High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90) Y-loaded glass microsphere radioembolization

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High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with ^{90}Y-loaded glass microsphere radioembolization

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Abstract

Background & Aims: Efficacy of radioembolization is derived from radioinduced damage, whereas tumour dosimetry is not considered as yet in prospective clinical trials.

Objectives: This study evaluates the impact of tumour dose (TD), based on ^{99m}Tc macroaggregated albumin (MAA) quantification, on response and overall survival (OS).

Materials and Methods: We consecutively included 85 patients with hepatocellular carcinoma treated with ^{90}Y-loaded glass microspheres. TD was calculated using a quantitative analysis of the MAA SPECT/CT. Responses were assessed after 3 months using the European Association for the Study of the Liver criteria. OS was assessed using Kaplan–Meier tests.

Results: Response rate was 80.3% on lesion-based analysis (n=132), and 77.5% on patient-based analysis. The response rate was only 9.1% for patients with TD <205 Gy against 89.7% for those with TD ≥205 Gy ($P<10^{-7}$). Non-portal vein thrombosis (PVT) patients exhibited a median OS of 11.75 m (95% CI: 3–30.7 m) for TD <205 Gy, and 25 m (95% CI: 15–34.7 m) for TD ≥205 Gy (P=.0391). PVT patients exhibited a 4.35 m median OS (95% CI: 2–8 m) for TD<205 Gy, and 15.7 m (95% CI: 9.5–25.5 m) for TD ≥205 Gy, (P=.0004), with HR of 6.99. PVT patients exhibited a median OS of 3.6 m (95% CI: 2–8 m) when PVT MAA targeting was poor or with TD <205 Gy (poor candidate), vs 17.5 m (95% CI: 11–26.5 m) for the others identified as good candidates (P<.0001), with HR of 12.85.

Conclusion: This study confirms the highly predictive value of MAA-based TD evaluation for response and OS. TD evaluation and PVT MAA targeting should be further evaluated in ongoing trials, whereas personalized dosimetry should be implemented in new trial designs.

KEYWORDS
overall survival, predictive dosimetry, radioembolization, response

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Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, with 500 000 new cases per year.[1] Radioembolization with ^{90}Y-loaded resin or glass microspheres is increasingly used in patients with unresectable tumours with promising clinical outcomes.[2–5] Also not yet recognized as a standard approach, radioembolization is currently recognized as a potential one by various scientific societies, such as the European Society of Medical Oncology.[6]

[90]Y-loaded microsphere radioembolization is preceded by a treatment simulation consisting of diagnostic angiography and hepatic perfusion scintigraphy with macroaggregated albumin (MAA), serving to identify lung and digestive shunts. The goal of radioembolization is to deliver a tumoricidal dose to the tumour while sparing healthy liver tissue.[7,8] Tumour-absorbed dose (TD) and that absorbed by healthy injected liver tissue (HILD) are two key parameters that should be defined when using radioembolization. However, these parameters are not currently used as yet in clinical trials.

When using glass microspheres in line with the product package insert,[9] the recommendation stipulates to deliver a radiation dose of 80–150 Gy to the injected liver volume (ILD), using a dose calculation based on the following accepted simplified formula:

$$ILD_{(Gy)} = IA_{(GBq)} \cdot (1 - LSF) \cdot 50 / M_{(Kg)}$$

where "IA" represents the activity to be injected, "LSF" the lung shunt fraction (as measured by MAA liver perfusion scan) and "M" the mass of the liver volume to be treated.

Tumour dose and healthy injected liver dose (HILD) can be assessed either prior to therapy, using MAA quantification as a surrogate of microsphere distribution,[10,11] or after therapy using a direct quantification of ^{90}Y-loaded microspheres.[12] MAA dosimetry is the only one available prior to therapy and able to impact the patient treatment schedule.[13,14]

When using local therapy as radioembolization, two of the most essential post-therapeutic parameters, besides toxicity, that must be evaluated are tumour response and overall survival.[5] It should be mentioned, however, that recurrence does not necessarily mean complete therapeutic failure, as this local therapy approach can often be repeated once more, yet with additional healthy liver exposure to radiation.

This study thus sought to evaluate the impact of predictive MAA-based dosimetry on response and survival in HCC patients treated with glass microspheres (TheraSphere®) using the product package insert's dosimetric recommendations, including a large sample of patients and tumours.

1 | MATERIALS AND METHODS

1.1 | Patient characteristics

Between December 2006 and December 2012, 108 HCC patients were treated in our centre; 23 were excluded from the analysis: 2 owing to having no MAA SPECT/CT evaluation, and 21 who were treated without using the product package insert's

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Key points

- Largest study with MAA dosimetry on HCC.
- High impact of tumour dose on response and OS.
- The higher the dose above the threshold, the greater the effect.
- Tumour dose evaluation should be used in the treatment schedule.

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recommendations and received treatment intensification (i.e. a lobe dose >150 Gy).

