Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation

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A multicenter analysis was conducted to evaluate the main prognostic factors driving survival after radioembolization using yttrium-90–labeled resin microspheres in patients with hepatocellular carcinoma at eight European centers. In total, 325 patients received a median activity of 1.6 GBq between September 2003 and December 2009, predominantly as whole-liver (45.2%) or right-lobe (38.5%) infusions. Typically, patients were Child-Pugh class A (82.5%), had underlying cirrhosis (78.5%), and had good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0-1; 87.7%), but many had multinodular disease (75.9%) invading both lobes (53.1%) and/or portal vein occlusion (13.5% branch; 9.8% main). Over half had advanced Barcelona Clinic Liver Cancer (BCLC) staging (BCLC C, 56.3%) and one-quarter had intermediate staging (BCLC B, 26.8%). The median overall survival was 12.8 months (95% confidence interval, 10.9-15.7), which varied significantly by disease stage (BCLC A, 24.4 months [95% CI, 18.6-38.1 months]; BCLC B, 16.9 months [95% CI, 12.8-22.8 months]; BCLC C, 10.0 months [95% CI, 7.7-10.9 months]). Consistent with this finding , survival varied significantly by ECOG status, hepatic function (Child-Pugh class, ascites, and baseline total bilirubin), tumor burden (number of nodules, alpha-fetoprotein), and presence of extrahepatic disease. When considered within the framework of BCLC staging, variables reflecting tumor burden and liver function provided additional prognostic information. The most significant independent prognostic factors for survival upon multivariate analysis were ECOG status, tumor burden (nodules >5), international normalized ratio >1.2, and extrahepatic disease. Common adverse events were: fatigue, nausea/vomiting, and abdominal pain. Grade 3 or higher increases in bilirubin were reported in 5.8% of patients. All-cause mortality was 0.6% and 6.8% at 30 and 90 days, respectively. *Conclusion:* This analysis provides robust evidence of the survival achieved with radioembolization, including those with advanced disease and few treatment options. (HEPATOLOGY 2011;54:868-878)

Hepatocellular carcinoma (HCC) is one of the most common malignancies and is increasingly affecting people at a younger age.[1] Treatment decisions are influenced as much by underlying liver disease as by tumor stage and take into account the risk/benefit analysis of whether tumor progression is more life-threatening than patients' advancing cirrhosis, with the attendant danger of worsening liver function through adverse effects of treatment. The Barcelona Clinic Liver Cancer (BCLC) staging system[2,3] defines five stages with progressively worse prognosis and has been validated in several western studies,[4-6] thus providing a robust framework for comparing the outcomes of different therapies.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; ^{90}Y, yttrium-90.

For patients who are not eligible for curative resection or liver transplantation but still have their disease confined to the liver, liver-directed therapies play an important role in reducing tumor burden, providing palliation of symptoms, and increasing survival.[7] Chemoembolization is the only liver-directed treatment that had shown a positive impact on survival in patients with unresectable disease.[8] Radioembolization (or selective internal radiation therapy) is another recognized liver-directed therapy[9,10] whose role in unresectable liver disease is still being refined. In radioembolization, implantable radioactive microspheres are delivered into the arteries that feed the tumors so that tumor nodules are treated irrespective of their number, size, or location. The high-energy radiation source yttrium-90 (^{90}Y) emits a tumoricidal dose of beta radiation (100-1,000+ Gy), far in excess of the doses delivered safely with external beam radiation therapy, over a finite range (mean tissue penetration, 2.5 mm; maximum, 11 mm) so that exposure to the surrounding normal parenchyma is limited.[11] Like other intra-arterial procedures, radioembolization has been evaluated where resection or ablation is not feasible, but mostly in patients with larger, infiltrating and/or multifocal disease.[12] Previous clinical experience has shown that radioembolization produces clinically significant reductions in tumor burden among patients with HCC[13,14] that may help downstaging patients for radical therapies,[15] can be performed in the presence of portal vein thrombosis,[16-18] and can be safely applied to patients who have cirrhosis with good liver function[13,19-21]; however, sinusoidal obstruction syndrome remains the main complication[22] in noncirrhotic livers. In this study, we combined the clinical experience from eight European centers to assess the main factors driving the prognosis of unresectable HCC treated with radioembolization using ^{90}Y-labeled resin microspheres (SIR-Spheres; Sirtex Medical Limited, Sydney, Australia). The results also provide relevant data for future comparisons of radioembolization with other treatment options across the different stages of HCC as defined by the BCLC staging system.

Materials and Methods

Study Design and Enrollment Criteria. This was a multicenter analysis of survival and the prognostic factors influencing survival following radioembolization with ^{90}Y-resin microspheres in patients with HCC. Authorization was received from Local Review Boards to conduct a retrospective analysis of consecutive patients with unresectable HCC who received radioembolization between September 25, 2003, and December 17, 2009, at eight European centers. Only those patients that had at least one follow-up visit after treatment were studied. Some centers recruited and followed all their patients prospectively. Patients were followed from the date of treatment until July 1, 2010, or until the date of death. The criteria for patient selection and some details of the treatment protocol (e.g., whether the ideal site for microsphere injection was considered to be the proper hepatic artery or one or more lobar or segmental arteries) varied between centers. Radioembolization was considered for those patients with HCC who were not suitable for radical therapies (e.g., resection, liver transplantation, local ablation) and were not considered good candidates for transarterial therapies (e.g., arterial embolization/chemoembolization) or systemic therapy based on clinical judgment by multidisciplinary teams in each center. These patients underwent radioembolization either as a first therapy or after having progressed to

