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Response Assessment by Volumetric Iodine Uptake Measurement: Preliminary Experience in Patients with Intermediate-Advanced Hepatocellular Carcinoma Treated with Yttrium-90 Radioembolization

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Abstract

Purpose To retrospectively compare early response to yttrium-90 radioembolization (Y90) according to volumetric iodine uptake (VIU) changes, Response Evaluation Criteria In Solid Tumor 1.1 (RECIST 1.1) and modified RECIST (mRECIST) in patients with intermediate-advanced hepatocellular carcinoma (HCC) and to explore their association with survival.

Materials and Methods Twenty-four patients treated with Y90 and evaluated with dual-energy computed tomography before and 6 weeks after treatment were included. VIU was measured on late arterial phase spectral images; 6-week VIU response was defined as: complete response (CR, absence of enhancing tumor), partial response (PR, ≥ 15% VIU reduction), progressive disease (PD, ≥ 10% VIU increase) and stable disease (criteria of CR/PR/PD not met). RECIST 1.1 and mRECIST were evaluated at 6 weeks and 6 months. Responders included CR and PR. Overall survival (OS) was evaluated by Kaplan–Meier analysis and compared by Cox regression analysis.

Results High intraobserver and interobserver agreements were observed in VIU measurements ($k > 0.98$). VIU identified a higher number of responders (18 patients, 75%), compared to RECIST 1.1 (12.5% at 6 weeks and 23.8% at 6 months) and mRECIST (29.2% at 6 weeks and 61.9% at 6 months). There was no significant correlation between OS and RECIST 1.1 ($P = 0.45$ at 6 weeks; $P = 0.21$ at 6 months) or mRECIST ($P = 0.38$ at 6 weeks; $P = 0.79$ at 6 months); median OS was significantly higher in VIU responders (17.2 months) compared to non-responders (7.4 months) ($P = 0.0022$; HR 8.85; 95% CI 1.29–88.1).

Conclusion VIU is highly reproducible; as opposite to mRECIST and RECIST 1.1, early VIU response correlates with OS after Y90 in intermediate-advanced HCC patients.

Keywords Hepatocellular carcinoma · Tumor response · Survival · Yttrium-90 · Radioembolization · Computed tomography · Dual energy

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Introduction

Over the last decade, modified radiological criteria have been proposed for the assessment of tumor response to treatment in hepatocellular carcinoma (HCC), based on bidimensional or unidimensional measurement of persistent arterially enhancing tumor. Both European Association for the Study of the Liver (EASL) criteria [1] and modified Response Evaluation Criteria In Solid Tumors (mRECIST) [2] have been validated after percutaneous ablation and

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trans-arterial chemoembolization [3–6], and mRECIST are today recommended for HCC response assessment [7].

However, the usefulness of these criteria after yttrium-90 selective internal radiation therapy (Y90) is controversial [8–11]. Several studies have proposed alternative response criteria, based on volumetric measurements and/or functional parameters derived from perfusion and diffusion imaging [12–17]. Although much sophisticated software is being developed allowing volumetric analysis of perfusion and diffusion metrics [14, 15, 18–22], in routine clinical practice functional parameters are measured on single regions of interest (ROIs), thus being poorly reproducible [23] and potentially not representative of the entire tumor burden.

Over the last years, dual-energy computed tomography (DECT) has gained clinical acceptance. DECT can differentiate and quantify the iodine content that represents a surrogate biomarker of tumor vascularity. Gordic et al. [24] demonstrated a significant intra-individual correlation between CT arterial perfusion (AP) and iodine density obtained from DECT. Since early AP variations are correlated to survival in liver tumors [25], a similar relation could be postulated using the iodine density measured by DECT.

Compared to perfusion CT, DECT offers several advantages. It does not require additional contrast administration and radiation exposure, and, by using commercially available software, it enables iodine quantification in a segmented volume, obtaining the so-called volumetric iodine uptake (VIU), that could represent an appealing tool for quantitative response assessment [26].

Purpose of this retrospective preliminary single-center study was to compare early response to Y90 in terms of VIU changes, RECIST 1.1 and mRECIST in patients with intermediate-advanced HCC and to explore the association of these criteria with survival.

Materials and Methods

Institutional review board approved the study, and written informed consent was waived. All patients provided written informed consent for CT examinations and Y90.

We retrospectively analyzed the data of HCC patients treated with Y90 from February 2013 (date of installation of DECT equipment) to December 2015, evaluated with DECT and spectral imaging less than 1 month before the procedure and 6 ± 2 weeks (mean 6.2 ± 1.7) after treatment.

