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CLINICAL INVESTIGATION

Low-Dose External Beam Radiation Therapy and Painful Hip Due to Coxarthrosis and Greater Trochanteric Pain Syndrome: Predictive Impact of Diagnosis, Target Volume Definition, and Season of Treatment

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Purpose: Coxarthrosis and greater trochanteric pain syndrome (GTPS) are common etiologies of hip pain. In this retrospective study, we analyzed the treatment response within the 3 to 12 months of low-dose external beam radiation therapy (LD-EBRT) for coxarthrosis and GTPS along with potential predictive factors.
Methods and Materials: We evaluated data from patients who were treated with radiation therapy for GTPS or coxarthrosis at our radiation centers between 2014 and 2024. In addition, all planning computed tomography scans were analyzed according to the Kellgren-Lawrence score. Subsequent univariate and multivariate analyses of the data were performed.
Results: The clinical response rate (overall response rate [ORR]) was approximately 64% in GTPS and 58% in coxarthrosis. Approximately 20% of the patients received a second series of LD-EBRT, and approximately 5% a third. In multivariate regression analyses of coxarthrosis, factors negatively correlated with ORR were an initial increase in pain, age $\geq$ 70 years, and body mass index (BMI) $\geq$ 25 kg/m^2. The outcome was independent of symptom duration, LD-EBRT season, and planning target volume. In GTPS, symptom duration >12 months, initial pain increase, and prior hip prosthesis were negatively correlated with ORR. No dependence on the LD-EBRT season or on the definition of the planning target volume was observed.
Conclusions: LD-EBRT may be an effective treatment option for GTPS and coxarthrosis. Early application of this therapy option appears to alleviate symptoms, regardless of season or planning target volume.

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Introduction

Pain in the hip because of degenerative disorders is a common medical problem. The most critical diagnoses are arthrosis of the hip joint (also known as "coxarthrosis") and tendinopathies of the gluteal muscles (referred to as "greater trochanteric pain syndrome," GTPS).

A recent meta-analysis estimated the prevalence of radiologically significant coxarthrosis (Kellgren-Lawrence score of "2" or higher) at 8.5%, and found that the prevalence increased with age.[1] Various national and international guidelines assess the diagnosis and treatment of coxarthrosis, but grade interventions differently in each case (see a current overview in Gray et al[2]). Common interventions include lifestyle changes, physical exercise, pharmacologic management (especially pain-reducing therapies), so-called "adjunctive therapies" (such as acupuncture, manual therapy, or transcutaneous electrical nerve stimulation), and surgical interventions.[2]

The prevalence of GTPS (defined as "tenderness to palpation over the greater trochanter") has been estimated to affect up to 10% of the population.[3] A current explanation for this symptomatology is a "tendinopathy" of the gluteal muscles that insert on the greater trochanter, leading to aseptic inflammation affecting the bursae and even the iliotibial tract.[4] Treatment options include lifestyle modifications, nonsteroidal anti-inflammatory drugs, hip-strengthening exercises with physical therapy, corticosteroid or platelet-rich plasma injections, and adjunctive therapies such as external shock wave therapy.[4-6] In cases where comprehensive conservative treatments have failed, surgical options such as bursectomy may be considered. However, even after surgical intervention, local complaints may persist, requiring further conservative therapies.[7]

Low-dose external beam radiation therapy (LD-EBRT) is frequently used in central Europe to treat tendinopathies and osteoarthritis symptoms that are refractory to other conservative therapies.[8] LD-EBRT consists of 6 fractions, given once or twice weekly, up to a total dose of 3 Gy. In vitro and in vivo studies have demonstrated diverse inhibitory effects of these low doses of radiation on various inflammatory effectors.[9] In painful heel spurs, a form of tendinopathy, the clinical efficacy of LD-EBRT has been demonstrated in prospectively randomized trials.[10,11] However, prospective evidence of LD-EBRT's effectiveness in treating osteoarthritis remains pending.

