

Scientific Article

Clinical Outcomes of Patients With Unresectable Primary Liver Cancer Treated With Yttrium-90 Radioembolization With an Escalated Dose



Re-I Chin, MD, MSCI,^a Anirudh Bommireddy, MD,^b Tyler J. Fraum, MD,^c Daniel R. Ludwig, MD,^c Yi Huang, MS,^a Jacqueline E. Zoberi, PhD,^a Jose L. Garcia-Ramirez, MS,^a Nichole M. Maughan, PhD, MS,^a William Chapman, MD,^d Kevin Korenblat, MD,^e Lauren E. Henke, MD, MSCI,^a Hyun Kim, MD,^a and Shahed N. Badiyan, MD^{a,*}

^aDepartment of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri; ^bSt. Louis University School of Medicine, St. Louis, Missouri; ^cMallinckrodt Institute of Radiology; ^dSection of Transplant Surgery, Division of General Surgery, Department of Surgery; ^eDivision of Gastroenterology, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri

Received January 19, 2022; accepted March 15, 2022

Abstract

Purpose: Yttrium-90 (90Y) radioembolization with an escalated dose has been shown to improve clinical outcomes compared with standard dose radioembolization, but there are few data on the local control of primary liver tumors. We reported the clinical outcomes of patients with unresectable primary liver tumors treated with 90Y radioembolization with an escalated dose.

Methods and Materials: Clinical data of patients with unresectable hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and biphenotypic tumors (cHCC-CC) treated with radioembolization with an escalated dose (≥ 150 Gy) between 2013 and 2020 with >3 months follow-up were retrospectively reviewed. The primary endpoint was freedom from local progression. Clinical response was defined by Modified Response Evaluation Criteria in Solid Tumours and toxic effects were assessed using Common Terminology Criteria for Adverse Events version 5.0.

Results: Fifty-three patients with HCC and 15 patients with CC/cHCC-CC were analyzed. The median dose delivered was 205 Gy (interquartile range, 183-253 Gy) and 198 Gy (interquartile range, 154-234 Gy) for patients with HCC and CC/cHCC-CC, respectively. The 1-year freedom from local progression rate was 54% (95% confidence interval [CI], 38%-78%) for patients with HCC and 66% (95% CI, 42%-100%) for patients with CC/cHCC-CC. For patients with HCC, United Network for Organ Sharing nodal stage 1 ($P = .01$), nonsolitary tumors ($P = .02$), pretreatment α -fetoprotein of >7.7 ng/mL ($P = .006$), and ≤ 268 Gy dose delivered ($P = .003$) were predictors for local progression on multivariate Cox analysis. No patients with HCC who received a dose >268 Gy had a local tumor progression. The 1-year overall survival for patients with HCC was 74% (95% CI, 61%-89%). After radioembolization, 5 (7%) patients had grade 3 ascites, and 4 (6%) patients had grade 3/4 hyperbilirubinemia.

Conclusions: Treatment of unresectable primary liver tumors with 90Y radioembolization with an escalated dose was safe and well tolerated. Delivery of >268 Gy may improve local tumor control of HCC. Determination of the maximum tolerated dose needs to be performed in the context of future prospective dose-escalation trials to further evaluate the safety and efficacy of such an approach.

Sources of support: Dr Chin received the American College of Radiation Oncology Resident Seed Grant (\$1000) in 2020.

Disclosures: Dr. Henke and Dr. Kim have received honoraria from ViewRay and VarianDr. Badiyan received speaker's honoraria from MEVION

Data sharing statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Shahed N. Badiyan, MD; E-mail: sbadiyan@wustl.edu

<https://doi.org/10.1016/j.adro.2022.100948>

2452-1094/© 2022 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

© 2022 The Authors. Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Primary liver cancer is the seventh most common malignancy and accounted for 781,631 liver cancer-related deaths globally in 2018.¹ For patients with early-stage disease, surgical resection and liver transplantation are considered potentially curative treatments.^{2,3} Patients with locally advanced disease who are not candidates for surgery have been shown to benefit from locoregional therapies, which can slow disease progression, prolong survival, and potentially bridge to liver transplantation.^{4,5}

Transarterial radioembolization is a locoregional liver-directed therapy that delivers radioactive microspheres containing β -emitting yttrium-90 (90Y) directly to the tumor via hepatic artery branches.⁶⁻⁹ There has been a steady increase in the use of radioembolization globally over the past decade,^{9,10} with multiple studies demonstrating clinical efficacy in hepatocellular carcinoma (HCC),^{10,11} intrahepatic cholangiocarcinoma (iCCA),¹²⁻¹⁴ and combined hepatocellular-cholangiocarcinoma (cHCC-CC).^{15,16} Compared with transarterial chemoembolization (TACE), radioembolization has been shown to increase time-to-progression while resulting in fewer toxic effects.¹⁷

The recommended treatment radiation dose range for standard radioembolization is 80 to 150 Gy.¹⁸ More recently, delivery of 90Y with an escalated dose of >150 Gy to tumor-containing segments of the liver for carefully selected patients has demonstrated improved tumor response and overall survival compared with standard 90Y dose delivery.¹⁹⁻²¹ However, the clinical response rate remains variable,²² and there are limited data on local tumor control. In this study, we retrospectively reviewed our clinical experience in a small cohort of patients treated with 90Y to an escalated dose (>150 Gy) who had surgically or medically inoperable primary liver tumors to assess the patterns and predictors of local tumor progression.

Methods and Materials

Patient and tumor characteristics

Between March 2013 and April 2020, 86 patients who received 90Y radioembolization with an escalated dose to a minimum of 150 Gy for primary liver tumors at a single academic institution were identified. Eighteen patients with <3 months of follow-up were excluded, leaving 68 analyzable patients. Institutional review board approval

was obtained before data collection, and informed consent was waived given the retrospective study design.

Patients with biopsy-proven or clinically diagnosed (by serum tumor markers, computed tomography [CT], and magnetic resonance imaging [MRI] abdomen) HCC, iCCA, and cHCC-CC were eligible for 90Y radioembolization after multidisciplinary consensus. Standard selection criteria for 90Y radioembolization included patients with unresectable primary liver tumors with disease progression or disease not amenable to alternative locoregional therapies, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, serum total bilirubin <2 mg/dL, Child-Pugh (CP) class A-B, and the ability to undergo angiography. Patients were generally considered inoperable due to medical comorbidities, underlying hepatic dysfunction, or tumor-related factors.

