Yes, it is time to redefine the role of low-dose radiation therapy for benign diseases! Response to Letter by Montero *et al*

We thank the authors, with affiliations of six departments of radiation oncology in Spain and Germany, for their interest in our randomised controlled trials (RCT) and their compliments on the study designs.[1] Our studies showed no substantial beneficial effect on symptoms of low-dose radiation therapy (LDRT) in patients with knee and hand osteoarthritis (OA).[2 3] These findings dispute the effectiveness of radiation therapy at low doses in OA as commonly used in certain parts of the world. However, the authors mention several aspects, which should be taken into account when definitively appreciating our results, which we like to reply on in this letter.

We agree that OA is a serious health problem considering its high clinical burden, the high and rising prevalence, and the growing impact on healthcare and future economic costs.[4] Subsequently, there is a clear need to improve management of OA that is supported by scientific evidence, as no effective disease-modifying treatments are available. Therefore, current treatment focuses primarily on the reduction of symptoms including pain and loss of function while the importance and efficacy of non-surgical treatment modalities have been described in several international clinical guidelines for the management of knee and hand OA.[5 6] Of note, the authors mention approaches (ie, local heat, magnetic therapy and shock wave) not supported by evidence or included in international guidelines for the management of OA.

The authors state that the analgesic effect of radiation therapy is smaller in OA than other osteoarticular disorders (eg, calcaneodynia, achillodynia, bursitis trochanterica). This statement is based on findings of two observational studies with heterogeneous populations using a single transition question (von Pannewitz scale) that is likely to be biased by social desirability, in particular when assessed by telephone. The inferior design of those studies does not allow evidence-based discrimination in effects between different patient groups. Therefore, well-designed randomised studies in well-defined patient groups are necessary.

Remarkably, the authors mention that the clinical effectiveness of LDRT has been recognised for several decades and that the clinical effectiveness is proven by a multitude of trials. However, the authors ignore the results of our systematic literature review summarising the results of seven clinical observational studies.[7] Indeed, high improvement rates were reported in those studies. However, the methodological quality of all studies was judged as weak (no blinding, retrospective designs, uncontrolled studies and non-validated single-item outcome measures). Therefore, we concluded that there is insufficient high-level evidence available to indisputably demonstrate the effectiveness of LDRT in patients with OA. In addition, two low-quality RCTs in patients with OA were published in the 1970s and showed no effect of a higher dose radiation therapy than recommended in current guidelines.[7] Thus, in our opinion there is insufficient evidence to justify the use of LDRT for OA in clinical practice, which was exactly the motivation for the setting up of our trials.

The authors question several methodological aspects of our study, that is, the assumed and found placebo effect (40% response in the sham group), the unbalance in body mass index (BMI) between groups, the timing of the primary endpoint (3 months after intervention), the validity of the treatment protocol, length of follow-up and lack of assessment of biochemical inflammatory parameters other than erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). We will address these comments point by point:

