Lipiodol Deposition and Washout in Primary and Metastatic Liver Tumors After Chemoembolization

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Abstract. *Background/Aim:* Lipiodol is the key component of conventional trans-arterial chemoembolization. Our aim was to evaluate lipiodol deposition and washout rate after conventional trans-arterial chemoembolization in intrahepatic cholangiocarcinoma and hepatic metastases originating from neuroendocrine tumors and colorectal carcinoma. *Patients and Methods:* This was a retrospective analysis of 44 patients with intrahepatic cholangiocarcinoma and liver metastasis from neuroendocrine tumors or colorectal carcinoma who underwent conventional trans-arterial chemoembolization. Lipiodol volume (cm³) was analyzed on non-contrast computed tomography imaging obtained within 24 h post conventional trans-arterial chemoembolization, and 40-220 days after conventional trans-arterial chemoembolization using volumetric image analysis software. Tumor response was assessed on contrast-enhanced magnetic resonance imaging 1 month after conventional trans-arterial chemoembolization.

Results: The washout rate was longer for neuroendocrine tumors compared to colorectal carcinoma, with half-lives of 54.61 days ($p<0.00001$) and 19.39 days ($p<0.001$), respectively, with no exponential washout among intrahepatic cholangiocarcinomas ($p=0.83$). The half-life for lipiodol washout was longer in tumors larger than 300 cm³ compared to smaller tumors (25.43 vs. 22.71 days). Lipiodol wash out half-life was 54.76 days ($p<0.01$) and 29.45 days ($p<0.00001$) for tumors with a contrast enhancement burden of 60% or more and less than 60%, respectively. A negative exponential relationship for lipiodol washout was observed in non-responders ($p<0.00001$). *Conclusion:* Lipiodol washout is a time-dependent process, and occurs faster in colorectal carcinoma tumors, tumors smaller than 300 cm³, tumors with baseline contrast enhancement burden of less than 60%, and non-responding target lesions.

Lipiodol is the key component of conventional trans-arterial chemoembolization (cTACE) for primary and metastatic liver tumors (1, 2). This agent serves as a tumor-seeking, embolic and drug carrier agent, and is used in combination with chemotherapy for cTACE (3). In addition, the radiopacity of lipiodol helps to easily visualize and track it (4, 5). It has been shown that lipiodol retention in the treated tumor is related to tumor necrosis (6). Therefore, it could be considered as an imaging surrogate for response (7). While there are different one-dimensional (1D), two-dimensional

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Figure 1. *Treatment and Imaging sequence. This timeline illustrates the sequence of imaging and treatment with conventional trans-arterial chemoembolization (cTACE) was performed. CT: Computed tomography.*

(2D), and three-dimensional (3D) methods to measure tumor response and lipiodol deposition, 3D or volumetric methods are more accurate for measuring lipiodol deposition within the targeted tumor (8).

Quantitative 3D metrics for tumor enhancement according to the European Association for the Study of the Liver (qEASL) have been introduced for evaluation and prediction of tumor response and survival (9), and have been shown to be better than 1D and 2D metrics in various tumor types, including neuroendocrine (NET), colorectal carcinoma (CRC) and hepatocellular carcinoma (HCC) (10-14). The qEASL metrics can be used for measurements of lipiodol deposition (15, 16). Our team previously showed that lipiodol deposition is higher in patients with HCC who responded to cTACE on both conventional and cone-beam computed tomography (CT) (8, 11). The degree of lipiodol deposition after cTACE in patients with NET was recently shown to predict response (17), although it is still unknown if lipiodol deposition is also a predictor of response in hepatic cholangiocarcinoma and liver metastases from colorectal tumors. Moreover, the rate of lipiodol washout (beyond absolute lipiodol uptake) has not been rigorously investigated as a potential indicator of response (18). A relationship between the rate of lipiodol washout and tumor response was first shown in a VX2 rabbit model of HCC (3). Tumor cells that remained viable after TACE showed washout of lipiodol through lysosomes, whereas dead tumor cells showed intra-cellular retention of small lipiodol droplets.

