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The Precision of Hepatic Arterial Infusion Scintigraphy as a Quantitative Biomarker of Tumor Microvasculature

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Abstract

OBJECTIVE—Optimal clinical development of new cancer therapies targeting tumor vasculature requires new target-specific response assays. This clinical study examined the test-retest repeatability of SPECT as an in vivo assay of angiogenic hepatic tumor microvasculature using an intraarterial infusion of ^{99m}Tc-macroaggregated albumin (MAA) delivered via a hepatic artery infusion (HAI) pump.

MATERIALS AND METHODS—Patients with primary or secondary cancerous liver tumors with HAI pump-catheter implants placed for HAI chemotherapy underwent hepatic SPECT after separate arterial infusions of 37 and 185 MBq of ^{99m}Tc-MAA via an HAI pump. Quantitative measures of hepatic tumor MAA uptake were obtained from paired test-retest SPECT datasets. Repeatability was defined by quotients of paired measurands with 95% CIs and coefficients of repeatability (CRs).

RESULTS—Test-retest HAI pump SPECT yielded highly repeatable measurements in quantitative indexes of tumor microvasculature. Variability in repeat test-retest measurements was small relative to the range of observed measurements between different tumors. The total hepatic tumor microvascular MAA accumulation (percentage injected dose) proved most repeatable, with test-retest value quotients near unity (quotients: median, 1.10 ± 0.09 [SD]; range, 1.03–1.32; 95% CI, 1.07–1.19) and 1.6% CR. Tumor MAA uptake values ranged from 5% to 18% injected dose.

CONCLUSION—This article describes the precision of HAI SPECT as a quantitative biomarker of tumor microvasculature under conditions of repeatability. The results support clinical testing of HAI SPECT as a radiologic response biomarker for angiotropic tumor therapy.

Keywords

angiogenesis inhibitors; liver neoplasms; microspheres; neovascularization; pathologic neovascularization; yttrium radioisotopes

The U.S. National Cancer Institute estimates that more than 500 million people worldwide will benefit from new anticancer therapies that target tumor blood vessels [1, 2]. A phenotypic pathologic hallmark of cancerous tumors is tumor angiogenesis, a tumor-stimulated proliferation of tumor microvasculature that nourishes tumor growth [3, 4]. Systemic treatment with tumor angiogenesis inhibitors has proven efficacy for a variety of cancer types [5]. Hepatic tumor angiogenesis and perfusion derive primarily from the

hepatic arterial system, whereas normal hepatic parenchyma derives perfusion predominantly from the portal venous system. For cancer patients with hepatic tumors (primary or secondary), an increasing number of treatment regimens involve direct infusion of therapeutic agents to the liver via an arterial catheter; infusates include chemotherapeutic drugs [6], radioactive microspheres [7–9], and embolizing agents [10]. Physicians, government agencies, and commercial industries are calling for new target-specific clinical assays that can detect the *in vivo* therapeutic response of tumor microvasculature to vascular-targeted cancer treatments [2, 11, 12].

High-microvessel-density angiogenic overgrowth within hepatic tumors can be visualized at hepatic arterial infusion (HAI) scintigraphy [7–9, 13–24]. HAI scintigraphy with a nontherapeutic radiotracer infusate is commonly performed before HAI chemotherapy and radioactive microsphere therapy to ensure the infused therapeutic agent will be successfully delivered only to the intended region or regions of the liver [6, 17, 25]. The standard infusate is ^{99m}Tc -macroaggregated albumin (MAA), a radiolabeled colloid particulate approximately 25–50 μm in mean diameter [26, 27], that physically occludes the first microvascular lumen it encounters [28]. Normal microvascular precapillary hepatic arteriole diameters range from 15 to 100 μm [28]. The luminal diameter of a normal hepatic capillary is 7–15 μm , whereas tumor capillaries are more dilated [4].

