Gastroenterology 2016;151:1155–1163

Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e24. Learning Objective: Upon completion of this exercise, successful learners will be able to define the role of two commonly used transarterial therapies for Barcelona Clinic Liver Cancer (BCLC) A/B hepatocellular carcinoma (HCC) patients: (1) radioembolization and (2) conventional transarterial chemoembolization (cTACE).

See Covering the Cover synopsis on page 1043; see editorial on page 1062.

BACKGROUND & AIMS: Conventional transarterial chemoembolization (cTACE) is used to treat patients with hepatocellular carcinoma (HCC). Radioembolization is a minimally invasive procedure that involves implantation of radioactive micron-sized particles loaded with yttrium-90 (Y90) inside the blood vessels that supply a tumor. We performed a randomized, phase 2 study to compare the effects of cTACE and Y90 radioembolization in patients with HCC. **METHODS:** From October 2009 through October 2015, we reviewed patients with HCC of all Barcelona Clinic Liver Cancer (BCLC) stages for eligibility. Of these, 179 patients with BCLC stages A or B met our enrollment criteria and were candidates for cTACE or Y90 therapy. Patients were assigned randomly to groups that received Y90 therapy (n = 24; 50% Child–Pugh A) or cTACE (n = 21; 71% Child–Pugh A). The primary outcome was time to progression (TTP), evaluated by intention-to-treat analysis. Secondary outcomes included safety, rate of response (based on tumor size and necrosis criteria), and Kaplan–Meier survival time. We performed inverse probability of censoring weighting and competing risk analyses. **RESULTS:** Patients in the Y90 radioembolization group had significant longer median TTP (>26 mo) than patients in the cTACE group (6.8 mo; $P = .0012$) (hazard ratio, 0.122; 95% confidence interval [CI], 0.027–0.557; $P = .007$). This was confirmed by competing risk and inverse probability of censoring weighting analyses accounting for transplantation or death. A significantly greater proportion of patients in the cTACE group developed diarrhea (21%) than in the Y90 group (0%; $P = .031$) or hypoalbuminemia (58% in the cTACE group vs 4% in the Y90 group; $P < .001$). Similar proportions of patients in each group had a response to therapy, marked by necrosis (74% in the cTACE group vs 87% in the Y90 group) ($P = .433$). The median survival time, censored to liver transplantation, was 17.7 months for the cTACE group (95% CI, 8.3–not calculable) vs 18.6 months for the Y90 group (95% CI, 7.4–32.5) ($P = .99$). **CONCLUSIONS:** In a randomized phase 2 study of patients with HCC of BCLC stages A or B, we found Y90 radioembolization to provide significantly longer TTP than cTACE. Y90 radioembolization provides better tumor control and could reduce drop-out from transplant waitlists. ClinicalTrials.gov no. NCT00956930.

Keywords: Randomized Trial; Chemoembolization; Radioembolization; Liver Cancer.

Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers, resulting in 740,000 deaths annually. It is the second most common cause of cancer mortality worldwide.[1] Patients with HCC often present beyond transplant or resection eligibility. Locoregional therapies now are applied for the full spectrum of patients who are not candidates for curative options. Locoregional therapies (ablation, conventional transarterial chemoembolization [cTACE], and radioembolization with yttrium-90 microspheres [Y90]), appear

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Abbreviations used in this paper: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CT, computed tomography; cTACE, conventional transarterial chemoembolization; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HR, hazard ratio; IPCW, inverse probability of censoring weighting; KM, Kaplan–Meier; OS, overall survival; TTP, time to progression; WHO, World Health Organization; Y90, yttrium-90.

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2016.08.029

in guidelines as treatment options for HCC.[2–4] For early disease (Barcelona Clinic Liver Cancer [BCLC] A), ablation is recommended. However, when contraindications to ablation exist, the stage-migration concept advocates the next best line of therapy (in this case cTACE) be applied. For intermediate disease (BCLC B), cTACE is the standard of care, with a demonstrated survival benefit.[5–7] Compared with cTACE, Y90 has shown increased time to progression,[8] good quality of life,[9] a neoadjuvant role before resection,[10–12] and high antitumoral activity in patients with portal vein invasion.[13] Consequently, experts have advocated strongly that Y90 be studied in randomized trials using cTACE as the control arm.[8,14,15]

The purpose of this study was to compare cTACE and Y90 in a prospective, randomized, phase 2 setting for the treatment of unresectable, unablatable HCC. As recommended by guidelines,[16] the primary end point was time to progression (TTP). Secondary end points included safety, response rate, and overall survival. Our hypothesis was that Y90 would prolong TTP when compared with cTACE.[8]

