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Yttrium-90 Radioembolization for Intermediate-Advanced Hepatocellular Carcinoma: A Phase 2 Study

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Yttrium-90 radioembolization (Y90RE) is a novel approach to radiation therapy for hepatocellular carcinoma (HCC), never tested in phase 2 studies. Fifty-two patients with intermediate (n.17) to advanced (n.35) HCC were prospectively recruited to assess, as the primary endpoint, efficacy of Y90RE on time-to-progression (TTP). Secondary endpoints were tumor response, safety, and overall survival (OS). All patients were Eastern Cooperative Oncology Group (ECOG) score 0-1, Child-Pugh class A-B7. Y90RE treatments aimed at a lobar delivery of 120 Gy. Retrospective dosimetric correlations were conducted and related to response. Fifty-eight treatments were performed on 52 patients. The median follow-up was 36 months. The median TTP was 11 months with no significant difference between portal vein thrombosis (PVT) versus no PVT (7 versus 13 months). The median OS was 15 months (95% confidence interval [CI], 12-18 months) with a nonsignificant trend in favor of non-PVT versus PVT patients (18 versus 13 months). Five complete responses occurred (9.6%), and the 2 year-progression rate was 62%. Objective response was 40.4%, whereas the disease control rate (78.8%) significantly affected survival (responders versus nonresponders: 18.4% versus 9.1%; $P = 0.009$). Tumor response significantly correlated with absorbed dose in target lesions ($r = 0.60$, 95% CI, 0.41-0.74, $P < 0.001$) and a threshold of 500 Gy predicted response (area under the curve, 0.78). Mortality at 30-90 days was 0%-3.8%. Various grades of reduction in liver function occurred within 6 months in 36.5% of patients, with no differences among stages. On multivariate analysis, tumor response was the sole variable affecting TTP ($P < 0.001$) and the second affecting survival (after Child-Pugh class). *Conclusion:* Y90RE is an effective treatment in intermediate to advanced HCC, particularly in the case of PVT. Further prospective evaluations comparing Y90RE with conventional treatments are warranted. (HEPATOLOGY 2013;57:1826-1837)

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Hepatocellular carcinoma (HCC) is a global health problem; it is the third most common cause of cancer-related mortality and the leading cause of death among patients with cirrhosis.[1,2] The coexistence of two life-threatening conditions such as cancer and cirrhosis makes it difficult to prognosticate the outcome of patients with HCC. The most used staging system is the Barcelona Clínic Liver Cancer (BCLC), endorsed by both American and European liver societies.[2,3]

The intermediate stage of HCC (BCLC-B) incorporates heterogeneous tumor burdens and liver function

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clínic Liver Cancer; CI, confidence interval; CT, computed tomography; DCR, disease control rate; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard-ratio; LD, liver decompensation; MRI, magnetic resonance imaging; OS, overall survival; PVT, portal vein thrombosis; RECIST, Response Evaluation Criteria in Solid Tumors; SPECT, single photon emission computed tomography; TACE, trans-arterial chemoembolization; ^{99m}Tc-MAA, technetium-99m macroaggregated albumin; TTP, time-to-progression; WHO, World Health Organization; Y90RE, yttrium-90 radioembolization.

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stages (Child-Pugh class A or B) resulting in a wide interval of expected survival after trans-arterial chemoembolization (TACE), from 14 to 45 months.[2] This suggests that not all intermediate-stage HCCs will derive a similar benefit from TACE, whereas some patients may benefit from other treatment options.[4]

In addition, patients with advanced HCC (BCLC-C stage), although sharing a median survival of less than a year, may present with heterogeneous performance statuses and different tumor burdens, from single nodules associated with limited portal vein thrombosis (PVT) amenable of curative attempts to bulky intrahepatic diffusion associated with extrahepatic spread (EHS). In all those patients, sorafenib significantly improves survival,[5] with subgroup analyses showing that different baseline characteristics may affect the expected survival.

Yttrium-90 radioembolization (Y90RE) is a novel transarterial approach to radiation therapy for liver cancer that has achieved in large series comparable or improved survival, time-to-progression (TTP) and toxicity with respect to chemoembolization,[6] and efficacious tumor control also in advanced patients with PVT.[7,8] According to published data, Y90RE could compete favorably with TACE or sorafenib in the appropriate setting. However, no prospective phase 2 or 3 studies confirming Y90RE results have been reported, hindering such a technique from its application in general practice.

The present phase 2 study was undertaken to assess the efficacy and safety of Y90RE—as for variations in TTP and overall survival (OS)—in a prospective cohort of intermediate and advanced HCC: namely, in a population of patients with well-compensated cirrhosis and cancer, associated or not with tumoral invasion of the portal system.

Patients and Methods

Study Design, Enrollment, and Patient Cohort. This is a single-center prospective phase 2 trial on a consecutive cohort of patients with liver cirrhosis and HCC confined to the liver and not eligible to conventional curative treatments (i.e., liver resection, ablative therapies or transplantation). The study was designed to capture intermediate to advanced HCC patients originally referred for liver transplantation but with a tumor extension that a multidisciplinary board precluded from both a transplant list or downstaging protocols. Patients were offered to enter the prospective clinical study with Y90RE after being informed on more conventional treatments available, such as sorafenib or TACE, whether or not PVT was found to be associated with the primary tumor.

Study design, enrollment criteria, and grouping are summarized in Fig. 1.

No patient showed an extrahepatic tumor spread on bone scan, chest and abdominal multiphase computed tomography (CT), or magnetic resonance imaging (MRI). Positron emission tomography scans were acquired for patients suspected to have extrahepatic spread. The cut-off in size of the shortest diameter for hepatic hilum lymph node enlargement to be defined as metastatic was 1.5 cm. Elevated alpha-fetoprotein (AFP) serum level did not represent a contraindication to treatment. Blood tests, AFP, and abdominal/thoracic CT or MRI were performed at 30 and 90 days and subsequently every 3 months. Contrast-enhanced ultrasound was added between each dynamic imaging and bone scan every 6 months. The primary endpoint of the study was to assess the efficacy of Y90RE as measured by time-to-progression (TTP); secondary endpoints were OS, tumor response, and safety. After progression, patients were treated according to physician judgement or received best supportive care. Even if progression or recurrence formally ended the per-protocol TTP response assessment, all enrolled patients were followed up until death. The study received Institutional Review Board approval and has been registered as ClinicalTrials.gov NCT00910572.

