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Pickering Lipiodol-emulsion for liver TACE with oxaliplatin

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Purpose

Poly(lactic-co-glycolic acid) (PLGA) nanoparticles (Nps) adsorb at the water/oil interface to stabilize emulsion (Pickering-emulsion). This study aimed to compare the release profiles of oxaliplatin from Pickering-emulsion and from Lipiodol-emulsion.

Materials/methods

Pickering-emulsions and Lipiodol-emulsions were both formulated with oxaliplatin (5mG/mL) and Lipiodol (Water/oil ratio: 1/3). For Pickering-emulsion only, PLGA-Nps (15mG/mL) were dissolved into oxaliplatin before formulation. In-vitro releases of platinum from both emulsions were evaluated. Then, 0.625 mG oxaliplatin was injected in left hepatic arteries of 18 rabbits bearing VX2 liver tumors using either 0.5 mL Pickering-emulsion (n=10) or 0.5 mL Lipiodol-emulsion (n=8). In each group, half rabbits were sacrificed at 1h and half at 24h. Platinum' plasmatic pharmacokinetic and quantification in tissues (tumors and left-liver lobes) were measured (ICP-MS mass-spectrometry) and compared.

Results

In-vitro, Pickering-emulsion demonstrated a slow oxaliplatin' release compared to Lipiodol-emulsion (15.8 \pm 3.0% vs. 85.3 \pm 3.3% at 24h). The platinum plasmatic-peak and the area under the curve were significantly lower with Pickering-emulsion, respectively 0.24 \pm 0.07 nG/mL vs. 0.53 \pm 0.20 nG/mL, p=0.01 and 9.7 \pm 2.9 vs. 15.6 \pm 7.3, p=0.03. Platinum' concentration in tumors was not different between the 2 emulsions neither at 1h (8.6 \pm 3.3 vs. 15.7 \pm 10.4 nG/mG, p=0.08) nor at 24h (5.1 \pm 4.8 vs. 2.2 \pm 1.9, p=0.06). The ratio tumors/left-livers platinum' concentrations was

significantly higher with Pickering-emulsion at 1h (33.2 ± 14.9 vs. 18.0 ± 10.8 , $p=0.02$) and 24h (43.4 ± 42.9 vs. 14.5 ± 6.6 , $p=0.04$).

Conclusion

Slow release of oxaliplatin from Pickering-emulsion results in significant decrease of systemic exposure and similar concentrations in the tumors at 1h and 24h.

Introduction

A drug delivery platform is currently used during liver Trans Arterial Chemo-Embolization (TACE). It acts as a transient reservoir, allowing slow release of the chemotherapy in the tumors' supply for a prolonged exposure of the cancer' cells while minimizing systemic effects. Lipiodol and drug eluding beads are the two drug delivery platforms, currently used in clinical practice for TACE of hepatocarcinoma ¹ or liver metastases from neuroendocrine or colorectal cancers. Various anticancer drugs such as doxorubicin, epirubicin, irinotecan, mitomycin C and cisplatin have been evaluated with one or the other or the both platforms.

Lipiodol (Guerbet, Aulnay-sous-bois, France) is an oily based radio-opaque contrast agent that is use as a drug delivery platform because of its radio-opacity and its preferential tumor uptake compared to surrounding liver tissue². Since most anticancer drugs are water-soluble, the vectorization mechanism consists in formulating a water-in-oil emulsion between the chemotherapy (aqueous-phase) and the Lipiodol (oily-phase)³. However, the release of chemotherapy occurs quite rapidly because lipiodol-emulsions have relatively poor stability. Within a few minutes – hours according the chemotherapy, the two phases of the emulsion separate and almost the entire water-soluble drug disappears very rapidly from the Lipiodol, resulting in high chemotherapy systemic exposure and inadequacy between the deposit of Lipiodol and of chemotherapy deposit ⁴.

Drug eluding beads are polyvinyl alcohol-based hydrogel beads that can be loaded with chemotherapy. The presence of the anionic sulphonate group enables the sequestering of positively charged drugs only (Coulomb charge interactions). Thus, doxorubicin, epirubicin or irinotecan are the only chemotherapies that can be used in clinical practice. In addition, because of variable ionic interaction' intensities

between beads and the chemotherapy, the release could be either incomplete and very slow (doxorubicin) or complete and very fast (irinotecan)⁵. Finally, the beads are not only a drug delivery platform but also an embolic medical device (different sizes available, ranging from 70 up to 700 μm) that blocks the arterial flow. This property helps in further increasing the tumor drug exposure but can induce hypoxia and unexpected development of new tumor blood vessels (tumor neo-angiogenesis). Although calibrated drug eluting beads have been developed to standardize the TACE procedure, the choice of loadable chemotherapies is limited to anionic drugs. Moreover, the release kinetics could be affected by chemical rearrangements of the drug inside the microsphere.

