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Yttrium-90 Radioembolization for Intrahepatic Cholangiocarcinoma: Safety, Response, and Survival Analysis

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BACKGROUND

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy, and while rare, is experiencing a rising incidence in North America and Europe (1). A malignancy of the intrahepatic biliary epithelium, ICC is rapidly fatal with a median survival of 3 to 8 months if left untreated (2, 3). This dismal prognosis stems from a clinically silent course, with many patients presenting with advanced disease not amenable to curative resection (3, 4). For these patients, several palliative therapies have been attempted to improve survival, with mixed results.

Systemic chemotherapy regimens do demonstrate a modest survival benefit over supportive care, but > 40% of patients experience significant clinical toxicities, and overall survival remains below 1 year (5–7). To minimize systemic toxicities, locoregional therapies have been employed with moderate success. The use of radiofrequency ablation (RFA) has been reported; however, most series involve small patient cohorts with limited survival data (8–10). Transarterial chemoembolization (TACE) has been demonstrated to improve overall survival over supportive care, but significant toxicities are observed in > 20% of patients (11, 12).

Given ICC's relative radiosensitivity (13, 14), Yttrium-90 (Y90) radioembolization has promise as a locoregional treatment for this disease. Preliminary analyses of safety and efficacy have been reported in several small studies, with a reported median survival ranging from 9 to 14 months (2, 15, 16). The current study was undertaken to expand upon or initial proof-of-concept report (15), and further delineate the safety, antitumoral response, and survival following Y90 radioembolization of patients with unresectable intrahepatic ICC.

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METHODS

Patients

We previously reported a pilot study in 24 patients with unresectable ICC (15). The current study expands upon the prior report, now including forty-six patients with unresectable ICC who were treated with Y90 radioembolization at a single institution from July 2003 – May 2011. We conducted a review of a prospectively collected database. Our Institutional Review Board approved this study, and all patients provided informed consent. Patients were referred for treatment by medical/surgical oncology and were discussed at multidisciplinary tumor board. Patient selection criteria included: 1) histologically proven ICC, 2) unresectable tumor, 3) an Eastern Cooperation Oncology Group (ECOG) performance status of 0–2, 4) adequate liver function with bilirubin <2.0 mg/dL, and 5) ability to undergo visceral angiography. Exclusionary criteria included: 1) flow to the gastrointestinal tract not correctable by coil embolization or 2) estimated radiation dose to the lungs > 30 Gray (Gy) in a single administration or 50 Gy cumulatively.

Treatment Protocol

Pretreatment mesenteric angiography and technetium-99m macroaggregated albumin scanning were performed according to previously published guidelines (17). The device used was TheraSphere (Ottawa, Ontario, Canada); the United States Food and Drug Administration (FDA) approved this brachytherapy device for hepatocellular carcinoma (HCC). This device was used off-label for this study.

Liver function tests, complete blood count, coagulation profiles, albumin and total bilirubin levels were obtained on the day of Y90 treatment for all patients. Y90 treatment was administered with a planned dose of 120 Gy. Patients with bilobar disease were treated in a sequential lobar fashion, treating the contralateral side 30–60 days after the first treatment. Patients were evaluated at 1 month, 3 months, and every 3 months on protocol after treatment. At each follow-up visit, patients were assessed for clinical and biochemical toxicities and imaging was obtained (either computed tomography (CT) or magnetic resonance imaging (MRI)). Patients were retreated if they demonstrated signs of incomplete tumor targeting, or progressive intra-hepatic disease as determined by imaging response.

Data Collection, Statistical Analysis, Outcome Measures

All medical, laboratory, clinical, and imaging data were acquired prospectively. The primary endpoint of this study was safety. Secondary endpoints included tumor response and overall survival (OS). Analyses were by intention to treat. The Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 4.0) was used to categorize toxicities (18). Biochemical toxicities that occurred any time after treatment, without time cutoff, are reported.