Finally, 85 HCC patients were included, treated consecutively with TheraSphere® using the package insert's recommendation of targeting a 80–150 Gy radiation dose to the lobe, each with an available MAA SPECT/CT dosimetric evaluation. Written informed consent was obtained from each patient, and the use of radioembolization was approved by the Rennes ethics committee. The indication for selective internal radiation therapy (SIRT) was decided upon by an HCC multidisciplinary tumour board specialized in liver malignancies. Patients were considered unsuitable for chemoembolization as a result of different conditions (PVT; multifocal or voluminous lesions; incomplete response or progression following chemoembolization). Portal vein thrombosis (PVT) occurred in 31 patients and was classified according to Mazzaferro et al.,[4] using the slightly modified classification of Shi et al.[15]

Portal vein thrombosis extended at the segmental level (PV1) in 6 patients (19.4%), at the branch level (PV2) in 16 (51.6%), into the main portal vein trunk (PV3) in 7 (22.5%) and into the mesenteric or splenic vein (PV4) in 2 cases (6.5%). Extrahepatic metastatic disease was detected in only one patient. Tumours were nodular or multinodular in 80 cases and diffuse in 5. Patient and tumour characteristics are detailed in Table 1.

1.2 | Planning and administration of ^{90}Y-loaded glass microspheres

For the simulation, diagnostic angiography was carried out for arterial mapping and catheter positioning to optimize tumour targeting while avoiding digestive shunts. Coil embolization was not performed systematically. A liver perfusion scan was conducted following injection of 185 MBq of MAA into the hepatic artery, with planar and SPECT/CT acquisition.

A quantitative uptake analysis of tumour and non-tumour liver tissue was performed as previously described.[11]

The activity to be injected was calculated conventionally to achieve the dosimetric end points described in the package insert,[9] i.e. 80–150 Gy to the treated liver (without exceeding 30 Gy to the lungs for one treatment and 50 Gy as cumulative dose).

Tumour dose was evaluated solely for lesions >2 cm to avoid error of quantification related to partial volume effect, as suggested by several authors.[10] PVT dose was not technically achievable (size often lower than 2 cm or delineation of PVT and main tumour not possible with MAA). However, MAA PVT targeting was evaluated visually and

TABLE 1 Demographic and baseline characteristics of the patients (n=85)

Clinical variable	Value
Age (year)	67.3±8.5
Gender	
Male	87%
Female	13%
Underlying liver disease	
Alcohol	48.2%
Hepatitis C	14.1%
Hepatitis B	2.3%
Haemochromatosis	7%
NASH	23.5%
Biliary	1.1%
Non-cirrhotic	2.3%
Child classification	
A5	72.9%
A6	22.3%
B7	4.7%
Tumour distribution	
Unifocal	41.1%
Multifocal	52.9%
More diffuse	5.8%
Tumoral size (mean±SD)	7.1±8.3 cm
Tumoral involvement	
Mean±SD	19.8±18.5%
≥70%	3.6%
≥50 and <70%	7%
≥25% and <50%	15.3%
<25%	75.1%
PVT	
Main	29%
Branch	51.6%
Segmental	19.4%
αFP level (kUI/L)	
Mean±SD	9374±57 807
Median	39
>400	23.5%
Bilirubin level (µmol/mL)	
Mean±SD	18.6±9.6
>34 µmol/mL	7%
ALT level (U/L)	
Mean±SD	52.6±32.2
>5N	5.8%
Albumin level (g/L)	
Mean±SD	39.5±4.9
<28 g/L	2.3%

(continues)

TABLE 1 (continued)

Clinical variable	Value
CLIP classification	
0	17.6%
1	43.5%
2	25.9%
3	9.4%
4	3.5%
BCLC classification	
A	7%
B	56.4%
C	36.4%
D	0%
ECOG performance status	
0	82.3%
1	17.7%
2	0%
Prior therapy	
No	50.6%
Yes	49.4%
Surgery	21.1%
Chemoembolization	17.6
Sorafenib	14.1%
[131]I-lipiodol	15.2%
Radiofrequency	7%

classified as poor in the event of PVT uptake lower or equal than to the healthy liver; or as high in the event of PVT uptake higher than to the healthy liver (Fig. 1).

Portal vein thrombosis patients were classified as good candidates for radioembolization if TD was ≥205 Gy and in the presence of good PVT targeting. They were classified as poor candidates if either TD was <205 Gy or PVT targeting was poor.

In the case of multiple treatments, the dosimetric analysis was performed for the first treatment only as previously described,[11] except for the only one patient who received two injections in the same lobe within 2 months where cumulative doses were calculated.

Twenty-four patients received two treatments. In case of bilateral disease (n=10), two lobar treatments were administered separately at an interval of 6–8 weeks. In case of incomplete response after a first injection, a second treatment was performed at least 6 months after the first one (n=8). For one patient with technical difficulty with incomplete tumour coverage a second injection in the same lobe was performed at 2 months and five patients received a second injection as a result of recurrence.

