Original Article

Use of yttrium-90 radioembolization for patients with unresectable liver metastases: experience from a single center

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Background: Yttrium-90 (Y-90) radioembolization is an intra-arterial, catheter-based therapy that delivers high doses of internal radiation to tumors while sparing normal surrounding tissue. Metastatic liver disease, in general, is associated with a poor prognosis from a variety of primary gastrointestinal malignancies. As a result, Y-90 radioembolization has an emerging role in locoregional control of patients with unresectable liver metastases.

Methods: Patients with cancer that metastasized to the liver and treated with Y-90 radioembolization between 2005 and 2015 (n=21) were evaluated retrospectively. Patients were selected based on multi-disciplinary evaluation; inclusion criteria included data that were abstracted from medical records including patient records, laboratory data, and radiographic studies. Toxicities were recorded using Common Terminology Criteria 3.0. Response was recorded according to mRECIST criteria.

Results: Twenty-one patients received treatments with SIR-Spheres Y-90 radioembolization. The median treatment activity delivered was 1.3 gBq (range, 0.7–1.7 gBq). The median treatment dose delivered was 95.5 Gy (range, 50–120 Gy). The median lung shunt fraction was 2.0% (range, 0.5–5.8%). Toxicities as measured by laboratory values were overall low, with alkaline phosphatase (Alk Phos) being most commonly elevated following treatment in 52% of patients, followed by AST and ALT derangements in 29% and 33% of patients, respectively. The most common clinical toxicities among all patients were abdominal pain (43%), followed by nausea/vomiting (38%), fatigue (19%), anorexia (14%), and diarrhea (10%). A clinical benefit response was seen in 71% [defined as patients achieving complete response (CR), partial response (PR), or stable disease (SD)]. PR was seen in 33% of cases; progressive disease (PD) was noted in 29%. Post-initial treatment, patients survived for a median 9 months (range, 6.01–14.1 months) after their first radioembolization treatment, and survival from the time of diagnosis of liver metastasis was 21.8 months (range, 14.2–40.2 months).

Conclusions: For patients with nonresectable metastasis of cancer to the liver, Y-90 radioembolization is a safe and well-tolerated procedure and a potentially useful option in hepatic malignancies that are not satisfactorily addressed by existing treatment modalities. This data suggest that a significant percentage of patients achieve clinical benefit including many with PR. Survival after treatment from this single-center is consistent with preexisting evidence. Prospective, randomized data is required to compare radioembolization with other therapies including chemoembolization and systemic chemotherapy.

Keywords: Metastatic liver cancer; radioembolization; yttrium-90 microspheres (Y-90 microspheres)

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Introduction

Yttrium-90 (Y-90) microspheres radioembolization is an intra-arterial, catheter-based technique that delivers high doses of internal radiation to liver tumors. Y-90 is embedded into non-biodegradable microspheres which are selectively administered to branches of the hepatic artery. The goal of radioembolization is to deliver tumoricidal doses of radiation to tumors while sparing surrounding liver parenchyma. Radioembolization takes advantage of the unique vascular supply of the liver and hepatic solid tumors. Liver metastases are hypervascular lesions deriving 80–100% of their blood supply from the hepatic artery as compared with the liver parenchyma which relies on the portal vein (1,2). Microspheres embedded with Y-90 when installed through the hepatic artery concentrate in liver tumors in a 3:1 to 20:1 ratio when compared with normal liver parenchyma. As a result, liver tumors in particular are favorable targets for intra-arterial therapies based on this preferential blood supply.

Y-90 is a pure beta-emitter with a mean tissue penetration of 2.5 mm. A dose of 1 GBq contains approximately 25 million microspheres and provides about 50 Gy per kilogram. Y-90 microspheres have been found to deliver highly effective radiation doses (100 to 1,000+ Gy) to tumor tissue (3). Conventional external beam radiation is limited by the extreme radiosensitivity of liver parenchyma; whole liver external beam radiation is limited to 30 Gy to avoid radiation-induced liver toxicity (4). At present, two commercially available products are available, SIR-Spheres and TheraSpheres. SIR-Spheres were approved for colorectal cancer with metastasis to the liver in conjunction with continuous intrahepatic infusion floxuridine (FUDR).