The objective of this study was to quantitatively measure lipiodol deposition and its washout rate after cTACE in patients with intrahepatic cholangiocarcinoma (ICC), hepatic metastasis from NET, and CRC.

Patients and Methods

Study design. This retrospective analysis of cases enrolled patients from three different clinical trials currently running at Yale New Haven Hospital (NCT02753881, NCT01877187, and NCT02994251). These trials are Institutional Review Board-approved, and the retrospective data review required for this study was compliant with the Institutional policy.

Study population. All patients were reviewed in our multidisciplinary Liver Tumor Board and referred for cTACE.

Inclusion criteria were: i) Intrahepatic cholangiocarcinoma or hepatic metastases from NET or CRC treated with cTACE; ii). non-contrast CT scan within 24 h after cTACE; iii). at least one follow-up non-contrast CT scan; iv). multiphasic contrast-enhanced MRI study 8 to 12 weeks after the first cTACE. Figure 1 demonstrates the study flow chart and sequence of CT and MRI studies in relation to cTACE.

Conventional trans-arterial chemoembolization protocol. All treatments were cTACE procedures performed by one of two interventional radiologists (K.H. and C.G.), each with more than 15 years of experience in intra-arterial hepatic interventions. According to our institutional standard protocol (1), cTACE was performed using an approximately 1-to-1 mixture of 10 cc lipiodol (Lipiodol; Guerbet, France) and water-soluble chemotherapy cocktail. The latter included 50 mg doxorubicin (Adriamycin; Pharmacia & Upjohn, Peapack, NJ, USA) and 10 mg mitomycin C (Intas Pharmaceuticals Limited, Pharmez, Ahmedabad, India). All cTACE procedures were followed by administration of Embospheres (diameter 100-300 μ m; Merit Medical Co., South Jordan, UT, USA) to near stasis. The angiographic and embolization steps have been reported before (11, 12, 19, 20). Patients were either treated with selective (lobar or segmental) or super-selective injections.

CT scan. Multidetector CT images were acquired on a 64-slice CT scanner (Somatom Sensation 64, Siemens Medical Solutions, Erlangen, Germany) approximately 24 h after the cTACE procedure and prior to discharge. Only non-contrast CT scans were obtained based on the study standard abdomen protocol using the following parameters: 120 kVp acquisitions, 545 mA, scan speed, 0.33 s/revolution; detector collimation, 0.6 mm/row; helical pitch factor, 0.575/revolution. After that, image reconstruction was performed using body kernel B30f, with a field of view of 400 $\times$ 400 $\times$ 220 mm (matrix size of 512 $\times$ 512 $\times$ 300) with a voxel size of 0.78 mm³.

MRI. MRI of the abdomen was obtained using a standardized MRI protocol for liver masses in all patients on a 1.5-Tesla scanner (Siemens Magnetom Avanto; Siemens, Erlangen, Germany) with a phased array torso coil (repetition time 5.77 ms/echo time 2.77 ms; field of view 320-400 mm; matrix, 192 $\times$ 160; slice thickness, 2.5 mm; receiver bandwidth, 64 kHz; flip angle, 10 $^\circ$). The protocol included single-shot breath-hold gradient-echo diffusion-weighted echo-planar images in the axial dimension, axial T2-weighted fast spin-echo images, and unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadopentetate; Magnevist; Bayer, Wayne, NJ, USA) breath-hold axial T1-weighted 3D fat-suppressed spoiled gradient-echo images in the hepatic arterial phase (20 s after contrast injection), portal venous phase (70 s after contrast injection) and delayed phase (180 s after contrast injection).