The inclusion criteria were as follows:

- naïve HCC diagnosed according to international guidelines [27] and excluded from curative treatments and

trans-arterial chemoembolization (TACE; main exclusion criteria for TACE represented by macrovascular invasion and/or tumors larger than 10 cm) after multidisciplinary tumor board discussion;
- preserved liver function (Child–Pugh A or B7);
- no contraindications to Y90 (e.g., severe allergy to contrast agents, hepato-pulmonary shunt > 20%, any other contraindication to angiography and selective catheterization).

Among 65 naïve HCC patients treated with Y90 during the study period, 41 patients did not undergo DECT with spectral imaging before and/or after treatment and were excluded from the study. The final population consisted of 24 patients (20 males; mean age 63.4 years), predominantly with liver cirrhosis (87.5%) and advanced-stage HCC (Barcelona Clinic of Liver Cancer, BCLC stage C, 87.5%) due to portal vein tumor thrombus (PVTT). Clinical and demographic data are summarized in Table 1.

Y90 Procedure

Y90 was preceded by a simulation procedure consisting of an angiographic study and a SPECT-CT examination after intraarterial injection of ^{99}Tc-labeled macroaggregated albumin.

Dosimetry was obtained according to the manufacturers' recommendation. Treatment was performed using resin ($n = 22$; Sir-Spheres®; Sirtex Medical Europe GmbH, Bonn, Germany) or glass particles ($n = 2$; TheraSphere®; Biocompatibles UK Ltd, Surrey, UK) labeled with Y90. Treatment was lobar in 19 (79.2%) cases, bi-segmental in two (8.3%) cases and segmental in three (12.5%) patients. The median treatment activity delivered was 1.25 GBq (range 0.35–4 GBq). The median dose delivered was 100 Gy (range 90–120 Gy). All the procedures were completed successfully, delivering the entire planned dose.

CT Protocol

CT protocol (Discovery CT750 HD system; GE Healthcare, Wisconsin, USA) included an unenhanced scan followed by tri-phasic acquisition, after injection of 110 mL non-ionic contrast medium (Iomeron 400; Bracco, Milan, Italy) through antecubital venous access at a flow rate of 4 mL/s, followed by 40 mL saline flush at the same flow rate, using an automatic injector (MEDRAD Stellant; MEDRAD, INC., Warrendale, PA, USA). Post-contrast imaging scan delay was determined by automated bolus triggering (SmartPrep; GE Healthcare). Late arterial phase was acquired in spectral imaging mode (Supplementary Table 1).

Table 1 Patients' demographics

Age (years)	
Median	68
Range	43–79
Gender	
Males	20 (83.3%)
Females	4 (16.7%)
ECOG performance status	
0	23 (95.8%)
1	1 (4.2%)
Cirrhosis	
Absent	3 (12.5%)
HCV	11 (45.8%)
HBV	2 (8.3%)
Dysmetabolic	4 (16.7%)
Cryptogenic	4 (16.7%)
Child–Pugh Class	
A5	16 (66.7%)
A6	7 (29.1%)
B7	1 (4.2%)
Hepatocarcinoma diagnosis	
Radiological	13 (54.2%)
Biopsy	11 (45.8%)
BCLC	
B	3 (12.5%)
C	21 (87.5%)
Tumor number	
1	6 (25.0%)
2	1 (4.2%)
3	1 (4.2%)
5	1 (4.2%)
7	2 (8.3%)
> 10	13 (54.1%)
Maximum tumor diameter (mm)	
Non-measurable[a]	9 (37.5%)
Median	93
Range	35–170
Tumor extension	
Unilobar	10 (41.7%)
Bilobar	14 (58.3%)
PVTT classification[b]	
Absent	3 (12.5%)
Ia	4 (16.7%)
Ib	8 (33.3%)
IIa	6 (25%)
IIIa	2 (8.3%)
IIIb	1 (4.2%)
Baseline tumor necrosis[c]	
Absent	19 (79.2%)
Present	5 (20.8%)

Table 1 continued

AFP (ng/ml)	
Median	12.25
Range	2–46,566

ECOG European Cooperative Oncology Group, *BCLC* Barcelona Clinic of Liver Cancer, *PVTT* portal vein tumor thrombus, *AFP* alfa-fetoprotein

[a]Lesions were considered truly non-measurable when appearing exclusively as PVTT

