


# BMJ Open Low-dose RaDiation therapy for patients with KNeE osteoArthritis (LoRD-KNeA): a protocol for a sham-controlled randomised trial

Byoung Hyuck Kim ,<sup>1,2</sup> Kichul Shin,<sup>3,4</sup> Min Jung Kim,<sup>3</sup> Hak Jae Kim,<sup>5</sup> Du Hyun Ro,<sup>6</sup> Joon Ho Wang,<sup>7</sup> Dae-Hee Lee,<sup>7</sup> Dong Hyun Kim,<sup>8</sup> Jiyu Sun,<sup>9</sup> Ji Hyun Lee,<sup>10</sup> Ji Young Kim,<sup>11</sup> Eun-Hee Hong,<sup>11</sup> Seong-Jun Cho,<sup>11</sup> Hyuk-Soo Han,<sup>6</sup> Won Park<sup>12</sup>

**To cite:** Kim BH, Shin K, Kim MJ, *et al.* Low-dose RaDiation therapy for patients with KNeE osteoArthritis (LoRD-KNeA): a protocol for a sham-controlled randomised trial. *BMJ Open* 2023;**13**:e069691. doi:10.1136/bmjopen-2022-069691

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-069691>).

BHK and KS contributed equally.

Received 29 October 2022  
Accepted 02 December 2022



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Won Park;  
wonro.park@samsung.com and  
Dr Hyuk-Soo Han;  
oshawks7@snu.ac.kr

## ABSTRACT

**Introduction** Low-dose radiation therapy (LDRT) for osteoarthritis (OA) has been performed for several decades. However, supporting evidence from randomised studies using modern methodologies is lacking, and a recently published randomised study failed to show the significant benefit of LDRT. The presented trial aims to evaluate the efficacy and safety of LDRT for patients with knee OA.

**Methods and analysis** This prospective, multicentre, randomised trial will be conducted in the Republic of Korea. A total of 114 participants will be randomly assigned (1:1:1) to receive sham irradiation, 0.3 Gy/6 fractions of LDRT or 3 Gy/6 fractions of LDRT. Key inclusion criteria are primary knee OA with Kellgren-Lawrence grade 2–3 and visual analogue scale 50–90 when walking at the baseline. The primary endpoint is the rate of responders at 4 months after LDRT according to the OARSI-OMERACT criteria. Concomitant use of analgesics is prohibited until the primary efficacy evaluation is scheduled.

**Ethics and dissemination** Currently, approval from the Ministry of Food and Drug Safety of the Republic of Korea and the institutional review board of each participating hospital has been obtained. Patient enrolment began in October 2022 and is ongoing at three participating sites. The results will be disseminated to academic audiences and the public via publication in an international peer-reviewed journal and presentation at conferences. This trial will provide valuable information on the safety and efficacy of LDRT for patients with knee OA.

**Trial registration number** NCT05562271.

## INTRODUCTION

Osteoarthritis (OA) is a representative degenerative disease in which the cartilage is gradually destroyed with ageing and structural deformation of the joint progresses. According to the WHO, OA is one of the fastest growing health problems and is the second leading cause of disabilities in the USA.<sup>1</sup> Although there is a difference in the preferred site according to gender, both men

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This multicentre, single-blinded, sham-controlled, superiority randomised controlled trial compares low-dose radiation therapy and sham radiation therapy for knee osteoarthritis.
- ⇒ The protocol includes two experimental groups for comparison with the sham control group, which has not been tested in a randomised setting for osteoarthritis.
- ⇒ The trial intends to reduce bias in pain assessment by specifically defining the restrictions or prohibitions of concomitant analgesic drugs.
- ⇒ One limitation of this protocol is that the results based on Asian patients might not be reproducible in other ethnic groups.

