90Y-Loaded Microsphere SIRT of HCC Patients With Portal Vein Thrombosis High Clinical Impact of 99mTc-MAA SPECT/CT-Based Dosimetry

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^{90}Y-loaded microsphere SIRT of HCC patients with portal vein thrombosis: high clinical impact of ^{99m}Tc-MAA SPECT/CT-based dosimetry.

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Abstract

Radioembolization with ^{90}Y-loaded microspheres based on classical prescription methods is increasingly applied to HCC patients with portal vein thrombosis (PVT). In recent years, pre-therapeutic predictive dosimetry based on technetium-99m macroaggregated albumin (MAA) quantitative scintigraphy using SPECT/CT has been developed. This paper presents an overview on the MAA-based dosimetry concept, discusses important confounding factors, such segmentation methods and specific angiographic considerations required for a simulation based dosimetric evaluation. The concept of "dosimetric angiography" is then introduced for the first time. Main results available are reported as a threshold tumor dose, allowing a response, between 100-120 Gy with ^{90}Y-loaded resin microspheres and between 205-257 Gy with ^{90}Y-loaded glass microspheres. Impact of MAA-based dosimetry and MAA PVT targeting on overall survival is also reported. Due to those dosimetric advances, personalized dosimetric approaches based on MAA dosimetry are now available, with specific endpoints, for both ^{90}Y-loadedresin or glass microsphere. The clinical impact of personalized dosimetry in PVT patients is particularly high as a median OS of 20.2 months has been reported for good PVT candidate treated with glass microspheres (TD ≥205 Gy and good PVT targeting) as against only 3 months for poor candidate (TD<205 Gy or poor PVT targeting), and as a significant amount of patients where down-staged towards surgery (12%) in the same study.

Introduction

Liver selective internal radiation therapy (SIRT) is primarily aimed to deliver a tumoricidal absorbed dose to tumors, while sparing the surrounding healthy liver tissues .[1,2] To achieve optimal efficacy along with the lowest possible toxicity, the tumor absorbed dose (TD) and absorbed dose by normal injected liver tissue (NLD) should be evaluated prior to therapy initiation. Despite this evidence, the rules applied for activity planning are still widely based on the BSA method for resin microspheres, with a mean dose of between 80 to 150 Gy to be delivered to the liver for glass microspheres, including tumors and healthy liver. This strategy is referred to as standard dosimetric approach.

SIRT must at all times be preceded by a workup consisting of a mapping angiography and technetium-99m macroaggregated albumin (MAA) scintigraphy. These techniques are designed to select the correct position for treatment and to verify the presence of lung and digestive shunts. Recent advances have been made while using quantitative MAA scintigraphy as an accurate dosimetric tool. [3-7]

This work-up combined with MAA-based dosimetry has become a real treatment simulation with potential impact on the treatment schedule and prescribed absorbed dosing, resulting in a fully-personalized approach.

This chapter has been meant to summarize the clinical results obtained so far with SIRT using standard dosimetric approaches, to review both the interest and limitation of MAA-based dosimetry, and to outline the clinical impact of a personalized dosimetric approach on HCC patients with PVT.

Clinical results obtained with SIRT using standard dosimetric approaches in PVT patients.

Non-comparative studies

Several studies using both resin or glass microspheres have produced interesting results concerning overall survival (OS) of PVT patients,[7-12] ranging from 10 to 13 months (mo), [10-12] thus comparing favorably with the 8.1-month OS achieved with sorafenib in the SHARP trial, considered the standard of care in this indication.

In all of these studies, several classical parameters have been demonstrated to significantly impact OS. The most important OS-impacting parameters from the two largest studies recently reported and involving 120 and 185 PVT patients, respectively,[9,10] comprised the following: Child-Pugh (CP) status, performance status, bilirubin level, ascites, tumor size, number of lesions (solitary vs multifocal), as well as PVT involvement level (Table 1). As example, in the Abouchaleh et al[8] study, median OS was 13.3 mo (95% confidence interval [CI]: 8.7–15.7 mo) for CP-A patients, 6.9 mo (95% CI: 5.3–10.1 mo) for CP-B7 patients, and only 3.9 mo (95% CI: 2.9–5.0 mo) for ≥CP-8 patients.[8] Regarding PVT extension, the larger the extension, the lower the results obtained, with the poorest OS observed for main PVT versus segmental PVT involvement. These figures clearly demonstrate the relevance of appropriate patient selection.

