Conventional Lymphangiography (CL) in the Management of Postoperative Lymphatic Leakage (PLL): A Systematic Review

Konventionelle Lymphangiografie (KL) beim Management postoperativer Lymphleckagen (PLL): Eine Systematische Übersicht

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ZUSAMMENFASSUNG


Schlussfolgerung Die KL ist technisch machbar und sicher und effektiv beim Management der PLL. Lipiodol als Kontrastmittel spielt für die KL eine essentielle Rolle, da das hochvisköse jodierte Mohnöl nicht nur diagnostische, sondern auch therapeutische Effekte aufweist. Leitlinien und randomisierte kontrollierte Studien sind weitere Schritte, um den tatsächlichen Nutzen der KL zu definieren.
**Kernaussagen:**
- Die PLL ist eine schwer behandelbare und potenziell lebensbedrohliche chirurgische Komplikation.
- Die KL entwickelte sich als Alternative zur konservativen/operativen Behandlung der PLL.
- Die KL ist technisch machbar und sicher und effektiv beim Management der PLL.
- Die Lipiodol-basierte KL kann als therapeutische Prozedur angesehen werden.
- Leitlinien und randomisierte kontrollierte Studien sind weitere wichtige Schritte.

**ABSTRACT**

**Background** Postoperative lymphatic leakage (PLL) is usually managed by conservative and/or surgical treatments but these procedures can be challenging to perform and potentially clinically ineffective. Therefore, conventional lymphangiography (CL) has emerged as an important alternative. The aim of this review is to present the available outcome data on CL in the management of PLL.

**Method** A systematic literature search (PubMed) using the MeSH term “lymphangiography” was performed and the search was restricted to literature published between January 2007 and August 2019. Identification, screening, and assessment for eligibility and inclusion were conducted in accordance with PRISMA.

**Results** From the initially obtained 1006 articles (identification), 28 articles with a total of 201 patients were finally included (inclusion). The methodological quality of all included articles corresponds to level 4 (Oxford Centre for Evidence-based Medicine – Levels of Evidence, March 2009). PLL occurs after oncological and non-oncological surgery in the form of chylothorax, chylous ascites, and cervical, thoracic, abdominal and peripheral lymph fistula and/or lymphocele. The technical success rate of CL is 75–100 %. Access for CL is transpedal (176 patients) or intranodal (25 patients). Lipiodol is used as the contrast material in all articles, with a maximum amount of 20 ml for transpedal CL and 30 ml for intranodal CL. The X-ray imaging modalities used for CL are fluoroscopy, radiography and/or CT. Two articles report CL-associated major complications and CL-associated morbidity and mortality. The PLL cure rate is 51–70 % for transpedal CL (time to PLL cure: 2–29 days) and 33–100 % for intranodal CL (time to PLL cure: 2–<30 days). Bailout procedures in the case of clinically ineffective CL include a range of treatments.

**Conclusion** CL is feasible, safe, and effective in the management of PLL. Lipiodol as the contrast material is essential in CL because the highly viscous iodinated poppy-seed oil has not only diagnostic but therapeutic effects. Guidelines and randomized controlled trials are further steps towards defining the ultimate value of CL.

**Key Points:**
- PLL is a difficult-to-treat and potentially life-threatening surgical complication.
- CL has emerged as an alternative to conservative/surgical treatment of PLL.
- CL is feasible, safe, and effective in the management of PLL.
- Lipiodol-based CL can be regarded as a therapeutic procedure.
- Guidelines and randomized controlled trials are further important steps.

**Citation Format**

the available outcome data on CL in the management of PLL as published between January 2007 and August 2019 are presented and catalogued with comments.

Materials and Methods

Our systematic review is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews [18]. A literature search was performed up to September 2019 in the PubMed database, using the Medical Subject Heading (MeSH) term “lymphangiography”. The search was restricted to literature published between January 2007 and August 2019. Titles and abstracts of retrieved articles were screened for data on CL, and defined as lymphangiography performed under X-ray imaging after contrast material injection. Full-length articles including reference lists of potentially relevant articles were evaluated for eligibility based on the following inclusion criteria: Only publications with original data on CL performed in the management of PLL were included. The following exclusion criteria were defined: (I) Alternative lymphangiography techniques (e.g., MR lymphangiography and indocyanine green lymphangiography), (II) CL performed in combination with second-line lymphatic interventions (e.g., thoracic duct embolization or interstitial embolization), (III) lack of adequate reporting of methodological details, and (IV) publication language other than English or German. Primary data extraction was performed by two experienced interventional radiologists, each with >10 years of experience in CL. Data were then reviewed and evaluated by all authors, and discrepancies were resolved by consensus. For better clarity and to increase the scientific informative value of the systematic review, the articles that were finally included were organized according to the number of patients that were included in the different articles: Category I data – large original case series (>10 patients); Category II data - small original case series (3–9 patients); Category III data – case reports and other short reports such as letters to the editor and technical notes (<3 patients). Outcome data with a special focus on clinical background and indications, technical aspects, complications, morbidity and mortality, PLL cure rate after CL, and bailout procedures in case of clinically ineffective CL were presented under results in the main body as well as in the form of tables. Category III data were summarized in the main body, whereby new or relevant additional information (e.g., new clinical indications, innovative technical aspects, or complications, morbidity or mortality) was emphasized.

