Radiation Segmentectomy: Potential Curative Therapy for Early Hepatocellular Carcinoma[1]

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Purpose: To report long-term outcomes of radiation segmentectomy (RS) for early hepatocellular carcinoma (HCC). The authors hypothesized that outcomes are comparable to curative treatments for patients with solitary HCC less than or equal to 5 cm and preserved liver function.

Materials and Methods: This retrospective study included 70 patients (median age, 71 years; range, 22–96 years) with solitary HCC less than or equal to 5 cm not amenable to percutaneous ablation who underwent RS (dose of >190 Gy) between 2003 and 2016. Patients who underwent subsequent curative liver transplantation were excluded to eliminate this confounding variable affecting survival. Radiologic response of time to progression and median overall survival were estimated by using the Kaplan-Meier method per the guidelines of the European Association for the Study of the Liver (EASL) and the World Health Organization (WHO).

Results: Seventy patients were treated with RS over 14 years. Sixty-three patients (90%) showed response by using EASL criteria, of which 41 (59%) showed complete response. Fifty patients (71%) achieved response by using WHO criteria, of which 11 (16%) achieved complete response. Response rates at 6 months were 86% and 49% by using EASL and WHO criteria, respectively. Median time to progression was 2.4 years (95% confidence interval: 2.1, 5.7), with 72% of patients having no target lesion progression at 5 years. Median overall survival was 6.7 years (95% confidence interval: 3.1, 6.7); survival probability at 1, 3, and 5 years was 98%, 66%, and 57%, respectively. Overall survival probability at 1, 3, and 5 years was 100%, 82%, and 75%, respectively, in patients with baseline tumor size less than or equal to 3 cm (n = 45) and was significantly longer than in patients with tumors greater than 3 cm (P = .026).

Conclusion: RS provides response rates, tumor control, and survival outcomes comparable to curative-intent treatments for selected patients with early-stage HCC who have preserved liver function.

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Curative approaches at the very early stage (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A) of hepatocellular carcinoma (HCC) include radiofrequency ablation, surgical resection, and transplantation (1). Resection and transplantation have provided excellent outcomes, with 5-year survival rates ranging between 60%–80% for well-selected BCLC stage 0 or A HCC (2). Radiofrequency ablation shows similar survival outcomes in HCC less than or equal to 3 cm in diameter, and it was recently added as the treatment of choice in BCLC stage 0 HCC (3). However, many patients are not candidates for these therapies at presentation; stage migration states patients should be offered the next-best therapy if the first-line therapy is not feasible (4). Based on two prospective randomized trials, the next-best therapy is transarterial chemoembolization (5,6).

An application of segmental, high-dose radioembolization provides selective ablative radiation doses to tumors (7). Radiation segmentectomy (RS) is a targeted form of radioembolization with yttrium 90 (^{90}Y), usually delivered to no more than two hepatic segments. The high tumor dose maximizes cytotoxic radiation delivery, whereas the focused delivery minimizes risk of collateral parenchymal damage (8). This threshold dose of 190 Gy has been confirmed by using pathologic correlation from transplant explants (9).

Implication for Patient Care

- Radiation segmentectomy (RS) may represent a curative treatment option for patients with early hepatocellular carcinoma with preserved liver function who cannot undergo liver resection or ablation.
- RS is an outpatient, minimally invasive intra-arterial therapy with a low toxicity profile that may represents a convenient treatment option for patients with comorbidities preventing liver resection.

In our study, we review our long-term outcomes (>10 years) of patients with HCC less than or equal to 5 cm not amenable to resection, radiofrequency ablation, or transplantation who underwent RS. We hypothesize that this approach could be considered potentially curative based on the same rationale as resection, radiofrequency ablation, and transplantation.

Materials and Methods

R.J.L. and R.S. are advisors to BTG International. There was no funding for this analysis and all authors had control of the data and information submitted for publication. Our study was approved by the institutional review board and was compliant with the Health Insurance Portability and Accountability Act. All patients provided written informed consent prior to receiving treatment after selecting RS over chemoembolization. We searched our prospectively acquired database of HCC (10) for patients treated with ^{90}Y radioembolization from December 2003 to 2016 (14 years). Inclusion criteria were as follows: solitary HCC less than or equal to 5 cm, preserved liver function (Child-Pugh class A), and no vascular invasion or extrahepatic metastases (7). Patients who underwent transplantation or resection were excluded to mitigate the potential confounding impact on overall survival (Fig 1). A subanalysis of patients with HCC less than or equal to 3 cm was also performed, creating a cohort potentially comparable to radiofrequency ablation. Twenty-four of the 70 patients have been previously reported (9). In that prior study, the concept of RS was introduced and validated by using results from pathologic explants. In our current study, all patients underwent updated long-term imaging and clinical follow-up, permitting mature survival and time-to-progression analyses.

