

Personalized dosimetry with intensification using ⁹⁰Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis

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ABSTRACT

To evaluate the response rate and survival of hepatocellular carcinoma (HCC) portal vein thrombosis (PVT) patients treated with ^{90}Y -loaded glass microspheres (Therasphere®) using a personalized dosimetry and intensification concept. **Material and methods:** Therasphere® was administered to 41 HCC PVT patients (main=12; lobar/segmental=29). $^{99\text{m}}\text{Tc}$ -Macroaggregated albumin (MAA) single-photon emission computed tomography (SPECT)/computed tomography (CT) quantitative analysis was used to calculate the tumor dose (TD), healthy injected liver dose (HILD), and injected liver dose (ILD). Response was evaluated at 3 months using European Association for the Study of the Liver (EASL) criteria, with CT follow-up lasting until disease progression or death. Survival was assessed using the Kaplan-Meier method. **Results:** The mean injected activity was $3.1 \pm 1.5 \text{ GBq}$ and mean ILD $143 \pm 49 \text{ Gy}$. Applying a TD threshold of 205 Gy , MAA SPECT/CT achieved a 100% sensitivity and 90% overall accuracy (0 false negatives; 4 false positives) in response prediction. Based on TD and HILD values, 37% of patients received an intensification of the treatment (increased injected activity with the aim of achieving a $\text{TD} \geq 205 \text{ Gy}$ and $\text{HILD} < 120 \text{ Gy}$, applying an $\text{ILD} > 150 \text{ Gy}$). This resulted in a high response rate (85%) without increased liver Grade $\geq \text{III}$ toxicity (6% versus 12% in the non-boosted patients, ns). For the total 41 patients, median overall survival (OS) was 18 months (m) (range: 11-25). For patients with a $\text{TD} < 205 \text{ Gy}$, median OS was 4.3m (3.7-5m) vs. 18.2m (8.5-28.7m) for those with a $\text{TD} \geq 205 \text{ Gy}$ ($p=0.005$). Median OS was 20.9m for patients with a $\text{TD} \geq 205 \text{ Gy}$ and good PVT targeting ($n=36$). OS was 12m (3- ∞) for patients with main PVT vs. 21.5m (12-28.7) for those with segmental or lobar PVT (ns). For the five patients with complete portal vein revascularization who underwent lobar hepatectomy, median OS was not reached, yet exceeded

24.5m and was significantly higher than that of other patients ($p=0.0493$). **Conclusion:** Using a MAA SPECT/CT personalized dosimetry and intensification concept with ^{90}Y -loaded glass microspheres induced prolonged OS for PVT patients as compared to the standard of care (sorafenib), without increasing liver toxicity. Prospective randomized studies are therefore warranted.

Key words: radioembolization, hepatocellular carcinoma, MAA dosimetry, personalization

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, with approximately 500,000 new cases per year (1). The prognosis is particularly poor in portal vein thrombosis (PVT) cases, with a reported spontaneous survival of 5.1 months (m) in Western countries (2) and 4.2m in Asia (3). Therapeutic care for PVT patients is difficult, owing to PVT constituting a contraindication for surgery and chemoembolization. Radioembolization using ¹³¹I-Lipiodol is the first therapeutic option that has proven effective in significantly increasing overall survival (OS) in a randomized study (4). The efficacy of sorafenib has also been validated in two positive randomized studies (2, 3). However, even with the administration of sorafenib, the OS for this patient population is very poor, remaining below 8.1m (4).

Several non-randomized studies applying radioembolization using ⁹⁰Y-loaded microspheres have reported promising results, with OS values ranging from 10 to 13m in PVT patients using the standard dosimetric approach (5-9). In a technique combining ⁹⁰Y-loaded glass microspheres and the standard dosimetric approach, the objective is to administer 120±20Gy to the treated liver, regardless of the tumoral dosimetry. Using macroaggregated albumin (MAA)-based dosimetry, a dose/response relationship was clearly identified (10, 11), and we found that a 205Gy tumoral dose threshold was necessary to reach to achieve a response (11). We have also recently described the lobar intensification concept in a cohort of unselected patients (12).

This retrospective study sought to report our results using a personalized dosimetric approach of ⁹⁰Y-loaded glass microspheres injections in PVT patients, with treatment intensification when required.

MATERIAL AND METHODS

This was a retrospective cohort study comprising 41 consecutive PVT patients treated using a personalized dosimetric evaluation between October 2008 and September 2012. This study was an extension of our previously published cohort of PVT patients (12). Written informed consent was obtained from each patient, and the use of selective internal radiation therapy (SIRT) was approved by our University Hospital's Ethics Committee. The indications governing SIRT use were defined during an HCC multidisciplinary staff meeting. SIRT was used as first-line treatment for 66% of patients, and for recurrences in the remaining 34%. Patients were considered unsuitable for chemoembolization due to PVT involvement. No patient presented with extrahepatic spread. Patient and tumor characteristics have been presented in Table 1.

Microspheres were administered as per current standard guidelines. Following diagnostic angiography, liver perfusion scan was conducted, then 185MBq of technetium 99^m radiolabeled macroaggregated albumin (MAA) were injected into the hepatic artery. Planar acquisitions were performed for lung shunt evaluation. Single-photon emission computed tomography (SPECT)/computed tomography (CT) acquisitions were conducted with the following parameters: window: 140 ± 7.5 KeV; 32 projections; 180°; 128 * 128; 30s/projection (Symbia T2 gantry, Siemens, Germany). Findings were reconstructed using an iterative method consisting of ordered subset expectation maximization, five iterations, and eight subsets, with attenuation using a low-dose CT attenuation map, and scatter corrections, applying the Jaszczak method (dual energy window scatter correction, with a scatter window of 120 ± 7.5 KeV). No correction of the volume effect was carried out due to the large lesion sizes. The images were then visualized with or without CT scan fusion.

