Scientific Research Publishing

Journal of Biosciences and Medicines, 2023, 11, 258-268
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Research Progress on the Prediction of TACE Efficacy by Lipiodol Deposition

Yi Qing, Yong Li

Zhuhai Intervention Medical Center, Zhuhai Hospital Affiliated with Jinan University (Zhuhai People's Hospital), Zhuhai, China
Email: Lorry5160@163.com

How to cite this paper: Qing, Y. and Li, Y. (2023) Research Progress on the Prediction of TACE Efficacy by Lipiodol Deposition. *Journal of Biosciences and Medicines*, **11**, 258-268.
https://doi.org/10.4236/jbm.2023.1111022

Received: October 16, 2023
Accepted: November 18, 2023
Published: November 21, 2023

Abstract

Primary hepatocellular carcinoma is one of the most common and deadliest malignant tumors in the world, and most patients are diagnosed after missing the optimal treatment period. TACE (Transcatheter arterial chemoembolization) is currently the preferred treatment for advanced HCC (Hepatocellular Carcinoma), as it can induce local ischemic necrosis of the tumor while reducing the systemic side effects of drugs by embolizing the tumor-feeding arteries. Lipiodol, with its unique comprehensive properties of imaging, drug loading, and embolization, has become a key component in the process of TACE. Therefore, analyzing the deposition of lipiodol in hepatic tumor tissues after TACE can effectively evaluate the treatment efficacy. This article summarizes and analyzes the metabolism of lipiodol in tumors and the clinical application of lipiodol deposition status in predicting patient prognosis, aiming to provide clearer diagnostic and treatment strategies for clinical doctors.

Keywords

Hepatocellular Carcinoma, Transcatheter Arterial Chemoembolization, Lipiodol, Interventional Treatment

1. Introduction

HCC is the sixth most common cancer worldwide and the third leading cause of cancer-related deaths. The incidence of HCC is still rapidly increasing, posing a significant threat to human life and health [1] [2]. Risk factors for HCC include hepatitis B virus, hepatitis C virus, obesity-related non-alcoholic steatohepatitis (NASH), alcohol-related liver cirrhosis, etc. [3] [4] [5]. Owing to a lack of typical manifestations of early stage HCC, most HCC patients present with abdominal pain and symptoms of hepatic failure and have already progressed to moderate or advanced stages by the time they are diagnosed, often at an advanced stage

where curative treatment options are lost, and most patients will die within 3 to 6 months. Common treatment methods for HCC include liver resection, liver transplantation, ablation therapy, transcatheter arterial chemoembolization (TACE), radiation therapy, and systemic anti-tumor therapy. The most important consideration for clinicians is to select appropriate treatment methods based on the different stages of HCC in different patients [6].

NCCN Clinical Practice Guidelines in Hepatobiliary Cancers (2021, Version) [7] and Standardization for Diagnosis and Treatment of Primary Hepatic Carcinoma (2022 Edition) both recommend TACE as the main treatment for patients with intermediate and advanced stages of HCC. The goal of TACE is to induce tumor ischemic necrosis by embolizing the tumor arteries with embolic agents and combining them with anti-tumor drugs, thereby achieving cytotoxic effects on tumor tissues [8] [9], it aims to achieve a high concentration of drug uptake in the tumor site while reducing uptake in other parts of the body [10]. In addition, TACE is also widely used in the treatment of HCC at other stages and patients with hepatic metastasis from other tumors [11] [12] [13].

Lipiodol is the most commonly used embolic agent in TACE. It can not only embolize the tumor-feeding vessels but also serve as a carrier for chemotherapy drugs, prolonging the duration of drug action. It can also activate the immune system of the liver and synergize with TACE treatment. The half-life period of lipiodol in the liver is approximately 4 - 6 weeks [14] [15]. Other embolic agents, such as gelatin sponge particles, can be added to enhance the embolization effect and improve treatment outcomes. The distribution and deposition of lipiodol in the tumor region directly affect the degree of tumor vascular embolization and the concentration of anticancer drugs in the tumor mass. Therefore, the assessment of post-TACE lipiodol deposition can provide clinicians with a direct and accurate evaluation of TACE efficacy and help determine the next step in patient treatment planning [16] [17].