Materials and Methods

The study was an investigator-initiated, open-label, single-center, phase 2 Prospective Randomized Study of Chemoembolization Versus Radioembolization for the Treatment of Hepatocellular Carcinoma. The study was institutional review board–approved, complied with the Health Insurance Portability and Accountability Act, and was registered (NCT00956930). All BCLC stage HCC patients were reviewed by the multidisciplinary tumor board (transplant surgery, hepatology, medical oncology, and interventional radiology) between October 2009 and October 2015. After excluding ineligible patients (portal vein invasion or infiltrative disease, n = 69; hyperbilirubinemia, n = 86; increased creatinine, n = 28; other abnormal laboratory results, n = 20; human immunodeficiency virus, n = 15; transjugular intrahepatic portosystemic shunting, n = 27; metastatic disease, n = 36; other health problems precluding treatment, n = 22; other treatment recommendations, n = 44; psychological/social issues, n = 49; previous liver or systemic treatment, n = 71; underwent resection, n = 155; or underwent ablation, n = 60), there were 179 BCLC A/B patients (eligible for cTACE or Y90) who were offered noninterventional studies, cTACE, Y90, or a 2-arm randomized clinical trial comparing cTACE with Y90 (Supplementary Figure 1). Of the 179 patients, 43 declined to participate in research, 29 selected other clinical trials, 49 requested Y90, and 13 requested cTACE. Forty-five patients agreed to be randomized. After discussion of the protocol and signing informed consent, they were randomized prospectively 1:1 to conventional chemoembolization (cTACE; control arm) or radioembolization (Y90; test arm). BCLC A patients were considered ineligible for ablation/resection because of lesion size/multifocality/location or portal hypertension/liver function. All BCLC B patients deemed appropriate for standard of care cTACE also were deemed eligible for Y90. The ultimate intent of treatment for these patients was liver transplantation with candidacy evaluated by transplant surgery.[17] No donor organs were obtained from executed prisoners or other institutionalized persons. The study was halted early because of slow accrual and competing studies. The last patient was enrolled on July 14, 2015, with complete imaging (TTP), transplant, and survival data updated on July 15, 2016. All authors had access to the study data and reviewed and approved the final manuscript.

Study Eligibility

In brief, inclusion criteria were image/biopsy-proven HCC by guidelines,[4] unablatable/unresectable disease, no vascular invasion, Child–Pugh A/B, bilirubin level of 2.0 mg/dL or less, and aspartate aminotransferase/alanine aminotransferase 5 times the upper limit of normal or less. Exclusion criteria were infiltrative/bulk disease (≥70% tumor burden), 50% or more tumor burden with albumin level less than 3 g/dL, cardiac comorbidities, major surgery within the past 4 weeks, or active infection.

Evaluation and Staging

Patient demographics, risk factors, etiology, performance status, staging (BCLC), albumin-bilirubin (ALBI) score, and Child–Pugh class were recorded.

Treatment Arms

cTACE. Chemoembolization was performed with 75 mg/m^2 (maximum, 150 mg) dosing. The drug/lipiodol combination was followed by embolic microspheres (Embospheres; Merit Medical Systems, South Jordan, UT). The percentage of drug administered was recorded, with confirmation of lipiodol deposition by noncontrast computed tomography (CT). Patients were admitted for 24–48 hours of observation, and discharged with antibiotics/analgesics/antiemetics as needed.

Y90. Angiography and technetium-99m scintigraphy were used to estimate lung shunting, identify extrahepatic perfusion, and perform coil embolization if necessary. Glass microspheres (TheraSphere; BTG International, West Conshohocken, PA) were used at a 120-Gy dose, with treatment on an outpatient basis.[18–20]

Outcome Variables

All clinical and laboratory adverse events (Common Terminology Criteria for Adverse Events, version 4.0)[21] were recorded, with censoring at transplantation.

Response rates were determined by contrast-enhanced magnetic resonance imaging (World Health Organization [WHO] bidimensional, and 3-dimensional European Association for the Study of the Liver [EASL]) and chest CTs.[22] Because lipiodol is not visible by magnetic resonance imaging, this was selected as the imaging modality to ensure treatment concealment. Scans were reviewed in a blinded manner by 2 board-certified radiologists. Third-reader adjudication was performed when necessary.

TTP and overall survival (OS) analyses were calculated from day of randomization by Kaplan–Meier (KM) analysis using intention-to-treat (ITT). Progression was defined as follows: (1) WHO: 25% increase in bidimensional cross-product, (2) EASL: 25% increase in arterial enhancement, (3) portal vein tumor thrombus development, (4) index lesion: lesions requiring retreatment because of worsening circumferential enhancement, and (5) new lesions or extrahepatic metastases. Small lesions that were difficult to characterize and eventually

Table 1. Baseline Characteristics

Characteristic	cTACE (n = 21)	Y90 (n = 24)	*P* value
Demographics			
Age, *y*[a]	64 (62–70)	62 (58–65)	.45
Sex			
Male	16 (76)	17 (71)	1.00
Female	5 (24)	7 (29)	
Ethnicity			
Caucasian	16 (76)	19 (79)	1.00
African American	3 (14)	3 (13)	
Hispanic	1 (5)	1 (4)	
Asian	1 (5)	1 (4)	
Risk factors			
Etiology			
Alcohol	1 (5)	4 (17)	.73
HCV	10 (48)	12 (50)	
HCV + alcohol	2 (10)	1 (4)	
HCV + hemochromatosis	1 (5)	0 (0)	
HBV	2 (10)	3 (13)	
NASH	1 (5)	1 (4)	
Cryptogenic	1 (5)	0 (0)	
Hemochromatosis	0 (0)	1 (4)	
Unknown	3 (14)	1 (4)	
Imaging cirrhosis			
Present	20 (95)	24 (100)	.47
Absent	1 (5)	0 (0)	
Tumor burden <25%	21 (100)	24 (100)	-
Distribution			
Unilobar	14 (67)	17 (71)	1.00
Bilobar	7 (33)	7 (29)	
Lesions, n			
Solitary	11 (52)	13 (54)	1.00
Multifocal	10 (48)	11 (46)	
Largest tumor size, *cm*			
Median (IQR)	2.6 (0.7)	3.0 (1.2)	.18
Mean (95% CI)	3.0 (2.3–3.6)	3.2 (2.7–3.7)	.55
AFP level, *ng/mL*			
<200	19 (90)	21 (88)	1.00
≥200	2 (10)	3 (12)	
Method of diagnosis			
Biopsy	8 (38)	7 (29)	.55
Imaging	13 (62)	17 (71)	
Liver function			
Bilirubin level, *mg/dL**	0.9 (0.8–1.5)	1.3 (1.2–1.7)	.058
Albumin level, *g/dL**	3.2 (2.9–3.4)	3.1 (2.7–3.3)	.58
ALBI grade			
1	1 (5)	0 (0)	.296
2	17 (81)	17 (71)	
3	3 (14)	7 (29)	
Portal hypertension			
Present	11 (52)	20 (83)	.051
Absent	10 (48)	4 (17)	
Stage			
BCLC			
A	17 (81)	18 (75)	.73
B	4 (19)	6 (25)	
Child–Pugh (at randomization)			
A	15 (71)	12 (50)	.30
B7	3 (14)	6 (25)	
B8	2 (10)	3 (12.5)	
B9	1 (5)	3 (12.5)	
Child–Pugh (day of first treatment)			
A	16 (76)	10 (42)	.085
B7	3 (14)	8 (33)	
B8	1 (5)	4 (17)	
B9	1 (5)	1 (4)	
C10	0 (0)	1 (4)	