and women are at high risk of developing OA in the knee.<sup>2</sup>

Usually, exercise, weight loss and lifestyle changes are implemented initially, and analgesic medications or local injections can be administered for pain; in some cases, joint replacement surgery is performed.<sup>3</sup> However, commonly used non-steroidal anti-inflammatory drugs (NSAIDs) can cause side effects such as gastrointestinal, renal or cardiovascular side effects following long-term use. Specifically, it has been reported that the use of NSAIDs by elderly patients can cause 2/1000 fatal cardiovascular side effects per year and can quadruple the risk of gastrointestinal bleeding.<sup>4 5</sup> In addition, around 25% of patients do not respond or lose effectiveness to NSAIDs over time. More invasive interventions such as intra-articular injection therapy, joint lavage, synovectomy and joint replacement can be considered; however, each has its own risks such as bleeding and infection. On the other hand, radiation has also been used in the treatment of OA since

the early 1900s especially in Europe because it has the potential advantage of non-invasively reducing pain and avoiding drug side effects.<sup>6</sup> Until now, low-dose radiation therapy (LDRT) is used for OA worldwide.<sup>7</sup>

Although radiation therapy for OA is being actively carried out in some countries including Germany, there are considerable regional differences in the use of LDRT.<sup>8</sup> A worldwide survey found that less than 10% of institutions in the USA use radiation for the treatment of arthritis, in contrast to more than 85% in German.<sup>8</sup> Despite the low probability of negative outcomes, concerns about the side effects of secondary cancer, vague negative perceptions of radiation and the various use of other conservative treatments seem to contribute to differences in clinical practice.

According to several clinical studies published mainly by German Society of Radiation Therapy and Oncology (DEGRO), LDRT had a symptom-reducing effect on 63%–90% of symptomatic patients with OA, and no notable clinical side effects were reported.<sup>2 6 9</sup> Although it is a traditional and common treatment, supporting evidence from randomised studies using relatively modern methodologies are lacking as the treatment has been routinely performed before the era of evidence-based medicine. Recently, small randomised studies (55 patients with knee OA, 54 patients with hand OA) were conducted on a Dutch population.<sup>10 11</sup> There was no difference in the pain response rate of the LDRT group (6Gy/6 fractions) compared with the control group (sham irradiation); thus, there was scepticism in recommending LDRT for OA. Several issues such as disproportionate allocation between groups, small number of patients and inadequate treatment dose were also raised; nevertheless, the recommendation of LDRT for OA by the DEGRO group was maintained.<sup>12</sup>

However, high-quality evidence is still lacking, and prospective studies in Asia have never been conducted.<sup>7</sup> Therefore, we aim to conduct a prospective randomised study to evaluate the efficacy and safety of LDRT for patients with knee OA, compared with sham irradiation.

