Diagnostic lymphangiography with therapeutic effect: Since more than 70 years Lipiodol is used as an off-label standard of care for chylothorax - why not convert to on-label use?

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Abstract

Purpose: The use of Lipiodol as a diagnostic agent and off-label therapeutic agent has been investigated in well over 395 publications listed in Pubmed under the key words: lymphangiography and chylothorax in the time period between 1921-2021.

While Lipiodol® ultra-fluid has been approved for use as a diagnostic agent in most countries, it can only be used off-label as a therapeutic agent for chylothorax, cholascos, and lymphatic leaks and fistulas. The therapeutic effects in chylothorax and the question why Lipiodol® ultra-fluid is still not approved for on-label use in the treatment of chylothorax are reviewed.

Background: Lipiodol was synthesized as iodized poppy seed oil by the French pharmacist Marcel Guerbet and first described by him in 1901. Over the past 12 decades, it has proven to be a reliable and versatile clinical theranostic agent. Lipiodol® ultra-fluid has been used (a) as a diagnostic contrast agent alone in the clarification and (b) so far only in off-label use as a therapeutic agent for chylothorax or cholascos, e.g. in cases of postoperative lymph leakages. Lipiodol® ultra-fluid has, to our knowledge, only very limited approvals as a therapeutic agent, in Switzerland only for transarterial chemoembolization (TACE) of liver cancer.

For decades and in numerous countries, Lipiodol® ultra-fluid has been in use as first-line treatment of chylothorax, cholascos, lymphatic leakage or lymphatic fistulae, avoiding additional interventions or surgery.

This review aims to assess in which countries Lipiodol® ultra-fluid is approved (a) as a primary diagnostic tool and (b) as a first line therapeutic agent. This review wants to reassess why the general therapeutic approval still lacks, and what could be done to achieve it.

Keywords: Lipiodol therapeutic agent; Lipiodol® ultra-fluid; theranostics; chylothorax; minimally invasive therapy; conversion from off-label use to approved therapeutic agent; on-label use.

Background

Lipiodol is a clear oily liquid, a mixture of long chain C16 and C18 di-iodinated ethyl esters of fatty acids of poppy seed oil (Papaver somniferum var. nigrum), the content of predominantly fatty acids amounts to 79%, of which 98% are unsaturated (20). It contains iodine at a concentration of 480 mg/ml L, the viscosity at 37°C is about 25 Pa•s and its density is 1.28 g/cm^3(20, 57)

It was first synthesized by the French pharmacist Marcel Guerbet in 1901, and was presented by his colleague Laurent Lafay in the same year as the world's first iodinated poppy seed oil (1,56). In 1921, the French radiologists Jean-Athanase Sicard and Jacques Forestier discovered the X-ray attenuating property of Lipiodol. Subsequently, this led to its first use as an X-ray contrast agent in the investigation of a spinal cord tumor by means of myelography, without any side effects occurring (1). Other radiological applications followed in fast sequence: Bronchography in 1922, dacryography in 1923, hysterosalpingography in 1924 and sialography, fistulography, ureterography and cystography in 1928 (56). The hysterosalpingography, i.e., contrast filling of the uterus and the fallopian tubes for ruling out occlusion as an infertility cause is a very interesting use case, and today every bit as important as it was a century ago. In 1937 lipiodol® ultra–fluid was even used to visualize the intrahepatic and extrahepatic bile ducts as part of a Percutaneous Transhepatic Cholecysto- and Cholangiography (PTC). Lipiodol® ultra-fluid was also used therapeutically in the treatment of goiter in the third decade of the last century, as reported by Wolff in his 2001 publication (20).

Lymphography

In 1952, Lipiodol® lymphography was first performed by Kinmonth and described as a clinically

