

Radiotherapy in benign pathology: treatment of lymphorrheas

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Research

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Abstract

Objective : To aim of the study is to determine the efficacy and safety of treatment with low-dose 3D external beam radiotherapy (EBRT) in patients with inguinal lymphorrhea. **Material and methods :** We retrospectively analyzed a total of 53 patients with persistent lymphorrhea after conservative treatment between 2008 and 2018. All patients were treated with 3D EBRT with photons of 6 - 18 MeV. The most common schedules were 7.5 Gy in 5 fractions (90.7%).

Results : The complete closure of the fistula was achieved in 100% (43/43) of the patients. Three patients required re-irradiation due to persistence. We did not find any acute toxicity.

Conclusions : Low-dose radiation therapy is effective and safe for treating persistent lymphorrheas.

Introduction

Lymphoceles are cavities filled with lymphatic fluid that occur after surgical interventions¹. Lymphorrhea is defined as the flow of lymph from lymphatic ducts that drains externally through persistent lymphocutaneous fistulas (FLC). The definition of FLC is not very well described in the literature. Giovannacci et al.² defined an FLC as the secretion outlet at a flow of 30 ml/day for more than 3 days after surgery or persistent discharge after the fifth postoperative day. FLC has been described 4 years after surgery with drains of 50 ml per day³.

Primary congenital lymph fistulas are quite rare. Invasive procedures, mostly vascular, abdominal, pelvic and cardiac, are more likely to cause secondary lymph fistulas. Persistent lymphocutaneous lymph fistulas carry a high risk of complication and infection of the wound resulting in prolonged hospitalization, delay in rehabilitation and an increase of costs associated with the treatment.

The incidence of lymphoceles and FLC is variable in the different studies published to date. It is estimated between 2% and 8% of all vascular and abdominal or pelvic procedures^{4,5}. There seems to be a higher rate in patients with comorbidities.

FLC management requires individualization. Initial conservative treatment should be established with immobilization, elevation and compression of the limb, if possible. Failure to this, different sclerosing drugs such as ethanol, tetracycline, iodine solution or bleomycin and other compounds such as yttrium-90 or rhenium-186^{6,7,8} may be injected percutaneously. Rates of conservative management success vary among the authors. Twineet⁹ published control rates with conservative management of 80–100%. Other authors report 82% after 3 weeks of conservative management¹⁰. However, there are authors who defend the early surgical reintervention, especially if the drainage rate is high, in wound infections or in the presence of foreign bodies. Surgical reintervention carries its own risks.

Radiation therapy (RT) for the management of benign diseases is usually performed with lower radiation dose than those used for malignant tumors¹¹. There are different indications for the use of RT in the

treatment of benign disorders. Some examples are chronic degenerative pain¹², soft tissue conditions like Dupuytren's disease or Peyronie's disease¹³, keloids scars, Grave's orbitopathy¹⁴ and lymphoceles or persistent FLC¹⁵. In complex and refractory cases, in addition to the measures described above, RT can be considered as a treatment for FLC. RT in these cases is believed to have an anti-inflammatory effect. In order to achieve this, low doses per fraction and total ionizing radiation have a anti-inflammatory effect by decreasing the discharge of cytokines in pro-inflammatory cells. This changes the permeability of the cell membranes in vascular cells, increasing reabsorption of lymph. In addition, fibroblasts differ in fibrocytes, which promote fibrosis, increase nitric oxide and locally decrease lymphatic flow¹⁶.

Doses of 1–2 Gy per fraction cause aseptic vasculitis in the endothelium that destroys vascular light. Recent studies have reported that even lower doses (0.3–0.5 Gy per fraction) could be effective in the lymphatic fistula treatment. The aim of this study is to analyze our results in the FLC treatment with RT and the rate of secondary complications.

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Material And Methods

The main objective of our study is to determine the efficacy and safety of treatment with low-dose 3D external beam radiotherapy (EBRT) in patients with inguinal lymphorrhea refractory to other treatments.

A cross-sectional and retrospective observational study was carried out for which the patient registry of the Radiation Oncology Department of the Marqués de Valdecilla University Hospital was reviewed from May 2008 to April of 2018. Patient selection and characteristics The sample consisted of 53 patients (5 women and 48 men) with FLC and persistent lymphorrhea (figure 1). The average age was 69 years (range 35-90 years). Patients were selected based on a series of criteria established and detailed below. § Diagnosis of refractory FLC to conservative treatments and referral to our service. The following exclusion criteria were also applied.

- Presence of oncological disease in the same anatomical area.
- General condition that prevents treatment with RT.
- Inability to remain immobile during treatment.