As previously described, “volumetric analysis” software (Syngo workstation, Siemens) was used for quantitative tumoral and non-tumoral liver tissue evaluation (11, 12). This software enables the semi-automatic generation of the volume-of-interest (VOI) in the injected liver and tumor by means of an isocontour method. For each VOI, the threshold value was adjusted to achieve good matching between the isocontours of the MAA distribution and the liver and tumor boundaries on fusion images. These VOIs were then used to measure the MAA volume of distribution in the injected liver and tumor, as well as the total activity contained therein.

Rather than absolute quantification of ^{99m}Tc -MAA in Bq/ml for each VOI relative quantification was performed (percentage of detected count in each VOI). The volume and activity values in the injected healthy liver were calculated by subtraction.

The doses in the selected VOIs (*i.e.*, tumor, injected liver, and healthy injected liver) were calculated using the classical medical internal radiation dose (MIRD) formula as below:

$$D_{\text{VOI}} \text{ (Gy)} = A_{\text{VOI}} \text{ (GBq)} \cdot 50 / W_{\text{VOI}} \text{ (kg)}$$

where D_{VOI} = mean dose in the VOI; A_{VOI} = total activity in the VOI; W_{VOI} = weight of the VOI, with W = volume (L) of 1.03

The injected activity (IA) was calculated based on the following personalized dosimetric endpoints:

- If possible, attain a tumoral dose (TD) $\geq 205\text{Gy}$,
- With a healthy injected liver dose (HILD) $< 120\text{Gy}$,
- And with a lung dose $< 30\text{Gy}$ or $< 50\text{Gy}$ for cumulative treatments.

Treatment intensification was defined as patients receiving an injected liver dose (ILD) ≥ 150 Gy (12).

For treatment intensification, the established endpoint was to achieve a TD ≥ 205 Gy. Treatment intensification was not aimed to reach 120Gy for the HILD. Conserving the HILD was only a matter of safety.

No intensification was performed if required to reach a HILD ≥ 120 Gy in order to attain the TD threshold of 205.

After 8 to 15 days, glass microsphere (TheraSphere[®], BTG) were injected using a lobar approach, typically on the following Wednesday, 3 days after calibration, during the first treatment week. In cases of bilateral disease, two lobar treatments were administered separately, with a 6-8 week interval between treatments.

Tumor response of treated lesions was assessed using the European Association for the Study of the Liver (EASL) criteria (13). Morphological responses using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria and α FP responses for patients with an α FP level ≥ 200 KUI/L were also provided. Triphasic CT scans were performed 3 months after treatment, and then every 3 months until disease progression or death. Toxicities were scored by applying the common terminology criteria for adverse events (CTCAE) (V4). Only permanent and clinically relevant Grade \geq III liver toxicities, which manifested within 6 months of radioembolization, were considered limiting factors. The imputability of the suspected toxicities was defined according to guidelines laid down by the International Conference on Harmonization (ICH E2B R3),

attributing toxicity to disease progression for patients with both liver toxicity and evidence of widely progressive disease.

Statistics

Quantitative values were expressed as mean \pm standard deviation (SD) and were compared between responding and non-responding patients using a distribution-free Wilcoxon-Mann-Whitney comparison test. Discontinuous data was compared by means of Chi-squared test (Fisher's exact test). This test was used in conjunction with univariate analysis in order to identify parameters associated with tumor response, progression-free survival (PFS), OS, and liver toxicity. Significant data from univariate analysis was then subjected to multivariate analysis using logistic regression testing. Survival rates were estimated using the Kaplan-Meier method and compared on the basis of log-rank testing. Survival rates were not censored for hepatectomies. SAS software was utilized for statistical analysis, with a significance threshold set at $p \leq 0.05$.

RESULTS

Of the total 41 treated patients, 15 (37%) received treatment intensification and 26 (63%) standard dose (ILD=120 \pm 20Gy, not exceeding 150Gy). In two standard dose cases, treatment intensification was warranted, yet impossible due to the HILD. Lung dose was not found to constitute a limit for intensification.

For the entire patient cohort, the mean IA was 3.1 \pm 1.5GBq and mean ILD 143 \pm 49Gy.

For the intensified patients, the mean IA increase was 58 \pm 39%, resulting in a mean ILD of 187 \pm 49Gy and mean HILD of 85 \pm 25% (Table 2).

Of all the intensified patients, 47% were intensified owing to a predictive TD, when using the standard dosimetric approach (120Gy to the treated lobe), which should have been below 205Gy; 40% due to a predictive TD between 205 and 250Gy; 13% despite a provisional TD >250Gy.

The EASL response rate of treated lesions was 85%, with five patients showing complete response (CR), 30 partial response (PR), and six stable disease (SD). The response rate was 81% for patients receiving intensification and 88% for those receiving none (ns), with a rate of 91% observed for those with lesions ≥ 10 cm (n=12). Five patients exhibiting good response and complete portal vein revascularization, including one with main portal vein thrombosis (**Figure 1**), underwent wide hepatectomy. Complete resection (R0) was achieved for all patients, although residual tumoral areas were revealed on microscopic examination in all patient tumors and in the portal veins of two. At the time of evaluation, two patients had died of disease progression and the remaining three were still alive with recurrences.