Seventy patients with solitary HCC less than or equal to 5 cm and Child-Pugh class A liver function underwent RS. No patient underwent curative treatment (transplantation, resection, or radiofrequency ablation) as of the date of data closure (Table 1). Among the 70 patients, 45 (64%) were men; median age of the cohort was 70 years (range, 22–96 years; 69 years for men and 72 years for women; P = .29). Long-term (>10 years) survival data were assessed.

Evaluation and Staging

A multidisciplinary team (hepatology, oncology, transplant surgery, interventional radiology) triaged patients to RS following a thorough discussion of all potential treatments. This approach was chosen as an alternative to radiofrequency ablation when the tumor was in an unfavorable location (dome, central near bile ducts, abutting gallbladder and/or stomach). Patients in this population were not deemed candidates for transplantation and/or resection secondary to comorbidities or older age (determined by transplant team).

All patients were evaluated in the interventional oncology clinic, and a history and physical examination were performed. Laboratory and imaging

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Abbreviations:
BCLC = Barcelona Clinic Liver Cancer
EASL = European Association for the Study of the Liver
HCC = hepatocellular carcinoma
RS = radiation segmentectomy
WHO = World Health Organization

Author contributions:
Guarantors of integrity of entire study, R.J.L., A.G., R.A., R.A.M., M.A., A.R., R.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, R.J.L., A.G., N.A., R.A., A.A., R.A.M., S.M., R.H., J.C.C., A.R., R.S.; clinical studies, R.J.L., A.G., N.A., R.A., D.G., K.D., B.T., S.M., M.A., A.R., R.S.; statistical analysis, R.J.L., A.G., N.A., R.A., A.A., R.A.M., S.M., A.R., R.S.; and manuscript editing, R.J.L., A.G., N.A., R.A., A.A., R.A.M., L.K., D.G., B.T., R.H., J.C.C., M.A., A.R., R.S.

Conflicts of interest are listed at the end of this article.

See also the editorial by Sofocleous and Boas.

Figure 1

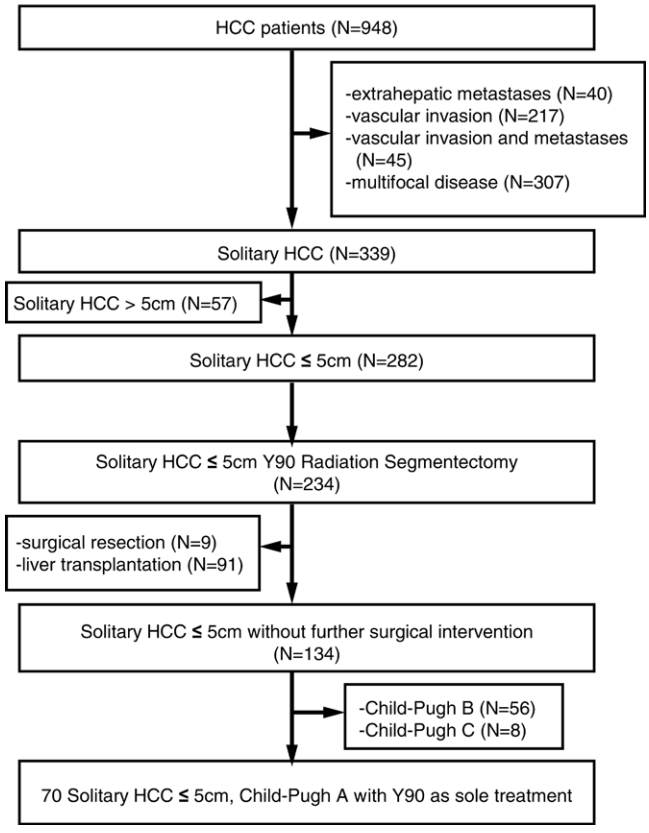

Figure 1: Study flowchart. HCC = hepatocellular carcinoma, Y90 = yttrium 90.

studies (contrast material–enhanced magnetic resonance [MR] imaging or computed tomography [CT]) were performed. The diagnosis of HCC was made per guidelines (11). Imaging findings of cirrhosis and portal hypertension (varices, splenomegaly with thrombocytopenia) were recorded. Liver function was assessed by using the Child-Pugh system. Tumor staging was performed per the United Network for Organ Sharing (UNOS) classification scheme for tumor size and/or number. All patients were classified as having BCLC stage 0 or A HCC.