Figure 2. A: Magnetic resonance imaging (MRI), segmentation of liver tumors and analysis of quantitative 3D European Association for the Study of the Liver metrics (qEASL). This figure demonstrates 2D and volumetric tumor segmentation and qEASL evaluation of the volume of tumor enhancement prior to conventional trans-arterial chemoembolization (cTACE) and in follow-up MRI studies. B: Computed tomographic imaging, and lipiodol deposition segmentation, and qEASL analysis. This figure demonstrates 2D and volumetric tumor segmentation and qEASL evaluation of lipiodol deposition pre cTACE and in follow-up computed tomography.

Image analysis. Measurements according to the response evaluation criteria in solid tumors (RECIST) and modified response evaluation criteria in solid tumors (mRECIST) metrics (21), as well as volumetric segmentation of the liver and targeted tumor, were carried out by a radiology resident (N.N., with 4.5 years of experience in abdominal MRI). All measurements were conducted using standard electronic calipers using Digital Imaging in Communications and Medicine files. To measure the diameter and area of tumor contrast enhancement, the reader re-evaluated the images in their different phases to distinguish the true extent of tumor burden. For 1D measurements, the two largest enhanced lesions were assessed. The arterial phase was used for NET, the venous phase was evaluated for CRC and the delayed phase for ICC.

A prototype 3D quantitative semiautomatic tumor analysis software (Medisys; Philips Research, Suresnes, France) was used for volumetric tumor assessment (9). 3D Segmentation masks of the tumors were created by three readers (I.R., J.M.M.v.B., and M.A.M.) each with 1 year of experience using the 3D tumor analysis program. The readers were supervised by a radiologist (N.N.). The area within the segmented mask was considered the total tumor volume measured in cubic centimeters. The volume of tumor enhancement (cm^3) was calculated by qEASL calculation, which has been described before in detail (9). Briefly, axial non-contrast and corresponding contrast-enhanced phases of MRI T1-weighted images were uploaded to the software. After subtraction, feeding the 3D tumor segmentation mask of the tumors, and placing a region of interest within healthy liver parenchyma, the software generated a color map of the enhanced tissue within the segmented 3D tumor mask automatically, with not enhanced, *i.e.*, necrotic, areas of the tumor being represented in blue and enhanced and thus viable parts of the tumor being represented in red (Figure 2A). The software also calculated the volume of tumor enhancement automatically.

A decrease of 65% or more in the volume of tumor enhancement on MRI was considered a response to cTACE (22). The same segmentation method was used to determine lipiodol deposition

(cm^3) using CT images (Figure 2B). Here, radiopaque lipiodol was represented by hyperdense voxels, in contrast to the previously mentioned MRI scans where hyperintense voxels represented the inflow of the contrast agent (*i.e.*, viable tissue).

The following formula was used for evaluation of lipiodol washout on non-contrast CT, and the result was calculated as the average change in lipiodol volume (cm^3) per day given by (*i.e.*, the slope) (2):

$$\lambda = \Delta V / \Delta t$$

where λ was the change in tumor lipiodol volume between the first (within 24 h of cTACE) and follow-up non-contrast CT, and was the follow-up time in days.

Statistical analysis. Statistical analysis and data management was performed to find the most significant cutoff values for tumor size and enhancing tumor volume while looking into the lipiodol deposition and washout. For comparison of groups, the Mann-Whitney *U*-test and Kruskal-Wallis tests were used, the former for pairwise comparisons, the latter for multiple comparisons. Additionally, non-parametric bootstrapped exponential regression was used to evaluate the existence of an exponential washout rate over time over various strata. Lastly, a non-parametric bootstrap was used to evaluate the Pearson correlation between lipiodol deposition and tumor volume. For both bootstrap estimates, 100,000 bootstrap samples were conducted. Bootstrapping was employed to overcome the small sample size and allow for valid asymptotic estimation of the parameters. Throughout, a *p*-value of less than 0.05 was considered statistically significant.

Results

Study population characteristics. The studied patients were a typical cohort population (Table I) with a median overall survival of 10 months and a median number of cTACE treatments of two sessions per patient. Six (25%) patients

Table I. Demographic characteristics of the studied population.

