Universitat de Girona
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FINAL DEGREE PROJECT

CAN PROPHYLACTIC REHABILITATION REDUCE THE OCCURRENCE OF LOWER LIMB LYMPHEDEMA IN PATIENTS WITH GYNECOLOGIC MALIGNANCES?

A MULTICENTER, CONTROLLED, OPEN-LABEL, RANDOMIZED CLINICAL TRIAL

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ABSTRACT

BACKGROUND: Secondary lymphedema is a chronic condition that often results from oncological treatment procedures. This condition can significantly impact the functionality and quality of life of gynecological cancer survivors. While decongestive therapies are available for the treatment of diagnosed lymphedema, there is a currently lack of evidence on prophylactic measures to prevent its onset after gynecological pelvic lymphadenectomy.

OBJECTIVE: The study aims to evaluate the effectiveness of prophylactic rehabilitation in reducing the risk of secondary lower limb lymphedema in patients undergoing surgery for gynecological cancer involving pelvic lymphadenectomy. Additionally, we will try to assess whether prophylactic rehabilitation leads to a higher quality of life compared to the control group, which will receive exclusively educational strategies.

DESIGN AND PARTICIPANTS: This study is a multicenter, controlled, open label, randomized clinical trial conducted in four Catalan hospitals. The study population consists of patients with any gynecologic tumor who undergo pelvic lymphadenectomy as part of their oncology treatment. The sample will be composed of 140 patients who meet the inclusion criteria, with 70 in the intervention group and 70 in the control group.

METHODS: The main dependent variable will be to assess the presence or absence of lower limb lymphedema. The secondary dependent variable will be the evaluation of quality of life. Covariates that may affect the outcomes will be included.
Patients will be randomly assigned into two groups: the control group, which will receive the current protocol based on educational strategies, and the intervention group, which will receive prophylactic decongestive therapy, in addition to the same educational strategy. The intervention will last for 12 weeks, and we will follow-up these patients for 24 months. The occurrence of lymphedema and quality of life will be analyzed and compared between the two different groups.

KEYWORDS: *secondary lymphedema, lower extremity, rehabilitation, gynecologic cancer, quality of life.*

ABBREVIATIONS

- CC: Clinical Coordinators
- CCMM: Comparative Circumferential Measurement Method
- CDT: Complex Decongestive Therapy
- CEIC: Comité de Ética de Investigación Clínica
- CTCAE: Common Terminology Criteria for Adverse Events
- DM: Data Manager
- EWB: Emotional Well-Being
- FACT-G: Functional Assessment of Cancer Therapy General
- FWB: Functional Well-Being
- GN: Gynecologic-oncology Nurse
- GS: Gynecologic-oncology Surgeons
- HUJT: Hospital Universitario Doctor Josep Trueta
- IS: Independent Statistician
- ISL: International Society of Lymphology
- LLL: Lower Limb Lymphedema
- MLD: Manual Lymphatic Drainage
- PI: Principal Investigators
- PWB: Physical Well-Being
- QoL: Quality of Life
- RP: Rehabilitation Physician
- SCOG: Societat Catalana d'Obstetrícia I Ginecologia
- SEGO: Sociedad Española de Ginecología y Obstetricia
- SLNB: Sentinel lymph node biopsy
- SWB: Social Well-Being

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INTRODUCTION

1. GYNECOLOGICAL CANCER

Gynecological cancer comprises different malignant tumors located in the female reproductive organs. These pathologies are categorized based on their primary site of origin. There are five main types of gynecological cancer: cervical cancer, ovarian cancer, uterine cancer, vaginal cancer, and vulvar cancer.

Table 1: Worldwide statistics for gynecological cancers among all cancers combined in 2020. Extracted from (1)

	Incidence rate	Mortality rate
Cervix uteri	3,1%	3,4%
Corpus uteri	2,2%	1%
Ovary	1,6%	2,1%
Vulva	0,2%	0,2%
Vagina	0,1%	0,1%

Cervical cancer stands as the most commonly diagnosed gynecological malignancy globally, ranking fourth in overall female cancer diagnoses, after breast cancer, colorectal cancer, and lung cancer. It is also the fourth leading cause of cancer-related mortality in females worldwide (1).

In developed countries, endometrial cancer represents the most frequent gynecological malignancy, excluding breast cancer. Advanced age and obesity are the main risk factors for its development. Currently, both factors are increasing, so is the incidence of this gynecological cancer. Meanwhile, ovarian cancer takes presence as the main cause of mortality for gynecological malignances in developed countries (2).

Gynecological malignances present a wide variety of characteristics, including specific signs and symptoms, risk factors, diagnostic methods, and therapeutic and preventive

management. It is important to note that each cancer is unique in its presentation and requires individualized care (2). A crucial aspect of gynecologic cancers involves recognizing that the dissemination of these tumor cells significantly influences the management of the disease. This spread can occur through continuity, through blood or through the lymphatic system (3).

2. LYMPHATIC SYSTEM

The lymphatic system comprises lymphatic organs, including lymph nodes, tonsils, thymus, and the spleen, all interconnected by a complex network of slender tubes, known as lymphatic vessels. Running parallel to the venous circulation, these vessels extend throughout the body, serving as an accessory pathway. Lymphatic system facilitates the drainage of excess fluids from the interstitial space to the bloodstream. This system operates as a low-pressure system, assisted by the contraction of skeletal muscle and the presence of unidirectional valves that prevent retrograde flow. The lymph is transported through collecting lymphatic vessels, filtered through lymph nodes, and eventually reintegrates into the circulatory system *(Figure 1)* (4–6).

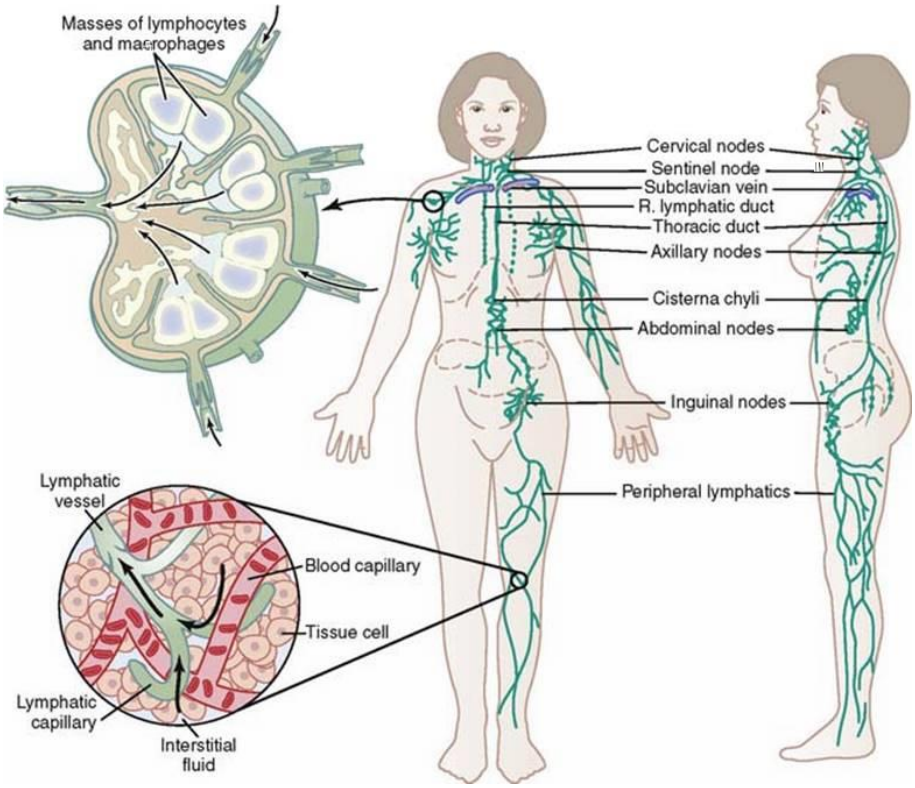


Figure 1: Lymphatic system (4)

The lymphatic drainage patterns of the gynecological organs are similar to the venous drainage, due to their shared embryological vascular origin. The gynecological lymphatic vessels follow the path of the uterine artery. Broadly speaking lymphatic drainage occurs in the parametrial and paracervical lymph nodes, progressing to the obturator lymph nodes and towards internal and external iliac lymph nodes. Ultimately, the lymphatic flow converges at the paraaortic lymph nodes. In contrast, posterior lymphatic vessels go through rectal muscles and urosacral ligaments to reach the rectal lymph nodes *(Figure 2)* (2).

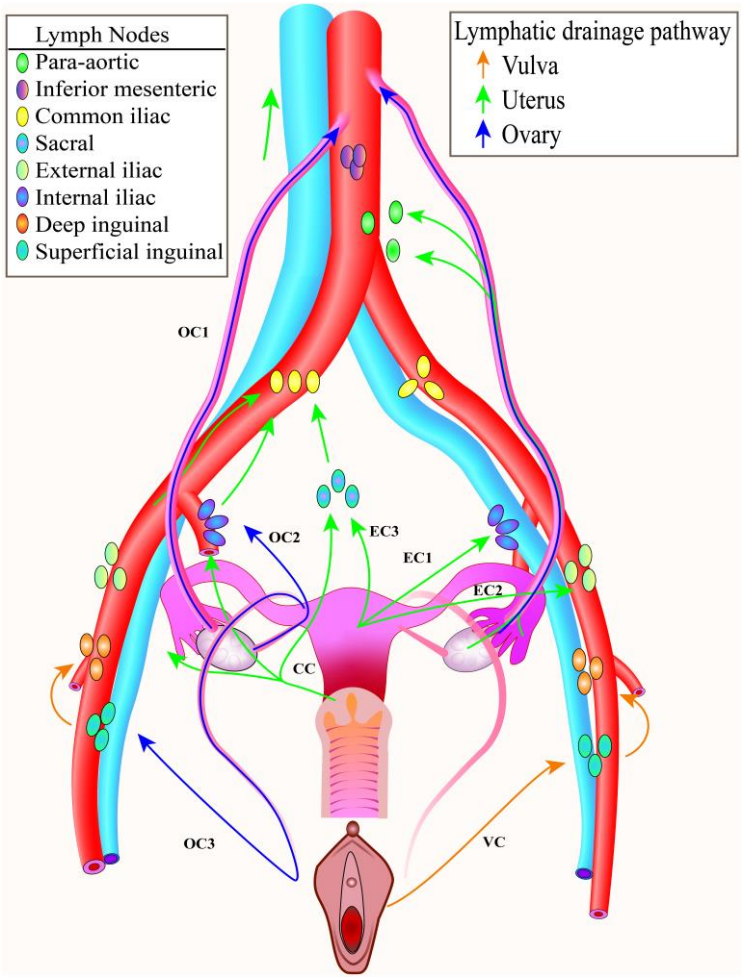


Figure 2: Pelvic lymphatic drainage. The common lymphatic drainage pathways of the ovary, the uterus, the cervix, the vagina and the vulva. To facilitate display, only one side lymphatic drainage route was drawn for each tumor. CC, cervical cancer; EC, endometrial cancer; OC, ovarian cancer; VC, vulva cancer (7).

All lymphatic vessels originating from the lower half of the organism converge to drain into the thoracic duct, which subsequently empties into the venous system at the junction between the internal jugular vein and the left subclavian vein *(Figure 1)* (4).

Lymphatic dissemination is the main pathway of tumor spread, contributing to therapeutic challenges and failures. The risk of lymphatic extension is determined by factors such as tumor´s localization, size and invasive stage. Therefore, removal and pathologist assessment of lymph nodes are essential for cancer staging, prognostication, guidance of surgical intervention and adjuvant therapy (3).

3. LYMPHEDEMA

Lymphedema is a localized form of tissue swelling resulting from lymphatic system insufficiency and disrupted lymph transport. Its incidence is approximately 20 million people worldwide, resulting in substantial discomfort, morbidity, and financial burdens for those affected (5,8).

Fluid accumulation in the interstitial space occurs as a result of an imbalance between lymph production and absorption, process regulated by Starling forces. These forces, oncotic and hydrostatic, dictate the movement of fluids across blood and lymphatic vessels. Disruption, backflow, or obstruction of lymphatic vessels impede the lymphatic reabsorption of proteins filtrated by the blood vessels. These proteins play an essential role in water accumulation in interstitial tissues due to increased osmotic pressure (9).

The persistence of lymphedema triggers inflammatory and immune responses, mediated by fibroblast, mononuclear cells, and adipocytes, leading to the deposition of adipose tissue and collagen in the skin and subcutaneous tissues. This complex interplay of factors contributes to the chronic nature of lymphedema and its complications (9).

3.1. Classification

Lymphedema is classified either primary or secondary.

A. <u>Primary Lymphedema</u>

Primary lymphedema arises from genetic mutations that lead to an incomplete development of lymphatic vessels and malfunction of the lymphatic drainage capacity.

The condition manifests in three clinical subtypes: congenital lymphedema, which is present from birth; early lymphedema, which initiates during puberty *(Figure 3);* and late lymphedema typically appearing around the age of 35 or later (5,9).

In most cases, it is inherited as an autosomal dominant trait, with incomplete penetrance and variable expression. Frequently, primary lymphedema presents in the lower extremities, and sometimes it can affect genitalia and arms. The incidence is higher in female than in males (5).