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previous surgical or nonsurgical treatments, but not prior external irradiation. These patients frequently presented with preserved or fairly preserved liver function, portal vein invasion, or thrombosis or extensive tumor burden (bilobar and/or main tumor >10 cm and/or an uncountable number of nodules). Published general recommendations for patient selection include unresectable liver-only or liver-dominant tumors, Eastern Cooperative Oncology Group (ECOG) performance status score 0-2, untreated life expectancy of at least 12 weeks and exclude patients with abnormal organ or bone marrow function (total bilirubin level >2.0 mg/dL in the absence of a reversible cause; serum albumin <3.0 g/dL), limited hepatic reserve, ascites, or other clinical signs of liver failure on physical examination.[23,24] However, under exceptional circumstances and with informed consent, some patients have been treated outside these criteria. Radioembolization was only undertaken after a detailed pretreatment workup (outlined below) and after review by a multidisciplinary team including hepatologists and/or oncologists, interventional radiologists, and nuclear medicine specialists. Diagnosis of HCC was either histologically proven or based on noninvasive European Association for the Study of the Liver criteria.[25] All patients provided informed consent prior to treatment planning.

Treatment Procedure. Radioembolization was performed using ^{90}Y-resin microspheres as described.[23,26] In addition to standard assessments, patients underwent a thorough angiographic evaluation to identify any extrahepatic vessel that may feed the tumors, to detect and occlude every collateral vessel that arose from the hepatic arteries selected for injection that may carry microspheres to the gastrointestinal tract or other extrahepatic organs and to assess the patency and blood flow characteristics in the portal vein and its branches. One center in this study delayed occlusion of extrahepatic feeding vessels until the day of treatment.

Depending upon the extent of tumor burden, patients were treated with either a segmental, lobar, or whole-liver treatment approach. Once the ideal sites for microsphere injection had been identified, a technetium-99m–labeled macroaggregated albumin scan was performed to calculate the degree of hepatopulmonary shunting, to further identify unnoticed collateral vessels, and eventually to calculate differential distribution of particles between tumor and nontumor tissue (tumor/nontumor ratio). Using this information, the activity was calculated as per the manufacturer's instructions using the empiric formula, body-surface area method, or modified partition model to optimize the dose of radiation delivered to liver tumors while safely preserving the nontumoral parenchyma. Patients were excluded from treatment if the above evaluations revealed that (1) the hepato-pulmonary shunt was >20%, as per the manufacturer's recommendation; (2) the hepato-pulmonary shunt would result in 30 Gy being delivered to the lungs with a single infusion or 50 Gy for multiple infusions; or (3) if embolization of microspheres into the gastrointestinal tract could not be prevented. Clinical judgment was used to assess the appropriateness of radioembolization in patients presenting with relative contraindications, including compromised pulmonary function and an inadequate liver reserve for whole-liver treatment. Typically 1 or 2 weeks later, patients were then implanted with ^{90}Y-resin microspheres. The ^{90}Y-resin microspheres were provided in a 3-GBq vial calibrated for 23:00 Greenwich Mean Time on the day of treatment. Patients with bilobar involvement were treated according to local protocols either in a single session or using sequential lobar therapies, typically 4-6 weeks apart. Patients were typically discharged the day after radioembolization, depending upon local regulations.

Data Collection and Analysis. Hematological, liver function, and blood biochemistry tests and physical examination were performed pretreatment. Data were collated from the medical records for baseline and 3, 6, 9, and 12 months following treatment for serum levels of liver aminotransferase, albumin, total bilirubin, prothrombin activity, creatinine, and alpha-fetoprotein levels. The nature and severity of all adverse events were accessed from the medical records from the day of radioembolization to day 180 posttreatment, although the analysis of clinical and laboratory adverse events was performed on baseline to day 90 data because this was the most representative for treatment related events. All adverse events were graded using National Cancer Institute Common Toxicity Criteria Adverse Events Version 3.0. Survival was calculated from the day of treatment to the day of death or last follow-up. Those patients in whom status could not be established were censored at the time of last follow-up. Patients undergoing resection, transplantation, or percutaneous ablation following radioembolization were censored at the time of surgery or ablation.

Statistical Analyses. Patient survival was summarized using the Kaplan-Meier product-limit method to compute nonparametric estimates of survivor function. Univariate Cox proportional hazards models were applied to identify single-vector prognostic factors associated with survival, and a log-rank test at an alpha error level of 0.05 was used to compare survival curves among strata. A univariate Cox proportional hazards

model was used to compare prognostic variables, summarized by the hazards ratio and its 95% confidence interval (CI). The multivariate proportional hazards model was applied to the statistically significant univariate variables by Kaplan-Meier (log-rank test) or Cox proportional hazards model at alpha 0.05, and the analysis model was constructed based on the maximum number of statistically significant variables (best subsets approach),[27] using the Akaike information criteria for model selection. A multivariate model was constructed to test the significance of prognostic indicators of survival in addition to BCLC. Associations between covariates (yes/no) and Common Terminology Criteria for Adverse Events (CTCAE) grade were tested by Fisher's exact test and Cochran-Mantel-Haenszel row mean score. Transitions in CTCAE grades were tested by the exact McNemar's test. All statistical analyses were conducted using SAS version 9.2 XP Pro statistical analysis software (SAS, Cary, NC).

Results

Patients. Data were collated on 325 consecutive patients with HCC (109 followed prospectively) who received radioembolization at eight European centers located in Pamplona, Spain (n = 97), Rome, Italy (n = 79), Bologna, Italy (n = 35), Latina, Italy (n = 31), Udine, Italy (n = 26), Bonn, Germany (n = 24), Munich, Germany (n = 19), and Napoli, Italy (n = 14). The median follow-up was 10.0 months (range, 0.2-48.0), and a total of 201 death events were recorded.