RS Protocol

Planning mesenteric angiography was performed as previously described (12). RS was performed with glass microspheres (BTG International, Ottawa, Canada) impregnated with ^{90}Y (13). Cone-beam CT (6-second imaging, 6-second injection delay) was performed to verify complete tumor targeting, to provide volumetric analysis for dosimetry, and to ensure complete coverage of the tumor margin. A tumoricidal dose delivery was performed by measuring the perfused volume with cone-beam CT and entering this into the glass-microsphere formula with a target dose of greater than 190 Gy. Selective high-dose radioembolization to the tumor-bearing hepatic segments was delivered, a dose previously demonstrated to provide complete pathologic necrosis (9). All patients were treated by K.D., B.T., S.M., R.H. (each with 3–5 years of experience), R.J.L. (with 10 years of experience), and R.S. (with >20 years of experience).

Toxicity Assessment

Hepatic enzymes, alkaline phosphatase, serum albumin, and bilirubin were assessed at 1 month and 3 months after RS. Treatment-related liver toxicities were assessed by using version 4.0 of the Common Terminology Criteria for Adverse Events.

Response Assessment

Patients were seen in the clinic 1 month after radioembolization and subsequently at 3-month intervals. Laboratory and imaging studies were obtained at each visit. Response status was blindly assessed by using the necrosis criteria of the World Health Organization (WHO) and the European Association for the Study of the Liver (EASL) by an interventional radiologist (A.R., with >5 years of experience); this reader did not treat any patient (14) (Table E1 [online]). Objective response rates were estimated by considering the patient's best radiologic response during his or her entire follow-up period. Patients were considered for additional radioembolization or other treatment if there were signs of tumor progression or development of new hepatic tumors.

Time to Progression

Tumor progression was defined as any of the following: 25% increase in bidimensional cross-product of the targeted tumor (WHO criteria), 25% increase in arterial enhancement of the targeted tumor (EASL criteria), development of portal vein tumor thrombus, and new intrahepatic or extrahepatic disease. Time to progression and time to target lesion progression were calculated by using the Kaplan-Meier method.

Survival Analysis

Overall survival was calculated by using the Kaplan-Meier method (log-rank) from the day of first treatment with ^{90}Y until the day of last follow-up or death. Multivariate analysis was not conducted because of insufficient death endpoints

Table 1

Baseline Characteristics

Parameter	No. of Patients (n = 70)
Sex	
Male	45 (64)
Female	25 (36)
Age (y)*	
All patients	70 (22–96)
Men	69 (22–87)
Women	72 (58–96)
Etiology of liver disease	
Hepatitis C virus	34 (49)
Alcohol	3 (4)
Cryptogenic	15 (21)
Hepatitis B virus	7 (10)
Autoimmune	3 (4)
Nonalcoholic steatohepatitis	7 (10)
Hemochromatosis	1 (1)
Child-Pugh score	
Class A5	27 (39)
Class A6	43 (61)
Cirrhosis	
Yes	64 (91)
No†	6 (9)
Imaging portal hypertension‡	
Yes	50 (71)
No	20 (29)
α-fetoprotein	
>200 μg/L	11 (16)
<200 μg/L	59 (84)
Method of diagnosis	
Imaging	51 (73)
Biopsy	19 (27)
Lesion size (cm)	
Median	2.6
Range	1.3–4.6
UNOS tumor number and size	
T1 (<2 cm)	15 (21)
T2 (2–3 cm)	35 (50)
T2 (3–5 cm)	20 (29)

Note.—Unless otherwise specified, data in parentheses are percentages. UNOS = United Network for Organ Sharing.

* Data are means, with ranges in parentheses. P = .29

† Six patients without cirrhosis had nonresectable hepatocellular carcinoma because of other comorbidities.

‡ Indicates the presence of varices, splenomegaly, or thrombocytopenia.

Table 2

Radiographic Response

Parameter	1 mo (n = 70)		6 mo (n = 63)		9 mo (n = 42)		12 mo (n = 35)	
	EASL	WHO	EASL	WHO	EASL	WHO	EASL	WHO
Partial response	32 (46)	15 (21)	26 (42)	28 (44)	9 (21)	27 (64)	7 (20)	21 (60)
Complete response	9 (13)	3 (4)	28 (44)	3 (5)	27 (64)	3 (8)	22 (63)	4 (11)
Stable disease	26 (37)	50 (71)	4 (6)	27 (43)	1 (3)	9 (21)	1 (3)	7 (20)
Progressive disease	3 (4)	2 (3)	5 (8)	5 (8)	5 (12)	3 (7)	5 (14)	3 (9)

Note.—Data are the number of patients, with percentages in parentheses. Best overall response according to European Association for the Study of the Liver (EASL) guidelines: responsive, 63 patients (90%) vs nonresponsive, seven patients (10%). Best overall response according to World Health Organization (WHO) guidelines: responsive, 50 patients (71%) vs nonresponsive, 20 patients (29%).

at the time of data closure. All analyses were performed by using SPSS Statistics (version 24; IBM, Armonk, NY).

