

# **Pharmacokinetics of $^{99m}\text{Tc}$ -MAA- and $^{99m}\text{Tc}$ -HSA-Microspheres Used in Pre-Radioembolization Dosimetry: Influence on the Liver–Lung Shunt**

Running title: Albumin Microspheres in Radioembolization

Oliver S. Grosser<sup>1</sup>, Juri Ruf<sup>1,2</sup>, Dennis Kupitz<sup>1</sup>, Annette Pethe<sup>1</sup>, Gerhard Ulrich<sup>1</sup>, Philipp Genseke<sup>1</sup>, Konrad Mohnike<sup>1</sup>, Maciej Pech<sup>1,3</sup>, Wolf S. Richter<sup>4</sup>, Jens Ricke<sup>1</sup>, and Holger Amthauer<sup>1</sup>

<sup>1</sup> Department of Radiology and Nuclear Medicine, University Hospital Magdeburg, Magdeburg, Germany

<sup>2</sup> Department of Nuclear Medicine, University Hospital Freiburg, Freiburg, Germany

<sup>3</sup> 2<sup>nd</sup> Department of Radiology, Medical University of Gdansk, Gdansk, Poland

<sup>4</sup> pharmtrace - clinical research, Berlin, Germany

## Corresponding Author:

Oliver Stephan Grosser

Department of Radiology and Nuclear Medicine

University Hospital Magdeburg

Leipziger Strasse 44

39120 Magdeburg, Germany

Phone: (+49) 391-67-13000

Fax: (+49) 391-67-13990

E-mail: [oliver.grosser@med.ovgu.de](mailto:oliver.grosser@med.ovgu.de)

Words: 2,496

## ABSTRACT

Perfusion scintigraphy using technetium-99m ( $^{99m}\text{Tc}$ )-labeled albumin aggregates is mandatory before hepatic radioembolization with yttrium-90-microspheres. As part of a prospective trial, the intrahepatic and intrapulmonary stability of two albumin compounds,  $^{99m}\text{Tc}$ -MAA (macroaggregated serum albumin, MAA) and  $^{99m}\text{Tc}$ -HSA (human serum albumin, HSA), was assessed.

**Methods:** In 24 patients with metastatic colorectal cancer, biodistribution (liver, lung) and liver–lung shunt (LLS) of both tracers (12 patients each) were assessed by sequential planar scintigraphy (1, 5, and 24 hr post injection [p.i.]).

**Results:** Liver uptake of both albumin compounds decreased differently. Although initial LLSs at 1h p.i. were similar in both groups, MAA-LLS increased significantly from 1 (3.9%) to 5 (7.7%) and 24 h p.i. (9.9%), respectively. HSA-LLS did not change significantly, indicating a steady state of pulmonary and intrahepatic degradation.

**Conclusion:** Compared with  $^{99m}\text{Tc}$ -MAA,  $^{99m}\text{Tc}$ -HSA-microspheres are likely more resistant to degradation over time, allowing a reliable LLS determination even at later time points.

**Keyword:** Radioembolization, dosimetry, biokinetics,  $^{99m}\text{Tc}$ -labeled albumin spheres, liver-lung shunt

## INTRODUCTION

Radioembolization with yttrium-90 ( $^{90}\text{Y}$ )-labeled microspheres is an established therapy for unresectable liver malignancies (1). Despite generally good tolerability, complications (e.g., gastrointestinal ulceration) due to misplaced microspheres may occur (2). In addition, an excessive liver–lung shunting (LLS) may cause radiation pneumonitis, potentially leading to a serious impairment of respiratory function (3,4). Proper estimation of the LLS is therefore a crucial component of pretherapeutic therapy simulation by perfusion scintigraphy (PS), including SPECT(-CT) (5). PS can be performed with technetium-99m macroaggregated serum albumin ( $^{99\text{m}}\text{Tc}$ -MAA) or technetium-99m human serum albumin ( $^{99\text{m}}\text{Tc}$ -HSA) (6,7), tracers formally approved for lung scintigraphy (8,9) used off-label in therapy simulation.

Both tracers are administered into the liver arteries, and the resulting planar and SPECT(-CT)-images are used (1) for the exclusion of extrahepatic tracer accumulation in organs at risk (stomach, gall bladder, etc.) (10) and (2) for the estimation of the LLS and/or lung doses (5). Based on the LLS determined, the activity of  $^{90}\text{Y}$ -microspheres administered is reduced by reference to look-up tables provided by the manufacturer. In the case of a very high LLS, radioembolization treatment may even be canceled to avoid an excessive pulmonary radiation exposure (11,12).