We have therefore developed a new concept of drug delivery platform that allows 1) the loading of various types of chemotherapies independently of their chemical structure and 2) their controlled release while keeping the value of Lipiodol in terms of a radio-opacity, preferential tumor' uptake⁶ and transient vessels' occlusion⁷. The principle is based on the Pickering technology^{8,9} that uses solid particles instead of surfactants to stabilize the water droplets. Pickering emulsions are known to display a high stability against coalescence. The use of solid particles (Pickering technology) in the formulation of an emulsion avoids the use of toxic synthetic surfactants and results in very stable interfaces between the aqueous phase and the oily phase.

The purpose of this study is to compare the release profiles of oxaliplatin from Pickering-emulsion and Lipiodol-emulsion.

Pickering emulsions stabilized by the irreversible adsorption of tiny solid particles at the interface have been drawn lots of attention since its appearance.

Pickering emulsion showed a special number of advantages over conventional surfactant emulsion, namely: (i) a high stability thanks to the robust and reproducible formulations,(ii) reduced foaming problems and (iii) a lower toxicity (at least compared to certain surfactants)

Materials/ methods

Two successive studies were performed to compare Pickering-emulsion and Lipiodol-emulsion. The first one was designed to compare the in vitro release profile of oxaliplatin from the 2 emulsions. The second study was an animal study designed to compare the plasmatic pharmacokinetics and tissues exposures of oxaliplatin in rabbit implanted with VX2 liver tumors.

Formulation of the emulsions:

Two different types of water-in-oil emulsions were formulated: Lipiodol-emulsion and Pickering-emulsion.

For both emulsions, the oily-phase was composed with Lipiodol and the aqueous phase was composed with oxaliplatin (5 mG/mL). The addition of poly(lactic-co-glycolic acid) (PLGA) nanoparticles in the aqueous-phase of Pickering-emulsion (15 mG/mL) was the only difference between the 2 emulsions. These nanoparticles adsorb at the water/oil interface to stabilize the emulsion (Figure-1). Oxaliplatin was the chosen chemotherapy in this study for two main reasons. First, several studies has already demonstrated that hepatic arterial infusion (HAI) of oxaliplatin is safe and effective in animal models and in humans. Second, the most appropriate drug delivery platform for oxaliplatin has not been investigated yet.

Water-in-oil emulsions were formulated by continuous injection of 1 volume of aqueous phase in 3 volumes of oily phase with an electric syringe-pump (flow-rate of

1 mL per minute) during repetitive pumping of two 10-mL syringes through a three-way stopcock¹⁰.

In vitro study:

In-vitro release of platinum from the 2 emulsions was evaluated. We did the experiments twice for each emulsion: an aliquot of 0.8 mL of emulsion (corresponding to 1 mG of oxaliplatin or to 0.49 mG of platinum) was loaded into mini GeBAflex tubes (molecular weight cut-off: 12–14 kDa; Gene Bio-Application Ltd., Kfar Hanagide, Israel). Those tubes were immersed in 40 ml of buffer solution (acetate buffer 25 mM, pH 6.8) and incubated in a shaking bath (37°C) rotated at a speed of 150 rpm. At predetermined times (1h, 4h, 24 h, 48h, 72h, 1 week, 2 weeks and 1 month), 0.5 ml of buffer solution were collected for platinum quantification.

Animal study:

This study was performed in accordance with our institutional Animal Care and Use Committee guidelines. VX2 liver tumors were percutaneously implanted in New Zealand White rabbits under general anesthesia (Intramuscular injections of Ketamine 20-40mg/kg and xylazine 3-5mg/kg, Isoflurane 3-5% for induction and 1.5-3% for maintenance mixed with O₂ at 1L/min). For this purpose, 1–2 mm freshly harvested tumor fragments, coming from the hind limb tumors of a donor rabbits were implanted under ultrasound guidance through a 18G needle and in 3 different locations of the left liver lobe. 1 week after the liver tumors' implantations, MR checkup scans were performed to confirm tumors growth and location in liver.

