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Intra arterial treatment of hepatocellular carcinoma: Comparison of MELD score variations between radio-embolization and chemo-embolization

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KEYWORDS
Hepatocellular carcinoma;
Chemo-embolization;
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Toxicity

Abstract
Purpose: The purpose of this study was to assess liver function deterioration, as assessed using the model for end-stage liver disease (MELD) score variations, following transarterial chemo-embolization (TACE) versus selective internal radiation therapy (SIRT) in patients with unresectable unilobar hepatocellular carcinomas (HCC).
Patients and methods: We retrospectively evaluated all patients who underwent a single conventional TACE or SIRT procedure in our department from May 2013 to May 2018 for unilobar unresectable HCC. A total of 86 patients (76 men, 20 women; mean age, 65.5 years) were included. There were 63 patients in the TACE group [56 men, 7 women; mean age, 65.1 ± 9.6 (SD) years] and 23 patients in the SIRT group [20 men, 3 women; mean age, 70 ± 9.2 (SD) years]. Delta MELD, defined as post treatment minus pre-treatment MELD score, was considered for liver function deterioration and compared between patients who underwent single lobar treatment of SIRT versus TACE.

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Results: Patients in SIRT group had significant higher tumor burden, alpha-fetoprotein serum level, and rates of macroscopic vessel invasion. Mean pre-treatment MELD scores did not differ between TACE [mean, 8.41 ± 1.71 (SD); range: 7.24—9.24] and SIRT groups [mean, 8.36 ± 1.74 (SD); range: 7.07—9.21] ($P = 0.896$) as well as Child-Pugh class and albumin-bilirubin (ALBI) grade distribution. However, following treatment, mean DeltaMELD was greater in TACE group (mean, 0.83 ± 1.83 [SD]; range: −0.30— − 1.31) than in SIRT group (mean, −0.13 ± 1.06 [SD]; range: −0.49—0.32) ($P = 0.021$). At multivariate analysis, SIRT treatment was independently associated with a lower DeltaMELD score than TACE (R = −0.955 [−1.68; − 0.406]; $P = 0.017$;).
Conclusion: Whereas performed in patients with higher tumor burden, SIRT resulted in lower degrees of liver function worsening as assessed using MELD score variations.

Treatment options for unresectable hepatocellular carcinomas (HCC) need to take into account both tumoral staging and liver function, as more than 90% of patients with HCC have underlying cirrhosis [1—3]. Indeed, patient prognosis is based on the 2 intertwined diseases and the choice for an adequate treatment relies on a reasonable balance between an optimal anti tumoral efficacy and an acceptable toxicity [2].

Intra arterial therapies are essential treatments for the management of patients with HCC [4,5]. They are mainly represented by transarterial chemo-embolization (TACE) and selective internal radiation therapy (SIRT). Both treatments aim at selectively treating tumors via arterial targeting, using ischemic mechanisms and cytotoxic effect for TACE, and local radiation therapy for SIRT.

TACE is the mainstay therapy for patients with Barcelona Clinic Liver Cancer (BCLC) B stages of disease [3]. This includes patients with multifocal disease, without vascular invasion or extra hepatic disease, and with good performance status and preserved liver function [3], whereas SIRT is an alternate option for patients with macroscopic vessel invasion or major tumor burden, or after failed TACE [6,7].

Current results in the literature did not demonstrate significant differences of tumor response rates or patient survival between SIRT and TACE in retrospective or prospective non-randomized studies [8—13]. Only one prospective randomized phase-2 trial has demonstrated an improvement of time to progression with SIRT versus TACE in 45 patients with BCLC A or B disease [14]. Nevertheless, if both treatments provide a good antitumoral efficacy, the choice of the more appropriate therapy may rely on their tolerance, so that comparison of liver toxicity induced by both procedures is a critical issue.

