

Original Article

Conditional survival analysis of hepatocellular carcinoma patients treated with radiofrequency ablation

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Aim: Survival estimates are commonly reported as survival from the first observation, but future survival probability changes based on the survival time already accumulated after therapy, otherwise known as conditional survival (CS). The aim of the study was to describe CS according to different prognostic variables in hepatocellular carcinoma (HCC) patients treated with radiofrequency ablation (RFA).

Methods: Data on 125 very early/early HCC patients treated with RFA between 1999 and 2007 were analyzed. Actuarial survival estimates were computed by means of Kaplan–Meier method and compared by log–rank test. The 5-year CS was calculated with stratification by several predictors for patients who had already survived up to 5 years from diagnosis.

Results: Median overall survival (OS) was 72 months (95% confidence interval [CI], 58–86). Age, Child–Pugh (CP), α -fetoprotein (AFP), Cancer of the Liver Italian Program (CLIP)

score and type of recurrence (early vs late) were significant predictors of OS. The 5-year CS rates of the entire study cohort assessed at 1, 2, 3 and 5 years from the treatment were 49%, 48%, 30% and 34%, respectively. Subgroup analysis confirmed age and CP as significant predictors of CS at all time points, while the CS of subgroups stratified by AFP and CLIP did not differ significantly from the 3rd year after RFA onward, as more advanced patients had probably escaped early recurrence.

Conclusion: CS analysis showed that the impact of different variables influencing OS is not linear over time after RFA. Information derived from the study can improve the current management of HCC patients.

Key words: cancer, cirrhosis, hepatocellular carcinoma, radiofrequency ablation

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) is the third most common cause of cancer-related death

worldwide and the main cause of mortality among patients with cirrhosis.^{1,2} Despite the recent improvements in surveillance protocols and diagnostic tools, HCC diagnosis at early stage (when curative treatments are feasible) is currently reported in only 30–60% of cases.³

Radiofrequency ablation (RFA) represents the standard of care for patients at very early and early stage, who are not suitable for surgical therapies (i.e. hepatic resection or orthotopic liver transplantation [OLT]).

The best outcomes have been reported in HCC classified as Barcelona Cancer of the Liver Clinic stage (BCLC) 0 (i.e. single nodule of ≤ 2 cm) for which RFA has demonstrated a competitive efficacy with respect to surgery in terms of overall survival (OS).^{4,5}

Recent data have shown a 5-year survival in 70% of patients after local ablation⁶ but these projections are not necessarily pertinent for patients who have survived the initial treatment period, as prognosis after initial management is not static, namely, patients who have

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survived an interval of time after treatment have a different probability of surviving for the following 5 years than was estimated at the time of diagnosis. Their prognosis is more accurately described using conditional survival (CS) analysis,⁷ based on the concept of conditional probability. Such analysis determines the probability that a patient, who has survived for a specific period, will still be alive at another fixed interval.

As in many other malignancies, HCC patients have been found to show higher hazard rates for death in the first few years, thereafter decreasing over time. In fact, it is well known that the evolutionary course of liver function along with tumor burden and recurrence influence both the therapeutic strategy and the assessment of prognosis; hence, the prognostic estimations made at the time of the initial diagnosis are usually valid for describing general groups but not likewise able to define individual prognosis.

Thus, a more accurate individual prognosis, based on the repeated reassessment of survival probability, would be important not only in the routine practice but also in the research setting to better understand the comparability of groups in treatment trials, especially in the setting of adjuvant strategies.

Studies on CS have been previously published in several fields of oncology^{8,9} and a recent paper has explored the CS pattern of HCC patients after hepatic resection.¹⁰

The aim of the present study was to describe how CS probability can change over time according to different prognostic variables, taking into consideration HCC patients submitted to a curative ablative therapy, such as percutaneous RFA.

METHODS

Patients

FROM FEBRUARY 1999 to November 2007, 694 patients were diagnosed with HCC by histology or radiological imaging (multiphase computed tomography [CT] or magnetic resonance imaging) at the University of Foggia. Among them, 471 did not meet the criteria for RFA, which were: (i) very early or early HCC (i.e. a single nodule or up to three nodules <3 cm), as classified by BCLC; and (ii) contraindications to surgical therapies, such as hepatic resection, due to comorbidities, liver function impairment or tumor location in deep liver segments.

