Estefanía Boza Moreno

Ana Casañ Alufre

Anna Pau Charles

"Prospective longitudinal observational study in patients with hand osteoarthritis (OA) treated with low-dose radiotherapy (LDRT): anti-inflammatory molecular effects, clinical outcomes, and their correlation."

Bachelor's Thesis

Supervised by Dr. Meritxell Arenas Prat

Co-supervisors: Marta Canela and Raquel García

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2. ABSTRACT

Introduction: Hand OA is a degenerative disease characterized by cartilage damage and local inflammatory processes. Preclinical studies have demonstrated the molecular anti-inflammatory effect of low-dose radiotherapy (LDRT). Elevated levels of serum inflammatory mediators have been reported in patients with OA. Moreover, studies have suggested clinical improvement of OA after LDRT, making it a potentially effective therapeutic alternative.

Objectives and Hypotheses: The aim of the study is to assess the correlation between clinical improvement and changes in TNF-α, IL-1β, and CCL2 (pro-inflammatory profile), PON1 (anti-inflammatory activity), and TGF-β (dual role in inflammation) following LDRT in hand OA. The hypothesis was that LDRT would improve clinical outcomes, reduce levels of TNF-α, IL-1β, CCL2, and increase PON1 and TGF-β1 levels.

Materials and Methods: The initial sample included 31 patients recruited between November 2020 and November 2024. However, the final sample comprised 12 patients diagnosed with hand OA (83.3% women; median age: 71 years), all recruited between February and November 2024, according to eligibility criteria. Blood samples were collected, and the Cochin questionnaire was administered before and one month after treatment. LDRT was applied in six sessions of 0.5 Gy on alternate days (total dose: 3 Gy; up to 6 Gy in case of re-irradiation). Pain was assessed one month later and classified into four categories. TNF-α and IL-1β were analyzed using ELISA. CCL2, TGF-β, and PON1 were not measured due to technical limitations. Data were analyzed using IBM SPSS Statistics 29.

Results: Blood samples were successfully collected from 12 patients out of the initial cohort of 31, in order to assess changes in the expression of the target molecules. Among these patients, 75% reported an improvement in pain ($p = 0.083$), and 50% reported an improvement in hand function ($p = 1.000$); both without statistical significance. IL-1β was not expressed in any case. TNF-α was detected in one patient before LDRT and in two after LDRT, with no statistically significant changes.

Discussion: Despite the observed trend toward clinical improvement, the results did not reach statistical significance. Serum cytokine measurement may not accurately reflect local joint inflammation. Methodological limitations, such as small sample size, absence of a control group, and short follow-up period, affect the strength of the conclusions.

Conclusions: In our small patient cohort, LDRT did not show statistically significant clinical or biochemical effects. No correlation could be established between clinical outcomes and biomarkers. Randomized, double-blind studies with larger sample sizes are needed to confirm its efficacy and molecular impact.

3. INTRODUCTION

3.1. DEFINITION OF OA

OA is a disorder characterized by an imbalance between the degradation and synthesis of the extracellular matrix of cartilage and subchondral bone. It begins with micro and macrolesions that trigger maladaptive repair responses, thereby promoting cartilage degradation, bone remodeling, osteophyte formation, joint inflammation, and loss of normal joint function (Blanco FJ et al., 2022).

According to its etiology, it is classified as primary (70–85% of cases) when the cause is unknown, and as secondary when it results from other conditions, mostly metabolic or endocrine diseases such as diabetes (Beltrán Fabregat et al., 2010).

Pain pattern

The condition is primarily associated with chronic pain of mechanical characteristics, which worsens with activity and improves with rest (eventually becoming present at rest in later stages) (Morehead K et al., 2004)

OA is accompanied by functional limitation, joint stiffness, and occasionally varying degrees of swelling or even synovial effusion. It may also be associated with joint deformity and misalignment. Specifically, hand OA is characterized by the involvement of the distal (DIP) and proximal interphalangeal joints (PIP) as well as the first carpometacarpal joints, with reduced grip strength being a characteristic symptom (Beltrán Fabregat et al., 2010)

Epidemiology

The EPISER16 study (a large-scale epidemiological study in Spain on rheumatic diseases) shows that the overall prevalence of OA in the population aged ≥40 years is 29.35%, with lumbar spine OA being the most common location. Specifically, the prevalence of hand OA is 7.73%. Additionally, prevalence increases with age, being more common in women, especially after the age of 60, reaching its peak at ages 80 or older. (Blanco FJ et al., 2021)

Risk factors

Although risk factors vary depending on the affected joint, some are common across different types of OA. These include age >50 years, obesity, genetics (which plays a role in approximately 50% of all OA cases), and female sex. (Morehead K et al., 2004).

Obesity disrupts the balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages, promoting chronic inflammation. In addition, it increases the secretion of chemokine ligand 2 (CCL2), leading to macrophage recruitment and the production of IL-1β, TNF-α and interleukin-6 (IL-6), which act as pro-inflammatory signals. (Nedunchezhiyan U et al., 2022). Other factors include traumatic injuries, anatomical joint abnormalities, intense physical activity, and certain occupational exposures. Regarding hand OA, jobs requiring repetitive manual activities, such as pinching movements, are associated with a higher risk. (Morehead K et al., 2004).

Moreover, it has been suggested that increased bone mineral density is associated with a higher risk of OA and a reduction in joint space. (Morehead K et al., 2004). Nutritional factors may also play a role, as deficiencies in vitamin C and D (antioxidant molecules) are believed to increase the risk by failing to counteract the production of reactive oxygen species by chondrocytes, which can damage cartilage collagen, hyaluronate, and synovial fluid. (Oteo Álvaro A, 2021). Additionally, a high-fat diet promotes increased macrophage infiltration and elevated levels of IL-1β, IL-6 and TNF in the synovial membrane. (Larrañaga-Vera A et al., 2017). It has been suggested that smoking decreases the risk of OA (Morehead K et al., 2004), although the association between smoking and OA remains a topic of debate (Blanco FJ et al., 2021).

Diagnosis

The diagnosis, staging, and prognosis of OA are primarily determined through medical history, physical examination, and simple radiography in most cases. (Beltrán Fabregat et al., 2010).

Although plain radiography remains the first-choice imaging technique (where the characteristic OA tetrad consists of joint space narrowing, marginal osteophytes, subchondral bone sclerosis, and subchondral cysts), other imaging tests include ultrasound (useful for assessing complications), bone scintigraphy (indicated in suspected hidden bone lesions), computed tomography (CT) (to confirm associated bone lesions), and magnetic resonance imaging (MRI) (which provides better visualization of soft tissue structures). (Beltrán Fabregat et al., 2010). There is not always a direct correlation between radiological abnormalities and clinical manifestations, as the degree of correlation varies depending on the joints examined, being higher for the knees, hips, and lumbar spine, and lower for the hands and cervical spine (Beltrán Fabregat et al., 2010).

Additionally, in cases where secondary OA of metabolic origin is suspected, laboratory studies may be useful. Other complementary tests, which have both diagnostic and therapeutic applications, include arthroscopy, which allows for joint lavage. (Beltrán Fabregat et al., 2010)

Disease assessment

Pain intensity is typically measured using a Visual Analogue Scale (VAS), ranging from 0 to 10 (0 = no pain, 10 = maximum pain). Likewise, the VAS is often used to assess the patient's overall health status, with 0 indicating very good health and 10 indicating very poor health (Beltrán Fabregat et al., 2010).

To evaluate quality of life, the WHO's Whoqol-Bref questionnaire (subjective patient assessment) can be used (Cardona-Arias JA et al., 2014). To assess joint function in hand OA, tests such as the Cochin questionnaire are available. (Molina MJ et al., 1997)

3.2. PATHOGENESIS OF OA AND INFLAMMATORY MOLECULES

Although cartilage degradation is the central event in the pathogenesis of OA, inflammation also plays a key role, especially in the hand (Beltrán Fabregat et al., 2010). This chronic inflammatory process can induce synovial hyperplasia and subchondral bone growth (which undergoes a process of sclerosis), as well as osteophyte formation (Oteo Álvaro A, 2021). An increase in inflammatory mediators is common, including cytokines (TNF-α, IL-1β, IL-6, TGF), chemokines (such as CCL2, also known as MCP-1), as well as nitric oxide (NO), all of which contribute to cartilage degradation (Marchev AS et al., 2017).

Several studies have shown that mechanical loading activates inflammatory pathways such as IL-1β, TNF-α, and oxidative stress (Nedunchezhiyan U et al., 2022). Moreover, chemokines, a type of cytokine, are believed to play a central role in the development and perpetuation of synovitis by promoting leukocyte infiltration (predominantly macrophages and lymphocytes) into the synovial membrane (Luo H et al., 2024). It has been shown that inhibiting the expression of these chemokines effectively alleviates symptoms and slows disease progression in OA (Luo H et al., 2024).

