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Low-dose radiotherapy for benign conditions: management of persistent inguinal lymphorrhea

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Abstract

Background Lymphorrhea is a complication that can arise after vascular, abdominal or pelvic interventions and is associated with significant morbidity. While conservative management is typically effective, some cases remain refractory.

Methods This retrospective cross-sectional study analyzed 43 patients with persistent inguinal lymphorrhea treated at a tertiary hospital between 2008 and 2018. All patients received external beam radiotherapy (EBRT) using 3D conformal techniques with photons (6–18 MV). The delivered dose was 7.5 Gy in five 1.5 Gy/fractions.

Results Complete closure of the lymphatic fistula was achieved in all patients. Three required reirradiation with the same schedule to reach complete resolution. No acute or late toxicity was observed in any case.

Conclusions Low-dose EBRT is a safe and effective treatment option for persistent lymphorrhea refractory to conservative measures. Its anti-inflammatory and fibrosing effects support its therapeutic use in benign lymphatic complications.

Trial registration Not applicable.

Keywords Lymphorrhea, Lymphatic fistula, Low-dose radiotherapy, Benign pathology, External beam radiation therapy

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Background

Lymphoceles are fluid-filled cavities that arise following surgical procedures, particularly those involving lymphatic disruption [1]. Lymphorrhea refers to the external leakage of lymphatic fluid through persistent lymphocutaneous fistulas (LCFs). However, the definition of LCF is inconsistently described in the literature. Giovannacci et al. [2] defined an LCF as persistent lymphatic drainage of ≥ 30 mL/day for more than three days postoperatively, or any continuous drainage beyond postoperative day five. In some cases, LCFs have been reported as late as four years after surgery, with drainage volumes up to 50 mL/day [3].

Primary congenital lymphatic fistulas are rare. Most LCFs are secondary and result from invasive procedures, particularly vascular, abdominal, pelvic, or cardiac surgeries. Persistent LCFs are associated with a high risk of wound complications, including infection, delayed healing, prolonged hospitalization, delayed rehabilitation, and increased healthcare costs.

The incidence of lymphoceles and LCFs (Fig. 1) varies across published series, but is generally estimated to occur in 2–8% of all vascular, abdominal, or pelvic interventions [4, 5]. The risk appears to be higher in patients with pre-existing comorbidities [6].

Management of LCFs should be individualized. First-line conservative treatment includes limb immobilization, elevation, and compression, where applicable [7]. If these measures fail, percutaneous instillation of sclerosing agents such as ethanol, tetracycline, iodine solution, or bleomycin may be considered, as well as radiopharmaceuticals like yttrium-90 or rhenium-186 [8–10]. Reported success rates for conservative management vary. Twine et al. [11] reported control rates between 80 and 100%, while others describe an 82% resolution rate after three weeks of conservative therapy [12]. Nonetheless, some authors advocate for early surgical

reintervention, particularly in cases with high output drainage, wound infection, or the presence of foreign material. However, surgical reintervention is not without risks.

Radiotherapy (RT) for benign conditions is typically administered at significantly lower doses than those used for malignant disease [13]. RT has been employed in a variety of benign indications, including chronic degenerative joint disease [14], soft tissue disorders such as Dupuytren's and Peyronie's disease [15], keloid scars, Graves' orbitopathy [16], and persistent lymphoceles or LCFs [17]. In complex or refractory LCFs, RT may be considered as a therapeutic option [18].

RT is thought to exert anti-inflammatory effects at low doses. These include reduced secretion of pro-inflammatory cytokines by immune cells, alterations in endothelial permeability, and increased lymphatic reabsorption. Moreover, radiation induces fibroblast differentiation into fibrocytes, promoting localized fibrosis, increasing nitric oxide production, and reducing lymphatic flow in the irradiated area [19].

Doses of 1–2 Gy per fraction are known to induce aseptic endophthalmitis and obliteration of lymphatic vessels. Emerging evidence suggests that even lower doses (0.3–0.5 Gy per fraction) may be sufficient for therapeutic effect in the context of LCFs [18–20].