Definition of Technical Success

Technical success of CL was defined as successful injection of the contrast material with the intention to selectively visualize the lymphatic system and the lymphatic pathology under X-ray imaging.

Definition of PLL Cure

As written in the different articles, PLL cure was defined as clinical disappearance of the PLL after CL without the need for further intervention.

Results

Literature Search and Selection

From the initially obtained 1006 articles, 858 were excluded due to the lack of information on CL. The remaining 148 articles as well as 46 further articles identified through detailed evaluation of the main bodies and reference lists were assessed for eligibility. Of these 194 articles, 166 articles not fulfilling the inclusion criteria or fulfilling the exclusion criteria were excluded. Finally, 28 articles with a total of 201 patients were included for detailed analyses (Fig. 1). These 28 articles included 5 large original case series with >10 patients (Category I data) and 3 small original case series with 3–9 patients (Category II data) [15, 19–25]. The other 20 articles included were case reports and other short reports such as letters to the editor and technical notes with <3 patients (Category III data) [14, 17, 26–43]. None of these articles included a prospective study or a randomized controlled trial. The methodological quality of all included articles corresponds to level 4 of the Oxford Centre for Evidence-based Medicine – Levels of Evidence, March 2009.
Outcome Data

Clinical Background and Indications of CL

Under consideration of Category I data and Category II data, PLL occurs after oncological (e.g. esophagectomy and radical prostatectomy) and non-oncological (e.g. thoraco-abdominal aortic repair and kidney transplantation) surgery of the thorax, abdomen, pelvis and spine. The clinical presentation of PLL is chylous thorax and chylous ascites as well as cervical, thoracic, abdominal and peripheral lymph fistula and/or lymphocele. The PLL volume is 10–3000 ml/day. Failed pretreatments to cure PLL include a range of procedures such as conservative management (e.g. compression bandage and total parenteral nutrition), conservative treatments (e.g. somatostatin analogues and sympathomimetic drugs), minimally invasive procedures (e.g. drainage/paracentesis and percutaneous thoracic duct embolization), and surgical management (e.g. surgical exploration). The interval “causal surgery – CL” is 1–183 days. Data are catalogued in Table 1.

Under consideration of Category III data, further types of causal surgery include different conventional (e.g. hemihepatectomy) and minimally invasive (e.g. exploratory laparoscopy including peritoneal washing and omental and peritoneal biopsies) procedures [31, 41]. Compared with Category I data and Category II data, the clinical presentation of PLL is extended, and includes also chyluria and a PLL volume of up to 6000 ml/day [26, 32]. As for Category I data and Category II data, failed pretreatments to cure PLL include a range of procedures such as conservative management (e.g. low fat/high protein enteral nutrition and factor XIII products [20 ml/day for 5 days]), percutaneous radiotherapy (midabdominal area [20 Gy for 2 weeks]), minimally invasive procedures (e.g. interstitial embolization by applying glue after intranodal CL), and surgical management (e.g. peritoneal-vesicular shunt implantation) [26, 33, 36, 38].

Technical Aspects of CL

Under consideration of Category I data and Category II data, the technical success rate of CL is 75–100 %, whereby reasons for technical failure include the inability to inject the contrast material selectively into the lymphatic system. Access for CL is transpedal for Category I data as well as intranodal (groin, neck and axilla) for Category II data. Lipiodol, injected selectively with a maximum injection speed of 0.13 ml/min for transpedal CL and 0.33 ml/min for intranodal CL, is used as the contrast material in all articles. The maximum amount of Lipiodol is 20 ml for transpedal CL and 15 ml for intranodal CL, irrespective of whether unilateral or bilateral CL was performed. The X-ray imaging modalities used for CL are fluoroscopy and radiography in 8/8 articles, and additionally CT in 5/8 articles. The time point of X-ray imaging to visualize the PLL is the filling phase in 8/8 articles, and additionally the nodal phase in 6/8 articles. X-ray imaging signs of PLL include direct signs (pathological contrast material extravasation) and/or indirect signs (e.g. pathological contrast material pooling and atypical opacification of the lymph ducts as a sign of lymphatic collateralization). Data are catalogued in Table 2.