AFP, α-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NASH, nonalcoholic steatohepatitis.
[a]Values are expressed as the median and 95% confidence intervals.

declared as HCC were adjudicated retrospectively to the earliest date of detection. Patients were censored on the day of last imaging for all TTP analyses. OS with censoring to liver transplantation was assessed.

Statistical Plan

Sample size was based on published literature and pilot data. Our estimated effect size was 6 months, assuming exponential survival, and a median TTP of 10 months for cTACE and 16 months for Y90 (hazard ratio [HR], 0.625). By using a 2-tailed α value of .10, a sample size of 55 per group would result in 80% power to detect this effect size. Ten percent was added to account for patient attrition, leading to an overall sample size of 124 patients (62 per group). Overall survival and TTP were compared using KM and the log-rank test. The hazard ratio and 95% confidence interval (CI) were estimated using proportional hazards regression. Inverse probability of censoring weighting (IPCW) was applied in the analysis of TTP using the censoring methods described by Hernan et al.[23] This method assigns higher weights to the outcomes of patients who were not censored, where censoring includes transplanted patients. The covariates used in this analysis included baseline sex, tumor distribution, number of lesions, largest tumor size, α-fetoprotein level, hepatitis C status, BCLC, and Child–Pugh.[24–26] The cumulative incidence of progression with transplant/death as competing risks also was compared using Gray's[27] test. Conditional power was calculated using the Proschan et al method,[28] as applied by Jitlal et al,[29] a statistical methodology permitting interpretation of data from trials terminated early. All analyses were performed using IBM SPSS Statistics v23.0 (Armonk, NY), STATA v14.0 (StataCorp, College Station, TX), and SAS/STAT software (SAS OnlineDoc 9.4, 2012; SAS Institute, Inc, Cary, NC); a *P* value less than .05 was considered significant.

Results

Baseline Characteristics

The groups were well matched. Y90 patients trended toward more portal hypertension ($P = .051$) and baseline bilirubin (1.3 vs 0.9; $P = .058$) (Table 1). More than 50% of all patients showed solitary lesions. No patient showed

cancer-related symptoms or weight loss at presentation. Supplementary Table 1 lists the baseline distribution of covariates used in the IPCW analysis, variables that may affect progression and transplantation. These covariates show no significant difference between treatment arms.

Treatment and Dosimetry

All 24 Y90 patients were treated successfully. Two of the 21 randomized cTACE patients received treatment off study but were included in the ITT analysis.

Y90. Selective Y90 was performed in 17 of 24 patients; 7 were lobar treatments. The median dose was 126 Gy (95% CI, 124–176) to a median of 405 ml (95% CI, 347–623) treatment volume. The median residual activity was 1.9% (95% CI, 1.6–3.5). The median lung shunt fraction was 5.1% (95% CI, 4.4–7.6), with a cumulative lung dose of 4 Gy (95% CI, 2.8–6.6). All treatments were as outpatients.

cTACE. Selective chemoembolization was performed in 16 of 19 patients; 3 were lobar infusions. On average, 52% of the total drug-lipiodol mixture was infused. The median number of days hospitalized at first procedure and cumulatively were 1 (95% CI, 0.9–2.2) and 1.5 (95% CI, 1.3–2.9), respectively.

cTACE vs Y90. Because of planning angiography, days from randomization to treatment were longer with Y90 compared with cTACE (18-day 95% CI, 15–26 vs 8-day 95% CI, 8–11, respectively; $P < .0001$). cTACE patients trended toward more treatments at 1.7 ± 1.1 (95% CI, 1.2–2.2) compared with 1.3 ± 0.5 (95% CI, 1.0–1.5) Y90 ($P = .098$). One cTACE patient crossed over to Y90 after 13.8 months because of continued progression after 3 cTACE treatments.

Clinical and Laboratory Toxicities

Supplementary Table 2 summarizes toxicities. The 30-day mortality rate was 0%. Vascular complications (n = 2) included common femoral artery pseudoaneurysm, 1 in each group ($P = 1.0$). There was a trend for more fatigue with Y90 ($P = .08$). The cTACE groups experienced more diarrhea ($P = .031$) and hypoalbuminemia ($P < .001$).

Delayed (>30 days) grade 3+ toxicities occurred in 3 cTACE patients: hyperbilirubinemia (day 49), abdominal pain from progression (day 183), and sepsis (day 309, early after the third cTACE cycle). Delayed grade 3+ toxicities occurred in 4 Y90 patients: ascites (days 68, 81, and 179) and bacterial peritonitis (day 54).

