ORIGINAL ARTICLE

Curative versus palliative treatments for recurrent hepatocellular carcinoma: a multicentric weighted comparison

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Abstract

Background: Management of recurrence after surgery for hepatocellular carcinoma (rHCC) is still a debate. The aim was to compare the Survival after Recurrence (SAR) of curative (surgery or thermoablation) versus palliative (TACE or Sorafenib) treatments for patients with rHCC.

Methods: This is a multicentric Italian study, which collected data between 2007 and 2018 from 16 centers. Selected patients were then divided according to treatment allocation in Curative (CUR) or Palliative (PAL) Group. Inverse Probability Weighting (IPW) was used to weight the groups.

Results: 1,560 patients were evaluated, of which 421 experienced recurrence and were then eligible: 156 in CUR group and 256 in PAL group. Tumor burden and liver function were weighted by IPW, and two pseudo-population were obtained (CUR = 397.5 and PAL = 415.38). SAR rates at 1, 3 and 5 years were respectively 98.3%, 76.7%, 63.8% for CUR and 91.7%, 64.2% and 48.9% for PAL (p = 0.007). Median DFS was 43 months (95%CI = 32-74) for CUR group, while it was 23 months (95%CI = 18-27) for PAL (p = 0.017). Being treated by palliative approach (HR = 1.75; 95%CI = 1.14–2.67; p = 0.01) and having a median size of the recurrent nodule>5 cm (HR = 1.875; 95%CI = 1.22–2.86; p = 0.004) were the only predictors of mortality after recurrence, while time to recurrence was the only protective factor (HR = 0.616; 95%CI = 0.54–0.69; p<0.001).

Conclusion: Curative approaches may guarantee long-term survival in case of recurrence.

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Introduction

Although surgery is the main curative approach for hepatocellular carcinoma (HCC), HCC has a very high rate of recurrence of up to 70% at 5 years.[1–3] Tumour recurrence is one of the most significant factors affecting mortality in patients with HCC,[4] and consequently its management after surgical resection is of capital interest to prolong overall survival. The treatment options include repeat liver resection, transarterial therapy, ablative therapy and systemic medical therapies.[5,6] Recently, salvage liver transplant has also been proposed to treat HCC recurrence,[7] but remains controversial due to organ shortage and the overall low rate of patients that may fulfill transplant criteria at the time of recurrence. Among the other treatments, there is a lack of evidence on which is the best option in case of relapse, and even if few reports are already available in literature, no clear indication has been provided. While redo-surgery (RS)[8–10] has been reported to achieve better long-term results than thermoablation (TA),[11] most studies have involved small samples, without a large control group or any comparison, and therefore the outcomes are still not fully supported by the data. Palliative treatments such as trans-arterial chemo-embolization (TACE) and systemic medical therapies such as Sorafenib (SOR) are largely employed in clinical practice albeit no clear survival benefit has been shown. Notwithstanding, in case of relapse, most physicians considered the recurrence as a failure of the curative intent, addressing those patients to palliative care. Therefore this study aimed to investigate the survival outcomes of curative versus palliative treatments in cases of recurrent HCC in a large multicenter cohort of surgical patients. This study was carried out by the Italian hepatocellular carcinoma Recurrence in the Liver Study (He.Rc.O.Le.S.) Group.

Methods

Register information

This retrospective study evaluated data from patients enrolled in the Italian Register of HCC recurrence, promoted by the hepatocellular carcinoma Recurrence in the Liver Study Group (He.Rc.O.Le.S. Group), which currently comprises 30 Italian liver surgery centres. The study was designed as a two-phase study: the first phase, *HERCOLES1*, enrolled patients who had been treated for HCC by surgery across the participating centers from January 2008 to December 2018. The second phase, *HERCOLES2*, is collecting the same data but in a prospective fashion, from September 2019. The study protocol was registered at clinicaltrials.gov (ID = NCT04053231) and followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013). The Ethical Committee of the coordinating centre (San Gerardo Hospital, Monza, Italy, "Monza e Brianza Ethical Committee") reviewed and approved the protocol on 21/12/2018. Data management and statistical analysis were carried out by the Bicocca Clinical Research Office (BiCRO), which actively participate and support the study Group. More information about the *HERCOLES Project* can be found at http://www.hercolesgroup.eu.