A high flow of arterial infusate to tumor microvasculature (relatively greater than flow to normal hepatic parenchyma), as visualized at HAI scintigraphy before treatment, is associated with an increased likelihood of hepatic tumor response to HAI chemotherapy [14, 29] and radioembolization [30]. The accuracy of clinical HAI scintigraphy to measure hepatic tumor microvascular MAA accumulation *in vivo* has been shown by correlation with *ex vivo* assay [22]. To our knowledge, the precision of clinical HAI scintigraphy to evaluate whether HAI scintigraphy can potentially detect and quantify therapy-induced changes in hepatic tumor microvasculature has not yet been explored. In this study, we evaluated the test-retest repeatability of quantitative indexes of hepatic tumor microvasculature derived from HAI scintigraphy as prerequisite validation for the potential clinical application of HAI scintigraphy in evaluating the response of tumor microvasculature to therapy.

Materials and Methods

Patients

HAI scintigraphy studies were ordered as part of standard care and were performed according to departmental standard procedure. Data analysis was approved by the institutional review board. For this type of study, formal patient consent is not required. All procedures that are performed in studies involving human participants are performed in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Adult patients with malignant hepatic tumors who underwent placement of subcutaneous hepatic arterial pumps with attached pump catheters inserted into the proper hepatic artery via a sacrificed gastroduodenal artery (*i.e.*, Watkin's technique [31]) as part of standard care

from December 4, 2006, to January 8, 2007, were included in the study. Study subjects underwent HAI scintigraphy before beginning HAI infusion chemotherapy. HAI SPECT data for nine patients with colorectal liver metastases were obtained. One patient was excluded because of extrahepatic delivery of infusate, so the final study group was composed of eight patients.

Hepatic Arterial Infusion Pump Scintigraphy

While the patient was in a supine position on the scanner bed, the HAI pump reservoir was accessed using sterile technique and 37 MBq of MAA (volume, 2 mL) was manually infused via the HAI pump-catheter over a 3-minute period, followed by SPECT. Next, 185 MBq of MAA (volume, 2 mL) was infused over 3 minutes; SPECT was repeated using the same camera (Precedence, Philips Healthcare). SPECT was acquired using a 360° orbit, 64 azimuths, and 30 seconds per azimuth. SPECT image reconstruction used the Astonish algorithm (Philips Healthcare) with 8 iterations, 8 subsets, and a cutoff of 0.5; a Hanning filter; order and zoom of 1.00; scatter correction; no attenuation correction; and $4.66 \times 4.66 \times 4.66$ mm voxel size.

SPECT Analysis

SPECT images were analyzed by an experienced nuclear medicine physician using ImageJ software (version 1.46r, National Institutes of Health) with the NucMed plugin (J. Anthony Parker). CT or MRI liver scans obtained less than 5 days before and after SPECT as part of standard care were available for correlation. For measurements of MAA tracer accumulation in the microvasculature of tumors, tumor-free liver, and whole liver, SPECT image volumes of interest (VOIs) were delineated by digital thresholding based on voxel intensity.

The tumor-free liver VOI was defined as liver without tumorlike foci of preeminent MAA uptake on SPECT or sites of tumor visualized at CT or MRI. For uniformity in SPECT analyses between patients, the tumor-free liver VOI was empirically defined per patient as the second quartile of liver counts determined by histogram counts in a whole-liver VOI. This quantitative threshold was empirically validated per patient by digital color highlighting of liver voxels within this second quartile to visually confirm that the defined tumor-free liver VOI excluded tumor sites and hepatic regions devoid of MAA accumulation (e.g., hepatic cysts).

For uniformity in SPECT analyses between patients, four different semiautomated methods of delineating hypervascular tumors on SPECT on the basis of pixel intensity were tested. Tumor VOI boundaries were defined by applying lower count thresholds of, first, the average counts in the second quartile of tumor-free liver VOI counts; second, 3 SDs above the tumor-free liver VOI counts second-quartile average; third, the lower boundary of the top quartile of tumor counts in an initial tumor VOI; and, fourth, the lower boundary of the top half of tumor counts in an initial tumor VOI.

Voxel counts from each VOI were quantified as mean, maximum, and total values. One tumor with visually distinct focal MAA uptake was analyzed per patient. Analyzed tumors ranged in size from 4.3 to 9.2 cm. Total tumor MAA accumulation was calculated as the percentage injected dose (%ID) by the quotient obtained from the total tumor VOI counts

divided by the total (whole) liver counts multiplied by 100. For calculation of the spatial extent of a hypervascular tumor, the total number of tumor VOI voxels was multiplied by voxel size. The quotient of tumor MAA accumulation (i.e., %ID) divided by tumor hypervascular volume (cm³) was calculated. Ratios of tumor-to-liver VOI counts were calculated using all combinations of tumor and liver (including tumor-free liver and whole liver) VOI types.