[b]Defined according to the classification of Shi et al. [28]

[c]Defined by the presence of extensive hypoattenuating areas in the context of the arterially enhancing tumor at baseline

Image Analysis

On an independent workstation (Advantage Windows 4.6, GE Healthcare), two independent radiologists (IB and FT, 13 and 10 years of experience) calculated VIU in treated liver lobe before and after treatments. Readers were allowed to compare the late arterial phase with the portal venous and delayed phases to recognize "viable" tumor, defined as the hyperattenuating areas in the arterial phase with washout in the subsequent phases. VIU measurement was taken by semi-automatic segmentation of the entire tumor load on the late arterial phase, including macrovascular tumor thrombosis, through manual definition of the margins of the enhancing tumor on the axial slices. Subtle and patchy hypoattenuating areas detected in the context of enhancing tumor were included in the segmented volume. Once the segmentation was completed, the software automatically calculated the overall tumor volume (cm^3) and its mean iodine content ($\mu g/cm^3$). The total VIU (mg) was obtained with the following formula: [(lesion volume × mean iodine concentration)/1000]. Segmentation was repeated three times, at an interval of at least 1 month, and the mean values were used for further analysis.

In the lack of published data, VIU response criteria were defined according to Dai et al. [26]: complete response (CR, complete disappearance of arterially enhancing tumor), partial response (PR, reduction of VIU of at least 15%), progressive disease (PD, increase in VIU of at least 10%) and stable disease (SD, criteria of CR/PR/PD not met).

Another radiologist (LC, 13 years of experience), blinded to VIU findings and original reports, retrospectively evaluated target tumor response within the treated liver lobe, at 6-week and 6-month follow-up, according to RECIST 1.1 [29] and mRECIST [2]. Response assessment was compared to the original report; in case of discrepancy, consensus was reached between three radiologists (LC, EB, RC).

For all criteria, responders included CR and PR.

Statistical Analysis

Data were analyzed using descriptive statistics (mean and standard deviation, SD) and compared with Chi square or Fisher exact test for categorical data and Student's t test for paired data. Intra- and interobserver agreements in VIU measurement were tested by Bland and Altman plot.

Survival curves were calculated as the time between first treatment and death or end of follow-up (December 15th, 2017) using Kaplan–Meier analysis, and compared with Wilcoxon signed rank test. Cox proportional hazards were used to test the association between overall survival (OS) and baseline factors and response criteria.

Statistical analysis was performed with dedicated software (SAS, Cary, NC USA) considering a P value < 0.05 as statistically significant.

Results

Radiological Tumor Response

The mean VIU values were 10.8 ± 12 mg before treatment and 8.1 ± 13.4 mg after treatment, with a mean VIU reduction of 15.7% (median 55.4%; 95% CI $-$ 33 to 64.4). Almost perfect intraobserver and interobserver agreements were observed in VIU measurements (Table 2).

By VIU criteria, PR was observed in 18 patients (75%) and PD in six cases (25%). Association between VIU response and baseline parameters is presented in Supplementary Table 2.

RECIST 1.1 and mRECIST responses are reported in Table 3. Three patients died within 6 months after

Table 2 Intraobserver and interobserver agreement in VIU measurement (Bland and Altman plot)

	Mean difference	95% CI	K
VIU before treatment			
Intraobserver			
Observer 1	$-$ 0.123	$-$ 0.79 to 0.55	0.992
Observer 2	0.231	$-$ 0.64 to 1.1	0.988
Interobserver	0.108	$-$ 0.22 to 0.44	0.998
VIU after treatment			
Intraobserver			
Observer 1	0.11	$-$ 0.77 to 1	0.988
Observer 2	0.14	$-$ 0.79 to 1.07	0.987
Interobserver	0.256	$-$ 0.21 to 0.72	0.997

Table 3 Radiological tumor response

	Volumetric iodine uptake		Total
	Non-responder	Responder	
6 weeks (24 pts)			
mRECIST			
CR	0	4 (16.7%)	4 (16.7%)
PR	0	3 (12.5%)	3 (12.5%)
SD	3 (12.5%)	11 (45.8%)	14 (58.3%)
PD	3 (12.5%)	0	3 (12.5%)
RECIST 1.1			
CR	0	0	0
PR	0	3 (12.5%)	3 (12.5%)
SD	3 (12.5%)	15 (62.5%)	18 (75.0%)
PD	3 (12.5%)	0	3 (12.5%)
6 months (21 pts)			
mRECIST			
CR	2 (9.5%)	5 (23.8%)	7 (33.3%)
PR	1 (4.8%)	5 (23.8%)	6 (28.6%)
SD	1 (4.8%)	4 (19.1%)	5 (23.8%)
PD	0	3 (14.3%)	3 (14.3%)
RECIST 1.1			
CR	0	0	0
PR	0	5 (23.8%)	5 (23.8%)
SD	2 (9.5%)	9 (42.9%)	11 (52.4%)
PD	2 (9.5%)	3 (14.3%)	5 (23.8%)