Liver toxicity following intra arterial therapy of unresectable HCCs is mainly expressed by the deterioration of the liver function that can be evaluated by the Child-Pugh score and/or the model for end-stage liver disease (MELD) score [15]. The latter allows a more linear and quantitative discrimination of liver function changes, without clinical evaluations that could incorporate subjective interpretation. The MELD score and its variations have clinically relevant impacts with an excellent accuracy for predicting the 3-months survival rate for patients with cirrhosis, and to a lesser extent the 6 and 12 months prognosis [16—19]. The MELD score has been specifically chosen for the allocation of liver transplant, having shown a greater precision than Child-Pugh score to evaluate and stratify large patients' population [19].

The aim of this study was to assess the liver function deterioration, as assessed using MELD score variations, following TACE versus SIRT procedure for unresectable unilobar HCCs, and to determinate predictive factors of severe function deterioration.

Methods

Study design

We retrospectively evaluated all TACE and SIRT procedures performed in our department from May 2013 to May 2018 for patients with unilobar unresectable HCC. Inclusion criteria were: (i) age between 18 and 89 years; (ii) unilobar unresectable HCC either biopsy-proven or based on radiologic features; (iii) first intra arterial treatment; (iv) TACE or SIRT performed in a lobar setting, i.e. targeting a liver lobe; (iv) clinical (including assessment of Child-Pugh score), biological (including liver blood tests), and radiological (either liver multiphasic computed tomography or magnetic resonance imaging) examinations within 1 month before procedure, (vi) clinical and biological examinations post treatment within 1 to 6 months after the procedure. Non-inclusion criteria were: MELD and Child-Pugh score non-computable or > 1 month before the procedure, absence of pre-treatment imaging, non-liver-related complication during follow-up, Child-Pugh score before treatment > B7, presence of HCC extra hepatic metastasis. Fig. 1 shows patient inclusion into the study. A total of 86 patients (76 men, 6 women; mean age, 65.5 years) were included.

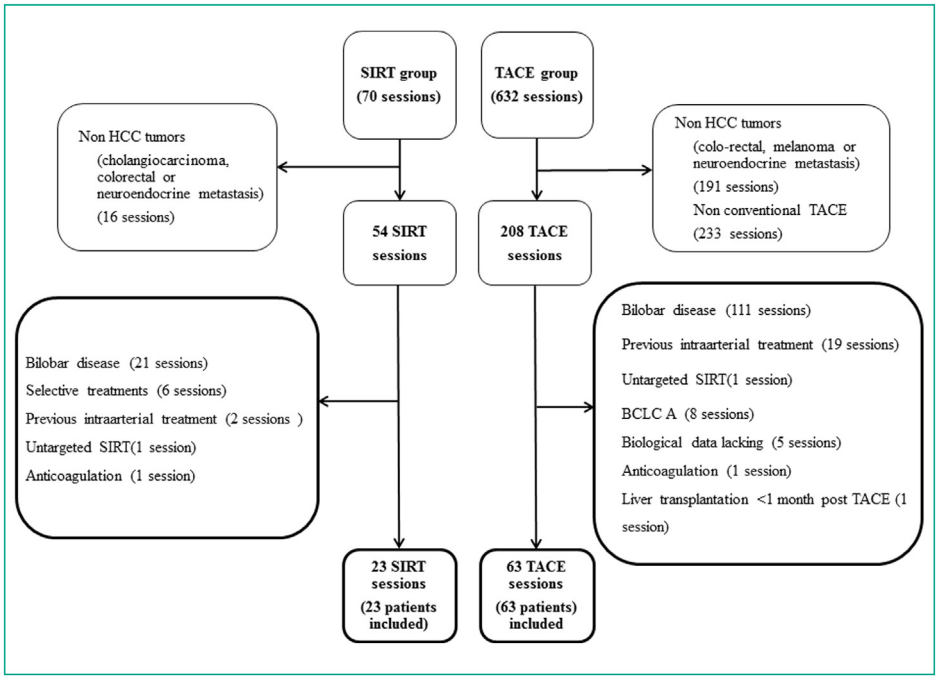

Figure 1. Flowchart shows study population.

