LIPIODOL® ULTRA FLUID

Ethyl ester of iodized fatty acids of poppy seed oil

Lipiodol® efficacy & safety for improved overall survival in HCC [1,2,3,4]

Endorsed by International HCC Treatment Guidelines [5,6,7,8]

Guerbet

Contrast for Life

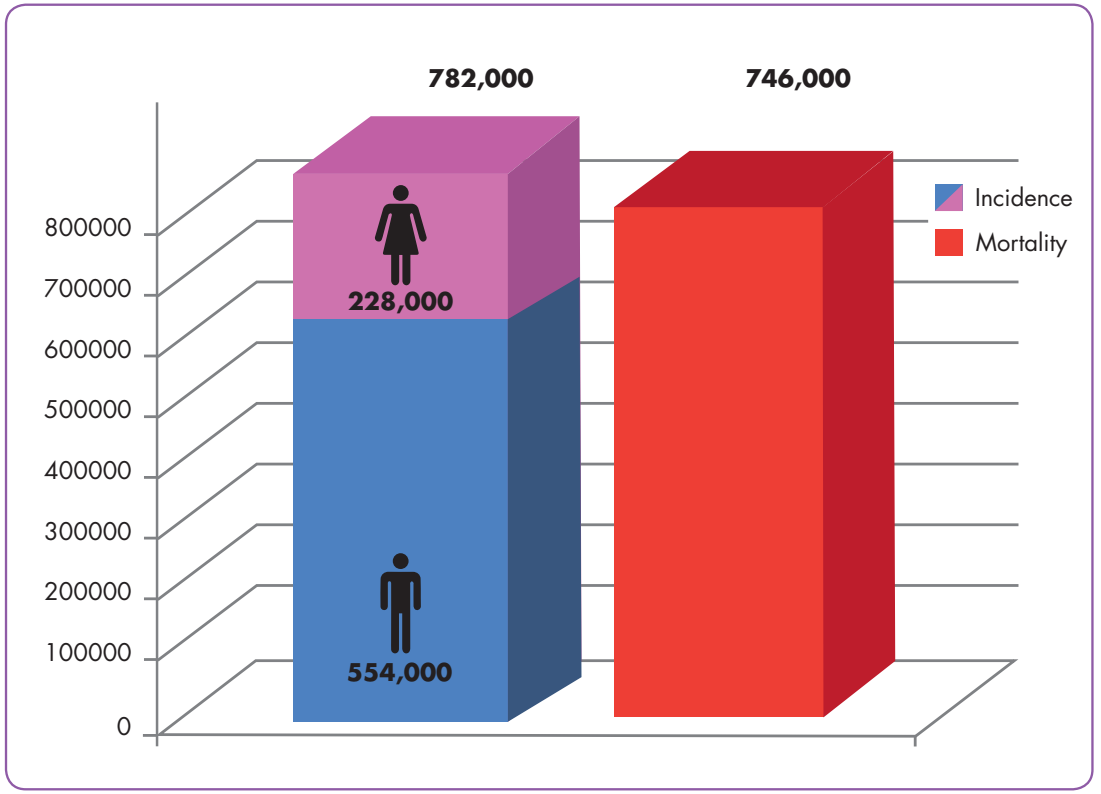
Indications and dosage may vary from country to country.
Countries in which cTACE indication is registered: France, Japan, South Korea, Austria, Peru, Turkey, Hungary, Czech Republic, Mongolia, Argentina, The Netherlands, Vietnam, Thailand, Mexico, Brazil & Taiwan.
For complete information please refer to country's local SPC.
For a copy of the SPC, please contact a member of Guerbet.

1. Ikeda M. et al., Prospective Study of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: An Asian Cooperative Study between Japan and Korea J. Vasc. Interv. Radiol. 2013; 24: 490-500
2. Lo C.M. et al. Randomized Controlled Trial of Transarterial Lipiodol Chemoembolization for Unresectable Hepatocellular Carcinoma Hepatology 2002; 35: 1164-1171
3. Llovet J.M. et al. arterial embolization or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial The Lancet 2002; 359: 1734-1739
4. Llovet J.M. et al . Systematic Review of Randomized Trials for Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival Hepathology 2003; 37: 429-442
5. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J. Hepatol. 2012; 56: 908-943
6. Japan Society of Hepatology, Recommendation, Chapter 5, Hepatology Research 2010; 40 (Suppl.1) 96-112
7. Bruix J. & Sherman M. AASLD Practice Guidelines; American Association for Study of the Liver Diseases; Hepatology 2011; 53: 1020-1022
8. Chinese guidelines 2011 edition, Chin. Clin. Oncol. 2012; 1:10