Three patients exhibiting response of treated lesions demonstrated progression at 3 months in areas outside the treated liver, one with contralateral progression and two with distant progression.

Using univariate analysis, only two factors were associated with EASL response of the treated lesions: a TD ≥ 205 Gy (p=0.0183) and T/NT ratio (p=0.0028), with a mean T/NT ratio of 7.8 for responding patients and only 2.8 for non-responders. None of these parameters continued to prove significant when evaluated on multivariate analysis (supplemental table).

The RECIST response of treated lesions was available for 40 patients and unavailable for one, who exhibited a diffuse not-well delineated HCC. The response rate was only 42%, with 15 PR and 35 SD.

α FP response evaluation was available for 19 of the 20 patients, with an α FP level >200. The response rate was 78.9%, with 15 PR, one SD, and three PD (contralateral liver: n=1; distant metastases: n=2).

Four clinically relevant and permanent Grade ≥ 3 liver toxicities were encountered (liver decompensation with abundant ascites), one in the intensified group (6%) and three in the conventional dose group (12%). The difference was found to be non-significant. Decompensations began within 6 weeks, worsening until inducing death in all four patients. Each had a Child Pugh score of A5 at baseline, transaminases <5N, and normal bilirubin values, with the exception of one patient with a value of 34 μ mol/ml. All four patients with liver toxicity exhibited poor MAA targeting of the PVT (three main, one branch). PVT targeting was the only tested parameter that was associated with liver toxicity on univariate analysis (p <0.0001). Other non-significant factors tested were α -fetoprotein (AFP) level, treatment line (first-line *versus* \geq second-line), bilirubin level (< or \geq 34 μ mol/mL), alanine aminotransferase (ALT) level (< or \geq 5N), Child-Pugh score (A5 or A6/B7), tumor involvement (< or \geq 50%), hepatic reserve (percentage of non-irradiated liver, < or \geq 30%), HILD, and a combination of HILD (\geq 40, 60, 80, 100, and 120Gy) and hepatic reserve <30%.

For all 41 patients, the median PFS and OS were 9m (95% CI: 6-11m) and 18m (95% CI: 11-24.5m), respectively. Median PFS and OS have been presented in relation with several parameters in Table 3.

PFS was found to significantly correlate with TD, α FP, Eastern Cooperative Oncology Group (ECOG) status and good or poor candidate status, the latter defined as patients with a TD \geq 205Gy

and good PVT targeting or a TD <205Gy and poor PVT targeting, respectively. A highly significant correlation was found between OS and TD (< *versus* $\geq 205\text{Gy}$, $p = 0.005$, Figure 2) and PVT targeting (good *vs.* poor, $p < 0.0001$, Figure 3), as well as with good or poor candidate status ($p < 0.0001$, Figure 4). A significant correlation was found between OS and Child status (A5 *vs.* A6, and B7) ($p = 0.015$). OS was significantly higher for patients who received lobar hepatectomy than for those who did not undergo surgery, not reach (yet exceeding 24.5m) *versus* 15m, respectively ($p = 0.0493$, Figure 5). Finally, OS did not statistically differ between main or branch/segmental PVT.

DISCUSSION

The radio-induced tumoricidal effect has been found to respond to the determinist rule, with a minimum absorbed tumoral dose necessary in order to induce response (tumoral threshold dose or TTD).

To date, two independent teams have described this dose/reponse relationship in the context of HCC with a clear TTD identification, based on MAA scintigraphy, while using ^{90}Y -loaded glass microspheres (10-12). By applying a biologically effective dose and a voxel approach, Chiesa *et al.* were the first to describe a dose/response relationship with a TTD of 257Gy (10). Using a simple MIRD approach and mean dose evaluation, we also described a TTD of 205Gy with sensitivity and accuracy in the prediction of response of 100% and 91%, respectively (11). TD has been described as the only predictive parameter of response at multivariate analysis (12).

More recently, post-therapeutic dosimetry has also identified a clear dose/response relationship (14) in HCC patients treated with ^{90}Y -loaded glass microspheres, thus confirming the significant relevance of TD.

MAA SPECT-CT-based dosimetry is, however, the only technique currently available that can be performed prior to microsphere injection, thus allowing for treatment schedule modifications, such as a personalized dosimetric approach with intensification in cases of low TD. We recently described this approach comprising personalized dosimetry and intensification at the lobar level with interesting results (79% response rate) in an unselected cohort of HCC patients (12). Using this approach, we found no evident correlation between tumor size and response (12). This is a highly relevant finding, as tumor size has been recognized as a critical parameter related to response using radioembolization with no personalized dosimetric approach. Previous studies have reported significant decreases in response rate as tumor size increased (7, 15). With the application of standard radioembolization, the complete histological response rate was 89% for lesions <3cm and only 33% for lesions >5cm (15). In another study, the morphological response rate was 82% for lesions <5cm, 17.6% for those between 5 and 10cm, and only 2% for those >10cm (7). This point underlines the fact that intensification should be considered for large lesions. Riaz *et al.* have also previously described an intensification approach at a segmental level called radiation segmentectomy, producing very good results (81% response rate; no clinical toxicity) and thus underlying the usefulness of the intensification concept (16, 17). Recent results by means of radiation segmentectomy have demonstrated that the rate of complete histological response was significantly higher for segments receiving a mean dose $\geq 190\text{Gy}$ (*i.e.*, 66.6% for a segment dose $\geq 190\text{Gy}$ compared to only 25% for a segment dose <190Gy, $p=0.03$) (17). Tumor doses were not provided in this study, thus rendering any direct comparison with our threshold