Liver disease and function

Etiologies of chronic liver diseases and patient history related to cirrhosis and portal hypertension complications were gathered. Pre-treatment and post treatment MELD and Child-Pugh scores were computed. Delta MELD [18] was considered for liver function deterioration. It was defined as post treatment MELD minus pre-treatment MELD score. When prothrombin time was recorded instead of international normalized ratio (INR) on blood test examination, INR was obtained based on the following published formula [17,20]: INR = (prothrombin index [% of normal]/94.9) − 0.81. Albumin-bilirubin (ALBI) score and ALBI grade were also calculated [21]. Pre-treatment alpha-fetoprotein (AFP) serum level, number/size of tumors were gathered and AFP score [22] was calculated.

Treatments

All treatment decisions were taken during multidisciplinary tumor board. TACE was proposed in first intention for BCLC B HCC patients. SIRT was proposed to patients with (i) no response following two TACE procedures, (ii) TACE contraindications, or (iii) macroscopic vascular invasion (portal) on pre-treatment imaging. Technical details about the procedures were gathered. They included the following items:

- liver portion treated (lobar/sectorial/segmental);
- for TACE: vector (either drug-eluding beads or conventional TACE with lipiodol); chemotherapeutic agent (either doxorubicin or idarubicin), embolization agent for conventional TACE;
- for SIRT: treatment with SIR-Spheres™ (Sirtex Medical Limited,) or TheraSphere® (Biocompatibles UK Limited, BTG International), administered radioactivity (in Mega Becquerel), post treatment tumor and targeted liver radiation dose, as assessed on single photon emission tomography/computed tomography scan performed the day following the procedure. Dose calculation was performed using body surface area method for SIR-Spheres and MIRD (Medical Internal Radiation Dose Committee) for TheraSphere®.

Statistical analysis

Categorical data were expressed as raw numbers, proportions and percentages and compared using the Chi^2 test or Fisher exact test, as appropriate. Quantitative data were expressed as mean ± standard deviation (SD) and ranges or median, interquartile range (Q1; Q3) according to data distribution and compared using either Student *t* test or Wilcoxon rank-sum test. The influence of parameters on MELD score modifications, as assessed by DeltaMELD value, was analysed using logistic and linear regressions as appropriate. Variables associated with the presence of liver function worsening, with a *P*-value < 0.15 in univariate analysis, were then included in a stepwise forward multivariate analysis. Variables with a *P*-value < 0.05 at multivariate analysis were considered significant. Statistical tests were performed with Biosta TGV and *P*-value.io (R software interface).

Results

Patients

Sixty-three patients in TACE group and 23 patients in SIRT group, for a total of 86 patients met the inclusion criteria. The clinical and demographic characteristics of the included patients as well as procedures details are shown in Table 1.

Table 1 Patients and treatments characteristics.

