Orthovoltage x-ray therapy significantly reduces disability risk in knee osteoarthritis patients: A decade-long cohort study

Maria V. Makarova 1, Mikhail Yu. Valkov 2, Andrey M. Grjibovski 1,2,3

1 Northern State Medical University, Arkhangelsk, Russia
2 North-Eastern Federal University, Yakutsk, Russia
3 Northern (Arctic) Federal University, Arkhangelsk, Russia

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Abstract:
Introduction — Osteoarthritis (OA) of the knee and hip joints affects 13% of the adult population in the Russian Federation. While medications can provide some relief from the pain associated with OA, they are often not enough. An alternative treatment option is orthovoltage radiation therapy (OVRT), which not only relieves pain, but can also help prevent disability. However, there is little evidence for the long-term effectiveness of OVRT.

Objective — We compared the incidence of disability among patients with OA who received standard treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with the symptomatic slow-acting drugs for osteoarthritis (SYSADOA), or in combination with OVRT for knee OA in the setting of an open randomized controlled trial with long-term follow-up.

Material and Methods — The sampling frame included patients with confirmed OA of the knee sensu Altman (1991), with radiographic grades of OA from 0 to 2 sensu Kellgren-Lawrence. A total of 292 patients were randomly distributed among two groups of equal sizes. The control group received combination therapy with NSAIDs and SYSADOA. In the experimental group, OVRT was additionally performed at a total dose of 4.5 Gy. Relationships between treatment regimen and time to disability were studied using actuarial analysis, Kaplan-Meier plots. Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI), as well as attributable fraction (AF) and population attributable fraction (PAF) were calculated.

Results — The cumulative time at risk for disability was 2,304.9 person-years. In total, 9.5% of patients in the experimental group became disabled during the observation period vs. 17.8% in the control group. In the experimental group, the level of disability was lower (HR=0.49, 95% CI: 0.26-0.95). Differences became more pronounced after adjusting for sex, age, radiographic grade of OA, pain intensity, and duration of OA before treatment (HR=0.24, 95% CI: 0.11-0.48). AF and PAF were 49.9% and 25.8%, respectively.

Conclusion — It has been shown that the introduction of OVRT in the treatment regimen can reduce the disability of patients with knee OA by almost 50%. One in four disability cases could be prevented if OVRT were used universally in the treatment of knee OA. Our results indicate that combining OVRT with standard care is a more effective approach to preventing disability in patients with knee OA than standard treatment alone.

Keywords: osteoarthritis, knee, disability, survival analysis, orthovoltage radiation therapy.

Introduction

Osteoarthritis (OA) of the knee joint is a common musculoskeletal disease. According to a meta-analysis of 88 epidemiological studies, approximately 654.1 million people 40 years of age worldwide were diagnosed with gonarthrosis [1]. In Russia, the prevalence of OA of the knee and hip joints was estimated at 13% in people 18 years of age and older [2].

OA is a painful condition that is typically treated with nonsteroidal anti-inflammatory drugs (NSAIDs) [3, 4]. The uncontrolled use of NSAIDs can lead to serious gastrointestinal complications [5]. In accordance with the clinical recommendations by the Association of Rheumatologists of Russia, symptomatic slow-acting drugs for osteoarthritis (SYSADOA), such as chondroitin sulfate, glucosamine, and other tissue repair stimulants and correctors of bone and cartilage metabolism, can also be used to treat knee OA [4]. However, meta-analyses of studies conducted without the support of pharmaceutical companies did not confirm the benefits of using both chondroitin and glucosamine sulfates, and therefore their use was not recommended by most of the international professional rheumatology communities. [3, 4, 7].

OA often progresses steadily, leading to high rates of disability and referrals for surgical treatment. Up to 15% of patients with OA become disabled. Furthermore, OA patients account for about a
third of all patients with permanent disability due to joint diseases [8].