Follow-Up Evaluation and Censoring

Patients were followed up until the last imaging date and for survival. For all 45 patients, the median length of follow-up evaluation was 17.2 months (range, 1.4–62.1 mo). For TACE, the median follow-up evaluation was 15.7 months (range, 1.4–62.1 mo). For Y90, the median follow-up evaluation was 21.0 months (range, 2.3–59.6 mo). For TACE, there were 7 transplants at a median of 7.6 months (range, 3.0–17.3 mo). For Y90, there were 13 transplants at a median of 8.8 months (range, 4.0–15.3 mo). For TTP, there were 12 progressions (TACE, 10; Y90, 2) and 33 censored (TACE, 11; Y90, 22). Of the 11 censored in TACE, 6 (54.6%) were transplanted after the last imaging for progression and were censored in the TTP analysis. Of the 22 censored in Y90, 12 (54.6%) were transplanted after the last imaging for progression and were censored in the TTP analysis. Of the 12 progressions, there was 1 patient in each group who had a transplant after the progression. All transplants occurred

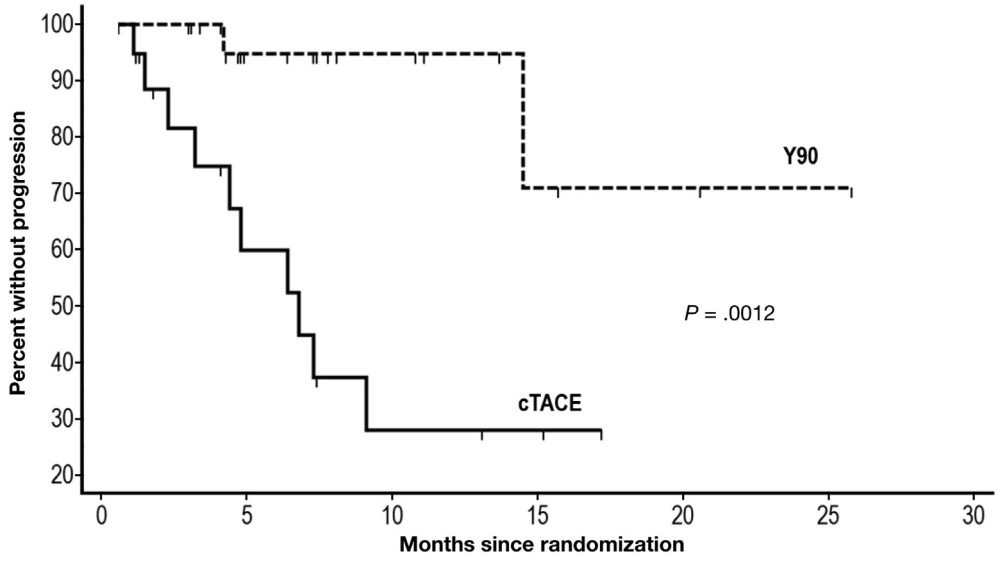

Figure 1. Time to progression.

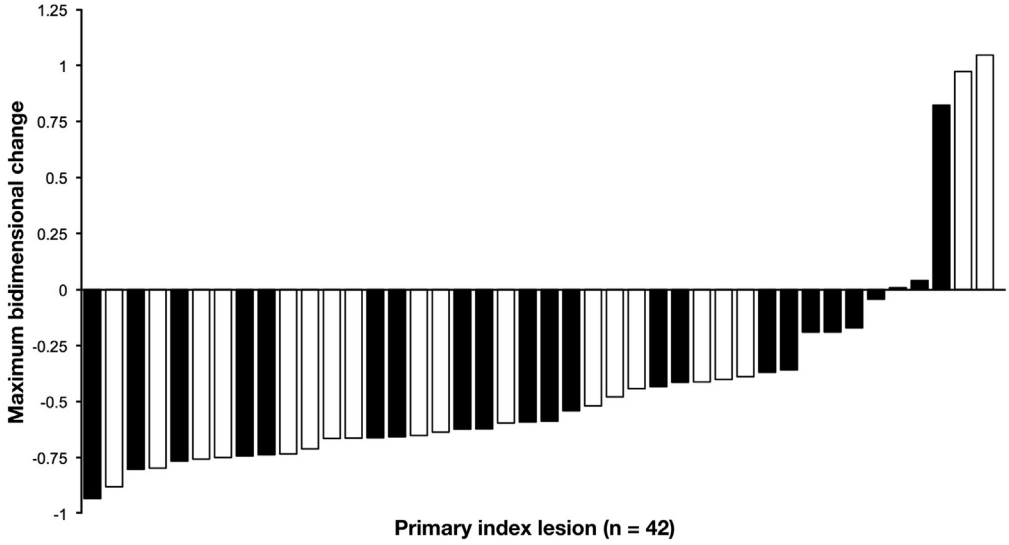

Figure 2. Waterfall plot of maximum size change for WHO measurements in (n = 42) primary index lesions after Y90 (*black bars*) vs cTACE (*white bars*). Negative values represent reductions in tumor size with a 50% or greater reduction (-) defined as a partial response and a more than 25% increase (+) in size defined as progressive disease.

after the time used in the TTP analysis. The data for the IPCW analysis may be summarized in 4 groups as follows: (1) censored, not subsequently transplanted: TACE, 5 (24%); Y90, 10 (42%); (2) censored, subsequently transplanted: TACE, 6 (29%); Y90, 12 (50%); (3) progressed, not subsequently transplanted: TACE, 9 (43%); Y90, 1 (4%); and (4) progressed, subsequently transplanted: TACE, 1 (5%); Y90, 1 (4%).