Two weeks after the liver tumors' implantations, TACE procedures were performed by an experienced interventional radiologist (FD), under general

anesthesia and under fluoroscopic guidance (OEC 9800 Plus Mobile C-arm, Milwaukee, Wisconsin, USA). The femoral artery was surgically exposed and catheterized with a 4F vascular sheath using a Seldinger approach. A micro-catheter (2.4F Merit Maestro Merit medical®, South Jordan, UT, USA) was used to selectively engage the left hepatic branch (Figure-2) and to inject 0.5 ml of emulsion corresponding to 0.625 mg of oxaliplatin. Attention was given to avoid any injection in the right hepatic artery and additional embolization with gelatin sponge was considered only in case of persistent flow in the left hepatic branch after completion of the injection.

Heparinized systemic blood samples (2 mL) were collected from the vascular sheath 5, 10, 20, 30 and 60 minutes after the injection of the emulsion to measure the plasma pharmacokinetics of oxaliplatin. The procedures were either non-recovery procedures (sacrifice at 1 hour, immediately after the last blood sample collection) or recovery procedures with sacrifice at 24 hours. Four different groups of rabbits were considered according to the type of emulsion they received and according to the delay before sacrifice:

- Group-1: rabbits received Lipiodol-emulsion and were sacrificed 1 hour after the injection.
- Group-2: rabbits received Pickering-emulsion and were sacrificed 1 hour after the injection.
- Group-3: rabbits received Lipiodol-emulsion and were sacrificed 24 hours after the injection.
- Group-4: rabbits received Pickering-emulsion and were sacrificed 24 hours after the injection.

Immediately after sacrifice, post-TACE MR scans (3T Magnetom Skyra; Siemens, Erlangen, Germany) using a 15 channels knee coil, was performed for each rabbit to measure and enumerate the liver tumors (Figure-2). Then, livers were resected. Tissues samples from the right and left liver lobes, as well as all the tumors were dissected separately and homogenized with a blender for platinum quantification.

Platinum quantification:

Quantification of platinum was accomplished using mass spectrometry ICP-MS of acid digested samples. Specifically, blood and tissues samples were digested in concentrated trace nitric acid (> 69%, Thermo Fisher Scientific, Waltham, MA, USA) and placed at 60 °C for 24 hours to allow for complete sample digestion. Ultra pure H₂O (18.2 MΩ·cm) is then added to produce a final solution of 3.0% nitric acid (v/v) and 4.0% hydrochloric acid (v/v) in a total sample volume of 5 mL. Quantitative standards were made using individual 1000 µg/mL Pt elemental standards (Inorganic Ventures, Christiansburg, VA, USA) which were combined to create a 100 ng/mL mixed element standard in 2.0% nitric acid (v/v) and 4.0% hydrochloric acid (v/v) in a total sample volume of 50 mL. ICP-MS was performed on a computer-controlled (QTEGRA software) Thermo iCapQ ICP-MS (Thermo Fisher Scientific, Waltham, MA, USA) operating in STD mode and equipped with a ESI SC-2DX PrepFAST autosampler (Omaha, NE, USA). Internal standard was added inline using the prepFAST system. Online dilution was also carried out by the prepFAST system and used to generate calibration curves consisting of 100, 50, 20, 10, 5, 2, 1 ng/mL Pt. Each sample was acquired using 1 survey run (10 sweeps) and 3 main (peak jumping) runs (40 sweeps).

Statistical Analysis

Data were presented as the mean value \pm SD. Prism® software version 5.0 was used to determine the Area Under the Curve (AUC) and to assess differences between means (t-test). $P < 0.05$ was considered statistically significant.

Results

In vitro study:

The platinum release profiles of the two different emulsions are shown in Figure-3. Lipiodol-emulsion demonstrated a rapid drug release compared with Pickering-emulsion. The percentage of platinum released from Lipiodol-emulsions and Pickering-emulsions were respectively: $12.0 \pm 6\%$ vs. $1.5 \pm 0.2\%$ at 1 h, $50.0 \pm 13.8\%$ vs. $4.7 \pm 0.9\%$ at 4h, $85.3 \pm 3.3\%$ vs. $15.8 \pm 3.0\%$ at 24h. Interestingly, the release of platinum from the Lipiodol-emulsions was almost complete after 24h whereas it was still on going from the Pickering-emulsions after 1 month ($72.0 \pm 2.1\%$).

Animal study:

A total of 18 rabbits (3.5 ± 0.3 kG) bearing a total of 33 liver VX2 tumors received selective left hepatic artery injection of 0.5 mL emulsion. No additional embolization with gelfoam was performed since the flow was already completely stopped by the emulsion. Nine rabbits were sacrificed at 1 hour and 9 rabbits were sacrificed at 24 hours. Four rabbits bearing 6 tumors were included in group-1, 5 rabbits bearing 9 tumors in group-2, 4 rabbits bearing 9 tumors in group-3 and 5

rabbits bearing 9 tumors in group-4. The maximal tumor diameter was 15.0 ± 6.4 mM without statistical difference between the 4 groups.