Study overview

Analyses were carried out on the retrospective register as per *HERCOLES1* protocol. After analysis, results and discussion were debated collegially with the aim to get the approval from each center. The local Ethical Committee review of the protocol deemed that particular formal approval was not required owing to the retrospective, observational and anonymous nature of this study. Results are reported according to principles of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[12]

Patient selection and study design

All consecutive adult patients (age $\geq$ 18 years) with histologically proven HCC who underwent surgery from January 2008 to December 2018, correctly enrolled in *HERCOLES1* database, were evaluated. Inclusion criteria in this particular study were: (1) patients who underwent surgery for first diagnosis of HCC without previous treatments, which experienced a recurrence; (2) patients whom follow-up was completed at the end of the observational period; (3) a recurrence which has been treated in the participating centers with redo-surgery (RS), thermoablation (TA), trans-arterial chemo-embolization (TACE) or medical treatment with Sorafenib (SOR). Exclusion criteria were (1) microscopic positive surgical margin after the first surgical approach confirmed at the histological specimen, (2) patient dead before first recurrence event; (3) a recurrence which has been treated by surgery as a bridge to transplantation; (4) being treated by salvage-transplant (5) being treated by Best Supportive Care. Patients were then divided according to the recurrence treatment: redo-surgery (RS), thermoablation (TA), trans-arterial chemo-embolization (TACE) and medical treatment with Sorafenib (SOR). Finally, RS and TA were merged to create a curative cohort (CUR), while TACE and SOR joined the palliative group (PAL). The treatment allocation was assessed by multi-disciplinary meetings patient by patient in each participating center - involving hepatobiliary surgeons, hepatologists, medical oncologists, radiologists, interventional radiologists, infectivologists - as the sum of different evaluations about underlying liver function, tumor burden and comorbidities, according to the local protocols of each participating center.

Study aim and end-points

The aim of the study was to retrospectively compare different hepatocellular carcinoma recurrence treatments (divided between curative and palliative approaches) in terms of survival and to identify which factors were associated with mortality and second recurrence after secondary treatments. The primary endpoint was to compare the Survival After Recurrence (SAR) in patients undergoing curative or palliative therapies. The Secondary end-point was to estimate the Disease-Free-Survival (DFS) after curative rather than palliative treatment of the first recurrence. Risk factors for SAR and DFS were also evaluated.

Variables and follow-up

Age, sex, Charlson Comorbidity Index and liver function at presentation were recorded and evaluated at the first visit. In particular, the presence of cirrhosis and its severity was evaluated by expert hepatologists during the disease work-up. Barcelona Clinical Liver Cancer stages (BCLC) were estimated after radiological evaluation. Model for end-stage liver disease (MELD) score, and Child-Pugh score were calculated on the basis of preoperative serum biochemical values and clinical examination. Biochemical tests as albumin and total bilirubin were collected at the time of recovery. Portal hypertension was diagnosed in case of varices at radiological imaging, or in case of platelet count $\leq$100.000 10−6/Liter and presence of splenomegaly ($\geq$ 22 cm in the major diameter at CT scan). The number and diameter of nodules were assessed through preoperative radiologic imaging and confirmed by intraoperative ultrasound either during the staging procedures at the first diagnosis and during the follow-up time in case of recurrence. Presence of concomitant local extrahepatic spread was assessed radiologically, and it has defined as the spread of the recurrence on the hilar lymphnodes or in the diaphragmatic muscle for contiguity. The extension of liver resection was defined as minor $\leq$3 segments and major >3 segments, based on Brisbane nomenclature.[13] A description of the surgical technique and the definition of Anatomic Resection (AR) and of Parenchyma-Sparing-Resection (PSR) have already been published,[14,15] and each centre involved in the study declared to follow the criteria.

All patients were followed-up by using local follow-up protocols including measurement of serum α-FetoProtein, abdominal ultrasound, contrast computed tomography (CT) or magnetic resonance imaging (MRI), and office visits as previously described.[3] Briefly, each patient was followed-up every 3 months for the first two years and then every six months. SAR was defined as the time interval in months from recurrence to death; if alive, patient data were censored at the last visit available. DFS was defined as the time interval in months from the date of the first recurrence to another recurrence event or death. In case of no recurrence or death, data were censored at the date of the last available follow-up. Time to recurrence was measured from the date of the first surgery to the date of the recurrence. Patient surveillance was closed at the end of March 2019.

Statistical analysis

Sample description was performed using median and interquartile range (IQR) for numeric variables and number and proportion for categorical variables. Mann−Whitney and Fisher test were used, respectively, to compare baseline patients' characteristics between the two treatment groups. Treatment-specific SAR curves over time were estimated using the Kaplan−Meier method and the log-rank test was used to compare the two treatment groups. Moreover, we run uni- and multivariate Cox regression analyses to test the association between patients' characteristics (including treatment) with the outcome. Of note, time elapsed between the first surgery and the first recurrence was included among the possible prognostic factors. Although this variable may appear as time-dependent it was actually treated as a fixed variable in our analysis because the starting point of our observation is the moment when the first recurrence occurs and thus the variable is well-defined for all the patients in our sample. The proportional hazard assumption was checked for all variables using the test based on Schoenfeld residuals. The problem of the presence of unmeasured values in some of the covariates (due reasonably to a "missing at random" mechanism[16]) was handled using multiple imputation based on the predictive mean matching algorithm.[17,18] Final estimates of the coefficients and standard errors were obtained by pooling model results on 20 imputed datasets. To overcome the likely presence of selection bias in comparing the marginal SAR between treatments, we performed an Inverse Probability Weighting (IPW) Kaplan−Meier analysis on the multiply imputed data.[19−21] A logistic regression model was fitted to each of the 20 datasets to estimate the probability of receiving palliative treatment conditional on possible confounders, chosen on the ground of univariate analysis and clinical knowledge. For every patient a weight was calculated as the inverse of the probability of the treatment actually received. Final weights were obtained averaging over the imputed datasets. Standardized mean differences of confounders were calculated on the original and weighted populations to check balance between treatment groups. Finally, treatment-specific marginal SAR curves were estimated by the weighted Kaplan−Meier estimator and compared using the robust score test. Sensitivity analyses were performed according to the intrahepatic or concomitant local extrahepatic spread of the recurrence, since the well-known importance of the tumor localization in predicting the survival benefit. Analogous analyses were performed on the DFS endpoint. All statistical tests were two tailed and a 5% significance level was considered. All the analyses were carried out using R software version 3.6.0.