B. Secondary lymphedema

Secondary lymphedema is significantly more widespread than primary lymphedema. It is defined by an acquired impairment or obstruction of a previously normal lymphatic system. Globally, the most prevalent cause of secondary lymphedema is due to an infection by the nematode *"Wuscheria bancrofti",* also known as filariasis. In industrialized world the most common cause is associated with malignancies. Less frequently, medical disorders such as chronic venous insufficiency, recurrent bacterial infection, trauma, or obesity may contribute to its occurrence *(Figure 3)* (5,9).

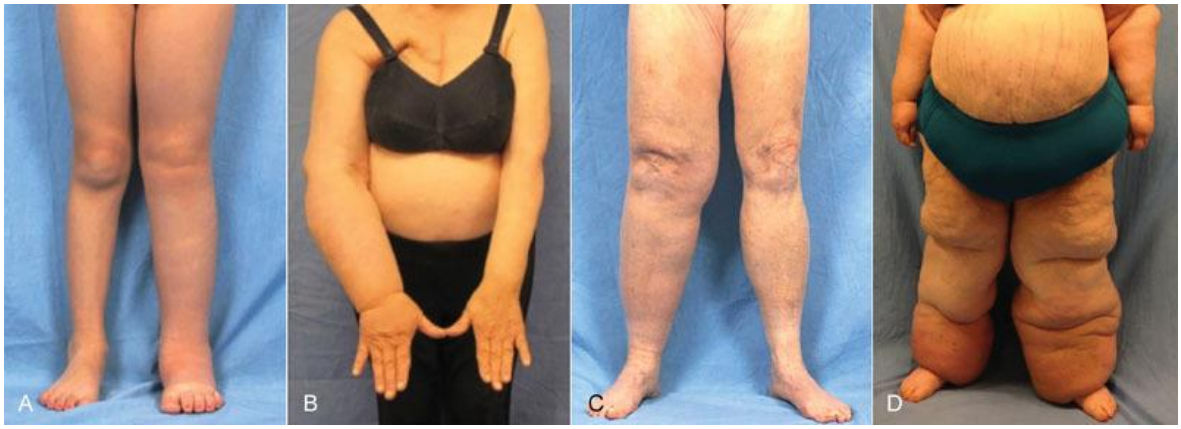


Figure 3: Types of lymphedema. (A) Pediatric primary lymphedema of the left lower extremity. (B) Secondary lymphedema of the right arm following breast cancer treatment. (C) Secondary lymphedema of the right leg following inguinal lymphadenectomy and radiation for cancer management. (D) Bilateral lower extremity obesity-induced lymphedema in a patient with a BMI of 72. BMI, body mass index (10).

Malignances may lead to lymphatic dysfunction through various mechanisms. Firstly, surgical excision of lymph nodes, known as lymphadenectomy, significantly increases the

risk of lymphedema. This is the strongest predictor of this condition, regardless of the cancer type. Tumor compression can also induce an obstruction of lymphatic vessels or nodes. Another contributing factor is the infiltration of tumor cells, recognized as lymphangitic carcinomatosis. Additionally, lymph node radiation therapy may also obliterate lymphatic vessels. Finally, the impact of certain medication, such as adjuvant taxanes, can be associated with secondary cancer-related lymphedema (6).

Some studies affirm that secondary cancer-related lymphedema often occurs within the first 12 months post-surgery, particularly between 4 and 6 months after surgery (11,12); while others advocate that lymphedema may emerge even up to 24 months after surgery (13,14).

Currently, there is a noticeable change in the medical landscape with the gradual displacement of lymphadenectomy by a more advanced technique, the sentinel lymph node biopsy (SNLB). This approach offers a less invasive evaluation of the lymph nodes, which aids in cancer staging and reduces potential complications of lymphadenectomy, such as lymphedema. Nevertheless, in gynecologic malignances, lymphadenectomy is still a necessary practice for the staging of initial ovarian cancer, ganglionar debulking during cytoreduction for advanced ovarian cancer, surgical management of cervical cancer, and selected cases of high-risk endometrial cancer where SNLB may not be feasible (3,7,15).

A systematic review and meta-analysis of cancer-related secondary lymphedema studied this condition. The incidence of lymphedema in patients undergoing pelvic lymph node dissection for gynecological cancers raged from 0% to 73%, with an **average incidence of 23.9%.** Due to the lack of consensus on a single diagnostic method, incidence rates vary between studies. Significantly, the risk increased when added radiation therapy, reaching an incidence of lymphedema as high as 34% (16). Estimates of the incidence of cancer-related secondary lymphedema vary for different types of gynecologic cancers. For endometrial cancer the range is approximately 1-38%, while for cervical cancer is between 17-81%, presenting the highest incidence. Similarly, vulvar and vaginal cancer estimated rates range from 6-75% and for ovarian cancer 5-21% (14).

3.2. Clinical manifestations

Clinical presentation of lymphedema is characterized by a persistent sensation of heaviness and discomfort in the affected limb. Typically, it initiates on the dorsal aspect of the feet and progresses gradually up the leg (*Figure 4)*. This condition is commonly asymmetric, diffuse and does not alleviate with changes in body position. Lymphedema can manifest unilaterally or bilaterally, and it often follows a progressive and irreversible course (9,17).

In the early stages of lymphedema, there is a transitory soft edema with a noticeable fovea upon pressure. Over time, there is an accumulation of subcutaneous adipose tissue, which gives a pitted or dimpled texture, known as "peau d´oragne". This process results in an increased size of the affected extremity and a loss of its original form, often accompanied by the characteristic square fingers. In chronic situations, the tissues become progressively indurated and fibrotic, assuming a woody appearance (5,9,17).
The Stemer sign becomes apparent in advanced stages, which is the inability to pinch the skin at the base of the second toe, pathognomonic for chronic lymphedema *(Figure 4)* (5).

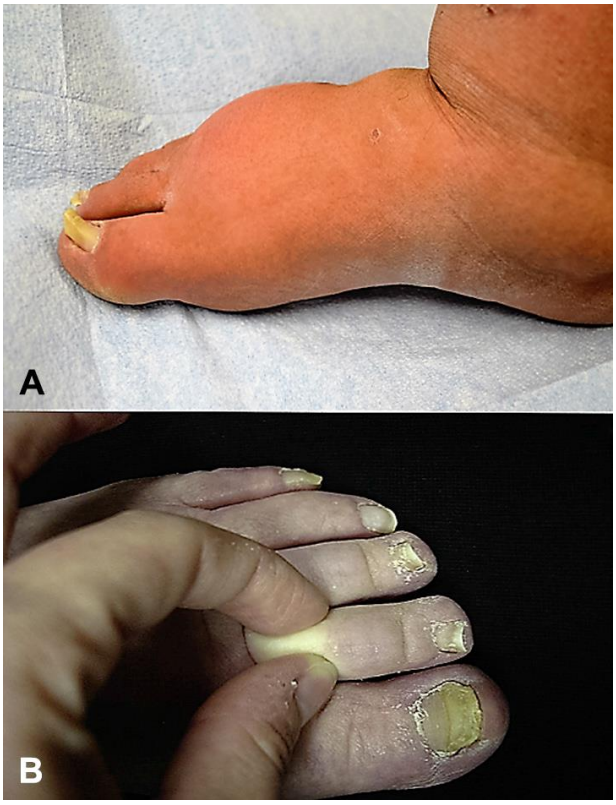


Figure 4: Lymphedema. A, Swelling on the dorsal aspect of the feet is typical for patients with lymphedema. B, The Kaposie-Stemmer sign is positive (5).

3.3. Complications

Frequently, lymphedema associate recurrent infections, such as lymphangitis, erysipelas, cellulitis, and mycosis. Each infection episode contributes to the obstruction of the lymphatic vessels and worsens the patient's situation. Tine pedis is significantly prevalent due to the chronic interdigital maceration. Furthermore, fissures and ulcerations are commonly manifested. In this context, lymphorrhea may occur, characterized by the leakage of amber-colored fluid from the skin, corresponding to lymph (5,17).

In the advanced stages, the limbs acquire a hyperkeratotic appearance, resulting not only in a significant physical limitation, but also in an unfavorable impact on the patient's psychological well-being (5).

Patients with severe chronic lymphedema persisting for over a decade have a 10% elevated risk of developing cutaneous angiosarcoma. This malignancy, though less common, is strongly aggressive leading to an unfavorable prognosis and a 5-year survival rate below 10%. Angiosarcoma typically presents as red-purple nodules, that may extend, ulcerate, and form satellite lesions *(Figure 5)* (5).

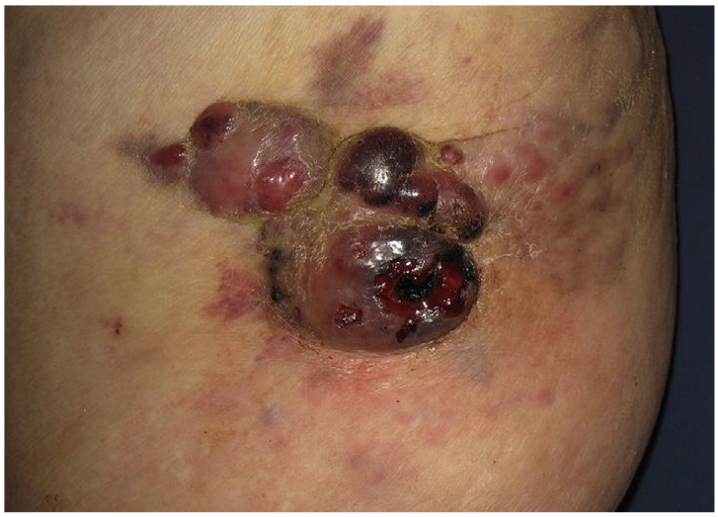


Figure 5: Cutaneous angiosarcoma. Right calf with 17-cm x 8-cm violaceous ulcerated, multifocal tumor (5).

In addition to the great physical impact secondary to lymphedema, these patients suffer important psychological affectation, such as anxiety, depression, and negative body image associated to the altered mobility and deformity of the extremities, as well as possible genitalia (5).

The Lymphedema and Gynecologic cancer (LeG) study has revealed that the health-related Quality of Life (QoL) for women experiencing lower limb lymphedema (LLL) after gynecologic cancer surgery is notably decreased when compared to patients without lymphedema. This decline is observed in various domains, emotional, physical, functional, and social well-being, indicating a negative impact on their daily lives. Additionally, these individuals have higher levels of lower limb dysfunction in routine activities, such as walking or getting out of the car. Moreover, the presence of LLL is associated with an elevated level of cancer-related distress. This may be due to the persistent reminder of their cancer experience, impeding the process of adapting to life after a cancer diagnosis (18).

3.4. Stages

Once lymphedema is diagnosed, it is important to categorize the stage of edema to effectively determine the best treatment strategies and evaluate treatment response.
The International Society of Lymphology (ISL) has defined four clinical stages of lymphedema progression (8,9):

- **Stage 0:** this stage is characterized by a latent or subclinical condition in which edema is not visibly apparent, despite disrupted lymphatic transport. It may associate slight alterations in tissue structure or subjective symptoms. This stage is often transitory and can persist for months to years before the manifestation of edema.
- **Stage I**: in this stage, there is an initial accumulation of fluid with a high proteins concentration, resulting in elastic edema. Limb elevation can lead to a reduction in edema. Pitting may be observed, as well as proliferating cells.

- **Stage II:** without intervention, lymphedema progresses over time, leading to fibrosis and hardening, causing irreversible damage. Elevating the extremity no longer reduces the edema. Pitting is usually evident at the onset of this stage.
- **Stage III:** this advanced stage is characterized by complicated lymphedema, associating cutaneous atrophic changes such as acanthosis, fat deposition, fibrosis, and warty overgrowths. This progression results in recurrent lymphangitis and elephantiasis.

This classification exclusively focuses on the physical condition of the lower limbs. In order to provide a more comprehensive evaluation, the ISL has complemented these stages with a quantitative functional severity assessment, using excess volume differences, referred to as ISL grade *(Figure 6)* (8).

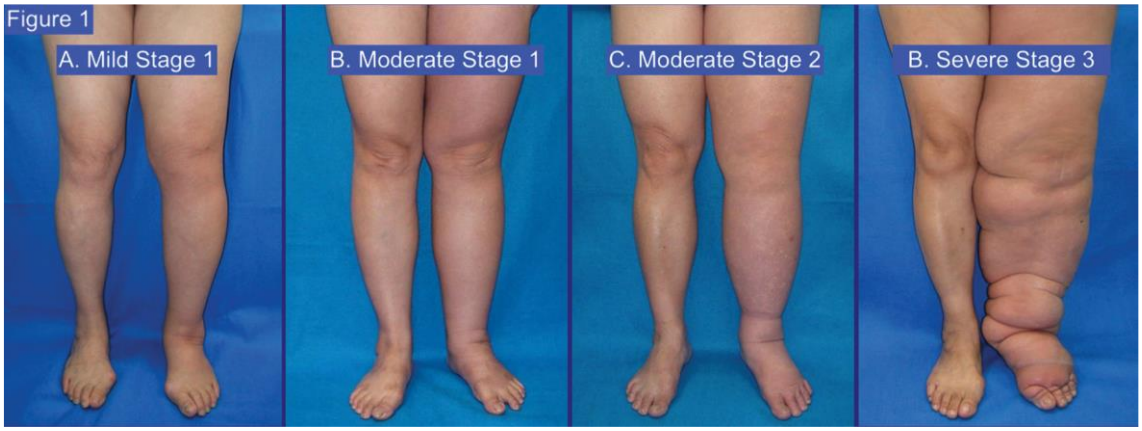


Figure 6: Photographs of the ISL stages/grade of lymphedema. (A) Stage 1 mild lymphedema with <20% difference in limb size. (B) Stage 1 moderate lymphedema with a 20–40% difference in limb size. (C) Stage 2 moderate lymphedema with a 20–40% difference in limb size with associated fibrosis and irreversible edema. (D) Stage 3 severe lymphedema with >40% limb difference, and abnormal fat deposits (19).