Based on these results, patients exhibiting one of the following items are not considered good PVT candidates for SIRT: bilirubin level higher than 2mg/dL, significant ascites, CP ≥CP-8, performance status ≥2, and complete occlusion of the main portal vein.

For MAA SPECT/CT-based dosimetry, two other major prognostic factors have been identified when using glass microspheres, namely TD and PVT targeting.[7] The relative risk (RR) of death was 6.99 (95% CI: 1.98–24.39) for TD< 205 Gy (vs TD≥ 205 Gy) and 14.7 (95% CI: 3.09–69.12) for patients with poor PVT MAA targeting (vs good PVT targeting).[7] Figure 1 shows a typical case of good MAA PVT targeting. These results underline the necessity of accurate dosimetric evaluation prior to treatment selection.

Comparative studies

To date, only a single retrospective study focused on PVT patients and comparing SIRT versus sorafenib has been published.[13] Overall, 24 patients treated using ^{90}Y-loaded glass microspheres along with a personalized approach applied in most cases were matched with 24 patients treated with sorafenib based on a propensity score. A trend towards superior OS was observed for SIRT, though between-group differences did not reach statistical significance, with an estimated median OS of 26.2 mo for SIRT- vs 8.7 mo for sorafenib-treated patients (p=0.054).

Considering randomized studies, only one single study involving PVT patients was published in 1994. [14] This study using ^{131}I-lipiodol SIRT versus best supportive care (BSC) revealed a significant improvement in the survival rate at 6 mo in the SIRT arm as compared to the BSC arm, with figures of 48% and 0%, respectively (p<0.01). These results have been considered to be the first prove supporting SIRT use in PVT patients. For ethical reasons owing to the dramatically-positive results, the study was stopped. On account of the small number of patients included (n=27), the outcome remains controversial, yet this is the sole randomized trial carried out in this setting, with positive and sustained results.

Three randomized studies, yet not focused on PVT patients, have been published to date.[15-17] The SARAH[15] and SIRveNIB[16] trials were designed to compare resin microspheres versus sorafenib, along with the SORAMIC trial[17] comparing resin microspheres combined along with sorafenib versus sorafenib alone. The primary endpoint was OS in all trials, with all of them failing to demonstrate any survival improvement in the SIRT arm, as based on either the intent-to-treat (ITT) or per-protocol approach (PP), **(Table 2).** No OS benefit was seen for PVT patients, with an OS disfavoring SIRT (RR of 1.19), even in the SARAH trial. [15] It

should, however, be emphasized that response rate and tolerance was significantly better with SIRT. [15,16]

The results of a fourth randomized Phase III study, namely the STOP-HCC study (NCT01556490), comparing glass microspheres associated with sorafenib versus sorafenib alone are still awaited and should be made available in the course of 2019.

Several parameters possibly related to trial failure have been discussed in the meantime, such as absence of dosimetric endpoints and inclusion of too-severely advanced patients.[18] The ITT approach used is similarly a matter of debate, given that excessive lung or digestive shunting are recognized contra-indications rather than ITT failures, with an abnormally high ITT failure rate in the SIRT arm (between 26 and %, depending on the studies).

The negativity of the Phase 3 trials without any dosimetric endpoints, along with the promising preliminary results obtained with MAA SPECT/CT-based dosimetry, clearly justify the further development of personalized dosimetry.

Dosimetry and MAA-based dosimetry

Dosimetry concept

From a physical perspective, an absorbed dose represents an energy (Joule) divided by a mass (Kg), expressed in either J/Kg or Gy with 1 Gy= 1 J/Kg. Several dosimetric approaches have been described to date, namely the classical medical internal radiation dose (MIRD) approach, biological effective dose evaluation (BED), uniform equivalent dose calculation (EUD), Monte Carlo simulation, and Kernel density estimation.[5]

The MIRD approach, the most widely applied, assumes a homogeneous dose distribution. Given that following initial embolization, microspheres are not biodegradable and remain trapped within the vessels, the effective half-life is supposed to be the physical half-life of ^{90}Y, and the MIRD equation can thus be simplified:

The absorbed dose D (Gy) to a volume of interest (VOI) of mass M (Kg) containing an activity A (GBq) of ^{90}Y is then calculated using the following simplified MIRD formula:

$$D_{(Gy)} = A_{(GBq)} \cdot 50 / M_{(Kg)}$$

Doses can be calculated for different VOIs, especially for tumor, perfused liver, normal perfused liver, and lung tissues. Typically, the liver mass (in Kg) is assumed to be equal to its volume (L) multiplied by a factor 1.03; the lung mass is assumed to be equal to 1 Kg. It must be underlined that this formula is used for both resin or glass microspheres.

