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Virologic control and severity of liver disease determine survival after radiofrequency ablation of hepatocellular carcinoma on cirrhosis

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ABSTRACT

Background: We aimed to identify the main determinants of long-term overall survival (OS), including virologic control, and recurrence after radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) on cirrhosis.
Methods: Cirrhotic patients treated by RFA for HCC within Milan criteria were included. Associations between patient features and events were estimated by the Kaplan–Meier method with the log rank test and using uni/multivariate Cox models.
Results: 389 cirrhotic patients (Child–Pugh A 86.6%, 473 tumors) were included. OS was 79.8%, 42.4% and 16%, and overall tumor recurrence 45%, 78% and 88% at 2, 5 and 10 years, respectively. In multivariate analysis, age, Child–Pugh, GGT, HCC near major vessels, esophageal varices, alkaline phosphatase and HBV predicted OS. Gender, ALT, AFP and alcohol intake were associated with tumor recurrence. Multinodular HCC (19.5%) was associated with risk of tumor recurrence outside Milan criteria. HBV patients had longer OS than other patients (P = 0.0059); negative HBV PCR at RFA was associated with decreased tumor recurrence (P = 0.0157). Using time-dependent analysis in HCV patients, a sustained virologic response was associated with increased OS (124.5 months) compared to other patients (49.2 months, P < 0.001).
Conclusion: Virologic response and severity of underlying liver disease were the main determinants of long-term OS after RFA for HCC developing on cirrhosis.

1. Introduction

Percutaneous radiofrequency ablation (RFA) is one of the main curative treatments available for hepatocellular carcinoma (HCC) developing on cirrhosis based on the Barcelona Clinic Liver Classification (BCLC) [1–3]. Several studies have confirmed the efficacy of RFA in HCC smaller than 3 cm, with 5-year overall survival (OS) ranging from 40 to 70%; however, controversy remains concerning the best therapeutic strategy, i.e. RFA or liver resection, for these patients [4–9]. New RFA techniques have emerged in the last few years, including no-touch multi-bipolar RFA associated with improved local control in larger HCC between 3 and 5 cm [10,11]. However, results of percutaneous RFA remain impaired by a high rate of tumor recurrence, varying from 55% to 80% at 5 years [4–7]. Tumor recurrence can be described based on spatial distribution with local (near the ablation site) or distant (far from the ablation site) recurrence, and also based on temporal distribution with early (within 2 years after treatment) and late recurrence (more than 2 years after treatment) [2,12].

Most studies reporting long-term outcome at 10 years after RFA for HCC included Asian patients with hepatitis B (HBV) or hepatitis C (HCV) liver disease [6,7]. European patients are usually older, with chronic alcohol intake and metabolic syndrome, more advanced

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liver failure, portal hypertension and co-morbidities, explaining the limited number of candidates for resection [13]. Moreover, while sustained virologic responses (SVR) and maintained virologic responses (MVR) in HCV and HBV cirrhotic patients without HCC have been associated with increased OS and decreased HCC occurrence, robust data are still lacking in cirrhotic patients with HCC treated by RFA [14,15].

The aim of this study was to describe long-term results of RFA as a first-line treatment in Western cirrhotic patients with HCC falling within Milan criteria. We also sought to determine prognostic factors in survival and recurrence, including the impact of antiviral treatments.

2. Materials and methods

2.1. Patients

We conducted a retrospective analysis of patients prospectively treated and followed up at a tertiary center at Jean Verdier Hospital, Bondy, France (see Section 2 for data recorded). Inclusion criteria were: (1) patients >18 years with cirrhosis (histologically proven); (2) HCC diagnosed by histology or non-invasive criteria using contrast-enhanced CT scan or MRI according to EASL criteria [16]; (3) HCC BCLC 0 or A within Milan criteria (a single nodule ≤5 cm or ≤3 nodules ≤3 cm without extrahepatic metastasis or tumor portal thrombosis); (4) no previous treatment for HCC; and (5) treatment by percutaneous RFA between 2005 and 2015. A description of RFA treatments is detailed in Supplementary data.

2.2. Follow-up and endpoints

Patients with HCC underwent a prospective follow-up in our unit with clinical, biological and triple-phase contrast material-enhanced CT or MR imaging, initially assessed 1 month after ablation, and thus every 3 months during the first 2 years and then every 6 months after 2 years; follow-up ended in December 2016. Adverse events related to RFA were classified using the Dindo Clavien classification [17].

OS was determined between the date of RFA until death or the date of the most recent follow-up visit prior to December, 2016. For patients who died during the follow-up period, cause of death was classified either as HCC-related, liver disease independently of HCC, not liver-related or unknown. Time to recurrence was determined between the date of RFA until tumor recurrence, or the date of the most recent follow-up visit prior to December, 2016. Data in patients who underwent liver transplantation were censored from the study at the date of transplantation. Primary efficacy rate was defined as the percentage of target tumors successfully eradicated following the initial procedure. Tumor recurrence patterns were defined as local (development of HCC next to or within the ablation zone, including treatment failure as previously defined), distant (new HCC in other segments or in the same segment distant from the treated area), early (within 2 years after ablation) or late recurrence (more than 2 years after ablation). Moreover, we classified tumor recurrence according to tumor burden, recurrence within Milan criteria and recurrence outside Milan criteria.

2.3. Statistical analyses

Characteristics of patients were presented as medians [range] for continuous variables, and as numbers (percentages) for categorical data.