tumor dose of 205Gy impossible. Nevertheless, this study brings to light new evidence of the dose/response relationship observed with radioembolization. It also demonstrates that intensification at a segmental level for small lesions (median size: 2.6cm) can be performed in an uncomplicated manner (not requiring evaluation of the tumor dose), producing good clinical results (safety and response rate of 86%), with the objective of delivering a threshold dose of 190Gy to the segment. Interestingly, the meanILD of our intensified patients was in the same range, namely 187Gy.

As PVT patients often present with large lesions, and owing to the existence of PVT itself, lobar intensification seemed particularly worth investigating in this selected patient cohort. In this study, intensification was applied in 37% of cases. For intensification, our primary endpoint was to achieve a TD ≥ 205 Gy, namely the threshold tumoral dose that had already been identified (11, 12). We had previously observed (12) that the response rate was higher for patients with a TD >275 Gy, in comparison with patients with a TD of 205-275 Gy. Intensification was therefore also performed for some patients with a predictive TD >205 Gy (as predicted using the standard dosimetric approach), with a little over 50% of intensified patients thus concerned. We can wonder if an interesting endpoint of intensification could be reaching the maximal tolerated dose to the healthy injected liver. One difficulty with this hypothesis is the fact that this maximal tolerated dose is not well-defined with radioembolization, especially for cirrhotic patients, and we currently do not know up to which level we can intensify patients. For these reasons, we conservatively decided to not use any potential maximal tolerated dose to reach as an endpoint.

Nevertheless, using this concept of intensification, we obtained a very high response rate (85%) in this cohort of PVT patients with large lesions (mean tumor size: 8.5 ± 3.1 cm). Once again, we

observed that TD clearly impacted the response rate, as previously described (10-12). Achieving high response rates is a crucial goal, as it has been associated with extended OS (7, 18). This is especially the case for PVT patients, with responders exhibiting a 3-year survival rate of 25%, compared to only 4.4% for non-responders ($p=0.02$) (7). In line with previous findings (11, 12), we found no evident correlation between response and size, and observed a high response rate (91%) for patients with lesions ≥ 10 cm. This finding demonstrates that, with a controlled TD (using a personalized dosimetric approach and intensification), we were able to restore, at least partially, the prognosis of patients with large lesions. An additionally interesting finding was that PFS and OS also strongly correlated with TD, with a median OS of only 4.3m (95% CI: 3.7-5m) for a TD < 205 Gy compared to 18.2m (95% CI: 8.5-28.7m) for a TD ≥ 205 ($p = 0.005$).

The other parameter that strongly correlated with OS in our study was PVT targeting. The four patients who underwent no MAA PVT targeting exhibited severe acute liver toxicity leading to death. One reason to explain this is that radioembolization induces transient portal hypertension (19), which can be poorly tolerated by PVT patients who present with poor liver function and no accurate treatment of PVT due to the absence of targeting. The median OS was only 3m (95% CI: 3-3.7m) for patients with poor PVT targeting, compared to 20.2m (95% CI: 12-25.1m) for those with good PVT targeting ($p < 0.0001$). Interestingly, we found that PVT location (main vs. branch/segmental) was not statistically related to OS. This finding is also of significant interest, since main PVT cases are often considered as a contraindication or poor candidates for radioembolization. In reality, the key parameter for PVT is MAA targeting and not PVT location. Thus, irrespective of PVT location, radioembolization should be considered and PVT targeting evaluated. Only poor PVT targeting should be considered a contraindication.

In this study, using intensification did not increase liver toxicity. Severe and permanent hepatic toxicities were no higher in intensified patients (6%) than in those treated with the standard approach (12%). The only parameter found to strongly correlate with liver toxicity was the presence of main or branch PVT without MAA targeting. No patient exhibited a combination of small hepatic reserve (<30%) with a HILD >120Gy, which represented a previously identified liver toxicity factor (12). It is for this reason that two patients did not receive intensification, given that the process would have induced this at-risk situation.

In this group of patients treated with a personalized dosimetric approach and intensification, where necessary, the global median OS was 18m, regardless of TD or PVT targeting. Such a prolonged OS in non-selected PVT patients has never previously been described, whether using radioembolization with a standard dosimetric approach or sorafenib. Previous studies have, in fact, reported a median OS of between 6.4 and 13m for PVT patients using glass or resin microspheres [6-10], which contrasts with values of only 6.5-8.1m with sorafenib (4, 9).

Child A and lobar PVT patients appeared very good candidates for radioembolization in our study, with a median OS of 23.3m (95% CI: 8-23.7m). Relatively long median OS ranging between 15.7 and 17m, have also been described in this type of patient subgroup in other studies (5, 7, 20), thus emphasizing the particular interest of radioembolization in this context.

The median OS was 20.9m for good radioembolization candidates identified prior to therapy, namely patients with both a fixed TD and good PVT targeting.

Lastly, OS was not attained for operated patients, though it did exceed 24.5m, and was significantly longer in these patients than non-operated ones (15m , $p=0.0493$) underlying the potential interest of surgery for PVT patients exhibiting good response to radioembolization.

