LIPIODOL® ULTRA FLUID
Ethyl ester of iodized fatty acids of poppy seed oil

Solution of Visualization & Embolization for Abnormal Lymphatic system

(1,2,3,4,5)

Guerbet
Contrast for Life
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**The Lymphatic system & Lymphography**

- **The Lymphatic system** is a part of the circulatory system and a vital part of the immune system, comprising a network of lymphatic vessels.

- **Lymphangiography /Lymphography** a valuable tool for the detection of various types of lymphatic leakages including chylothorax, chylous ascites, and lymphatic fistulae. \(^\text{(1)}\)

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**The incidence of postoperative chylothorax ranges from 0.5% to 5%**

**Postoperative chylous ascites ranges from 0.03% to 11%** \(^\text{(2)}\)
**Lipiodol® indication in lymphography**

*Indications in diagnostic radiology* - Lymphography.

*Indications in interventional radiology* - Selective embolization in combination with Histoacryl glue (particularly for arteriovenous malformation or aneurysms).

**Lipiodol® site of injection for lymphangiography**

2 methods:

A. *Intranodal Lymphangiography:*
   - Inject Lipiodol® into *inguinal lymph node*

B. *Pedal Lymphangiography:*
   - Inject Lipiodol® into *isolated vessel on the dorsum foot below the ankle*
Lymphography—Detecting lymphatic system impairment recommended by International Clinical Guidelines

International Union IUA guideline (International Union of Angiology)\(^{(3)}\)

« Oil contrast standard Lymphangiography /Lymphography
LAG* is still advantageously employ in selected patients with chylous dysplasia and gravitational reflux disorders in order to define more clearly the extension of the pathologic alteration and site of lymphatic and chylous leak. These are the only diagnostic investigation that can clearly demonstrate pathologies of chylous vessels, chylous cyst and thoracic duct in cases of chylothorax, chylous ascites, protein losing enteropathy. »

American APTA guideline (American Physical Therapy Association)\(^{(4)}\)

« ...Lymphography may be used to detect lymphatic system impairment… Diagnostic accuracy in patients with known lymphedema demonstrated a sensitivity of 1.0 and a specificity of 1.0 when compared with CT and MRI... »

*LAG: Lymphangiography

LYMPHOGRAPHY ENDORSED BY INTERNATIONAL GUIDELINES
A lipid-soluble ultrafluid contrast medium (Lipiodol® Ultra fluid) is injected into lymphatic vessel after isolation and cannulation of the lymphatics of the dorsum of foot with microsurgical technique so that the lymphatic network and lymph nodes can be seen. When this conventional oil contrast lymphangiography is coupled with CT scan, it allows a more accurate assessment of disease extension, as well as the site of the obstacle and source of chylous leakage. The main indications for the use of direct oil contrast lymphangiography are represented by the pre-operative assessment of patients affected by lymphatic and chylostatic disorders: chyloperitoneum, chylothorax, chyluria, chylo-colpometrorrhrea, and chylous joint effusion.
Lipiodol® mixture with cyanoacrylate (polymer) glue

- Example of mixture

Tools necessary to obtain Lipiodol® and NBCA (n-Butyl cyanoacrylate) mixture:
- Two clean and dry syringes
- Three-way stopcock
- Non-ionic solution (10% dextrose) to flush the catheter

LIPIODOL® & NBCA MIXTURE EASY TO PREPARE
## Two lymphangiography techniques with Lipiodol® described in 2016