A retrospective series of LD-EBRT in the therapy of coxarthrosis showed a pain reduction in 24% to 89% of patients.[8] However, this improvement in symptoms was often of limited duration. The German guideline for radiation therapy of benign diseases recommends LD-EBRT for symptomatic coxarthrosis as "can be performed," citing evidence level 4 (case series, cohort, and case-control studies of low study quality).[8]

Table 1[12-17] summarizes the treatment results of LD-EBRT in GTPS. Overall, >50% of the irradiated patients can expect a complete/good response of the symptoms in the further course, with approximately 30% experiencing treatment failure. The German guideline recommends LD-EBRT after failure of other conservative therapies as "can be performed," referring to evidence level 4.[8]

The present study is intended to analyze and compare the efficacy of LD-EBRT in coxarthrosis (as an example of osteoarthritis) and GTPS (as an example of a tendinopathy) within, to our knowledge, the largest patient collective published to date, which was treated according to the same standards and fractionation schedule. Furthermore, predictive factors for treatment response will be analyzed. In particular, the robustness of the diagnosis (clinical and radiologic), radiologically detectable osteoarthritis of the hip joint on the planning computed tomography (CT) scan, target volume definition, and the season of the year when LD-EBRT is applied are to be correlated with treatment results.

Methods and Materials

The clinical courses of all patients diagnosed with "symptomatic coxarthrosis" (International Classification of Diseases, 10th Revision, [ICD]-10 codes: M16.0-M16.9)[18] and "GTPS" (ICD-10 codes: M70.6, M76.0, M76.1, M76.3, M76.8, and M76.9),[18] who were treated between January 1, 2014 and December 31, 2024, at our radiotherapeutic centers, were retrospectively analyzed.

Patients had previously been referred to an orthopedic surgeon and had received clinical and radiologic confirmation of the diagnosis. LD-EBRT was indicated in accordance with the S2e guideline if other conservative treatment options had been exhausted or were not feasible.[8] In the context of LD-EBRT, invasive therapies (eg, cortisone injection and arthroscopy) were not permitted in parallel with LD-EBRT. Only the continuation of analgesic treatment and accompanying physical therapies were allowed.

Patients who provided consent allowing their data to be used for anonymized retrospective analysis were included, as established during their regular consultations before LD-EBRT.

The processing and evaluation of such data adhered to the guidelines of the Ethics Committee of Hannover Medical School, Germany, No. 11816-B0-K2025.

The examined patients were divided into 2 groups. In addition to radiologic changes in the hip joint of at least Kellgren-Lawrence grade "1," the prerequisite for the diagnosis of coxarthrosis was typical clinical symptoms such as painful internal rotation or pain radiating from the hip into the groin or toward the knee joint ("Cox" group, n = 262).[19]

The diagnosis of GTPS was clinical in all cases, with typical pain history/radiation and trigger on palpation ("GTPS" group, n = 549). From the "GTPS" group, all patients with radiologic signs of coxarthrosis but clinically inapparent were assigned to a new subgroup ("GTPS∩Cox" group, n = 380).

A substantial number of patients also underwent magnetic resonance imaging (MRI) to confirm the diagnosis as part of their LD-EBRT referral.

All patients received at least 2 conservative treatments with insufficient success before referral to LD-EBRT. Patients aged <40 years were generally not treated with LD-EBRT for coxarthrosis, and only in exceptional cases (long-lasting courses refractory to other conservative therapies) for GTPS.

All patients underwent a planning CT scan with 5-mm axial slices for LD-EBRT planning. The target volume definition was performed according to the diagnosis and the morphologic changes observed on the CT scan (Fig. 1).

In the case of coxarthrosis, the entire hip joint and the medial part of the femoral neck (anteriorly, including the intertrochanteric line, and posteriorly, slightly above the intertrochanteric crest) were encompassed as the clinical target volume, including any effusions, osteophytes, or sclerosis in the acetabular region. For GTPS, the inserting areas of the gluteal muscles at the greater trochanter down to the lesser trochanter at the lateral femoral neck, including the cranial part of the fascia lata, had to be included. The clinical target volume volume was expanded by 10 mm to create the planning target volume (PTV), but only by 5 mm medially to protect the intrapelvic organs. A 5-mm distance was also kept from the body surface. However, because several consultants performed the target volume contouring, deviations from these guidelines occurred. This is why a substantial number of patients received the dose to the gluteal insertions, although only the hip joint was intended to be treated.

LD-EBRT consisted of 6 fractions, usually twice weekly over 3 weeks, with a single dose of 0.5 Gy up to 3 Gy, according to International Commission on Radiation Units and Measurements Report 50 (ICRU-50). Patients who received a different dose or fractionation were excluded from this study.