One difficulty is that the radiobiological effect depends not only on the absorbed dose but also on the dose rate, and on the heterogeneity of dose distribution as well.

On account of this property, external bean radiotherapy (EBR) and selective internal radiation therapy (SIRT) are critically different.[5,19] This is mainly due to a high difference in radiation exposure rate (high in EBR and low in SIRT) and in dose distribution homogeneity (homogeneous with EBR; heterogeneous with SIRT depending of the therapeutic agent's bio-distribution). Therefore, it is impossible to compare the radiobiological effect provided by 1 Gy of EBRT with the radiobiological effect provided by 1 Gy of SIRT, or by 1 Gy of glass or resin SIRT, as previously demonstrated in a stimulation study.[7] In this study, for a whole liver irradiation, the dose to the liver producing 50% of toxicity was 40 Gy for resin microspheres and slightly >60 Gy for glass microspheres.
Another example of the differing radiobiology observed between glass and resin microspheres consists in the reported threshold dose for HCC resulting in a response, ranging between 100 and 120 Gy for resin microspheres[3,4] and being around 200 Gy for glass microspheres. [5-7] These results are further supported by the high difference in specific activity observed among ^{90}Y-loaded microspheres (50 Bq/ sphere for resin and 2500 Bq/sphere for glass, at qualibration time), leading to differences in dose distribution heterogeneity.[7]

At present, two dosimetric approaches can be applied for SIRT, namely a simulation-based dosimetry (*e.g.*, MAA-based dosimetry) enabling treatment personalization, and a direct dosimetric evaluation based on ^{90}Y-PET quantification recognized as gold standard approach, because based on direct therapeutic compound quantification. However, as ^{90}Y-PET dosimetry cannot be used for treatment personalization, this approach will not be further developed in this paper.

Technical considerations regarding dosimetry evaluation

Several issues concerning dosimetry evaluation have been reported,[19] including tumor histology, tumor size, tumor vascularity, product used as previously mentioned, previous therapy, response and toxicity criteria applied, underlying cirrhosis, and hepatic reserve.
Two technical considerations that have not yet been fully evaluated must be highlighted here, namely the segmentation method used and angiographic considerations for simulation-based dosimetry.

Segmentation approach

For the segmentation of VOIs, two approaches are presently available.[19]
The gold standard approach is based on diagnostic imaging using CT, MRI, or CBCT. This imaging is then co-registered with SPECT or SPECT/CT, with solely the counts within the anatomically delineated VOIs taken into consideration for dose calculation of this VOI. The presumed advantage of this approach is to achieve the most accurate and reproducible volume definition. However, in case of coregistration error, a significant amount of counts of the SPECT image is possibly excluded from the VOI, leading to a significant underestimation of the absorbed dose of this VOI.

The second approach available is based on full SPECT/CT segmentation. It has been demonstrated in a phantom study that the mean error in the volume measurement was lower than 7%, with good reproducibility (inter-observer concordance: 99%). The approach's advantage is that coregistration with a diagnostic imaging is not mandatory, while the counts include in the VOI are taken into account, thereby resulting in a lower risk of underestimation of the absorbed dose. In cases of hepatic vascularization variability or aberration, using MAA SPECT/CT for volume measurement offers the advantage of providing a more functional evaluation of the truly perfused volume.[21] As a result, cases of full liver perfusion identified with MAA SPECT/CT despite a lobar injection were reported in the literature.[21] However, in complex clinical cases, the thresholding required for segmentation may prove difficult to perform, thereby leading to volume definition errors.

As for glass microsphere use in HCC, it must be emphasized that one study using ^{90}Y-PET dosimetry based on CT segmentation and PET co-registration failed to reveal a dose response relationship, with segmentation errors impacting tumor dose as main explanation.[22] On the other hand, in several studies using a full SPECT/CT segmentation, a clear dose response relationship has been evidenced.[4-7]

The key message is that the segmentation method used has a direct impact on the dosimetric evaluation and must, therefore, be carefully described in the studies. This will likely enable us to confirm the results' validity and to additionally compare the results of different studies.