The cohort represented patients across a wide age range (22-87 years; mean, 64.5 years). The majority were Child-Pugh class A (82.5%), had underlying cirrhosis (78.5%), and had a good performance status (ECOG status 0-1; 87.7%) (Table 1). Hepatitis B or C was recorded as the etiology in 13.0% and 44.3% of patients, respectively. Typically, because transarterial embolization had failed to control disease or was considered unsuitable, patients had multinodular disease (75.9%), and more than a third (38.6%) had >5 nodules. The majority of patients had disease confined to the liver (90.8%), although over half (53.1%) had disease invading both lobes and nearly a quarter had portal vein occlusion (13.5% branch or 9.8% main). Over half of the patients were classified according to the BCLC staging system[2,3] as advanced (BCLC stage C, 56.3%), one-quarter were intermediate (BCLC stage B, 26.8%), and the remainder were mostly early (BCLC stage A, 16.0%), with a marginal number of patients being in the terminal stage (BCLC stage D, 0.9%). A total of 135 (41.5%) patients had failed or

Table 1. Baseline Patient and Disease Characteristics, Prior Procedures, and Treatment Parameters Among 325 Patients

Characteristics	Values
Sex, male/female, no. (%)	265 (81.5)/60 (18.5)
Age, years, mean ± SD (range)	64.5 ± 10.8 (22-87)
ECOG performance status, no. (%)*	
0	176 (54.3)
1	108 (33.3)
2	37 (11.4)
3	3 (0.9)
Prior procedures, no. (%)	
Surgery	59 (18.2)
Vascular	89 (27.4)
Percutaneous ablation	30 (9.2)
Presence of cirrhosis, no. (%)	255 (78.5)
Child-Pugh class, no. (%)	
A	268 (82.5)
B	57 (17.5)
Tumor burden (nodules), no. (%)*	
1	78 (24.1)
2-5	121 (37.3)
>5	125 (38.6)
Bilobar, no. (%)	172 (53.1)*
Presence of extrahepatic metastases, no. (%)	30 (9.2)
Portal vein occlusion, no. (%)	
Patent	249 (76.6)
Branch	44 (13.5)
Main	32 (9.8)
Presence of ascites, no. (%)	37 (12.7)‡‡
Presence of encephalopathy, no. (%)	7 (2.4)‡‡
BCLC stage, no. (%)	
A	52 (16.0)
B	87 (26.8)
C	183 (56.3)
D	3 (0.9)
AFP >400 ng/mL, no. (%)	109 (34.9)¶
Total bilirubin >1.5 mg/dL, mean ± SD, no. (%)	1.1 ± 0.58, 55 (17.0)†
Albumin, g/dL, mean ± SD	3.6 ± 0.98††
INR >1.2, mean ± SD, no. (%)	1.2 ± 0.25,§ 75 (23.4)‡
ALT, U/L, mean ± SD	61.3 ± 49.12§
Creatinine, mg/dL, mean ± SD	0.9 ± 0.33‖
Treatment parameters	
Activity administered, GBq, median (range)	1.6 (0.3-4.0)
Target treatment, no. (%)	
Whole liver	147 (45.2)
Right lobe	125 (38.5)
Left lobe	29 (8.9)
Segmental	24 (7.4)
Target tumor volume, mL, median (range)	224 (2.2-4,000)#
Target liver volume, mL, median (range)	1416 (27.0-5,566)**
Number of treatments, no. (%)	
1	303 (93.2)
2	19 (5.8)
3	3 (0.9)

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase.

Prior procedures include surgery (resection or transplantation), percutaneous ablation (radiofrequency or ethanol injection), and intraarterial procedures (transarterial embolization, chemoembolization, or hepatic arterial chemotherapy). Sites of extrahepatic disease included mainly lymph nodes but also bone, adrenal, and lung.

Missing baseline data were not available for *1 patient, †2 patient, ‡4 patients, §5 patients, ‖11 patients, ¶13 patients, #22 patients, **23 patients, ††29 patients, and ‡‡34 patients.

Table 2. Main Procedure-Related Clinical Adverse Events by Severity

CTCAE	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	177 (54.5)	152 (46.8)	17 (5.2)	8 (2.5)	0	0
Nausea and/or vomiting	104 (32.0)	89 (27.4)	14 (4.3)	1 (0.3)	0	0
Abdominal pain	88 (27.1)	70 (21.5)	13 (4.0)	5 (1.5)	0	0
Fever	40 (12.3)	36 (11.1)	4 (1.2)	0	0	0
Gastrointestinal ulceration	12 (3.7)	3 (0.9)	3 (0.9)	5 (1.5)	0	1 (0.3)
Pneumonitis	0	0	0	0	0	0

Procedure-related events (fatigue, nausea/vomiting, abdominal pain, and fever) were evaluated from day 1 to day 7. Radiation-related events (long-term fatigue, gastrointestinal ulceration, and pneumonitis) were evaluated from day 8 to month 3. Data are expressed as no. (%).

progressed to a prior locoregional therapy, mostly as a single procedure (29.2% of the overall cohort), including transarterial embolization or chemoembolization (27.4%), surgical resection or transplantation (18.2%), or percutaneous ablation (9.2%).

Treatment Procedures and Complication Rate. The majority of patients received a single administration of microspheres. The remaining patients had two or three treatments (5.8% and 0.9%, respectively), mostly to improve a partial tumor response or to treat tumors arising in a contralateral lobe. The median activity administered was 1.6 GBq (range, 0.3-4.0 GBq), with predominantly whole-liver (45.2%) and right-lobe (38.5%) infusions (Table 1). The majority of whole-liver treatments were performed in a single session (141/147 [95.9%]) through one or more injections. The median hepato-pulmonary shunt was 6.0% (range, 0%-32.5%).