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<th>Performed</th>
<th>Intranodal Lymphangiography</th>
<th>Pedal Lymphangiography</th>
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<tr>
<td><strong>Volume of Lipiodol®</strong></td>
<td>2-10 mL</td>
<td>6-12 mL</td>
</tr>
<tr>
<td><strong>Injection rate</strong></td>
<td>Lipiodol® was injected manually at an injection rate of 0.2–0.4 mL/min on one side</td>
<td>Lipiodol® was injected at a rate of 0.2–0.4 mL/min by using a dedicated lymphangiogram pump</td>
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<tr>
<td><strong>Needle</strong></td>
<td>Ultrasound guidance using a 26-gauge needle</td>
<td>Using a 30-gauge lymphangiography needle</td>
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<tr>
<td><strong>Operation</strong></td>
<td>The needle tip was positioned in the transitional zone between the cortex and the hilum of the inguinal lymph node under sonographic guidance</td>
<td>The needle and lymphatic vessel were firmly tied together by using 3–0 silk thread and then secured with adhesive strip</td>
</tr>
<tr>
<td><strong>Considered technically successful</strong></td>
<td>If the target lymph node is successfully selected and the lymphatic channels of interest are adequately visualized by using Lipiodol®</td>
<td>If the lymphatic vessel is successfully selected and the lymphatic channels of interest are adequately visualized by using Lipiodol®</td>
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Clinical Applications – 1. Lymphatic leak

Direct lymphangiography as treatment option of lymphatic leakage: indications, outcomes and role in patient’s management (6)

A 54-year-old patient with lymphatic fistula after inguinal lymphadenectomy due to metastasis in lymph nodes from cutaneous malignant melanoma. The daily amount of drained lymph was 150 mL. Ten days after lymphography the lymphatic fistula was occluded.

(a) CT of pelvis before lymphography. Documentation of the lymphatic fistula in the right inguinal region.
(b) X-ray image documenting contrasted lymph vessels of the right feet after injection of iodized oil.
(c) X-ray image documenting lymph leakage in the right inguinal region.
(d) CT of the pelvis one day after lymphography. Documentation of lymphatic leakage.

Outcome: ...Of 64 patients, 45 patients (70.3%) were treated and cured after lymphography. Based on the lymphography findings, 19 patients (29.7%) underwent surgical intervention with a completely occlusion of lymphatic leakage. The lymphatic leak could be completely occluded in 96.8% of patients...
2. Chylous leak

Therapeutic strategy for chylous leakage after esophagectomy: focusing on lymphangiography using Lipiodol® (7)

(a) Main trunk type: the patient underwent esophagectomy with a combined resection of the thoracic duct. A chest radiograph shows that the thoracic duct was visualized in the lower mediastinum (black arrow). A large pooling of contrast medium leaked from the stump of thoracic duct (white arrow).

(b) Branch type: the patient underwent esophagectomy with the combined resection of thoracic duct. The black arrowhead shows the stump of the right-sided thoracic duct which was successfully ligated in the preceded esophagectomy. However, the left-sided thoracic duct (black arrow) was patent, and the segmental plexus formation of the lymphatic vessels was observed in the lower mediastinum. Pooled contrast medium was leaked from the plexus formation of the lymphatic vessels (white arrow).

Outcome: In all 33 patients, the therapeutic management was determined after lymphangiography, and all patients were finally healed.
A novel algorithm proposed for determining the optimal therapeutic strategy for the treatment of refractory chylous leakage after esophagectomy, focusing on lymphangiography using Lipiodol® (7).

The management algorithm for the treatment of refractory post-esophagectomy chylous leakage.
3. Chyloous ascites – Case report

Ultrasound-guided intranodal lymphangiography with ethiodized oil to treat chyloous ascites (8)

(1) Abdominal CT showing marked ascites.
(2) Fluoroscopic image showing injected Lipiodol® through the bilateral inguinal lymph nodes.
(3) The follow-up CT visualizing abdominal lymphatic vessels including cisterna chyli (arrow) without Lipiodol® leakage into the abdominal cavity.

Outcome: After the lymphangiography, the persistent abdominal pain was significantly reduced within a day. Moreover, the triglyceride level decreased to 21 mg/dL, and CA was resolved within 3 days…

LIPIODOL® – FOR CHYLOUS ASCITES
4. Lymphedema – Case reports

Transnodal lymphangiography in the diagnosis and treatment of genital lymphedema

(A) A lymphangiography image at 30 min showing lymphatic hyperplasia in the pelvis (curved arrows) and lymphatic plevic fistula (arrowhead).

