



Contemporary lymphatic interventions for post-operative lymphatic leaks

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Abstract: Post-operative lymphatic injuries are uncommon but increase morbidity and mortality in vulnerable patient populations. Post-surgical lymphatic leaks are most commonly a consequence of radical neck dissection, esophagectomy, and lung cancer resections or retroperitoneal surgeries such as radical nephrectomy and lymphadenectomy. Injury may occur anywhere along the lymphatic chains with most serious leaks occurring along the axial skeleton between the inguinal region and the left venous angle. The resultant clinical manifestations of a lymphatic leak are dependent on the location and severity of the lymphatic injury as well as patient factors. Treatment strategies are tailored toward the causative etiology, symptom severity, and daily leak volume with higher volume leaks warranting a more aggressive approach. Lymphangiography and lymphatic interventions, such as embolization, are increasingly applied for both the diagnosis and as a minimally invasive therapy for lymphatic injuries. Herein, a review of lymphatic anatomy, lymphangiography, and lymphatic interventions for the treatment of post-operative chylothorax, chylous ascites, and lymphocele is presented.

Keywords: Lymphangiography; chylothorax; chylous ascites; post-surgical; lymphocele

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Introduction

While historically uncommon, the incidence rate of chylothorax, chylous ascites, and lymphocele is rising likely due to longer survival of cancer patients and the potential for aggressive surgery. For instance, chylous ascites complicates between 0.3–11% of major abdominal operations and lymphoceles complicate between 0.6–32% of renal transplants, urologic lymphadenectomies, and gynecologic lymphadenectomies (1-6). Manifestations may range from asymptomatic, small lymphoceles incidentally found on follow-up imaging to a recalcitrant high volume and debilitating chylous ascites. Traditionally, conservative therapy for lymphatic injuries consists of dietary

modification with either a non-fat diet or total parenteral nutrition, drainage of the affected area, and supportive care. If the lymphatic leak persists, open or laparoscopic surgical approaches could be pursued at the risk of longer hospitalization and recovery, increased morbidity, and higher mortality (7-9).

Over the last two decades, lymphatic intervention has been a new frontier in interventional radiology brought to the forefront by Constantin Cope in 1999 with a prospective trial of thoracic duct embolization for chylothorax (10). Multiple subsequent techniques and applications have arisen from Cope's initial work including successful treatment of chylous ascites, lymphoceles, plastic bronchitis, and protein losing enteropathy (11-14). Herein, an overview

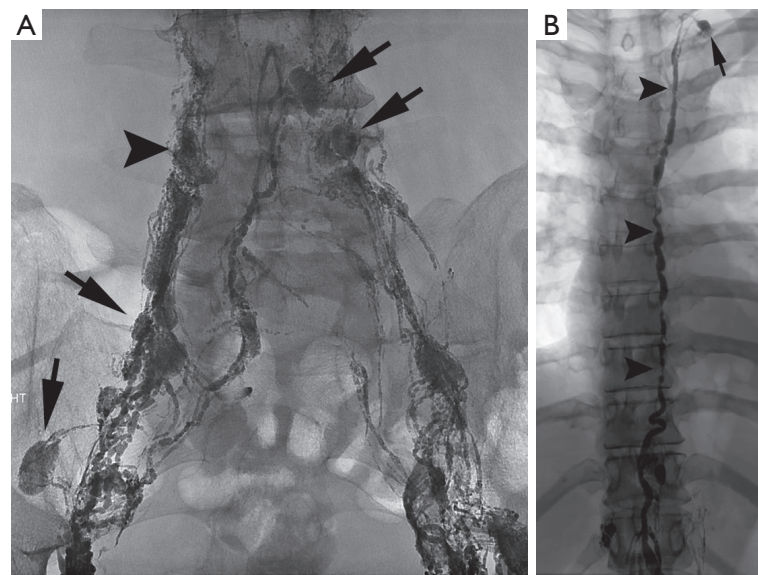


Figure 1 Conventional lymphatic anatomy. (A) Lymphatic vessels are interspersed with lymph nodes (arrows and arrowhead) as they course along and around the iliac vasculature; (B) the retroperitoneal lymphatics coalesce to form the cisterna chyli (bottom of image) which gives rise to a single thoracic duct (black arrowheads), terminating at the left venous angle (arrow).

of lymphatic anatomy is followed by a discussion of the evolution of lymphangiography from a “lost-art” to a necessary precursor for lymphatic intervention. The current status of lymphatic intervention for traumatic chylothorax, chylous ascites, and lymphocele are then summarized followed by a suggested treatment algorithm.