Patient age, sex, ethnicity, ECOG performance status, American Joint Committee on Cancer 8th edition staging, United Network for Organ Sharing (UNOS) staging, tumor size, solitary versus multifocal lesions, unilobar versus bilobar tumor involvement, portal vein tumor invasion/thrombus, cirrhosis, and total liver volume were collected for all patients. CP class was determined for patients with cirrhosis. Albumin-bilirubin liver index and Barcelona Clinic liver cancer (BCLC) staging were determined for patients with HCC.

Preprocedure evaluations

Clinical examination and baseline laboratory evaluation, including complete blood count, comprehensive metabolic panel, and coagulation tests, were performed for all patients. α -Fetoprotein (AFP) was obtained for patients with HCC and biphenotypic liver primary tumors. All patients underwent baseline imaging, including triphasic contrast-enhanced hepatic CT or multiphase MRI. The maximum lesion size was defined as the greatest dimension of the largest lesion or the largest diameter of tumor arterial enhancement for HCC per the staging radiology report.

Hepatic arteriography was performed to assess the hepatic vascular anatomy, and if needed, coil embolization was performed on any collateral arteries to prevent the extrahepatic distribution of microspheres.²³ Patients were evaluated for pulmonary and extrahepatic shunting with the use of planar and single-photon emission CT (SPECT) imaging after technetium-99m macroaggregated albumin infusion through hepatic artery branches as determined by the planned treatment site and patient anatomy.^{24,25} Patients with significant nontarget perfusion of the bowel,

>20% lung shunt, or >30 Gy to the lung based on technetium-99m macroaggregated albumin infusion imaging results were ineligible for radioembolization.

90Y radioembolization planning and administration

A total of 75 radioembolization procedures were performed in 68 patients. All patients were treated with 90Y glass microspheres (TheraSphere; BTG International, London, United Kingdom).²⁴ The majority (61 of 68; 90%) of the patients were planned with a prescribed dose between 150 and 200 Gy. Five (7%) patients were planned with a prescribed dose of 300 Gy, and 2 (3%) patients were planned with a prescribed dose of 500 Gy. 90Y dosage for each patient was calculated using the medical internal radiation dose equation according to the liver target treatment volumes contoured on triphasic CT or MRI scans with the use of Eclipse (Varian, Palo Alto, CA) treatment planning system.²⁶ The prescribed dose was administered into segmental branches of the hepatic arteries for segmental treatment and the left or right hepatic artery for unilobar treatment.²³ C-arm cone beam CT and digital subtraction angiography were used intraoperatively to determine vascular supply to the tumor and detect potential extrahepatic vessels.^{27,28} Postradioembolization imaging was performed with 90Y bremsstrahlung SPECT or 90Y positron emission tomography to verify microsphere distribution at the treating physician's discretion.

Clinical follow-up

Patients were generally followed with clinical, laboratory, and imaging (CT or MRI) every 3 months for the first year after radioembolization. Further locoregional treatments were delivered for select patients who had partial response, stable disease, or progressive disease at the target lesions. Clinical and biochemical toxic effects were evaluated at clinical follow-up visits using the Common Terminology Criteria for Adverse Events version 5.0.²⁹

Clinical response assessment

Clinical tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumours version 1.1 for patients with HCC at 3 months after radioembolization.^{30,31} Independent imaging review was performed by 2 fellowship-trained abdominal radiologists, T.J.F. and D.R.L., for the assessment of initial clinical response of the treated tumor(s), and disagreements were reviewed together to obtain a consensus. Subtractions were generated for all MRI studies for modified Response

Evaluation Criteria in Solid Tumours assessment. For typical HCCs, arterial phase and arterial-phase subtractions were preferentially used. For iCCA/cHCC-CCs and atypical HCCs, delayed phase and delayed-phase subtractions were preferentially used. Posttreatment 90Y SPECT (or Tc-MAA SPECT if 90Y SPECT was not performed) was reviewed to determine whether a new lesion occurred within or outside the treatment zone, if applicable. In cases where the radiologists agreed on the presence of viable tumor in a treated target lesion but disagreed on whether there was partial response versus stable disease, an average of the pre- and posttreatment viable tumor measurements was used for final response assessment.

Statistical analysis

The primary endpoint was freedom from local progression (FFLP). The secondary endpoints were clinical response rate, toxic effects, freedom from elsewhere liver progression (FFELP), regional control (RC), distant progression-free survival (DPFS), and overall survival (OS). Survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test.

FFLP was defined as time from the date of 90Y radioembolization to local progression, which was determined either by imaging review at initial clinical response or by any increase in tumor size or enhancement or development or expansion of vascular invasion in subsequent clinical imaging reports. Patients who had undergone further liver-directed locoregional therapy to the same lesion were also censored for FFLP. FFELP was defined as time from the date of 90Y radioembolization to the earlier of disease progression in the untreated liver or development of new liver lesions, excluding progression in the segment (s) treated by 90Y. RC was defined as time from the date of 90Y radioembolization to the earlier of disease progression of existing metastatic lymph nodes or development of new metastatic lymph nodes. DPFS was defined as time from the date of 90Y radioembolization to the earlier of disease progression of existing distant extrahepatic metastatic disease or development of new distant extrahepatic metastatic disease. FFELP, RC, and DPFS were determined by retrospective review of radiology reports. OS was defined as time from the date of 90Y radioembolization to death from any cause. Patients who did not develop events (ie, local progression, elsewhere progression, regional progression, distant progression, and death from any cause for FFLP, FFELP, RC, DPFS, and OS, respectively) during the study period were censored at last follow-up.

Univariate Cox regression was used to assess the ability of various factors to predict survival times in patients with HCC. Univariate analysis was not performed for patients with iCCA/cHCC-CC owing to a small sample size. Multivariate Cox proportional hazards model was

performed to assess for predictors of FFLP and OS in patients with HCC. AFP and delivered dose were analyzed both as continuous variables and as dichotomized variables with low and high groups based on cut-point analysis using the `surv_cutpoint` function in R, version 4.0.2 (R Foundation for Statistical Computing). Multivariate analysis was performed using a forward stepwise method ($P = .10$ for entry, $P = .05$ for removal). Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. A 2-sided P value $<.05$ was considered statistically significant.

Results

Patient, tumor, and treatment characteristics

Baseline patient and tumor characteristics are detailed in Table 1. Fifty-three (78%) patients had HCC, 11 (16%) patients had iCCA, and 4 (6%) patients had cHCC-CC. Prior locoregional liver-directed treatments are summarized in Table 2. Six (9%) patients received multiple types of prior hepatic locoregional therapies. Prior systemic therapy with sorafenib was delivered to 3 (4%) patients with HCC, all of whom had metastatic disease at the time of 90Y with an escalated dose. Gemcitabine-based systemic therapy was administered to 3 (4%) patients with iCCA and 2 (3%) patients with cHCC-CC before 90Y with an escalated dose.