Regarding OA pain, its origin is multifactorial, depending on both articular and periarticular structures. However, it has been postulated that angiogenesis in the subchondral bone is an initial event in pain development, as blood vessels provide nutrients for axonal growth and neo-innervation at the osteochondral junction. The synovial membrane contributes to pain by secreting pro-inflammatory factors such as TRKB (the receptor for brain-derived growth factor-BDNF), CCL14, and ADAMTS15, as well as angiotensinogen, angiotensin-converting enzyme and CCL2 (Sanchez-Lopez E et al., 2022).

Specifically, MCP-1/CCR2 signaling is involved in neuropathic pain and neuroinflammation. (Scanzello CR, 2017). There is not always a consistent correlation between pain intensity and the degree of structural joint damage (Morehead K et al., 2004)

The expression of vascular endothelial growth factor (VEGF) is believed to be upregulated in osteoarthritic joints, potentially linking it to catabolic processes in chondrocytes and synovial cells, thereby contributing to cartilage destruction (Sanchez-Lopez E et al., 2022).

Many studies have shown that proliferating M1 macrophages can be observed in the synovial membrane and cartilage affected by OA, and they can promote synovial angiogenesis by secreting VEGF, exacerbate local joint inflammation by producing tumour necrosis factor (TNF)-α, IL-1β, IL-6, matrix metalloproteinases (MMPs) and inducible nitric oxide synthase (iNOS). They can also induce osteophyte formation in OA by producing TGF-β (Luo H et al., 2024). On the other hand, M2 has an anti-inflammatory effect, as it blocks the IL-1β and iNOS activity (Nedunchezhiyan U et al., 2022)

Molecules Involved in the Pathogenesis of OA

Proinflammatory cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) play a critical role as mediators in cartilage degradation and pain modulation. These cytokines can induce their own production and stimulate synoviocytes and chondrocytes to release IL-6, nitric oxide (NO), matrix metalloproteinases (MMPs), and aggrecanases (ADAMTS), while also promoting the synthesis of proteases and prostaglandin E2 (PGE2), and simultaneously suppressing the synthesis of collagen and proteoglycans (López-Armada MJ et al., 2004; Blaney Davidson EN et al., 2007).

IL-1 is a family of inflammatory cytokines, among which IL-1β—primarily released by monocytes and M1 macrophages—is the most potent inducer of cartilage degradation (Vincent TL et al., 2019). IL-1 can also induce the expression of nerve growth factor (NGF), a key pain sensitizer in OA (Jenei-Lanzl Z et al., 2019). Moreover, adipocytes are also known to secrete proinflammatory cytokines such as IL-1β and TNF-α, thereby contributing to cartilage degradation (Jenei-Lanzl Z et al., 2018). In advanced stages of OA, matrix-degrading enzymes and inflammatory mediators induced by IL-1β and TNF-α contribute to an increase in bone volume, leading to subchondral bone sclerosis. This condition is characterized by thickening of the subchondral bone plate and alterations in the subchondral trabecular structure (Jenei-Lanzl Z et al., 2018).

Transforming growth factor beta 1 (TGF-β1) is the predominant isoform of TGF-β in articular cartilage, accounting for 60–85% of the total TGF-β present (van der Kraan PM, 2018). This cytokine exerts a dual effect: in healthy synovial joints, TGF-β has anti-inflammatory properties and acts as a potent antagonist to IL-1. However, under inflammatory conditions such as OA, cartilage degradation results in the release of TGF-β. Elevated levels of TGF-β contribute to synovial hyperplasia, fibrosis, inflammation, and osteophyte formation in osteoarthritic joints. Additionally, it promotes chondrocyte hypertrophy and further cartilage damage (Blaney Davidson EN et al., 2007).

IL-1β, TNF-α, and TGF-β have the capacity to stimulate both bone resorption and formation. In the context of normal bone remodeling and fracture healing, these cytokines play dual roles: initially promoting bone resorption, followed by stimulation of bone formation to maintain skeletal homeostasis (Xu Z et al., 2019).

IL-6 is a cytokine with both anti-inflammatory and pro-inflammatory properties, exhibiting protective or degenerative effects on joint tissues depending on the activated signaling pathway. It can stimulate the production of other pro-inflammatory cytokines, such as IL-1β and TNF-α, thereby exacerbating the inflammatory process in the joints (Scheller J et al., 2011).

CCL2, also known as monocyte chemoattractant protein-1 (MCP-1), is a key inflammatory mediator predominantly secreted by M1 macrophages in the synovial membrane. It is also produced in large quantities by chondrocytes under osteoarthritic conditions, in contrast to moderate expression under physiological conditions (Luo H et al., 2024). Elevated expression of CCL2 facilitates the recruitment of memory T lymphocytes, natural killer (NK) cells, and monocytes to the site of inflammation. The latter differentiate into macrophages upon interaction between chemokine receptor CCR2 and CCL2. These macrophages, in turn,

release IL-1β, IL-6, and TNF-α, further promoting the local inflammatory microenvironment within the synovial membrane (Camps J et al., 2021).

Paraoxonase 1 (PON1) is an enzyme associated with high-density lipoproteins (HDL) that is considered part of the innate immune system. Notably, PON1 inhibits the synthesis of CCL2; therefore, PON1 deficiency leads to increased production of CCL2, which in turn induces immune cell migration and infiltration into target tissues and disrupts normal metabolic function (Camps J et al., 2021).

Serum Detection of Molecules in Patients with OA

Previous studies have shown that serum levels of IL-1β, TNF-α, CCL2, and TGF-β are elevated in patients with OA, whereas PON1 levels are decreased

One study reported elevated levels of IL-1β and TNF-α in patients with articular cartilage lesions in the knee (Wang ZW et al., 2019). Similarly, two other studies also identified increased serum IL-1β levels in patients with knee OA (Mao et al., 2021; Nguyen TTT et al., 2021). Likewise, elevated serum concentrations of TNF-α have been detected in patients with knee OA (Min S et al., 2017). Studies on CCL2 and TGF-β have also confirmed elevated serum levels of these molecules in osteoarthritic patients compared to healthy controls. These elevations have been associated with disease progression (Zhang Y et al., 2023; van der Kraan PM, 2022, respectively). Finally, lower serum levels of PON1 have been observed in patients with knee OA compared to healthy individuals, suggesting that reduced expression of this molecule may play a role in the progression of the disease (Ertürk C et al., 2017).

3.3. OA TREATMENT

The treatment of OA encompasses a wide range of therapeutic measures, although not all are supported by the same level of evidence.

Firstly, non-pharmacological measures, which include adequate health education consisting of an explanation of the process, prognosis and self-care exercises (Glyn-Jones et al., 2015). Other measures would be weight loss in obese patients or exercise focused on gaining muscle strength; in both cases, a reduction in symptoms has been demonstrated (Glyn-Jones et al., 2015). In addition, depending on the case of each patient, joint unloading with orthopedic devices or support techniques such as occupational therapy may be recommended. The measures previously discussed have a high level of recommendation (Miguéns, 2021).

Secondly, there are pharmacological measures, mainly analgesics. Among these, paracetamol stands out, although recent studies indicate that its level of evidence remains of uncertain significance. Although it is recommended as the first therapeutic step in various guidelines, its effect is minimal compared to placebo, and it has been associated with elevated transaminase levels (Giménez et al., 2016). Non-steroidal anti-inflammatory drugs (NSAIDs), on the other hand, have demonstrated a high level of evidence for the treatment of moderate pain and are recommended when used at the lowest effective dose, with careful monitoring of adverse effects (Miguéns, 2021). The recommendation of opioids remains controversial across clinical guidelines (Giménez et al., 2016), with a clear distinction between tramadol—considered a minor opioid and generally recommended for moderate to severe pain—and major opioids, which are largely discouraged. On the other hand, infiltrated corticosteroids are

recommended during acute phases of the condition (Giménez et al., 2016). Platelet-rich plasma shows highly variable outcomes, and there is no clear or consistent stance across clinical guidelines (Miguéns, 2021). Finally, chondroitin sulfate is positively recommended for nodular OA of the hands and knees (Giménez et al., 2016).

Thirdly, there are physical therapies with different levels of evidence for the treatment of OA. The recommended ones include thermotherapy, self-administered massage therapy and paraffin in nodular OA (Miguéns, 2021). Others present an uncertain level of evidence, with very heterogeneous results, such as ultrasonic therapy, laser, interferential current therapy, extracorporeal shock waves and cryotherapy. Transcutaneous electrical nerve stimulation (TENS) is strongly discouraged (Miguéns, 2021).