Lymphatic anatomy

Despite dramatic advances in medical knowledge, the lymphatic circulation remains mysterious and difficult to study. Ancient Greeks were aware of the presence of lymphatic vessels, but incompletely understood their function. Autopsy and animal vivisection by multiple scholars throughout the 17th century led to a fuller understanding of lymphatic anatomy and physiology, particularly within the abdominal cavity (15). In the 19th century, the structure and function of lymph nodes and their interplay with lymphatic vessels was described. This was followed by the theory for the formation of lymph by diffusion across blood vessels by a balance of hydrostatic and oncotic pressures, the Starling equation. With the understanding that the lymphatic system functions to return fluid and nutrients from interstitial tissues to the venous system, three distinct subdivisions within the lymphatic circulation are now recognized: soft tissue/extremity,

hepatic, and enteral lymphatics (15).

Functionally, the lymphatics are a unidirectional drainage system channeling 1.5–4 L of fluid back to the central circulation daily. Hepatic and enteral lymphatics produce approximately 80% of lymphatic fluid, while the upper and lower extremities give rise to the remaining 20% of daily lymph volume. While the hepatic lymphatics are rich in protein and the enteral lymphatics are rich in fat droplets, the extremity lymphatics have a low concentration of nutrients and a preponderance of lymphocytes (15). Lymphatic circulation is vital for the return of serum protein and lipids to the systemic circulation and is central to fluid balance and immune response.

The fluid from each network courses through lacelike vessels and interspersed lymph nodes to the retroperitoneum where they coalesce to form a dilated sac-like structure, the cisterna chyli. The cisterna chyli in turn gives rise to the thoracic duct, which is the largest lymphatic vessel in the body at approximately 40 cm long and terminates at the left venous angle (*Figure 1*). The right head, neck, thorax, and upper extremity lymphatics drain through a right lymphatic duct. All remaining lymphatics including the hepatic, enteral, lower extremities, left upper extremities, and the left head and neck drain into the thoracic duct. This standard anatomy is present in approximately 50% of the population (15).

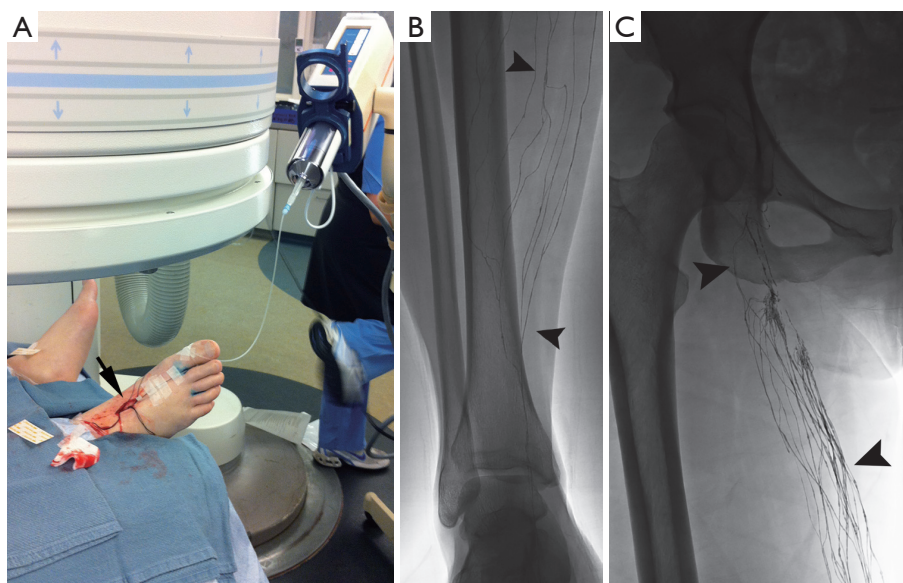


Figure 2 Pedal lymphangiography. (A) Cutdown on the dorsum of the foot is performed (arrow) and a lymphatic vessel is cannulated with a needle attached to a contrast injector; (B) spot radiograph of the lower leg reveals normal lace-like lymphatic vessels (arrowheads); (C) spot radiograph of the thigh reveals multiple lymphatic vessels coursing together (arrowheads) and coalescing into lymph nodes before continuing into the inguinal canal.

