Is it time to redefine the role of low-dose radiotherapy for benign disease?

It is estimated that 24% of the general adult population is currently suffering from osteoarthritis (OA), affecting 10% of men and 18% of women over 60 years of age in high-income countries. A WHO report predicted that degenerative OA will become the fourth leading cause of disability by 2020.[1] This may not only affect the individuals who suffer from the diseases, but will undeniably have an impact on national health systems in social and economic terms.

There is no specific or definitive treatment for the early and late stages of degenerative OA. Weight loss, maintaining moderate levels of exercise and physical rehabilitation approaches (local heat, magnetic therapy and shock waves, among others) are some of the conservative therapies applied. Analgesics and non-steroidal anti-inflammatory drugs, symptomatic slow-acting drugs for OA, corticosteroids, anaesthetics and other local injections have been proposed for the relief of the symptoms before a prosthetic replacement of the damaged joint would finally be carried out at the end of a long road. None of these options have demonstrated high efficacy, and even more importantly can provoke multiple side effects and acute and late morbidities (ie, gastrointestinal bleeding, kidney and cardiac disorders, and so on) which may become serious and even compromise the patient's life.[2]

The clinical effectiveness of low-dose radiation therapy (LD-RT) in the range of 0.3–0.7 Gy single dose and 3–10 Gy total dose for pain relief and subsequent improvement of joint functionality has been recognised for several decades. Further, the anti-inflammatory efficacy of LD-RT has been confirmed in several experimental models, both in vitro and in vivo.[3–7] The first clinical evidence of its efficacy in non-cancerous osteoarticular disorders dates from the end of the 19th century, although there has traditionally been some resistance for its widespread use due to the fear of its possible side effects and carcinogenesis. However, the clinical experience of using LD-RT acquired in recent years regarding its radiobiological and immunological mechanisms of action,[8 9] its low toxicity profile and its proven effectiveness in degenerative OA has reinforced its role as a therapeutic alternative in these patients without other options. This has been evidenced by a multitude of trials. In addition, radiotherapy is a non-invasive treatment that does not interfere with other therapies, something of great importance considering most candidate patients' multimorbidity characteristics.

In 2017, at the 37th European SocieTy fo Radiotherapy and Oncology (ESTRO) Annual Congress, Minten *et al*[10–12] presented and has since published the results of two double-blinded randomised trials on the effect of LD-RT therapy for symptomatic relief and functional improvement of degenerative OA of the hand or knee joints. They provided the first clinical studies that compared a modern radiation therapy technique with a sham irradiated group with identical patient and disease characteristics. In the first study, the authors analysed the results observed in 56 patients with OA of the hand (finger joint OA or rhizarthrosis), while in the second study 55 patients with OA of the knee were enrolled, applying the same randomised, double-blinded design of radiotherapy at low dose (6 Gy in fractions of 1 Gy, 3 fractions/week) versus sham radiotherapy. In both studies, the authors evaluated the clinical response at 3 months of treatment according to the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) response criteria, including evaluation of pain and functionality of the treated joints. At 3 months' follow-up, the authors did not observe any differences in any of the response parameters analysed between the group of patients who received radiotherapy and those who did not (sham treatment).

The results of these two well-designed studies raise some questions regarding the effectiveness of radiotherapy at low doses in degenerative osteoarticular disorders from the perspective of radiation oncologists with several years of clinical experience in the use of LD-RT for the symptomatic relief of these diseases. Several aspects should be taken into account when definitively evaluating the possible negative impact of these findings.

First, under the term 'osteoarticular pathology', very different entities are included, covering both OA and enthesopathies. Although radiotherapy is effective in the symptomatic treatment of osteoarticular disorders, it is well described that a higher rate of complete pain remissions is achieved in the treatment of patients with calcaneodynia, achillodynia, bursitis trochanterica and shoulder syndrome (enthesopathies) than in the treatment of gonarthrosis. Degenerative OA of the knee or of the interphalangeal joints of the hand is a chronic disorder with destruction of the bone and cartilage; although radiotherapy can alleviate the inflammation and pain symptoms secondary to the joint destruction, the underlying pathophysiological mechanisms will continue without evident changes. Therefore, the analgesic effect is lower than that observed in other disorders.[13 14]