Results

Baseline Characteristics

Among 70 patients, 50 (71%) had tumors less than or equal to 3 cm, whereas 20 (29%) had tumors of 3–5 cm. Eleven (16%) patients exhibited elevated α-fetoprotein levels greater than 200 μg/L. Forty-six of 70 (66%) patients underwent RS to one segment bearing the tumor, whereas 24 of 70 (34%) patients underwent RS to two segments. Mean follow-up time was 29 months ± 25 (95% confidence interval: 6, 117.8).

Adverse Events

At 1-month follow-up, one (1.4%) patient developed grade 3 bilirubin toxicity, and one (1.4%) patient developed grade 3 albumin toxicity. At 3 months, one (1.4%) patient developed grade 3 aspartate aminotransferase toxicity. One patient (1.4%) developed rapidly progressive disease, exhibited grade 3 bilirubin and albumin at month 3, and died 4 months after ^{90}Y. No other grade 4 toxicities were found at month 3 (Table E2 [online]).

Radiographic Response

Among 70 patients, 63 (90%) responded according to EASL criteria, of whom 41 (59%) showed complete response. Response with concomitant new lesions or metastases was considered progression.

Fifty (71%) patients achieved radiologic response according to WHO criteria, with 11 of 70 (16%) successfully achieving complete WHO response. Similar to EASL, patients with responding tumors and new lesions or metastases were considered nonresponders.

Time-dependent radiologic response showed 59%, 86%, 85%, and 83% response according to EASL criteria and 26%, 49%, 72%, and 71% response according to WHO criteria at 1, 6, 9, and 12 months, respectively (Table 2).

Time to Progression

Median time to progression was 2.4 years (95% confidence interval: 2.1, 5.7). Further stratification by using size (≤3 cm and >3 cm) did not show a significant difference (P = .2) (Fig 2). For local tumor control, median time to target lesion progression was not reached regardless of tumor size, with a 5- and 7-year progression-free probability of 72% (Fig 3). Only one patient received treatment after progression in the form of conventional transarterial chemoembolization. Table E3 (online) describes progression pattern after complete response, demonstrating that local recurrence in complete responders occurred in four patients (9.8%).

Survival

At data closure, 17 of 70 (24%) patients died, whereas 53 of 70 (76%)

patients were censored to last day of follow-up. Median overall survival for the entire 70-patient cohort was 6.7 years (95% confidence interval: 3.1, 6.7), with a 1-, 3-, and 5-year survival probability of 98%, 66%, and 57%, respectively (Fig 4). A subanalysis of patients with tumor size less than or equal to 3 cm (n = 45) resulted in 1-, 3-, and 5-year survival probabilities of 100%, 82%, and 75%, respectively (Table 3). Table 4 lists seminal studies of ablation, resection, and transplantation with corresponding 1-, 3-, and 5-year survival probabilities. Figure 5 shows a patient at 9-year follow-up after RS who presents with complete necrosis. This person is considered cured.

Discussion

The BCLC system identifies patients with limited disease as candidates for curative-intent therapies. Patients at a very early stage (stage 0) present with a single HCC less than 2 cm and preserved liver function (Child-Pugh class A). Patients with early-stage (stage A) HCC present with either a solitary tumor (of any size) or up to three tumors, all less than 3 cm in diameter with either Child-Pugh class A or class B liver function. Designating HCC therapies as "curative" (transplantation, resection, or radiofrequency ablation) is controversial and relates to the level of evidence; guideline recommendations are not uniformly derived from randomized level I studies (11). The National Comprehensive Cancer Network guidelines recognize radioembolization as one of the treatment options for HCC (15).

Rationale for Curative Designation of Transplantation, Resection, or Ablation

Liver transplantation is considered the reference standard curative therapy in appropriately selected patients, with 5-year survival exceeding 70% (16), an overall recurrence rate between 8%–15% (17), and 1-year morbidity and/or mortality reaching 10% (18,19). Surgical resection is also considered curative for patients with preserved liver function (20) and resectable HCC (11), provided adequate future liver remnant. Five-year survival rates vary between 60%–80%, with recurrence rates of 70% and 30-day mortality of 11% (21–23). Radiofrequency ablation is also considered curative and comparable to resection for patients