For evaluation of the potential impact of residual activity from the first MAA injection contributing to SPECT images after the second MAA injection, VOI counts from the first SPECT dataset were subtracted from those of the second SPECT dataset for each VOI variable tested as a separate analysis. Adjusting measured VOI counts in the second SPECT dataset for residual counts from the first MAA injection yielded similar tumor values (differed by < 1%).

Statistics

Tumor and liver VOI radioactive counts obtained at HAI scintigraphy were statistically robust with 0.2% uncertainty in total counts for all VOI types for the initial and retest SPECT data. Paired measurements from test-retest SPECT were compared by dividing the greater value by the lesser value, with a quotient of 1.00 indicating perfect agreement, and calculating 95% CIs for each parameter. Coefficients of repeatability (CRs) were calculated using the following standard formula [32]:

$$CR = 1.96 \times \sqrt{\frac{\sum (d_2 - d_1)^2}{n}},$$

where d_2 and d_1 are paired measurands from test-retest measurements of a single patient and n is the total number of patients studied.

Results

HAI SPECT parameters with high test-test repeatability were identified with wide ranges of observed tumor values relative to CR values (Table 1). Tumor total MAA accumulation (percentage injected dose) was highly repeatable (Fig. 1) using hypervascular tumor VOI defined by tumor voxels with counts above the mean value of second-quartile liver counts. Repeat tumor percentage injected dose measurements differed by a mean quotient of 1.16 ± 0.27 (median, 1.06; range, 1.00–1.82; 95% CI, 0.97–1.35), with 1.00 indicating identical percentage injected dose values on repeat measurements. Population tumor percentage injected dose values ranged from 5% to 18% (median, 10%; mean $\pm$ SD, $10\% \pm 4\%$), with a CR of 1.6%. A change in tumor percentage injected dose of greater than 1.6% on serial HAI SPECT scans (e.g., baseline vs posttreatment) is thus predicted to not be a mere artifact of test-retest variability, under conditions of repeatability. This CR (1.6%) is small relative to the observed range of tumor percentage injected dose values (up to 18%), which indicates that HAI SPECT hypothetically can detect true biologic microvascular changes in tumor microvasculature of varying magnitudes. For example, a post-treatment decrease in tumor percentage injected dose from 18% to 15% would be a true but relatively minor change,

compared with a decrease to 0% (tumor necrosis with no uptake after treatment [e.g., see Fig. 2]). Tumor percentage injected dose using other tested tumor VOI thresholds (see Materials and Methods) yielded lower quotients of the magnitude of the range of observed tumor values (maximum – minimum) divided by CR (i.e., range/*CR*) (data not shown).

The spatial extent of hypervascular tumor (cm^3) measured at HAI SPECT was repeatable using a tumor VOI defined as the top quartile of counts in the (initial) tumor VOI. Repeat measurements differed by a mean factor of 1.09 ± 0.13 (median factor of 1.04; range, 1.00–1.38; 95% CI, 1.00–1.18). SPECT hypervascular tumor volumes averaged $49.9 \pm 41.7 \text{ cm}^3$ (range, 12.8–139.0 cm^3 ; median, 35.6 cm^3) with a CR of 10.3 cm^3 . Hypervascular tumor volume using other tested tumor VOI thresholds yielded less agreement between paired measurements (data not shown).

SPECT tumor microvascular density when considered as the quotient of tumor percentage injected dose divided by tumor hypervascular volume ($\% \text{ID}/\text{cm}^3$), using the tumor VOI thresholds described earlier, proved highly repeatable. Repeat measurements differed by a mean factor of 1.13 ± 0.09 (median factor, 1.10; range, 1.03–1.32; 95% CI, 1.07–1.19). Tumor $\% \text{ID}/\text{cm}^3$ values ranged from 0.07 $\% \text{ID}/\text{cm}^3$ to 0.75 $\% \text{ID}/\text{cm}^3$ (mean, 0.30 $\% \text{ID}/\text{cm}^3 \pm 0.20\% \text{ID}/\text{cm}^3$; median, 0.26 $\% \text{ID}/\text{cm}^3$) with a CR 0.08 $\% \text{ID}/\text{cm}^3$. This CR is small relative to the observed range of tumor $\% \text{ID}/\text{cm}^3$ values (0.68% difference [i.e., maximum – minimum]), indicating HAI SPECT can quantitatively differentiate tumors of greater microvascular density from those of lesser microvascular density.