Contents

Primary liver cancer epidemiology

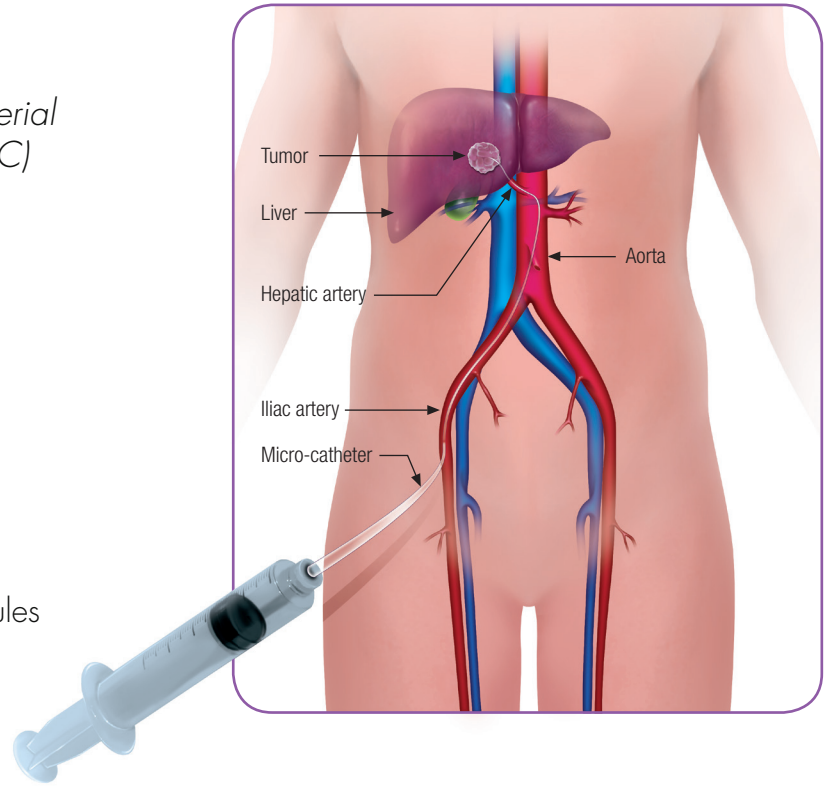
- 782,000 new cancer cases worldwide occurred in 2012 [1]
- 5th most common cancer in men (554,000 cases) and the 9th in women (228,000 cases) [1]
- 2nd most common cause of death from cancer worldwide, 746,000 deaths in 2012 [1]
- HCC represents more than 90% of primary liver cancers [2]
- Very poor prognosis

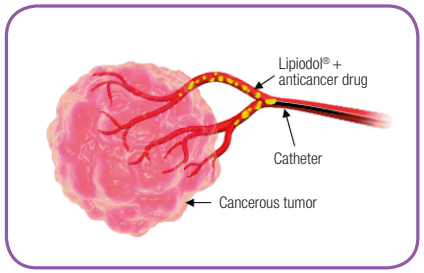


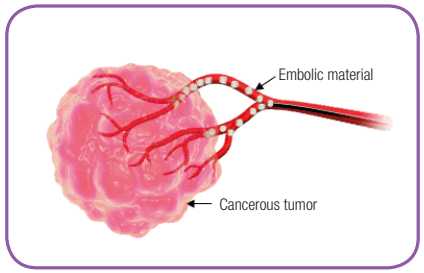
Lipiodol® indication in HCC

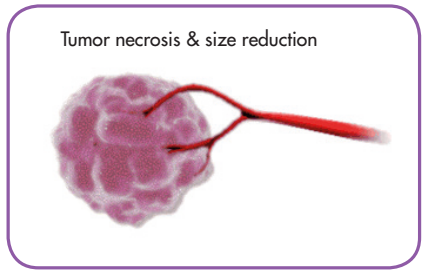
Visualization, Localization *and* ***Vectorization*** *during Trans-Arterial* ***Chemoembolization*** *(TACE) of hepatocellular carcinoma (HCC) at intermediate stage, in adults*

- HCC etiology
  - Hepatitis B & C
  - Prolonged alcohol abuse
  - Non alcoholic steato hepatitis (NASH)
- Conventional Trans Arterial Chemoembolization (cTACE)
  - cTACE = Lipiodol® TACE
  - Intratumor injection of Lipiodol® + anticancer agent
  - Complementary embolization with gelatin sponge or particules





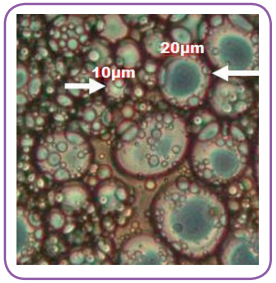




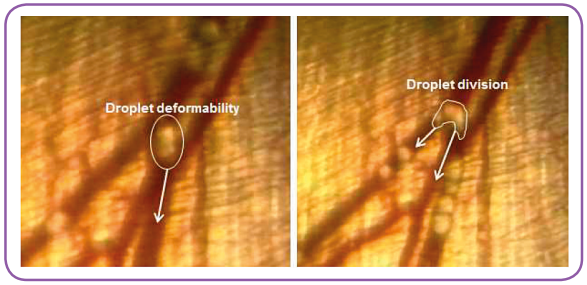
LIPIODOL® – INDICATED TO FIGHT HCC

Lipiodol® mechanisms-of-action

- Lipiodol®-drug droplets are deformable & heterogeneous in size [3-4]

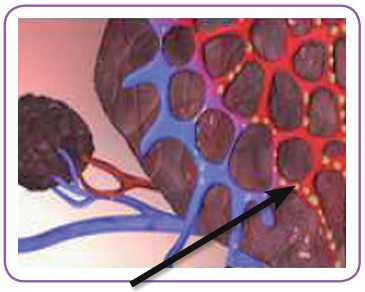


- Microscopic image
- Lipiodol® + doxorubicin droplets
- Source: Guerbet Group

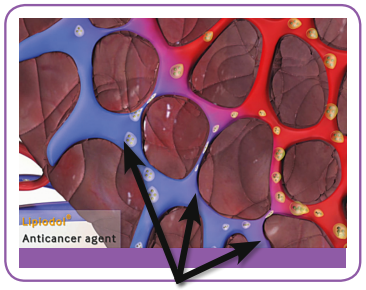


- Extract of in vivo video microscopy of rat cremastervessels perfused with Lipiodol®
- Courtesy of Prof. Th. de Baère

- Lipiodol®-drug droplets allow both proximal & distal anticancer drug delivery [3]

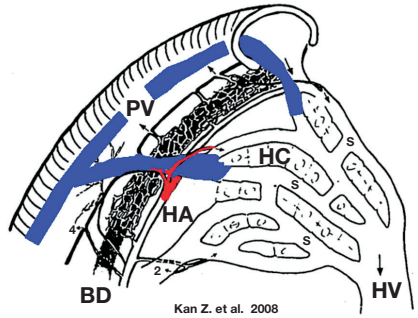


Lipiodol® + anticancer agent



Droplet deformability

- Lipiodol®-drug droplets achieve transient dual embolization (arterial & portal vessels) [5]

