**OPTIMIZATION OF FRACTIONATION SCHEDULES OF HEEL SPUR RADIOTHERAPY: MONOCENTRIC PROSPECTIVE RANDOMIZED OPEN-LABEL TRIAL**

**Project introduction including relevance and topical issues**

***Heel spur syndrome as an important socioeconomic disorder***

About 26 000 patients are treated per year with radiotherapy for non-malignant diseases in the Czech Republic. Approximately 75% of them are treated on X-ray therapy units and most of these patients undergo radiotherapy of heel spurs [1]. Painful heel spur is a major part of the heel spur syndrome (HSS). It is reportedly the most common cause of pain in the inferior heel and is estimated to account for 11% to 15% of all foot symptoms requiring professional care among adults [2]. Healthcare providers involved in the treatment of painful heels may include general medical practitioners, podiatrists, rheumatologists, physiotherapists, orthopedic, general and trauma surgeons, sports doctors, radiation oncologists, orthotists and osteopaths.

The prevalence of HSS ranges from 8%-10% in the general population at some point during a lifetime [3]. In addition, 10% of runners are affected. HSS is probably the second most common foot complaint (after toenail problems), and about 2 to 6 million cases are estimated in the U.S. each year [4]. Usually, the affected patients are older than 40 years. The epidemiology underlines the importance of the socioeconomic damages caused by HSS, because the patients suffering from heel pain are younger and more active compared to those with other painful skeletal disorders [5].

***Diagnosis and conventional therapy***

Conventional x-rays are the gold standard in the diagnosis of a heel spur, usually lateral pictures of the calcaneus are performed (Figure 1). They show a calcified spur at the inferior side of the calcaneus. The intensity of pain is not regarded to be dependent on the size of the spur.

*Figure 1: heel spur*

A great variety of therapy methods have been tested in the past but none of them has provided a high level of evidence [6]. Ice, heat, ultrasound, radiofrequency, laser beams and extracorporal shock wave therapy have been applied. Steroids and local anesthetics injected into the plantar fascia, and oral analgetic medication have been prescribed. Immobilization of the foot using special splints and adjustable shoes were applied. Physiotherapy was performed. Most of these methods and their results have been summarized in a Cochrane review [7]. Radiotherapy is often recommended after several unsuccesfull courses of treatment based on other conventional modalities [8, 9]. As a general consensus, patients will only undergo surgery in the case that conservative therapy methods have not yielded sufficient pain relief.

***Radiotherapy in the treatment of heel spur syndrome***

The anti-inflammatory effect of radiation therapy has been known for a long time and has been reported in numerous publications. Nevertheless, the exact mechanism is still unclear. Some of the models discussed are: Improvement of blood perfusion in the tissue due to an influence of radiation on the endothelium, release of cytokines and enzymes, influence on the local parts of the vegetative nervous system, and modification of the pH value in the tissue [10]. Low-dose radiation effects can be explained by an influence on molecular mechanisms and inflammation mediators.

Single doses of external beam radiotherapy (EBRT) in the range of 0.3–1 Gy are called “low dose EBRT” (LD‐EBRT). These single fractions are applied two or three times a week until a total dose of about 3–6 Gy is reached. Such radiotherapeutic concepts are used for diverse nonmalignant conditions. In contrast, EBRT in oncology is characterized by much higher single and total doses. “Normofractionation” describes single doses of 1.8–2 Gy, applied about five times a week. From a radiobiological point of view, these high cumulative doses are used to induce DNA double strand breaks. Due to errors in a repair mechanism (nonhomologous end joining), dicentric chromosomes can occur. These can result in unfinished mitoses, the so‐called “mitotic catastrophe,” the main mechanism to reduce clonogenic survival in tumor cells [11]. The much lower doses of LD‐EBRT act via different mechanisms. In the last two to three decades, several anti‐inflammatory effects have been discovered, contrary to the effects of the above‐mentioned high EBRT doses. LD‐EBRT has been shown to induce apoptosis in peripheral blood mononuclear cells (PBMC) [12]. Furthermore, doses between 0.1 and 0.5 Gy reduced the adhesion of PBMC significantly to endothelial cells in vitro, probably by suppressing the expression of L‐selectin on the surface of PBMC [13].