Reference Parameters for Staging and Response. Diagnosis of HCC was made on noninvasive imaging criteria or biopsy according to European Association for the Study of the Liver (EASL)–American Association for the Study of Liver Diseases guidelines.[3,9] Each patient's performance status was monitored with the Eastern Cooperative Oncology Group (ECOG) score.[10] Tumor-related PVT was defined at baseline CT or MRI as a filling defect, partially or completely occluding the vessel in the portal venous phase, with

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Additional Supporting Information may be found in the online version of this article.

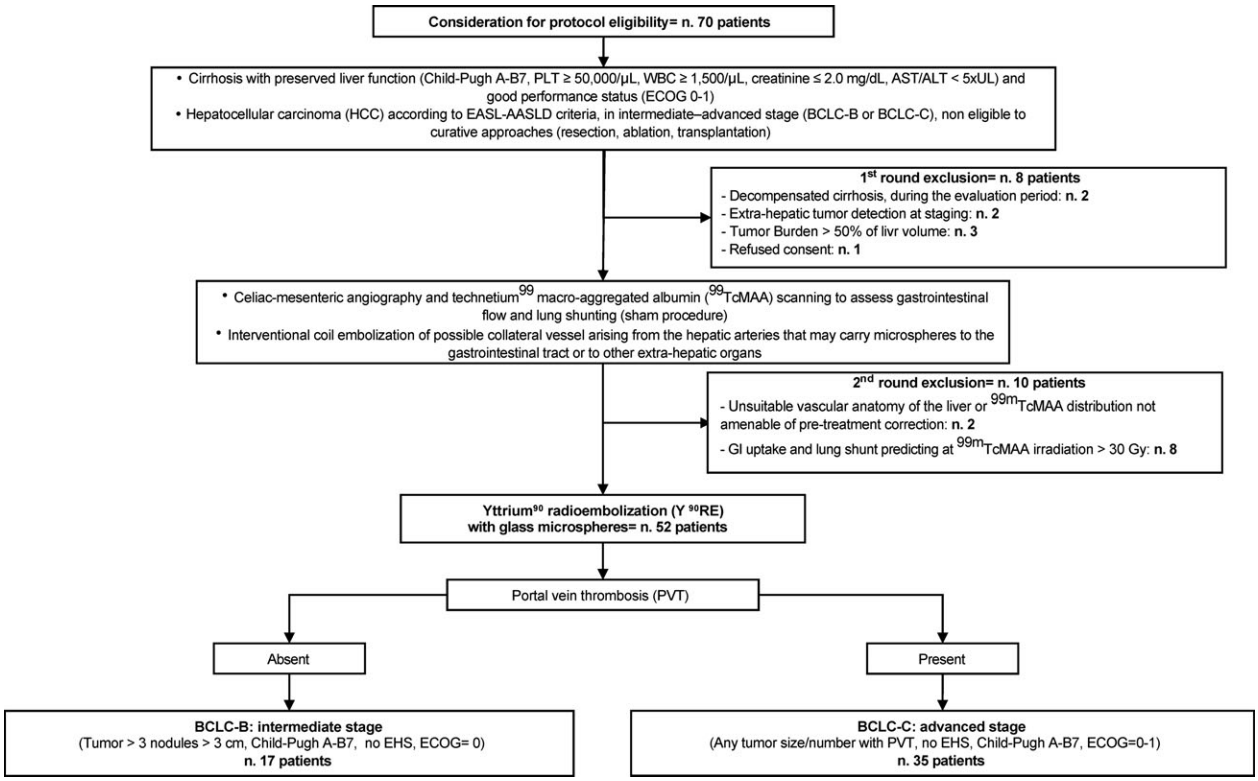

Fig. 1. Study design, enrollment criteria, and patient grouping.

clear evidence of enhancement during the arterial phase of dynamic imaging. PVT extension was classified according to slight modification of the proposal by Shi et al.[11] (Supporting Fig. 1). Tumor burden—measured as percentage—was assessed at patient entry as a visual estimate, and at treatment planning objective mathematic measurements of the liver/tumor volumes were conducted. Adverse events and toxicity assessment were graded according to National Cancer Institute Common Toxicity Criteria (CTCAE version 3.0).[12] The composite clinical laboratory parameter of liver decompensation (LD) was added and defined as the occurrence of any of the following features during follow-up: clinically detectable ascites, bleeding from esophageal varices, hepatic encephalopathy, total bilirubin >3 mg/dL, and prothrombin time international normalized ratio >2.2. Any LD occurring within 180 days of radioembolization was considered treatment-related. Incidentally, the chosen definition of treatment-related LD included all previously described toxicities related to Y90RE[13–15] (Supporting Information).

Assessment of tumor response after Y90RE was made on anonymized scans reviewed by two radiologists on staff; whenever response classification was not obvious, agreement was reached with a third radiologist. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[16] World Health Organization (WHO) criteria[17] and EASL criteria,[9] hence assessing dimensions, cross-products of lesions, and reduction in viable tumor volume. For each criterion, the objective response was defined as partial response + complete response, whereas the disease control rate (DCR) was defined as stable disease to partial response + complete response. According to EASL, progression was defined as the appearance of new lesions (intra- or extrahepatic) or increase of enhancing tissue in the target lesions of at least 25%; partial response was defined as a decrease of at least 50% in the enhancement of the target lesions. The variations of PVT extension during follow-up were not considered in tumor response evaluation, with the sole exception of complete disappearance in case of complete response. AFP serum level was recorded but was not considered a parameter of response.

Procedure and Dosing. Y90RE was performed according to standard practice[7,18] in two sessions (Fig. 1): (1) a simulation session, through celiac-mesenteric angioscintigraphy with 160 MBq technetium-99m macroaggregated albumin (^{99m}Tc-MAA) scanning, and (2) a treatment session 3 to 4 weeks later using ^{90}Y-microspheres (TheraSphere; Nordion, Ottawa,

Canada). Depending on tumor characteristics, a maximum of two treatments per patient were allowed (Supporting Information). The treatment planning goal was a lobar delivery of 120 Gy, as described.[14,19] After injection, planar and single photon emission computed tomography (SPECT) scintigrams were acquired with the ^{90}Y Bremsstrahlung technique to check therapeutic biodistribution.