Tumor response by CT/MRI was determined using the World Health Organization (WHO) classification for all measurable lesions (>1 cm) in which the sum of pretreatment and post-treatment cross products were calculated by multiplying the greatest lesion dimension and its maximum orthogonal distance. Definitions of responses were: 1) complete response (disappearance of all lesions); 2) partial response (>50% reduction in cross product); 3) progressive disease (>25% increase in cross product); and 4) stable disease (any tumor size between criteria for partial response and progressive disease). The European Association for the Study of Liver Disease (EASL) modification of WHO response criteria was implemented (19). Tumors that exhibited >50% necrosis on post-treatment imaging were categorized as EASL responders. Definitions of response were: 1) complete response (100%

of treated lesion non-enhancing) and 2) partial response (between >50% and <100% of treated lesion non-enhancing).

Median survival was calculated using the Kaplan-Meier method from the time of first treatment and was stratified by: 1) performance status, 2) portal vein thrombosis (PVT), 3) extrahepatic metastases, 4) prior systemic chemotherapy, 5) tumor morphologic variant (peripheral, well-defined mass-like versus infiltrative, ill-defined); and 6) tumor distribution. Patients were censored if they were alive at the end of the study period. Additionally, patients who underwent either resection or transplantation were also censored. The log-rank test was used to assess differences in survival estimates between groups. A P value < 0.05 was considered significant.

RESULTS

Baseline Patient Characteristics

Table 1 summarizes baseline patient characteristics. During an 8-year period, 46 patients (25 men and 21 women) were treated. The median patient age was 68 years (range: 44–86). Eighteen patients (39%) were treatment naïve. The majority of patients were ECOG 0 (n=24, 52%), exhibited solitary (n=29; 65%), peripheral ICC (n=26; 57%) without portal vascular invasion (n=34; 74%) or extrahepatic metastases (n=30; 65%).

Treatment

All patients were treated on an outpatient basis and were discharged 2–6 hours following the procedure. The study population underwent a total of 92 treatments (average: 2/patient). Fourteen patients received 1 treatment, 8 patients received 2 treatments, and 24 patients received 3 treatments. Table 2 summarizes treatment data for all patients.

Biochemical and Clinical Toxicity

Clinical toxicities included fatigue in 25 patients (54%); transient, vague abdominal pain in 13 patients (28%); nausea in 6 patients (13%); vomiting in 4 patients (9%) and anorexia in 2 patients (4%). Four patients (9%) developed grade 3 albumin toxicity, and three patients (7%) experienced grade 3 bilirubin toxicity. No other serologic toxicities were observed. One patient (2%) developed a gastroduodenal ulcer that was refractory to medical management and necessitated an antrectomy and gastrojejunostomy. This was secondary to non-target microsphere administration to the lesser curvature of the stomach via an unrecognized small right gastric artery. Postprocedural imaging findings (available in 45 patients) of ascites and pleural effusions were demonstrated in 7 (15%) and 2 patients (4%), respectively.

Response and Imaging Findings

Figure 1 illustrates response as a waterfall plot. Follow-up imaging demonstrated an overall objective tumor response (any decrease in size) in 44 patients (98%); mean tumor reduction was 35%. By WHO criteria, a partial response was seen in 11 patients (25%), stable disease in 33 patients (73%), and disease progression in 1 patient (2%). According to EASL criteria, a complete response was observed in 4 lesions (9%), and a partial response was observed in 28 lesions (64%). No patient had disease progression by EASL.

Post Y90 resection

Five patients (11%) were downstaged to resection after treatment. Within this subset of patients, all were ECOG 0 with solitary peripheral tumors without portal vascular invasion. All patients within this subset were treatment naïve prior to radioembolization, and deemed

unresectable by a multidisciplinary tumor board including surgical oncology/transplant surgery. Three patients underwent right lobectomy, and 2 patients underwent trisegmentectomy (Table 3). The median time from radioembolization to surgical resection was 113 days, with a median follow-up after resection of 979 days. All patients were alive at the conclusion of the study. One patient (2%) with a known history of ulcerative colitis and primary sclerosing cholangitis underwent orthotopic liver transplantation after demonstrating a favorable response to radioembolization.

