Lymphatic Embolization versus Sclerotherapy for Symptomatic Post-operative Pelvic Lymphocele (LESPOL): A Randomized Pilot Study

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Abstract

This study was performed to compare clinical outcomes of lymphatic n-butyl cyanoacrylate (NBCA) embolization and ethanol sclerotherapy in patients with symptomatic postoperative pelvic lymphoceles.

This prospective, open-label, randomized, and controlled trial took place at two medical centers in Korea. Patients ≥18 years old with symptomatic postoperative pelvic lymphoceles were randomly assigned (1:1) to one of two study arms: lymphatic embolization or sclerotherapy. A target of 44 patients was set for each group to assess clinical outcomes.

The trial began in August 2018 but ended as a pilot study in February 2020. Problematic patient enrollment precluded full population recruitment, only 11 patients (lymphatic embolization, 5; sclerotherapy, 6) eventually participating. Clinical success and drainage tube removal rates were 100% in both arms. To achieve clinical success, significantly more procedures were needed in the sclerotherapy group than in the lymphatic embolization group (4.5±1.23 vs 2.0±1.00; $p<0.001$). The time to achieve daily drainage reduction thresholds (<20 mL or <20% of initial daily drainage) was also less in the sclerotherapy (vs embolization) group but fell short of statistical significance (4.8±2.63 days vs 7.0±3.67 days; $p=0.267$). No significant adverse events or recurring symptomatic lymphoceles were evident at 3-month follow-up visits.

Both lymphatic NBCA embolization and ethanol sclerotherapy might be safe and effective in treating symptomatic postoperative pelvic lymphoceles, showing no significant difference in clinical outcomes. In a future randomized prospective study, it is essential to establish better inclusion criteria to selectively include intractable lymphoceles to find out the difference in the outcome between the two treatments.

Introduction

Postoperative pelvic lymphoceles occur as complications of nodal dissections performed during various pelvic surgeries [1, 2]. Although a majority are asymptomatic, symptomatic lymphoceles may prolong hospitalization, increase medical costs, and delay postoperative adjuvant treatment (chemotherapy or irradiation) [3, 4].

Percutaneous catheter drainage (PCD) is the principal treatment for pelvic lymphoceles [5]. It relieves symptoms and induces mural adhesions through decompression. However, protracted catheter placement is often required, and some lymphoceles are refractory to simple PCD. Consequently, there is a clinical need for more active treatment. Interventional remedies, such as sclerotherapy and lymphatic embolization, are safe, effective, and less invasive compared with surgical treatment. Various sclerosing agents are known to enhance the therapeutic effects of PCD, ostensibly by irritating lymphocele walls, inciting local inflammation and fibrosis of lymphatic channels [6, 7].

The recent introduction of intranodal lymphangiography, which is a much faster and easier approach than conventional bipedal lymphangiography [8, 9], has enabled a lymphatic embolization as an alternative treatment, using n-butyl cyanoacrylate (NBCA) [10–12]. However, only one observational study comparing clinical outcomes of these two methods has been reported to date. [13].

This randomized controlled trial was intended to compare clinical outcomes of ethanol sclerotherapy and lymphatic NBCA embolization in patients with symptomatic postoperative pelvic lymphoceles.

Methods

Study design and randomization

This study was a prospective, open-label, randomized, and controlled trial conducted at two medical centers in Korea (registered as KCT0003078 at the Clinical Research Information Service [http://cris.nih.go.kr]). The protocol conformed to ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (No. 1802-100-924) and the National Cancer Center (No. NCC2018-0144). All patients granted written informed consent.

Qualifying patients were ≥18 years old and had developed symptomatic, sterile postoperative pelvic lymphoceles. Infected, chylous, or low-output (<100 mL/day) lymphoceles; urinomas; and ruptured lymphoceles presenting as ascites were grounds for exclusion. Patients were screened in the course of active PCD tube management, checking for these conditions and testing tubal drainage fluids (Fig. 1).