Time to Progression

Figure 1 compares TTP. The median TTP (primary end point) was significantly longer in the Y90 group: 6.8 months for cTACE vs not reached for Y90 (>26 mo; $P = .0012$; HR, 0.122; 95% CI, 0.027–0.557; $P = .007$). By competing risk analysis, Y90 again showed a significantly reduced hazard of progression compared with cTACE (subdistribution HR, 0.13; 95% CI, 0.03–0.57; $P = .006$), with transplant/death as competing events. By IPCW analysis, risk reduction of progression in the Y90 group was more pronounced (HR, 0.071; 95% CI, 0.008–0.645; $P = .019$).

Supplementary Table 3 summarizes the pattern of progression, showing that Y90 showed better local tumor control by enhancement criteria and new lesions. The median time to new hepatic lesions was 7.3 months for cTACE vs not reached for Y90 ($P = .017$). Two cTACE vs zero Y90 patients developed extrahepatic osseous progression ($P = .16$). The median time to extrahepatic spread was not reached.

Imaging Outcomes

Supplementary Table 4 presents the imaging response. Primary index lesions (n = 43) were defined in 184 reviewed studies (mean, 4.3 scans/patient), with follow-up imaging available in 42 of 43 patients (98%). Figure 2 represents a waterfall plot of maximal response. WHO response was 12 of 19 (63%) for cTACE vs 12 of 23 (52%) for Y90 ($P = .542$), with comparable median times with PR by group (7.3 mo; 95% CI, 3.9–12.6 after cTACE vs 7.6 mo; 95% CI, 4.5–11.3 after Y90; $P = .85$, log-rank). EASL response was 14 of 19 (74%) for cTACE vs 20 of 23 (87%) for Y90 ($P = .433$), with comparable median times to partial/complete response of 1.7 mo after Y90 (95% CI, 1.6–3.4) vs 1.4 mo after cTACE (95% CI, 1.3–4.9) ($P = .62$, log-rank).

Bridge to Transplant: Subgroup Analysis in Listed Patients

All transplanted patients were BCLC A at baseline; 18 Y90 vs 17 cTACE patients were within Milan criteria at baseline. The rates of transplantation in listed patients were 87% (13 of 15) after Y90 vs 70% (7 of 10) after cTACE. For cTACE, there were 7 transplants at a median of 7.6 months (range, 3.0–17.3 mo), and for Y90, there were 13 transplants at a median of 8.8 months (range, 4.0–15.3 mo).

TTP Analysis in Nontransplanted Patients

Twenty-five patients did not receive a liver transplant. TTP remained significantly longer with Y90 (median not reached at 26 months; 95% CI, 14.5–not calculable) vs cTACE (4.8 mo; 95% CI, 1.5–7.3; $P = .0002$) in nontransplanted patients.

Overall Survival

Figure 3 shows the KM curves (censored to liver transplantation) showing the median of 17.7 months (95% CI, 8.3–not calculable) and 18.6 months (95% CI, 7.4–32.5) OS for cTACE and Y90, respectively ($P = .99$).

Conditional Power

Overall TTP was compared using KM analysis and the log-rank test. The hazard ratio and 95% CI were estimated using proportional hazards regression. Because of slow accrual, the data safety monitoring committee recommended we close the study at 45 patients. The original power calculation determined that 55 patients per arm (110