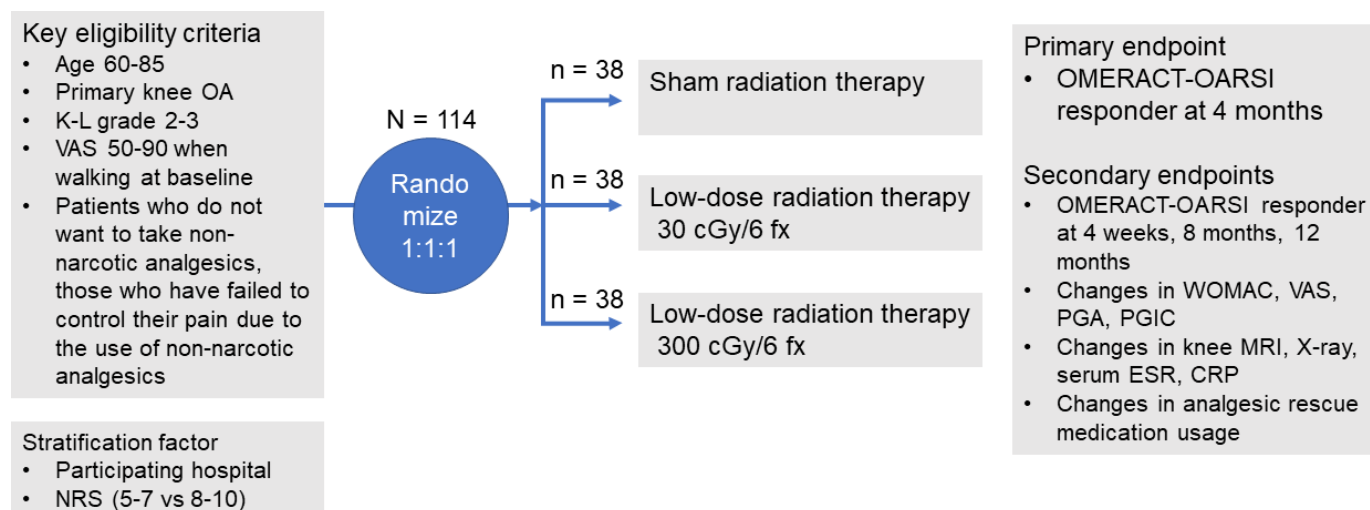
## METHODS AND ANALYSIS

### Study design and registration

This multicentre, single-blinded, sham-controlled, superiority randomised controlled trial compares LDRT and sham radiation therapy for knee OA. The trial is registered on the clinicaltrials.gov website. In this study, patients with knee OA are randomised at a ratio of 1:1:1 to receive sham irradiation, 0.3Gy/6 fractions of LDRT or 3Gy/6 fractions of LDRT (figure 1). In the case of bilateral knee OA, only the one with more severe pain is selected as the index knee and included in this study. If both sides have the same symptoms, the researcher objectively selects one knee with more severe arthritis and defines it as the affected side. The study design and protocol adhere to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines<sup>13</sup> (online supplemental table 1).

### Recruitment and eligibility criteria

In the Republic of Korea, three academic hospitals (Seoul National University Hospital, Samsung Medical Center and SMG-SNU Boramae Medical Center) will recruit study subjects. The recruitment process targets knee patients with OA who have visited the orthopaedic surgery or rheumatology department of each participating institution following the recommendation of a medical doctor. In addition, research subjects may be recruited by posting a notice of recruitment inside and outside the hospital.



**Figure 1** LoRD-KNeA trial design. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; K-L, Kellgren-Lawrence; LoRD-KNeA, Low-dose RaDiation therapy for patients with KNeE osteoarthritis; NRS, Numeric Rating Scale; OA, osteoarthritis; OMERACT-OARSI, Outcome Measures in Rheumatology-Osteoarthritis Research Society International; PGA, Patient Global Assessment; PGIC, Patient Global Impression of Change; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

**Table 1** The inclusion and exclusion criteria for LoRD-KNeA trial

Inclusion	Exclusion
Age 60–85 years old	A history of knee irradiation in the past
Kellgren-Lawrence grade 2–3 and diagnosed as a patient with primary knee osteoarthritis according to the ACR knee OA diagnostic criteria	Patients participating in other degenerative arthritis clinical trials
Patients with VAS 40 or higher when walking, with or without medication at the time of screening	Kellgren-Lawrence grade 4
Patients who have VAS 50 or more and 90 or less when walking at the baseline	A history of malignancy within the last 5 years
Among patients who were previously taking analgesic drugs at the time of screening, those with an increase in pain of 10 points or more at the baseline	A history of knee or hip surgery in the past
Patients who do not want to take non-narcotic analgesics, those who have failed to control their pain due to the use of non-narcotic analgesics, or candidates for invasive treatment (intra-articular injection, arthroplasty, etc.)	Patients who have received systemic steroid treatment or intra-articular steroid/hyaluronic acid injection within 2 months of screening
A person who has a will to discontinue all pain medications except for rescue medications throughout screening, baseline, and clinical trials related to knee arthritis	Patients with hip degenerative arthritis or other diseases of NRS 5 or higher that may affect functional score evaluation
A person who gives consent to use an approved contraceptive method from screening to 3 months after the end of the clinical trial	Patients who are scheduled for surgical treatment of the knee joint during the clinical trial period
A person who understands the eligibility requirements for the study and has signed the consent form	BMI >39 kg/m <sup>2</sup>
	Known history of analgesic or substance abuse within 2 years of screening
	History, diagnostic signs or symptoms of any of the following clinically significant psychiatric disorders that would render the study ineligible (psychotic disorder, depression, somatic disorder)
	History, diagnostic signs, or symptoms of any of the following clinically significant heart diseases that would render the study ineligible (surgery or stenting for ischaemic heart disease and coronary artery disease within 6 months prior to screening)
	History of other diseases that may affect the index joint, including autoimmune diseases (lupus, rheumatoid arthritis, etc.)
	Fibromyalgia history or diagnosis
	If the researcher judges that a person with significant trauma or other findings considered clinically important is inappropriate for participation in this study

ACR, American College of Rheumatology; BMI, body mass index; NRS, Numeric Rating Scale; OA, osteoarthritis; VAS, Visual Analogue Scale.