The results of our study were observed with the use of glass microspheres on Day 3, post-calibration, applying a specific activity of approximately 1250 Bq/sphere. A recent simulation (21) has demonstrated that the specific activity of microspheres is hugely influential, from a radiological point of view, with lower radiobiological effects observed with high specific activity due to the more heterogeneous distribution of radiation. Lewandowski *et al.* (22) proposed using glass microspheres on Week Two, typically 8 days following calibration, with a lower specific activity of approximately 393 Bq/sphere. This technique has been shown to provide good clinical results with a high response rate (57%) and low hepatic toxicity profile (2% of Grade 3/4 bilirubin toxicity). This approach also provides a good opportunity to optimize glass microsphere radioembolization. The use of glass microsphere with extended shelf-lives, combined with a personalized dosimetric approach, could be a promising method for further improving therapeutic effectiveness. New TTD and maximal HILD values will, however, have to be defined for the use of glass microspheres with a specific activity of 393 Bq/spheres.

Only one retrospective non-randomized study has to date sought to compare sorafenib and ^{90}Y -loaded resin microsphere radioembolization (9). No statistical difference regarding OS was identified between the therapeutic options (8.6m for sorafenib *versus* 6.4m for resin microsphere radioembolization, $p=0.879$). Nevertheless, this study's findings should be interpreted with caution, given the major bias against radioembolization that was present (9). The body surface area method was used for activity calculation, despite the partition method now being the

preferred technique of several experts (23,24). Moreover, some patients were treated with radioembolization despite presenting with inappropriate high lung shunting, leading to death, with no personalized dosimetric approach used.

The main drawback of this study was its retrospective and uncontrolled nature. Despite the valuable data it has provided regarding the potential use of radioembolization in PVT patients, as in other trials, further randomized studies are still warranted.

CONCLUSION

Using an MAA SPECT/CT personalized dosimetry and intensification concept with ⁹⁰Y-loaded glass microspheres, radioembolization offers a fully-customized oncological therapeutic option. It appears to be of particular interest in PVT patients, as it induces prolonged OS without increasing liver toxicity. TD and PVT targeting are the most relevant parameters to control in order to achieve good clinical results, even in main PVT cases. Surgery was performed on 12.2 % of the patients, achieving significantly higher OS. Prospective randomized studies are therefore now warranted in order to clearly define the application of this new personalized therapeutic approach.

CONFLICT OF INTEREST

E Garin is a consultant for BTG and has received lecture fees from Bayer

JL Raoul is a consultant for Bayer

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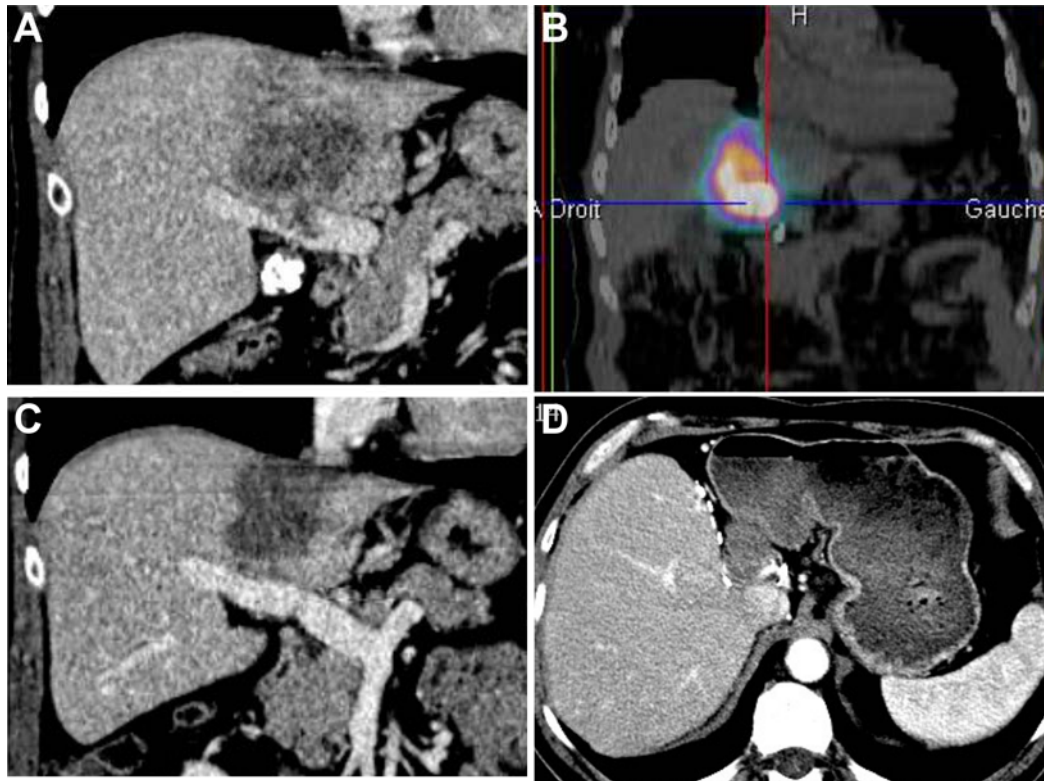
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Figure 1



Example of intensified PVT patient with major response with revascularization of the portal vein and prolonged overall survival