An alternative noninvasive treatment for OA is orthovoltage radiation therapy (OVRT). According to our randomized controlled trial, OVRT had a significant advantage over standard treatment, such as NSAIDs and SYSADOA, both in terms of immediate results [9] and long-term effects over a period of three years [10]. In Germany and Spain, radiation therapy is already included in the standards of pain management in OA and is recommended for the treatment of knee OA [11, 12]. However, it is not yet included in the therapeutic standards for the treatment of OA in Russia and many other countries. Its long-term analgesic effect has the potential to prevent disability and delay the need for surgery, but the lack of evidence regarding the long-term efficacy of OVRT is the main reason why it is not universally recommended for the treatment of OA [3, 4], which requires further research.

In publications examining the efficacy of OVRT, its safety was pointed out [13, 14], but its effect on disability was not reported.

We conducted a 10-year follow-up of patients with knee OA participating in a previously published randomized controlled trial (RCT) [3, 4] to assess whether the use of OVRT in addition to standard therapy reduces the risk of disability, compared with conventional treatment.

Material and Methods

Group recruitment procedure

This was a randomized controlled study with a long-term follow-up. Our study included all patients with confirmed knee OA sensu 1991 Altman criteria [15], with or without laboratory and radiographic manifestations, with radiographic grades of OA 0-2 sensu Kellgren-Lawrence [16], and an initial pain level of 30 mm or more based on the visual analog scale (VAS). Patients were recruited from outpatient clinics in Arkhangelsk, Northwestern Russia, between October 2012 and October 2014. Exclusion criteria were as follows: post-traumatic osteoarthritis, systemic connective tissue disease, a history of knee arthroplasty, and any condition precluding participation in the study. The selected patients were randomly assigned to two groups by blind randomization. Patient details and randomization procedure have been described previously [9, 10].

A total of 292 patients were included in the analysis, 146 in each group. The patients of the groups were comparable in terms of age and sex composition (Table 1). Participants in the control group received conventional therapy with a combination of SYSADOA glucosamine (500 mg) and chondroitin (400 mg) sulates according to the following scheme: 1 capsule 3 times a day for three weeks, then 1 capsule 2 times a day for up to twelve weeks. After an eight-week break, a second course was prescribed for twelve weeks according to the same scheme.

In the experimental group, in addition to standard conservative drug therapy, patients underwent orthovoltage X-ray therapy. The single focal dose was 0.45 Gy. A total of 10 sessions 48 hours apart resulted in a cumulative dose of 4.5 Gy. Both groups of patients were allowed to take selective NSAIDs.

Measuring the effect

The clinical endpoint of the follow-up was the established disability due to the knee joint OA. Data on the onset of disability were obtained from the Unified State Information System in the Field of Healthcare in Arkhangelsk. Patients without disabilities were censored by the date of the last check-up or by the date of their last registered visit to the doctor, or else by the specified date of 31 December 2021.

Statistical data processing

The incidence of disability in both groups was calculated per 100 person-years. Attribute fraction (AF) and population attributable fraction (PAF) were calculated to estimate the proportion of disability that could be prevented if all patients received OVRT in addition to standard treatment in the study and in the general population. Disability-free survival in the experimental and control groups was assessed using actuarial analysis. Differences between groups were assessed using the Gehan-Wilcoxon procedure. Cumulative disability risks were plotted using Kaplan-Meier plots. Although the groups were similar in age, radiographic grade of OA, body mass index, pain intensity, and duration of OA prior to study entry, we additionally controlled for these characteristics in proportional hazards analysis. Crude and adjusted hazard ratios (HR) were calculated. Survival analysis results were presented with 95% confidence intervals due to their superiority over traditional p-values [17].

For all calculations, the Stata software package version 17 (Stata Corp., TX, USA) was employed [18].