Furthermore, a retrospective dose-response correlation analysis on tumor versus nontumor tissue was performed on CT-based, attenuation-corrected ^{99m}Tc-MAA SPECT images. Accordingly, the absorbed dose was calculated in each 4.42 side volumetric pixel (voxel) of the liver evaluating the absorbed dose as proportional to the ^{99m}Tc-MAA SPECT count fractions in each voxel. SPECT raw data were imported to a Siemens e.soft workstation and manually coregistered and reconstructed with CT-based attenuation correction, using an *ad hoc* optimized iterative algorithm. Reconstructed SPECT images were then exported to a MATLAB code (SilvyAnnMart), where the uptaking liver regions were separated into tumor lesions (excluding necrotic regions) and nontumor parenchyma, by regions of interest drawn comparing SPECT and CT images. The mean absorbed dose was the arithmetic mean of the absorbed dose in voxels belonging to the tumor regions of interest. Parenchyma absorbed dose was averaged on both uptaking and nonuptaking voxel of the organ. Lesions with a volume of <3 cc (diameter <1.8 cm) were excluded to avoid absorbed dose underestimation induced by the partial volume effect.[19]

Statistical Analysis. To test an increase in median survival in a cohort of intermediate to advanced HCCs from 10 months with conventional treatments to 15 months with 90YRE, a sample size of 50 patients enrolled over a 2-year period, followed by 2 years of additional follow-up, was predicted. This provided sufficient power (85%) on the assumption of exponential distribution of survival time, and type 1 error = 10% (one-tailed test): a distribution and error within the accepted variances of phase 2b studies, aimed at avoiding underestimation of possible treatment-related beneficial effects on outcome.

TTP was calculated from the first 90YRE to the first progression at any site. OS was calculated from the first 90YRE to death from any cause.

Data were summarized using descriptive statistics. Univariate and multivariate analyses were conducted with Kaplan-Meier and Cox proportional hazard models, respectively. Receiver operating characteristic curve analysis was used to determine the optimal cut-off of mean absorbed dose predicting response. Analyses were conducted using SAS version 8.0.2 (SAS Institute Inc., Cary, NC). $P < 0.05$ was considered significant.

Results

Patient Population and Treatment. Seventy patients were evaluated for the study between February 2007 and June 2009, 52 of whom received Y90RE for an eligibility rate of 74%, which increased to 80% when the sole unfitting technicalities were considered. A study flowchart and the reasons for Y90RE exclusion are shown in Fig. 1.

Patient and tumor baseline characteristics are outlined in Table 1. Tumors presenting with either early-stage (BCLC-A) or end-stage (BCLC-D) HCC were excluded, but of the 52 patients enrolled in the study, 35 (67.3%) had advanced HCC with PVT and 17 (32.7%) had intermediate stage HCC with PVT. None of the patients met United Network for Organ Sharing stage T1-T2 (i.e., Milan Criteria for transplantation) being 43 cases (82.7%) in stage T4. The median age of the patients was 64 years (range, 27-82 years); all of the patients had compensated cirrhosis, with Child-Pugh stage distributed as A5-A6 in 43 (82.7%) patients, B7 in 9 (17.3%) patients, and B8-C in 0 (0%) patients; all patients had an ECOG score of 0-1. Liver disease was mainly related to hepatitis C virus infection (40%). Fifteen patients (28.9%) had received other treatments prior to Y90RE (liver resection, n = 8; radiofrequency ablation, n = 7). A total of 69.2% exhibited multifocal disease, whereas tumor burden never exceeded 50% of the total liver volume. The mean ± SD and median size of the largest tumor were 61 ± 31 mm and 56 mm (range, 20-150), respectively.

The anatomic location of PVT in advanced patients was mostly in the right portal vein (74.3%). PVT extended at the segmental or main branch level in 29 patients (PV1-PV2, 82.8%), whereas the tumor expanded into the main portal vein trunk (PV3) in five patients (14.3%) or the mesenteric or splenic vein (PV4) in one (2.9%). Baseline AFP, bilirubin, and platelet count did not differ among patients with or without PVT, whereas tumor size was significantly larger in PVT patients with respect to those who were PVT-free (69 ± 30 versus 44 ± 27 mm, respectively; $P = 0.0048$), with the largest treated HCC measuring 150 versus 120 mm.

Overall, 88.4% of patients received a single treatment with a total number of 58 treatments, representing most of the patients affected by unilobar disease

Table 1. Baseline Characteristics of the Study Population

Characteristics	Study Population N = 52)	No PVT (n = 17)	PVT (n = 35)
Age, years	64 (27-82)	62 (27-73)	64 (32-82)
Sex			
Female	3 (5.8)	2	1
Male	49 (94.2)	15	34
Etiology of liver disease			
HBV	16 (30.8)	4	12
HCV	21 (40.4)	10	11
Alcohol and other	15 (28.8)	3	12
Child-Pugh class			
A5-A6	43 (82.7)	15	28
B7	9 (17.3)	2	7
Portal hypertension*			
No	31 (59.6)	11	20
Yes	21 (40.4)	6	15
ECOG performance status			
PS 0	31 (59.6)	17	14
PS 1	21 (40.4)	–	21
BCLC stage			
B	17 (32.7)	17	–
C	35 (67.3)	–	35
UNOS stage			
T3	9 (17.3)	9	–
T4a	8 (15.4)	8	–
T4b	35 (67.3)	–	35
CLIP score			
0	4 (7.7)	2	2
1	19 (36.5)	11	8
2	16 (30.8)	4	12
3	9 (17.3)	–	9
4	4 (7.7)	–	4
Okuda stage			
I	37 (71.2)	14	23
II	15 (28.8)	3	12
Tumor distribution			
Unilobar	49 (94.2)	15	34
Bilobar	3 (5.8)	2	1
Number of nodules			
1	16 (30.8)	1	15
2-3	25 (48.1)	8	17
>3	11 (21.1)	8	3
Largest tumor diameter, mm	56 (20-150)	39 (20-120)	66 (22-150)
Tumor burden			
0-25%	17 (32.7)	8	9
26-50%	35 (67.3)	9	26
AFP, ng/mL	49 (0-126560)	11 (0-20043)	253 (0-126560)
Previous treatment			
None	37 (71.1)	10	27
Radiofrequency ablation	7 (13.5)	2	5
Liver resection	8 (15.4)	5	3

Data are expressed as the median (range) or absolute number (%) as appropriate.

