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

Hintergrund Die postoperative Lymphleckage (PLL) wird meist konservativ und/oder chirurgisch behandelt, jedoch können diese Behandlungen anspruchsvoll und potenziell klinisch ineffektiv sein. Die konventionelle Lymphangiografie (KL) entwickelte sich zur wichtigen Alternative. Ziel der vorliegenden Übersicht ist es, die verfügbaren Outcome-Daten zur KL beim Management der PLL darzustellen.

Methode Eine systematische Literaturrecherche (PubMed) unter Verwendung des MeSH-Begriffs „lymphangiography“ wurde durchgeführt, wobei ausschließlich Artikel berücksichtigt wurden, die zwischen Januar 2007 und August 2019 publiziert wurden. Identifikation, Screening sowie Beurteilung auf Eignung und Einschluss erfolgten in Übereinstimmung mit PRISMA.

Ergebnisse Von den ursprünglich erhaltenen 1006 Artikeln (Identifikation) wurden letztendlich 28 Artikel mit insgesamt 201 Patienten eingeschlossen (Einschluss). Die methodische Qualität aller eingeschlossenen Artikel entspricht Level 4 (Oxford Centre for Evidence-based Medicine – Levels of Evidence, March 2009). Die PLL tritt nach onkologischen und nicht-onkologischen Operationen in Form von Chylothorax, chylösem Aszites sowie zervikalen, thorakalen, abdominellen, pelvinen und peripheren Lymphfisteln und/oder Lymphozelen auf. Die technische Erfolgsrate der CL liegt bei 75–100 %. Der Zugang für die CL ist transpedal (176 Patienten) oder intranodal (25 Patienten). Lipiodol wird in allen Artikeln als Kontrastmittel verwendet, mit einer Maximaldosis von 20 ml für die transpedale CL und 30 ml für die intranodale CL. Röntgen-Bildgebungsmodalitäten beinhalten Fluoroskopie, Radiografie und/oder CT. 2 Artikel berichten über CL-assoziierte Major-Komplikationen sowie CL-assoziierte Morbidität und Mortalität. Die PLL-Abheilungsrate beträgt 51–70 % für die transpedale CL (Abheilungszeit: 2–29 Tage) bzw. 33–100 % für die intranodale CL (Abheilungszeit: 2–<30 Tage). Rettungsprozeduren im Fall der klinisch ineffektiven CL beinhalten unterschiedliche Behandlungen.

Schlussfolgerung Die KL ist technisch machbar und sicher und effektiv beim Management der PLL. Lipiodol als Kontrastmittel spielt für die KL eine essenzielle 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.

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Introduction

Different types of surgical procedures may injure lymph ducts and lymph nodes, resulting in postoperative lymphatic leakage (PLL) as a difficult-to-treat and potentially life-threatening complication [1]. PLL can occur anywhere in the body along the lymphatic system, leading to the pathological accumulation of lymph or chyle (e.g. chylothorax and lymphatic ascites or chylous ascites) [1, 2]. Lymph can also leak through percutaneous tracts in the form of a lymph fistula, which is associated with or without diffuse or localized lymph collections (e.g. lymphocele) [3]. Refractory PLL can significantly affect postoperative recovery time, wound healing, and quality of life. High-output PLL increases morbidity and mortality among patients due to lymphocytopenia, protein loss, fat loss, malnutrition, respiratory distress, and immune suppression [1, 3–5]. For the past three decades, conservative and surgical treatments have defined the standard for managing PLL. Conservative management includes parenteral nutrition, medium-chain triglycerides diet, administration of somatostatin analogues

(e.g. octreotide), repeated paracentesis, and percutaneous drainage procedures. Surgical management comprises different and at least in parts non-standardized approaches such as lymph duct ligation, shunt implantation, sclerotherapy with doxycycline or thrombin, plastic surgery, and wound vacuum therapy [6, 7]. Depending on the type, degree and location of PLL, both conservative and surgical management can be challenging to perform, time-consuming and expensive as well as clinically ineffective, whereby surgery-related complication and mortality rates of up to 38 % and 25 %, respectively, have been described [1, 3, 4, 6, 8–13]. Conventional lymphangiography (CL), a radiological examination performed under X-ray imaging after contrast material injection, has emerged as an alternative to the aforementioned treatments. In different articles, CL was described as a minimally invasive diagnostic tool for determining the precise location of the PLL but more importantly there are multiple articles outlining the therapeutic effects of CL [3, 4, 10, 14–17]. Although CL is increasingly applied in clinical practice, the technique, safety, and efficacy have not been analyzed in a systematic review. In this article,

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 (PRIS-MA) 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). Category I data were first analyzed, and then the analysis was extended to Category II data. 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.

► **Fig. 1** Flow Chart on the Selection of Articles. Note: ¹Category I data – large original case series (> 10 patients); ²Category II data – small original case series (3–9 patients); ³Category III data – case reports and other short reports such as letters to the editor and technical notes (< 3 patients).