62 year old patient with a large HCC and main PVT

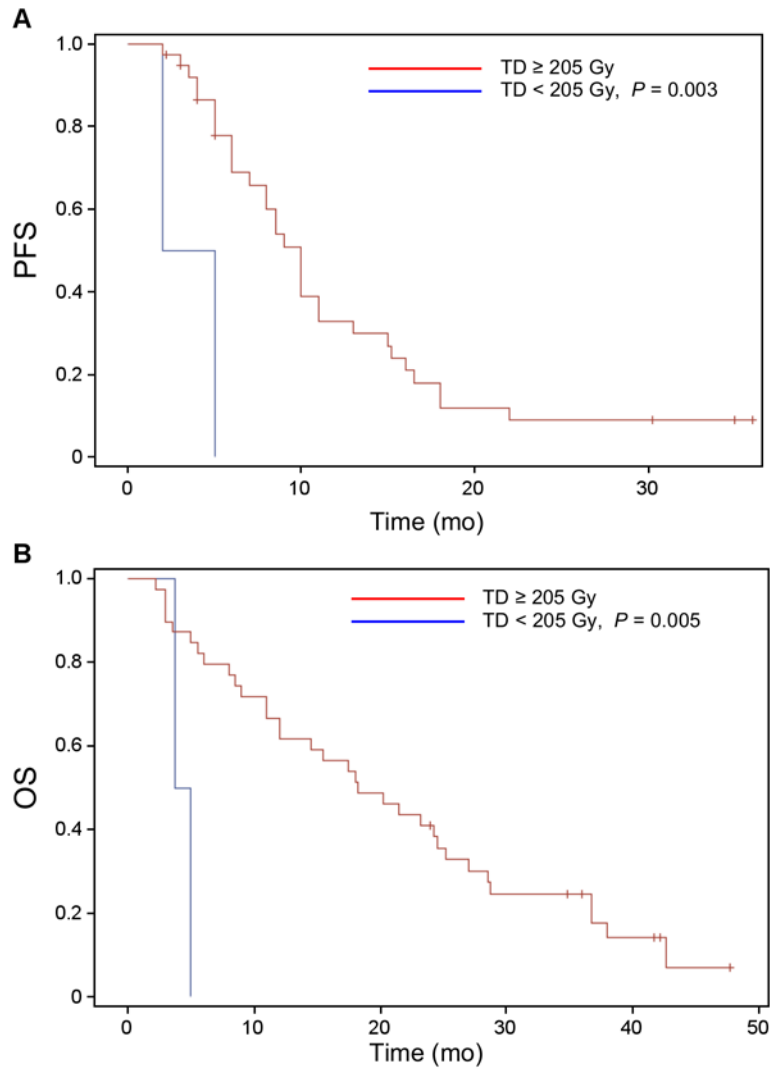
Initial CT slice: infiltrative HCC of 9.6 cm with main PVT (A)

MAA SPECT/CT with high uptake in the tumor and main PVT (B)

Using the standard approach only 0.56 GBq of ^{90}Y loaded glass microspheres should have been used to achieve an ILD of 120 Gy (TD should have been only 162 Gy and HILD 37 Gy). The patient was then intensified and received twice the standard activity (1.16 GBq, ILD was 211 Gy, TD was 285Gy and HILD 65 Gy).

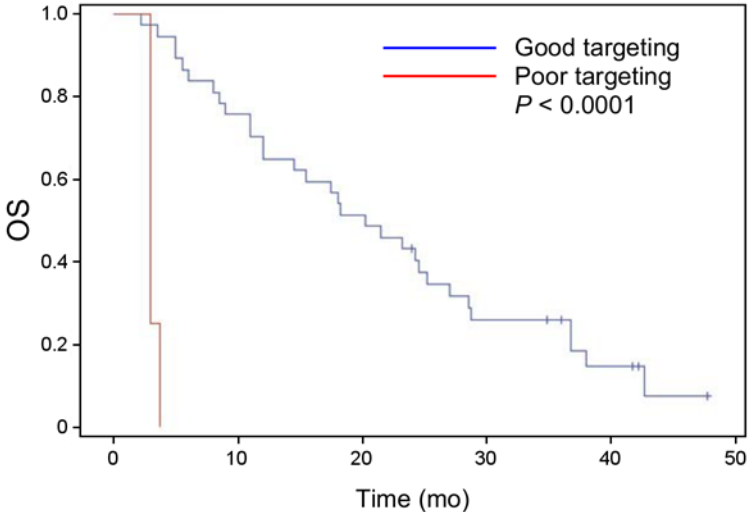
CT slices 6 weeks after injection: EASL partial response of the tumor and main portal vein revascularization (C). The patient subsequently received a left hepatectomy (with complete tumoral resection). PFS was 15 months with lung recurrence only. The patient was still alive at 36.2 months with still only lung recurrences and no liver recurrence (D).

