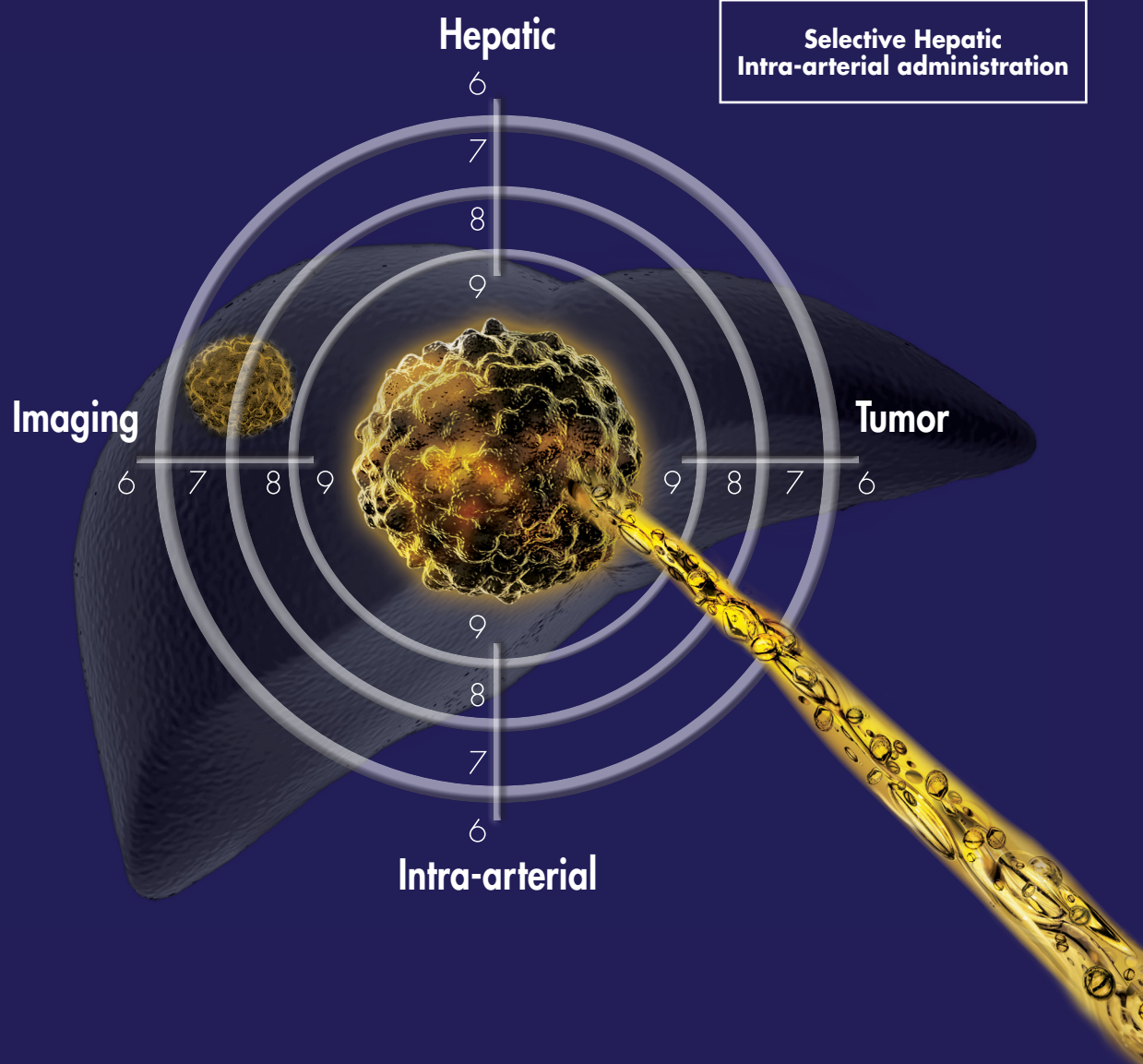




# LIPIODOL® ULTRA FLUID

Ethyl ester of iodized fatty acids of poppy seed oil

## Imaging tumors in adults with known HCC



**Guerbet** |   
Contrast for Life

Indications and dosage may vary country to country.  
Countries with indication of Lipiodol® for liver imaging : France, USA, Brazil, Mexico,  
Argentina, Chile, Colombia, Peru, Uruguay, Venezuela, India, Vietnam, Burkina Faso, Egypt, Iraq, Morocco, Tunisia.  
For complete information please refer to country's local SPC.  
For a copy of the SPC, please contact a member of Guerbet.