Common procedure-related adverse events were usually mild (grade 1/2) and included nausea/vomiting (32.0% all grades) and abdominal pain (27.1% all grades), with very few grade 3 events (Table 2). These adverse events are easily controlled with medication if necessary and usually subside in less than 48 hours. Fatigue was reported in 54.5% of patients (all grades), typically occurring in the first few weeks after radioembolization and lasting 1-2 weeks, with few (2.5%) grade 3 events. As summarized in Supporting Table 1, fatigue was reported most commonly in patients with advanced stage (61.2%) compared with those with intermediate (41.4%) or early stage disease (50.0%) ($P = 0.021$). Recorded adverse effects were not more frequent among that third of patients followed prospectively, indicating that an underestimation of adverse events is unlikely. Events related to radiation of nontarget tissues (primarily grade 1/2) included gastrointestinal ulcerations and liver-related events. Gastrointestinal ulceration (3.7% all grades) was grade 3 in five patients (1.5%) and was the cause of death in one patient at 3 months. Regarding liver-related events, elevated bilirubin (all grades) was recorded in 22.6% of patients at baseline, increasing to 48.6% of patients up to day 90 ($P < 0.001$), with a minority experiencing grade ≥ 3 events (5.8% up to day 90). A minor increase in the proportion of patients with grade >0 values for international normalized ratio (INR) and platelet levels to day 90 was observed (Table 3). There were no significant differences in the transitions in CTCAE for laboratory values among BCLC stages (Supporting Table 2). All-cause mortality was 0.6% and 6.8% (2 and 22 patients) at 30 and 90 days, respectively.

Survival Analyses. The median overall survival was 12.8 months (95% CI, 10.9-15.7), which did not diminish significantly with increasing age or sex. Survival varied significantly by ECOG performance status, hepatic function (Child-Pugh class, ascites, and baseline total bilirubin), tumor burden (number of nodules, alpha-fetoprotein), presence of extrahepatic disease, and BCLC disease stage (Table 4). Median survival

Table 3. Main Procedure-Related Laboratory Adverse Events By Severity

		Preradioembolization		Month 3		Change of CTCAE Grade at Month 3			
CTCAE	n	All Grades	Grade ≥ 3	All grades	Grade ≥ 3	Decreased	Same	Increased	*P**
Total bilirubin	292	22.6%	0.0%	48.6%	5.8%	4.8%	59.2%	36.0%	<0.001
Albumin	237	38.0%	0.0%	39.7%	0.8%	12.2%	68.8%	19.0%	0.500
ALT	272	59.6%	1.8%	57.4%	3.3%	15.4%	69.5%	15.1%	0.289
INR	277	22.4%	0.0%	31.4%	1.8%	4.0%	81.2%	14.8%	0.063
Creatinine	276	8.3%	0.4%	11.6%	1.4%	1.8%	90.9%	7.2%	0.250
Platelets	268	44.4%	2.2%	52.6%	3.4%	9.3%	72.4%	18.3%	0.581

Abbreviation: ALT, alanine aminotransferase.

All events were evaluated from baseline to month 3.

*Exact McNemar test comparing grade 3-4 CTCAE at month 3 versus grade 3-4 preradioembolization.