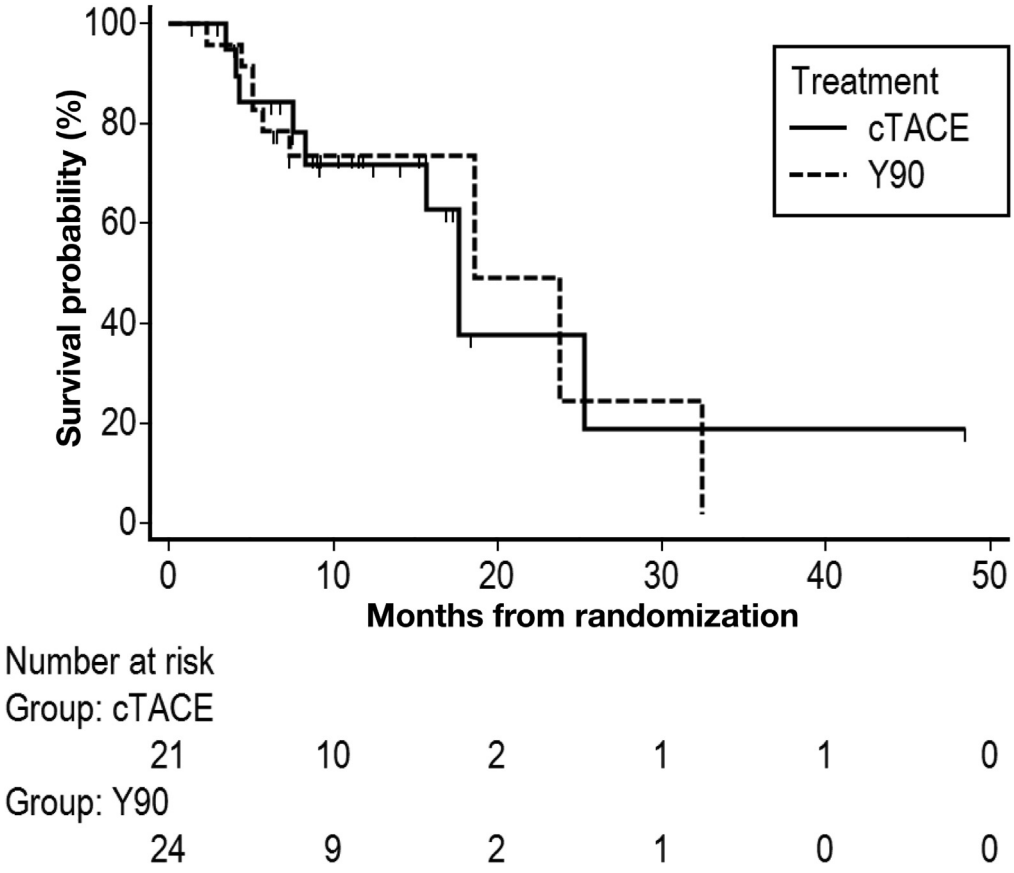

Figure 3. Overall survival from randomization censored to liver transplantation.

total) were needed to have 80% power to detect a median 10-month TTP for cTACE and 16-month TTP for Y90 (HR, 0.625) (2-tailed type I error rate, 10%), with an additional 10% to account for attrition (total planned sample size of 124). There was no provision for a formal interim analysis. Because exponential survival was assumed, the power calculation expected that all 110 patients would be followed up to progression events. At study halting, the actual observed median TTP after 45 patients was 6.8 months for cTACE vs not reached for Y90 (>26 mo; $P = .0012$; HR, 0.122; 95% CI, 0.027–0.557; $P = .007$). There were 12 progression events (10 cTACE, 2 Y90). Conditional power was calculated using the method of Proschan et al[28] as applied by Jitlal et al.[29] The information fraction was calculated as the observed number of events divided by the protocol expected number of events, or $12/110 = 0.11$. As described in the original study design, a 0.625 HR applied to both past and future data, the probability of achieving statistical significance at the end of 110 patients (conditional power) was 80%; this is the original protocol unconditional power. However, when the observed HR of 0.122 was used for accrued data but, conservatively, the original protocol HR of 0.625 for future data, the conditional power was 96.8%. Therefore, cautiously assuming that there is attenuation of the current HR of 0.122 treatment effect observed in the 45 enrolled patients to HR of 0.625 for an additional hypothetical 79 patients, there is a 96.8% chance that statistical significance in favor of Y90 still would be declared.

Discussion

Y90 prolongs TTP when compared with cTACE for early intermediate stage HCC, suggesting more complete treatment of targeted lesions and tumor control. Longer TTP did not translate to increased OS, suggesting local control (as an isolated variable) is insufficient for survival improvement in cirrhotic patients with competing risks of death. However, improved tumor control potentially could decrease the drop-out rate from transplant listing. With the exception of more diarrhea and hypoalbuminemia in the cTACE group, adverse events were similar between groups and compared favorably with previous retrospective reports.[8,30]

Response Rate

Baseline lesion size was relatively small and, hence, PRs and CRs were similar between groups. This is consistent with prior reports and emphasizes differences in assessing response with Y90 compared with cTACE when enhancement is used. Investigators have highlighted the pitfall of using an early enhancement pattern in assessing response for Y90 in large lesions.[31] cTACE is embolic and, hence, the vascularity that permits enhancement during cross-sectional imaging (arterial hypervascularity) is occluded by the drug/embolic. Y90, on the other hand, is a microembolic therapy that does not occlude the vasculature. The results of our study herein suggest that the time to response by enhancement criteria for small lesions are equivalent.

Time to Progression, Overall Survival

Despite longer time from randomization to treatment, overall treatment failure was lower with Y90, suggesting improved cytotoxicity. Technically, cTACE and Y90 have become more similar since the adoption of cone-beam CT and microcatheter technologies, allowing improved intraprocedural visualization of tumor coverage. Although coil embolization before radioembolization initially was common, contemporary practices require coiling infrequently.[32] Therefore, we attribute TTP improvement to mechanistic differences in antitumor activity rather than technique; both groups were treated predominantly with selective techniques. Survival was lower than expected in both groups, explained by the 29%/50% Child–Pugh B advanced cirrhotic patients included in this clinical trial (at randomization).

Curative Transplantation

Survival inherently is linked to transplantation.[17] Progression of HCC directly impacts transplant eligibility through waiting list drop-out. Therefore, a locoregional therapy prolonging TTP should reduce waitlist drop-out and provide higher rates of successful bridging to transplantation. This theory is supported by our findings, in which patients randomized to Y90 showed better tumor control and listed Y90 patients received transplantation at a rate of 87%. Moreover, some centers are hesitant to perform ablation in transplant candidates because of the risk of tract seeding. In these settings, intra-arterial therapy such as Y90 eliminates the risk of tract seeding, prolongs TTP, and potentially offers a higher chance for transplantation.

Study Rationale

Chemoembolization is considered the standard of care for BCLC B patients based on improved survival compared with best supportive care.[5–7] Also, the applicability of cTACE is acknowledged for BCLC A patients ineligible for recommended treatments (stage migration). We followed these principles during Prospective Randomized Study of Chemoembolization Versus Radioembolization for the Treatment of Hepatocellular Carcinoma, recognizing we could ethically randomize unablatable BCLC A and BCLC B patients eligible for cTACE.