Under consideration of Category III data, the technical success rate of CL is 100 % in 20/20 articles, whereby in 1 article groin intranodal CL was performed under CT guidance and with a 1 ml test injection of water-soluble iodinated contrast material because ultrasound-guided puncture of the inguinal lymph nodes was not feasible (due to the patient’s thick edematous skin preventing precise detection and taping of the inguinal lymph nodes). Access for CL is transpedal in 5/20 articles and intranodal (groin) in 14/20 articles. In 1/20 articles, intranodal (mesentery) was the access for CL [38]. Lipiodol is used as the contrast material in all articles, being injected selectively with a maximum injection speed of 0.14 ml/min for transpedal CL and 0.5 ml/min for intranodal CL [41, 43]. The maximum amount of Lipiodol is 12 ml for transpedal CL and 30 ml for intranodal CL, irrespective of whether unilateral or bilateral CL was performed [30, 36]. X-ray imaging modalities used for CL, time point of X-ray imaging to visualize the PLL and X-ray imaging signs of PLL are comparable with Category I data and Category II data.

Complications, Morbidity, and Mortality during/after CL

Under consideration of Category I data and Category II data, 5 articles specify complications, morbidity and mortality during/after CL. CL-related minor and major complication rates are 0–3 % and 0 % for transpedal CL as well as 0 % and 0 % for intranodal CL, respectively. One article described CL-associated minor complications (contrast material emboli in the pulmonary artery in 2 patients) after transpedal CL [20]. 30-day CL-related morbidity and mortality rates are 0 % and 0 % for transpedal CL as well as 0 % and 0 % for intranodal CL, respectively. Data are catalogued in Table 3.

Under consideration of Category III data, the complication, morbidity and mortality rates during/after CL can be regarded as low, as is the case for Category I data and Category II data. CL-related minor and major complication rates are 0 % and 0 % in 13/20 articles (and n.s. in 5/20 articles). The 30-day CL-related mortality rate is 0 % in 9/20 articles (and n.s. for 10/20 articles) [28, 36–40, 42, 43]. The 30-day CL-related mortality rate is 0 % in 10/20 articles (and n.s. for 8/20 articles) [28, 32, 33, 36–40, 42, 43]. In 2 articles, however, significant complications, morbidity and/or mortality are described [29, 41]. In the article of Taki et al., acute respiratory distress syndrome was reported as a CL-related major complication after transpedal CL, and the patient developed pulmonary fibrosis necessitating domiciliary oxygen therapy due to permanent hypoxemia [41]. In the article of Sheybani et al., Lipiodol embolization to the brain and to the lung was reported as a CL-related major complication after intranodal CL, and the patient died 69 days after CL (because all supportive care was withdrawn due to a very low probability of meaningful recovery after a complicated clinical course including deteriorating mental status and pneumonia) [29].

PLL Cure Rate after CL and Bailout Procedures

Under consideration of Category I data and Category II data, the PLL cure rate is 51–70 % for transpedal CL and 33–100 % for intranodal CL. Subgroup analyses as performed in the original articles present a deeper insight into the PLL cure rates. For the patients without surgical revision < 4 weeks after transpedal CL, Kos et al. described a PLL cure rate of 75 % for chylothorax, 86 % for lymph...
### Table 1 Clinical background and indications for CL.

<table>
<thead>
<tr>
<th>Study/Number of Patients</th>
<th>Clinical Presentation of PLL</th>
<th>PLL Volume</th>
<th>Type of Causal Surgery</th>
<th>Failed Pretreatments to Cure PLL</th>
<th>Interval &quot;Causal Surgery – CL&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category I Data (Large Original Case Series with &gt; 10 Patients)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22</td>
<td>Chylothorax, chylous ascites, thoracic, abdominal and peripheral lymph fistula, thoracic, abdominal and peripheral lymphocele</td>
<td>200–3000 ml/day</td>
<td>Thymectomy, pneumectomy, esophagectomy, partial gastrectomy, nephrectomy, prostatectomy, soft tissue resection, bypass surgery, endoaneuromyomaphy, lymphadenectomy, semicastration</td>
<td>N.a.</td>
<td>5–154 days</td>
</tr>
<tr>
<td>Alejandro-LaFont E et al., 2011. Acta Radiol [15]/50</td>
<td>Chylothorax, chylous ascites, lymph fistula, lymphocele</td>
<td>≤2500 ml/day</td>
<td>Pneumectomy, esophagectomy, pancreaticoduodenectomy, gastrectomy, appendectomy, hysterectomy, cystectomy, transplantation surgery, coronary bypass surgery, spondylodesis, lymphadenectomy</td>
<td>Compression bandage, diuretics, dietary modification (including total parenteral nutrition and medium-chained triglycerides diet), drainage/paracentesis, sclerotherapy (doxycycline)</td>
<td>1–120 days</td>
</tr>
<tr>
<td>Gruber-Rout T et al., 2014. Eur J Radiol [20]/71</td>
<td>Chylothorax, chylous ascites, lymph fistula, lymphocele</td>
<td>10–1000 ml/day</td>
<td>Esophagectomy, gastrectomy, splenectomy, cystectomy, kidney transplantation surgery, radical prostatectomy, lymphadenectomy</td>
<td>Conservative treatment (unspecified)</td>
<td>&gt;21 days</td>
</tr>
<tr>
<td>Kawasaki R et al., 2013. AJR [21]/14</td>
<td>Chylothorax, chylous ascites, lymph fistula, lymphocele</td>
<td>300–3000 ml/day</td>
<td>Esophagectomy, gastrectomy, thoracic and thoracoabdominal aortic repair</td>
<td>Dietary modification (including total parenteral nutrition), somatostatin analogues1,2 (300 μg of octreotide per day), drainage/paracentesis</td>
<td>3–62 days</td>
</tr>
</tbody>
</table>

