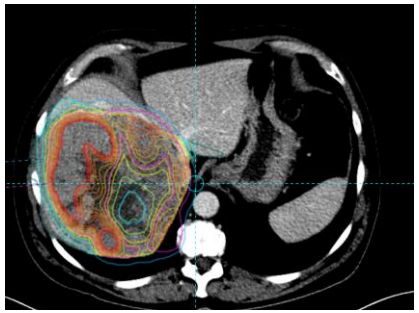
Clinical impact of personalized dosimetry for SIRT of liver cancers

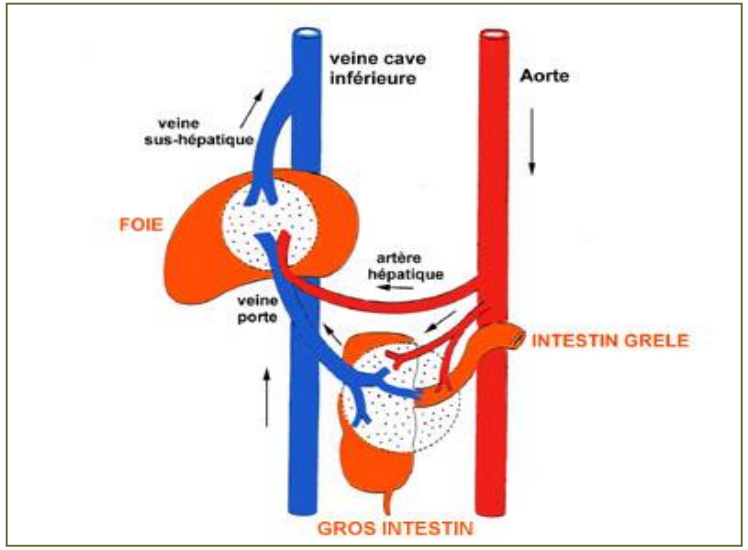


Centre Eugène Marquis RENNES

Etienne Garin, MD-PhD,
Médecine Nucléaire
Rennes

SIRT of liver tumors principle

- **Administration of a high amount of radioactivity directly in the hepatic artery**
  - ⇒ Optimisation of tumoral targeting
  - ⇒ Sparing healthy liver tissue



- **Available oing to the double hepatic vascularization**
  - Liver 80% : portal vein, 20% hepatic artery
  - tumor (CHC) : 80% hepatic artery, 20% portal vein => arterial **hypervascularization**

- **Treatment preceded by a simulation :**

  - Diagnostic angiography with 3 main goals:

  Optimization of the catheter position (tumoral targeting, avoiding organ at risk)

  MAA injection

  Digestive shunt identification : ± embolization

  - MAA scan : quantification of lung shunt, identification of digestive shunts, tumoral targeting, dosimetry

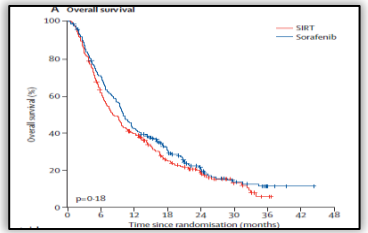
Products available

- ^{90}Y loaded resin microspheres (SIR-Sphere®, Sirtex)
- ^{90}Y Loaded glass microspheres (TheraSphere®, Boston)

Parameter	Glass[1]	Resin[1]
Size	20-30 µm	20-60 µm
Isotope	^{90}Y in the glass matrix	^{90}Y on the microbead surface
Specific gravity[2]	3.6 g/dl	1.6 g/dl
Activity/sphere (at calibration)	**2,500 Bq**	**50 Bq**
No of dose sizes	6 (3, 5, 7, 10, 15, 20 GBq) + personalised doses	1 (3 GBq)
No of spheres/vial	1.2-8 million	40-80 million
No of spheres/dose of 3 GBq	1.2 million	40-80 million
Authorization from the EU	Yes (hepatic neoplasia)	Yes

Negativity of all randomized phase III studies in HCC using ^{90}Y loaded microspheres

- **SARAH trial** *(Vilgrin et al. Lancet Oncol 2017) :* Median OS: **9.9 m** (8-12.7) for SIRT vs **9.9 m** (I 9-11.6) for sorafenib
- **SIRveNIB** *(Cho et al. JCO 2018)* : Median OS: **11.3 m** (9.2-13.6) for SIRT vs **10.4 m** (8.6-13.8) for sorafenib
- **SORAMIC** *(Ricke et al. 2018)* : Median OS: **14.0 m** (11.5-17) for SIRT vs **11.1 m** (CI 9.8-13.8) for sorafenib alone

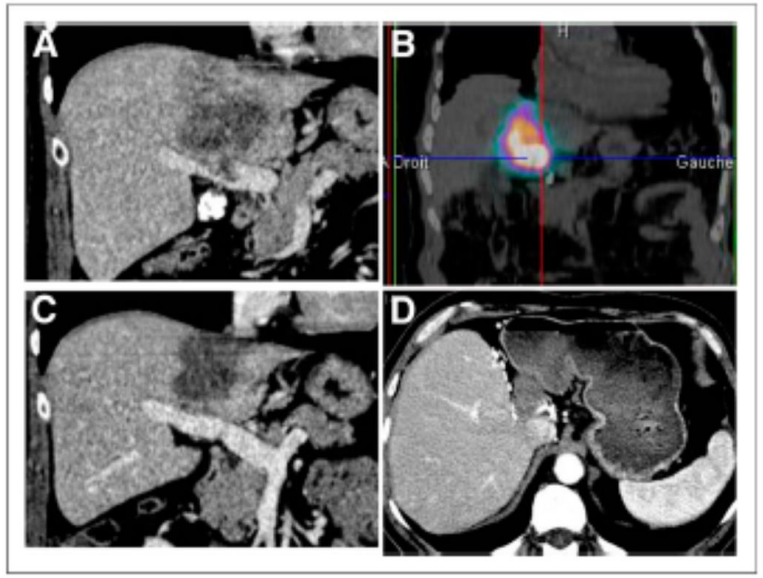


No dosimetry :

^{90}Y resine : body surface area

^{90}Y glass : 80-150 Gy to the liver

< 30 Gy to the lungs



Standard planning
IA = 0.77 GBq (ILD = 120 Gy)

=> Tumoral dose = 162 Gy

Personalised planning
IA = 1.16 GBq (x 1.5)

=> Tumoral dose = 285 Gy

Left hepatectomy
TTP: 15.2 m
0S = 49 m

Complete EASL response with PV revascularisation

Dose computing

- **The Medical Internal Radiation Dose Committee (MIRD) equation is used** to calculate de Dose for injected radiolabelled compounds

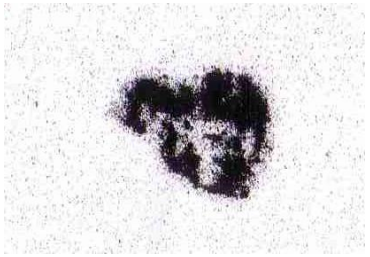
1 GBq of ^{90}Y delivers 50 Gy to a tissue mass of 1 kg

- **The simplified MIRD formula for Y-90 is used to calculate the dose in a volume of interest** (lobe, tumor, healthy liver, lungs, …)

$$D_{(Gy)} = A_{(GBq)} \times 50 / \text{mass}_{(kg)}$$

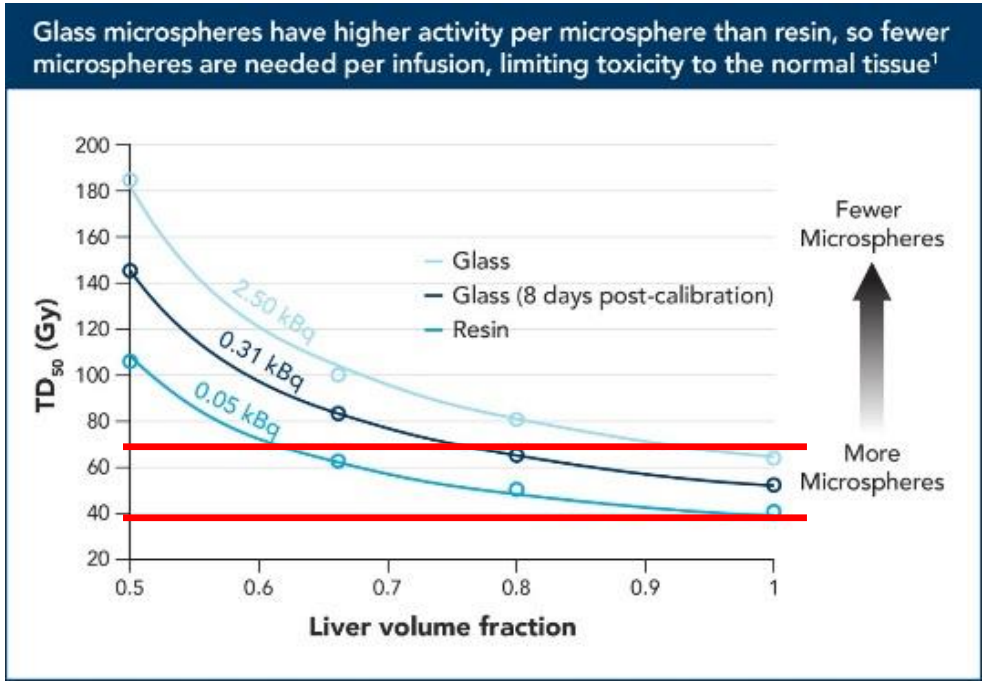
Radiobiology = radio-induce tissue damage

- **Tissue damage depends not only on the absorbed dose, but also on :**
  - **The dose rate** : equal for Y-90 resin and glass microspheres
  - **The heterogeneity of the dose distribution :**
    different between resin and glass due to a highly different specific activity :
    50 Bq/sphere (resin) vs 2500 Bq/sphere (Glass)



- **Dose rate and heterogeneity are not taken into account in the MIRD formula :**

**Radiobiology of glass and resin microspheres is different:
Not the same effect for the same physical absorbed dose.
(not the same threshold doses for both products)**



Walrand S et al. *J Nucl Med* 2014

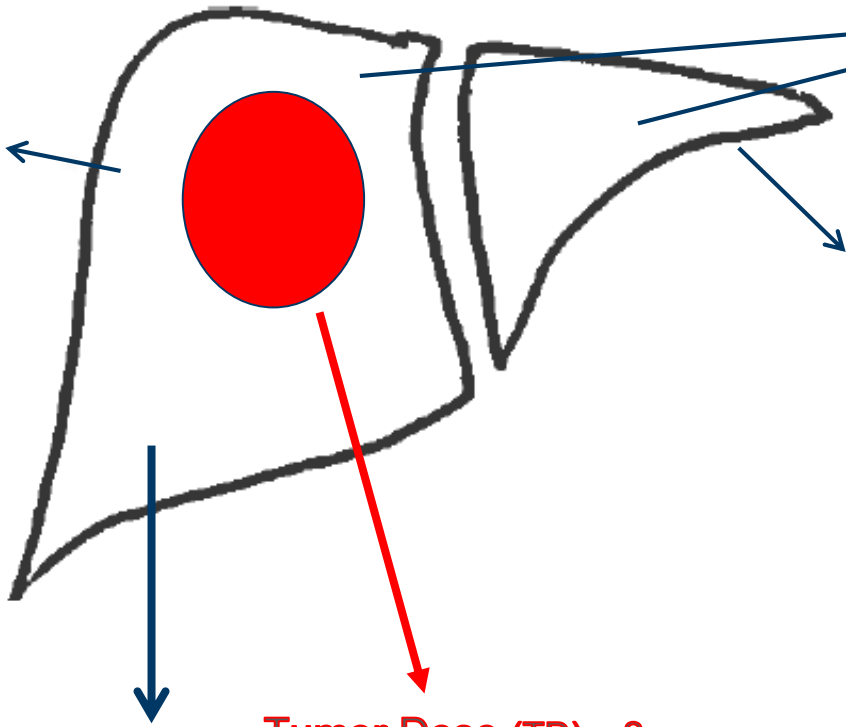
Dosimetry usual metrics for liver SIRT

Exemple for a right treatment

Whole Liver Dose (WLD) : Perfused Liver + Hepatic Reserve

Liver Absorbed Dose

Perfused liver Dose (PLD)



Whole Normal* Liver Dose (WNLD)
Normal Perfused Liver +
Normal Hepatic reserve

Hepatic Reserve= %
Non Perfused Normal Liver
Dose = 0 Gy
Safety issue

Single compartment Dosimetry

Tumor Dose (TD) = ?
Normal Perfused Liver Dose (NPLD) = ?