2. The Theoretical Basis of Lipiodol Application in the Treatment of HCC

2.1. Vascular Characteristics of Hepatocellular Carcinoma

Approximately 75% of the blood supply to normal liver tissue is derived from the portal vein, while approximately 25% is derived from the hepatic artery [18] [19]. However, in the growth of malignant tumor tissue, a large number of abnormal neovascularization occurs, resulting in more than 90% of the blood supply to hepatocellular carcinoma originating from the hepatic artery, with only about 10% supplied by the portal vein. Therefore, TACE selectively targets the tumor-feeding arteries to deliver chemotherapy agents, thereby achieving local treatment of the tumor while minimizing damage to normal liver tissue.

2.2. Metabolism of Lipiodol in the Liver

It has been suggested that there is a pump in the tumor cell membrane that can

take up lipiodol and transfer it into the cell via cytosolic drinking, and that the pump subsequently fails due to hypoxia in the tumor, and the lipiodol is thus deposited in the cell. It has been hypothesized that Kupffer cells can actively capture and phagocytose iodine oil, and the decrease in the number of Kupffer cells in hepatocellular carcinoma cells, which may prolong the clearance time of lipiodol, when administered through the hepatic artery, lipiodol will be deposited in the tumor tissue for months or even up to a year due to the overvascularization of tumor vasculature and the lack of a siphon effect of the Kupffer cells in the tumor tissues, whereas in the normal or cirrhotic tissues, iodine oil is gradually cleared within 4 weeks is gradually removed. The time required for hepatic clearance of iodized oil and restoration of microcirculation is closely related to the patency of the hepatic arteries. Twisted and irregular blood vessels and poorly developed lymphatic vessels in hepatocellular carcinoma tissues result in a slower loss of lipiodol from tumor lesions compared to normal liver tissues [20]. In contrast, lipiodol deposited in tumor tissues may be consumed by tumor cells that maintain a differentiated state and retain the ability to consume foreign substances.

2.3. The Metabolic Process of Lipiodol in the Liver

Lipiodol not only exhibits stronger accumulation and longer retention characteristics in liver tumors and highly vascularized liver metastases, but it can also temporarily embolize both the hepatic artery and the portal vein branches through the peribiliary capillary plexus and the drainage pathway of the tumor. In cases where tumors invade the blood flow pathway in the liver, hepatic arteriovenous fistulas (HAVFs) may occur, which can not only cause portal hypertension but also increase the chances of tumor cell dissemination to distant organs. In interventional therapy, hemodynamic changes caused by abnormal shunting can directly affect the efficacy of TACE, and lipiodol can even cause pulmonary and systemic embolism through abnormal shunt pathways [20]. Therefore, understanding the blood supply to the liver and tumor lesions in patients is of great significance for clinicians in selecting treatment methods and predicting patient prognosis.

Lipiodol not only exhibits stronger accumulation and longer retention characteristics in liver tumors and highly vascularized liver metastases, but it can also temporarily embolize both the hepatic artery and the portal vein branches through the peribiliary capillary plexus and the drainage pathway of the tumor. In cases where tumors invade the blood flow pathway in the liver, hepatic arteriovenous fistulas (HAVFs) may occur, which can not only cause portal hypertension but also increase the chances of tumor cell dissemination to distant organs [21]. In interventional therapy, hemodynamic changes caused by abnormal shunting can directly affect the efficacy of TACE, and lipiodol can even cause pulmonary and systemic embolism through abnormal shunt pathways. Therefore, understanding the blood supply to the liver and tumor lesions in patients is

of great significance for clinicians in selecting treatment methods and predicting patient prognosis.