Survival

At final survival analysis (May 2012), 7 patients (15%) remained alive, and 39 patients (85%) had succumbed to their disease. The median follow-up was 29 months. Figure 2 displays survival stratified by tumor morphology using a Kaplan-Meier survival curve.

Table 4 summarizes univariate/multivariate analyses according to baseline characteristics. Univariate analyses revealed portal vein thrombosis, multifocal disease, infiltrative pattern, and tumor burden >25% as negative prognosticators of survival. Of these variables, however, portal vein thrombosis was not found to be significant in a multivariate model. The median survival was 14.6 months for patients with solitary tumors (n=29), versus those with multifocal tumors (P<0.005). The median survival for patients with peripheral tumor morphology (n=26) versus infiltrative tumor morphology (n=20), was 15.6 months and 6.1 months, respectively (P=0.006). The median survival for patients (n=36) with <25% disease burden was 14.4 months, versus 5.3 months in those with >25% disease burden (P=0.028).

DISCUSSION

ICC accounts for 10–20% of all primary liver cancers, and presents with a clinically silent course, portending a poor prognosis (20). If left untreated, median survival ranges from 3–8 months (3). Over 60% of patients are not candidates for curative therapy due to advanced disease and comorbidities (4). For those with non-operative disease, multiple palliative therapies exist to control tumor growth and prolong survival, with no consensus on a standard of care.

Systemic chemotherapy regimens incorporating gemcitabine demonstrate marginal survival benefit, with a median overall survival of 8 months, at the cost of Grade 3–4 toxicities in > 40% of patients (6, 7). With limited response and significant toxicities associated with systemic approaches, locoregional therapies have been explored for these patients.

Several studies have examined the use of TACE in the setting of unresectable ICC (21). A prospective study by Kiefer et al involved 62 patients (11). Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), demonstrating partial response in 11%, stable disease in 64%, and progression in 24% of patients. Five patients experienced major complications. Post-embolization syndrome (CTCAE grade 1 or higher of post-procedural pain, fever, nausea or vomiting) occurred in 65% of patients. Median OS was 15 months from time of first treatment. Park et al (12) compared the benefits of TACE over supportive care in the management of ICC in 155 patients. By RECIST criteria, 23% experienced a partial response, 66% had stable disease, and 11% had progressive disease. Major hematologic and non-hematologic toxicities (CTCAE>grade 3) were observed in 13% and 24% of patients, respectively. TACE exhibited a survival benefit over supportive care, with a median OS of 12.2 vs. 3.3 months (p<0.001). These results corroborate prior smaller studies, with median OS ranging from 9–12 months (22, 23). More recently, 2 small studies from Aliberti et al (24) and Poggi et al (25) have revealed a potential therapeutic role for drug-eluting microspheres, however sample size and survival data is very limited.

Prior to the current study, three studies have examined the utility of Y90 radioembolization in patients with unresectable ICC (2, 16), including one preliminary study from our own institution (15). Hoffman et al (16) retrospectively reported on 33 patients who underwent Y90 radioembolization as inpatients. These patients had largely failed other therapies, with 79% of patients receiving prior chemotherapy, 37% receiving prior surgery, and 18% receiving prior RFA, TACE, or external beam radiation. Using RECIST criteria, disease control (partial response or stable disease) was noted in 85% of patients. Median OS was 10 months from time of first treatment. Patients with favorable functional status (ECOG=0) and limited tumor burden (<50%) experienced significantly better prognosis. A study by Saxena et al (2) in 25 patients revealed similar results, demonstrating disease control in 74% of patients by RECIST, with a median OS of 9.3 months. The majority of this cohort had received prior chemotherapy (68%), with many having had prior liver resections (40%). The presence of favorable functional status (ECOG=0) and non-infiltrative tumors improved survival in these patients. Our original pilot study (15), represented a proof-of-concept, and demonstrated safety in a limited patient cohort. The current study confirms our initial results, and represents a more mature cohort of these patients, with long-term follow-up. As such, the current survival data does not demonstrate early censoring bias. In our current study 35% of patients had previous systemic chemotherapy, while 15% had previous liver-directed therapies. By WHO imaging criteria, disease control was evident in 98% of patients, and by EASL guidelines, 73% of patients demonstrated >50% necrosis on follow-up imaging. The most common post treatment clinical symptoms were fatigue (54%) and abdominal pain (28%), which is in line with other studies utilizing radioembolization for hepatic tumors (26). After multivariate analyses, several prognostic factors were noted to negatively affect survival: multifocal disease, infiltrative disease, and tumor burden >25%.