RECIST Response Evaluation Criteria In Solid Tumors, *mRECIST* modified RECIST, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

treatment; thus, the 6-month CT control was available in 21 patients. Out of 90 retrospective assessments, consensus reading was required in five cases (5.6%).

At 6 weeks, by RECIST 1.1 three cases (12.5%) were considered PR, while 75% of cases were SD. According to mRECIST, seven (29.2%) patients were defined as responders with four cases (16.7%) of CR. Six-month CT controls demonstrated an increased number of responders, with 7 (33.3%) CR and six (28.6%) PR according to mRECIST, and 5 (23.8%) PR according to RECIST 1.1. Using two-tailed Fisher's exact test, no statistically significant correlation was found between early VIU response and RECIST 1.1 ($P = 0.13$ at 6 weeks; $P = 0.19$ at 6 months) or mRECIST ($P = 0.55$ at 6 weeks; $P = 0.64$ at 6 months). Of notice, 11 cases of SD according to mRECIST and 15 cases according to RECIST 1.1 were defined as responders by VIU at early follow-up (Figs. 1, 2).

Fig. 1 74-Year-old female patient with large, single HCC nodule in segment 1 evaluated before (axial scan arterial phase, **A**; VIU measurement, **B**) and 6 weeks after (axial scan arterial phase, **C**; VIU measurement, **D**) Y90 radioembolization. Early after treatment, the lesion does not show well-defined areas of necrosis; the maximum axial diameter is reduced by 11.5% (**A**, **C**); thus, the case is defined as SD according to RECIST and mRECIST. VIU (**B**, **D**; ROI1: volume; Av: average iodine content) is reduced by 43.7% (from 8.07 to 4.54 mg); thus, the patient is considered as VIU responder. The patient died 17 months after Y90

Overall Survival

One patient was lost to follow-up 9 months after Y90. The remaining patients were followed until death or end of follow-up (December 15th, 2017). At latest follow-up, 20 patients (83.3%) had died, with a median survival of 11 months (95% CI 7.9–29.4).

Among all baseline factors, OS was significantly associated with Child–Pugh score and AFP values (Table 4).

There was no significant correlation between OS and RECIST 1.1 ($P = 0.45$ at 6 weeks and $P = 0.21$ at 6 months; Fig. 3A, B) or mRECIST ($P = 0.38$ at 6 weeks and $P = 0.79$ at 6 months; Fig. 3C, D). Conversely, VIU response was significantly associated with survival ($P = 0.0022$), with a median survival of 7.4 months (95% CI 3.1–10.7) in non-responders and 17.2 months in responders (95% CI 10.8–41) (Fig. 3E).

Factors identified at univariate analysis (Child–Pugh score, AFP and VIU response) were confirmed to be independently associated with survival in the multivariate model (Table 4).

Discussion

In the present study, a new criterion was investigated that combines volumetry and iodine content measurement as the expression of tumor vascularity. Our preliminary results demonstrate that VIU can represent a reliable tool for the early assessment of tumor response after Y90.

RECIST 1.1 have a limited role in HCC response assessment [30], and mRECIST are currently recommended by European guidelines for HCC follow-up [7].