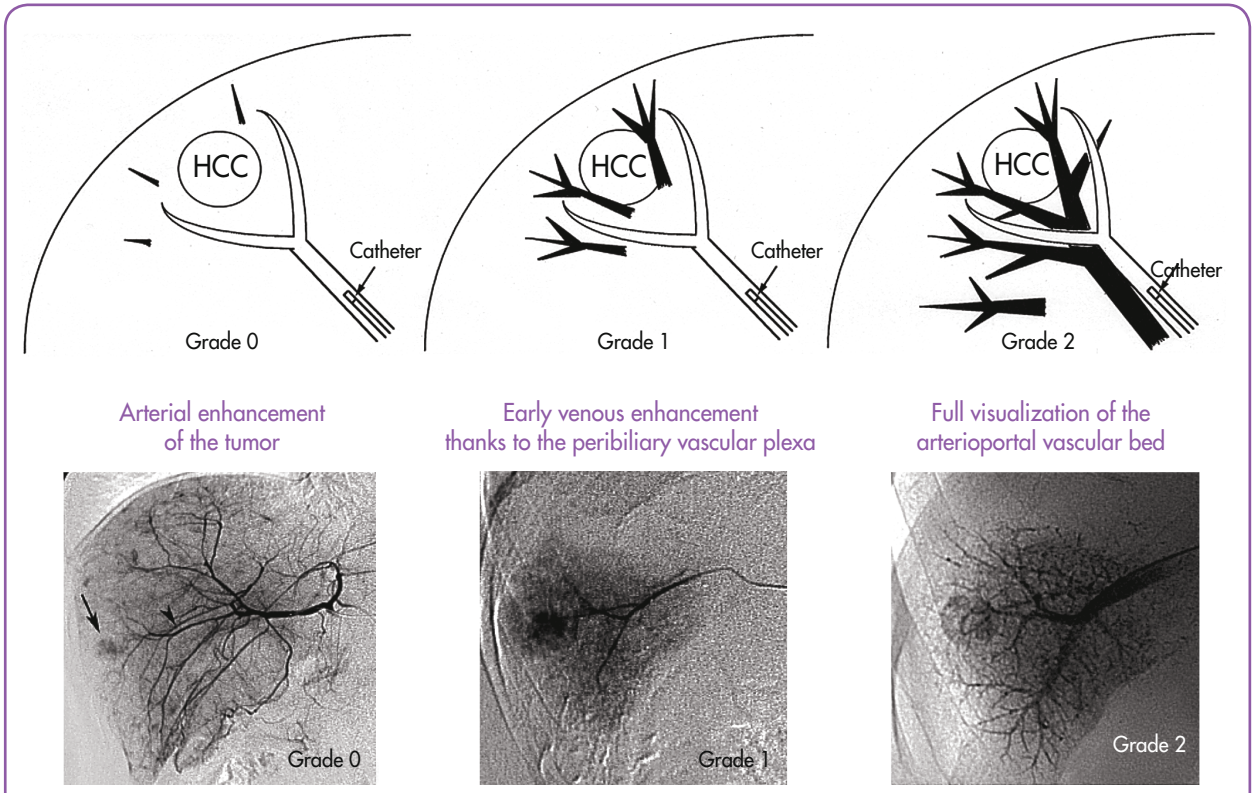


PV = Portal Venule
HA = Hepatic Arteriole
BD = Bile Duct
HV = Hepatic Venule
HC = Hepatocytes

LIPIODOL®-DRUG DROPLETS DEFORMABILITY & SIZE DIVERSITY FOR OPTIMAL DRUG DELIVERY & DUAL EMBOLIZATION

Dual arterial & venous perfusion for efficient cTACE[6]

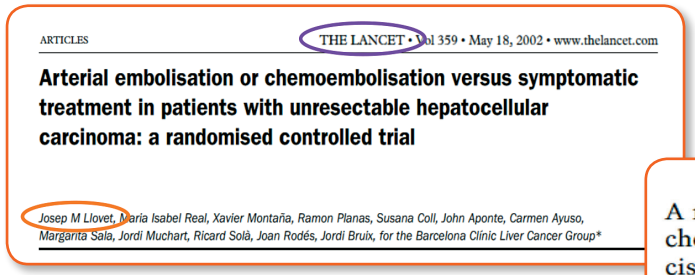
Radiological evidence of dual vascularization of HCC



Grades of portal vein visualization & size of tumors treated with ultraselective cTACE

PERIBILIARY PLEXA ALLOW LIPIODOL®–DRUG DROPLETS SHUNTING FROM HEPATIC ARTERY TO PORTAL VEIN

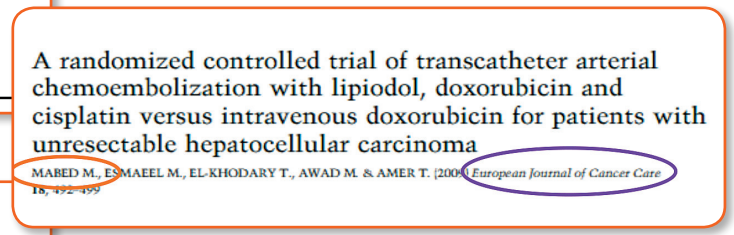
Landmark clinical studies



ARTICLES THE LANCET • Vol 359 • May 18, 2002 • www.thelancet.com

Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial

*Josep M Llovet, Maria Isabel Real, Xavier Montaña, Ramon Planas, Susana Coll, John Aponte, Carmen Ayuso, Margarita Sala, Jordi Muchart, Ricard Solà, Joan Rodés, Jordi Bruix, for the Barcelona Clínic Liver Cancer Group**