Table 4. Survival by Baseline Characteristic and BCLC Stage

	Median Survival															
	All Patients				BCLC A Patients				BCLC B Patients				BCLC C Patients			
Characteristic	n	Mo.	95% CI	*P*	n	Mo.	95% CI	*P*	n	Mo.	95% CI	*P*	n	Mo.	95% CI	*P*
All	325	12.8	10.9-15.7	NA	52	24.4	18.6-38.1	NA	87	16.9	12.8-22.8	NA	183	10.0	7.7-10.9	NA
Age, years																
<65	142	12.8	10.4-17.9	0.933	20	24.4	10.9-46.8	0.481	40	19.0	11.9-23.2	0.625	79	9.5	7.2-11.8	0.613
>65	183	13.6	10.9-16.8		32	27.4	18.6-45.9		47	16.9	10.9-25.0		104	10.2	7.4-11.7	
Sex																
Female	60	15.5	8.6-18.8	0.631	15	19.4	12.4-33.7	0.163	8	19.1	6.8-NR	0.386	36	8.6	6.2-17.9	0.817
Male	265	12.8	10.9-15.7		37	30.9	19.6-46.8		79	16.9	12.8-22.8		147	10.0	7.7-10.9	
ECOG status																
0	176	16.9	13.6-19.6	<0.001	52	24.4	18.6-38.1	NA	87	16.9	12.8-22.8	NA	37	10.8	6.5-11.9	0.844
1-2	145	9.9	7.4-10.9										145	9.9	7.4-10.9	
3-4	3	5.2	2.2-NR													
Cirrhosis																
No	70	17.9	12.4-20.8	0.189	9	33.7	12.4-46.8	0.308	24	19.1	15.4-34.2	0.195	37	11.4	6.5-18.8	0.891
Yes	255	11.9	10.4-14.9		43	24.4	15.8-38.1		63	14.9	10.8-19.4		146	9.9	7.4-10.8	
Total bilirubin, mg/dL																
≤1.5	268	15.1	12.4-17.9	0.002	45	23.7	15.8-33.7	0.232	80	16.9	12.8-22.8	0.050	140	10.4	7.6-13.1	0.009
>1.5	55	8.8	5.5-11.7		6	NR	2.3-NR		7	4.1	2.4-25.0		42	8.3	5.5-10.3	
INR																
≤1.2	246	15.5	12.6-18.4	<0.001	46	30.9	22.1-45.9	0.001	71	18.4	12.8-23.2	0.822	126	10.9	9.3-13.1	0.037
>1.2	75	8.6	7.0-10.9		6	13.8	4.9-18.6		14	19.0	8.3-NR		55	7.3	5.8-9.5	
ALT, IU/L																
≤median	160	15.8	12.8-19.6	0.044	25	23.7	18.6-46.8	0.548	44	19.1	12.8-23.2	0.726	90	9.3	7.5-13.8	0.312
>median	160	10.9	9.9-14.5		25	24.4	12.4-NR		43	16.9	10.6-29.5		90	10.2	6.9-10.9	
Albumin, g/dL																
>3.5	170	13.1	10.2-16.6	0.686	28	24.4	19.4-46.8	0.270	49	18.4	12.8-22.8	0.164	91	8.3	6.5-10.2	0.035
≤3.5	126	11.7	10.4-15.8		17	27.4	10.4-33.7		26	10.8	7.0-23.2		82	10.9	9.3-15.7	
Ascites																
No	254	14.1	11.8-17.9	<0.001	36	30.9	18.6-45.9	0.077	75	18.4	13.6-23.2	<0.001	141	10.4	8.2-11.8	0.007
Yes	37	6.1	4.4-8.6		3	19.4	2.0-27.4		3	3.6	3.0-4.5		30	7.4	4.8-9.9	
Child-Pugh class																
A	268	14.9	11.9-17.1	0.006	47	30.9	18.6-45.9	0.131	82	18.4	13.6-23.2	<0.001	137	9.7	7.6-10.9	0.668
B	57	10.0	6.1-13.8		5	19.4	6.5-27.4		5	3.6	2.4-10.8		46	10.0	6.1-14.5	
No. of nodules																
1-5	199	16.8	13.6-22.1	<0.001	52	24.4	18.6-38.1	NA	39	22.8	13.6-36.0	0.058	107	10.3	7.6-14.5	0.020
>5	125	10.0	7.7-11.4						48	16.6	8.3-19.0		75	9.3	7.0-10.7	
Bilobar																
No	152	16.8	11.9-22.5	0.005	35	38.1	15.8-46.8	0.116	32	23.2	13.6-NR	0.123	84	10.2	7.4-16.8	0.431
Yes	172	11.4	9.9-13.8		17	22.1	12.4-30.9		55	15.4	10.6-19.1		98	9.7	7.4-10.8	
Portal vein occlusion																
Patent	249	15.3	12.4-18.4	0.003	52	24.4	18.6-38.1	NA	87	16.9	12.8-22.8	NA	110	9.3	7.4-11.4	0.826
Branch/Main	76	10.0	6.5-11.8										73	10.2	7.7-11.8	
Extrahepatic disease																
No	295	14.1	11.7-16.8	0.001	52	24.4	18.6-38.1	NA	87	16.9	12.8-22.8	NA	155	10.2	8.2-11.7	0.137
Yes	30	7.4	4.8-13.1										28	7.4	4.3-13.1	
AFP, ng/mL																
≤400	203	18.4	15.1-20.8	<0.001	41	24.4	19.4-45.9	0.696	60	19.4	16.9-29.5	<0.001	101	10.8	8.3-15.7	0.224
>400	109	9.7	7.4-11.7		9	21.6	8.6-46.8		25	9.0	6.8-12.8		73	9.5	7.0-11.7	
No prior procedures	190	12.5	10.4-16.6	0.533	37	22.1	15.1-38.1	0.119	42	18.4	11.2-19.4	0.815	110	9.5	7.1-11.7	0.896
Any prior procedure	135	12.8	10.8-18.8		15	33.7	19.6-46.8		45	22.8	10.9-34.2		73	10.7	7.7-12.6	
BCLC stage																
A	52	24.4	18.6-38.1	<0.001	52	24.4	18.6-38.1	NA								
B	87	16.9	12.8-22.8						87	16.9	12.8-22.8	NA				
C	183	10.0	7.7-10.9										183	10.0	7.7-10.9	NA
D	3	5.2	2.2-NR													

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; NA, not applicable; NR, not reached.
Survival was calculated by way of Kaplan-Meier analysis.