Simulation-based dosimetry, specific angiographic requirements, and dosimetric angiography concept.

An essential fact we must consider is that a simulation-based dosimetry, irrespective of the surrogate used, represents a global approach including angiographic considerations. Therefore, this approach cannot be limited to an accurate quantification of the surrogate itself.

The difficulty in performing a simulation angiography with a full dosimetric purpose, including tumor and healthy liver dose evaluation, is that several specific endpoints are required, as compared to a classical work-up. The concept of "dosimetric angiography" should thus be introduced.

Initially, the only dosimetric endpoint of the work-up was to evaluate both LSF and lung dose. Given this context, it was admitted that, in case of bilobar disease and two treatments separated by 4-6 weeks, one work-up with MAA injection into the common or the proper hepatic artery was proven sufficient.

For a dosimetric angiography, the situation proves quite different, given that the blood flow must be kept similar between both simulation (namely dosimetric angiography) and treatment itself (namely therapeutic angiography). To this end, the following four technical issues must be taken into account: spams occurrence, proximity of arterial bifurcation, slow surrogate injection, and catheter repositioning:

- A direct impact of spasm occurrence on simulation angiography has previously been reported.[19,23] Limiting the risk of spasm occurrence as much as possible necessitates both of the following: 1) avoiding whenever technically possible coil embolization; 2) favoring whenever technically possible the use of catheter as floppy.[16]
- The arterial bifurcation proximity, within 1cm of the catheter tip, has also been reported to impact the blood flow.[25]
- A slow injection of the microsphere surrogate has been recommended, namely over 20 to 30 seconds for a 5mL syringe, in order to mimic the microspheres injection flow.[19]

- Lastly, injecting the surrogate and ^{90}Y-microspheres must be carried out exactly at the same position, with the same catheter tip orientation in the arterial tree, given that catheter repositioning have been reported to result in a poor correlation between surrogate and microsphere uptakes.[22,25]

In an effort for accuracy, a simulation-based dosimetry thus requires a multidisciplinary approach where IRs must be highly involved while taking into account the specific angiographic endpoints required for a dosimetric angiography.

Additional limitation when using MAA as microsphere surrogate

The physical properties of MAA and microspheres are not exactly the same. MAA is made up of biodegradable particles, with sizes estimated to range from 10 to 150μm, without being well calibrated. The majority, namely about 90%, measure between 10 and 40μm, whereas 1 to 2% measure <15μm. The fact that MAA causes an overestimation of lung shunting, along with an underestimation of tumor and liver doses, is no longer a matter of debate. This observation has been clearly demonstrated in a recent study comparing lung shunt measurement by either MAA or by holmium microsphere quantification.[26] However, it must be noted that high lung shunting is not very common, occurring is less than 10% of HCC cases.

Several disappointing study results have been obtained to date. However, it should be noted that these studies were primarily carried out in patients with metastatic disease using either resin microspheres[25,27,28] or encountering several technological issues not clearly assessed like catheter repositioning[27-29] or absence of spasm evaluation.[22,25,27-29] Nevertheless, MAA-based dosimetry has so far been proven to accurately predict treatment response for HCC, when using either glass[5-7] or resin microspheres,[3-4] yet in studies not focused on HCC with PVT.

Different studies based on ^{90}Y-PET-dosimetry have confirmed the accuracy of MAA-based dosimetry in HCC. Kao et al[30] demonstrated a strong correlation between MAA SPECT/CT tumor and ^{90}Y-PET doses when using resin microspheres. The median relative error between both dosimetric evaluations was only 3.8%, with a trend towards a slight tumor dose

overestimation observed with ^{99m}Tc-MAA SPECT/CT. A recent prospective study using PET found a threshold dose of 200 Gy for glass microspheres,[31] while another study using glass microspheres demonstrated a very good correlation between the T/NT ratio calculated on MAA and on ^{90}Y PET, being 5.6±3.2 versus 5.9±3.5, r=0.918, respectively.[32]

Evidence of a close MAA-based dose response relationship in HCC and OS impact.