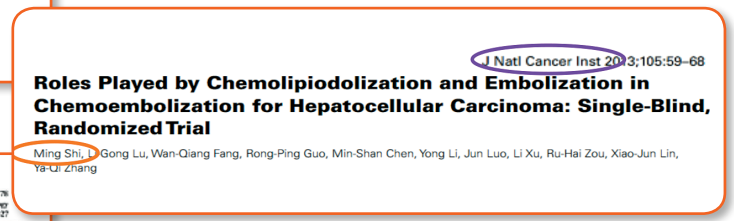
A randomized controlled trial of transcatheter arterial chemoembolization with lipiodol, doxorubicin and cisplatin versus intravenous doxorubicin for patients with unresectable hepatocellular carcinoma

MABED M., ESMAEEL M., EL-KHODARY T., AWAD M. & AMER T. (2004) *European Journal of Cancer Care* 13, 492–499

HEPATOLOGY 2002;35:1164-1171

Randomized Controlled Trial of Transarterial Lipiodol Chemoembolization for Unresectable Hepatocellular Carcinoma

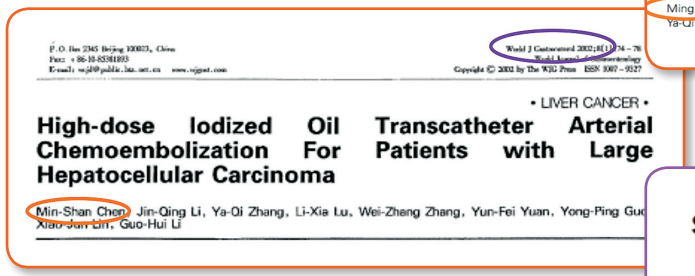
Chung-Mau Lo, Henry Ngan, Wai-Kuen Tso, Chi-Leung Liu, Chi-Ming Lam, Ronnie Tung-Ping Poon, Sheung-Tat Fan, and John Wong



J Natl Cancer Inst 2003;105:59–68

Roles Played by Chemolipiodolization and Embolization in Chemoembolization for Hepatocellular Carcinoma: Single-Blind, Randomized Trial

Ming Shi, Li-Gong Lu, Wan-Qiang Fang, Rong-Ping Guo, Min-Shan Chen, Yong Li, Jun Luo, Li Xu, Ru-Hai Zou, Xiao-Jun Lin, Ya-Qi Zhang

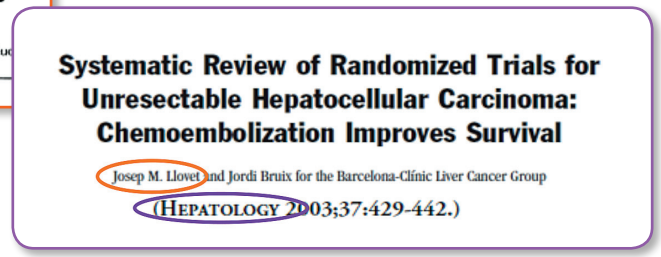


World J Gastroenterol 2002;8(1):74–76

• LIVER CANCER •

High-dose Iodized Oil Transcatheter Arterial Chemoembolization For Patients with Large Hepatocellular Carcinoma

Min-Shan Chen, Jin-Qing Li, Ya-Qi Zhang, Li-Xia Lu, Wei-Zhang Zhang, Yun-Fei Yuan, Yong-Ping Guo, Xiao-Jun Lin, Guo-Hui Li



Systematic Review of Randomized Trials for Unresectable Hepatocellular Carcinoma: Chemoembolization Improves Survival

Josep M. Llovet and Jordi Bruix for the Barcelona-Clínic Liver Cancer Group

(HEPATOLOGY 2003;37:429-442.)

5 MAJOR RANDOMIZED CONTROLLED TRIALS & 1 META-ANALYSIS

Efficacy

Llovet J. M. et al. The Lancet (2002)[8]

Multicenter, randomized, controlled clinical trial.

112 patients with unresectable HCC (Child-Pugh class A or B)

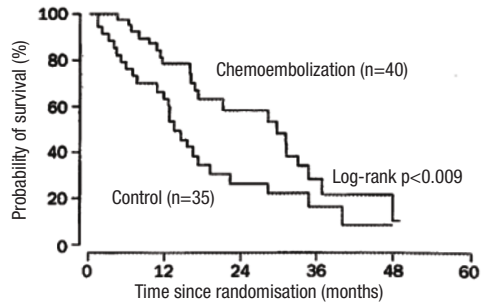
- Arterial embolization group (TAE without cytotoxic drug): 37 patients
- Chemoembolization group (cTACE with Lipiodol® + doxorubicin): 40 patients
- Control group (conservative treatment): 35 patients.

1ary endpoint = survival, 2ary endpoint = treatment response.

Objective:
«… to assess the survival benefit of regularly repeated arterial embolization (gelatin sponge) or chemoembolization (gelatin sponge plus doxorubicin) compared with conservative treatment. »

Results:
«…chemoembolization with gelfoam & doxorubicin improves survival in selected candidates with unresectable hepatocellular carcinoma. »

	TAE	cTACE	Control
1-year survival (%)	75	82	63
2-year survival (%)	50	63	27
3-year survival (%)	29	29	17
Mean survival (mo)	**25.3**	**28.7**	**17.9**
		p = 0.009	
Deaths	67% 25/37	52% 21/40	71% 25/35



cTACE IMPROVED THE SURVIVAL OF PATIENTS WITH UNRESECTABLE HCC

Efficacy

Lo C.M. et al. Hepatology (2002)[7]

Single center, open-label, randomized, controlled clinical trial

79 Asian patients with unresectable HCC (Okuda I/II stage)
- Chemoembolization group (cTACE with cisplatin+Lipiodol® repeated every 2-3 months): 40 patients
- Control group (symptomatic treatment): 39 patients

1ary endpoint = survival, 2ary endpoints = tumor response, tolerance, liver function

Objective:
«… assessed the efficacy of transarterial Lipiodol® (Lipiodol® Ultrafluide, Laboratoire Guerbet, Aulnay-Sous-Bois, France) chemoembolization in patients with unresectable hepatocellular carcinoma. »

Results:
«… transarterial Lipiodol® chemoembolization […] prolongs the survival of a selected group of Asian patients with unresectable hepatocellular carcinoma & is an effective palliative treatment option. »

Probability of survival	cTACE (%)	Control (%)
1-year	57	32
2-year	31	11
3-year	26	3

Much higher probability of survival with cTACE rather than control.