Our current study demonstrates a subset of patients with peripheral solitary tumors may be downstaged to surgical resection. The ability to downstage offers a clear advantage with regard to survival, as resection offers the only potentially curative therapeutic option (20). Five-year survival following resection ranges from 27–48% (4, 20). Eleven percent of our patients (5/46) initially presented with localized unresectable tumors, which were downstaged to surgical resection. All patients within this subset were treatment naïve. None of these patients received cytotoxic therapies following radioembolization, and therefore maintained good performance status. Three patients had right lobe tumors abutting the middle hepatic vein. None had adequate future liver remnant to allow for a right trisegmentectomy. Following Y90 radioembolization, two of these patients experienced tumor retraction from the middle hepatic vein, allowing for a right hepatectomy. The third patient also experienced tumor retraction from the middle hepatic vein but required portal vein embolization prior to right hepatectomy. Two patients were deemed unresectable due to a central tumor abutting both the right and left hepatic veins. Following radioembolization, tumor retraction from the left hepatic vein permitted right trisegmentectomy. The fifth patient had a mass abutting the IVC precluding surgical resection. Following radioembolization, a clear margin between the tumor and IVC was evident on CT and confirmed with intravascular ultrasound.

As demonstrated in prior studies (4, 27, 28), patients who undergo curative (R0) resection have the best long-term survival, which was seen in our small subset. Similar to HCC, progression-free survival following radioembolization for ICC may yield insight into tumor biology (29, 30). These patients may possess less biologically aggressive tumors, and may benefit from adjuvant curative resection. Based on the published literature, and our current report, adjuvant resection rates are higher following radioembolization (2, 16) than TACE (11, 12, 22, 23). These results, taken together, suggest that therapeutic and patient selection can be further refined to improve the efficacy of downstaging.

There are several limitations to this study. This is a single institution study at a tertiary-level center reporting on a small patient cohort, thereby making definitive treatment recommendations difficult. Second, the majority of the patients (61%) had undergone prior therapy. Isolating any survival effect achieved by the radioembolization is not possible. In order to investigate a survival benefit with radioembolization, randomized studies will be necessary.

This study confirms that in patients with unresectable ICC, radioembolization is safe, and demonstrates a significant anti-tumoral response and survival benefit. These survival benefits are dependent on baseline patient characteristics, especially disease burden. Results are most pronounced in patients with solitary tumors, who can be downstaged to curative resection. For patients with limited disease burden, our multi-disciplinary team prefers first line therapy with Y90 radioembolization; systemic chemotherapy is utilized in the adjuvant setting. Progression-free survival following radioembolization may be indicative of less biologically aggressive tumors, and may be used to expand the criteria for curative resection. As many patients present with advanced disease outside resection criteria, the possibility of downstaging disease burden via radioembolization should be further explored in future studies.

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Abbreviations

ICC	Intrahepatic cholangiocarcinoma
CR	Complete Response
CI	95% Confidence Interval
CT	triphasic contrast-enhanced computerized tomography
ECOG	Eastern Cooperative Oncology Group
EASL	European Association for the Study of the Liver
HCC	Hepatocellular Carcinoma
MRI	gadolinium-enhanced magnetic resonance imaging
OS	Overall Survival
PVT	Portal venous thrombosis
PD	Progressive Disease
PR	Partial Response
RCT	RECIST, Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
TACE	Transarterial Chemoembolization
WHO	World Health Organization