Several studies using MAA-based dosimetry have demonstrated a dose response relationship in HCC (Table 2). Reported threshold doses were 100-120 Gy for resin microspheres[3,4] and 205-257 Gy for glass microspheres.[5,7]

In the larger study with resin microspheres involving 109 patients evaluated for response (RECIST 1.1), the mean TD for patients with disease control was 121.4 Gy versus only 85.1 Gy for patients with progression, p=0.0204.

In the larger study with glass microspheres involving 130 evaluated lesions,[7] the response rate based on EASL criteria was 91% for lesion with a TD≥205 versus only 5.5% for a TD<205, $p<10^{-3}$. In addition, it has been demonstrated that the false-positive rate was proven high, corresponding to non-responding lesions with a TD≥205 Gy, 33.3% for TDs ≥205 Gy and <260 Gy, and very low, 3.2% only, for TD ≥260 Gy (p=0.0012), in accordance with a fundamental radiobiology law: “the higher the dose above the threshold dose, the more severe the damage”.

Its impact on OS has likewise been demonstrated in several studies. When using resin microspheres, a median OS of 14.1mo (95% CI: 9.6–18.6 mo) has been reported for patients with a TD >100 Gy versus only 6.1mo (95% CI: 4.9–6.8 mo) for those with a TD <100 Gy, p<0.0001.[4] For glass microspheres, the largest study involving 85 patients reported an OS of 21 mo (95% CI: 15–27 mo) for a TD ≥ 205 Gy versus 6.5 mo (95% CI: 3–24 mo) for a TD < 205 Gy, the difference being statistically significant (p=0.0052); the relative risk of death (RR) was 2.35 (95% CI: 1.26–4.4) for a TD < 205 Gy (p=0.0053).[7]

The TD’s impact on OS was proven to be even higher for PVT patients with a median OS of 15.7 mo (95% CI: 9.5–25.7) for a TD ≥205 Gy versus 4.35 mo (95% CI: 2–8) for a TD <205 Gy, p=0.0004; the RR of death was 6.99 (95% CI: 1.98–24.39) for a TD < 205 Gy (p=0.0025).[7]

Normal liver dose and liver toxicity

The maximal liver tolerated dose is more complex to define, as several confounding factors must be taken into account, such as toxicity definition, treatment line, severity of underlying liver disease, and hepatic reserve;[19]

For resin microspheres, based on Bremsstrahlung ^{90}Y SPECT dosimetry, a treated normal liver dose of 52 Gy has been reported to provide a risk of G2 liver toxicity in 50% of cases.[33] For glass microspheres, Chiesa et al[34] calculated the global dose to the healthy liver, including both the irradiated and non-irradiated parenchyma. Based on the authors' assumptions, fixing a limit of 75 Gy for the global healthy liver dose corresponded to a 15% probability of liver decompensation consisting of any liver decompensation, irrespective of its severity and eventual reversibility, with glass microspheres implanted 3.75 days after the calibration date with a defined specific activity.

A published study has evaluated the normal injected liver dose (NLD),[35] with the mean dosimetric evaluation performed as standard using the MIRD approach. The patient cohort comprised 71 carefully-selected patients, with 94.4% of them exhibiting a CP-A score. The normal NLD and hepatic reserve did not correlate with severe (CTCAE V3, G $\geq$3) clinical permanent liver toxicity. Only the association of a NLD >100 Gy or >120 Gy with a hepatic reserve <30% correlated with severe permanent liver toxicity upon univariate analysis ($p = 0.032$ and 0.017, respectively). Upon multivariate analyses, only the association of a NLD dose >120 Gy with a hepatic reserve <30% remained significantly correlated with severe permanent liver toxicity ($p<0.0001$).