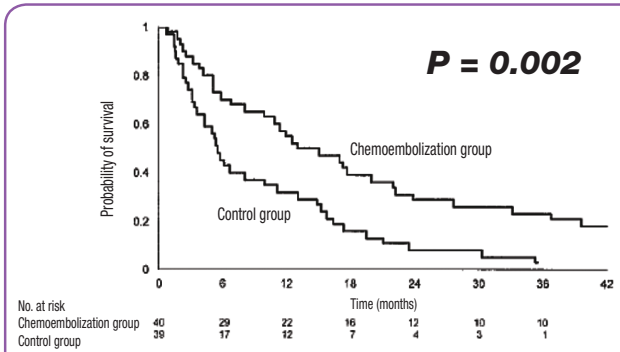
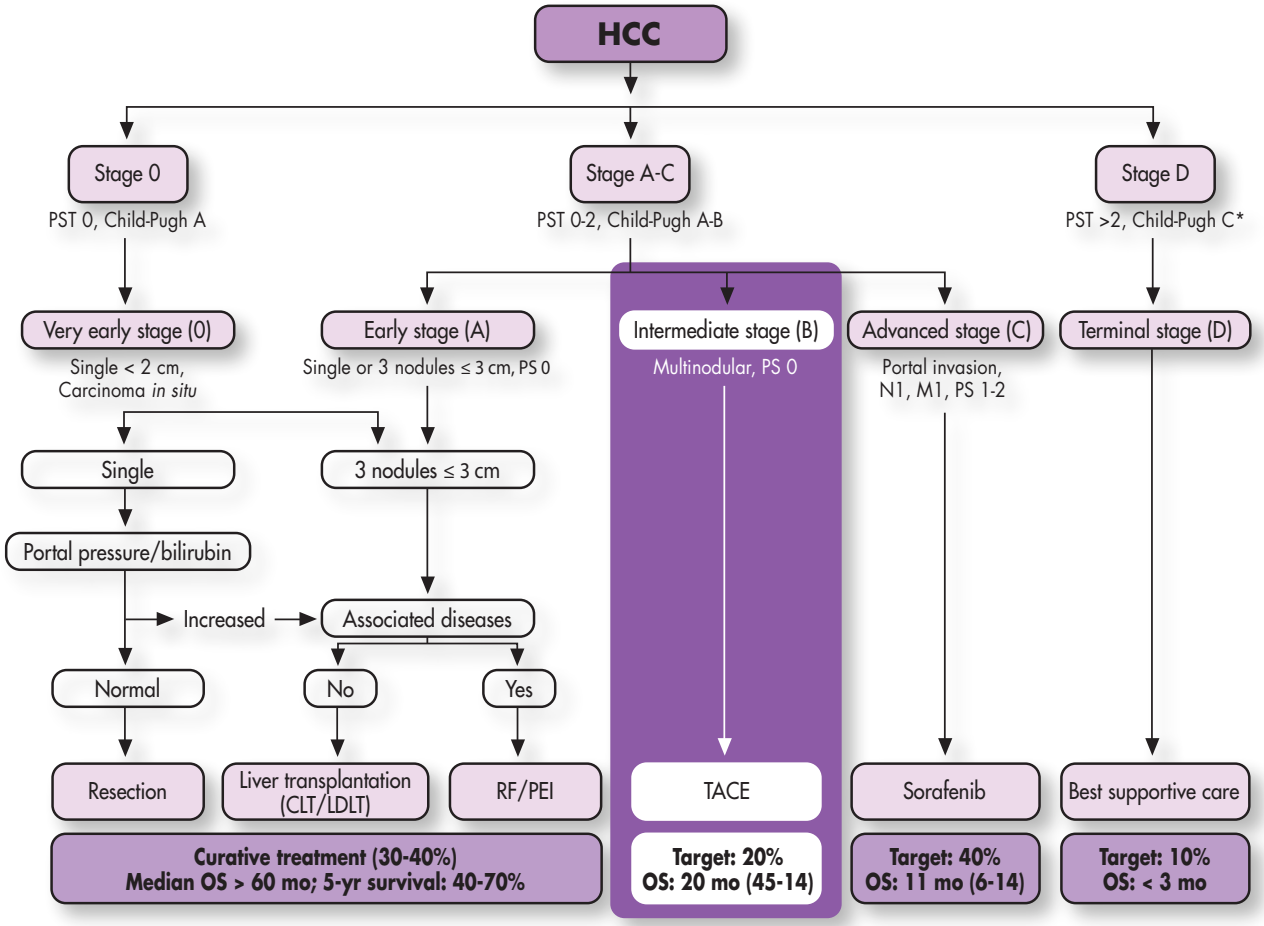


Fig. 2. Probability of survival in patients treated with chemoembolization & in patients of the control group (log-rank test, P = .002).

cTACE IMPROVED THE SURVIVAL OF ASIAN PATIENTS WITH UNRESECTABLE HCC

BCLC staging system & treatment strategy [2]