For the therapeutic phase, glass microspheres were usually injected on Day 3 after calibration, each time using a lobar approach. Injections were performed 1 week after the simulation in 93% of cases, and 2–3 weeks after the simulation in only 7%.
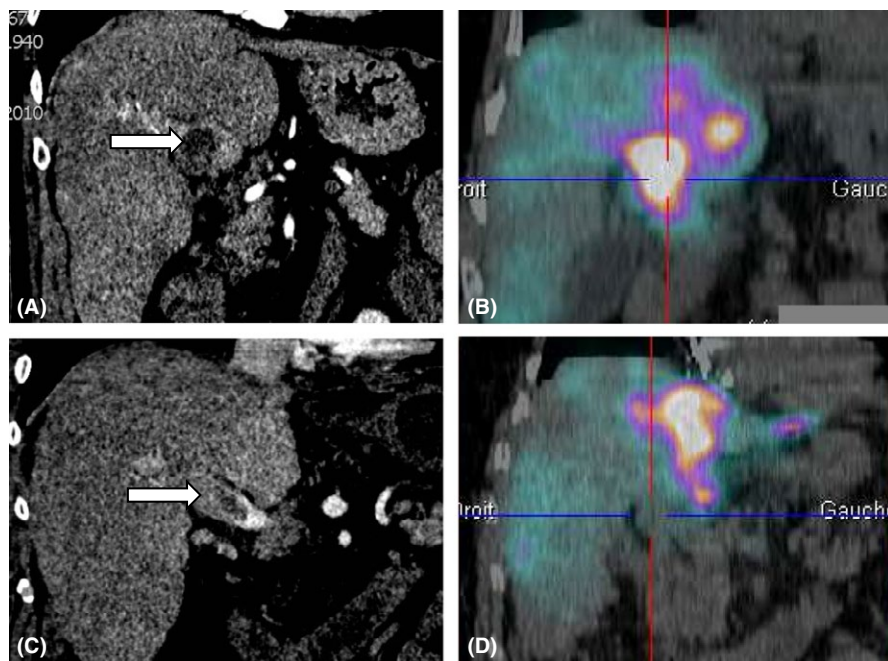
FIGURE 1 Portal vein thrombosis (PVT) macroaggregated albumin (MAA) targeting evaluation. Example of good targeting (PVT uptake higher than the liver) of a main branch PVT (CT scan, white arrow: A) with high MAA uptake on the SPECT CT (B). Example of poor targeting (PVT uptake lower or equal than the liver) of a main branch PVT (CT scan, white arrow: C) with no MAA uptake on the SPECT CT (D)

1.3 | Response evaluation

Response evaluation was performed using both lesion-based and patient-based analyses, yet only for the delineable treated lesions. As radioembolization is a local therapy, the analysis of a potential dose/response relationship requires a response analysis only of the treated lesions.

Response of treated tumours was assessed using European Association for the Study of the Liver (EASL) criteria. Accordingly, progression was defined as new lesion occurrence or increased enhancing tissue size of at least 25% in the target lesions on the arterial phase; partial response was defined as decreased enhancing tissue size of at least 50% in the target lesions; a complete response was defined as disappearance of hypervascularization and stable disease by the others situations. An objective response was defined by a partial or complete response, whereas no response was defined by stable disease or progression. The PVT extension variations during follow-up were not considered in tumour response evaluation, excepting complete disappearance (complete revascularization of the portal vein), as previously described.[5]

Triphasic CT scans were performed 3 months after treatment, then every 3 months until disease progression or death.

The mean follow-up duration was 22.2±16.3 months.

Potential variables associated with response in univariate analysis were as follows: TD as continuous and dichotomized variable <205 vs ≥205 Gy, as well as tumour size as continuous or dichotomized variable <5 vs ≥5 cm and <10 vs ≥10 cm. Multivariate analysis was performed for variables that were significant in univariate analysis.

The threshold TD of 205 Gy, described in a preliminary study,[11] was used to calculate the diagnostic performances of MAA dosimetry to predict the response status. A "true positive" (TP) was defined as an objective response obtained with a TD ≥205 Gy; a "true negative" (TN)

was defined as no objective response with a TD <205 Gy; a "false negative" (FN) was defined as an objective response with a TD <205 Gy; a "false positive" (FP) corresponded to no objective response with a TD ≥205.

1.4 | Toxicity analysis

Toxicities were scored using the common terminology criteria for adverse events (CTCAE) (V4). Only permanent and clinically relevant Grade ≥III liver toxicities, manifesting within 6 months of radioembolization, were considered limiting factors. The imputability of the suspected toxicities was defined according to the International Conference of Harmonization (ICH, E2B R3). Potential variables associated with toxicity analysed in univariate analysis were as follows: treatment line (first line vs ≥second line), Child-Pugh (A5 vs A6+B7), Cancer of the Liver Italian Program (CLIP) classification (≤2 vs ≥3), bilirubin level (<35 μmol/L vs ≥35 μmol/L), aspartate aminotransferase (AST) level (<5N vs ≥5N), World Health Organization (WHO) status (0 vs 1 and 2), MAA PVT targeting for PVT patients, TD (<205 Gy vs ≥205 Gy), severe underlying biliary disease (yes or no), HILD as a continuous and dichotomized variable (>40, 60, 80, 100 and 120 Gy), hepatic reserve (HR) calculated as the volume of the not irradiated liver divided by the volume of the whole liver (<30% or ≥30%) as well as a combined parameter associating the HILD (>40, >60, >80, >100 or >120 Gy) and HR <30%. Multivariate analysis was performed for variables that were significant in univariate analysis.

1.5 | Survival

Overall survival was defined as the time between treatment and last follow-up or death. Several variables were tested (see Tables 2 and 3).