In a recent study NLD evaluated either alone or associated with a low hepatic reserve, was not associated with liver toxicity for PVT patients.[7] For PVT patients, the only parameter strongly associated with liver toxicity was the absence of MAA PVT targeting.[7]

Development of a MAA-based personalized dosimetry

When using resin microspheres, one expert group has recommended targeting 120 Gy for delineable HCC, without exceeding a NLD of 50 or 70 Gy, depending on the underlying disease. [1]

When using glass microspheres, a personalized dosimetric approach concept, along with treatment intensification as necessary, has been previously described, targeting a tumor dose >205 Gy.[35] The patients who underwent treatment intensification were administered an injected liver dose ≥150 Gy, contrasting with the 80-150 Gy delivered in the classical approach. In this concept, the NLD was kept <120 Gy. In this study, 38% of patients underwent treatment intensification. The response rates were significantly higher when using the personalized dosimetric approach versus the standard dosimetric approach, estimated at 86% versus only 55%, respectively (p=0.01). The toxicity rate did not differ between patients who underwent treatment intensification and those who did not, respectively 5.8% vs 9.2%.[35]

This intensification concept proves to be of particular value for PVT patients. Personalized dosimetry, as previously described,[35] was evaluated in a study involving 41 PVT cases.[36] In this study, 37% of patients received treatment intensification. A high 85% response rate was achieved without causing any concomitant increase in permanent liver Grade ≥III toxicity (6% in the intensified patients *versus* 12% in the non-intensified ones, ns). The TD was found to significantly impact OS, which was 4.3 mo (95% CI: 3.7-5) vs 18.2 months (95% CI: 8.5-28.7) for patients with a TD below 205 Gy or over 205 Gy, respectively (p=0.005). Patients with a TD ≥205 Gy and good PVT targeting (n=36, ie 87%) exhibited an OS of 20.2 mo. It has to be underlined that in this study using treatment intensification, tumor size was not correlated with OS, as in several studies using a standardized dosimetric approach, indicating that it has been possible to provide a sufficient amount of radiation in large lesions. Five patients exhibiting a complete portal vein recanalization were downgraded towards surgery and resected at a later time. The objective median OS was not reached, though exceeding 24.5 mo and being significantly longer (p=0.0493) for the five patients who underwent lobar hepatectomy. [36] Figure 1 shows an interesting case of PVT patient down-staged by 1 ^{90}Y loaded glass microspheres injection followed by surgery.

A randomized multicenter Phase 2 study, DOSISPHERE-01 trial (2015-A00894-45), was designed to compare a personalized dosimetric arm targeting at least 205 Gy to the tumor (and if possible, TD higher than 250-300 Gy) against a standard dosimetric arm targeting 120±20 Gy to the injected liver, involving HCC patients treated with glass microspheres. For this study, patient recruitment has presently been completed, with results possibly available in 2019.

Take home messages

PVT patients prove to be good candidates for SIRT, provided that patient selection is accurately performed. Treatment has been proven associated with better results in CP A patients, with no ascites and bilirubin levels <2mg/dL.

In several studies, MAA SPECT/CT-based dosimetry has been demonstrated to be a good predictor of treatment response and OS, with a threshold dose between 100-120 Gy for resin microspheres and between 205-257 Gy for glass microspheres.

For accuracy, MAA SPECT/CT-based dosimetry must meet several requirements:

- Consider several diagnostic angiography specifications, including limitation of spasm occurrence, main bifurcation proximity, slow MAA injection, as well as accurate catheter positioning;
- Use an accurate segmentation method (CT based or MAA SPECT/CT based), with superior results described based on full SPECT/CT segmentation.

MAA PVT targeting proves to be paramount, as as absence of PVT targeting for lobar and main PVT were previously reported correlating with a high risk of liver failure.

The clinical impact of MAA personalized dosimetry is high as prolonged OS reaching up to 20.2 mo and down-staging rate of 12% have been reported.

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Table 1 :
Median OS (mo) and CI 95% for the main prognostic parameters reported to be associated with OS at multivariate analysis.