| **Category II Data (Small Original Case Series with 3–9 Patients)** | | | | | |
| Kariya S et al., 2015. Lympholgy [23]/3 | Cervical lymphocele, chylous ascites, inguinal lymph fistula | 300–400 ml/day | Esophagectomy, colectomy including ileocecal resection, inguinal lymphadenectomy | Conservative treatment (unspecified), drainage/paracentesis, surgical exploration, percutaneous embolization of the thoracic duct (performed 21 days after causal surgery) | 61–183 days |
| Liu J et al., 2016. Int J Surg Case Rep [24]/3 | Chylothorax | 500–2500 ml/day | Esophagectomy | Dietary modification (including total parenteral nutrition), somatostatin analogues1,2 (500 μg of octreotide subcutaneously every 8 hours each day for 2 weeks), sympathomimetic drugs (100–120 mg of etilefrine as continuous infusion for 9 days), drainage/paracentesis | 12–93 days |

n.s. = not specified; Category III data (case reports and other short reports such as letters to the editor and technical notes with <3 patients) are summarized in the main body.

1 Somatostatin is secreted from the pancreas, stomach, and duodenum, and it exerts inhibitory actions on stomach acid and bile secretion, and thus reduces chyle flow by suppressing the absorption of fat, which is the raw material for chyle [47].

2 Somatostatin acts on somatostatin receptors present in lymphoid tissues and it reduces chyle flow by shrinking lymph ducts [48].
Table 2  Technical aspects of CL.

<table>
<thead>
<tr>
<th>study/number of patients</th>
<th>technical success rate of CL (and reason for technical failure)</th>
<th>access for CL</th>
<th>type/amount of injected contrast material</th>
<th>injection speed of contrast material</th>
<th>X-ray imaging modalities used for CL</th>
<th>site of PLL according to X-ray imaging</th>
<th>X-ray imaging signs of PLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22</td>
<td>91% (impossible to obtain transpedal access for selective contrast material injection [due to fragile and very thin lymph ducts or lymph edema])</td>
<td>transpedal (also bilateral)</td>
<td>Lipiodol/1 ml per 10 kg of body weight per foot, ≤ 14 ml per foot</td>
<td>0.07 – 0.1 ml/min per foot</td>
<td>fluoroscopy, radiography/filling phase, nodal phase</td>
<td>thorax, abdomen, periphery</td>
<td>direct² (pathological contrast material extravasation), indirect³ (contrast material detection in the drainage reservoir, pathological disruption of the centripetal contrast material distribution with consecutive masking of the extravasating contrast material due to dilution, atypical opacification of the lymph ducts as a sign of lymphatic collateralization)</td>
</tr>
<tr>
<td>Alejandre-Lafont E et al., 2011. Acta Radiol [15]/50</td>
<td>94% (impossible to obtain transpedal access for selective contrast material injection [unspecified])</td>
<td>transpedal (also bilateral)</td>
<td>Lipiodol/1 ml per 10 kg of body weight per foot, ≤ 10 ml per foot</td>
<td>0.07 – 0.1 ml/min per foot</td>
<td>fluoroscopy, radiography, CT/filling phase, nodal phase⁴</td>
<td>thorax, abdomen</td>
<td>n.s.⁶</td>
</tr>
<tr>
<td>Gruber-Rouh T et al., 2014. Eur J Radiol [20]/71</td>
<td>90% (impossible to obtain transpedal access for selective contrast material injection [due to fragile lymph ducts or lymph edema])</td>
<td>transpedal (unilateral for lymphocele and lymph fistula; bilateral for chylothorax and chylous ascites)</td>
<td>Lipiodol/≤ 1 ml per 10 kg of body weight per foot, ≤ 20 ml for both feet</td>
<td>0.1 – 0.13 ml/min</td>
<td>fluoroscopy, radiography, CT/filling phase, nodal phase⁷</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kawasaki R et al., 2013. AJR [21]/14</td>
<td>100% (–)</td>
<td>transpedal (bilateral)</td>
<td>Lipiodol/8 ml per foot</td>
<td>n.a.</td>
<td>fluoroscopy, radiography, CT/filling phase, nodal phase⁹</td>
<td>n.s.</td>
<td>direct (pathological iodized oil extravasation, pathological iodized oil pooling)⁴¹,¹²</td>
</tr>
<tr>
<td>Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14</td>
<td>100% (–)</td>
<td>transpedal (bilateral)</td>
<td>Lipiodol/≤ 8 ml per foot, ≤ 12 ml for both feet</td>
<td>0.1 ml/min</td>
<td>fluoroscopy, radiography, CT/filling phase, nodal phase¹⁰</td>
<td>n.s.</td>
<td>direct (pathological iodized oil extravasation)⁵, indirect (pathological iodized oil pooling)⁹</td>
</tr>
</tbody>
</table>

