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ORIGINAL ARTICLE • HIP - RADIOTHERAPY

Short-term pain reduction after low-dose radiotherapy in patients with severe osteoarthritis of the hip or knee joint: a cohort study and literature review

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Abstract

Background Low-dose radiotherapy (LDRT) for pain reduction in osteoarthritis (OA) is a frequently used treatment in Germany and Eastern European countries. The evidence on the effects of LDRT on pain in patients with OA remains unclear. This study evaluated the effect of LDRT on pain in patients with severe OA of the hip or knee joint.

Methods This prospective study included a total of 16 joints in 12 patients (4 hips and 12 knees). The inclusion criteria were: patients older than 50 years, severe OA (Kellgren–Lawrence grade III–IV) of the hip or knee joint, patients not responding to conservative treatment and patients who are inoperable or not willing to undergo surgery. The joint was irradiated with a total dose of 6.0 Gray. The Numeric Rating Scale for pain (NRS-pain) and patient-reported outcome measures were obtained at pre-, 6, 13, 26, 39 and 52 weeks post-radiation. A decrease of two points on the NRS-pain was defined as clinical relevant.

Results The median age of the included patients was 74 years (range 58–89). In 50% of the joints ($n = 8$, 3 hip and 5 knee joints), a clinical relevant difference in pain at 6 weeks post-radiation was observed. This clinical relevant difference decreased to 25% at 52 weeks post-radiation.

Conclusion LDRT showed a clinical relevant pain relief at 6 weeks after radiotherapy. The long-term effect of LDRT, however, was limited. A randomized placebo-controlled trial is necessary to assess the effect of LDRT on pain in patients with OA of the hip or knee joint.

Keywords Hip · Irradiation · Knee · Low-dose radiotherapy · Osteoarthritis · Pain

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Introduction

Osteoarthritis (OA) is a degenerative joint disease which often leads to disability and pain [1]. OA of the hip and knee joint is the most common with a prevalence of 30% of patients above the age of 65 years [2]. The prevalence of elderly patients with OA will furthermore increase as a result of aging of the population [3]. As frailty is highly prevalent in the elderly, these patients are vulnerable for adverse outcomes after surgery. As such, it is of importance to have effective noninvasive treatment options.

Currently, noninvasive treatment options for OA include analgesics, weight loss, physical therapy and ambulatory aids [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injections are considered to be preferred agents for the pharmacological management of OA. However, NSAIDs are associated with an increased risk of cardiovascular events and gastrointestinal problems [4]. Local corticosteroid injections showed no long-term benefits [1].

Low-dose radiotherapy (LDRT) for pain reduction in OA is a frequently used treatment in Germany and Eastern European countries [5, 6]. Despite the use of LDRT in the treatment of OA, the evidence on the effects of LDRT on pain and functioning in patients with severe OA remains unclear. The main goal of this study was to evaluate the effect of LDRT on patients with severe OA of the hip or knee joint who are inoperable or not willing to undergo surgery.

Methods

This study included a total of 16 joints in 12 patients (4 hips and 12 knees). The inclusion criteria were: patients older than 50 years, pain based on severe OA (Kellgren–Lawrence grade III–IV) of the hip or knee joint, patients not responding to conservative treatment and patients who are inoperable or not willing to undergo surgery. Patients with rheumatoid arthritis, ipsilateral prosthetic surgery, lumbar pain or spinal referred pain were excluded.

A computed tomography (CT) scan of the affected joint was performed for treatment planning. The clinical target volume was defined as the affected joints including synovium, bone and surrounding muscle and connective tissue. Furthermore, a planning target volume margin of 1.5 cm was added (Fig. 1). The dose specifications are according to ICRU50 aiming a dose of 95–107% of the calculated dose [7]. The treatment consisted of low-dose irradiation using two parallel-opposed 6 megavolt photon beams. A total dose of 6.0 Gray (Gy) was given in 6 fractions of 1.0 Gy during a period of 2 weeks.