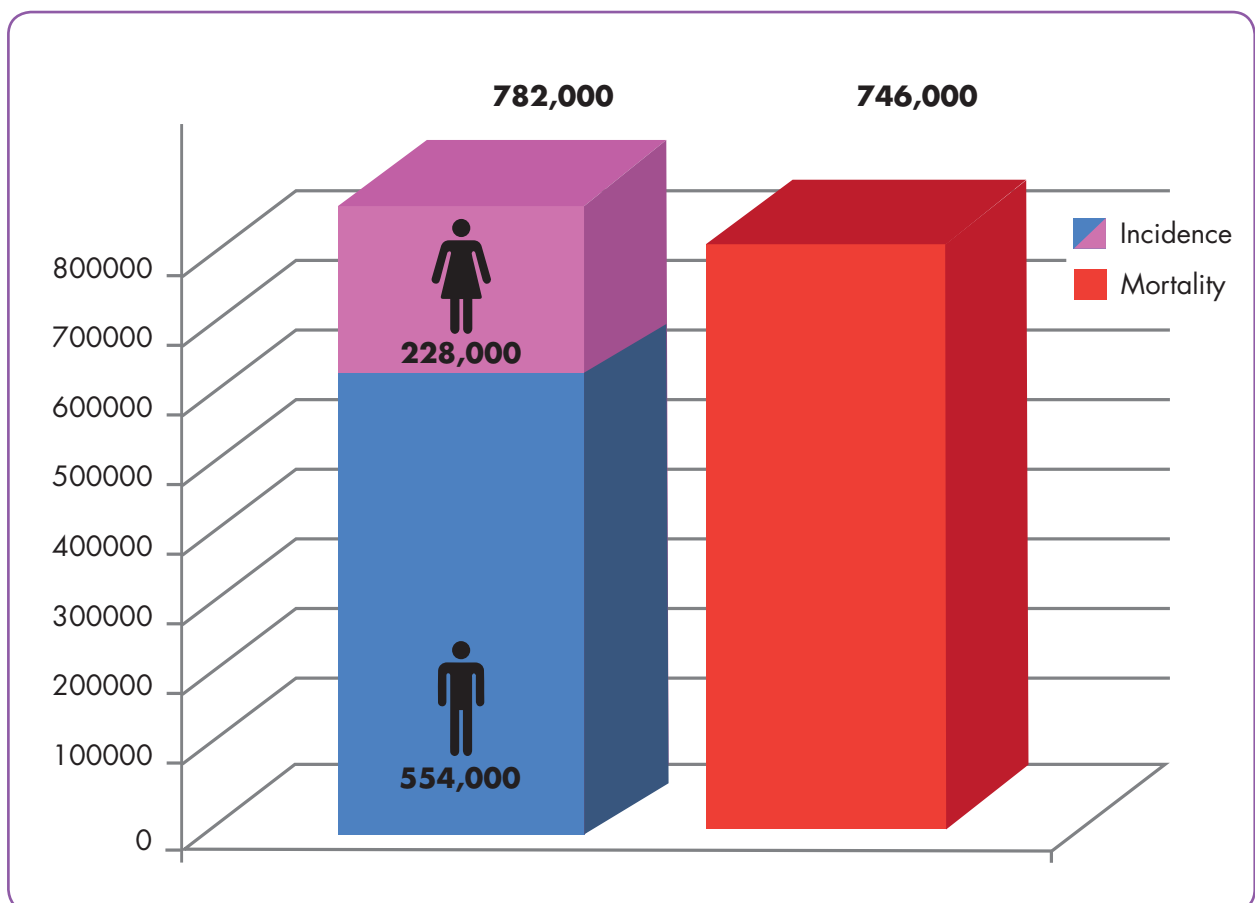


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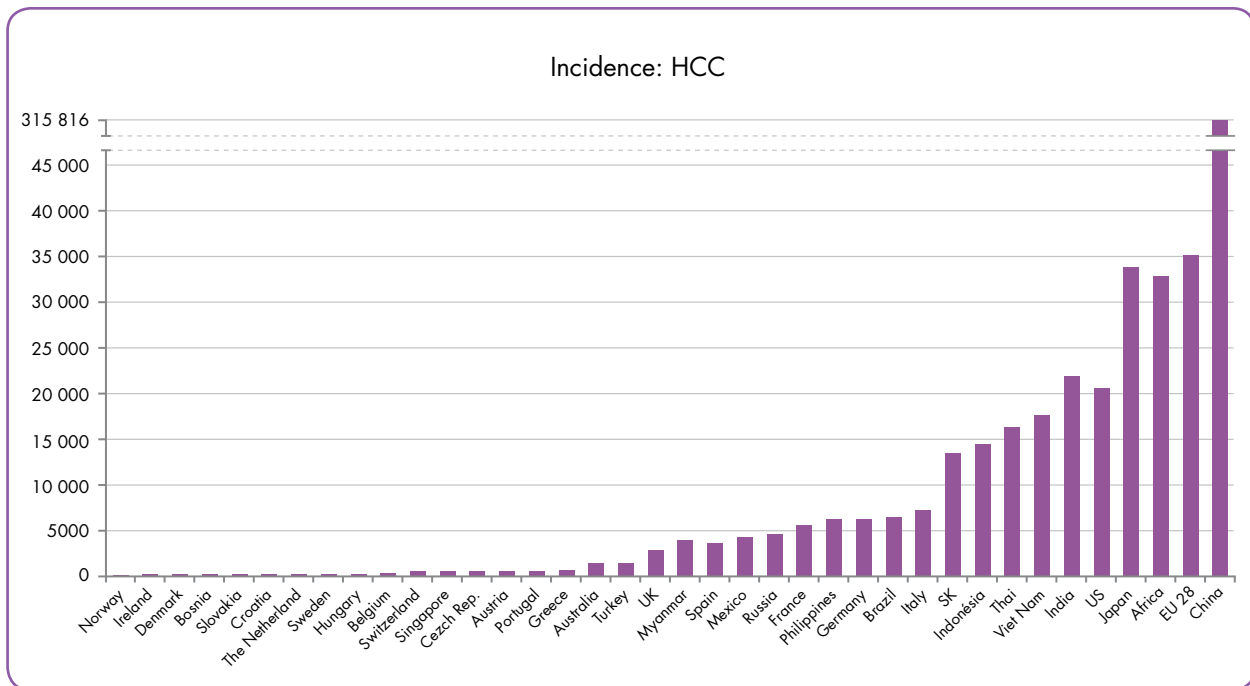
# Primary liver cancer epidemiology

- 782,000 new primary liver cancer cases reported worldwide occurred in 2012 <sup>(1)</sup>
- 5th most common cancer in men (554,000 cases) ; 9th in women (228,000 cases) <sup>(1)</sup>
- 2nd most common cause of death from cancer worldwide : 746,000 deaths in 2012 <sup>(1)</sup>
- HCC represents more than 90% of primary liver cancers <sup>(2)</sup>
- Very poor prognosis



## PRIMARY LIVER CANCER – A DEADLY DISEASE

# HCC incidence – global snapshot



Sources Globocan 2012 + Extrapolation  
 EU = 28 European Union Countries  
 Africa = 50 countries