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clínic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; PVT, portal vein thrombosis; UNOS, United Network for Organ Sharing.

*Portal hypertension is defined by the presence of a platelet count below 100,000/mm^3 associated with significant splenomegaly, or presence of varices at endoscopy.

(94.2%). Of the six patients that underwent two sessions of Y90RE, three patients were treated in both lobes, whereas the other three underwent a second session because of local progression. A total of seven (13.5%) patients required pretreatment embolization of intra- or extrahepatic vessels to prevent gastrointestinal/lung shunting or to induce redistribution of the tumor blood supply.

The median injected activity was 2.6 GBq (range, 1.1-5.7 GBq), and the median dose to liver lobe was 101 Gy per treatment (range, 34-146 Gy). The median lung dose per treatment was 0.2 Gy (range, 0-15 Gy) as for a nonattenuation corrected median lung shunt of 1% (range, 0-26%). The median follow-up time of the studied population was 36 months.

Tumor Response and Outcomes. A median of six scans per patient was collected, and overall, 398 scans were reviewed. Response rates, TTP, and patient OS stratified by stage are summarized in Table 2.

The objective response to Y90RE was about 40% according to any of the adopted criteria (21 patients: 40.4%), whereas the DCR reached 75%-78.8% (WHO and EASL criteria, respectively). On average, both objective response and DCR were higher in PVT-negative versus PVT-positive patients, although not significantly, being at WHO criteria the objective response 47% versus 37.1% and the DCR 82.3% versus 71.4%. Similarly, using EASL criteria, the objective response was 52.9% versus 34.3% and the was DCR 88.2% versus 74.3.% in intermediate versus advanced HCC, respectively.

The best tumor response as described by density variation (EASL criteria) is summarized in Fig. 2A.

Five complete responses (9.6%) were registered: three in PTV patients and two in non-PVT patients, with an AFP reduction from a mean of 3,856 to 20 ng/mL. Complete responders had a mean survival of 36 months (range, 12-52 months). According to dimensional criteria (RECIST and WHO), the number of registered complete responses diminished to four.

In responding patients, the median time to response was 3 months (95% confidence interval [CI], 3-4) at any assessment criteria. Nonsignificant differences were found in objective response between patients with Child-Pugh A versus Child-Pugh B7 disease (37.2% versus 55.5% at both WHO and EASL criteria). WHO objective responses varied by largest baseline tumor size ($\leq$5 cm, 82.4%; 5-10 cm, 17.6%; >10 cm, 2%).

Tumor response evaluation did not consider AFP. However, in the overall series, a median decrease of 20% in AFP values was observed from the time of treatment to the lowest registered level. Such variation

Table 2. Tumor Response and Patient Outcomes

	No. of Patients	EASL (CR+PR), n (%)	WHO (CR+PR), n (%)	Disease Control Rate* (CR+PR+SD)	Median TTP, Months, 95% CI	Median OS, Months, (95% CI)
Overall series	52	21 (40.4)	21 (40.4)	41 (78.8)	11 (6-NC)	15 (12-18)
PVT absent						
BCLC B	17	9 (52.9)	8 (47)	15 (88.2)	13 (6-NC)	18 (12-38)
Child A	15	7 (46.7)	6 (40)	13 (86.7)	13 (6-NC)	18 (13-38)
Child B	2	2 (100)	2 (100)	2 (100)	No PD†	NC
PVT present						
BCLC C	35	12 (34.3)	13 (37.1)	26 (74.3)	7 (6-12)	13 (9-17)
PV1-PV2	29	11 (37.9)	12 (41.4)	23 (79.3)	7 (6-2)	14 (11-18)
PV3-PV4	6	1 (16.6)	1 (16.6)	3 (50)	NC	8 (5-10)
BCLC C/Child-Pugh A	28	9 (32.1)	10 (35.7)	20 (71.4)	6 (6-2)	16 (11-21)
PV1-PV2	23	8 (34.8)	9 (39.1)	18 (78.3)	7 (6-2)	17 (13-21)
PV3-PV4	5	1 (20)	1 (20)	2 (40)	3 (2-NC)	9 (4-NC)
BCLC C/Child-Pugh B	7	3 (42.9)	3 (42.9)	6 (85.7)	NC	6 (5-12)
PV1-PV2	6	3 (50)	3 (50)	5 (83.3)	NC	6·5 (5-12)
PV3-PV4	1	–	–	1 (100)	No PD†	5

Abbreviations: BCLC, Barcelona Clínic Liver Cancer; CR, complete response; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCV, hepatitis C virus; NC, not calculable; OS, overall survival; PR, partial response; PV1, tumor thrombi involving segmental branches of portal vein or above; PV2, tumor thrombi involving right/left portal vein; PV3, tumor thrombi involving the main portal trunk; PV4, tumor thrombi involving the superior mesenteric vein PVT, portal vein thrombosis; SD, stable disease; TTP, time-to-progression.

*According to EASL criteria.

†No progression of disease observed during follow-up.

was even more evident in the PVT population, which showed a 48% decrease in AFP levels following Y90RE. In particular, out of 22 patients expressing an AFP value >200 ng/mL (PVT, n = 20; no PVT, n = 2), 15 (68.2%) patients (PVT, n = 13; no PVT, n = 2) showed an AFP reduction of more than 50% after treatment.

Sixty-five tumor lesions were included in the retrospective dosimetric analysis. The lesion median absorbed dose was 387 Gy (range, 24-1,478 Gy); radiological response correlated with absorbed dose into the target lesions (Spearman's $r = 0.60$; 95% CI, 0.41-0.74; $P < 0.001$). Lesions lacking objective response received a median dose of 275 Gy, whereas responding tumors were found to absorb 490 Gy. An efficacy threshold of 500 Gy (Fig. 2B) significantly predicted the observed objective response and limited to 20% the rate of nonresponders (area under the curve, 0.78).