Lymphangiography

Dating back to the 1930s, contrast material was directly injected into lymph nodes for radiographic visualization (16). Kinmonth *et al.* described the technique of lymphangiography of the lower extremity in 1955 and Fischer and Zimmerman tested different radio-opaque contrast agents in the lymphatics, including ethiodized oil, which is used to the present day (17,18). Traditional trans-pedal lymphangiography, “the Kinmonth method”, was regularly used since 1955 for various indications including lymphoma staging, differentiation of inflammatory from neoplastic processes, evaluation of metastatic disease, and determination of chemotherapy response. Following injection of blue dye in the webspaces between the toes, surgical cutdown of the dorsum of the foot was performed to expose a lymphatic vessel, which was subsequently cannulated with a 30-gauge needle (*Figure 2*). An injection of approximately 5 cc/hour of ethiodized oil would then be initiated in each foot and serial spot radiographs were taken from the foot to the chest, following the progression of the contrast. However, pedal lymphangiography could take several hours to yield elegant images of lymphatic vessels and the retroperitoneal circulation. With the advent of new imaging technologies including ultrasound (US), computed

tomography (CT), and magnetic resonance imaging (MRI) diagnostic lymphangiography fell out of favor (19,20). By the 1990s, only a few medical centers performed lymphangiography as a diagnostic exam and technical proficiency of radiologists began to wane. Constantin Cope is largely credited with transitioning lymphangiography from a diagnostic test to a precursor for lymphatic interventions. Additionally, reports from other authors emerged on the therapeutic efficacy of lymphangiography in successfully treating approximately 50% of patients with various lymphatic leaks (21).

Although these initial lymphatic interventions reinvigorated interest in pedal lymphangiography, the technical difficulty, invasive nature, and time-consumption of the modality precluded wide adoption. Moreover, given the low demand for pedal lymphangiography over decades, infusion pumps necessary for the procedure became difficult to locate and service. Intranodal lymphangiography was initially described in children in 2011 and subsequently in adults in 2012, as an easier alternative with shorter procedure time (22,23). Under ultrasound guidance, a 25–27-gauge spinal needle is positioned into inguinal lymph nodes at the junction between the hilum and cortex. Subsequent slow injection (approximately 0.2–0.4 mL per minute) of ethiodized oil is then followed