In a radiological–pathological analysis of 15 patients transplanted after Y90 with or without, Vouche et al. [10] demonstrated that, although EASL and mRECIST detected a higher number of responders compared to WHO and RECIST, none of these criteria could reliably predict complete pathological necrosis.
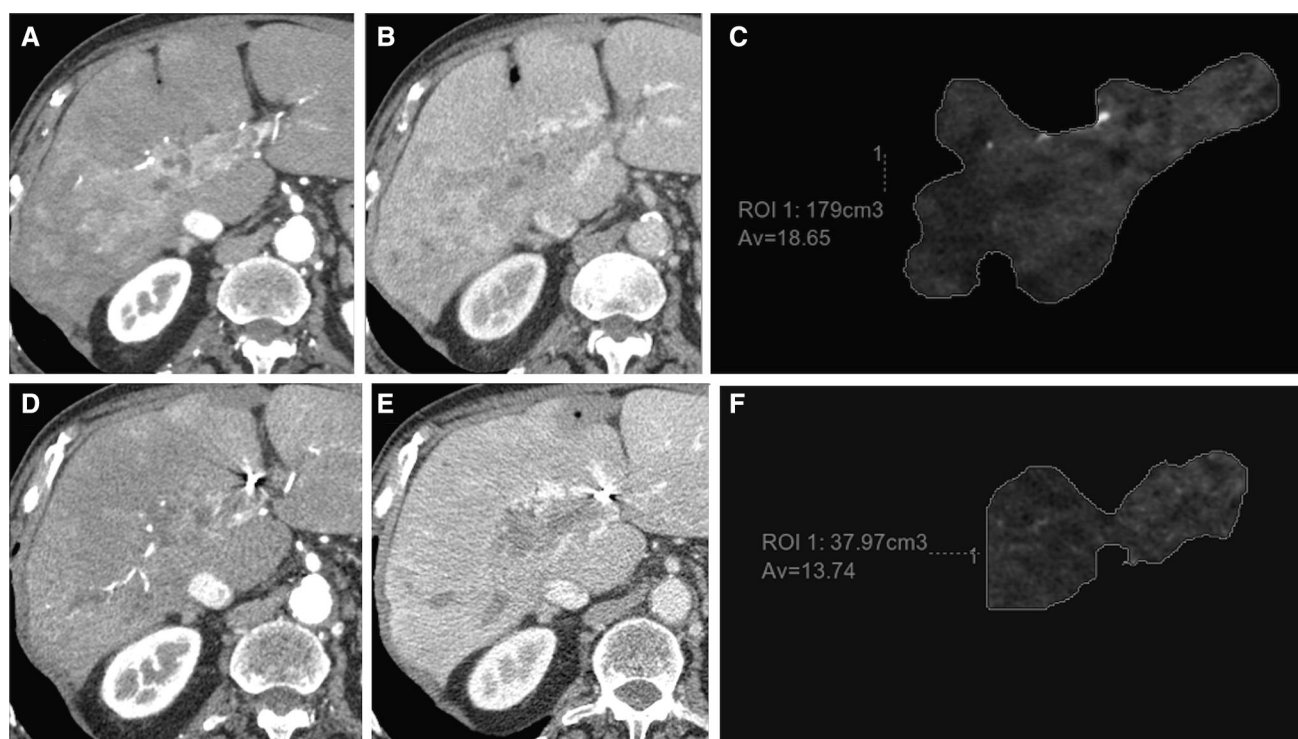
Fig. 2 75-Year-old male patient with bioptically proven HCC invading the right portal vein and extending into the left portal vein; CT images performed before (late arterial phase, **A**; portal venous phase, **B**; VIU measurement **C**) and after (late arterial phase, **D**; portal venous phase, **E**; VIU measurement, **F**) Y90. After treatment, at visual assessment, the extension of portal vein infiltration is reduced with concomitant reduction in arterial enhancement. However, as portal vein thrombosis is a non-target lesion, the patient was considered stable both by RECIST 1.1 and mRECIST. VIU is reduced from 3.33 to 0.52 mg (reduction of 84%), defining the patient as responder. The patient died 17.5 months after Y90

The limitations of RECIST and mRECIST are partially related to the treatment's nature. The main effect of Y90 is the exposure to very high radiation doses, while the embolic effect is minimal, particularly when using glass spheres compared to resin spheres. Hence, at early follow-up tumor necrosis may not be macroscopically evident or may be inhomogenously distributed, and, therefore, difficult to quantify, despite effective therapy. Moreover, radiation-induced inflammation is often appreciated in the treated area as arterially enhancing tissue that may be difficult to differentiate from "viable" tumor [8–10, 31].

HCC stage may also play a role in defining usefulness of size criteria. A recent study on 134 BCLC A patients with single HCC demonstrated that EASL criteria outperform RECIST 1.1 in predicting survival [32]. However, Y90 is frequently indicated in patients with PVTT and infiltrative HCC [33–36], which are defined non-measurable and non-target lesions (Fig. 2) [2, 29]. Thus, in more advanced stages, a relatively high number of patients will be classified as having SD at early follow-up using conventional criteria. In our series, 54.2 and 70.8% of patients were defined as SD with mRECIST and RECIST 1.1, respectively, while the majority of these SD cases were VIU responders.