Out of 223 patients fulfilling the aforementioned criteria, 73 presented contraindication to RFA due to liver decompensation (58 patients) or at-risk locations

(superficial lesions adjacent to any part of the gastrointestinal tract; 15 patients). Among 150 patients actually treated with RFA, 25 who underwent previous treatments for HCC (17 patients) or with incomplete clinical data (five patients) and presenting severe life-threatening comorbidities that could affect life expectancy (three patients) were excluded from the analysis.

Finally, data on 125 patients treated with percutaneous RFA were retrieved and analyzed.

The detailed flow diagram of the study population is summarized in Figure 1.

This study was approved by our institutional review board for retrospective evaluation of de-identified patients.

Follow-up analysis ended in June 2014 with a 89-month median follow-up time (95% confidence interval [CI], 88–108).

The following parameters were recorded: demographics and medical history, etiology of the underlying liver disease, treatments performed at recurrence after RFA, liver function according to Child–Pugh (CP) score and Model for End-Stage Liver Disease (MELD), Eastern Cooperative Oncology Group performance status, tumor stage according to BCLC, Cancer of the Liver Italian Program (CLIP), Okuda and American Liver Tumor Study Group staging systems, presence of portal hypertension (defined by at least one of the following: esophageal varices, platelet count <100 000/ μ L and splenomegaly).¹¹

Treatment protocol

The technical details of the ablative procedures performed in our center have been described elsewhere.¹²

Briefly, all the procedures had been performed under ultrasonographic guidance with a 150-W generator (Model 1500L; RITA Medical System, Mountain View, CA, USA), connected to an expandable 15–14-G electrode with a 2.0-cm long exposed tip (expandable by means of seven hooks). After administration of analgesia (50–60 mg propofol and 0.05–0.1 mg fentanyl) as well as local anesthesia (5–15 mL of 1% lidocaine) by an anesthesiologist, an RFA needle had been first inserted into the tumor. The electrode had been placed into the center of the lesion maintaining the temperature of the needle tip at 80–110°C for 10–12 min. After ablation, the needle had been retracted maintaining its tip hot in order to prevent by thermal coagulation seeding or hemorrhage along the electrode track. For larger nodules, different applicator positions had been adopted to create overlapping coagulation zones. For patients with multiple nodules, all lesions had been

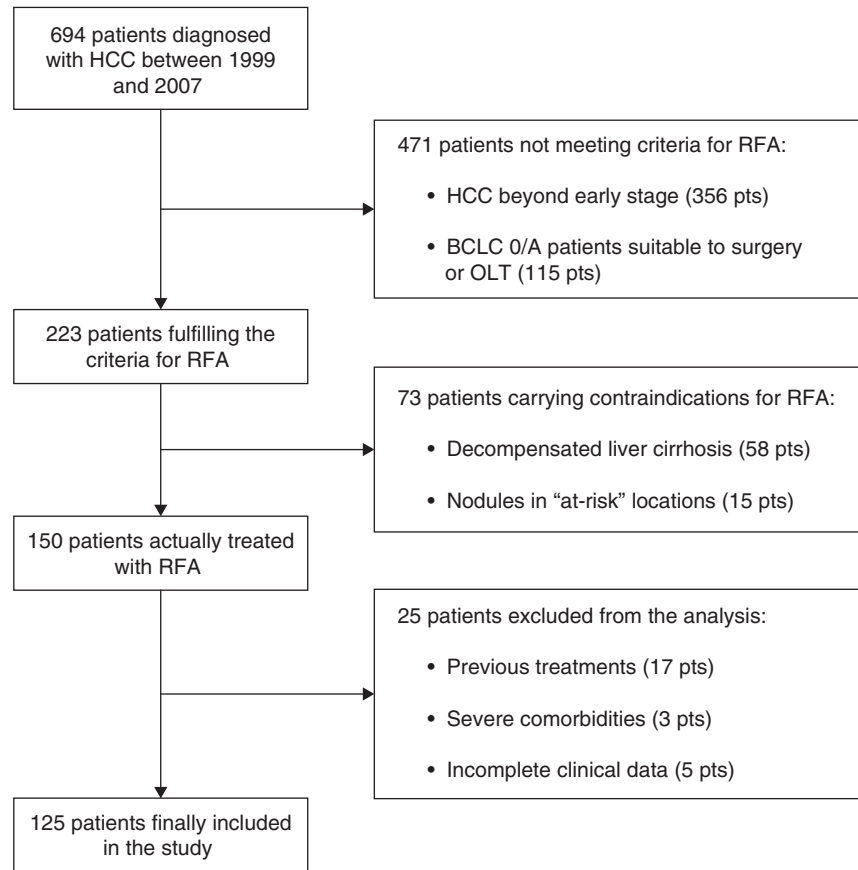


Figure 1 Study flow chart. One hundred and twenty-five patients were finally included in the study. BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; RFA, radiofrequency ablation.

treated in one single session. Every procedure had been aimed at obtaining a 5-mm safety margin around the treated lesions. No antibiotic prophylaxis or anti-inflammatory drugs had been administered prior to therapy.