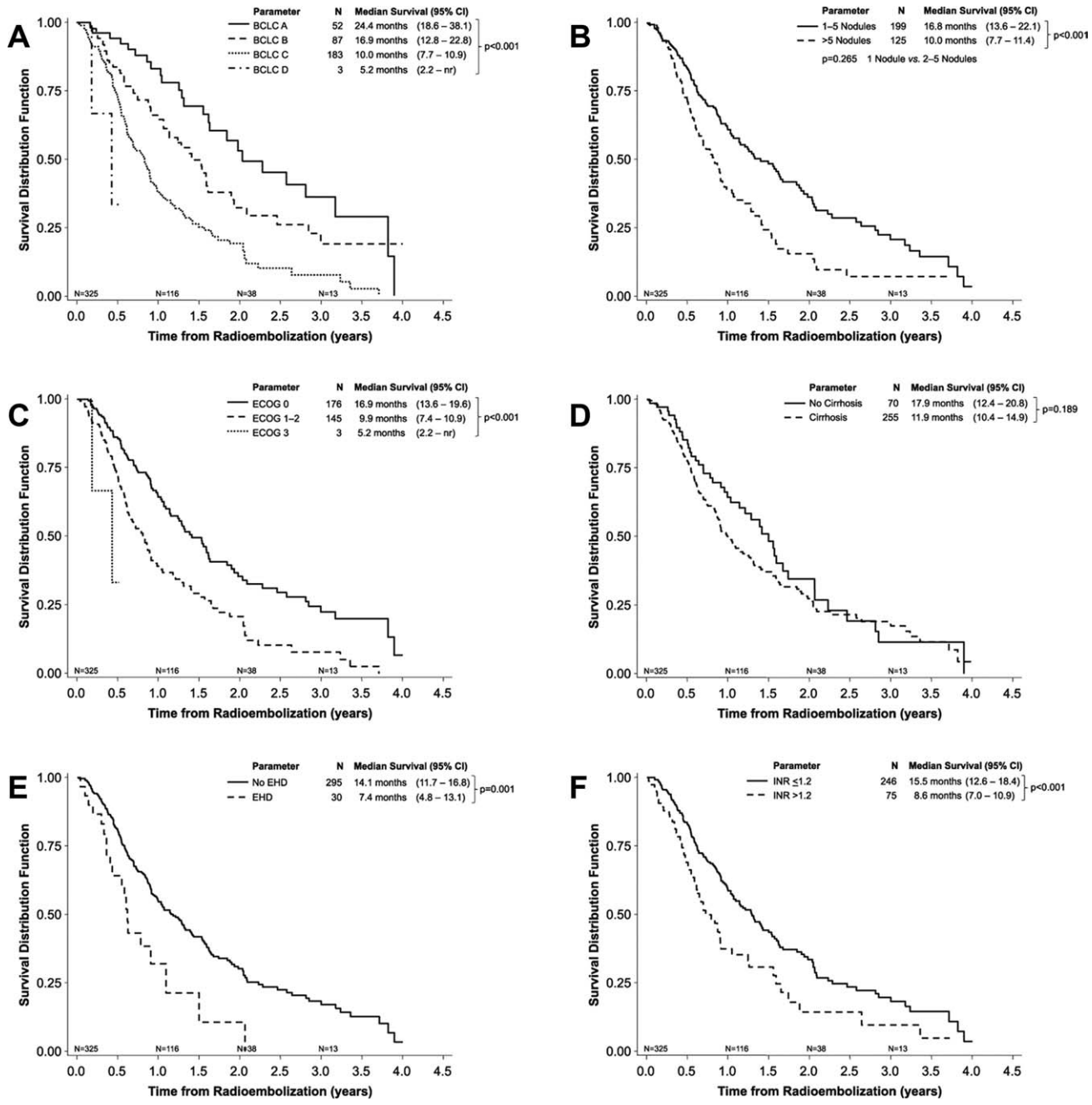

Fig. 1. Kaplan-Meier survival curves of patients with HCC treated with ^{90}Y-resin microspheres radioembolization stratified by various prognostic variables. (A) BCLC stage. (B) Tumor burden in the liver, by number of nodules. (C) ECOG performance status. (D) Presence or absence of cirrhosis. (E) Presence or absence of extrahepatic disease (EHD). (F) INR higher or lower than 1.2.

was significantly better in patients with one to five nodules (16.8 months; 95% CI, 13.6-22.1) compared with those with more than five nodules (10.0 months; 95% CI, 7.7-11.4; $P < 0.001$) (Fig. 1); in patients with ECOG 0 (16.9 months; 95% CI, 13.6-19.6) compared with ECOG 1-2 (9.9 months; 95% CI, 7.4-10.9; $P < 0.001$); in patients without extrahepatic disease compared with those with extrahepatic disease (14.1 months; 95% CI, 11.7-16.8 versus 7.4 months; 95% CI, 4.8-13.1; $P = 0.001$); and in patients with an INR $\leq$1.2 compared with those with INR >2 (15.5 months; 95% CI, 12.6-18.4 versus 8.6 months; 95% CI, 7.0-10.9; $P < 0.001$). Overall survival diminished in patients with portal vein occlusion (branch or main) compared with those with patent vessels (10.0 months; 95% CI, 6.5-11.8 versus 15.3 months; 95% CI, 12.4-18.4; $P = 0.003$), with no significant difference in survival between patent portal

Table 5. Multivariate Analysis of Significant Single-Vector Prognostic Indicators

Variable	HR (95% CI)	P
All patients		
No. of nodules >5	1.76 (1.32-2.35)	<0.001
ECOG performance status	1.39 (1.14-1.70)	0.001
Extrahepatic disease	1.91 (1.17-3.13)	0.010
INR >1.2	1.47 (1.04-2.09)	0.028
BCLC stage A		
INR >1.2	5.26 (1.72-16.09)	0.004
BCLC stage B		
AFP >400 ng/mL	2.98 (1.62-5.48)	<0.001
Total bilirubin >1.5 mg/dL	2.91 (1.20-7.06)	0.019
BCLC stage C		
No. of nodules >5	1.59 (1.10-2.29)	0.014
INR >1.2	1.52 (1.05-2.21)	0.028

Abbreviation: AFP, alpha-fetoprotein.

Model selection was made according to the best subsets approach using input variables that are statistically significant in the univariate Cox proportional hazards model ($P < 0.05$). Data contributing to the multivariate model: n = 319/325 (98.2%).

vein and branch occlusion ($P = 0.124$). Reflecting this influence of tumor burden and liver function, the median survival was 24.4 months (95% CI, 18.6-38.1) in patients with BCLC stage A compared with 16.9 months (95% CI, 12.8-22.8) in patients with BCLC stage B and 10.0 months (95% CI, 7.7-10.9) in patients with BCLC stage C (Fig. 1). Prior procedures (surgical, ablative, or vascular procedures) did not significantly affect the duration of survival following radioembolization compared with those without prior treatments (12.81 versus 12.5 months, respectively; $P = 0.533$). Survival for different subgroups of patients according to other prognostic factors is shown in Supporting Table 3.

Univariate Cox proportional hazards modeling indicated that liver function and Child-Pugh class were significant predictors of survival, whereas the presence of cirrhosis did not significantly adversely impact survival following radioembolization. With increasing tumor burden (as measured by the number of nodules in the liver and alpha-fetoprotein), survival diminished significantly. This was reflected in the stratification of patients by BCLC stage, which was a highly significant predictor of clinical outcome (Table 4). Compared with the whole cohort, median survivals were similar for patients who received whole-liver treatment or only right- or left-lobe treatment (hazard ratio [HR] 1.12, 1.06, and 1.04, respectively), although segmental treatment was associated with increased survival (median, 23.7 months; 95% CI, 9.0 to not reached; HR, 0.52; 95% CI, 0.28-0.96; $P = 0.038$). Notably, however, elevated lung shunting (greater than median) did not affect overall survival (HR, 1.03; 95% CI, 0.77-1.37).