To ensure correct patient positioning, either 2D portals were generated or a cone beam CT was performed during the LD-EBRT simulation. Daily positioning was initially performed on isocenter markers on the patient's skin; later (from 2021 onward), using a surface guidance system, alignRT (Vision RT). The quality requirements for these treatments were consistent with those of oncologic radiation therapy.

"Initial increase of pain" was defined as an increase in symptoms after 3 fractions of LD-EBRT. All patients were interviewed accordingly, and the results were documented in the file. For statistical evaluation, treatment efficacy was assessed at 2 time points.

First, at the end of LD-EBRT. Treatment effects were grouped using the modified "von Pannewitz" score[8,20] as

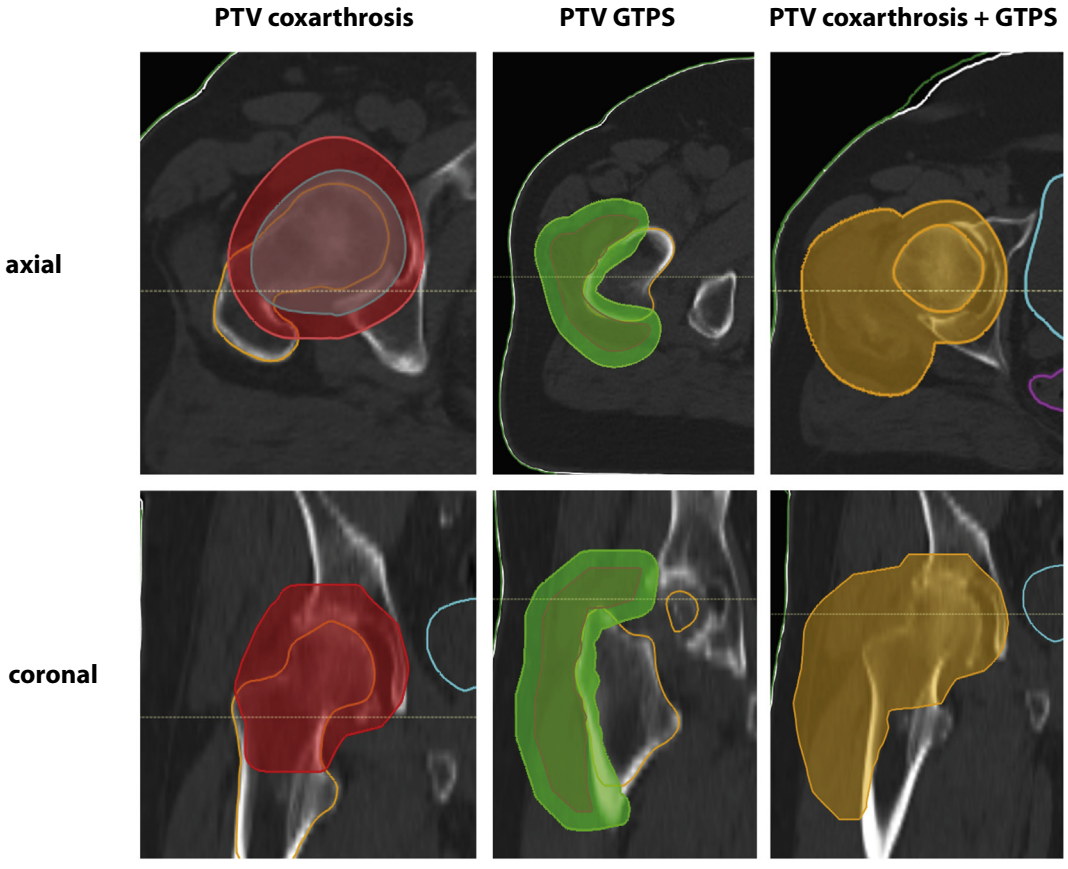

Fig. 1. Planning target volume for coxarthrosis and GTPS. Graphical representation of then syndrome;ward selection (Wald) xncluded treated areas in the axial and coronal plane in LD-EBRT for coxarthrosis, GTPS, and GTPS with coxarthrosis. *Abbreviations:* GTPS = greater trochanteric pain syndrome; LD-EBRT = low-dose external beam radiation therapy; PTV = planning target volume.

"no change" (including persistent deterioration of symptoms during or at the end of LD-EBRT), "partial response," and "complete response."