Multi compartment dosimetry

* Non tumoral

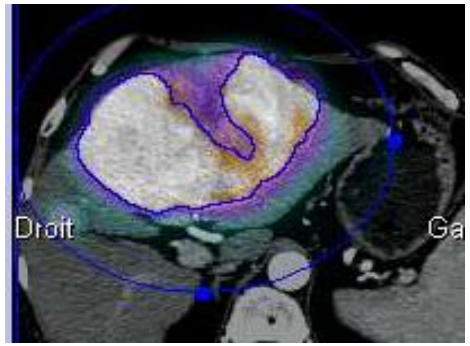
Computing the dose : how can we proceed?

$$D_{(Gy)} = A_{(GBq)} \times 50 / mass_{(kg)}$$ and liver mass = volume x 1.03

FUNCTIONAL (scintigraphy)

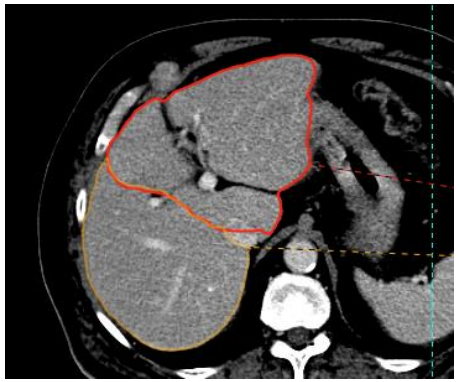
- **Simulation based dosimetry (work up)= treatment personalization**
  MAA scintigraphy
  (other surrogate or scout dose)

- **Post therapeutic dosimetry = confirmatory**
  Y-90 PET/CT (or SPECT/CT)



ANATOMICAL SEGMENTATION

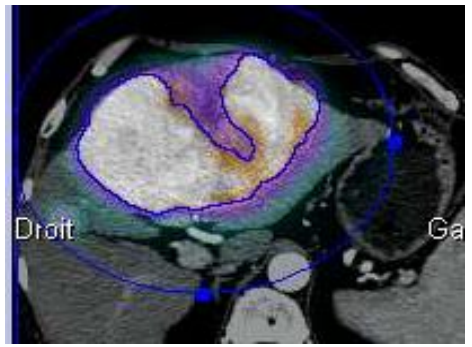
- **CT/MRI**
- **CBTC**



FUNCTIONAL SEGMENTATION

- **MAA or Y-90**

quantitative analysis



Technical note

Nuclear Medicine Communications 2011, 32:1245–1255

Nuclear Medicine Communications

Effectiveness of quantitative MAA SPECT/CT for the definition of vascularized hepatic volume and dosimetric approach: phantom validation and clinical preliminary results in patients with complex hepatic vascularization treated with yttrium-90-labeled microspheres

Etienne Garin[a,e,f], Laurence Lenoir[a], Yan Rolland[b], Sophie Laffont[a,f], Marc Pracht[c], Habiba Mesbah[d], Philippe Porée[d], Valérie Ardisson[a,f], Patrick Bourguet[a,e], Bruno Clement[f] and Eveline Boucher[c,f]

- **Phantom study validation of scintigraphic volume evaluation**
- **SPECT alone not accurate**
- **SPECT/CT accurate with a Mean error < 7%**

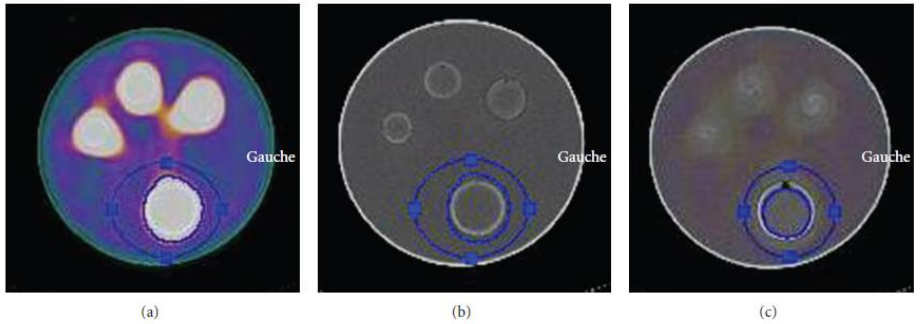
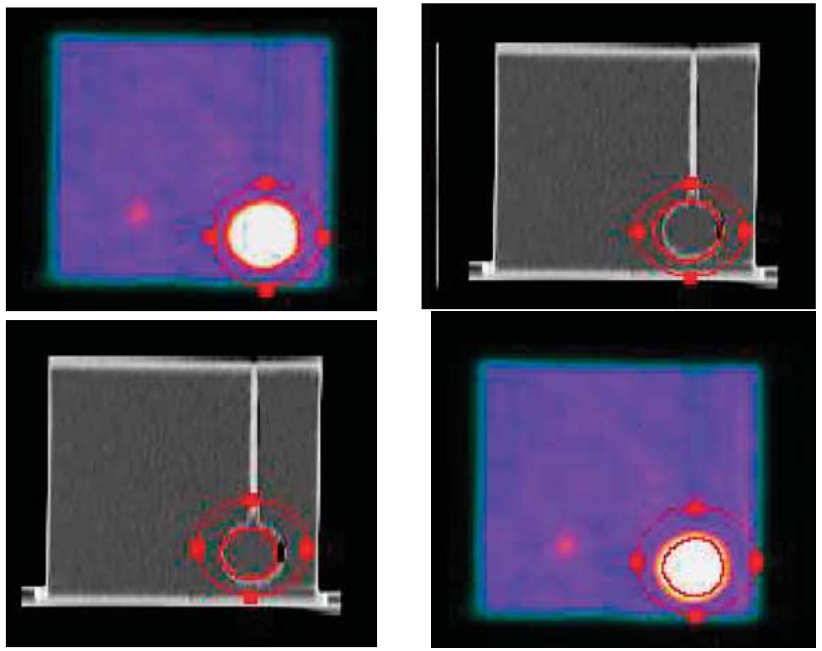


FIGURE 1: Delineation of VOIs used for quantitative analysis of SPECT and SPECT/CT analysis (a, b): VOI defined on SPECT hot spot alone.



Technical Considerations and Confounding Factors for dosimetry with direct impact on doses evaluation

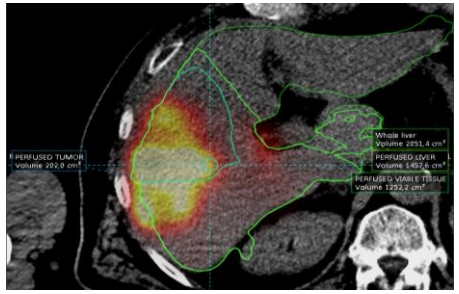
Garin E, et al. Eur J Nucl Med Mol Imaging. 2016;43:559-575.

- **MAA based dosimetry or post therapeutic (bremsstrahlung or PET) dosimetry**
  - **MAA :**
    - Major advantage : available prior theray => threatment schedule impact
    - Drowback : over estimation of LSF (10% of large HCC)
  - **Post therapeutic :**
    - Most accurate dosimetric evaluation (direct microspheres quantification),
    - But available after therapy (Validation of a tretment for a selected patient)
- **Product used (**Threshold TD for HCC ~ 100/120 Gy for resin, ~ 200 Gy for glass)
- **Response and toxicity criteriae used**
- **Segmentation method used**
- **Blood flow during surrogate/micropsheres injection**

Segmentation

- **CT/MRI/CBCT co-registered with SPECT/CT** : Risk of co-registration errors
- **SPECT/CT** *(validated by DOSISPHERE trial) :* No co-registration, but thresholding difficulties in some cases

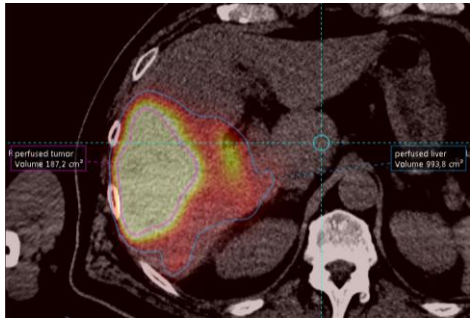
CT segmentation,



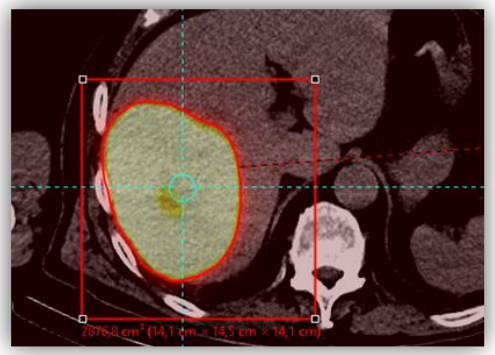
PLD= 120 Gy
TD= 253 Gy

PLD= 180 Gy
TD= 504 Gy

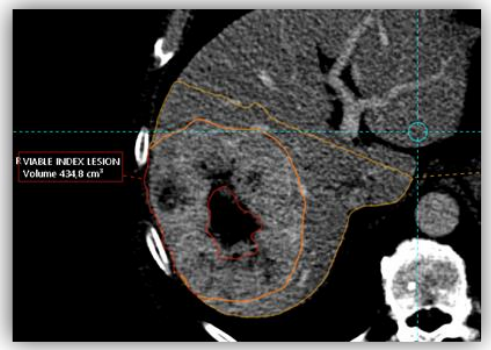
MAA SPECT/CT segmentation



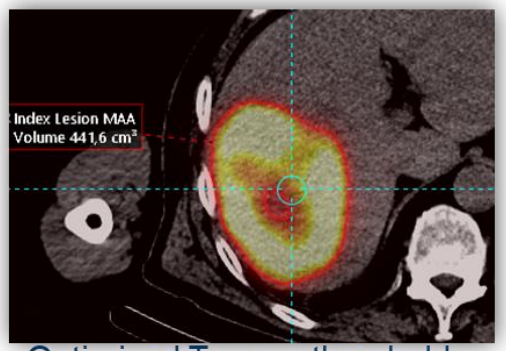
- **SPECT/CT optimized by anatomical volumetry (CT/MRI)**



Tumour threshold 6%
tumour volume 555 cc



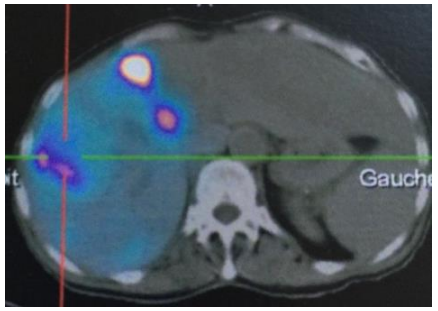
Viable tumour volume on CT : 434 cc



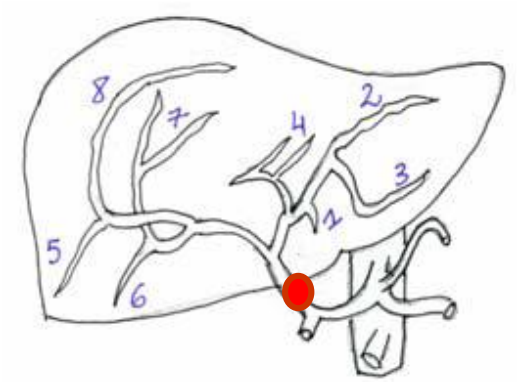
Optimised Tumour threshold
based on CT volume : 10%
Tumour volume 441 cc

Blood flow preservation

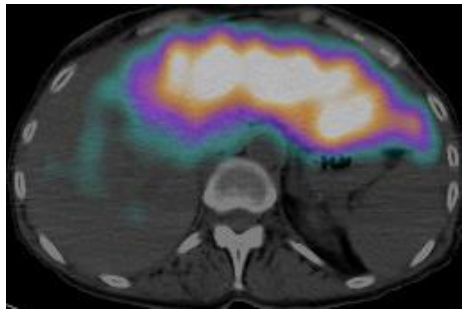
Specific endpoints are required for an angiography with simulation based dosimetry purpose



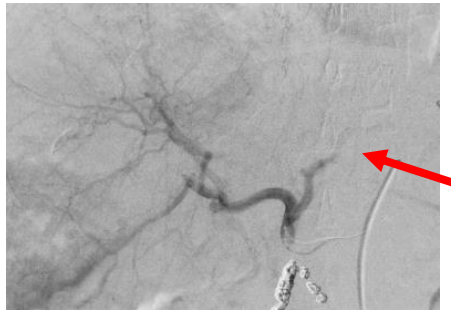
MAA



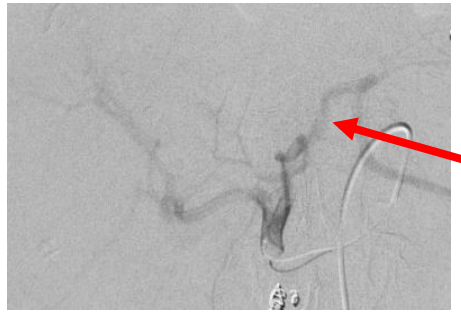
90 Y



Treatment simutation



Diagnostic angio after coiling, spasm of the LHA



Treatment

Therapeutic angio, same cath Position, no spasm

- **Blood flow preservation (avoiding spasm, microthrombi…): floppy catheter, less coiling as possible, less time as possible…** *(Garin et al. JNM 2016, Semin Nucl Med 2019)*
- **Slow MAA injection, over 20-30s,** *(Garin et al. Eur J Nucl Med 2016)*
- **Catheter position and rigorous repositioning at the same place MAA/Y-90** *(Wondergem et al. JNM 2013, Haste et al. JVIR2017)*

Simulation based dosimetry requires a multidisciplinary approach +++

Impact of technical concerns : negativity of several studies

^{99m}Tc-Macroaggregated Albumin Poorly Predicts the Intrahepatic Distribution of ^{90}Y Resin Microspheres in Hepatic Radioembolization

J Nucl Med 2013; 54:1294–1301
DOI: 10.2967/jnumed.112.117614

Conclusion: In current clinical practice, MAA distribution does not accurately predict final ^{90}Y activity distribution.

But

80% metastasis, Resin microspheres

5-French catheter was used (too large, increase probability of spams occurrence)

Coil-embolization generally performed (increase probability of spams occurrence)

No spasm evaluation

J Vasc Interv Radiol 2017; 28:722–730

CLINICAL STUDY

Correlation of Technetium-99m Macroaggregated Albumin and Yttrium-90 Glass Microsphere Biodistribution in Hepatocellular Carcinoma: A Retrospective Review of Pretreatment Single Photon Emission CT and Posttreatment Positron Emission Tomography/CT

Conclusion : MAA was found to be a poor surrogate to quantitatively predict subsequent ^{90}Y AD to hepatocellular tumors.

But also no Dose response relationship with 90Y PET dosimetry on 62 HCC patients !!!!

SPECT alone, CT segmentation and coregistration, whole tumor segmentation only (not viable tumor)
No spasm evaluation

Main results with standard dosimetry : BSA for resin, 80-150 Gy for glass.