Tumor-to-liver ratios were also evaluated as indexes for quantifying relative tumor hypervascularity. These parameters proved less repeatable than the $\% \text{ID}/\text{cm}^3$ parameter, with large CR values relative to the range of tumor-to-liver ratios observed. For example, using tumor counts from tumor VOI voxels with activity above the second quartile of tumor-free liver activity versus hepatic counts from tumor-free liver VOI voxels within the second quartile of tumor-free liver activity yielded tumor-to-liver ratios with a CR of 3.9. Tumor-to-liver ratios obtained with these VOIs ranged from 2.9 to 6.9 (median, 4.9; mean, 4.8 ± 1.7) with test-retest quotients that differed by an average factor of 1.44 ± 0.18 (median factor, 1.43; range, 1.17–1.68; 95% CI, 1.32–1.56).

Discussion

This study indicates HAI scintigraphy can provide quantitative indexes of hepatic tumor microvasculature with high precision. The clinical relevance of visualizing hepatic tumor hypervascularity at pretherapy HAI scintigraphy is well recognized: Scintigraphic tumor hypervascularity predicts tumor response to infusional chemotherapy [15, 29], radioactive microspheres [7–9], and arterial embolization [10]. However, the predictive value of pretherapy HAI scintigraphy is not a substitute for detecting response posttherapy. Daly et al. [15] showed that tumor hypervascularity before treatment indicates the potential to benefit from hepatic chemotherapy but does not guarantee tumor response. To our knowledge, no trial has investigated pre- versus posttherapy HAI scintigraphy for detecting tumor response. Detecting changes or lack of changes in tumor hypervascularity early after

treatment with angiotropic therapy might predict subsequent tumor response and positively impact patient management.

To our knowledge, this study is the first clinical study evaluating the test-retest repeatability of quantitative indexes of tumor microvasculature derived from HAI scintigraphy. In the study population, the observed ranges of values for experimental HAI SPECT indexes of tumor microvasculature were wide relative to small CR values for tumor total MAA uptake (percentage injected dose), tumor hypervascular volume (cm^3), and the derived quotient ($\%\text{ID}/\text{cm}^3$) as shown in Table 1. These results suggest HAI SPECT potentially has precision sufficient for the detection and quantification of therapy-induced changes in tumor microvasculature. The CR statistic quantifies absolute reliability measurement error in the same units as the measurement tool, providing an index of the smallest change in a measurand that represents a true change, not merely an artifact of test-retest variability [32]. Tumor percentage injected dose can be considered an index of the total mass of perfused microvasculature within a tumor. Normalizing tumor percentage injected dose to tumor volume can be viewed as a SPECT index of tumor microvascular density and provides complementary information. For example, two tumors in different patients had similar total MAA accumulation (percentage injected dose) values, but one tumor was half the size of the other. However, the smaller tumor had a $\%\text{ID}/\text{cm}^3$ quotient approximately twice that of the larger tumor consistent with denser tumor microvasculature (Fig. 2).

This study accomplished a necessary preliminary validation of the precision of HAI SPECT parameters of hepatic tumor microvasculature in a highly controlled setting. The repeat SPECT study was performed immediately after the initial SPECT study on a single scanner, patients were immobile between SPECT examinations, and each MAA dose was administered slowly via an implanted pump-catheter system (as opposed, for example, to intermittent hepatic artery catheterization using a minimally invasive approach) [33]. In this study design, intrinsic variability in hemodynamics within the hepatic arterial tree would have the greatest potential impact on intrahepatic MAA uptake and the test-retest repeatability of scintigraphic measurements. Intrahepatic distribution of MAA delivered via HAI is reported to be potentially susceptible to hemodynamic effects, such as laminar flow with slow infusions or retrograde flow artifact with rapid bolus injections [34–36]. The observed minimal test-retest repeatability of hepatic tumor MAA uptake indicates that intrinsic variability in hemodynamics within the hepatic vascular tree has minimal impact on the potential use of HAI scintigraphy as a radiologic biomarker of tumor microvasculature.

