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TITLE PAGE

First-Line Selective Internal Radiation Therapy in Patient with Uveal Melanoma Liver Metastases

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Abbreviations:

SIRT: Selective Internal Radiation Therapy; RECIST: Response Evaluation Criteria in Solid Tumors; WHO: World Health Organization; EASL: European Association for the Study of Liver Disease; OS: overall survival; ECOG: Eastern Cooperative Oncology Group; 99mTc-MAA: Technetium-99m macroaggregated albumin; PFS: progression-free survival.

ABSTRACT

Survival of patients with uveal melanoma liver metastases is strongly correlated with disease control in the liver. Unfortunately, there are no standardized treatments for this chemo-resistant disease. Selective Internal Radiation Therapy (SIRT) has been tested as salvage therapy but no data exist about its use as first-line therapy. The purpose of this study was to investigate the safety and efficacy of SIRT used as first-line therapy in patients with uveal melanoma metastatic to the liver. **Methods:** This retrospective analysis of a prospectively collected cohort included 22 patients treated with first-line SIRT. Biochemical and clinical toxicities were recorded. Tumor response included European Association for the Study of Liver Disease (EASL) criteria. Predictive factors of survival were analyzed by uni-/multivariate analysis. Overall survival was calculated using the Kaplan-Meier method with the log-rank test. **Results:** Grade 3-4 biological and clinical toxicities occurred in 24% of patients (for both). According to EASL, disease control at 6 months after SIRT was achieved in 15 (52%) of the 29 SIRT and was predictive of survival. Median overall survival from the first SIRT was 18 months [95% confidence interval (95%CI), 8-28]. At the time of the analysis, 5 patients (23%) were still alive. In multivariate analysis, largest lesion size [1.22 hazard ratio (HR); 95%CI, 0.98-1.53], liver tumor volume [1.002 HR; 95%CI, 1.0004-1.003], subsequent systemic [0.04 HR; 95%CI, 0.006-0.24] and liver-directed locoregional therapies [0.204 HR; 95%CI, 0.04-0.94] were predictive of survival. **Conclusion:** First-line SIRT is safe and demonstrated promising outcomes in patients with uveal melanoma liver metastases. Subsequent systemic and liver-directed locoregional therapies ameliorated survival, highlighting the potential for improved outcomes with combinatorial approaches. The

results of this study suggest that prospective trials using first-line SIRT should be considered.

Keywords:

Uveal melanoma, Radioembolization, SIRT, Tumor Response, Overall survival

INTRODUCTION

Uveal melanoma is a rare disease with an incidence of 5.1 per million in the United States but constitutes the most common primary intraocular malignant tumor in adults. The 5-year survival rate is approximately 80% (*1*). However, 10-30% of patients with uveal melanoma will develop systemic metastases within 5 years and up to 45% within 15 years, predominantly in the liver (70-90% of cases) (*2*,*3*). After diagnosis of metastases, the prognosis is greatly reduced with a median overall survival (OS) of only 2 months without treatment and 6-13 months for treated patients (*2*,*4*). Therefore, patient survival is strongly correlated with hepatic tumor control.

While local eye treatments (proton beam, plaque brachytherapy) of the primary tumor are generally successful in eliminating cancer tissue and preventing local recurrence, there are no effective systemic therapies for metastatic uveal melanoma (*5*). Because patient prognosis is highly dependent on progression of liver metastases, various liver-directed locoregional treatments have been tested with the goal of extending survival. Despite encouraging results, surgery or local ablations are only rarely performed as most of the patients develop widespread liver metastases. Thus, treatments capable of covering the whole liver such as transarterial chemoembolization, isolated hepatic perfusion and selective internal radiation therapy (SIRT) – also called yttrium-90 (Y^{90}) radioembolization - are usually carried out (*6*).

The scientific rationale for SIRT is twofold. SIRT consists of the administration in the hepatic artery of Y^{90}-radioactive microspheres. As liver metastases receive their blood supply mainly from neovessels arising from the hepatic artery, administered

microspheres are preferentially trapped into the tumor microvasculature minimizing damage to the surrounding normal liver parenchyma (*7*). Moreover, uveal melanoma is a radiosensitive tumor as demonstrated by treatment success of the primary eye tumor, thus SIRT holds significant promise in achieving meaningful results in the treatment of liver metastases. Few studies have reported the use of SIRT in uveal melanoma patients with liver metastases as salvage therapy (*8*–*14*). SIRT demonstrated to be safe in patients with liver dominant disease, unresectable and refractory to other treatment modalities such as systemic chemotherapy, with a reported median OS ranging from 3.1-12.3 months (*8*–*14*).