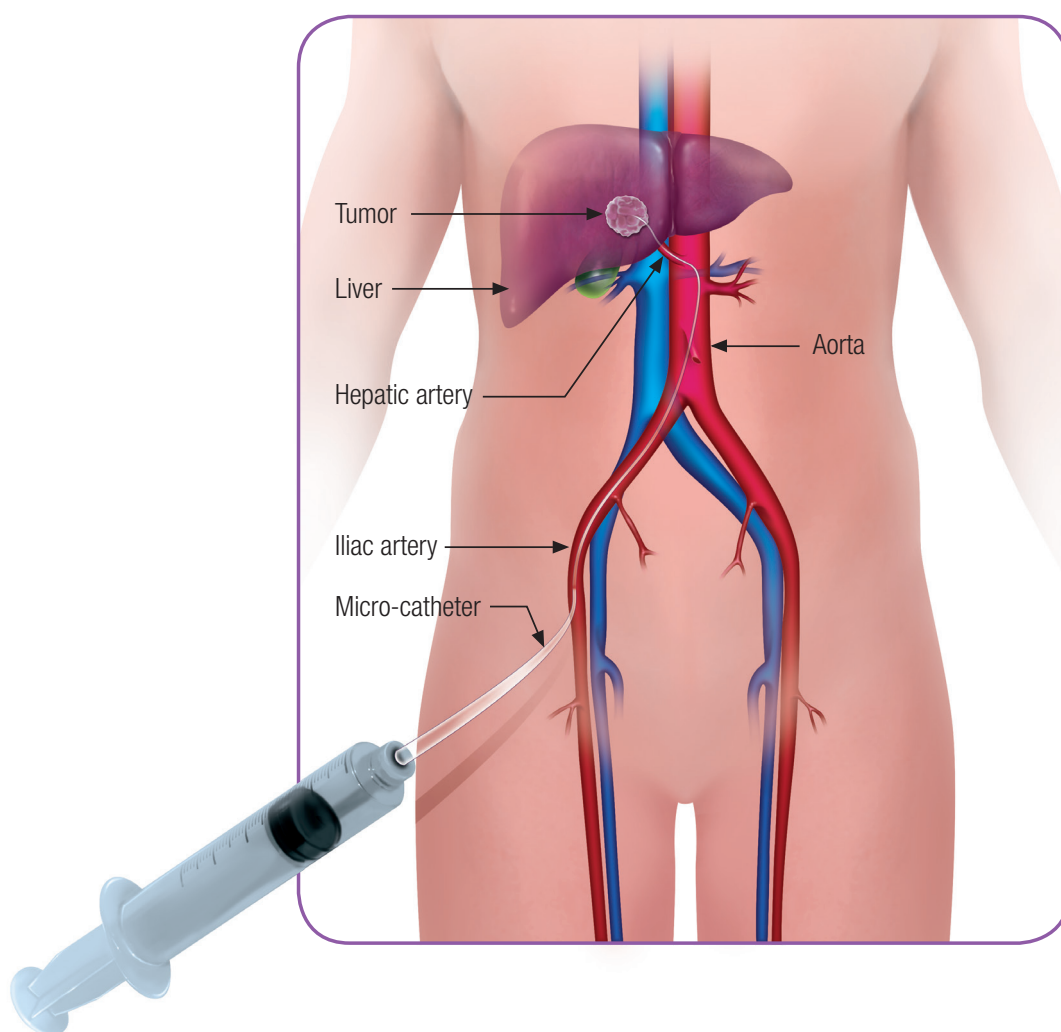
## HCC etiology

- Hepatitis B & C
- Prolonged alcohol abuse
- Non alcoholic steato hepatitis (NASH)

## PRIMARY LIVER CANCER – A WORLDWIDE BURDEN

# Lipiodol® indication in HCC patients

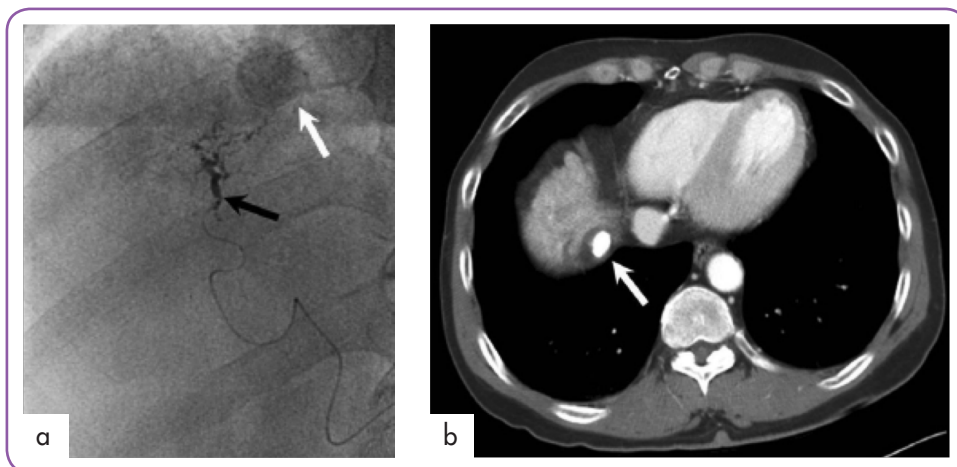
Lipiodol® is indicated for *selective hepatic intra-arterial* use for *imaging tumors* in adults with known *HCC*.