Furthermore, The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) can also be correlated with lymphedema stages, evaluating the physical impediments experienced by patients as a result of secondary lymphedema *(Table 2)* (19,20).

Table 2: Grading Systems for Lymphedema. Adapted from (19).

ISL Stage	ISL Grade	CTCAE Grade
0: subclinical impairment of lymphatic transport	-	-
1: high protein edema, reversible with limb elevation. It may present pitting	**Mild**: >5% and <20% increased limb volume difference	**Grade 1**: Traces of thickening or slight discoloration of the skin
2: dermal fibrosis that do not improve with leg elevation	**Moderate**: 20-40% increased limb volume difference	**Grade 2**: limited daily life functions. Visible skin discoloration, coriaceous texture, formation of papillae
3: Atrophic skin changes and elephantiasis	**Severe**: >40% increased limb volume difference	**Grade 3**: Severe symptoms are a barrier to self-care and daily activities.

3.5. Diagnosis

The timely diagnosis of lymphedema is key to prevent the irreversible consequences associated with advanced stages and providing optimal therapeutic intervention.

In cancer-related secondary lymphedema both a detailed medical history and a comprehensive physical examination play a crucial role in the diagnosis. Indicators include localized, gradually progressive edema, as well as the presence of cutaneous thickening and fibrosis in advanced stages, as previously discussed; a documented history of cancer treatment (e.g. surgery, lymph node dissection, radiation therapy) and the absence of underlying causes for generalized edema, such as heart failure, hepatic failure or renal failure. These data suggest the likelihood of secondary lymphedema. However, we must complement the clinical diagnosis with the appropriate objective tools (6).

The **comparative circumferential measurement method** (CCMM) is the predominantly used objective evaluation in assessing LLL. This method uses a non-elastic tape to compare the affected extremity with its opposite. The way measurements are taken differs among authors, one commonly employed involves the measurement of four designated zones: metatarsal-phalangeal joints, two centimeters (cm) up to the medial

malleolus, and ten cm both above and below the patella. A discrepancy of 2 to 2.5 cm at multiple levels between the limbs is considered indicative of lymphedema. This is an inexpensive and easily taught form of measurement. However, certain limitations exist, as this measurement may not discern subtle changes, and it requires a normal contralateral limb, nonexistent in bilateral lymphedema (16,19,21).

Circumferential measurement can be used to calculate individual **limb volume** and **excess limb volume** by employing a specialized computer program or calculator equipped with mathematical formulas, such as de truncated cone formula. This approach enables to obtain a reliable measurement that facilitates comparisons. Additionally, limb volume changes is useful to classify lymphedema according to the ISL grade (19,21,22).

The **water volumeter** stands as the gold standard for direct volumetric measurement, employing the displacement of water within a standardized container. This method can detect volume changes below 1%. A discrepancy of 200 ml between the two limbs serves as the diagnostic for identifying LLL. It is simple and easily reproducible but inconvenient for patients, with hygienic issues and difficult to use in routine practice (19,21).

The **perometer** is an optoelectronic volumetry device that uses infrared light to scan extremity diameter throughout the length of the limb, allowing for volumetric assessment. This complex tool has a higher interobserver reliability but the high cost difficult its use (19,21).

Bioimpedance spectroscopy is a valuable tool in the examination of tissue changes. This technique is based on the measure of tissue's resistance to a low-intensity electric current over a spectrum of frequencies. By obtaining specific parameters, we can calculate the volumes of extracellular and intracellular fluid. Its utility extends to the early detection of lymphedema and monitoring its initial phases to avoid irreversible stages. Despite its usefulness, this is an expensive method that requires an expert for data analysis and curve calculation (19,23).

Tissue tonometry is another tool that measures the impedance of soft tissues to compression and quantifies compliance, correlating these results with the swelling and degree of fibrosis in the extremities. However it also requires an internal control and a normal contralateral limb for comparison (16,19).

Imaging techniques, such as lymphangioscintigraphy with technetium-99, provides qualitative and quantitative information on lymph transit. Computed tomography and magnetic resonance imaging exhibit notable sensitivity and specificity in studying soft tissue edema. Ultrasound is valuable in excluding confounding disorders, such as deep venous thrombosis and venous insufficiency. Additionally, near-infrared imaging using indocyanine green is a contemporary technology employed intraoperatively for identifying sentinel lymph nodes in cancer staging. It can also be used to visualize lymphatic pathways and transit in real time (19,21).
However, these imaging techniques are expensive and should be considered as a secondary approach when the diagnosis of lymphedema remains unclear. Since perimetral and volumetric measurements serve as a reliable and universally applicable method for diagnosing and evaluating LLL (19,23).

Given that patients often report symptoms before clinical identification of lymphedema, the LeG study have examined patient-reported lymphedema in gynecologic malignancies using validated surveys, known as The **Gynecologic Cancer Lymphedema Questionnaire** (GCLQ). They have shown that patients experiencing a score change greater than 4 from their baseline exhibited poorer QoL, body image, sexual and vaginal function, limb function, and cancer distress. These questionnaires combined with objective measurements demonstrate good sensitivity and specificity in diagnosing this condition (18,24).

As mentioned, the decline in QoL becomes significant in cases of LLL. The evaluation of health-related QOL in cancer patients employs the **Functional Assessment of Cancer Therapy-General** (FACT-G). This is a 27-item scale validated, reliable and sensible to clinical change, as demonstrated by the American Society of Clinical Oncology (18,25).

3.6. Treatment

The current consensus document from the ISL has classified peripheral lymphedema treatment into conservative (non-operative) and operative methods (8):

A. Non operative treatment

Non operative treatment relied on three main pillars: physical therapy, drug therapy and psychosocial rehabilitation.

Within physical therapy, **Complex Decongestive Therapy** (CDT) plays a crucial role. This therapy comprises two phases, the initial one involves skin care, manual lymphatic drainage (MLD), and, depending on the stage, may include muscle pumping exercises and compression with multilayered bandage wrapping, ideally administered by trained professionals. The second phase aims to maintain and enhance the achieved results from the previous phase. It involves the use of a low-stretch elastic stocking compression, along with skin care and exercise. Physical exercise promote lymphatic flow, mobilize joints and strengthen muscles, it is essential both in the initial treatment and during the maintenance phase (8,21,26). About a 60% of reduction in limb volume could be achieved in moderate to severe lymphedema using this physical therapy (27).

Compression garments have been useful in the early stages of breast cancer-related lymphedema treatment and as a preventive measure against fluid accumulation and volume changes. **Intermittent pneumatic compression** is another alternative for physical therapy, simulating manual massaging with compression and decompression cycles. They are more convenient devices that can improve treatment adherence. **Kinesio taping** seems to be another useful way to reduce lymphedema but still requires further study (8,21).

In this context, **educational strategies** are indispensable. Patient education in the anatomy and functioning of lymphatic system, definition and risk factors of secondary lymphedema, possible symptoms and signs, self-assessment, learning about aids in compression treatment, skincare practices, weight control and exercise routines (8).

Drug therapy, such as diuretics, may also be used in the initial phase of CDT, but only for short periods of time due to the risk of inducing electrolyte imbalances. These agents are recommended exclusively for patients with specific comorbid situations or complications. The role of benzopyrones as adjuvant therapy to CDT has not been clearly determined yet. Antimicrobials should be employed in cases of related infections, such as cellulitis, lymphangitis or erysipelas (8).

Finally, **psychosocial support** and life quality enhancement programs are essential for a comprehensive treatment of secondary lymphedema (8).

B. Operative Treatment

In gynecologic cancer patients, operative management serves as an alternative when conservative measures have not been successful, always employed in conjunction with CDT. Two primary approaches exist: physiologic and ablative procedures. **Physiologic surgeries** include lymphatic collector implantation, vein and lymph segments transplantation, and lymphatic venous or lymph nodal venous shunt. These should be exclusively utilized in early LLL. By contrast, **ablative surgical techniques**, such as liposuction and direct excision, are reserved for advanced lymphedema, considering potential adverse effects, such as pain, infections, healing complications, and fistulas (21).

3.7. Prevention

Prevention in secondary lymphedema can be classified in primary, secondary and tertiary. Primary prevention focuses on preventing the onset of lymphedema, while secondary prevention involves treating lymphedema in its early stages to prevent its progression into chronic and severe stages. Tertiary prevention aims to improve lymphedema in its advanced stages (8).

Currently, due to the significantly repercussion of lymphedema in cancer patients, more attention is paid to mitigate the progression of this condition. The ISL consensus document about lymphedema underline the significance of early detection in preventing lymphedema from becoming chronic. It emphasizes the necessity of continuous

assessment before and after cancer treatment, monitoring limb volume and functional mobility to detect early fluid accumulation. Early stages identification allows to a conservative intervention, reducing the probability of progression to a chronic stage, thus enhancing treatment outcomes and cost-effectiveness (8).

However, considering the substantial and debilitating consequences associated with lymphedema following gynecologic tumor surgeries, the challenge lies in developing measures to establish effective primary prevention. The ISL has identified some risk factors for lymphedema, such as, an elevated body mass index (BMI), a high number of lymph node dissection, extensive surgeries, adjuvant therapy and a sedentary lifestyle. Despite these recognized factors, currently, there is not enough evidence to support any specific measure to prevent LLL after gynecological surgeries (8,19).

A randomized clinical trial has demonstrated the effectiveness of early physiotherapy in avoiding secondary lymphedema following breast cancer surgery involving axillary lymph node dissection. The physiotherapy regimen comprised MLD, massage of scar tissue, and progressive active and action assisted shoulder exercises. Both the therapy group and the control group received an educational strategy. The statistical outcomes were significant, revealing a difference in the incidence of lymphedema of 25% in the control groups versus 7% in the intervention group (28).
The Department of Physiotherapy in Melbourne conducted a study on this condition and published a paper supporting the prophylactic use of compression sleeves in women at high risk of breast cancer-related lymphedema. The clinical trial concluded that compression sleeves are a successful intervention in reducing the incidence of secondary lymphedema in the upper limbs (29).

These are some examples that show that secondary lymphedema research has focused on upper extremity after breast cancer, leaving a gap in knowledge regarding prevention of secondary lymphedema after gynecological cancer treatment. Wang et al have recognized this problem and have conducted a randomized clinical trial to assess the efficacy of prophylactic modified complex decongestive therapy in preventing LLL after radical surgery for cervical cancer. The physiotherapy regimen included MLD,

compression bandage, regular exercise and health education. The results demonstrated a significant advantage, with an incidence of lymphedema in the control group of 23.9% compared to the intervention group, which showed a lower incidence of 13.6% (13).

Based on available studies, a comprehensive assessment throughout the surgical process, combined with a prophylactic physiotherapy approach before the onset of lymphedema, could constitute an effective program to prevent secondary lymphedema in gynecologic patients undergoing lymph node dissection. This intervention aims not only to avoid its occurrence but also improve the overall quality of life for these patients.

JUSTIFICATION

Secondary lymphedema is a debilitating, chronic and progressive condition that frequently occurs after cancer treatment. The appearance of this complication has been identified as one of the most relevant sequelae after surgical interventions for gynecological cancers in which lymph node excision is performed, either with a staging or therapeutic purpose (5,8). A systematic review and meta-analysis of cancer-related secondary lymphedema revealed that the average incidence of lymphedema in these cases was reported to be approximately 24% (16).

Lymphedema is characterized by chronic edema of the extremities and thickening of the skin. As it progresses, the tissues become indurated and fibrotic, which can cause discomfort and functional disability. Additionally, patients may experience ulcerations and recurrent bacterial and fungal infections in the affected extremity (5,9,17). This lymphatic disease has a significant psychological impact on patients due to functional limitations and aesthetic changes. Research has consistently shown that lymphedema is associated with a decrease in patients' quality of life, affecting their physical, mental, and emotional well-being (18).

Research on lymphedema in the domain of oncology has concentrated on upper extremity lymphedema in individuals undergoing treatment for breast cancer (19). These studies have shown that mobility and early rehabilitation can efficiently prevent secondary lymphedema of the upper limbs after oncologic surgery involving axillary lymph node dissection. Therefore, a protocol with a series of rehabilitative measures has been developed to prevent its occurrence in the upper extremity (28,30,31).

Limited evidence from randomized clinical trials is available for patients undergoing surgery for other gynecological malignancies. As previously mentioned, a singular study conducted in China has explored the effectiveness of prophylactic physiotherapy in reducing the incidence of lymphedema in women undergoing surgery for cervical cancer, obtaining favorable results (13). This study has inspired the objective of our project: to stablish a postoperative program for the prevention of lymphedema in all type of gynecological cancer survivors through early rehabilitation therapies.

Women undergoing pelvic lymphadenectomy as part of oncologic surgeries received only post-operative education, which is insufficient to prevent the development of lower extremity lymphedema. Consequently, affected individuals do not undergo treatment until symptoms manifest. While some improvement is possible at this point, reversing the effects of this chronic evolutionary process becomes challenging (19).