The detailed inclusion and exclusion criteria are listed in [table 1](#). Key inclusion criterias are (1) age 60–85 years old, (2) primary knee OA with Kellgren-Lawrence grade 2–3, (3) patients who have visual analogue scale (VAS) 50–90 when walking at the baseline, (4) person who has a will to discontinue all pain medications except for rescue medications throughout screening, baseline, and clinical trials related to knee arthritis. Key exclusion criteria are (1) Kellgren-Lawrence grade 4, (2) history of knee or hip surgery in the past, (3) patients with hip degenerative arthritis or other diseases of NRS 5 or higher that may affect functional score evaluation, (4) history of other

diseases that may affect the index joint, including autoimmune diseases.

### Randomisation and masking

Participants will complete a consent form at the study site during visit 1 (screening). The participants are randomised at visit 2 (baseline) using a pre-defined randomisation sheet after confirming that they fulfil the inclusion criteria (patients with VAS 50 or more and 90 or less when walking at baseline; among patients previously taking analgesic drugs at the time of screening, those with an increase in pain of 10 points or more at baseline). The

randomisation sheet is generated by the stratified block randomisation method using R programme. Stratification factors are participating hospital and baseline pain score (NRS 5–7 vs 8–10) in order to include a balanced number of patients per group with respect to pain score. Owing to radiation therapy planning differences, this trial is single-blinded, and the subjects of the study would not know whether they would be assigned to a specific arm.

### Allocation and treatment procedures (intervention)

All patients will receive non-contrast enhanced CT simulation for the index knee using personalised immobilisation devices. Three-dimensional treatment planning will be conducted based on the simulation CT. Patients are randomised (1:1:1) to receive sham irradiation, 0.05 Gy per fraction of LDRT, or 0.5 Gy per fraction of LDRT. Patients will receive a total of 6 fractions of LDRT. The index knee of the enrolled patients is subjected to irradiation with 6 MeV energy using a linear accelerator. Sham radiation therapy is given to patients in the control group, who will undergo CT of the index knee with the same treatment setup as in the experimental group but without the beam from the linear accelerator. Sham radiation therapy will be identical to LDRT of experimental groups in all aspects including simulation, positioning, RT schedule, in-room setup procedures, and gantry positions. Treatments are delivered two times per week for 3 weeks. Target volumes include 8 cm superior/inferior to the knee joint space and 3 cm medial to the medial femoral condyle, 3 cm lateral to the lateral tibial condyle including the articular cartilage, neighbouring bone, and entire synovium, as well as the periarticular connective tissue according to expert consensus.<sup>29</sup> To clearly demonstrate the efficacy of single course LDRT, reirradiation for patients with insufficient response is not allowed in this study.

### Acceptance of concomitant drugs

Concomitant use of analgesics is prohibited until 4 months after irradiation when the primary efficacy evaluation is scheduled. During this period, only the use of a rescue drug (acetaminophen) may be permitted if the subjects need it for OA or other types of pain or disease (if pain relief is inadequate). As pain evaluation is scheduled at the screening visit and follow-up after LDRT, the use of a rescue drug is also temporally prohibited 48 hours before each visit. Specifically, other than the rescue drug, the following drugs and therapies are prohibited until 4 months after LDRT when the primary efficacy evaluation is scheduled: Cox2-selective inhibitors, NSAIDs, narcotic analgesics (including weak opioid combinations), systemic corticosteroids, injection into the knee joint (corticosteroids, platelet-rich plasma, hyaluronic acid), and acupuncture, procedures, and surgical treatments for knee OA. Concomitant drugs other than analgesics can be permitted at the discretion of the investigator if medically necessary. All medically prescribed drugs are not prohibited after the primary efficacy evaluation;

however, all concomitant drugs administered during the clinical trial period should be recorded in the case report form, including the ingredient name, daily dose, dosage unit, administration route, administration period, and purpose of administration.