During the study follow-up, 28 progressions were observed: extrahepatic disease in seven (25%) patients; appearance of new nodules or progression in the treated lobe in eight (27.6%) patients; and contralateral or bilobar progression in 13 (46.4%) patients. Overall, the tumor progression rate at 2 years was 62% (Fig. 3A) and the median TTP for the entire cohort was 11 months (range, 6-11) with no significant difference observed on whether or not patients had PVT, even though a trend in lengthening the median TTP was registered for patients without PVT (13 months) versus those with PVT (7 months) (Table 2). Similarly, no statistical difference was determined comparing patients with high versus low AFP serum level at presentation, although a trend was observed from a DCR and a TTP of 68.7% and 6 months, respectively, in patients with pretreatment AFP serum level >400 ng/mL to 83.3% and 11 months, respectively, in patients with nonelevated AFP. A total of 15 patients received treatments other than Y90RE after progression: 13 patients retaining a good performance status were treated with sorafenib because of extrahepatic or untreatable progression, and two patients underwent radiofrequency ablation for a single nodule appearing in the contralateral liver lobe.

Results on survival are reported in Table 2 and Fig. 3. The median OS of the entire series was 15 months (95% CI, 12-18) with a nonsignificant trend in favor of non-PVT patients (18 versus 13 months with respect to advanced stages). Survival observed in patients with PVT type 1-2 (17 months; 95% CI, 13-21) was remarkably similar to patients without PVT (18 months; 95% CI, 13-38). Overall survival at 3 years was about 16% (Fig. 3B) ranging from 31% to 11.4% in non-PVT versus PVT, respectively. In each BCLC strata, survival tended to favor patients with Child-Pugh class A disease over patients with Child-Pugh class B disease (Table 2). Within the BCLC-C category, median survival and TTP deteriorated as the level of PVT extended (14 months for PV1-2 versus 8 months for PV3-4; $P = 0.052$).

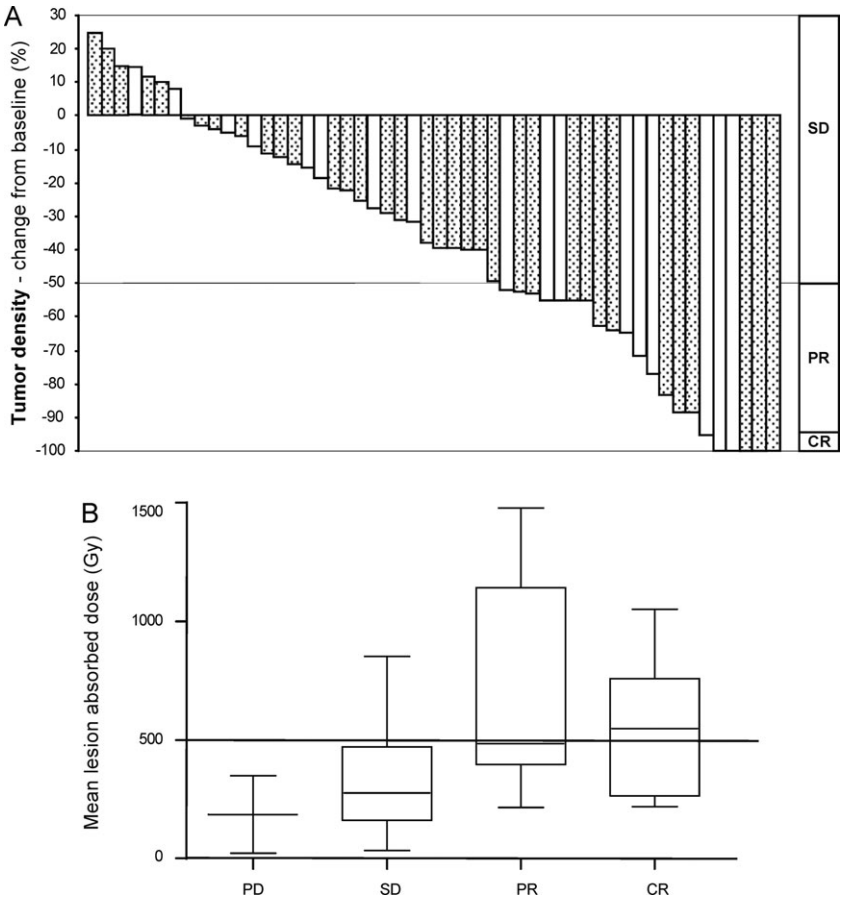

Fig. 2. Tumor response and dose correlation. (A) Best tumor response after Y90RE (waterfall plot). The response in each treated patient was assessed according to EASL criteria.[12] No progression was detected in target lesions. Five complete responses were registered. Dotted bars represent patients with PVT; blank bars represent patients without PVT. (B) Tumor absorbed dose and response (box plot). Maximum, minimum, and median values of mean absorbed dose together with quartile (first and third) distribution of values according to tumor response. A threshold of 500 Gy absorbed dose predicted objective responses (area under the curve, 0.78). CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease.

Tumor control rate by Y90RE significantly affected patient outcome (Fig. 3C). In responders versus nonresponders, a significant 3-year survival difference was registered (18.4% versus 9.1%; $P = 0.009$). This related to the positive effect of Y90RE in the more consistent sample of HCCs with PVT (25% versus 4.4% in responders versus nonresponders, respectively; $P = 0.02$), whereas in intermediate stage patients, survival comparison among responders versus nonresponders did not show significant differences (Fig. 3D).

Predictors of tumor progression and patients' survival are summarized in Table 3.

Tumor characteristics (size >6 cm: hazard ratio [HR], 4.42 [1.95-10.00]; extension involving >25% of the liver: HR, 3.46 [1.31-9.13]) and tumor control rate (HR, 37.43 [7.73-181.35]) were significantly related to TTP at univariate analysis. In the multivariate model, tumor response by EASL criteria was the sole variable affecting TTP ($P < 0.001$) and the second ($P = 0.048$) after Child-Pugh class independently affecting survival outcomes.