Results

By the end of January 2019, 16 centres had correctly submitted data to the HERCOLES1 register. Between January 2008 and December 2018, 1560 patients treated by surgery for HCC first presentation were correctly enrolled in the database. Median follow-up was 46 (IQR 21–77) months. Six-hundred and seventy-nine patients experienced a recurrence after the first treatment at the end of follow-up. Of these, 150 were excluded because of a positive surgical margin (R1). Five-hundred and twenty-nine patients were further screened: overall survival could not be estimated for eight of these because of missing data and they were consequently excluded. Of the 521 remaining patients, 412 underwent curative (redo-surgery or thermoablation, n = 156) or palliative (trans arterial chemo-embolization or Sorafenib, n = 256) treatments and were included in the analyses. In detail, 77 (18.7%) patients underwent surgery, 79 (19.2%) were submitted to thermoablation, while 104 (25.2%) underwent TACE and 152 (36.9%) were treated with Sorafenib. The flow chart is depicted in Fig. 1. A brief description of the characteristics of the four treatments is given in Supplementary Table 1.

The curative and palliative groups differed in several variables at baseline: the rate of cirrhosis was higher in the curative group (79.7% vs 69% in palliative group, p = 0.025) and the intermediate stage according to the BCLC classification was more frequent in the palliative cohort while the very early–early stage was more frequent in the curative group (p = 0.014). Furthermore, the rate of concomitant local extrahepatic spread after the first surgery was much higher in the palliative group (22.5% vs 10.9% in curative group, p = 0.003). The median number of recurrent nodules was 3 (IQR 2–5) in the palliative group while it was 1 (IQR 1–2) in the curative group (p < 0.001). The median size was 2.00 cm (IQR 1.5–3.5) and 1.90 cm (IQR 1.5–2.5) respectively (p < 0.001). The localization of the recurrent nodules was more frequently bilateral in the palliative group (43.2%) than in the curative (17.0%) cohort (p < 0.001). These data are summarized in Table 1. To account for the fact that these differences might be due to selection biases when marginally comparing the outcome of the two treatments, an inverse probability weighting approach was employed. These significantly unbalanced variables (cirrhosis, BCLC stage, number of recurrent nodules and the relative size, intrahepatic and/or concomitant local extrahepatic recurrence, bilobar recurrence) plus "age" (a strong predictor of mortality, even if not heavily unbalanced between treatments in our sample) were used to estimate the patients' weights. The distribution of the treatment weights in the two factual treatment groups is shown in Supplementary Fig. 1a and b. After weighting, we obtained two pseudo populations (curative pseudo group = 397.5440 patients; palliative pseudo-group = 415.3843 patients) with balanced

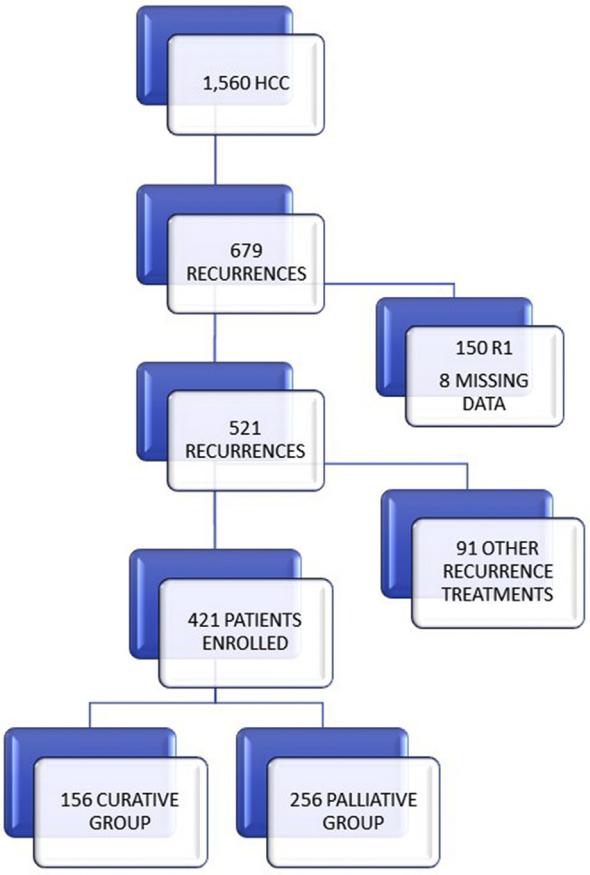

Figure 1 Flow chart of the enrolment for the study

potential confounding factors. As reported in Table 2 and Supplementary Fig. 2a, the standardized absolute mean difference between treatment groups was <0.1 for all variables, indicating good balance between the two groups.