Results

The cumulative time at risk for disability was 2,304.9 person-years. In total, 9.5% (n=14) of patients became disabled in the experimental group vs. 17.8% (n=26) in the control group. The total numbers of disabled OA patients at baseline by radiographic grade are presented in Table 2.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experimental group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numeric variables, mean (95% CI)</td>
<td></td>
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<tr>
<td>Age, years</td>
<td>37.3 (35.1–39.4)</td>
<td>39.8 (37.7–41.9)</td>
<td>0.103</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.0 (25.9–28.2)</td>
<td>26.6 (25.8–27.5)</td>
<td>0.667</td>
</tr>
<tr>
<td>Duration of OA, months</td>
<td>9.7 (8.8–10.6)</td>
<td>9.2 (8.1–10.4)</td>
<td>0.068</td>
</tr>
<tr>
<td>Pain intensity as measured by VAS, mm</td>
<td>57.1 (54.7–59.9)</td>
<td>55.7 (52.7–58.8)</td>
<td>0.574</td>
</tr>
<tr>
<td>Categorical variables, n (%)</td>
<td></td>
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<tr>
<td>Proportion of females</td>
<td>64 (43.8)</td>
<td>77 (52.7)</td>
<td>0.274</td>
</tr>
<tr>
<td>Radiographic grade 0 of OA, n (%)</td>
<td>15 (10.3)</td>
<td>24 (16.4)</td>
<td>0.346</td>
</tr>
<tr>
<td>Radiographic grade 1 of OA, n (%)</td>
<td>89 (60.9)</td>
<td>86 (58.9)</td>
<td>0.667</td>
</tr>
<tr>
<td>Radiographic grade 2 of OA, n (%)</td>
<td>42 (28.8)</td>
<td>36 (24.7)</td>
<td>0.724</td>
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CI, confidence interval; OA, osteoarthritis; VAS, visual analog scale.

Table 2. Absolute numbers and proportion of patients who developed disability over the follow-up period, by radiographic grades of knee osteoarthritis (OA)

<table>
<thead>
<tr>
<th>Radiographic grade of OA</th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0, n (%)</td>
<td>0/15 (0.0%)</td>
<td>1/24 (4.2%)</td>
</tr>
<tr>
<td>Grade 1, n (%)</td>
<td>1/89 (1.1%)</td>
<td>5/86 (5.8%)</td>
</tr>
<tr>
<td>Grade 2, n (%)</td>
<td>13/42 (30.9%)</td>
<td>20/36 (55.6%)</td>
</tr>
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</table>
The incidence of disability due to knee OA was 1.17 per 100 person-years in the experimental group vs. 2.34 per 100 person-years in the control group. The incidence rate ratio was 0.50 (95% CI: 0.25-0.99), p=0.018. The AF and PAF were 50% and 24%, respectively, suggesting that only one in four disability cases would occur if all patients received OVRT in addition to standard care.

The actuarial analysis yielded the following results: 96.6% (95% CI: 92.0%-98.6%) and 90.2% (95% CI: 84.0%-94.1%) of patients in the treatment group had no disability through 5 and 10 years of follow-up, respectively, while the corresponding proportions in the control group were 91.1% (95% CI: 85.2%-94.7%) and 79.6% (95% CI: 70.9%-86.0%), p=0.030. The cumulative risks of developing disability in both groups are shown in Figure 1.

Crude HR estimated via proportional hazards analysis was 0.49, 95% CI: 0.26-0.95, p=0.033. Adjusting for differences between groups in age, sex, radiographic grade of OA, pain intensity, and duration of OA prior to treatment significantly increased the effect of OVRT in addition to standard treatment, compared with standard treatment alone (HR=0.24, 95% CI: 0.11-0.48). This implies that OVRT with standard care is a more effective treatment option in preventing disability than standard treatment alone.

Discussion
This is the first article analyzing long-term follow-up of patients with grade 0-2 gonarthrosis in our RCT until the establishment of a disability. Our findings suggest that OVRT in combination with conventional therapy significantly delays disability and has potential for clinical practice. The incidence of disability in our study is comparable with worldwide data [19].

Radiation therapy is not a widely accepted approach to the treatment of OA due to conflicting data on its effectiveness. A double-blind, randomized study involving 55 patients with knee OA conducted in the Netherlands showed that after three months of low-dose radiation, there was no reduction in pain in the radiation therapy group (HR 1.09; 95% CI 0.37-3.19). Furthermore, the authors found no changes in the synovial membrane according to ultrasound and MRI examination in both groups [20].