### Outcome measures (assessment)

Pain/function test scores including VAS score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Patient Global Assessment (PGA) score and Patient Global Impression of Change (PGIC) score are measured at the screening visit and at follow-up visits at 4 weeks, 4 months, 8 months and 12 months after the end of LDRT. Laboratory data including white blood cell (WBC), red blood cell (RBC), haemoglobin, haematocrit, platelet count, WBC differential count, AST/ALT, blood urea nitrogen (BUN), creatinine, glucose, protein, albumin, total bilirubin, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are collected at the screening visit and at follow-up visits at 4 weeks, 4 months, 8 months and 12 months after the end of LDRT. Precontrast and postcontrast MRI of the index knee is performed during the screening period, at 4 months and at 12 months. Knee X-ray examination is performed during the screening period and at 12 months.

### Primary endpoint: OMERACT-OARSI criteria

The primary endpoint is the rate of responders at 4 months after LDRT according to the Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OARSI-OMERACT) criteria.<sup>14</sup> The responder definition according to the OMERACT-OARSI criteria is (1) an improvement in WOMAC pain or WOMAC function  $\geq 50\%$  and an absolute change  $\geq 20$  mm or (2) an improvement of  $\geq 20\%$  with an absolute change  $\geq 10$  mm in at least two of the following three categories: WOMAC pain, WOMAC function and PGA.

### Secondary endpoints

The secondary endpoints include OMERACT-OARSI response rate at 4 weeks, 8 months and 12 months, changes in WOMAC subscale (pain, stiffness, physical function), changes in VAS score, PGA score and PGIC score, radiological changes evaluated by knee MRI, radiological changes evaluated by knee X-ray, changes in serum inflammatory factors (ESR, CRP), changes in the amount of analgesic rescue medication usage and efficacy evaluation dropout rate.

### Safety evaluation

Potential toxicities related to knee irradiation are evaluated as grade 1–5 according to the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 scale for all enrolled subjects. The potential adverse events during this trial are as follows: skin rash, discolouration or irritation, joint oedema, decreased joint range of motion and other unpredicted adverse events.

### Sample size calculation

For sample size calculation, a randomised, comparative, parallel, three-arm design is used with 80% power and a two-sided alpha of 0.025 considering the comparison of the control group to each of the two types of experimental groups; a total of two tests are planned, and Bonferroni correction is performed. According to the ArthroRad trial, when doses of 0.05 Gy and 0.5 Gy per fraction (similar to this trial) were applied to degenerative arthritis of the hand and knee, the combined response rate of 'markedly improved' and 'improved' was around 60%.<sup>15</sup> In addition, when the results of several retrospective studies were combined, clinical symptom improvement was observed in 63%–90% of cases after LDRT.<sup>2</sup> Therefore, the number of samples for this study may be determined by the following hypothesis test: assuming that the proportion of responders is 65% in the experimental groups and 30% in the control group, when the power is 80% and the alpha error is 5%, 34 patients are needed in each group. Considering a 10% dropout rate, each arm requires 38 patients. A total of 114 patients will be enrolled in this study.

### Data collection and statistical analysis

A standardised case report form is designed before study. Well-trained clinical research coordinators will retrieve all required data from medical records and study questionnaires. Prior to analysis, comprehensive data check will be conducted by a second study researcher. External data monitoring committee is not required for this investigator-initiated type trial.

Efficacy is evaluated in the full analysis set (FAS), which includes subjects enrolled in this clinical trial with randomisation and those who have received at least one assigned treatment and have confirmed the primary efficacy endpoint at least once. Safety is assessed for all patients who have received at least one fraction of radiation therapy. The per protocol set (PPS) is implemented as an auxiliary set. The PPS is an analysis of patients included in the FAS who have received the assigned treatment without major research protocol violation.

The analysis of baseline characteristics and group comparison is conducted with an independent t test or non-parametric test. Changes during the study period in all outcomes are analysed by a paired t test or non-parametric equivalent.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct or reporting or dissemination plans of this research.

