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Low-Dose Radiation Therapy for Painful Osteoarthritis: An Emerging Treatment Modality

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Abstract

Osteoarthritis is the most common degenerative joint disease worldwide, and its prevalence is steadily rising due to an aging population and increased risk factors such as obesity and sedentary lifestyles. Despite the increase in investigative research on Low-Dose Radiation Therapy (LDRT) occurring in other countries and current clinical use, LDRT is inappreciably used in the United States.

Numerous studies published outside the U.S. indicate moderate to long-term pain relief and increased mobility following the treatment of joints affected by osteoarthritis with LDRT. Here, we discuss the pathophysiology, risk factors, and current recommendations for the treatment of osteoarthritis. Also, included is a brief outline of the anti-inflammatory and immune modulatory effects of LDRT as well as a synopsis of relevant clinical outcomes in patients being treated with LDRT for osteoarthritis? LDRT is a non-invasive, pain-relieving treatment with minimal risk of side effects to patients.

Further investigation and research into using LDRT as an alternative therapeutic agent for patients with osteoarthritis is recommended.

Introduction

Since the discovery of X-Rays, many advances have been made in our understanding of the benefits of Radiation Therapy (RT). It has become apparent that RT has different biological effects at different doses [1].

Osteoarthritis (OA) is a degenerative disease in which the cartilage is gradually destroyed with aging and structural deformation. According to the World Health Organization (WHO), OA is one of the fastest growing health problems, and is the second leading cause of disabilities in the United States [2].

OA can be caused by overweight and/or improper loading of the joint, injuries, dysplasia, or other arthropathy. Progressive destruction of the joint cartilage may potentially involve the bone, the joint capsule, and the adjacent muscles. OA may be the cause of pain.

Initially, repeated movements of the joint may be painful; but, as time progresses, pain may occur during rest. Later we may observe deformation of the joint, as well as impaired movement [3].

There are several treatment options including Physical Therapy (PT), NSAIDS, Intra-articular Corticosteroid or Hyaluronic Acid Injections, and surgical interventions such as joint replacement or arthrodesis [4].

Reports in the medical literature indicate that Low Dose Radiotherapy (LD-RT) may have moderate to long-term efficacy in the treatment of OA with minimal clinical side effects [5,6]. This paper will explore the use of low dose radiation therapy, as an emerging treatment modality for painful osteoarthritis.

Pathophysiology of OA

OA is a disabling and progressive joint disease that commonly affects weight-bearing joints including the knees, hips, hands, and vertebrae. While osteoarthritis was previously categorized exclusively as an age-related, “wear and tear” degenerative joint disease, recent research suggests that proinflammatory markers are heavily involved in the disease process. OA pathology involves the complex interactions between multiple pathological events including oxidative stress, synovitis, and immune-mediated responses, all which result in the degradation of cartilage. The underlying disease process and pathogenesis of OA is not entirely understood and has continued to evolve over the years.

One of the primary functions of chondrocytes is to detect mechanical stress *via* receptors located within the extracellular matrix. Repeated stress placed on a joint over time may result in increased signaling of chondrocytes receptors, creating inflammation and up regulation of enzymes, such as aggrecanase and collagenase. The primary function of these enzymes is to degrade collagen, and when they are consistently up regulated irreversible cartilage breakdown results.

Additionally, progressive chondrocytes loss causes remodeling of subchondral bone, which involves the formation of new vascular channels. These channels facilitate the interaction and communication between bone and cartilage. In response to repeated chondrocytes stimulation, proinflammatory markers travel through the vascular channels and act asparagines factors when they reach the synovial fluid. This process triggers an inflammatory response by up regulating macrophages that reside in the synovial fluid of the joint, further perpetuating the cycle of cartilage breakdown.

It is significant to note that vascular channels contain various sensory nerve endings which may be over stimulated in response to chronic inflammation. The repeated stimulation of the vascular nerve endings, in addition to the associated innervations and stimulation of the articular cartilage is thought to be a contributing factor to the pain patients experience with OA.