Fourthly, surgery is a therapeutic option for severe OA or when the underlying cause can be addressed surgically (Glyn-Jones et al., 2015). Notable surgical techniques include cartilage repair via arthroscopy and prosthesis implantation in more advanced cases. However, surgical intervention should only be considered when the patient's surgical risk is low.

Finally, an emerging therapeutic alternative currently under investigation is LDRT, which will be examined in detail throughout this study.

3.4. RADIOTHERAPY. FUNDAMENTALS AND BIOLOGICAL EFFECTS

Radiotherapy is based on the action of ionising radiation on the patient's tissues (Rizo Potau et al., 2016).

The effects of ionising radiation on tissues can be stochastic (random) or non-stochastic (deterministic). Stochastic effects are due to genetic mutations, have no dose threshold, their severity is also independent of dose and are characterised by a long latency period. In contrast, non-stochastic effects are due to accumulated cell death, appear after a certain threshold dose, their severity depends on the dose and can be of both early and late onset (Rizo Potau et al., 2016) (Ramos-Prudencio et al., 2023).

The unit of dose absorbed per session is referred to as fractionation (Rizo Potau et al., 2016).

Conventional radiotherapy in cancer treatment uses a fractionation of 2 Gy to complete total doses of between 30 Gy in palliative treatments and 80 Gy in radical treatments (Rizo Potau et al., 2016). Alternatively, LDRT, a fractionation of less than 1 Gy, has been shown to have an anti-inflammatory effect (Dove et al., 2022).

LDRT is currently used as a therapy for inflammatory pathologies, including OA. It is noteworthy that more than one third of radiotherapy treatments in Germany are for benign pathology, including more than 15,000 patients with OA (Dove et al., 2022).

Treatment scheme in LDRT

In 2018, the German Society for Radiation Oncology (DEGRO) published the latest national guideline for non-malignant disorders. In it, the therapeutic basis for dosing and fractionation for OA is laid down. The recommendation is 0.5-1 Gy per fraction up to total doses of 3-6 Gy. In addition, if pain control is not achieved, retreatment can be performed following the same dose guidelines (Mücke et al., 2018; Arenas et al., 2013).

Adverse effects associated with LDRT

The DEGRO, performed an update stating that no cases of malignant disease caused by LDRT for the treatment of OA have been reported (Mücke et al., 2018). The exact risk of stochastic effects is very difficult to define (Mücke et al., 2018). Therefore, to assess the potential risk of malignant disease from low-dose radiotherapy, the location, sex and especially the age of the patient must be taken into account (Jansen et al., 2005). So much so that the DEGRO recommends this treatment for patients over 40 years of age (Mücke et al., 2018).

Regarding the acute non-stochastic effects of LDRT, only one patient reported skin erythema in a review of 1000 patients (Abdus-Salam et al., 2020). Furthermore, it has been shown not to impair the functionality of healthy joints (Deloch et al., 2018).

Radiobiological Mechanism of LDRT

As for the radiobiological mechanism by which the anti-inflammatory effect occurs, it has been shown to modulate macrophages through inhibition of nitric oxide synthase (Hildebrandt et al., 1998). Furthermore, it predisposes their differentiation to the M2 anti-inflammatory phenotype (Calabrese et al., 2019). It has also been shown in preclinical studies to reduce leukocyte adhesion to endothelial cells, which decreases their migration (Trott et al., 1999). Radiotherapy may also increase apoptosis of these leukocytes (Lödermann et al., 2012; Arenas M et al., 2006).

Effects of LDRT on Molecular Expression

Regarding the effects of LDRT on TNF-α and IL-1β, current studies are based on experimental models using mice or in vitro systems. All of them support that the levels of these cytokines tend to decrease after treatment administration. In an experimental study by Weissmann T et al., involving transgenic mice with arthritis treated with LDRT, a reduction in serum levels of TNF-α and IL-1β was observed (Weissmann T et al., 2022). Another study by Hong EH et al. demonstrated that LDRT applied to an experimental model of chondrocytes cultured in plates reduced IL-1β levels without causing any side effects (Hong EH et al., 2014). Similarly, Kim BH et al. showed that LDRT decreases TNF-α expression in the culture medium of human chondrocytes (Kim BH et al., 2022).

Concerning TGF-β, various studies agree that LDRT induces a localized increase in this cytokine as part of a controlled anti-inflammatory mechanism, limiting the inflammatory response (Weissmann T et al., 2023; Donaubauer AJ et al., 2021; Niewald M et al., 2024; Arenas M et al, 2008).

As for CCL2, an in vitro study using murine cell cultures demonstrated that LDRT can variably modulate its expression depending on the time elapsed post-irradiation and the state of cell activation. In activated cells, a significant decrease in CCL2 expression was observed 24 hours after irradiation (Schröder S et al., 2018).

Regarding PON1, a study involving 30 patients with COVID-19 pneumonia treated with LDRT showed that PON1 levels decreased after 24 hours and increased after one week—coinciding with the peak inflammatory state of the disease (Rodríguez-Tomás et al., 2022). So far, no further studies have investigated PON1 activity following LDRT, but its effects at full radiation doses can be evaluated based on a clinical trial involving 200 breast cancer patients and 200 healthy women. Prior to radiotherapy, women with breast cancer had lower PON1 levels than the controls. After radiotherapy, an increase in the molecule's concentration was observed, although this increase was smaller in women with metastases (Arenas et al., 2017).

Clinical effects of LDRT

A recent review states that LDRT has been shown to improve pain in 60-90% of patients with OA (Mücke et al., 2018).

A retrospective study analysed the pain reduction of 159 patients with OA in different joints after treatment with radiotherapy, there was a progressive reduction in the visual analogue scale and pain reduction was maintained 24 months later in 64% of patients. In this study, no significant difference in long-term pain response was found between patients who received one cycle of radiotherapy and those who received two or three cycles of radiotherapy (Hautmann et al., 2020).

Another retrospective study in patients with OA evaluated the action of radiotherapy for pain reduction in 598 patients, and found a reduction of the visual analogue scale from 7 to 5 at the end of treatment, with a score of 1 in 62.4% 3 months later (Juniku et al., 2019).

3.5. LDRT STUDIES IN HAND OA

Specifically in cases of hand OA, there are several studies showing a favourable symptomatic outcome. A prospective study analysed 100 patients with hand OA treated with low-dose radiotherapy, based on the visual analogue scale. Of these, 94% showed a reduction in pain from an average of 8 points before treatment to 3 points after 6 months (Alvarez et al., 2022).

In an *Atlas guide* based on computed tomography images of benign diseases treated with low-dose radiotherapy, it is described that there is pain relief in 56-90% of irradiated patients with hand OA, and that this improvement is greater when the first metacarpophalangeal joint is involved compared to the second and fifth fingers (Álvarez et al., 2021).

The 2014 guideline of the German Society of Radiology mentions the same percentage of pain relief in irradiated patients with hand OA as the first article, 63-75% (Ott OJ et al., 2015).

In a study looking at 483 patients with hand OA treated at Erlangen Hospital with low-dose radiotherapy, 70% of patients showed pain relief. Factors such as age, gender, number of affected fingers, and single and cumulative doses were analysed, without finding a significant difference in pain relief between these factors. However, in contrast to the *Atlas guideline*

results mentioned above, this study found that patients with involvement of the first finger had worse outcomes than those with involvement of other fingers (Donaubauer et al., 2020).

4. HYPOTHESIS

Low-dose radiotherapy (LDRT) in patients with hand OA improves clinical outcomes and reduces levels of TNF-α, IL-1β and CCL2, while increasing levels of PON1 and TGF-β1.

5. OBJECTIVES

5.1. MAIN OBJECTIVE

To assess the correlation between clinical improvement and changes in TNF-α, IL-1β, and CCL2 (pro-inflammatory profile), PON1 (anti-inflammatory activity), and TGF-β (dual role in inflammation) following low-dose radiotherapy in hand OA.

5.2. SECONDARY OBJECTIVES

To assess clinical changes after radiotherapy.

To assess changes in TNF-α, IL-1β, CCL2, TGF-β and PON1 molecules in blood after radiotherapy.

6. MATERIALS AND METHODS

6.1. STUDY DESIGN

This is a prospective, longitudinal observational pilot study involving patients with OA at different locations, with a specific focus on hand OA.

The aim of the study is to analyze TNF-α, IL-1β, CCL2, PON1, and TGF-β levels, along with clinical markers of function and pain, both before and one month after LDRT.