Given the elevated cure rate and extended survival resulting from advances in oncologic treatment, we emphasize the importance of prioritizing efforts to prevent complications that may arise from the therapeutic process.

The primary goal of this study is to improve the morbidity and quality of life for patients who have undergone lymph node dissection as part of any gynecologic tumour surgery at Hospital Doctor Josep Trueta. We aim to provide objective evidence of the advantages of prophylactic rehabilitation in secondary cancer-related lymphedema, thus contributing to the overall well-being of these patients.

HYPOTHESIS

1. MAIN HYPOTHESIS

- Prophylactic rehabilitation will reduce the **occurrence of lower-limb lymphedema** in patients undergoing surgery for gynecological cancer involving dissection of pelvic lymph nodes.

2. SECONDARY HYPOTHESIS

- Prophylactic rehabilitation will provide a **higher quality of life** in patients undergoing surgery for gynecological cancer involving dissection of pelvic lymph nodes.

OBJECTIVES

1. MAIN OBJECTIVE

- To determine the effectiveness of prophylactic rehabilitation in reducing the risk of **secondary lymphoedema** in patients undergoing surgery for gynecological cancer involving dissection of pelvic lymph nodes.

2. SECONDARY OBJECTIVE

- To assess whether prophylactic rehabilitation provides a **higher quality of life** in patients undergoing surgery for gynecological cancer involving dissection of pelvic lymph nodes.

MATERIAL AND METHODS

1. STUDY DESIGN

This study will be performed as a multicenter, prospective, longitudinal, randomized, controlled and open-label clinical trial. It will be carried out in four hospitals in Catalonia, all affiliated to the Institut Català d'Oncologia (ICO), ensuring access to specialized materials and personnel trained in gynecologic oncology. The participant hospitals are:

- Hospital Universitari Doctor Josep Trueta, Girona
- Hospital Universitari de Bellvitge, Hospitalet de Llobregat
- Hospital Universitari Germans Trias i Pujol, Badalona
- Hospital Universitari Joan XXIII, Tarragona

Hospital Universitario Doctor Josep Trueta will serve as the reference center. Each hospital would have a clinical coordinator responsible for supervising the correct adherence to the protocol and maintaining contact with the principal investigators of the study to ensure a well-coordinated implementation.

This study aims to assess the effectiveness of prophylactic physiotherapy in reducing the occurrence of lymphedema in patients diagnosed with any gynecological cancer requiring pelvic lymph node dissection as a component of their surgical treatment. A more detailed description of both interventions is provided in the section *Study variables*.

2. STUDY POPULATION

Study population of this study will be based on patients undergoing pelvic lymph node excision as part of their gynecological cancer treatment. Patients will be selected and included in the study after having met the inclusion criteria.

2.1. Inclusion criteria

- Patients over 18 years old.
- Patients diagnosed with gynecological cancer requiring pelvic lymph node excision as part of their surgical treatment.
- Patients with the capacity to comprehend and carry out the necessary rehabilitation exercises.
- Signed consent form.

2.2. Exclusion criteria

- Patients diagnosed with acute cellulitis or active deep vein thrombosis.
- Patients diagnosed with another type of cancer concurrently.
- Patients physically or mentally unable to complete de intervention program and following recommendations.

2.3. Withdrawal of patients

Patients who agree to participate in the study must commit to the established follow-up and the investigators should encourage their adherence. However, patients may exit the study under the following circumstances:

- Voluntary withdrawal by patients, who request to leave the study by communicating it to the research team.
- Patients who, at any point during the clinical trial, meet exclusion criteria after their inclusion.
- Participants who do not attend scheduled visits despite multiple attempts to contact them.
- Tumor recurrence or thrombotic events that interfere with the planned study follow-up.
- Any severe health condition preventing the patient from continuing in the study.
- Dead of the patient.

The patient's withdrawal will be documented in a record with the date.

3. SAMPLING

3.1. Sample selection

A consecutive non-probabilistic sampling method will be caried out. Thus, patients who meet the inclusion criteria and none of the exclusion criteria, should be included in the study as they become conveniently available in a consecutive way.

3.2. Sample size

The sample size was estimated using GRANMO software.

Considering the limited existing literature by the time, a Chinese clinical trial reported a 23,9% incidence of secondary LLL in patients undergoing radical hysterectomy for cervical cancer with pelvic lymphadenectomy. Among these patients 34,5% developed lymphedema in the control group, while the intervention group, who received prophylactic physiotherapy, exhibited a lower rate at 13,6% (13).

Accepting an alpha risk of 0.05 and a power of 0.8 in a two-tailed test 70 subjects are necessary in the first group and 70 in the second to find as statistically significant a proportion difference, expected to be of 0.345 in group 1 and 0.136 in group 2. A drop-out rate of 10% has been anticipated.

3.3. Estimated time of recruitment

According to the data provided by the gynecologic-oncology unit at HUJT, approximately 35 patients per year undergo pelvic lymphadenectomy as part of gynecological cancer treatment at Hospital Doctor Josep Trueta de Girona. To achieve our goal of 140 patients, considering the involvement of 4 participating hospitals, it is estimated a one- year period of recruitment.

3.4. Randomization

Patients scheduled for pelvic lymphadenectomy as part of their gynecological cancer treatment will be randomized in a 1:1 ratio into two groups:

- Control group: these patients will receive the current protocol, which is based on educational strategies.

- Intervention group: these patients will receive prophylactic decongestive physiotherapy which consist of manual lymphatic drainage, and compression bandaging. In addition to the same educational strategies as the control group.

More detailed information about the strategies in both groups are detailed in the section *Study variables*.

Randomization will be performed using computer-generated random numbers to minimize bias in the assignment of subjects into both groups.

This study adheres to the "intention-to-treat" principle. Under this principle, study participants are analyzed based on their original assignment to the treatment group, regardless of whether they adhered to or received the intended treatment. This method preserves the benefits of randomization and increases internal and external validity.

3.5. Masking techniques

This study will adopt an open label design. In this clinical trial, blinding the rehabilitation physician or the patient is unfeasible due to the different nature of the procedures: the intervention group will receive specific physical therapy not provided to the control group.

Ideally, the gynecologic oncology nurse responsible for performing the limb follow-up assessment should be blinded. However, these oncology nurses have a strong relationship with the oncology patients, providing immediate professional assistance in the event of any adverse effects or unexpected symptoms. In addition, all members of the oncology functional unit have unlimited access to the clinical history. Therefore, blinding the gynecologic oncology nurse in this clinical trial is challenging.

Despite this lack of blinding the statistician in charge of the analysis, will be unaware of whether the patient underwent rehabilitation or received only educational intervention.

4. STUDY VARIABLES

4.1. Independent variable

The independent variable is a dichotomic qualitative variable that depends on the type of intervention performed.

- Group 1 - Control group: Patients will receive health education.

The educational strategy will involve a series of instructions and information about the anatomy and functioning of the lymphatic system, the definition and risk factors of secondary lymphedema, as well as possible symptoms, signs and complications. Additionally, general advice for prevention will be provided, including avoiding scratches, bites, trauma or injury, prevention of infection, avoiding prolonged periods of standing or sitting, wearing appropriately fitting shoes, maintaining toenail and skincare, practicing weight control and following exercise routines. The exercise program adheres to the current protocol of HUJT, involving breathing exercises and lower extremity mobilization *(Annex I).*

This educational session will be explained by a rehabilitation physician post-surgery while the patient is hospitalized, along with printed materials to assist the patient in the recovery process. A follow up will be conducted to ensure comprehension of the program and to address any concern. The first follow-up will take place in-person with the rehabilitation physician one week after discharge, follow by another in-person session one-month post-surgery, and two more follow-up sessions from the rehabilitation physician will be conducted two and three months after surgery via telephone. Always explaining the possibility to advance the visit if any incident occurs.

- Group 2 - Intervention group: Patients will receive prophylactic physiotherapy for 12 weeks, complemented by the same educational strategy as the control group.

The physiotherapy protocol will consist in manual lymphatic drainage massage, used for the treatment of postoperative oedema, and a gradual scar massage. Initially administered by the rehabilitation physician while the patients are hospitalized. Patients will later be instructed to independently perform the technique at home for

45 minutes daily, following physician guidance. Additionally, to enhance patient understanding and execution, a video explanation of the manual massage will be provided.

The intervention group will also receive stretch elastic compression stockings (15-30 mmHg). Patients will be recommended to wear the compression stockings for approximately 6 hours daily, after lymphatic massage is completed.

The follow up protocol for the intervention group will be identical to the control group. Two in-person follow-up sessions will be conducted, one at one week after discharge and another one-month post-surgery. Two more follow-up sessions will occur two and three months after surgery via telephone. The final call will mark the conclusion of the rehabilitation process. There will be the option during all the process for an earlier visit if any incidents or concerns arise.

A follow-up document will be completed by the physician after every visit *(Annex VII)*.

In both cases, if lymphedema is diagnosed during the program, we will interrupt follow-up and we will initiate the appropriate treatment for secondary lymphedema, as previously detailed in the introductory section under *Treatment*.

4.2. Main dependent variable

The main dependent variable to study will be the presence or absence of lymphedema, which is a dichotomous qualitative variable.

There are several methods of assessing lymphedema (detailed in the *Diagnosis* section), but no standard recommended method has yet been established.

Based on the reliability, accessibility and easily reproducible technique by trained professionals, we have opted to use measurements of the lower extremities, following the existing literature of the Lymphedema and Gynecologic cancer (LEG) study from the Society of Gynecologic Oncology (32).

Measurements will be taken with the patient in a bipedal position or seated with both feet firmly on the ground. The heel will be flexed at a 90-degree-angle to the leg, and we

will mark 10 cm above the bottom of the patient's heel on the medial aspect of each extremity. Subsequently, the patient will be asked to rest on a stretcher with legs straight in a relaxed position. We will continue measuring 10 cm intervals progressing until the inferior aspect of the inguinal crease in the groin area *(Figure 7)*. This measurement process will be applied bilaterally. Circumference measurements will be taken twice at each marked level and verified, with a permissible variance of 1.0 cm accounted for human error.

Before the commencement of the study, the professionals responsible for these measurements will undergo specialized training.

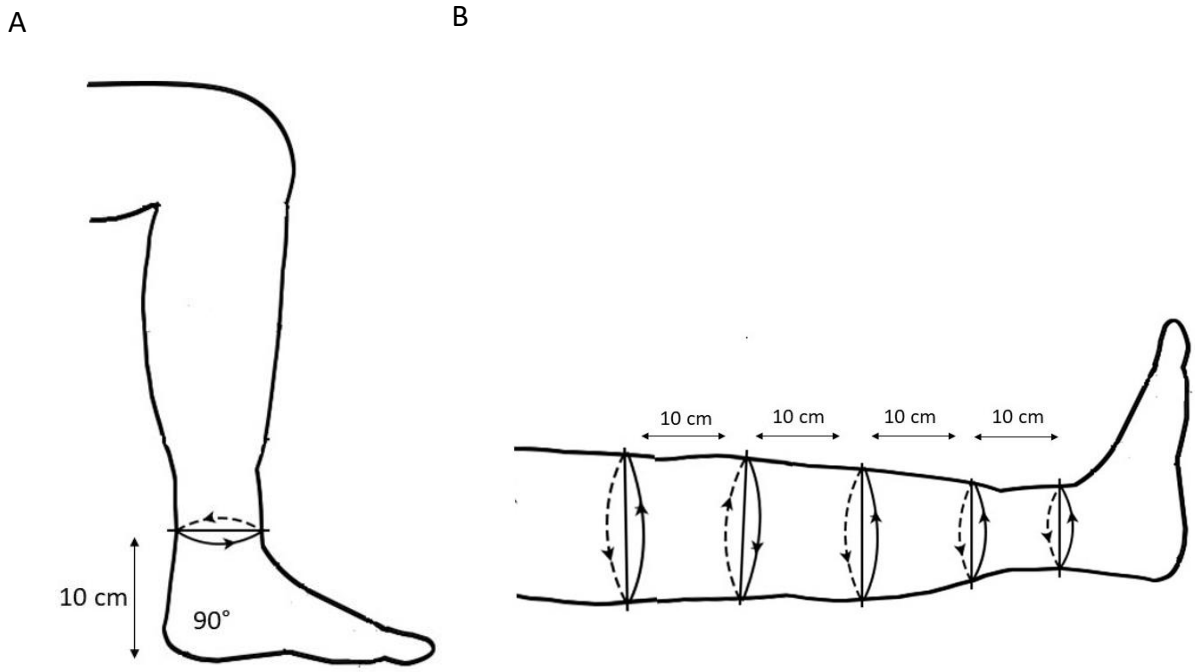


Figure 7: Limb assessment. A) Seated position; B) Supine position.

Volume will be calculated with the truncated cone formula, as described by Casley-Smith:

$$V = h\frac{(C^2 + Cc + c^2)}{12\pi}$$

V is the volume of an extremity segment, C represents the circumference at the top of the segment, c denotes the circumference at the bottom of the segment, and h is the distance between the ends.

Leg volume will be determined by summing the volumes of each truncated cone. These formulas will be integrated into a specific program, wherein the professional responsible for measurements will only need to introduce perimeter measures and the total volume result will be automatically calculated.

To diagnose lymphedema is required a **minimum change in limb volume of 5%,** compared to the unaffected limb or the baseline measurement if bilateral lymphedema.