Figure 2

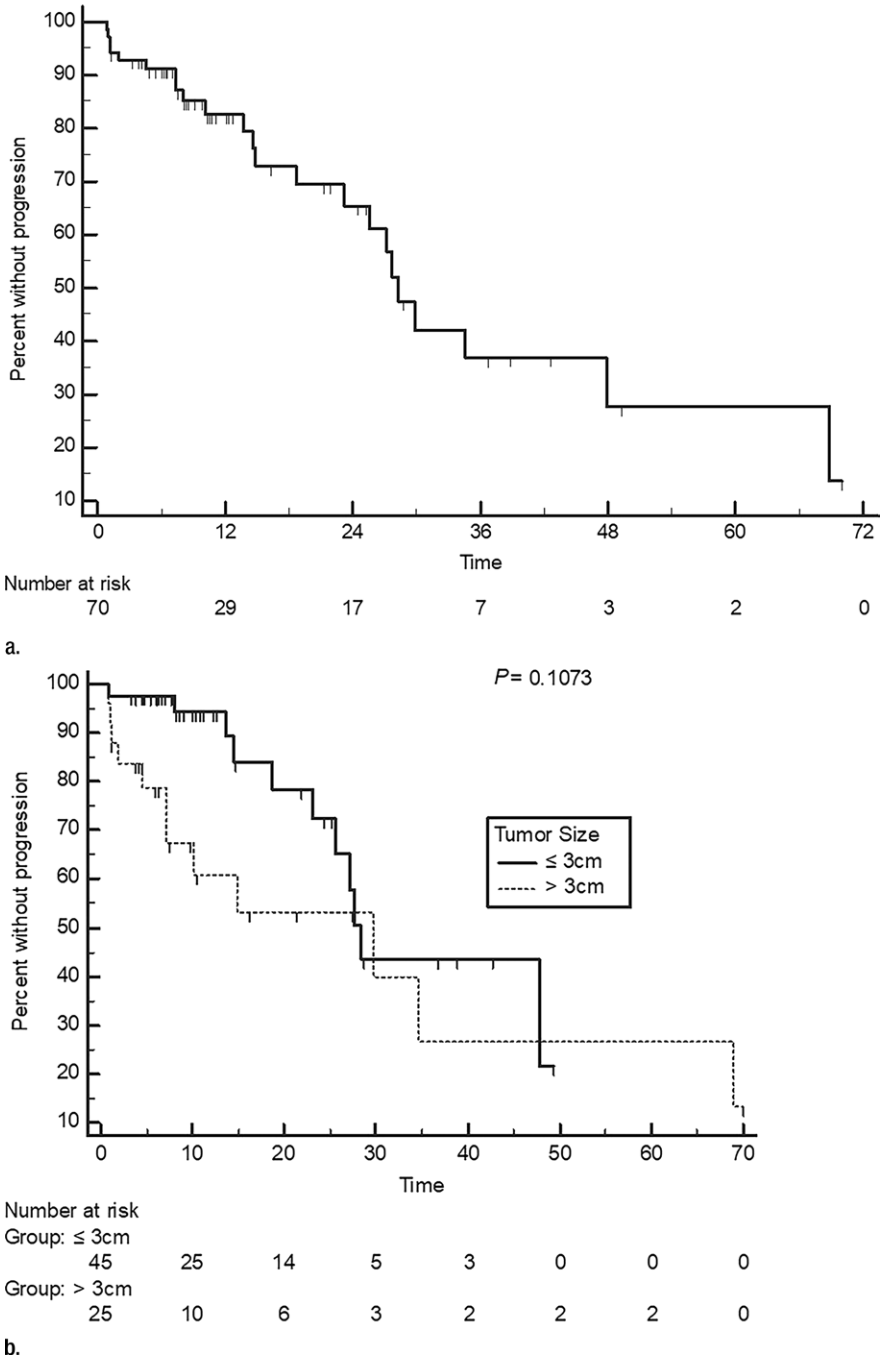

Figure 2: Graphs show **(a)** time to progression for all patients and **(b)** time to progression stratified by using tumor size (≤3 cm and >3 cm).