The patient collection was conducted through the outpatient radiotherapy consultations, as well as through referrals from consultations in other specialties. All participants with hand OA received LDRT at the Radiation Oncology Department of HUSJR between February and November 2024. A total dose of 3 Gy was administered, following a fractionation schedule of 0.5 Gy per session on alternate days, for a total of six sessions. Prior to the start of treatment, a blood draw and Cochin functionality test were performed, and both were repeated one month after completion of radiotherapy. One month after completing radiotherapy, participants assessed their pain, which was categorized into four levels: no improvement, mild improvement, moderate improvement, and no pain. Pro-inflammatory markers (TNF-α and IL-1β) from the two blood samples were analyzed using ELISA. Due to limited resources, CCL2,

TGF-β, and PON1 were not analyzed. Follow-up was conducted through medical records, Radiation Oncology consultations, and telephone interviews.

6.2. SETTINGS AND STUDY SUBJECTS

Patients were selected based on specific inclusion and exclusion criteria, as outlined below. Although the initial sample consisted of 31 patients, the final number of participants was reduced to 12. To ensure data anonymization, each case was assigned a unique identification number.

INCLUSION	EXCLUSION
• Age ≥ 18 years • Diagnosis of hand osteoarthritis • Previous trial of other therapeutic alternatives • Signed informed consent	• Pregnancy • Skin lesion in the irradiated area • Refusal to participate in follow-up

Table 1. Inclusion and Exclusion Criteria.

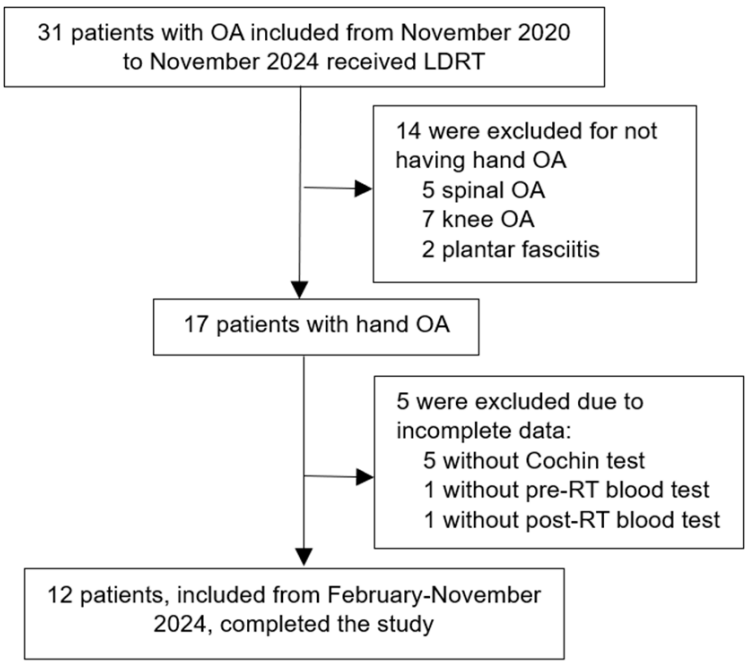

Fig 1. Trial profile

6.3. VARIABLES

A total of 45 clinical variables have been defined in the study.

The main study variables are those related to OA:

- Inflammatory markers (TNF-α, IL-1β, CCL2, TGF-β and PON1) pre- and post-radiotherapy.
- Cochin Functionality Scale scores pre- and post-radiotherapy.
- Post-radiotherapy pain categorisation.

Secondary variables include:

- 18 parameters were analyzed from pre- and post-radiotherapy blood samples, including: 6 hematological (hemoglobin, total leukocytes, neutrophils, lymphocytes, platelets, ESR), 10 biochemical (blood glucose, LDL, HDL, triglycerides, total cholesterol, albumin, GFR calculated from creatinine, GOT, GPT, GGT), 1 inflammatory (CRP), and 1 immunological (IL-6) marker.
- 3 variables relating to the treatment used (total dose, fractionation, sessions administered).
- Age at the time of treatment, sex and anthropometry.
- Occupation.
- Comorbidities (underlying conditions) and cardiovascular events: Hypertension, Diabetes Mellitus (DM), Dyslipidemia (DLP), Acute Myocardial Infarction (AMI), Congestive Heart Failure (CHF), and Stroke
- Toxic habits (tobacco and alcohol).
- Consumption of analgesia, Non-steroidal anti- inflammatory drugs (NSAIDs) or corticosteroids.
- Follow-up.

Additionally, the date of the patient's last medical check-up (defined as the most recent visit to a health center or contact with a healthcare professional) was reviewed, as it is essential for calculating the patient's follow-up time.

6.4. ELISA PROTOCOL FOR THE ANALYSIS OF MARKERS

Plate preparation

- Dilute the capture antibody in phosphate buffered saline (PBS). Immediately coat a microplate with 100 microlitres per well of the diluted capture antibody. Seal and incubate the plate at room temperature overnight.
- Aspirate each well and wash with wash buffer. Repeat the process for a total of 3 washes.
- Block the plate by adding reagent diluent (300 microlitres in each well). Incubate at room temperature for one hour.
- Repeat the washing.

Assay procedure

- Add 100 microlitres of sample or standards together with the reagent diluent to each well. Then incubate for 2 hours at room temperature.
- Perform a wash.
- Add 100 microlitres of detection antibody to each well together with the reagent diluent. Then incubate for 2 hours at room temperature.
- Wash.
- Add 100 microlitres of streptavidin-HRP solution to each well. Incubate for 20 min at room temperature avoiding direct light.
- Perform a wash.
- Add 100 microlitres of substrate solution to each well. Incubate for 20 min at room temperature, avoiding direct light.
- Add 50 microlitres of stop solution to each well.
- Determine the optical density of each well immediately.

6.5. COCHIN'S TEST OF HAND FUNCTIONALITY

To assess hand joint function, the Cochin Test was used. It consists of 18 questions related to basic activities of daily living (BADL), with scores ranging from 0 (no difficulty) to 5 (unable to perform), for a maximum score of 90. A higher score indicates worse functionality (Molina MJ et al., 1997). The complete questionnaire can be found in Annex 1."

6.6. DATA COLLECTION

The collection of clinical information for the creation of the database (including the original sample of 31 patients) was obtained from blood tests and follow-up visits in the Radiation Oncology service of HUSJR, as well as from the patients' medical records using SAP and HNet software.

6.7. STATISTICAL ANALYSIS

Statistical analysis was performed using *IBM SPSS Statistics 29*, which allows for the calculation of descriptive statistics. The pre-specified continuous quantitative variables are presented as median (interquartile range) and the discrete quantitative variables as absolute value (percentage). To obtain information on the differences between the values of the variables before and after radiotherapy, different statistical tests were used. The Wilcoxon test was used for continuous quantitative variables while the χ^2 test, Mc Nemar test and binomial test were used for discrete quantitative variables. Statistical significance was set at $P < 0.05$.

6.8. ETHICAL ASPECTS

This study was approved by the Ethics Committee for Research with Medicines (CEIM) of the Pere Virgili Health Research Institute (IISPV), under code RadBenigna Ref.120/2018.

The study participants had signed the informed consent prior to the first blood sample extraction and start of radiotherapy. In this document, it was explained to them that some data from their clinical history would be transferred to a database to be studied anonymously under an identification code. Maintaining the confidentiality of personal data: Organic Law 15/1999,

of 13 December, on the protection of personal data LODP and Organic Law 3/2028, of 5 December, on the protection of personal data and guarantee of digital rights.