	SIRT ($n=23$)	TACE ($n=63$)	P
Male	20 (87)	56 (88.9)	0.804
Age (year)	70 ± 9.2	65.1 ± 9.6	0.648
Performance status			0.017
0	23 (100)	50 (79.4)	
1	0 (0)	13 (20.6)	
BCLC			< 0.001
B	6 (30.4)	49 (77.8)	
C	16 (69.6)	14 (22.2)	
Underlying cirrhosis	21 (91.3)	57 (90.5)	0.907
Bilirubin (μmol/l)	12.77 ± 10.2 [5—17.5]	14.78 ± 6.6 [9—19]	0.419
INR	1.12 ± 0.1 [1.01—1.18]	1.12 ± 0.11 [1—1.19]	> 0.999
Creatinin serum level (μmol/l)	77.1 ± 20 [64—85.5]	78.7 ± 21.9 [64—91.5]	0.752
Child-Pugh class	22 (95.7)	57 (90.5)	0.669
A			
B	1 (4.3)	6 (9.5)	
MELD score	8.36 ± 1.74 [7.07—9.21]	8.41 ± 1.71 [7.24—9.24]	0.896
ALBI score	−2.61 ± 0.43 [−3.01− − 2.36]	−2.53 ± 0.51 [−2.92− − 2.13]	0.477
ALBI grade			0.931
1	10 (43.5)	28 (44.4)	
2	13 (56.5)	35 (55.6)	
3	0 (0)	0 (0)	
Portal hypertension (endoscopic signs/previous variceal rupture)	3 (13)	22 (34.9)	0.062
Platelets < 100,000	4 (17.4)	20 (31.7)	0.278
HCC			
Multifocal	5 (21.7)	37 (58.7)	0.005
Infiltrative	8 (34.8)	3 (4.8)	< 0.001
Tumor characteristics			
AFP (UI/ml)	884 ± 2661 [11.9—232]	945 ± 3368 [4.4—126]	0.931
Tumor number	2.9 ± 3.1 [1—3]	4.9 ± 4.5 [2.5_5]	0.002
Largest nodule (mm)	79.7 ± 29.8 [58.5—99.5]	44.4 ± 33.1 [21.5—53.5]	< 0.001
Macroscopic vessel invasion	16 (69.6)	1 (1.6)	0.017
AFP score	4.3 ± 1.7 [3.5—6]	3.2 ± 2.2 [2-5]	0.003
AFP score > 2	20 (87)	32 (50.8)	
Previous HCC treatment			
None	10 (40.4)	26 (41.3)	> 0.999
Targeted therapy	3 (13)	7 (11.1)	> 0.999
Surgery	0 (0)	13 (20.6)	0.017
TACE	8 (34.8)	15 (23.8)	0.350
SIRT	1 (4.3)	1 (1.6)	0.452
Percutaneous ablation	5 (21.7)	16 (25.4)	> 0.999
Additional embolization: None/microspheres/Gelfoam		6/22/35 (9.5/34.9/55.6)	
SIR-Spheres/TheraSpheres	10/13 (40.5/56.5)		
Yttrium 90 delivered dose (MBq)*	2080 ± 1361		

Quantitative variables are presented as mean ± standard deviation (SD); numbers in brackets are ranges; qualitative variables are expressed as proportions followed by percentages in parentheses. * 22 patients; SD: standard deviation; ALBI: albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; NASH: non-alcoholic steato-hepatitis; AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma; SIRT: selective internal radiation therapy; TACE: transarterial chemo-embolization; INR: international normalized ratio; MELD: model for end-stage liver disease.

Pre-treatment imaging showed a significant higher tumor burden in SIRT patients [mean tumor size, 79.7 mm ± 29.8 (SD); range: 58.5—99.5 mm] than in TACE patients [mean tumor size, 44.4 mm ± 33.1 (SD); range: 21.5—53.5 mm] ($P < 0.001$). An AFP score > 2 was found in 20/23 patients (87%) of SIRT group and 32/63 patients (51%) of TACE group ($P = 0.003$). Macroscopic vessel invasion was present in 16/23 patients (70%) of SIRT group and 1/63 patient (2%) of TACE group ($P < 0.001$).

Mean pre-treatment MELD scores did not differ between TACE group (8.14) and SIRT group (8.36) ($P = 0.896$). Child-Pugh score distribution (A or B) was not different between the two groups; 22/23 patients (96%) were grade A in SIRT group and 57/63 patients (91%) in TACE group ($P = 0.669$). The ALBI score and grade [21] distribution did not differ between both groups: mean ALBI score was −2.61 ± 0.43 [SD] (range: −3.01— −2.36) in SIRT group and −2.53 ± 0.51 (SD) (range: −2.92— −2.13) in TACE group ($P = 0.477$), with 13/23 patients (57%) and 35/63 patients (56%) grade 2 respectively in SIRT and TACE groups ($P = 0.931$). Mean time from procedure to post treatment clinical and biological evaluation was not different between TACE group [mean time, 53 days ± 38 (SD); range: 30—62.7 days] and SIRT group [mean time, 40 days ± 20 (SD); range: 28—49 days] ($P = 0.148$).