Category II data (small original case series with 3–9 patients)

<p>| Kariya S et al., 2015. Lymphology [33]/3 | 100% (–) | groin, neck or axilla | intranodal (unilateral or bilateral)¹⁷ | Lipiodol/1–6 ml | n.a. | fluoroscopy, radiography/filling phase | left venous angle, pelvis, groin | direct (pathological iodized oil extravasation) |</p>
<table>
<thead>
<tr>
<th>Study/Number of Patients</th>
<th>Technical Success Rate of CL (and Reason for Technical Failure)</th>
<th>Access for CL</th>
<th>Type/Amount of Injected Contrast Material</th>
<th>Injection Speed of Contrast Material</th>
<th>X-Ray Imaging Modalities Used for CL/Time Point of X-Ray Imaging to Visualize the PLL</th>
<th>Site of PLL According to X-Ray Imaging</th>
<th>X-Ray Imaging Signs of PLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu J et al., 2016. Int J Surg Case Rep [24]/3</td>
<td>100% (-) groin intranodal (unilateral)</td>
<td>Lipiodol/ 8–15 ml</td>
<td>n.a.</td>
<td>Fluoroscopy, radiography, CT/filling phase 18, nodal phase</td>
<td>Behind the common hepatic arterial trunk, paravertebral/mediastinal at the level of T5 and T7</td>
<td>Direct (pathological iodized oil extravasation), indirect (pathological iodized oil pooling)</td>
<td></td>
</tr>
<tr>
<td>Iwai T et al., 2018. Transplant Proc [25]/4</td>
<td>75% (impossible to obtain intranodal access for selective contrast material injection [due to lack of identification of a groin lymph node under ultrasound])</td>
<td>Lipiodol/ 8–10 ml</td>
<td>0.33 ml/min</td>
<td>Fluoroscopy, radiography/filling phase</td>
<td>Pelvic</td>
<td>Direct (pathological iodized oil extravasation), indirect (pathological iodized oil pooling)</td>
<td></td>
</tr>
</tbody>
</table>

n.s. = not specified; Category III data (case reports and other short reports such as letters to the editor and technical notes with <3 patients) are summarized in the main body.