Patient monitoring and response evaluation

Clinical visits, including physical examination, laboratory analyses, imaging evaluation and adverse event (AE) monitoring, were performed on an outpatient basis at 30–50 days after the procedure and every 4 months thereafter. In case of incomplete response, a second treatment was planned in patients with a CP score of B7 or less.

Tumor response was assessed by means of thoracoabdominal multiphase CT according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.¹³

Safety parameters were classified following the Common Terminology Criteria for Adverse Events (CTCAE) 4.0.¹⁴

Patients with recurrence were submitted to transarterial chemoembolization (TACE) in the case of multiple or large nodules, RFA in the presence of recurrence within BCLC stage A and percutaneous ethanol injection (PEI) when nodules were adjacent to a major vessel. Systemic chemotherapy and, from the end of 2008, sorafenib (Nexavar; Bayer, Leverkusen, Germany) were conducted in selected patients with extrahepatic metastatic or neoplastic portal vein thrombosis.

Statistical analysis

Categorical variables were described as frequencies and percentages while continuous variables as median and range. Times to event data, namely OS and time to recurrence (TTR), were estimated from the first procedure until the event or the last follow-up visit by Kaplan–Meier with plots and median (95% CI), compared by means of log-rank test and used in the calculation of the survival rate (SR), 5-year CS and 3-year conditional recurrence-free survival (RFS).

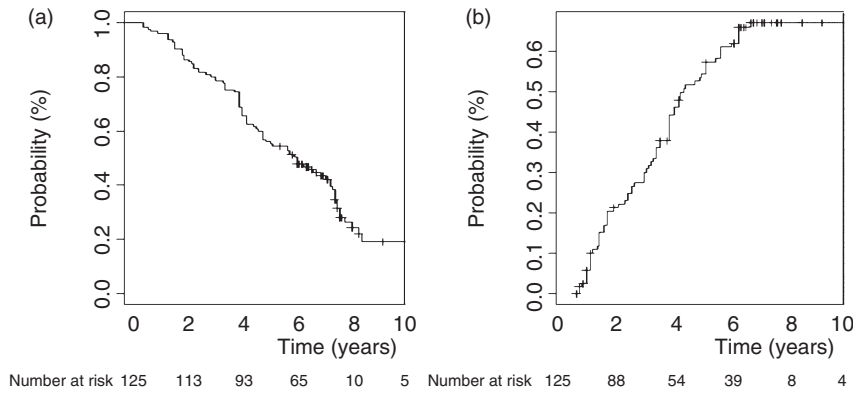


Figure 2 Actuarial overall survival and time to recurrence curves of the whole study population. (a) Overall survival. Median overall survival was 72 months (95% confidence interval, 58–86). (b) Time to recurrence. Median time to recurrence was 48 months (95% confidence interval, 42–64).

Conditional RFS was assessed at 3 years and computed within a shorter time-span (until 3 years elapsed since the treatment) due to the negligible number of events occurring from 5 years after RFA onwards (see Fig. 2b for details).

Only variables that were significantly related to patient survival at log-rank analysis were used for 5-year CS calculation.

Conditional survival is derived from the concept of conditional probability in biostatistics.⁷ Its mathematical definition can be expressed as follows: CS ($y | x$) is the probability of surviving for an additional y years, given that the person has already survived x years. Let $S(t)$ be the traditional actuarial survival at time t , CS can be expressed as: $CS(y | x) = S(x + y) / S(x)$. For example, in computing the 5-year CS for a patient who has already survived 2 years, that is, the survival at $5 + 2$ years, $S(7)$, is divided by the survival at 2 years, $S(2)$.¹⁰

The CS differences observed between subgroups were compared with the calculation of standardized differences (d), used as terms of effect size. Standardized differences were computed as follows:

$$d = (p_p - p_e) / \sqrt{([p_p[1 - p_p] + p_e[1 - p_e]]) / 2}$$

where p_p and p_e denote the proportion of a binary baseline variable in two groups.¹⁵

Effect size is a measure which is independent of the sample size and can give a more robust estimation of a difference in means or proportions: a value of less than 0.1 indicates very small differences between groups, values between 0.1 and 0.3 indicate small differences, d values between 0.3 and 0.5 indicate moderate differences, and d values greater than 0.5 indicate considerable differences.¹⁰

The analysis was performed using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) and significance was established at the 0.05 level (two-sided).