### Ethics and dissemination

Currently, approval from the Ministry of Food and Drug Safety of the Republic of Korea (No. 20220084855) and the institutional review board of each participating hospital (Seoul National University Hospital, Samsung Medical Center, SMG-SNU Boramae Medical Center)

has been obtained. Informed consent form is attached in online supplemental file 1. Patient enrolment began in October 2022 and is ongoing at three sites in the Republic of Korea. Participants will be provided informed consent following discussion regarding study procedures with a physician of the research team. The planned sample size is 114 patients, and the accrual duration of this trial is approximately 1 year and 12 months of follow-up (after enrolment of the last patient) for the evaluation of the safety and efficacy endpoints. The results will be disseminated to academic audiences and the public via publication in an international peer-reviewed journal and presentation at various conferences. This trial will provide valuable information on the safety and efficacy of LDRT for patients with knee OA.

### Composition, roles and responsibilities

Trial processes and data are managed and audited within the research team. The study sponsor (Korea Hydro & Nuclear Power) will have access to anonymised trial data following the completion of all data collection. Trial analysis will be completed by the research team within SMG-SNU Boramae Medical Center or an independent statistician.

### Protocol modifications

Trial registries, research ethics committee, study sponsor and participants will be informed of any protocol modifications by a member of the study team from SMG-SNU Boramae Medical Center.

## DISCUSSION

If pain and movement restrictions caused by OA are not adequately addressed, several detrimental health effects can occur. As a result, patients with OA patients could incur a significant amount of medical expenses annually, which would be a socioeconomic burden on the national medical system. In order to promote LDRT in countries that do not typically use it, convincing medical evidence should be provided. In addition to our trial, more prospective randomised studies with controlled analgesic medications, relevant endpoints, standardised response evaluation and adequate sample sizes should be conducted to offer LDRT as an alternative conservative treatment option for OA.

We believe that the restriction of concomitant drugs is the biggest difference and strongest point of the present trial compared with previous studies. In previous studies, pain and function scores are mainly evaluated for outcome measurement; however, the use of analgesics can cause the greatest bias, making it difficult to interpret the results. In a randomised study by Mahler *et al*, there were no specific concomitant drug restrictions.<sup>10</sup> Patients were encouraged not to change analgesics and were discouraged from receiving other active treatments during the study; however, their use was allowed and monitored when needed.<sup>10</sup> As a result, unspecified analgesics were

used by approximately half of the patients (56% in the LDRT group and 43% in the sham group) for 3 months, and this uncontrolled part may have resulted in a study with bias. In the recent ArthroRad trial, the use of analgesics during the trial was also not limited despite patients having undergone surgical interventions or injections to the involved joint after LDRT were excluded as soon as this therapy became known.<sup>15</sup> They commented that limiting the intake of oral analgesics was unrealistic. In our study, we may be able to test whether inhibiting of concomitant analgesics is practically feasible through our study.

In determining the radiation dose of the experimental groups, although 1 Gy per fraction (as used in randomised studies involving a Dutch population) is the dose clinically used in Europe, its effectiveness was not confirmed; thus, 1 Gy per fraction was not used in the present study. Considering that a clinical dose of 0.5–1 Gy per fraction is mainly used, a dose of 0.5 Gy per fraction still needs to be verified by a randomised study for OA. In addition, a dose of 0.05 Gy per fraction, which was suggested in the ArthroRad trial to have similar efficacy to that of 0.5 Gy per fraction in the short term, should be further verified. A control group should receive sham irradiation as placebo effects cannot be ruled out. Therefore, the present study planned to validate treatment efficacy using two experimental groups of 0.05 Gy per fraction (a total of 0.3 Gy/6 fractions) and 0.5 Gy per fraction (a total of 3 Gy/6 fractions), which will be compared with the control group (sham irradiation).

Meanwhile, the other randomised RAGOCO trial is currently underway in Spain, which is designed to compare 0.5 Gy and 1 Gy per fraction (ClinicalTrials.gov identifier NCT04424628). Together with our trial, the findings are expected to form an important basis for optimising the dose of LDRT in the future.

In conclusion, the LoRD-KNeA trial will provide valuable information on the safety and efficacy of LDRT for patients with knee OA.