Because pharmacokinetic data on both MAA and HSA spheres after intravenous (i.v.) injection showed an in vivo pulmonary instability of the radiopharmaceutical (13), a timely performed PS is also recommended after intra-arterial (i.a.) injection of  $^{99\text{m}}\text{Tc}$ -labeled albumin compounds (14).

The aim of this analysis is to compare changes in the intrahepatic and intrapulmonary biodistribution and the resulting LLS determination of  $^{99m}\text{Tc}$ -MAA- and  $^{99m}\text{Tc}$ -HSA- microspheres over time in patients scheduled for radioembolization.

## **MATERIAL AND METHODS**

### **Patients**

The present subanalysis of data from both PS tracers was performed as part of a prospective phase 2 clinical trial evaluating the predictability of the accumulation of  $^{90}\text{Y}$ -labeled resin microspheres (SIR-Spheres; Sirtex Medical Ltd, Sydney, Australia) from preceding PS.

In a two-armed study design, patients scheduled for  $^{90}\text{Y}$ -radioembolization of hepatic metastases from colorectal cancer were randomized for one of the two tracers for PS: patients in arm A ( $n = 12$ , male (m)/female (f): 10/2; 66.1 y: range = 46.6–82.2 y) received  $^{99m}\text{Tc}$ -MAA, and patients in arm B ( $n = 12$ , m/f: 8/4; 58.6 y: range = 46.2–76.2 y) received  $^{99m}\text{Tc}$ -HSA (Supplemental Table 1). Trial-specific inclusion criteria were the presence of metastases in both liver lobes and a life expectancy of longer than 6 months. Trial-specific exclusion criteria were an LLS > 10%, concomitant chemotherapy, and variants of the arterial hepatic blood supply that would not allow bilobar evaluation by a single tracer administration into the common hepatic artery.

This monocenter study was approved by the local ethics committee (registration number: 77/09) and supervised by responsible national regulatory agencies (ClinicalTrials.gov Identifier: NCT01186263). Informed written consent was obtained from all participants enrolled.

### **Microspheres Preparation and Application**

Labeling and quality control of the  $^{99m}\text{Tc}$ -MAA (Mallinckrodt Medical B.V., Petten, The Netherlands) and  $^{99m}\text{Tc}$ -HSA (ROTOP-HSA microspheres B20, ROTOP Pharmaka, Radeberg, Germany) were performed according to the manufacturer's recommendations (Supplemental Table 2) (8,9).  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -HSA were injected i.a. into the common hepatic artery during the angiographic evaluation procedure before radioembolization. In order to avoid nonspecific gastric uptake of free  $^{99m}\text{Tc}$ -pertechnetate, 600 mg sodium perchlorate was administered beforehand.

### **Planar Imaging and Analysis of Biodistribution**

Planar imaging was performed in 6 patients (MAA/HSA=4/2) with a dual-head SPECT gamma camera (e.cam, Siemens Medical, Hoffman Estates, IL, USA) and in 18 patients (MAA/HSA=8/10) with a SPECT-CT (NM/CT 670, GE Medical, Haifa, Israel). For both systems, planar imaging was performed with an imaging matrix of 256 x 1024, an energy window at 140 keV  $\pm$  15%, and a scan speed of 8 cm/min. PS imaging was performed nominally at three time points: 1 (PS1), 5 (PS2), and 24 h (PS3) after the angiographic application of the  $^{99m}\text{Tc}$ -labeled particles (Supplemental Table 3).

Semi-quantitative analysis for LLS determination was performed with regions of interest (ROI) analysis on planar data. ROIs for liver and lung were drawn in anterior and posterior projections. The geometric mean of the ROIs was calculated, and time activity curves were estimated for each ROI. All data were corrected for radioactive decay to estimate the uptake of particles (percentage-injected particles) within the ROIs at the different imaging time points and to estimate the in vivo pharmacokinetics of the tracers.

### **Statistics**

The R software package (version 3.1.3, R Foundation for Statistical Computing, Vienna, Austria) was used for statistical evaluations. Analysis of variance (ANOVA) was used to

assess the impact of the liver volume, tumor load, and tracer on the LLS estimated at PS1. Liver volume and tumor load were subdivided into two groups (levels:  $\leq$  median, and  $>$  median) each to test potential impact on LLS. Differences in tracer uptake were tested for significance by unpaired  $t$ -tests at single time points. Change in uptake of each tracer between different time points was tested by paired  $t$ -tests.