**LIPIODOL® – OPTIMAL TUMOR VISUALIZATION IN HCC**

# Lipiodol® in liver CT

- Has a high affinity for primary hepatic tumors<sup>(3)</sup>
- Moves as oil droplets in the feeding vessels of HCCs
- Deposits in the tumor<sup>(3)</sup> when injected into the hepatic artery<sup>(4)</sup>
- Optimizes visualization of HCCs compared to the surrounding liver parenchyma<sup>(3)</sup>
- Retained in 85% of HCCs<sup>(5)</sup>
- Prolonged retention in liver tumors<sup>(6)</sup>



**(a)** A radiograph obtained during intra-arterial Lipiodol® injection. 2 mL of Lipiodol® was injected via the subsegmental branch of the right anterior hepatic artery (black arrow). Note the Lipiodol® retention in the subphrenic tumour (white arrow)<sup>(7)</sup>

**(b)** On 1-month follow-up CT showing a focal Lipiodol® accumulation (arrow)<sup>(7)</sup>

**LIPIODOL® – ENHANCED VISUALIZATION OF HCC TUMOR ON CT SCAN**



## Safety

Bruneton JN. et al. *Gastrointest. Radiol.* (1988) <sup>(6)</sup>

**Aims:** To evaluate the tolerance and value of HIAL (Hepatic IntraArterial Lipiodol®)

**Materials and Methods:** Single center prospective study

**138 patients** with hepatic tumors (n=118) or non-complicated cirrhosis (n=20) received HIAL.

« Once the catheter was correctly positioned, a 3-way valve was used to obtain the emulsion: 10 ml serum, 10 ml water-soluble contrast medium, 10 ml Lipiodol® [...]. The CT scans were obtained 2 h following Lipiodol® injection. »

### Results:

« **Patients' tolerance of HIAL examination was excellent**, with no abdominal or thoracic clinical signs in cases of selective hepatic artery injection. »

« When injection was nonselective, certain side effects were observed immediately after injection. One-third of patients in whom the product was injected into the celiac trunk experienced nausea or vomiting that regressed spontaneously in less than 15 min. »

« In 2 patients, the product was injected into the upper mesenteric artery for the work-up of hepatic metastases: both developed diarrhea that lasted for 6 h, then disappeared without any sequelae. »

« No respiratory complications were observed, even in patients with chronic respiratory insufficiency. »

### Conclusion:

« HIAL combined with CT seems the imaging technique of choice when a malignant liver tumor is suspected or a known lesion requires investigation. In addition to providing valuable information on the location of lesions, the technique differentiates various semiologic types that can serve as the basis for deciding on endovascular therapy. »

« ...All patients received 10 ml Lipiodol® emulsion injected by an arterial route; **there were no serious complications.** »

**LIPIODOL® – NO SERIOUS ADVERSE EVENTS FOLLOWING HEPATIC INTRA-ARTERIAL INJECTION**





## Efficacy

Rizvi S. et al. *Transplant. Proc.* (2006)<sup>(3)</sup>

**Aim:** To correlate the post Lipiodol® CT scan findings with respect to tumor size in the explanted liver

**Materials and Methods:** Retrospective, single center study

**21 patients** with end stage liver disease (ESLD) with high preoperative suspicion of HCC who had an hepatic arteriogram with Lipiodol® injection as part of their pretransplant work-up.

**Results:**

« Overall accuracy of Lipiodol® CT scan test was found to be 0.91, which is considered superior to the IV contrast CT alone. »

**Conclusion:**

« ... Lipiodol® injection can be considered during the pre-transplantation workup of high-risk cirrhotic patients, since the current model for End-Stage Liver Disease scoring system for HCC is built on the ultimate bulk of the tumor. »

**LIPIODOL® – ALLOWS ACCURATE ASSESSMENT OF DISEASE EXTENT**



## Efficacy

Ngan H. et al. Br. J. Radiol. (1990) <sup>(8)</sup>

**Aim:** To evaluate the sensitivity & specificity of the techniques of Lipiodol® – CT

**Materials and Methods:** Prospective, single center study

- 60 patients suspected of having an HCC
- Lipiodol®-CT was performed 6-13 days following intra-arterial injection of Lipiodol®