Times to events were estimated from the last procedure, and the incidence of events was estimated by the Kaplan–Meier method and compared between the groups of patients using the log-rank test. Association between variables and events was conducted using univariate Cox proportional hazards regression models. All variables with a P value <0.10 were included in a multivariate Cox regression model using backward stepwise elimination, computing the estimate of the hazard ratio (HR) along with their 95% CI. The association between variables and tumor recurrence outside and inside Milan criteria was performed using univariate and multivariate logistic regression models in patients developing HCC. An extensive description of statistical analysis is detailed in Supplementary data.

3. Results

3.1. Characteristics of the population, technical efficacy and safety of radiofrequency ablation

A total of 389 consecutive patients with cirrhosis and HCC within Milan criteria received percutaneous RFA as a first-line treatment between 2005 and 2015 (main characteristics of patients are summarized in Table 1). Patients were mainly male (76.6%), with a median age of 66 years [39–90]. Cirrhosis was due to chronic alcohol intake in 54.6%, HCV in 42.8%, metabolic syndrome in 32.0% and HBV in 11.1% of cases (40.6% with mixed etiologies), and was classified as Child–Pugh A in 86.6% of cases. Mean tumor size was 25 mm [7–50], with a median serum AFP level of 7 ng/ml [1–19, 442]; 19.5% of patients had multiple HCC.

Primary efficacy rate of the procedure was 86.1%, and 13.9% of patients required more than one procedure to achieve complete ablation (obtained in 99.5% of patients using one or more procedures). We observed 17 severe complications classified Dindo Clavien IIIa–V (4.4%) (liver failure, n = 6; digestive perforation, n = 6; hepatic abscess, n = 3; Tako-tsubo, n = 1; hemothorax, n = 1; drained pleural effusion, n = 1), including 2 deaths due to RFA (0.5%, 1 due to liver failure and 1 due to colon perforation).

3.2. Risk factors in long-term overall survival

Median OS was 52.0 months, while OS at 2, 5 and 10 years was 79.8%, 42.4% and 15.8% (Fig. 1A), respectively; 205 patients died, related to HCC in 49.5% of cases, to liver disease independently of HCC in 24.0% of cases, not liver-related in 18.1% of cases and unknown in 8.3% of cases (Fig. 1B). Forty-five patients (11.6%) were lost to follow-up. A total of 35 patients were transplanted during follow-up (20 for HCC recurrence and 15 for liver failure; median time from RFA ablation to transplantation was 18 months); 5-year OS post-liver transplantation was 84%, and only 1 patient had tumor recurrence post-transplantation.

In multivariate analysis, age (HR = 1.06 [95%CI: 1.04; 1.08]), Child–Pugh B/C score (HR = 2.75 [95% CI: 1.80; 4.20]), GGT >2N (HR = 1.53 [95%CI: 1.10; 2.13]), esophageal varices grade 2 or 3 (HR = 1.86 [95%CI: 1.29; 2.69]) and alkaline phosphatase >1.5N (HR = 2.68 [95%CI: 1.73; 4.15]) were independently associated with higher risk of death (Table 2 and Fig. 2). However, among the 389 HCC patients, only 224 had a single etiology (HBV, HCV, chronic alcohol intake or NASH alone) and we observed a non-significant statistical difference in overall survival between the 4 groups of patients with only one etiology (Supplementary Fig. 7).

Patients considered as resectable had longer median OS (70.1 months) than patients considered as non-resectable (49.3 months, P = 0.008) (Supplementary Fig. 1A), with no significant differences in term of overall tumor recurrence (Supplementary Fig. 1B). The 2, 5- and 10-year OS rates were, respectively, 87.2%, 61.9% and 32.3% for resectable patients and 78.2, 38% and 12.5% for non-operable patients.

Table 1
Baseline characteristics of the 389 cirrhotic patients.

Baseline characteristics		Available data	Total N = 389
Gender (male)[a]		389	298 (76.6)
Age (years)[b]		389	66 [39–90]
Etiologies of cirrhosis	Chronic alcohol intake[a]	388	212 (54.6)
	Metabolic syndrome[a]	388	124 (32.0)
	Hepatitis B[a]	388	43 (11.1)
	Hepatitis C[a]	388	166 (42.8)
Child–Pugh classification	A[a]	389	337 (86.6)
	B[a]	389	49 (12.6)
	C[a]	389	3 (0.8)
Signs of portal hypertension	Ascites[a]	389	18 (4.6)
	Esophageal varices grade II–III[a]	329	75 (22.8)
	Platelet count <100,000 mm^3[a]	386	144 (37.3)
Biology at time of RFA	Alk P (xN)[b]	378	1.0 [0.3–5.0]
	GGT (xN)[b]	386	2.6 [0.3–40.0]
	AST (xN)[b]	386	1.2 [0.1–18.0]
	ALT (xN)[b]	386	1.0 [0.3–8.5]
	Total bilirubin (μmol/l)[a]	386	13 [3–93]
	Albumin (g/L)[a]	344	38.4 [24–54.1]
	Prothrombin time (%)[a]	387	76 [39–100]
HCC features	1 nodule[a]	389	313 (80.5)
	2 nodules[a]	389	68 (17.5)
	3 nodules[a]	389	8 (2.0)
	Tumor size (mm)[b]	389	25 [7–50]
	Larger nodule >30 mm[a]	389	98 (25.2)
	Histologically proven HCC[a]	389	270 (69.4)
	Serum AFP (ng/ml)[b]	377	7 [1–19,442]
RFA treatment	Complete ablation[a]	389	387 (99.5)
	>1 RFA for complete ablation[a]	380	53 (13.9)
Complications (Dindo Clavien classification)	Dindo Clavien I[a]	386	38 (9.8)
	Dindo Clavien II[a]	386	24 (6.2)
	Dindo Clavien IIIa[a]	386	7 (1.8)
	Dindo Clavien IIIb[a]	386	2 (0.5)
	Dindo Clavien IVa[a]	386	6 (1.6)
	Dindo Clavien V[a]	386	2 (0.5)

Alk P, GGT, AST and ALT were reported using fold of the upper limit of normal.
[a] Number (percentage).
[b] Median [range].