Change in Local Practice

Our findings have motivated an institutional change in local practice. Patients bridged to transplantation now receive Y90 based on our finding of lower progression and potentially reduced drop-out. Therefore, Y90 may influence survival positively by increasing the rate of curative transplant. Currently, we reserve cTACE when combination therapy with radiofrequency ablation is planned, lipiodol uptake will assist in HCC diagnosis, nontarget perfusion precludes radioembolization, or when transplantation is imminent (thereby mitigating handling a radiated specimen).

Competing Risk Analysis

In the presence of competing risks of death and liver transplantation, Kaplan–Meier may not estimate TTP sufficiently because either of these 2 events precludes recording of subsequent cancer progression. A sensitivity analysis was performed in which TTP also was analyzed using Gray's[27] test for comparing cumulative incidence curves, with liver transplant as the competing event, generating a cause-specific hazard ratio for TTP. By competing risk analysis, Y90 showed longer TTP compared with cTACE.

IPCW Analysis

To address the potential issue of dependent censoring by therapy, we applied IPCW. For this study, IPCW assigns increasing weights to patients the longer they remain on follow-up evaluation. As they proceed through follow-up evaluation, the probability of remaining on follow-up evaluation decreases. By using logistic regression, IPCW assigns the inverse of these probabilities, which are a function of baseline characteristics, to each month of follow-up evaluation, thereby increasing the weight of the months representing longer follow-up evaluation. If there is an imbalance between groups in the rate of informative or noninformative censoring, then the group with more censoring would be weighted less in this analysis, thereby equalizing the effect of censoring in the analysis. In our study, IPCW confirmed longer TTP in the Y90 group.

Strengths, Limitations

Strengths included the randomized nature, comprehensive imaging review, and real-world clinically relevant patient flow of unablatable BCLC A and B patients intended for standard of care cTACE, but randomized to test arm Y90. The study also showed longer TTP with Y90 despite longer time to initial treatment compared with the cTACE group. Limitations included required censoring of imaging/survival to transplant. However, given the increasing complexity of this disease, it is recognized that patients only rarely receive 1 HCC treatment. Patients do not move along the BCLC algorithm in a linear A→B→C→D fashion, but rather cycle from stage to stage in multiple directions as they receive treatment. Censoring to liver transplant is the correct statistical method to determine TTP. Survival in such cases is confounded by cross-over to alternate therapies, an increasingly challenging end point when studying BCLC A and B.[33] Therefore, TTP was used as a surrogate end point to extract meaningful data most closely linked to the intervention. Also, because transplantation and death precluded future observation of progression, competing risk and IPCW analyses were performed, confirming the findings favoring Y90 over cTACE. Although our enrollment rate of 25% was encouraging (45 of 179), the study was halted at the recommendation of our cancer center given accrual difficulties common to interventional studies. Historically, these challenges arise because of the following: (1) referral patterns for specific therapies or studies (43 patients declined the research, 29 selected other trials, 49 requested Y90, and 13 requested cTACE), (2) the rapid improvement

of technology and clinical science obviating the initial trial research questions because of updates in standard of care, (3) difficulties of patient compliance with follow-up evaluation and imaging as part of a strict protocol and, (4) compared with other cancers, the low incidence of HCC in the United States. To overcome these limitations, we advocate the following: (1) multidisciplinary tumor boards to review eligibility for studies, (2) shorter trial activation times and increased institutional support, (3) requisite imaging quality and frequency of scans needed for TTP analyses, (4) inclusion of neighboring hospitals referring patients for study consideration, and (5) use of composite data pooling studies. Finally, we acknowledge the slightly lower than expected survival. This is explained by the percentage of Child–Pugh B patients in both groups at randomization.

Despite accrual issues, post hoc analysis (Proschan et al[28] method) suggested that, with a 5.1-fold HR increase (0.122–0.625) associated with Y90 for the 79 remaining hypothetical patients (for complete target enrollment), there would be a 96.8% chance of a significant result at the end of the study. When controlling for dependent censoring between the 2 treatment arms with IPCW analysis, we found that the TTP benefit with Y90 was maintained by competing risk and amplified by IPCW analyses. Although the relatively low sample size is acknowledged, the seminal studies establishing cTACE as the standard of care also were limited in sample size, single center, and enrolled mostly Child–Pugh A patients. Although our TTP results favoring Y90 are in line with other uncontrolled retrospective reports in patients with compromised liver functions, our study validates such findings with prospective randomized level I evidence.[34–38]

Conclusions

Intra-arterial embolotherapy is safe and has high antitumor activity. This study represents a real-world, comparative effectiveness analysis of Y90 and cTACE by ITT. In light of competing risks of liver transplantation and death, Y90 significantly increased TTP compared with cTACE in a randomized phase 2 setting, translating to significantly improved local tumor control that could reduce drop-out from transplant waitlists.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.08.029.

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Received June 22, 2016. Accepted August 23, 2016.