	Abouchaleh et al[8]	Spreafico et al[9]	Garin et al[7]
Overral population	na	14.1 (10.7-17.5)	12 (8-20.2)
Child Pugh	A : 13.3 (8.7-15.9) B7 : 6.9 (5.3-10.1) B : 3.9 (2.9-5)	A : 14.1 (10.9-17.3) B7 : 7.5 (3.8-11.2) ns	A5 : 15 (8-25.5) A6 + B7 : 9 (3-26.5) ns
Bilirubin	<2 mg/dl : 8 (7.3-11) ≥2 mg/dl : 5 (2.2-9.7) $p<10^{-3}$	<1.2 mg/dl : 16 (13-18) ≥1.2 mg/dl : 9.5 (9-10) ns	<2 mg/dl : 15 (14-27) ≥2 mg/dl : 11 (5-8) ns
ECOG	0 : 8 (6.7-13.8) 1 : 7.7(5.2-9.5) p=0.01	na	0 : 15.7 (9.5-25.5) 1 : 11 (3.5-26.5) ns
Ascites	Absent : 8.8 (7.7-12) Present : 4.6 (3.5-6.4) p=0.01	na	na
Size	< 5cm : 13.9 (11-20) ≥ 5cm : 6.4 (5-7.8) p=0.037	< 5cm : 21.7 (12.6-30) ≥ 5cm : 11.6 (7.8-15.4) ns	< 10cm : 20.2 (8-29) ≥ 10cm : 11.5 (3.7-17) p=0.045
Tumor burden	Solitary : 12.6 (7.7-19) Multifocal : 6.5(5-7.9) p=0.04	<50% : 16 (13.7-18.3) ≥ 50% : 6.4 (5.2-7.6) $p<10^{-3}$	<50% : 15 (8-23 .9) ≥ 50% : 4.2 (2-29) ns
PVT extension	Seg : 13.8 (8.5-15.7) Lobar : 7.7 (5.3-10.4) Main : 5 (4-7.7) ns	PV1: 28 (10.7-45.3) PV2 : 12 (6.1-19.7) PV3 : 8.2 (5.7-10.8) $p<10^{-3}$	na
αFP	< 100 : 11.4 (7.9-13.9) ≥100 : 6.5 (5-7.7) p=0.037	<1000 : 16.4 (1.9-21) ≥1000 : 9.2 (7.2-12.2) p=0.003	<400 : 13.8 (8 .26.5) ≥400 : 12 (13-18) ns
TD	na	na	≥205 Gy : 15.7 (9.5-25) < 205 Gy : 4.35 (2-8) p=0.0004

na= non available, seg = segmentary, PV1 = segmentary, PV2 = second order branch, PV3 = first order branch

Table 2.
Randomized studies using ^{90}Y loaded resin microspheres SIRT and sorafenib (S) in advance HCC (not focussed on PVT patients).

	SARAH trial[15]	SIRveNIB trial[16]	SORAMIC Trial[17]
Treatment	SIRT alone vs S	SIRT alone vs S	SIRT + S vs S
% of patients not receiving the assigned treatment	22% for SIRT	28.6% for SIRT 9.0% for S	47.2% for SIRT+S 16. 3% for S
OS ITT	8 mo (6.7-9.9) for SIRT vs 9.9 mo (8.7-11.4) for S ns	8.8 mo for SIRT vs 10 mo for S ns	12.1 mo (12.6-14.6) for SIRT+S vs 11.5 mo (9.8-13.8) for S ns
OS per protocol	mo 9.9 (8-12.7) for SIRT vs 9.9 mo (9-11.6) for S ns	11.3 mo vs for SIRT vs 10.4 mo for S ns	14.1mo (10.9-16.4) for SIRT+S 11.1 mo (9.7-13.9) for S ns
OS and PVT	HR = 1.19 (0.92–1.54) for SIRT	na	na
Response rate	19% for SIRT vs 12% for S p=0.0421	16.5% for SIRT vs 1.7% for S p<0.001	na
% patient with at least one Grade ≥3 AE	41% for SIRT vs 63% for S	27.7% for SIRT vs 50.6% for S p<0.001	72.3% for SIRT+S vs 68.5% for S
Quality of life	Significantly improved for the SIRT arm	na	na