Second, at the last visit/contact, at least 3 months later (in almost half of the patients, additionally significantly later), as patients were followed up in accordance with internal procedures and a defined protocol system established at the study centers and documented in the patient files. In the event of an inadequate subjective response, a second series of LD-EBRT was offered.

After completing the second series, patients received another follow-up at least 3 months later. In individual cases, a third series of LD-EBRT was also provided in the subsequent clinical course, primarily if symptoms worsened after an initially favorable clinical response, in accordance with the German guideline.[8]

The primary endpoint was "treatment response" at the end of clinical follow-up after the last treatment series. It consisted of "partial" and "complete" responses, as described above.

For the evaluation of predictive factors, clinical and therapeutic parameters related to treatment volume definition were documented, including the volume of the PTV, the distance between the greater trochanter and the cranial field border, the distance between the lesser trochanter and the inferior field border, and the anatomic location of the PTV (hip joint vs GTPS vs. both anatomic areas). Furthermore, in the planning of CT scans, 1 observer (P.K.) reevaluated all affected hip joints and classified them according to the Kellgren-Lawrence score[21,22]:

Grade 0: no obvious pathologic findings;
Grade 1: possible osteophytic formation, "doubtful" joint space narrowing;
Grade 2: definite osteophytes, "possible" joint space narrowing;
Grade 3: moderate osteophytes, "definite" joint space narrowing, some sclerosis;
Grade 4: large osteophytes, "marked" joint space narrowing, definite bone ends deformity.

The aim was to analyze the influence of osteoarthritic changes on treatment success in patients who underwent LD-EBRT for confirmed GTPS, treating these radiologic changes as independent predictors.

The treatment season (and evaluation of treatment efficacy during follow-up) was classified as "spring:" (01.03-31.05), "summer:" (01.06-31.08), "autumn:" (01.09-30.11), and "winter:" (01.12-28.02). The start date of the LD-EBRT defined the season, even if the duration of the LD-EBRT exceeded the seasonal boundary.

Statistics

"Partial" and "complete" responses were combined into an "overall response rate" (ORR) to contrast with "no change," thereby improving statistical power. "ORR" was referred to in the present study as "response group."

Furthermore, patients were grouped according to their initial and pretherapy diagnosis (coxarthrosis vs GTPS). Additionally, we evaluated patients with GTPS who presented a radiologic coxarthrosis of at least Kellgren-Lawrence grade "1" separately ("GTPS∩Cox"). The aim was to determine whether this clinically unrecognized coxarthrosis affected treatment results.

Following the group allocation, we tested the metric variables for normal distribution using the Shapiro-Wilk test (SPSS, IBM, version 30). This strategy showed that all variables were not normally distributed. Accordingly, unrelated groups with at least ordinal-scaled characteristics were examined using the Wilcoxon-Mann-Whitney test. If the result was significant ($P< .05$), the effect size "r" was also calculated to better assess clinical relevance.

A Pearson χ^2 test was performed to analyze dichotomous characteristics of 2 unrelated groups. Then, to improve the interpretability of the results, the effect size, "Phi" (ϕ), was also calculated when the required significance level ($P< .05$) was reached. In some cases, if categorical variables were significant in the Pearson χ^2 test, dummy variables were created, and a new Pearson χ^2 test was performed for each parameter. If the sample size (n) was <20, the Fisher-Yates test was performed instead of the Pearson χ^2 test, following convention. The significance level was set at $P< .05$.

Multiple regression analyses were conducted using GraphPad Prism, version 10.4.2. For categorical variables with >2 levels, dummy coding was applied.

For the logistic regression analysis with backward selection (Wald) of the GTPS and coxarthrosis subgroup, only variables that showed a statistically significant result ($P< .05$) in the univariate tests were included. A 2-tailed Pvalue of <.05 was considered statistically significant throughout all analyses.

Results

During the study period, 1575 patients received radiation therapy to the hip region for a benign underlying disease. Of these, 821 patients were excluded because they had received single-dose EBRT as ossification prophylaxis before surgical implantation of a hip prosthesis. Fifty-one patients had received LD-EBRT at a higher dose or alternative fractionation. Five patients were excluded because they discontinued LD-EBRT after the first or second fraction.