7. RESULTS

7.1. ORIGINAL SAMPLE

This study aims to analyze the effect of low-dose radiotherapy on several patients with hand OA. However, these patients come from a sample of 31 patients with benign inflammatory diseases (OA in various locations and plantar fasciitis) and were recruited through the Radiation Oncology Department. The characteristics of the study sample are as follows:

Original sample	Total
n	31 (100)
Location	
Spine OA	5 (16,1)
Hands OA	17 (54,8)
Toe (plantar fasciitis)	2 (6,5)
Knees OA	7 (22,7)
Sex	
Female	24 (77,4)
Male	7 (22,6)
Age	71,31 ± 14
Weight (kg)	73,5 ±17*
Height (cm)	163,5 ± 17*
Body mass index (kg/m2)	27,61 ± 4*
Tobacco	
Active smoking	6 (19,4)
Ex smoker	8 (25,8)
Non smoker	17 (54,8)
Alcohol	
Alcohol consume	1 (3,2)
Non alcohol consume	30 (96,8)
Analgesia	
Use of acetaminophen	22 (71,0)*
Use of NSAIDs	18 (58,1)
Use of corticosteroids	7 (22,6)
Comorbidities	
Hypertension	18 (58,1)
Diabetes mellitus	10 (32,3)
Hyperlipidemia	16 (51,6)
Ischemic event	2 (6,5)
Cardiac insufficiency	3 (9,7)
Stroke	2 (6,5)

Estatus	
Alive	30 (96,8)
Dead	1 (3,2)
Profession*	
Administrative	3 (9,7)
Housewife	1(3,2)
Locksmith	1 (3,2)
Discapacity	2 (6,5)
Cleaner	1 (3,2)
Teacher	2 (6,5)
Sheperd	1 (3,2)
Retired	5 (16,1)
Machinery repairman	1 (3,2)
Follow-up (years)	3,63 ± 0,4

Table 1. Descriptive table of the clinical characteristics of the patients in the original sample. *The continuous quantitative variables are presented as median +/- interquartile range and the discrete quantitative variables as absolute values (percentage). The asterisk indicates missing data: the weight, height, and Body Mass Index (BMI) of one patient, and the height and BMI of four, the occupation of 12 patients and the type of analgesia used by one patient.*

As shown in Table 1, only one patient—diagnosed with knee OA—did not survive, having passed away due to COVID-19 pneumonia. Hand OA was the most common manifestation, affecting 54.8% of the patients. The majority of the cohort were female (77.4%). The median age was 71 years, with an interquartile range (IQR) of 14. The median body mass index (BMI) was 27.61, falling within the overweight category, with an IQR of 4. Cardiovascular risk factors included active smoking (19.4%), alcohol consumption (3.2%), hypertension (58.1%), diabetes mellitus (32.3%), hyperlipidemia (51.6%), ischemic events (6.5%), stroke (6.5%), and heart failure (9.7%). In terms of analgesic use, 71% of patients reported using acetaminophen, while 58.1% used nonsteroidal anti-inflammatory drugs (NSAIDs). Regarding occupational status, the most common was retirement, accounting for 16.1% of the sample.

7.2. HAND OA SAMPLE

Of the original sample, the last 12 patients were recruited by our team and underwent blood sampling both before and after radiotherapy, and were administered the COCHIN questionnaire at these same time points. The sample characteristics are as follows:

Hand OA sample	Total
n	12 (100)
Sex	
Female	10 (83,3)
Male	2 (16,7)
Age	71,57±12,14
Weight (kg)	69 ±16,7*
Height (cm)	161±12*

Body mass index (kg/m2)	26,95 ± 7,22*
Tobacco	
Active smoking	4 (33,3)
Ex smoker	1 (8,3)
Non smoker	7 (58,3)
Alcohol	
Alcohol consume	1 (8,3)
Non alcohol consume	11 (91,7)
Analgesia	
Use of acetaminophen	9 (75) *
Use of NSAIDs	9 (75)
Use of corticosteroids	4 (33,3)
Comorbidities	
Hypertension	6 (50)
Diabetes mellitus	3 (25)
Hyperlipidemia	4 (33,3)
Ischemic event	0 (0)
Cardiac insufficiency	0 (0)
Stroke	0 (0)
Estatus	
Alive	12 (100)
Dead	0 (0)
Profession*	
Housewife	1 (8,3)
Administrative	1 (8,3)
Retired	1 (8,3)
Follow-up (years)	1,1 ± 0,2

Table 2. Descriptive table outlining the clinical characteristics of patients in the hand OA sample. *The continuous quantitative variables are presented as median +/- interquartile range and the discrete quantitative variables as absolute values (percentage). The asterisk indicates missing data: the weight, height, and BMI of one patient, the height and BMI of one patient, the occupation of 9 patients and the type of analgesia used by one patient*.

As shown in Table 2, all patients survived throughout the study period. The majority of the sample were women (83.3%). The median age was 72 years, with an interquartile range of 12. Patients had a median BMI of 27.1, which corresponds to the overweight category, with an interquartile range of 7.22. Cardiovascular risk factors included active smoking (33.3%), alcohol consumption (8.3%), hypertension (50%), diabetes mellitus (25%), and hyperlipidemia (33.3%). Notably, this sample did not present with ischemic events, stroke, or heart failure.

In terms of analgesic use, 75% of patients reported using acetaminophen, while 75% also used nonsteroidal anti-inflammatory drugs (NSAIDs). Regarding occupational status, the sample was evenly distributed between administrative workers, retirees, and housewives.

Clinical data in the hand OA sample

Clinical data	Frequency	P
Pain relief detailed		
No pain relief	3 (25)	0,572
Slight pain relief	4 (33,3)	
Moderate pain relief	4 (33,3)	
Absence of pain	1 (8,3)	
Pain relief		
Pain relief	3 (25)	0,083
Non pain relief	9 (75)	
Cochin test		
Functional improvement	6	1
Non functional improvement	6	

Table 3. Descriptive table of pain and functional improvement after radiotherapy in the hand OA sample. *The discrete quantitative variables are presented as absolute values (percentages) and were analyzed using the binomial test for pain improvement, the Chi-square test for pain relief grading and for the COCHIN test. P values ≤ 0.05 indicate a statistically significant difference; however, in this case, no statistically significant differences were observed in any of the variables.*

As shown in Table 3, 75% of patients reported some degree of pain relief: mild (33.3%), moderate (33.3%), and complete pain relief (8.3%). However, 25% of patients reported no improvement in pain. This difference was not statistically significant. Regarding functionality, the proportion of patients who experienced improvement was equal to the proportion who showed no amelioration.

Pain relief	Functional	improvement	Total	
	No	Yes		P
No	3	0	3	0,172
Slight	1	3	4	
Moderate	2	2	4	
Absence of pain	0	1	1	

Table 4. Descriptive cross table of pain and functional improvement after radiotherapy in the hand OA sample. *The discrete quantitative variables are presented as absolute values analyzed with Chi square. P values ≤ 0.05 indicate a statistically significant difference; in this case, there are no statistically significant differences.*

As shown in Table 4, patients who did not experience pain improvement also did not show improvement in functionality. However, 75% of those with mild pain improvement demonstrated functional improvement, 50% of those with moderate pain improvement showed functional improvement, and 100% of those who reported no pain also experienced functional improvement.

Blood values in hand osteoartritis sample

Plasma variables	Median		
	Pre	Post	p
Hemoglobin (g/dl)	13,95 ± 2,50	13,50 ± 2,10	0,099
Leukocytes (x10^3/ u/mc)	7,11 ± 0,64	7,11 ± 2,14	0,695
Neutrophils (x10^3/ u/mc)	4,51± 1,35	4,25± 2,18	0,346
Lymphocytes (x10^3/ u/mc)	1,97± 0,96	1,83± 0,91	0,637
Platelets (x10^3/ u/mc)	247± 76	260± 96	0,285
Glicemia (mg/dl)	102± 41	103± 53	0,799
LDL (mg/dl)	132,50± 56	114± 79	0,255
HDL (mg/dl)	64,50± 25	62± 33	0,720
Triglycerides (mg/dl)	129,50± 64	109± 64	0,347
Total cholesterol (mg/dl)	211± 89,80	196,30± 104,90	0,117
Albumin (g/dl)	4,55± 0,40	4,45± 0,2	0,107
CPR (mg/dl)	0,25± 0,37	0,23± 0,64	0,929
VSG (mm/h)	16± 19	18± 22	0.266
IL-6 (pg/ml)	3,5± 14	3,5± 9,4*	0,553
GF (ml/min/1,73 m2	88± 16,80	89,50± 17,90	0,969
AST (U/l)	22± 9	21,50± 6	0,050
ALT (U/l)	17,50± 10	16± 10	0,874
GGT (U/l)	17± 23	16± 21	0,132

Table 5. Descriptive table of the blood values in the hand OA sample. *The continuous quantitative variables are presented as median +/- interquartile range analyzed with the Wilcoxon test. P values ≤ 0.05 indicate a statistically significant difference; however, in this case, no statistically significant differences were observed in any of the values. The asterisk (*) denotes missing data: IL-6 levels after radiotherapy in one patient.*

Table 5 presents the laboratory values before and after radiotherapy. Notable inflammatory parameters include the leukocyte count, which remained constant at 7110 both before and after radiotherapy. Neutrophil counts decreased from 4510 to 4250, although this reduction was not statistically significant. Similarly, lymphocyte counts declined from 1970 to 1830, but this change was also not statistically significant. C-reactive protein (CRP) levels decreased slightly from 0.25 to 0.23, with no statistical significance. The erythrocyte sedimentation rate (ESR) increased from 16 to 18, but this change was not significant. Furthermore, interleukin-6 (IL-6) levels remained stable.