► **Abb. 1** Flussdiagramm mit Selektion der Artikel.

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 for 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 chylothorax 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 radiation therapy (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-venous 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 tapering 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 morbidity 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.						
► Tab. 1 Klinischer Hintergrund und Indikationen für die KL.						
study/number of patients	clinical presentation of PLL	PLL volume	type of causal surgery	failed pretreatments to cure PLL	Interval "causal surgery – CL"	
category I data (large original case series with > 10 patients)						
Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22	chylothorax, chylous ascites, thoracic, abdominal and peripheral lymph fistula, thoracic, abdominal and peripheral lymphocele	200–3000 ml/day	thymectomy, pneumectomy, esophagectomy, partial gastrectomy, nephrectomy, prostatectomy, soft tissue resection, bypass surgery, endoaneurysmorrhaphy, lymphadenectomy, semicastration	n.a.	5–154 days	
Alejandro-Lafont E et al., 2011. Acta Radiol [15]/50	chylothorax, chylous ascites, lymph fistula, lymphocele	≤ 2500 ml/day	pneumectomy, esophagectomy, pancreaticoduodenectomy, gastrectomy, appendectomy, hysterectomy, cystectomy, transplantation surgery, coronary bypass surgery, spondylosis, lymphadenectomy	compression bandage, diuretics, dietary modification (including total parenteral nutrition and medium-chained triglycerides diet), drainage/paracentesis, sclerotherapy (doxycycline)	1–120 days	
Gruber-Rout T et al., 2014. Eur J Radiol [20]/71	chylothorax, chylous ascites, lymph fistula, lymphocele	10–1000 ml/day	esophagectomy, gastrectomy, splenectomy, cystectomy, kidney transplantation surgery, radical prostatectomy, lymphadenectomy	conservative treatment (unspecified)	> 21 days	
Kawasaki R et al., 2013. AJR [21]/14	chylothorax, chylous ascites	300–3000 ml/day	esophagectomy, gastrectomy, thoracic and thoraco-abdominal aortic repair	dietary modification (including total parenteral nutrition), somatostatin analogues ^{1,2} (300 µg of octreotide per day), drainage/paracentesis	3–62 days	
Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14	chylothorax, chylous ascites, lymph fistula, lymphocele	200–3000 ml/day	esophagectomy, aortic root replacement, gastrectomy, resection, colectomy, lymphadenectomy, surgery for scoliosis	dietary modification (including total parenteral nutrition), drainage/paracentesis	n.a.	
Category II data (small original case series with 3–9 patients)						
Kariya S et al., 2015. Lymphology [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 analogues ^{1,2} (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	
Iwai T et al., 2018. Transplant Proc [25]/4	pelvic lymph fistula, lymphocele	169–361 ml/day	kidney transplantation	drainage/paracentesis	10–15 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.► **Tab. 2** Technische Aspekte der KL.

study/number of patients	technical success rate of CL (and reason for technical failure)	access for CL	type/amount of injected contrast material	injection speed of contrast material	X-ray imaging modalities used for CL/time point of X-ray imaging to visualize the PLL	site of PLL according to X-ray imaging	X-ray imaging signs of PLL
Category I data (large original case series with > 10 patients)							
Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22	91 % (impossible to obtain transpedal access for selective contrast material injection [due to fragile and very thin lymph ducts or lymph edema])	transpedal (also bilateral)	Lipiodol/1 ml per 10 kg of body weight per foot, ≤ 14 ml per foot	0.07–0.1 ml/min per foot	fluoroscopy, radiography/filling phase, nodal phase ¹	thorax, abdomen, periphery	direct ² (pathological contrast material extravasation), indirect ³ (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)
Alejandro-Lafont E et al., 2011. Acta Radiol [15]/50	94 % (impossible to obtain transpedal access for selective contrast material injection [unspecified])	transpedal (also bilateral)	Lipiodol/≤ 1 ml per 10 kg of body weight per foot, ≤ 10 ml per foot	0.07–0.1 ml/min per foot	fluoroscopy, radiography, CT/filling phase ⁴ , nodal phase ⁵	thorax, abdomen	n.s. ⁶
Gruber-Rough T et al., 2014. Eur J Radiol [20]/71	90 % (impossible to obtain transpedal access for selective contrast material injection [due to fragile lymph ducts or lymph edema])	transpedal (unilateral for lymphocele and lymph fistula; bilateral for chylothorax and chylous ascites)	Lipiodol/≤ 1 ml per 10 kg of body weight per foot, ≤ 20 ml for both feet	0.1–0.13 ml/min	fluoroscopy, radiography, CT ⁷ /filling phase ⁸ , nodal phase ⁷	n.s.	n.s.
Kawasaki R et al., 2013. AJR [21]/14	100 % (–)	transpedal (bilateral)	Lipiodol/8 ml per foot	n.a.	fluoroscopy, radiography, CT/filling phase ⁹ , nodal phase ¹⁰	n.s.	direct (pathological iodized oil extravasation, pathological iodized oil pooling) ^{11,12}
Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14	100 % (–)	transpedal (bilateral)	Lipiodol/≤ 8 ml per foot, ≤ 12 ml for both feet	0.1 ml/min	fluoroscopy, radiography, CT/filling phase ¹³ , nodal phase ¹⁴	n.s.	direct (pathological iodized oil extravasation) ¹⁵ , indirect (pathological iodized oil pooling) ¹⁶
Category II data (small original case series with 3–9 patients)							
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)