3. Lipiodol Application in Clinical Practice

3.1. Dosage of Lipiodol

Using excessive dosage of lipiodol in TACE treatment can damage the liver parenchyma. Conversely, if the lipiodol dosage used during the procedure is too low, it may not achieve complete tumor arterial embolization, leading to the possibility of tumor neovascularization and accelerated tumor progression. Therefore, the ultimate goal for clinicians is to maximize the targeted embolization effect on the tumor while minimizing liver damage. Studies have shown that the best long-term prognosis is achieved when administering lipiodol at a dosage equivalent to 1.0 to 1.5 times the absolute value of the tumor diameter (in cm) in milliliters. Additionally, for highly vascularized tumors, a dosage of lipiodol 2 - 3 times the tumor diameter has been recommended, while for tumors with poor vascularity or avascularity, filling the tumor with lipiodol to achieve therapeutic goals is preferred [22] [23]. With the emergence of the concept of precision intervention and the advancement of treatment techniques, there is a new requirement for precise quantitative dos.

3.2. Impact of Lipiodol on Prognosis

Accurate and timely assessment of the efficacy of Transarterial Chemoembolization (TACE) is crucial for treatment planning. For patients who respond well to TACE, it can help them decide whether early repeat treatment is necessary to eliminate residual viable tumors or opt for delayed treatment to reduce drug toxicity and treatment-related complications. On the other hand, for patients who do not respond effectively to initial treatment, a timely transition to second-line local or systemic therapy is beneficial.

3.2.1. Predicting Prognosis by Lipiodol Deposition on Images

In practice, due to the difficulty of radiation penetration through lipiodol, radiologists find it challenging to directly assess the degree of tumor necrosis post-TACE. Therefore, post-procedural lipiodol uptake is often used to evaluate the efficacy of TACE. The improved mRECIST (modified Response Evaluation Criteria in Solid Tumours) has been recommended for reliable assessment of treatment response in HCC patients after TACE, making it the preferred radiological response evaluation method. Studies have shown that combining the tumor enhancement on preoperative MRI with the lipiodol deposition range on postoperative CT can better predict tumor necrosis and tumor response in the treatment of liver cancer lesions [24].

Lipiodol angiography and post-interventional CT scans provide a non-invasive examination basis for differentiating between benign and malignant tumors [25]. By combining follow-up imaging examinations with histopathological data,

it has been found that lipiodol deposition in tumors is closely related to tumor necrosis, and the accumulation of Hounsfield Units (HU) in lipiodol deposition areas on CT images is of significant importance in predicting pathological necrosis [26]. Baseline imaging characteristics, especially those showing tumor vascularity features such as arterial enhancement, have been considered predictive of tumor response to conventional TACE. Tumors with obvious enhancement in the arterial phase of CT images and those diagnosed as highly vascularized in angiography show a stronger response to conventional TACE [27] [28]. Numerous studies have found that patients with more or even dense lipiodol deposition in tumors have a better prognosis after TACE, while patients without deposition or with scattered lipiodol deposition have a higher risk of early recurrence.

3.2.2. Predicting Prognosis by Lipiodol Washout Rate on Images

In follow-up examinations, a faster reduction in lipiodol deposition density indicates a higher risk of early tumor recurrence [29]. Compared to hypovascular tumor lesions, lesions with rich blood supply have a higher uptake of chemotherapy drugs and greater potential for embolization. These studies suggest that repeat TACE treatment may be less effective in patients with hypovascular liver cancer who show an incomplete response after TACE, while combination therapy may improve the treatment efficacy for patients with rich blood supply [30].

3.2.3. Predicting Prognosis by Blood Supply of the Liver and Tumors

The dual blood supply of the liver, the shunt between the hepatic artery and portal vein, and the complex microvascular structure of malignant liver tumors affect the treatment efficacy, allowing lipiodol distribution to extend beyond the liver tumor lesions. Patients with lipiodol deposition around the tumor exhibit a higher reduction rate of viable tumor tissue after TACE, and infiltrative tumors show less lipiodol deposition compared to tumors with clear contours [25]. Additionally, the presence of lipiodol deposition in portal vein tumor thrombus is considered to indicate better treatment efficacy of TACE [31].