A total of 698 patients with 811 irradiated hips were examined in the analysis. Two hundred sixty-two hips were treated for coxarthrosis, and 549 hips for GTPS (for details, see Table 2). However, in the GTPS group, 380 hips showed signs of osteoarthritis of at least Kellgren-Lawrence grade "1" on the planning CT scan (GTPS∩Cox, Table E2).

Patients irradiated for coxarthrosis were older (71.5 years) in comparison to GTPS (65.2 years). In more patients with GTPS, the diagnosis was confirmed with MRI. As

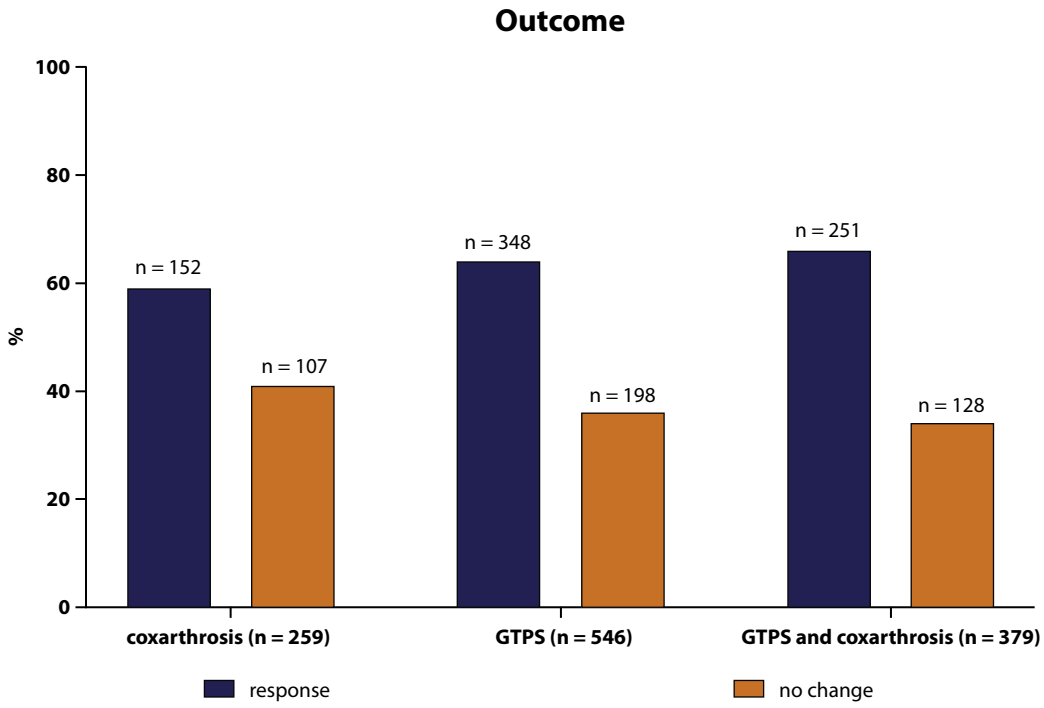

Fig. 2. Treatment success at the end of clinical follow-up.Presentation of the overall response rates for coxarthrosis (58.02%), GTPS (63.39%), and GTPS and coxarthrosis (66.05%) in relation to the outcome. *Abbreviation:* GTPS = greater trochanteric pain syndrome.

expected, radiologic signs of coxarthrosis were significantly pronounced in the coxarthrosis group with a Kellgren-Lawrence score of "2" (1-4) compared with "1" (0-4).

The characteristics of the GTPS∩Cox group did not differ significantly from those of the GTPS group.

Regarding LD-EBRT treatment characteristics for coxarthrosis, the target volume only comprised the femoral head and the medial part of the femoral neck in approximately 40% of cases, whereas 60% received additional treatment of the peripheral neck. For GTPS, nearly 60% of patients received treatment of the gluteal muscle insertion areas at the greater trochanter, whereas 40% received an additional dose to the femoral head. PTV volume was significantly larger in GTPS than in coxarthrosis, with longer distances between the superior and inferior field borders relative to the trochanteric structures.

No significant differences were observed in the seasons of LD-EBRT administration, with approximately one-fourth of patients treated in each season.

Approximately 13% of patients reported an initial increase in pain sensation at the end of the first LD-EBRT series, whereas >50% reported a response, regardless of the diagnosis. No differences were observed between GTPS and GTPS∩Cox.