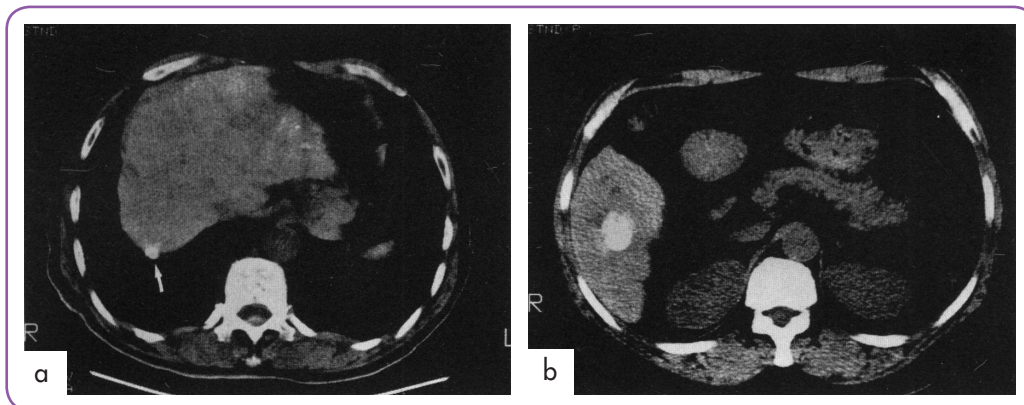
**Objectives:**

- To investigate the specificity of Lipiodol®-CT
- To see if Lipiodol® can detect an HCC while it is small and asymptomatic
- To see if resectability rate can be improved
- To analyze the pattern of uptake of Lipiodol® by the tumor

**Results:**

«The size of the HCCs ranged from 0.8 cm to 11 cm in diameter with the median size at 2.2 cm.»  
« Four uptake patterns were found: homogeneous, patchy, no uptake, faint uptake by the liver.»  
«...In the diagnosis of HCC, Lipiodol®-CT had an overall **sensitivity of 97.1%**, an accuracy of 88.3% and a **specificity of 76.9%** [...].»

**LIPIODOL® – CAN DETECT SMALL HCCs NOT SEEN ON CT OR ANGIOGRAPHY**



**(a)** A 0.8 cm HCC with dense homogeneous uptake of Lipiodol® (arrow) in right lobe of the liver  
**(b)** An HCC 2.5 x 1.8 cm with dense homogeneous uptake in the right lobe.

**Conclusion:**

« ... for high risk patients, Lipiodol®-CT is useful in the detection of HCCs while they are relatively small. In view of its ability to demonstrate daughter nodules at times not seen by conventional CT or hepatic angiography, the technique helps to determine whether the tumor is suitable for surgical resection or whether it would better treat with chemotherapy, including trans-arterial chemo-embolization. »

«... by detecting the tumor earlier, improvement in the previously reported resectability rate could be achieved. »

**LIPIODOL® – ENABLES A BETTER TREATMENT CHOICE**



## Efficacy

Kim J. et al. Clin. Radiol. (2015) (7)

**Aim:** To compare the therapeutic efficacy of fluoroscopy-guided radiofrequency ablation (F-RFA) and ultrasound-guided RFA (US-RFA) in treatment of small HCCs.

**Materials and Methods:** Prospective, single center study

**93 patients** with small HCCs underwent percutaneous RFA.

- Group A: 42 patients with 46 HCCs invisible on US → F-RFA was performed following intra-arterial iodized oil injection
- Group B: 51 patients with 58 HCCs → US-RFA was performed

**Endpoints:** technical effectiveness, complications, local tumor progression, and patient survival

### Results:

- « Technical effectiveness rates were 97.8% in group A and 96.6% in group B. There was no significant difference of technical effectiveness between the two groups ( $p = 0.65$ ).
- There was no major complication in both groups. »

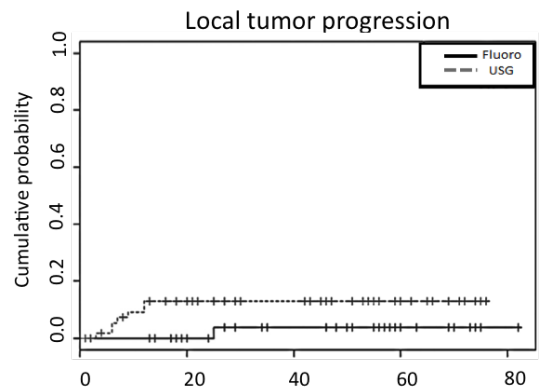
### Conclusion:

« ...F-RFA following intra-arterial iodized oil injection is a feasible and safe therapeutic option for small HCC. Most US-invisible HCCs, including tumors in unfavorable locations, could be successfully treated using this technique. Its therapeutic efficacy was comparable to that of US-RFA. »