(mainly retrospectives studies)

HCC Tumouricidal Dose with 90Y glass microspheres

Author and Year of Publication	Chiesa et al. Q J Nucl Med 2011	Garin et al. J Nucl Med 2012	Garin et al. Liver Int 2017	Ho et al. Eur JNM2018	Chan et al. Int J Radiat Oncol Biol Phys 2018	Kappadath et al. Int J Radiat Oncol Biol Phys 2018
Nb of patients/lesions	48/65	36/58	85/132	62/na	27/38	**34/53**
Lesion size (cm)	5.6	7.1	7.1	na	7.3	**4.1**
Macroaggregated albumin (MAA)- or ^{90}Y-based dosimetry	MAA-based	MAA-based	MAA-based	MAA-based	^{90}Y PET	**^{90}Y SPECT/CT**
Response evaluation	EASL	EASL	EASL	^{18}FDG or ^{11}C-acetate PET	mRECIST	**mRECIST**
Tumouricidal Tumor Dose (TTD)	mean TD 257 Gy	mean TD 205 Gy	mean TD 205 Gy	mean TD 152/174/262 Gy	mean TD 200 Gy	**mean TD 160 Gy**
RR for TD ≥ TTD vs. < TTD	85% vs. na	na	91% vs. 5.5% $p < 10^{-3}$	na	84% vs. na	**50% TCP**
Prediction of response for TTD	se = 85% spe = 70%	se = 100% acc = 91%	se = 98.3% acc = 88.7%	se = 89.2% spe = 88%	se = 66% PPV = 100%	**na**
OS for TD ≥ vs. < TTD	**na**	**18m vs. 9m p = 0.032**	**21m vs. 6.5m p = 0.0052**	**na**	**na**	**na**

HCC Tumouricidal Dose with 90Y resin microspheres

Author and Year of Publication.	Lau et al. Br J Cancer 1994	Hermann et al. Radiology 2020	Kao et al. J Nucl Med 2012	Strigari et al. JNM2010	Allimant et al. JVIR 2018
Nb patients/lesions	18/na	121/na	10/na	73/na	**37/na**
Lesion size (cm)	na	na	na	2.9	**5**
MAA or ^{90}Y Based dosimetry	MAA based	MAA based	^{90}Y SPECT/CT	^{90}Y SPECT/CT	**^{90}Y PET**
Response evaluation	WHO	RECIST1.1	RECIST1.1	EASL	**mRECIST**
Tumouricidal Tumor Dose (TTD	Mean TD 120 Gy	Mean TD 100 Gy	Mean TD <91 Gy	BED 110 Gy	**AUDVH$_T$ 61 Gy**
RRs for TD ≥ TTD vs. TD < TTD	87.5% vs. 12% p=0.005	DCR 74% vs 51% p=0.05	100% vs. na	TCP of 73%	**TCP of 76.5%**
Prediction of response for TTD	na	na	na	na	**se = 76.5% spe= 75%**
OS for TD ≥ TTD vs. TD < TTD	**55 w vs. 26.6 w p = 0.005**	**14.1 m vs. 6.1 m p = 0.0001**	**na**	**na**	**na**

Normal Liver tolerated dose with 90Y microspheres

- **More complexe to evaluate**
- **Low number of events**
- **Difficulty of the event collection (delayed) and imputability (cirrhosis)**
- **Many confounding factors**
  - Underlying cirrhosis (and severity : Child classification, bilirubin level)
  - Hepatic reseve
  - Definition of liver toxicity
    - Any liver decompensation (Chiesa et Al.), reversible or not
    - Clinically relevant ≥ G3 and permanent

- **Results available only after a firt SIRT (no evaluation of cummulative dose)**

Normal Liver tolerated dose with 90Y microspheres

Author and Year of Publication	Strigari et al. JNM 2010	Allimant et al. JVIR 2018	Garin et al. Eur JNM et 2013	Chiesa et al. Eur JNM 2015	Garin et al. Liver Int 2017	Chan et al. Cardiovasc Intervent Radiol 2018
Nb of patients	73	37	71	52	85	35 (27 HCC, 7 metastasis)
Product	resin	resin	glass	glass	glass	glass
MAA- or ^{90}Y-Based dosimetry	^{90}Y SPECT/CT	^{90}Y PET	MAA based	MAA based	MAA based	^{90}Y PET
Toxicity evaluation	G ≥2	REILD	Clinically relevant, G ≥3 and permanent	Any liver decompensation	Clinically relevant, G ≥ 3 and permanent	G ≥ 2
NLD parameter/normal liver threshold dose (NLTD)	NPLD 52 Gy	$AUDVH_{NPL}$ na	NPLD 100 Gy + HR of <30% p = 0.032	WNLD 75 Gy*	NPLD na	NPLD 54 Gy
NTCP for an NLD larger than an NLTD	50%	na	na	15%	na	50%
NLD parameters for patients with toxicity and no toxicity	na	78.9 Gy vs 53.8 Gy p = 0.04	na	na	104.7 Gy vs 79.5 Gy p = 0.028	na

* Value revised in 2021 : < 90 Gy if bilirubin < 1.1mg/dL and < 50 Gy if bilirubin > 1.1 mg/dL

Uni-compartment Personalized dosimetry

Radiation segmentectomy

Radiation Lobectomy

Radiation segmentectomy (Glass Microspheres)

- Ojective : Increase the absorbed to one/two segment (efficacy), Spare normal paranchyma (safety)
- Usually for small lesion

Riaz et al. *In J Radiat Oncol Biol Phys 2010*

84 patients

Mean dose = 521Gy

RR (EASL) : 81%

No toxicity, particularly biliary

OS = 26.9 m (20.5-30.2)

Vouche et al. *Hepatology 2014*

102 patients

Solitary lesion < 5cm

Mean dose = 242Gy

RR (EASL) : 86%

Complete Pathological response :

66.6% vs 25%

for segment dose ≥ 190 Gy

vs< 190 Gy, *(p=0.03)*

Gabr et al. Eur JNM 2021

45 operated patients

Median size : 2.5 cm

Median dose : 240 Gy

CPR:

100% vs 55%

for segment dose ≥ 400 Gy

vs< 400 Gy, *(p=0.01)*

Radiation Lobectomy : princeps publication (Glass Microspheres)

Ann Surg Oncol (2009) 16:1587–1596
DOI 10.1245/s10434-009-0454-0

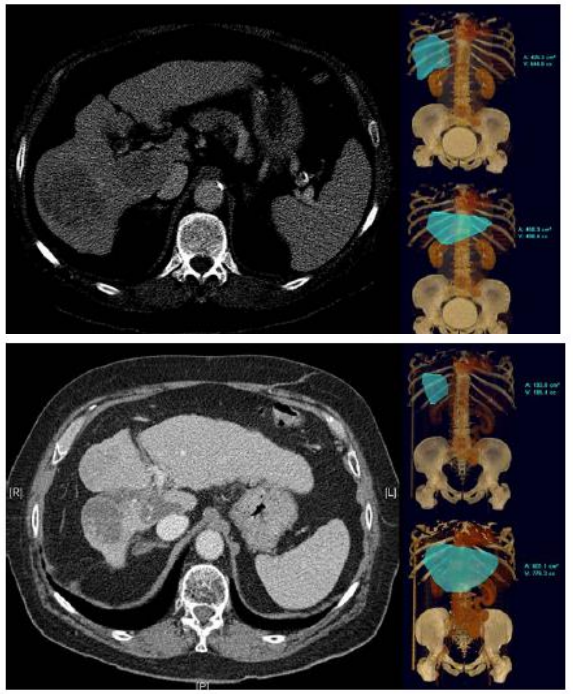
Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC TUMORS

Radiation Lobectomy: Preliminary Findings of Hepatic Volumetric Response to Lobar Yttrium-90 Radioembolization

Ron C. Gaba, MD[1], Robert J. Lewandowski, MD[2], Laura M. Kulik, MD[3], Ahsun Riaz, MD[2], Saad M. Ibrahim,

- 101 right unilobar treatments, 20 «radiation lobectomy » observed
  - Atrophy of 52% of the treated liver
  - Hypertrophy of 40% of the untreated liver (FRL)
- Three goals in only one procedure :
  - effective treatment of lesions
  - preparation of eventual surgery : Hypertrophy of the FRL
  - « Biological test of time » : identification of patients with early controlateral or extrahepatic recurrence (not candidate to surgery)
- Initial recommendation lobar dose for glass microspheres : 140-150 Gy



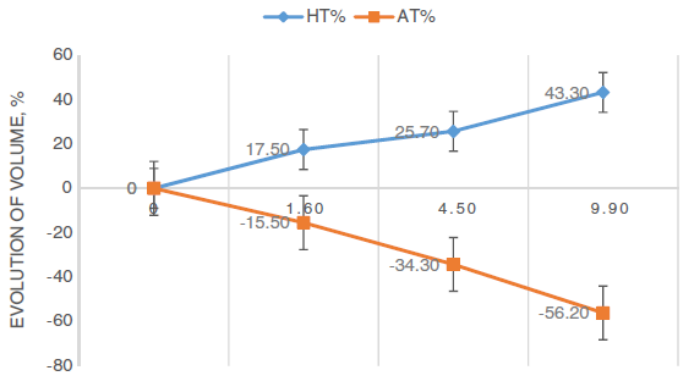
MAA based Dosimetry and FLR Hypertrophy

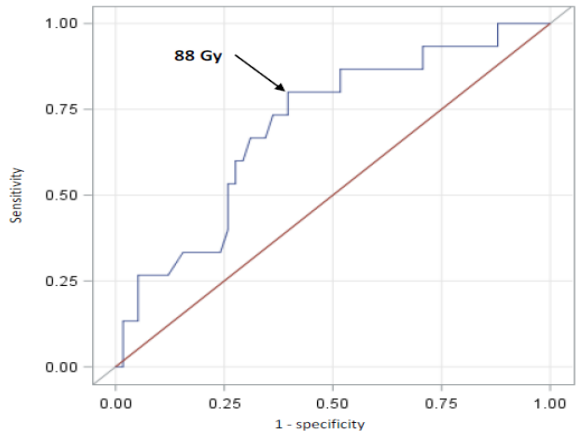
Dosimetric parameters predicting contralateral liver hypertrophy after unilobar radioembolization of hepatocellular carcinoma

Xavier Palard[1,2] · Julien Edeline[2,3,4] · Yan Rolland[5] · Samuel Le Sourd[4] · Marc Pracht[4] · Sophie Laffont[1] · Laurence Lenoir[1] · Karim Boudjema[6] · Thomas Ugen[7] · Vanessa Brun[8] · Habiba Mesbah[9] · Laure-Anne Haumont[9] · Pascal Loyer[3] · Etienne Garin[1,2,3]

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3845-7

- **Retrospective study on 73 patients treated with TheraSphere™**
- **MAA-based dosimetry**
- **Hypothesis of 2 targets:**
  - The healthy liver and the tumour
  - Hypertrophy may be associated with Normal Perfused Liver Dose and/or with high doses in large lesions
- **Mean Maximal Hypertrophy (MHT) was 35.4 ± 40.4 % at 5.9 ± 3.4 m**
- **88 Gy Normal Perfused Liver Dose best predicting MHT greater than 10% MHT** identified using ROC *(included in Recommendation Paper)*



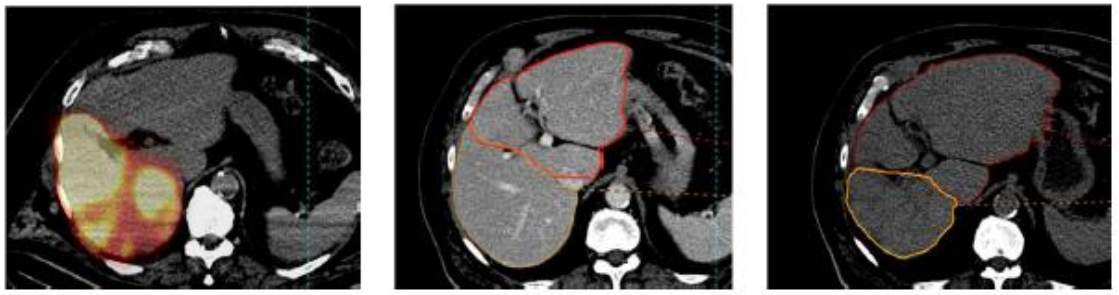


Maximal Hypertrophy > 10% was significantly more frequent:

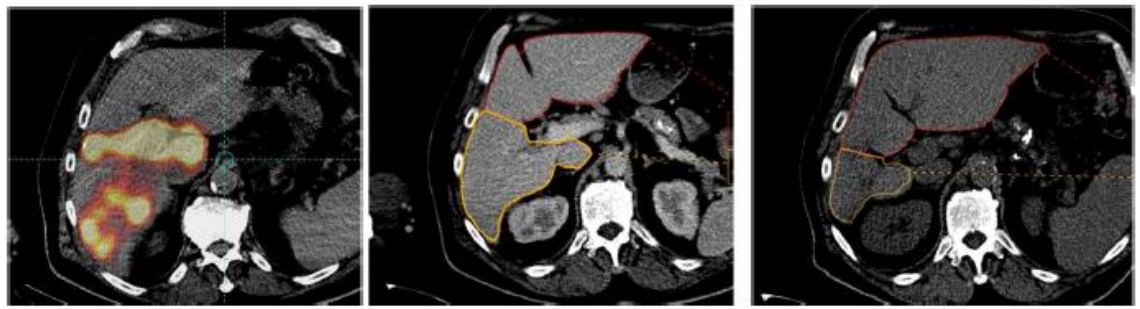
- For Normal Perfused Liver Dose **(NPLD) > 88 Gy** (52% of the population) :
  92.2% versus 65.7% for Healthy injected Liver Dose <88 Gy, *p=0.032*

- For patients with hepatic reserve <50% : for **Tumor Dose (TD) ≥ 205Gy & Tumor Volume (TV) ≥ 100 cc**
  62.3%, versus only 29.1% if TD < 205Gy or TV < 100 cc, *p=0.0329*,

- **For patients with either an NPLD≥ 88 Gy or a TD≥ 205Gy for TV≥ 100cc (85% of the population): 83.9%, versus only 54.5% for the others, *p=0.0265***



NPLD= 114 Gy
Maximal Hypertrophy = 66 % at 9 m
TD= 346 Gy and TV = 43 cc



NPLD= 21 Gy only
Maximal Hypertrophy = 82 % at 6.5 m
TD= 361 Gy and TV = 150 cc

Multicompartment Personalized dosimetry

Personalized dosimetry : princeps publication

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2395-x
Received: 17 January 2013 / Accepted: 7 March 2013

ORIGINAL ARTICLE

Boosted selective internal radiation therapy with ^{90}Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept

E. Garin · L. Lenoir · J. Edeline · S. Laffont ·

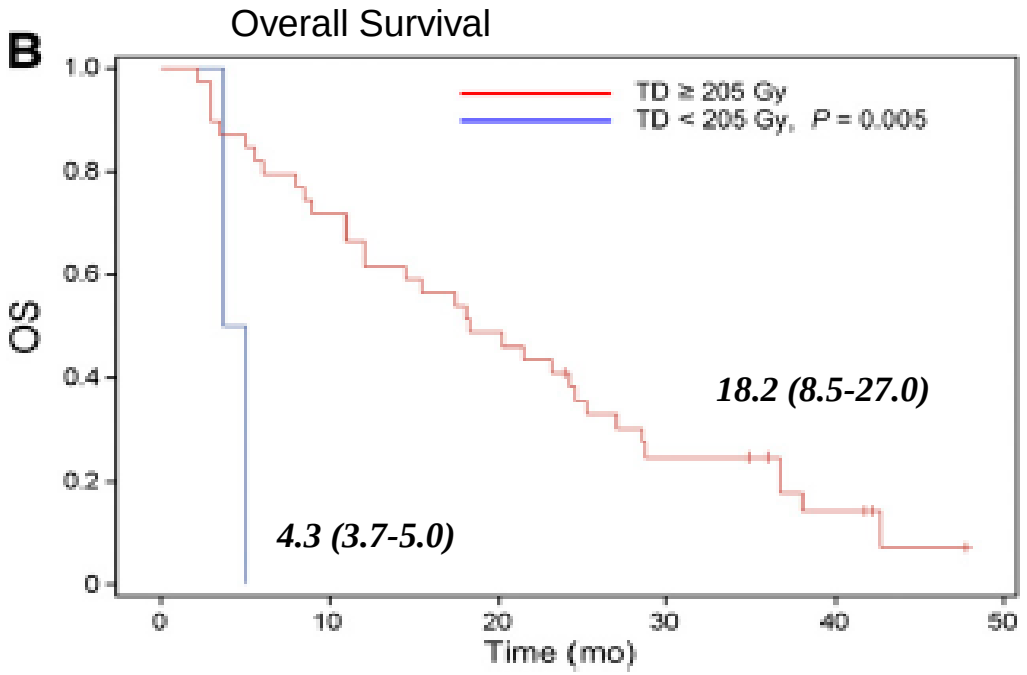
- 71 patients, Lobar approach, glass microspheres
- MAA SPECT/CT based personalised dosimetry endpoints for 51 patients : Goal to achieve a Tumor Dose ≥ 205 Gy
- **Intensification in 24% of the cases with unilobar disease = lobar dose > 150 Gy, BUT Liver dose < 150 Gy**
- **RR = 86 % using personalised dosimetry *vs*. 55% with standard approach, *p=0.001***
- **No toxicity increase** *(5.8 % for intensified patients vs 9.2%, ns)*

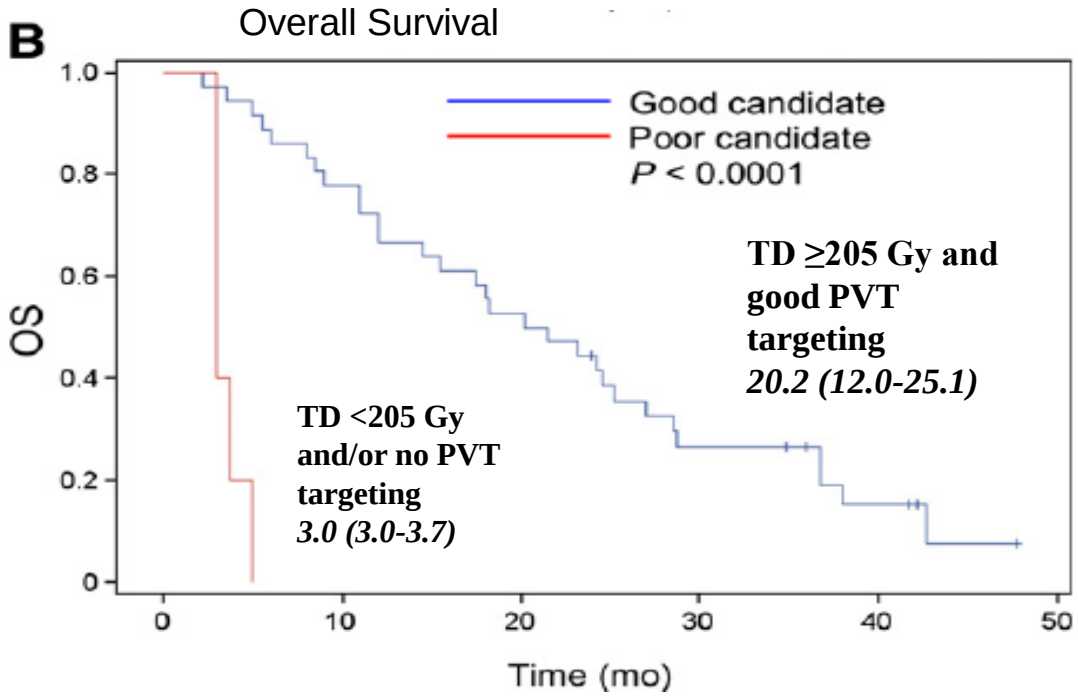
Personalized Dosimetry with Intensification Using ^{90}Y-Loaded Glass Microsphere Radioembolization Induces Prolonged Overall Survival in Hepatocellular Carcinoma Patients with Portal Vein Thrombosis

J Nucl Med 2015; 56:339–346
DOI: 10.2967/jnumed.114.145177

Etienne Garin*[1–3], Yan Rolland*[4], Julien Edeline[2,3,5], Nicolas Icard[1], Laurence Lenoir[1]–

- Retrospective study of 41 PVT patients, MAA SPECT/CT based Dosimetry
- Tumor dose intensification rate: 37%,
- **5 patients downstaged toward surgery**





Personalized Dosimetry based on Maximal Normal liver Tolerated Dose

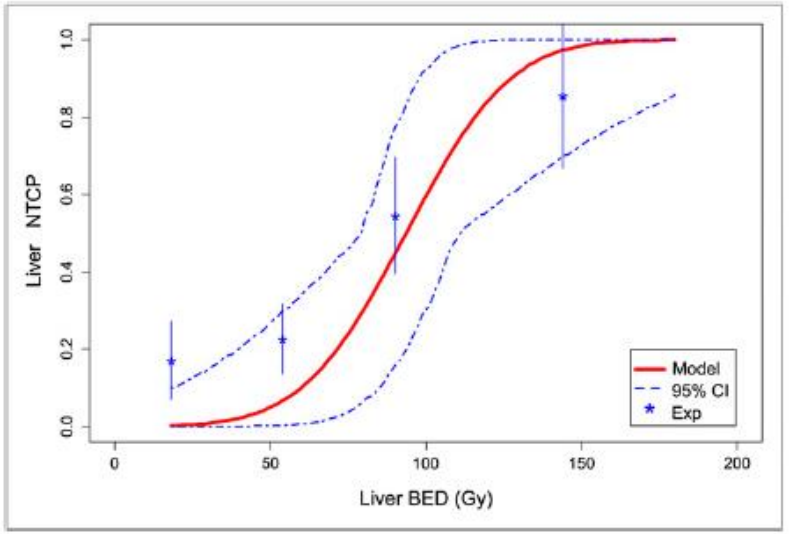
Eur J Nucl Med Mol Imaging (2015) 42:1718–1738
DOI 10.1007/s00259-015-3068-8

ORIGINAL ARTICLE

Radioembolization of hepatocarcinoma with ^{90}Y glass microspheres: development of an individualized treatment planning strategy based on dosimetry and radiobiology

C. Chiesa [1] · M. Mira [2] · M. Maccauro [1] · C. Spreafico [3] · R. Romito [4] · C. Morosi [3] ·

- **Toxicity Probability (modeling) of 15% for a Healthy liver dose of 75 Gy and Child A patients**
- **Any decompensation (reversible or not)**
- **MAA Mean absorbed dose of the Normal Liver (irradiated + not irradiated)**

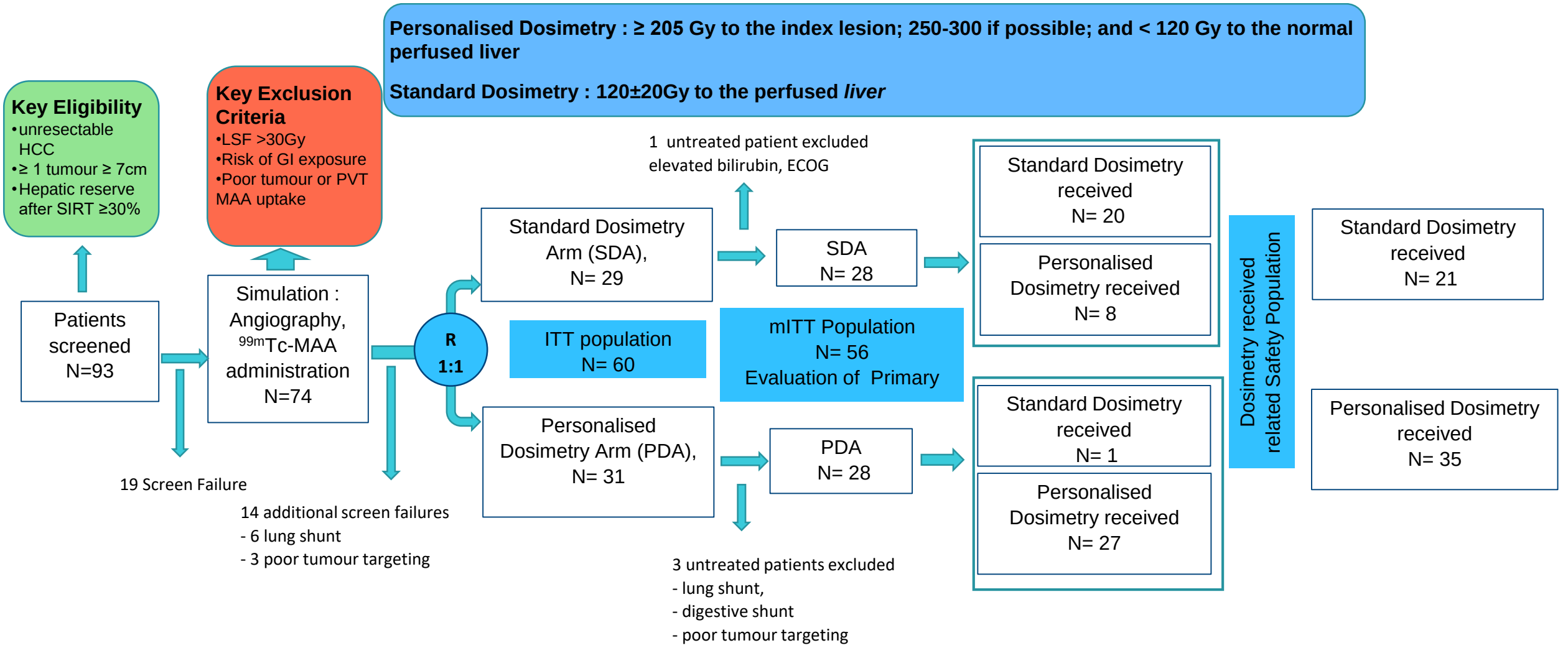


Multi-compartment Personalised Dosimetry
Latest Level 1 evidence :
DOSISPHERE trial

Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial

Etienne Garin*, Lambros Tselikas*, Boris Guiu, Julia Chalaye, Julien Edeline, Thierry de Baere, Eric Assenat, Vania Tacher, Corentin Robert,

Lancet Gastroenterol Hepatol 2020



Demographic and baseline characteristics

	Intention-to-treat population		Modified intention-to-treat population	
	Personalised dosimetry group (n=31)	Standard dosimetry group (n=29)	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)
Mean age, years	65·0 (10·1)	63·2 (13·4)	64·8 (10·1)	62·5 (13·1)
Sex				
Female	3 (10%)	2 (7%)	2 (7%)	2 (7%)
Male	28 (90%)	27 (93%)	26 (93%)	26 (93%)
Child-Pugh liver function classification				
A5	25 (81%)	23 (79%)	22 (79%)	22 (79%)
A6 or B7	6 (19%)	6 (21%)	6 (21%)	6 (21%)
ECOG performance status				
0	18 (58%)	14 (48%)	16 (57%)	13 (46%)
1	13 (42%)	15 (52%)	12 (43%)	15 (54%)
BCLC classification				
B	4 (13%)	3 (10%)	3 (11%)	2 (7%)
C	27 (87%)	26 (90%)	25 (89%)	26 (93%)
Portal vein invasion				
Absent	11 (36%)	8 (27%)	10 (36%)	7 (25%)
Present	20 (65%)	21 (72%)	18 (64%)	21 (75%)
Index tumour size, cm				
Mean	10·6 (2·8)	11·1 (2·8)	10·5 (2·4)	10·9 (2·57)
≥10	17 (55%)	18 (62%)	15 (54%)	17 (61%)
<10	14 (45%)	11 (38%)	13 (46%)	11 (39%)

Table 1: **Demographic and baseline characteristics of patients in the intention-to-treat and modified intention-to treat populations**

Primary endpoint : Response Rate index lesion
Investigator evaluation confirmed by central evaluation

	Investigator evaluation		
	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value
Objective response	20 (71%)	10 (36%)	..
Complete response	6 (21%)	3 (11%)	..
Partial response	14 (50%)	7 (25%)	..
No response	8 (29%)	18 (64%)	..
Stable disease	4 (14%)	14 (50%)	..
Progressive disease	1 (4%)	0	..
Other	3 (11%)*	4 (14%)†	
Objective response rate (95% CI)	71% (51–87)	36% (19–56)	0·0074

Data are n (%), unless otherwise stated. *Two patients were evaluated at 3 months after the introduction o month 3. †One patient was evaluated at 3 months after the introduction of systemic treatment, and three who had died due to progressive disease.