Patient-reported outcome measures (PROMs) were obtained at pre-, 6, 13, 26, 39 and 52 weeks post-radiation. PROMs included the Numerical Rating Scale for pain (NRS-pain, 0 to 10, 10 being 'worst pain'). A decrease of two points or more on the NRS-pain was defined as clinical relevant [8]. Other PROMs included the EuroQol-5D (EQ-5D; 0 to 1, 1 indicates the best health state) and the Oxford Knee and Hip Score (OKS or OHS; 12 to 60, 12 being the best outcome) [9–11]. In patients with bilateral OA of the hip or knee joint, PROMs were analyzed separately. Furthermore, the presence of side effects of LDRT (e.g., pain induction and local tenderness) was documented.

Statistical analysis

All statistical analyses were done with the use of Statistical Package for the Social Sciences version 20.0 for windows (SPSS Inc., Chicago, IL). Descriptive statistics were used to summarize the data. Results are presented as either with median (range) or proportions (%). Significance levels were set at $p \leq 0.05$.

Results

A total of 12 patients (4 hip and 12 knee joints) with a median age of 74 years (range 58–89) were included. The patients' characteristics are presented in Table 1. In Fig. 2, the median NRS-pain during each follow-up is presented. In 50% of the joints ($n = 8$, 3 hip and 5 knee joints), a clinical relevant difference in pain was observed at 6 weeks post-radiation. This clinical relevant difference decreased to 25% ($n = 4$, 2 hip and 2 knee joints) at 52 weeks post-radiation. No differences in EQ-5D, OKS and OHS were observed after radiotherapy (Table 2). Furthermore, no side effects have been reported.

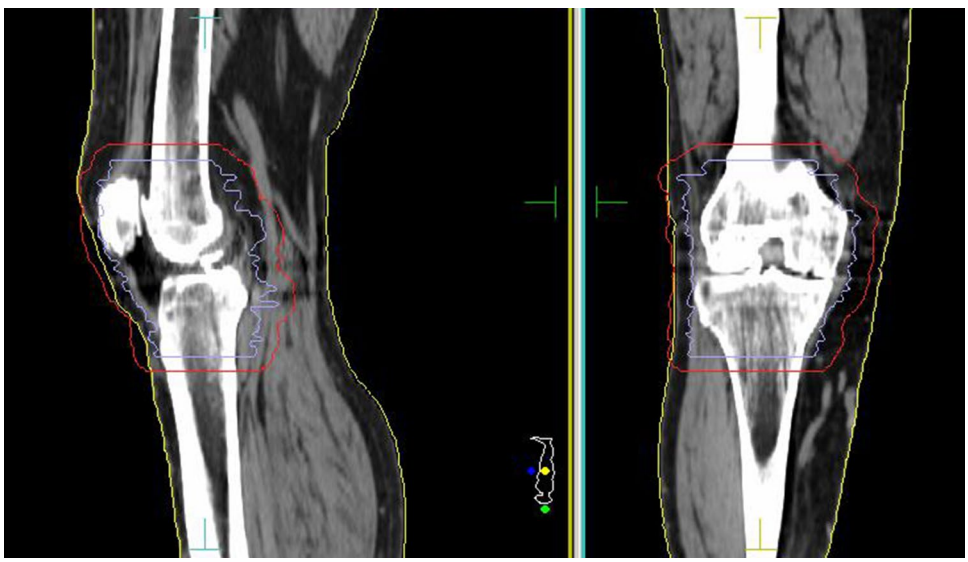

Fig. 1 An example of treatment planning with the use of a CT scan of the knee joint. The red outline represents the clinical target volume, and the purple outline represents the planning target volume (color figure online)