Figure 2



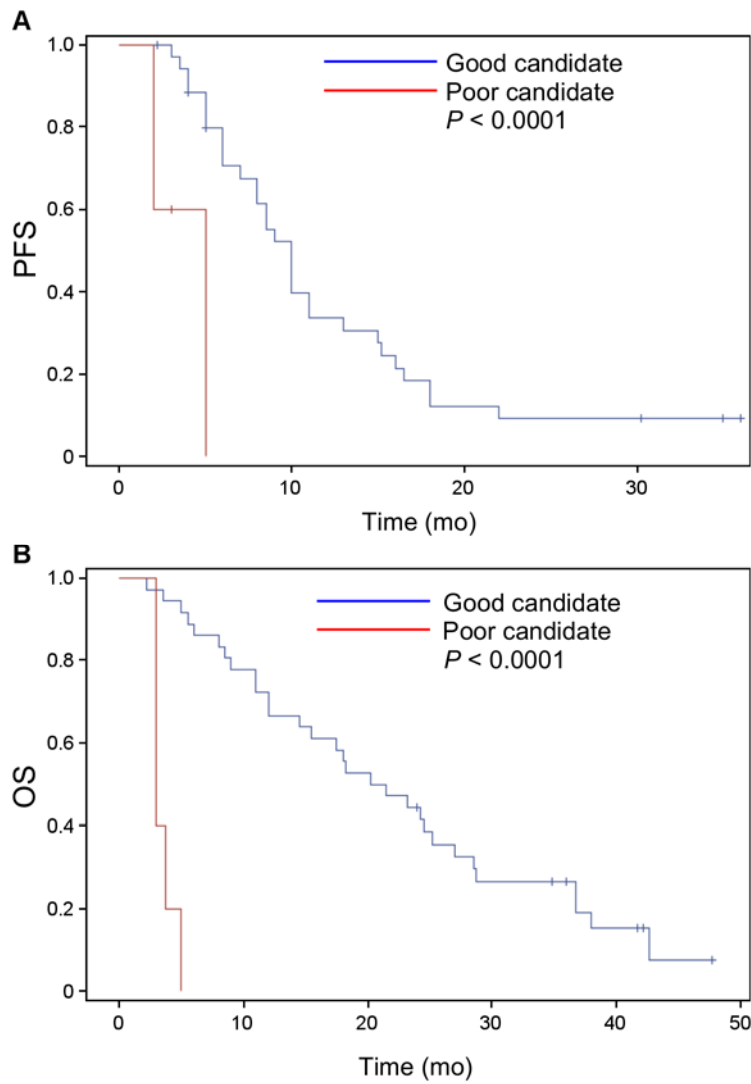
Kaplan Meyer estimates of PFS (A) and OS (B) stratified by TD

Figure 3



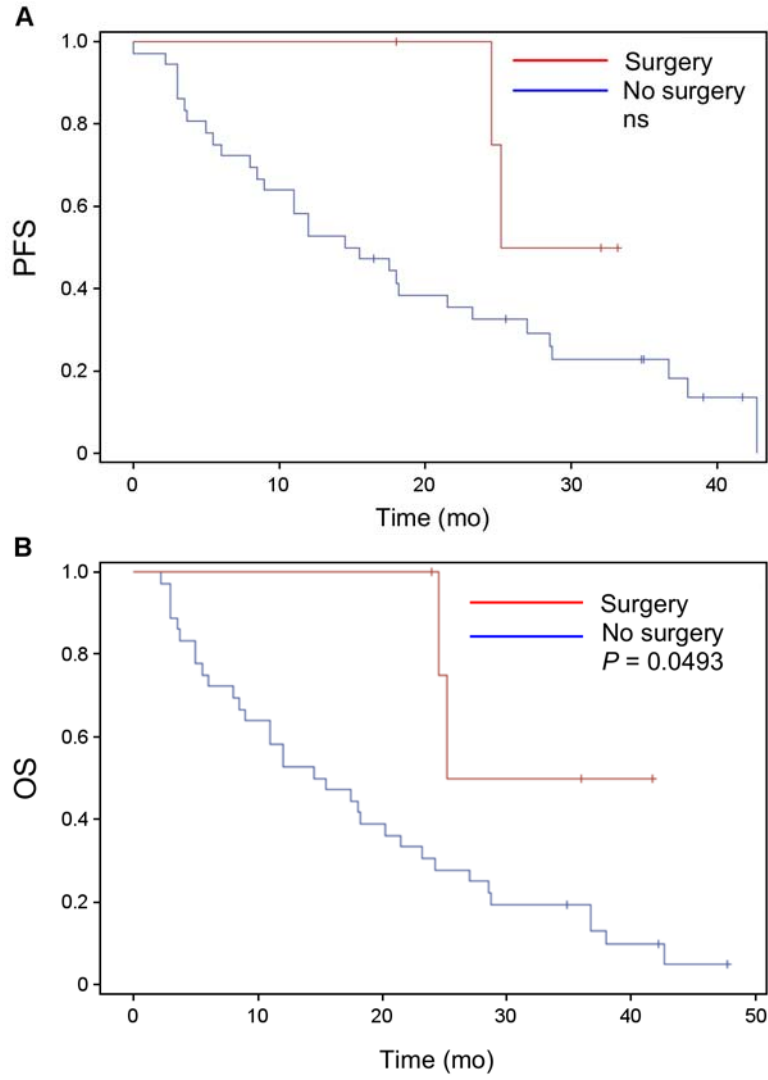
Kaplan Meyer estimates of OS stratified by PVT targeting (good, n= 37 ; poor, n=4)

Figure 4



Kaplan Meyer estimates of PFS (A) and OS (B) for poor (n=5) or good (n=36) candidates to radioembolization

Figure 5



Kaplan Meyer estimates of PFS (A) and OS (B) stratified by surgery.