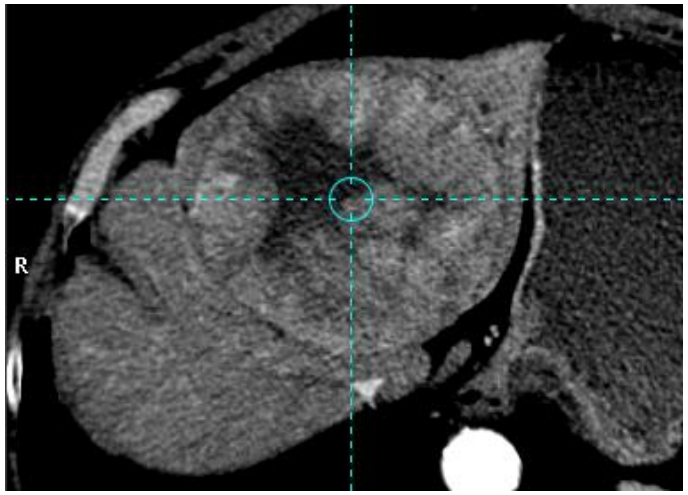
Table 3: **Objective response evaluation of the index lesion at 3 months by investigator and cent population**

Dose response correlation

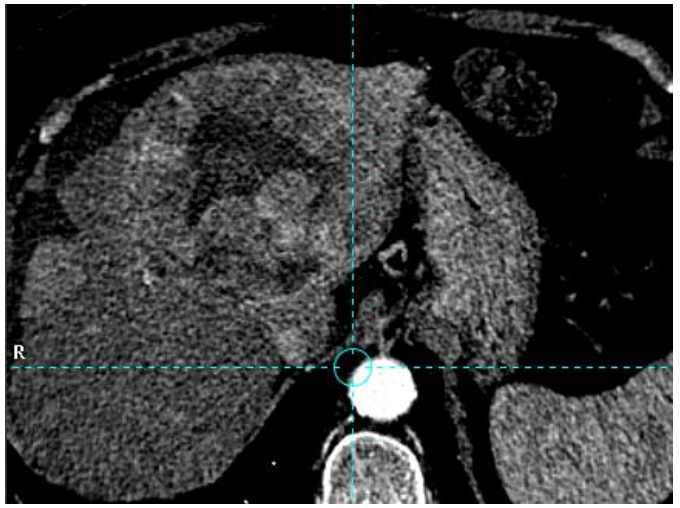
	Response Rate (CR+PR)			
Dosimetry	**Investigator Evaluation**		**Centralised Evaluation**	
Absorbed tumour Dose ≥ 205 Gy (%)	**76.6**		**81.8**	
Absorbed tumour Dose <205Gy (%)	**22.2**	*P=0.0002*	**20**	*P<0.0001*
Perfused Liver Dose ≥150Gy (%)	**80.9**		**86.2**	
Perfused Liver Dose <150 Gy (%)	**40.0**	*P=0.0028*	**33.3**	*P<0.0001*

Case 1 , SDA :

Index lesion of 10.7cm at baseline, **Perfused liver dose = 125Gy , TD= 140 Gy**,



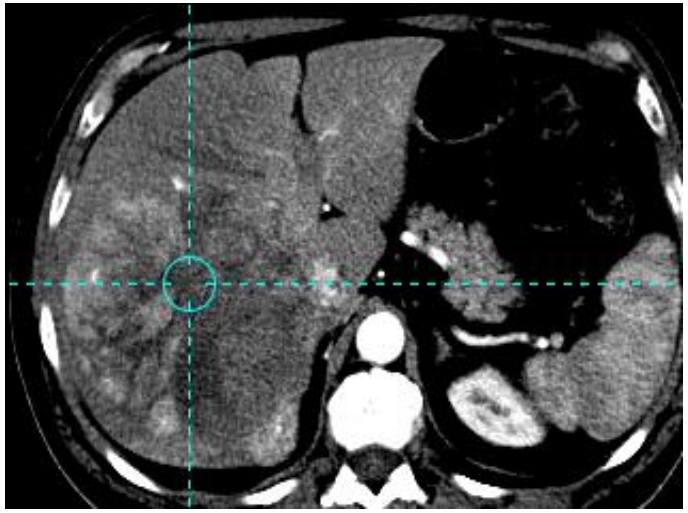
Baseline



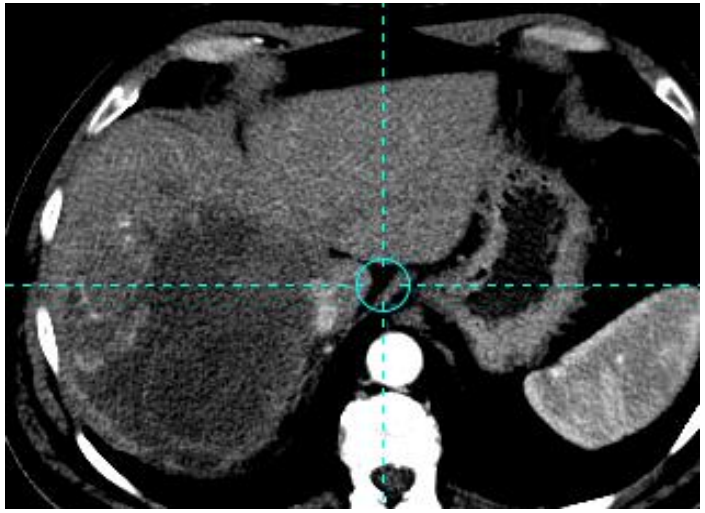
SD at M3

Case 2, PDA :

Index lesion of 15 cm at baseline, **Perfused liver dose = 235 Gy, TD= 294 Gy,**



Baseline



Good PR at M3

No degradation of the safety profile

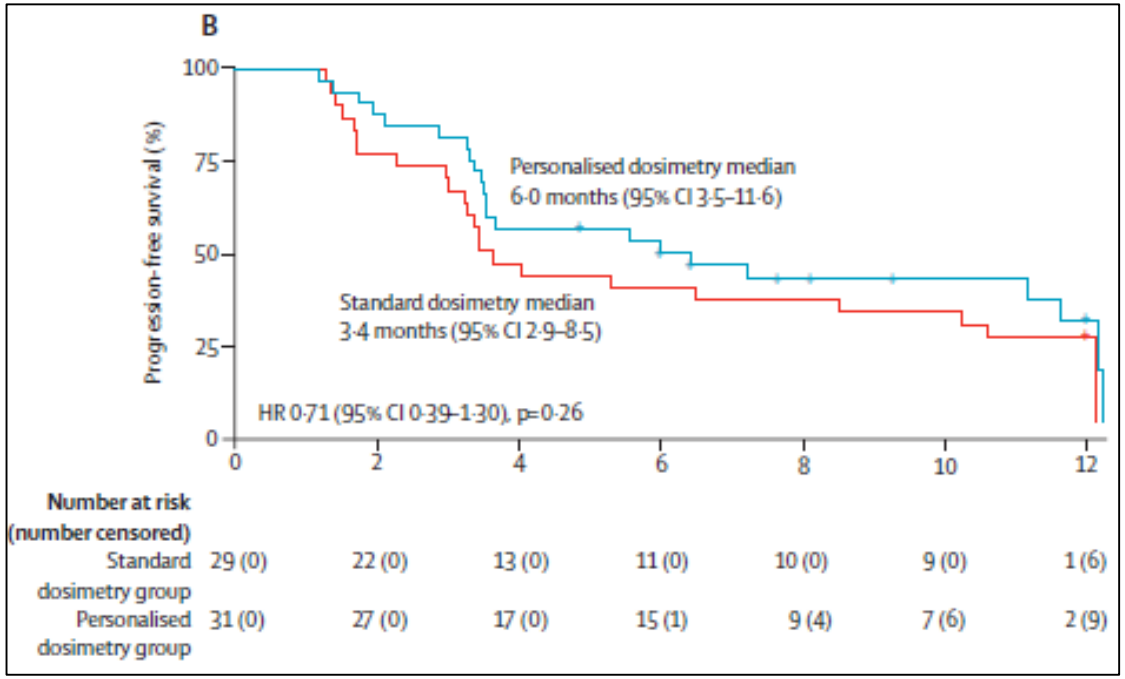
	Personalised dosimetry treatment (n=35)		Standard dosimetry treatment (n=21)	
	Patients	Events	Patients	Events
Any adverse event	31 (89%)	158	19 (90%)	83
Grade 3	20 (57%)	30	14 (67%)	26
Grade ≥3	21 (60%)	36	16 (76%)	31
Grade 4	3 (9%)	3	2 (10%)	2
Grade 5	2 (6%)*	3	3 (14%)†	3
Any serious adverse event	7 (20%)	10	7 (33%)	10
Serious treatment-related adverse events	3 (9%)	4	3 (14%)	3

Adverse events occurring in patients who reported one or more adverse event. 35 patients received personalised dosimetry treatment (>150 Gy to the perfused liver) and 21 patients received standard dosimetry treatment (<205 Gy to the index lesion). * One patient died due to hepatic failure (related to treatment) and the other patient died due to encephalopathy associated with deterioration of their general condition (unrelated to treatment; counted as two grade 5 events). †These patients died due to ascitis (related to treatment), spinal cord compression (unrelated to treatment), and cachexia (unrelated to treatment).

Table 4: **Adverse events in the safety analysis population**

Liver decompensation (G≥3): 8.6% (PDA) vs 9.5% (SDA)

PFS, ITT population

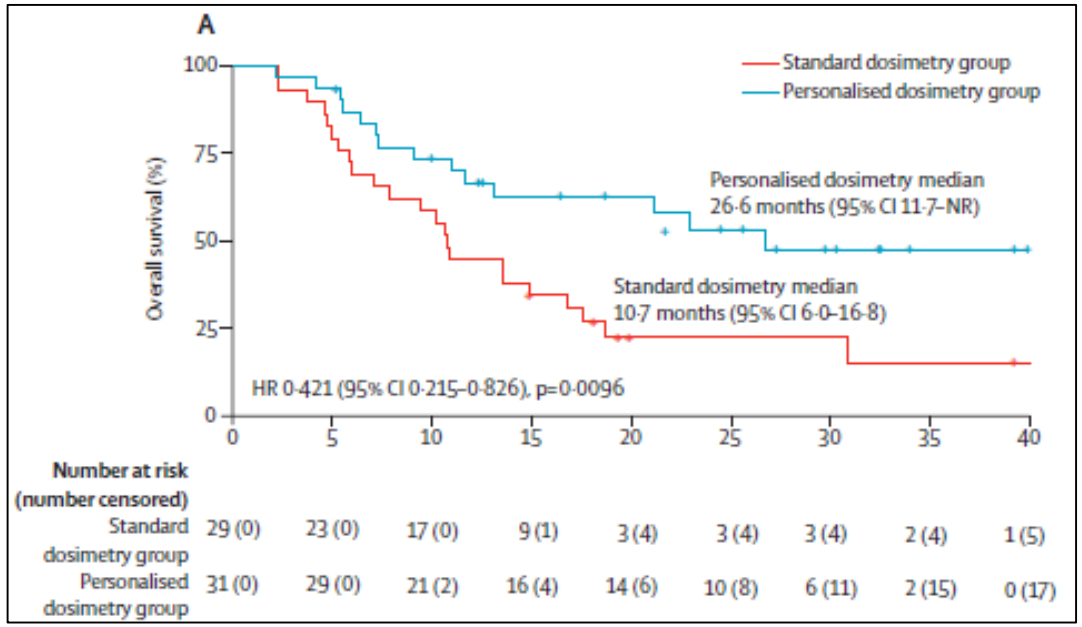


Censored at time of surgery,

Surgery rate : 34% in PDA 4% in SDA

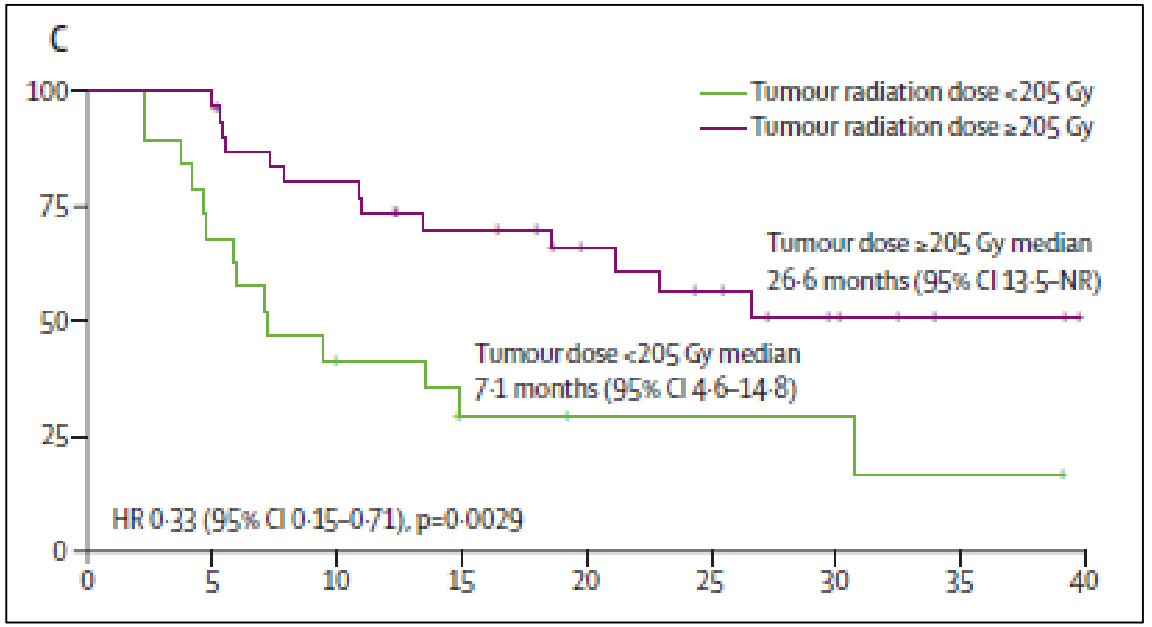
ITT population :

26.6 (11.7-NR) in the PDA vs **10.7m** (6-16.8) in the SDA



Based on TD :

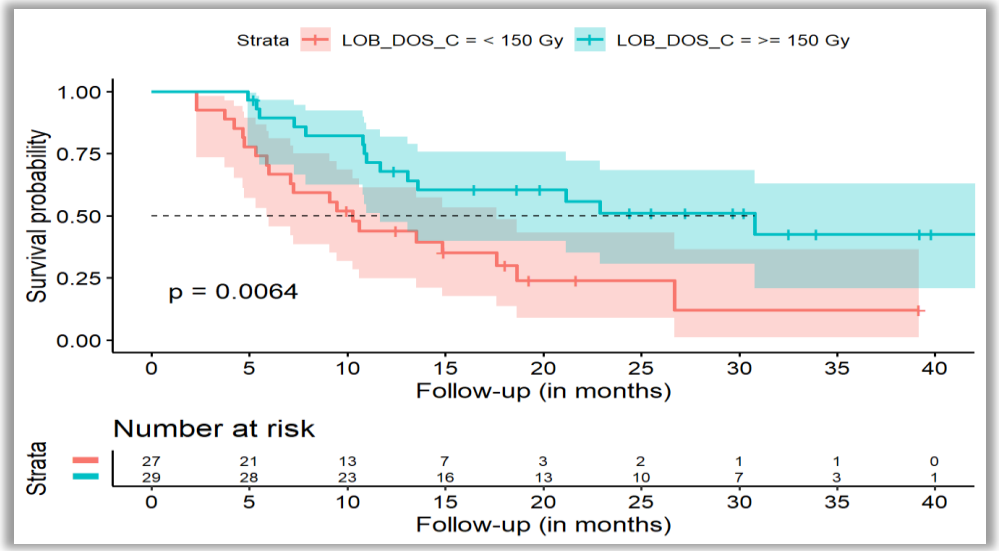
26.6 (13.5-NR) for TD ≥ 205Gy vs **7.1m** (4.6-14.8) for TD < 205 Gy,