The aim of our study was to investigate the safety and efficacy of SIRT used as first-line therapy in patients with uveal melanoma metastatic to the liver.

MATERIALS AND METHODS

This single-institution retrospective study of a prospectively collected patient cohort was approved by the Institutional Review Board. Informed consent was waived.

Patient Population

Twenty-nine consecutive patients were considered for SIRT for liver metastases of uveal melanoma between 2010-2017. Baseline extra-hepatic metastases were not considered a contraindication as survival is related to hepatic disease control (*2*,*15*). All patients were discussed at our multidisciplinary liver tumor board and provided informed consent for the procedure.

Inclusion criteria included: 1) biopsy-proven liver metastases, 2) Eastern Cooperative Oncology Group (ECOG) ≤2, 3) adequate liver (bilirubin ≤2mg/dL), hematologic (granulocyte count ≥1.5x10^9/L, platelets ≥50x10^9/L)) and renal (creatinine <2mg/dL) functions (*16*). Seven patients were excluded for the following reasons: previous systemic or liver-directed therapies (n=2), absence of follow-up after SIRT (n=3), estimated pulmonary shunt fraction >20% (n=1), and rapidly progressive liver metastases and worsening of liver function during treatment planning precluding SIRT (n=1). Thus, the final study population included 22 patients.

Patient assessment and toxicity analysis

Patients underwent assessment of medical history and imaging, and physical examination. Baseline complete laboratory tests (including liver, renal and hematologic functions) and imaging (whole body PET/CT, contrast-enhanced thoracoabdominal CT and liver MRI) were performed. From this data, patient baseline characteristics were

obtained. Patients were followed by clinical assessment, laboratory tests, and CT/MRI) to assess treatment toxicity and tumor response. The advent of extrahepatic spread, if any, was recorded. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.0).

Treatment

Pre-procedure simulation angiography allowed embolization of non-target extra-hepatic vessels (when appropriate) followed by injection of Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) in proper, left or right hepatic artery depending on tumor distribution and treatment planning. Single-photon emission CT with integrated CT (SPECT/CT) permitted to quantify the tumor volume to be treated, tumor-to-liver uptake ratio, pulmonary and systemic shunt fraction and dosimetry planning. The tumor volume to be treated was also calculated by contouring the metastases on pretreatment imaging (liver MRI/CT, PET/CT or SPECT/CT after 99mTc-MAA injection). SIRT (TheraSphere; Biocompatibles, UK and SIR-Spheres; Sirtex Medical, Australia) was performed in the weeks following the simulation angiography and on an outpatient basis (*16*,*17*). Methods used for calculating the required activity for injection and the actual dose delivered (partition model) have been reported elsewhere (*17*–*19*). Depending on tumor distribution and vascular access, Y^{90}-microspheres were administered either to one lobe or to the whole liver. In case of bilobar disease and sequential lobar treatment, the contralateral side was treated 1-2 months after the first treatment. Depending on subsequent imaging follow-up, patients with incompletely treated disease or progressive liver disease were retreated.

Response Assessment

Image analysis was performed on MRIs/CTs by two radiologists during the same session to ensure careful comparison between pre- and post-SIRT findings. Any discrepancy was resolved in consensus. Up to 2 target liver lesions (≥1cm) were chosen per patient. The two largest target lesions were evaluated (*20*). Tumor response was evaluated by World Health Organization (WHO), Response Evaluation Criteria in Solid Tumors (RECIST), modified RECIST (mRECIST), and European Association for the Study of Liver Disease (EASL) guidelines (*21–24*). Patients were classified as responders (complete response, (CR); partial response, (PR)) or non-responders (stable disease, (SD); progressive disease; (PD)) according to each tumor response criteria (*20–24*). Disease control rate (DCR) was defined as PR+CR+SD.

Statistical Analysis

Statistical analysis was performed using Anaconda 2.7 (Python Language Reference), the python module lifelines and Rpy2 to link python with R 3.1.3 (R Foundation for Statistical Computing, Austria). Data were summarized using descriptive statistics. Overall survival, progression-free survival (PFS), and hepatic PFS were calculated from the first SIRT until death or last follow-up. Patients alive were censored at the end of the study period. Survival times were analyzed by the Kaplan-Meier method and differences were calculated using log-rank test. Univariate/multivariate Cox proportional hazard ratios (HR) were performed to identify factors associated with survival. Factors with a *P*-value <.1 in univariate analysis were included in multivariate analysis. A *P*-value <.05 was considered significant.