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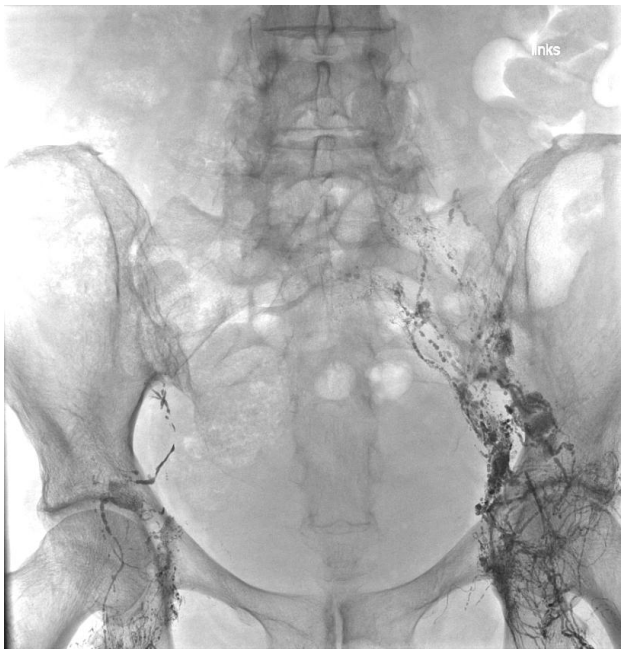

Figure 1: *Lymphangiography, bi-pedal access, normal findings.*

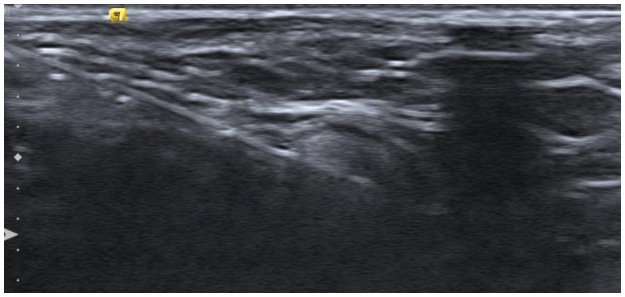

Figure 2: *US guided inguinal intranodal lymphography.*

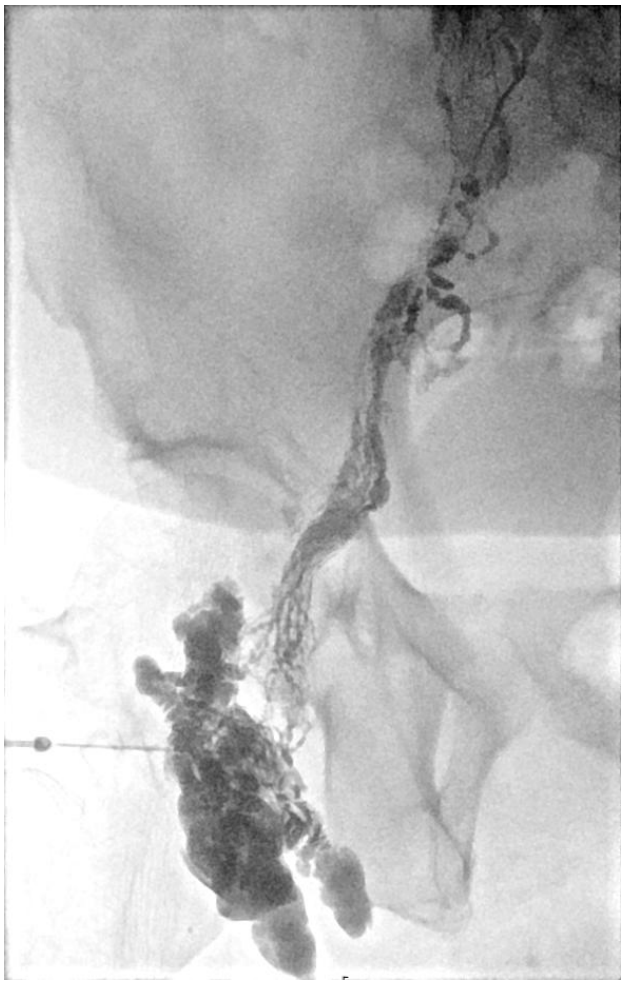

Figure 3: *Intranodal ultrasound-guided puncture of inguinal lymph node and fluoroscopic controlled injection of Lipiodol® ultra-fluid.*

relevant method (2,6). In the 1960s, lymphangiography was of great importance for the anatomically precise visualization of the lymphatic system (48), i.e., the lymph nodes and lymphatic vessels and detection of tumors (3-13), which nowadays is an emerging domain of MR lymphography (37).