As mentioned earlier in the *Classification* section, it is not clear whether lymphedema presents within the first 12 months or even up to 2 years after surgery. Therefore, in our clinical trial, the follow-up period for lymphedema assessment will be extended to 24 months to completely capture any potential occurrences.
A specialized nurse from the gynecologic-oncology unit will conduct in-person visits to take limb measurements at the 1st, 3rd, 6th, 12th and 24th month after surgery. This data will be used to compare limb volume evolution between the control and intervention group.
All the obtained information will be collected in the follow up document (*Annex VI*) and will be included in the study's database.

4.3. Secondary dependent variable

The secondary dependent variable in this study is the Quality of Life, a quantitative discrete variable.
When assessing cancer patients, a validated and reliable health-related QoL patient-reported outcome questionnaire is utilized, known as The Functional Assessment of Cancer Therapy (FACT) defined by the American Society of Clinical Oncology *(Annex II)* (25).

There exists a general scale, FACT-G, applicable to all types of cancer, along with disease-specific subscales such as FACT-cervix, FACT-endometrial and FACT-vulva. These subscales include additional items depending on the specific cancer characteristics. Given that our study focuses on lymphadenectomy in various gynecological cancers rather than a specific cancer type, we will employ the FACT-G scale.

This scale comprises 27-items divided into four subscales:

- Physical well-being (PWB)- consisting of 7 items.
- Functional well-being (FWB) - consisting of 7 items.
- Social well-being (SWB) - consisting of 7 items.
- Emotional well-being (EWB) - consisting of 6 items.

Participants will rate each item on a scale from 0 to 4 (0 = not at all, 1= a little bit, 2=somewhat, 3= quite a bit, 4= very much). The summation points across all subscales results in a total score of 108, with a higher outcome indicative of better QOL (18).

The same specialized nurse from the gynecologic-oncology unit that will take the limb measurements will administer this questionnaire to patients. Participants will be requested to fill out the questionnaire during the preoperative visit, 15 days prior to surgery, and it will be completed again 12- and 24-months post-surgery.

We will conduct an initial assessment of the patient's baseline QoL status 15 days prior to surgery to account for any pre-existing psychological distress and consider it in case of getting a significant altered final score. Additionally, we are also aware of the possible influence of some factors in these baseline questionnaires, such as recent oncologic diagnosis and surgery-related anxiety.

The objective is to compare QoL in both groups at 12 and 24-months post-surgery, assessing whether early physiotherapy could improve QoL for patients undergoing pelvic lymphadenectomy, thus verifying our hypothesis.

4.4. Covariates

The covariates are additional participant characteristics that will be taking into account to control possibles confounding effects, thus enhancing the validity and interpretation of the study.

- Age: it is a quantitative continuous variable measured in years.
- Body mass index (BMI): it is a quantitative continuous variable measured in kilograms/ metre^2.

- History of chronic venous insufficiency: it is a dichotomic qualitative variable, categorized as either “yes” or “no”.
- History of cardiac congestive failure, renal failure or hepatic failure: it is a dichotomic qualitative variable, categorized as either “yes” or “no”.
- Gynecological cancer type: it is a qualitative polytomous nominal variable that can be classified into endometrial, ovarian, cervical or vaginal cancer.
- Number of lymph nodes removed: it is a quantitative discrete variable.
- Lymph node invasion: it is a dichotomic qualitative variable, categorized based on the absence (N0) or presence (N1) of lymph node tumor invasion.
- Adjuvant treatments: It is a qualitative polytomous nominal variable presenting the following categories: radiotherapy, chemotherapy or hormonal therapy.
- Hospital: qualitative polytomous nominal variable.

Given that we are conducting a clinical trial, we expect that equitable randomization distributes this covariates uniformly among both groups.

Table 3: Covariates Summary

COVARIATES	DESCRIPTION	MEASUREMENT	CATEGORIES OR VALUES
Age	Quantitative continuous variable	Self-referred	Years
Body Mass Index	Quantitative continuous variable	Weight and height	kilograms/ metre^2
Chronic venous insufficiency	Dichotomic qualitative variable	Medical History	Yes or No
Cardiac/renal/hepatic failure	Dichotomic qualitative variable	Medical History	Yes or No
Gynecological cancer type	Qualitative polytomous nominal variable	Histological diagnosis	Endometrial, ovarian, cervical or vaginal cancer
Lymph nodes removed	Quantitative discrete variable	Surgical sheet	Number
Lymph node invasion	Dichotomic qualitative variable	Anatomo-pathological assessment	Absence (N0) or Presence (N1)
Adjuvant treatment	Qualitative polytomous nominal variable	Multidisciplinary comittee decision	Radiotherapy, chemotherapy or hormonal therapy
Hospital	Qualitative polytomous nominal variable		Trueta, Bellvitge, Germans Trias i Pujol, Joan XXIII

5. PROCEDURE SCHEDULE AND DATA COLLETION

This program will be implemented at the chosen hospitals and data collection will be obtained from the assessment and medical histories, then recorded in a dedicated database created for the clinical trial, which will be later analyzed.

RECRUITMENT

Patients with suggestive symptoms of malignant gynecological process will be referred to the gynecological-oncology unit at their reference hospitals. The professional team of the unit will conduct a comprehensive assessment to establish a diagnosis, including detailed clinical history, physical examination, and the necessary medical test such as

blood analysis, gynecological echography, computerized tomography, magnetic resonance, PET-TC or colposcopy. Each patient's case will be carefully reviewed by the gynecologic-oncology committee, and a personalized treatment plan will be determined based on the specific type of cancer and its stage.

If a patient requires pelvic lymph node excision as part of their surgical treatment for the gynecologic tumor and meets the inclusion criteria and none of the exclusion criteria, they will be invited to participate in the clinical trial. A comprehensive explanation of the surgical procedure, the potential postoperative consequences, such as lymphedema, and the current treatment measures will be provided. Additionally, necessary information for participation will be communicated, including the intervention program, its duration, follow-up visits and confidentiality measures.

Should the patient choose to enroll in the study, they will receive patient information sheet (*Annex III*) and will be required to sign the informed consent form (*Annex IV*). Following, patients will be randomized in the control group and the intervention group.

All personal information and clinical history, including covariates, such as previous gynecologic surgeries, type of cancer, and specific interventions, will be filled out in the respective document (*Annex V*) and will be registered in the database created for the clinical trial.

INTERVENTION

- **Pre surgery assessment**: 15 days before undergoing the pelvic surgery, patients will attend a preoperative visit in the gynecologic-oncology unit. During this visit, a specialized nurse will take the initial limb measurements and provide a QoL questionnaire to be filled out. This process is detailed in the *Main dependent variable* and *Secondary dependent variable* sections. Additionally, patients will undergo a preoperative visit with the anesthesiologist to verify their suitability for the surgery.

- **Surgical procedure**: The surgical team from the gynecologic-oncology unit, specialized in oncological procedures, will perform the surgery. The tumor excision will be adapted based on the specific characteristics of the cancer, and

necessary lymph nodes will be dissected and analyzed by an anatomic pathologist to confirm the extent of cancer. The count of dissected nodes will be documented in the patient's surgical sheet. After the surgery, patients will be hospitalized for a minimum of 2 days to facilitate proper recovery.

- **Hospitalization**: while hospitalized, the rehabilitation physician will provide all patients with consistent health education recommendations and an informative sheet. For those included in the intervention group, the rehabilitation physician will conduct manual drainage massage daily and apply a compression bandage while in the hospital. Patients will receive detailed instructions on continuing the program at home. A video will also be provided to enhance the comprehension of physiotherapy techniques. Further information about the control and the intervention group is outlined in the *Independent variable* section.

FOLLOW UP

There will be to lines of follow up:

- **Limb measurement and QOL questionnaire**: both assessments will be conducted by the same specialized nurse of the gynecologic oncology unit. Limb measurement will be taken the 1st, 3rd, 6th, 12th and 24th months after surgery and it will be properly documented *(Annex VI).* QOL questionnaire will be completed approximately 12 and 24 months after surgery *(Annex II).*

- **Physiotherapy and educational strategy control**: supervised by the same rehabilitation physician at each hospital, it will consist of a total of three assessments. There will be two in-person follow up visits, one week after discharge and one month after surgery and two more final follow up sessions, two and three months after surgery via telephone. A follow-up document will be completed by the physician to ensure the patient is following the recommendations (*Annex VII*).

All visits that coincide in time will be attempted to be scheduled on the same day to facilitate the patient's attendance.

DATA COLLECTION

The entire circuit will be implemented across all hospitals and data will be consolidated in a share database. Principal investigators by meetings with clinical coordinators of each participant hospital will ensure uniform adherence to the protocol. Furthermore, a statistician will analyze results and supervise correct randomization.

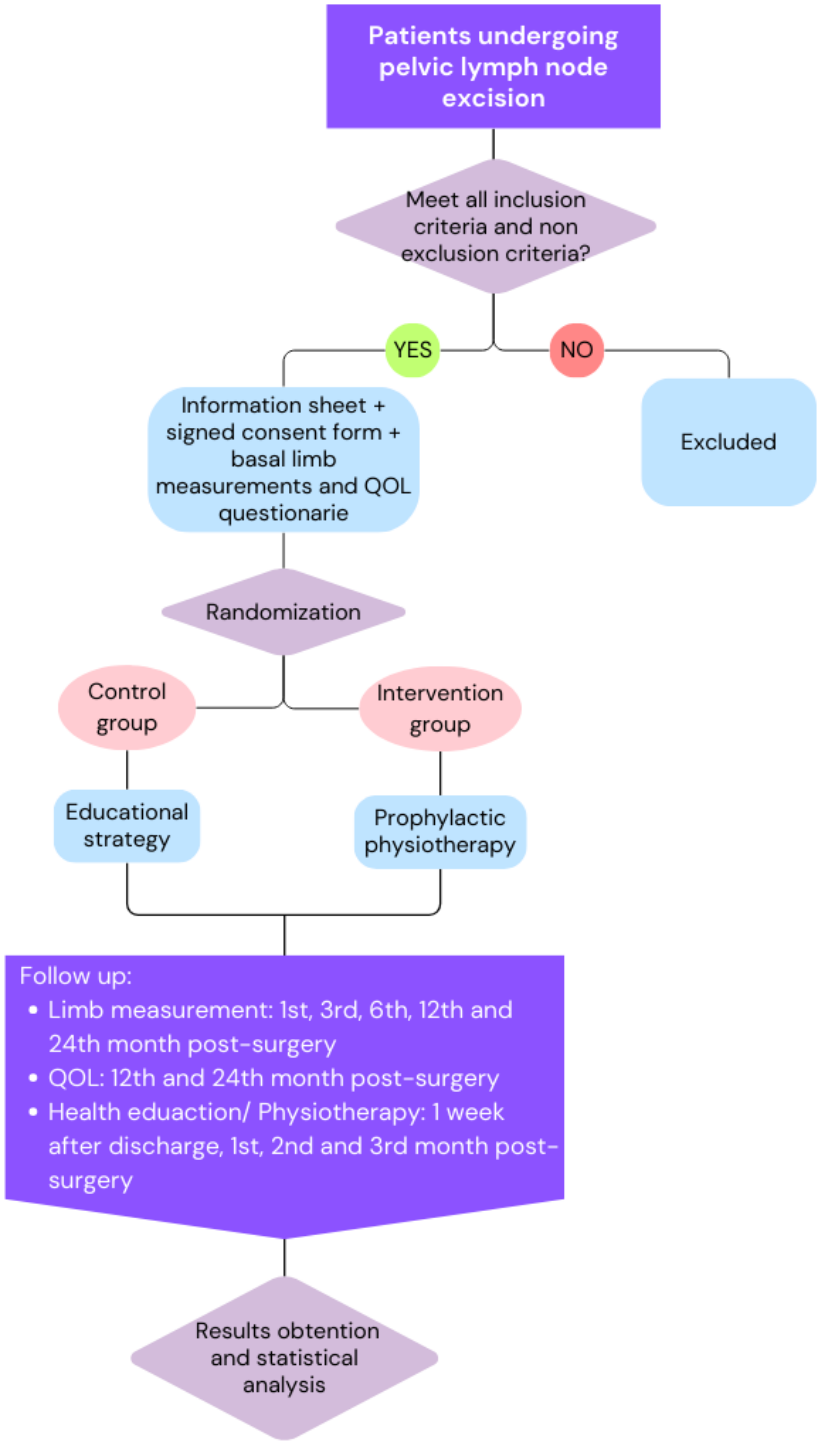


Figure 8: Data collection flow diagram

STATISTICAL ANALYSIS

The statistical analysis will be carried out by the statistician, and it will be done using the Statistical Package for Social Sciences (SPSS) software version 29.0.1.

We will establish a $p < 0,05$ value as statistically significant, defining a 95% confidence interval for all analyses.

1. DESCRIPTIVE ANALYSIS

In order to compare the characteristics of both groups, a descriptive analysis of the variables will be carried out.

The qualitative variables, including both dependent (presence or absence of lymphedema) and covariates will be summarized using proportions. For the quantitative discrete variables, both dependent (Quality of Life) and covariates, summaries will be provided using medians and interquartile range.

All these analyses will be stratified according to the intervention and the control group. Additional stratification will be done for the covariates. Age will be categorized in quartiles. BMI will be categorized in low weight (<18 kg/m^2), norm-weight (≥18 and <25 kg/m^2), overweight (≥25 and <30 kg/m^2), obese (≥30kg/m^2).