Survival after recurrence (SAR) and risk factors for mortality after second treatment

By the end of follow-up, 159 (38.6%) patients had died after the second treatment. The median SAR was not reached in the curative group while it was 58 months (95%CI: = 47–68) in the palliative group. The 1-, 3- and 5-year SAR was 97.4%, 80.6% and 64.9% in the curative group, while it was 91.9%, 65.1% and 47.8% in the palliative cohort (p < 0.001). After IPW, these significant trends were confirmed: the median SAR was not reached in the curative group while it was 59 months (95%CI: 48–68) in the palliative group (p: 0.007). SAR rates at 1-, 3- and 5-year were respectively 98.3%, 76.7% and 63.8% for the curative group and 91.7%, 64.2% and 48.9% for the palliative group. The results before and after IPW are depicted in Fig. 2 a-b. As a

Table 1 Baseline characteristics of the two groups in the observed cohort

N	Curative	Palliative	p
	156	256	
First Presentation before Recurrence Treatment			
Age (median [IQR])	71.00 [66.00, 75.00]	70.00 [62.50, 75.50]	0.260
Female (%)	36 (23.1)	66 (25.8)	0.618
Charlson Comorbidity Index (median [IQR])	6.00 [5.00, 7.00]	6.00 [4.00, 7.00]	0.445
ChildPugh B (%)	13 (8.8)	24 (9.5)	0.962
Cirrhosis (%)	122 (79.7)	176 (69.0)	0.025
BCLC stage (%)			0.014
0	10 (6.8)	11 (4.4)	
A	96 (64.9)	134 (54.0)	
B	23 (15.5)	74 (29.8)	
C	19 (12.8)	29 (11.7)	
HBV+ (%)	36 (25.4)	52 (21.5)	0.457
HCV+ (%)	72 (50.7)	130 (53.7)	0.642
Albuminemia g/dl (median [IQR])	3.80 [3.47, 4.20]	3.70 [3.40, 4.20]	0.892
Total Bilirubin mg/dl (median [IQR])	0.89 [0.60, 1.23]	0.91 [0.70, 1.24]	0.377
Major Hepatectomy (%)	34 (21.8)	57 (23.5)	0.662
Portal Hypertension (%)	30 (26.3)	49 (27.5)	0.926
Microvascular invasion (%)	44 (28.4)	95 (37.5)	0.074
Satellitosis (%)	12 (12.9)	34 (26.8)	0.020
Grading Edmondson (%)			0.116
1	12 (7.7)	8 (3.1)	
2	111 (71.2)	185 (72.5)	
3	31 (191.9)	61 (23.9)	
4	2 (1.3)	1 (0.4)	
Recurrence Presentation			
Time to Recurrence, months (median [IQR])	20.52 [10.68, 35.56]	17.34 [7.45, 39.50]	0.32
Bilobar Recurrence (%)	16 (17.0)	51 (43.2)	<0.001
Recurrence Localization (%)			0.003
Intrahepatic	139 (89.1)	196 (77.5)	
Intrahepatic and Local Extrahepatic Spread	17 (10.9)	57 (22.5)	
Number of Recurrent Nodules (median [IQR])	1.00 [1.00, 2.00]	3.00 [2.00, 5.00]	<0.001
Size of the Recurrent Nodule (median [IQR])	1.90 [1.50, 2.50]	2.00 [1.50, 3.50]	<0.001
Type of Recurrence Treatment			
Surgery	77 (49.3%)	–	–
Thermoablation	79 (50.7%)	–	–
TACE	–	104 (40.6%)	
Sorafenib	–	152 (59.4%)	

BCLC Barcellona Clinic Liver Cancer Staging System; HBV hepatitis B virus; HCV hepatitis C virus; TACE transarterial chemoembolization.

sensitivity analysis, SAR estimation was made according to the localization of the recurrent HCC (intrahepatic or concomitant local extrahepatic spread). In the observed cohort, 335 patients showed an intrahepatic spread only, and 139 were treated by curative approach, while 196 by palliative therapies. One, three and five years SAR were 97.1%, 81.9%, 66.3% and 91.7%, 66.8%, 51.0% for CUR and PAL groups respectively (p: 0.001). After IPW, the difference between the two groups were still significant (p: 0.025). The curves are depicted in Supplementary Fig. 3. In case of concomitant local extrahepatic spread of the recurrent HCC (n = 74), 17 patients were submitted to a curative approach, while 57 to a palliative one. One, three and five years SAR was 100%, 70.3% and 52.7% for CUR and 92.8%, 48.7% and 33.3% for PAL groups in the observed population (p: 0.100). In the weighted pseudopopulation, the trend was still not significant (p: 0.275). The survival curves are reported in Supplementary Fig. 4.