The clinical presentation of OA includes joint stiffness, pain, and decreased mobility that occurs with activity, or in the more advanced stages of disease, occurs at rest. Radiographically, patients may present with visibly reduced joint space, osteophytes, bone deformities, and thickening of subchondral bone [7].

Risk Factors for OA

The risk of developing OA depends on both joint-specific factors and systemic factors. Joint specific factors are related to mechanical stress that is placed on the joint, while systemic factors include a combination of inflammatory and metabolic processes. OA is more prevalent among women than men, is more frequently diagnosed in patients between 40-50 years of age and has a higher prevalence in developed rather than developing countries.

Specific risk factors for OA include aging, obesity (BMI > 30 kg/m^2), a sedentary lifestyle, smoking, sarcopenia, osteoporosis, various genetic factors (including genes

encoded for IGF-1, collagen, or the vitamin D receptor), diets low in vitamin D, C, and K, abnormal weight bearing and loading of the joints, and structural malalignment of the joints [8].

Traumatic knee injuries are considered one of the most important risk factors in the development of knee OA. Injuries that include, but are not limited to ACL and meniscus tears, joint dislocations, and fractures increase the risk of developing OA. Similarly, physical activities that include excessive loading of the joint and mechanical stress, repetitive kneeling, and squatting increase the risk of developing OA [9].

Current Treatment Available for OA

The exact disease process involved in OA is multi-factorial, and therefore, there is no definitive treatment protocol that has been established. Typically, treatment for patients with OA begins with a conservative approach that consists of physical and exercise therapy, lifestyle modifications (i.e., weight loss), and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Additionally, intra-articular joint injections of glucocorticoids and other substances have been explored with the goal of reducing systemic side effects, as the drug is introduced directly into the joint. Being a pathologically complex disease, OA typically requires a multifaceted treatment approach to have an impactful effect on pain reduction.

According to the Osteoarthritis Research Society International and American College of Rheumatology, treatment modalities for OA currently include, but are not limited to, land and water-based exercise, walking with a cane, transcutaneous electrical nerve stimulation, weight control, acetaminophen, duloxetine, oral or topical NSAIDs, intra-articular corticosteroids, and opioids.

Unfortunately, conservative approaches (i.e., physical therapy, NSAIDs) may become less effective over time, ultimately requiring patients to undergo surgical intervention (i.e., arthroplasty, osteotomy). The goal of surgical interventions is to reduce pain, decrease disability, improve patients' ability to perform their activities of daily living, and to increase their quality of life. As a whole, treatment for OA should be tailored and individualized to the needs of each patient according to their symptoms, disease progression, pain severity, and personal goals regarding treatment [7].

Low Dose Radiation Therapy

In the field of radiation oncology, low dose radiation therapy is used in the treatment of various benign cancers and conditions including meningioma, vestibular schwannoma, paraganglioma, hidradenitis suppurativa, orbital pseudo tumor, fascial fibromatosis, and as preventative therapy against keloids. Radiation is a form of energy that is targeted to damage the genes in DNA cells. Damaged cells are rendered unable to replicate and divide, causing programmed cell death, or apoptosis, to occur. This effect is favorable in the treatment of cancer, as radiation therapy is designed to prevent the growth and division of rapidly dividing cancer cells. However, radiation also damages normal, healthy, rapidly dividing cells, thus increasing the risk of significant side effects in patients undergoing this therapy [10].

LDRT involves the use of radiation at lower doses than those used in traditional radiation therapy. The use of low-dose radiation therapy is proposed to be immune modulatory and anti-inflammatory by way of modulating several inflammatory pathways that involve macrophages, leukocytes, and endothelial cells. On the other hand, high-dose radiation therapy is proposed to be immune suppressive and pro-inflammatory. Additionally, HDRT produces cytotoxic effects that are less prominent with the use of LDRT. The anti-inflammatory effect of LDRT has rendered it an effective therapeutic treatment for chronic inflammatory and degenerative diseases such as OA [11].