TNF alpha expression	Pre-radiotherapy	Post-radiotherapy	Total	p
Yes	1	2	3	1
No	11	10	21	

Table 6. Descriptive table of the TNF alpha expression in the hand OA sample. *The discrete quantitative variables have been expressed as absolute values analyzed with Mc Nemar test. P values ≤ 0.05 indicate a statistically significant difference; however, in this case, no statistically significant differences were observed*.

As shown in Table 6, TNF-alpha expression was observed in only one patient before radiotherapy, with a value of 2.26 pg/ml. After radiotherapy, two patients expressed TNF-alpha, with values of 3.13 and 5.6 pg/ml, though these differences were not statistically significant. The remaining patients did not express TNF-alpha; however, it is important to note that we cannot assume a value of 0, as doing so would introduce analytical bias.

IL 1 expression	Pre-radiotherapy	Post-radiotherapy	Total	p
Yes	0	0	0	1
No	12	12	24	

Table 7. Descriptive table of the IL-1 expression in the hand OA sample. *The discrete quantitative variables are presented as absolute values analyzed with Mc Nemar test. P values ≤ 0.05 indicate a statistically significant difference; in this case, no statistically significant differences were observed*.

As shown in Table 7, no expression of IL-1 was detected in any patient. However, we cannot assume that the value for all these patients was 0 pg/ml, as this would introduce analytical bias. Therefore, the results are presented as frequencies in Tables 6 and 7.

PON1 expression	Pre-radiotherapy	Post-radiotherapy
Yes	NA	NA
No	NA	NA
TGF-β expression	**Pre-radiotherapy**	**Post-radiotherapy**
Yes	NA	NA
No	NA	NA
CCL2 expression	**Pre-radiotherapy**	**Post-radiotherapy**
Yes	NA	NA
No	NA	NA

Table 8. Descriptive table of CCL2, TGF-β, and PON1 expression in the hand OA sample. NA refers to "not applicable."

As presented in Table 8, these three molecules could not be measured using the ELISA method due to limitations in resources.

8. DISCUSSION

The aim of this study was to evaluate the evolution of pain, function and inflammation (TNF-α, IL-1β) in patients with hand OA after LDRT. A sample of 12 patients was analysed.

Of the cases studied, 83.3% were women. This proportion of women in the sample is higher than in the population with OA, where they represent 60%. The median age of the patients in the study was 71 years, consistent with the peak prevalence of OA occurring between 60 and 70 years of age.

Regarding prior treatment for OA, 100% of participants had received anti-inflammatory drugs, 75% had used NSAIDs, and 33.3% had been treated with intralesional glucocorticoids. In comparison, Domínguez-Gil et al. conducted an observational, descriptive, cross-sectional study in Spain involving 3,002 patients with OA, reporting NSAID use in 44.8% and intralesional corticosteroid use in 8.6% of cases (Domínguez-Gil et al, 2003). Similarly, in 2023, Yang Z et al. published a meta-analysis of international observational studies, reporting that 68% of patients with OA received NSAIDs (Yang Z et al, 2023). The higher proportion of NSAID and glucocorticoid use observed in our study sample may be attributed to the inclusion criterion requiring participants to have previously undergone therapeutic alternatives.

Occupation was recorded for 2 of the 12 participants: one clerical worker and one housewife. Both occupations involve repetitive manual tasks, which have been associated with an increased risk of hand OA (Morehead K et al., 2004). In future studies with larger sample sizes, it is recommended to systematically collect occupational data to enable risk factor analysis.

Although the follow-up of the 31 patients treated with LDRT is considerable, the follow-up in the hand OA subgroup is more limited. Despite this limitation, the results show that 1 month after the administration of radiotherapy, pain has been reduced in 77.6% of patients, with improvement in function as measured by Cochin's test in 50% of patients. Although the proportion of pain improvement is high, the difference does not reach statistical significance at 5% ($p=0.083$), so it cannot be ruled out that the observed improvement is attributable to chance. In terms of functionality ($p=1.00$) there is no evidence of differences.

In the first determination prior to radiotherapy, IL-1β was not expressed in 100% of the patients and TNF-α in only one of them. It should be noted that the patient who expressed the latter cytokine had tenosynovitis in the third finger of the right hand. Following radiotherapy treatment, IL-1β remained undetectable in 100% of patients. TNF-α was expressed in two patients post-treatment, and it became negative in the one patient who had tested positive before treatment. No statistically significant changes in inflammatory molecules were found before and after radiotherapy. As a result, no relationship could be established between changes in inflammatory markers and clinical improvement, as measured by pain reduction and improved function.

For the statistical analysis of the molecules, they have been categorised as dichotomous qualitative variables (expressed/not expressed), as most of them were not expressed. Representing them with a numerical value, such as 0 in case of no expression, could induce bias in the results. There is a higher proportion of functional improvement among those with

improved pain (55.6%) compared to those with no improvement in pain 33.3%. This suggests a possible positive relationship between improved pain and improved function, but is not statistically significant (p= 0.172).

Similar results of pain reduction and clinical improvement of function in hand OA after radiotherapy have been found in published literature. In a review published by Seegenschmiedt et al, a total of 17 retrospective clinical studies were evaluated, encompassing 809 patients with hand OA treated with LDRT (Seegenschmiedt et al, 2015). A marked and complete reduction of pain was observed in 63-75% of irradiated patients. In another study published by Rühle et al, they performed a retrospective analysis with a sample of 970 patients with OA in joints of different sizes, including the hand. The administration of LDRT showed a similar decrease in pain with no differences in joint type (Rühle et al, 2021). In contrast, there are studies that contradict our pain reduction results such as the clinical trial published by Mahler et al., where a randomised, blinded, placebo-controlled clinical trial was conducted with 55 patients with knee OA, where they found no difference between radiotherapy and placebo in the reduction of pain and inflammatory signs (Mahler et al, 2019). Another randomised, blinded, two-arm, placebo-controlled clinical trial conducted in 2018 with 56 patients with hand OA found no significant difference between the groups in terms of function or pain reduction (Minten et al, 2018). These two studies advise against the use of LDRT for the treatment of OA. In response to these two clinical trials, an article published in 2019 considers that the number of patients is too small to reach this conclusion and cannot invalidate the existing clinical evidence in numerous publications on LDRT for the treatment of OA (Ott OJ et al, 2019). Due to the discrepancy of the results, more research is needed to discern the role of LDRT in pain relief and improved function in OA.

Regarding the expression of cytokines in the study, a systematic review by Kellesarian et al. analyzes cytokine profiles in the synovial fluid of patients with temporomandibular joint (TMJ) OA. The results show elevated levels of IL-6, IL-1β, and TNF-α in the synovial fluid of these patients, indicating localized inflammation in the joint that may not necessarily be reflected in peripheral blood (Kellesarian et al, 2016). Ulmner M et al. compared the concentrations of IL-1β and TNF-α in synovial tissue and synovial fluid, correlating them with clinical parameters of local inflammation in patients with TMJ OA. The results show that concentrations of IL-1β and TNF-α in the synovial tissue correlate with clinical signs of local inflammation, while this correlation is not observed in the synovial fluid. This suggests that synovial tissue may better reflect local inflammation than synovial fluid or peripheral blood (Ulmner M et al., 2022).

There are studies that could explain why the patients recruited in the study do not express these molecules as expected. On the one hand, Meehan RT et al. point out that in patients with OA, blood concentrations of cytokines such as IL-1β, TNF-α, and IL-6 may not accurately reflect levels in the synovial fluid, since these cytokines can be produced at various sites outside of the arthritic joints (Meehan RT et al., 2021). On the other hand, Mabey T et al. compared serum concentrations of pro-inflammatory and anti-inflammatory cytokines in patients with knee OA and healthy controls. This study found no significant differences in serum levels of IL-1β and TNF-α between OA patients and controls (Mabey T et al., 2016).

Considering the findings of the aforementioned publications, further research is needed to evaluate whether measuring IL-1β and TNF-α in peripheral blood is useful for studying local

inflammation in OA. Current scientific evidence supports that synovial fluid and, especially, synovial tissue do reflect local inflammation. However, it is important to note that measuring cytokines in synovial fluid or tissue is an invasive procedure, making it a less accessible technique than assessment through peripheral blood.

9. CONSTRAINTS AND LIMITATIONS

The study has several limitations that constrain the ability to draw statistically significant conclusions, primarily due to limited statistical power associated with a small sample size ($n < 50$). Specifically, only 12 patients diagnosed with hand OA were available for both functional assessment using the Cochin Hand Function Scale and for blood sampling before and after the application of LDRT. The study design was neither randomized nor blinded—neither for participants nor evaluators—which may introduce both selection and assessment biases. Furthermore, the absence of a control group prevents the determination of whether the observed improvements in pain and functionality are attributable to the radiotherapy intervention itself or to confounding factors such as the natural course of the disease or placebo effects. The reported improvements may have been influenced by patients' expectations regarding the treatment.