RESULTS

Patient Data

Patient characteristics are summarized in table 1. Mean patient age was 59 years (range, 30-82). Most patients had an ECOG 0 (73%), bilobar disease (91%) with no extrahepatic disease (82%). The median diameter of the largest metastasis was 2.6 cm (range, 1.4-18.6) and the median SUVmax was 7.4 (range, 3.3-22.1). Overall, 77% and 41% of the patients received systemic and liver-directed locoregional therapiesafter SIRT, respectively (supplemental table 1). Seventeen patients (77%) developed extrahepatic metastases after SIRT. The median follow-up period from first SIRT was 15 months (range, 1-65).

Treatment Data

Treatment characteristics are summarized in table 2. Twenty-nine SIRTs were performed (1.3 procedures per patient, range 1-3). 15 patients (68%) required prophylactic coil embolization. A majority of patients (73%) underwent only one SIRT. 41% received whole liver treatment in one session, 23% received fractioned whole liver treatment (sequential right and left lobes) and 36% received only single lobe treatment. Whole liver SIRT was repeated in one patient. One patient was planned for bilobar treatment in two sessions but a celiac trunk dissection after right liver SIRT prevented left liver treatment. In another patient, activity and dose were calculated for whole liver SIRT but post-treatment SPECT/CT showed only right liver Y^{90}-microspheres deposition. In another patient, activity and dose were estimated for right liver SIRT but post-treatment SPECT/CT demonstrated whole liver Y^{90}-microspheres deposition (under-treatment).

Activities and doses administered are shown in table 2. Median activity infused per patient was 1.8GBq. Median radiation doses to tumor, healthy liver and lungs were 155.4, 46.2 and 1.1 Gy, respectively.

Toxicities

Toxicities are summarized in supplemental table 2. Grade 1 and 2 clinical toxicities included mainly mild to moderate abdominal pain and fatigue (9 patients, 41%). Grade 3 toxicities (7 patients, 32%) included more severe abdominal pain requiring hospitalization (2 patients), radiation cholecystitis (3 patients) and clinical symptoms of liver failure (2 patients). There were no grade 4 clinical toxicities. Grade 3 and 4 laboratory perturbations were observed in 4 (18%) and 3 (14%) patients, respectively. No difference in toxicity was noted between glass and resin microspheres. All patients were either treated conservatively with satisfactory evolution or asymptomatic. There were no treatment-related deaths.

Tumor Response and Survival Prediction

Supplemental table 3 summarizes tumor response. All responses criteria categorized a majority of the patients as SD at 3 months post SIRT. However, the number of responders (PR and CR) increased at 6 months. The absolute number of responders at 6 months was higher for mRECIST and EASL criteria (47% and 58%, respectively) than for RECIST and WHO criteria (16% and 26%, respectively). None of the response criteria was predictive of survival at 3 months post SIRT except for EASL that was the only criteria that showed a significant difference in responders and non-responders with a median survival of 26 vs. 11 months, respectively (table 3). At 6

months post SIRT, mRECIST and EASL were able to accurately stratify patients responders from non-responders (27 versus 11.5 months and 26 versus 11.5 months, respectively) and were predictive of survival (both *P*<.05, table 3) (figure 1). Stratification of response by DCR was not discriminant at 3 months for any of the response criteria (all: *P*>.05), whereas EASL was the only criteria to accurately predict survival at 6 months post therapy (*P*=0.002 figure 2).

Survival Outcomes

At the time of the analysis, 17 patients (77%) had died and 5 (23%) were alive. Median OS after the diagnosis of liver metastases and after the first SIRT was 20 months (95% confidence interval (95%CI), 11-31) and 18 months (95%CI, 8-28), respectively. The median HPFS was found to be 8 months (95%CI, 5-26) and overall PFS 5 months (95%CI, 2-17).

Parameters used for univariate and multivariate analyses are reported in table 4. In univariate analysis, liver tumor burden estimated by the largest lesion size [HR: 1.3; 95%CI, 1.08-1.57], treated tumor volume [HR: 1.0008; 95%CI, 1.0001-1.002], post-SIRT systemic [HR: .33; 95%CI .12-.86] and liver-directed locoregional [HR: .21; 95%CI, .07-.62)] therapies were significant predictors of survival (all: *P*<.05), whereas ECOG status [HR: 2.73; 95%CI, .88 - 8.44] showed a trend (*P*=.08). The mean activity administered per patient was omitted because of collinearity with the treated tumor volume, the latter being directly used to calculate the activity to be administered (*17*). All these parameters remained significantly correlated with survival in multivariate analysis (*P*<.05) but ECOG (*P*=.38) (table 4).

DISCUSSION

The main finding of this study is that first-line SIRT is safe and demonstrate promising outcomes in patients with uveal melanoma liver metastases.