In the classical approach, lymphangiography is performed via a lymphatic vessel stained by patent blue at the dorsum of the foot unilaterally or bilaterally, while the more modern approach is an inguinal intranodal US guided lymph node puncture, which is much less invasive (4,8–10). After gaining access to a lymph vessel, slow Lipiodol® ultra-fluid injection is monitored under fluoroscopy with contrast volumes ranging from 10 to 20 ml in total. Contraindications of i.v. Lipiodol® ultra-fluid are summarized in Tab. 2. Before cross-sectional imaging became widely available in clinical practice, lymphangiography, due to its anatomic depiction quality, was the mainstay diagnostic tool in the workup of lymphatic diseases, such as lymphogranulomatosis, Hodgkin's disease, and sarcoidosis (11–13). Lipiodol® lymphography also rendered possible a valid examination answering the question of metastatic spread in the lymph vessel system, based on marginal and central Lipiodol storage defects in the lymph nodes (12,14,15).

Main Part

Lymphography or lymphangiography as a diagnostic method was first performed by Kinmonth in 1952 and described as a clinical method (2). With the beginning of the 1960s, it became increasingly important as a diagnostic tool for imaging the lymphatic vasculature with contrast enhancement of lymphatic vessels and lymph nodes (16). After introduction of cross-sectional imaging, lymphangiography experienced even an increase in its diagnostic value. Together with cross-sectional imaging it is widely used in the detection and therapy of lymphatic leakage. In a 2018 review, Kim et al. reported a technical success rate of lymphography and thoracic duct emboliza-

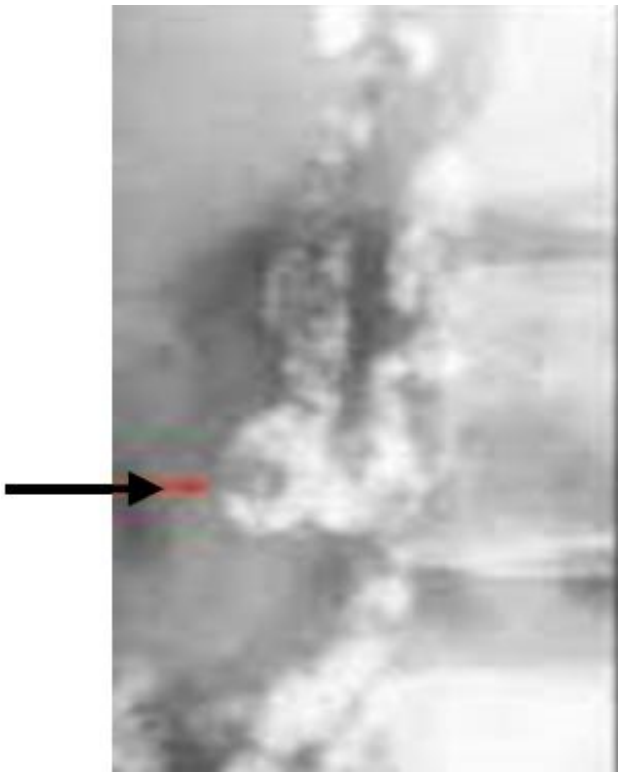

Figure 4: *Lymphadenogram revealing a metastasis in an enlarged lymph node (lack of Lipiodol enhancement, blue arrow).*

tion of 92.2% from their analysis of 9 studies with a total of 407 patients (52). The pooled clinical success rate of lymphography (LAG), thoracic duct disruption (TDD) and thoracic duct embolization (TDE) on a pre-protocol basis were 56.6%, 79.4% and 60.8%, respectively (47,52).

Today, when it comes to pathological changes such as metastatic involvement of lymph nodes or detection of metastases, the various modalities of cross-sectional imaging as a diagnostic tool, both non-invasive or semi-invasive (i.v. contrast agent), have undoubtedly become the methods of first choice. They have largely replaced Lipiodol® ultra-fluid lymphangiography as a first step diagnostic tool in screening examinations (rule-out metastases) in lymph nodes. However, Lipiodol lymphangiogram defends its role as a highly sensitive (99%) and highly accurate (98%) method for detecting lymphatic leakages (18). Hence, the role of Lipiodol lymphangiogram should focus on lymphatic leakage cases and be performed in combination with cross-sectional imaging (computed tomography (CT) and magnetic resonance imaging (MRI), or without (11,56).

The importance of Lipiodol® ultra-fluid as a diagnostic agent is underlined by the high number of publications (395) listed on Pubmed forthe years 1921-2021.

