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EDITORIAL

Low-dose radiotherapy: Mayday, mayday. We've been hit!

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For more than a hundred years the ship cruised through the sea totally unfazed, mighty and big. Over the decades, tens of thousands became acquainted with the luxury and wellness on board. Suddenly, two small icebergs appeared on the horizon ...

Low-dose radiation therapy (LDRT) for benign degenerative inflammatory disorders is well established among German-speaking radiotherapists and a growing number of orthopedic specialists. Nationwide, several thousand patients with painful joints or enthesopathies experience significant pain relief every year using this treatment modality [1–5]. The treatment costs are completely covered by the insurance companies without any doubt. Recently, two randomized, blinded, and sham-controlled trials on knee and hand joint osteoarthritis, however, provided evidence that LDRT does not provide any measurable additional benefit [6, 7]. Could it all be about a placebo effect?

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Mahler et al. [6] evaluated the effect of LDRT on symptoms and inflammation in patients with knee joint osteoarthritis. Patients aged ≥50 years, a pain score ≥5/10, and no response to analgesics and exercise therapy were randomized to receive LDRT (single dose 1 Gy, total dose 6 Gy within 2 weeks; $n = 27$) or sham intervention six times in 2 weeks with a recorded playback of a radiotherapy session instead ($n = 28$). Primary outcome was the proportion of responders at a 3-month post-intervention interval. Secondary outcomes included pain, function, and inflammatory signs assessed by ultrasound, MRI, and serum inflammatory markers (erythrocyte sedimentation rate, C reactive protein). The authors reported no substantial beneficial effect on symptoms and inflammatory signs of LDRT compared with sham treatment.

Minten et al. [7] performed a similar randomized, blinded, and sham-controlled trial in a total of 56 patients with hand osteoarthritis. Likewise, the authors did not demonstrate a substantial beneficial effect of LDRT on symptoms and inflammation compared to sham treatment.

Both trials were well designed, balanced between the treatment arms, and conducted with high quality. As the first published sham-controlled evaluations regarding both entities, these two trials set a standard for the performance of upcoming randomized studies in the field of radiotherapy for degenerative inflammatory disorders. Based on the results of both trials and the absence of other high-quality evidence, the authors advised against the use of LDRT as a treatment option for knee and hand joint osteoarthritis. However, there are several reasons why we think that the results presented are not strong enough to initiate a change in clinical practice. From our point of view, the final conclusion of the authors that future efforts should mainly be focused on "deimplementation" of LDRT is not justified based on the data presented. As the authors stated themselves, both studies have several limitations, such as low patient numbers, the short-term follow-up of only 3 months, and a very optimistic prognosis assessment for the success evaluation in their study design.

The total numbers of patients included in the studies were 55 and 56, respectively. Although the results are interesting and may serve as a good contribution to the discussion of the role of LDRT for benign disorders, they do not have the power to totally delete the existing body of clinical evidence of numerous publications on LDRT for the treatment of painful arthrosis or other benign disorders such as enthesopathies. Of course, well-conducted randomized controlled trials offer a higher level of evidence, but in both trials, the patient numbers were indeed too small for such a clear conclusion advising against the use of LDRT in knee or hand joint osteoarthrosis.

From our own large clinical experience with randomized trials for inflammatory degenerative disorders (Erlangen Dose Optimization Trial, $n = 1080$) we know that the effect of pain control increases over time [8]. Fig. 1 depicts the response rates directly after radiotherapy (early response), and after a 2- (delayed response) and a 30-month (late response) follow-up. There was a clear increase in the rate of patients with complete pain remission during long-term follow-up. A time interval of 3 months after the completion of LDRT is suitable for response evaluation, but it is definitely too early to advise against a treatment which is still regarded as good clinical practice in German-speaking and other countries, especially when arguing with these limited patient numbers.

Another critical point is the patient selection. In both studies, patients with osteoarthrosis and a severe pain syndrome (pain score ≥5 on a 0–10 numeric rating scale for at least 15 of the last 30 days, despite analgesic use and occupational and/or physical therapy) were enrolled. The rationale and concept behind the pain-resolving potential of LDRT is an anti-inflammatory modulation of pain perception on a molecular level. Obviously, advanced osteoarthritis with already fixed bony joint destruction and periarticular soft tissue damage may be less accessible to a certain pain-controlling effect of LDRT as, for example, compared to enthesopathies. These findings were considerably demonstrated in a recent prospective clinical quality assessment [9].