1 performed 24 hours after contrast material injection.
2 observed in 75% of patients.
3 observed in 25% of patients.
4 acquired during the first 2 hours of after contrast material injection.
5 acquired 24 hours after contrast material injection.
6 for the 12 patients with clinically ineffective CL and undergoing subsequent surgical ligation of the thoracic duct or lymphocele resection, the site of PLL could be determined on the basis of X-ray imaging signs in 10 of 12 patients (for these 10 patients, surgical exploration confirmed the correct site of PLL in 100%).
7 performed 24 hours after contrast material injection in the case of a lack of X-ray imaging signs of PLL in the filling phase.
8 performed under fluoroscopy/radiography only.
9 radiography and CT were performed immediately after contrast material injection, and additionally 2–3 hours after contrast material injection in the case of a lack of opacification of the upper mediastinum or the left infraclavicular region in the first filling phase X-ray imaging.
10 radiography and CT were performed 24 hours after contrast material injection in the case of a lack of opacification of the upper mediastinum or the left infraclavicular region in the second filling phase X-ray imaging.
11 3 different degrees of PLL were defined: major PLL (detectable under both fluoroscopy/radiography and CT), minor PLL (detectable under CT only but not under fluoroscopy/radiography), and undetectable PLL.
12 in this study, pathological contrast material pooling was categorized as a direct X-ray imaging sign of PLL.
13 performed under fluoroscopy, radiography, and/or CT (CT was performed up to 26 hours after contrast material injection).
14 performed under CT (CT was performed up to 26 hours after contrast material injection).
15 under CT, PLL was detected in 64% of patients.
16 CT was used to classify the type of PLL (nodular [4 patients] vs. beaded [5 patients]) and to predict the clinical effectiveness of CL (a nodular appearance was discussed as a positive predictor for clinical effectiveness; see also ▶ Table 4).
17 CL was performed after nuclear scintigraphy (technetium-99m labeled human serum albumin).
18 performed under radiography or CT, or both.
19 performed under ultrasonic guidance applying a 25 G cathelin needle.
fistula, and 0 % for lymphocele [19]. After transpedal CL, Alejandre-Lafont et al. observed a PLL cure rate of 70 % for the patients with a PLL volume of < 500 ml/day compared with 35 % for the patients with a PLL volume of > 500 ml/day [15]. Gruber-Rouh et al. presented a PLL cure rate of 96.8 % for the patients with a PLL volume of < 200 ml/day compared with 58.1 % for the patients with a PLL volume of > 200 ml/day after transpedal CL [20]. Kawasaki et al. could achieve a PLL cure in 2 of 7 major PLLs (annotation: major PLLs were defined as detectable under both fluoroscopy/radiography and CT) as well as in all minor PLLs (annotation: minor PLLs were defined as detectable under CT only but not under fluoroscopy/radiography) and undetectable PLLs after transpedal CL [21]. Kariya et al. repeated intranodal CL once in a patient with cervical lymphocele (22 days after the first intranodal CL), once in a patient with chylous ascites (4 days after the first intranodal CL), and 3 times in a patient with a lymph fistula in the groin (4, 10, and 17 days after the first intranodal CL) which resulted in a PLL cure rate of 100 % [44]. Time to PLL cure is 3 – 29 days for transpedal CL and 2 – 20 days for intranodal CL. Bailout procedures in the case of clinically ineffective CL include a range of treatments such as conservative management and surgical revision (e. g. lymph duct ligation and lymphocele fenestration). Data are catalogued in Table 3.

<table>
<thead>
<tr>
<th>study/number of patients</th>
<th>CL-related minor complications</th>
<th>CL-related major complications</th>
<th>30-day CL-related morbidity</th>
<th>30-day CL-related mortality</th>
<th>overall morbidity</th>
<th>overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kos et al., 2007. Cardiovasc Intervent Radiol [19]/22</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alejandre-Lafont E et al., 2011. Acta Radiol [15]/50</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gruber-Rouh T et al., 2014. Eur J Radiol [20]/71</td>
<td>3 %†</td>
<td>0 %</td>
<td>n.s.</td>
<td>0 %</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Kawasaki R et al., 2013. AJR [21]/14</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14</td>
<td>0 %</td>
<td>0 %</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
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</table>

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<th>study/number of patients</th>
<th>CL-related minor complications</th>
<th>CL-related major complications</th>
<th>30-day CL-related morbidity</th>
<th>30-day CL-related mortality</th>
<th>overall morbidity</th>
<th>overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kariya S et al., 2015. Lymphology [44]/3</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Liu J et al., 2016. Int J Surg Case Rep [24]/3</td>
<td>0 %</td>
<td>0 %</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Iwai T et al., 2018, Transplant Proc [25]/4</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>0 %</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. – not specified; Category III data (case reports and other short reports such as letters to the editor and technical notes with < 3 patients) are summarized in the main body.

† contrast material emboli in the pulmonary artery in 2 patients (rated as minor complications).

Under consideration of Category III data, the PLL cure rate is 100 % in 4 articles with transpedal CL and 14 articles with intranodal CL (and n.s. in 2/20 articles [1 article with transpedal CL and 1 article with intranodal CL]) [17, 26–28, 30–43]. In the article of Hara et al. with 1 patient with chylothorax (PLL volume of 1000 ml/day), intranodal CL was performed twice at an interval of 1 month (bilateral groin access for the first CL and bilateral groin and bilateral axilla access for the second CL) until PLL cure was observed [37]. The time to PLL cure is 2–5 days for transpedal CL and 3–<30 days for intranodal CL.