A second LD-EBRT series was applied in 59 patients (22.5%) with coxarthrosis, 3 months after the first series, and in 177 patients (32.2%) with GTPS, after 4 months (131 patients, 34.5%, in the GTPS∩Cox). A third series was rarely given: 12 patients (4.6%) with coxarthrosis, and 16 patients (2.9%) with GTPS (n = 12 patients, 3.2% in the GTPS∩Cox).

The mean follow-up time between the first LD-EBRT and the evaluation of treatment success at the end of clinical follow-up was 3 months in the Cox study and about 7 months in the GTPS study. Approximately, 48% of all cases were followed up for longer because of further treatment and subsequent follow-up, resulting in a mean follow-up time of about 7 months for GTPS. Nearly 14% were followed for more than 1 year.

Symptom response in up to 3 series was reported in 58% of patients with coxarthrosis, nearly 64% with GTPS, and 66% in the GTPS∩Cox group (Fig. 2).

Univariate analysis of potential predictive factors

Table E1 shows the "ORR" versus "no change" after LD-EBRT of patients with coxarthrosis and GTPS.

In coxarthrosis, an age ≥ 70 years was associated with a significantly lower "ORR" (53% vs "no change" 47%, P= .025), whereas no such correlation was found in GTPS. Similarly, a body mass index (BMI) ≥ 25 kg/m^2 was associated with worse treatment results in coxarthrosis, but not in GTPS ("ORR" 58% vs "no change" 74%, P= .013). In GTPS, a prior hip prosthesis was negatively correlated with treatment outcome.

Surprisingly, in both groups, the certainty of the clinical diagnosis, confirmed by MRI, was not predictive of treatment response. Concerning pain characteristics, no influence on treatment outcomes was found in coxarthrosis. In

GTPS, a duration of symptoms <6 months before LD-EBRT was significantly associated with response (80% "ORR" vs 20% "no change," $P < .001$; $\phi = 0.15$), compared with a duration over 1 year with more "no change" (55% "ORR" vs 45% "no change," $P < .001$; $\phi = 0.18$). Furthermore, pretreatment with WHO-level II analgesics was associated with "no change" (51%, $P = .031$).

Almost all specifications related to LD-EBRT planning (target volume definition and distance of field boundaries to anatomic landmarks) showed no correlation with treatment outcomes, whereas the target volume definition was directly related to the diagnosis. Nevertheless, these data also show that GTPS irradiated only peripherally (61% vs 39%) had a good effect comparable to simultaneous coirradiation of the femoral head (peripheral + femoral head: 67% vs 33%).

Interestingly, the time of year (season) of LD-EBRT or the season of evaluation treatment results did not affect LD-EBRT efficacy.

An initial increase of pain during LD-EBRT was significantly associated with "no change" in all diagnoses studied (Cox $P = .009$; $\phi = 0.16$; GTPS $P = 6.00E\text{-}5$; $\phi = 0.17$; GTPS∩Cox $P = .001$; $\phi = 0.17$).

No correlation was observed between the outcome and the severity of coxarthrosis in either the GTPS group ($P = .93$) or the GTPS∩Cox group ($P = .68$). In contrast, the median Kellgren-Lawrence score in patients with coxarthrosis in "response" was "2," significantly lower than in patients without a treatment response (median "3;" $P = .023$; $r = 0.14$).

Regarding potential influencing factors in the group of patients with GTPS who had radiologic signs of coxarthrosis incidentally identified on the planning CT scan ("GTPS∩Cox"), no significant differences were observed compared with the overall GTPS group (Table E3).

Multivariate analysis

All significant factors in the univariate tests were included in the multivariate logistic regression with backward selection (Table 3, Fig. 3). In GTPS, significantly poorer treatment results were confirmed for a duration of symptoms > 12 months [odds ratios (OR), 1.943; 95% CI, 1.326-2.848], an initial increase in pain during LD-EBRT (OR, 2.091; 95% CI, 1.245-3.514), and a prior hip prosthesis (OR, 1.864; 95% CI, 1.125-3.090). In the Cox group, the initial increase of pain was also statistically significant (OR, 2.928; 95% CI, 1.332-6.436). Furthermore, there was a worse outcome for BMI ≥ 25.0 kg/m^2 (OR, 2.091; 95% CI, 1.168-3744) and an age ≥ 70 years (OR, 2.411; 95% CI, 1.330-4.368).