Plasmatic pharmacokinetics of platinum

Plasmatic pharmacokinetics of platinum after injection of the two emulsions are shown in Table-1 and Figure-4. We observed a significantly lower peak of platinum concentrations in the blood (C_{max}) after injection of Pickering-emulsion (0.24 ± 0.07 nG/mL) compared to Lipiodol-emulsion (0.53 ± 0.2 nG/mL, $p < 0.01$). The AUC at 1 hour was significantly lower for the Pickering-emulsion (9.7 ± 2.9 vs. 15.6 ± 7.3 , $p = 0.03$).

Platinum concentration in livers and tumors tissues

Platinum concentrations in livers and tumors tissues are respectively presented in Table-1 and in Table-2. We observed a significantly lower concentration of platinum in the left liver lobe for Pickering-emulsion (0.29 ± 0.07 nG/mG) compared to the Lipiodol-emulsion at 1 hour (1.29 ± 0.77 nG/mG, $p = 0.04$). No difference was observed for the platinum' concentration in right lobe between the different groups. The platinum' concentrations in tumors were not significantly different between the Pickering-emulsion and the Lipiodol-emulsions, neither at 1 hour (8.6 ± 3.3 vs. 15.7 ± 10.4 nG/mG, $p = 0.08$) nor at 24h (5.1 ± 4.8 vs. 2.2 ± 1.9 , $p = 0.06$). The platinum' concentrations ratio between the tumor and the left liver was significantly higher with Pickering-emulsion compared to Lipiodol-emulsion at 1 hour ($(33.2 \pm 14.9$ vs. 18.0 ± 10.8 , $p = 0.02$) and at 24 hours (43.4 ± 42.9 vs. 14.5 ± 6.6 , $p = 0.04$).

Discussion

The terms “water-in-oil emulsion” refers to fine droplets’ dispersions of an aqueous-phase in a continuous oily-phase. The high interfacial energy of the dispersed droplets in the oily-phase contributes to thermodynamic instability and results in a coalescence process when droplets bump into each other and combine to form a larger droplet, so the average droplet size increases over time. However, stable Lipiodol-emulsion are necessary for TACE, allowing slow release of the chemotherapeutic agent into the liver’ tumor feeders for prolonged exposure, while minimizing systemic exposure^{11,12,13}. Stable emulsions can be obtained using substances known as emulsifiers that are able to decrease the interfacial tension between the two phases and are usually included in emulsion formulations. Until now, synthetic surfactants have been used to stabilize Lipiodol-emulsions¹¹. However, these surfactants raise directly or indirectly toxicity issues. On the other hand, Pickering-emulsion uses solid particles as emulsifiers. The adsorption of the solid particles at the water/oil interface lead to the formation of a protective film that resist droplet coalescence and phase separation. The low toxicity and high stability of Pickering-emulsions lend unique properties when compared against classical emulsions stabilized by synthetic surfactants and make them very attractive especially for biomedical applications such as TACE.

We demonstrated that the use of fully biodegradable and biocompatible solid PLGA-nanoparticles in the formulation of emulsion results in a slow release of the oxaliplatin in-vitro. Indeed, the release of oxaliplatin from Lipiodol-emulsion was almost complete within 24 hours whereas it was only 15% when nanoparticules were added into the aqueous-phase. Based on our in-vitro study, we can also see that after 1 month, the total release of oxaliplatin from the Pickering-emulsion was around

72%. This slow release results in a significant decrease of the systemic exposure in vivo with a significant decrease of the plasmatic peak and of the area under the curve. Interestingly, this slow release doesn't result in any significant difference in the tumor drug exposure, neither at 1 hour nor at 24 hours. We can observe a trend for higher platinum concentration in the tumor with Lipiodol-emulsion at 1 hour. Although non significant, this difference is consistent with the "bolus" release of oxaliplatin from the Lipiodol-emulsion demonstrated in-vitro. On the opposite, there is a trend for higher platinum concentration in the tumor with Pickering-emulsion at 24 hours. This prolonged tumor exposure is consistent with the slow release of oxaliplatin demonstrated in-vitro. Interestingly, Pickering-emulsion keeps the value of the Lipiodol in terms of predominant accumulation in hyper vascularized liver tumors. We found that the platinum' concentration ratio between the tumors and the left liver lobe was as high as 33.2 ± 14.9 at 1 hour, significantly higher than the ratio obtained with Lipiodol-emulsion (18.0 ± 10.8 , $p=0.02$).