The aim of this study is to evaluate the efficacy and safety of low-dose radiotherapy in the treatment of persistent lymphocutaneous fistulas, and to report the rate of secondary complications.

Methods

Study design and setting

This was a retrospective, single-center, observational study conducted at a tertiary hospital in northern Spain. The study included patients with persistent inguinal lymphocutaneous fistulas (LCFs) who were treated with external beam radiotherapy (EBRT) between January 2008 and December 2018.

Eligibility criteria

Patients were eligible if they met all of the following criteria:

- Presence of a persistent lymphocutaneous fistula unresponsive to conservative management.
- Absence of active malignancy in the irradiated region.
- Adequate general condition to undergo outpatient radiotherapy.
- Capacity to remain immobilized during simulation and treatment.



Fig. 1 Persistent lymphocutaneous fistula and persistent lymphorrhea

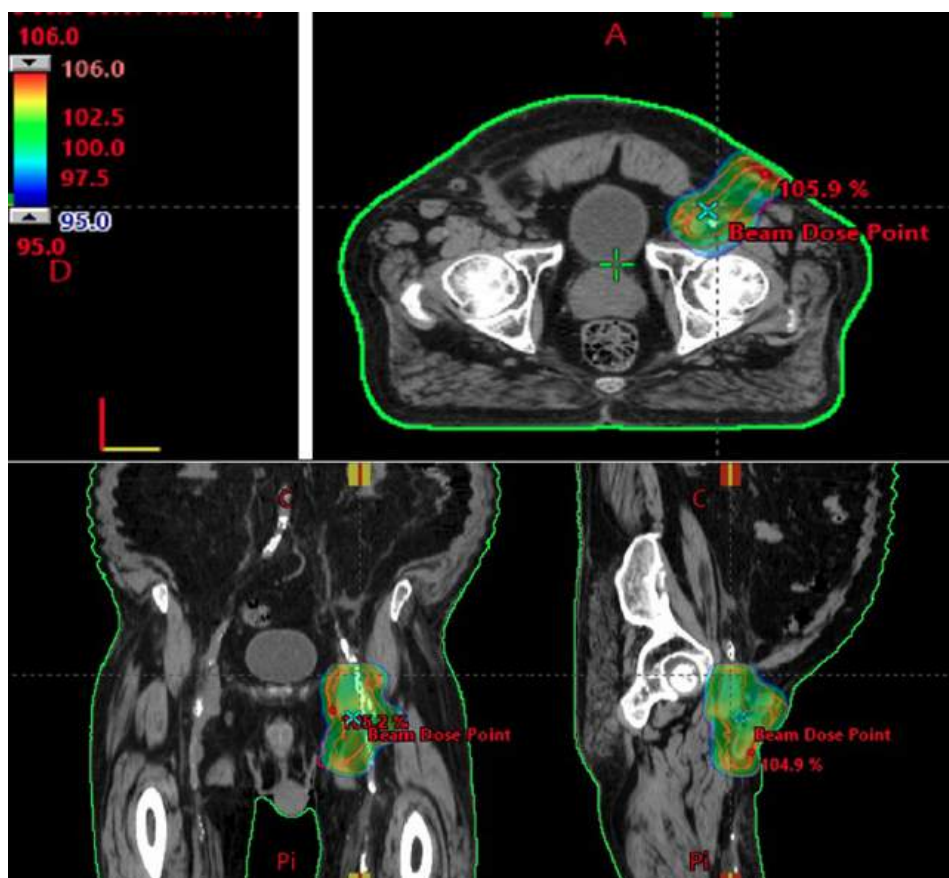


Fig. 2 External beam radiotherapy. Dosimetry

Patients were excluded if they had received prior radiotherapy to the same anatomical region, had a poor performance status preventing EBRT, or presented with non-inguinallymphorrhea.

Radiotherapy planning and delivery

All patients underwent CT-based simulation for treatment planning. The clinical target volume (CTV) included the lymphatic vessels, the fistulous tract, and the associated seroma or lymphocele when present, as well as the overlying skin scar. A margin of 3–5 mm was applied around these structures to ensure adequate coverage. A planning target volume (PTV) was generated by applying a 0.5–1.0 cm isotropic margin to the CTV to account for setup uncertainties. In all cases, the surgical scar at the skin level had to be properly included in the treatment volume. The use of a bolus was applied whenever necessary to optimize skin dose coverage.