Discussion

The ORR was approximately 64% for GTPS and 58% for coxarthrosis. In the Cox group, the ORR increased from 55% to 58% after 2 or 3 series of LD-EBRT, in the GTPS group from 55% to 63% and in the GTPS∩Cox group from 57% to 66% (Table E1/E3). Because the therapy was repeated only in the absence of a sufficient response, a cumulative effect on success was within the expected range. However, in all groups, some patients reported improvement after the first series but had a new increase in

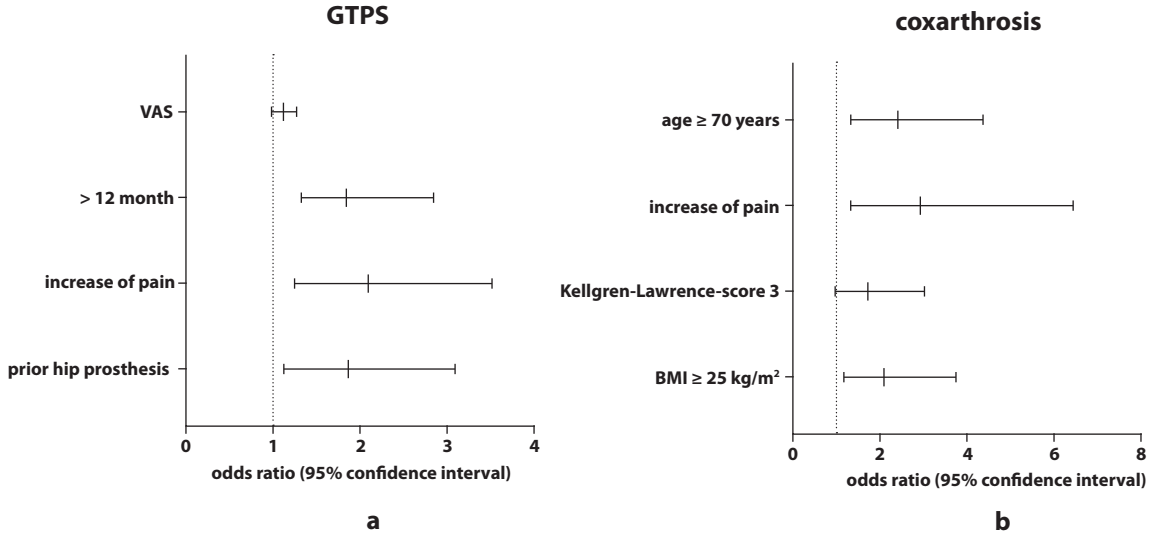

Fig. 3. Multivariate logistic regression analysis (odds ratios) with backward selection (Wald) of prognostic factors. This graph illustrates the final model of the multivariate logistic regression analysis with backward selection (Wald) for the researched entities. **(A)** GTPS: In the multivariate regression analysis, initial increase in pain, a prior hip prosthesis, and a symptom duration of more than 12 mo were confirmed as negative influencing factors. **(B)** Coxarthrosis: In this study, this significance could only be demonstrated for the factor the factor thesis, and age ≥70 year, and a body mass index ≥25.0 kg/m^2. *Abbreviations:* BMI = body mass index; GTPS = greater trochanteric pain syndrome; VAS = Visual Analog Scale.

symptoms during further follow-up, which was to be expected given the pathogenesis of the clinical pictures investigated as chronic degenerative or inflammatory diseases with habitual pathogenesis.[23-25]

These results for LD-EBRT in GTPS compare favorably with those of other retrospective studies, despite differences in endpoints and follow-up periods (see Table 1). One other study compared LD-EBRT outcomes for both diagnoses in smaller cohorts (n = 54 patients with GTPS, 57% "response;" n = 30 with coxarthrosis, 27% "response").[15] The discrepancy may be because of differences in the definition of efficacy.