3.3. Risk factors in tumor recurrence

Median time to overall recurrence was 26.9 months, and cumulative overall tumor recurrence at 2, 5 and 10 years was 45.6%, 78.4% and 87.7%, respectively (Fig. 1C). In multivariate analysis, male gender (HR = 1.47 [95%CI: 1.05; 2.04]), AFP level >200 ng/ml (HR = 1.57 [95%CI: 1.11; 2.20]) and ALT >2N (HR = 1.47 [95%CI: 1.08; 2.00]) were independently associated with more frequent tumor recurrence, whereas HBV (HR = 0.63 [95%CI: 0.40; 0.98]) was independently associated with lower risk of tumor recurrence (Table 2 and Supplementary Fig. 2). Among the 240 patients with tumor recurrence, 29% harbored a recurrence outside Milan criteria. A multinodular tumor (HR = 2.00 [95%CI: 1.02; 3.85]) was the only variable independently associated with a higher rate of tumor recurrence outside Milan criteria (Supplementary Table 1). After HCC relapse, 171 patients (71%) were retreated using percutaneous ablation, with a lower rate of patients amenable to percutaneous treatments (38%) for relapse outside Milan criteria compared to 88% of patients re-treated by percutaneous ablation after relapse within Milan criteria. Among the 20 patients transplanted for HCC recurrence, 19 were transplanted after tumor relapse within Milan criteria, whereas only 1 patient was transplanted after tumor recurrence outside Milan criteria following efficient tumor downstaging.

The cumulative incidence of local tumor recurrence was 11.9% at 2 years, and then reached a plateau of 17.5% local recurrence after 3 years of follow-up (Fig. 1D). HCC localized near major vessels (HR = 2.11 [95%CI: 1.52; 6.36]) and the presence of esophageal varices grade 2 or 3 (HR = 2.40 [95%CI: 1.52; 4.59]) were independently associated with a higher rate of local tumor recurrence (Supplementary Table 5 and Supplementary Fig. 3). In contrast, a serum AFP level >200 ng/ml (HR = 1.65 [95%CI: 1.10; 2.46]), male gender (HR = 1.48 [95%CI: 1.05; 2.09]), Child–Pugh B/C (HR = 1.78 [95%CI: 1.14; 2.78]) and ALAT >2N (HR = 1.58 [95%CI: 1.15; 2.17]) were independently associated with increased distant tumor recurrence, whereas HBV infection (HR = 0.55 [0.34; 0.90]) was associated with a lower incidence of distant tumor recurrence (Supplementary Table 5 and Supplementary Fig. 4).

Overall tumor recurrence (HR = 4.57 (CI95% = 3.24–6.44), P < 0.001), local tumor recurrence (HR = 2.08 (CI95% = 1.41–3.07) P < 0.001) and distant tumor recurrence (HR = 4.23 (CI95% = 3.04–5.88) P < 0.001) were associated with poor overall survival using a univariate Cox model and time-dependent analysis.

We observed 42.2% of early tumor recurrence during the 2 years following treatment. An AFP level >200 ng/ml, ascites and GGT >2N were predictive factors for early tumor relapse (Supplementary Table 6 and Supplementary Fig. 5). In contrast, ALAT >2N (HR = 2.00 [95%CI: 1.24; 3.24]) was independently associated with a higher rate of late tumor recurrence, whereas HBV infection (HR = 0.30 [95%CI: 0.12; 0.73]) was associated with a lower incidence of late tumor recurrence in multivariate analysis (Supplementary Table 6 and Supplementary Fig. 6).

3.4. Effects of the virologic response on outcome in patients with HBV- or HCV-related cirrhosis

As shown in previous analyses, patients with chronic HBV infection (n = 43) had increased OS (median 119.6 months) compared to patients with other etiologies of liver disease (median 51.0 months, P value = 0.0059) (Fig. 3A), as well as decreased distant tumor