RESULTS

Clinical characteristics of patients

CLINICAL AND DEMOGRAPHIC characteristics are summarized in Table 1. Patients had a median age of 70 years (range, 39–86), were mostly male (80%) and hepatitis C virus (HCV) was the predominant etiology of the underlying liver disease (62%). Out of 77 HCV patients, 55 had been previously treated with interferon but none of them obtained a sustained virological response; on the other hand, all 26 hepatitis B virus patients were under nucleoside/nucleotide treatment at the time of RFA. Liver function was preserved with 87% of the patients of CP A status. The median MELD score was 9 (range, 6–14). Almost 90% of patients were of BCLC stage A with a median maximum diameter of 31 mm (range, 10–45). Median α -fetoprotein (AFP) was 25.7 UI/mL (range, 1.1–2100).

Tumor response and safety data

Complete responses (CR), assessed by mRECIST criteria, were 90.4% (113/125). Among the 125 treated patients, 77 underwent a single RFA, 42 underwent two consecutive procedures and six patients were treated with three consecutive treatments in order to achieve the CR.

The mean number of RFA treatments needed to achieve the CR was 1.4 ± 0.61 with a median time to response of 3 months (95% CI, 2–4).

No treatment-related deaths were observed. Within 1 month, six patients (4.8%) experienced a transient

Table 1 Baseline characteristics

Variable	All patients (<i>n</i> = 125)
Age (years)	70 (39–86)
Sex (male)	100 (80%)
Etiology (HCV/HBV/other)	77 (62%)/26 (21%)/22 (17%)
Child–Pugh (A/B)	109 (87%)/16 (13%)
AFP (UI/mL)	25.7 (1.1–2100)
Portal hypertension†	92 (74%)
MELD	9 (6–14)
No. of nodules (1/2/3)	100 (80%)/23 (18%)/2 (2%)
Maximum diameter (mm)	31 (10–45)
BCLC (0/A)	14 (11%)/111 (89%)
ALTSG (I/II)	14 (11%)/111 (89%)
CLIP (0/1/2)	70 (56%)/48 (38%)/7 (6%)
OKUDA (I/II)	110 (88%)/15 (12%)
ECOG performance status (0/1)	121 (97%)/4 (3%)

Values are expressed as median (range) in case of continuous variables and absolute number (percentage) in case of categorical variables.

†Defined by at least one of the following: esophageal varices, platelet count of <100 000/μL and splenomegaly.

AFP, α-fetoprotein; ALTSG, American Liver Tumor Study Group; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.

episode of liver decompensation and eight (6.4%) severe adverse events (grade 3/4), specifically one case of abdominal abscess and seven cases of abdominal pain, rapidly resolved after a brief hospitalization and short-term antibiotic and analgesic therapy.

Actuarial OS and disease recurrence

During the follow-up period, 84 of the 125 (67.2%) patients died. Tumor recurrence represented by far the most frequent cause of death (55 cases; 44%), followed by liver failure (28 cases; 22.4%) and other causes that accounted for the remaining patient (one case; 0.8%).

The median OS was 72 months (95% CI, 58–86) and actuarial SR was 80%, 56% and 19% at 3, 5 and 10 years, respectively. (Fig. 2a).

During the study follow up, 75 recurrences (60.3%) were observed. The median TTR, as computed from the first RFA performed, was 48 months (range, 42–64) with a RFS rate of 86%, 48% and 40% at 1, 5 and 10 years, respectively (Fig. 2b). In particular, early recurrence (≤ 2 years from the treatment) was observed in 29 patients (38.7%) and late recurrence (>2 years from the treatment) in 46 cases (61.3%). Factors significantly

related to the occurrence of early tumor relapse were CP score, AFP and maximum tumor diameter (data not shown).

Treatment at recurrence was RFA in 21 patients (28.3%), PEI in two (2.8%), TACE in 32 cases (42.9%) and sorafenib or systemic therapy in 10 (13%). Out of 75 patients who experienced tumor recurrence, 10 (13%) were not amenable to further treatments due to impaired liver function ($n = 8$ of them) or huge tumoral burden ($n = 2$).

CS

Actuarial 3-, 5- and 10 year SR, in relationship to the clinical and tumoral characteristics taken into consideration, are reported in Table 2. The following variables were found to be significantly related to OS: age ($P = 0.01$), CP score ($P < 0.001$), AFP ($P = 0.01$), CLIP score ($P = 0.002$) and type of recurrence (i.e. whether early or late, $P < 0.001$).