The liver is the most common site of metastases in primary gastrointestinal malignancies because of hematogenous spread of malignant cells through the portal circulation. In addition, the presence of unresectable hepatic metastases is an independent sign of poor prognosis (5,6). The five year survival rate for patients with hepatic metastases ranges from 23–45% (7). Surgical resection is the treatment of choice for eligible patients as it may potentially result in clinical cure. Candidacy for surgical resection of liver metastases is generally based upon medical fitness for surgery, the functional reserve of the liver, the number and size of lesion lesions, lymph node/vascular involvement, and the presence of extra-hepatic disease, although criteria differ among individual surgeons and institutions (8,9).

Unfortunately, only 10% to 20% of metastatic colorectal carcinoma is resectable (10). Without intervention, colorectal liver metastases have a reduced median survival of 9 months (11). Cholangiocarcinoma and other biliary cancers are often diagnosed at an advanced stage, requiring resection of both primary and metastatic disease, which is associated with high operative mortality. For endocrine tumors with liver metastases, the 5-year survival for untreated disease is 13–54%, but only 10–20% of these cases are candidates for complete resection with curative resection often not possible (12). As a result, there has been continued interest in defining the role of alternative regional treatments for disease control including local tumor ablation, regional hepatic intra-arterial chemotherapy or chemoembolization, radiation therapy, and intra-arterial radioembolization.

To date the safety and efficacy of Y-90 radioembolization in the management of liver metastases has been promising. In a 2014 review of 20 studies (979 patients), patients with unresectable metastatic colorectal cancer who failed chemotherapy had a median survival of 12 months after Y-90 treatment, with 0% complete response (CR), 31% partial response (PR), and 40.5% stable disease (SD); median time to intrahepatic progression was 9 months (13). A prospective study by Rafi *et al*. treated 19 patients with cholangiocarcinoma with liver involvement, with 0% CR, 11% PR, 68% SD, and 21% progression of disease; median survival of 12 months after start of Y-90 (14). A prospective study by Cao *et al*. examined 51 patients with neuroendocrine metastases treated with radioembolization, with 12% CR, 27% PR, 27% SD, and 33% progression of disease; median survival was 36 months (15). However, a 2009 Cochrane review concluded that well-designed, large, phase III clinical trials were still needed to confirm the effectiveness of radioembolization of colorectal metastasis to the liver (16).

Methods

Patient cohort

Between 2005 and 2015, 21 patients with unresectable liver metastases were treated with Y-90 microspheres at Scripps Clinic. Eligibility for radioembolization was determined by treating providers involving a multi-disciplinary team of medical oncologists, radiation oncologists, interventional radiologists, and surgeons. Selection criteria included the

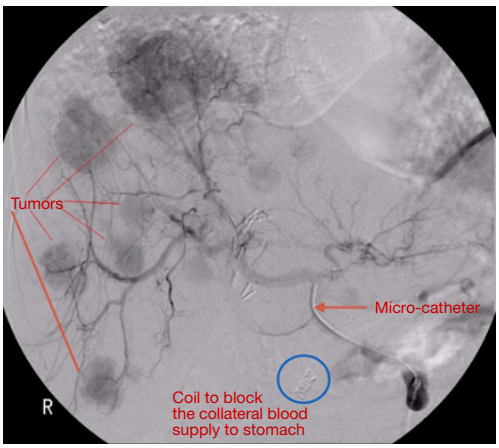

Figure 1 A hepatic angiogram on a patient with multiple liver metastases. There was a coil embolization of the left gastric artery to prevent delivery of Y-90 to the gastrointestinal system. Y-90, yttrium-90.

following: the presence of unresectable liver dominant metastases, progressive disease (PD) despite systemic therapy, disease not amenable to alternative locoregional therapies, age greater than 18 years old, clinically acceptable pretreatment performance status, and ability to undergo pretreatment angiography. Exclusion criteria included uncorrectable blood flow to the gastrointestinal tract, significant extra-hepatic disease, and applied lung dose greater than 30 Gy in a single treatment fraction.

A comprehensive review of each patient's medical record was performed including baseline patient characteristics, toxicities, radiographic imaging, and survival outcomes. Data were collected retrospectively. The study was approved by our institutional review board, and patient data were deidentified compliant with the Health Insurance Portability and Accountability Act. This work conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

Pretreatment evaluation and staging

All patients included in this study were diagnosed with secondary metastatic liver cancer with tumor biopsy, radiographic imaging, or a combination thereof. Pretreatment evaluation included comprehensive history and physical, routine laboratory tests, and baseline imaging studies. Primary tumor staging was accomplished by American Joint Committee on Cancer (AJCC) TNM staging system.