The parameters for 90Y treatment with an escalated dose are also summarized in Table 2. Of the 47 patients who received radioembolization to specific segments, 35 (74%) received a dose >190 Gy. The median follow-up was 8.9 months (interquartile range [IQR], 5.0-22 months) for all patients with HCC and 10.4 months (IQR, 5.3-22 months) for living patients with HCC. The median follow-up was 6.1 months (IQR, 4.8-20 months) for all patients with iCCA/cHCC-CC and 7.0 months (IQR, 5.4-12 months) for living patients with iCCA/cHCC-CC.

Initial clinical response

Status of the treated tumor region assessed at a median of 2.9 months (IQR, 2.2-3.2 months) after radioembolization revealed a complete response (CR) in 11% (7 of 68), partial response (PR) in 41% (27 of 68), stable disease (SD) in 30% (20 of 68), and progressive disease (PD) in 18% (12 of 68). Two patients with HCC did not have repeat imaging at the time of initial clinical follow-up. Of the 51 patients with HCC who had repeat imaging, the initial clinical response included 6 (12%) patients with CR, 20 (39%) with PR, 16 (31%) with SD, and 9 (18%) with PD. Of the 15 patients with iCCA/cHCC-CC who

had repeat imaging at 3 months, the initial clinical response included 1 (6%) patient with CR, 7 (47%) with PR, 4 (27%) with SD, and 3 (20%) with PD.

FFLP

Local progression of the index tumor treated with radioembolization with an escalated dose was observed in 34% (18 of 53) of patients with HCC at a median time of 4.0 months (IQR, 2.2-10.7 months) and in 33% (5 of 15) of patients with iCCA/cHCC-CC at a median time of 4.1 months (IQR, 3.1-15.6 months). The 1- and 2-year FFLP rates for patients with HCC were 54% (95% CI, 38%-78%) and 48% (95% CI, 32%-74%), respectively (Fig. 1a). The 1- and 2-year FFLP rates for patients with iCCA/cHCC-CC were 66% (95% CI, 42%-100%) and 50% (95% CI, 24%-100%), respectively (Fig. 1a). For patients with HCC, UNOS T4 tumors had lower FFLP rates compared with UNOS T2-3 tumors (2-year FFLP: 31% [95% CI, 14%-72%] vs 66% [95% CI, 43%-100%], $P = .03$ by log-rank; Fig. 2). There was no difference in FFLP between patients who received >190 Gy of delivered dose compared with ≤ 190 Gy ($P = .23$ by log-rank).

Univariate Cox analysis of predictors of FFLP is summarized in Table 3. On multivariate analysis, UNOS nodal stage 1 (HR, 27.8; 95% CI, 2.24-346; $P = .01$), nonsolitary lesions (HR, 12.4; 95% CI, 1.49-102; $P = .02$; Fig. 1b), AFP >7.7 ng/mL (HR, 26.3; 95% CI, 2.61-265; $P = .006$; Fig. 1c), and delivered dose of >268 Gy (HR, 0; 95% CI, 0.00-0.11; $P = .003$; Fig. 1d) were significant predictors of FFLP after adjusting for bilobar tumor involvement and pretreatment total bilirubin level (Table 3). The 1- and 2-year FFLP rates for patients who received ≤ 268 Gy were 37% (95% CI, 18%-73%) and 27% (95% CI, 11%-67%), respectively, whereas the 1- and 2-year FFLP rates for patients who received >268 Gy were 100% (95% CI, 100%-100%) for both (Fig. 1d). Of the 7 patients who were treated with >268 Gy (median, 328 Gy; IQR, 271-505 Gy), the median tumor size was 6.7 cm (IQR, 4.5-9.5 cm). Five (71%) patients received radioembolization to 2 segments and 2 patients (29%) received radioembolization to the left hemiliver.

Survival outcomes

The 1- and 2-year FFELP rates for patients with HCC were 59% (95% CI, 46%-76%) and 50% (95% CI, 36%-71%), respectively (Fig. 3a). The 1- and 2-year FFELP rates for patients with iCCA/cHCC-CC were 53% (95% CI, 32%-86%) and 21% (95% CI, 7%-68%), respectively (Fig. 3a).

The 1- and 2-year RC rates for patients with HCC were 91% (95% CI, 82%-100%) and 86% (95% CI, 75%-99%), respectively (Fig. 3b). The 1- and 2-year RC rates for patients with iCCA/cHCC-CC were 59% (95% CI,

Table 1 Baseline patient and tumor characteristics

Characteristic	HCC n = 53*	iCCA/cHCC-CC n = 15*	Characteristic	HCC n = 53*	iCCA/cHCC-CC n = 15*
Age	68 (62-74)	66 (62-71)	BCLC		
Sex			A	8 (15)	NA
Male	38 (72)	11 (73)	B	8 (15)	NA
Female	15 (28)	4 (27)	C	36 (68)	NA
Ethnicity			D	1 (2)	NA
White	44 (83)	13 (87)	Child-Pugh class		
Black	7 (13)	2 (13)	A	38 (90)	7 (100)
Asian	2 (4)	0 (0)	B	4 (10)	0 (0)
ECOG			ABLI grade		
0	23 (44)	5 (33)	1	27 (64)	NA
1	24 (45)	9 (60)	2	15 (36)	NA
2	5 (9)	1 (7)	Lobe involvement		
3	1 (2)	0 (0)	Unilobar	39 (74)	11 (73)
Staging [†]	UNOS	AJCC 8th edition	Bilobar	14 (26)	4 (27)
T stage			Lesion number		
1	0 (0)	10 (67)	≤3	43 (81)	10 (67)
2	11 (21)	5 (33)	>3	10 (19)	5 (33)
3	19 (36)	0 (0)	Solitary lesion		
4	23 (43)	0 (0)	Solitary	32 (60)	8 (53)
N stage			Nonsolitary	21 (40)	7 (47)
1	4 (8)	6 (40)	Tumor size (cm)	5.8 (3.3- 7.7)	5.9 (5.1-9.5)
M stage			Tumor size		
1	5 (9)	0 (0)	<5 cm	20 (38)	3 (20)
Group stage			≥5 cm	32 (62)	12 (80)
1	0 (0)	5 (33)	Portal vein invasion/thrombus	16 (30)	4 (27)
2	11 (21)	4 (27)	Main	2 (12)	0 (0)
3	15 (28)	5 (33)	Lobar	11 (69)	3 (75)
4	27 (51)	1 (7)	Segmental	3 (19)	1 (25)
AFP (ng/mL) [‡]	8 (5-463)	45 (15- 151)			
Bilirubin, total (mg/dL) [‡]	0.7 (0.5- 1.0)	0.5 (0.4- 0.9)			
Albumin (g/dL) [‡]	4.0 (3.7- 4.3)	4.2 (3.8- 4.4)			

Abbreviations: AFP = α -fetoprotein; AJCC = American Joint Committee on Cancer; ABLI = albumin-bilirubin liver index; BCLC = Barcelona Clinic liver cancer; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; iCCA/cHCC-CC = intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma; IQR = interquartile range; NA = not applicable; UNOS = United Network for Organ Sharing.