All participants were informed of the purpose and the study methodology as well as the probable side effects. Patients provided written informed consent. All patients referred to our service met the inclusion criteria and none of the exclusion criteria; therefore they were all included in the study.

Radiotherapy treatment

RT treatment was administered by external linear RT accelerators (Varian Truebeam or Elekta Precise). In both cases, the energy used was 6 Mv or 18 Mv photons. Prior CT simulation was performed.

The treated area included the vessels under the scar and the seroma, if still present (CTV). A safety margin was considered (PTV) between 0.5 and 1 cm depending on the immobilization and image system for positioning (EPID or CONEBEAM). Protection of the nearby organs was provided. Conformal RT (3D) was used for all patients (figure 2).

The efficacy of the treatment was evaluated clinically as no response or complete response (complete closure of the fistula). We measured acute toxicity according to toxicity scales of RTOG cancer treatments. All patients were reviewed at the end of treatment and a month later in the Radiation Oncology Service. If the treatment was not satisfactory, the patients were referred back to our Service for a new evaluation. Subsequently, further follow-ups were done by their referral service.

Study variables

The variables collected and studied were the following.

- Age (mean and range) (Discrete quantitative variable)
- Sex (male and female) (Qualitative categorical dichotomous variable)
- FLC closure (Yes / No) (Qualitative categorical dichotomous variable)
- Complications (Yes / No) (Qualitative dichotomous qualitative variable)

Statistical analysis

Statistical analysis was performed in the Statistical Package for Social Sciences (SPSS) version 22.0. The descriptive analysis was applied for ordinal variables using the median as a measure of central tendency and percentage for nominal variables.

Results

Long-term outcome

Ten patients were not treated due to the self-limited process. The average time between surgery and RT was 38 days with a range between 7 and 110 days. The average duration of treatment was 5 consecutive days (range 2-7 days). 90.7% (39) of the patients were treated with a dose of 7.5 Gy in 5 daily sessions (1.5 Gy / session). Other dose fractionations used were: 5.5 Gy in 3 fractions in 1 patient (1.5 Gy + 1.5 Gy + 2.5 Gy), 8 Gy to 4 Gy / fraction in 2 patients and 15 Gy to 3 Gy / fraction in 1 patient. 40 of the 43 patients achieved a complete response of the persistent FLC. Three patients showed partial response

needing reirradiation, with the same treatment plan, and also achieved complete response. Therefore, the complete closure of the fistula was achieved in 100% (43/43) of the patients.

Acute and late toxicity

No related acute or late side effects were observed with the treatment.

Discussion

There are few articles in the literature regarding the schemes of RT treatment for this type of ailments. However, everyone seems to be in agreement on the effectiveness of radiotherapy in these cases. The treatment for FLC with low doses of radiotherapy per session (lower than cytoreductive doses normally used for malignant tumors such as 1.8-2 Gy / session) has a radiobiological basis¹⁷.

Seegenschmiedt et al¹¹ made one of the first approaches to this in 1999 with the document "Radiotherapy for benign diseases". We have focused on persistent lymphorrhea since this pathology is quite common after certain types of frequent interventions, as cardiac catheterization.

Mayer et al¹⁸ showed that the late side effects of radiation of FLC were not significant and the results showed the complete closure of the fistula. Despite the heterogeneity between patients and the administered doses, they obtained very good results and achieved complete responses.

Dietl et al³ analyzed a cohort of 28 treated patients with 3 fractions of 3 Gy in 3 consecutive days, with a voltage of 120–300 kV. Due to the good results, they concluded radiotherapy is a valid therapy to treat lymphatic fistulas. In this study neither early nor late side effects caused by RT were reported.

In our series of 43 patients we did not observe any side effects. Most of the patients (39) were treated with 5 fractions of 1.5 Gy with a total dose of 7.5 Gy.

To this date, there is little evidence about the treatment of lymphorrheas and there are no protocols with well-defined schemes. In addition, the incidence of cases of persistent lymphorrhea after conservative treatment is low.

Radiation therapy as a treatment in these cases is safe, fast and effective. It would be convenient to conduct prospective and multicenter studies in this regard that include more patients so as address the best fractionation. Quality of life studies, in addition to cost analysis should be performed since it leads to shorter hospital stays and less infectious complications.

Conclusions

Our retrospective analysis shows that an irradiation dose of 7.5 Gy with small fractions such as 1.5 Gy can completely solve lymphatic fistulas in most patients. RT in these situations has a good safety profile.