Treatment-Related Toxicities and Liver-Related Events. In Table 4, the observed grade 3-4 clinical and laboratory toxicities at 3 and 6 months are reported.

Among post-Y90RE relevant clinical toxicities, the most common included anorexia (15.4%) and clinically detectable ascites (9.6%), whereas at laboratory sampling, altered bilirubin affected 27% of the series, paralleled by alkaline phosphatase elevation in 19.2% and lymphocyte count reduction in 15.4%. No significant differences in toxicity were registered within each category when PVT patients were compared with non-PVT patients. There were no gastroduodenal ulcers or pulmonary toxicities. Within 6 months of therapy, 36.5% of the patients suffered from at least one episode of liver decompensation, with no difference among PVT versus non-PVT patients: seven out of 19 patients eventually recovered with no need of hospitalization, whereas in 12 patients (27.3% of the entire series), liver decompensation led to death.

Forty-four patients died during the median 3 years of follow-up. The causes of death were tumor progression in 28 cases (63.6%), liver failure in 12 cases (27.3%) and non liver–non tumor-events in 4 cases (9.1%). Thirty- and ninety-day mortality were 0% and 3.8% (n=2) respectively: both deaths were not treatment-related as occurred at 3 months in tumor progressing PVT patients.

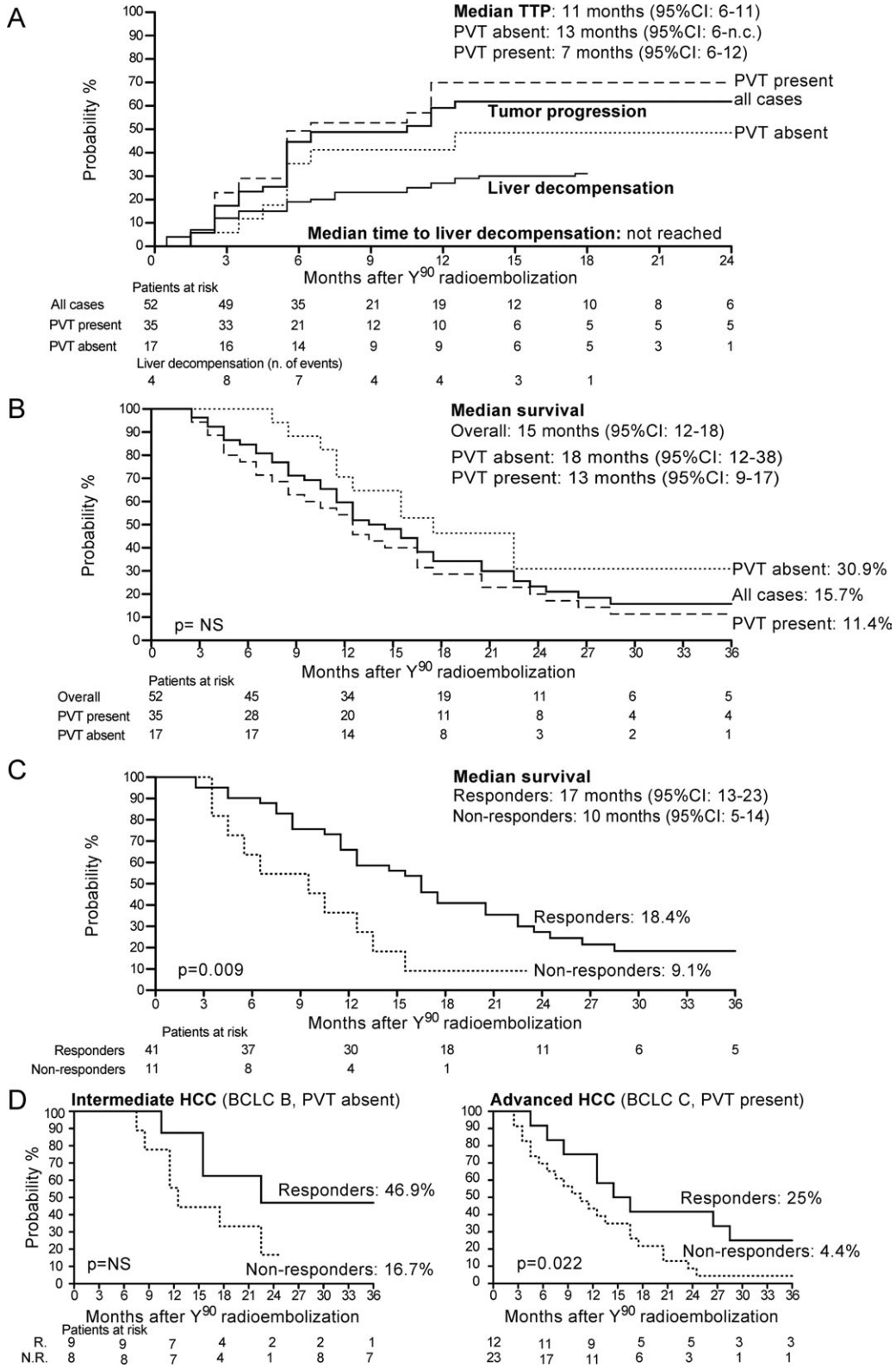

Fig. 3. Outcome after Y90RE. (A) Probability of tumor progression (TTP) and liver decompensation after Y90RE. The overall rate of tumor progression was 62%, with no difference between PVT versus non-PVT patients. The median time to liver decompensation is not calculable, because at the end of the observation period, less than 50% of patients experienced such event. (B) Patient OS. No difference between PVT versus non-PVT patients was found. (C) Survival according to tumor control rate (EASL criteria).[12] Responders to Y90RE showed to be favored with respect to nonresponders. (D) Survival according to tumor stage (BCLC) and objective response. Responders to Y90RE showed to be favored in survival, particularly in the case of PVT.