Based on PLD :

30.8m (11.7-NR) for PLD ≥ 150 Gy vs

10.3m (5.617.6) for PLD < 150 Gy,

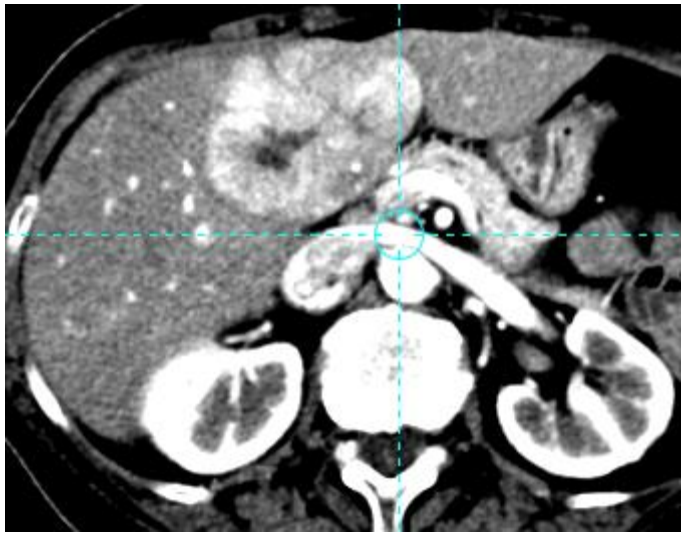


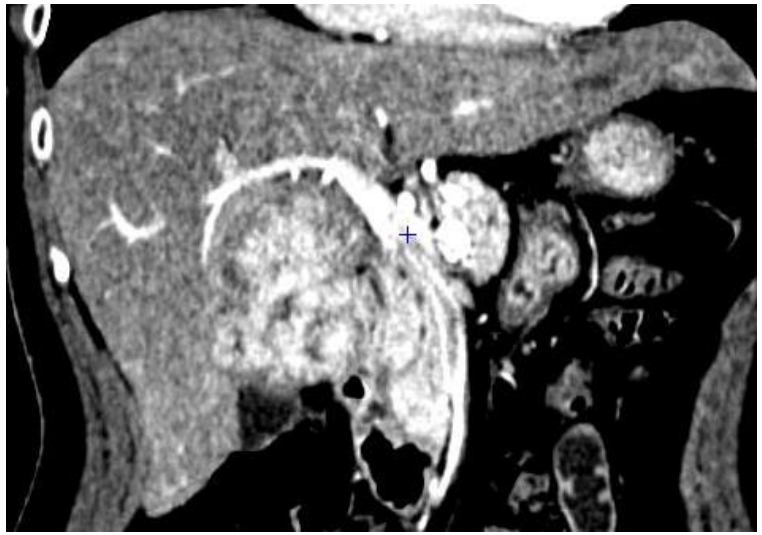
67 Year old female

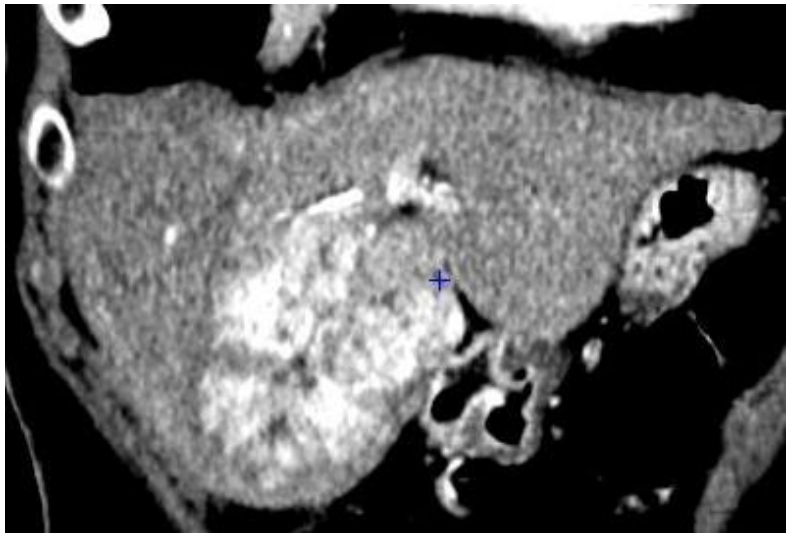
ECOG 0,
Child A5, bilirubin 0.5 mg/dL
No underlying Cirrhosis

Large unifocal segment IV HCC (7cm)
BCLC A

AFP : 78 000ng/ml







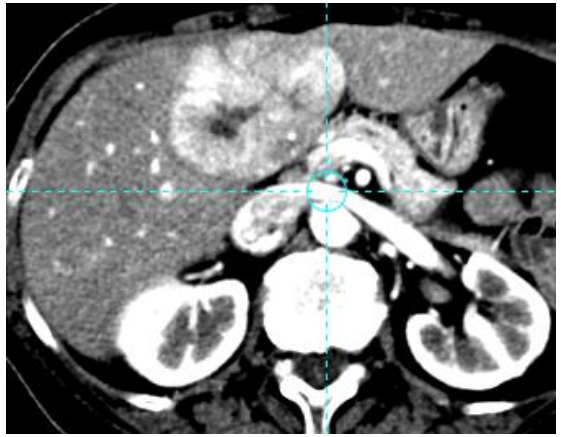
Tumor bord proposal:

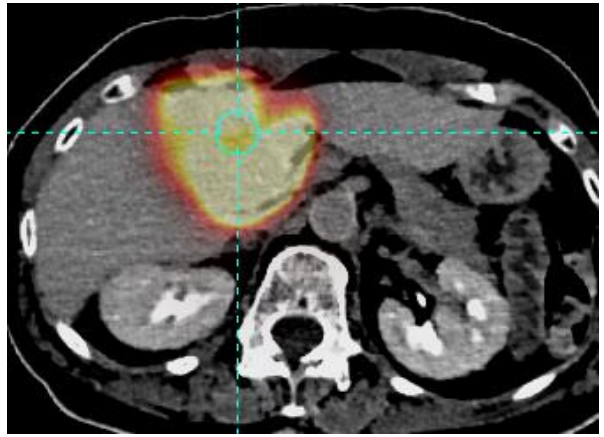
The surgeon asked for a neoadjuvant SIRT before central Hepatectomy, with the intent of :

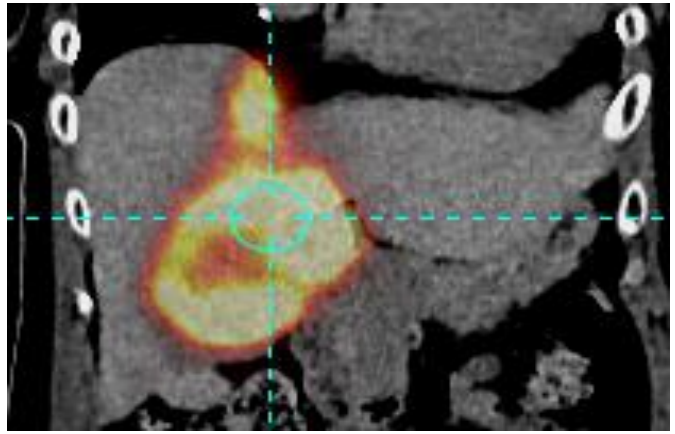
Retracting the tumor from vessels and Biological Test of time

Proposal validated

Treatment planning/ Treatment







Good tumor targeting, concordant with CT

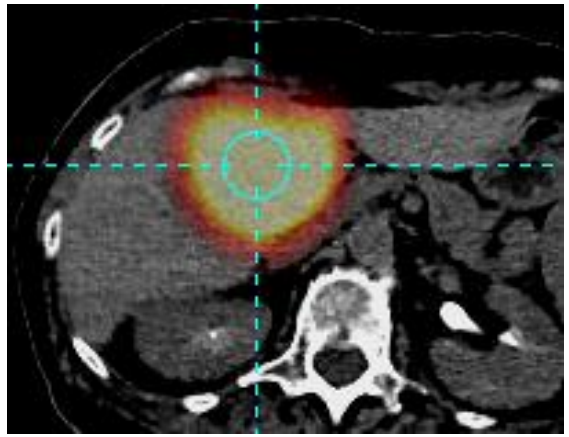
MAA based dosimetry :

Activity to inject 1.95 GBq

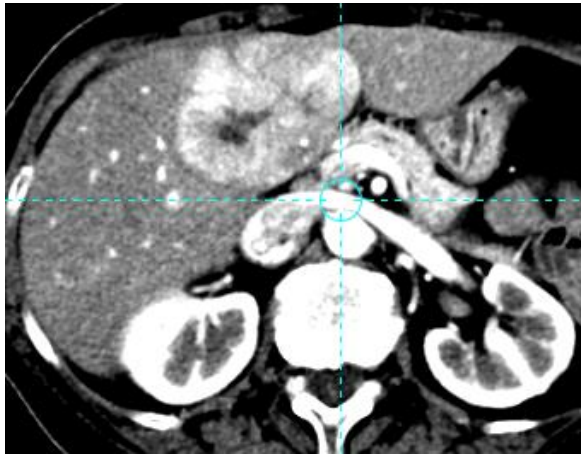
Perfused Liver dose (segment IV) : 450 Gy
Whole Liver dose : 95 Gy *(< 150 Gy)*
Tumor dose : 615 Gy

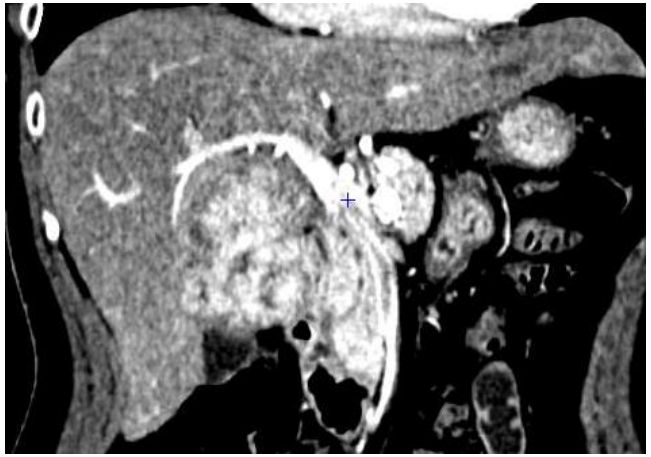
Normal Perfused Liver dose: 166 Gy *(> 100 Gy but HR 78.4%)*
Whole Normal Liver dose : 44 Gy *(<90 Gy)*

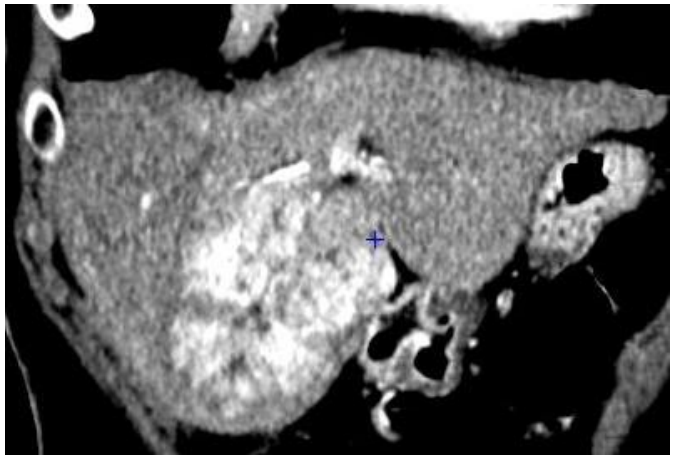
90Y SPECT/CT



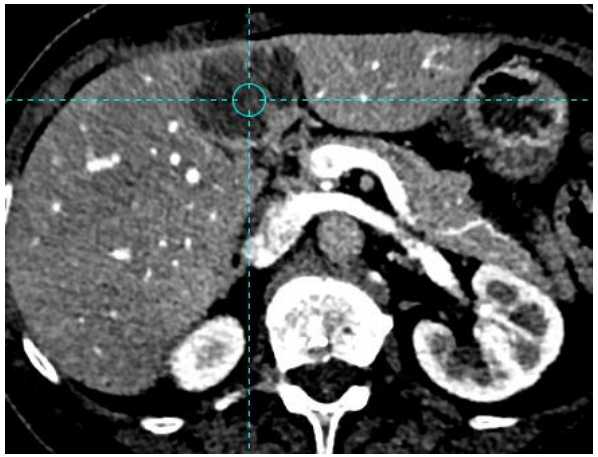
Baseline

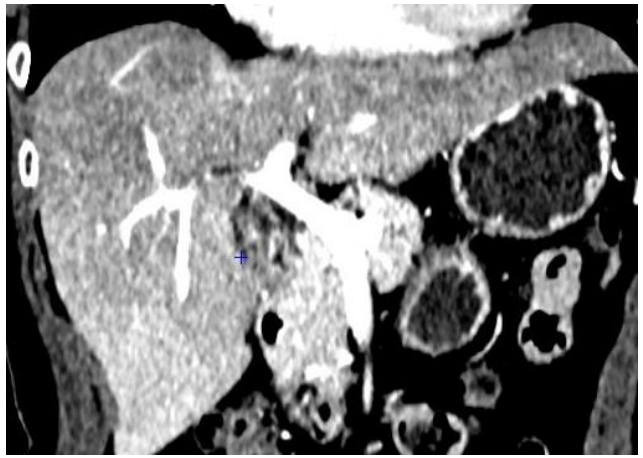


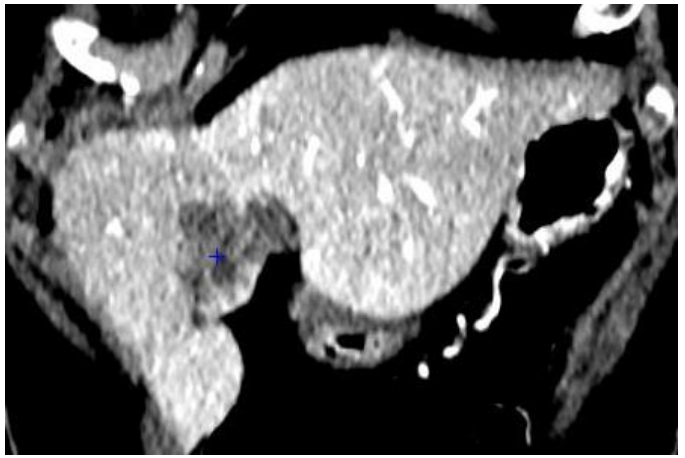




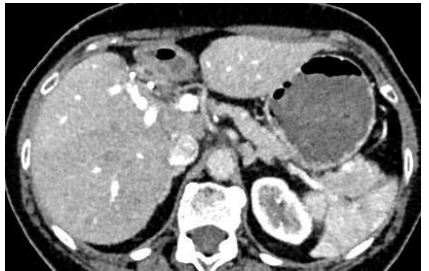
Follow up at 3 month: Compleate EASL response, **Normalisation of the AFP (3ng/ml)**