Despite being a clinically tried and tested therapeutic agent, in Switzerland Lipiodol can only be utilized off-label for the treatment of lymphatic leaks.

The selection from the present literature further emphasizes its value as the most accurate method alone and in combination with cross-sectional imaging in the accurate detection of lymphatic leakage with fluoroscopy, CT and MRI (48–58).

Pediatric Populations

Lymphangiography is used not only in adults but also in the diagnostic workup of children for the detection of lymphatic leaks, with subsequent thoracic duct embolization or thoracic duct disruption (2,43,44,50,51). These are mainly individual cases or small case series with a maximum of 11 children (22,43).

A search of the Pubmed database with the keywords: chylothorax lymphangiography lipiodol children yields, as compared to the large number of publications in adults, only a negligible number of publications in pediatric patients (19,22,23,43,50,51,53). Of note, Lipiodol based investigations or interventions are technically more demanding in children as compared to adults, due in part to lack of cooperation (in awake patients) or the need of general anesthesia.

Chylothorax

In adults, the basis for a minimally invasive therapy for chylothorax rests on (a) chest drainage drawing fluid macroscopically consistent with chyle, (b) laboratory confirmation of chyle composition and (c) lymphangiography confirmed lymphatic leakage (12,57,58). The natural history of an untreated chylothorax leads, via malnutrition, to increased morbidity and mortality risk (31,40,46). The volume of chyle fluid leakage into the interpleural space can exceed 1.5 L per day. Treatment often is performed by percutaneous minimally invasive embolization of the thoracic duct via puncture of the cisterna chyli and insertion of a microcatheter.Transcatheter embolization of the thoracic duct is performed with a tissue adhesive injection, e.g. Histoacryl, (n-Butyl-2-Cyanoacrylate) (49,55) alone, or more often in combination with embolization coils. The intervention is monitored with fluoroscopy and finally controlled with cross-sectional imaging (18). Above procedure is considered much less invasive than open surgical or endoscopic thoracic duct ligation, with comparable closure success rates: Percutaneous minimally invasive thoracic duct closure in 89% (9 patients), open surgical closure by ligation in 95% (in 21 of 22 patients),thoracoscopically or in a newer retroperitoneoscopic approach by ligation with closure in 75% (in 3 of 4 patients), with significant reduction of chyle leakage (22,44,45,54).