Furthermore, the current state-of-the-art treatment schedule for LDRT for inflammatory degenerative disorders involves 6 fractions of 0.5 Gy/2–3 times per week and a second radiotherapy series after 12 weeks if necessary because of, e. g., insufficient pain relief [8]. It appears not prudent to advise against a treatment well established in a different country unless it is tested according to the current state-of-the-art concept, which was not done in either trial. Many pre-clinical studies have proven that a single dose between 0.3 and 0.7 Gy is significantly more effective in amelioration of inflammation compared to a dose of 1.0 Gy. Discontinuous dose–effect relationships have been widely accepted in the low and intermediate dose range for many years [10].

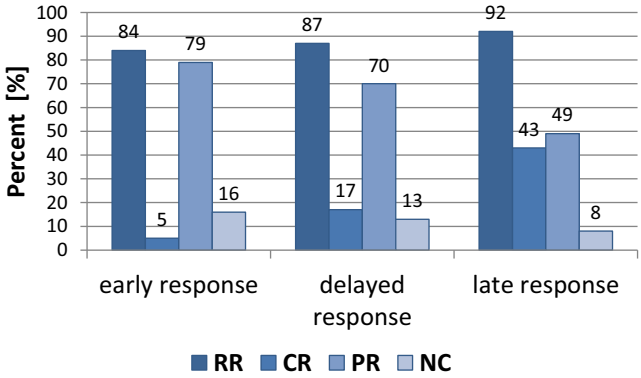

Fig. 1 Overall response rates of 1080 patients of the randomized Erlangen Dose Optimization Trial with low-dose radiotherapy for benign inflammatory disorders. *RR* response rate, *CR* complete response, *PR* partial response, *NC* no change

Just recently, it was demonstrated that particularly a single dose of 0.5 Gy positively impacts on bone metabolism [11]. Clinically, it was proven that radiotherapy with lower single dose of 0.5 Gy and a total dose of 3 Gy is at least as effective as 1.0 Gy/6 Gy total dose [12].

Since the patient numbers are very low in each study arm, the inclusion of patients with a higher BMI in the LDRT group might further falsify the results in the knee joint osteoarthritis trial. It has become obvious that overweight persons have a permanently higher basal level of inflammation, and a direct comparison with the control group is therefore difficult [13].

Another point of criticism is the fact that in both studies, about 50% of the patients had a pain history of ≥5 years before irradiation. Own experience has shown that the response rate of LDRT is rather worse in such clinical situations [14].

Despite the weaknesses of both clinical studies [6, 7], we agree that future optimized randomized trials with higher patient numbers are needed for inflammatory degenerative diseases that are currently routinely treated with LDRT in Germany. Furthermore, additional randomized data are definitely needed to better define the anti-inflammatory and pain-controlling potential of LDRT as well as its beneficial impact on bone metabolism for arthrosis and enthesopathies. Additionally, we will have to learn more about which patients will most probably benefit from LDRT. Currently, detailed immune monitoring is performed within the IMMO-LDRT01 trial (NCT02653079), which might contribute to improved patient stratification in the future. First results of another German randomized and blinded multicenter trial for knee and hand joint arthrosis (ARTHRORAD trial: 6×0.5 Gy vs. 6×0.05 Gy) are expected in 2019.

For us, the two Dutch studies were not convincing enough to change clinical practice in Germany, but they clearly brought the level of clinical trials using LDRT to

a higher level than before and have opened the door for improved design and performance of future randomized trials. We summarize that future randomized trials should include patients with less advanced joint osteoarthrosis, with shorter pain intervals, longer follow-up evaluation (at least 1 year), and with a higher patient number and a reduced response difference estimate between the two or three randomized groups.

The ship passed the two floating icebergs. It was hit but not seriously damaged. The icebergs did not reach deep enough. But it would be a good strategy for captains to strengthen the walls of the ship by designing and initiating better trials, because the next iceberg may be much more bulky.

Conflict of interest O.J. Ott, O. Micke, R. Mücke, M. Niewald, F. Rödel, U. Schäfer, M.H. Seegenschmiedt, M. Arenas, B. Frey, and U.S. Gaipl declare that they have no competing interests. None of the authors had a relationship with an entity that has a financial interest in the subject matter discussed in this manuscript.

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