In order to predict the role of each of these significant variables at different time points during the follow up, depending on whether each of them had already impacted or not, 5-year CS probability after 1, 2, 3 and 5 years had elapsed since treatment was computed (Table 3, Fig. 3).

As described in Table 3, the CS of the entire study population showed a mild decrease after the first 2 years elapsed since RFA and, subsequently, a sharper impairment of SR from the 3rd year onward: this characteristic was explored by analyzing the relationship between CS and the degree of liver disease and tumor features.

Clinical and demographic parameters, namely, age and CP score, did not show any decrease in standardized mean differences over time, being younger patients with preserved liver function always having a better prognosis with a CS 5-year survival greater by at least 10% at all time points with respect to those aged more than 65 years and of CP stage B. Such a difference tended to even increase from the 3rd year onward.

On the other hand, tumor factors (AFP and CLIP) had an impact on shortening survival only for the first 2 years from RFA. In particular, 5-year CS rates of patients of CLIP stage 0 were more than doubled as compared with more advanced individuals in the first 2 years after treatment and presented only mild differences from the 3rd year onward ($d = 0.27$ and 0.18 at 3 and 5 years after RFA, respectively). AFP, dichotomized by the median value, showed a similar behavior, although with lower mean differences between subgroups ($d = 0.44$, 0.18 and 0.11 after 2, 3 and 5 years had elapsed since RFA, respectively).

Table 2 Three-, 5- and 10-year survival rates in relationship to patients' characteristics

Variable	3 years	5 years	10 years	<i>P</i>
All patients (<i>n</i> = 125)	80%	56%	19%	–
Age, years				0.01
≤65 (<i>n</i> = 39)	89%	74%	33%	
>65 (<i>n</i> = 86)	75%	47%	0%	
Sex				0.25
Male (<i>n</i> = 100)	76%	51%	10%	
Female (<i>n</i> = 25)	84%	60%	29%	
Etiology				0.6
HCV (<i>n</i> = 77)	88%	61%	27%	
HBV (<i>n</i> = 26)	69%	50%	9%	
Other (<i>n</i> = 22)	63%	41%	14%	
Child–Pugh				<0.001
A (<i>n</i> = 109)	82%	61%	40%	
B (<i>n</i> = 16)	52%	19%	14%	
AFP				0.01
≤25 UI/mL (<i>n</i> = 62)	84%	72%	40%	
>25 UI/mL (<i>n</i> = 63)	79%	52%	14%	
Portal hypertension†				0.8
Yes (<i>n</i> = 92)	80%	58%	19%	
No (<i>n</i> = 33)	79%	51%	18%	
MELD				0.44
≤9 (<i>n</i> = 70)	80%	58%	21%	
>9 (<i>n</i> = 55)	80%	53%	16%	
Maximum diameter				0.47
≤35 mm (<i>n</i> = 94)	81%	57%	23%	
>35 mm (<i>n</i> = 31)	74%	51%	0%	
BCLC				0.24
0 (<i>n</i> = 14)	93%	71%	33%	
A (<i>n</i> = 111)	78%	54%	17%	
CLIP				0.002
0 (<i>n</i> = 70)	86%	74%	23%	
1 (<i>n</i> = 48)	75%	31%	16%	
2 (<i>n</i> = 7)	57%	43%	0%	
Time to recurrence‡				<0.001
Early (<i>n</i> = 29)	38%	10%	0%	
Late (<i>n</i> = 46)	93%	61%	8%	

P-values are on the basis of Kaplan–Meier estimates and log–rank test. Bolding indicates statistical significance.

†Portal hypertension was defined by at least one of the following: esophageal varices, platelet count of <100 000/μL and splenomegaly.

‡Early recurrence was defined as recurrence within 2 years from surgery and late recurrence as beyond 2 years.

BCLC, Barcelona Clinic Cancer of the Liver; CLIP, Cancer of the Liver Italian Program; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.

As expected, time to tumor relapse (early vs late) showed high standardized mean differences at all time points with a decreasing trend due to the occurrence of late recurrences beyond 2 years after RFA ($d = -0.94$, -0.45 and -0.32 at 2, 3 and 5 years elapsed since the treatment, respectively).

Conditional 3-year RFS is detailed in Table 4. Unlike CS, conditional RFS remained substantially

stable as time elapsed from the treatment and a slight decrease was observed only when assessed since the 3rd year after the treatment. Not unexpectedly, when stratifying the analysis according to clinical and tumoral features, the higher standardized differences were found to be related to AFP, CLIP, maximum diameter (tumor-related factors) together with CP score.