Table 3. Univariate and Multivariate Analysis on TTP and OS

	TTP				OS			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (>65 years versus ≤65 years)	0.64 (0.29-1.37)	0.249			0.90 (0.49-1.65)	0.726		
Sex (female versus male)	0.45 (0.06-3.33)	0.437			0.88 (0.27-2.86)	0.826		
Etiology (other versus HCV)	1.81 (0.80-4.11)	0.154			0.73 (0.40-1.34)	0.310		
Child-Pugh score (B versus A)	0.41 (0.10-1.75)	0.230			2.43 (1.10-5.36)	**0.027**	3.66 (1.56-8.58)	**0.0028**
Portal hypertension* (yes versus no)	0.92 (0.43-1.94)	0.819			1.37 (0.74-2.54)	0.310		
ECOG performance status (1 versus 0)	0.71 (0.32-1.57)	0.402			1.18 (0.65-2.16)	0.587		
BCLC stage (C versus B)	1.70 (0.75-3.85)	0.204			1.59 (0.82-3.10)	0.172		
UNOS stage (T4b versus T3-T4a)	1.70 (0.75-3.85)	0.204			1.59 (0.82-3.10)	0.172		
CLIP score (2-4 versus 0-1)	0.90 (0.44-1.88)	0.789			1.48 (0.81-2.71)	0.199		
Tumor burden (26%-50% versus 0%-25%)	3.46 (1.31-9.13)	**0.012**	1.13 (0.38-3.34)	0.830	2.19 (1.08-4.44)	**0.030**	2.06 (0.84-5.05)	0.112
Tumor distribution (bilobar versus unilobar)	0.95 (0.23-4.02)	0.949			1.19 (0.36-3.90)	0.774		
No. of nodules (multiple versus single)	0.93 (0.42-2.04)	0.853			1.46 (0.74-2.88)	0.272		
Largest tumor diameter (>60 mm versus ≤60 mm)	4.42 (1.95-10.00)	**0.0004**	3.65 (1.39-9.59)	**0.0087**	2.13 (1.15-3.93)	**0.016**	1.67 (0.79-3.53)	0.183
AFP at presentation (>400 versus ≤400)	0.88 (0.37-2.06)	0.762			1.19 (0.63-2.26)	0.594		
Treatments prior to Y90RE (yes versus no)	0.54 (0.22-1.33)	0.182			1.27 (0.68-2.38)	0.453		
Response (PD versus CR + PR + SD)†	37.43 (7.73-181.35)	**0.0002**	22.48 (4.53-111.61)	**0.0001**	2.564 (1.21-5.31)	**0.013**	2.01 (0.91-4.44)	**0.048**

Boldface values are statistically significant.

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clínic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HCV, hepatitis C virus; HR, hazard ratio; OS, overall survival; TTP, time to progression; UNOS, United Network for Organ Sharing; Y90RE, yttrium-90 radioembolization.

*Portal hypertension is defined by the presence of a platelet count below 100,000/mm^3 associated with significant splenomegaly, or presence of varices at endoscopy.

†According to EASL criteria.

Discussion

Intra-arterial tumor injection of biocompatible Yttrium-90–loaded microspheres represents a new concept in radiation therapy, able to contribute to the treatment of liver cancer. Differently from TACE, radioembolization does not depend on embolic induced hypoxia as the Yttrium-90 microspheres endure within the microvascular bed of HCCs and allow a pure radiotherapeutic effect also in patients with PVT.

Despite a wide range of studies and applications of radioembolization (e.g., downstaging/bridging to transplantation or resection, macrovascular-invading tumors, advanced and even metastatic disease), the lack of prospective phase 2 investigations have impeded a precise identification of a specific population of patients with HCC who may benefit from Y90RE as a first-line treatment.

Long before its current use, Y90RE relied on individual basis and local expertise, but in the last few years the standardization of practice and indications yielded a progressive improvement of results. According to the most recent studies, a median survival of about 17 months (range, 16.9-17.2 months) in intermediate HCC and 11 months (range, 10-13.8 months) in advanced HCC are expected after Y90RE, with a disease control rate of 37%-60%, a severe (bilirubin) toxicity of 6%-20%, and a mortality rate of 3-6.8% at 30-90 days, respectively.[6,7,15,18] The acceptable safety profile and the efficacy of Y90RE in controlling tumor progression has been acknowledged in several guidelines,[2,3] and the device is approved for treatment of HCC with or without PVT both in Europe and America.

This is the first phase 2 trial sought to determine efficacy and safety of Y90RE in intermediate and advanced HCC. To a large extent, the study captured HCCs with precluded access to curative options (such as transplantation) because of tumor-related portal invasion in patients with good performance.

The consistent median follow-up (36 months) allowed the collection of reliable data across well-established prognostic groups of HCC, especially in the presence of PVT. The observed outcomes, which accounted for 9.6% of complete responses, revealed a high degree of concordance with previous investigations.

The obtained results (i.e., rate of tumor progression at 2 years, 62%; median TTP, 11 months; disease control rate, 79%; median OS, 15 months—with the lower limit of the CI interval being higher than the

Table 4. Cumulative Toxicity Analysis

Event	Within 3 Months	Within 6 Months
Clinical toxicities		
Fatigue		
Total	1 (1.9)	3 (5.8)
PVT	1 (2.9)	3 (8.6)
No PVT	–	–
Abdominal pain		
Total	2 (3.8)	3 (5.8)
PVT	1 (2.9)	2 (5.7)
No PVT	1 (5.9)	1 (5.9)
Nausea/vomiting		
Total	3 (5.8)	5 (9.6)
PVT	2 (5.7)	3 (8.6)
No PVT	1 (5.9)	2 (11.8)
Anorexia		
Total	5 (9.6)	8 (15.4)
PVT	3 (8.6)	5 (14.3)
No PVT	2 (11.8)	3 (17.6)
Fever		
Total	2 (3.8)	2 (3.8)
PVT	1 (2.8)	1 (2.8)
No PVT	1 (5.9)	1 (5.9)
Ascites		
Total	4 (7.7)	5 (9.6)
PVT	1 (2.9)	2 (5.7)
No PVT	3 (17.6)	3 (17.6)
Variceal hemorrhage		
Total	1 (1.9)	2 (3.8)
PVT	1 (2.9)	2 (5.7)
No PVT	–	–
Cholecystitis		
Total	1 (1.9)	1 (1.9)
PVT	1 (2.9)	1 (2.9)
No PVT	–	–
Bile duct stenosis		
Total	2 (3.8)	3 (5.8)
PVT	2 (5.7)	3 (8.6)
No PVT	–	–
Laboratory toxicities		
Bilirubin		
Total	7 (13.5)	14 (26.9)
PVT	5 (14.3)	10 (28.6)
No PVT	2 (11.8)	4 (23.5)
Alkaline phosphatase		
Total	6 (11.5)	10 (19.2)
PVT	4 (11.4)	6 (17.4)
No PVT	2 (11.8)	4 (23.5)
Albumin		
Total	6 (11.5)	9 (17.3)
PVT	4 (11.4)	6 (17.1)
No PVT	2 (11.7)	3 (17.6)
Lymphocyte count		
Total	6 (11.5)	8 (15.4)
PVT	4 (11.4)	6 (17.1)
No PVT	2 (11.7)	2 (11.7)
Liver decompensation*		
Total	12 (23.1)	19 (36.5)
PVT	8 (22.8)	13 (37.1)
No PVT	4 (23.5)	6 (35.3)