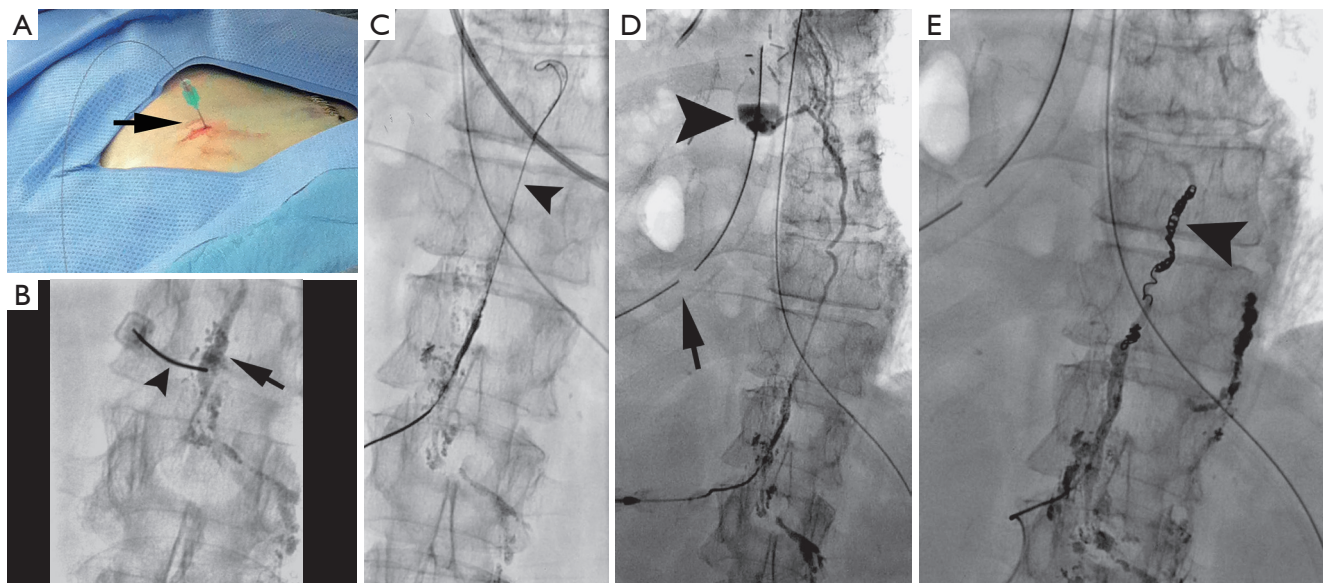


Figure 3 A 62-year-old patient with post-operative right chylothorax undergoing thoracic duct embolization. (A) Percutaneous trans-abdominal puncture is performed with a 21-gauge needle (arrow) and microwire; (B) spot radiograph of the 21-gauge needle (arrowhead) puncturing the cisterna chyli (arrow); (C) spot radiograph of a microwire (arrowhead) navigating into the thoracic duct; (D) after exchanging the needle for a microcatheter, central lymphangiography can be performed revealing extravasation into the right thoracic cavity (arrowhead). Note right chest tube in situ (arrow); (E) thoracic duct embolization was performed with coils (arrowhead) and glue, mechanically occluding the leak.

with fluoroscopy and spot radiographs from the inguinal lymph nodes through the pelvic lymphatic chain and into the retroperitoneal lymphatic vessels. Further, the application of intranodal lymphangiography technique with gadolinium-based contrasts have revolutionized the ability to dynamically visualize lymphatic anatomy under MRI and will allow for continued technical innovation and better understanding of lymphatic pathophysiology (24,25).

Chylothorax

Historically described by Bartholin in 1651, chylothorax occurs when chylous fluid leaks into the pleural space (26). Presently, the incidence of this disorder is estimated at 1:6,000 hospital admissions (27-29). While older reports list nontraumatic causes of chylothorax, such as lymphoma, lung cancer, or tuberculosis as the most common etiologies, more recent reports note the increase in post-surgical chylothorax. For instance, chylothorax complicates 0.42% of general thoracic surgeries and up to 3.9% of esophagectomies (1,2,27-29). Patients present with symptoms related to pleural effusions including dyspnea, chest pain, fever, and/or fatigue (29). Pleural fluid that

has a milky appearance with a triglyceride concentration greater than 110 mg/dL or the presence of chylomicrons on lipoprotein electrophoresis confirms the diagnosis of chylothorax (30). Traditional treatment consists of a non-fat diet or total parenteral nutrition, drainage, and supportive care often lasting for weeks or months. Leakage of chyle is associated with increased mortality due to significant loss of essential proteins, immunoglobulins, fat, vitamins, electrolytes, and water (31). For example, the mortality of chylothorax post-esophagectomy can reach 50% (32). These poor outcomes, particularly for patients with a chyle leak post-esophagectomy, served as an impetus for early and aggressive treatment to improve patient outcomes (33).

In 1998, Cope demonstrated the safety and feasibility of lymphangiography to facilitate percutaneous trans-abdominal puncture of retroperitoneal lymphatics (34). After passing a microwire into the lymphatic circulation, a microcatheter can be inserted to facilitate lymphatic imaging and subsequently perform thoracic duct embolization to mechanically occlude the site of injury and its inflow (*Figure 3*). These reports culminated in a 2002 retrospective study of 42 patients with chylothorax in which clinical success after thoracic duct embolization