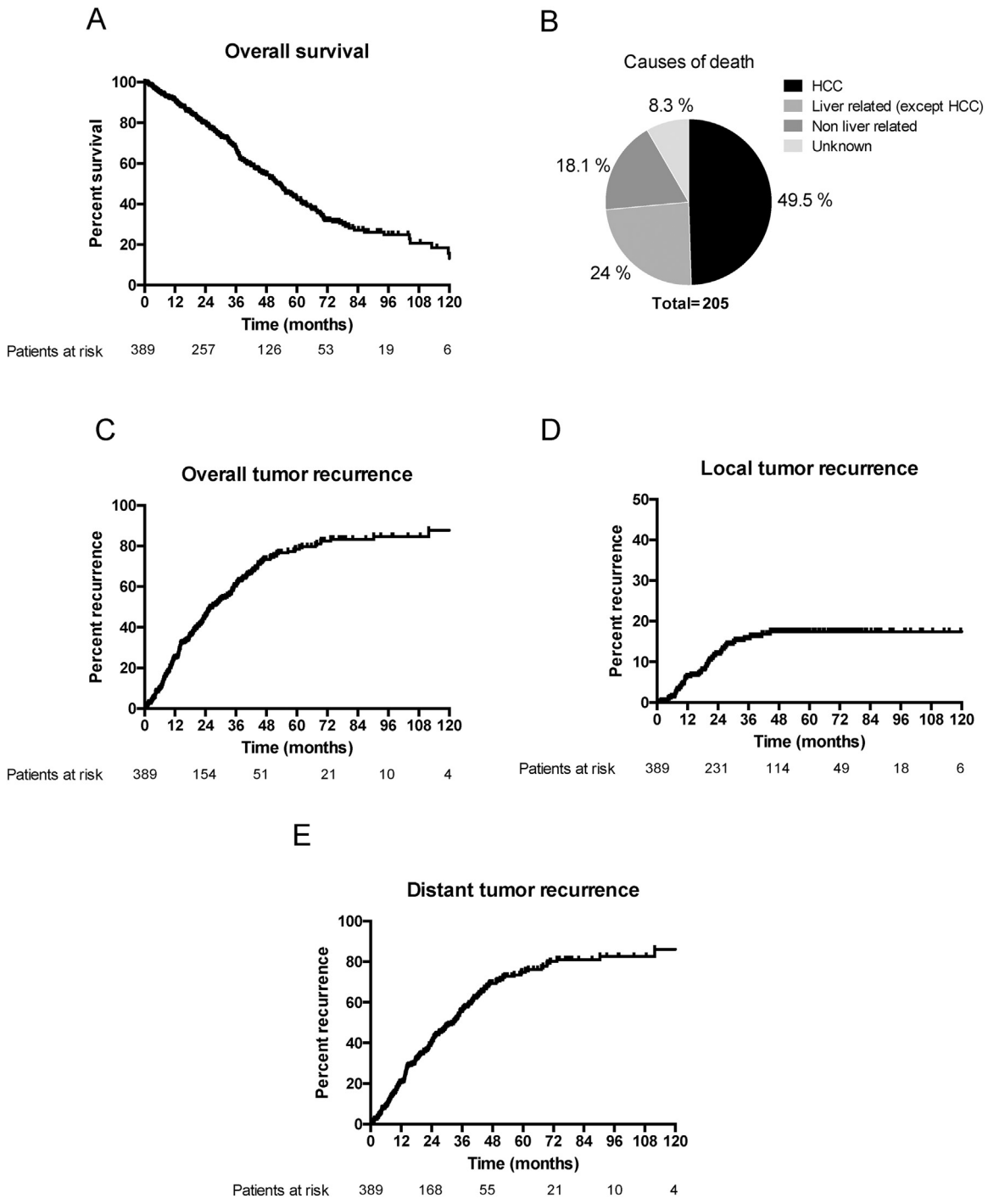

Fig. 1. OS and tumor recurrence.
OS (A) and causes of death are reported (B). We also considered overall tumor recurrence (C), local tumor recurrence (D) and distant tumor recurrence (E) using the Kaplan–Meier method.

recurrence (median time to distant recurrence was 59 months for HBV patients versus 32 months for other patients; P value = 0.024) (Fig. 3B), and all persisted in multivariate analysis (Tables 2 and supplementary Table 5).

A decrease in tumor recurrence in HBV patients was mainly observed for late tumor recurrence but not for early tumor recurrence (Supplementary Fig. 6B and Supplementary Table 6).

Data on AVT and HBV PCR were available for 41 patients: 9 patients received no AVT at the time of RFA due to spontaneous negative HBV PCR or negative HBV PCR induced by previous AVT, and 32 patients received AVT introduced before (n = 30) or after RFA (n = 2). Thirty out of 32 patients receiving AVT obtained an MVR response before RFA or during follow-up after RFA. Taking into account HBV PCR at the time of RFA, patients with negative PCR (MVR or negative PCR without treatment) had longer median time to tumor recurrence (92 months) than patients with positive PCR (14 months, P value = 0.02) (Fig. 3D). No significant difference was observed in terms of median OS (121 months for patients with negative PCR versus 70 months for patients with positive PCR, P value = 0.11) (Fig. 3C).

Table 2
Univariate and multivariate analysis of overall survival and overall tumor recurrence (Cox proportional hazard regression models).