**LIPIODOL® + RFA – A FEASIBLE AND SAFE THERAPEUTIC OPTION**

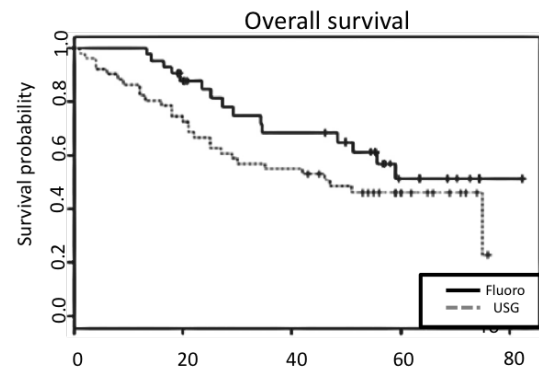
**Results:**

**Local tumor progression:** « The 1, 3, and 5-year local tumour progression rates were 0%, 3.7%, and 3.7% (group A) and 13%, 13%, and 13% (group B). **The local tumour progression rates of group A were lower** than those of group B with marginal significance ( $p=0.05$ ). »



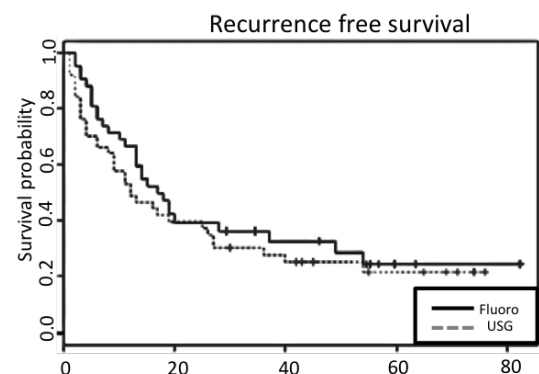
**Results:**

**Patient overall survival:** « In group A, the cumulative overall survival rates at 1, 3, and 5 years were 100%, 68.3%, and 51.2% (group A) and 82.4%, 54.9%, and 46.1% (group B). The overall survival rates were not significantly different between the two groups ( $p=0.26$ ). »



**Results:**

**Recurrence-free survival:** « The 1, 3, and 5 year recurrence-free survival rates were 68.8%, 37.5% and 25.3% in group A and 48.7%, 27.8%, and 21.6% in group B, respectively. The recurrence-free survival rates were not significantly different between the two groups ( $p=0.38$ ). »



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- (3) Rizvi S. et al. Is post-Lipiodol CT Better Than IV Contrast CT Scan for Early Detection of HCC? A Single Liver Transplant Center Experience, Transplant. Proc., 2006; 38: 2993-2995
- (4) Gonsalves C.F. et al. Chemoembolization of hepatic malignancy, Abdom. Imaging, 2009; 34:557-65
- (5) Pourgholami M. et al. Regression of Novikoff rat hepatocellular carcinoma following locoregional administration of a novel formulation of clofazimine in Lipiodol, Cancer Letters, 2004; 207: 37-47
- (6) Bruneton JN. et al. Hepatic Intraarterial Lipiodol: Technique, Semiologic Patterns, and Value for Hepatic Tumors, Gastrointest. Radiol., 1988; 13:45-51
- (7) Kim J. et al, Fluoroscopy-guided radiofrequency ablation for small hepatocellular carcinoma: a retrospective comparison with ultrasound-guided ablation, Clin. Radiol., 2015; 70, 1009-1015
- (8) Ngan H. et al. Lipiodol computerized tomography: how sensitive and specific is the technique in the diagnosis of hepatocellular carcinoma? Br. J. Radiol., 1990; 63: 771-775





**LIPIODOL® ULTRA-FLUID. Composition:** Ethyl esters of iodized fatty acids of poppy seed oil 10 mL, corresponding to an iodine content of 480 mg/mL.

**Indications(\*\*):** In diagnostic radiology - Hysterosalpingography - Ascending urethrography - Lymphography - Sialography - Fistulography and exploration of abscesses - Exploration of frontal sinuses - Pre and post-operative cholangiography. In interventional radiology - Visualisation and localization (by selective intra-arterial use during CT) of liver lesions in adults with known or suspected hepatocellular carcinoma - Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma at intermediate stage, in adults - Selective embolization in combination with Histoacryl glue (particularly for arteriovenous malformation or aneurysms) - Selective injections of LIPIODOL® ULTRA-FLUID into the hepatic artery for diagnostic purposes where a spiral CT scan is not practical. In endocrinology - Prevention of severe cases of iodine deficiency.