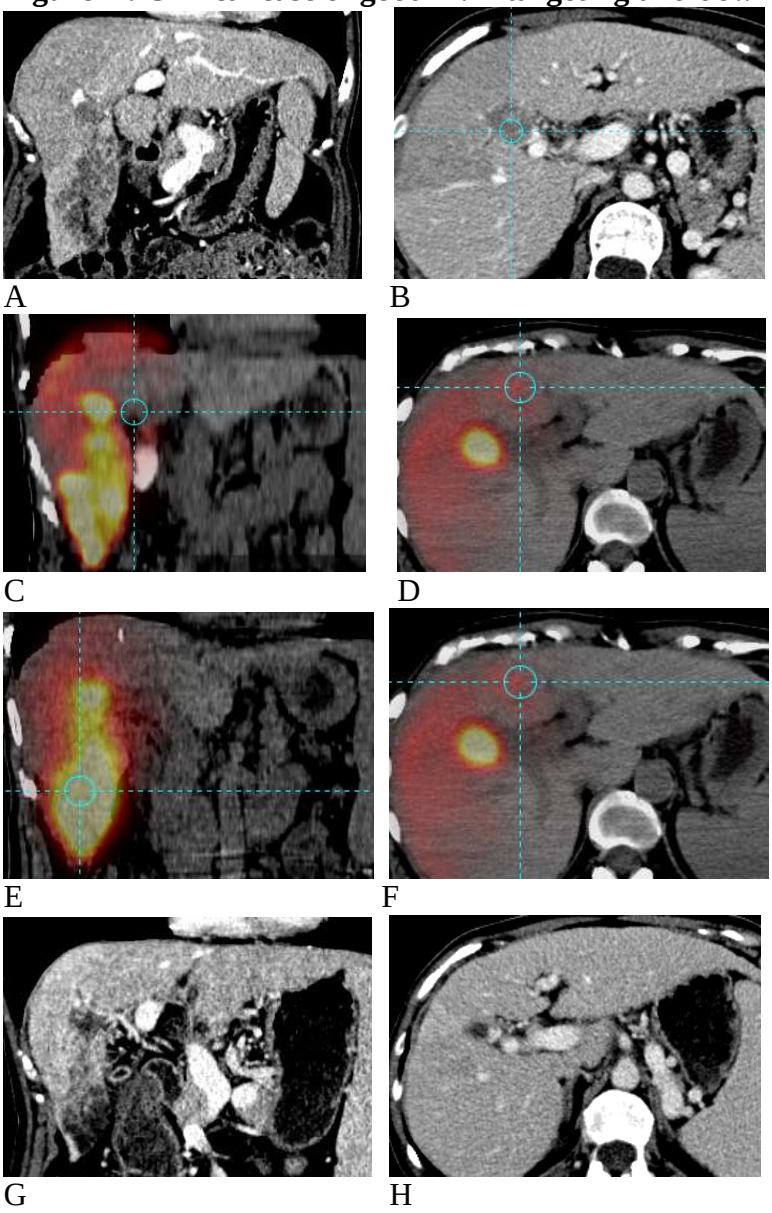
ITT= intent to treat, HR= hazard ratio, Response rate was evaluated using RECIST

Table 3: Studies with MAA based tumor dose/response corelation in HCC

	Lau[3]	**Kao**[30]	**Chiesa**[5]	**Garin**[35]	**Garin**[36]
Product	resin	resin	glass	glass	glass
Nb patients/ Nb lesions	18/ na	10/ na	48/ 65	71/ na	41 PVT patien
Lesion size (cm)	na	na	5.6	7.1	8.5
Prior therapy	na	50%	28.9%	51%	34%
Response Evaluation	WHO	RECIST1.1	EASL	EASL	EASL
Threshold TD (Gy)	120	< 91	257	205	205
RR for TD ≥TTD Vs < TTD	87.5% vs 12.5% p=0.005	100%	85% vs na	na	na
OS for TD ≥Thresold TD Vs < Thresold TD	55.9w vs 26.6w p=0.005	na	na	23m (17.5-28.5) Vs 11.5m (2–30.7) ns	18.2m (8.5-28.7) vs 4.3m (3.7-5) p=0.005

Nb= number, na = non available, TTD= Threshol tumor dose, w = week, m = months

Figure 1 : Clinical case of good PVT targeting and down-staging



59-Year hold woman, hepatitis B cirrhossis (Child Pugh A5), with a large HCC (8.9 cm) of the right lobe (A) and bisegmental PVT involvement (B). High level of αFP (30548 kUI/l).
MAA SPECT/CT evidencing high tumor uptake (C) and a good PVT targeting (D).
She received one injection of 2,45 GBq of ^{90}Y loaded glass microspheres with a MAA-based TD of 270 Gy.
^{90}Y bremsstrahlung SPECT/CT demonstrating a good concordance with MAA simulation, both regarding tumoral uptake (E) and PVT targeting (F).
Follow up CT scan at 4 months evidencing a partial response of the HCC (G) and a complete necrosis of the PVT (H), associated with a 97% reduction of αFP (909 kUI/l).
She underwent a right hepatectomy, she finally died of progressive disease 24.5 months after microspheres injection of progressive disease (first recurrence within peritoneum).