The results presented here show the precision of HAI scintigraphy under conditions of repeatability with optimal control of variables that might affect MAA delivery and scintigraphic measurements. If poor results had been obtained, further study would not have been warranted, but only a small study population was required to show the high precision of HAI scintigraphic measurements of tumor microvasculature, under these conditions. The high-precision results obtained provide a clear justification for prospective study of the precision of HAI scintigraphy when performed on separate dates and with other HAI approaches.

Conclusion

This study provides preliminary clinical validation of the precision of HAI scintigraphy as a quantitative radiologic biomarker of tumor microvasculature under conditions of repeatability. Quantitative scintigraphic biomarker measurements of tumor microvasculature showed a wide range of observed tumor values with small CR values, indicating the potential clinical use of HAI scintigraphy for detecting and quantifying therapy-induced changes in tumor microvasculature.

Acknowledgments

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References

1. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med*. 1971; 285:1182–1186. [PubMed: 4938153]
2. National Cancer Institute. Angiogenesis initiative fueling collaboration. *NCI Cancer Bulletin*. Feb 28.2006 3
3. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000; 100:57–70. [PubMed: 10647931]
4. Folkman, J., Kalluri, R. Tumor angiogenesis. In: Kufe, D.Pollock, R.Weichselbaum, R.Bast, R., JrHolland, J., Frei, E., III, editors. *Cancer medicine*. Hamilton, ON, Canada: BC Decker; 2003. p. 161-194.
5. Zhao Y, Adjei AA. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. *Oncologist*. 2015; 20:660–673. [PubMed: 26001391]
6. Power DG, Healey-Bird BR, Kemeny NE. Regional chemotherapy for liver-limited metastatic colorectal cancer. *Clin Colorectal Cancer*. 2008; 7:247–259. [PubMed: 18650193]
7. Ho S, Lau WY, Leung TW, et al. Tumour-to-normal uptake ratio of ⁹⁰Y microspheres in hepatic cancer assessed with Tc99m macroaggregated albumin. *Br J Radiol*. 1997; 70:823–828. [PubMed: 9486047]
8. Gulec SA, Mesoloras G, Dezarn WA, McNeillie P, Kennedy AS. Safety and efficacy of Y-90 microsphere treatment in patients with primary and metastatic liver cancer: the tumor selectivity of the treatment as a function of tumor to liver flow ratio. *J Transl Med*. 2007; 5:15. [PubMed: 17359531]
9. Ho S, Lau WY, Leung TW, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. *Eur J Nucl Med*. 1996; 23:947–952. [PubMed: 8753684]
10. Civalleri D, Scopinaro G, Balletto N, et al. Changes in vascularity of liver tumours after hepatic arterial embolization with degradable starch microspheres. *Br J Surg*. 1989; 76:699–703. [PubMed: 2765804]
11. Brower V. Evidence of efficacy: researchers investigating markers for angiogenesis inhibitors. *J Natl Cancer Inst*. 2003; 95:1425–1427. [PubMed: 14519742]
12. Food US Drug Administration. Memorandum of understanding between the United States Food and Drug Administration, the National Cancer Institute, and the Centers for Medicare and Medicaid Services. 2006Memorandum of understanding number 225-06-8001
13. Ridge JA, Bading JR, Gelbard AS, Benua RS, Daly JM. Perfusion of colorectal hepatic metastases: relative distribution of flow from the hepatic artery and portal vein. *Cancer*. 1987; 59:1547–1553. [PubMed: 3828954]
14. Sigurdson ER, Ridge JA, Kemeny N, Daly JM. Tumor and liver drug uptake following hepatic artery and portal vein infusion. *J Clin Oncol*. 1987; 5:1836–1840. [PubMed: 3681370]
15. Daly JM, Butler J, Kemeny N, et al. Predicting tumor response in patients with colorectal hepatic metastases. *Ann Surg*. 1985; 202:384–393. [PubMed: 2931055]