Therefore, RT is a solid, effective, safe and economic treatment option for the persistent lymphorrheas.

Declarations

Conflicts of interest

The authors declare that they have no competing interests" in this section.

AUTHORS' CONTRIBUTIONS

Verónica Cañón M.D.: conception and design.

Javier Anchuelo M.D.: acquisition of data.

Nicolás Sierrasesumaga M.D.: revising references.

Lucia Alonso M.D.: acquisition of data.

Ana Rivero M.D.: acquisition of data.

Piedad Galdós M.D.: revising references.

Iván Diaz de Cerio M.D.: alignment and drafted the manuscript.

Ana Garcia Blanco M.D.: revising references.

Maria Ferri: acquisition of data.

Juan Cardenal M.D.: analysis of data.

Héctor Vidal M.D.: acquisition and processing of Magnetic resonance image

Rosa Fabregat Ph.D.: analysis of data.

Samuel Ruiz Ph.D: analysis of data.

Pedro J. Prada M.D, Ph.D: revising, alignment and drafted the manuscript.

DECLARATIONS

Ethics approval and consent to participate. Not applicable.

Consent for publication. Not applicable.

Availability of data and materials. Not applicable.

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Figures

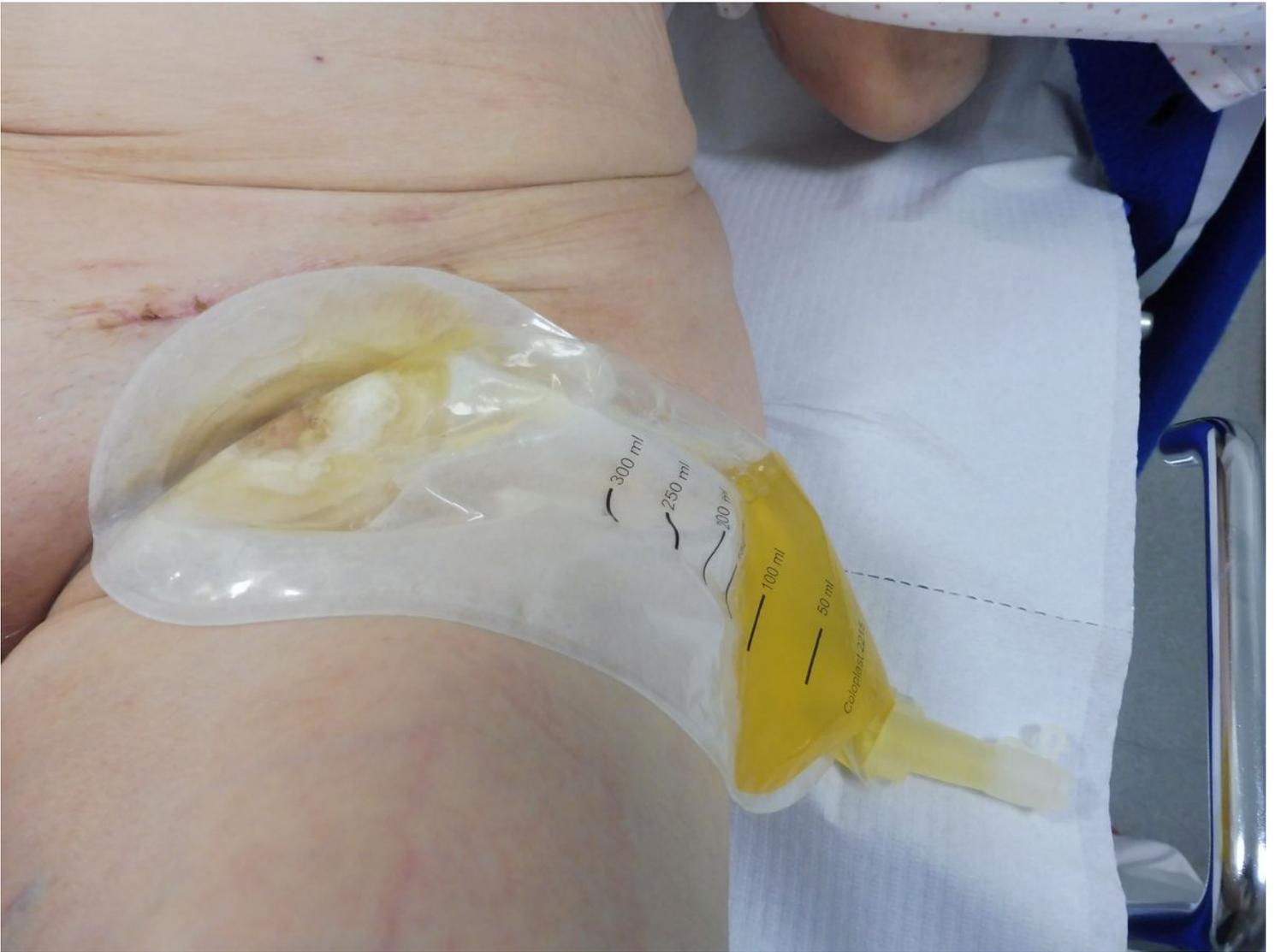


Figure 1

Persistent lymphocutaneous fistula (FLC) and persistent lymphorrhea.