To assess the risk factors for mortality after the second treatment, multivariate Cox regression analysis was performed as summarized in Table 3. Being treated by palliative therapy (HR = 1.744; 95%CI = 1.14–2.66; p = 0.010) and having a recurrent nodule > 5 cm in size (HR = 1.835; 95% CI = 1.182–2.833; p = 0.007) were the only independent predictors of mortality, while every additional year after the second treatment without recurrence was found to decrease the hazard of mortality by 38% (HR = 0.621; 95%CI = 0.548–0.704; p < 0.001). Results of the Schoenfeld test to check the proportional hazards assumption are reported in Supplementary Table 2.

Disease-free survival (DFS) and risk factors for recurrence after second treatment

As a secondary analysis, DFS from the first recurrence to the second one was evaluated after treatment. In this case, data on second recurrence was available in 393 cases, of whom 317 were treated either by curative (n = 116) or palliative (n = 201) treatment. Inverse probability weighting was performed on this population as in the primary analysis to weight baseline

Table 2 Comparing the distribution of the baseline predictors of SAR between treatments in the original and weighted samples. The table reports the average values calculated accross 20 analogous balance check tables, one for each imputed dataset

Factors	Original sample N = 412			Weighted sample N = 812.928		
	Curative N = 156	Palliative N = 256	Standardized difference	Curative N = 397.544	Palliative N = 415.384	Standardized difference
Age, mean (SD)	69.82 (8.39)	68.27 (10.0)	−0.1689	69.17 (8.13)	68.88 (9.64)	−0.0321
Cirrhosis, N (%)	124.3 (79.68)	176.6 (68.98)	−0.107	300.95 (75.7)	307.36 (73.99)	−0.0171
BCLC stage 0-A, N (%)	111.95 (71.76)	150.05 (58.61)	−0.1315	249.92 (62.87)	263.94 (63.54)	0.0068
BCLC stage B, N (%)	24.4 (15.64)	76 (29.69)	0.1405	98.08 (24.67)	101.44 (24.42)	−0.0025
BCLC stage C, N (%)	19.65 (12.6)	29.95 (11.7)	−0.009	49.54 (12.46)	50 (12.04)	−0.0042
Number of Recurrent Nodules >1, N (%)	39.75 (25.48)	192.55 (75.21)	0.4973	216.39 (54.43)	231.89 (55.83)	0.0139
Size of Recurrent Nodule >5 cm, N (%)	11 (7.05)	43.95 (17.17)	0.1012	39.87 (10.03)	53.67 (12.92)	0.0289
Concomitant Local Extrahepatic Recurrence, N (%)	17 (10.9)	57.85 (22.6)	0.117	62.79 (15.8)	73.98 (17.81)	0.0201
Bilobar Recurrence, N (%)	29.95 (19.2)	126.35 (49.36)	0.3016	137.67 (34.63)	156.51 (37.68)	0.0305

BCLC Barcellona Clinic Liver Cancer Staging system.

differences (age, presence of cirrhosis, BCLC stage, number and size of recurrent nodules, localization of the recurrence and presence of bilobar disease). These results are reported in Supplementary Fig. 1c and d and 2b.

The median DFS after second treatment was 57 months (95% CI: 31−not evaluable) for the curative group, while it was 19 months (95%CI = 15−25) for the palliative cohort ($p < 0.001$). DFS rates at 1, 3 and 5 years were respectively 85.1%, 57.0% and 48.1% for the curative group and 64.7%, 37.4% and 30.3% for the palliative group. After weighting, two pseudo populations were created: 309.060 curative and 317.453 palliative pseudo patients were obtained. Survival outcomes were confirmed in the pseudo populations: the median DFS after second treatment was 43 months (95%CI = 32−74) in the curative group, while it was 23 months (95%CI = 18−27) in the palliative group ($p = 0.017$). DFS rates at 1, 3 and 5 years were respectively 86.1%, 52.0% and 43.3% for the curative group and 65.9%, 40.5% and 32.7% for the palliative group. Curves are presented in Fig. 2 c-d.

The results of the uni- and multivariate Cox regression analyses are summarized in Table 3. Briefly, being treated by palliative therapies (HR = 1.743; 95%CI = 1.104−2.753; $p = 0.022$), and a recurrent multinodular presentation (HR = 1.574; 95% CI = 1.04−2.38; $p = 0.032$) were the only independent predictors of further recurrence, while each year without relapse after the first treatment was the only significant protective factor (HR = 0.801; 95%C = 0.695−0.922; $p = 0.002$). The size of a recurrent nodule >5 cm was slightly but not significantly associated with relapse (HR = 1.558; 95%CI = 0.961−2.526; $p = 0.072$). Results of the Schoenfeld test to check the proportional hazards assumption are reported in Supplementary Table 2.