All tests performed were two-sided, and statistical significance was assumed at a  $P$ -value  $<0.05$ . Biological half-life times were estimated by regression analysis.

## RESULTS

### Preparation and Application of $^{99m}\text{Tc}$ -MAA and $^{99m}\text{Tc}$ -HSA

Due to constraints imposed by kit preparation, the number of injected spheres differed significantly between both radiopharmaceuticals ( $P < 0.0001$ , Supplemental Table 2). Furthermore, significant differences between groups were observed for free  $^{99m}\text{Tc}$ -pertechnetate ( $P = 0.002$ ), the residual activity in the syringe ( $P = 0.03$ ), and the injected activity ( $P = 0.014$ , all Supplemental Table 2).

### Tracer Uptake (Liver and Lung) Over Time

Between PS1 and PS2, furthermore to PS3, a significant release of particles from the liver was observed for both pharmaceuticals ( $P \leq 0.0002$ , Fig. 1A, B). The liver and lung uptake at PS1 was not significantly different for both pharmaceuticals ( $P > 0.11$ , Fig. 1A, B). The MAA initially showed a fast and then a slower release from liver, which is best fitted by a bi-exponential decay curve (Fig. 2;  $T_{\text{half-life, fast}} = 7.9 \text{ h}$ ,  $T_{\text{half-life, slow}} = 22.4 \text{ h}$ , adjusted (adj.)  $R^2 = 0.77$ ). In contrast, HSA revealed a slow release from liver (Fig. 2; mono-exponential decay curve,  $T_{\text{half-life}} = 41.7 \text{ h}$ , adj.  $R^2 = 0.76$ ).

The median MAA uptake in the lung increased significantly from PS1 to PS2 (2.7% to 3.8%,  $P = 0.0007$ , Fig. 1C) and decreased significantly during the following interval (PS2 to PS3), the median being 3.0% ( $P = 0.002$ , Fig. 1C).

The median HSA uptake in the lungs did not change significantly over time ( $P \geq 0.64$ , Fig. 1D).

### **Liver–Lung Shunt**

For both tracers, ANOVA showed no significant dependency between LLS measured at PS1 and liver volume, tumor load, and tracer ( $P \geq 0.26$ ). For MAA, the absolute LLS increased significantly from PS1 (LLS<sub>PS1</sub> = 3.9%) to PS2 by 3.6% ( $P = 0.0005$ , Fig. 3A and Supplemental Table 4). For HSA, there was no significant change in LLS over the same time period ( $P = 0.74$ , LLS<sub>PS1</sub> = 3.2%, Fig. 3B). This increase in LLS in the MAA group at PS2 was significant compared with the corresponding LLS determined in the HSA-group ( $P < 0.0001$ , Fig. 3A, B).

LLS further increased from PS2 to PS3 in the MAA group (mean increase = 5.0%,  $P < 0.0001$ ; Fig. 3A), whereas the corresponding increases in the HSA group (mean increase: 1.3%,  $P < 0.0001$ ) were significantly smaller ( $P < 0.0001$ , Fig. 3A, B).

### **DISCUSSION**

The aim of the study was to compare the intrahepatic and intrapulmonary pharmacokinetics of  $^{99m}\text{Tc}$ -MAA and  $^{99m}\text{Tc}$ -HSA microspheres after i.a. injection and their influence on estimating LLS.

Although uptake in liver and lung did not significantly differ between the two radiopharmaceuticals at the first imaging time point (1 h p.i), we observed a significant,

time-dependent redistribution of both tracers from the capillary bed of the liver to the capillary bed of the lung. This effect was significantly more pronounced for MAA particles, with a maximal pulmonary uptake at 5 h p.i. In contrast, the pulmonary uptake of HSA particles was almost constant for up to 24 h after injection.

Although theoretically more time points would have been desirable for the assessment of tracer biokinetics, the low number of imaging time points was chosen to guarantee patient compliance after a long and tedious angiographic procedure.

We do admit that the entire biokinetic tracer degradation and redistribution, including interactions such as compartment inflow and outflow, cannot be derived from this simplified two-compartment model (lung, liver). Nevertheless, this model is in our opinion reliable to estimate LLS and demonstrate the effects from particle degradation.