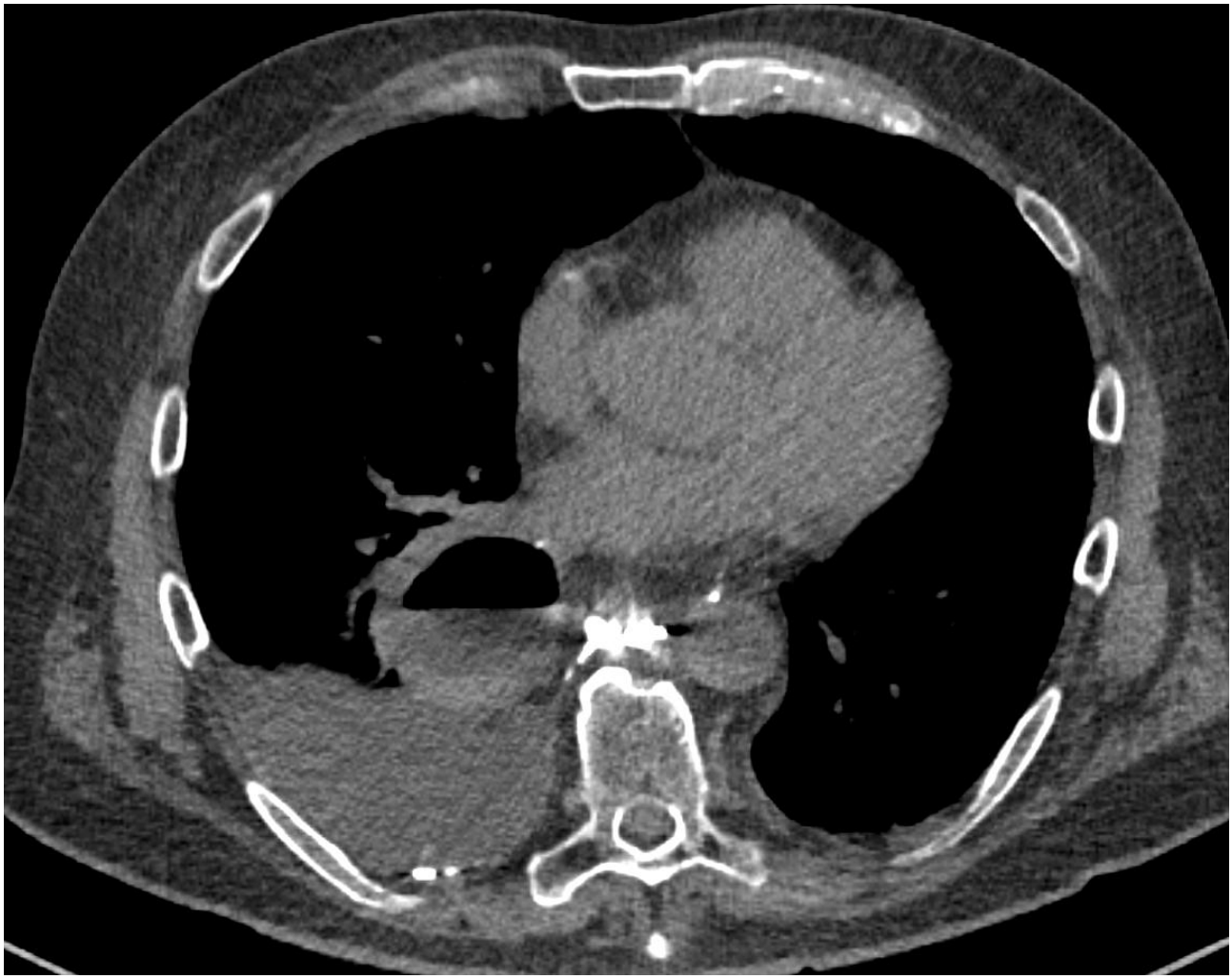

Figure 5: *CT-Lymphangiography in Chylothorax, with massive lymph vessel leakage 6 hours past Lipiodol® ultra-fluid injection.*

Table 1: *Overview of lymphatic diagnostic and interventional techniques, from Pieper et al, 2019 (56).*

TABLE 1. Overview of Lymphatic Imaging Techniques and Interventional Treatment Options

Clinical Problem	Lymphatic Imaging Techniques	Lymphatic Interventional Treatment Options
Peripheral leakage	X-ray lymphangiography (transpedal), MRL	Lipiodol injection/lymphangiography
Pelvic leakage/lymphocele	X-ray lymphangiography (transpedal/transnodal), MRL	Lipiodol injection/lymphangiography, lymph vessel/node embolization
Chylous ascites	X-ray lymphangiography (transpedal/transnodal), MRL	Lipiodol injection/lymphangiography, lymph vessel/node embolization
Protein-losing enteropathy	Hepatic lymphangiography	Hepatic lymphangiography, lymph vessel embolization
Hepatic lymphorrhea	Hepatic lymphangiography	Hepatic lymphangiography, lymph vessel embolization
Chylothorax	X-ray lymphangiography (transpedal/transnodal), MRL	Lipiodol injection/lymphangiography, lymph vessel disruption, lymph vessel (thoracic duct) embolization

MRL indicates magnetic resonance lymphangiography (note: MRL is an off-lable use of MR contrast media).

