

Supplementary Materials: Anatomical Quantitative Volumetric Evaluation of Liver Segments in Hepatocellular Carcinoma Patients Treated with Selective Internal Radiation Therapy: Key Parameters Influencing Untreated Liver Hypertrophy

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Text S1: Treatment

A simulation angiography allowed embolization of any potential non-target extrahepatic vessels, followed by selective injection of technetium-99m-macroaggregated albumin (99mTc-MAA) into the tumor feeding arteries (depending on tumor location) and treatment planning. Imaging with single emission computed tomography with integrated CT (SPECT/CT) allowed quantification of treatment volume, dosimetry planning and lung shunt fraction. Predictive therapy planning based on partition model defined several compartments: whole liver volume, perfused volume, tumor perfused volume and non-tumoral perfused volume. Perfused volume was defined for each injection position. Healthy non-perfused liver volume was obtained after the global perfused volume was subtracted to the whole liver. To achieve personalized dosimetry, we calculated the required 90Y-microspheres activity to obtain the desired mean absorbed dose (Gy) in each perfused volume. SIRT (TheraSphere; Boston Scientific and SIR-Spheres; Sirtex), was performed 2–4 weeks following the simulation angiography.

Text S2: MRI Acquisition

All MRIs were conducted on 1.5T and 3T devices (Siemens Healthcare GmbH, Erlangen, Germany). Examinations were performed with a surface body array coil. Liver MRI protocol included: a breath-hold axial and coronal T2WI half-Fourier acquisition single-shot turbo spin-echo (T2WI HASTE), a respiration-triggered fat-suppressed turbo spin-echo T2WI, a free breathing fat-suppressed single-shot echoplanar DWI with tridirectional diffusion gradients using b-factors of 50, 400, 800s/mm² and a breath-hold axial dynamic T1WI using a fat-suppressed three-dimensional spoiled gradient-echo sequence, volumetric interpolated obtained before contrast material injection. An intravenous injection of 0.1 mmol/kg (0.2 ml/kg) of gadoterate meglumine (Dotarem; Guerbet, Villepinte, France), at a rate of 3ml/second was then performed. Triple arterial phase images were acquired after a delay of 20 seconds with a Caipirinha (controlled aliasing in parallel imaging results in higher acceleration) Dixon TWIST (time-resolved angiography with stochastic trajectories) VIBE volume interpolated breath-hold examination sequence. Portal and late phase followed, at 70 seconds and 3 minutes respectively.

Text S3: Tumor and Spleen Volume

Baseline tumor volume was similar between glass-microspheres vs resin-microspheres treated patients (mean, 93.7 mL vs 140.2 mL, $p=0.19$). Tumor volume correlated with absolute and relative spleen volumes at 6-months post-SIRT ($\rho=0.352$, $p=0.018$; $\rho=0.307$; $p=0.043$). However, absolute tumor volume increase at 6-months positively correlated with spleen volume increase at 3- and 6-months ($\rho=0.325$; $p=0.032$; $\rho=0.289$, $p=0.060$ (trend), respectively).

Baseline spleen volume inversely correlated with baseline platelet count ($\rho=-0.658$, $p<0.001$), albumin ($\rho=-0.312$, $p=0.005$) and PT ($\rho=-0.424$, $p<0.001$). It correlated with

baseline total bilirubin ($\rho=0.365$, $p<0.001$) and Child-Pugh score ($\rho=0.385$, $p<0.001$), but not with ASAT, ALAT, ALP, or GGT. No correlation was found between spleen volume evolution and platelet variation over time post-SIRT.

Administered non-tumoral liver activity correlated with spleen volume increase at 3- and 6-months ($\rho=0.269$, $p=0.029$ and $\rho=0.398$, $p=0.016$), but not at 12-months. Administered ^{90}Y -activity also impacted spleen volume increase at 3-months ($\rho=0.221$, $p=0.049$). Whereas late decrease in spleen volume at 12-months was observed with high delivered tumor activity ($\rho=-0.771$, $p<0.001$). No relationship was found with the other dosimetric parameters.