(B) Lymphangiography image at 45 min demonstrating vaginal leak (arrow).

(C) CT scan 24 h after lymphangiography depicting Lipiodol® within the parenchyma of the kidney indicating lymphatic pelvic fistula (arrow).

(D) Coronal reconstruction of the same CT scan showing Lipiodol® within the kidney parenchyma due to lymphopelvic fistula (arrow) and lymphatic hyperplasia in the pelvic organs (curved arrows).

Outcome: Sclerosing activity of Lipiodol is expected to gradually decrease the amount of leakage or the severity of inflammation. Genital lymphedema also progressively decreased, and the patient’s discomfort disappeared...
5. Lymphatic anomalies

Interventional treatment of pulmonary lymphatic anomalies (10)

(A) Dynamic contrast–enhanced magnetic resonance lymphangiography (DCMRL) of the patient with neonatal chylothorax, demonstrating abnormal pulmonary lymphatic flow toward lung parenchyma (white arrows).

(B) Fluoroscopy image of the chest again demonstrating abnormal flow of the Lipiodol® injected through groin lymph nodes toward lung parenchyma (black arrows).

Outcome: Percutaneous embolization of these abnormal pulmonary lymphatic vessels results in alleviation of the symptoms of plastic bronchitis in close to 100% of the patients with minimal complications…
6. Lymphatic Leak

Lymphatic leak occurring after surgical lymph node dissection: a preliminary study assessing the feasibility and outcome of lymphatic embolization

(A) Technique 1: the leak (white arrow) was targeted under fluoroscopic guidance using a 22-gauge needle (black arrow) through which NBCA was injected.

(B) Technique 2: the inflow vessel leading to the leak (white arrow) was punctured using a 22-gauge needle (black arrow) and NBCA was injected.

(C) Technique 3: NBCA was injected into a pelvic lymph node (black arrows) to treat multifocal leaks (white arrows).

Embolization technique. For embolization, a 1:1 mixture of NBCA and Lipiodol® was used for the first two techniques, while the mixture was between 1:6 and 1:8 for the third technique.

Outcome: Intranodal lymphangiography was successfully performed on both sides in 19 patients (90.5 %) [...] 17 patients (81.0 %) showed initial response to treatment. Three patients underwent repeated embolization with successful results. The overall success rate was 95.2 %.
7. Chylous Leak – Case report
CT-guided injection of N-butyl cyanoacrylate glue for treatment of chylous leak after aorto-mesenteric bypass

A 68-year-old man with chronic mesenteric ischemia underwent aortohepatic and superior mesenteric artery bypass with placement of a tunneled superior mesenteric artery (SMA) graft within the left para-aortic retroperitoneum. Under CT guidance, a 22-gauge Chiba needle (A) was targeted at the lymphatic leak, and (B) 1 ml of NBCA glue and Lipiodol® (arrow) was injected.

NBCC/Lipiodol® ratio 1:1

Outcome: The patient was discharged home soon after procedure with no recurrence of either the pleural effusion or ascites during 3 months of clinical follow-up. There were no complications from the intranodal lymphangiogram or the NBCA:Lipiodol® injection.

LIPIODOL® & NBCA – FOR CHYLOUS LEAK
8. Chylothorax – Case reports

Embolization for thoracic duct collateral leakage in high-output chylothorax after thoracic surgery (13)

A 67-year-old man who had undergone esophagectomy for esophageal cancer. Despite conservative treatment, his postoperative chylous output was 2300 mL/day.

(A) Lymphangiography. No rupture is evident in the thoracic duct (black arrows). Extravasation of lipiodol is apparent on the left of the thoracic duct, and rupture of a lymphatic duct (white arrow) forming a collateral route bypassing the thoracic duct is seen. The collateral routes comprise lymphatic ducts that form a reticulate network (black arrowheads) continuing to the lumbar lymphatics. The ruptured lymphatic duct is supplied with lipiodol from the lumbar lymphatics and cisterna chyli via the collateral routes.