Post treatment liver function worsening

Following intra arterial therapy, mean DeltaMELD score was + 0.83 ± 1.83 (SD) in the TACE group and −0.13 ± 1.06 (SD) in the SIRT group ($P = 0.021$) (Fig. 2). INR did not significantly increase in both groups (Table 2). No significant differences in increase of bilirubin and creatinine serum levels were observed between the two groups. INR variation (Delta INR) was greater in TACE group than in SIRT group ($P = 0.002$) whereas no differences in bilirubin and creatinine serum levels variations were observed between the two groups.

Factors influencing Delta MELD

Univariate analysis demonstrated positive association between DeltaMELD and TACE treatment ($P = 0.029$) and portal vein thrombosis ($P = 0.096$) (Table 3). For multivariate analysis, the variable ''portal vein thrombosis'' had to be excluded due to multicollinearity bias with SIRT treatment as patients with portal vein thrombosis were mainly treated using SIRT. In multivariate analysis and after bootstrapping (1000 iterations), SIRT treatment was independently associated with a lesser DeltaMELD [R = −0.955 (−1.68; −0.406)] ($P = 0.017$).

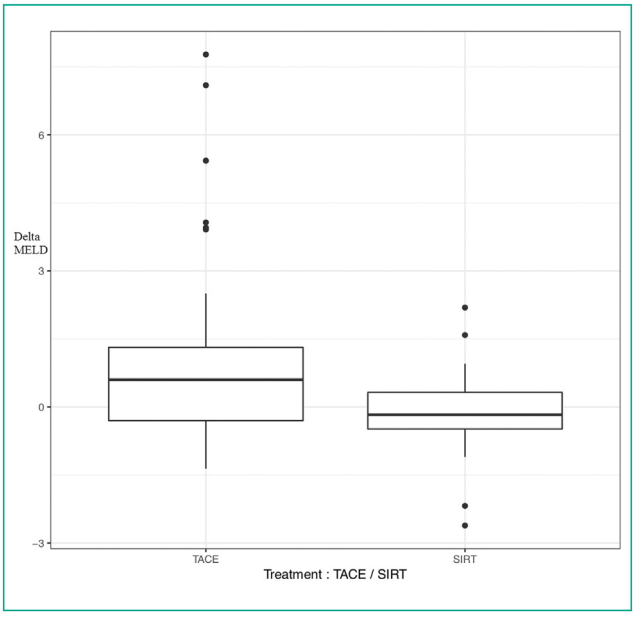

Figure 2. DeltaMELD box plots for Transarterial chemo-embolization (TACE) and Selective internal radiation therapy (SIRT) groups. Box plots show Delta Model for end-stage liver disease (MELD) distribution after TACE and SIRT treatments in the study population. The top and bottom of the box are the 25th and 75th percentiles, respectively. The length of the box is the interquartile range and the median (50th percentile) is the line drawn through the box. TACE indicates transarterial chemo-embolization. SIRT indicates selective internal radiation therapy.

Discussion

The results of our study show that worsening of liver function following loco regional treatment of HCC is variable and depends on the type of intra arterial treatment performed. Indeed, worsening of the MELD score was regularly noted following TACE, whereas it did not vary following SIRT. TACE procedure was the single variable associated with DeltaMELD at multivariate analysis, whereas SIRT treatment was the single variable independently associated with a lesser liver function worsening. Interestingly, no other variables were associated at multivariate analysis, even not the pre-treatment MELD score or the ALBI score or grade. Based on retrospectives and non-randomized prospective studies, TACE and SIRT show close results in terms of response and survival [8—13], particularly for BCLC B patients. Assessment of liver function impairment resulting from either technique might help in some cases to select the most appropriate therapy. This point is all the more crucial as these treatments (especially TACE) may be repeated, leading to cumulative toxicity, with parenchymal and/or arterial injuries.