	Univariate analysis			Multivariate analysis		
	HR	CI 95%	P value	HR	CI 95%	P value
Overall survival						
Age	1.03	1.01–1.05	<0.001	1.06	1.04–1.08	<0.001
Sex (male)	1.12	0.80–1.56	0.512			
Chronic alcohol intake	1.35	1.02–1.79	0.034	1.52	1.09–2.13	0.015
Metabolic syndrome	0.91	0.68–1.23	0.557			
HBV	0.46	0.26–0.81	0.007			
HCV	0.99	0.76–1.32	0.998			
Child–Pugh B	2.70	1.86–3.92	<0.001	2.75	1.80–4.20	<0.001
GGT >2N	1.73	1.30–2.31	<0.001	1.53	1.10–2.13	0.011
Alk P >1.5N	2.68	1.87–3.84	<0.001	2.68	1.73–4.15	<0.001
ALT >2N	1.08	0.76–1.53	0.664			
AST >2N	1.06	0.76–1.49	0.716			
Platelet count >100,000 mm^3	1.09	0.81–1.46	0.574			
Ascites	3.34	1.92–5.81	<0.001			
EV grade II or III	1.60	1.13–2.28	0.008	1.86	1.29–2.69	0.001
AFP >200 ng/ml	1.12	0.74–1.70	0.586			
Uninodular HCC	0.84	0.59–1.19	0.327			
HCC >30 mm	1.37	1.04–1.81	0.024			
Subcapsular	1.25	0.93–1.68	0.143			
Under diaphragm	1.31	0.84–2.05	0.236			
Close to colon	1.72	0.76–3.90	0.192			
Close to gall bladder	0.99	0.41–2.41	0.980			
Close to major vessels	1.44	0.93–2.23	0.103			
Overall tumor recurrence						
Age	1.01	0.99–1.02	0.452			
Sex (male)	1.40	1.02–1.93	0.038	1.47	1.05–2.04	0.024
Chronic alcohol intake	0.95	0.74–1.23	0.717			
Metabolic syndrome	0.86	0.65–1.14	0.290			
HBV	0.66	0.43–1.03	0.069	0.63	0.40–0.98	0.040
HCV	1.31	1.02–1.69	0.037			
Child–Pugh B or C	1.41	0.92–2.17	0.111			
GGT >2N	1.29	1.00–1.67	0.050			
Alk P >1.5N	1.00	0.65–1.52	0.990			
ALT >2N	1.44	1.07–1.95	0.017	1.47	1.08–2.00	0.014
AST >2N	1.42	1.05–1.92	0.024			
Platelet count >100,000 mm^3	1.05	0.81–1.37	0.701			
Ascites	1.55	0.82–2.92	0.179			
EV grade II or III	1.15	0.82–1.61	0.417			
AFP >200 ng/ml	1.64	1.12–2.39	0.011	1.57	1.11–2.20	0.010
Uninodular HCC	0.81	0.59–1.12	0.200			
HCC >30 mm	1.29	1.00–1.67	0.052			
Subcapsular	0.96	0.73–1.26	0.752			
Under diaphragm	1.07	0.70–1.64	0.746			
Close to colon	2.11	0.99–4.49	0.052			
Close to gall bladder	1.46	0.75–2.86	0.265			
Close to major vessels	1.29	0.86–1.93	0.216			

AFP: alphafetoprotein; ALT: alanine transaminase; Alk P: alkaline phosphatase; AST: aspartate transaminase; EV: esophageal varices; GGT: gamma glutamyl transferase; HBV: hepatitis B virus; HCV: hepatitis C virus.

Among 163 patients with HCV-related cirrhosis and available data on AVT, SVR were obtained in 54 patients (33%), either before RFA (n = 24) or during follow-up after RFA (n = 30). Using time-dependent analysis, no significant difference was observed in time to tumor recurrence between patients who achieved SVR and patients who did not achieve SVR (Fig. 4A and Supplementary Table 2). Among the 20 DAAs patients who achieved SVR, 3 started DAAs before RFA and 17 after RFA; none of the 3 patients treated by DAA before RFA developed an HCC recurrence. Among the other 17 patients, 13 developed a HCC recurrence, of whom 5 after DAA initiation (3.7 months to 24 months after DAA) (Supplementary Table 7). Moreover, we did not observe an increase in tumor recurrence in patients who achieved SVR using DAA regimens compared to other patients (Fig. 4B), even after using an IPTW-adjusted approach to control for indication bias associated with DAA prescription (Supplementary Table 3).

In contrast, using time-dependent analysis, patients with SVR had increased median OS (median survival not reached at 124.5 months) compared to patients without SVR (49.2 months, P value <0.001) (Fig. 4C). Together with age, Child–Pugh score and esophageal varices grades 2 or 3 and alkaline phosphatase level, SVR (HR = 0.41 [95%CI: 0.21; 0.80], P = 0.009) was independently associated with survival in multivariate analysis (Supplementary Table 4). No significant difference was observed in risk of death between patients with SVR using DAA and other patients (Fig. 4D), even after using an IPTW-adjusted approach (Supplementary Table 3).

4. Discussion

Here we provide the long-term outcome of a large homogeneous cohort of 389 patients with cirrhosis and HCC falling within Milan criteria, naive of previous oncologic treatment and treated by first percutaneous RFA. Most series available in the literature reporting outcomes of up to 8–10 years after RFA were conducted in Asia, mainly in HBV patients in Korea and HCV patients in Japan [6,7]. Extensively described large series of cirrhotic patients from western countries with follow-up of at least 10 years are lacking [4,5,10].