Surgery at 4 months: R0, complete histological response

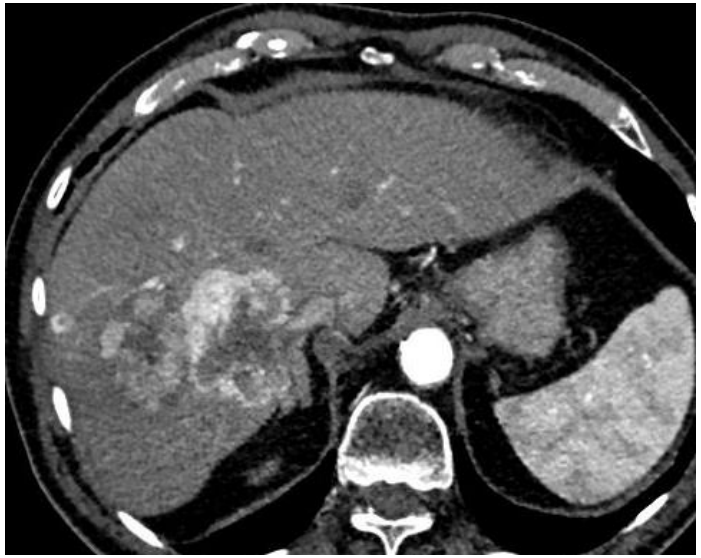


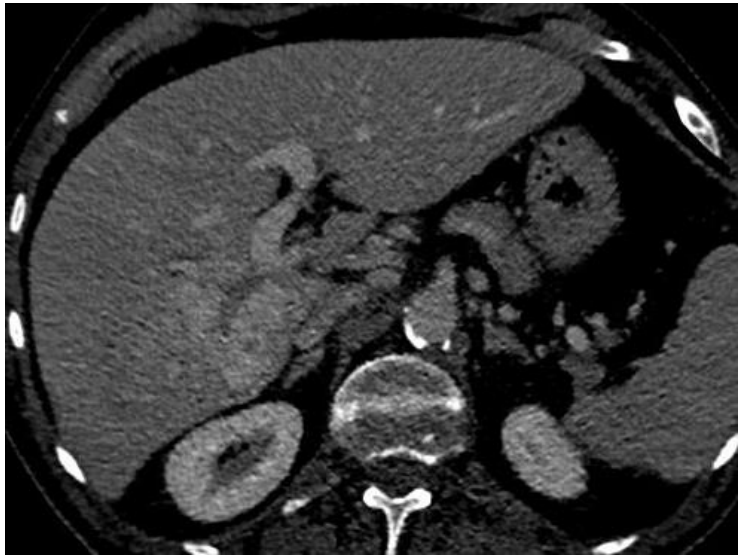
Case HY : 73 year old patient, BCLC C

ECOG 0,
Child A5, bilirubin : 0.58 mg/dL
No cirrhosis

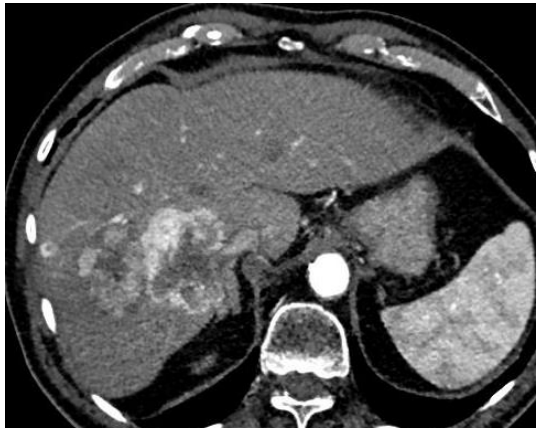
2 confluent HCCs 8 cm, Right PVT
No ascites at all TDM
No Portal Hypertension
Hepatic reserve : 50.6 %

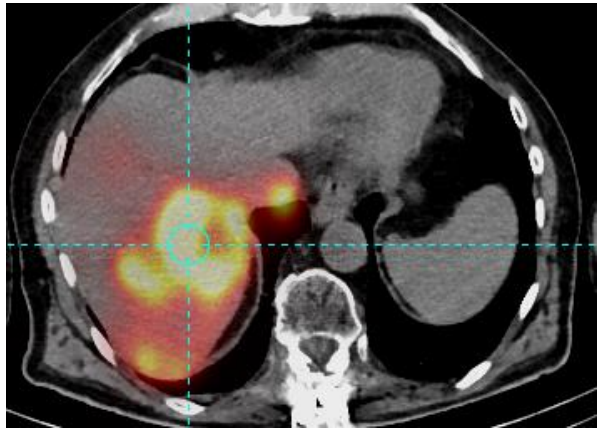
AFP normal

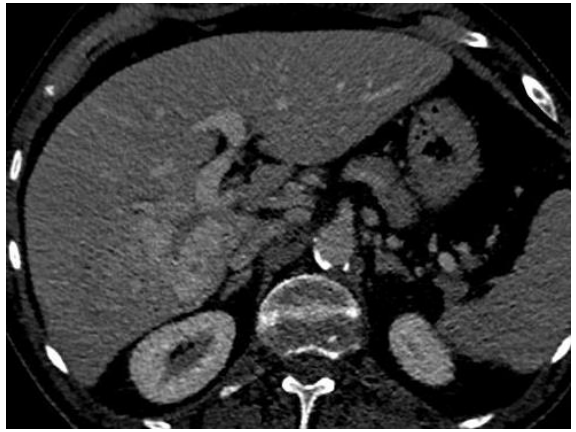


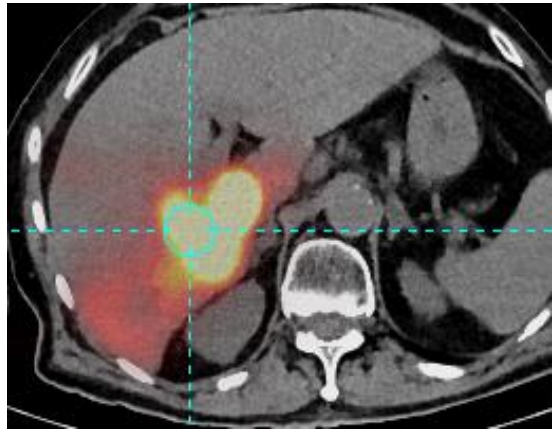


Simultion and treatment









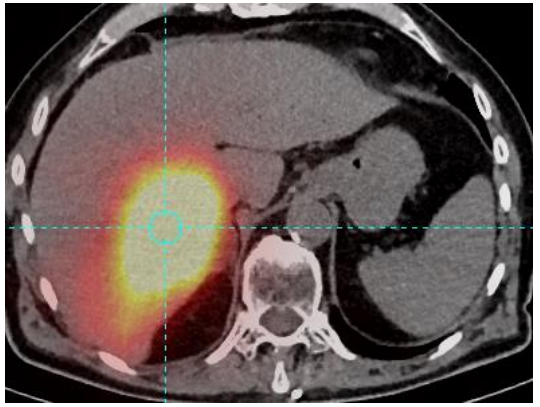
Good tumor targeting,
Concordant with CT

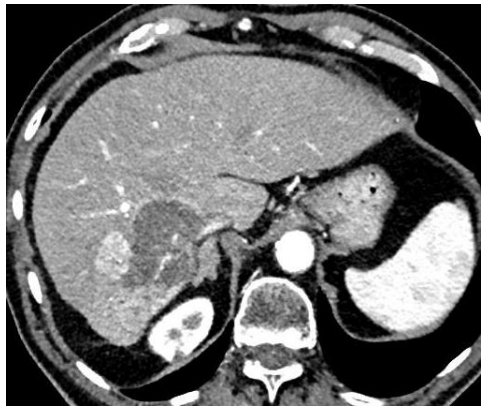
Good PVT targeting,

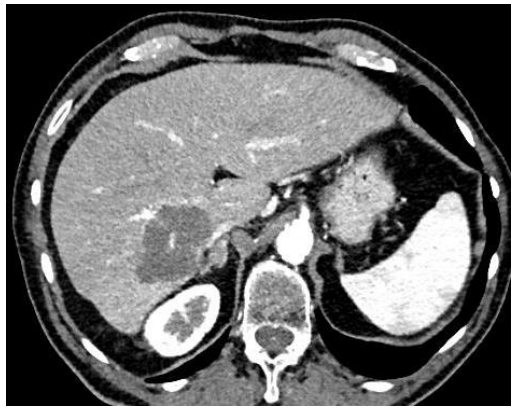
Dosimetry planning : activity to inject 3.16 GBq

Perfused Liver Dose (Right lobe): 222 Gy **(treatment intensification)**
Whole Liver Dose : 110 Gy ***(<150 Gy)***
Tumor Dose: 552 Gy
Normal Perfused Liver Dose : 126Gy , but HR > 30% (50.6%)
Whole Normal Liver Dose : 65 Gy, ***(<90 Gy)***

90Y SPECT/CT

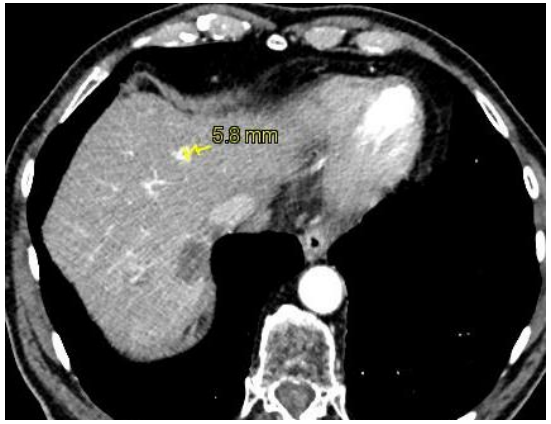


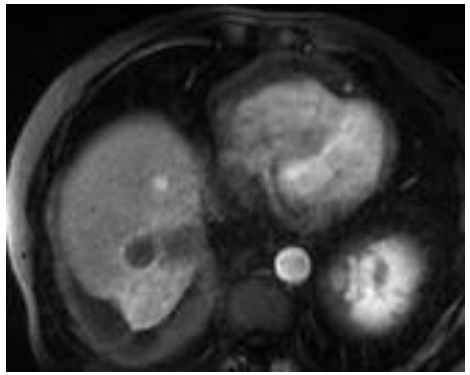


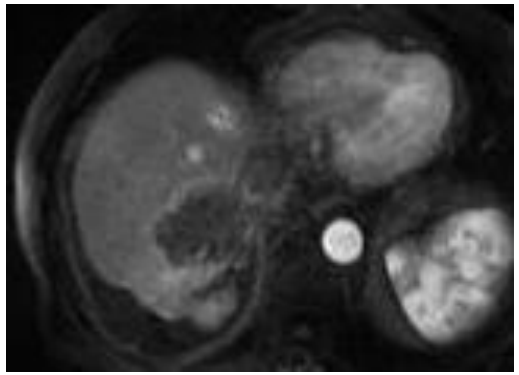


At 4 months :

Partial response,
Doubtfull 6mm lesion seg 4
Still ECOG 0 and Child A5





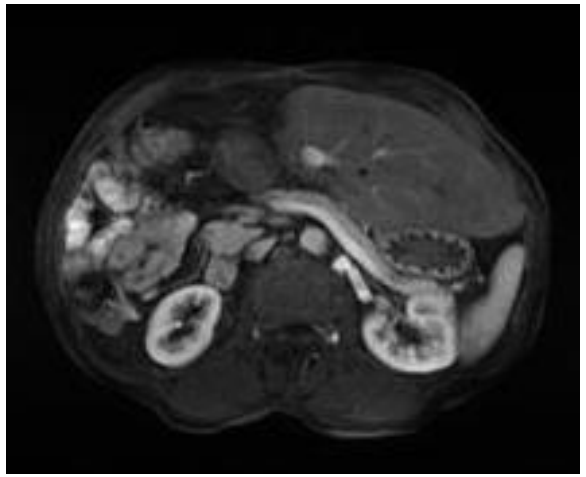


At 7 months :

CR of treated lesions
2 recurences seg 4
Still ECOG 0 and Child A5

Tumor board proposal : surgery (at month 10, R0)

MRI 5 months post surgery, 15 months post SIRT : still RC



International recommendations for Personalized Dosimetry

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-019-04840-5

GUIDELINES

Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group

Riad Salem[1] ·
Joseph Herman[7]

Received: 19 February

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-05163-5

GUIDELINES

International recommendations for personalised selective internal radiation therapy of primary and metastatic liver diseases with yttrium-90 resin microspheres

Hugo Levillain
Oliver S. Gros
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Bruno Sangro

Received: 11 Sept

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05600-z

GUIDELINES

EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds

M. Weber[1] · M. Lam[2] · C. Chiesa[3] · M. Konijnenberg[4] · M. Cremonesi[5] · P. Flamen[6] · S. Gnesin[7] · L. Bodei[8] · T. Kracmerova[9] · M. Luster[10] · E. Garin[11] · K. Herrmann[1]