Effects on Immune System

The use of ionizing radiation as a therapeutic has significant implications on the immune system. LDRT contributes to reduced inflammation, increased tissue regeneration,

inhibition of atypical immune responses, and pain relief. As a result, this therapy is particularly useful for patients diagnosed with chronic, inflammatory, degenerative diseases like osteoarthritis.

The initial step in the inflammatory response includes the recruitment and adhesion of leukocytes to the endothelium located at a site of tissue damage. LDRT reduces the adhesion of leukocytes to the endothelium. In response to decreased adhesion, endothelial cells secrete the highly anti-inflammatory cytokine TGF-B1. Further, lack of adhesion contributes to the modulation of reactive oxygen species *via* E2 related factor (Nrf2) and *via* anti-oxidative enzymes including superoxide dismutase, catalase, and glutathione peroxidase. This cascade of events can significantly reduce the inflammation, and subsequently, can help reduce the pain experienced by patients with degenerative joint disease. Another key mechanism of the inflammatory response involves the differentiation of monocytes into macrophages. Macrophages function to produce various inflammatory compounds, nitric oxide being one of the most notable. Nitric oxide propagates vascular permeability, edema, and inflammatory pain. LDRT targets and impairs activated macrophages, thus decreasing the synthesis of nitric oxide. This reduction *via* treatment with LDRT may contribute significantly to the reduction in inflammatory pain for patients with osteoarthritis [11].

It is important to note that while LDRT has been used for many years, the precise effects of radiation on the immune system are still rather unclear. The IMMO-LDRT01 trial analyzed the effects of LDRT on the immune system, pain reduction, and impact on quality of life in patients. In the trial, 125 patients had their blood drawn after irradiation with 0.5 Gy and during follow-up appointments. The findings from this study indicated that the total number of leukocytes in the blood did not change, there was a slight reduction of eosinophils, basophils and dendritic cells, and the number of B cells increased. Most notably, monocytes and monocytes-related cells significantly decreased following treatment with LDRT. This study concluded that the treatment of patients with LDRT reduces pain through modulation of specific immune cells and biomarkers [12].

Clinical Outcomes

For several decades, LDRT has been evidenced by several clinical trials as an effective alternative treatment for patients with OA. The existing clinical trials indicate symptom anticipant relief displayed in 63% to 90% of all patients treated with LDRT [13].The University Hospital Erglangen conducted a study between 2004 and 2019, comprising a total of 483 patients with degenerative joint disease of the fingers and/or thumb who underwent LDRT. About 461 patients received a total dose of 3 Gy of radiation, and 22 patients received a total dose of 6 Gy. The study concluded that 70% of patients reported a reduction in their subjective pain immediately after treatment and during follow-up appointments at 8 weeks, 12 weeks, and 6 months. Additionally, patients who received dosages in increments of 0.5 Gy had better outcomes than patients who received dosages in increments of 1.0 Gy [14].

In a study conducted between April 2015 and March 2021, a total of 100 patients (median age of~60) suffering from OA of the hand and/or fingers were treated with LDRT consisting of 6 fractions of 0.5-1 Gy every other day until reaching a total dose of 3-6 Gy. The Visual Analogue Scale (VAS) was used to assess patient pain level and the Von Pannewitz Score (VPS) was used to assess joint functionality. At a median follow-up of 10.5 months, 94% of patients reported decreased pain indicated by a reduction in the VAS level. Approximately 70 patients had functionality improvements after treatment with LDRT as measured by the VPS score [15].

Finally, it is important to note that other smaller scale studies have found no significant differences compared to placebo or conservative treatments. For example, a randomized control trial published in the Cochrane Central Register of Controlled Trials assigned a total of 55 patients to two groups. The first group received LDRT (1 Gy per fraction) six times in 2 weeks, and the second group received a “sham” treatment. After 3 months, 44% of

patients treated with LDRT and 43% of patients in the control group responded to treatment according to the OMERACT-OARSI criteria. The study concluded that there was no significant difference in response between the two groups [16].