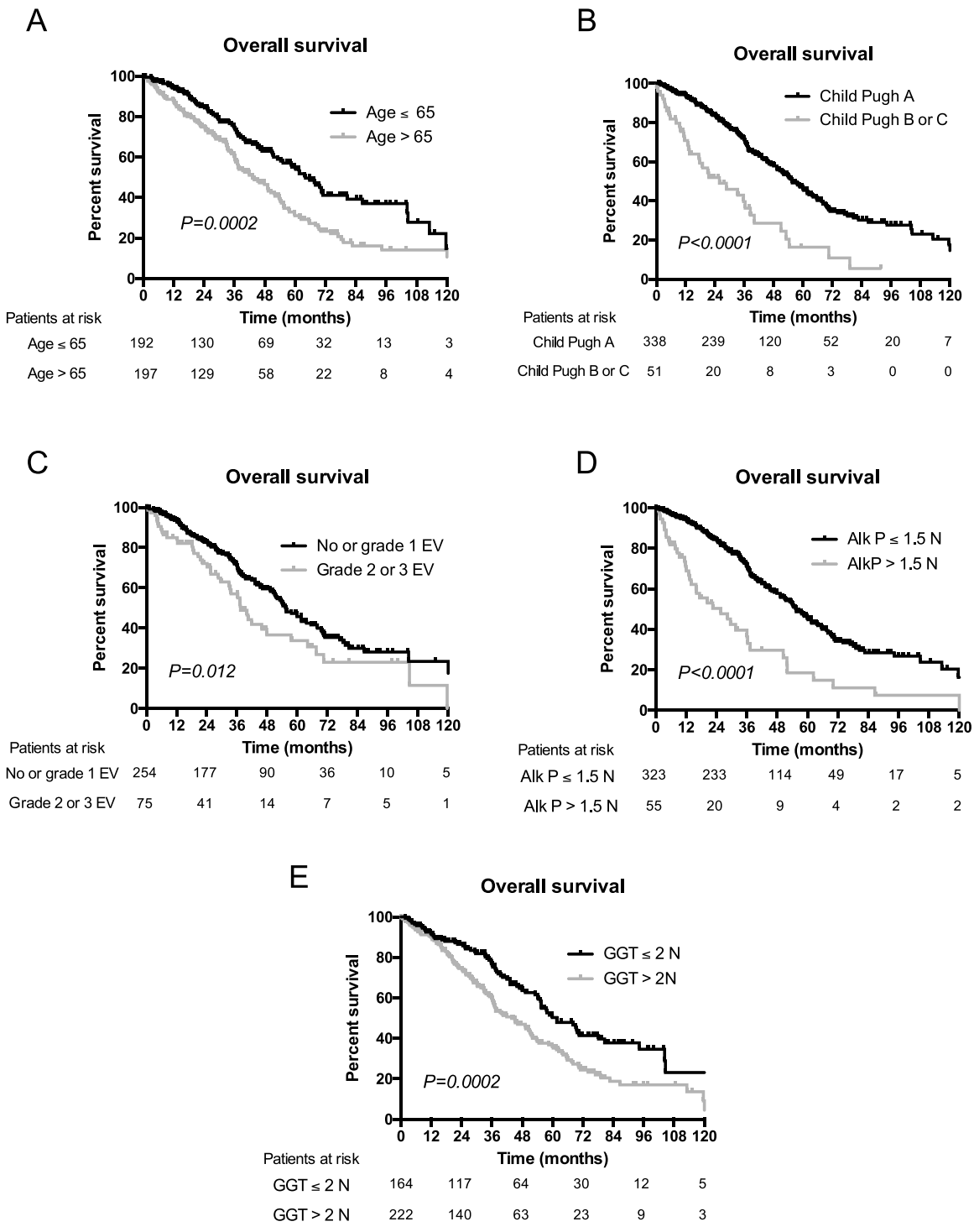

Fig. 2. Survival curves for prognostic factors in OS significant in multivariate analysis.
Prognostic factors associated with OS via multivariate analysis are represented using the Kaplan–Meier method with log rank test: according to age (A), Child–Pugh score (B), grade of esophageal varices (C), level of alkaline phosphatase (D) and level of gamma glutamyl transferase (E).

We obtained 5- and 10-year OS of 42.4% and 15.8%, respectively, with low mortality (0.5%) and morbidity (4.4%). Interestingly, we observed virtually the same outcome in Western cirrhotic patients treated by resection, who showed around 45% survival at 5 years [18]. Patients considered as resectable in our series had longer OS than non-resectable patients, but a similar rate of tumor recurrence. This suggests that differences in survival are mainly due to the degree of liver failure, portal hypertension and co-morbidities, rather than to differences in tumor control [19]. Our series grouped together patients with various etiologies of liver disease (HBV, HCV, metabolic syndrome and excessive alcohol intake) that permitted analysis of the impact of etiology on outcome. Alcohol-related cirrhotic patients had the same OS as patients with HCV-related or metabolically related diseases, suggesting that percutaneous RFA is an effective curative HCC treatment in alcohol-related cirrhotic patients, who are frequently non-resectable due to the presence of portal hypertension and co-morbidities, or are non-transplantable due to persistent alcohol consumption.