Variable		Value
Gender, n (%)	Male/female	14/10 (58.3%/41.7%)
Age	Mean±SD	59.63±14.36
Ethnicity, n (%)	White	20 (83.3%)
	African American	1 (4.2%)
	Asian	3 (12.5%)
Median overall survival	Months, range	10.00 (3-81)
ECOG	0	18
	1	6
Number of cTACE	Median (range)	2 (1-6)
Laboratory findings	Serum bilirubin, mg/dl	0.65±0.37
	Serum bilirubin, mg/dl	3.93±0.49
	INR	1.00±0.08
Ascites, n (%)	Yes	5 (20.8%)
Encephalopathy, n (%)	Yes	0 (0%)

cTACE: Conventional trans-arterial chemoembolization; ECOG: Eastern Cooperative Oncology Group; INR: international normal ratio; SD: standard deviation.

had ICC, four (16.67%) patients had NET and 14 (58.33%) patients had CRC. Nine patients had a single lesion, while 15 patients had multiple hepatic lesions. While single target lesions were analyzed in all patients with ICC and NET, two different target lesions were analyzed in three patients with CRC; in total, six (22.22%) ICC, four (14.82%) NET and 17 (62.96%) CRC target lesions were evaluated.

Baseline liver, tumor and lipiodol measurements. Table II demonstrates the baseline liver volume, largest tumor diameter, largest diameter of tumor enhancement, tumor volume, volume of contrasted-enhanced tumor based on tumor types and post cTACE response. Lipiodol volume within the tumor and the percentage of coverage is also shown in Table II, based on tumor type and post cTACE response.

Lipiodol washout. There was a negative exponential relationship between the lipiodol washout rate and the time interval between the initial and follow-up lipiodol imaging ($p<0.0001$; Figure 3) for all tumors. This exponential curve showed lipiodol washout to be a time-dependent process with an estimated half-life of 23.09 days [95% confidence interval (CI)=20.34-25.85 days].

Lipiodol deposition and washout based on tumor type. No significant differences were identified in the volume of lipiodol deposition between NET, CRC, and ICC ($p=0.96$; Figure 4A). However, the lipiodol washout rate was different between different types of tumors ($p<0.001$; Figure 4B-D). No exponential relationship with respect to time was observed in the washout rate among ICC tumors ($p=0.83$). However, an exponential relationship was observed for CRC

Figure 3. Tumor lipiodol washout for the entire cohort. This exponential curve shows lipiodol washout is a time-dependent process, with R^2 of 0.78. Dotted lines indicate the 95% confidence interval of the fitted line.

($p<0.0001$) and NET ($p<0.001$). The lipiodol washout rate was slower in NET than in CRC, with half-lives for lipiodol washout of 54.61 days (95% CI=42.63-75.97 days) and 19.39 days (95% CI=17.56-21.64 days), respectively.

Lipiodol deposition and washout based on tumor size. There was a direct linear correlation between lipiodol deposition and tumor size (Pearson correlation $r=0.63$, $p<0.01$). The tumor volume of 300 cm³ was determined as the most significant cutoff value to differentiate for lipiodol deposition based on tumor size. Lipiodol deposition was significantly higher in tumors larger than 300 cm³ ($p=0.031$; Figure 5A). In both groups (≥ 300 cm³ and <300 cm³), a negative exponential relationship was observed over time for the lipiodol washout rate ($p<0.00001$, Figure 5B; and $p<0.01$, Figure 5C, respectively). In patients with tumors 300 cm³ or larger, the lipiodol washout half-life was 25.43 days (95% CI=18.32-41.54 days), while it was 22.71 days (95% CI=20.27-25.80) in smaller tumors.