Therefore, in the clinical management of liver cancer, clinicians should consider the lipiodol deposition status in post-TACE imaging examinations as a reflection of treatment efficacy and evaluate the reasons for poor lipiodol deposition within the tumor, such as difficulties in identifying the supplying artery or inadequate lipiodol retention due to arteriovenous shunting.

3.3. Factors Affecting the Deposition of Lipiodol

Factors affecting the deposition of lipiodol include anatomical factors such as the size, density, and structure of tumor microvessels, tumor size, presence of ischemia, and necrosis. Physiological factors such as local flow, shear stress, blood pressure, permeability, and physical-chemical parameters related to the drug itself can also influence the deposition of lipiodol. Studies have found that the washout pattern of different types of tumors may be related to their unique his-

topathological characteristics [20], such as the degree of fibrosis, vascular distribution, lymphatic vessels, Kupffer cells, and phagocyte density in different types of liver cancer tumor tissue.

The volume of lipiodol deposited in the tumor is related to the subsequent reduction in necrotic tumor volume or even the entire tumor volume. Sophie Stark *et al.* [25] analyzed the deposition of lipiodol through CT imaging 24 hours after cTACE and found that the deposition pattern and density of lipiodol could be used to predict the reduction of tumor tissue and the subsequent imaging response. They also found that the deposition of lipiodol in target lesions could be predicted based on the tumor enhancement pattern on baseline MRI, and that lipiodol loss in viable tumors was faster compared to necrotic tumors, which may be related to tumor cell consumption as mentioned earlier. Yin-Chen Tsai *et al.* [32] found that the parenchyma-to-lipiodol ratio (PLR) evaluated by Cone-beam CT (CBCT) was a useful predictor of tumor response 1 year after cTACE, and the lesion-to-lipiodol ratio (LLR) provided an objective evaluation of the extent of HCC tumor shrinkage. Furthermore, their study results indicated that previous liver resection, radiofrequency ablation (RFA), and ethanol ablation (EI) were not major influencing factors on cTACE outcomes. If a COV of PLR < 0.149, it suggests that these incomplete or difficult embolized tumors need additional treatment in a short time because of the extremely high progression risk. The phenomenon of vascular lakes, observed as a continuous contrast agent pool in the venous phase during TACE, is associated with tumor size, pseudo capsule, and alpha-fetoprotein levels. Studies have reported that patients with the presence of vascular lakes have better local and tumor responses, indicating more lipiodol deposition [33] [34].

4. Summary

Many studies have shown that TACE treatment has good efficacy for intermediate to advanced liver cancer and even other malignant tumors [35]. However, in clinical practice, tumor recurrence often occurs after TACE treatment. This may be due to the exacerbation of tumor hypoxia, increased expression of vascular endothelial growth factor (VEGF), and local inflammation after embolization of tumor-feeding arteries.

As liver cancer progresses, the expression of VEGF gradually increases, and angiogenesis is believed to affect tumor survival after TACE by influencing the VEGF signaling pathway. TACE can also induce the expression of VEGF in residual tumor cells, and there is a direct relationship between lipiodol retention and decreased plasma VEGF levels in HCC patients. Therefore, targeted drugs such as sorafenib and brivanib, which are anti-angiogenic inhibitors, are often used in combination with TACE in clinical treatment. Although lipiodol has viscosity, it is difficult to completely block blood flow. Over time, the mixture of lipiodol and chemotherapy drugs deposited in the tumor will gradually decrease, and tumor blood vessels may regenerate or reopen. Under the action of pro-

angiogenic factors, new collateral circulation is established around the tumor, leading to tumor recurrence. Therefore, multiple TACE treatments are needed to delay disease progression, but repeated treatments can aggravate liver function damage, induce a local ischemic and hypoxic environment, and increase the expression of hypoxia-induced factors and vascular endothelial growth factors in HCC. Hypoxia may also allow tumor cells to escape from TACE and anti-angiogenic treatments, ultimately leading to tumor recurrence. Therefore, targeting hypoxia, such as inhibiting HIF-1a activity, provides a new direction for the treatment of liver cancer.