⁹⁰Y Yttrium-90 radioembolization

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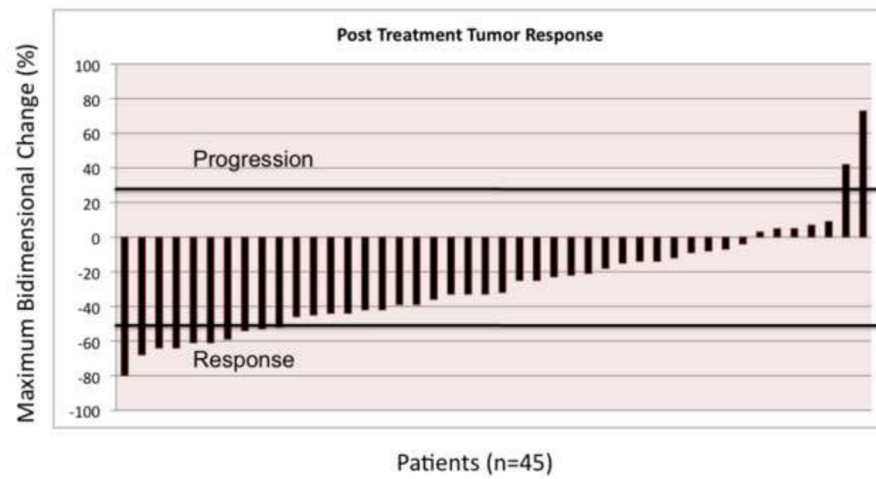


Figure 1. Tumor response using World Health Organization criteria are presented here as a waterfall plot. Bar values demonstrate the maximum change in tumor size from baseline in 45 patients after yttrium-90 radioembolization. Thresholds for disease progression and response are marked.

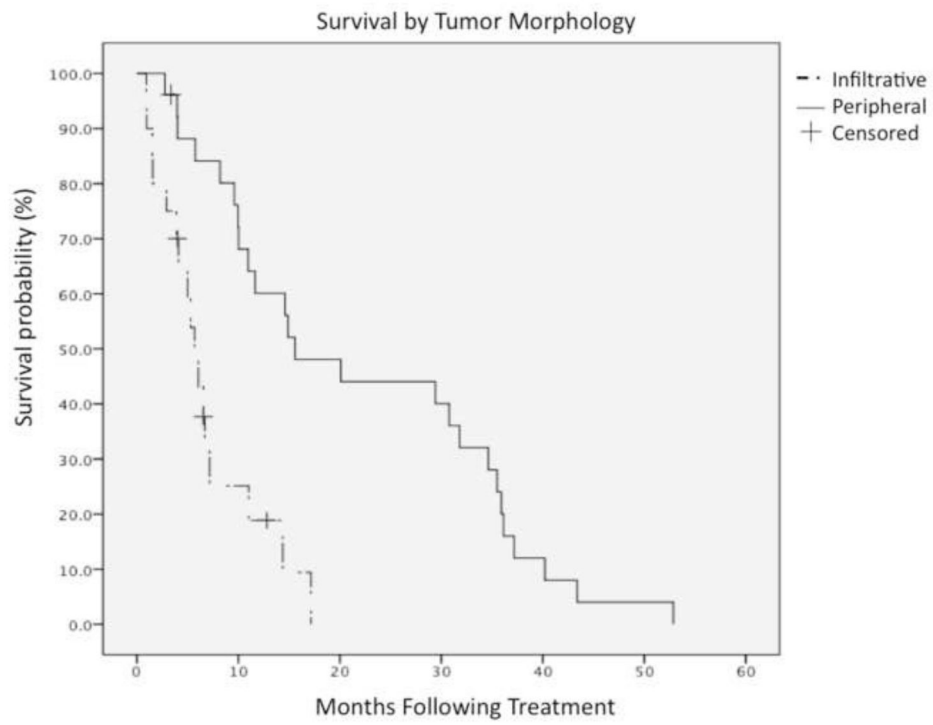


Figure 2. Overall survival as stratified by tumor morphology, peripheral versus infiltrative. Median survival with peripheral tumor morphology was 15.6 months, versus 6.1 months for infiltrative morphology (P=0.006).