A total of 88 patients was projected to achieve a power of 0.80 and a significance level of 0.05 in assessing clinical successes of both treatment methods. This was based on success rates of 80% for lymphatic embolization and 50% for sclerotherapy, as indicated by a prior retrospective observational study [13]. The dropout rate was estimated at 10%. Eligible patients were expected to randomly undergo either ethanol sclerotherapy or lymphatic embolization in a 1:1 ratio, using dedicated web-based software of the Medical Research Collaborating Center at Seoul National University Hospital for assignment purposes. We adopted a crossover design for this trial (Fig. 1).

Interventional procedures

In all patients with symptomatic lymphoceles, PCD was implemented using 10.2-Fr catheters. Lymphocele contents were completely evacuated (to collapse the sacs) and measured, recording amounts as initial volumes. Following placement, PCD tubes were actively managed as needed through periodic checks, repositioning, changes, and irrigation.

Lymphatic embolization or sclerotherapy was performed on a randomized basis by two specialists (SH and IJL), each with >8 years of experience in interventional radiology, adhering to a strict predefined study protocol. Assigned interventions were conducted for a maximum 10 days (Fig. 1). Serial procedures were freely allowed during the 10-day treatment period at operator discretion, and the total number of sessions was recorded. PCD tubes were clamped at Day-10 if daily drainage was <20 mL or <20% of the initial daily drainage.

In the lymphatic embolization arm, intranodal lymphangiography was performed using iodinated contrast (Lipiodol Ultra Fluid; Laboratoire Guerbet, Aulnay-sous-Bois, France) to trace regional lymphatics and identify sites of leakage (Fig. 2). Once leakage was demonstrated, the closest upstream lymph node (among those supplying afferent flow to leakage sites) was embolized, delivering a variable mix of NBCA and contrast (1:3 to 1:6 ratios) to the punctured node and/or lymphatic vessels as in previous investigations [10, 13].

In the sclerotherapy arm, a baseline cavitogram was obtained at the onset of every treatment session (Fig. 3). Intracavitary absolute ethanol was then instilled into fully aspirated lymphoceles, emptied of their contents to achieve maximum concentration of sclerosant [7, 13]. The volume of absolute ethanol used was half the amount of fluid aspirated but no more than 100 mL. Patients were repositioned every 5 min for a 20-min duration as follows: supine, left lateral decubitus, right lateral decubitus, and supine again. All instilled ethanol was completely aspirated thereafter.

Assessment of clinical outcomes

Therapeutic outcomes were assessed 2 weeks after initial interventions. If successful, PCD tubes were removed. In clinical failures, other treatment options were available (Fig. 1), so a maximum treatment period of 4 weeks was feasible. Patients were scheduled for office visits 3 months after removal of PCD tubes. The status of treated lymphoceles was assessed by computed tomography, magnetic resonance imaging, or ultrasonography.

Clinical success was defined as resolution of lymphocele-related symptoms while achieving predetermined daily drainage reduction thresholds (<20 mL/day or <20% of initial daily drainage) within 10 days from first interventions and by catheter removal at 2 weeks without recurrence of symptoms. Fluid reduction ratios were calculated based on drainage volumes measured immediately prior to first sessions of assigned interventions. In patients treated successfully by either method, times to achieve daily drainage reduction thresholds were calculated.

Adverse events were recorded for every patient from the point at which signed informed consent was obtained until the end of study. The list of potential complications included cellulitis/lymphadenitis, skin necrosis, aggravation of lymphedema, venous thrombosis, pulmonary embolism, cardiopulmonary symptoms, inadvertent distal arterial embolization of NBCA, and anaphylaxis to any agents used in treatment.

Statistical analysis

Categorical variables were expressed numerically and in percentages. Continuous variables were reported as means and standard deviations. Mann-Whitney U test was applied for group-wise comparison of times to achieve clinical success, driven by commercially available software (MedCalc v19.8; MedCalc Software Ltd, Ostend, Belgium). A two-tailed *p*-value <0.05 was deemed statistically significant.