BCLC = Barcelona-Clinic Liver Cancer

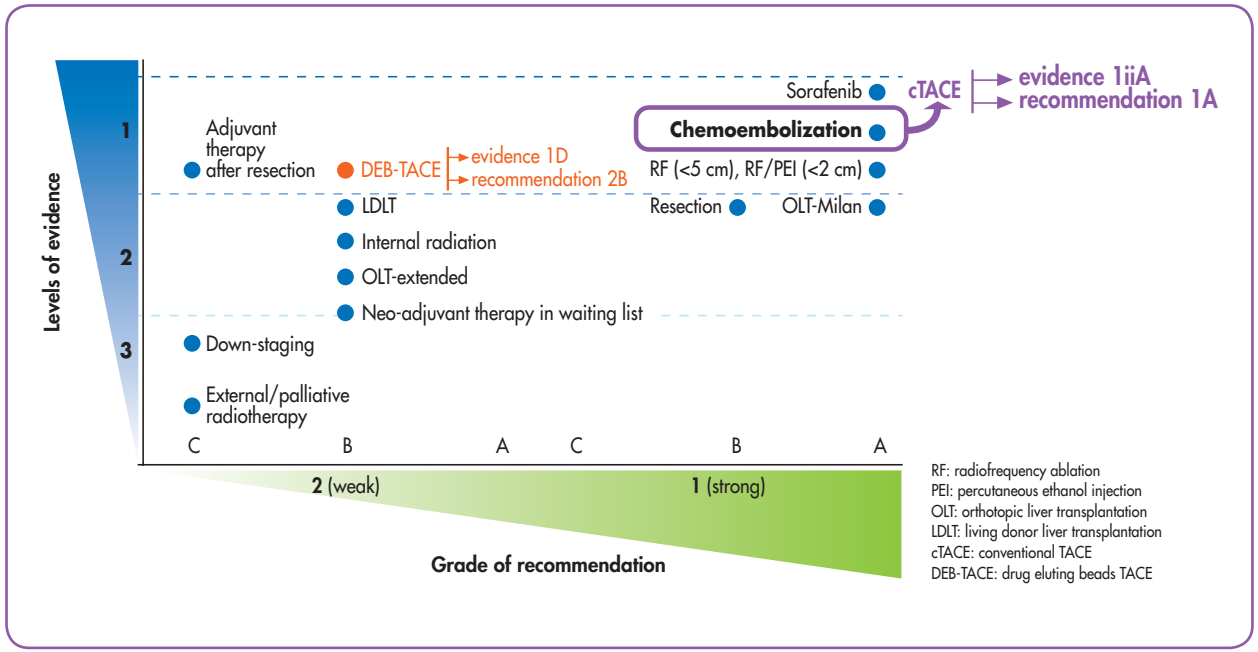
cTACE: "STANDARD-OF-CARE" FOR STAGE B HCC PATIENTS

Clinical practice guidelines for HCC management [2]

Recommendations on chemoembolization & transcatheter therapies[1]

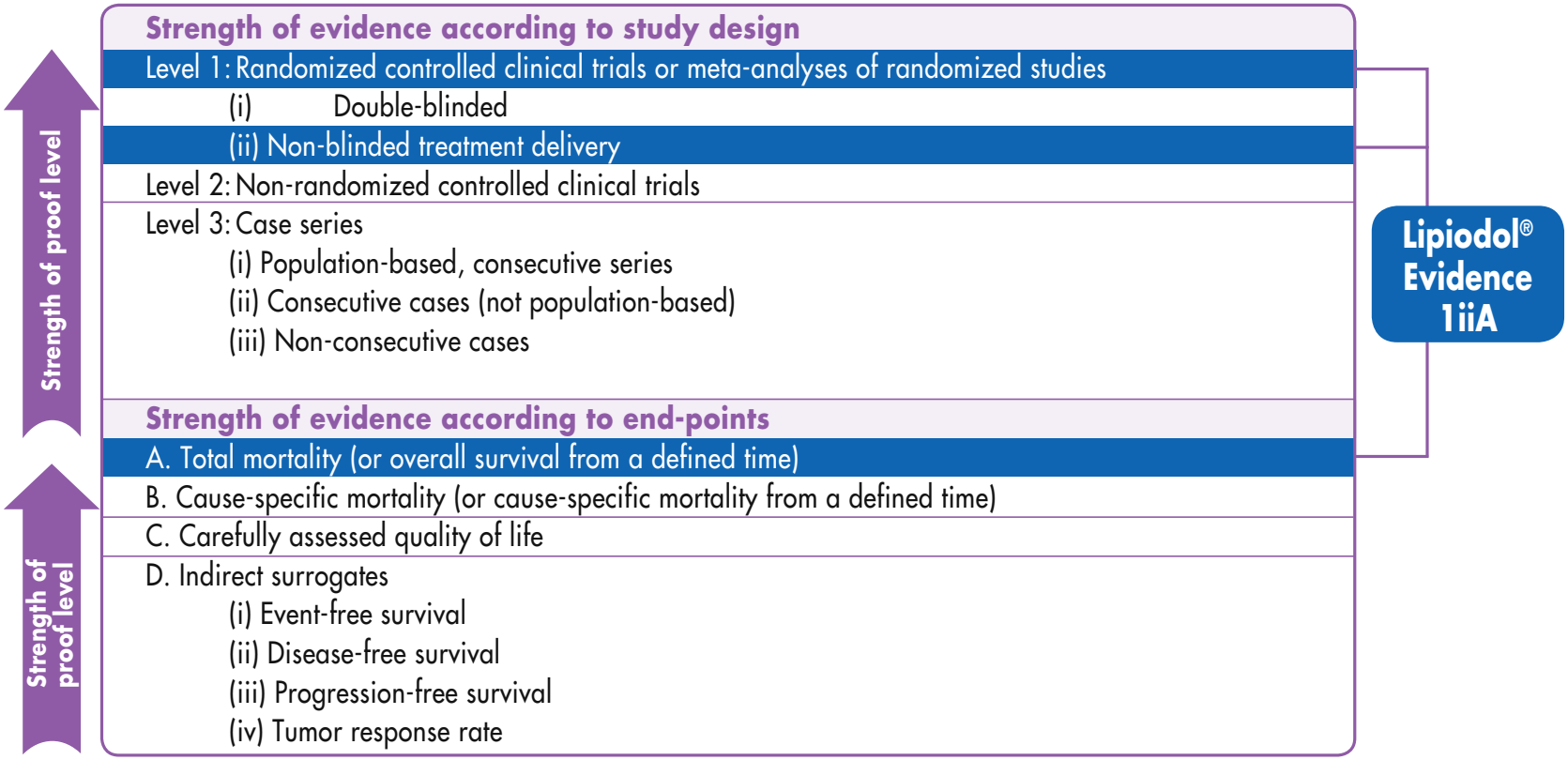
*« Chemoembolization (Lipiodol®) **is recommended** for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra hepatic spread (evidence 1iiA; recommendation 1A). »*