Figure 3

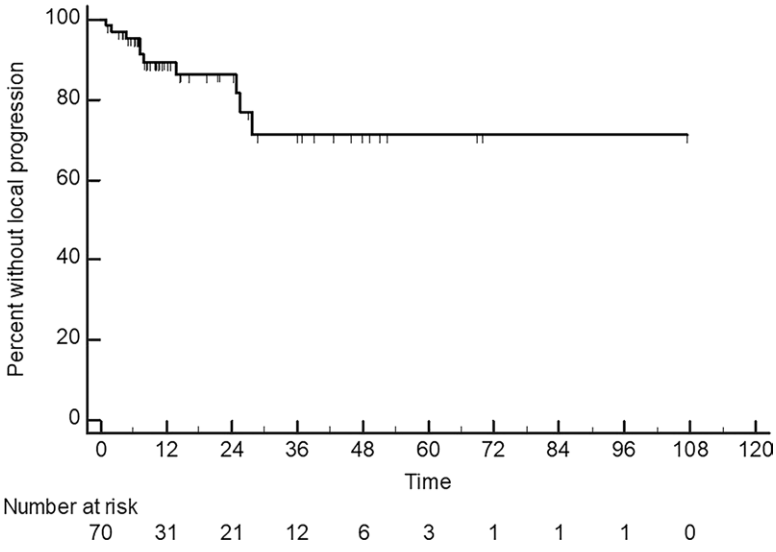

Figure 3: Graph shows local tumor control represented by using time to target lesion progression.

with BCLC stage 0 or A HCC. It is recommended in poor candidates for resection with limited disease (24), exhibiting 3- and 5-year survival rates in solitary HCC less than 5 cm of 89% and 61%, respectively (25), and recurrence rates reaching 39% in 3–5-cm lesions (26). Combined with embolization, the curative aspect of ablation may be further enhanced (27). Effectively, all three of the above options, despite limitations in long-term outcomes, recurrence rates, and postoperative morbidities, are considered potentially curative based on phase 2 studies with limited data demonstrating improved survival with randomized studies (28,29).

Rationale for RS

Stage migration occurs when a patient with HCC is not suitable for the recommended therapy or therapies (4). According to BCLC, patients with early-stage disease would be offered conventional transarterial chemoembolization, migrating from a curative to a palliative treatment. In our current study, the application of radioembolization by using an ablative dose with RS for the treatment of unablatable lesions that are Child-Pugh class A BCLC stage 0 or A was evaluated. This targeted form of radioembolization provides ablative radiation doses to the targeted tumor and margin (7). A previous radiologic-pathologic study demonstrated a dose >190 Gy was associated with achieving 100% necrosis, arguably a curative pathologic endpoint (9). Although chemoembolization was also discussed with patients as an option, they selected RS after informed consent.

Rationale for Curative Potential of RS

The question that emerges from our study is what constitutes a curative treatment. RS was found to generate outcomes consistent with treatments considered to be curative: 71% response per WHO criteria and 90% response per EASL criteria, local tumor control rate at 5 years of 72%, time to progression of 2.4 years, overall survival at year 5 of 55%, and median overall survival of 80 months (6.7 years). 5-year survival was 75% for patients with HCC less than or equal to 3 cm. These outcomes compare favorably with pivotal studies establishing other curative therapies for early HCC.

Our outcomes suggest that RS may be considered curative in patients with unablatable BCLC stage 0 or A lesions less than or equal to 5 cm. First, any survival benefit in this cohort was solely attributable to ^{90}Y and exceeds the expected survival of 36–60 months for BCLC stage A HCC. Second, when applying strict selection criteria in a manner analogous to other curative treatments, prolonged survival is noted. Third, the favorable adverse event profile in a treatment that can be performed on an outpatient same-day basis should be considered competitive to more invasive traditional curative treatments (30). Fourth, a dose of greater than 190 Gy has been shown to achieve complete pathologic necrosis (9). Finally, from a statistical standpoint, curative therapies all exhibit one common characteristic: a flattening of the Kaplan-Meier curve (31). With RS, this flattening occurs along 55% at year 5. The amalgamation of these data suggests that RS, in select patients, exhibits curative outcomes.

RS is technically simple, especially with the advent of the cone-beam CT, and should be considered in patients with unablatable or unresectable HCC (29). Furthermore, as expected, patients with Child-Pugh class A disease rarely experience hepatic toxicity (1.4%); this finding was borne out in our study.

Strengths include the homogeneity of the patient cohort, long-term follow-up (>10 years), prospective data collection, and strict patient selection (≤5 cm, Child-Pugh class A). When individualizing patient care, this cohort was stage migrated to RS by using a multidisciplinary tumor board. Limited therapy after progression permits the attribution of survival outcome solely to RS without confounders. Finally, the time to progression of 2.4 years (29 months) is comparable to the Prospective Randomized Trial of Radioembolization and Chemoembolization in HCC (or PREMIERE) trial, where greater than 26 months of time to progression was validated in a randomized setting (32). Also, the mean follow-up