Comment

In this systematic review, the outcome data regarding CL in the management of PLL have been presented and catalogued with comments. On the basis of Category III data, no firm conclusions can be drawn, but Category I data and Category II data suggest that CL is feasible, safe, and effective. CL is performed in the management of PLL occurring in multiple different locations. Accordingly, clinical background and indications are inconsistent: Type of PLL (e. g. peripheral percutaneous lymph fistula, pelvic lymphocele, or chylothorax), PLL volume (ranging from 10 ml/day to 6000 ml/day), type of causal surgery (e. g. exploratory laparoscopy including biopsy, hemihepatectomy, kidney transplantation,
or esophagectomy), failed pretreatments to cure PLL (ranging from conservative management [e. g. dietary modification] to surgical revision [e. g. wound vacuum therapy]), and interval “causal surgery – CL” (ranging from 1 day to 4 years). Regarding technical aspects, transpedal CL and groin intranodal CL are the most frequently used accesses, both being performed with a high technical success rate and with Lipiodol as the contrast material. Lipiodol is a highly viscous ethyl ester of iodinated poppy-seed oil fatty acid with the potential to not only visualize but also to cure the PLL [45, 46]. There are two potential mechanisms leading to PLL cure: Lipiodol-induced selective blockage of the leaking lymph ducts and/or lymph nodes as well as induction of a sterile inflammation process with subsequent scarring at the site of the pathological Lipiodol extravasation leading to closure of the PLL over time [16, 25]. Alternative access for intranodal CL is the neck, axilla and the mesentery [37, 38, 44]. X-ray imaging modalities that are regularly used for CL are not only fluoroscopy and radiography but also CT, the latter demonstrating also the subtle-direct (pathological contrast material extravasation) and indirect (e. g. pathological contrast material pooling) signs of PLL, especially in complex anatomic regions (e. g. thorax or abdomen) [21]. The time point or window of X-ray imaging with which to visualize the PLL is the filling phase (performed during contrast material propagation into the central lymphatic system), and additionally the nodal phase (performed in multiple articles 24 hours after contrast material injection if X-ray imaging in the filling

<table>
<thead>
<tr>
<th>study/number of patients</th>
<th>PLL cure rate after CL</th>
<th>time to PLL cure</th>
<th>follow-up interval after CL</th>
<th>bailout procedures in case of clinically ineffective CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>category I data (large original case series with &gt;10 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22</td>
<td>55 %1</td>
<td>21–28 days</td>
<td>n.s.2</td>
<td>surgical occlusion of the thoracic duct, lymphocele fenestration (inclusive of insertion of a Salem drain), wound debridement</td>
</tr>
<tr>
<td>Alejandro-Lafont E et al., 2011. Acta Radiol [15]/50</td>
<td>51 %3</td>
<td>≤ 14 days</td>
<td>n.s.</td>
<td>surgical ligation of the thoracic duct, lymphocele resection</td>
</tr>
<tr>
<td>Gruber-Rouh T et al., 2014. Eur J Radiol [20]/71</td>
<td>70 %4</td>
<td>10–28 days</td>
<td>1–24 months</td>
<td>surgical occlusion of the PLL5</td>
</tr>
<tr>
<td>Kawasaki R et al., 2013. AJR [21]/14</td>
<td>64 %6</td>
<td>3–29 days</td>
<td>12–104 days</td>
<td>surgical pleurodesis, surgical thoracic duct ligation</td>
</tr>
<tr>
<td>Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14</td>
<td>57 %</td>
<td>n.s.</td>
<td>n.s.</td>
<td>surgical pleuro-sclerosis, conservative treatment</td>
</tr>
</tbody>
</table>

Category II data (small original case series with 3–9 patients)

<table>
<thead>
<tr>
<th>study/number of patients</th>
<th>PLL cure rate after CL</th>
<th>time to PLL cure</th>
<th>follow-up interval after CL</th>
<th>bailout procedures in case of clinically ineffective CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kariya S et al., 2015. Lymphology [44]/3</td>
<td>100 %1,6</td>
<td>2–14 days</td>
<td>n.s.</td>
<td>–</td>
</tr>
<tr>
<td>Liu J et al., 2016. Int J Surg Case Rep [24]/3</td>
<td>33 %</td>
<td>20 days</td>
<td>n.s.</td>
<td>surgical lymph duct ligation5,10</td>
</tr>
<tr>
<td>Iwai T et al., 2018. Transplant Proc [25]/4</td>
<td>100 %</td>
<td>8–13 days</td>
<td>8–16 months</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. – not specified; Category III data (case reports and other short reports such as letters to the editor and technical notes with <3 patients) are summarized in the main body.