Lipiodol is often used in combination with chemotherapy drugs, and monotherapy and combination chemotherapy have become part of the TACE drug regimen. Commonly used chemotherapy drugs include anthracyclines, platinum compounds, taxanes, fluoropyrimidines, and others. When lipiodol is combined with chemotherapy drugs, it can alter their pharmacokinetic characteristics, prolong the metabolism time of drugs in tumor lesions, and thus extend the contact time between tumor cells and chemotherapy drugs. Therefore, lipiodol can increase the local concentration of drugs while reducing the systemic drug load. Pan He *et al.* [36] designed a novel nanostructure called nanoDOX, which was uniformly mixed with lipiodol through ultrasound to produce a lipiodol-DOX compound (SHIFT & DOX). Compared to traditional embolic agents, SHIFT & DOX has stronger stability and hydrophobicity, as well as good drug release behavior, providing a novel, safe, efficient, and economical treatment option for advanced liver cancer patients. Nanoparticle technology, by combining different drugs to improve drug efficacy, provides a promising future for liver cancer treatment [37].

Although TACE has beneficial effects on the survival of liver cancer patients, it still has many limitations as a palliative treatment. Inadequate vascular embolization or incomplete tumor necrosis may occur, requiring patients to undergo repeated embolization treatments, which can lead to worsening liver function and gradual narrowing of tumor-feeding arteries [26]. Therefore, multimodal combination therapy provides better survival opportunities for liver cancer patients. The type of lipiodol deposition, as one of the indicators for evaluating patient prognosis, should prompt clinicians to promptly switch treatment modalities or combine other treatments, such as radiofrequency ablation, radioactive particle implantation, targeted therapy, and immunotherapy, to achieve better treatment outcomes for patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al.* (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and

Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Kocarnik, J.M., Compton, K., Dean, F.E., Fu, W.J., Gaw, B.L., Harvey, J.D., *et al.* (2021) Cancer Incidence, Mortality, Years of Life Lost, Years Lived with Disability, and Disability-Adjusted Life Years for 29 Cancer Groups from 2010 to 2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *JAMA Oncology*, **8**, 420-444.

[3] Petrick, J.L., Florio, A.A., Znaor, A., Ruggieri, D., Laversanne, M., Alvarez, C.S., *et al.* (2020) International Trends in Hepatocellular Carcinoma Incidence, 1978-2012. *International Journal of Cancer*, **147**, 317-330. https://doi.org/10.1002/ijc.32723

[4] Farhad, I., Kimberly, D.M., Rebecca, L.S., Stacey, A.F., Elizabeth, M.W. and Ahmedin, J. (2017) Disparities in Liver Cancer Occurrence in the United States by Race/Ethnicity and State: Liver Cancer in the United States. *CA*: *A Cancer Journal for Clinicians*, **67**, 273-289. https://doi.org/10.3322/caac.21402

[5] Akinyemiju, T., Abera, S., Ahmed, M., Alam, N., Alemayohu, M.A., Allen, C., *et al.* (2017) The Burden of Primary Liver Cancer and Underlying Etiologies from 1990 to 2015 at the Global, Regional, and National Level: Results from the Global Burden of Disease Study 2015. *JAMA Oncology*, **3**, 1683-1691. https://doi.org/10.1001/jamaoncol.2017.3055

[6] Llovet, J.M., Robin, K.K., Augusto, V., Amit, G.S., Eli, P., Sasan, R., *et al.* (2021) Hepatocellular Carcinoma. *Nature Reviews Disease Primers*, **7**, Article No. 6. https://doi.org/10.1038/s41572-020-00240-3

[7] Benson, A.B., D'Angelica, M.I., Abbott, D.E., Anaya, D.A., Anders, R., Are, C., *et al.* (2021) Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, **19**, 541-565. https://doi.org/10.6004/jnccn.2021.0022