Oxaliplatin is an effective chemotherapy for patients suffering from colorectal cancer. The Hepatic Arterial Infusion (HAI) of oxaliplatin and its association with systemic chemotherapy has yielded overall response rate of 64% in patients having survived one or more lines of IV chemotherapy¹⁴ and 62% in patients who have progressed on IV oxaliplatin¹⁵. In addition, HAI of oxaliplatin limits systemic and especially neurological toxicities, thanks to a greater hepatic clearance. The HAI of oxaliplatin has demonstrated significant pharmacokinetic advantages over the systemic route (IV) in rabbit VX2 liver tumor models¹⁶. It has been demonstrated that HAI of oxaliplatin results in tissue concentrations that are significantly higher in the tumor versus healthy hepatic tissue in a ratio of 4.3 at 24h. In our study this ratio was even higher at 24h, with a value of 43.4 ± 42.9 for Pickering-emulsions and $14.5 \pm$

6.6 for Lipiodol-emulsions, suggesting a real potential benefit of using a drug delivery platform for the HAI of oxaliplatin in terms of tumor response and systemic toxicities.

We acknowledge some limitations. The first one is that we consider Lipiodol-emulsion as a gold standard to evaluate the release of oxaliplatin from Pickering-emulsion. However, there is no other drug delivery system that we could have used for comparison since oxaliplatin cannot be loaded in drug eluting beads so far. A high ratio of Lipiodol/oxaliplatin (3/1) and a continuous and slow incorporation of oxaliplatin in the Lipiodol were considered in order to obtain the best stability of the Lipiodol-emulsion^{3,10}. Another limitation is that no embolic agent has been injected during TACE procedures. However, the flows in the arteries were always completely stopped at the end of the emulsion' injections and additional embolizations would have resulted in back-flow in extra-hepatic arteries. In addition, we believed that additional embolizations would have introduced bias for the evaluation of the oxaliplatin' release from the emulsions.

Emulsions:			
	<u>Conventional</u>	<u>Pickering</u>	
• <u>Pharmacokinetic</u>	<i>n= 8 rabbits</i>	<i>n= 10 rabbits</i>	
C max (nG/mL)	0.53 ± 0.2	0.24 ± 0.07	p<0.01
AUC	15.6 ± 7.3	9.7 ± 2.9	p=0.03
• <u>Sacrifice: H+1</u>	<i>n= 4 rabbits (group-1)</i>	<i>n= 5 rabbits (group-2)</i>	
Platinum (nG/mG) - Left liver lobe	1.29 ± 0.77	0.29 ± 0.07	p=0.04
- Right liver lobe	0.76 ± 0.49	0.28 ± 0.12	p=0.07
• <u>Sacrifice: H+24</u>	<i>n= 4 rabbits (group-3)</i>	<i>n= 5 rabbits (group-5)</i>	
Platinum (nG/mG) - Left liver lobe	0.14 ± 0.10	0.15 ± 0.08	p=0.4
- Right liver lobe	0.09 ± 0.05	0.10 ± 0.02	p=0.3

[Table-1:](#) Mean platinum concentration (nG/mG) in liver tissues according to the type of emulsion injected and according to the delay before sacrifice.

Emulsions:			
	<u>Conventional</u>	<u>Pickering</u>	
• <u>Sacrifice: H+1</u>	<i>n= 6 tumors (group-1)</i>	<i>n= 9 tumors (group-2)</i>	
Maximal tumor diameter (mM)	14.1 ± 11.1	16.0 ± 5.9	p=0.6
Platinum : - in tumors (nG/mG)	15.7 ± 10.4	8.6 ± 3.3	p=0.08
- ratio tumor/ left liver lobe	18.0 ± 10.8	33.2 ± 14.9	p=0.02
• <u>Sacrifice: H+24</u>	<i>n= 9 tumors (group-3)</i>	<i>n= 9 tumors (group-4)</i>	
Maximal tumor diameter (mM)	15.0 ± 2.9	14.5 ± 5.0	p=0.4
Platinum: - in tumors (nG/mG)	2.2 ± 1.9	5.1 ± 4.8	p=0.06
- ratio tumor/ left liver lobe	14.5 ± 6.6	43.4 ± 42.9	p=0.04

Table-2: Mean platinum concentration (nG/mG) in liver tumors according to the type of emulsion injected and according to the delay before sacrifice.