* Statistics presented: median (IQR); n (%).

† UNOS staging for patients with HCC and AJCC 8th edition staging for patients with cholangiocarcinoma and biphenotypic tumor.

‡ Pretreatment laboratory values.

33%-100%) and 44% (95% CI, 20%-99%), respectively (Fig. 3b). The 1- and 2-year DPFs rates for patients with HCC were 79% (95% CI, 67%-93%) and 62% (95% CI, 45%-85%), respectively (Fig. 3c). The 1- and 2-year DPFs for patients with iCCA/cHCC-CC were 59% (95% CI, 34%-100%) for both (Fig. 3c).

Twenty (38%) patients with HCC and 5 (33%) patients with iCCA/cHCC-CC died in the follow-up period. The

1- and 2-year OS among patients with HCC were 74% (95% CI, 61%-89%) and 59% (95% CI, 44%-79%), respectively (Fig. 3d). The 1- and 2-year OS among patients with iCCA/cHCC-CC were 76% (95% CI, 55%-100%) for both (Fig. 3d). Univariate Cox analysis of predictors of OS is summarized in Table E1. On multivariate analysis, CP class B (HR, 25.4; 95% CI, 1.92-336; $P = .01$), ECOG 1 (HR, 5.55; 95% CI, 1.13-27.3; $P = .04$), ECOG 2 (HR, 13.4;

Table 2 Treatment parameters of 90Y with an escalated dose

Characteristic	HCC n = 53*	iCCA/cHCC-CC n = 15*
Prior liver-directed therapy	12 (23)	1 (7)
Chemoembolization	12 (100)	0 (0)
Cryoablation	2 (17)	0 (0)
Bland embolization	1 (8)	0 (0)
Standard dose radioembolization	0 (0)	1 (100)
Prescribed dose (Gy)	200 (170-250)	200 (150-225)
Delivered dose (Gy)	205 (183-253)	198 (154-234)
Delivered dose		
150-189 Gy	17 (32)	7 (47)
≥190 Gy	36 (68)	8 (53)
Treatment target		
1 segment	14 (26)	3 (20)
2 segments	22 (42)	4 (27)
3 segments	4 (8)	0 (0)
Left hemiliver	5 (9)	3 (20)
Right hemiliver	8 (15)	5 (33)
Target volume (cc)		
1 segment	324 (199-362)	194 (139-413)
2 segments	480 (326-672)	470 (393-548)
3 segments	275 (258-324)	-
Left hemiliver	559 (473-1132)	319 (316-984)
Right hemiliver	865 (722-1256)	1123 (522-1384)
Total liver volume (cc)		
1 segment	1677 (1540-1897)	1575 (1430-1741)
2 segments	1739 (1500-2349)	1603 (1486-2205)
3 segments	2512 (1685-2751)	-
Left hemiliver	1849 (1736-2347)	1649 (1343-2039)
Right hemiliver	1561 (1270-2186)	1330 (1237-1890)
Target to total liver volume ratio		
1 segment	0.2 (0.1-0.2)	0.1 (0.1-0.2)
2 segments	0.3 (0.2-0.3)	0.3 (0.2-0.3)
3 segments	0.1 (0.1-0.2)	-
Left hemiliver	0.3 (0.3-0.5)	0.2 (0.2-0.5)
Right hemiliver	0.6 (0.4-0.7)	0.7 (0.4-0.8)
Lung shunt (%)	4.9 (3.8-8.5)	4.2 (2.7-6.8)

Abbreviations: 90Y = yttrium-90; HCC = hepatocellular carcinoma; iCCA/cHCC-CC = intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma; IQR = interquartile range.

* Statistics presented: median (IQR); n (%).

95% CI, 1.38-129; $P = .03$), initial progressive disease (HR, 57.2; 95% CI, 1.53-2132; $P = .03$), and liver transplant (HR, 0.03; 95% CI, 0.00-0.66; $P = .03$) were significant predictors of OS after adjusting for nonsolitary lesion (Table E1).

Toxic effects and subsequent treatments

Table 4 summarizes the clinical and biochemical toxic effects after treatment. The most frequently noted acute grade 1 and 2 clinical toxic effects within