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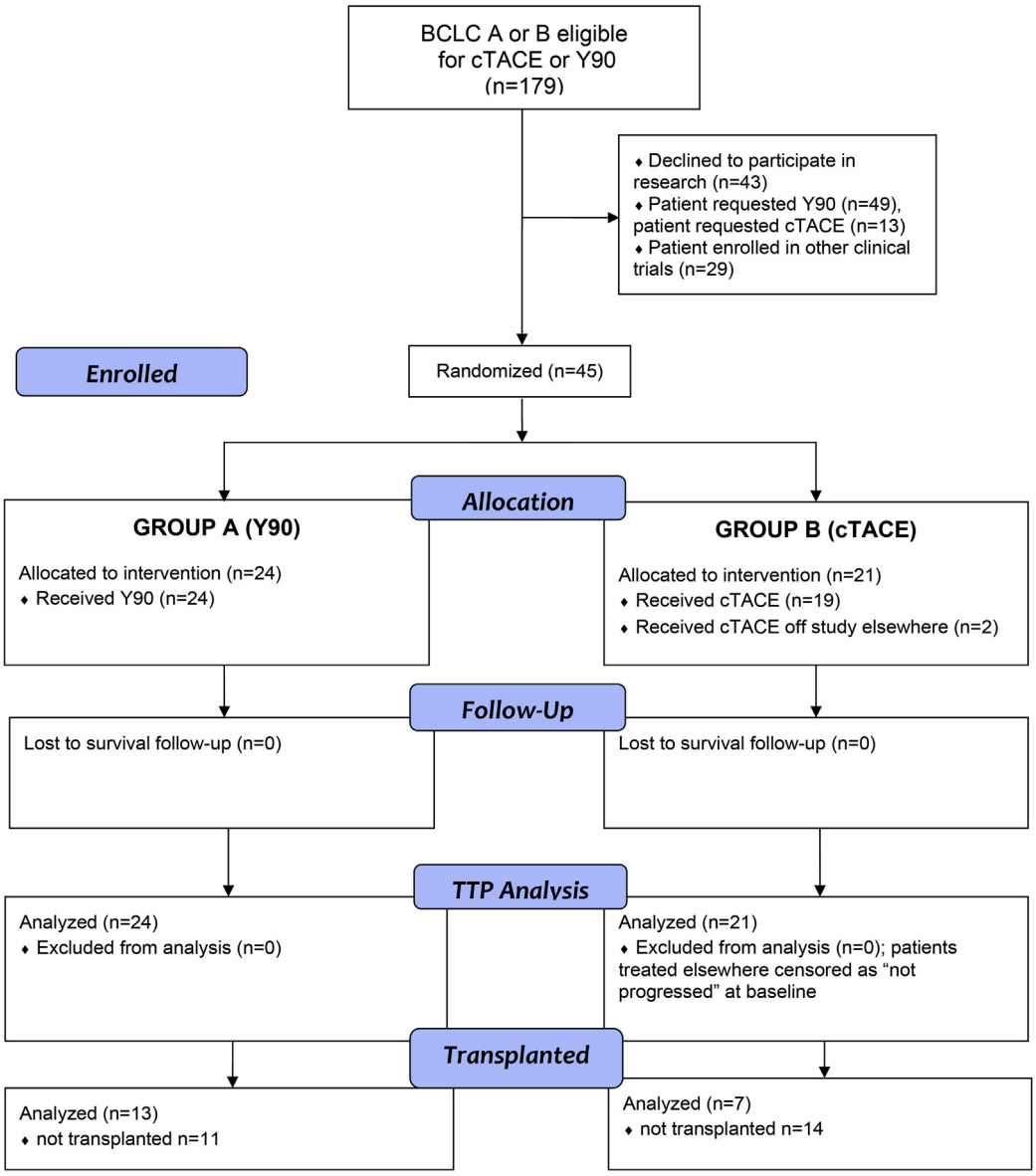
Acknowledgments
The authors thank Carlene del Castillo, Karen Marshall, Krystina Salzig, Melissa Williams, and Jenny Karp for their commitment to patient care and dedication to clinical research.

Conflicts of interest
These authors disclose the following: Robert J. Lewandowski, Laura Kulik, and Riad Salem serve as advisors to BTG International. The remaining authors disclose no conflicts.

Funding
This study was supported in part by National Institutes of Health grant CA126809. Also supported by a Medical Scientist Training Program student (T32GM008152 to A.C.G.) with support for research provided by an Allied Scientist grant from the Society of Interventional Radiology Foundation.



Supplementary Figure 1. CONSORT study flowchart.

Supplementary Table 1. Baseline Characteristics: Inverse Probability of Censoring Weighting

Characteristic	cTACE (n = 21)	Y90 (n = 24)	Odds ratio (95% CI)
Demographics			
Sex			
Male	16 (76)	17 (71)	0.76 (0.20–2.89)
Female	5 (24)	7 (29)	1.0
Distribution			
Bilobar	7 (33)	7 (29)	0.82 (0.23–2.92)
Unilobar	14 (67)	17 (71)	1.0
Lesions, n			
Solitary	11 (52)	13 (54)	1.07 (0.33–3.47)
Multifocal	10 (48)	11 (46)	1.0
Largest tumor size, *cm*[a]			
Median (IQR)	2.6 (0.7)	3.0 (1.2)	1.08 (0.84–1.38)
Means (95% CI)	3.0 (2.3–3.6)	3.2 (2.7–3.7)	1.0
AFP level, *ng/mL*			
$<$200	19 (90)	21 (88)	0.74 (0.09–4.91)
$\geq$200	2 (10)	3 (12)	1.0
HCV			
Yes	13 (62)	13 (54)	0.73 (0.22–2.39)
No	8 (38)	11 (46)	1.0
BCLC			
A	17 (81)	18 (75)	0.71 (0.17–2.91)
B	4 (19)	6 (25)	1.0
Child–Pugh (at randomization)			
A	15 (71)	12 (50)	1.0
B7	3 (14)	6 (25)	2.50 (0.52–12.14)
B8	2 (10)	3 (12.5)	1.88 (0.27–13.09)
B9	1 (5)	3 (12.5)	3.75 (0.34–40.81)

NOTE. Odds ratio = 1.0, indicates reference group.
AFP, α-fetoprotein; HCV, hepatitis C virus; IQR, interquartile range.
[a]Odds ratio per 0.50-cm change.