Treatment Risks

A main consequence associated with the use of ionizing radiation is DNA damage to normal tissues positioned in the area receiving radiation. Effects of radiation on normal tissue often vary, as toxicity is dependent on the affected organs' cellular characteristics and function. Adverse effects include but are not limited to dermatitis, fibrosis, lymphedema, bone pain, cognitive effects, mucositis, xerostomia, osteoradionecrosis, gastritis, pneumonitis, pericarditis, esophagitis, and cystitis. Further research is needed to establish the safety and effectiveness of LDRT, as the evidence supporting its use is currently limited and conflicting, and little is known about its long-term effects [17].

Current research and clinical trials indicate that the use of LDRT in the treatment of OA does not pose a significant risk of side effects. Experiments have shown that at a low dose, ionizing radiation may up regulate cytoprotective mechanisms that improve a cell & # 39s; ability to better survive a subsequent, high dose of radiation. This is the basis for which oncologists pretreat cancer patients with low dose radiation before administering high dose radiation [18]. However, the long-term effects for patients being treated with LDRT for OA remain unclear due to the limited number of clinical trials that have been conducted, and subsequently, the limited number of patient follow-up and evaluation after an extended period post-treatment.

Conversely, the current treatments available for OA carry certain risks of their own. NSAID use is associated with gastrointestinal bleeding, myocardial infarction, stroke, bronchospasm, and acute kidney injury [19]. Intra-articular corticosteroid injections are associated with the risk of subcutaneous atrophy, cushingoid appearance, joint infections, post-injection flare, tendinopathy, albicans arthritis, asymptomatic hydroxyapatite calcifications, and saphenous neuropathy [20].

Surgical interventions, such as total hip/knee replacements carry risk of bleeding, interventional complications, deep joint infection, pulmonary embolism, and dislocation, to name a few [10].

Discussion

OA is the most common degenerative joint disease across the world, and it places a large burden on the population. Patients experience debilitating pain, stiffness in weight bearing joints, and eventual disability that ultimately may require surgical correction. OA causes a significant reduction in physical functionality and interferes with activities of daily living.

Decreased activity may contribute to the development of multiple comorbid conditions, an increased need for medication and subsequent side effects, plus increased financial burdens on afflicted patients and society [9].

Additionally, the burden of this disease has numerous psychological effects, potentially increasing the incidence of anxiety and depression [21].

LDRT is currently being used and investigated in other countries; however, it is only minimally used in the United States. There have been many recent studies indicating that LDRT provides pain reduction, increased joint mobility, and subsequently, increased quality of life in patients with degenerative joint disease. Given the nature, severity, and trajectory of OA, along with the limited effectiveness of current treatment modalities, it is reasonable to consider LDRT as a possible alternative therapeutic treatment option.

In the United States, multiple smaller scale studies have produced positive outcomes in terms of pain relief, improved joint function, and reduced inflammation in patients with OA, while others have found no significant differences compared to placebo or conservative treatments. To further expand, evaluate, and develop the existing literature regarding the treatment of OA with LDRT, it is necessary to increase the sample size of patients enrolled in clinical trials. Additionally, to determine the effectiveness of

LDRT for OA, a larger population of patients should receive education about this alternative treatment and be given the opportunity to participate in randomized controlled trials with the approval of their physician [13].

Conclusion

Despite the utilization of LDRT for OA in other countries, this treatment is rarely used in the United States. As indicated by many clinical trials and studies published in other countries, LDRT as an alternative therapeutic agent signifies moderate to long term pain relief, increased joint functionality and mobility, and increased quality of life for patients with OA. Further, recent research suggests that LDRT is associated with few adverse effects and is relatively non-invasive. Efforts to expand and develop the current literature and explore alternative treatment modalities for OA are recommended.

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