was achieved in over 70% (35). Multiple authors from various institutions have since contributed large patient series since this initial manuscript, in both pediatric and adult populations (36-39). A recent meta-analysis of nine studies on lymphatic interventions for chylothorax from 2008–2017 included 407 patients and found that a pooled clinical success rate of thoracic duct embolization approached 80% with a pooled major complication rate of 2.4% (40). Based on these results, the American College of Radiology recommends lymphangiography and thoracic duct embolization in the treatment planning of chylothorax and as an effective, minimally invasive alternative to surgery (28). Different approaches to access the central lymphatics including direct trans-cervical and retrograde trans-venous approaches have now been described, further increasing the probability of technical success and extending the breadth of possible interventions to include balloon occlusion and stent placement within the thoracic duct (41-44). Given the widespread acceptance of thoracic duct embolization, increased clinical application and innovation is likely.

Chylous ascites

A report of tuberculous chylous ascites in a 2-year-old stands as the initial description of this uncommon condition (15). While chylous ascites was estimated to occur once in every 50,000–187,000 hospital admissions through the 1930–1950s, a single institution review estimated the incidence at nearly 1 per 11,589 in the 1970s (8,45). Patients present with symptoms of ascites including disproportionate weight gain, abdominal discomfort or fullness, dyspnea, or leakage of milky fluid from drains or incisions. Chylous ascites fluid analysis is similar to chylothorax. Underlying etiologies may be traumatic or non-traumatic, which along with daily output, guide therapy. In general, chylous ascites due to malignancy has a poor prognosis compared with non-malignant etiologies, which have a 40% 1-year mortality (8,45).

Since the initial work by Cope in 1998 to treat chylothorax and chylous ascites, hundreds of patients have been reported in the literature with successful lymphatic embolization for chylothorax (35-40). In contrast, the published experience for percutaneous image-guided interventional treatment of chylous ascites has been scarce and comprises fewer than 150 patients, many in case reports or small series. There has been an increased interest in image-guided therapies for post-operative chylous ascites,

with three recently published retrospective series each with greater than 20 patients (11,12,46). In total, 63 patients with iatrogenic chylous ascites were reported having undergone lymphangiography and a variety of lymphatic embolization techniques and approaches with a collective clinical success rate exceeding 80% with only one major complication, transient hypoglycemia, reported (46). A recent manuscript reviewed the collective literature for image-guided treatment of traumatic chylous ascites and found 18 other manuscripts in addition to their cohort detailing treatment of 96 patients (46). Procedure specific information was available on 82 of the patients, with a leak visualized in 60 of the procedures (73%). Lymphangiography without embolization was performed in 40 of 82 patients with cessation of leakage in 28 of 40 patients (70%). Embolotherapy with coils, glue, or sclerosants was performed in the 42 of 82 patients with clinical success in 37 of 42 patients (88%). Although reporting bias is present in technical notes and case reports, the potential for successful treatment, particularly in patients who underwent diagnostic lymphangiography without therapeutic intent cannot be discounted. Generally, pedal or intranodal lymphangiography is followed through the pelvis and retroperitoneum to evaluate for a lymphatic injury. Often, lymphangiography alone is diagnostic and therapeutic (*Figure 4*). Injuries below the lumbar spine may be difficult to access with a wire and microcatheter, but needle-based glue embolization may be performed from adjacent inflow lymph nodes if necessary (*Figure 5*). An advanced technique, balloon occluded retrograde abdominal lymphatic embolization, can be used in recalcitrant cases and involves retrograde lymphatic access from the left venous angle, balloon occlusion near the level of injury, and subsequent sclerotherapy (43). Generally, the experience with treatment of chylous ascites will continue to grow as caregivers realize the potential for image-guided minimally invasive treatment options in this difficult to treat patient population.