It is also important to highlight that the initial research design proposed the inclusion of a sample of 50 patients with OA affecting various anatomical sites. Patient recruitment began in 2020; however, our involvement in the project commenced in 2023 upon joining the Department of Radiation Oncology as internal medical trainees. Between September 2023 (the start of our involvement) and December 2024 (the end of the recruitment period), the number of OA cases recorded at *Hospital Universitari Sant Joan de Reus* (HUSJR) was insufficient to meet the initial recruitment target. Given the higher prevalence of patients presenting with hand OA, the study was ultimately focused on this specific joint location. Prior to our involvement in the study, no standardized scale had been employed to assess joint functionality. Consequently, four patients diagnosed with hand OA were later identified as not having undergone the Cochin Hand Function Scale assessment and were therefore excluded from the statistical analysis.

It is also important to note that several challenges arose during data collection. Among these was the absence of relevant clinical information—such as weight and height—for certain patients, as these data were not documented in their medical records. With regard to the blood analyses, not all parameters were available for all participants, as the samples collected prior to our involvement did not include all the variables that were subsequently deemed relevant for the study. In the case of one patient with hand OA, no pre-treatment blood sample was obtained prior to radiotherapy, requiring their exclusion from the study. Similarly, the follow-up blood sample scheduled for one month after radiotherapy was not collected in another patient, who was consequently excluded from the analysis. This issue was primarily due to non-adherence by some patients to the scheduled blood test appointments. Finally, the proportion of female participants in the study does not reflect the gender distribution typically observed in the OA population, introducing a potential gender bias. Potential confounding variables that may have influenced our results include the individual medical histories of each patient, as

well as factors not accounted for in the study, such as dietary habits, which were not investigated.

IL-1β was not expressed in any patient either before or after treatment, and TNF-α was expressed in only three patients. This considerably limits the study's capacity to assess significant changes in inflammatory markers. It is also relevant to note that the original study design proposed the analysis of a broader range of cytokines than were ultimately included. These included CCL2, PON1, and TGF-β, as previously outlined in the introduction. It was decided not to proceed with its analysis due to resource limitations and the consideration that it was not justified, particularly after observing that neither IL-1β nor TNF-α were expressed at the levels anticipated based on the initial hypotheses.

Finally, another limitation is the relatively short follow-up period after radiotherapy for hand OA (1.1 ± 0.2 years), compared to a longer follow-up for OA at other locations (3.63 ± 0.4 years). Given that OA is a chronic condition, it is important to assess whether the observed improvements are sustained in the medium and long term.

10. CONCLUSIONS

Following radiotherapy in patients with hand OA, no statistically significant changes were observed in function, pain, or inflammatory biomarkers.

Due to the limitations of this study, no correlation can be established between clinical improvement and serum levels of TNF-α, IL-1β, CCL2, TGF-β and PON1 following LDRT in this patient population.

Future studies are warranted to further investigate the effects of LDRT on functional outcomes, pain, and inflammatory markers. A larger sample size representative of the target population is recommended, and the study design should follow a randomized, double-blind clinical trial format. Additional aspects to consider include non-invasive indirect assessment of inflammation via ultrasound; evaluation of hand grip strength to measure function (as recommended by Kloppenburg et al., 2015); direct assessment of patients' perceived functional impairment; and analysis of potential changes post-radiotherapy.

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12. APPENDICES

12.1. Appendix 1: Cochin Test

TEST COCHIN DE FUNCIONALIDAD DE MANOS						
	DIFICULTAD					
COCINA	Sin	Poca	Alguna	Mucha	Casi imposible	Imposible
¿Puede sujetar un tazón?						
¿Puede coger una botella llena y levantarla?						
¿Puede coger un plato lleno?						
¿Puede servirse un vaso de una botella llena?						
¿Puede abrir un bote que ya haya sido abierto?						
¿Puede cortar la carne con un cuchillo?						
¿Puede pinchar con el tenedor de manera eficaz?						
¿Puede pelar la fruta?						
VESTIRSE						
¿Puede abrocharse la camisa?						
¿Puede abrir y cerrar cremalleras?						
HIGIENE						
¿Puede apretar un tubo de pasta dentífrica?						
¿Puede sujetar su cepillo de dientes de manera eficaz?						
ESCRITURA						
¿Puede escribir una frase corta con un lápiz o un bolígrafo?						
¿Puede escribir una carta con un lápiz o un bolígrafo?						
VARIOS						
¿Puede girar la manija de la puerta?						
¿Puede cortar un trozo de papel con las tijeras?						
¿Puede coger unas monedas que están en la mesa?						
¿Puede girar la llave en su cerradura?						

12.2. Appendix 2: Favorable Opinion from the CEIm of the IISPV

IISPV
INSTITUT D'INVESTIGACIÓ SANITÀRIA PERE VIRGILI

CEIm
Comitè Ètic d'Investigació amb medicaments

DICTAMEN COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS

DOÑA Mª TERESA AUGUET QUINTILLA, PRESIENTA DEL COMITÉ ÉTICO DE INVESTIGACIÓN CON MEDICAMENTOS DEL INSTITUT D'INVESTIGACIÓ SANITÀRIA PERE VIRGILI.

HACE CONSTAR QUE:

Este Comité, en su reunión de fecha **25/10/2018** acta número **9** se ha evaluado y decidido emitir **Informe Favorable** para que se realice el estudio titulado:

"EFECTES ANTIINFLAMATORIS DEL TRACTAMENT RADIOTERÀPIC A DOSIS BAIXES EN PACIENTS AMB PATOLOGIA BENIGNA"

Código: RADBENIGNA
Versión Protocol: v. n. 1
Versión HIP Y CI: v. n. 1
Ref. CEIM: 120/2018

CONSIDERA QUE:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.

La capacidad del investigador y los medios disponibles son apropiados para lleva a cabo el estudio.

Son adecuados tanto el procedimiento para obtener el consentimiento informado como la compensación prevista para los sujetos por daños que pudieran derivarse de su participación en el estudio.

El alcance de las compensaciones económicas previstas no interfiera con el respeto a los postulados éticos.

Este comité **acepta** que dicho estudio sea realizado en el Hospital Universitari Sant Joan de Reus por la Dra Meritxell Arenas Prats del Servicio de **Oncología Radioterápica.**

En el caso que se evalúe algún proyecto en el que participe como investigador/colaborador algún miembro de este comité, se ausentará de la reunión durante la discusión del estudio.

La composición actual del CEIm del Institut d'Investigació Sanitària Pere Virgili es la siguiente:

Presidente
Dra. Maria Teresa Auguet Quintilla
Servicio de Medicina Interna. Hospital Universitari Joan XXIII. Representante de la Comisión de Investigación.

Secretario
Dr. Josep Mª Alegret Colomé
Cardiólogo. Hospital Universitari Sant Joan de Reus

Vocales

Dr. Xavier Ruiz Plazas
Urólogo. Servicio de Medicina Interna del'Hospital Universitari Joan XXIII.
Sra. Montserrat Boj Borbonés
Servicio de Farmacia del Hospital Universitari Sant Joan de Reus.
Sra. Anna Borruel Llovera
Diplomada Universitaria en Enfermería. UAU
Sra. Immaculada de Molina Fernández
Diplomada Universitaria en Enfermería. Hospital Universitari Joan XXIII.
Dr. Joaquín Escribano Súblas.
Médico del Servicio de Pediatría. Representante de la Comisión de Bioètica Assitencial. Miembro de la Comisión de Investigación.
Dr. Joan Fernández Ballart
Catedrático de Medicina Preventiva i Salud Pública. Facultad de Medicina i Ciències de la Salut. Universitat Rovira i Virgili.
Sra. M. Mar Granell Barceló
Abogada i Asesora Jurídica del Comité.
Dr. Josep M. Crespo Bernabeu
Servicio de Farmacia del Hospital Universitari Joan XXIII.
Dr. Jesús Miguel López-Dupla
Servicio de Medicina Interna Hospital Universitari Joan XXIII
Sr. Jordi Mallol Mirón
Catedrático de Farmacología, Facultad de Medicina, Universitat Rovira i Virgili.
Sra. Isabel Rosich Martí
Farmacéutica Atenció Primaria
Sr. Francesc Xavier Sureda Batlle
Profesor Titular de Farmacología. Universitat Rovira i Virgili.
Dr. Vicente Valentí Moreno
Oncólogo. Hospital Sant Pau i Santa Tecla.
Dra. Elisabet Vilella Cuadrada
Departamento de Formación e Investigación del Hosptal Psiquiàtric Universitari Institut Pere Mata. Representante de la Comisión de Investigación.
Sra. Mercè Vilella Papaseit
Representante de la Sociedad Civil.