Intervention

All patients underwent pretreatment computed tomography (CT) scan of the chest and abdomen in order to determine liver lobe volumes. Celiac and hepatic angiography was performed to define hepatic vascular anatomy. Patients with hepatic arteries supplying gallbladder, stomach, or intestine underwent coil embolization of collateral arteries or were otherwise excluded from therapy (*Figure 1*). A Tc-99-macro-aggregated albumin (MAA) was performed at the time of the planning angiogram to determine lung shunting for planning purposes to avoid complications of radiation pneumonitis (*Figure 2*).

The prescribed activity of Y-90 for resin microsphere was determined according to body surface area (BSA) method outlined in the User's Manual and Package Insert provided by the manufacturer. The method varies the prescribed activity based upon the size of the patient as well as the proportion of tumor involvement of the liver. The activity delivered was reduced if there was evidence of increased lung shunt. Microspheres activity was determined utilizing conventional Medical Internal Radiation Dose (MIRD) Committee technique adjusted according to the calculated shunt of lung particles.

Post-treatment evaluation

Tumor response was assessed by post-treatment CT scan (*Figure 3*). Response was determined according to guidelines from RECIST 1.1 (17,18). CR was defined as the disappearance of any intra-tumoral arterial enhancement in all target lesions. PR was defined as an at least 30% decrease in the sum of the diameters of viable target lesions. PD was defined as an at least 20% increase in diameters of enhancing target lesions or evidence of new lesion. SD was defined as any tumor response between PR and PD. If a patient expired before repeat imaging could be performed, they were considered to have PD.

Clinical and laboratory toxicities

Patients were followed up with regular visits at regular intervals as determined by the treating provider. Clinical and laboratory adverse events were recorded from medical records, following the National Cancer Institute Common Terminology Criteria (NCI CTC) version 3.0. Toxicities were measured and followed for both clinical symptoms and derangement of laboratory measurements of total bilirubin, albumin, aspartate aminotransferase (AST), alanine

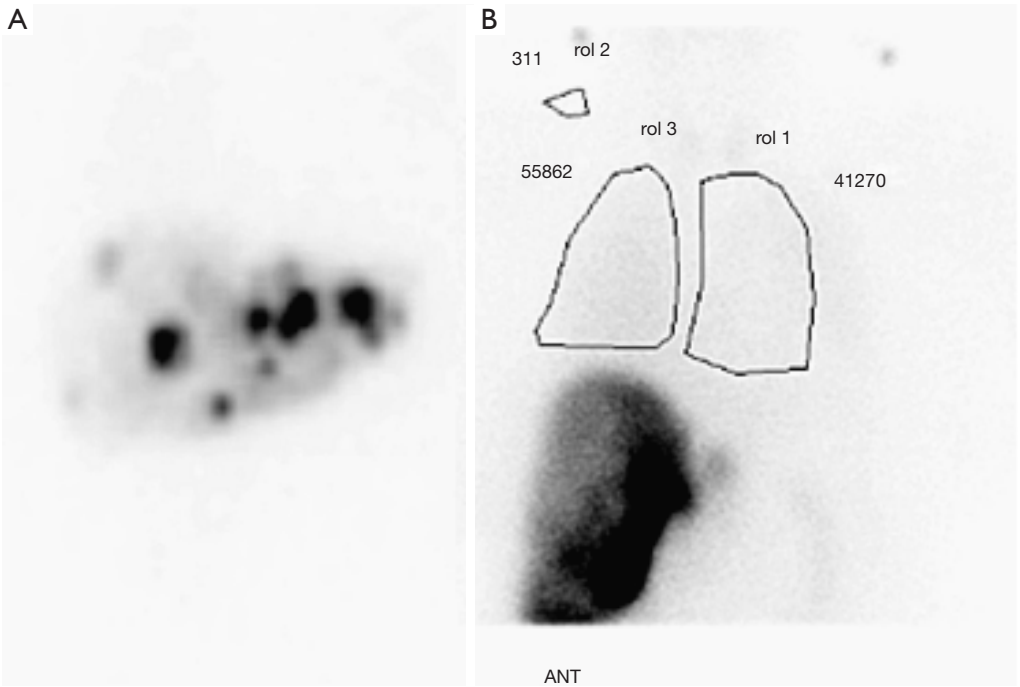

Figure 2 Nuclear medicine planar image for a typical Tc-99m MAA scan to determine the percent of lung shunting. (A) The left figure shows how MAA can also be used to further delineate the hepatic anatomy; (B) the right figure shows a study where there was negligible lung shunting, and treatment with Y-90 could proceed. MAA, macro-aggregated albumin; Y-90, yttrium-90.