Our study showed that first-line SIRT was safe. Our complication rate (grade 3-4 clinical and laboratory toxicities observed in 32% of patients for both) may seem higher than in previous studies (0-25%) (*8*–*13*). A potential explanation is that we adopted a conservative methodology and reported toxicities at any time during the 6-month period following SIRT and we did not use the 30-day time cut-off used in many reports. Moreover, patients with pre-existing laboratory toxicities were counted as toxicities at follow-up, even if there was no change in grade. Furthermore, this could be attributed to the administered activity which was higher in our study when compared to previously published data for SIRT as salvage therapy (median, 1.8GBq vs. 0.33-1.55GBq, respectively) (*8*–*11,13*). Indeed, in the absence of previous hepatic treatment in our patients, no dose reduction was deemed necessary as opposed to when SIRT was used as salvage (*9*,*13*). Importantly, observed adverse events in our study were self-limited and either asymptomatic or managed conservatively.

Our study included a thorough analysis of size-based (WHO/RECIST) and enhancement-based (mRECIST/EASL) criteria. WHO and RECIST categorized a majority of the patients as non-responders following SIRT and were unable to predict survival. However, when using enhancement-based criteria, at 3 months post therapy for EASL (a trend was observed for mRECIST, *P*=.052) and at 6 months for both mRECIST and EASL, an accurate survival prediction could be done. Taken together these results

show, as demonstrated previously (*20*,*25*,*26*), that response criteria assessing viable tumor (i.e. enhancement) outperform response criteria assessing anatomic size-based changes in the tumors in terms of their ability not only to correctly identify responders from non-responders, but also to do it at an earlier time point, and that response to therapy may be delayed and some patients who do not respond early following SIRT may still exhibit response at 6 months. Published reports in a salvage setting used RECIST (also WHO/EASL (*11*)) (*8*–*14*,*27*). Our results of DCR using RECIST compares favorably when compared to SIRT as salvage therapy at 3 months, 84% vs. 43-78% (*10*,*12*,*13*). When using mRECIST or EASL the DCR at 3 months were 92% and 87.5%, respectively. The interval between SIRT and radiological response evaluation was not clearly mentioned in the other studies (*8*,*9*,*11*,*14*), and 2 of them reported altogether ocular, cutaneous and other melanomas (*11*,*14*), which makes any comparison hazardous.

Median OS ranging from 3.1-12.3 months have been obtained in previous studies about SIRT used as salvage therapy (*8*–*14*). Consequently, our results are promising with a median OS of 18 months (95%CI, 8-28) following first-line SIRT and are similar to a recently published small cohort of uveal melanoma patients also treated with first-line SIRT (*27*). Of note, at the end of our follow-up period, 5 patients (23%) were still alive underlying the fact that reported outcomes might still improve further. Our survival time is longer than 14.9 months estimated by a prognostic model with the most favourable parameters (i.e. high Karnofsky index, low dimension of the largest metastasis and low alkaline phosphatase level) (*28*). Our results are also encouraging in light of the fact that patients treated with first-line SIRT may have good or aggressive cancer biology,

whereas when salvage SIRT is used, some patients with aggressive disease and initially treated with, e.g. systemic chemotherapy, will die before undergoing salvage SIRT, while other patients will have hepatic disease progression precluding SIRT. So these patients are not captured in the salvage SIRT studies (patient selection bias). Importantly, the median HPFS of 8 months (95%CI, 5-26) also compares favorably to 4.2-5.9 months found in previous studies (*9*–*11*,*14*). Collectively, these results confirm the radiosensitivity of uveal melanoma liver metastases and highlight SIRT's ability to effectively control liver disease. The absence of dose reduction performed in a salvage setting (*9,13*) may potentially explain part of the increased efficacy of first-line SIRT in view of the link between the dose and tumor response (*29*). Moreover, we found that the tumor burden was negatively correlated with survival. This is consistent with previously published data in uveal melanoma patients treated with SIRT as salvage therapy (*9*,*14*). This sheds light on the importance of surveillance programmes screening for liver metastases, since the earlier they are detected the better the chances of getting effective treatment (*28*). Of note, baseline extra-hepatic metastases or development of extrahepatic metastatic disease during follow-up were not correlated with survival, highlighting not only the importance of hepatic disease control on survival but also that extrahepatic metastases should not be considered a contraindication for patients to undergo SIRT.