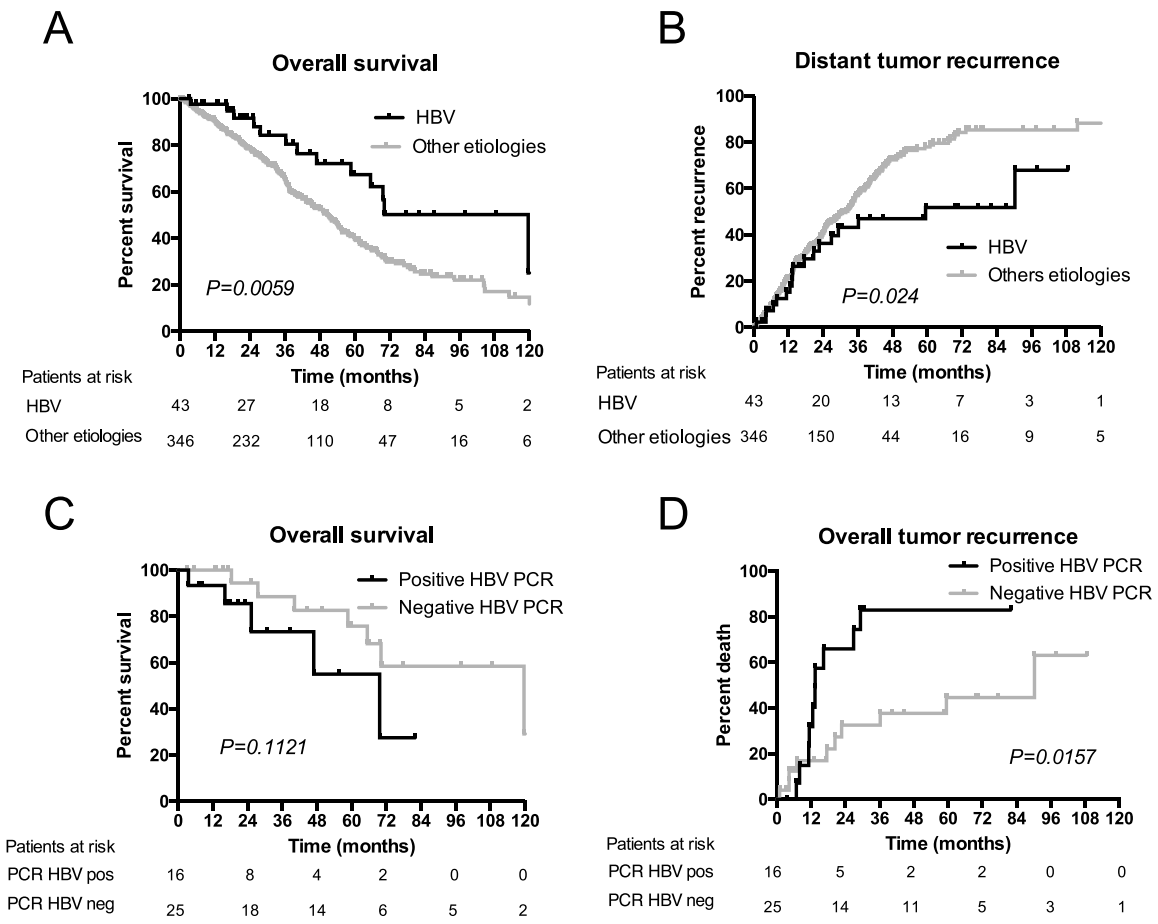

Fig. 3. Survival and tumor recurrence in HBV patients.
OS and distant tumor recurrence according to the presence of HBV infection ((A) for OS and (B) for distant tumor recurrence), and according to the presence of a negative or positive PCR at the time of RFA ((C) for OS and (D) for overall tumor recurrence) are represented using the Kaplan–Meier method with the log rank test.

Severity and activity of underlying liver disease, represented by the Child–Pugh score, endoscopic portal hypertension, GGT level (a marker of the activity of the liver disease due to metabolic syndrome or active alcohol consumption) and HBV infection were the main determinants of long-term survival, whereas classical tumor features at baseline, such as serum AFP, tumor size and number, were not predictive of death.

Analysis of the pattern of recurrence revealed the complex interplay of risk factors linked to spatial and temporal tumor recurrence [20]. We confirmed HCC localized near major vessels as a risk factor in local recurrence due to the decreased temperature induced by blood flow (heat sink effect) [21]. We also found that the presence of portal hypertension at endoscopy was associated with increased risk of local tumor recurrence. A previous study had shown that portal hypertension was associated with increased dropout in HCC patients waiting for liver transplantation due to a weaker response to transarterial chemo-embolization [22].

In contrast, predictors of distant tumor recurrence were a mixture of tumor features such as AFP level and characteristics of underlying liver disease such as ALT, that reflect viral disease activity, HBV infection and Child–Pugh score.

Interestingly, the AFP level was the main predictor of early tumor recurrence in patients treated by RFA, confirming the observation, made after resection, on the role of tumor biology as a key determinant in early recurrence. On the other hand, HBV infection and ALT were the main predictors of late tumor recurrence, emphasizing the role of underlying liver disease and de novo carcinogenesis in late recurrence [20].

Interestingly, tumor size between 3 to 5 cm and multinodular disease were not associated with tumor recurrence or OS in our study, indicating that patients with such tumor features can be efficiently treated by RFA [10,11]. In our series, liver transplantation performed after tumor relapse following a first RFA treatment was associated with satisfactory results, with a 5-year OS following transplantation of 84% and only one patient with recurrence. Based on current results, we need to stress that multinodular HCC was associated with a higher risk of tumor recurrence outside Milan criteria that would thus exclude these patients from salvage liver transplantation. Consequently, in patients with multifocal HCC eligible for liver transplantation, transplantation should be discussed as a first line, with RFA as potential bridge therapy, whereas patients with uninodular HCC could have the sequence RFA first, followed by salvage liver transplantation after tumor recurrence.

We also assessed the impact of viral response in hepatitis B and C patients. In HBV patients, we were unable to compare patients who received treatment to patients without treatment, since all patients received treatment or had spontaneous negative PCR, and nearly all patients receiving AVT obtained MVR during follow-up. However, decreased distant and late tumor recurrence and increased OS in HBV patients independently of other prognostic factors, when compared to patients with other etiologies of liver disease, suggested that viral control in HBV patients could improve prognosis. Moreover, the association between negative HBV PCR at the time of RFA and longer time to tumor recurrence suggests that HBV patients who develop HCC after efficient viral control have a better outcome.