Table 1 Patient characteristics

No.	Gender	Age	ASA	OA	Uni- or bilateral	KL grade
1.	Female	67	3	Hip	Bilateral	3
2.	Female	89	3	Hip	Unilateral	4
3.	Female	86	3	Hip	Unilateral	3
4.	Male	59	2	Knee	Unilateral	3
5.	Male	77	3	Knee	Bilateral	3
6.	Male	58	2	Knee	Bilateral	3
7.	Female	80	2	Knee	Unilateral	4
8.	Female	74	2	Knee	Unilateral	4
9.	Female	87	3	Knee	Bilateral	4
10.	Female	73	3	Knee	Unilateral	4
11.	Female	66	3	Knee	Unilateral	4
12.	Female	72	3	Knee	Unilateral	4

ASA classification American Society of Anesthesiologists classification, *OA* osteoarthritis, *KL grade* Kellgren–Lawrence grade

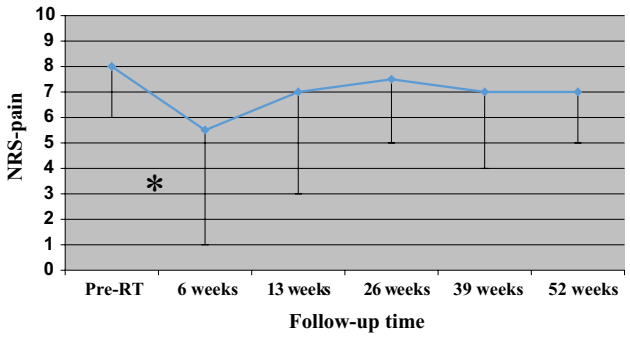

Fig. 2 Median (range) NRS-pain during follow-up. NRS, Numeric Rating Scale; RT, radiotherapy; *clinical relevant

Discussion

The most important finding of this study was that patients showed a clinical relevant pain relief in almost 50% of the joints at 6 weeks after LDRT. However, the long-term effect of LDRT was limited. Furthermore, no improvement in functioning was observed, and no side effects of LDRT were reported.

In the literature, a number of studies described the effect of LDRT on pain reduction in patients with OA of the hip or knee joint (Table 3) [12–20]. Short-term pain relief was observed in 24–91% of patients [13–16, 18–20]. Three studies reported pain relief in 61–78% of patients at 52 weeks post-radiation [12, 16, 18]. These results were higher than in the present study reporting only 25% clinical relevant pain relief at 52 weeks post-radiation. However, these studies had a retrospective observational design, and no validated PROMs were used [12, 16, 18]. Furthermore, the severity of OA was not reported. A recently published randomized double-blinded study showed no effect of LDRT in patients with OA of the knee [20]. The absence of an effect of LDRT in this study can be argued, as the included patients had no synovitis of the knee. The median synovial thickness of the included patients was less than 4 mm corresponding to an absence of synovitis [21]. As the mechanism of LDRT is believed to be anti-inflammatory, the absence of synovitis could have reduced the effect of LDRT in the randomized double-blinded study [20]. The anti-inflammatory effect of LDRT is due to radiation-induced modulation of cells that are involved in the pathogenesis of OA [22–24].

In addition, the total doses of radiotherapy are of importance to minimize side effects such as pain and tumor induction. Directly following radiation, the joint might be slightly more painful, but this effect normally disappears in the first week after radiotherapy. The reported lifetime risk of an induced fatal tumor is < 0.001% in patients at the age of 50. The risk of a fatal tumor decreases with increasing age and lower total doses of radiotherapy [25]. The Deutsche Gesellschaft fur Radioonkologie (DEGRO) guideline for

Table 2 Median (range) pre- and post-radiation: Oxford Knee and Hip Score (OKS, OHS) and the EuroQol-5D (EQ-5D)