[8] Makary, M.S., Umang, K., Jordan, M.C., Khalid, M. and Joshua, D.D. (2020) Locoregional Therapy Approaches for Hepatocellular Carcinoma: Recent Advances and Management Strategies. *Cancers*, **12**, E1914. https://doi.org/10.3390/cancers12071914

[9] Makary, M.S., Stuart, R., Eric, M., Eliza, W.B. and Joshua, D.D. (2021) Hepatocellular Carcinoma Locoregional Therapies: Outcomes and Future Horizons. *World Journal of Gastroenterology*, **27**, 7462-7479. https://doi.org/10.3748/wjg.v27.i43.7462

[10] Hulin, A., Jeanick, S. and Mohamed, B. (2019) Clinical Pharmacokinetics and Pharmacodynamics of Transarterial Chemoembolization and Targeted Therapies in Hepatocellular Carcinoma. *Clinical Pharmacokinetics*, **58**, 983-1014. https://doi.org/10.1007/s40262-019-00740-w

[11] Galle, P.R., Forner, A., Llovet, J.M., Mazzaferro, V., Piscaglia, F., Raoul, J.L., Schirmacher, P. and Vilgrain, V. (2018) EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma. *Journal of Hepatology*, **69**, 182-236. https://doi.org/10.1016/j.jhep.2018.03.019

[12] Vogl, T.J. and Gruber-Rouh, T. (2019) HCC: Transarterial Therapies—What the Interventional Radiologist Can Offer. *Digestive Diseases and Sciences*, **64**, 959-967. https://doi.org/10.1007/s10620-019-05542-5

[13] Gaba, R.C., Lokken, R.P., Hickey, M.R.M., Lipnik, A.J., Lewandowski, R.J., Salem, R., *et al.* (2017) Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy. *Journal of Vascular and Interventional Radiology*, **28**, 1210-1223. https://doi.org/10.1016/j.jvir.2017.04.025

[14] Schicho, A., Hellerbrand, C., Krüger, K., Beyer, L.P., Wohlgemuth, W., Niessen, C.,

et al. (2016) Impact of Different Embolic Agents for Transarterial Chemoembolization (TACE) Procedures on Systemic Vascular Endothelial Growth Factor (VEGF) Levels. *Journal of Clinical and Translational Hepatology*, **4**, 288-292. https://doi.org/10.14218/JCTH.2016.00058

[15] Idée, J.M. and Boris, G. (2013) Use of Lipiodol as a Drug-Delivery System for Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma: A Review. *Critical Reviews in Oncology/Hematology*, **88**, 530-549. https://doi.org/10.1016/j.critrevonc.2013.07.003

[16] Thierry, D.B., Alban, D., Renè, B., Patrick, C., Jacques, D. and Alain, R. (1998) Modification of Arterial and Portal Hemodynamics after Injection of Iodized Oils and Different Emulsions of Iodized Oils in the Hepatic Artery: An Experimental Study. *Journal of Vascular and Interventional Radiology*, **9**, 305-310. https://doi.org/10.1016/S1051-0443(98)70273-8

[17] Kan, Z., Ivancev, K., Hägerstrand, I., Chuang, V.P. and Lunderquist, A. (1989) *In Vivo* Microscopy of the Liver after Injection of Lipiodol into the Hepatic Artery and Portal Vein in the Rat. *Acta Radiologica*, **30**, 419-425. https://doi.org/10.1177/028418518903000418

[18] Matsui, O., Kadoya, M., Kameyama, T., Yoshikawa, J., Takashima, T., Nakanuma, Y., *et al.* (1991) Benign and Malignant Nodules in Cirrhotic Livers: Distinction Based on Blood Supply. *Radiology*, **178**, 493-497. https://doi.org/10.1148/radiology.178.2.1846240