1 for the patients without surgical revision <4 weeks after CL, the PLL cure rate after CL was 69.2 % (75 % for chylothorax, 86 % for lymph fistula and 0 % for lymphocele).
2 PLL recurrence after 8 wks in 1 patient with combined chylothorax/chyloous ascites initially treated effectively with CL.
3 PLL cure rate of 70 % for the patients with a PLL volume of < 500 ml/day compared with 35 % for the patients with a PLL volume of > 500 ml/day.
4 PLL cure rate of 96.8 % for the patients with a PLL volume of < 200 ml/day compared with 58.1 % for the patients with a PLL volume of > 200 ml/day.
5 performed on the basis of X-ray imaging presenting degree and location of PLL.
6 PLL cure in 2 of 7 major PLLs (defined as detectable under both fluoroscopy/radiography and CT) as well as cure in all minor (defined as detectable under CT only but not under fluoroscopy/radiography) and undetectable PLLs.
7 CT was repeated once in the patient with the cervical lymphocele 22 days after the first CL, once in the patient with the chylous ascites 4 days after the first CL, and 3 times in the patient with the lymph fistula in the groin 4, 10, and 17 days after the first CL.
8 PLL cure in 2 of 7 major PLLs (defined as detectable under both fluoroscopy/radiography and CT) as well as cure in all minor (defined as detectable under CT only but not under fluoroscopy/radiography) and undetectable PLLs.
9 performed on the basis of X-ray imaging presenting degree and location of PLL.
10 in both patients with clinically ineffective CL, surgical lymph duct ligation was performed 2 or 13 days after CL (showing a time to PLL cure of 16 and 2 days, respectively).
phase remains unclear). Transpedal and intranodal CL can be regarded as safe procedures. CL-associated complications are occasional and in the vast majority of cases there are minor complications that are self-limiting or well manageable with standard treatment. Contrast material emboli in the pulmonary artery are a relevant complication. However, this was rated as a minor complication due to the lack of clinical sequelae in 1 article [20]. CL-associated morbidity and mortality are extremely rare, but were described in 1 article with acute respiratory distress syndrome and in 1 article with cerebral contrast material embolism, respectively [29, 41]. The PLL cure rate after CL – as written in the different articles – should be interpreted with caution. With respect to Category I data and Category II, the PLL cure rate is indicated as 51–70 %, 57–64 % and 33–100 %, respectively [15, 19–22, 24, 25, 44]. However, these data do not necessarily consider the rate of technical failure. After recalculation under specific consideration of the rate of technical failure of CL, the real PLL cure rate – the PLL cure rate on an intent-to-treat basis – decreases in 3/5 articles for Category I data (from 55 % to 50 %, from 51 % to 48 % and from 70 % to 63 %, respectively) and in 1/3 articles for Category II data (from 100 % to 75 %) [15, 19, 20, 25]. The predictors of PLL cure after CL include PLL volume, PLL morphology, and type of PLL. PLL volumes of > 500 ml/day or > 200 ml/day are associated with decreased PLL cure rates [15, 20]. Minor PLLs detectable under CT only (but not under fluoroscopy/radiography) are associated with increased PLL cure rates [21]. CL for the treatment of lymphoceles is associated with decreased PLL cure rates [15, 19]. Practical experience, however, repeatedly shows that the aforementioned positive and negative predictors of clinical success are not necessarily reliable. Notwithstanding, one cannot emphasize enough the fact that one or multiple repetitions of CL can lead to an increased PLL cure rate as was demonstrated by Kariya S et al. and Hara H et al. [37, 44]. Bailout procedures after clinically ineffective CL include conservative management and different types of surgical treatments (e.g. thoracic duct ligation, wound debridement and lymphocele fenestration). Interestingly, second-line percutaneous lymphatic interventions such as thoracic duct embolization by applying coils or interstitial embolization by applying glue are not mentioned as bailout procedures [3, 45]. A possible explanation is that the different second-line percutaneous lymphatic interventions are performed virtually always in combination with CL, whereby CL is then intended exclusively to visualize the lymphatic system (e.g. cisterna chyli) and the lymphatic pathology (e.g. leaking lymph ducts and/or lymph nodes) to guide specifically subsequent second-line percutaneous lymphatic interventions [3, 9, 10, 13, 45]. Because of the multiple types and high complexity of second-line percutaneous lymphatic interventions, presentation of these outcome data would exceed the scope of this manuscript and therefore they were not considered in this review (according to the exclusion criteria). However, a dedicated systematic review of articles with second-line percutaneous lymphatic interventions is strongly warranted and should be performed and published in the near future.

The primary limitation of this systematic review is the source data itself, which are available on the level of study data but not on the level of patient data. All analyzed articles are retrospective analyses with limited sample size and, therefore, the presented level of evidence is low (level 4 of the Oxford Centre for Evidence-based Medicine – Levels of Evidence, March 2009). The lack of standardization of reporting criteria and terminology impedes the precise communication in the field of CL, which has to be listed as another limitation. These facts made the implementation of a meta-analysis of the presented original data impossible. Nevertheless, detailed analysis of the 28 articles was performed in order to present the status quo of CL in the management of PLL as accurately as possible.

In conclusion, CL is feasible, safe, and effective in the management of PLL. Lipiodol as the contrast material is essential in CL because the highly viscous iodinated poppy-seed oil features not only diagnostic but also therapeutic effects. Accordingly, Lipiodol-based CL can be regarded as a therapeutic procedure. Position papers, interdisciplinary guidelines, and randomized controlled trials are future steps to define the ultimate value of CL in the interdisciplinary management of PLL. Furthermore, the role of second-line percutaneous lymphatic interventions such as thoracic duct embolization or interstitial embolization must be specified.

Conflict of Interest

Guerriet, Villepinte, France financially supported professional language editing. The sponsor had no influence over the content of the manuscript. All authors report no conflict of interest regarding this manuscript.

References