Subsequent liver-directed and systemic therapies performed after SIRT were also positively correlated with survival. In our study, 4 patients (18%) underwent chemoembolization and 5 (23%) thermal ablations. Transarterial chemoembolization demonstrated to increase OS particularly in patients with a limited tumor burden,

preserved liver function and good performance status (*30*). Similarly to surgery, thermal ablations demonstrated to be effective in case of localized disease (*31*). Although most of our patients had diffuse involvement of liver parenchyma, in some of them, tumor burden was predominant in one lobe allowing the ablation of contralateral isolated lesions. Taken together these results show the importance of patient selection and combination therapies. Although the heterogeneity of therapies that our patient cohort received does not allow us to draw definite conclusions about one particular post-SIRT treatment, first-line SIRT not only does not preclude subsequent treatments (liver-directed and systemic), but it might have synergistic abilities, in particular with immunotherapies (*32*). Further studies combining first-line SIRT with systemic therapies are needed.

Strengths of this study include a comprehensive safety/toxicity, tumor response and survival analysis of a clinically relevant scenario - first-line SIRT in uveal melanoma patients - in a real-life setting at a comprehensive cancer center. A long follow-up was performed to provide mature data. There were several limitations to this research. First, it is a retrospective single-center study with a limited number of patients. However, uveal melanoma is a rare disease and our sample size is larger than most published data (*8*,*10–12*,*14*,*27*,*33*). Moreover, our cohort is composed of prospectively collected patients as first-line SIRT is performed systematically whenever possible, leaving its use as second-or more-line depending on patient's referral. Second, patients lost to follow-up (3/25, 12%) might have had potential unrecognized outcomes. Third, most of our patients received different additional therapies after SIRT which may have biased the results. However, this reflects real-life practice of a highly resistant disease with no

established treatment. Fourth, post-SIRT PET-CT was not available for all patients and functional response could not be evaluated. Fifth, stratification of uveal melanoma according to their genetic subtypes was not available. Yet, this is of great interest for the development of molecularly targeted therapies.

In conclusion, first-line SIRT is safe and demonstrated promising outcomes in patients with uveal melanoma liver metastases. Importantly, subsequent systemic and liver-directed locoregionally therapies were not only possible after first-line SIRT but improved survival, highlighting the potential for improved outcomes with combinatorial approaches. The results of this study suggest that prospective trials using first-line SIRT should be considered.

DISCLOSURE

The authors have no potential conflicts of interest to report.

KEY POINTS

Question

Is first-line SIRT a safe and effective option for patients with uveal melanoma liver metastases?

Pertinent findings

First-line SIRT for patient with uveal melanoma liver metastases is safe and achieves promising survival outcomes. Subsequent liver-directed and systemic therapies positively influenced survival and a combined approach seems therefore crucial. Lower tumor burden is associated with longer survival so early detection and treatment with SIRT are essential for improved outcomes.

Implications for patient care

First-line SIRT for patient with uveal melanoma liver metastases achieves promising survival and does not preclude subsequent liver-directed and systemic therapies, highlighting that combinatorial approaches may improve existing survival outcomes.

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TABLES

TABLE 1 – Baseline characteristics

Characteristic		Value (%)
No. of patients		22 (100)
Sex		
	Male	11 (50)
	Female	11 (50)
Age*		
	All patients	59 (range, 30-82)
	Female	58 (range, 39-73)
	Male	61 (range, 30-82)
Ethnicity		
	White	22 (100)
ECOG status		
	0	16 (73)
	1	6 (27)
Time from diagnosis of uveal melanoma to liver metastases (months)		
	Mean	34.9 (95%CI, 19.7-50.1)
	Median	19 (range, 0-144)
Time from diagnosis of liver metastases to first SIRT (months)		
	Mean	2.7 (95%CI, 2.3-3.1)
	Median	3 (range, 1-5)
No. of patients with extrahepatic metastases before SIRT		4 (18)
Liver tumor distribution		
	Whole liver	20 (91)
	Unilobar	2 (9)
Liver tumor burden		
- Liver tumor volume (cm^3)		
	Mean	318.1 (95%CI, 82.6-553.6)
	Median	130 (range, 10-2750)
- Largest lesion (cm)		
	Mean	4.1 (95%CI, 2.4-5.8)
	Median	2.6 (range, 1.4-18.6)
- Number of metastases		
	0-10	13 (59)
	>11	9 (41)
Tumor-to-healthy liver uptake ratio (MAA SPECT/CT)		
	Mean	4.0 (95%CI, 3.1-4.9)
	Median	3.5 (range, 1-10)
SUV max		
	Mean	7.5 (95%CI, 5.6-9.4)
	Median	7.4 (range, 3.3-22.1)

Note: Except where indicated, data represent number of patients and numbers in parentheses are percentages.
*Data are represented as means.