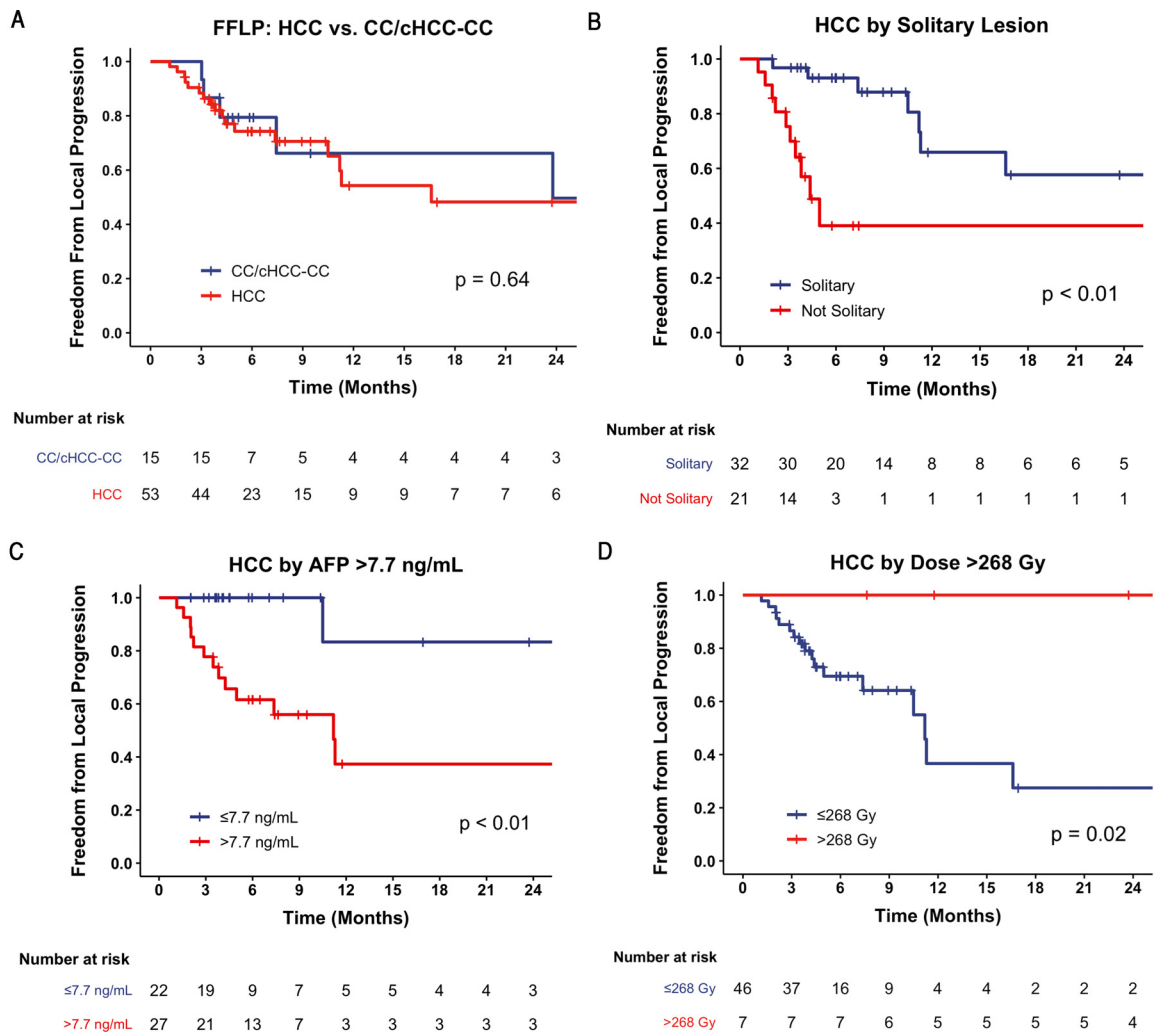


Figure 1 Kaplan-Meier estimates of (A) freedom from local progression (FFLP) stratified by patients with hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma (iCCA/cHCC-CC). For patients with HCC, FFLP was stratified by (B) solitary lesions, (C) pretreatment α -fetoprotein (AFP) >7.7 ng/mL, and (D) delivered dose >268 Gy.

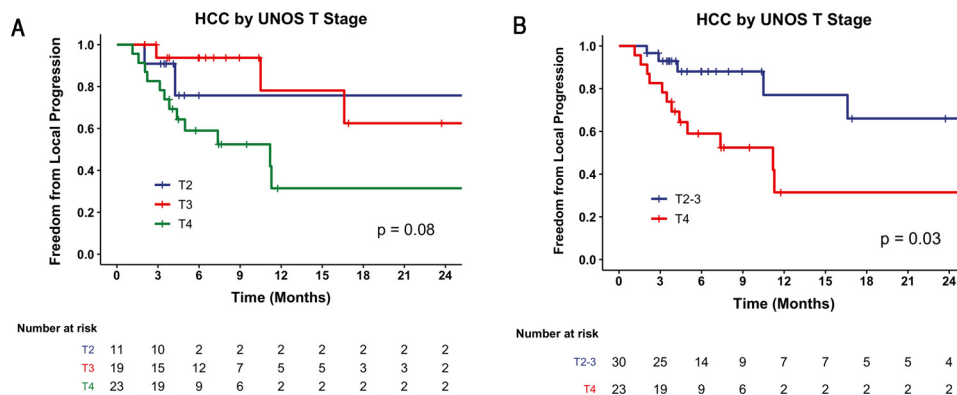


Figure 2 Kaplan-Meier estimates of freedom from local progression for patients with hepatocellular carcinoma (HCC) stratified by (A) United Network for Organ Sharing (UNOS) T2, T3, and T4, and (B) UNOS T2-T3 and T4.

Table 3 Univariate and multivariate analyses for factors predicting FFLP in patients with HCC

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Ethnicity						
White	1.00	-		-	-	-
Black	10.5	3.41, 32.3	<.001	-	-	-
Asian	1.25	0.15, 10.1	.83	-	-	-
UNOS T stage						
2 or 3	1.00	-		-	-	-
4	2.91	1.09, 7.81	.03	-	-	-
UNOS N stage						
1	3.27	0.91, 11.8	.07	27.8	2.24, 346	.01
UNOS M stage						
1	2.28	0.65, 7.96	.20	-	-	-
UNOS group stage						
2 or 3	1.00	-		-	-	-
4	2.42	0.86, 6.79	.09	-	-	-
Bilobar involvement	4.69	1.82, 12.1	.001	0.13	0.01, 1.13	.06
BCLC						
A	1.00	-		-	-	-
B	2.82	0.45, 17.7	.27	-	-	-
C	1.52	0.34, 6.81	.58	-	-	-
D	1.65	0.14, 18.9	.69	-	-	-
Child-Pugh class						
A	1.00	-		-	-	-
B	0.98	0.12, 7.66	.98	-	-	-
Nonsolitary lesion	5.90	2.16, 16.1	<.001	12.4	1.49, 102	.02
Tumor size ≥ 5 cm	0.84	0.32, 2.21	.72	-	-	-
AFP >7.7 ng/mL	11.7	1.54, 89.3	.02	26.3	2.61, 265	.006
Pretreatment total bilirubin (mg/dL)	0.31	0.08, 1.16	.08	0.04	0.00, 1.26	.07
Delivered dose (Gy)	0.99	0.98, 1.00	.08	-	-	-
Delivered dose >268 Gy	0.1	0.01, 0.85	.04	0	0.00, 0.11	.003
Portal vein invasion/thrombus	2.41	0.95, 6.16	.07	-	-	-
Abbreviations: AFP = α -fetoprotein; BCLC = Barcelona Clinic liver cancer; CI = confidence interval; FFLP = freedom from local progression; HCC = hepatocellular carcinoma; HR = hazard ratio; UNOS = United Network for Organ Sharing. Bolded p-values indicate statistical significance of smaller than $p = 0.05$.						

the first 3 months were fatigue, nausea, and abdominal pain. No patients had grade 4 or higher clinical toxic effects.