Three-dimensional conformal radiotherapy (3D-CRT) was used in all cases, with photon beams of 6 or 18 MV (Fig. 2). The most frequently used dose schedule was 7.5 Gy in 5 daily fractions ($n=39$). Alternative regimens included 5.5 Gy in 3 fractions ($n=1$), 8 Gy in 2 fractions ($n=2$), and 15 Gy in 5 fractions ($n=1$). Image guidance

was performed using electronic portal imaging (EPID) or cone-beam CT, according to local protocols.

Outcome measures

The primary endpoint was clinical resolution of the lymphorrhea, defined as complete cessation of lymphatic discharge at the treated site. Secondary outcomes included the need for reirradiation and the incidence of acute or late treatment-related toxicities.

Toxicity assessment

Toxicities were prospectively assessed during treatment and follow-up visits using the Radiation Therapy Oncology Group (RTOG) grading system. Both acute (within 90 days post-treatment) and late (after 90 days) effects were recorded.

Statistical analysis

Descriptive statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were summarized using median and interquartile ranges (IQR), while categorical variables were presented as frequencies and percentages. Due to the descriptive nature

of the study and the lack of a comparison group, no inferential statistical tests were conducted.

Results

A total of 43 patients with persistent inguinal lymphocutaneous fistulas were treated with external beam radiotherapy (EBRT) during the study period. The median age was 69 years (range: 48–84), and the majority were male ($n = 38$; 88.4%).

The most commonly prescribed radiotherapy schedule was 7.5 Gy delivered in 5 daily fractions, which was used in 39 patients (90.7%). Alternative dose-fractionation regimens included 5.5 Gy in 3 fractions ($n = 1$), 8 Gy in 2 fractions ($n = 2$), and 15 Gy in 5 fractions ($n = 1$).

The mean time between surgery and initiation of radiotherapy was 30 days (range: 25 to 70 days). Treatment efficacy was evaluated between the third and fourth week after completion of radiotherapy.

All patients achieved complete clinical resolution of the lymphatic fistula. In three cases (7.0%), reirradiation using the same schedule (7.5 Gy in 5 fractions) was required due to initial incomplete response. Following reirradiation, complete closure of the fistula was successfully achieved in all three patients. Reirradiation was considered only in cases of persistent fistulous drainage after an initial course of EBRT. In all three cases requiring reirradiation, a minimum interval of three weeks had elapsed since the first treatment. Additionally, reirradiation was only performed when the volume of lymphatic output remained equal to or greater than prior to the initial radiotherapy course.

No acute or late toxicities related to radiotherapy were observed. Specifically, no patients experienced radiation-associated skin reactions, infections, or delays in wound healing. All treatments were well tolerated, and all scheduled radiotherapy sessions were completed without interruption.

Discussion

This retrospective series demonstrates that low-dose external beam radiotherapy (EBRT) is an effective and well-tolerated treatment for persistent lymphocutaneous fistulas (LCFs) unresponsive to conservative measures. All 43 patients included in this study achieved complete closure of the fistula, and no radiation-related toxicities were observed. These findings support the integration of radiotherapy into the therapeutic algorithm for benign lymphatic complications in selected patients.

Our results are consistent with previous reports suggesting that low-dose radiotherapy promotes lymphatic closure through multiple mechanisms, including endothelial apoptosis, reduced inflammatory cytokine production, enhanced lymphatic reabsorption, and stimulation of fibroblast differentiation [13]. Mayer et al. was among

the first to report successful outcomes with radiotherapy in the management of lymphatic fistulas, although the evidence remains scarce and limited to small series or case reports [18].

Several recent publications have provided more robust data supporting the use of radiotherapy for LCFs. Habermehl et al. described the effectiveness of radiotherapy as a non-invasive yet underutilized option for managing lymphatic fistulas, advocating its broader adoption. They support the efficacy of very low-dose RT (0.3–0.5 Gy per fraction) in controlling lymphatic leakage with no reported acute toxicity and a negligible risk of carcinogenesis. Importantly, the authors recommend discontinuing treatment immediately after resolution of lymphorrhea, reinforcing the safety and clinical utility of RT as a minimally invasive alternative in complex settings [21].