Figure 4

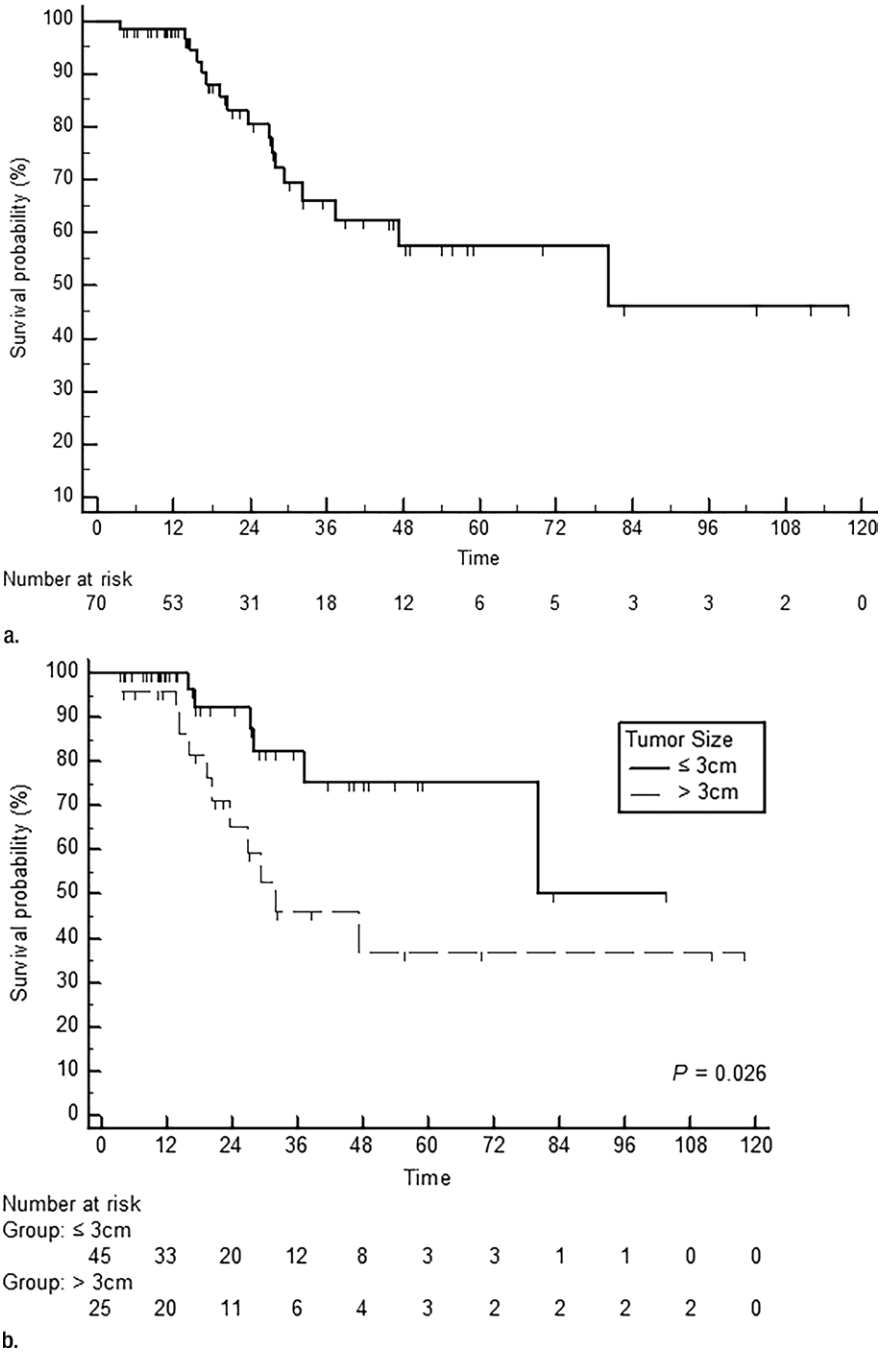

Figure 4: Graphs show **(a)** survival for all patients and **(b)** survival stratified by using tumor size (≤3 cm and >3 cm).

Table 3

Overall Survival

Overall Survival Rate	≤3 cm (*n* = 45)	>3 cm (*n* = 25)	All ≤5 cm (*n* = 70)
1 y	100	96	98
3 y	82	46	66
5 y	75	37	57

Note.—Data are percentages.

of 29 months reported in our study exceeds two of the seminal descriptions of radiofrequency ablation as curative, where they reported mean follow-up of 24 months and 27 months, respectively (25,33).

Limitations include the retrospective and nonrandomized nature of the analysis, selection bias, and comparison to published literature rather than to an internal control group. A long-term follow-up report may be necessary to provide a survival update on patients more recently treated. Finally, limited death endpoints also prevent multivariate analyses.

In conclusion, RS provides local tumor control, prolonged time to progression, and overall survival outcomes comparable to radiofrequency ablation, resection, and transplantation for patients with BCLC stage 0 or A HCC. RS should be considered curative for the treatment of solitary HCC less than 5 cm.