Table 1: Demographic and baseline characteristics of the patients (n=41)

Clinical Variable	Value
Age (year)	64.4±9.5
Gender (number of cases) Male / Female	33 / 8
Underlying liver disease	
- Alcohol	16
- Hepatitis C	9
- Hepatitis B	1
- Hemochromatosis	5
- NASH	8
- Non cirrhotic	2
Child classification (number of cases) A / B7	38 / 3
Tumor distribution (number of cases)	
- Unifocal	19
- Multifocal	15
- Diffuse	7
- Unilateral	32
- Bilateral	9
Tumoral size (mean±SD)	8.5±3.1 cm
Tumoral involvement	
- mean±SD	27.4±18.5%
- ≥ 70%	2.4%
- ≥50 and < 70%	9.7%
- ≥ 25% and < 50%	36.5%
- < 25%	51.2%
PVT (number of cases) Main / Branch / segmental	12 / 21 / 8

αFP level (kUI/l) Mean±SD / Median	6480±17734 / 145
Bilirubin level (μmol/ml) - Mean±SD - > 34 μmol/ml	17.6±8.8 3 cases
ALT level (U/l) - Mean±SD - > 5N	80±47 0 case
Albumin level (g/L) - Mean±SD - < 28 g/L	38.7±4.5 1 case
CLIP classification (number of cases) 0 / 1 / 2 / 3 / 4	0 / 11 / 21 / 6 / 3
BCLC C classification (number of cases)	41
ECOG performance status (number of cases) 0 / 1 / 2 / 3	30 / 10 / 1 / 0
Prior therapy No / yes	66% / 34%

ALT: alanine aminotransferase; CLIP: cancer of the liver Italian program; ECOG: Eastern Cooperative Oncology Group; NASH: NASH: non-alcoholic steatohepatitis; PVT: portal vein thrombosis; SD: standard deviation

Table 2: Boosted patients (n=15), baseline characteristics, percentage of intensification, dosimetry and response

Tumoral involvement	35.6±15.6%
Tumoral size (mean±SD)	8.8±3.5cm
Child A/B	15/1
IA (mean±SD)	3.3±1.8 GBq
% Boost (mean±SD)	56±40%
ILD (mean±SD)	187±48Gy
TD (mean±SD)	353±103Gy
HILD (mean±SD)	85±25Gy
RR	81%

IA: injected activity; % boost: % of increase of the injected activity with reference of the standard activity that should have been injected to achieve an ILD of 120Gy; ILD: injected liver dose; HILD: healthy injected liver dose; TD: tumoral dose; RR: response rate

Table 3 : Factors associated with PFS and OS (with univariate analysis)

	PFS (months)	OS (months)
TD (< versus ≥205Gy)	3.5 [2-5] versus 10 [7-11] P=0.0029	4.3 [3.7-5] versus 18.2 [8.5-28.7] p=0.005
PVT targeting (good versus poor)	NA*	3 [3-5] versus 20.9 [12-27] p <0.0001
Good versus poor candidate**	5 [2-5] versus 10 [7-11] p <0.0001	3 [3-3.7] versus 20.2 [12-25.1] p <0.0001
Main PVT versus lobar or segmental	5.5 [3-13] versus 10 [6-11] ns	11.5 [11-25.2] versus 21.5 [11-28.5] ns
Child A and lobar PVT versus others	10 [7-16] versus 8 [4-10] ns	13.75 [3-27] versus 23.2 [8-23.7] ns
Child-Pugh (A5 versus A6+B7)	6 [3.5-11] versus 10 [7-15.2] ns	23.7 [12-36.7] versus 7 [3-21.5] p=0.015
Type (U versus M and D)	10 [6-11] versus 8 [2-15.2] ns	11.5 [3.7-23] versus 25.2 [12-36.7] ns
Unilateral versus bilateral disease	10 [7-13] versus 6 [2-11] ns	17.85 [9-25.2] versus bilateral 18 [0-∞] ns
Tumoral involment < or ≥ 50%	8 [2-15.2] versus 10 [6-11] ns	17.5 [11-25.2] versus 38 [3-38] ns
size (≤5 versus > 5cm)	7 [3-∞] versus 9 [6-11] ns	30 [2.2-∞] versus 17 [11-25.2] ns
CLIP (stage 0-2 versus 3 and 4)	9 [2-10] versus 10 [5-15.2] ns	21.5 [8.5-28.7] versus 15.5 [3-27] ns

aFP level (≤ 400 versus > 400)	11 [5-16.5] versus 8.5 [5-10] p=0.02	21.5 [11-36.7] versus 14.5 [3-25.2] ns
Bilirubin level (≤ 36 versus $> 36 \mu\text{mol/l}$)	9 [6-11] versus 5 [3.5- ∞] ns	18.2 [12-27] versus 3.2 [0-36.7] ns
ECOG status (0 versus 1 or 2)	10 [8-15] versus 5 [2.10] p=0.02	18.2 [12-27] versus 11 [3- ∞] ns
Treatment line (first versus others)	8.5 [5-11] versus 10 [5-16.5] ns	24.5 [3-36.7] versus 14.5 [8.5-25.2] ns
Surgery (yes versus no)	10 [8-16] versus 8.5 [6-11] ns	15.0 [8.5-21.5] versus not reached [24.5-∞] p=0.0493

U: unifocal; M: multifocal; D: diffuse; PFS: progression free survival; OS: overall survival;

CLIP: cancer of the liver Italian program; ECOG: Eastern Cooperative Oncology Group; PVT:

portal vein thrombosis; TD: tumor dose

*Patients with no PVT targeting died before progression

** A good candidate is defined as a patient with both a TD ≥ 205 Gy and good PVT targeting

A poor candidate is defined as either exhibiting a TD < 205 Gy or poor PVT targeting or both