Lymphocele

In contrast to chylothorax and chylous ascites, which were both described in the 17th century, the first report of lymphocele dates to 1950 (47). Functionally, lymphoceles are a collection of lymphatic fluid encased within a fibrotic wall without a true epithelial lining, histologically differentiating them from a cyst. Lymphoceles are most commonly iatrogenic, occurring after pelvic or retroperitoneal

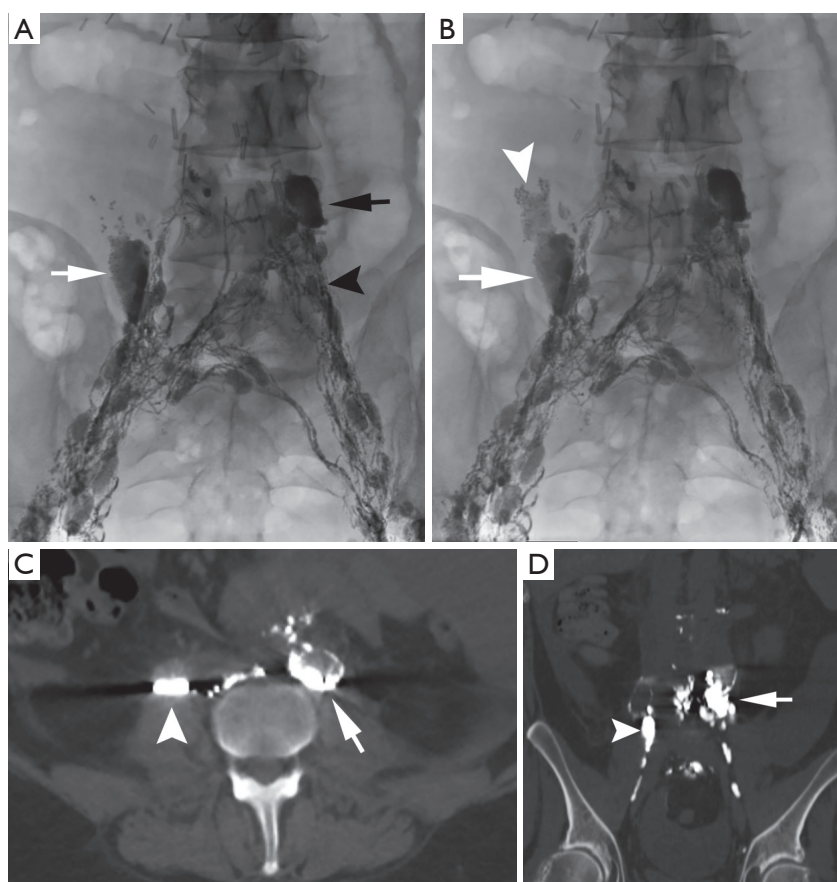


Figure 4 A 41-year-old male post retroperitoneal lymphadenectomy has recalcitrant chylous ascites undergoing lymphangiography. (A) Amorphous leakage of contrast material is seen bilaterally (white and black arrow), which is different in shape from lymph nodes (arrowhead). Multiple surgical clips are seen overlying the spinal column; (B) additional injection of contrast confirms the free extravasation (white arrow) and the beading of oily contrast (white arrowhead); intraprocedural axial (C) and coronal (D) computed tomography images further confirm the multiple leakage sites (white arrow and arrowhead) which are freely leaking into the peritoneal space.

lymphadenectomy during renal transplantation or urologic/gynecologic malignancy staging (48). Surgical exposure of the groin for vascular access, bypass grafting, and extracorporeal membrane oxygenation cannulation are all known causative procedures as well (49). The incidence and location of lymphocele formation varies widely based on the extent of lymphadenectomy, open versus laparoscopic approach, and surgical technique. To achieve diagnosis and differentiate a lymphocele from a seroma or hematoma, the anechoic fluid filled contents are aspirated, which normally yield clear or light, yellow fluid with a lymphocyte predominance on cell count (>70%) and low creatinine level (50). While most lymphoceles are asymptomatic, particularly if small, larger lymphoceles are more likely to have a wide range of symptoms related to structures they

compress including ureters, veins, rectosigmoid colon, nerves, or the bladder.