Results

Between August 1, 2018 and November 31, 2019, 50 patients underwent PCD for symptomatic postoperative pelvic lymphoceles (Fig. 4). After excluding patients with infected, chylous, or low-output lymphoceles, only15 potential study candidates remained. Three patients then declined participation, and one sclerotherapy assignee withdrew consent, leaving a study population of 11 patients. Five and six patients underwent lymphatic embolization and sclerotherapy, respectively. Owing to problems with patient enrollment, the trial ended prematurely in February 2020 but continued as a pilot study.

Patient characteristics and treatment outcomes are summarized in Table 1. The two groups did not differ significantly in mean drainage volumes before interventions began (lymphatic embolization, 302.0±77.91 mL; sclerotherapy, 323.3±128.63 mL; p=0.854). All procedures (100%) were technically successful. Clinical success and PCD tube removal rates were 100% in both groups. There were no recurring lymphoceles at 3-month follow-up in either group.

Table 1
Patient characteristics and treatment outcomes (lymphatic NBCA embolization vs ethanol sclerotherapy)

Group	Sex/ Age	Surgery	Time from PCD to 1st treatment session (days)	Daily drainage volume before treatment (mL)	Number of sessions	Time to clinical success (days)	Time to PCD tube removal (days)
Embolization	F/65	Ultralow anterior resection	2	250	1	10	14
	F/66	TAH+BSO+PLND+PaLND	7	410	1	1	12
	M/80	Radical cystectomy	9	360	2	10	16
	M/75	Excision of retroperitoneal tumor	7	240	3	7	19
	F/43	TAH+BSO+PLND+PaLND, low anterior resection, metastasectomy of multiple peritoneal seeding	37	250	3	7	13
Sclerotherapy	M/75	Radical prostatectomy	2	330	4	4	14
	F/58	TAH+BSO+PLND+PaLND	4	200	4	4	14
	F/70	TAH+BSO+PLND	4	550	4	7	14
	M/72	Radical cystectomy	3	200	4	3	13
	M/76	Radical cystectomy	6	310	4	2	14
	M/65	Radical cystectomy	22	350	7	9	16
Note: no patients experienced adverse events							
NBCA, n-butyl cyanoacrylate; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; PLND, pelvic lymph node dissection; PaLND, paraaortic lymph node dissection							

Time to achieve daily drainage reduction thresholds (<20 mL or <20% of initial daily drainage) was less for sclerotherapy than for lymphatic embolization, although the difference was not statistically significant (4.8±2.63 days vs 7.0±3.67 days; p=0.267). However, the number of sessions required for clinical success was significantly greater in the sclerotherapy (vs lymphatic embolization) group (4.5±1.23 vs 2.0±1.00; p<0.001).

Two patients in the lymphatic embolization group and three patients in the sclerotherapy group had existing lower-extremity edema at study enrollment. No worsening or new edema of the lower extremities developed in either group after receiving interventional treatments. Otherwise, no significant adverse events emerged by end of study, whether during periods of treatment or follow-up.

Discussion

In the present study, both lymphatic embolization and sclerotherapy showed excellent safety and efficacy in the treatment of symptomatic postoperative pelvic lymphocele, showing no statistical difference in clinical outcomes.

However, significantly more sessions were needed for sclerotherapy than for lymphatic embolization.

Unfortunately, this trial ended prematurely due to patient enrollment difficulties, continuing as a mere pilot study. The incidence of symptomatic pelvic lymphocele seems to have declined in our medical centers for various reasons. Extensive pelvic nodal dissections are often rife with complications, particularly lower limb edema. Mapping of sentinel pelvic lymph nodes is now common practice in pelvic surgery, and the survival benefit of extensive (vs standard) pelvic lymph node dissection is subject to debate, especially in early stage cancers [14, 15]. Consequently, extensive dissections of this sort have dwindled in number.