2. BIVARIATE INFERENCE

The difference in proportions of the presence/absence of lymphedema between the intervention and the control groups will be tested using the chi-square test or the Fisher's exact test (if the expected number of cases in a cell is less than 5).

For the Quality-of-Life scores, the difference in medians between the intervention and control groups will be evaluated using the Mann-Whitney's U test.

These analyses will be stratified by the covariates.

3. MULTIVARIATE ANALYSIS

While conducting a clinical trial, it may not be necessary to control for confounding. However, the possibility of interactions between confounders and, more importantly, changes in the distribution of confounders between groups during the follow-up, even

after randomization, cannot be ruled out. Therefore, we will adjust those confounders in multivariate models.

The effect of the intervention on the presence/absence of lymphedema will be assessed estimating a logistic regression controlling for the covariates.
For the Quality of Life, a Poisson regression will be estimated, adjusting for the covariates.

ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial will adhere to the ethical principles and guidelines established by The World Medical Association in the Declaration of Helsinki for *Ethical Principles for Medical Research Involving Human Subjects* (1964, last reviewed in 2013) and *The Principles of Biomedical Ethics* by Beauchamp and Childress (1979, reviewed in 2009).

- The principle of **justice** entails the fair distribution of the benefits of vital well-being, ensuring that no patient faces discrimination based on ethnicity, socioeconomic status, or any other factors that might result in unfair treatment.
- Patient's **autonomy** will be respected, with individuals participating voluntarily in the study. They will receive comprehensive information, including a written information sheet (*Annex III*) and a consent form (*Annex IV*), which will be freely signed if participants wish to do so.
- The principle of **non-maleficence** will be preserved, ensuring that no harm is intended towards the participating patients. The intervention will be performed in accredited hospitals by qualified healthcare personnel.
- The principle of **beneficence** is expected to be respected, aiming to reduce incidence rates of LLL through the application of studied rehabilitation techniques.

The protocol will undergo evaluation and approval by to the *CEIC (Comité Ético de Investigación Clínica)* of each hospital involved in the project before starting the project. The committee will verify that the protocol aligns with the ethical requirements, considering and incorporating any proposed modifications.

Privacy and confidentiality will be preserved as all patient personal information and medical history will be anonymous. Each patient will be assigned a code number, and these codes and data will be stored in a database accessible only to the research team. The information will be handled in accordance with:

- *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales"*

- *“Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relative a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos”.*

Autonomy will be respected according to the *"Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica."*
As this clinical trial consist in a medical research and does not involve the use of any drug or medical device, it will comply with the *"Ley 14/2007, de 3 de julio, de Investigación biomédica".*

All data collected will be used for the intended purpose of this study. Investigators must declare no conflict of interest, and commit to publishing all data and results transparently, including unfavorable data or events.

STUDY LIMITATIONS AND STRENGTHS

We believe that our clinical trial can provide valuable evidence regarding the positive impact of prophylactic rehabilitation in the prevention of secondary LLL. However, the study does have certain limitations.

- One limitation of our study is that we are conducting an open label study due to the inability to mask patients or professionals regarding the type of intervention received. Consequently, we will be introducing a possible **detection bias**. To mitigate this limitation, the statistician responsible for analyzing the results will be blinded.

- Another important limitation is the multicenter nature of the study, which may introduce variability between hospitals. Our main objective, assessing the incidence of lymphedema, relies on specific operator-dependent measurements of the extremity, as well as the prophylactic rehabilitation program, that must be carried out in the same way across all hospitals. **Inter-observer biases, information biases and detection biases** may occur. We will try to minimize variability by standardizing the protocol and with training sessions for all participating professionals. Before starting the clinical trial, we will do a meeting with all participating physicians, and we will explain properly all the protocol and solve any concern. In addition, we will adjust for hospital in the multivariate models.

  On the other side, one advantage of a multicenter study is that results can be generalized more easily than a single-center study.

- Since a non-probabilistic consecutive recruitment method has been employed, the whole population is not represented, potentially leading to **selection bias** and compromising external validity. To minimize this bias, participants will be randomized into both groups, ensuring an equitable distribution of patients and facilitating the extrapolation of the results.

- This study is presented as a prospective clinical trial, making patients **withdrawals** possible. We have anticipated this issue calculating a drop-out rate

of 10% in our sample size. Additionally, telephone calls will be initiated if a participant is absent from follow-up visits, encouraging them to continue participating in the study.

- Despite the extended duration and the cost of this clinical trial, implementing a preventive rehabilitation program could avoid the expenses of treating a chronic, life-long condition such as severe lymphedema.

WORKING PLAN AND CHRONOGRAM

1. RESEARCH TEAM PERSONNEL

The study will be conducted by the following personnel:

- Principal investigators (PI): Marta Mariño and Anna Taltavull will be the research team responsible for developing the protocol, supervising the intervention, obtaining conclusions and publishing the results.
- Clinical coordinators (CC): will be oncologic gynecologists assigned to each participant hospital. They are the professionals in charge of overseeing the specific procedures at each hospital and ensuring compliance with the study protocols.
- Data manager (DM): responsible for applying the randomization and creating a database.
- Independent statistician (IS): responsible for the statistical analysis of the study and creating the calculator program.
- Gynecologic-oncology specialized surgeons (GS), a gynecologic-oncology specialized nurse (GN) and a rehabilitation physician (RP).
- Collaborators: nursing staff, oncology team, gynecology team, laboratory team, pathology team, radiology team and anesthesiology team.

Meetings and training sessions will be done before starting the clinical trial to guarantee the uniformity of the study.

2. STUDY STAGES

Recruitment of patients will last 12 months, with a follow-up period of 24 months for each patient. This clinical trial is expected to last 4 years and will be divided in the following stages:

STAGE 0: ELABORATION OF THE PROTOCOL AND STUDY DESIGN (duration of 2 months)

- **Elaboration of the protocol**: the principal investigators will conduct bibliographic research and will carry out the objectives, hypothesis, and methodology of the study.

- **Selection of participating hospitals and clinical coordinators:** the research team will purpose the selected hospitals to participate in the study and will recruit the clinical coordinators for each center. All of them will receive some copies of the protocol.

STAGE 1: ETHICAL EVALUATION OF THE PROTOCOL (duration of 3 months)

- **Presentation to the CEIC**: before initiating the study, the protocol must be accepted by Ethics Committee of Clinical Investigation (CEIC) of each hospital. Considering and incorporating any proposed modifications.

STAGE 2: PREPARATION, COORDINATION AND TRAINING (duration of 2 months)

- **General meetings**: a meeting with the investigators and all clinicians participating in the study will be held at HUJT to explain the protocol, the chronogram, and data collection methods. Clinical coordinators and principal investigators will meet every 3 months to ensure the correct implementation of the protocol.
- **Creation of the database and the calculator program**: the data manager will establish the database. The statistician will develop a program to automatically calculate limb volume using mathematical formulas.
- **Training sessions**: physicians involved in the study will undergo training sessions. Nurses responsible for assessing lower extremity volume will participate in a course on lymphedema, where the measurement method will be standardized. Rehabilitation physicians will be trained to familiarize with lymphedema and the physical intervention they are tasked with. All collaborators will be instructed on how to collect and register information in the database.

STAGE 3: RECRUITMENT, INTERVENTION AND DATA COLLECTION (duration of 36 months)

- **Patients recruitment**: patients will be recruited following a non-probabilistic consecutive method. It will be mandatory to meet the inclusion criteria and none of the exclusion criteria. Individuals participating will be required to sign the consent form and the information sheet. The patient recruitment period is anticipated to last 12 months.

- **Intervention and follow-up:** patients participating in the study will undergo measurements of limb perimeter and complete a QOL questionnaire. Then, they will be randomly assigned to either the control or intervention group. Each group will receive the respective intervention for 12 weeks and a 24 months follow-up by limb and QOL assessment will be conducted.
- **Data collection:** the rehabilitation physician and the responsible nurse will record data in the designated follow-up sheet (*Annex VI*) and (*Annex VII*). Clinical coordinators will supervise this information, and they will meet the principal investigators every three months to evaluate the correct application of the protocol.

STAGE 4: DATA ANALYSIS AND INTERPRETATION OF RESULTS (duration of 3 months)

- **Statistical analysis**: the analysis of the information existent in the database will be realized by the independent statistician.
- **Interpretation and conclusion**: data will be discussed and interpretated by the principal investigators trying to arrive to a conclusion.

STAGE 5: EDITION AND PUBLICATION (duration of 2 months)

- **Paper redaction**: the principal investigators will write an article with a detailed explanation of the process, the results and the conclusions obtained.
- **Publication and dissemination:** The paper will be published and presented at the SCOG ("Societat Catalana d'Obstetrícia I Ginecologia") and SEGO ("Sociedad Española de Ginecología y Obstetricia").

3. CHRONOGRAM

Table 4: Chronogram. PI, principal investigators; CEIC, Comité de Ética de Investigación Clínica; CC, clinical coordinators; GN, gynecologic-oncology nurse; GS, gynecologic-oncology surgeons, RP, rehabilitation physician; DM, data manager; IS, independent statistician; M1, M2, M3, M4…,M12, refers to months.

STAGE AND ACTIVITIES	STAFF	YEARS AND MONTHS																	
		1st YEAR												2nd YEAR		3rd YEAR	4th YEAR		
		M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M 1-M 7	M 8-M 12	M 1-M 12	M 1-M 7	M8-M10	M11-M12
STAGE 0: ELABORATION OF THE PROTOCOL AND STUDY DESIGN																			
Bibliographic research	PI																		
Protocol elaboration	PI																		
Contact participating hospitals and physicians	PI																		
STAGE 1: ETHICAL EVALUATION OF THE PROTOCOL																			
Ethical evaluation and approval	CEIC																		
STAGE 2: : PREPARATION, COORDINATION AND TRAINING																			
General meeting	CC, GN, GS, PI, RP																		
Creation of databases and calculation programs	DM, IS																		
Training sessions	GN, RP																		
STAGE 3: RECRUITMENT, INTERVENTION AND DATA COLLECTION																			
Patient recruitment	CC, GS																		
Intervention	CC, GN, RP																		
Follow-up	CC, GN, RP																		
Data collection	CC, GN, RP																		
STAGE 4: DATA ANALYSIS AND INTERPRETATION OF RESULTS																			
Statistical analysis	IS																		
Interpretation of results and conclusion	PI, CC																		
STAGE 5: EDITION AND PUBLICATION																			
Paper redaction	PI																		
Publication and dissemination	PI																		

BUDGET

Table 5: Budget.

EXPENSES	UNIT COST	UNIT	TOTAL
PERSONNEL AND TRAINING			
Data manager	40€/h	40h	1.600 €
Hired statistician	40€/h	40h	1.600 €
Rehabilitation trainer	60€/h	10h	600 €
Lymphedema course	50€/attendee	4 nurses	200 €
MEETINGS			
Initial informative meeting (travel and food cost)	100€ / attendee	12 persons	1.200 €
MATERIAL			
Information sheet and consent document impression	0,03€/page	6 pages x 140 patients	840 €
QoL questionnaire	0,03€/page	2 pages x 140 patients x 3 times	25,20 €
Exercise recommendations	0,03€/page	3 pages x 140 patients	12,60 €
Tape measure	7€/unit	4 hospitals	28 €
Compressive stockings	20€/unit	140 patients	2.800 €
PUBLISHING			
English correction	500€/article	1	500 €
Article publication and open acess	1.500€/article	1	1.500 €
DISSEMINATION COST			
SOG (inscriptions, travels and acommodations)	400€/attendee	2 attendees	800 €
SEGO (inscriptions, travels and acommodations)	500€/attendee	2 attendees	1.100 €
		TOTAL	**12.805,80 €**

The principal investigators, clinical coordinators and medical personnel are employees of each participant hospital, so there will be no additional cost.

Procedures involved in cancer treatment, such as diagnostic tools, surgery and adjuvant treatment, have not been considered as an internal cost, as they will be carried out as necessary for all patients, independent of our intervention.
Regarding team meetings, there will be an initial general meeting at the HUJT, attended by the principal investigators, involved nurses, rehabilitation physicians and gynecologic surgeons, who represent the clinical coordinators of each hospital. The following meetings will be conducted via videoconference between the investigators and de clinical coordinators.

For this clinical trial no insurance will be contracted, as no high-risk interventions are performed on the patients.

FEASIBILITY

We find this study to be feasible for different reasons.

Firstly, the clinical trial will be conducted in four Catalan hospitals, all of which are members of the ICO. This ensures that each hospital has the necessary resources and healthcare teams to perform the study. Within each center, there is a specialized gynecologic oncology functional unit that performs a multidisciplinary approach between gynecologic surgeons, nurses, medical oncologists, radiotherapists and radiologists. Our goal is to integrate rehabilitation physicians into this team to improve cancer care for oncology patients. Moreover, we plan to conduct training session to uniform the interventions and improve internal validation.

The prophylactic rehabilitation program is a safe and easily replicable therapy, that most patients can perform at home. The program aims to improve the sequelae of cancer treatment and the quality of life with practical and feasible procedures.

Furthermore, the number of patients needed to conduct the study is 140, and given it is a multicenter study, we estimate a recruitment period of 1 year and a follow-up period of 2 years. Requiring a total duration of 4 years, which is both reasonable and feasible.