**Posology and method of administration (\*):** have to be adapted according to the type of examination, the territories explored, the age and weight of the patient. The volume to be administered depends on the particular requirements of the technique and the size of the patient. Contraindications: Hypersensitivity to LIPIODOL® ULTRA-FLUID - Confirmed hyperthyroidism - Patients with traumatic injuries, recent haemorrhage or bleeding - Hysterosalpingography during pregnancy or acute pelvic inflammation - Bronchography. In interventional radiology (Trans-Arterial Chemo-Embolization), Administration in liver areas with dilated bile ducts unless drainage has been performed.

**Special warnings and special precautions for use(\*):** There is a risk of hypersensitivity regardless of the dose administered. **Lymphography:** Pulmonary embolism may occur immediately or after few hours to days from inadvertent systemic vascular injection or intravasation of LIPIODOL® ULTRA-FLUID: Perform radiological monitoring during LIPIODOL® ULTRA-FLUID injection and avoid use in patients with severely impaired lung function, cardiorespiratory failure or right-sided cardiac overload. **Hypersensitivity:** all iodinated contrast agents can lead to minor or major hypersensitivity reactions, which can be life-threatening. These hypersensitivity reactions are of an allergic nature (known as anaphylactic reactions if they are serious) or a non-allergic nature. They can be immediate (occurring within 60 min) or delayed (not occurring until up to 7 days later). Anaphylactic reactions are immediate and can be fatal. They are dose-independent, can occur right from the first administration of the product, and are often unpredictable: avoid use in patients with a history of sensitivity to other iodinated contrast agents, bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to LIPIODOL® ULTRA-FLUID. **Thyroid:** can cause hyperthyroidism in predisposed patients. Lymphography saturates the thyroid with iodine for several months and thyroid exploration should be performed before and after the procedure. Oesophageal varices must be carefully monitored. Hepatic intra-arterial treatment can progressively cause an irreversible liver insufficiency in patients with serious liver malfunction and/or undergoing close multiple sessions. The risk of superinfection in the treated area is normally prevented by administration of antibiotics. **Embolization with glue:** An early polymerisation reaction may exceptionally occur between LIPIODOL® ULTRA-FLUID and certain surgical glues, or even certain batches of glue. Before using new batches of LIPIODOL® ULTRA-FLUID or surgical glue, the compatibility of LIPIODOL® ULTRA-FLUID and the glue must be tested in vitro. **Interaction with other medicinal products and other forms of interaction (\*):** Metformin, Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, Diuretics, Interleukin II. **Fertility, pregnancy and lactation (\*):** LIPIODOL® ULTRA-FLUID must only be used in pregnant women if absolutely necessary and under strict medical supervision. Breastfeeding should be discontinued if LIPIODOL® ULTRA-FLUID must be used. **Effects on ability to drive and use machines:** The effects on ability to drive and to use machines have not been investigated. **Undesirable effects(\*)** most adverse effects are dose-related and dosage should therefore be kept as low as possible: hypersensitivity, anaphylactic reaction, anaphylactoid reaction, vomiting, diarrhea, nausea, fever, pain, dyspnea, cough, hypothyroidism, hyperthyroidism, thyroiditis, pulmonary embolism, cerebral embolism, retinal vein thrombosis, lymphoedema aggravation, hepatic vein thrombosis, granuloma. **Overdose (\*)** The total dose of LIPIODOL® ULTRA-FLUID administered must not exceed 20 mL. **Pharmacodynamic properties (\*)** Pharmacotherapeutic group: X-ray contrast media, iodinated; ATC code: V08A D01. Water-insoluble iodinated contrast medium. **Presentation (\*\*)** - 10 mL glass ampoule, box of 1 - 10 mL glass ampoule, box of 50. **Marketing authorization holder (\*):** Guerbet - BP 57400 - F-95943 Roissy CdG cedex - FRANCE. **Information:** tel : 33 (0) 1 45 91 50 00. **Revision:** September 2, 2015.

(\*) For complete information please refer to the local Summary of Product Characteristics

(\*\*) Indications, volumes and presentations may differ from country to country.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

Guerbet



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