(B) Transcatheter thoracic ductography. Iodinated contrast agent is injected through a microcatheter inserted in the thoracic duct by a percutaneous transabdominal approach. The white arrowhead indicates the microcatheter tip. Similar to lymphangiography, a ruptured lymphatic duct (white arrow) is present, and extravasation of iodinated contrast agent is evident. Injection of a 5-mL bolus of iodinated contrast agent visualizes the ducts as far as collateral routes that communicate with the lumbar lymphatics (black arrowheads).

(C) Thoracic duct embolization. This image represents a digital-subtraction image taken during injection of N-butyl cyanoacrylate mixed with Lipiodol® (N-butyl cyanoacrylate:lipiodol=1:10) into the thoracic duct. The N-butyl cyanoacrylate reaches the rupture site (white arrow) in the lymphatic duct and travels via a collateral route that communicates with the lumbar lymphatics (black arrowhead).

(D) Plain radiograph the day after thoracic duct embolization. N-butyl cyanoacrylate mixed with Lipiodol® was retained in the injected lymphatic vessel and embolization remained intact the day after TDE.

Outcome: Clinical success was achieved in all patients […] No recurrence of chylous effusion was seen for any of the five patients in this period. No complications requiring treatment were encountered.

LIPIODOL® & NBCA – FOR THORACIC DUCT COLLATERAL LEAKAGE
9. Lymphatic Ascites

Risk factor analysis for massive lymphatic ascites after laparoscopic retroperitoneal lymphadenectomy in gynecologic cancers and treatment using intranodal lymphangiography with glue embolization[14]

Outcome: successful treatment for massive lymphatic ascites [...] this procedure may be an alternative treatment options for massive lymphatic ascites after retroperitoneal lymphadenectomy…

LIPIODOL® & NBCA – FOR MASSIVE LYMPHATIC ASCITES
# Lipiodol® Ultra Fluid in Lymphography

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| Visualizer & localizer | - Immediate visualization of lymphatic leak or lymphatic anomalies  
                          - Localization for real time procedure guiding\(^{(6,7,8)}\) |
| Embolizer         | - Decrease the amount of leakage  
                          - Improve Lymphedema\(^{(9)}\)                                      |
| Vectorizer & Timer | - Gives radiopacity & modification polymerization time according to the Lipiodol® & glue ratio\(^{(13)}\) |
Bibliography

(14) Tae-Wook Kong, et al., Risk factor analysis for massive lymphatic ascites after laparoscopic retroperitonal lymphadenectomy in gynecologic cancers and treatment using intranodal lymphangiography with glue embolization, J Gynecol Oncol., 2016;Jul;27(4):e44.
LIPIODOL® ULTRA-FLUID. Composition: Ethyl esters of iodoxy 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 - Stenography - 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 (partially 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 hypothyroidism - 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 radiological examination. Chemo-Embolization: Trans-Arterial Chemo-Embolization is not recommended in patients with decompensated liver cirrhosis (Child-Pugh ≥B), 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 is 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, diarrhoea, nausea, fever, pain, dyspnoea, 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. Marketing authorization holder (*): Guerbet - BP 57400 - F-95943 Roissy Cedex - FRANCE. Information: tel: 33 (0) 1 45 91 50 00. Revision: April 24th, 2018.

(*) For complete information please refer to the local Summary of Product Characteristics
(**) Indications, volumes and presentations may differ from country to country.

Countries in which Lymphography indication is registered: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Cambodia, Czech Republic, Denmark, Egypt, France, Germany, Hong Kong, Hungary, India, Indonesia, Iran, Ireland, Israel, Japan, Luxembourg, Malaysia, Mexico, Mongolia, Morocco, Netherlands, New Zealand, Peru, Philippines, Portugal, Russian Federation, Singapore, South Africa, South Korea, Switzerland, Taiwan, Thailand, Tunisia, Turkey, United Kingdom, United States Of America, Uruguay, Vietnam.

For a copy of the SPC, please contact a member of Guerbet.