Lipiodol deposition and washout based on tumor enhancement burden. Based on receiver operating characteristics analysis, a tumor enhancement burden of 60% was determined as the most significant cutoff value to detect differences in lipiodol deposition. Lipiodol deposition was moderately higher in tumors with tumor enhancement burden of 60% or higher than when compared to tumors with lower tumor enhancement burden ($p=0.067$, Figure 6A).

In both groups (tumor enhancement burden $\geq 60\%$ and $<60\%$), a negative exponential relationship was observed over time in lipiodol washout ($p<0.01$; Figure 6B) and ($p<0.0001$; Figure 6C), respectively. In particular, in patients

Table II. Baseline liver volume, tumor and lipiodol measurements (mean $\pm$ SD).

Variable	Total	Tumor type			Response status	
		ICC	NET	CRC	Response	No response
Liver volume, cm ³	2,268.9 $\pm$ 923.62	2,234.0 $\pm$ 961.9	2,946.5 $\pm$ 3.5	2,173.5 $\pm$ 979.2	2,427.3 $\pm$ 1,550.2	2,229.4 $\pm$ 769.2
Tumor largest diameter, cm	12.6 $\pm$ 4.0	13.0 $\pm$ 5.1	13.2 $\pm$ 1.5	12.4 $\pm$ 3.9	10.0 $\pm$ 4.0	12.8 $\pm$ 3.6
Enhancement, largest diameter, cm	7.0 $\pm$ 1.9	7.1 $\pm$ 2.6	8.9 $\pm$ 1.4	6.7 $\pm$ 1.5	5.4 $\pm$ 2.6	7.4 $\pm$ 1.4
Tumor volume, cm ³	751.6 $\pm$ 770.0	1,047.5 $\pm$ 975.2	1,349.3 $\pm$ 529.8	553.6 $\pm$ 664.4	772.1 $\pm$ 1,139.3	779.3 $\pm$ 715.9
Enhancement volume, cm ³	248.7 $\pm$ 254.0	406.0 $\pm$ 315.9	666.5 $\pm$ 45.1	130.2 $\pm$ 122.6	86.4 $\pm$ 77.4	309.7 $\pm$ 280.8
Tumor lipiodol volume, cm ³	235.9 $\pm$ 211.0	198.4 $\pm$ 112.6	215.0 $\pm$ 223.9	254.2 $\pm$ 240.8	228.1 $\pm$ 263.1	246.5 $\pm$ 214.4
Tumor lipiodol coverage, %	49.8 $\pm$ 23.4	43.9 $\pm$ 18.9	50.3 $\pm$ 44.4	51.7 $\pm$ 19.9	41.6 $\pm$ 20.5	48.5 $\pm$ 18.0

CRC: Colorectal carcinoma; ICC: intrahepatic cholangiocarcinoma; NET: neuroendocrine tumor; SD: standard deviation.

Figure 4. Tumor lipiodol deposition and washout based on tumor type. A: Lipiodol deposition was not different between colorectal cancer (CRC), intrahepatic cholangiocarcinoma (ICC), and neuroendocrine tumor (NET). The lipiodol washout curves for CRC (B), NET (C), and ICC (D) had R^2 of 0.8985, 0.8909, and 0.0322, respectively. Dotted lines indicate the 95% confidence interval of the fitted line. No fit is provided for ICC given the absence of an exponential relationship.

Figure 5. Lipiodol deposition and washout based on tumor volume. A: The lipiodol deposition was greater in tumors larger than 300 cm³. Using a tumor volume cut-off of 300 cm³ patients were divided into groups with ≥300 cm³ (B) and <300 cm³ (C), with R² of 0.8496 and 0.5731, respectively. Dotted lines indicate the 95% confidence interval of the fitted line.

with 60% or more tumor enhancement burden, the lipiodol washout half-life was 54.76 days (95% CI=34.76-130.18 days), while lipiodol washout half-life was 29.45 (95% CI=26.03-33.92 days) in patients with less than 60% tumor enhancement burden. Furthermore, the absence of an overlap between CIs for the two groups suggests that patients with a tumor enhancement burden of greater than 60% had a statistically higher washout half-life.