TABLE 2 Kaplan-Meyer estimates of overall survival

	Overall population (n=85) OS (months) Median (CI 95%)	PVT patients (n=31) OS (months) Median (CI 95%)
TD (<205 vs ≥205 Gy),	6.5 (3–24) vs 21 (15–27) P=.0052	4.35 (2–8) vs 15.7 (9.5–25.7) P=.0004
Child-Pugh (A6+B7 vs A5)	17.5 (6–26.5) vs 20.6 (12–27) ns	9 (3–26.5) vs 15 (8–25.5) ns
CLIP (>1 vs 0 and 1)	12 (3.5–18) vs 22.1 (14–26.5) P=.0453	12 (3–18) vs 13.5 (5.5–26.5) ns
Bilirubin level (≤35 vs >35 µmol/L)	18.95 (14–25.5) vs 8 (5–∞)ns	15 (8–23.2) vs 6.5 (5–8) ns
ECOG status (0 vs 1 or 2)	19.45 (14–27) vs 11 (3.7–24.2) ns	15.7 (9.5–25.5) vs 11 (3.5–26.5) ns
aFP level (≤400 vs >400)	23.2 (14–27) vs 10.75 (3.5–25) ns	13.8 (8–26.5) vs 12 (13–18) ns
Tumour size (<5 vs ≥5 cm)	25.5 (14–38.3) vs 15 (11–23.2) ns	29.9 (2.2–46.2) vs 12 (8–18) ns
Tumour size (<10 vs ≥10 cm)	23.7 (14–27) vs 12 (6–18.5) P=.0241	20.2 (8–29) vs 11.5 (3.7–17.5) P=.0405
Tumour involvement (≥50 cm vs <50%)	9.5 (2–47.5) vs 19.6 (15–25.5) ns	4.25 (2–29) vs 15 (8–23.9) ns
Tumour type (diffuse vs nodular)	9.5 (3–24.2) vs 21 (14–28) P=.0126	9.5 (3–15.7) vs 16.2 (8–25.5) ns
PVT involvement, yes vs no (overall population only)	12 (8–20.2) vs 24 (14–29) P=.0391	–
PVT targeting, poor vs good (PVT patients only)	–	4.35 (2–8) vs 15.7 (9.5–25.5) P=.0004
Poor vs good PVT candidate	–	3.6 (2–8) vs 17.5 (11–26.5) P<.0001

TABLE 3 Univariate and multivariate analysis of factors associated with overall survival (Cox model)

	Overall population (n=85)		PVT patients (n=31)	
	Relative risk (CI 95%)	Mulivariate analysis	Relative risk (CI 95%)	Mulivariate analysis
TD (<205 vs ≥205 Gy),	2.35 (1.26–4.4) P=.0072	P=.0053	6.99 (1.98–24.39) P=.0025	ns
Child-Pugh (A6+B7 vs A5)	1.37 (0.81–2.31) ns	–	1.72 (0.79–3.74) ns	–
CLIP (>1 vs 0 and 1)	1.90 (0.99–3.64) ns	–	1.76 (0.76–4.06) ns	–
Bilirubin level (≤35 vs >35 µmol/L)	0.82 (0.29–2.28) ns	–	0.29 (0.06–1.35) ns	–
ECOG status (0 vs 1 or 2)	0.72 (0.39–1.32) ns	–	0.41 (0.16–1.06) ns	–
aFP level (≤400 vs >400)	0.67 (0.38–1.18) ns	–	0.69 (0.32–1.47) ns	–
Tumour size (<5 vs ≥5 cm)	0.65 (0.40–1.70) ns	–	0.57 (0.19–1.71) ns	–
Tumour size (≥10 vs <10 cm)	1.85 (1.07–3.23) P=.0271	ns	2.28 (1.01–5.17) P=.0485	ns
Tumour involvement (≥50% vs <50%)	1.12 (0.32–1.32) ns	–	2.04 (0.69–6.01) ns	–
Tumour type (diffuse vs nodular)	1.77 (1.07–2.95) P=.0238	ns	2.38 (0.84–6.75) ns	–
PVT involvement, yes vs no (overall population only)	1.63 (1.01–2.62) P=.0428	ns	–	–
PVT targeting, poor vs good (PVT patients only)	–	–	14.7 (3.09–69.12) P=.0007	P=.0254
Poor vs good PVT candidate	–	–	12.85 (3.68–44.77) P<.0001	–[a]

–, not performed; Good PVT candidate, TD ≥205 Gy and good PVT targeting; Poor PVT candidate, TD <205 Gy or poor PVT targeting; TD, tumour dose.
[a]Not performed as this variable is a combination of TD and PVT targeting.

1.6 | Statistics

Quantitative values were expressed as mean±standard deviation (SD), compared between responders and non-responders using both lesion-based and patient-based analysis, and a distribution-free Wilcoxon comparison test. Discontinuous data were compared by means of Chi-squared test (Fisher's exact test). This test was used in conjunction with univariate analysis to identify parameters associated with tumour response and liver toxicity. Significant data from the univariate analysis were then subjected to multivariate analysis using logistic regression testing. OS values were estimated using the Kaplan-Meier method and compared based on log-rank testing. Univariate analysis of variables potentially associated with

OS was performed using a Cox Model. Multivariate analysis also using a Cox model was performed for variables that were significant in univariate analysis. SAS software (Version 9.3, SAS Company, Singapore) was used for the statistical analyses, with a significance threshold set at P≤.05.