Upon multivariate analysis using statistically significant ($P < 0.05$) single-vector variables from the univariate Cox proportional hazards model or by Kaplan-Meier analysis, ECOG performance status, tumor burden (number of nodules >5), INR >1.2, and extrahepatic disease were found to be the most significant independent prognostic factors for survival after radioembolization (Table 5). When BCLC staging was included in the multivariate analysis, BCLC (HR, 1.74; 95% CI, 1.41-2.16; $P < 0.001$), INR >1.2 (HR, 1.46; 95% CI, 1.05-2.01; $P = 0.022$), and bilobar disease (HR, 1.36; 95% CI, 1.02-1.82; $P = 0.036$) remained the significant independent prognostic factors for survival. In patients with BCLC stage A, INR >1.2 was the only significant independent predictor for survival, whereas alpha-fetoprotein >400 ng/mL and total bilirubin >1.5 mg/dL were significant for patients with BCLC stage B, and tumor burden and INR >1.2 were significant for patients with BCLC stage C.

Regarding postradioembolization therapy, some patients received radical treatments including liver transplantation (n = 5), resection (n = 3), and percutaneous ablation (n = 3). These were censored for survival analysis at that time. A total of 34 patients (10.5%) received sorafenib a median of 6.0 months after radioembolization (range, 2.1-36.0 months) and for a median duration of 2.8 months (range, 1.4-5.5 months). When patients were censored at the start of sorafenib treatment, the median survival after radioembolization was 13.1 months (95% CI, 10.9-17.1) compared with 12.8 months (95% CI, 10.9-15.7) for the noncensored overall cohort, including those who had received sorafenib. This finding was consistent for each BCLC stage, with median survivals in censored and noncensored cohorts of 30.9 months (95% CI, 19.4-45.6) and 24.4 months (95% CI, 18.6-38.1) for BCLC stage A (including three sorafenib patients in the noncensored cohort), 19.0 months (95% CI, 12.8-25.0) and 16.9 months (95% CI, 12.8-22.8) for BCLC stage B (including 11 sorafenib patients in the noncensored cohort), and 10.0 months (95% CI, 8.0-10.9) and 10.0 months (95% CI, 7.7-10.9) for BCLC stage C (including 20 sorafenib patients in the noncensored cohort).

Discussion

A considerable amount of information has been published in the last decade regarding the use of radioembolization with ^{90}Y-loaded microspheres for the treatment of HCC.[28] Median survivals, however, vary widely (between 7 and 27 months) between phase II studies, depending on performance status, extent of

disease involvement, degree of hepatic functional reserve, and presence or absence of cirrhosis.[13,14,19,20,29] Very recently, Salem et al.[17] reported a large prospective study in 291 patients treated with glass-based ^{90}Y microspheres (TheraSphere; MDS Nordion, Ottawa, Ontario, Canada) showing that liver function and portal vein thrombosis were main predictors of survival. However, a consistent analysis of safety and survival according to the BCLC staging system has yet to be published.

In this study, we present the largest series of HCC patients receiving radioembolization and the first large, multicenter evaluation. Data were analyzed in a way that allows comparison with other treatment options, taking into account the natural course of the disease across different well-established prognostic groups. This analysis may help to better understand the potential effect of radioembolization on survival and to aid in the design of future clinical studies. It should be noted that the outcomes of this evaluation reveal a high degree of concordance with those of ^{90}Y-glass microspheres in patients with unresectable HCC.[17] Taken together, the results of these two series provide reliable data regarding the potential use of radioembolization for the treatment of HCC.

Overall, a low incidence of severe (grade >3) adverse events was observed with radioembolization in a cohort with a high incidence of cirrhosis. The procedure itself was well tolerated, with mild-to-moderate nausea and/or vomiting, abdominal pain, and fever of limited duration occurring in less than one-third of patients. As would be expected in a population of patients with underlying chronic liver disease, many patients had grade 1 or 2 abnormal values in liver-associated parameters such as INR, bilirubin, platelets, and alanine aminotransferase prior to radioembolization, and the majority experienced no change in grade at 3 months posttreatment. In contrast with other liver function tests, a grade 3 or higher increase in bilirubin was observed in 5% of patients, suggesting a potential for radioembolization-induced liver disease in a small number of patients.[22] However, it should be noted that progression of tumor disease or liver cirrhosis cannot be ruled out as the cause of this derangement in liver function. Put into perspective, treatment-emergent grade 3 or 4 liver dysfunction was documented in 5% of placebo-treated and 7% of sorafenib-treated patients in the pivotal SHARP (Sorafenib HCC Assessment Randomized Protocol) trial.[30]

Regarding survival analysis, when the joint contribution of single-vector prognostic factors are considered in a multivariate model, the performance status, disease burden (intrahepatic and extrahepatic) and liver function (as measured by total bilirubin >1.5 mg/dL) provide further indications of predicted clinical outcome. Because these factors are considered by the BCLC staging system, it is no surprise that survival is progressively worse for each BCLC stage. In the background of BCLC staging, increased tumor burden (as reflected by multinodularity and bilobar involvement) or aggressiveness (as determined by high alpha-fetoprotein, portal vein thrombosis , or poor performance status) and worsened liver function (as reflected by increased bilirubin or INR) provide additional prognostic information. The survival outcomes in specific cohorts compare favorably with other locoregional treatment options (chemoembolization and arterial embolization) that would typically be considered for unresectable patients in BCLC stages A and B, as has also been shown recently.[31] Data from our series show that survival after radioembolization appears particularly promising for the subset of patients with intermediate stage HCC who are considered poor candidates for chemoembolization (i.e., those with bilobar and/or multiple [>5] tumors; median, 15.4-16.6 months) as well as for those who had failed prior chemoembolization or arterial embolization (median, 15.4 months). Survival is also promising for the group of patients with advanced stage disease (BCLC C), particularly those with portal vein thrombosis , where radioembolization compares well to that observed after sorafenib treatment and is well tolerated. A potential confounding effect on survival due to sorafenib therapy given after radioembolization was ruled out.