- We based our assumption of a high placebo effect on previous research reporting on the power of placebo for pain relief in OA, in particular for rather invasive interventions such as sham LDRT, which are associated with higher placebo effects.[8] The 3-month response in knee OA was about 40% in both groups, confirming our assumption and illustrating the substantial effect of placebo and regression to the mean. In addition, LDRT can only have a place in clinical practice when its effect would outweigh the time investment, patients' burden, radiation exposure and costs. It is very likely that placebo and regression to the mean effects are also responsible for the reported improvements of LDRT on symptoms in previous studies suffering from methodological shortcomings.
- The authors assume that a higher BMI in the LDRT group (knee OA) could have affected our results because overweighed persons have a higher level of inflammation. We agree on this point as we cannot rule out BMI as potential confounder due to potential unbalanced randomisation considering the limited sample size. However, as median BMI (and thus inflammation level) was higher in the LDRT group than in the sham group, a potential overestimation of effect is more likely than an underestimation as regression to the mean effect is more likely in the LDRT group. As described in the results section, additional analyses adjusting for BMI did not modify our results. In summary, we do not have any reasons to assume that differences between groups in BMI might jeopardise the results.
- The authors challenge our choice of primary endpoint at 3 months. We hypothesised that short-term effects of LDRT on inflammation (and thus on pain) are more likely than long-term effects. Moreover, we followed the 2015 guidelines for radiation therapy of benign diseases of the German Society for Radio-oncology (DEGRO) stating that evaluation of the treatment effect should be performed after 2–3 months. Nevertheless, clinical results at 6 and 12 months (manuscript in preparation) show invariably no relevant differences between groups in both knee and hand OA trials after long-term follow-up.
- Furthermore, the authors state that low response rates could be attributed to the limited size of the radiation fields. We followed the 2015 DEGRO guidelines recommending that target volumes should include joint cartilage adjoining bony structures, synovial tissue, and adjoining muscles and connective tissues. The total dose should range from 3.0 to 6.0 Gy, with fraction sizes of 0.5–1.0 Gy, applied two to three times per week. All these recommendations were followed in both our studies. A new RCT would be necessary to examine the hypothesis of the authors that a larger field or a smaller fraction size would have resulted in a more positive effect.
- Other than suggested by the authors we did not exclude patients on the basis of symptom duration. In line with the DEGRO guidelines we included the relevant patients, being patients who failed to respond to conservative treatment. Nevertheless, additional analysis with adjustment for symptom duration as potential confounder yielded similar results.
- The authors suggest to use biochemical inflammatory parameters other than ESR and CRP (eg, T and B cells, monocytes)

to assess the inflammatory response. Indeed, previous in vitro and in vivo studies of OA in animal models have shown that LDRT exerts anti-inflammatory effects.[9] However, in humans there is currently no high-level evidence that supports the hypothesis that an anti-inflammatory response leads towards substantial reduction of symptoms in OA. Of note, we did not observe a substantial reduction of symptoms or inflammatory signs. We plan to assess the effect of LDRT on the proinflammatory protein S100A8/A9. To our knowledge, the use of monocytes and T cells to assess inflammatory response in OA is not yet generally accepted and the results reported by Rühle *et al* did not confirm the usefulness of those parameters to assess inflammation in OA.[10] They only observed small fluctuating changes in some parameters during a period of 30 weeks in a heterogeneous sample without data on the clinical diagnosis.

Recently, the evidence for the effectiveness of LDRT for benign (musculoskeletal) diseases has been reviewed.[11] McKeown *et al* conclude that in the UK the use of radiation therapy for benign conditions is limited, in contrast to practice in Germany.[11] They also conclude that interpretation of the literature on radiation therapy for benign conditions is problematic because much of the evidence is based on case reports and single institution case series, although some randomised studies and systematic reviews do exist. There is a need to question and discuss the necessity of treatments commonly used but not supported by evidence. In recent years, this problem has gained more attention and the internationally expanding Choosing Wisely campaign is a good example of the effort taken to decrease tests and treatments that do not have additional value for patients and may even cause harm.[12] We therefore recommend to add LDRT treatment for other benign (musculoskeletal) disorders to the Choosing Wisely list of the European Society for Radiotherapy and Oncology.

Finally, when taking a more reflective and contemplating position, it should be noted that the scenario that unfolds here is not uncommon in history of medicine. There are numerous examples of treatments that have been used for decades and were considered beneficial, based on uncontrolled studies, until higher quality evidence demonstrated that the treatment was not effective. Well-known examples include, for example, hormone replacement therapy for cardiovascular disease in postmenopausal women,[13] steroids after head trauma[14] and surgery in lumbosacral radicular syndrome in the acute phase of the disease.[15] The first results regarding those treatments from high-quality trials were received by disbelief, much alike the current situation. However, arguments that the clinical effectiveness of LDRT has been recognised for several decades and that results of observational studies are positive are not valid. The way forward is clear: the burden of proof to demonstrate effectiveness of LDRT in OA lies with its proponents, and until then, use of this treatment should not be advocated.

In conclusion, considering the consistency of findings of both our trials and the lack of high-level evidence showing the opposite, we feel that it is time indeed to redefine the role of LDRT in knee and hand OA and that deimplementation of LDRT in clinical practice should be seriously and urgently considered. However, we acknowledge the importance of replication to further strengthen the body of knowledge by conducting preregistered well-designed randomised trials with validated outcomes.

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