PROMs	Pre-radiation	6 weeks	13 weeks	26 weeks	39 weeks	52 weeks
OKS/OHS	50 (29–58)	47 (20–55)	40 (17–56)	42 (20–57)	40 (24–56)	40 (29–56)
EQ-5D	0.19 (0.03–0.78)	0.57 (0.02–0.89)	0.57 (0.20–0.89)	0.57 (0.20–0.78)	0.57 (0.20–0.78)	0.57 (0.20–0.78)

Table 3 Overview of literature on the effect of low-dose radiotherapy in patients with osteoarthritis of the hip or knee joint

	No. of patients (hip/knee)	Intervention (SD/TD Gy)	Short-term outcome	Long-term outcome
Lidner et al. [12]	158 (53/105)	1.0 or 2.0/4.0–10.0	–	> 12 months: 61% improved
Keinert et al. [13]	290 (0/290)	0.5 or 1.0/3.0–8.0	6 weeks: 81% free of complaints or better	–
Yaneva et al. [14]	373 (32/341)	–	End of treatment: 81–91% good or excellent effect	–
Gärtner et al. [15]	26 (5/21)	0.75 or 1.0/3.75–5.0	End of treatment: 24–37% improved or free of complaints	3 months after treatment: 12–35% improved or free of complaints
Sautter-Bihl et al. [16]	42 (0/42)	0.5–1.0/2.6–6.0	End of treatment: 62% satisfying, good or very good effect	> 12 months: 71% satisfying, good or very good effect
Keilholz et al. [17]	37 (6/31)	0.5 or 1.0/6.0 or 12.0	–	> 6 months: 64–72% improved or free of complaints
Mucke et al. [18]	5069 (0/5069)	0.25–3.0/3.0–12.0	< 3 months: 60% partial or complete pain relief	> 12 months: 78% partial or complete pain relief
Keller et al. [19]	1037 (0/1037)	0.5–1.5/0.5–10.0	Immediately or 2 months after therapy: 79.3% improved	–
Mahler et al. [20]	55 (0/55)	1.0/6.0	3 months after therapy: no significant differences in NRS-pain, WOMAC and patient global assessment between the low-dose radiotherapy and sham group.	–
Current study	12 (4/12)	1.0/6.0	6 weeks: 50% clinical relevant pain reduction measured with NRS-pain No differences in EQ-5D, OKS and OHS	52 weeks: 25% clinical relevant pain reduction measured with NRS-pain No differences in EQ-5D, OKS and OHS

SD single dose, *TD* total dose, *NRS-pain* Numeric Rating Scale for pain, *WOMAC* Western Ontario and McMaster University Osteoarthritis Index scale, *EQ-5D* EuroQol-5D, *OKS* Oxford Knee Score, *OHS* Oxford Hip Score

the radiotherapy of non-malignant disorders recommends total doses of 3.0–6.0 Gy [5]. Although five previous studies reported total doses of 8.0–12.0 Gy, none of these studies collected information regarding side effects [12, 13, 17–19]. In the present study, a total dose of 6.0 Gy was given, and no side effects have been reported.

There are some limitations to the current study. First, due to the lack of validated outcome measures in the previous studies no sample size calculation could be performed. Second, the duration of complaints, previous conservative treatment, co-medication and presence of synovitis were not documented. As the mechanism of low-dose radiotherapy is believed to be anti-inflammatory, an absence of synovitis could have reduced the effect of low-dose radiotherapy. Therefore, the current results should be interpreted with caution. However, the purpose of this study was to initiate awareness about the possible role of LDRT in patients with OA not responding to conservative treatment who are inoperable or not willing to undergo surgery. Furthermore, there was no blinding, and no control group was included. A randomized, doubled-blinded, sham-controlled trial of patients with synovitis of the hip or knee joint will be needed to confirm our current results.

Conclusion

This study showed a clinical relevant pain relief at 6 weeks after radiotherapy in patients with severe OA of the hip or knee joint. The long-term effect of LDRT was limited. A randomized placebo-controlled trial of patients is necessary to assess the effect of LDRT on pain in patients with synovitis of the affected joint.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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