Figures legends:

Figure-1: Confocal scanning laser microscopy of Pickering-emulsion. Nanoparticules appears in blue (rhodamine) and surrounded the dispersed aqueous droplets in the countinuous oily-phase (Lipiodol), confirming that nanoparticules adsorbed at the interface to stabilize the emulsion.

Figure-2: Trans-Arterial Chemo-Embolization (TACE) with oxaliplatin in a New Zealand White rabbit: angiography in the celiac trunk (A) and in the left-hepatic artery (B), post-TACE MR scan (C) and resected liver (D) showing a 15 mM large VX2 liver tumor (white arrow).

Figure-3: In-vitro release of platinum from the Lipiodol-emulsion and from Pickering emulsion : masse released (A) and percentage released (B).

Figure-4: Platinum plasmatic pharmacokinetics after injection of the emulsions in the left hepatic arteries.

References:

1. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908-943.
2. Takayasu K, Arii S, Matsuo N et al. Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. *AJR Am J Roentgenol* 2000; 175: 699-704.
3. de Baere T, Arai Y, Lencioni R et al. Treatment of Liver Tumors with Lipiodol TACE: Technical Recommendations from Experts Opinion. *Cardiovasc Intervent Radiol* 2015.
4. Gaba RC, Baumgarten S, Omene BO et al. Ethiodized oil uptake does not predict doxorubicin drug delivery after chemoembolization in VX2 liver tumors. *J Vasc Interv Radiol* 2012; 23: 265-273.
5. Jordan O, Denys A, De Baere T et al. Comparative study of chemoembolization loadable beads: in vitro drug release and physical properties of DC bead and hepasphere loaded with doxorubicin and irinotecan. *J Vasc Interv Radiol* 2010; 21: 1084-1090.
6. de Baere T, Zhang X, Aubert B et al. Quantification of tumor uptake of iodized oils and emulsions of iodized oils: experimental study. *Radiology* 1996; 201: 731-735.
7. de Baere T, Dufaux J, Roche A et al. Circulatory alterations induced by intra-arterial injection of iodized oil and emulsions of iodized oil and doxorubicin: experimental study. *Radiology* 1995; 194: 165-170.
8. Pickering EC. Emulsion. *J Chem Soc* 1907; 91.
9. Ramsden. Separation of Solids in the Surface-layers of Solutions and 'Suspension' (Observations on surface-membranes, Bubbles, Emulsions, and

Mechanical Coagulation). Preliminary Account. *Proc. R. Soc. Lond.* 1903; 72: 156-164.

10. Deschamps F, Moine L, Isoardo T et al. Parameters for Stable Water-in-Oil Lipiodol Emulsion for Liver Trans-Arterial Chemo-Eembolization. *Cardiovasc Intervent Radiol* 2017.

11. Deschamps F, Farouil G, Gonzalez W et al. Stabilization Improves Theranostic Properties of Lipiodol(R)-Based Emulsion During Liver Trans-arterial Chemo-embolization in a VX2 Rabbit Model. *Cardiovasc Intervent Radiol* 2017; 40: 907-913.