Additional locoregional therapy targeted to the same lesion was delivered in 17 (25%) patients, of whom 14 (82%) had HCC and 3 (18%) had iCCA. These treatments included TACE (65%), radiofrequency ablation (12%), and repeat radioembolization (24%). Of the 17 patients who received additional locoregional therapy, 9 (53%) patients remained free of local progression at the last follow-up, 5 (29%)

patients had progression elsewhere in the liver, 2 (12%) had distant progression, and 1 (6%) did not have adequate follow-up to assess treatment response. Eight (12%) patients received orthotopic liver transplant after radioembolization with an escalated dose, 7 (88%) of whom were disease-free at the last follow-up. Seven (88%) of the 8 patients who received a liver transplant were outside of the Milan criteria before radioembolization with an escalated dose. Three (4%) patients underwent a partial hepatectomy after 90Y; all 3 remained disease-free at the last follow-up.

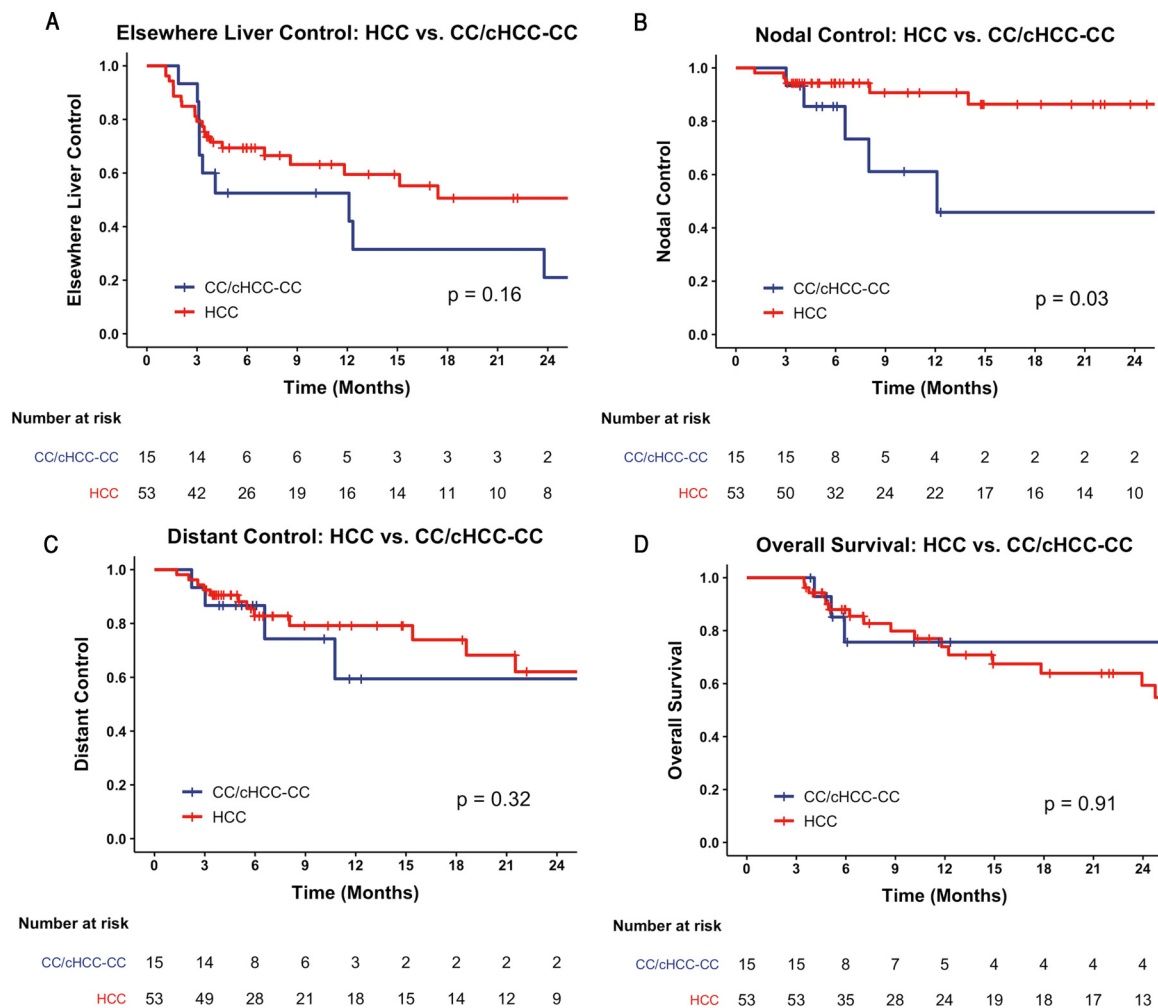


Figure 3 Kaplan-Meier estimates of (A) freedom from elsewhere liver progression, (B) regional control, (C) distant progression-free survival, and (D) overall survival stratified by patients with hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma (iCCA/cHCC-CC).

Table 4 Clinical and biochemical toxic effects for all patients assessed using CTCAE version 5.0

	Grade 1/2*	Grade 3/4*	Grade 5*
Clinical toxic effects			
Fatigue	15 (22)	-	-
Abdominal pain	9 (13)	-	-
Nausea	9 (13)	-	-
Decreased appetite	6 (9)	-	-
Ascites	-	5 (7)	-
Encephalopathy	-	4 (6)	-
Biochemical toxic effect			
Total bilirubin elevation	1 (1)	4 (6)	-

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

* Statistics presented: n (%).

Discussion

90Y radioembolization with an escalated dose has emerged as a promising approach that allows for treatment intensification to the tumor-containing liver segments while minimizing radiation exposure to the nontargeted liver parenchyma.²² To date, there has been a limited number of studies that have evaluated the rate and pattern of local progression in patients who receive radioembolization with an escalated dose. In this study, we reported a 2-year freedom from local progression rate of 48% (95% CI, 32%-74%) in patients with HCC.

Most of the reported clinical experiences of radiation segmentectomy (RS) to a minimum dose of 190 Gy involve patients with early-stage HCC (single tumor or tumors confined to ≤ 2 segments). In this setting, curative-intent RS can help bridge or downstage tumor to enable liver transplant for patients with tumors that were originally outside the Milan criteria.^{9,20,21,32} In patients with more advanced disease, radioembolization with an escalated dose also has been shown to be a viable treatment approach in a small sample of patients.³² Tumor progression occurred in 50% of the patients at a median of 319 days, and only 5% of the patients experienced local progression at the first site of failure, though local tumor progression was not analyzed as an independent endpoint.³² In the HCC subset of our study, which comprised 36 patients with BCLC stage C disease, complete response was observed in 6 patients, of whom 4 were BCLC stage C.