► **Table 2** (Continuation)

study/number of patients	technical success rate of CL (and reason for technical failure)	access for CL	type/amount of injected contrast material	injection speed of contrast material	X-ray imaging modalities used for CL/time point of X-ray imaging to visualize the PLL	site of PLL according to X-ray imaging	X-ray imaging signs of PLL
Liu J et al., 2016. Int J Surg Case Rep [24]/3	100 % (–)	groin intranodal (unilateral)	Lipiodol/ 8–15 ml	n.a.	fluoroscopy, radiography, CT/filling phase ¹⁸ , nodal phase ³	behind the common hepatic arterial trunk, paravertebral/ mediastinal at the level of T5 and T7	direct (pathological iodized oil extravasation), indirect (pathological iodized oil pooling)
Iwai T et al., 2018. Transplant Proc [25]/4	75 % (impossible to obtain intranodal access for selective contrast material injection [due to lack of identification of a groin lymph node under ultrasound])	groin intranodal (unilateral) ¹⁹	Lipiodol/ 8–10 ml	0.33 ml/min	fluoroscopy, radiography/filling phase	pelvic	direct (pathological iodized oil extravasation), indirect (pathological iodized oil pooling)

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 at the earliest 0.5 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 ultrasound guidance applying a 25 G catheter needle.

► **Table 3** Complications, morbidity, and mortality during/after CL.► **Tab. 3** Komplikationen, Morbidität und Mortalität während/nach KL.

study/number of patients	CL-related minor complications	CL-related major complications	30-day CL-related morbidity	30-day CL-related mortality	overall morbidity	overall mortality
category I data (large original case series with > 10 patients)						
Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Alejandro-Lafont E et al., 2011. Acta Radiol [15]/50	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gruber-Rouh T et al., 2014. Eur J Radiol [20]/71	3 % ¹	0 %	n.s.	0 %	n.s.	n.s.
Kawasaki R et al., 2013. AJR [21]/14	0 %	0 %	0 %	0 %	n.s.	n.s.
Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14	0 %	0 %	n.s.	n.s.	n.s.	n.s.
category II data (small original case series with 3–9 patients)						
Kariya S et al., 2015. Lymphology [44]/3	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Liu J et al., 2016. Int J Surg Case Rep [24]/3	0 %	0 %	n.s.	n.s.	n.s.	n.s.
Iwai T et al., 2018, Transplant Proc [25]/4	0 %	0 %	0 %	0 %	n.s.	n.s.
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 contrast material emboli in the pulmonary artery in 2 patients (rated as minor complications).						

fistula, and 0 % for lymphocele [19]. After transpedal CL, Alejandro-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 4**.

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,

► **Table 4** PLL cure rate after CL and bailout procedures.

► **Tab. 4** PLL-Abheilungsrate nach KL und Rettungsprozeduren.

study/number of patients	PLL cure rate after CL	time to PLL cure	follow-up interval after CL	bailout procedures in case of clinically ineffective CL
category I data (large original case series with > 10 patients)				
Kos S et al., 2007. Cardiovasc Intervent Radiol [19]/22	55 % ¹	21–28 days	n.s. ²	surgical occlusion of the thoracic duct, lymphocele fenestration (inclusive of insertion of a Salem drain), wound debridement
Alejandro-Lafont E et al., 2011. Acta Radiol [15]/50	51 % ³	≤ 14 days	n.s.	surgical ligation of the thoracic duct, lymphocele resection
Gruber-Rouh T et al., 2014. Eur J Radiol [20]/71	70 % ⁴	10–28 days	1–24 months	surgical occlusion of the PLL ⁵
Kawasaki R et al., 2013. AJR [21]/14	64 % ⁶	3–29 days	12–104 days	surgical pleurodesis, surgical thoracic duct ligation
Yoshimatsu R et al., 2013. Jpn J Radiol [22]/14	57 %	n.s.	n.s.	surgical pleuro-sclerosis, conservative treatment
Category II data (small original case series with 3–9 patients)				
Kariya S et al., 2015. Lymphology [44]/3	100 % ^{7,8}	2–14 days	n.s.	–
Liu J et al., 2016. Int J Surg Case Rep [24]/3	33 %	20 days	n.s.	surgical lymph duct ligation ^{9,10}
Iwai T et al., 2018. Transplant Proc [25]/4	100 %	8–13 days	8–16 months	n.s.

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 CLL 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/chylous 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 CL 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 volume decreased to 40/20/0 ml/day after the last CL.

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).

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 poppyseed 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

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

Guerbet, 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.

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