Several more modern trials have shown the analgetic effect of radiotherapy. The landmark study to prove the efficacy of LD‐EBRT was performed by the German cooperative group on the radiotherapy for benign diseases (GCGBD) under the responsibility of Niewald et al. [14]. A very low dose EBRT (6 × 0.1 Gy applied twice a week up to a total dose of 0.6 Gy) was randomized to a standard dose LD‐EBRT (6 × 1 Gy twice a week up to a total dose of 6 Gy). The significant benefit of standard dose 6x1 Gy was proven. In conclusion, this randomized trial established a dose‐response‐relationship of the analgesic effect of LD‐EBRT, thus providing a clinical and methodological proof of the efficacy of 6 × 1 Gy LD‐EBRT on the clinical course of painful heel spurs.

Two randomized studies investigated the efficacy of 0.5 Gy single dose in comparison to 1 Gy. The first trial was conducted by Heyd et al. [15]. They randomized 130 patients between 6 × 0.5 Gy twice weekly (low dose) and 6 × 1 Gy (standard dose). Both regimen were similarly effective. These results were confirmed by a second randomized trial by Ott et al. [16].

In conclusion, LD‐EBRT for painful plantar fasciitis/heel spur is an effective and safe treatment option for patients over 30 years of age and after exclusion of pregnancy. A fractionation of 6 × 0.5 Gy twice weekly up to a total dose of 3 Gy should be currently recommended based on randomized clinical trials. In the case of an insufficient response a second course of radiotherapy can be offered to the patient. Nevertheless, in many radiotherapeutic departments, kilovoltage X‐ray sources are less and less available and all modernization is focused mainly on megavoltage linear accelerators which are less usefull for non-malignant diseases related to bones (because of better radiobiology effects of kilovoltage comparing to megavoltage irradiation). This is why most patients are nowadays treated with linear accelerators, which were initially developed for the treatment of oncological diseases. Nevertheless, with increasing incidence of cancer, it may be assumed that availability of radiotherapy service for heel spur patients will be further limited.

This represents **upcoming** **unmet clinical need,** where alternative approaches with dramatically abbreviated fractionation schedules are needed in order to keep availability as well as effectivity of heel spur (and other non-malignant disorders) radiotherapy.

The aim to presented study is to evaluate low dose radiotherapy delivered in single fraction manner in the treatment of heel spur syndrome.

**Hypothesis and motivation**

We hypothesize that the very low total doses of radiotherapy (single fraction) applied in antiflogistic radiotherapy of heel spurs are non-inferior in pain relief compared to the overall higher doses applied by fractionated radiotherapy.

The topicality of single-fraction radiotherapy in non-malignant disorders is currently highly relevant in relation to the significantly limited availability of this treatment method due to insufficient equipment and capacity of radiotherapy workplaces (also related to dramatically increasing incidence of cancer) and also due to limitations given by restrictive measures in connection with a possible epidemiological situation or other causes of emergency.

Presented project proposal has very convenient cost/benefit ratio (small budget comparing to other projects submitted to this funding agencywith direct clinical impact on health care (applicability).

**Aims of the project**

The aim is to realize a monocentric prospective randomized open-label study, the output of which will be the objectification of the effect of various fractionation schedules of orthovoltage anti-inflammatory radiotherapy of heel spurs. The primary aim is to evaluate non-inferiority of one-day (single fraction) irradiation in the time horizon of three months after radiotherapy. The secondary goal is to analyze the technique of heel spur radiotherapy at individual workplaces performing this type of treatment in Czechia (questionnaire survey), resulting in the publication of a review article in the Czech language aimed at supporting the standardization of this treatment in the Czech Republic.

Aim1: To prepare all necessary documentation needed for prospective randomized clinical trial,

especially randomization table, patients documentation folders including printed quality of life questionnaires etc. The most time-consuming will be the preparation of printed as well as electronic case report forms.

Aim2: To initiate the monocentric prospective randomized open-label study of different radiotherapy

fractionation schedules for treatment of heel spur.

Aim3: To compare Calcaneodynia sum score at 3 months after radiotherapy between fractionated vs.

single fraction radiotherapy (**Primary objective of trial – to prove non-inferiority of single fraction radiotherapy of heel spur**)

Aim4: To compare Calcaneodynia sum score at 3 months after radiotherapy between different single

fraction radiotherapy prescription.

Aim5: To compare the need for reirradiation till 1 year after radiotherapy between fractionated vs.

single fraction radiotherapy. To compare the need of reirradiation till 1 year after radiotherapy between different single fraction radiotherapy prescription.