Although prior studies have detailed the clinical response, tumor progression, and toxic effects associated with radioembolization with an escalated dose, they offered limited insight to the patterns and predictors of local tumor control. In this study, UNOS nodal stage 1, nonsolitary lesions, pretreatment α -fetoprotein of >7.7 ng/mL, and ≤ 268 Gy dose delivered were associated with worse local control. In another study that evaluated the predictors of tumor recurrence, Manzia et al³³ found that 2 cm or greater remnant vital tissue after locoregional therapy at the pathologic examination in the explanted liver during liver transplant was an important predictor of disease-free survival and recurrence. Notably, that study included TACE, percutaneous ethanol injection, and radio-frequency ablation and excluded patients who received radioembolization.³³

The rationale for dose-escalation in primary liver cancer originated in studies with external beam radiation therapy that demonstrated a dose-response relationship.³⁴ In the 90Y space, Garin et al³⁵ reported a significantly increased response rate and OS in patients with HCC who were treated with a dose ≥ 205 Gy compared with patients receiving 120 Gy in the DOSISPHERE-01 trial. Additional studies support the importance of a threshold dose on tumor control^{36,37} and have correlated 90Y deposition/activity with individual tumor response in patients with primary and metastatic liver tumors.³⁸ In this study,

there was no benefit in local progression for patients with HCC who were treated with a dose ≥ 190 Gy compared with 150 to 190 Gy; however, patients who received a radioembolization dose >268 Gy had a significantly decreased rate of local progression. Together, these results indicate that higher doses of radioembolization may be needed to achieve better local control due to heterogeneity of 90Y microsphere deposition.

Although this study suggests that dose-escalation may be needed to improve local tumor control, the retrospective and heterogenous nature of this study preclude the determination of a maximal dose limit. Emerging evidence demonstrates that radioembolization with an even further escalated dose may be achieved in highly selected patients. The recently reported Local radioEmbolization using Glass Microspheres for the Assessment of Tumor Control with Y-90 (LEGACY) study retrospectively evaluated patients with solitary unresectable HCC ≤ 8 cm, CP A cirrhosis, and ECOG status 0 to 1 treated with radioembolization to a median dose of 410 Gy.³⁹ The objective response rate was 88.3% (CI, 82.4%-92.4%) with 62.2% (CI, 54.1%-69.8%) exhibiting a duration of response ≥ 6 months.³⁹ In a subset dose-pathology correlation of resection/transplantation, all LEGACY patients exhibited complete pathologic necrosis when the dose exceeded 400 Gy to the tumor-bearing tissue, suggesting 400 Gy as a possible "threshold dose" for an ablative effect.⁴⁰ Local control was not reported. Compared with the LEGACY study, the patients in this study had larger tumors (median: 5.8 vs 2.7 cm). Additionally, this study comprised patients with more severe underlying comorbidities: 68% of patients in this study were BCLC C and 61% of the LEGACY study were BCLC A. Considering these differences, the outcomes from this study are not surprising and add important information to the literature regarding 90Y with an escalated dose in the real-world management of primary liver cancers. Determination of the maximum tolerated dose needs to be performed in the context of future prospective dose-escalation trials to further evaluate the safety and efficacy of such an approach.

For iCCA and cHCC-CC, the majority of the published studies for these histologies used standard-dosing radioembolization.^{15,16,41} In our study, patients with iCCA/cHCC-CC had a high rate of nodal progression. This result is consistent with recent literature highlighting the risk of regional metastases in patients with unresectable cholangiocarcinoma.⁴² Surgical series also corroborate the pattern of regional recurrences and support the use of additional therapies to the elective nodal region.⁴³ Together, these results suggest that local liver-directed therapies such as 90Y may not adequately address nodal control in patients with iCCA/cHCC-CC.⁴²⁻⁴⁴

There are limitations to this study. A significant proportion of the patients treated with 90Y radioembolization were excluded for having fewer than 3 months of follow-up, which is due to the incomplete data available

in the retrospective study. This study had a small sample size, which limited the subgroup analyses that could be performed and the robustness of the statistics presented. The small number of patients with iCCA and cHCC-CC also precluded the statistical evaluation of predictors of local tumor progression for these primary tumors. Twelve (26%) patients received a dose between 150 and 190 Gy, below the generally accepted cutoff of >190 Gy for RS, but there was no difference in local tumor control between patients receiving >190 Gy compared with <190 Gy. It was also difficult to comprehensively capture grade 1 to 2 adverse events given the retrospective nature of this study, though the majority of clinically significant grade 3 to 5 events should be included. Despite these limitations, this study demonstrated that 90Y with an escalated dose was safe and well tolerated even in a relatively high-risk population with mostly BCLC stage C disease, with no grade 4 or 5 clinical toxic effects and low rates of grade 3 and 4 biochemical toxic effects, which is consistent with previously published data.^{20,21,32,45}

Conclusion

Treatment of unresectable primary liver tumors with 90Y with an escalated dose microsphere radioembolization was safe and well tolerated in this study, and delivery of greater than 268 Gy may improve local tumor control of HCC. Further investigations are necessary to optimize patient selection criteria, determine dose prescription, and refine its role in conjunction with additional forms of liver-directed therapy and systemic therapy.

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2022.100948](https://doi.org/10.1016/j.adro.2022.100948).