Lipiodol washout and response. Based on both mRECIST and qEASL criteria, 5 (22.7%) target lesions showed response to cTACE.

The lipiodol deposition in responders was not significantly higher than the deposition in non-responders ($p=0.19$; Figure 7A). There was no statistically significant exponential fit for

the responders ($p=0.20$; Figure 7B). In contrast, among the non-responders, a statistically significant negative exponential washout rate was observed ($p<0.00001$; Figure 7C). Correspondingly, the lipiodol half-life in non-responders was found to be 34.42 days (95% CI=28.30-43.93 days).

Discussion

Our findings showed that lipiodol washout is a time-dependent process which proceeds in a negative exponential pattern, *i.e.*, a faster initial washout phase followed by a later slower washout phase. Lipiodol is an oil-based contrast medium composed of fatty acid ethylic esters conjugated with iodine (37-48% concentration) (23). The mechanism of selective deposition of lipiodol inside hepatic primary and

Figure 6. Tumor lipiodol deposition and washout based on the burden of tumor enhancement. A: Tumor lipiodol deposition was higher in tumors with an enhancement burden of 60% or greater. Lipiodol washout based on tumor enhancement burden of $\geq 60\%$ (B) and $< 60\%$ (C) had R^2 of 0.8283 and 0.7459, respectively. Dotted lines indicate the 95% confidence interval of the fitted line.

metastatic tumors is only partially known. Hepatic tumors have a different degree of vascularization based on their nature and self-promoting angiogenesis. These tumors are usually vascularized with arterial supply mediated by the secretion of factors such as vascular endothelial growth factor. Tumor arterial supply dominates over portal venous supply with progressive involution creating a ‘siphon effect’. This increased tumor neo-vascularity has an affinity for lipiodol (24, 25). Furthermore, arterial vessels produced through tumor neo-angiogenesis are tortuous and irregular, with their caliber moderately increased and segments lacking *tunica muscularis*. This anomalous neo-angiogenesis allows leakage of contrast into the perivascular, intercellular space (25). Lastly, during neoplastic transformation, the plasma membrane may undergo a biochemical modification,

rendering it more lipophilic; this would favor adhesion of lipiodol to the membrane and its subsequent endocytosis into neoplastic cells (26). A combination of these changes results in varying degrees of lipiodol deposition and washout within the tumor, which is best imaged on CT scans post cTACE.

Lipiodol washout from embolized lesions occurs slowly because of insufficient portal vascularization (the main mechanism responsible for non-neoplastic washout), absence of reticuloendothelial cells such as Kupffer cells, and lack of lymphatic vessels (5, 27). These histopathological characteristics are different in various tumor types. Our findings showed that the rate of lipiodol washout followed a negative exponential curve, *i.e.*, a faster initial phase followed by a later slower phase. In addition, we demonstrated that the lipiodol washout rate was fastest in CRCs as compared to

Figure 7. Tumor lipiodol washout rate for the entire cohort based on response to conventional trans-arterial chemoembolization (cTACE). A: Lipiodol deposition was not significantly different between the responders and non-responders. Tumor lipiodol washout rate for the entire cohort for (B) responders and (C) non-responders, with R^2 of 0.3792 and 0.6866, respectively. Dotted lines indicate the 95% confidence interval of the fitted line. No fit is provided for non-responders given the absence of an exponential relationship.

NETs and ICCs. In fact, we did not find clear lipiodol washout pattern for ICCs, which is likely related to the fibrotic nature of ICC tumor. The pattern of washout across the different types of tumors may be related to unique histopathological characteristics of ICCs, NETs, and CRCs, including the extent of fibrotic tissue, vascularity, lymphatic vessels, Kupffer and phagocytosing cell density (28-31), each of which can facilitate or slow lipiodol washout and clearance from the tumor.