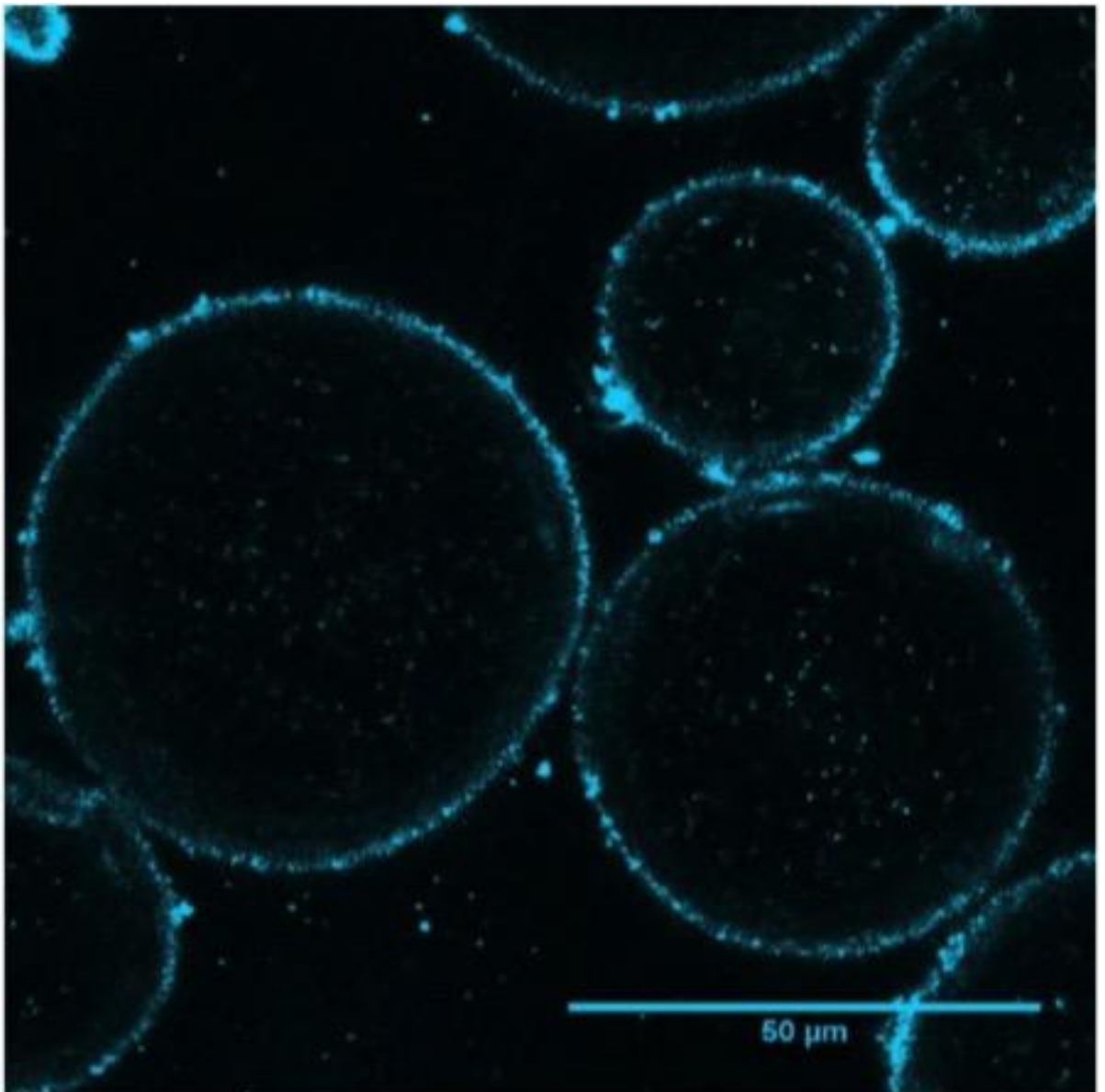
12. Choi JW, Cho HJ, Park JH et al. Comparison of drug release and pharmacokinetics after transarterial chemoembolization using diverse lipiodol emulsions and drug-eluting beads. *PLoS One* 2014; 9: e115898.