Aim6: To compare quality of life (SF-36 questionnaires – sum score) and VAS score at 1.5, 3, 6, 9 and

12 months and Calcaneodynia sum score at 1.5, 6, 9 and 12 months between fractionated vs. single fraction radiotherapy. To compare the quality of life (SF-36 questionnaires – sum score) and VAS score at 3, 6, 9 and 12 months and Calcaneodynia sum score at 1.5, 6, 9 and 12 months between different single fractions radiotherapy prescription.

Aim7: Evaluation of individual (not sum) parts of Calcaneodynia score and individual domains of

quality of life as per Aim 3, 4 and 6.

Aim7: To conduct a questionnaire survey analyzing the technique of heel spur radiotherapy at

individual workplaces performing this type of treatment in Czechia

**Methods and approaches**

*Pretreatment evaluation*

All patients referred to medical attention for non-malignant radiotherapy at the Department of Radiation oncology, Masaryk Memorial Cancer Institute (MMCI), will be screened for eligibility, and if all inclusion/exclusion criteria are met, they will be invited to participate in the present study.

Inclusion criteria: 1) Patients aged over 40 years who have been diagnosed clinically and radiologically to be suffering from a painful unilateral plantar heel spur for at least six months, 2) indication to heel spur radiotherapy, 3) 40 years or older patient, good performance status (Karnofsky index ≥ 70), 4) exclusion of other local diseases by the orthopaedic surgeon, 5) willingness of the patient to provide telephone or email contact to maintain follow up.

Exclusion criteria: 1) Prior radiotherapy of heel spur (even if prior radiotherapy was performed on the contralateral heel spur because of possible bias given patient's expectations and experiences related to previous radiotherapy, 2) corticosteroid local application during last 4 weeks prior to planned radiotherapy, 3) rheumatic or vascular diseases, lymphatic edema of lower limb, 4) former trauma or surgery of ipsilateral foot, 5) any systemic illness (collagen vascular diseases) or unstable medical condition that might pose additional risk for performance of radiotherapy including claustrophobia or jactation, 6) any other factors that, in the opinion of the site investigators, would interfere with adherence to study requirements, 7) pregnancy or breastfeeding, 8) inability or unwillingness of subject to sign written informed consent.

*Treatment and follow up approaches*

After consultations with eligible patients and answering all questions, informed consent approved by the Institutional Review Board will be signed by each patient and investigator before study enrollment and randomization. After obtaining written informed consent, a patient will be randomized by the statistician to one of the arms mentioned below.

After radiotherapy, follow-up examinations consist of a personal examination (3 months after radiotherapy) and questionnaire survey (1.5, 3, 6, 9 and 12 months after radiotherapy). Every single patient is followed-up for 1 year. This duration of follow-up was chosen on the basis of the retrospective experience that the vast majority of beneficial effects became apparent after less than 1 year.

In the case of an unfavorable response to the radiation therapy after 3 months or more, the patient will be offered a second treatment series applying a standard fractionated dose of 6 Gy, single fraction 1.5 Gy twice weekly. Irrespective of the outcome of this second series, these patients remained in their arms, with the result classified as “Insufficient pain relief”.

The effect is measured using several target variables (scores): Calcaneodynia-score according to Rowe et al. [8, 17], quality of life questionnaire Short-form 36 (SF-36) score, and visual analogue scale of pain. The most important endpoint is the pain relief expressed by Calcaneodynia-score three months after therapy.

Calcaneodynia score form is attached in separate file in this project proposal. Sum score (100 = free of symptoms, 0 = very intense symptoms) is calculated by evaluation of Pain symptoms (up to 30 points), Use of appliances (up to 15 points), Professional activities (up to 20 points), Daily/leisure activities (up to 15 points) and Gaint/limp (up to 20 points).

Visual analogue scale (VAS) score is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain." (0 = no pain, 100 = maximum imaginable pain intensity).

SF-36 questionnaire (form as well as evaluation description is attached in separate file in this project proposal) score taps eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. High values indicates good quality of life.

Additionally, "Complete pain relief" will be assumed if patients will be completely free of pain and regained full ability to walk and function well. “Insufficient pain relief” will be assumed, if the patient's subjective evaluation (VAS score) of improvement of pain will be less than 80%, or if the temporal pattern of clinical response will be unsatisfactory (ie, response will be delayed > 3 months or there will be need for second radiotherapy course. Skin toxicity will be evaluated according Common Terminology Criteria for Adverse Events (CTCAE) v5.