#### Author affiliations

<sup>1</sup>Radiation Oncology, Seoul National University College of Medicine, Seoul, Republic of Korea

<sup>2</sup>Radiation Oncology, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

<sup>3</sup>Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

<sup>4</sup>Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

<sup>5</sup>Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Republic of Korea

<sup>6</sup>Department of Orthopaedic Surgery, Seoul National University College of Medicine, Seoul, Republic of Korea

<sup>7</sup>Department of Orthopedic Surgery, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

<sup>8</sup>Department of Radiology, Seoul National University Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea

<sup>9</sup>Medical Research Collaborating Center, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

<sup>10</sup>Department of Radiology, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

<sup>11</sup>Radiation Health Research Institute, Korea Hydro & Nuclear Power Co Ltd, Seoul, Republic of Korea

<sup>12</sup>Department of Radiation Oncology, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea

**Acknowledgements** The authors would like to thank all the investigators, study coordinators, study participants, and their families for their support in this trial.

**Contributors** BHK is the principal investigator of the present trial. KS, MJK, HJK, DHR, JHW, D-HL, DHK, JS, JHL, JYK, E-HH, S-JC, H-SH and WP contributed to the development and implementation of this protocol and have approved this manuscript.

**Funding** This study was supported by grant (A22LP05) from Korea Hydro & Nuclear Power Co., Ltd.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Byoung Hyuck Kim <http://orcid.org/0000-0002-6156-0744>

#### REFERENCES

- Sebbag E, Felten R, Sagez F, *et al*. The world-wide burden of musculoskeletal diseases: a systematic analysis of the world health organization burden of diseases database. *Ann Rheum Dis* 2019;78:844–8.
- Dove APH, Cmelak A, Darrow K, *et al*. The use of low-dose radiation therapy in osteoarthritis: a review. *Int J Radiat Oncol Biol Phys* 2022;114:203–20.
- Bannuru RR, Osani MC, Vaysbrot EE, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.
- Bhala N, Emberson J, *et al*, Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382:769–79.
- Masclee GMC, Valkhoff VE, Coloma PM, *et al*. Risk of upper gastrointestinal bleeding from different drug combinations. *Gastroenterology* 2014;147:784–92.
- Seegenschmiedt MH, Micke O, Willich N. Radiation therapy for nonmalignant diseases in Germany. current concepts and future perspectives. *Strahlenther Onkol* 2004;180:718–30.
- Javadinia SA, Nazeminezhad N, Ghahramani-Asl R, *et al*. Low-dose radiation therapy for osteoarthritis and enthesopathies: a review of current data. *Int J Radiat Biol* 2021;97:1352–67.
- Leer JW, van Houtte P, Davelaar J. Indications and treatment schedules for irradiation of benign diseases: a survey. *Radiother Oncol* 1998;48:249–57.
- Micke O, Seegenschmiedt MH, Adamietz IA, *et al*. Low-dose radiation therapy for benign painful skeletal disorders: the typical treatment for the elderly patient? *Int J Radiat Oncol Biol Phys* 2017;98:958–63.
- Mahler EAM, Minten MJ, Leseman-Hoogenboom MM, *et al*. Effectiveness of low-dose radiation therapy on symptoms in patients

- with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial. *Ann Rheum Dis* 2019;78:83–90.
- 11 Minten MJM, Leseman-Hoogenboom MM, Kloppenburg M, *et al*. Lack of beneficial effects of low-dose radiation therapy on hand osteoarthritis symptoms and inflammation: a randomised, blinded, sham-controlled trial. *Osteoarthritis Cartilage* 2018;26:1283–90.
  - 12 Ott OJ, Micke O, Mücke R, *et al*. Low-dose radiotherapy: mayday, mayday. we've been hit! *Strahlenther Onkol* 2019;195:285–8.
  - 13 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
  - 14 Pham T, van der Heijde D, Altman RD, *et al*. OMERACT-OARSI initiative: osteoarthritis research society international set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* 2004;12:389–99.
  - 15 Niewald M, Müller LN, Hautmann MG, *et al*. ArthroRad trial: multicentric prospective and randomized single-blinded trial on the effect of low-dose radiotherapy for painful osteoarthritis depending on the dose—results after 3 months' follow-up. *Strahlenther Onkol* 2022;198:370–7.