16. Gyves JW, Ziessman HA, Ensminger WD, et al. Definition of hepatic tumor microcirculation by single photon emission computerized tomography (SPECT). *J Nucl Med*. 1984; 25:972–977. [PubMed: 6088735]
17. Ziessman HA, Thrall JH, Yang PJ, et al. Hepatic arterial perfusion scintigraphy with Tc-99m-MAA: use of a totally implanted drug delivery system. *Radiology*. 1984; 152:167–172. [PubMed: 6233632]
18. Vogel SB, Drane WE, Ros PR, Kerns SR, Bland KI. Prediction of surgical resectability in patients with hepatic colorectal metastases. *Ann Surg*. 1994; 219:508–516. [PubMed: 8185401]
19. Bledin AG, Kantarjian HM, Kim EE, et al. Tc99m-labeled macroaggregated albumin in intrahepatic arterial chemotherapy. *AJR*. 1982; 139:711–715. [PubMed: 6214932]
20. Goldberg JA, Bradnam MS, Kerr DJ, et al. Single photon emission computed tomographic studies (SPECT) of hepatic arterial perfusion scintigraphy (HAPS) in patients with colorectal liver metastases: improved tumour targeting by microspheres with angiotensin II. *Nucl Med Commun*. 1987; 8:1025–1032. [PubMed: 3502422]
21. Kerr DJ, Goldberg JA, Anderson JR, et al. The effect of angiotensin II on tumor blood flow and the delivery of microparticulate cytotoxic drugs. *EXS*. 1992; 61:339–345. [PubMed: 1617236]
22. Lau WY, Leung TW, Ho S, et al. Diagnostic pharmaco-scintigraphy with hepatic intra-arterial technetium-99m macroaggregated albumin in the determination of tumour to non-tumour uptake ratio in hepatocellular carcinoma. *Br J Radiol*. 1994; 67:136–139. [PubMed: 8130973]
23. Leung TW, Lau WY, Ho SK, et al. Determination of tumour vascularity using selective hepatic angiography as compared with intrahepatic-arterial technetium-99m macroaggregated albumin scan in hepatocellular carcinoma. *Cancer Chemother Pharmacol*. 1994; 33(suppl):S33–S36. [PubMed: 8137482]
24. Andrews JC, Walker-Andrews SC, Juni JE, Warber S, Ensminger WD. Modulation of liver tumor blood flow with hepatic arterial epinephrine: a SPECT study. *Radiology*. 1989; 173:645–647. [PubMed: 2813766]
25. Hildebrandt B, Pech M, Nicolaou A, et al. Interventionally implanted port catheter systems for hepatic arterial infusion of chemotherapy in patients with colorectal liver metastases: a phase II study and historical comparison with the surgical approach. *BMC Cancer*. 2007; 7:69. [PubMed: 17456240]
26. Hung JC, Redfern MG, Mahoney DW, Thorson LM, Wiseman GA. Evaluation of macroaggregated albumin particle sizes for use in pulmonary shunt patient studies. *J Am Pharm Assoc (Wash)*. 2000; 40:46–51. [PubMed: 10665249]
27. Mallol J, Diaz RV. Particle size and its mathematical distribution in six human albumin macroaggregate (MAA) kits. *Nucl Med Commun*. 1997; 18:87–88. [PubMed: 9061708]
28. Rappaport AM. Hepatic blood flow: morphologic aspects and physiologic regulation. *Int Rev Physiol*. 1980; 21:1–63. [PubMed: 6993392]
29. Kaplan WD, Ensminger WD, Come SE, et al. Radionuclide angiography to predict patient response to hepatic artery chemotherapy. *Cancer Treat Rep*. 1980; 64:1217–1222. [PubMed: 7471113]
30. Garin E, Lenoir L, Rolland Y, et al. Dosimetry based on Tc99m-macroaggregated albumin SPECT/CT accurately predicts tumor response and survival in hepatocellular carcinoma patients treated with Y90-loaded glass microspheres: preliminary results. *J Nucl Med*. 2012; 53:255–263. [PubMed: 22302962]
31. Watkins E Jr, Khazei AM, Nahra KS. Surgical basis for arterial infusion chemotherapy of disseminated carcinoma of the liver. *Surg Gynecol Obstet*. 1970; 130:581–605. [PubMed: 5436597]
32. Vaz S, Falkmer T, Passmore AE, Parsons R, Andreou P. The case for using the repeatability coefficient when calculating test-retest reliability. *PLoS One*. 2013; 8:e73990. [PubMed: 24040139]
33. Kaplan WD, D’Orsi CJ, Ensminger WD, Smith EH, Levin DC. Intra-arterial radionuclide infusion: a new technique to assess chemotherapy perfusion patterns. *Cancer Treat Rep*. 1978; 62:699–703. [PubMed: 657155]