Discussion

In this large multicentric Italian study on the current approach to HCC recurrence after curative treatment, surgery and thermoablation demonstrated an advantage in achieving long-term survival – even after recurrence – when compared with palliative strategies such as chemo-embolization or systemic therapies. While surgical resection and ablation are the first-line strategy for curing HCC at diagnosis, their role in cases of recurrence remains unclear, although several comparisons between curative and palliative treatments have already been published.[10,22–25] However, most of those studies were based on a small sample size, which limits the generalizability of their conclusions. To our knowledge, the present study is the first large, comprehensive analysis comparing curative and palliative recurrence procedures for HCC. Interestingly, our results showed a clear survival advantage when the recurrence is intrahepatic and treated again by a curative approach. But when a concomitant local extrahepatic spread was present, even if a trend in favour of curative was reasonably deducible, the survival difference was not significant. Of note, these trends were in line with the literature reported in the European guideline[2] when HCC spreads outside the liver, the prognosis is always very poor, without clear indications to invasive treatments.

Disease recurrence is the main factor associated with increased mortality[4] in HCC patients, indicating that understanding how and when to retreat in cases of recurrence should be a research priority with the aim of achieving stable and prolonged survival. To avoid clinical and statistical differences between the two cohorts, we adopted the IPW methodology to weight all the relevant covariates, such as those related to liver function and

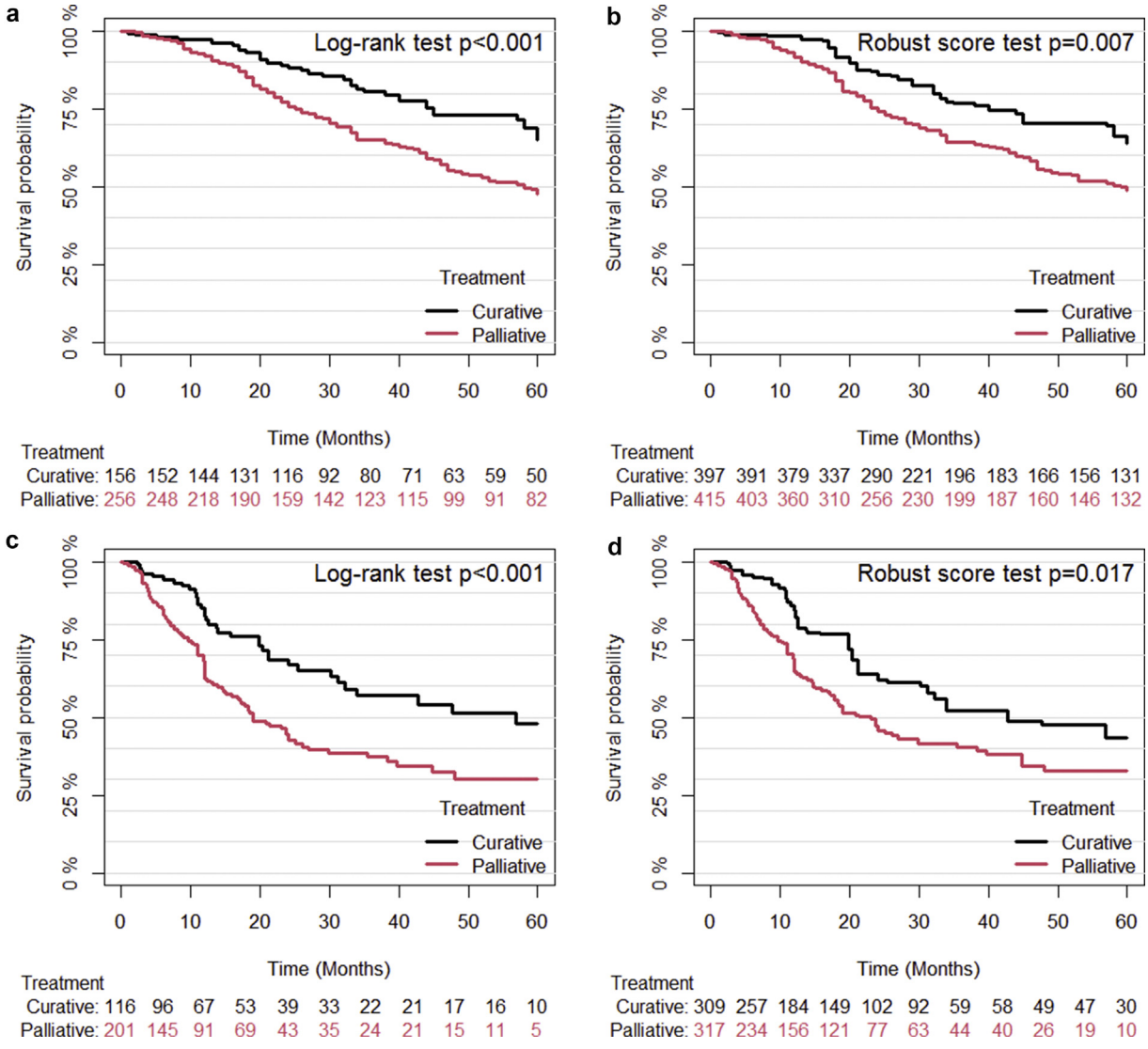

Figure 2 Survival after Recurrence (SAR) curves before (a) and after (b) Inverse Probability Weighting. Disease/Progression Free Survival (DFS) curves before (c) and after (d) Inverse Probability Weighting