PCD itself may well help resolve lymphatic leakages and thus offset any differing results of sclerotherapy and lymphatic embolization. There are many reports that drainage or even simple aspiration alone is effective in managing pelvic lymphoceles [5]. For optimal analysis of these two interventions, only lymphoceles refractory to PCD (ascertained by prolonged monitoring of drainage after PCD) were targeted in the original study design. It was impossible to foresee the impact of such a rationale when the study was launched. This stipulation was abandoned as enrollment faltered, but early termination was not prevented.

The findings herein conflict with those of a previous retrospective study in which lymphatic embolization clinically outperformed ethanol sclerotherapy [13]. The therapeutic efficacy of sclerotherapy was actually greater in the present study than in this earlier report. One explanation for the disparity is that our procedures and evaluations were performed by two experts adhering to a strict predefined protocol, whereas the prior retrospective analysis involved a nonstandard approach. Our total enrollment (N=11) was also quite low and no doubt insufficient to demonstrate any minor differences that might exist. Finally (and as already mentioned), the inclusion of less intractable lymphoceles amenable to simple PCD may have skewed patient outcomes.

Regardless of the pitfalls implicit in an underpowered study, both sclerotherapy and lymphatic embolization seemed safe and effective for treating the majority of patients with symptomatic pelvic lymphoceles. Either treatment may then be initiated in accord with clinical dictates and treatment availability. Sclerotherapy was easier to perform than lymphatic embolization and addressed multiple leakage points at once although significantly more treatment sessions were needed. It would also have good therapeutic effectiveness as far as the appropriate protocol is followed. Therefore, active PCD tube management and sclerotherapy can be worth trying initially. However, there are, for sure, lymphoceles, which are intractable or unsuitable for sclerotherapy; those with high flow (>1.5 L/day), ruptured lymphocele communicating with peritoneal space, and direct intraperitoneal lymphorrhea manifesting as lymphatic ascites [13]. Lymphatic embolization can be the last resort for these cases except for surgery. However, lack of a uniform intervention strategy, the technical difficulty entailed, and inordinate dependency on operator skills are hurdles of lymphatic embolization that must be overcome in the future.

The major limitation of this study was its premature termination before an adequate population was reached. Intractable lymphoceles, unresponsive to either treatment method, and patients with complications might not be thereby included. Therapeutic efficacy was 100%, with 0% complications, in both study arms. A definitive randomized, prospective study is warranted to rectify these shortcomings.

Conclusion

Both lymphatic NBCA embolization and ethanol sclerotherapy might be safe and effective for treating symptomatic postoperative pelvic lymphoceles and each method might yield similar clinical outcomes. In a future randomized

prospective study, it is essential to establish better inclusion criteria to selectively include intractable lymphoceles to find out the difference in the clinical outcome between the two treatments.

Abbreviations

PCD = percutaneous catheter drainage, NBCA = N-Butyl Cyanoacrylate

Declarations

Funding

This study was funded by a grant from the Guerbet Korea Research Fund.

Competing interests

None of the authors has any conflicts to disclose.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. 1802-100-924) and the National Cancer Center (No. NCC2018-0144). All patients granted written informed consent and all data were de-identified after collection.

Trial registration: The study is registered as KCT0003078 at the Clinical Research Information Service (http://cris.nih.go.kr). Registered April 2, 2018.

Consent for participate

Informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors contributions

In Joon Lee: Project management, data collection and analysis, manuscript writing and editing

Jinoo Kim: Project development and management, data analysis, manuscript editing

Gyoung Min Kim: Project management, manuscript editing

Ji Hoon Shin: Project management, manuscript editing

Hee Seung Kim: Data collection, manuscript editing

Cheol Kwak: Data collection, manuscript editing

Ho Kyung Seo: Data collection, manuscript editing

Myong Cheol Lim: Data collection, manuscript editing

Saebeom Hur: Project development and management, data collection and analysis, manuscript writing and editing