Table 3 Five-year conditional survival rates in relationship to patients' characteristics

Variable	Time elapsed since radiofrequency ablation				
	0-year	1-year	2-year	3-year	5-year
All patients (<i>n</i> = 125)	56%	49%	48%	30%	34%
Age, years					
≤65 (<i>n</i> = 39)	74%	79%	63%	57%	44%
>65 (<i>n</i> = 86)	47%	45%	41%	27%	0%
d	0.64	0.54	0.49	0.55	0.78
Sex					
Male (<i>n</i> = 100)	51%	53%	48%	36%	33%
Female (<i>n</i> = 25)	60%	58%	46%	33%	28%
d	−0.09	−0.04	0.01	0.02	0.12
Etiology					
HCV (<i>n</i> = 77)	61%	57%	42%	38%	35%
HBV (<i>n</i> = 26)	50%	48%	39%	29%	26%
Other (<i>n</i> = 22)	41%	43%	33%	26%	24%
d	0.35	0.18	0.32	0.38	0.29
Child–Pugh					
A (<i>n</i> = 109)	61%	52%	50%	32%	33%
B (<i>n</i> = 16)	19%	25%	27%	0%	0%
d	0.89	0.64	0.54	0.94	0.94
AFP					
≤25 UI/mL (<i>n</i> = 62)	72%	68%	63%	62%	56%
>25 UI/mL (<i>n</i> = 63)	52%	45%	41%	54%	47%
d	0.47	0.52	0.44	0.18	0.11
Portal hypertension†					
Yes (<i>n</i> = 92)	58%	41%	37%	29%	25%
No (<i>n</i> = 33)	51%	47%	41%	33%	38%
d	0.11	−0.28	−0.12	−0.19	−0.37
MELD					
≤9 (<i>n</i> = 70)	58%	49%	41%	31%	30%
>9 (<i>n</i> = 55)	53%	38%	31%	25%	19%
d	0.12	0.42	0.34	0.29	0.31
Maximum diameter					
≤35 mm (<i>n</i> = 94)	57%	57%	53%	46%	38%
>35 mm (<i>n</i> = 31)	51%	46%	38%	36%	34%
d	0.21	0.34	0.51	0.23	0.11
BCLC					
0 (<i>n</i> = 14)	71%	64%	59%	45%	33%
A (<i>n</i> = 111)	54%	49%	42%	38%	21%
d	0.42	0.38	0.39	0.22	0.25
CLIP					
0 (<i>n</i> = 70)	74%	65%	66%	37%	31%
1 (<i>n</i> = 48)	31%	28%	18%	21%	25%
2 (<i>n</i> = 7)	43%	20%	0%	0%	0%
d	0.55	0.50	0.68	0.27	0.18
Time to recurrence‡					
Early (<i>n</i> = 29)	10%	6%	9%	0%	0%
Late (<i>n</i> = 46)	61%	45%	38%	28%	13%
d	−0.87	−0.83	−0.94	−0.45	−0.32

The 5-year conditional survival represents the probability of surviving an additional 5 years, given that the person has already survived *x* years (*x* = time elapsed since radiofrequency ablation).

d is the standardized difference; d values lower than 0.1 indicate very small differences, d values between 0.1 and 0.3 indicate small differences, d values between 0.3 and 0.5 indicate moderate differences, and d values greater than 0.5 indicate large differences.

†Portal hypertension was defined by at least one of the following: esophageal varices, platelet count of <100 000/μL and splenomegaly.

‡Early recurrence was defined as recurrence within 2 years from radiofrequency ablation and late recurrence as beyond 2 years.

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.

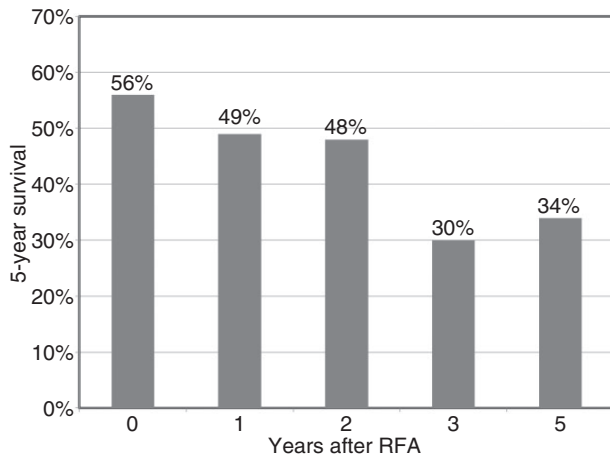


Figure 3 Five-year conditional survival of the whole study population, estimated at baseline, 1, 2, 3 and 5 years from the treatment.