A significant increase in the median LLS was observed for MAA particles from 3.9% (1 h p.i) to 7.7% (5 h p.i.). In contrast, the LLS estimated with HSA particles was not significantly affected by the redistribution process within this clinically relevant time frame (1 to 5 h p.i.). In light of the known pulmonary in vivo degradation of labeled albumin particles after i.v. injection, it is recommended to perform PS not later than 4 h p.i., preferably within the first 60 min after administration, to avoid an artificial overestimation of LLS (15,16), which could result in an unnecessary reduction of the prescribed activity or even unnecessary exclusion of patients from therapy (12,13).

According to our data, reported 4-h tolerance intervals appear to be too long for PS with MAA.

In accordance to the longer in vivo pulmonary half-life reported for HSA (7.2 h) and in comparison with MAA (4.2 h) after i.v. injection for pulmonary scintigraphy (9,17), we observed a longer half-life of labeled HSA in the liver, thus suggesting a better



intrapulmonary and intrahepatic stability of labeled HSA. One of the consequences of this longer half-life is a pulmonohepatic steady state when addressing the LLS estimations, remaining more or less constant even 1 day after tracer administration. However, PS is required not only for LLS determination but also for excluding extrahepatic abdominal tracer accumulation; an acquisition as early as possible is still recommended to retain optimal imaging statistics.

## **CONCLUSION**

When using  $^{99m}\text{Tc}$ -MAA and for  $^{99m}\text{Tc}$ -HSA microspheres for PS prior to radioembolization,  $^{99m}\text{Tc}$ -HSA-microspheres are likely more resistant to degradation over time, allowing a representative LLS determination even at later time points.

## **ACKNOWLEDGMENTS**

We thank SIRTEx Medical for funding of the clinical trial.

## **DISCLOSURE**

Oliver S. Grosser, Maciej Pech, Wolf S. Richter, Jens Ricke, and Holger Amthauer declare that they have received research grants and honoraria by Sirtex Inc. Juri Ruf, Dennis Kupitz, Annette Pethe, Gerhard Ulrich, Philipp Genseke, and Konrad Mohnike declare that they have no conflict of interest.

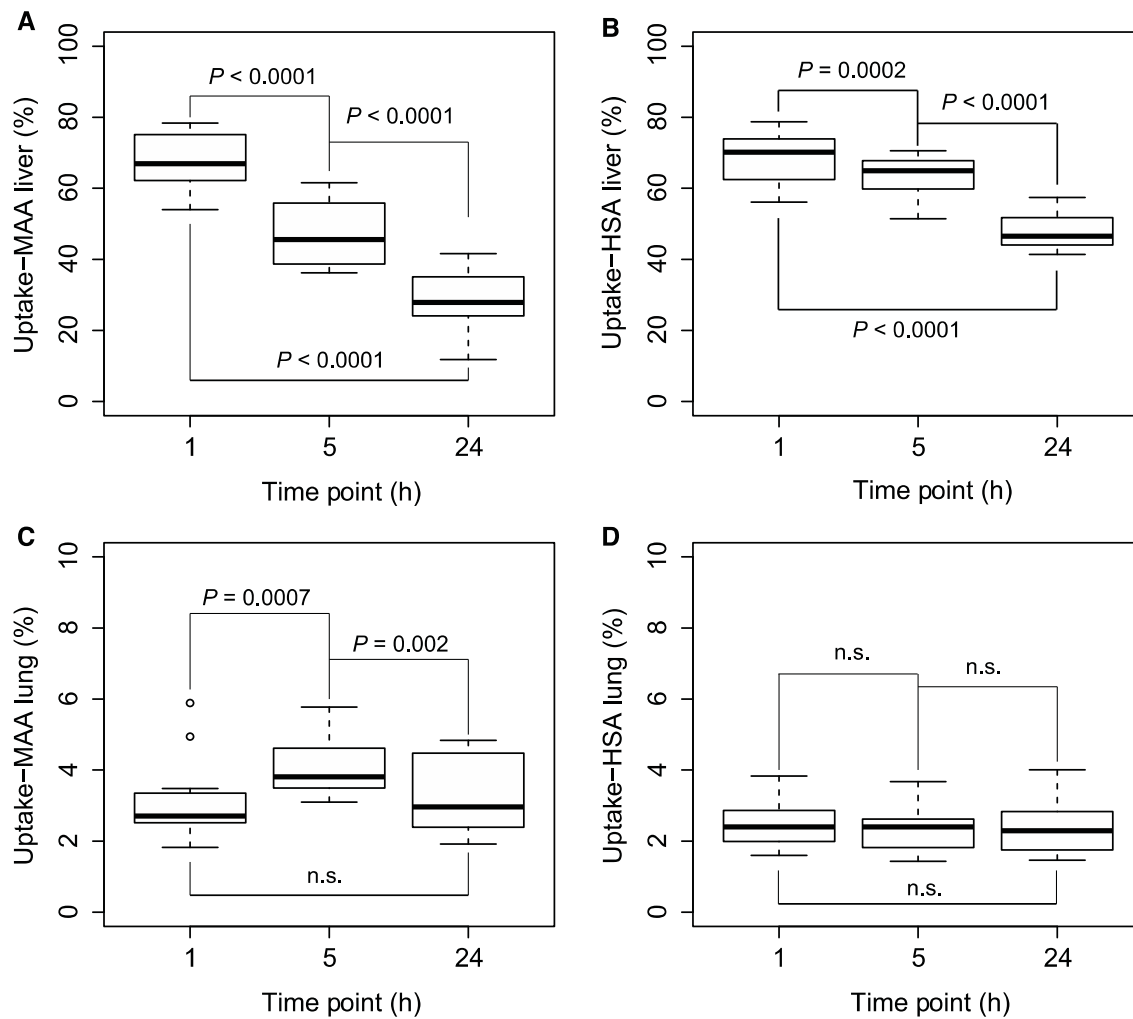
## REFERENCES:

1. Coldwell D, Sangro B, Salem R, Wasan H, Kennedy A. Radioembolization in the treatment of unresectable liver tumors: experience across a range of primary cancers. *Am J Clin Oncol*. 2012;35:167–177.
2. Riaz A, Lewandowski RJ, Kulik LM, et al. Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol*. 2009;20:1121–30.
3. Wright CL, Werner JD, Tran JM, et al. Radiation pneumonitis following yttrium-90 radioembolization: case report and literature review. *J Vasc Interv Radiol*. 2012;23:669–674.
4. Dancey JE, Shepherd FA, Paul K, et al. Treatment of nonresectable hepatocellular carcinoma with intrahepatic <sup>90</sup>Y-microspheres. *J Nucl Med*. 2000;41:1673–1681.
5. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. In *J Rad Oncol Biol Phys*. 2007;68:13–23.
6. Theysohn JM, Müller S, Schlaak JF, et al. Selective internal radiotherapy (SIRT) of hepatic tumors: how to deal with the cystic artery. *Cardiovasc Intervent Radiol*. 2012;36:1015–1022.
7. Ilhan H, Goritschan A, Paprottka P, et al. Systematic Evaluation of Tumoral <sup>99m</sup>Tc-MAA Uptake Using SPECT and SPECT/CT in 502 Patients Before <sup>90</sup>Y

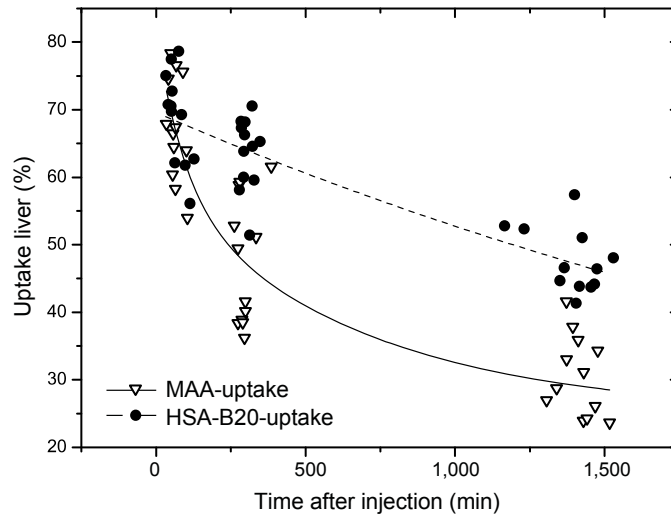
- Radioembolization. J Nucl Med. 2015;56:333–338.
8. Mallinckrodt Medical B.V. Product information TechneScan LyoMAA. May 2007.
  9. Rotop Pharma AG. Product information ROTOP-HSA Microspheres B20. Radeberg, Germany; 2008.
  10. Ahmadzadehfar H, Sabet A, Biermann K, et al. The significance of <sup>99m</sup>Tc-MAA SPECT/CT liver perfusion imaging in treatment planning for <sup>90</sup>Y-microsphere selective internal radiation treatment. J Nucl Med. 2010;51:1206–1212.
  11. SIRTEX MEDICAL Ltd. SIR-Spheres® Microspheres package insert. North Sydney, Australia; 2013.
  12. Biocompatibles UK Ltd. TheraSpheres Yttrium-90 glass microspheres: package insert. Farnham, UK; 2014.
  13. Zolle I. Technetium-99m pharmaceuticals. Berlin: Springer; 2007.
  14. Giammarile F, Bodei L, Chiesa C, et al. EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. Eur J Nucl Med Mol Imaging. 2011;38:1393–1406.
  15. Salem R, Parikh P, Atassi B, et al. Incidence of radiation pneumonitis after hepatic intra-arterial radiotherapy with yttrium-90 microspheres assuming uniform lung distribution. Am J Clin Oncol. 2008;31:431–438.
  16. Dezarn WA, Cessna JT, DeWerd LA, et al. Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality

assurance procedures for  $^{90}\text{Y}$  microsphere brachytherapy in the treatment of hepatic malignancies. *Med Phys*. 2011;38:4824–4845.

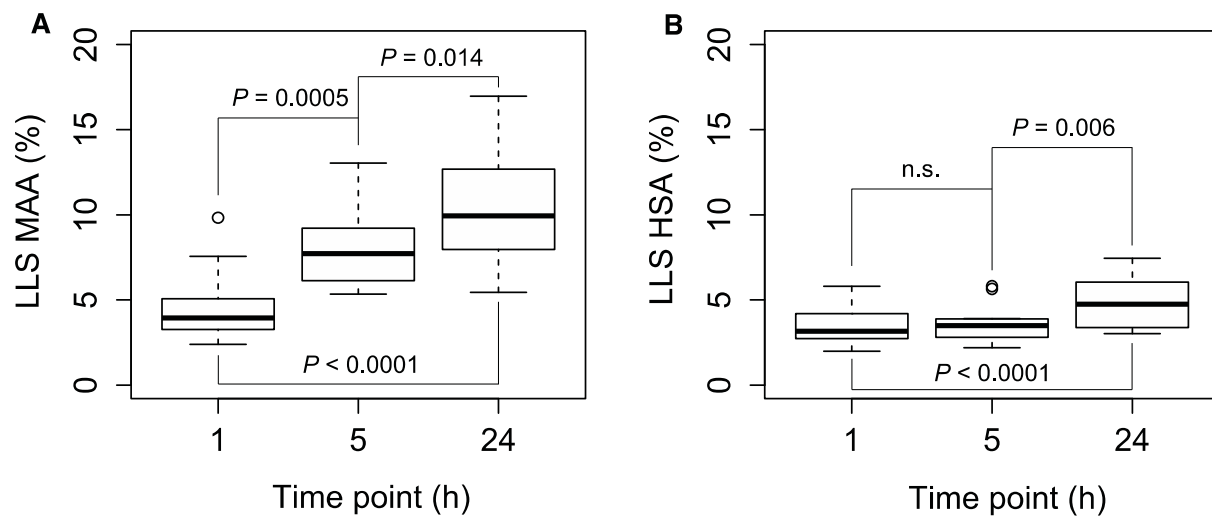
17. Blau M, Wicks R, Thomas SR, Lathrop KA. Radiation absorbed dose from albumin microspheres labeled with technetium-99m. *J Nucl Med*. 1982;23:915–917.



**FIGURE 1.** Uptake of  $^{99m}\text{Tc}$ -MAA (A, C) and  $^{99m}\text{Tc}$ -HSA (B, D) in the liver (A, B) and the lung (C, D) from PS at 1, 5, and 24 h after i.a. injection.



**FIGURE 2.** Liver uptake of MAA- and HSA-particles versus time. MAA uptake fitted by bi-exponential decay ( $T_{\text{half-live, fast}} = 7.9$  h,  $T_{\text{half-live, slow}} = 22.4$  h, adj.  $R^2 = 0.77$ ). HSA revealed a mono-exponentially decay ( $T_{\text{half-live}} = 41.7$  h, adj.  $R^2 = 0.76$ ).



**FIGURE 3.** LLS over time assessed with (A)  $^{99m}\text{Tc}$ -MAA and (B)  $^{99m}\text{Tc}$ -HSA