Furthermore, the costs of the clinical trial are low and affordable, as there is no need for numerous additional materials and the study follows a person-dependent procedure.

CLINICAL AND HEALTCARE IMPACT

Nowadays, advancements in diagnostic and therapeutic technologies for gynecologic cancers have relevant elevated survival rates. However, the morbidity associated with this type of cancer and its treatment plays an important impact on the quality of life for oncology survivors. Secondary lymphedema is a significant chronic sequela derived from oncological treatment procedures. This chronic condition severely affects emotional and physical well-being of patients, leading to important limitations on mobility and causing physical discomfort.

Changes have been made to try to reduce the risk of LLL with sentinel lymph node biopsy. However, for certain patients, pelvic lymphadenectomy remains the only viable alternative as part of the surgical treatment, thereby exposing them to an increased risk of lymphedema development. In this context, there is a lack of assessment of prophylactic measures to prevent secondary lymphedema.

If the results obtained in our clinical trial support the efficacy of prophylactic rehabilitation in preventing LLL following gynecologic cancer treatment, the incidence of lymphedema would be significantly reduced. By intervening before its onset, we aim to prevent the establishment of a long-term and challenging sequelae. This proactive approach not only deals with the high risk of its occurrence, but also improves the quality of life of oncology survivors.

BIBLIOGRAPHY

1. Sung H, Ferlay J, Siegel R, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.

2. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, editors. Oncología Ginecológica. In: Williams Ginecología. 3rd ed. Ciudad de Mexico: McGraw-Hill Global Education; 2017.

3. Bakkum-Gamez JN. Lymphadenectomy in the Management of Gynecologic Cancer. Clin Obstet Gynecol. 2019 Dec;62(4):749–55.

4. Hall ME, Hall JE, editors. Microcirculación y sistema linfático: intercambio de líquido capilar, líquido intersticial y flujo linfático. In: Guyton y Hall Tratado de fisiología médica. 14th ed. Barcelona: Elsevier; 2021. p. 193–204.

5. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. J Am Acad Dermatol. 2017 Dec;77(6):1009–20.

6. Mehrara B. Clinical features and diagnosis of peripheral lymphedema. In: UpToDate [Internet]. Alphen aan den Rijn: Wolters Kluwer; 2023 [cited 2023 Dec 2]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-peripheral-lymphedema

7. Wang T, Xu Y, Shao W, Wang C. Sentinel Lymph Node Mapping: Current Applications and Future Perspectives in Gynecology Malignant Tumors. Front Med. 2022 Jun 29;9:922585.

8. The diagnosis and treatment of peripheral lymphedema: 2020 consensous document of the International Society of Lymphology. Lymphology. 2020 Jun 2;53(1):3–19.

9. Creager M, Loscalzo J. Enfermedad venosa crónica y linfedema. In: Kasper, Fauci, Hauser, Longo, Jameson, Loscalzo, editors. Harrison Principios de Medicina Interna. 19th ed. México D.F.: McGraw-Hill Interamericana Editores; 2018. p. 1650–5.

10. Greene AK, Goss JA. Diagnosis and Staging of Lymphedema. Semin Plast Surg. 2018 Feb;32(1):12–6.

11. Beesley V, Janda M, Eakin E, Obermair A, Battistutta D. Lymphedema after gynecological cancer treatment. Cancer. 2007;109(12):2607–14.

12. Rebegea LF, Stoleriu G, Manolache N, Serban C, Craescu M, Lupu MN, et al. Associated risk factors of lower limb lymphedema after treatment of cervical and endometrial cancer. Exp Ther Med. 2020 Dec;20(6):181.

13. Wang X, Ding Y, Cai HY, You J, Fan FQ, Cai ZF, et al. Effectiveness of modified complex decongestive physiotherapy for preventing lower extremity lymphedema after

radical surgery for cervical cancer: a randomized controlled trial. Int J Gynecol Cancer. 2020 Jun;30(6):757–63.

14. Hayes SC, Janda M, Ward LC, Reul-Hirche H, Steele ML, Carter J, et al. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. Gynecol Oncol. 2017 Sep;146(3):623–9.

15. Wisner KPA, Ahmad S, Holloway RW. Indications and techniques for robotic pelvic and para-aortic lymphadenectomy with sentinel lymph node mapping in gynecologic oncology. Best Pract Res Clin Obstet Gynaecol. 2017 Nov 1;45:83–93.

16. Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer. Cancer. 2010;116(22):5138–49.

17. Lozano F. Linfedema. In: Rozman C, Lopez FC, editors. Farreras-Rozman Medicina Interna. 19th ed. Barcelona: Elsevier; 2020. p. 617–20.

18. Carter J, Huang HQ, Armer J, Carlson JW, Lockwood S, Nolte S, et al. GOG 244 - The Lymphedema and Gynecologic cancer (LeG) study: The impact of lower-extremity lymphedema on quality of life, psychological adjustment, physical disability, and function. Gynecol Oncol. 2021 Jan;160(1):244–51.

19. Dessources K, Aviki E, Leitao MM. Lower extremity lymphedema in patients with gynecologic malignancies. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2020 Feb;30(2):252–60.

20. Common Terminology Criteria for Adverse Events (CTCAE). Washington DC: U.S. Department of Health and Human Services; 2017.

21. Biglia N, Zanfagnin V, Daniele A, Robba E, Bounous V. Lower Body Lymphedema in Patients with Gynecologic Cancer. Anticancer Res. 2017 Jul 20;37(8):4005–15.

22. Lymphoedema Framework. Best Practice for the Management of Lymphoedema. International consensus. London: Medical Education Partnership; 2006.

23. Cuello-Villaverde E, Forner-Cordero I, Forner-Cordero A. Linfedema: métodos de medición y criterios diagnósticos. Rehabilitación. 2010 Oct;44:21–8.

24. Carter J, Raviv L, Appollo K, Baser RE, Iasonos A, Barakat RR. A Pilot Study Using the Gynecologic Cancer Lymphedema Questionnaire (GCLQ) as a Clinical Care Tool to Identify Lower Extremity Lymphedema in Gynecologic Cancer Survivors. Gynecol Oncol. 2010 May;117(2):317–23.

25. Cella D, Tulsky D, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;volume 11(3):570–9.

26. Maldonado AA, Ramos E, García-Alonso P, Jover JJ, Holguín P, Fernández-Cañamaque JL, et al. Abordaje multidisciplinar en el paciente con linfedema: de la rehabilitación a la microcirugía. Rehabilitación. 2022 Apr 1;56(2):150–8.

27. Lasinski BB, Thrift KM, Squire D, Austin MK, Smith KM, Wanchai A, et al. A Systematic Review of the Evidence for Complete Decongestive Therapy in the Treatment of Lymphedema From 2004 to 2011. PM&R. 2012;4(8):580–601.

28. Torres Lacomba M, Yuste Sánchez MJ, Zapico Goñi Á, Prieto Merino D, Mayoral del Moral O, Cerezo Téllez E, et al. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. The BMJ. 2010 Jan 12;340:b5396.

29. Spittle A. Critically appraised paper: For women at risk of breast cancer-related lymphoedema, prophylactic compression sleeve usage reduces and delays arm swelling. J Physiother. 2022 Jul 1;68(3):205.

30. Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM. Physiotherapy After Breast Cancer Surgery: Results of a Randomised Controlled Study to Minimise Lymphoedema. Breast Cancer Res Treat. 2002 Sep;75(1):51–64.

31. Soran A, Ozmen T, McGuire KP, Diego EJ, McAuliffe PF, Bonaventura M, et al. The Importance of Detection of Subclinical Lymphedema for the Prevention of Breast Cancer-Related Clinical Lymphedema after Axillary Lymph Node Dissection; A Prospective Observational Study. Lymphat Res Biol. 2014 Dec;12(4):289–94.

32. Carlson JW, Kauderer J, Hutson A, Carter J, Armer J, Lockwood S, et al. GOG 244- The Lymphedema and Gynecologic cancer (LEG) study: incidence and risk factors in newly diagnosed patients. Gynecol Oncol. 2020 Feb;156(2):467–74.

ANNEXES

1. ANNEX I. LYMPHEDEMA PREVENTION EXERCISES

EXERCICIS PER PREVENIR EL LIMFEDEMA DE MEMBRES INFERIORS

Servei de Rehabilitació

Què es un limfedema

Es tracta d'una malaltia de curs crònic que es manifesta per l'edema (augment de líquid) en una extremitat superior o inferior per obstrucció de les vies limfàtiques.

Les causes són múltiples. Entre les més freqüents són les infeccions i l'excisió quirúrgica dels vasos limfàtics (per exemple després d'una resecció d'un tumor).

Un cop s'estableix el limfedema, no existeix tractament curatiu, i per tant els objectius es centren a disminuir l'edema, reduir la simptomatologia i evitar la seva progressió i possibles complicacions.

Per aquest motiu li recomanem realitzar els següents exercicis 2-3 vegades al dia, a poc a poc, amb una durada màxima de 30 minuts. És recomanable fer-los amb la peça de contenció.

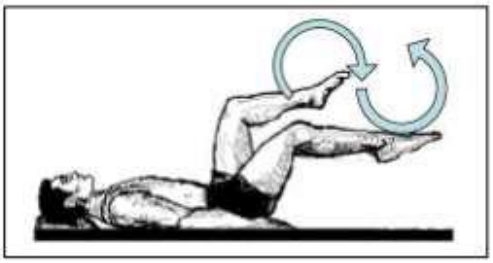
1er. Exercicis respiratoris. El/la pacient ha d'estar tombat/da, amb els braços avall i recolzats damunt del llit.

- Inspiració: Agafar tot l'aire que es pugui pel nas, aixecant l'abdomen
- Espiració: Anar expulsant l'aire molt lentament per la boca, afluixant l'abdomen.

Repetir-ho tres vegades.

2on. Exercicis de membres inferiors: Realitzar entre 5 i 20 repeticions de cadascun. És recomanable fer-los amb ambdós membres, no només amb l'afectat.

Exercici estirat



Fer la bicicleta:
1. Panxa enlaire, pedalar endavant
2. Panxa enlaire, pedalar enrere
3. De costat, pedalar cap als costats

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Girona

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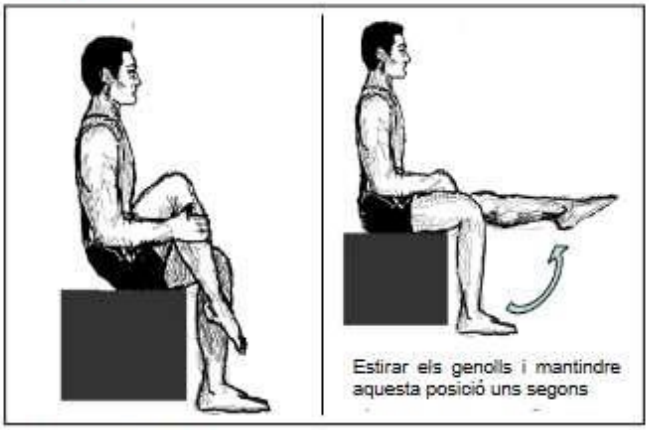
Exercicis per prevenir el limfedema de membres inferiors

Servei de Rehabilitació

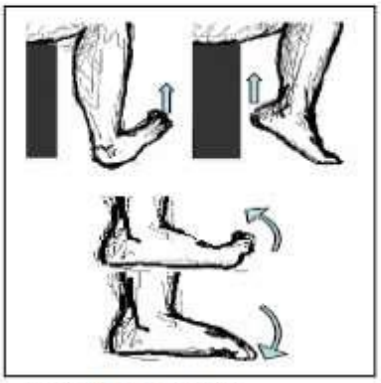
Exercicis assentat



Acostar els genolls al cos.

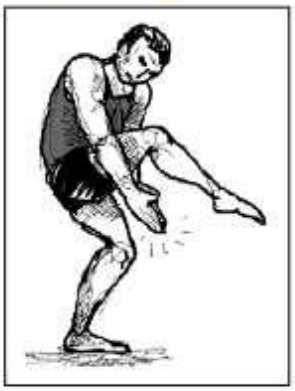
Estirar els genolls i mantindre aquesta posició uns segons

Els turmells cap enlaire i cap avall

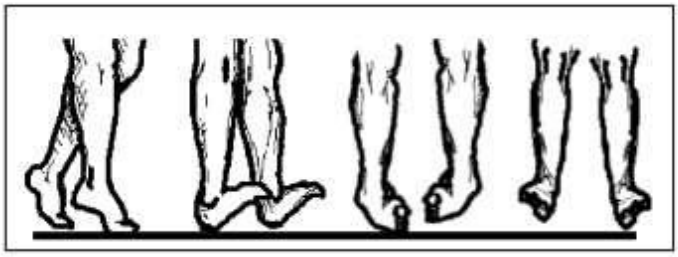


Flexionar i estirar els dits

Exercicis dempeus



Caminar aixecant el genoll i picant de mans per sota fent la cigonya



1. Caminar normal, marcant les puntes i els talons
2. Caminar de puntetes
3. Caminar de talons
4. Caminar amb la part externa del peu
5. Caminar amb la part interna del peu

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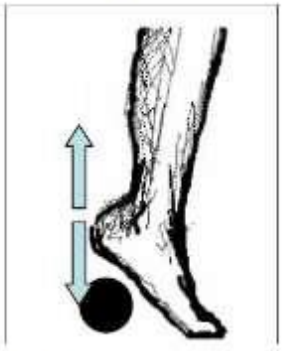
Exercicis per prevenir el limfedema de membres inferiors

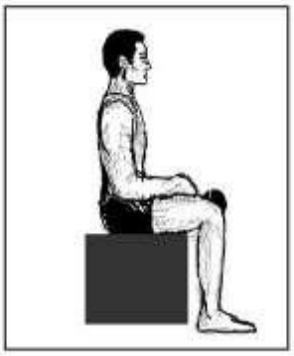
Servei de Rehabilitació

Exercicis amb una pilota d'escuma



Aixafar la pilota amb el taló, amb la punta i amb tot el peu

Dempeus, dibuixar una rodona amb la cama dreta i la cama esquerra al voltant de la pilota



Assentat, prémer la pilota amb els genolls

3r. Repetir els exercicis respiratoris: El/la pacient estarà tombat/da, amb els braços avall i recolzats damunt del llit.