Historically, treatment of lymphoceles was achieved surgically through open and subsequently laparoscopic internal marsupialization or external drainage (48). Since the 1990s, percutaneous aspiration and drainage has been performed and later combined with transcatheter sclerotherapy with success rates equivalent to or higher than surgery without anesthesia allowing treatment on an outpatient basis with faster recovery (49). Using CT or US guidance, a needle is directed into the lymphocele and after confirming location, a wire is placed over which the needle is exchanged for a drain (*Figure 6*). The fluid is aspirated to collapse the cavity and a variety of sclerosants may be instilled ranging from ethanol and povidone-

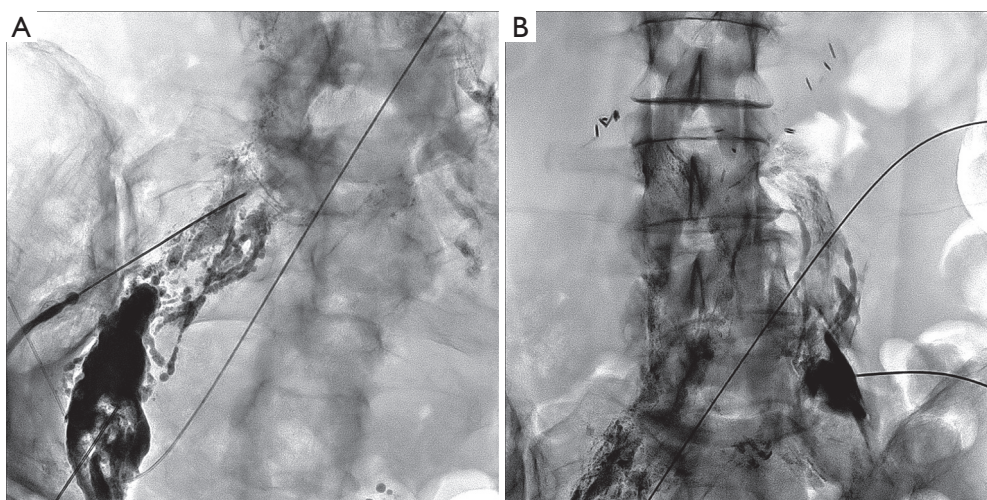


Figure 5 A 37-year-old male post retroperitoneal lymphadenectomy had recalcitrant chylous ascites despite prior lymphangiography. A 21-gauge needle was positioned in common iliac chain lymph nodes on the right (A) and left (B) and glue embolization was performed successfully treating the leak.

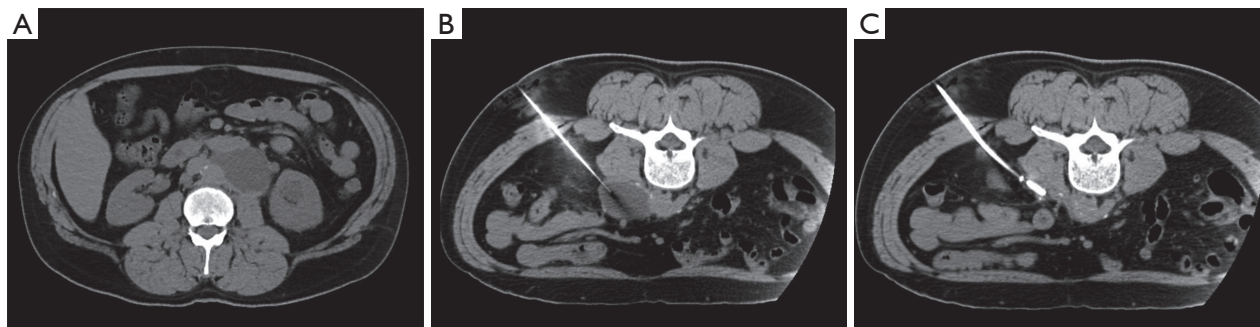


Figure 6 A 47-year-old male status post retroperitoneal lymphadenectomy for testicular cancer had persistent left flank pain. (A) Computed tomography image detects a fluid attenuation collection in the retroperitoneum overlying the left psoas and between the aorta and left kidney; (B) the patient was positioned prone, and a needle was placed from a posterior approach for fluid sampling and drain placement; (C) a drain was placed, collapsing the lymphocele and allowing for subsequent ethanol sclerotherapy.

iodine (the two most common) to bleomycin, doxycycline or many others depending on operator preference. Success rates for ethanol range from 88–97% and for povidone-iodine from 62–89%. Repeat treatment increases overall success rates above 90% and can be performed on an outpatient basis as well (49). Uncommonly, a recalcitrant lymphocele may recur despite drainage and sclerotherapy. Recent reports describing lymphangiography and lymphatic vessel embolization are documenting success (51). In this approach, lymphangiography is performed to reveal an area of leak into the lymphocele and glue embolization is either performed through the inflow lymph node or lymphatic

vessel. Several case series have been published revealing success rates in excess of 80% for recalcitrant lymphoceles with few major complications documented (51,52). Treatment algorithms for post-operative lymphatic leaks are shown in *Figure 7*.