DISCUSSION

TRADITIONALLY, THE TUMOR outcome is described as median OS time or 5-year SR, which reflect the survival of an entire cohort and are not informative for individual patients. All that the tumor survivors care about is the probability of surviving the next years given survival to a specific period of time. The observed SR cannot answer this important question. In contrast, the conditional probability of survival can predict yearly SR when patients survive for a specific period of time.⁷ Accordingly, CS information is potentially of great interest to patients, clinicians and researchers as it quantifies a patient's changing risk profile over time.

A number of previously published studies revealed increasing trends of CS from the first years after treatment onward in several fields of oncology, exploring CS patterns in cancer of the central nervous system, ovary, head and neck, breast, colorectum and other sites.^{8,9,16–18}

Recently, a paper published by the Bologna group has found that the impact of different variables influencing survival in HCC patients after hepatic resection is not linear over time: in particular, the 5-year CS of patients with preserved liver function (without portal hypertension and with MELD <9) always remained better at all time points while tumor factors had an impact on shortening survival only for the first 2 years.¹⁰

To the best of our knowledge, the current study is the first analysis aimed at defining CS patterns in HCC patients undergoing non-surgical ablative therapies, specifically percutaneous RFA.

It is well known that patients treated with loco-regional therapies constitute a different subset with respect to surgical ones, as they often present a more deteriorated liver function; therefore, it would be of interest to define the impact of different variables, particularly those related to liver function, in the field of ablative treatments.

In fact, in our series, 74% of patients presented clinical features of portal hypertension and 13% were of CP stage B, such percentages being dramatically higher in comparison with those reported by Cucchetti *et al.*¹⁰

In this study, in a setting of patients with more advanced underlying liver disease, we confirm that conventional tumor features, namely, AFP and CLIP score, are indeed, as expected, predictors of survival but only in the first 2 years. Patients remaining tumor recurrence-free for the first 2 years return to the same survival estimates as patients with more favorable tumor features. On the other hand, liver function and clinical parameters, such as CP score and age, maintained an important difference between subgroups at all time points, thus meaning a constant impact of these variables on CS over time.

All these differences could not be captured by conventional assessment modalities of survival; hence, the importance of our analysis in this field.

It is common knowledge that survival after radical therapies in HCC patients is affected by time to tumor recurrence, as those that recur within 2 years from treatment have a poorer prognosis with respect to those experiencing late recurrence.^{19–21} Such a finding is confirmed in our series, as the higher standardized mean differences in CS between subgroups are determined by this variable (Table 3). Thus, the careful follow up and optimal management of earlier recurrences are of great importance after RFA, because they influence long-term survival regardless of other clinical or tumoral features, as shown in our series.

Overall, as a consequence of the more advanced characteristics of our patients in comparison with previous published series, CS of the entire study cohort showed a decreasing trend over time elapsed since RFA. This finding, in contrast to the data published by Cucchetti *et al.*,¹⁰ explains how even in RFA patients who achieve the radical treatment of neoplasia, the long-term prognosis is affected by the evolutionary clinical course of the underlying liver disease. Instead, in surgical patients, both short- and long-term survival are mainly affected by tumor recurrence, as only those with preserved liver function are operated, thus meaning a marginal role of

Table 4 Three-year conditional recurrence-free survival rates in relationship to patients' characteristics