References

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin*. 2018;68:394–424.
- Iwatsuki S, Gordon RD, Shaw BW, et al. Role of liver transplantation in cancer therapy. *Ann Surg*. 1985;202:401–407.
- Fortner JG, Maclean BJ, Kim DK, et al. The seventies evolution in liver surgery for cancer. *Cancer*. 1981;47:2162–2166.
- Heckman JT, Devera MB, Marsh JW, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. *Ann Surg Oncol*. 2008;15:3169–3177.
- Sapisochin G, Barry A, Doherty M, et al. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. *J Hepatol*. 2017;67:92–99.
- Salem R, Thurston KG, Carr BI, et al. Yttrium-90 microspheres: Radiation therapy for unresectable liver cancer. *J Vasc Intervent Radiol*. 2002;13:223–229.
- Lewandowski RJ, Salem R. Yttrium-90 radioembolization of hepatocellular carcinoma and metastatic disease to the liver. *Semin Intervent Radiol*. 2006;23:64–72.
- Padia SA, Lewandowski RJ, Johnson GE, et al. Radioembolization of hepatic malignancies: Background, quality improvement guidelines, and future directions. *J Vasc Intervent Radiol*. 2017;28:1–15.
- Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: Recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging*. 2019;46:1695–1704.
- Tohme S, Bou Samra P, Kaltenmeier C, et al. Radioembolization for hepatocellular carcinoma: A nationwide 10-year experience. *J Vasc Intervent Radiol*. 2018;29:912–919.e2.
- Salem R, Gabr A, Riaz A, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. *Hepatology*. 2018;68:1429–1440.
- Saxena A, Bester L, Chua TC, et al. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: A preliminary assessment of this novel treatment option. *Ann Surg Oncol*. 2010;17:484–491.
- Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: Safety, response, and survival analysis. *J Vasc Intervent Radiol*. 2013;24:1227–1234.
- Gangi A, Shah J, Hatfield N, et al. Intrahepatic cholangiocarcinoma treated with transarterial yttrium-90 glass microsphere radioembolization: Results of a single institution retrospective study. *J Vasc Intervent Radiol*. 2018;29:1101–1108.
- Chan LS, Sze DY, Poultides GA, et al. Yttrium-90 radioembolization for unresectable combined hepatocellular-cholangiocarcinoma. *Cardiovasc Intervent Radiol*. 2017;40:1383–1391.
- Malone CD, Gibby W, Tsai R, et al. Outcomes of yttrium-90 radioembolization for unresectable combined biphenotypic hepatocellular-cholangiocarcinoma. *J Vasc Intervent Radiol*. 2020;31:701–709.
- Salem R, Gordon A, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. 2016;151:1155–1163.
- Cremonesi M, Chiesa C, Strigari L, et al. Radioembolization of hepatic lesions from a radiobiology and dosimetric perspective. *Front Oncol*. 2014;4.
- Garin E, Tzelikas L, Guiu B, et al. Major impact of personalized dosimetry using 90Y loaded glass microspheres SIRT in HCC: Final overall survival analysis of a multicenter randomized phase II study (DOSISPHERE-01). *J Clin Oncol*. 2020;38:516.
- Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation segmentectomy: Potential curative therapy for early hepatocellular carcinoma. *Radiology*. 2018;287:1050–1058.
- Vouche M, Habib A, Ward TJ, et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: Multicenter radiology-pathology correlation and survival of radiation segmentectomy. *Hepatology*. 2014;60:192–201.
- Jia Z, Wang C, Paz-Fumagalli R, et al. Radiation segmentectomy for hepatic malignancies: Indications, devices, dosimetry, procedure, clinical outcomes, and toxicity of yttrium-90 microspheres. *J Intervent Med*. 2019;2:1–4.
- Liu DM, Salem R, Bui JT, et al. Angiographic considerations in patients undergoing liver-directed therapy. *J Vasc Intervent Radiol*. 2005;16:911–935.
- Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: A consensus panel report from the Radioembolization Brachytherapy Oncology Consortium. *Int J Radiat Oncol Biol Phys*. 2007;68:13–23.
- Haste P, Tann M, Persohn S, et al. Correlation of technetium-99m macroaggregated albumin and yttrium-90 glass

- microsphere biodistribution in hepatocellular carcinoma: A retrospective review of pretreatment single photon emission CT and posttreatment positron emission tomography/CT. *J Vasc Interv Radiol.* 2017;28:722–730. e1.
26. Loevinger R, Budinger T, Watson E. *MIRD Primer for Absorbed Dose Calculations*. New York: Society of Nuclear Medicine; 1991.
 27. Orth RC, Wallace MJ, Kuo MD. C-arm cone-beam CT: General principles and technical considerations for use in interventional radiology. *J Vasc Interv Radiol.* 2008;19:814–820.
 28. Louie JD, Kothary N, Kuo WT, et al. Incorporating cone-beam CT into the treatment planning for yttrium-90 radioembolization. *J Vasc Interv Radiol.* 2009;20:606–613.
 29. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0*. 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed March 15, 2022.
 30. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis.* 2010;30:52–60.
 31. Seyal AR, Gonzalez-Guindalini FD, Arslanoglu A, et al. Reproducibility of mRECIST in assessing response to transarterial radioembolization therapy in hepatocellular carcinoma. *Hepatology.* 2015;62:1111–1121.
 32. Padia SA, Kwan SW, Roudsari B, et al. Superselective yttrium-90 radioembolization for hepatocellular carcinoma yields high response rates with minimal toxicity. *J Vasc Interv Radiol.* 2014;25:1067–1073.
 33. Manzia TM, Lai Q, Iesari S, et al. Impact of remnant vital tissue after locoregional treatment and liver transplant in hepatocellular cancer patients, a multicentre cohort study. *Transpl Int.* 2018;31:988–998.
 34. Park HC, Seong J, Han KH, et al. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2002;54:150–155.
 35. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): A randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol.* 2021;6:17–29.
 36. Kappadath SC, Mikell J, Balagopal A, et al. Hepatocellular carcinoma tumor dose response after 90 y-radioembolization with glass microspheres using 90 Y-SPECT/CT-based voxel dosimetry. *Int J Radiat Oncol Biol Phys.* 2018;102:451–461.
 37. Chan KT, Alessio AM, Johnson GE, et al. Prospective trial using internal pair-production positron emission tomography to establish the yttrium-90 radioembolization dose required for response of hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2018;101:358–365.
 38. Badiyan S, Bhooshan N, Chuong MD, et al. Correlation of radiation dose and activity with clinical outcomes in metastatic colorectal cancer after selective internal radiation therapy using yttrium-90 resin microspheres. *Nucl Med Commun.* 2018;39:915–920.
 39. Salem R, Johnson GE, Kim E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: The LEGACY study. *Hepatology.* 2021;74:2342–2352.
 40. Gabr A, Riaz A, Johnson GE, et al. Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: Confirmatory multicenter analysis in 45 explants. *Eur J Nucl Med Mol Imaging.* 2021;48:580–583.
 41. Hoffmann R-T, Paprottka PM, Schön A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: Factors associated with prolonged survival. *Cardiovasc Interv Radiol.* 2012;35:105–116.
 42. Kozak MM, Toesca DAS, von Eyben R, et al. Stereotactic body radiation therapy for cholangiocarcinoma: Optimizing locoregional control with elective nodal irradiation. *Adv Radiat Oncol.* 2020;5:77–84.
 43. Ghiassi-Nejad Z, Tarchi P, Moshier E, et al. Prognostic factors and patterns of locoregional failure after surgical resection in patients with cholangiocarcinoma without adjuvant radiation therapy: Optimal field design for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys.* 2017;99:805–811.
 44. Song S, Kim K, Chie EK, et al. Locoregional recurrence after curative intent resection for intrahepatic cholangiocarcinoma: Implications for adjuvant radiotherapy. *Clin Transl Oncol.* 2015;17:825–829.
 45. Riaz A, Gates VL, Atassi B, et al. Radiation segmentectomy: A novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys.* 2011;79:163–171.