- Inspiració: Agafar tot l'aire que es pugui pel nas, aixecant l'abdomen
- Espiració: Anar expulsant l'aire molt lentament per la boca, afluixant l'abdomen.

Repetir-ho tres vegades.

2. ANNEX II. QoL QUESTIONNAIRE

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

3. ANNEX III. PARTICIPANT INFORMATION SHEET

DOCUMENTO DE INFORMACIÓN PARA LA PACIENTE

Nombre del estudio: Investigación sobre la eficacia de la rehabilitación profiláctica en la prevención de linfedema de los miembros inferiores en pacientes que han sido sometidas a una linfadenectomía pélvica como parte de tratamiento para el cáncer ginecológico.

Centro asistencial:

Investigador principal: Marta Mariño Pérez

Bienvenida,

Nos dirigimos a usted para informarle que actualmente se está realizando un estudio de investigación en el cual nos gustaría solicitar su participación. Este estudio se lleva a cabo en el Servicio de Obstetricia y Ginecología, en la Unidad Funcional de Ginecología Oncológica, de 4 hospitales de Cataluña.

El estudio ha sido aprobado por el Comité de Ética e Investigación Clínica de cada uno de los hospitales participantes en el proyecto. La aprobación se ha realizado de acuerdo con la legislación vigente y respetando los principios enunciados en la Declaración de Helsinki y en las guías de buena práctica clínica.

Nuestra intención es explicarle detalladamente el motivo de la realización de este estudio y en que consiste su participación, con el fin de que pueda decidir libremente si desea formar parte. En esta hoja informativa se recoge toda la información necesaria sobre la participación en el estudio. Le rogamos que la lea con atención y si le surge cualquier consulta, no dude en ponerse en contacto con el equipo investigador.

PARTICIPACIÓN EN EL ESTUDIO

La participación en este estudio es completamente voluntaria, y puede decidir no participar o cambiar su decisión y revocar el consentimiento en cualquier momento sin necesidad de explicación comunicándoselo al equipo investigador.

No participar o revocar el consentimiento, no afectará ni modificará de ninguna manera el plan asistencial que ha de recibir ni la relación con los profesionales sanitarios.

DESCRIPCIÓN DEL ESTUDIO

Objetivo y finalidad del estudio

Este estudio tiene como principal objetivo investigar la eficacia de la rehabilitación profiláctica en mujeres sometidas a una linfadenectomía pélvica (escisión de los ganglios linfáticos pélvicos) como parte del tratamiento oncológico por algún cáncer ginecológico (cáncer de ovario, cáncer de endometrio, cáncer de cérvix o cáncer vaginal).

Una de las secuelas más importantes derivadas del tratamiento quirúrgico es la aparición de linfedema de miembros inferiores. Este trastorno, crónico y debilitante, se caracteriza por la inflamación y el aumento de volumen en las extremidades, teniendo un impacto directo en la funcionalidad y en la calidad de vida de las pacientes.

Actualmente, el manejo tras dicha intervención quirúrgica es una educación sanitaria con recomendaciones para disminuir el riesgo de padecer linfedema. Estas recomendaciones no llegan a ser suficientes y hasta un 24% de las pacientes intervenidas desarrollan esta patología. Nuestro objetivo con este ensayo clínico es establecer un protocolo de rehabilitación profiláctica postquirúrgica, con el fin de evitar la aparición de linfedema y mejorar la calidad de vida de las pacientes.

Metodología e intervención

En este estudio participarán un total de 140 pacientes que serán distribuidas de manera aleatoria en dos grupos:

- Grupo intervención: realizará la rehabilitación postquirúrgica, bajo la supervisión de un médico rehabilitador, junto con la educación sanitaria correspondiente.
- Grupo control: recibirá el protocolo actual que incluye únicamente la educación sanitaria.

A todas las pacientes se les realizará un seguimiento clínico durante 24 meses. Las visitas con el médico rehabilitador se realizarán los tres primeros meses, incluyendo dos visitas presenciales y dos telefónicas. Las visitas con la enfermera de la unidad funcional

encargada de las mediciones de las extremidades se realizarán de manera presencial el primer mes postoperatorio, y posteriormente, en los meses tercero, sexto, duodécimo y vigésimo cuarto.

Paralelamente, las pacientes seguirán el protocolo convencional de seguimiento por parte de los servicios de ginecología y oncología. Además, teniendo en cuenta la posible necesidad de terapias adyuvantes, este estudio contempla la opción de que las pacientes las reciban, siempre y cuando el comité multidisciplinario de tumores lo determine como apropiado.

BENEFICIOS Y RIESGOS DEL ESTUDIO

El principal beneficio que se espera de este estudio es disminuir la incidencia de linfedema en mujeres sometidas a linfadenectomía pélvica como tratamiento de su cáncer ginecológico y, por ende, mejorar su calidad de vida.

No se anticipan riesgos significativos para las pacientes, ya que la rehabilitación preventiva empleada en el grupo intervención es la misma técnica terapéutica utilizada en caso de diagnóstico de linfedema. Esta técnica, no invasiva, es fácilmente replicable, para llevar a cabo por la paciente en casa, y ha demostrado ofrecer resultados positivos como terapia.

PROTECCIÓN DE DATOS PERSONALES Y CONFIDENCIALIDAD

La confidencialidad de la información del paciente estará resguardada, y los datos recopilados en este estudio se gestionarán conforme a la Ley Orgánica de Protección de Datos de Carácter Personal y Garantía de los Derechos Digitales (3/2018) y al Reglamento 2016/679 del Parlamento y del Consejo Europeo.

Los datos recopilados serán tratados de manera confidencial, sin posibilidad de acceso por parte de terceros, y únicamente se emplearán con fines de investigación.

Los datos e información personal se asociarán a un código cuyo conocimiento estará exclusivamente en manos del equipo investigador, con el fin de mantener la máxima confidencialidad posible.

DIFUSIÓN DE RESULTADOS

Una vez finalizado el estudio los resultados y las conclusiones obtenidas se divulgarán en revistas científicas y se presentarán en congresos médicos, con el fin de que otros centros y pacientes puedan beneficiarse de dichos hallazgos. Durante el proceso, se garantiza el tratamiento anónimo de los datos de carácter personal, respetando la confidencialidad de la información de la paciente.

COMPENSACIÓN ECONÓMICA

El equipo de investigación responsable de este ensayo clínico no obtiene ningún beneficio económico.

Como paciente, la participación en el estudio es totalmente voluntaria y, por tanto, no se obtendrá ninguna compensación económica.

Si está de acuerdo con este estudio, se le entregará una copia de este documento y el Consentimiento Informado, que deberá firmar para aceptar su participación.

CONTACTO

Ante cualquier duda o pregunta sobre el estudio, estamos a su disposición. Puede ponerse en contacto con el equipo investigador de las siguientes maneras:

- Teléfono:……
- Correo electrónico:……

Gracias por su atención.

4. ANNEX IV. INFORMED CONSENT FORM

CONSENTIMIENTO INFORMADO

Nombre del estudio: Investigación sobre la eficacia de la rehabilitación profiláctica en la prevención de linfedema de los miembros inferiores en pacientes que han sido sometidas a una linfadenectomía pélvica como parte de tratamiento para el cáncer ginecológico.

Centro asistencial:

Investigador principal: Marta Mariño Pérez

Declaración de la paciente:

Yo, _____,

con DNI_____, declaro haber revisado el material informativo acerca de la investigación y haber recibido la suficiente información por parte del miembro encargado del equipo de investigación.

Entiendo que la participación es totalmente voluntaria y no remunerada, y que tengo la opción de cambiar de opinión en cualquier momento, retirando mi consentimiento informado sin que eso afecte a mi atención sanitaria.

Concedo autorización para que el equipo de investigación utilice los datos de mi historial clínico con fines relacionados al estudio, garantizando la confidencialidad de dicha información.

Asimismo, he tenido la oportunidad de plantear todas las preguntas pertinentes y mis inquietudes respecto al estudio han sido resueltas.

Certifico haber recibido una copia del Documento de Información para la Paciente y una copia de este Consentimiento Informado.

Firma de la participante: Firma del investigador:

Fecha: ___ /___ /___ Fecha: ___ /___ /___

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____,

Con DNI _____, retiro mi consentimiento para participar en el estudio previamente mencionado.

Firma de la participante: Firma del investigador:

Fecha: ___ /___ /___ Fecha: ___ /___ /___

5. ANNEX V. DATA COLLECTION FORM

DOCUMENTO DE RECOGIDA DE DATOS

Nombre del estudio: Investigación sobre la eficacia de la rehabilitación profiláctica en la prevención de linfedema de los miembros inferiores en pacientes que han sido sometidas a una linfadenectomía pélvica como parte de tratamiento para el cáncer ginecológico.

Fecha de recogida de datos: ___ / ___ / ___

Centro sanitario:

☐ Hospital Universitari Doctor Josep Trueta, Girona

☐ Hospital Universitari de Bellvitge, Hospitalet de Llobregat

☐ Hospital Universitari Germans Trias i Pujol, Badalona

☐ Hospital Universitari Joan XXIII, Tarragona

Responsable de recoger información: _____

Código de la paciente: _____

Datos a recopilar:

- Edad: _____ años
- IMC: _____ kg/m^2
- Historia de insuficiencia venosa crónica:
  - ☐ Si ☐ No
- Historia de insuficiencia cardíaca, insuficiencia renal o insuficiencia hepática:
  - ☐ Si ☐ No

    En caso afirmativo especificar patología: _____
- Tipo de cáncer ginecológico: _____
- Número de nódulos linfáticos extraídos: _____
- Afectación linfática mediante estudio anatomopatológico:
  - ☐ Si (N1) ☐ No (N0)
- Tratamiento adyuvante:
  - ☐ Si ☐ No

    En caso afirmativo especificar tratamiento: _____

6. ANNEX VI. LIMB MEASSUREMENT FOLLOW-UP DOCUMENT

SEGUIMIENTO DE LA MEDICIÓN DE LAS EXTREMIDADES

Nombre del estudio: Investigación sobre la eficacia de la rehabilitación profiláctica en la prevención de linfedema de los miembros inferiores en pacientes que han sido sometidas a una linfadenectomía pélvica como parte de tratamiento para el cáncer ginecológico.

Fecha de recogida de datos: ___ / ___ / ___

Centro sanitario:

- ☐ Hospital Universitari Doctor Josep Trueta, Girona
- ☐ Hospital Universitari de Bellvitge, Hospitalet de Llobregat
- ☐ Hospital Universitari Germans Trias i Pujol, Badalona
- ☐ Hospital Universitari Joan XXIII, Tarragona

Responsable de recoger información: _____

Código de la paciente: _____

Visita:

- ☐ Preoperatoria
- ☐ 1 mes postcirugía
- ☐ 3 meses postcirugía
- ☐ 6 meses postcirugía
- ☐ 12 meses postcirugía
- ☐ 24 meses postcirugía

Intervención:

- ☐ Grupo Intervención (rehabilitación)
- ☐ Grupo Control

Medición del volumen (cálculo mediante programa informático):

- Extremidad inferior derecha: _____
- Extremidad inferior izquierda: _____

7. ANNEX VII. REHABILITATION FOLLOW-UP DOCUMENT

SEGUIMIENTO DEL PROGRAMA DE REHABILITACIÓN

Nombre del estudio: Investigación sobre la eficacia de la rehabilitación profiláctica en la prevención de linfedema de los miembros inferiores en pacientes que han sido sometidas a una linfadenectomía pélvica como parte de tratamiento para el cáncer ginecológico.

Fecha de recogida de datos: ___ / ___ / ___

Centro sanitario:

☐ Hospital Universitari Doctor Josep Trueta, Girona

☐ Hospital Universitari de Bellvitge, Hospitalet de Llobregat

☐ Hospital Universitari Germans Trias i Pujol, Badalona

☐ Hospital Universitari Joan XXIII, Tarragona

Responsable de recoger información: _____

Código de la paciente: _____

Visita:

☐ 1 mes postcirugía

☐ 2 meses postcirugía

☐ 3 meses postcirugía

Intervención:

☐ Grupo Intervención (rehabilitación)

☐ Grupo Control

Datos a recopilar:

- ¿Realiza los ejercicios de movilidad diariamente?
  - ☐ Sí ☐ No

En caso de pertenecer al grupo intervención:

- ¿Realiza el masaje de drenaje linfático diariamente?
  - ☐ Sí ☐ No
- ¿Utiliza las medias compresivas diariamente durante 6h?
  - ☐ Sí ☐ No