« The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol® particles associated with less systemic adverse events (evidence 1D; recommendation 2B). »



cTACE STRONGLY RECOMMENDED FOR STAGE B HCC PATIENTS

Level of evidence[2]



STRONG LEVEL OF EVIDENCE OF IMPROVED OVERALL SURVIVAL

Grade of recommendation[2]

Strength of proof level

Grading of evidence[1]	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimation of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C

Strength of proof level

Grading recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty: higher cost or resource consumption	2

Lipiodol® Recommendation 1A

STRONG GRADE OF RECOMMENDATION BASED ON HIGH-QUALITY EVIDENCE

cTACE endorsement by international clinical practice guidelines

American guidelines[9]

« TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extra hepatic spread (level I). »

« Chemotherapy has to be injected prior to arterial obstruction. It is usual to suspend chemotherapy in Lipiodol®, an oily contrast agent used for lymphographic studies. Lipiodol® is selectively retained within the tumor and this expands the exposure of the neoplastic cells to chemotherapy… »

Chinese guidelines[10]

« Superselective catheterization is preferred whenever possible, in combination with proper embolization agents. An emulsion mixture of super-liquid Lipiodol® and chemotherapeutic agents is commonly used for this therapy. The dosage of iodized oil should depend on the size, blood supply, and tumor of feeding arteries of the tumor. »

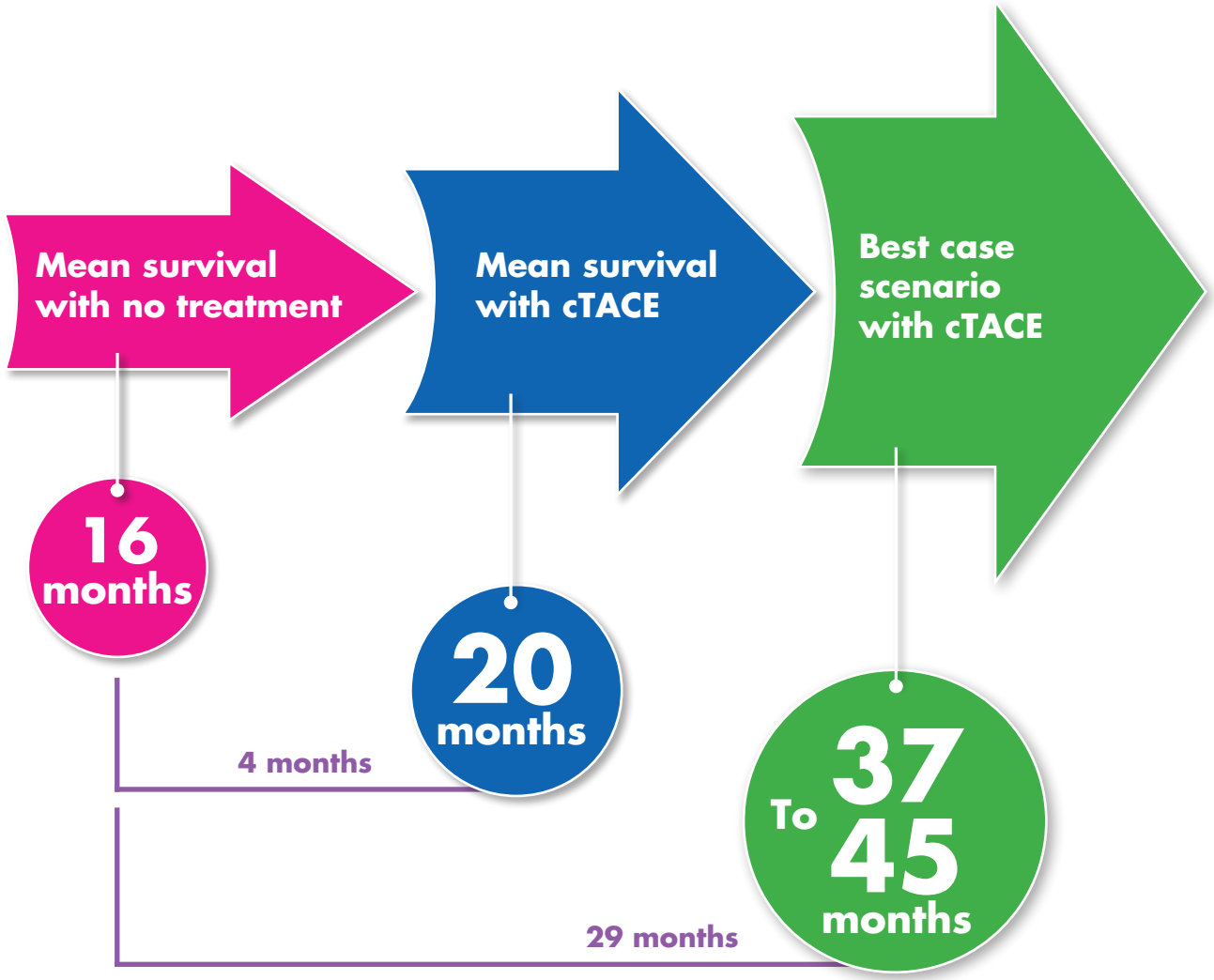
Japanese guidelines[11]

« Transcatheter arterial chemoembolization/TAE is recommended as treatment for advanced hepatocellular carcinoma with liver damage stages A and B (inoperable and not candidates for local ablation therapy)… (grade A). »