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Figures

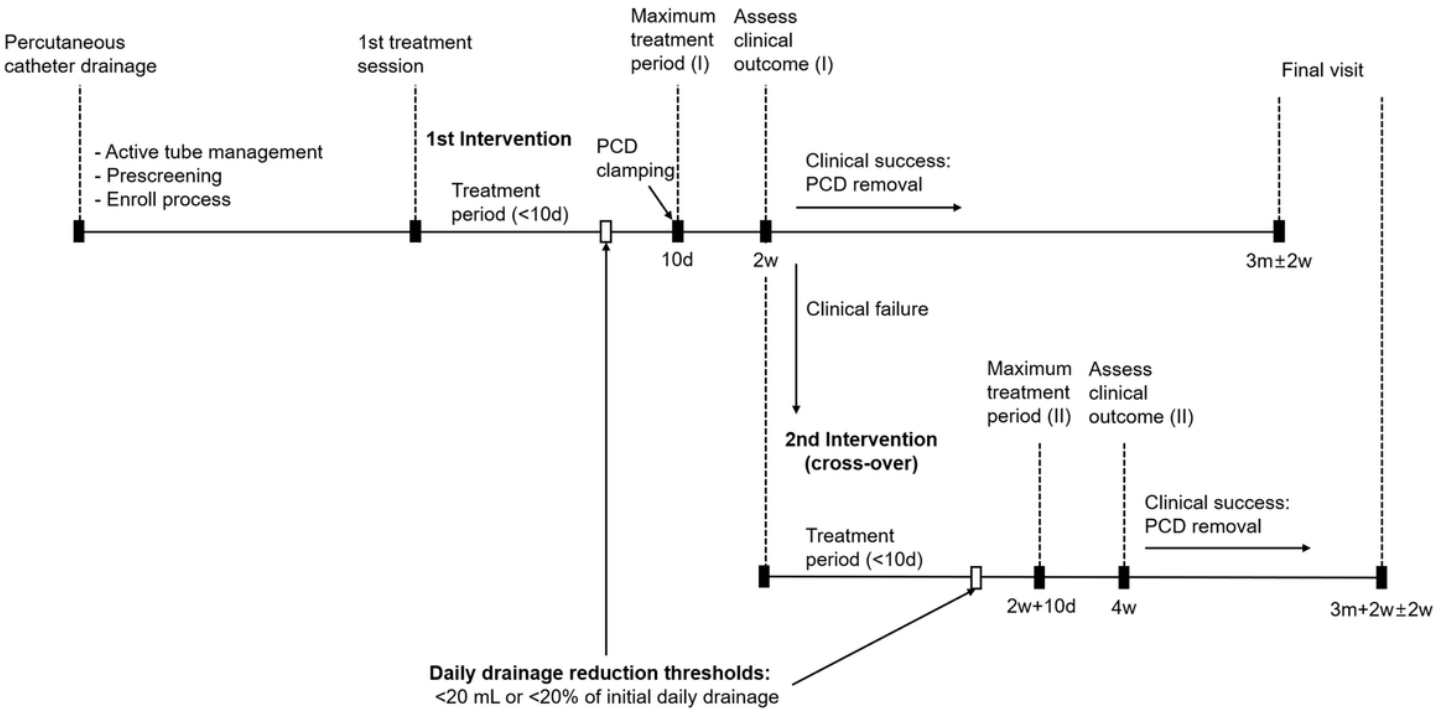

Figure 1

Schematic of study protocol

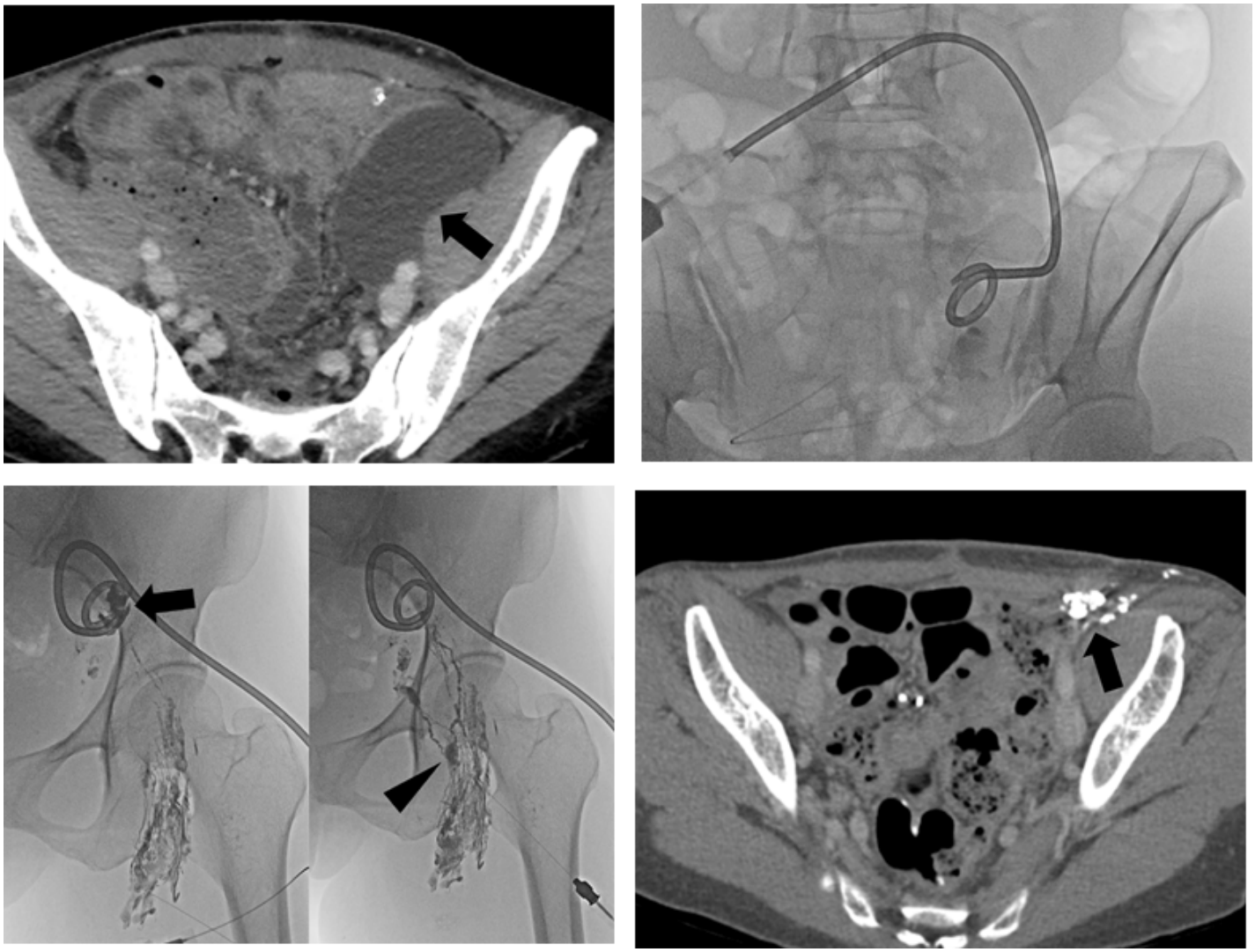

Figure 2

Lymphatic embolization in a 43-year-old woman

(A) Pelvic CT image shows left side pelvic lymphoceles (arrow).

(B) Percutaneous catheter drainage (PCD) was done for the pelvic lymphocele.

(C) In spite of PCD for 37 days, the daily amount was more than 250 mL. The lymphangiography which is taken through left inguinal lymph nodes shows leakage around the tip of PCD tube (arrow on left side image). Lymphatic embolization was performed through a closest lymph node (arrowhead) with glue/Lipiodol mixture.

(D) 3-month follow-up CT image just shows Lipiodol deposition (arrow) around left iliac vessels without recurrence of the pelvic lymphocele.