Only grade 3-4 clinical and laboratory toxicities are reported (CTCAE version 3·0). Data are expressed as the absolute number of events (%). No significant differences in toxicity were registered within each category when patients with versus without PVT were compared.

Abbreviation: PVT, portal vein thrombosis.

*Defined as the occurrence of any of the following conditions: clinically relevant ascites, total bilirubin >3 mg/dL, hepatic encephalopathy, prothrombin time international normalized ratio >2.2, variceal hemorrhage.

10-month survival estimated for these patients—with no difference between non-PVT versus PVT patients) demonstrated the competitive potentials of Y90RE with respect to conventional therapeutic options for HCC at similar stages and support further studies focused within each tumor category treated with radioembolization.

At first glance, the results of Y90RE compare quite favorably with sorafenib in PVT patients (BCLC-C) and seem to achieve similar outcomes in intermediate stage HCC (BCLC-B) if compared with TACE (median survival, 14-16.5 months).[4,20] This study captured patients accepting Y90RE as an experimental treatment because they were suboptimal candidates for both TACE and sorafenib and were refused transplantation due to tumor extension. The small number of patients and the possible bias in selecting intermediate stages with tumor extension judged ineligible for TACE reduces the strength of the study, particularly for non-PVT patients.[21,22]

Conversely, this study proves that prognosis of PVT may be improved with Y90RE at the level of non-thrombotic patients (Fig. 3B) and confirms the observations of other series indentifying the presence of PVT as the HCC presentation that benefits the most from Y90RE. In this respect, the influence of the interval (3 to 4 weeks) between screening and actual treatment of such a population of fairly advanced tumors may have contributed to a certain underestimation of the Y90RE efficacy.[8,15]

In patients with PVT, the median TTP of 13 months, associated with a significant survival benefit in responding patients, confirmed the results of previous cohorts[7,15,18] and compared favorably with the 4.1 and 8.9 months observed for TTP and survival, respectively, in similar patients aided by sorafenib.[5] Combination of sorafenib with radiation has shown to be efficacious in experimental models,[23] and the present data, combined with the observed manageable toxicity, may justify proper randomized comparisons[24] in the specific subset of HCC with PVT in patients retaining good hepatic function.

The efficacy of Y90RE was confirmed by a DCR above 75% (Table 2) and the tumor response significantly related to both TTP and survival at univariate and multivariate analysis (Table 3). As previously stated, the effect of tumor response on TTP and survival considered response as a baseline characteristic rather than a time-dependant covariate,[25] and that may have caused a guarantee-time bias, reflected by the wide HRs observed for the TTP of the study. However, the first assessment of tumor response was

done 30 days after treatment and only two deaths were registered within 3 months, namely at the time of the second radiologic assessment. Considering that the median time to response of the entire series was 3 months (95% CI, 3-4) and that 96.3% of patients were alive at that time, we considered clinically meaningful our conclusions on the efficacy of Y90RE in eliciting tumor response and eventually prolonging survival.

Overall, our data on objective tumor response (40.4%) and complete responses (9.6%) showed to be slightly reduced with respect to previous series,[15,18] but that is justified in light of the unbalanced distribution of tumor stages in the Milan series, containing significantly more PVT patients and T4b tumors than others.

It is worth noting that tumor response to Y90RE was related to tumor absorbed dose, 500 Gy being the threshold significantly associated with objective response (Fig. 2B). These data support the current search for innovative treatment planning based on tumor/nontumor dosimetry methods applied to ^{99m}Tc-MAA SPECT as pretreatment forecast on efficacy and toxicity.[19,26]

All targeted HCC lesions of this series were controlled by Y90RE (Fig. 2A), whereas tumor progression in nontarget lesions or new nodules of HCC were associated with outcome deterioration. These findings support refinements in radiation delivery within each tumor nodule while preserving the surrounding parenchyma, a line of research that is currently under investigation in several centers.

Low incidence of complications and persistence of response after a single treatment are attractive features of Y90RE. This study presents Y90RE as a treatment with a reasonable toxicity profile and a rate of adverse events that is comparable to systemic molecular-targeted agents.

In particular, no treatment-related deaths were registered, and grade 3-4 bilirubin toxicities remained below 14% at 3 months, similar to previous findings.[6] Using a comprehensive definition of liver decompensation[13] that considers as treatment-related any event occurring within 6 months of Y90RE treatment, 36.5% of our patients suffered some adverse event, none of which was fatal (Fig. 3A). Overall, only 27.3% of the registered deaths were due to liver decompensation; this is within the acceptable range observed after treatment in patients with mostly advanced tumors, even though the small sample size of this study prevents a more precise determination of Y90RE-related influence on various causes of death, whether tumor or cirrhosis progression prevailed in outcome determination.

In conclusion, this is the first prospective phase 2 study assessing efficacy of Y90RE in intermediate and advanced HCC. On the basis of our findings, particularly in case of tumor-related PVT, patient outcome and tumor control rate confirmed to be competitive with respect to conventional treatments, while the toxicity profile proved to be manageable. On these premises, further prospective evaluations that focus on the benefit of radioembolization in HCC patients are warranted.[27]

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