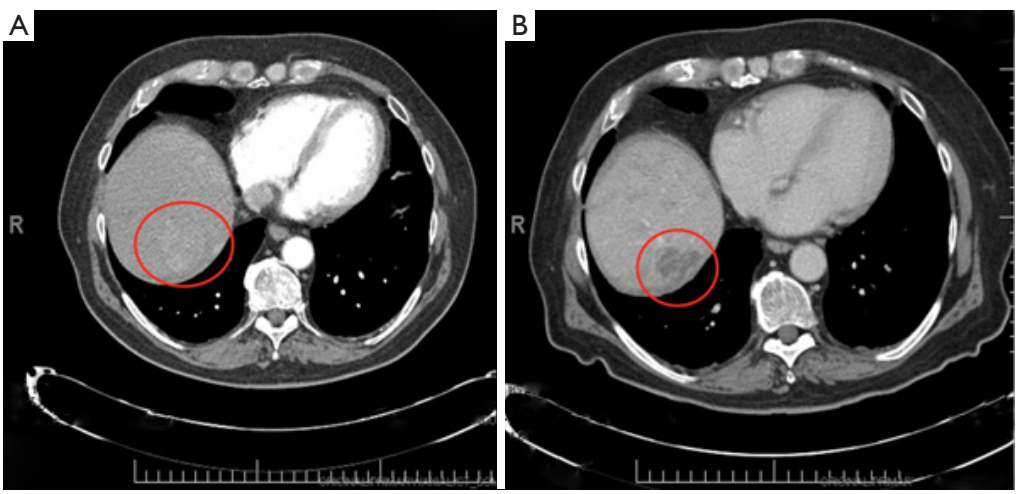

Figure 3 A CT scan of a patient before and after Y-90 treatment. (A) In the pre-treatment CT on the left, the arterial phase shows a tumor with early arterial enhancement; (B) the post-treatment CT in the washout phase, on the right, shows exaggerated decreased contrast enhancement in the area of the tumor due to necrosis after Y-90 treatment. CT, computed tomography; Y-90, yttrium-90.

Table 1 Baseline demographics, tumor characteristics, and treatment characteristics of the 21 patients studied

Patient characteristics	n (%)
Age (years)	63.4 (14.3)
Female	12 (57.1)
Caucasian	21 (100.0)
Karnofsky performance status	
100	4 (19.0)
90	11 (52.4)
80	6 (28.6)
Tumor type	
Neuroendocrine	5 (23.8)
Carcinoid	3 (14.3)
Insulinoma	1 (4.8)
Merkel cell carcinoma	1 (4.8)
Pancreaticobiliary	7 (33.3)
Pancreatic ductal adenocarcinoma	4 (19.0)
Cholangiocarcinoma	3 (14.3)
Colorectal	9 (42.9)
Colon adenocarcinoma	7 (33.3)
Rectal adenocarcinoma	2 (9.5)
Tumor characteristics	
Tumor size, largest (cm)	5.1 (2.6)
Nodal involvement	9 (42.9)
Distant metastasis	10 (47.6)
Distribution	
Unifocal	1 (4.8)
Multifocal	20 (95.2)
Tumor location	
Unilobar	6 (28.6)
Bilobar	15 (71.4)
Treatment characteristics	
Prior therapy	
Resection	4 (19.0)
Radiofrequency ablation	1 (4.8)
Chemotherapy	15 (71.4)
External beam radiation	1 (4.8)
None	2 (9.5)
Number of treatments	
One	13 (61.9)
Two	8 (38.1)
Activity	1.30 (0.27)
Percent lung shunting	2.00 (1.41)

All patients were Caucasian and received one or two treatments of Y-90. Most patients had multifocal distribution of their tumors and had undergone prior treatment of their tumors. Y-90, yttrium-90.

aminotransferase (ALT), and Alk Phos.