Functional biomarkers derived from perfusion and diffusion imaging are under investigation for tumor response assessment [15, 16, 25, 37]. However, they are usually calculated on single axial planes and may not be representative of the entire tumor volume. In the future, volumetric measurement of diffusion and/or perfusion parameters could become the reference for tumor response evaluation [20–23]. However, these measurements require complex algorithms and dedicated software that are not yet widely available.

DECT is gaining acceptance as a valid technology providing high-quality images and allowing identification of different materials [38], with promising clinical applications. By dedicated software provided by the manufacturer, iodine content can be measured within a segmented volume, representing an appealing biomarker of tumor vascularity. Iodine uptake has been investigated in patients under sorafenib [26], and it has been demonstrated to be significantly associated with arterial perfusion [24]. Compared to perfusion CT, it does not require additional acquisitions and contrast administrations, representing an

Table 4 Univariate and multivariate analyses of factors associated with survival

Variable	Univariate		Multivariate	
	OS HR (95% CI)	*P*	OS HR (95% CI)	*P*
Age	1.01 (0.98–1.05)	0.41		
Gender		0.22		
Males (*n* = 20)	1.00			
Females (*n* = 4)	2.17 (0.58–6.42)			
ECOG performance status		0.27		
0 (*n* = 23)	1.00			
1 (*n* = 1)	4.08 (0.21–25.3)			
Cirrhosis		0.79		
Absent (*n* = 3)	1.00			
HCV (*n* = 11)	0.39 (0.10–1.88)			
HBV (*n* = 2)	0.66 (0.08–4.05)			
Dysmetabolic (*n* = 4)	0.43 (0.08–2.40)			
Cryptogenic (*n* = 4)	0.53 (0.11–2.75)			
Child–Pugh Class		**0.047**		**0.02**
5 (*n* = 16)	1.00		1.00	
6 (*n* = 7)	3.64 (1.22–10.6)		14.98 (2.14–300.1)	
7 (*n* = 1)	1.74e–8 (0–10.0)		1.42e − 7 (0–696)	
BCLC		0.22		
B (*n* = 3)	1.00			
C (*n* = 21)	2.32 (0.65–14.8)			
Number of lesions		0.35		
Single (*n* = 6)	1.00			
Multiple (*n* = 18)	1.66 (0.60–5.83)			
Number of lesions		0.39		
< 5 (*n* = 8)	1.00			
≥ 5 (*n* = 16)	1.52 (0.60–4.35)			
Maximum tumor diameter		0.72		
< 90 mm (*n* = 7)	1.00			
≥ 90 mm (*n* = 8)	1.55 (0.49–5.08)			
Non-measurable (*n* = 9)	1.43 (0.46–4.58)			
Tumor extension		0.87		
Unilobar (*n* = 10)	1.00			
Bilobar (*n* = 14)	1.07 (0.44–2.75)			
PVTT[a]		0.30		
Absent (*n* = 3)	1.00			
I–II (*n* = 18)	2.61 (0.71–16.78)			
III (*n* = 6)	1.32 (0.16–11.16)			
Baseline tumor necrosis		0.33		
Absent (*n* = 19)	1.00			
Present (*n* = 5)	1.83 (0.50–5.40)			
AFP (ng/ml)		**0.04**		**0.0002**
≤ 200 (*n* = 18)	1.00		1.00	
> 200 (*n* = 6)	3.62 (1.04–12.1)		37.6 (4.81–868)	
Treatment extension		0.78		
Segmental (*n* = 5)	1			
Lobar (*n* = 19)	1.17 (0.42–4.14)			

Table 4 continued

Variable	Univariate		Multivariate	
	OS HR (95% CI)	P	OS HR (95% CI)	P
VIU		**0.0026**		**0.03**
Responders (n = 18)	1.00		1.00	
Non-responders (n = 6)	7.59 (2.07–31.08)		8.85 (1.29–88.1)	
RECIST 1.1 (6 weeks)		0.15		
Responders (n = 3)	1.00			
Non-responders (n = 21)	2.75 (0.73–18.2)			
mRECIST (6 weeks)		0.13		
Responders (n = 7)	1.00			
Non-responders (n = 17)	2.33 (0.79–8.65)			
RECIST 1.1 (6 months)		0.07		
Responders (n = 5)	1.00			
Non-responders (n = 16)	3.47 (0.93–22.5)			
mRECIST (6 months)		0.64		
Responders (n = 8)	1.00			
Non-responders (n = 13)	1.28 (0.44–3.61)			