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Table 4

Survival Rates Compared with Other Curative Treatments

Tumor No. and Size, Treatment Modality, and Clinical Study	No. of Patients	Survival (%) 1 y	3 y	5 y	Median Overall Survival (mo)
Solitary ≤3 cm					
Radiation segmentectomy					
Current study	45	100	82	75	Not reached
Surgical resection					
Pompili et al (34)	246	95	82	74*	Not reached
Huang et al (35)	45	100	96	82	Not reached
Radiofrequency ablation					
Pompili et al (34)	298	98	81	66*	Not reached
Huang et al (35)	57	87	77	55	Not reached
Solitary ≤5 cm					
Radiation segmentectomy					
Current study	70	98	66	57	80
Surgical resection					
Chen et al (36)	91	93	73	64*	Not reached
Radiofrequency ablation					
Lencioni et al (25)	145	100	89	61	65
Chen et al (36)	91	94	69	66*	Not reached
Single ≤5 cm or ≤3 nodules, all ≤3 cm†					
Liver transplantation					
Mazzaferro et al (16)	48	…	…	75*	Not reached
Llovet et al (37)	58	84	74	74	Not reached
Jonas et al (17)	120	90	…	71	Not reached

* Indicates 4-year survival probability.

† Based on Milan criteria.

tific, and Cook for lectures including service on speakers bureaus. Other relationships: disclosed no relevant relationships. **B.T.** disclosed no relevant relationships. **S.M.** disclosed no relevant relationships. **R.H**. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for Bayer. Other relationships: disclosed no relevant relationships. **J.C.C.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for and receives payment from Novartis for lectures including service on speakers bureaus; has grants/grants pending with National Institute of Diabetes and Digestive and Kidney Diseases (R01). Other relationships: disclosed no relevant relationships. **M.A.** disclosed no relevant relationships. **A.R.** disclosed no relevant relationships. **R.S.** Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for Boston Scientific, BTG, and Terumo; receives payment from BTG for travel/accommodations/meeting expenses unrelated to activities listed; money paid to institution by BTG for grants/grants pending. Other relationships: disclosed no relevant relationships.

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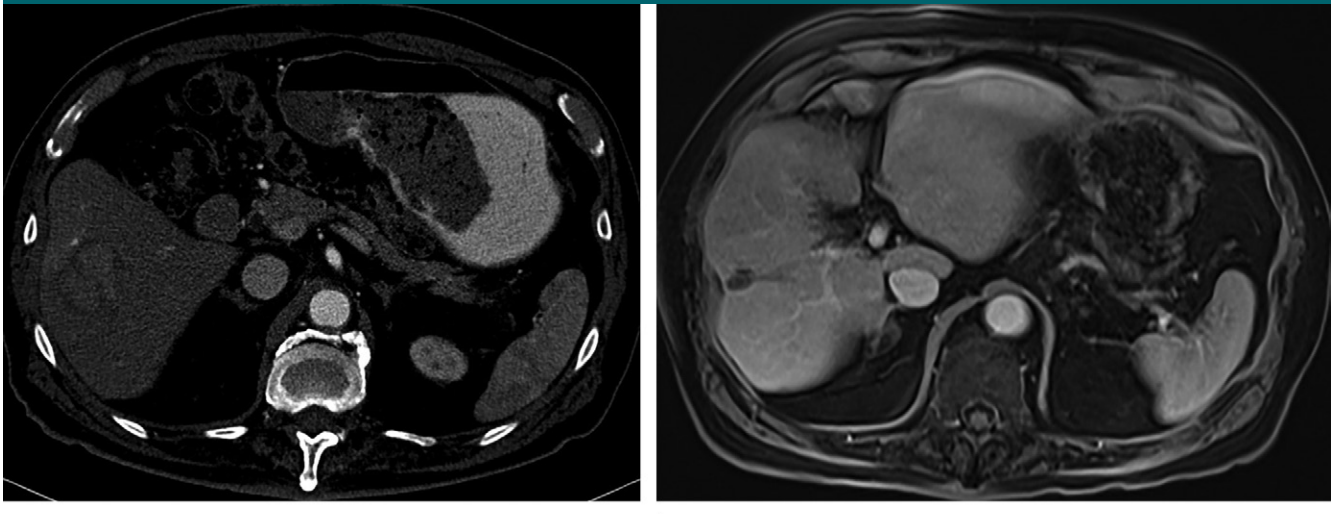
Figure 5



a. b.

Figure 5: Images show **(a)** contrast material–enhanced CT scan before yttrium 90 of an 87-year-old man with 4-cm hepatocellular carcinoma in right lobe. **(b)** Contrast-enhanced MR image at subsequent 9-year follow-up (now aged 96 years) shows complete necrosis.

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