Second, since 2000, at least six clinical studies have been published on the efficacy of LD-RT in degenerative knee or hand OA, including a total of 1508 patients who were analysed retrospectively[13 15–17] or prospectively[14 18]. Irradiation doses ranged from 3 to 6 Gy total dose with a fractionation of 0.5–1 Gy single dose and 2–3 fractions per week. With a median follow-up of 3–48 months (median 29 months), the response rate mainly referring to pain relief ranged from 63% to 90% in the different clinical series. However, between 7% and 100% of the patients (median 15%) required a second course of radiotherapy 6–12 weeks later to reach a positive clinical outcome if the initial result had not been completely satisfactory. Further, Mücke *et al*[19] collected data from 238 institutions in Germany, of which 188 (79%) used LD-RT for the treatment of knee OA. The authors reviewed data from 4544 patients treated in 2008 with a median dose of 6 Gy (range 3–12 Gy) by two or three weekly fractions of 1 Gy of median dose (range 0.25–3 Gy). Thirty per cent of patients received a second series of radiotherapy 6–12 weeks after completion of the first. The authors observed symptomatic pain relief in 79.5% of patients.[19] Thus, we believe that these studies clearly show the real achievable goals that LD-RT can produce.

Third, the striking question raised by the two articles is whether LD-RT has to be definitively dropped from our protocols for OA, as suggested by the authors, or it has to be restricted only to the most refractory patients. Usually LD-RT for OA is delivered to patients with very chronic disease and is unsuitable for other treatments. Thus, the assumed goal of improvement in 40% of the patients in the LD-RT arm is considered too highly optimistic, being a drawback of the studies. Another important aspect is that the small number of patients could raise doubts regarding the statistical results. The percentage of patients who responded to the placebo was unexpectedly high. Further, the inclusion of patients with a higher body mass index in the LD-RT group might falsify the results. It has become obvious that overweight persons do have a permanent higher basal level of inflammation (summarised in ref 20) and a direct comparison with the placebo group is therefore difficult.

Furthermore, a delayed onset of the analgesic effects of LD-RT was established previously and results showed a significant improvement in long-term efficacy compared with results obtained immediately after radiotherapy.[8 9 13] In the two randomised studies, however, the evaluation of the outcome was limited to 3 months after completion of treatment. Thus, no long-term benefit was evaluated at 6 or 12 months. In addition, the studies did not offer to carry out a second series of irradiation, which, according to the experience of previous clinical studies, can benefit a high percentage of patients.[13–19]

The design and evaluation of both randomised trials, including different clinical questionnaires and the assessment of quality of life, are good, but the additional biochemical inflammatory parameters (erythrocyte sedimentation rate and C reactive protein serum levels) do not appear to be very useful criteria for assessing inflammatory response in chronic arthrodegenerative disease. Against this background, Rühle *et al*[9] recently reported on a modulation of T cells and monocytes and a reduction of the activation marker CD69 on T, B and NK cells in the blood of patients with chronic painful musculoskeletal diseases following radon spa treatment.[19] Comparable assays are currently running in patients with LD-RT (NCT02653079) and complementary ones are planned in Spain in the near future.

Additionally, it is important to further take into consideration the very long clinical history and treatment prior to the application of LD-RT, while both studies restricted the inclusion criteria to the duration of symptoms of more than or equal to 5 years in 68% in the LD-RT group and 54% in the sham-treated group.

Finally, the clinical data provided on irradiation volumes, at least with regard to the treatment of arthrosis of the thumb, raise concerns about their suitability, given that a certain relationship had been established previously between the size of the field and response to treatment, with larger fields than those used by Minten *et al* associated with a higher response to treatment, and that to some extent might contribute to the low rate of responses observed in these patients.[17]

In conclusion, the two studies raise very interesting questions, and their extraordinarily accurate design should serve as a basis for future clinical studies that contemplate on the efficacy of LD-RT, and not only restricted to the hand and knee joints. Moreover, the adequate definition of volumes of irradiation, inclusion of a second series of treatment and the evaluation of a long-term response beyond 3 months after the treatment might further contribute to a more accurate selection of patients that most probably will benefit from LD-RT. The future work from these studies is to define the patients who are prone to clinical improvement after LD-RT and to develop biomarkers to predict responses to LD-RT.

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Handling editor Josef S Smolen

Contributors All the authors wrote and reviewed the manuscript.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Montero A, Sabater S, Rödel F, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2018-214873

Received 4 December 2018
Accepted 8 December 2018

Ann Rheum Dis 2018;**0**:1–2. doi:10.1136/annrheumdis-2018-214873

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