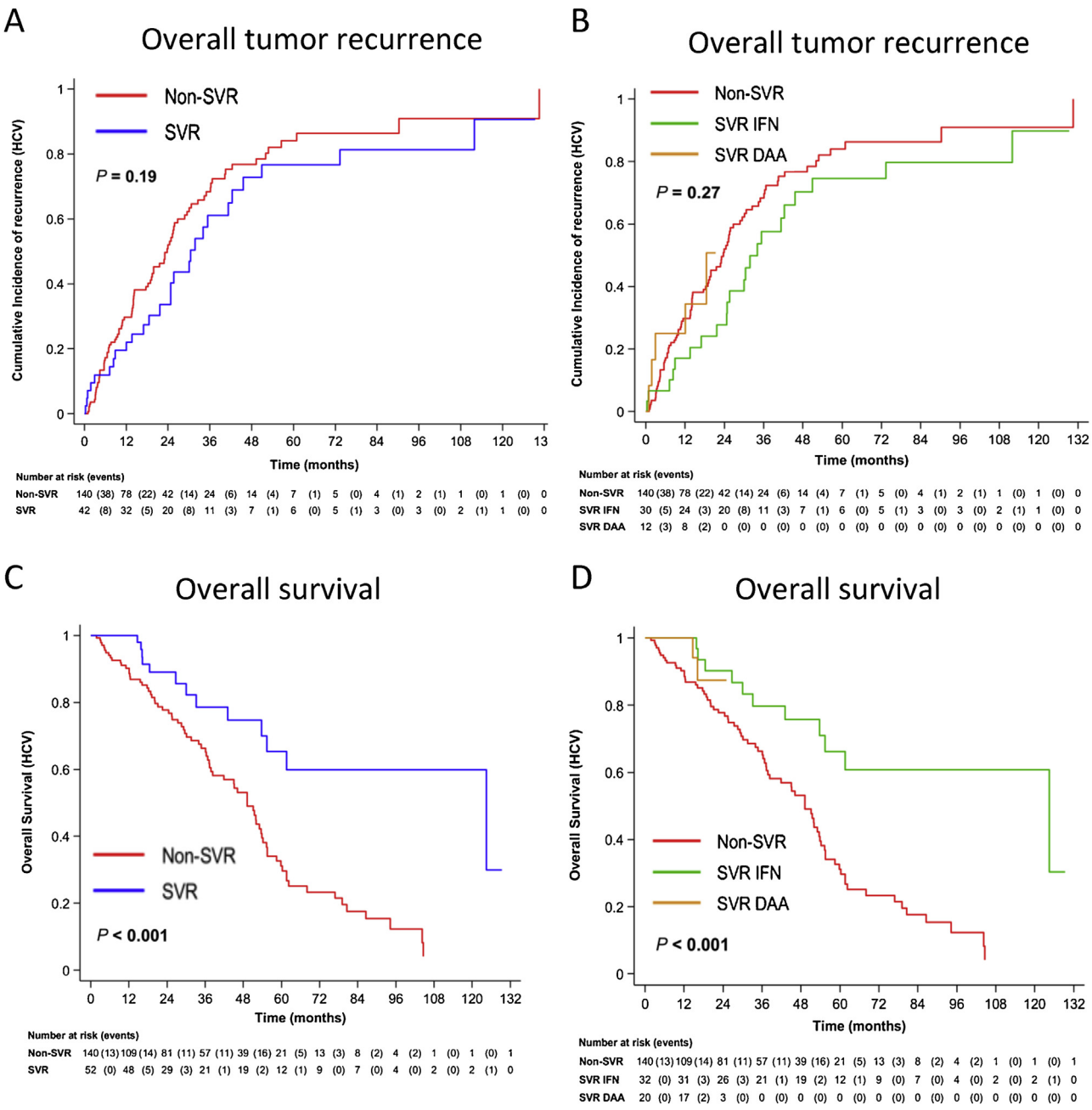

Fig. 4. Effect of sustained virologic response on survival and tumor recurrence in HCV patients.
OS according to the presence or absence of SVR (A), or according to the presence of SVR using an interferon regimen, versus SVR using DAA versus patients without SVR (B) using time-dependent analysis. Overall tumor recurrence according to the presence or absence of SVR (C) or according to the presence of SVR using an interferon regimen, versus SVR using DAA versus patients without SVR (D) using time-dependent analysis. Curves are represented using the Kaplan–Meier method and the log rank test.

Using time-dependent analysis, we also showed that SVR in HCV patients was associated with increased OS independently of other prognostic factors, whereas tumor recurrence was not significantly reduced. This suggests that the main benefit of SVR in HCV patients was related to decreased risk of liver failure. A recent controversy arose concerning an association between DAA treatment and HCC recurrence in patients with HCV-related cirrhosis and previously treated for HCC [23]. Some studies showed an increase in recurrence of HCC shortly after DAA treatment, whereas others did not find any such association [23–26]. Unfortunately, at the time, we did not have enough patients or follow-up to precisely and robustly evaluate a potential role of new DAA upon recurrence of HCC after RFA treatment in HCV-related cirrhosis. More data based on a dedicated multicentric prospective study are required to answer this important question.

Our study underlines the fact that HCC treatment is fundamental, but management of underlying disease is imperative for achieving long-term survival. OS in HBV patients and in HCV patients with SVR rose to 60% at 10 years, suggesting that a subgroup of patients with efficient control of underlying liver disease and efficient initial treatment of their HCC by RFA could attain the same results in OS as with liver transplantation alone, thereby avoiding the need for graft in the context of organ shortage.

In conclusion, despite a high rate of tumor recurrence, the main prognostic factors in long-term survival after RFA for HCC developing on cirrhosis remain the severity of underlying liver disease and

the ability to obtain a virologic response, suggesting that prevention of complications of cirrhosis and treatment of etiology are crucial for improving survival after efficient percutaneous treatment of HCC on cirrhosis. Patients who achieved viral control had prolonged long-term OS close to results obtained after liver transplantation.

Conflict of interest

O Seror received personal fees and non-financial support from Angiodynamics, Olympus and Bayer Schering Pharma and received personal fees from GE as a consultant; N Ganne and P Nahon received personal fees from Bayer Schering Pharma. Other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.07.014.

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