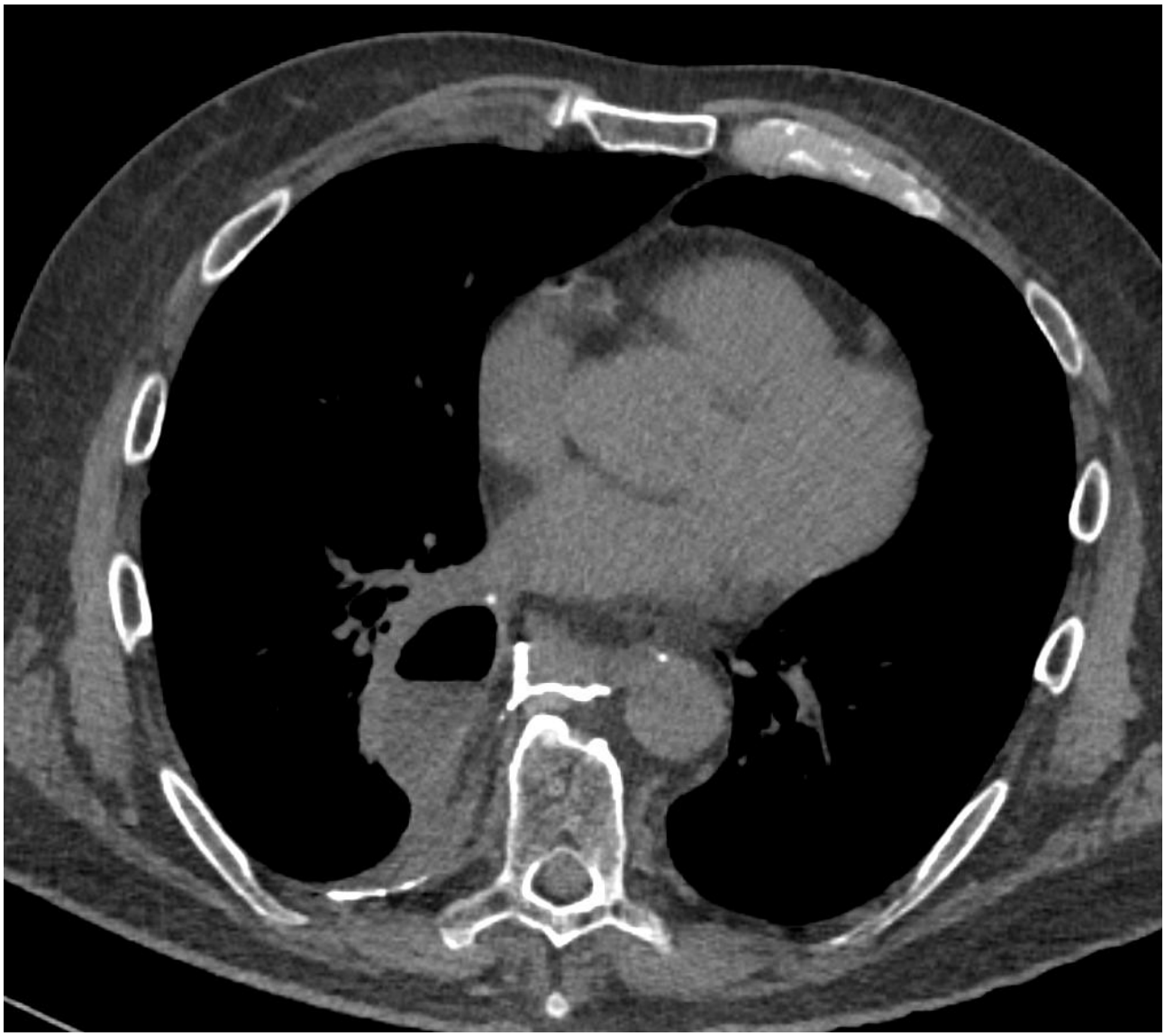

Figure 6: *CT-Lymphangiography in Chylothorax, with stopped lymph vessel leakage 12 hours past Lipiodol® ultra-fluid injection proving therapeutic success.*