Firma

CEIM
COMITÈ ÈTIC D'INVESTIGACIÓ AMB MEDICAMENTS
Edifici de Nutrició i Salut
Avda. de la Universitat, 1, 2a planta
43204 Reus (Tarragona)
Tel. 977 75 93 94

Dra. Mª Teresa Auguet
Presidenta CEIm IISPV

Reus, 25 de octubre de 2018

12.3. Appendix 3: Completed and Signed Supervisor's Report

TREBALL DE FI DE GRAU. FMCS. FITXA D'AVALUACIÓ DEL TUTOR

L'avaluació del treball pràctic tindrà en compte la nota referida pel tutor respecte a la memòria impresa i el seguiment del treball. El resultat de l'avaluació del tutor ha de ser favorable per tal que l'alumne pugui presentar i defensar el treball i representa el 25 % nota total del TFG.

ENSENYAMENT: Grau de Medicina

NOM DE L'ALUMNE: Estefanía Boza Moreno, Ana Casañ Alufre, Anna Xiang Pau Charles

TÍTOL DEL TREBALL: "Prospective longitudinal observational study in patients with hand osteoarthritis (OA) treated with low-dose radiotherapy (LDRT): anti-inflammatory molecular effects, clinical outcomes, and their correlation."

SEGUIMENT I AVALUACIÓ DEL TREBALL PER PART DEL TUTOR DEL TREBALL PRÀCTIC (0-10)	
Ha mostrat capacitats d'anàlisis i síntesi i raonament al llarg del treball	10
Ha mostrat iniciativa durant tot el procés d'elaboració del Treball	10
El procés d'elaboració del Treball ha estat continuat	10
Ha mostrat habilitat de cerca i gestió de la informació	10
Ha mostrat capacitat d'organització i planificació	10
Ha seguit la normativa pròpia del Centre en quan a la presentació escrita del treball	10
El treball és ordenat i redactat amb cura, expressant-se correctament amb la llengua escollida	10
Els resultats del treball són originals	10
El treball presentat supera les expectatives del tutor	10
Comentaris del tutor si s'escau	
MITJANA DE LA NOTA DEL TUTOR (0-10)	10

AVALUACIÓ: FAVORABLE X NO FAVORABLE ☐

AUTORITZA a que el treball sigui públic i visible al repositori institucional de la URV*?

SI X NO ☐

* Desaconsellat en casos de treballs amb dades de pacients i amb treballs potencialment publicables

NOM I SIGNATURA DEL TUTOR:** ARENAS PRAT MERITXELL - 77306678K Digitally signed by ARENAS PRAT MERITXELL - 77306678K Date: 2025.05.15 20:58:53 +02'00'

Reus a 15 de maig de 2025

**Lliurar una còpia al tutor i adjuntar una còpia amb la signatura original al Treball escrit. La suplantació de la signatura original està tipificada com a falta greu i serà objecte d'expedient.

12.4. Appendix 4: Data Protection Requirements. Participant Information Sheet and Informed Consent Form

FULL D'INFORMACIÓ AL PARTICIPANT

Naturalesa del Projecte

El Projecte d'Investigació per al que li demanem la seva participació té per títol **"Efectes del tractament radioteràpic a dosis baixes en pacients amb patologia benigna."**

L'objectiu de l'estudi és valorar la resposta clínica dels pacients amb patologia benigna tractats amb radioteràpia a dosis baixes i correlacionar-la amb biomarcadors d'activitat inflamatòria.

Per l'estudi es demanarà la seva participació durant el període que realitzi el tractament amb radioteràpia (6 Gy a 0.6 Gy 5 sessions per setmana) i 1 mes després d'acabar aquest tractament radioteràpic.

Els investigadors responsables d'aquest estudi pertanyen al Servei d'Oncologia Radioteràpica de l'Hospital Universitari Sant Joan de Reus i compten amb la col·laboració d'investigadors de la Unitat de Recerca Biomèdica de l'Hospital Sant Joan de Reus.

Procediments

La participació en l'estudi consisteix en:

- Permetre que els investigadors puguin conèixer i treballar amb dades com el diagnòstic, l'edat, l'evolució de la malaltia, entre d'altres.
- Respondre a tests i qüestionaris específics d'investigació, a més de l'entrevista i proves necessàries per l'estudi.
- Permetre que li practiquin una extracció sanguínia abans del tractament radioteràpic i un mes després de finalitzar-lo.

Totes les dades recollides per a al recerca es guarden en uns fitxers informatitzats especialment dissenyats per a la Recerca i en cap d'ells apareix ni el seu nom ni cap dada que pugui identificar-lo.

Les mostres de sang són processades per separar el plasma de les cèl·lules. El plasma es guarda congelat per les anàlisis bioquímiques.

Beneficis i Riscos

El benefici de l'estudi és aprofundir en el coneixement del tractament de la malaltia amb la finalitat de millorar-lo. A curt termini no es preveu que els resultats obtinguts en l'estudi puguin beneficar directament al participant, sinó que seran uns resultats que beneficiïn a la població en general.

Aquest estudi pot contribuir a conèixer millor el mecanisme del tractament radioteràpic a dosis baixes, però en cap cas vostè com participant rebrà cap compensació econòmica. L'estudi no suposa cap risc que no sigui el derivat de l'extracció de sang.

Garantia de Participació voluntària

Els investigadors li garantim que sigui quina sigui la seva decisió respecte a la participació en el projecte, la seva atenció sanitària per part del personal de l'Hospital no es veurà afectada. A més, en el cas de que vostè accepti participar, l'informem que es pot retirar en qualsevol

moment sense haver de donar explicacions i en aquest cas la seva mostra seria retirada així com també, les seves dades dels fitxers informàtics.

Confidencialitat

L'hospital i els investigadors es responsabilitzen de que en tot moment es mantingui la confidencialitat respecte a la identificació de les dades del participant. El nom i les dades que permeten identificar al pacient només consten en la història clínica. Els investigadors utilitzen codis d'identificació sense conèixer el nom de la persona a la que pertany la mostra. Aquests procediments estan subjectes al que disposa la Llei Orgànica 15/1999 del 13 de desembre de Protecció de Dades de Caràcter personal i el Reglament (UE) 2016/679 del Parlament Europeu i del Consell de 27 d'abril de 2016 de Protecció de Dades (RGPD).

Preguntes

Arribat aquest moment li donem la oportunitat de fer preguntes. Li respondrem el millor que puguem.

CONSENTIMENT INFORMAT

El/La.....
Informa el Pacient o Representant Legal (familiar de referència o tutor) Sr./Sra
.....
de l'existència d'un projecte d'investigació sobre:
"Efectes antiinflamatoris del tractament radioteràpic a dosis baixes en pacients amb patologia benigna". I se li demana la seva participació.

Aquest projecte té per objectiu valorar la resposta clínica al tractament dels pacients amb patologia benigna tractats amb radioteràpia a dosis baixes i correlacionar-la amb biomarcadors d'activitat inflamatòria.

També és necessari treballar amb algunes dades de la història clínica.

L'estudi no suposa cap risc que no sigui el derivat de l'extracció de sang.

El benefici de l'estudi és aprofundir en el coneixement de la malaltia per millorar i el tractament. A curt termini no es preveu que els resultats obtinguts de l'estudi puguin beneficiar el subjecte participant, sinó que en tot cas seran uns resultats que beneficiaran a tota la població.

Els responsables de l'estudi, i per tant de les mostres i les dades, són investigadors de l'Hospital Universitari Sant Joan de Reus, l'Institut d'Investigacions Pere i Virgili i la Universitat Rovira i Virgili que poden establir col·laboracions científiques amb altres institucions acadèmiques o empreses privades. La col·laboració amb altres institucions pot suposar que se cedeixi part de la mostra, procediment que es farà sota les normes de confidencialitat i seguretat que li hem explicat.

L'equip investigador garanteix la confidencialitat respecte a la identitat del participant i d'altra banda garanteix que la mostra i els resultats derivats de la investigació seran utilitzades per a les finalitats descrites i no unes altres.

He estat informat de la naturalesa de l'estudi que es resumeix en aquest full, he pogut fer preguntes que aclareixin els meus dubtes i finalment he pres la decisió de participar, sabent que la decisió no afecta a la meva atenció terapèutica al centre i que em puc retirar de l'estudi en qualsevol moment.

	Nom i cognoms	Data	Signatura
Pacient			
Familiar o tutor			
Informant			