recurrent tumour burden. Patients who experienced HCC recurrence and who were consequently retreated with curative intent by surgery or thermoablation achieved a 5-year survival after recurrence of almost 64% versus only 49% in the case of palliative approaches. This advantage of curative treatment was confirmed in the IPW cohort. In this sense, a recurrent event should not be considered as a failure on the road to cure, but an expected event that can be effectively treated by a series of consecutive curative treatments.

In the available literature SAR ranges between 22% and 84%, with a median 5-year SAR of 35.2%.[4] The better SAR found in the current study may be explained by differences in the stratification of patients (our study merged surgery and thermoablation), and different baseline characteristics. Treating patients with a palliative approach increased the risk of mortality after second relapse by 74%, suggesting the need to carefully evaluate which patients should be excluded from the chance to achieve long-term survival. This decision should be based on the recurrence tumour burden, as our analysis suggests, as for the first diagnosis. Notably, our findings are consistent with another report[26] that recommended restaging the disease recurrence using the same parameters as in the first evaluation. Interestingly, pathological findings at initial resection were not related to the risk of mortality after second treatment: this result is consistent with the report of Yoh et al.,[10] but this feature needs more investigation since contradictory results have been reported in the literature.[27] This difference may be attributed to heterogeneity in the study population.

Importantly, the time of recurrence after the first treatment played a pivotal role in both the risk of mortality and relapse after

Table 3 Uni and Multivariate Cox Regression Analysis to identify factors predicting mortality and recurrence after second treatment

	Risk of mortality after second treatment				Risk of recurrence after second treatment			
	Univariate Cox models		Multivariate Cox model		Univariate Cox models		Multivariate Cox model	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Palliative therapies (vs curative)	1.95 (1.366; 2.783)	<0.001	1.744 (1.14; 2.667)	0.01	1.959 (1.334; 2.877)	0.001	1.743 (1.104; 2.753)	0.022
Age (per year of increase)	1.024 (1.004; 1.044)	0.018	1.019 (0.997; 1.042)	0.097	1.014 (0.993; 1.035)	0.19		
Female (vs male)	0.877 (0.605; 1.272)	0.489	0.745 (0.499; 1.111)	0.149	0.8 (0.53; 1.208)	0.289	0.695 (0.449; 1.077)	0.104
Child B (vs A)	0.621 (0.344; 1.121)	0.114	0.675 (0.338; 1.345)	0.264	0.763 (0.422; 1.378)	0.369	0.793 (0.419; 1.489)	0.467
Presence of Cirrhosis (vs not)	0.781 (0.553; 1.103)	0.161	0.757 (0.517; 1.109)	0.153	0.942 (0.632; 1.403)	0.769	0.971 (0.63; 1.494)	0.892
HBV+ (vs negative)	0.876 (0.591; 1.298)	0.51			0.747 (0.452; 1.235)	0.256		
HCV + (vs negative)	0.929 (0.675; 1.277)	0.65			1.129 (0.793; 1.607)	0.501		
Portal hypertension (vs not)	1.188 (0.826; 1.709)	0.355			1.180 (0.790; 1.764)	0.419		
BCLC stage B (vs 0-A)	0.964 (0.66; 1.407)	0.849	0.865 (0.575; 1.301)	0.485	0.925 (0.61; 1.404)	0.715	0.805 (0.517; 1.254)	0.338
BCLC stage C (vs 0-A)	0.683 (0.402; 1.161)	0.159	0.975 (0.557; 1.706)	0.929	0.514 (0.258; 1.021)	0.057	0.638 (0.314; 1.294)	0.213
Recurrent Nodules >1 (vs 1)	1.608 (1.142; 2.263)	0.007	1.425 (0.957; 2.122)	0.081	1.955 (1.355; 2.823)	<0.001	1.574 (1.04; 2.381)	0.032
Recurrent Nodule Size ≥5 cm (vs < 5 cm)	1.781 (1.205; 2.631)	0.004	1.83 (1.182; 2.833)	0.007	1.842 (1.169; 2.903)	0.008	1.558 (0.961; 2.526)	0.072
Previous Major Hepatectomy (vs minor)	1.098 (0.781; 1.545)	0.590			1.111 (0.743; 1.662)	0.607		
Concomitant Local Extrahepatic Spread (vs intra only)	1.608 (1.104; 2.341)	0.013	1.388 (0.932; 2.068)	0.107	1.355 (0.881; 2.084)	0.167	1.268 (0.8; 2.008)	0.312
Bilobar Recurrence (vs not)	1.209 (0.809; 1.805)	0.356			1.464 (0.969; 2.213)	0.072		
Time to Recurrence (per year of increase)	0.653 (0.582; 0.732)	<0.001	0.621 (0.548; 0.704)	<0.001	0.825 (0.721; 0.944)	0.005	0.801 (0.695; 0.922)	0.002
Charlson Comorbidity Index ≥ 9 (vs < 9)	1.006 (0.536; 1.888)	0.986	1.021 (0.519; 2.01)	0.951	1.072 (0.62; 1.852)	0.803		
Microvascular Invasion (vs not)	1.086 (0.775; 1.522)	0.633			1.049 (0.733; 1.501)	0.793		
Satellitosis (vs absence)	1.67 (1.04; 2.681)	0.036	1.11 (0.655; 1.881)	0.698	1.489 (0.931; 2.381)	0.098		
Histological Grading ≥3 (vs < 3)	1.543 (1.087; 2.192)	0.015	1.058 (0.718; 1.557)	0.777	1.125 (0.768; 1.649)	0.544		