Statistical analyses

Overall survival was the primary endpoint used in this study defined as the time between the date of first treatment and date of death. Secondary endpoints included survival since diagnosis, as well as proportion of patients with CR, PR, SD, and PD. Data were analyzed using descriptive methods. Median overall survival (including corresponding 95% confidence interval) was determined through Kaplan-Meier survival-analysis. Statistical analysis was performed with the software program R (19).

Results

Baseline characteristics

The 21 patients studied were predominantly between the ages of 50 and 75 years old and Caucasian (*Table 1*). The types of cancers studied were neuroendocrine (n=5), pancreaticobiliary tract (n=7), and colorectal (n=9). A majority of patients had undergone prior therapy, including chemotherapy (n=15), resection (n=4), and radiofrequency ablation (n=1). Most of the tumors were multifocal and bilobar, and in approximately half of the cases, the typical tumor size was 5 cm or smaller, commonly with extrahepatic and lymph node involvement.

Clinical and laboratory toxicities

The most common clinical toxicities were abdominal pain in 9 (43%) patients, followed by nausea and vomiting in 8 patients (38%). Anorexia and fatigue occurred in only 3 (14%) and 4 (19%) patients, respectively, and diarrhea occurred in only 2 cases (10%). About 33% of patients experienced no clinical side effects whatsoever.

The most common toxicity measured by laboratory values was Alk Phos, which showed mild toxicity in 11 patients, or 52% of our cohort (*Table 2*). Mild AST and ALT toxicities occurred in 6 and 7 patients respectively (29% and 33%). Bilirubin toxicity was mild in 3 patients (14%) and severe in 1 case (5%), and albumin toxicity was mild in 3 cases (14%) and severe in only 1 case (5%).

Tumor response

In this 21 patient cohort, 15 patients (71%) experienced

Table 2 Clinical and laboratory toxicities of Y-90 treatment graded according to the National Cancer Institute Common Terminology Criteria (NCI CTC) version 3.0. The most common toxicities were mild alkaline phosphatase elevation, abdominal pain, and nausea/vomiting

Clinical toxicities	n (%)
Fatigue	4 (19.0)
Abdominal pain	9 (42.9)
Nausea/vomiting	8 (38.1)
Anorexia	3 (14.3)
Diarrhea	2 (9.5)
Gastric ulcer	1 (4.8)
None	7 (33.3)
Laboratory toxicities	
Grade 1/2	
Bilirubin	3 (14.3)
Albumin	3 (14.3)
AST	6 (28.6)
ALT	7 (33.3)
Alk Phos	11 (52.4)
Grade 3/4	
Bilirubin	1 (4.8)
Albumin	1 (4.8)
AST	0 (0)
ALT	0 (0)
Alk Phos	0 (0)

Y-90, yttrium-90; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alk Phos, alkaline phosphatase.

a clinical benefit (either SD or PR). Eight patients (38%) experienced SD, and 7 patients (33%) experienced a PR (*Table 3*). A CR was not seen in any of these cases.

For patients with neuroendocrine tumors (n=6), 2 patients had a PR, 2 patients had SD, and 1 patient had progression of disease; the clinical benefit was 80%. Of the pancreatobiliary tumors (n=7), 3 patients had SD, and a single patient had a PR, for a total of 57% clinical benefit. Colorectal cancer (n=9) had a higher clinical benefit of 78% (3 with SD; 4 with PR).

Survival

Overall survival for this patient cohort was 22.5 months. Survival since the time of diagnosis for patients with neuroendocrine, pancreaticobiliary, and colorectal tumors were 40.2, 14.2, and 22.5 months respectively (*Table 3*). Kaplan-Meier curves for overall survival from diagnosis are demonstrated in *Figure 4*.

Prognosis

Unsurprisingly, the presence of increased index tumor size, extrahepatic metastases, and derangements in any lab value prior to treatment were significant predictors of poorer prognosis and survival rate (*Table 4*). However, the presence or absence of neoplasm-invaded lymph nodes did not seem to strongly correlate with survival.

While derangement of any of five lab values (total bilirubin, serum albumin, AST, ALT, and Alk Phos) would

Table 3 Tumor response to Y-90 treatment since diagnosis and first treatment according to RECIST 1.1 guidelines and survival

Variable	Neuroendocrine	Pancreaticobiliary	Colorectal	Overall
Tumor response, n (%)				
Complete response	0 (0)	0 (0)	0 (0)	0 (0)
Partial response	2 (40.0)	1 (14.3)	4 (44.4)	7 (33.3)
Stable disease	2 (40.0)	3 (42.9)	3 (33.3)	8 (38.1)
Progressive disease	1 (20.0)	3 (42.9)	2 (22.2)	6 (28.6)
Survival				
Survival since diagnosis (months)	40.2	14.2	22.5	21.8
Survival since Y-90 (months)	14.1	6.01	9.5	9

Y-90, yttrium-90.