[19] Wu, X.Z., Xie, G.R. and Chen, D. (2007) Hypoxia and Hepatocellular Carcinoma: The Therapeutic Target for Hepatocellular Carcinoma. *Journal of Gastroenterology and Hepatology*, **22**, 1178-1182. https://doi.org/10.1111/j.1440-1746.2007.04997.x

[20] Nezami, N., Van Breugel, J.M.M., Konstantinidis, M., Chapiro, J., Savic, L.J. and Miszczuk, M.A. (2021) Lipiodol Deposition and Washout in Primary and Metastatic Liver Tumors after Chemoembolization. *In Vivo* (*Athens, Greece*), **35**, 3261-3270. https://doi.org/10.21873/invivo.12621

[21] Ngan, H. and Peh, W.C.G. (1997) Arteriovenous Shunting in Hepatocellular Carcinoma: Its Prevalence and Clinical Significance. *Clinical Radiology*, **52**, 36-40. https://doi.org/10.1016/S0009-9260(97)80303-0

[22] Cheng, H.Y., Shou, Y., Wang, X., Xu, A.M., Chen, D. and Jia, Y.C. (2004) Adjustment of Lipiodol Dose According to Tumor Blood Supply during Transcatheter Arterial Chemoembolization for Large Hepatocellular Carcinoma by Multidetector Helical CT. *World Journal of Gastroenterology*, **10**, 2753-2755. https://doi.org/10.3748/wjg.v10.i18.2753

[23] Nakao, N., Uchida, H., Kamino, K., Nishimura, Y., Ohishi, H., Takayasu, Y., *et al.* (1994) Determination of the Optimum Dose Level of Lipiodol in Transcatheter Arterial Embolization of Primary Hepatocellular Carcinoma Based on Retrospective Multivariate Analysis. *Cardio Vascular and Interventional Radiology*, **17**, 76-80. https://doi.org/10.1007/BF00193921

[24] Varzaneh, F.N., Pandey, A., Ghasabeh, M.A., Shao, N.N., Khoshpouri, P., Pandey, P., *et al.* (2018) Prediction of Post-TACE Necrosis of Hepatocellular Carcinoma Usingvolumetric Enhancement on MRI and Volumetric Oil Deposition on CT, with Pathological Correlation. *European Radiology*, **28**, 3032-3040. https://doi.org/10.1007/s00330-017-5198-9

[25] Stark, S., Wang, C., Savic, L.J., Letzen, B., Schobert, I., Miszczuk, M., *et al.* (2020) Automated Feature Quantification of Lipiodol as Imaging Biomarker to Predict Therapeutic Efficacy of Conventional Transarterial Chemoembolization of Liver Cancer. *Scientific Reports*, **10**, Article No. 18026.

https://doi.org/10.1038/s41598-020-75120-7

[26] Park, C., Gwon, D., Chu, H.H., Kim, J.W., Kim, J.H. and Ko, G.Y. (2021) Correlation of Tumor Response on CT with Pathologically Proven Necrosis in Hepatocellular Carcinom Treated by Conventional Transcatheter Arterial Chemoembolization: Threshold Value of Intratumoral Lipiodol Accumulation Predicting Tumor Necrosis. *Abdominal Radiology*, **46**, 3729-3737. https://doi.org/10.1007/s00261-020-02845-4

[27] Park, H.J., Kim, J.H., Choi, S.Y., Lee, E.S., Park, S.J., Byun, J.Y., *et al.* (2017) Prediction of Therapeutic Response of Hepatocellular Carcinoma to Transcatheter Arterial Chemoembolization Based on Pretherapeutic Dynamic CT and Textural Findings. *American Journal of Roentgenology*, **209**, 211-220. https://doi.org/10.2214/AJR.16.17398

[28] Langenbach, M.C., Thomas, J.V., Gulia, S., Scholtz, J.E., Renate, H. and Tatjana, G.R. (2021) Lipiodol as a Predictive Indicator for Therapy Response to Transarterial Chemoembolization of Hepatocellular Carcinoma. *Cancer Biotherapy and Radiopharmaceuticals*. https://doi.org/10.1089/cbr.2020.4137