The main limitation of this study is its retrospective nature, although many patients were in fact followed prospectively and more than 98% of the data were available for the multivariate model. Due to this retrospective nature, we could not assess intention-to-treat patients who were evaluated for radioembolization but were considered inappropriate due, for instance, to insufficient liver function or technical considerations such as uncorrectable vasculature that would have led to the misdirection of microspheres to the gastrointestinal tract and other nontarget organs or excessive shunting of radiation to the lung. In addition, strict recommendations from the manufacturer and consensus guidelines[23] were not always followed (e.g., patients compromised by poor liver function or with ECOG performance status >2 were treated showing unsurprising poor outcomes). In contrast, this study assessed the results from radioembolization outside of clinical trials and consequently included a potentially broader cohort of patients than would hitherto have been recruited in a clinical trial.

In conclusion, our results provide a sound indication that radioembolization may well produce a clinically relevant survival benefit across different tumor stages, including those with advanced disease who have few treatment options. Further prospective evaluations of the clinical benefit for radioembolization in these patient populations are warranted. Although a head-to-head comparison of chemoembolization and radioembolization among patients in the intermediate stage is probably unfeasible due to the large number of patients needed (>1,000 according to Salem et al.[31]), radioembolization should be tested in the advanced stage either alone or, more reasonably, in combination with sorafenib.

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References

1. El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. Arch Intern Med 2000;160:3227-3230.
2. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100:698-711.
3. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 2010;30:61-74.
4. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, et al. Prognosis of hepatocellular carcinoma: Comparison of 7 staging systems in an American cohort. HEPATOLOGY 2005;41:707-716.
5. Cillo U, Vitale A, Grigoletto F, Farinati F, Brolese A, Zanus G, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006;44:723-731.
6. Grieco A, Pompili M, Caminiti G, Miele L, Covino M, Alfei B, et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda,CLIP, and BCLC staging systems in a single Italian centre. Gut 2005;54:411-418.
7. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. HEPATOLOGY 2011;53:1020-1022.
8. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. HEPATOLOGY 2003;37:429-442.
9. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Hepatobiliary guidelines. V.2.2010. www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf last accessed June 8th, 2011.
10. Jelic S, Sotiropoulos GC,on behalf of the ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2010;(21 Suppl. 5): v59-v64.
11. Kennedy A, Nutting C, Coldwell D, Gaiser J, Drachenberg C. Pathologic response and microdosimetry of ^{90}Y microspheres in man: review of four explanted whole livers. Int J Radiat Oncol Biol Phys 2004;60: 1552-1563.
12. Sangro B, D'Avola D, Iñarrairaegui M, Prieto J. Transarterial therapies for hepatocellular carcinoma. Exp Opin Pharmacother 2011;12:1057-1073.
13. Sangro B, Bilbao JI, Boan J, Martinez-Cuesta A, Benito A, Rodriguez J, et al. Radioembolization using ^{90}Y-resin microspheres for patients with advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2006;66:792-800.
14. Geschwind JF, Salem R, Carr BI, Soulen MC, Thurston KG, Goin KA, et al. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. Gastroenterology 2004;127:S194-S205.
15. Ettorre GM, Santoro R, Puoti C, Sciuto R, Carpanese L, Antonini M, et al. Short-term follow-up of radioembolization with yttrium-90 microspheres before liver transplantation: new perspectives in advanced hepatocellular carcinoma. Transplantation 2010;90:930-931.
16. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of ^{90}Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. HEPATOLOGY 2008;47: 71-81.
17. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010;138:52-64.
18. Iñarrairaegui M, Thurston KG, Arbizu J, Martinez-Cuesta A, Bilbao JI, Sangro B, et al. Radioembolization using ^{90}Y resin microspheres in patients with hepatocellular carcinoma and portal vein thrombosis. J Vasc Interv Radiol 2010;21:1205-1212.
19. Goin JE, Salem R, Carr BI, Dancey JE, Soulen MC, Geschwind JF, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: factors associated with liver toxicities. J Vasc Interv Radiol 2005;16:205-213.
20. Carr BI. Hepatic arterial ^{90}Yttrium glass microspheres (Therasphere) for unresectable hepatocellular carcinoma: interim safety and survival data on 65 patients. Liver Transpl 2004;10:S107-S110.
21. Kennedy AS, McNeillie P, Dezarn WA, Nutting C, Sangro B, Wertman D, et al. Treatment parameters and outcome in 680 treatments of internal radiation with resin ^{90}Y-microspheres for unresectable hepatic tumors. Int J Radiat Oncol Biol Phys 2009;74:1494-1500.
22. Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, Viudez A, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. Cancer 2008;112:1538-1546.
23. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, 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.
24. Coldwell D, Sangro B, Wasan H, Salem R, Kennedy A. General selection criteria of patients for radioembolization of liver tumors: an international working group report. Am J Clin Oncol 2011;34:337-341.
25. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions

of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421-430.
26. Bilbao JI, Reiser MF, eds. Liver Radioembolization with ^{90}Y Microspheres. New York, NY: Springer Verlag; 2008.
27. Hill T, Lewicki P. Statistics: methods and applications: a comprehensive reference for science, industry, and data mining. Tulsa, OK: StatSoft, Inc.; 2006.
28. Sangro B, Salem R, Kennedy A, Coldwell D, Wasan H. Radioembolization for hepatocellular carcinoma: a review of the evidence and treatment recommendations. Am J Clin Oncol 2010; doi:10.1097/COC.0b013e3181df0a50.
29. Kulik LM, Atassi B, Van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol 2006;94:572-586.
30. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al.; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
31. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, et al. Radioembolization results in longer time to progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140:497-507.