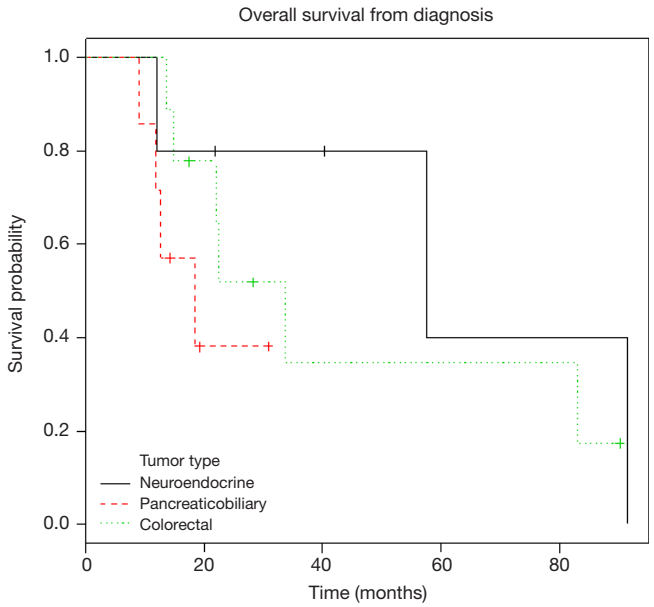

Figure 4 Kaplan-Meier curves depicting overall survival as well as survival for different tumor types.

be a strong predictor of poorer outcome, total bilirubin and serum albumin were abnormal in very few of our patients prior to treatment.

Conclusions

The growing literature on radioembolization shows that Y-90 is an effective treatment for the management of metastatic tumors (20). The median survival of chemorefractory, metastatic liver disease from colorectal, neuroendocrine, and biliary cancer after treatment with Y-90 radioembolization in our retrospective cohort was 9.5, 14.1, and 6.01 months, respectively. This is comparable to median survival times of 4.5–17 months for metastatic colorectal cancer and 23–45 months for metastatic neuroendocrine tumors (21-23). Overall median survival after treatment with Y-90 radioembolization in the biliary tract group varied depending on the specific primary malignancy; however a median survival 11.3–16.3 months for patients with intrahepatic cholangiocarcinoma has been reported in other similar studies (24,25).

A clinical benefit, defined as the presence of CR, PR, or

Table 4 Comparison of survival with regards to tumor type, laboratory toxicity, lymph node involvement, extrahepatic metastases, and index tumor size

Variable	Number of patients (%)	Since treatment		
		Mean	Median	Range
Total survival (months)	13 (100.0)	17.9	8.2	2.2–82.3
Etiology				
Biliary	4 (31.0)	5.7	5.4	3.9–8.2
Colorectal	6 (46.0)	12.6	8.5	2.2–41.8
Neuroendocrine	3 (23.0)	44.9	43.3	9.0–82.3
Bilirubin				
≤1.0	11 (85.0)	20.0	9	2.2–82.3
>1.0	2 (15.0)	6.5	6.5	4.8–8.2
Albumin				
≥3.4	10 (77.0)	22.1	9.3	4.3–82.3
<3.4	3 (23.0)	4.0	3.9	2.2–6.0
AST				
≤40	6 (46.0)	31.5	25.8	3.9–82.3
>40	7 (54.0)	6.3	6	2.2–9.5
ALT				
≤72	7 (54.0)	26.6	7.5	2.2–82.3
>72	6 (46.0)	7.8	8.6	4.3–9.9
Alkaline phosphatase				
≤126	7 (54.0)	27.5	9	3.9–82.3
>126	6 (46.0)	6.7	7.1	2.2–9.9
Nodes				
Negative	6 (46.0)	20.1	8.9	4.8–82.3
Positive	7 (54.0)	16	7.5	2.2–43.3
Extrahepatic metastases				
Negative	6 (46.0)	31.5	25.7	3.9–82.3
Positive	7 (54.0)	6.3	6	2.2–9.9
Index tumor size				
≤5 cm	8 (62.0)	25.4	9.7	3.9–82.3
5–10 cm	3 (23.0)	6.2	6	4.3–8.2
≥10 cm	2 (15.0)	5.6	5.6	2.2–9.0