A systematic review of 26 studies on the analgesic efficacy and safety of low-dose radiation therapy revealed a lack of high-quality studies, as well as a high heterogeneity in the used doses, schemes, and study designs [21]. Besides, published data on long-term side effects were nonexistent. Hence, the effectiveness of low-dose radiation therapy as a treatment for OA in clinical practice still needs confirmation through well-planned RCTs [3, 11].

On the other hand, in several countries, long-term use of radiation therapy for knee OA has already entered practice, as evidenced by the data of non-randomized trials included in national recommendations [11]. In our study, we observed the most pronounced effect from the use of radiation therapy for a longer period after the end of treatment: it persisted for at least three years [9, 10]. We believe that the long-term analgesic effect of OVRT significantly contributed to the reduction of persistent pain syndrome and objective pathological changes in the affected joints, which are drivers of disability.

The frequency of detecting disability in our study was significantly influenced by the initial radiographic grade of OA. When determining the disability grade, we considered the limitation of vital activities in patients with persistent disorders of static and dynamic functions (grades 3 and 4), because these disorders progressed faster with more severe radiographic grade of OA at baseline [22].

Several studies demonstrated that weight loss led to a decrease in the risk of developing OA of the knee joint and was associated with a decrease in pain and improved function of the knee joint [23, 24]. In our research, patients of the experimental group did not differ from those in the control group in terms of body mass index; however, adjustment for BMI and other characteristics substantially facilitated the detection of associations.

Patient outcomes were tracked over a long period, which was a major strength of our study. Most of the other studies had a limited follow-up period of one to three years [7, 8] without examining the long-term effects of treatment.

The main limitation of this study was its relatively small sample size (292 patients). However, this was enough to show the superiority of the experimental treatment over the control group. Moreover, it was sufficient to include five potential confounding factors in a multivariate proportional hazards analysis. Although our results provided sufficient evidence in favor of experimental treatment, it is necessary to replicate these findings in other clinical settings. In addition, longer follow-up is required.

Another limitation was the lack of mandatory registration of patients with OA, which can be considered as a dropout risk. However, as a risk reduction strategy, we had access to patients’ medical records, and they were regularly called in for appointments to assess long-term outcomes of treatment. The use of medical information systems for dynamic monitoring of patients or the development of a register of patients with OA using a model of population-based cancer registers [25] can be useful for studying the long-term effects of treatment.

Conclusion
We established that the introduction of OVRT into treatment regimens reduced the disability of patients with OA of the knee joint by almost 50%. One in four disability cases could be
prevented if OVRT were used universally in the treatment of knee OA. Our findings suggested that combining OVRT with standard care is a more effective approach to preventing disability in patients with knee OA than conventional treatment alone.

Ethical approval

The study was approved by the local Ethics Committee of the Northern State Medical University (Protocol No. 10 of 21 December 2011). All procedures complied with the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest

The authors declare no conflicts of interest.

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References


Authors:
Maria V. Makarova – MD, PhD, Associate Professor, Department of Diagnostic Radiology, Radiotherapy and Oncology, Northern State Medical University, Arkhangelsk, Russia. https://orcid.org/0000-0002-9144-3901.
Mikhail Yu. Valkov – MD, Dsc, Professor, Chair of the Department of Diagnostic Radiology, Radiotherapy and Oncology, Northern State Medical University, Arkhangelsk, Russia. https://orcid.org/0000-0003-3220-9638.
Andrey M. Grjibovski – MD, MPhil, PhD, Head of the Directorate for Research and Innovations, Northern State Medical University, Arkhangelsk, Russia; Professor, Department of Public Health, North-Eastern Federal University, Yakutsk, Russia; Professor, Department of Biology, Ecology and Biotechnology, Northern (Arctic) Federal University, Arkhangelsk, Russia. http://orcid.org/0000-0002-5464-0498.