« Lipiodol®-TACE taking account of hepatic functional reserve and the area of non-cancerous liver tissues to be chemoembolized is recommended for current TACE (grade B). […] »

cTACE ENDORSED BY INTERNATIONAL GUIDELINES WORLDWIDE

Overall survival data[2, 12]



SIGNIFICANT IMPROVEMENT OF STAGE B HCC PATIENT OVERALL SURVIVAL

Safety data[13]

Single center, retrospective clinical trial
Patients with HCC (n=198) treated by TACE
Endpoints: CT/MRI assessed liver/biliary injuries

Objective:
«… this study describes & compares liver/biliary injuries encountered with TACE in tumours developed in cirrhotic (hepatocellular carcinoma (HCC) […] livers. »

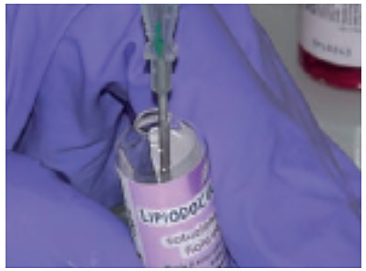
	HCC-group (n=198)	
n(%)	**cTACE** (n=142)	**DEB-TACE** (n=56)
Dilated bile duct (n=13)	3 (2.1)	10 (17.9)
Portal vein narrowing (n=6)	2 (1.4)	4 (7.1)
Portal vein thrombosis (n=7)	2 (1.4)	5 (8.9)
Biloma/liver infarct (n=1)	1 (0.7)	0
Session with at least one liver/biliary injury, (n=23)	**6 (4.2)**	**17 (30.4)**

Results:
« At least one liver/biliary injury was observed after 30.4-35.7% of DEB-TACE sessions while it occured after 4.2-7.2% of Lipiodol®-TACE (p<0.001).
We suggest caution when using DEB-TACE in the non cirrhotic liver. »

LOWER INCIDENCE OF LIVER/BILIARY INJURIES AFTER cTACE VS. DEB–TACE

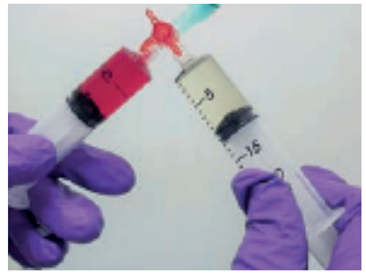
Lipiodol®–drug mixture preparation*

1



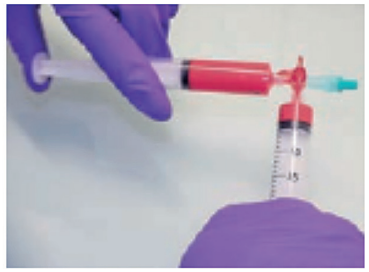
Prepare a syringe containing Lipiodol® Ultra Fluid & a syringe containing the anticancer agent

2



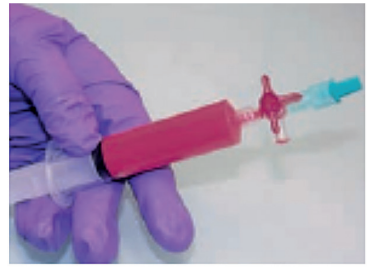
Connect both syringes to a three-way stopcock

3



Perform 15 to 20 back & forth movements between the two syringes to obtain a homogeneous mixture

4



Obtain a mixture of Lipiodol® Ultra Fluid + anticancer agent

The mixture should be extemporaneously prepared & used immediately after preparation (within 3 hours)

Mixture preparation recommendation

- Anticancer drug should be first pushed towards the syringe containing Lipiodol® [14]
- Volume of anticancer drug should be lower than the volume of Lipiodol®, ideally 1 volume of drug to 2 volume of Lipiodol® [15]
- Vigorous mixing of the anticancer drug and Lipiodol® via a 3-way stopcock [14]

* Example of a preparation with doxorubicin according to clinical practices. Guerbet pictures

Anticancer drugs associated with Lipiodol®

Several anticancer drugs may be associated with Lipiodol® Ultra Fluid			
Cisplatin [7]	Doxorubicin [8]	Epirubicin [16]	Mitomycin [17]
The instructions & precautions for use relating to anticancer drug must be strictly followed according to local SmPC			

Lipiodol® Ultra Fluid

FEATURES	BENEFITS
Tumor visualizer & localizer	- Immediate tumor visualization & localization for real time procedure guiding[16] - Per-procedure complete tumor filling visual confirmation for patient prognosis[20]
Chemotherapeutic drug vectorizer	- Proximal & distal drug delivery thanks to droplets deformability & size diversity[3] - Improved patient Overall Survival up to 45 months[2-12] - Endorsed by international guidelines as Standard-of-Care[2-9-10-11]
Transient dual embolizer	- Index & daughter nodules necrosis thanks to dual arterioportal embolization[19] - Transient occlusion authorizing repeated treatment[18]

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(9) US Guidelines: Bruix J. AASLD Practice Guidelines; American Association for Study of the Liver Diseases; Hepatology 2011; Vol. 53, No. 3.

(10) Chinese guidelines 2011 edition, Chin. Clin. Oncol. 2012; 1:10.

(11) Japanese Guidelines: Hepatology Research 2010; 40 (Suppl. 1): 96–112.

(12) Ikeda M. et al. Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma : an Asian cooperative study between Japan and Korea 2013; J. VAc. Interv. Radiol.; 24: 490-500.

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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 haemorrage 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 radiological examination. Chemo-Embolization: Trans-Arterial Chemo-Embolisation is not recommended in patients with decompensated liver cirrhosis (Child-Pugh ≥8), advanced liver dysfunction, macroscopic invasion and/or extra-hepatic spread of the tumour. Renal insufficiency must be prevented by correct rehydration 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.

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