34. Borzutzky CA, Turbiner EH. The predictive value of hepatic artery perfusion scintigraphy. *J Nucl Med.* 1985; 26:1153–1156. [PubMed: 2931505]
35. Ricke J, Hildebrandt B, Miersch A, et al. Hepatic arterial port systems for treatment of liver metastases: factors affecting patency and adverse events. *J Vasc Interv Radiol.* 2004; 15:825–833. [PubMed: 15297586]
36. Copur MS, Capadano M, Lynch J, et al. Alternating hepatic arterial infusion and systemic chemotherapy for liver metastases from colorectal cancer: a phase II trial using intermittent percutaneous hepatic arterial access. *J Clin Oncol.* 2001; 19:2404–2412. [PubMed: 11331319]

Fig. 1.

Paired test-retest hepatic arterial infusion (HAI) scintigraphic measurements of hepatic tumor macroaggregated albumin (MAA) uptake quantified as percentage injected dose (%ID) of radiotracer. For each patient (*x*-axis), tumor microvascular MAA-uptake is plotted (*y*-axis) as quantified by first SPECT examination (*diamonds*) and repeat SPECT examination (*boxes*).

Fig. 2.

Hepatic tumors in two patients with colorectal cancer metastases to liver.

A–D, Transaxial ^{99m}Tc –macroaggregated albumin (MAA) hepatic arterial infusion (HAI) SPECT image (**A**) and corresponding axial CT image (**B**) of 61-year-old man and transaxial ^{99m}Tc -MAA HAI SPECT image (**C**) and corresponding axial CT image (**D**) of 42-year-old woman. Dense microvasculature in periphery of hepatic tumors is visualized as rings of concentrated ^{99m}Tc -MAA (*arrows*, **A** and **C**). Tumors show center devoid of ^{99m}Tc -MAA, which is consistent with nonperfused necrotic cores. One patient had small tumor (4.3×4.0 cm) (*arrow*, **B**); other patient had larger tumor (9.2×7.8 cm) (*arrows*, **D**). Both tumors had similar total ^{99m}Tc -MAA uptake (tumor percentage injected dose [%ID] values); however, small tumor had higher concentration of ^{99m}Tc -MAA uptake (%ID/cm³) consistent with higher tumor microvessel density.

TABLE 1
Investigational Quantitative Scintigraphic Parameters of Tumor Microvasculature Obtained From Hepatic Arterial Infusion SPECT

Parameter	Observed Values		Mean Test-Retest Quotient (95% CI)	CR of Paired Test-Retest SPECT Measurements for Tumors	Range/CR ^a
	Mean $\pm$ SD	Range			
Percentage injected dose (%ID)	10 $\pm$ 4	5–18	1.16 (0.97–1.35)	1.6	9.5
Tumor hypervascular volume (cm ³)	49.9 $\pm$ 41.7	12.8–139.0	1.09 (1.00–1.18)	10.3	12.3
Quotient ^b (%ID/cm ³)	0.30 $\pm$ 0.20	0.07–0.75	1.13 (1.07–1.19)	0.08	8.1
Relative amount of MAA accumulation in equal volumes of tumor vs normal liver (tumor-to-liver ratio)	4.8 $\pm$ 1.7	2.9–6.9	1.44 (1.32–1.56)	3.9	1.0

Note—CR = coefficient of repeatability, MAA = macroaggregated albumin.

^aQuotient of the magnitude of the range of observed tumor values (maximum – minimum) divided by CR.

^bQuotient of tumor total MAA accumulation (%ID) and tumor hypervascular volume (cm³).