BCLC Barcellona Clinic Liver Cancer Staging System; HBV hepatitis B virus; HCV hepatitis C virus; TACE transarterial chemoembolization.

second treatment. Thus, the longer the interval between the first and second treatment, the lower the risk of mortality due to the occurrence of a second disease. This is consistent with previously reported observations[24,28,29] and the peculiarity of the oncological history of HCC, in which relapse in the first year after therapy should be considered as real metastases from the primary tumour, while a distant-in-time recurrence may be a de-novo occurrence caused by the underlying liver damage[30]; this timing seems to be a sort of indirect expression of tumour biology, as already confirmed in other tumour types.[31,32]

As a secondary end-point, our results clearly show that a curative approach to recurrence may also achieve longer disease-free-survival: this is of interest, because relapse is a well-known predictor of mortality, and indeed may be indirectly associated

with patients' quality of life, reducing the time spent in hospitals and consequently the overall disease costs.[33] The morphological presentation of the recurrence was again the only predictor of an increased risk of recurrence even after second treatment, together with treating the first relapse with palliative intent. These results confirm previous observations that led to the recommendation that restaging of recurrence should be carried out as per the first occurrence, addressing the therapies accordingly without avoiding curative intent only on the basis of a relapse of the disease.

This study had several limitations. First, among the available curative treatments for recurrence, salvage liver transplant (SLT) was not included as per inclusion/exclusion criteria of the study. Indeed, several studies compared SLT and redo-surgery and concluded that SLT is the best option for relapse treatment.[7,34] However, only a small number of patients received this treatment in the HERCOLES dataset (n = 5/412), and the relative data were not available because they were outside the purpose of the study and the register. Moreover, fulfilling the transplant criteria (according to age rather than Milan Criteria) at the time of recurrence[35] rather than the availability of organs is the main concern when using this approach, and consequently other curative treatments such as surgery and thermoablation should be considered as alternative first-line treatments in cases of recurrence, as shown by our analysis. Thus, in our series SLT was rolled out by a multidisciplinary meeting in each center, which have indicated the best treatment for each single case: all patients enrolled, consequently, were judged not feasible for transplant. Second, this was a retrospective study on patients already treated by surgery: this means that they had a very favourable first presentation of the disease when compared to other patients who had not been candidates for curative intent, which probably influenced further analysis of recurrent treatment indications. Thus, in liver surgery has been reported a high heterogeneity on the definition of resectability,[36] and consequently one of the limit of a retrospective multicentric study is the limited but present fluctuation of the resectability among the centers: this fact is not accounted by the present study. However, the goal of our study was to address how to retreat patients who had already been considered curable at the first presentation, stressing how this aim should not be ruled out in the case of HCC recurrence. Third, there was a clear risk of selection bias, which we sought to minimize by using the IPW statistics. Moreover, the retrospective nature of our data may raise doubts about whether other variables that were not recorded might have affected our results; however, all the well-known variables associated with the endpoint events selected in this study were included. Finally, we did not perform competing risk analysis, which would have required the cause of death for each patient that unfortunately was not always reported in the registry. However, competing risks should be balanced among groups (CUR vs. PAL) indicating that standard Cox regression and Kaplan–Meier analyses should be considered adequate.[37]

In conclusions, in cases of recurrence after surgery for HCC, redohepatectomy and thermoablation could play a key role in guaranteeing the continuation of curative intent when they are technically feasible, and particularly in case of intrahepatic relapse only. Tumour burden at the time of the relapse determines the most suitable treatment for achieving long-term results. Once confirmed in prospective studies, our findings could be used to refine patients' stratification and improve the therapeutic outcome of HCC patients.

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Conflict of interest

None declared.

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Appendix A1.

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Appendix A2. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.10.007.