2 | RESULTS

2.1 | Treatment parameters

The mean ^{90}Y-loaded glass microsphere injected activity was 2.6 (±1.2) GBq, the mean injected liver dose 117.2 (±22.4) Gy and the mean healthy injected liver dose 82.3 (±30.3) Gy.
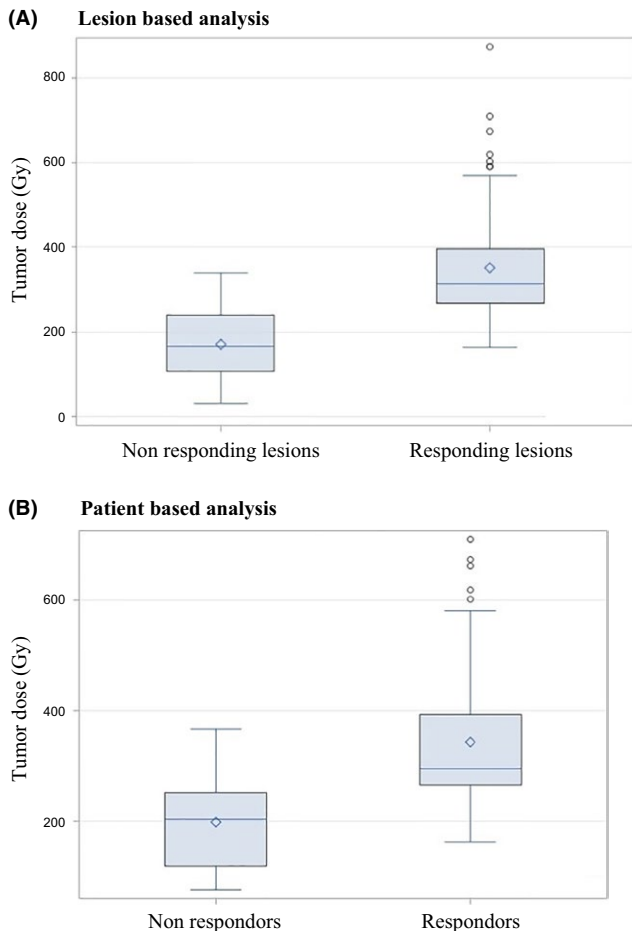
2.1.1 | Lesion-based analysis

A total of 132 delineable tumours were analysed. The 3-month response rate was 80.3% (CR: 17.4%, 23/132 lesions; PR: 62.8%, 83/132; SD 15.9%, 21/132; PD: 3.7%, 5/132). As demonstrated by univariate analysis, TD was significantly higher for responding lesions than non-responding ones, at 353±120 Gy vs 171±85 Gy respectively (*P*<.0001) (Fig. 2). Response rate was 92.1% for lesions with TD ≥205 Gy (105 responses over 114 lesions) vs only 5.5% for those with TD <205 Gy (1/18 lesions), *P*<10[−13].

Tumour size was significantly smaller for responding lesions (5.2±2.9 cm) than non-responding ones (7.9±3.8 cm), *P*=.0011. Response rate was 88.2% for lesions <5 cm (60/68 lesions) vs 71.8% for those ≥5 cm (46/64 lesions), *P*=.0182, and 83.2% for a size <10 cm (94/113 lesions) vs 63.1% for that ≥10 cm (12/19 lesions), *P*=.0430.

On multivariate analysis using continuous variables, only TD remained significantly associated with response (*P*<.00001).

Using the threshold tumoral dose of 205 Gy, TD was predictive of response with a sensitivity of 99.1%, a positive predictive value of 91.5% (10 false-positive results) and an accuracy of 91.6%.

The false-positive rate was highly impacted by tumour dose, recorded at 33.3% for TD ≥205 Gy and <260 Gy (7 FP/21 lesions), vs only 3.2% for TD ≥260 Gy (3 FP/93 lesions), *P*=.0012.

In the event of false-positive results, visual comparison of MAA and ^{90}Y microsphere distribution revealed a clear mismatch in only four cases (one partial arterial dissection during the therapeutic angiography, two cases with slightly different catheter repositioning and one case without specific angiographic abnormality).

2.1.2 | Patient-based analysis

Response

Response evaluation was available for 80 patients, as 5 patients had diffuse and non-evaluable lesions according to EASL criteria.

In total, 18 patients did not respond to treatment, whereas 62 did. The 3-month response rate was 77.5%, comprising 12.5% CR (10/80 patients), 63.7% PR (51/80), 17.5% SD (14/80) and 5% PD (4/80).

Tumour dose was significantly higher for responding lesions than non-responding ones, i.e. 343±123 Gy vs 198±85 Gy respectively (*P*<.0001) (Fig. 2). Response was also affected by tutor size with a mean largest tutor size of 5.9±3.1 cm for responding patients vs 9.8±2.8 cm for non-responding ones. Response rate was 100% for patients with a lesion <5 cm vs 64.7% for those with that ≥5 cm (33/51 patients), *P*<.0001, and 83.1% for a size <10 cm (54/65 patients) vs 46.6% for that ≥10 cm (7/15 patients), *P*=.0129.

Using the threshold tumoral dose of 205 Gy (11 patients, i.e. 13.7%, had a TD <205) TD was predictive of response with a sensitivity of 98.3% (only one false negative), a positive predictive value of 88.4% (eight false positives) and an accuracy of 88.7%.

On multivariate analysis using continuous variables, only TD remained significantly correlated with response (*P*<.0014).

Survival

At time of analysis, 74 patients were deceased and 11 still alive, with no patient lost to follow-up.