Statistically significant results are reported in bold

ECOG European Cooperative Oncology Group, *BCLC* Barcelona Clinic of Liver Cancer, *PVTT* portal vein tumor thrombus, *AFP* alfa-fetoprotein, *VIU* volumetric iodine uptake, *RECIST* Response Evaluation Criteria In Solid Tumors, *mRECIST* modified RECIST

[a]Defined according to the classification of Shi et al. [28]

interesting tool in daily clinical practice. Moreover, VIU is a reproducible quantitative parameter, as demonstrated by the excellent intra- and interobserver agreement in our study.

Our results show that, using the VIU cutoff value proposed by Dai et al. [26], it is possible to identify a higher number of responders compared to RECIST 1.1 and mRECIST at early follow-up after Y90 and that VIU response has a significant correlation with OS, as opposite to mRECIST and RECIST 1.1.

In view of the limitations of conventional size criteria in the early follow-up after Y90, most experts suggest that response should be assessed 3–6 months after treatment [32]. In the present study, 6-month RECIST 1.1 and mRECIST responses were not significantly associated with OS, despite the higher number of responders. Besides, evaluating tumor response later on follow-up implies a minimum time of 6–9 months before considering any other therapeutic approach in non-responders, with a dropout risk due to clinical deterioration and tumor progression. A much sensitive response parameter (such as VIU) used early after Y90 might allow prompt recognition of non-responders, who may be considered for alternative treatments.

Our study is limited by the retrospective design and the low number of patients. Population was heterogeneous in terms of clinical and tumor characteristics, influencing our results. Although well-known prognostic factors such as

Fig. 3 Kaplan–Meier curves comparing overall survival between responders and non-responders according to RECIST 1.1 at 6 weeks (**A**) and at 6 months (**B**), mRECIST at 6 weeks (**C**) and at 6 months (**D**) and VIU (**E**). Only VIU response showed a statistically significant association with overall survival (P = 0.0026)

Child–Pugh score and AFP values were confirmed in our study, other parameters, such as BCLC stage and PVTT extent, were not identified as significantly associated with OS, because of the small sample size. Due to the limited sample size, VIU cutoff values were not calculated by statistical means and were derived from the only publication proposing VIU response criteria in HCC patients [26]. Although these criteria seem to be reliable, given the significant association with OS, prospective larger studies are needed to calculate VIU cutoff values. Finally, mRECIST and RECIST were evaluated by a single radiologist; however, results were compared to the original reports and, in case of disagreement, consensus was reached.

Despite these limitations, our preliminary study demonstrates that, while mRECIST and RECIST 1.1 fail to demonstrate a correlation with post-treatment OS, VIU may represent a highly reproducible and useful tool for the early assessment of tumor response in intermediate-advanced HCC patients treated with Y90. Prospective studies are needed to confirm our preliminary findings.
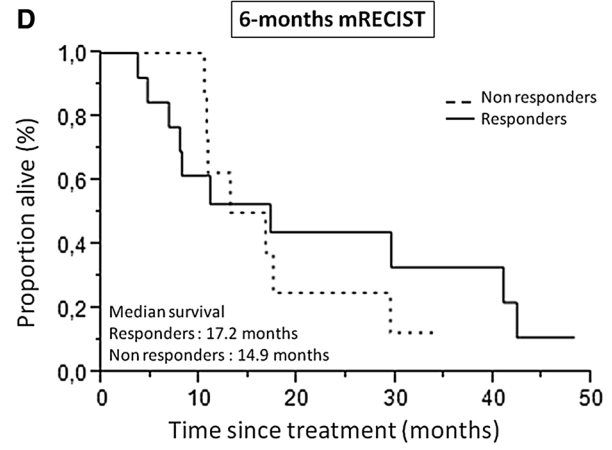
A 6-weeks RECIST 1.1
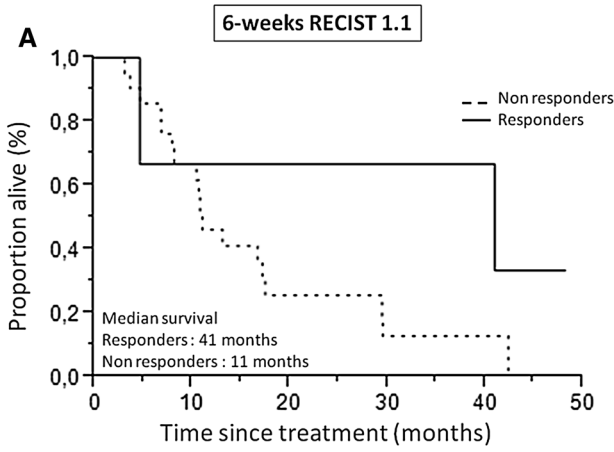
Number at risk	0	6 mo	12 mo	18 mo	24 mo
Non responders	21	19	10	6	5
Responders	3	3	3	3	3