TABLE 2 – Treatment characteristics

Characteristic	Value (%)
No. of SIRT	29 (100)
Number of SIRT per patient	
1	16 (73)
2	5 (23)
3	1 (5)
Liver treatment	
Whole liver in single session	9 (41)
Whole liver in multiple sessions	5 (23)
Lobar only	8 (36)
Sum of administered activities per patient (GBq)	
Mean	2.1 (95%CI, 1.7-2.5)
Median	1.8 (range, 1-2.8)
Mean administered activity per patient (GBq)	
Mean	1.7 (95%CI, 1.5-1.9)
Median	1.6 (range, 0.7-2.8)
Highest administered activity per patient (GBq)	
Mean	1.8 (95%CI, 1.5-2.1)
Median	1.6 (range, 1-3)
Dose to tumor (Gy)	
Mean	171.7 (95%CI, 142.5-200.9)
Median	155.4 (range, 43.9-356)
Dose to healthy Liver (Gy)	
Mean	50.4 (95%CI, 42.6-58.2)
Median	46.2 (range, 21-99.1)
Dose to lungs (Gy)	
Mean	1.3 (95%CI, 1.0-1.6)
Median	1.1 (range, 0.1-2.9)
Y^{90}**-microspheres**	
TheraSphere	5 (23)
SIR-Spheres	19 (86)
Both	2 (9)
Post-SIRT systemic therapies	
Chemotherapy	11 (50)
Immunotherapy	13 (59)
Both	7 (32)
Post-SIRT locoregional therapies	
TACE	4 (18)
Thermal ablation	5 (23)
Both	0 (0)

Note: Except where indicated, data represent number of patients and numbers in parentheses are percentages.

TABLE 3 – Treatment response analysis

Response Criteria	3 months				6 months			
	Survival (months)	**HR (95%CI)**	**R^2 (%)**	***P-value***	**Survival (months)**	**HR (95%CI)**	**R^2 (%)**	***P-value***
RECIST								
R	-	[1]	-	-	26	0.27 (0.03-2.08)	13	0.207
NR	20				22			
WHO								
R	24	0.76 (0.16-3.50)	0	0.723	26	0.47 (0.13-1.76)	8	0.264
NR	12				18			
mRECIST								
R	26	0.27 (0.07-1.01)	21	0.052	27	0.15 (0.04-0.60)	40	***0.007***
NR	11.5				11.5			
EASL								
R	26	0.30 (0.10-0.95)	20	***0.040***	26	0.22 (0.07-0.75)	29	***0.016***
NR	11				11.5			
RECIST								
DC	23	0.16 (0.02-1.65)	8	0.124	25.5	0.24 (0.05-1.24)	13	0.088
PD	7.5				14			
WHO								
DC	24	0.23 (0.04-1.24)	10	0.088	25.5	0.24 (0.05-1.24)	13	0.088
PD	8				14			
mRECIST								
DC	24	0.22 (0.04-1.15)	12	0.072	25	0.51 (0.06-4.27)	2	0.537
PD	9.5				22			
EASL								
DC	24	0.22 (0.04-1.15)	12	0.072	25.5	0.07 (0.01-0.56)	27	***0.011***
PD	9.5				8.5			

R = Responders, NR = Non-Responders, DC = Disease Control, PD = Progressive Disease, HR = Hazard Ratio, 95%CI = 95% Confidence Interval