The median OS was 18.7 m (95% CI: 12–25 m) for the global population (non-PVT patients: 24 m; 95% CI: 14–29 m; PVT patients: 12 m; 95% CI: 8–20.2 m, *P*=.0391).
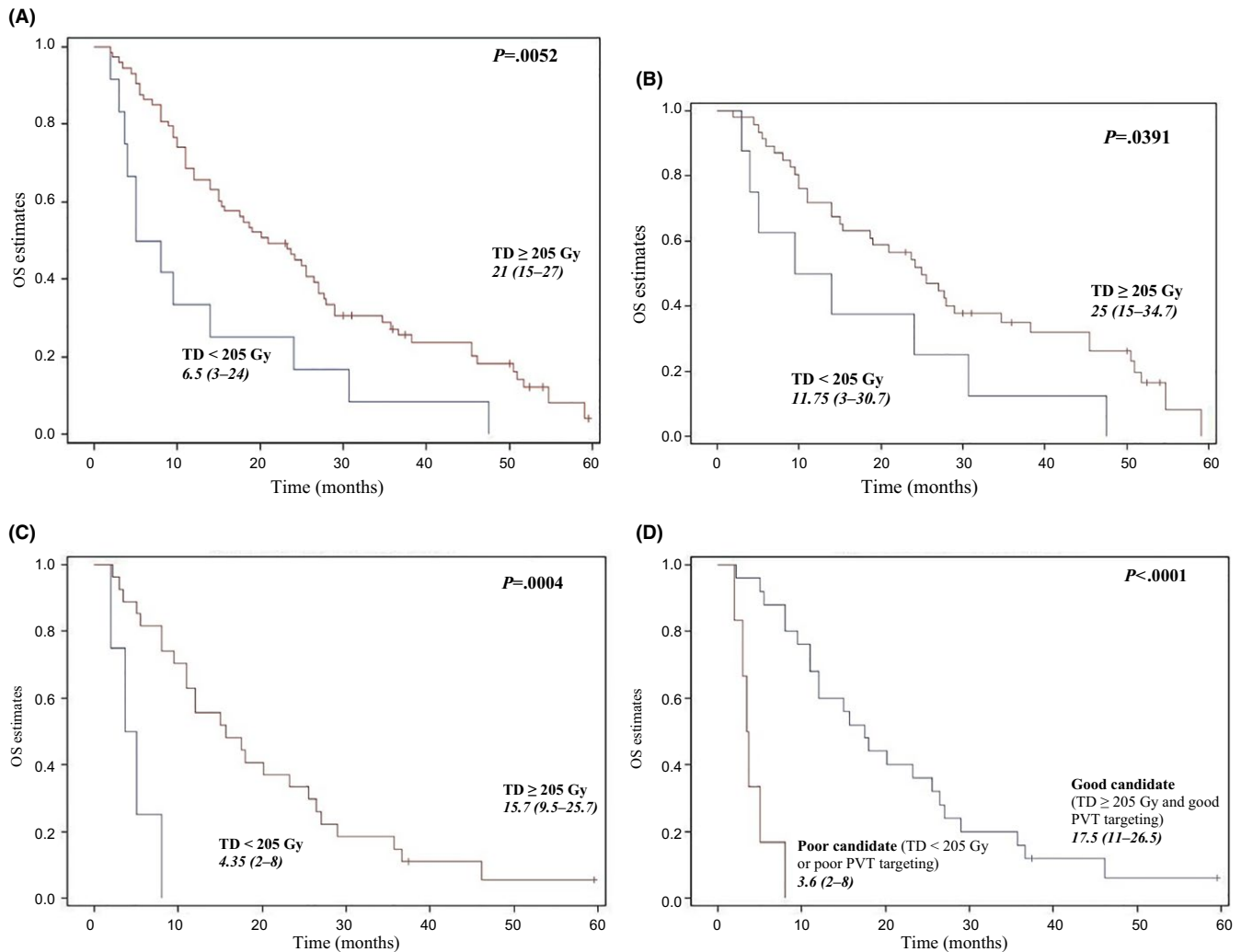
All causes taken into account, the mortality rate was 0% at 1 month, and 5.8% at 3 months.

The median OS values stratified using tested parameters are displayed in Table 2. TD was significantly associated with OS for the overall cohort as for both BLCC B and BLCC C patients (Fig. 3A–C). Other parameters associated with OS were CLIP classification (overall population only), tumour size <10 or ≥10 cm, tumour type (overall population only), PVT involvement, MAA PVT targeting as well as good or poor candidate for PVT patients (Table 2).

On multivariate analysis for the global cohort, TD was the only variable remaining significantly associated with OS (Table 3).

Regarding the 31 PVT patients, 25 were good candidates to radioembolization (i.e. 80.6%) and 6 poor candidates (i.e. 19.4%). One patient was a poor candidate as a result of TD <205 Gy only, two because of poor PVT targeting only and three on account of both TD

(A) Lesion based analysis

(B) Patient based analysis

FIGURE 2 Tumour dose distribution regarding EASL response status. (A) Lesion-based analysis. (B) Patient-based analysis

FIGURE 3 Kaplan-Meier estimates of OS. (A) OS for the overall population accordingly to tumour dose (TD) (85 patients). (B) OS for patients without portal vein thrombosis (PVT) accordingly to TD (54 patients i.e. 63.5%). (C) OS for PVT patients accordingly to TD (31 patients, i.e. 36.5%). (D) OS for PVT patients accordingly to the good or poor candidate to RE status

<205 Gy and poor PVT targeting. OS was only 3.6 m (95% CI: 2–8) for poor candidates, compared to 17.5 m (95% CI: 11–26.5) for good ones, (P<.0001), with an HR of 12.85 (95% CI: 3.68–44.77) (Fig. 3D).