Variable	Time elapsed since radiofrequency ablation			
	0-year	1-year	2-year	3-year
All patients (<i>n</i> = 125)	58%	54%	52%	45%
Age, years				
≤65 (<i>n</i> = 39)	60%	59%	53%	47%
>65 (<i>n</i> = 86)	47%	39%	42%	37%
d	0.64	0.59	0.39	0.56
Sex				
Male (<i>n</i> = 100)	41%	43%	40%	38%
Female (<i>n</i> = 25)	68%	58%	51%	45%
d	−0.59	−0.34	−0.31	−0.32
Etiology				
HCV (<i>n</i> = 77)	54%	43%	41%	38%
HBV (<i>n</i> = 26)	63%	57%	59%	47%
Other (<i>n</i> = 22)	41%	43%	40%	40%
d	−0.25	−0.28	−0.22	−0.21
Child–Pugh				
A (<i>n</i> = 109)	69%	65%	58%	49%
B (<i>n</i> = 16)	38%	33%	36%	28%
d	0.72	0.74	0.64	0.74
AFP				
≤25 UI/mL (<i>n</i> = 62)	72%	68%	63%	52%
>25 UI/mL (<i>n</i> = 63)	38%	35%	26%	14%
d	0.87	0.72	0.84	0.88
Portal hypertension†				
Yes (<i>n</i> = 92)	48%	41%	47%	39%
No (<i>n</i> = 33)	61%	57%	54%	48%
d	−0.21	−0.28	−0.11	−0.12
MELD				
≤9 (<i>n</i> = 70)	59%	57%	54%	48%
>9 (<i>n</i> = 55)	52%	49%	45%	39%
d	0.04	0.12	0.18	0.24
Maximum diameter				
≤35 mm (<i>n</i> = 94)	67%	58%	53%	49%
>35 mm (<i>n</i> = 31)	38%	33%	38%	31%
d	0.51	0.49	0.51	0.43
BCLC				
0 (<i>n</i> = 14)	75%	68%	63%	55%
A (<i>n</i> = 111)	52%	49%	47%	38%
d	0.31	0.38	0.21	0.38
CLIP				
0 (<i>n</i> = 70)	68%	65%	59%	47%
1 (<i>n</i> = 48)	51%	48%	41%	36%
2 (<i>n</i> = 7)	33%	31%	19%	15%
d	0.45	0.54	0.62	0.57

The 3-year conditional recurrence-free survival represents the probability of surviving without experiencing tumor recurrence an additional 3 years, given that the person has already survived *x* years (*x* = time elapsed since radiofrequency ablation).

d is the standardized difference; d values lower than 0.1 indicate very small differences, d values between 0.1 and 0.3 indicate small differences, d values between 0.3 and 0.5 indicate moderate differences, and d values greater than 0.5 indicate large differences.

†Portal hypertension was defined by at least one of the following: esophageal varices, platelet count of <100 000/μL and splenomegaly.

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CLIP, Cancer of the Liver Italian Program; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease.

underlying liver disease in defining prognosis in such patients.^{10,20}

Unlike CS, conditional RFS remained substantially stable as time elapsed from the treatment and a slight decrease was observed only at 3 years after RFA (Table 4). Such a finding confirms the need for a careful surveillance program in HCC patients treated with radical therapies, in particular in the first years after the treatment when recurrences are more aggressive. Not unexpectedly, the higher standardized differences were found related to AFP, CLIP, maximum diameter (tumor-related factors) together with CP score, factors well-known to be predictors of tumor recurrence in HCC patients.

This information may be of interest for further discussion in the field of the best therapeutic choice in HCC patients within the conventional tumor transplant criteria who are also eligible for curative ablative treatments, such as RFA. Percutaneous ablative treatments are radical therapies in BCLC 0/A patients but, unlike hepatic resection, are often performed in the presence of portal hypertension and other clinical features of liver cirrhosis; therefore, the long-term prognosis is invariably affected by the underlying liver disease. OLT obviates the aforementioned problems as it represents a definitive cure for both HCC and chronic hepatopathy, hence our results speak in favor of a more aggressive management of these patients. Furthermore, a better knowledge of the role played by different variables on survival at different time points after cure could be extremely important in judging the opportunity and the correct timing, as well as the length of therapy, of adjuvant treatments actually under investigation.

Our study has a number of strengths. It is the first work that focuses on the analysis of CS in HCC patients treated with an ablative therapy, specifically, percutaneous RFA. Furthermore, our paper analyzes the main prognostic variables for survival at baseline and at different time points in a subset of patients with more advanced liver disease and so with more confounders in comparison with previous studies. Lastly, the results of our series, strengthened by the very long follow up, outline the need for a redefinition of the correct therapeutic choice, particularly of the indications to transplant, based on the better knowledge of patients' long-term prognosis influenced by either baseline and evolutionary parameters. We think that the broad evaluation of patient survival based on tumoral and clinical variables captured not only at baseline but in their trend throughout a long time-span may be of value in both the proper planning of a therapeutic algorithm and the

prevention of recurrences (adjuvant setting and post-RFA surveillance).

On the other hand, our study presents some weaknesses, mainly due to the retrospective nature of our analysis and the small number of patients. However, complete information was obtained and verified for all patients in the study and this, in addition to the long study follow up, can obviate possible biases.

In summary, we have shown that CS for HCC patients changes over time and can be used as an important adjunct to traditional survival statistics.

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