Table S1. 3D quantitative image analysis of treated liver segments evolution.

| Liver Segments | Absolute median volume [mL] (range) | | | | p-value | | | | |
|----------------|-------------------------------------|---------------|---------------|----------------|---------------|---------------|----------------|--------|---------|
| | Baseline (n = 88) | 3 mo (n = 88) | 6 mo (n = 47) | 12 mo (n = 23) | Baseline—3 mo | Baseline—6 mo | Baseline—12 mo | 3–6 mo | 6–12 mo |
| I | 73 (28-169) | 61 (20-195) | 71 (13-118) | 78 (30-109) | 0.485 | 0.11 | 0.25 | 0.455 | 0.625 |
| II | 224 (85-402) | 189 (57-413) | 225 (79-468) | 143 (100-227) | 0.068 | 0.791 | 0.188 | 0.233 | 0.625 |
| III | 195 (59-1000) | 150 (18-787) | 151 (86-719) | 106 (68-125) | 0.061 | 0.092 | 0.062 | 0.11 | 0.062 |
| IV | 210 (59-528) | 177 (38-425) | 172 (69-320) | 150 (47-214) | 0.112 | 0.002 | 0.125 | 0.002 | 0.188 |
| V | 133 (27-342) | 113 (17-232) | 85 (34-258) | 66 (27-143) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| VI | 174 (66-417) | 144 (23-419) | 124 (64-384) | 85 (17-316) | <0.001 | <0.001 | 0.005 | 0.001 | <0.001 |
| VII | 257 (59-455) | 185 (63-479) | 191 (92-522) | 124 (48-273) | 0.001 | 0.001 | <0.001 | 0.028 | 0.024 |
| VIII | 207 (63-399) | 162 (67-396) | 158 (44-523) | 113 (50-310) | 0.001 | 0.001 | <0.001 | 0.042 | 0.025 |
| Liver Segments | Relative mean volume [%] (SD) | | | | p-value | | | | |
| | Baseline (n = 88) | 3 mo (n = 88) | 6 mo (n = 47) | 12 mo (n = 23) | Baseline—3 mo | Baseline—6 mo | Baseline—12 mo | 3–6 mo | 6–12 mo |
| I | 5 (1) | 5 (2) | 4 (2) | 5 (2) | 0.869 | 0.455 | 1 | 0.542 | 1 |
| II | 13 (5) | 12 (5) | 12 (5) | 9 (3) | 0.269 | 0.85 | 0.125 | 0.97 | 0.438 |
| III | 13 (7) | 11 (7) | 11 (7) | 6 (2) | 0.093 | 0.204 | 0.125 | 0.424 | 0.062 |
| IV | 14 (5) | 13 (6) | 11 (3) | 9 (4) | 0.21 | 0.042 | 0.188 | 0.021 | 0.438 |
| V | 9 (3) | 8 (3) | 7 (3) | 5 (3) | <0.001 | <0.001 | <0.001 | 0.001 | <0.001 |
| VI | 13 (5) | 11 (5) | 10 (5) | 8 (6) | 0.002 | <0.001 | 0.007 | 0.004 | 0.127 |
| VII | 16 (4) | 14 (5) | 13 (5) | 10 (5) | 0.002 | 0.005 | 0.002 | 0.159 | 0.175 |
| VIII | 12 (3) | 11 (4) | 10 (2) | 9 (4) | 0.002 | 0.002 | 0.004 | 0.191 | 0.068 |

Table S2. D quantitative image analysis of *untreated* liver segments evolution.

| Liver Segments | Absolute median volume [mL] (range) | | | | p-value | | | | |
|----------------|-------------------------------------|---------------|---------------|----------------|---------------|---------------|----------------|--------|---------|
| | Baseline (n = 88) | 3 mo (n = 88) | 6 mo (n = 47) | 12 mo (n = 23) | Baseline—3 mo | Baseline—6 mo | Baseline—12 mo | 3–6 mo | 6–12 mo |
| I | 80 (9-247) | 86 (19-290) | 107 (17-328) | 60 (22-198) | <0.001 | 0.011 | 0.117 | 0.694 | 0.865 |
| II | 221 (57-527) | 240 (34-520) | 260 (102-521) | 257 (91-501) | 0.132 | 0.09 | 0.027 | 0.004 | 0.712 |
| III | 206 (21-556) | 224 (42-564) | 260 (60-674) | 257 (42-572) | 0.001 | 0.007 | 0.002 | 0.022 | 0.89 |
| IV | 231 (98-587) | 247 (88-599) | 253 (68-574) | 221 (73-2208) | 0.098 | 0.225 | 0.393 | 0.948 | 0.678 |
| V | 171 (40-290) | 184 (66-345) | 168 (68-352) | 125 (112-252) | 0.019 | 0.453 | 0.866 | 0.325 | 0.641 |
| VI | 252 (27-421) | 253 (53-493) | 230 (72-465) | 179 (30-350) | 0.126 | 0.097 | 0.82 | 0.927 | 0.359 |
| VII | 292 (129-560) | 298 (120-643) | 292 (188-620) | 278 (171-502) | 0.482 | 0.089 | 0.765 | 0.585 | 0.147 |
| VIII | 207 (116-485) | 208 (19-478) | 215 (117-511) | 201 (161-307) | 0.158 | 0.489 | 0.039 | 0.33 | 0.547 |
| Liver Segments | Relative mean volume [%] (SD) | | | | p-value | | | | |
| | Baseline (n = 88) | 3 mo (n = 88) | 6 mo (n = 47) | 12 mo (n = 23) | Baseline—3 mo | Baseline—6 mo | Baseline—12 mo | 3–6 mo | 6–12 mo |
| I | 5 (2) | 6 (3) | 6 (3) | 5 (3) | 0.001 | 0.007 | 0.145 | 0.533 | 0.734 |