On multivariate analysis involving the PVT cohort, only PVT targeting remained significantly associated with OS (Table 3).

Toxicity

Severe permanent liver toxicity was found in nine patients (10.5%), Table 4. The toxicity rate was 6.3% for Child-Pugh A5 patients (4/62), 21% for A6 (4/19) and 25% for B7 (1/4), (ns), reaching 40% for patients with a bilirubin level >35 μmol/mL. No other severe clinically relevant toxicity was demonstrated, especially no gastroduodenal ulceration or lung damage.

For the global population, parameters associated with liver toxicity in univariate analysis were Eastern Cooperative Oncology Group (ECOG) performance status (P=.0474), underlying biliary disease (P=.0286), HILD continuous with a HILD of 79.5±29.1 Gy for patients without toxicity compared to 104.7±33.1 Gy for those with toxicity (P=.0283), in addition to those with a HILD ≥100 Gy (P=.0375) and

those with a HILD ≥120 Gy and a HR <30% (P=.0286). For PVT patients, only ECOG (P=.0164) and PVT targeting (P=2.95×10^{-4}) were associated with toxicity. In particular, the difference in HILD, exhibiting a value of 73.3±28.1 Gy vs 88.7±20.9 Gy for patients without and with toxicity, respectively, was not statistically significant.

For the overall population, three multivariate analyses were performed including successively one of the three linked variables proven significant in univariate analysis (+ the others significant variables): HILD as continuous variable (no significant variable found), HILD ≥100 Gy (only biliary disease was significant, P=.0352) and HILD ≥120 Gy with an HR <30% (only HILD ≥120 Gy with an HR <30% was significant, P=.0473).

For the PVT patients, only poor MAA PVT targeting was highly predictive of liver toxicity at multivariate analysis, P<10^{-3}.

3 | DISCUSSION

The first significant finding derived from this study is the clear and highly significant correlation between TD and response, with a

TABLE 4 characteristics of patients with liver toxicity

CASE/ Number of treatment	Child status/ Bilirubin (μmol/L)	ECOG status	PVT/ Classification/ Targeting	ILD (Gy)	HILD (Gy)	HILv mL	HR %	Toxicity beginning (week)	First symptoms/ CTCAE grade	OS (months)
1/1	A5/26	0	No	116	92	1219	20.2	11	A2/bil 3	7.0
2/1	A6/28	1	No	145	126	564	16.8	6	A3/bil 4	2.0
3/2	A5/6	0	No	218[a]	174[a]	1160	0	22	A2/bil 3	14.0
4/1	A6/17	0	Yes/4/poor	128	63	1788	63	5	DH3/bil 4	3.0
5/1	A5/22	1	Yes/3/poor	146	80	501	47	8	A2/bil 3	3.5
6/1	B7/14	0	No	132	119	485	27	18	A3/bil 3	4.5
7/1	A6/44	0	No	112	76	737	70	5	A2/bil 3	6.0
8/1	A5/29	1	Yes/2/poor	106	100	1755	38	2	A3/bil 3	3.7
9/1	A6/36	1	Yes/3/poor	134	111	319	62	7	A2/bil 4	5.0

A, ascites; Bil, bilirubin; DH, digestive haemorrhage; HILD, healthy injected liver dose; HILv, healthy injected volume; HR, Hepatic reserve; ILD, injected liver dose; PVT, PVT present, yes or no.

[a]Cumulative dose as this patient received two treatments of the same lobe separated by 2 months owing to an incomplete tumour coverage after the first one.

response rate of only 9.1% for patients with TD <205 Gy against 89.7% for those with TD ≥205 Gy, $P<10^{-7}$. TD was the only variable tested that significantly correlated with response on multivariate analysis. A tumoral threshold dose of 205 Gy for ^{90}Y glass microsphere radioembolization, obtained with the dosimetric method used in this study, was predictive of response with a sensitivity of 91.5% and 98.3% in tumour- and patient-based analyses respectively (only one lesion with a TD <205 Gy responded to radioembolization). We also demonstrated that the false-positive rate was high, 33.3% for TDs ≥205 Gy and <260 Gy, and very low, −3.2% only for TD ≥260 Gy (P=.0012), in accordance with a fundamental radiobiology law: "The higher the dose above the threshold dose, the more severe the damage (till the maximal achievable damage is obtained)". Thus, our results suggest that we should target a TD of at least 205 Gy, yet with an even better response achieved if we are able to target TD higher to this threshold (with the limitation that we also have to take into account the dose delivered to the healthy injected liver). This result, obtained on over 130 evaluated lesions, confirms preliminary published data obtained on smaller numbers of lesions treated with both glass or resin microspheres, even if the threshold doses applied were different.[10,11,16,17]

A broad evidence demonstrating the accuracy of MAA as a surrogate for microsphere distribution and quantification has thus now become available. This point is of great relevance given that it is still a controversial concept with several studies performed with resin microspheres claiming the contrary.[18,19] It must nevertheless be underlined that numerous confounding factors may cause bias in MAA dosimetric evaluation, including two angiographic parameters with a major potential impact: rigorous catheter repositioning and spasm occurrence.[19] It must be stressed that neither the precise position of the catheter nor the occurrence of vasospasm was analysed in the two cited negative studies.[18,19] In spite of a recently published example pertaining to a dramatic vasospasm with huge impact on tumour uptake quantification,[20] this parameter has almost never been discussed,

and it has recently been proposed to employ an as minimally invasive as possible angiographic procedure when using MAA as dosimetric tool.[20,21]