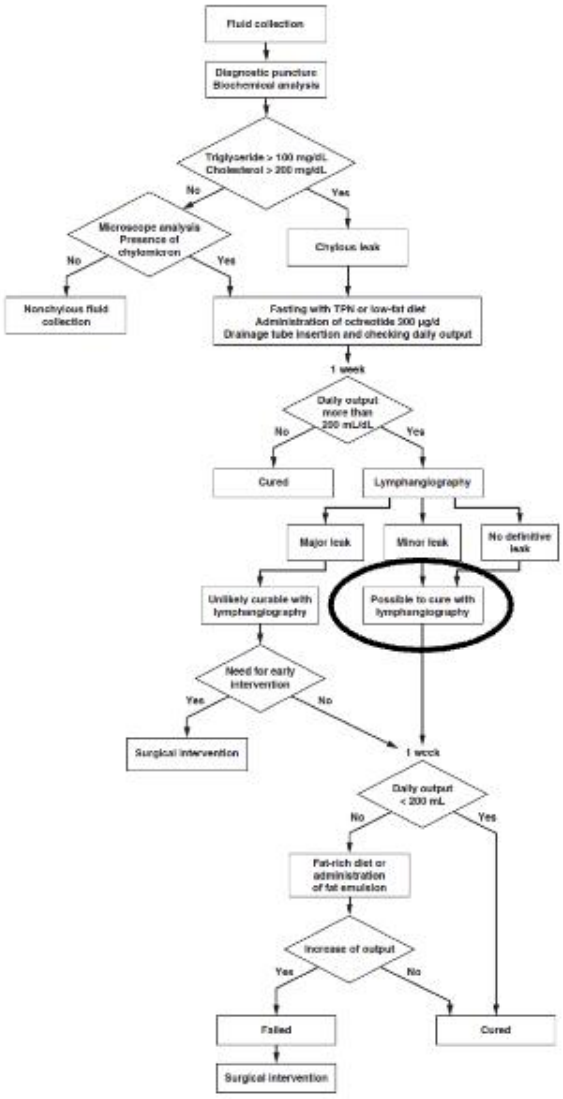

Figure 7: *Algorithm in the therapy of chylothorax using Lipiodol® ultra-fluid by means of lymphangiography as proposed by Kawasaki et al. in 2013 (37).*

Lipiodol® ultra-fluid is chosen for intention-to-treat use as a minimally invasive therapeutic method in chylothorax or general treatment of lymph leakage only in off-label use in these patients in combination with glue or coil embolization or needle disruption (41). However, it may also be repeatedly administered in off-label use, if final closure of the lymph leakage has not occurred after first application (56). Single or even repeated Lipiodol lymphangiography has been described as an effective therapyfor chylothorax (2,7,16,18,36,46).

Regulations

Off-label use is permitted in individual cases as a curative attempt to close a chyle leak under certain conditions and each case can be medicolegally challanged. The responsibility lies with the treating physician, who must provide detailed information for each case. Profound medical reasons for off-label use in that specific case and indication must be provided to the patient prior to the procedure. This means that all pertinent pros and cons must be discussed, and all the patient's questions must be answered. Alternative therapeutic options must be explained to the patient. Informing the patient about the off-label use of Lipiodol ® ultra-fluid is of utmost importance and must also be documented.

The process of dialogue, explanations and gaining informed consent is time consuming for physician and patient. If the physician fails to get an informed patient consent, including the off-label usage, he might be held liable.. Many malpractice suits hinge on the fact of missing and/or insufficient patient consent documentation. The authors have noticed that in the majority of publications reviewed there is no express mention of how and whether the off-label use was explained to the patient, or whether consent for this off-label use was obtained and documented, with one notable exception (56). However, if one implies a high standard of good clinical practice and knowledge of the medicolegal situation of the respective authors, it should be assumed that a comprehensive information and written consent of the patients were presumably carried out but just not mentioned. However, from a psychological point of view, having to explain to the patient that an off-label drug employment is the best therapeutic option, might put a strain on the trustworthy relation between patient and physician. For example, the patient cannot get the same reinsurance from a physician's statement that a drug is off-label as she or he would get if it were on-label. Hence, even if the physician is experienced in the therapeutic use of Lipiodol® ultra-fluid, he cannot fully convey this to the patient. If Lipiodol® ultra-fluid is de facto used as first-line therapeutic option for chylothorax in the described variations since 1951, why does it still not have an according approval 70 years later?

For the interventional radiologist, there are two other minimally invasive options for occlusive therapy of chylothorax when the primary attempt to treat the lymphangiographically precisely localized point of origin of the chylothorax by conventional dietary medical measures fails:
(a) Targeted percutaneous CT-guided alcohol ablation of a lymphatic leak previously detected with Lipiodol® ultra-fluid (52).
(b) Minimally invasive percutaneous needle dissection of the lymphatic leakage site (38).

In addition to the primary diagnostic indication and according to its package insert, Lipiodol® ultra-

Table 2: *(from package insert, Lipiodol® ultra-fluid, Guerbet Group, Villepinte, France) Where lies the responsibility for the limited approval of Lipiodol® ultra-fluid as a therapeutic agent of lymphatic leaks? Should Lipiodol® ultra-fluid still have to undergo further clinical trials? The empiric employment over the last 120 years and the published scientific data from all over the world (24-35) speak in favor of Lipiodol getting an approval as anon-label use therapeutic agent for chylos leakages (21,39,42).*