B 6-months RECIST 1.1
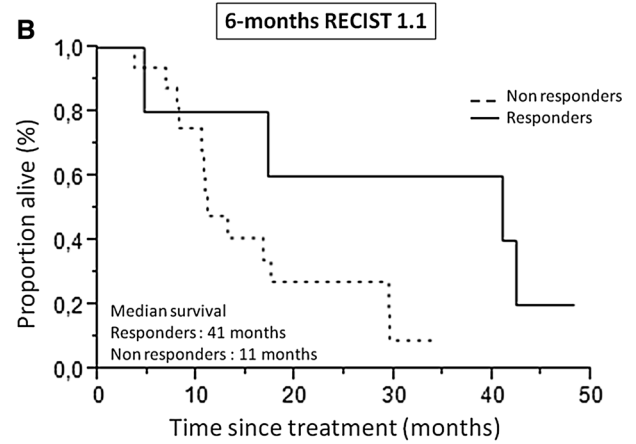
Number at risk	0	6 mo	12 mo	18 mo	24 mo
Non responders	16	16	8	5	5
Responders	5	5	5	4	4

C 6-weeks mRECIST
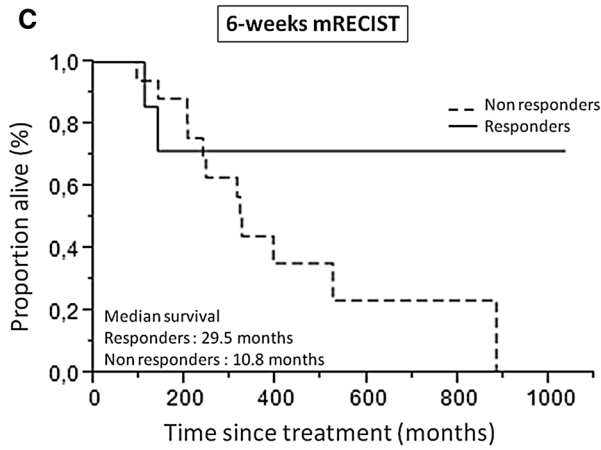
Number at risk	0	6 mo	12 mo	18 mo	24 mo
Non responders	17	16	8	4	4
Responders	7	6	5	5	5

D 6-months mRECIST

Number at risk	0	6 mo	12 mo	18 mo	24 mo
Non responders	8	8	6	3	3
Responders	13	12	7	6	6

E 6-weeks VIU response
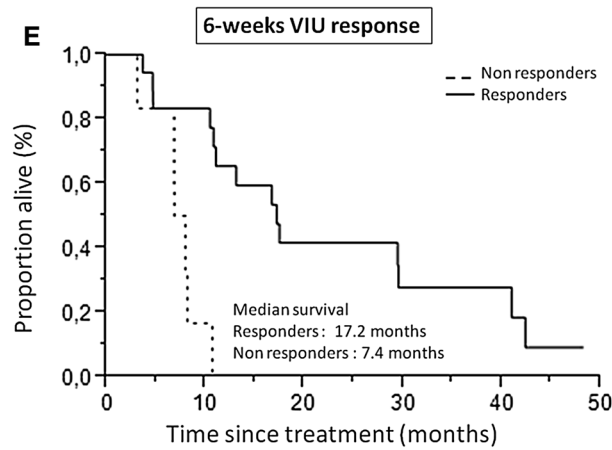
Number at risk	0	6 mo	12 mo	18 mo	24 mo
Non responders	6	6	0	0	0
Responders	18	16	12	8	8

Compliance with Ethical Standards

Conflict of interest Irene Bargellini received honoraria from GE Healthcare, Biocompatibles UK LTD, Sirtex, Bayer Spa; Laura Crocetti received honoraria from GE Healthcare; the remaining authors have no conflict of interests to declare.

Ethical Approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent For this type of study, informed consent was waived by the Local Ethical Committee.

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