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Treatment Options for Osteoarthritis: Using Ultra Low-dose Radiation

Osteoarthritis is a problem and problematic complaint of patients especially elderly patients. The current recommendation is anti-inflammatory medications or biologics to address severe osteoarthritis. However, in many cases, the long-term use of anti-inflammatories or biologics still does not address the patient's complaint of particular pain in particular areas. The side effects of long-term anti-inflammatory medications are numerous that have been reported in literature. Amongst them include gastric upset or ulceration and blood or platelets alterations. Biological treatment also has numerous side effects as well as chemotherapy agents, such as methotrexate.

In the decades before prevalent use of anti-inflammatory agents when no other agents were available, low-dose radiation for benign conditions including severe arthritis was instituted. However, this practice faded with the development and use of anti-inflammatory agents and later biologics and/or chemotherapy agents.
However, long-term use of these medications produces significant morbidity in some patients and did not specifically address the patients' complaint of particular areas. The patients become sometimes frustrated because of the lack of palliation of their pain.

Radiation therapy has different biological effects in different doses. In normal fractionation schedule, it has anti-tumor proliferative effect in the treatment of malignant disorders. **Alternatively smaller doses, radiation therapy has been shown to have strong anti-inflammatory effects. By using the anti-inflammatory properties of low-dose radiation, it has been used successfully treat painful musculoskeletal conditions, such as plantar fasciitis, trochanteric bursitis, medial and lateral epicondylitis, tendinopathies of various joints, and osteoarthritis of both the large and small joints have been shown to benefit.**

With more than 32 million Americans affected by osteoarthritis, the need for treatment of disease is significant. Osteoarthritis is characterized as a progressive disorder particularly presenting with signs of joint stiffness, pain and loss of mobility. It is also known that osteoarthritis results in degeneration of the cartilage between the bones and the joints. The underlying pathogenesis and mechanism of osteoarthritis are complex and the understanding of exact mechanisms is evolving. It is hypothesized that the pro-inflammatory mechanisms drive the recruitment of proteolytic enzymes, which lead to degradation of extracellular matrix. This results in damage to bone, articular cartilage, menisci, ligaments, and synovium, which is further exacerbated by excessive joint loading.

Osteoarthritis is more likely to be diagnosed in individuals with the risk factors, such as older age, female sex, higher body mass index, family history of osteoarthritis, anatomic factors including joint alignment and shape or previous joint injury. Although poorly understood, there appears to be a genetic predisposition for osteoarthritis in patients who have a family history of disease. Additionally, previous joint injury has been shown to increase the risk of osteoarthritis.

Current Treatment:
The exact disease mechanism is unknown and the etiology appears multifactorial. There is no definitive intervention for early stage degenerative osteoarthritis and treatment for late stage is focused on palliation of symptoms with the aim to restore the patient's mobility and thus improve their quality of life. Which interventions to implement varies among patients and no universal guidelines exist for the specific sequencing or combination of interventions across all patients. Weight loss, moderate levels of physical activity and physical rehabilitation are some of the conservative therapies. Non-steroidal anti-inflammatory drugs (NSAIDS) are usually the first-line treatment after a trial of conservative management and are typically helpful in alleviating pain, but also carry the risks with long term use including cardiovascular events, gastrointestinal bleeds and chronic or acute renal failure. In older patients who are more likely to be affected by osteoarthritis, the risk of NSAID use has been shown to have an excess risk of 7 in 1000 non-fatal CV events per year, 2 in 1000 fatal CV events per year and a four-fold increased risk of gastrointestinal bleeds. Additionally, about 25% of all patients will not respond to these therapies or lose their responsiveness over time.

Intra-articular NSAIDs, corticosteroids and biologic therapies can provide some relief. For a small portion of patients, surgical intervention such as joint lavage, debridement, synovectomy, radiofrequency ablation, or even prosthetic replacement might be indicated, carrying their own inherent risks of bleeding, infection or other interventional complications.

Use of very low doses of radiation:
In other countries, such **as Germany, over one-third of all radiation therapy treatments are for benign diseases including 15,000 patients with osteoarthritis**. In the US, thousands of patients are treated each year for various benign diseases, such as meningioma, schwannoma, paraganglioma, hidradenitis suppurativa, orbital pseudotumor, fascial fibromatosis, prevention of recurrent keloids, and prevention of heterotopic ossification. For several decades, low-dose radiation therapy has been used in the treatment of a wide variety of inflammatory conditions including symptomatic osteoarthritis. **Low-dose radiation therapy has been positioned as an effective therapeutic alternative for osteoarthritis evidenced by multiple clinical trials with symptomatic pain relief shown in 63% to 90% of all irradiated patients, with almost no acute side effects.**

Radiobiological Mechanism:
The exact pathophysiologic mechanisms of pain relief after radiation therapy are continuing to be investigated. However, radiobiological studies show that low doses of radiation have anti-inflammatory effect based on the modulation of a multitude of inflammatory pathways and cellular components including endothelial cells, leukocytes and macrophages. Macrophages have been shown to play an integral role in the inflammatory pathway via multiple pathways including ability to secrete proinflammatory cytokines, reactive oxygen species and nitric oxide.

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Risk of Secondary Malignancy:
Low doses of radiation therapy have the potential for the induction of secondary malignancy, believed to occur as a stochastic effect with no threshold point and an increased risk proportional to increased dose. When evaluating the carcinogenic risk of low-dose radiation therapy in the treatment of osteoarthritis, factors such as age and anatomic location of treatment is considered. One study published in Radiotherapy and Oncology estimated the risk of fatal tumor induction with radiation therapy with total dose of 6 Gy for knee osteoarthritis at the age of 25, 50 and 70 was 2 in 1000, 0.7 in 1000, and 0.3 in 1000 patients, respectively, when assuming an estimated effective dose of 13 mSv (which is an effective dose similar to an abdominal and pelvic CT scan).

Discussion:
Low-dose radiation therapy historically was used within the US and subsequently abandoned, advancements in our understanding of the radiobiology of low-dose radiation therapy and its anti-inflammatory effects could lead to prospective reinvestigation of the efficacy of low-dose radiation therapy. There is strong data to suggest low-dose radiation therapy in plantar fasciitis is about 80% effective in reducing pain. There is data to suggest benefits in other musculoskeletal disorders, such as trochanteric bursitis, medial and lateral epicondylitis, tendinopathies of various joints, Dupuytren contracture, Ledderhosen disease, heterotopic ossification, and other disorders.

The American Society for Radiation Oncology suggest a criterion for use of low-dose radiation therapy in treatment. There is extensive experience in this and the German study as well as other studies outside the US which have showed moderate to long-term pain relief and improved mobility after treatment with low-dose radiation therapy to joints, which is highly cost effective with minimal side effects.