TABLE 4 – Overall survival

Parameter	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	***P*-value**	**Hazard ratio (95%CI)**	***P*-value**
Sex	1.22 (0.47 - 3.17)	0.68	-	-
Age	1.03 (0.99 - 1.07)	0.1003	-	-
ECOG status	2.73 (0.88 - 8.44)	0.08	1.85 (0.47-7.24)	0,38
Primary tumor treatment (surgery vs. proton-therapy)	1.22 (0.39 - 3.84)	0.74	-	-
Time between eye tumor diagnosis and metastases	0.99 (0.97 - 1.00)	0.12	-	-
Time between metastases diagnosis and SIRT	0.89 (0.50 - 1.61)	0.72	-	-
Largest lesion (cm)	1.30 (1.08 - 1.57)	0.005	1.22 (0.98 - 1.53)	0,08
Estimated number of lesions	1.28 (0.48 - 3.45)	0.62	-	-
Metastases distribution (unilobar/bilobar)	1.41 (0.32 - 6.22)	0.65	-	-
Baseline SUVmax	1.02 (0.91 - 1.15)	0.72	-	-
Extrahepatic metastases before SIRT	1.21 (0.34 - 4.29)	0.77	-	-
Y^{90}-microspheres (SIR-Spheres vs. TheraSphere)	0.75 (1.34 - 2.12)	0.34	-	-
Treated tumor volume (cm^3)	1.0008 (1.0001 - 1.002)	0.02	1.002 (1.0004 - 1.003)	0,007
Liver treated (lobar vs. whole)	0.72 (0.25 - 2.09)	0.55	-	-
Liver treated (whole in 1 session, whole in multiple session, lobar)	0.91 (1.10 - 1.43)	0.54	-	-
Number of SIRT per patient	1.001 (0.42 - 2.37)	0.99	-	-
Mean of all SIRT session activity administered per patient (GBq)	2.54 (0.96 - 6.73)	0.06	-*	-
Sum of all SIRT session activities administered per patient (GBq)	1.19 (0.77 - 1.86)	0.42	-	-
Mean dose to healthy liver (Gy)	0.98 (0.95 - 1.01)	0.18	-	-
Mean dose to tumor (Gy)	0.99 (0.98-1.01)	0.56	-	-
Tumor-to-liver uptake ratio	1.11 (0.89 - 1.38)	0.36	-	-
Pulmonary shunt fraction (%)	0.43 (0.15 - 1.21)	0.11	-	-
Post-SIRT systemic therapies	0.33 (0.12 - 0.86)	0.02	0.04 (0.006 - 0.24)	0,0005
Post-SIRT locoregional therapies	0.21 (0.07 - 0.62)	0.005	0.204 (0.04 - 0.94)	0,04
Extrahepatic metastases after SIRT	0.98 (0.28 - 3.48)	0.98	-	-
Highest complication grade (CTCAE)	1.37 (0.86 - 2.18)	0.19	-	-

Note: -* Omitted from multivariate analysis as it is highly correlated with the treated tumor volume.

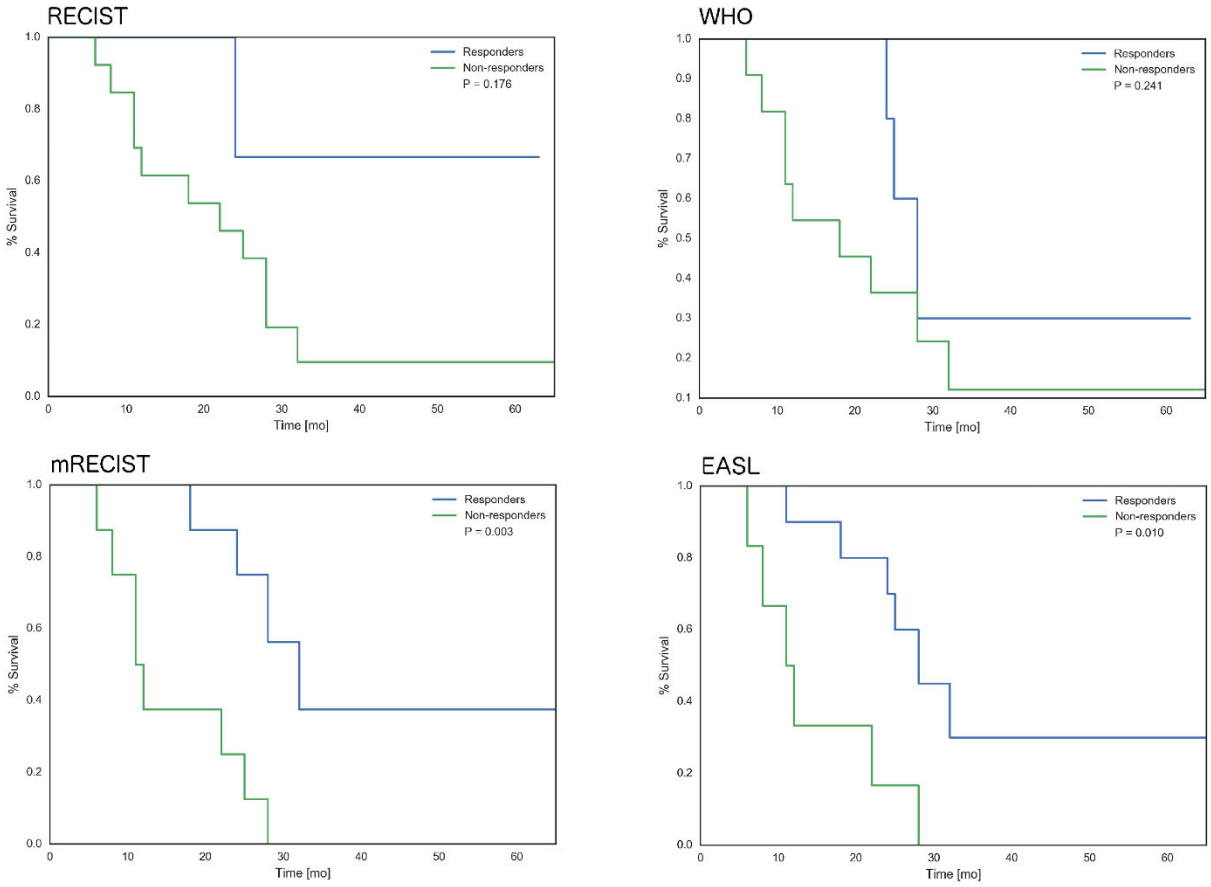

FIGURE 1: Survival analysis at 6 months post-SIRT.