After enrolment and filling in the SF-36 questionnaire, Calcaneodynia and VAS pain score forms, the patient is randomly assigned to either of the following therapy protocols:

Group A: Total dose of 6 Gy in 4 single fractions of 1.5 Gy applied twice weekly (most commonly

 used regimen, considered standard arm in this trial)

Group B: Total dose of 3 Gy in 2 single fractions of 1.5 Gy applied twice weekly

Group C: Total dose of 0.5 Gy in 1 single fractions of 0.5 Gy

Group D: Total dose of 1 Gy in 1 single fractions of 1 Gy

Group E: Total dose of 1.5 Gy in 1 single fractions of 1.5 Gy

Group F: Total dose of 2 Gy in 1 single fractions of 2 Gy

Arm A (standard fractionated dose): Groups A–B

Arm B (experimental single dose): Groups C–F

*Radiotherapy procedures:*

Technical aspects of X-ray heel spur radiotherapy will be in full concordance to our institutional Standard Operation Procedures. Patients are irradiated by GULMAY D 3225 kilovoltage X-ray irradiator. Patient is placed on the treatment couch in two possible positions according to location of maximal pain – in supine or in prone position. In supine position, beams are arranged as two laterolateral 90° and 270° fields and this technique is more commonly employed in patients localizing maximal pain to medial or lateral part of foot. Alternatively, the technique of so-called “plantar field” with the patient lying in prone position is employed for patients localizing maximal pain to plantar parts, Figure 2.

Most commonly, the bundle shaping using rectangular applicators 6x8cm or 6x10cm are utilized with skin-source-distance of 50cm for irradiation by energy of 150 kV.

**Statistical consideration** *Figure 2: heel spur radiotherapy*

The project aims to design a randomized trial that compared fractionated and single fraction radiotherapy. The patient will be randomized into 6 groups according to the total dose. Considered trial arms will be in the ratio 1:2. Patients will be randomized employing stratified permuted block randomization to ensure equal distribution of patients according to possible biases. Stratification factors will be 1) treatment prior to radiotherapy (none, light intervention, advanced intervention) and 2) Calcaneodynia sum score prior to radiotherapy (0–20, 21–40, 41–60, 61–100).

The primary endpoint is achieving a Calcaneodynia sum score over 75 at 3 months after radiotherapy. The study is designed to declare that the single fraction radiotherapy is not inferior to the fractionated radiotherapy at a -10% margin of non-inferiority. Assuming that 65% of the patients in both arms would achieve sufficient Calcaneodynia sum score (over 75), the study would require a sample size of 585 for the Arm B and 293 for Arm A (i.e., a total sample size of 878) to achieve a power of 90% and a level of significance of 5%. With an assumed drop-out of 10%, the project will include 966 patients in total, 161 in each dose group. The proposed number of patients corresponds to the actual incidence of patients meeting the eligibility criteria who are treated in our institution.

Patient characteristics will be described using standard summary statistics, i.e., median and interquartile range or mean and standard deviation for continuous variables and frequencies and proportions for categorical variables. Depending on the data type, common statistical tests such as Fisher's exact test or chi-square test for comparing categorical variables and nonparametric Mann-Whitney test or Kruskal-Wallis test for comparing continuous variables or their parametric alternatives, if the assumption of data normality will be met, will be used for comparison between groups. All statistical analyses will be performed employing a common significance level of 0.05.

**Time schedule and milestones of the project, justification of project duration**

The entire project is planned for the period from May 2022 to December 2025, that means 44 months. The subjects' enrollment is planned to start immediately after preparation of all administrative documentation (information materials for patients, printed as well as electronic Care Report Forms in collaboration with statistician etc), not later than at the beginning of last quarter of 2022. The overall time needed for patients enrollment is 21 months reflecting the patients' throughput in our department and reflecting the time needed for follow-up (1 year). It is estimated to finish patients recruitment in the middle of 2024. The length of the project also reflects the estimated number of enrolled patients needed for satisfactory power of final statistical tests.

We expect inclusion of 140 patients till December 31, 2022. During 2023, other cca 580 patients will be included. After 9 month of enrollment, with estimated cca 430 patients included, we plan the control analysis. The main reason is to identify eventual delay in enrollment and to assess standardization of all study processes. During first half of 2024, last 246 patients will be enrolled. The databases will be completed for comprehensive statistical analysis. The results will be also presented at national and international conferences.

The overall schedule of the project presents a Gantt chart in Figure 3.



*Figure 3: Gantt chart of the project*

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