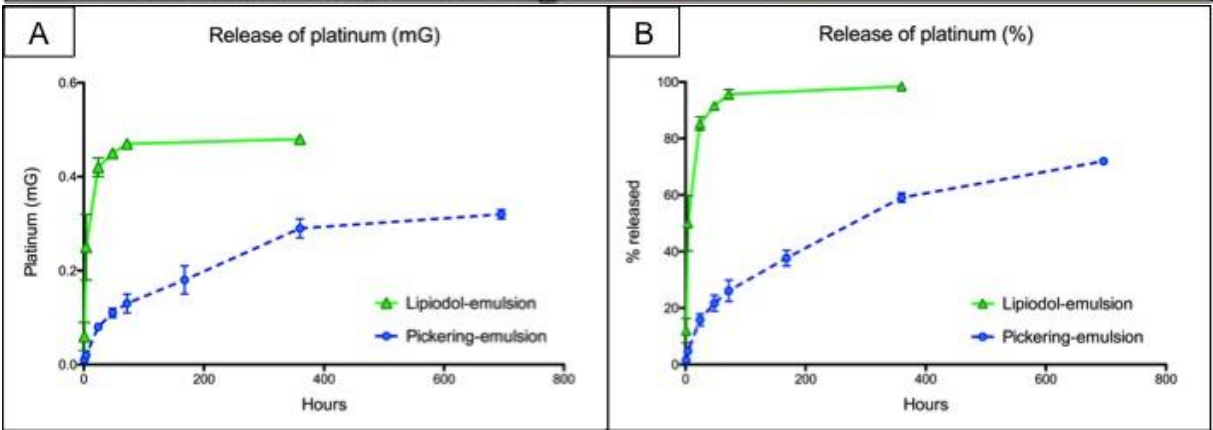
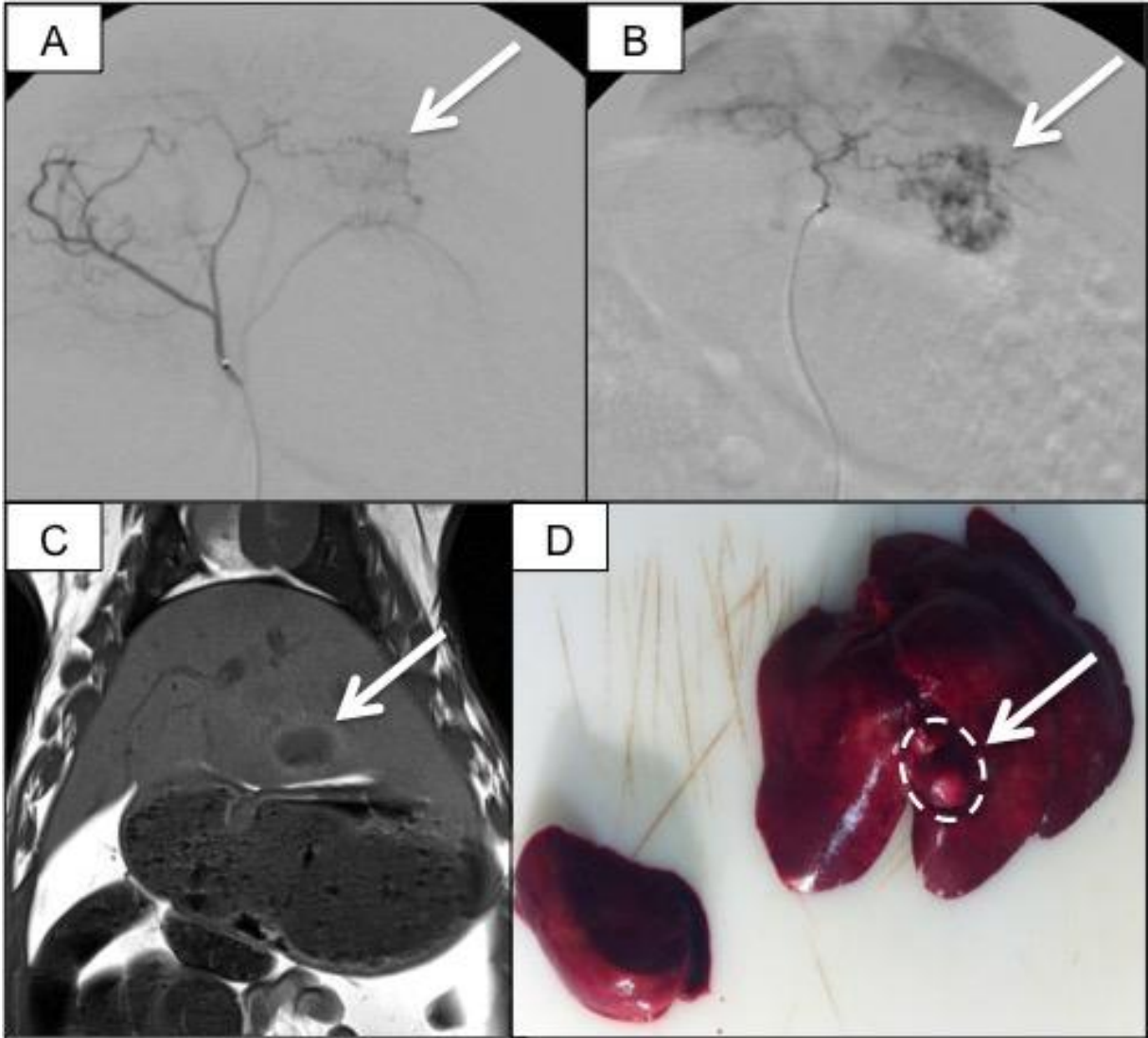
13. Boulin M, Schmitt A, Delhom E et al. Improved stability of lipiodol-drug emulsion for transarterial chemoembolisation of hepatocellular carcinoma results in improved pharmacokinetic profile: Proof of concept using idarubicin. *Eur Radiol* 2016; 26: 601-609.

14. Ducreux M, Ychou M, Laplanche A et al. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol* 2005; 23: 4881-4887.

15. Boige V, Malka D, Elias D et al. Hepatic arterial infusion of oxaliplatin and intravenous LV5FU2 in unresectable liver metastases from colorectal cancer after systemic chemotherapy failure. *Ann Surg Oncol* 2008; 15: 219-226.

16. Dzodic R, Gomez-Abuin G, Rougier P et al. Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: comparative results with cisplatin using a rabbit VX2 tumor model. *Anticancer Drugs* 2004; 15: 647-650.





Pharmacokinetics