Regarding worsening of liver function following intra arterial liver therapy, only one prospective study analysed Child-Pugh and MELD score changes for 86 BCLC B patients treated with TACE ($n = 42$) or SIRT ($n = 44$) [23]. This non-controlled prospective study did not found any significant increase of post treatment MELD scores in TACE and SIRT groups for stage BCLC B patients. However, the results focused on MELD variations per patient and not per session, with a DeltaMELD calculation done between pre-treatment MELD and last MELD available. Other studies did not demonstrate differences between TACE and SIRT regarding biological toxicity, including bilirubin [12,13,24—26], but none evaluated MELD score variation or evaluated the possibility of session repetition. Another study compared pre and post treatment MELD scores (at 1 month) in TACE groups, comparing Child-Pugh class A patients versus Child-Pugh B or C [27]. Pre-treatment MELD was 8.7 for CP A and 13.7 for CP B or C patients, with a variation of + 0.71 point

Table 2 Liver and renal function tests variations following SIRT and TACE procedures.

Variations between baseline and post treatment (Q1; Q3)

	SIRT ($n=23$)			TACE ($n=63$)		
	Baseline	Post treatment	*P*	Baseline	Post treatment	*P*
MELD score	8.36 ± 1.74 [7.07—9.21]	8.23 ± 1.59 [7.05—9.30]	0.800	8.41 ± 1.71 [7.24—9.24]	9.24 ± 2.44 [7.53—10.50]	0.029
Bilirubin (μmol/l)	12.77 ± 10.2 [5—17.5]	14.88 ± 8.8 [7.5—20.05]	0.456	14.78 ± 6.6 [9—19]	17.28 ± 11.8 [8—22.75]	0.146
INR	$1.12 \pm 0.$ [1.01—1.18]	1.11 ± 0.1 [1.05—1.15]	0.783	1.12 ± 0.11 [1—1.19]	1.17 ± 0.16 [1.05—1.25]	0.091
Creatinine serum level (μmol/l)	77.1 ± 20 [64—85.5]	71 ± 21.5 [60.5—84.5]	0.316	78.7 ± 21.9 [64—91.5]	76.94 ± 23.2 [60.5—90]	0.663

Comparison of these variations between SIRT and TACE groups (Q1; Q3)

	SIRT ($n=23$)	TACE ($n=63$)	*P*
Delta MELD	0.13 ± 1.06 [−0.49—0.32]	0.83 ± 1.83 [−0.30—1.31]	0.021
Delta bilirubin (μmol/l)	2.11 ± 7.29 [−0.5—6.8]	2.60 ± 8.38 [−2—4]	0.795
Delta INR	-0.01 ± 0.06 [−0.05—0.015]	0.05 ± 0.11 [0—0.08]	0.002
Delta creatinine serum level (μmol/l)	-6.08 ± 11.26 [−13—0.5]	-1.76 ± 11.08 [−6.3—4.5]	0.122

Quantitative variables are presented as mean ± standard deviation (SD), followed by ranges in brackets; ALBI: albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; NASH: non-alcoholic steato-hepatitis; AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma; SIRT: selective internal radiation therapy; TACE: transarterial chemo-embolization; INR: international normalized ratio; MELD: model for end-stage liver disease.

Table 3 Univariate analysis using logistic and linear regression to search for variables associated with DeltaMELD.

Logistic regression	Regression coefficient(Q1; Q3)	*n*	*P*
Sex			
Male	0.36 (−0.44; 1.04)	76	0.889
Female	0.092 (−0.14; 0.24)	10	—
Cirrhosis	0.22 (−0.37; 1.11)	78	0.824
NASH	0 (−0.30; 0.50)	15	0.402
Alcohol	0.39 (−0.33; 0.91)	50	0.229
Viral (HBV/HCV)	0 (−0.63; 1.16)	34	0.7
ALBI grade			
1	0.15 (−0.29; 0.84)	38	0.564
2	0.39 (−0.45; 1.22)	48	—
Portal hypertension			
Endoscopic	0.68 (−0.22; 1.10)	24	0.266
Platelet count < 100000 g/l	0.11 (−0.68; 1.26)	24	0.682
Previous treatment			
None	0.17 (−0.49; 0.85)	36	0.911
Surgery	0.78 (0; 1.44)	13	0.408
Percutaneous ablation	0.39 (−0.17; 1.15)	21	0.421
TACE	0.59 (−0.27; 1.22)	23	0.508
Macroscopic portal vein thrombosis	−0.09 (−0.65; 0.39)	17	0.096
Treatment			
TACE	0.60 (−0.30; 1.31)	63	0.029
SIRT	−0.17 (−0.49; 0.32)	23	—
Linear regression	**Correlation coefficient[95%CI]**	**n**	***P***
Pre-treatment MELD score	−0.108 [−0.313; 0.106]	86	0.316
Pre-treatment ALBI score	0.0954 [−0.119; 0.301]	86	0.384
Nodule number	−0.0582 [−0.267; 0.156]	86	0.592
Main nodule diameter (mm)	0.0493 [−0.164; 0.259]	86	0.652