Table 1

Baseline Characteristics

Characteristic	Category	N (%)
Age (years)	<65	25 (54)
	65	21 (46)
Gender	Male	25 (54)
	Female	21 (46)
Tumor Burden	<25%	36 (78)
	25–50%	8 (17)
	>50%	2 (4)
Distribution	Unilobar	30 (65)
	Bilobar	16 (35)
Number of lesions	Solitary	30 (65)
	Multifocal	16 (35)
Portal Vein Invasion	No	35 (76)
	Yes	11 (24)
Extrahepatic Metastases	No	30 (65)
	Yes	16 (35)
Pattern	Peripheral	26 (57)
	Infiltrative	20 (43)
ECOG	0	24 (52)
	1	21 (46)
	2	1 (2)
Previous chemotherapy	No	30 (65)
	Yes	16 (35)
Previous Liver-directed Therapy	None	39 (85)
	Resection	5 (11)
	RFA	1 (2)
	Transplant	1(2)

Abbreviation: ECOG, Eastern Cooperative Oncology Group; RFA, Radiofrequency ablation; TACE, Trans-arterial chemoembolization,

* patients may exhibit 1 or more symptom

Table 2

Yttrium 90 Dosimetry

Treatment	# Patients	Treatment	Median Dose (95% CI), Gy
Overall	46		
Right	25	70	95.4, 73.8–115.0
Left	8	23	114.7, 97.7–129.8
Bilobar	13	60	90.9, 68.0–103.7
Lung, Overall	46	90	3.9, 3.4–4.9

Gy indicates Gray; 95% CI, 95% confidence interval.

Table 3

Y90 Resection Cohort

Patient	Resection Type	Time Y90 to Resection (days)	Follow-up (days)
1	Right lobectomy	155	979
2	Trisegmentectomy	78	1412
3	Right lobectomy	77	1344
4	Trisegmentectomy	113	169
5	Right lobectomy	262	905

* All patients in the resection cohort were alive at the conclusion of the study

Table 4

Uni/Multivariate Analysis

Variable	Category	Univariate analysis (Survival)			Multivariate analysis (Cox Proportional Hazards Model)**		
		Median Survival in months	Hazard Ratio (CI)	P value	Adjusted P* Value	CI	P
ECOG	0	14.3	0.56 (0.07 – 4.27)				
	1	7.2	0.68 (0.08 – 5.01)	0.804			
	2	9.9	1.00				
Number of lesions	Solitary	14.6	0.37 (0.17 – 0.81)	0.0016	0.014	0.28 (0.12 – 0.65)	0.0031
	Multifocal	5.7	1.00			1.00	
Prior Chemotherapy	No	14.6	0.48 (0.22 – 1.05)	0.0262	0.235	0.62 (0.25 – 1.49)	0.28
	Yes	5.7	1.00			1.00	
PVT	No	14.4	0.32 (0.11 – 0.86)	0.0007	0.0063	0.96 (0.38 – 2.38)	0.919
	Yes	5.3	1.00			1.00	
Tumor Distribution	Unilobar	11.7	0.72 (0.36 – 1.44)	0.370			
	Bilobar	10.9	1.00				
Tumor Type	Peripheral	15.6	0.35 (0.16 – 0.78)	0.0005	0.0045	0.24 (0.09 – 0.66)	0.006
	Infiltrative	6.1	1.00			1.00	
Extrahepatic	No	11.7	0.78 (0.40 – 1.53)	0.448			
	Yes	10.0	1.00				
Central Lesion	No	10.0	1.19 (0.62 – 2.27)	0.605			
	Yes	14.6	1.00				
Tumor Burden	<25%	14.4	0.01 (0.001–0.13)			0.46 (0.17 – 1.23)	0.124
	25–50%	5.3	0.03 (0.002–0.35)	<0.0001	0.0009	0.05 (0.004 – 0.72)	0.028
	>50%	1.23	1.00			1.00	

Abbreviations: CI: Confidence Interval; ECOG: Eastern Cooperative Oncology Group; PVT: Portal Venous Thrombosis

* Adjusted for multiple comparison (correction factor=9)

** Factors were included in multivariate analysis if $P < .25$ in univariate analysis (unadjusted for multiple comparisons)