The high accuracy of MAA dosimetry in response prediction is of major interest, as MAA dosimetry is available prior to therapy it can be used for treatment personalization.[8,13,14,16] It has to be highlighted that the target TD of 120 Gy recommended by a panel of expert for resin microspheres[8] is different than the threshold doses observed for glass microsphere, i.e. between 205 and 217 Gy depending on the studies.[11,16] The great difference in the specific activity of microspheres (50 Bq per sphere for resin; 2500 Bq per sphere for glass) results in a high difference in the number of spheres to be injected for the same activity, with then a high difference regarding dose distribution heterogeneity, as recently demonstrated in a simulation study.[22] As the radiobiological effect depends not only on the absorbed dose but also highly on dose distribution heterogeneity,[16,22] this point may account—at least partially—for the difference in the threshold TD identified between glass and resin microspheres.

The second key finding of this study was the impact of TD on OS, observed for the first time in all patient categories, i.e. both PVT and non-PVT patients. On multivariate analysis for the overall population, only TD remained significantly linked to OS, P=.0053.

The impact of TD was particularly high for PVT patients, with a median OS of only 4.35 m (95% CI: 2–8) for TD <205 Gy vs 15.7 (95% CI: 9.5–25.7) for TD ≥205 Gy (P=.0004), HR of death of 6.99 (95% CI: 1.98–24.39) for TD <205 Gy. However, PVT targeting also proved to be a key parameter. When using multivariate analysis for PVT patients, only PVT targeting (and not TD alone) remained significantly associated with OS. Good or poor PVT candidate classification, taking into account both TD and PVT targeting, appears to be an interesting variable that should be further evaluated. OS dramatically differed between these two groups, at only 3.6 m (95% CI: 2–8) for poor candidates vs 17.5 m (95% CI: 11–26.5) for good ones (P<.0001). This point highlights the impact of TD and PVT targeting on patient selection,

and poor candidates should be excluded from this approach owing to impairment of their OS reducing it below that of the spontaneous OS reported for PVT patients in the Sharp trial, i.e. 5.1 months for patients treated with placebo.[23]

A third finding of particular interest was the parameters associated with toxicity in this study. Tolerance was acceptable with clinically limiting liver toxicity found in 10.5% of patients, and no other clinically relevant toxicity.

For the overall population, HILD as continuous variable, dichotomized or associated with hepatic reserve was parameters associated with liver toxicity in univariate analysis (with ECOG status and underlying biliary disease), and one of the two parameters still remaining significant on two of the three multivariate analyses performed, along with underlying biliary disease.

For PVT patients, MAA PVT targeting seems to be the most crucial parameter associated with toxicity in our study, as it was the only one still remaining highly significant using multivariate analysis ($P<.0001$). HILD was not correlated with toxicity (even in univariate analysis) in this patient group, probably because of the limited HILD received by those patients exhibiting huge tumours and tumoral radioactivity incorporation.

The typical recognized factors of toxicity like Child-Pugh status, bilirubin level and ECOG performance status were not found to be significant in our study, probably as a result of our very careful patient selection, including only 4.7% with Child-Pugh B status, only 5.8% with bilirubin levels >35 μmol/mL and none with a performance status ≥2.

Tumour dose is currently not taken into account in ongoing Phase 3 studies (SORAMIC, STOP HCC and SARAH), this may negatively impact trial results, which should be kept in mind. It could thus be advisable to, even retrospectively, perform TD evaluation in these trials and evaluate its impact on response and survival to ensure that no significant results are missed for a subgroup of patients who could be good candidates for radioembolization. It could also be recommended to introduce PVT MAA targeting evaluation in these trials.

Finally, regarding our global clinical results, this study confirms previously published data supporting the potential value of ^{90}Y-loaded microsphere radioembolization in HCC. The more favourable outcomes reported in this study (high response rate, quite long median OS for PVT patients) are probably because of our patient selection with only 25% of the patients with a tumour involvement >25%, only 6% of infiltrative tumours and less than 5% of the patients with a Child-Pugh B status.

Further works, especially prospective studies, are now warranted to evaluate dosimetry and the potential impact of a personalized dosimetric approach. Nevertheless, this concept will be of particularly great interest in improving radioembolization effectiveness.

4 | CONCLUSION

This study highlights the impact of MAA-based tumour dose evaluation on both response and OS for HCC patients treated with glass microspheres. Those results suggest that TD should be analysed in the large phase III ongoing trials (at least retrospectively), to avoid missing the group of patient best candidate to radioembolization. While further prospective studies are now warranted to evaluate MAA dosimetry, these results open up the possibility of using a personalized dosimetric approach that could potentially strongly improve radioembolization effectiveness.

CONFLICT OF INTEREST

Etienne Garin is a consultant for BTG.

ABBREVIATIONS

EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HILD, healthy injected liver dose; HR, hazard ratio; IA, activity to inject; ILD, injected liver dose; MAA,^{99m}Tc macroaggregated albumin; M, mass; OS, overall survival; PVT, portal vein thrombosis; S, lung shunt fraction; SPECT/CT, single photon emitted computed tomography coregistered with CT scan; TD, tumour dose.

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