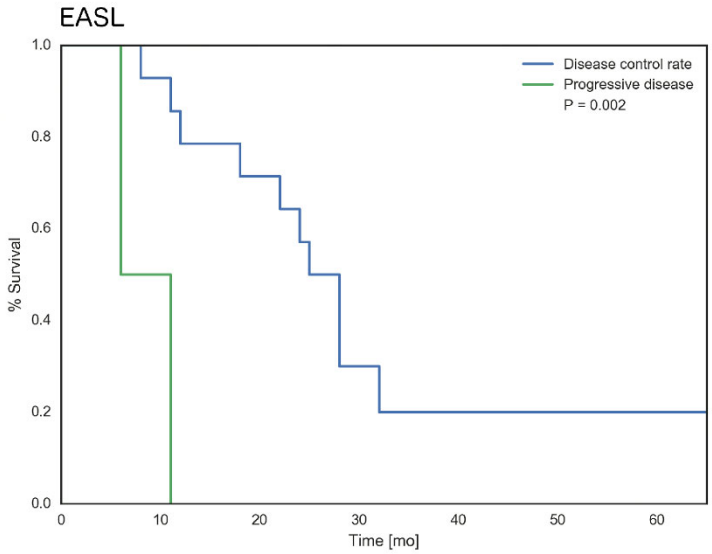

FIGURE 2: Survival analysis according to EASL response criteria when patient are stratified according to disease control rate vs. progressive disease at 6 months post-SIRT.

SUPPLEMENTAL TABLE 1 – Post-SIRT systemic and liver-directed locoregional therapies

Patients	Systemic therapies	Locoregional therapies
1	-	TACE
2	Ipilimumab Dacarbazine	MWA
3	Sorafenib	RFA MWA
4	Ipilimumab Pembrolizumab	TACE
5	Ipilimumab	-
6	-	-
7	Sorafenib Ipilimumab	-
8	Sorafenib Ipilimumab Nivolumab	RFA
9	Sorafenib	TACE
10	Sorafenib	-
11	Sorafenib Ipilimumab p53/HDM2 inhibitor CGM097	-
12	Ipilimumab Nivolumab	-
13	Sorafenib Ipilimumab	-
14	Sorafenib Ipilimumab Nivolumab	TACE
15	Sorafenib Ipilimumab Nivolumab Trametinib	-
16	Sorafenib	-
17	-	-
18	Ipilimumab Nivolumab	-
19	Nivolumab	RFA
20	Ipilimumab Nivolumab	RFA
21	-	-
22	-	-

TACE = Transarterial Chemoembolization, RFA = Radiofrequency Ablation, MWA = Microwave Ablation

SUPPLEMENTAL TABLE 2 – Toxicities

Clinical (CTCAE v4.0 grading scale)	No. of patients
None	6 (28)
1	4 (18)
2	7 (32)
3	7 (32)
4	0 (0)
Biological (CTCAE v4.0 grading scale)	**No. of patients**
None	1 (5)
1	5 (23)
2	4 (18)
3	4 (18)
4	3 (14)
Missing	5 (23)

Note: Data represent number of patients and numbers in parentheses are percentages

SUPPLEMENTAL TABLE 3 – Tumor response assessment after SIRT in target lesions

	RECIST		WHO		mRECIST		EASL	
	3 months	6 months	3 months	6 months	3 months	6 months	3 months	6 months
Complete Response (CR)	0 (0)	0 (0)	0 (0)	0 (0)	3 (12.5)	3 (16)	3 (12.5)	3 (16)
Partial Response (PR)	0 (0)	3 (16)	3 (12)	5 (26)	5 (21)	6 (31)	7 (29)	8 (42)
Stable Disease (SD)	21 (84)	12 (63)	16 (64)	10 (53)	14 (58.5)	7 (37)	11 (46)	4 (21)
Progressive Disease (PD)	4 (16)	4 (21)	6 (24)	4 (21)	2 (8)	3 (16)	3 (12.5)	4 (21)

Note: Data represent number of SIRT session and numbers in parentheses are percentages. Some patients had missing imaging or imaging with artefacts.