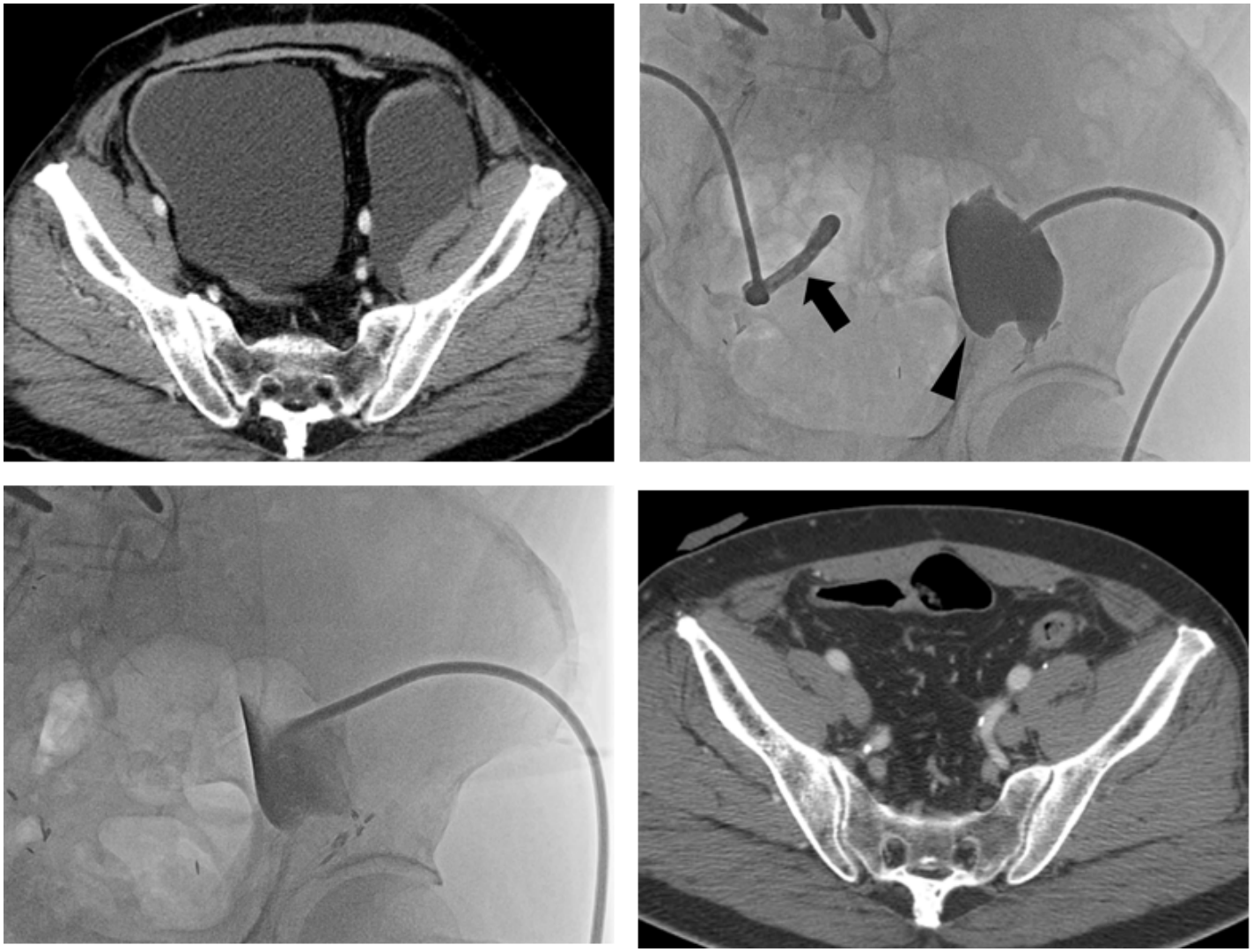

Figure 3

Ethanol sclerotherapy in a 64-year-old man

(A) Pelvic CT shows bilateral pelvic lymphoceles.

(B) 22 days after percutaneous catheter drainage, right side pelvic lymphocele is completely collapsed (arrow) but left side cavity (arrowhead) is still demonstrated around the tube placement with more than 300 mL of the daily drainage.

(C) After seven session of ethanol sclerotherapy, the lymphocele cavity is decreased and the daily drainage amount was less than 10 mL. Therefore, the tube was able to be removed.