Contraindications
Hypersensitivity to Lipiodol® ultra-fluid (fatty acid ethyl ester of iodinated poppy seeds oil)
Known hypersensitivity to iodinated contrast media
Severe pulmonary insufficiency in progressed pulmonary diseases
Patients after irradiation therapy of pulmonary tumors
Severe cardiac insufficiency
Known lymph duct occlusion
Right or left sided cardiac shunt
Intravenous injection
Intrathecal administration
Intrabronchial administration
Severe hyperthyroidism
Multinodular enlargement of the thyroid gland
During lactation period
Patient after traumata, status after hemorrhagic episodes or acute bleedings in the area of planned lipiodol injection (increased chance for pulmonary emboli)
Additional contraindication for the use during the trans arterial chemoembolization (TACE): Selective administration into liver tissues with dilated bile ducts, allowed use is possible after having performed a bile duct drainage prior to it (PTCD).

fluid has the second and unrestricted approval to date, for therapy of a hepatocellular carcinoma (HCC) of the liver. Lipiodol® ultra-fluid for this purpose is injected as contrast agent in order to localize and mark the tumor in the liver and secondly as a carrier for the chemotherapeutic agent, which is then injected super selectively into the nutritive vessels of the tumor via microcatheter (17). Lipiodol® ultra-fluid has a vaso-occlusive effect, which contributes to an additional improvement of chemoembolization in the treatment of the tumor, whose arterial blood supply should be eliminated totally, if possible, by capillary embolization inducing complete tumor necrosis.

Trivial as it may be, coevery potent drug tends to have its contraindications. For Lipiodol® ultra- fluid these are summarized in Tab. 2: As far as the efficiency of Lipiodol® ultra-fluid as a single theranostic agent is concerned, this would mean that the use of Lipiodol® ultra-fluid as a medication in an emergency such as a therapy-resistant postoperative chylothorax would be the liability of the interventional radiologist performing the procedure, without creating the legal uncertainty of an off-label use. The main alternative, avoiding these medicolegal liabilities, is the established surgical therapy, with repetition of general anesthesia and surgery, running an increased risk of morbidity and mortality especially in aged patients or in those with significant co-morbidities. Therefore, from an ethical and medicolegal standpoint and for the creation of a trusting doctor-patient relationship, it would be in the patients' best interest for Lipiodol® ultra-fluid to be approved as a lymph leakage-closing drug, as soon as possible. The answer to the question posed at the beginning, in which countries there is a license for Lipiodol® ultra-fluid as a therapeutic agent for chyle leakage can be answered swiftly: There is worldwide no such license or approval for Lipiodol® ultra-fluid as therapeutic agent for chyle leakage (Personal note from Guerbet to FM). In the package insert for Lipiodol® ultra-fluid from Guerbet Company, Villepinte, France, which is valid for Switzerland, only two indications are listed: 1. Lymphangiography with Lipiodol® ultra-fluid for the visualization of the lymphatic vascular system and thus for the detection of lymphatic fistulas, lymphatic leaks, chylothorax occurring postoperatively, as a result of trauma or spontaneously, and finally cholascos. 2. Super selective angiography with Lipiodol® ultra-fluid in the context of TACE to mark and treat a hepatocellular carcinoma (HCC) (17).

Conclusions

1. The existing clinical radiological experience of decades using Lipiodol® ultra-fluid as a safe therapeutic agent for the closure of lymphatic leaks should make it possible to convert the existing off-label use of Lipiodol®ultra-fluid into a regular approval for an intention to treat use in a chylothorax, a cholascos, a lymph fistula or lymph vessel leakage.
2. If this is not possible according to the regulations of the responsible authorities, despite of the already existing data on the efficiency of Lipiodol ® ultra-fluid in the treatment of a lymph vessel leakage, then:
   a. a retrospective study and/or
   b. a prospective single center study and/or, if necessary
   c. a multicenter study
   are the possibilities to convert the existing off-label use into a regular, intention-to-treat (theranostic) on-label use, with quite some urgency

after 120 years of clinical usage and good experiences

3. In our opinion it is mandatory for the manufacturer of Lipiodol®ultra-fluid to protect physicians from potential legal issues when using Lipiodol®ultra-fluid with intention to treat on patients by an official FDA-admittance for ON-LABEL use with intention to treat of their product. This special FDA-admittance procedure is of course long lasting and very expensive for the manufacturer.
4. Obviously, financial reasons should not interfere with legalization of very long known and commonly accepted standard of care procedures.

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