Improved survival associated with normal labs, negative lymph node involvement, no extrahepatic involvement, and index tumor sizes of 5 cm or less. Neuroendocrine tumors had longer survival than biliary or colorectal tumors. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

SD by RECIST criteria, was seen in 71% of patients in our cohort. A 78% clinical benefit was seen in the metastatic colorectal cancer subgroup, consistent with prior studies (13). A 57% clinical benefit was seen in the metastatic biliary tract cancer subgroup, and an 80% clinical benefit was seen in the metastatic neuroendocrine cancer subgroup; however, a clinical benefit has been previously reported as high as 90% in metastatic disease to the liver from primary sites other than colorectal cancer (26). CR in metastatic liver disease is exceedingly uncommon as demonstrated in our series, consistent with prior reports. Evaluation of treatment response by mRECIST criteria involves monitoring changes in lesion size post treatment. These radiographic changes may not reflect the true effectiveness of treatment due to changes that occur after Y-90 radioembolization such as hemorrhage, peritumoral edema, and ring enhancement within and surrounding the tumor site (27). Cianni *et al*. suggest that tumor response may be better determined with a volumetric assessment, using FDG-PET or fMRI with diffusion-weighted sequences as a means to evaluate tumor response.

This sample of patients confirms that Y-90 radioembolization is a generally safe and well-tolerated procedure. The majority of the laboratory toxicities noted in our study included low-grade derangements in albumin, transaminase, bilirubin and Alk Phos levels. The most common clinical toxicities were abdominal pain in 9 patients (43%), followed by nausea and vomiting in 8 patients (38%). These symptoms are consistent with the well-described complication of radioembolization known as post embolization syndrome (PES). Symptoms of PES include nausea, fevers, right upper quadrant pain, and vomiting; given these findings, PES is most likely the cause of the clinical toxicities experienced by our cohort (28). Radioembolization can cause serious complications including gastrointestinal ulceration, pancreatitis and cholecystitis (29); however, these complications were not experienced in our patient sample.

Radioembolization has been shown to be comparable to other locoregional therapies as a salvage regimen for metastatic liver disease. Hong *et al*. reported a similar survival benefit and fewer complications with radioembolization compared to chemoembolization for liver-dominant metastatic colorectal adenocarcinoma in 36 patients (30). To date, no randomized controlled trials have compared radioembolization and chemoembolization for cholangiocarcinoma. However, trials are currently underway comparing the two treatment approaches as a first line therapy for inoperable cholangiocarcinoma confined to the liver (31). A twenty-article meta-analysis evaluating median overall survival and tumor response to therapy in patients with unresectable intrahepatic cholangiocarcinoma showed that median overall survival was 22.8 months with hepatic arterial infusion (HAI), 13.9 months in Y-90 radioembolization, and 12.4 months in transcatheter arterial chemoembolization (TACE). Additionally, Y-90 radioembolization response rates (27.4%) were inferior to HAI (56.9%), but superior to TACE (17.3%) (32). For metastatic neuroendocrine tumors within the liver, several studies suggest that radioembolization may be the preferred option over other intra-arterial based therapies. Studies of moderate quality evidence evaluated by a multidisciplinary group of experts suggest that radioembolization may cause fewer side effects compared to transcatheter arterial embolization (TAE) and TACE; however the quality and strength of the reports from this study were limited when comparing survival, symptomatic response, and imaging response (33).

There were several limitations to our study. Our small sample size, lack of control or comparison group, and heterogeneous primary cancer types within the study limits the ability to generalize our findings. Additionally, a majority of patients in our cohort had multifocal metastatic disease, which is a poor prognostic indicator; however this factor is inherent to the patient population typically selected for radioembolization. Despite these limitations, our data adds to the growing body of evidence suggesting that radioembolization is a reasonable treatment option to stabilize or improve the burden of metastatic liver disease in patients with chemorefractory liver metastases and is generally well tolerated.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2016.01.13). HG serves as an unpaid Co-Editor-in-Chief of *Translational Cancer Research*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Data were collected retrospectively. The study was approved by our institutional review board, and patient data were deidentified compliant with the Health Insurance Portability and Accountability Act. Individual consent was waived. This work conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

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