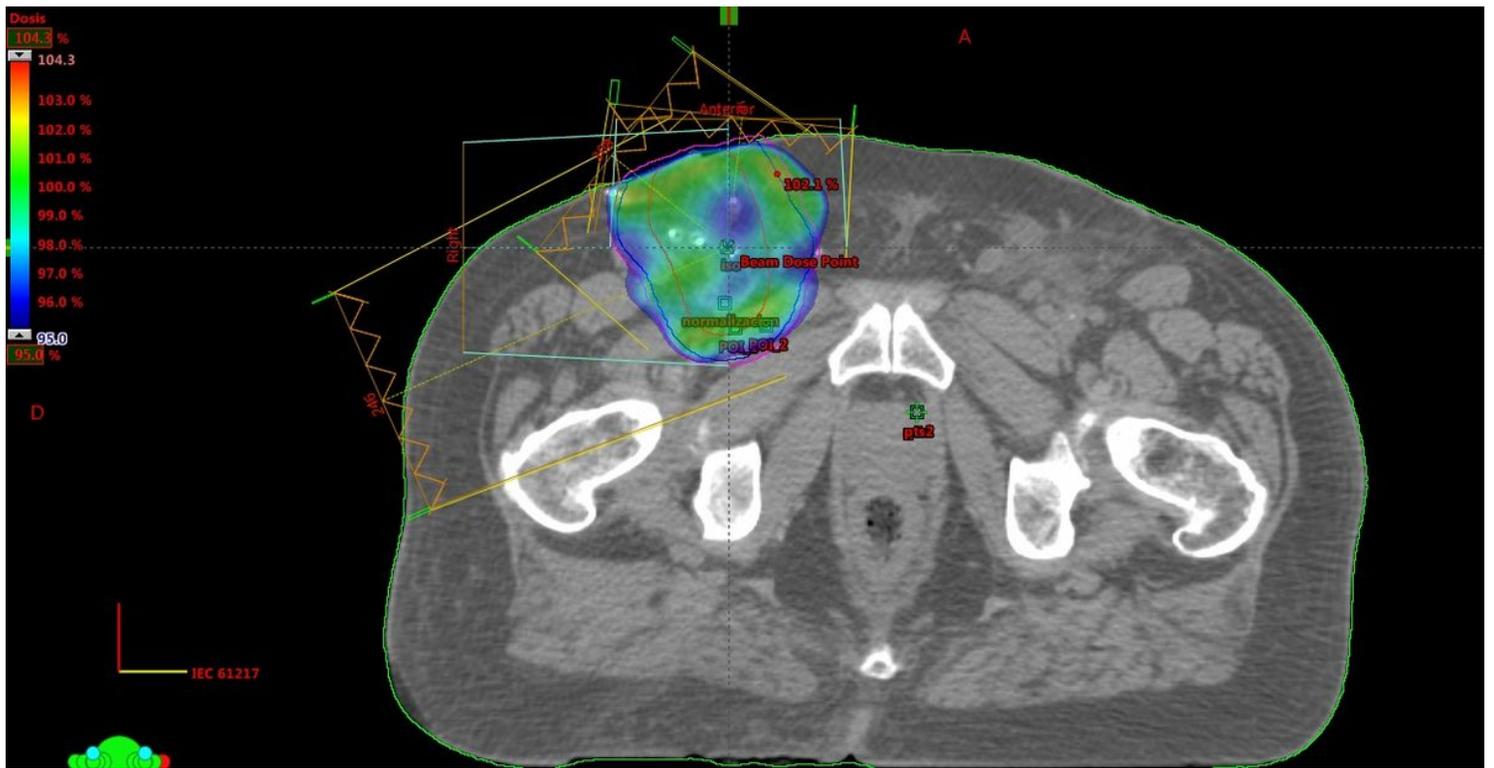


Figure 2

External Beam Radiotherapy. Axial dose distribution.