(D) 3-month follow-up CT image just shows complete disappearance of bilateral pelvic lymphoceles.

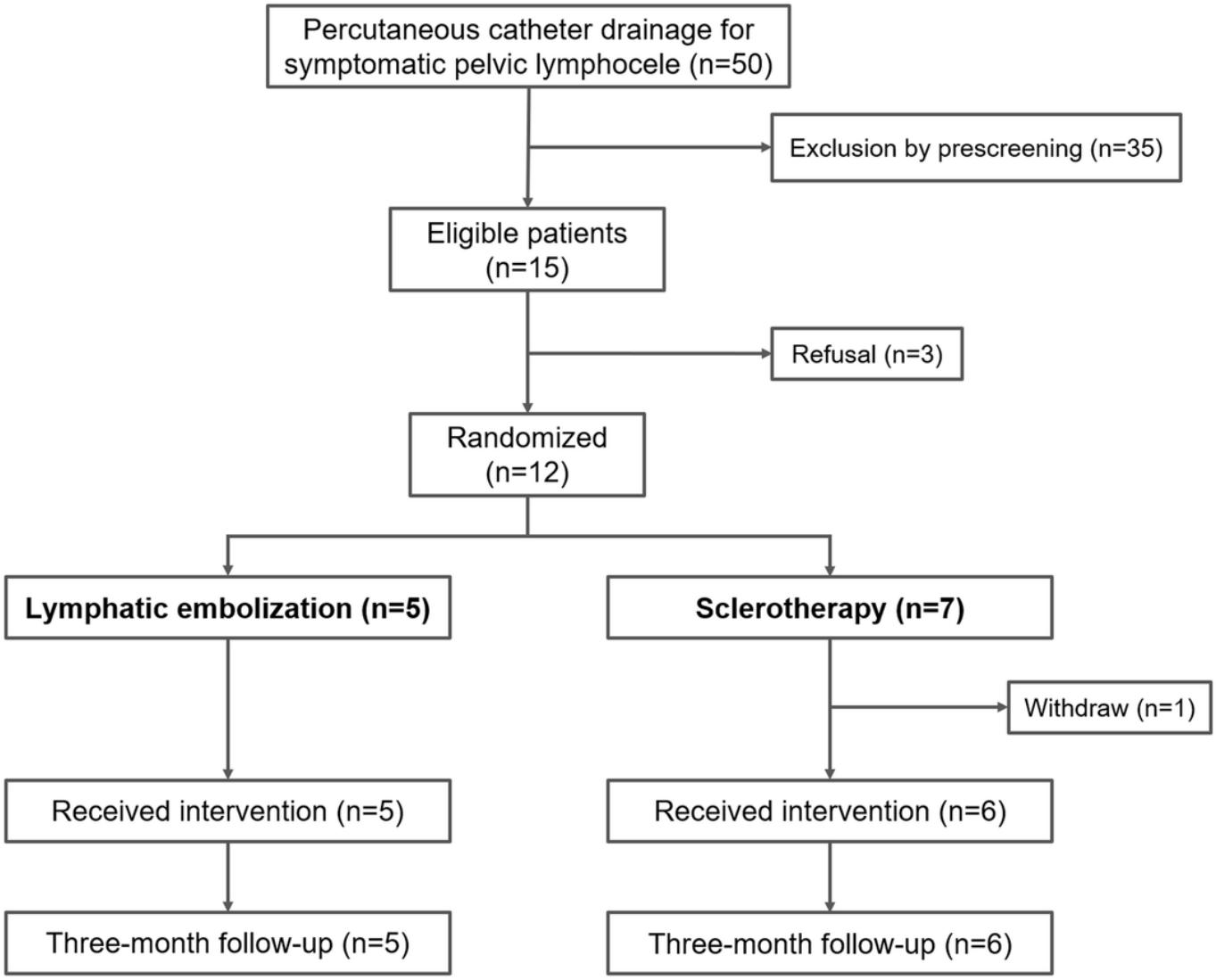

Figure 4

Patient enrollment and randomization algorithm