| | | | | | | | | | |
|------|--------|--------|--------|---------|--------|--------|--------|--------|-------|
| II | 14 (5) | 16 (5) | 16 (6) | 18 (8) | 0.033 | 0.005 | 0.005 | <0.001 | 0.071 |
| III | 14 (6) | 16 (7) | 17 (7) | 20 (9) | <0.001 | <0.001 | <0.001 | 0.003 | 0.243 |
| IV | 15 (4) | 16 (5) | 16 (6) | 19 (14) | 0.029 | 0.017 | 0.002 | 0.043 | 0.089 |
| V | 10 (4) | 11 (3) | 10 (4) | 11 (4) | 0.017 | 0.523 | 0.844 | 0.832 | 0.312 |
| VI | 14 (5) | 15 (5) | 14 (5) | 13 (5) | 0.049 | 0.123 | 0.57 | 0.648 | 0.301 |
| VII | 19 (5) | 21 (6) | 20 (5) | 22 (3) | 0.06 | 0.137 | 0.042 | 0.272 | 0.831 |
| VIII | 14 (3) | 14 (4) | 14 (3) | 15 (2) | 0.256 | 0.277 | 0.109 | 0.72 | 0.078 |

Table S3. Evolution of relative volumes.

| SIRT | Volume region | Relative volume [%] - mean (SD) | | | | <i>p</i> -value | | | | |
|--|---------------|---------------------------------|----------|----------|-----------|-----------------|---------------|----------------|--------|---------|
| | | Baseline | 3-months | 6-months | 12-months | Baseline—3 mo | Baseline—6 mo | Baseline—12 mo | 3–6 mo | 6–12 mo |
| All (<i>n</i> = 88) | Treated | 45 (29) | 40 (29) | 35 (27) | 26 (20) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | Untreated | 63 (21) | 68 (20) | 71 (19) | 78 (12) | <0.001 | <0.001 | <0.001 | 0.095 | 0.401 |
| | Spleen | - | - | - | - | - | - | - | - | - |
| | Tumor | 10 (18) | 11 (24) | 5 (13) | 2 (2) | 0.552 | 0.176 | 0.006 | 0.206 | 0.031 |
| Whole liver (<i>n</i> = 11) | Treated | 100 (0) | 100 (0) | 100 (0) | 100 (0) | - | - | - | - | - |
| | Spleen | - | - | - | - | - | - | - | - | - |
| | Tumor | 25 (33) | 19 (24) | 2 (2) | 1 (0) | 0.185 | 0.089 | - | 0.848 | - |
| Right/left liver and lobe (<i>n</i> = 49) | Treated | 47 (16) | 41 (17) | 37 (15) | 28 (11) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | Untreated | 53 (16) | 59 (17) | 63 (15) | 72 (11) | <0.001 | <0.001 | <0.001 | 0.005 | 0.038 |
| | Spleen | - | - | - | - | - | - | - | - | - |
| | Tumor | 9 (17) | 13 (30) | 6 (16) | 1 (1) | 0.304 | 0.102 | 0.015 | 0.004 | 0.247 |
| Others* (<i>n</i> = 28) | Treated | 20 (19) | 17 (16) | 18 (20) | 14 (9) | <0.001 | 0.025 | 0.178 | 0.847 | 0.213 |
| | Untreated | 80 (19) | 83 (16) | 82 (20) | 86 (9) | <0.001 | 0.025 | 0.178 | 0.865 | 0.653 |
| | Spleen | - | - | - | - | - | - | - | - | - |
| | Tumor | 4 (4) | 4 (4) | 5 (7) | 2 (3) | 0.808 | 0.71 | 0.017 | 0.599 | 0.06 |

Note.– *Others correspond to sectorial (V–VIII or VI–VII), segmental or subsegmental treatments.