Received: 9 September 2021 / Accepted: 19 October 2021

Table 2 Absorbed dose recommendations for ^{90}Y glass microspheres and the respective level of evidence (LOE)

	Single compartment		Multi-compartment		
Clinical scenario	Perfused volume dose	LOE	Normal liver dose	Tumour dose	LOE
HCC					
Segmentectomy	> 400 [83]	3	*Not applicable*		
Lobectomy	> 150 if whole liver dose <150 [67]	1*	≥ 88** [85]	≥ 205 [67]	3
	140–150 [84]	3	< 75 (range: 50/90***) [86]	≥ 250–300****	
Unilobar	> 150 if whole liver dose <150 [67]	1*	< 120** if HR < 30% [67]	≥ 205 [67]	1*
	80–150 [61, 74]	3	< 75 (range: 50/90***) [86]	≥ 250–300****	3
Bilobar	80–150**** [13, 69, 87]	1, 4	< 50/90*** [86]	≥ 205 [62]	3
ICC					
Segmentectomy	> 400 [60]	4	*Not applicable*		
Lobectomy	140–150	4	< 75 (range: 50/90***)	≥ 260 [88]	3
Unilobar	80–150 [89]	3	< 75 (range: 50/90***)	≥ 260 [88]	3
Bilobar	80–150 [89]	3	< 75 (range: 50/90***)	≥ 260 [88]	3
mCRC					
Segmentectomy	> 400 [90]	3	*Not applicable*		
Lobectomy	140–150	4	< 75 (range: 50/90***)	≥ 189 [91]	3
Unilobar	80–150 [92]	3	< 75 (range: 50/90***)	≥ 189 [91]	3
Bilobar	80–150 [92]	3	< 75 (range: 50/90***)	≥ 189 [91]	3

HR, hepatic reserve, i.e. untreated liver fraction

*In patients comparable to the DOSISPHERE-01 [67] study population (Child-Pugh A, large lesions, at least 30% of hepatic reserve)

**Dose to the normal perfused liver, based on the first treatment

***Dose to the whole normal liver. In HCC patients with total bilirubin levels >1.1 mg/dl, an upper threshold of 50 Gy should be used; in patients with total bilirubin levels <1.1 mg/dl, the whole normal liver dose should be kept below 90 Gy. Data are derived from unilobar treatments without prior RE only. Since these thresholds have been established in mostly cirrhotic HCC patients, they can be considered safe for non-HCC patients; however, caution is warranted particularly in ICC patients with underlying cirrhosis and after chemotherapy

****For large lesions [67]

Table 3 Absorbed dose recommendations for ^{90}Y resin microspheres and the respective level of evidence (LOE)

	Single compartment		Multi-compartment		
Clinical scenario	Perfused volume dose	LOE	Normal perfused liver dose	Tumour dose	LOE
HCC					
Segmentectomy	> 150 [93]	4	*Not applicable*		
Lobectomy	*Not recommended*		> 70 [93]*	≥ 100–120 [93]	4
Unilobar			< 40 [93]	≥ 100–120 [65]	3 4
Bilobar			< 30**/40 [93]	≥ 100–120 [65]	3 4
ICC					
Segmentectomy	> 150 [93]	4	*Not applicable*		
Lobectomy	*Not recommended*		> 70 [93]	≥ 100–120 [94]	3 4
Unilobar			< 40 [93]	≥ 100–120 *** [94]	3 4
Bilobar			< 30**/40 [93]	≥ 100–120 *** [94]	3 4
mCRC					
Segmentectomy	> 150 [93]	4	*Not applicable*		
Lobectomy	*Not recommended*		> 70 [93]	> 100 **** [93]	4
Unilobar			< 40 [93]	> 100 **** [95]	3 4
Bilobar			< 30**/40 [93]	> 100 **** [95]	3 4

Modified from Levillain et al. [93]

*Dose to the normal perfused liver with a hepatic reserve of >30%

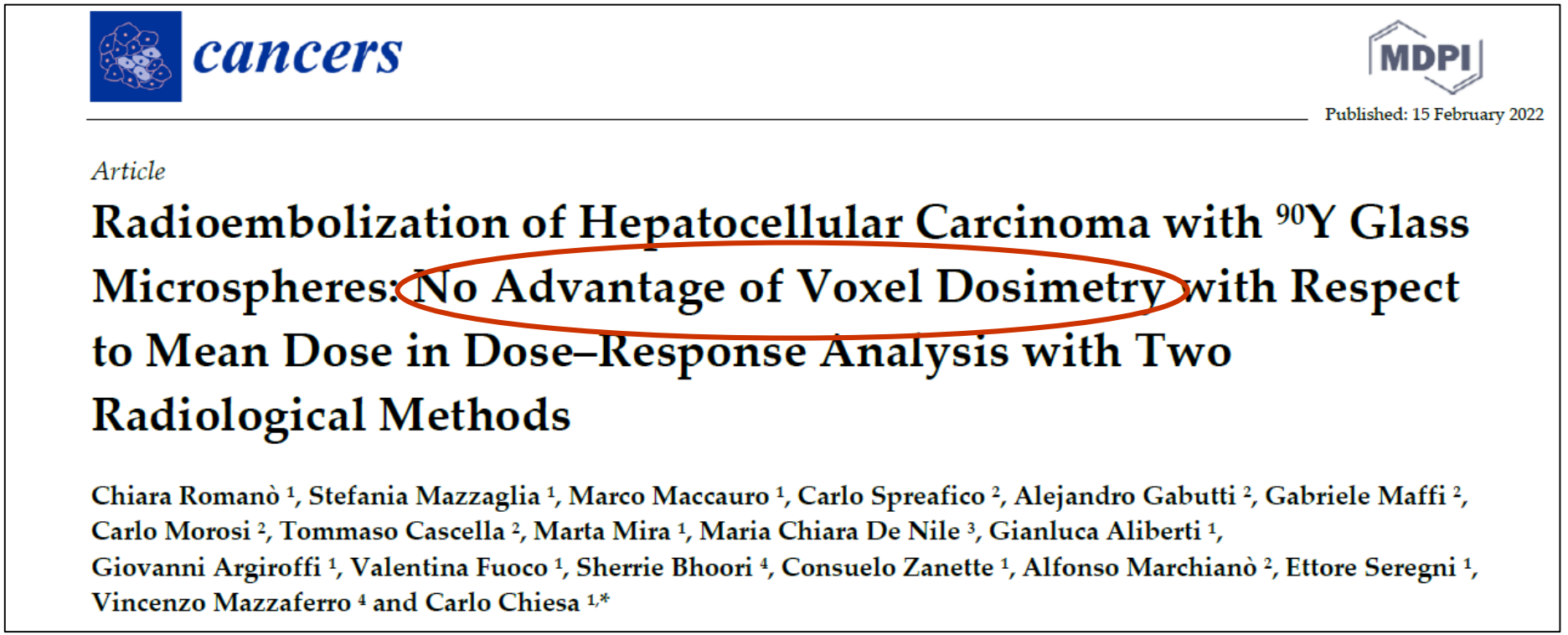
**In pretreated patients or those with compromised liver function

***Longer OS for patients treated with a partition model-derived mean tumour dose of 86 Gy vs. BSA-derived tumour dose of 38 Gy

****Tumour absorbed doses >100 Gy have been associated with higher rates of metabolic complete response, whereas a lower threshold of >40–60 Gy predicted metabolic partial response

Next steps : voxel based dosimetry ?

- **Theoretical advantage to use DVH and related metrics**
- **Dose correlation with Dx and Vx have to be evaluated as their potential clinical impact**



cancers

MDPI

Published: 15 February 2022

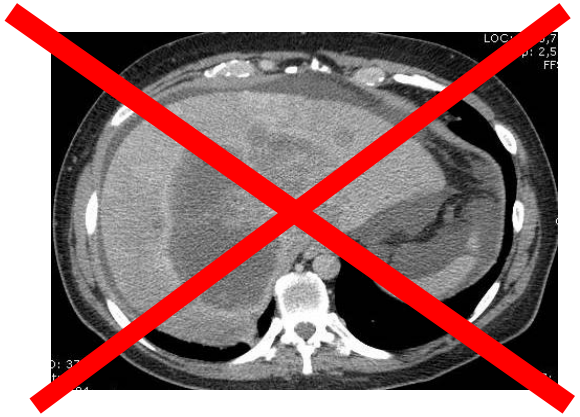
Article

Radioembolization of Hepatocellular Carcinoma with ^{90}Y Glass Microspheres: No Advantage of Voxel Dosimetry with Respect to Mean Dose in Dose–Response Analysis with Two Radiological Methods

Chiara Romanò [1], Stefania Mazzaglia [1], Marco Maccauro [1], Carlo Spreafico [2], Alejandro Gabutti [2], Gabriele Maffi [2], Carlo Morosi [2], Tommaso Cascella [2], Marta Mira [1], Maria Chiara De Nile [3], Gianluca Aliberti [1], Giovanni Argiroffi [1], Valentina Fuoco [1], Sherrie Bhoori [4], Consuelo Zanette [1], Alfonso Marchianò [2], Ettore Seregni [1], Vincenzo Mazzaferro [4] and Carlo Chiesa [1,*]

Challenging point : accurate patient selection

- **Good candidate to consider for treatment intensification to increase the tumor absorbed dose and the probability of response :**
  - ✓Large lesion and unilobar disease
  - ✓Hepatic reserve > 30%
  - ✓Child A
  - ✓No ascites at all (even if only depictable on CT)
  - ✓Curative intent



- **Good candidate to consider at dose reduction to preserve liver function :**
  - ✓Whole liver treatment in one session
  - ✓Bilobar disease with small lesions
  - ✓Child B patients

Challenging point : Quality control for Personalized Dosimetry

Simulation (work-up)

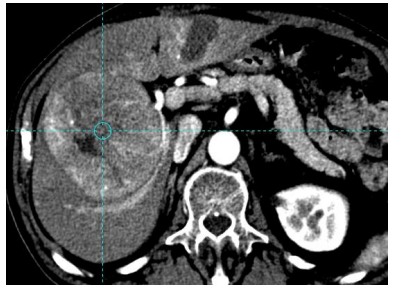
- **Dosimetric Angiography recommendations (work up)**
  - Blood flow preservation (caution regarding spasm)
  - CBCT on the treatment position (targeting evaluation)
  - Concordance of CBCT targeting and CT/MRI tumoral varcularistion (spasm?)
  - Slow MAA infusion
- **MAA SPECT/CT dosimetry :**
  - **Concordance of MAA targeting and CT/MRI tumoural vascularisation :**

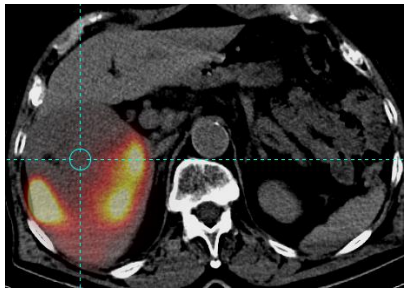
    if not accurate, MAA based dosimetry not accurate (spasm? Bifurcation incidence?) **and consider a new simulation**
  - Full tumour targeting ; PVT targeting
  - SPECT/CT segmentation (DOSISPHERE)

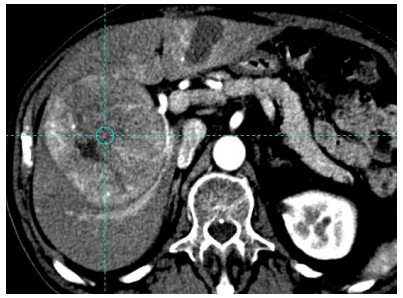
Treatment

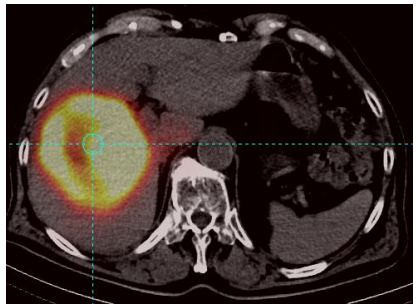
- **Therapeutic angiography**
  - Blood flow preservation (caution regarding spasm)
  - Accurate catheter repositioning
  - CBCT on the treatment position to evaluate the concordance of the targeting with the simulation CBCT
- **^{90}Y PET or SPECT/CT**
  - Concordance with MAA targeting, if not analyse the case (angio)

Example of simulation-based dosimetry quality control







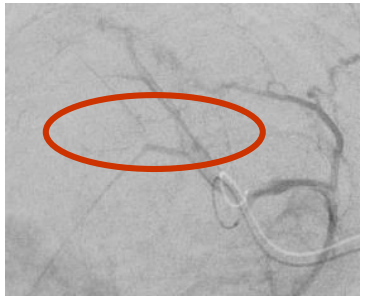


First simulation :
Discordance MAA/CT

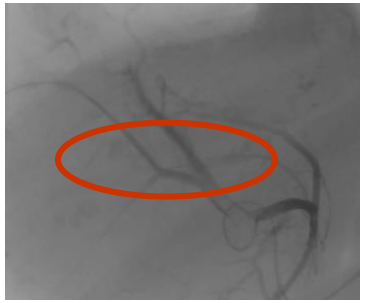
Simulation not accurate

Second simulation :
concordance MAA/CT

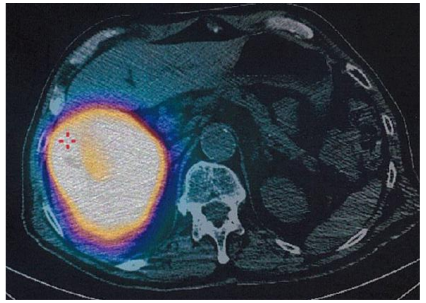
Simulation accurate



Blood flow impairement



Better blood flow



^{90}Y SPECT/CT

Take home messages

- **Multidisciplinarity of MAA based dosimetry is mandatory +++**
- **Level 1 Evidence that MAA SPECT/CT based dosimetry is accurate for large HCC prediction of response and OS, if it is rigorously performed (DOSIPHERE trial)**
- **Personalized multi-compartment dosimetry, targeting to the tumor more than 205Gy, if possible more than 250-300Gy, strongly increases RR and OS (DOSIPHERE trial) with glass microspheres**
- **New EANM recommendations for advanced dosimetry for both products**
- **Importance of accurate patient selection and quality control**
- **Voxel based dosimetry has to be evaluated**