ALBI: albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; NASH: non-alcoholic steato-hepatitis; AFP: alpha-fetoprotein; HCC: hepatocellular carcinoma; SIRT: selective internal radiation therapy; TACE: transarterial chemo-embolization; INR: international normalized ratio; MELD: model for end-stage liver disease; CI: confidence interval.

and −0.01, respectively. Non-selective TACE were more frequently performed in Child-Pugh A patients, with a higher tumor burden.

Whether SIRT or TACE exhibits the highest degrees of liver toxicity remains to be investigated by a comparison between two similar populations to better define the place of each treatment for HCC. With the recent increase in the number of available options, treatment strategy and the place of each treatment for HCC will become a critical issue. Our study focused on unilobar HCC disease and more specifically on lobar treatments, which are a reproducible and frequent situation. Unilobar but unresectable disease could become in next years a good indication of SIRT, in first intention, in order to obtain a good efficacy while preserving liver function and arterial patency, with the condition of a full tumor targeting [28,29]. It can also point out the possibility to treat with SIRT patients not suitable for a second TACE considering the ART [30,31] or ABCR [32] scores that include an assessment of radiological tumor response and liver function based on the change in the Child-Pugh score.

Our study has several limitations. First, its retrospective design implies multiple biases. However, strict inclusion criteria were chosen, such as the selection of lobar treatments only, which had the benefit to make comparison possible between both groups, but the disadvantage of restricting the size of the study population. Second, precise tools assessing liver function variations are not available yet. The MELD score was chosen for this study, as it has proven its superiority compared with the Child-Pugh score in the general population, and represents a widely used and accepted score to objectively evaluate liver function [19]. MELD modifications have clinical relevant impact, with a variation strongly related to mortality [17,18] at 6 and 12 months. The increase of one point MELD score a month, in a time-dependent model on waiting transplantation list [17], increases mortality of 22%. Third, due to the retrospective design, a lack of standardization in procedures can be noted. Indeed, SIRT treatments were performed using either Sir-Spheres or TheraSphere and TACE was performed using idarubicin, which is not yet the main drug used for cTACE worldwide [33]. Finally, the development of arteriopathy after treatment was not analyzed [34].

In conclusion, the results of our study demonstrate significant differences in liver function deterioration following lobar SIRT versus lobar cTACE procedures in unilobar HCC disease. A worsening of the MELD score was regularly observed

following cTACE, whereas it did not vary following SIRT, even though PVT and tumor burden were higher in patients undergoing SIRT. TACE procedure was the only variable positively associated with DeltaMELD on multivariate analysis, and conversely, SIRT treatment was the only variable independently associated with a lesser liver function degradation. These results could help to better define the place of SIRT in the armamentarium against HCC.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patients.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Julien Delicque: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing — original draft; Writing — reviewing and editing.

Margaux Hermida: Data curation.

Lauranne Piron: Data curation.

Carole Allimant: Data curation.

Ali Belgour: Data curation.

Georges Philippe Pageaux: Writing — reviewing and editing.

Fayçal Ben Bouallegue: Writing — reviewing and editing.

Eric Assenat: Writing — reviewing and editing.

Denis Mariano Goulart: Writing — reviewing and editing.

Boris Guiu: Supervision; Validation.

Christophe Cassinoto: Writing — reviewing and editing; Validation; Formal analysis.

Disclosure of interest

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