Table S4. Dosimetric parameters of glass- vs. resin-microspheres

| Dosimetric parameter | Glass-microspheres | | Resin-microspheres | | t-test | |
|---|--------------------|-----------|--------------------|-----------|---------|-----------------|
| | Median | Range | Median | Range | T-value | <i>p</i> -value |
| Administered ⁹⁰ Y activity (GBq) | 1.6 | 0.25-3.5 | 1.1 | 0.6-2.5 | 1.98 | 0.048 |
| Non-tumoral liver activity (GBq) | 0.98 | 0.17-3 | 0.7 | 0.07-1.35 | 2.07 | 0.038 |
| Non-tumoral liver dose (Gy) | 62.2 | 7.7-801 | 39.8 | 14.8-83.5 | 3.58 | <0.001 |
| Tumor activity (GBq) | 0.87 | 0.03-3 | 0.41 | 0.06-1.56 | 2.9 | 0.004 |
| Tumor dose (Gy) | 274.5 | 11.1-1267 | 184.9 | 95.5-903 | 2.04 | 0.042 |

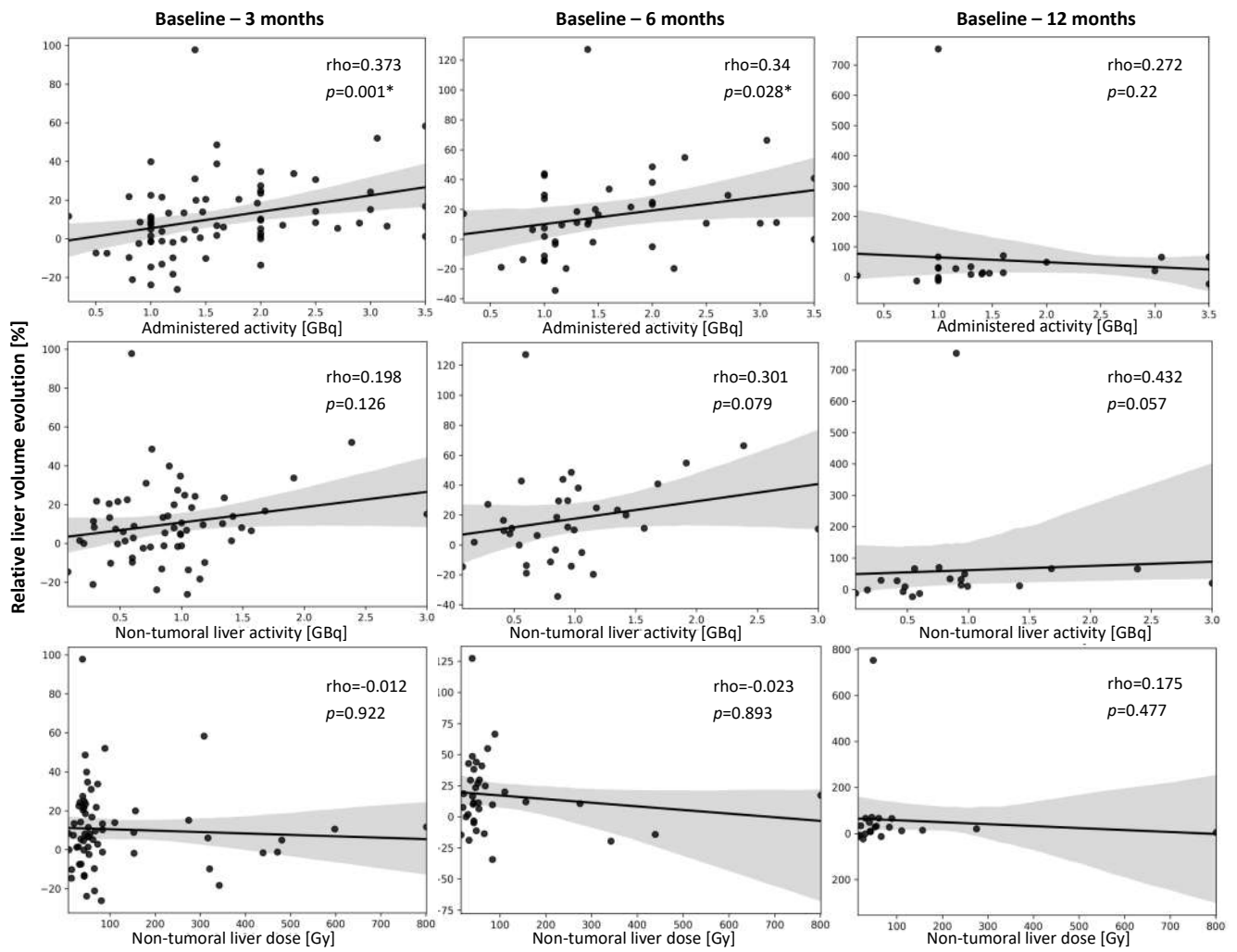


Figure S1. Linear regression analysis at 3-, 6- and 12-months of untreated liver volume evolution according to administered activity, non-tumoral liver activity and dose. * $p < 0.05$.