Our findings also showed that the lipiodol washout rate was slower in tumors with a tumor enhancement burden of 60% or greater. The burden of tumor enhancement reflects the vascularized part of the tumor with anomalous neo-angiogenesis that favors leakage of lipiodol into the intercellular space (24, 25) and adhesion of lipiodol to the tumor cell membrane with its subsequent endocytosis into

neoplastic cells (26). This might be related to the speed at which the tumor microenvironment can clear lipiodol. The larger the volume of tumor enhancement, the more lipiodol can be deposited during cTACE and the more lipiodol to be cleared.

Our findings indicated that there was not a statistically significant lipiodol washout in responders to cTACE; however, non-responders did experience some degree of washout. Absence of washout in responders is suggestive of successful trans-arterial delivery of lipiodol, resulting in embolization of arterial and portal vessels supplying the tumor, tumor cell necrosis, and lipiodol retention within the tumor (32, 33). This should be an indirect indicator of efficient delivery of chemotherapeutic agents (33), better induction of ischemia and necrosis, and consequently prolonged lipiodol retention and slower washout.

Although tumors with a volume of 300 cm³ or larger than had more lipiodol deposition, the lipiodol washout rate was slightly faster. Since only a predetermined volume of lipiodol (10 ml) is commonly used for cTACE, faster lipiodol washout may suggest that the standard volume of lipiodol might be suboptimal for sufficient embolization of supplying arteries, leaving residual blood flow behind and resulting in faster lipiodol washout. It is expected that larger tumors would accommodate larger volumes of lipiodol, which was seen in our study in tumors with a volume of 300 cm³ or more. Studies have shown that larger ICCs, NETs and CRCs are more likely to have larger areas of central necrosis which cannot retain lipiodol (29-31). Therefore, the necrotic proportion and vascularity of the tumor should be considered while correcting for lipiodol deposition.

This study shows lipiodol deposition and washout rates in the three most common non-HCC types of hepatic lesions treated by cTACE. Furthermore, to our knowledge, this is the only study examining the difference in the rate of lipiodol washout between these three types of hepatic tumors. The study is limited by the small sample size, a limitation partially mitigated by the use of non-parametric methods and bootstrap statistical methods. Furthermore, given the small sample size, regression estimates were not adjusted for possible confounding, a consideration which ought to be accounted for in future studies. Additionally, although we used a volumetric method to analyze lipiodol deposition, we did not evaluate the homogeneity, density, coverage and pattern of lipiodol deposition in tumors.

In conclusion, lipiodol washout is a time-dependent, negative exponential process that varies in tumors with different histopathology, resulting in faster lipiodol washout rates in CRCs than NETs. Lipiodol washout occurs faster in patients with tumors smaller than 300 cm³ and tumor enhancement burden of less than 60%. When lipiodol deposition is used to predict the response to cTACE, tumor types and features should be considered as factors which potentially influence lipiodol washout and deposition.

Conflicts of Interest

JC reports grant support from the Society of Interventional Oncology, Guerbet Pharmaceuticals, Philips Healthcare, Boston Scientific, Yale Center for Clinical Investigation, and the NIH R01CA206180 outside the submitted work. M.L. is a current employee and stockholder of Visage Imaging, Inc. and former Philips Research North America employee, and has grant support from NIH R01CA206180. All other Authors declare no conflicts of interest.

Authors' Contributions

Nariman Nezami: Concept, qualitative and quantitative analyzes, drafting, review and revision. Johanna Maria Mijntje van Breugel: Concept, and review. Menelaos Konstantinidis: Statistical analysis. Julius Chapiro: Concept and review. Lynn Jeanette Savic: Review and revision. Milena A. Miszczuk: Quantitative analysis and review.

Irvin Rexha: Quantitative analysis and review. MingDe Lin: supervised and reviewed. Kelvin Hong: supervised and reviewed. Christos Georgiades: Supervision and revision.

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