Hautmann et al. [22] conducted a large retrospective analysis involving 206 lymphatic fistulas in 191 patients following vascular surgery in the groin region. Their findings showed that radiotherapy significantly reduced lymphatic secretion volumes (from a median of 150 mL/day to 60 mL/day) and enabled early drain removal in most cases, with 75% of patients avoiding further surgical interventions. Interestingly, the timing of radiotherapy (before or after postoperative day 10) did not influence outcomes, supporting its flexibility in clinical practice.

More recently, Jazmati et al. [20] reported excellent results using extremely low-dose fractionated radiotherapy (0.3–0.4 Gy per fraction, median total dose 1.2 Gy) in 12 patients with persistent lymphatic fistulas after groin vascular surgery. Complete resolution was achieved in all cases, without adverse events. The authors emphasized the importance of initiating RT early—ideally within 72 hours of diagnosis—and highlighted the benefit of modern planning techniques such as intensity-modulated arc therapy (VMAT) using high-energy photons (6–15 MV).

While the optimal dose and fractionation scheme have not been standardized, regimens delivering total doses between 3 and 12 Gy appear effective. In our cohort, the most frequently prescribed scheme was 7.5 Gy in 5 daily fractions, which proved sufficient in the majority of cases. Notably, three patients (7.0%) required reirradiation with the same regimen, after which complete closure was achieved. These cases suggest that a second low-dose course may be safely administered if the initial response is suboptimal.

The absence of both acute and late toxicity in our study confirms the safety profile of low-dose RT in this setting [18, 21]. Importantly, treatment was delivered on an outpatient basis and completed without interruptions, making it a feasible and cost-effective option for patients who

may not be candidates for surgery or in whom further invasive procedures are undesirable.

This study has several limitations, including its retrospective nature, lack of a control group, and absence of long-term functional or quality-of-life assessments. Nonetheless, it represents one of the largest series published to date focusing specifically on radiotherapy for inguinal lymphorrhea.

Future prospective studies are warranted to confirm these findings, establish standardized dose and fractionation protocols, and explore the role of radiotherapy earlier in the treatment algorithm for persistent lymphatic fistulas.

Conclusions

Low-dose external beam radiotherapy (EBRT) appears to be a safe, well-tolerated, and highly effective treatment option for persistent inguinal lymphocutaneous fistulas, achieving complete clinical resolution in all patients in this cohort. The treatment was associated with minimal toxicity and excellent compliance. Given these favorable outcomes, EBRT may be considered a valuable therapeutic tool in the multidisciplinary management of this challenging complication, particularly when conservative measures have failed.

Prospective studies are needed to further define the optimal dose and fractionation, assess long-term outcomes, and establish standardized treatment protocols.

Abbreviations

VC	Verónica Cañón
JA	Javier Anchuelo
CL	Claudia Laborda
AGa	Ana Galán
ALR	Ana Laura Rivero
FP	Frandeína Pinto
MG	Mara García
PN	Paola Navarrete
PG	Piedad Galdós
AAlí	Ana Aliaga
AAye	Arantxa Ayete
CG	Cristina García
GL	Gemma Liria
MC	Maria Cerrolaza
RF	Rosa Fabregat
PJPr	Pedro José Prada

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Author contributions

VC, JA, and PJPr conceived the study and supervised the clinical coordination. CL, AGa, ALR, FP, MG, PN, PG, AAlí, AAye, CG, GL, MC, and RF participated in patient data collection and treatment delivery. JA and CL performed the data analysis and interpretation. JA drafted the manuscript. All authors critically reviewed the content, contributed to revisions, and approved the final version of the manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article. Additional anonymized data may be available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki. Ethical approval was obtained from the local ethics committee of the participating center. Written informed consent for radiotherapy treatment was obtained from all patients at the time of treatment.

Consent for publication

Not applicable. This study does not contain identifiable personal data from any individual participant.

Competing interests

The authors declare no competing interests.

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