[29] Matsui, Y., Horikawa, M., Noudeh, Y.J., Kaufman, J.A., Kolbeck, K.J. and Farsad, K. (2017) Baseline Tumor Lipiodol Uptake after Transarterial Chemoembolization for Hepatocellular Carcinoma: Identification of a Threshold Value Predicting Tumor Recurrence. *Radiology and Oncology*, **51**, 393-400. https://doi.org/10.1515/raon-2017-0030

[30] Tao, P.Y., Zhang, Z.S., Wang, T.C., Yu, M.Q. and Xiao, Y.D. (2021) A Predictive Model of Incomplete Response after Transarterial Chemoembolization for Early or Intermediate Stage of Hepatocellular Carcinoma: Consideration of Hepatic Angiographic and Cross-Sectional Imaging. *Abdominal Radiology*, **46**, 581-589. https://doi.org/10.1007/s00261-020-02701-5

[31] Yang, Z., Zou, R., Zheng, Y., Qiu, J., Shen, J., Liao, Y., *et al.* (2019) Lipiodol Deposition in Portal Vein Tumour Thrombus Predicts Treatment Outcome in HCC Patients after Transarterial Chemoembolisation. *European Radiology*, **29**, 5752-5762. https://doi.org/10.1007/s00330-019-06157-0

[32] Tsai, Y.C., Shih, J.H., Hwang, H.E., Chiu, N.C., Lee, R.C., Tseng, H.S., *et al.* (2021) Early Prediction of 1-Year Tumor Response of Hepatocellular Carcinoma with Lipiodol Deposition Pattern through Post-Embolization Cone-Beam Computed Tomography during Conventional Transarterial Chemoembolization. *European Radiology*, **31**, 7464-7475. https://doi.org/10.1007/s00330-021-07843-8

[33] Cavalcante, R.N., Nasser, F., Motta-Leal-Filho, J.M., Affonso, B.B., Galastri, F.L., Fina, B.D., Garcia, R.G. and Wolosker, N. (2017) Occurrence of Vascular Lake Phenomenon as a Predictor of Improved Tumor Response in HCC Patients That Underwent DEB-TACE. *CardioVascular and Interventional Radiology*, **40**, 1044-1051. https://doi.org/10.1007/s00270-017-1678-1

[34] Hu, B., Zhong, B.Y., Zhang, L., Dai, C., Li, W., Shen, J., *et al.* (2020) Occurrence of Vascular Lake Phenomenon Before Embolization for the Prediction of Lipiodol Uptake for Intermediate-Stage Hepatocellular Carcinoma Patients That Underwent cTACE. *CardioVascular and Interventional Radiology*, **43**, 1460-1467. https://doi.org/10.1007/s00270-020-02501-w

[35] Wang, Z., Ren, Z., Chen, Y., Hu, J., Yang, G., Yu, L., *et al.* (2018) Adjuvant Transarterial Chemoembolization for HBV-Related Hepatocellular Carcinoma after Resection: A Randomized Controlled Study Adjuvant TACE for HCC after Resection. *Clinical Cancer Research*, **24**, 2074-2081. https://doi.org/10.1158/1078-0432.CCR-17-2899

[36] Pan, H., Ren, E., Chen, B.Q., Chen, H., Cheng, H.W., Gao, X., *et al.* (2022) A Super-Stable Homogeneous Lipiodol-Hydrophilic Chemodrug Formulation for Treatment of Hepatocellular Carcinoma. *Theranostics*, **12**, 1769-1782. https://doi.org/10.7150/thno.68456

[37] Anwanwan, D., Santosh, K.S., Shriti, S., Varma, S. and Rajesh, S. (2020) Challenges in Liver Cancer and Possible Treatment Approaches. *Biochimica et Biophysica Acta* (*BBA*)—*Reviews on Cancer*, **1873**, Article ID: 188314. https://doi.org/10.1016/j.bbcan.2019.188314