Conclusions

Iatrogenic lymphatic leaks may result in chylothorax, chylous ascites, or lymphoceles and are a consequence of oncologic surgeries. The evolution of lymphangiography and lymphatic interventions allows for successful diagnosis

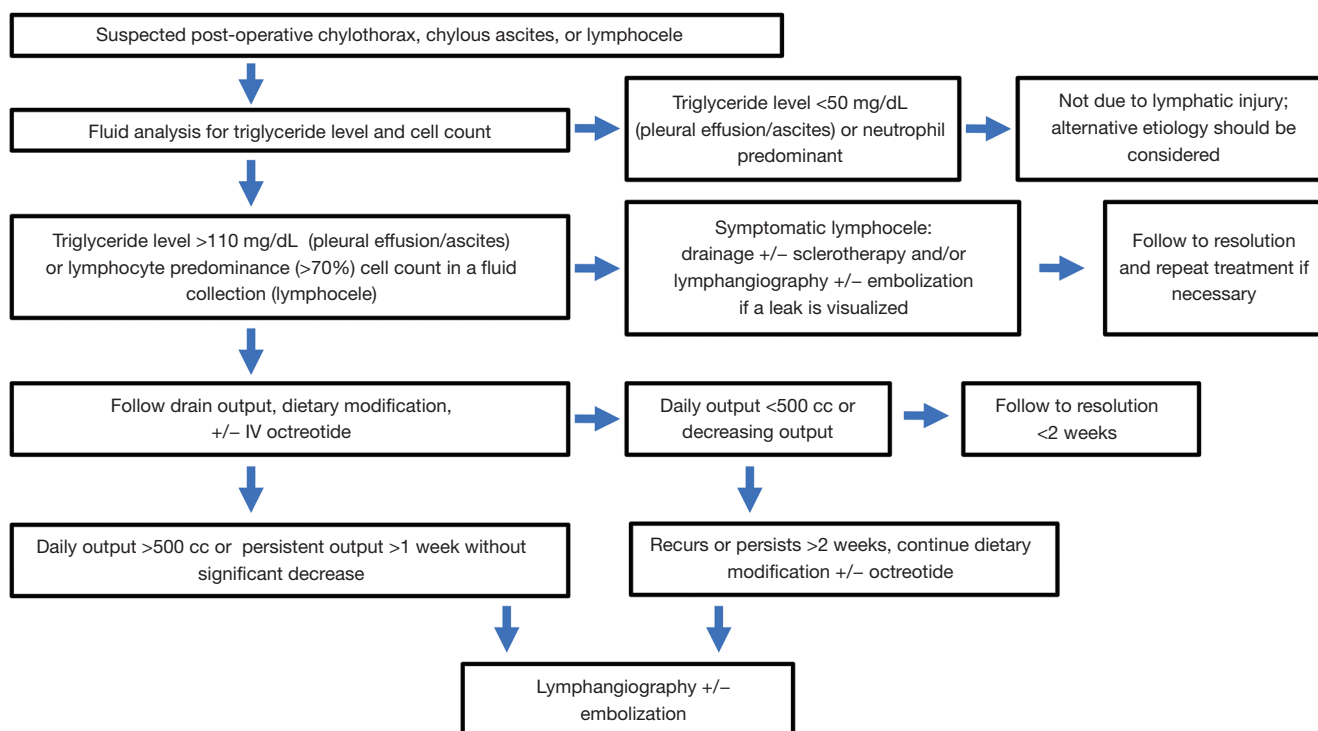


Figure 7 Treatment algorithm for post-operative lymphatic leaks.

and treatment in the large majority of post-surgical leaks with minimal risk to patients. Consideration should be given to the early interventional treatment to hasten patient recovery and potentially improve outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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