Age was a significant factor influencing treatment success for coxarthrosis, but not in GTPS. The patients with "no change" were older (53% vs 47%). One explanation may be that as coxarthrosis progresses degenerative processes increase.[26-28] LD-EBRT primarily inhibits inflammatory processes.[9] Therefore, a better response to LD-EBRT can be expected in the early phases of osteoarthritis, where inflammation predominates over degeneration. An earlier phase of the disease is often associated with a younger age.[26-28] Comparable results were shown in a study with 970 patients.[29]

Furthermore, a lower BMI was associated with a better outcome in coxarthrosis. A direct correlation between the prevalence of bilateral coxarthrosis and increasing BMI has been shown before.[30] Furthermore, a higher risk of hip replacement was correlated with a higher BMI.[31] Based on these findings, it is reasonable to correlate a higher BMI with a poorer outcome after LD-EBRT.

We categorized GTPS as a tendinopathy because of its pathogenesis.[32] In this context, inflammatory processes play a crucial role, particularly in the early phase.[25,33] In our study, early LD-EBRT after symptom onset was more likely to result in a response, whereas symptom duration exceeding 12 months was associated with a poorer overall outcome. Patellar tendinopathy has been studied in detail to differentiate its stages.[34] The acute stage lasts up to 6 weeks, the subacute stage up to 12 weeks, culminating in the chronic stage. Extrapolation of these findings to GTPS may explain our findings. Staruch et al[17] also drew similar conclusions from treatment results in n = 65 patients with GTPS, in whom a response to a previous injection with steroids was associated with a later response to LD-EBRT. Consistent with our results, LD-EBRT for plantar fasciitis was associated with better treatment outcomes when applied within 6 months of symptom onset.[35] Hence, after an insufficient response to initial therapies, prompt presentation of the patient for LD-EBRT may lead to a better response. This strategy should be considered when determining the indication and planning treatment.

In contrast, our study showed no correlation between symptom duration and ORR in coxarthrosis. Several studies indicate that osteoarthritis also has an inflammatory component, in addition to its degenerative component.[26-28] These findings may explain our results. The median Kellgren-Lawrance score for "no change" to LD-EBRT was "3," and it was "2" in the response group. As coxarthrosis grade "3" according to Kellgren-Lawrence is characterized by significant osteophyte formation, it is assumed that, in this "chronic phase," degenerative processes predominate over inflammatory processes, leading to a lower response to LD-EBRT.[22]

The apparent effects of LD-EBRT on inflammation led us to question whether there are correlations between seasons and the impact of LD-EBRT, either in terms of when LD-EBRT is performed or when the therapy results are evaluated. A recent meta-analysis found correlations between weather factors and clinical symptoms of osteoarthritis. In other words, relative humidity was positively associated with pain intensity.[36] However, in our collectives, the season did not affect the treatment results. To our knowledge, this question has not been investigated in the context of LD-EBRT before.

Interestingly, significant differences were observed in the subjective perception of pain before LD-EBRT in our collective with GTPS. Although patients with a response reported a median Visual Analog Scale (VAS) score of 7 of 10 before starting LD-EBRT, patients without improvement in

Table 1. Summary of the treatment results of LD-EBRT in GTPS published as full-text papers

Study	n	Fractionation of LD-EBRT	Follow-up	Main results
Micke et al[12]	27	SD 0.5 Gy/1 Gy, TD 6 Gy	29 mo	Response: 70%
Kaltenborn et al[13]	60	SD 0.5/1 Gy, TD 3/6 Gy	18 mo	CR, 21%, PR: 51%, NC, 28%
Micke et al[14]	70	SD 0.5 Gy, TD 6 Gy	29 mo	Good response: Gyat
Juniku et al[15]	54	SD 0.5 Gy, TD 3-5 Gy, 60% 2 series	36 mo	Good response: Gyat
Biete et al[16]	155	10 x 1 Gy (6 x 1 Gy)	4 mo	VAS reduction from 8 to 4
			5 y	53% long-lasting pain reduction
Staruch et al[17]	65	SD 0.5-1 Gy, TD 3-4 Gy, 66% 2 series	2 mo	Good response: 60% 2 series: > 70% - Neg. prognostic factor: regional structural abnormality - No effect of MRI imaging

Abbreviations: CR = complete response; GTPS = greater trochanteric pain syndrome; LD-EBRT = low-dose external beam radiation therapy; NC = no change; PR = partial response; SD = single dose; TD = total dose; VAS = Visual Analog Scale.

Table 2. Patient characteristics

Patient characteristics	Coxarthrosis Percent of n = 262	GTPS Percent of n = 549
Age, y*	71.53 (42-96)	65.28 (33-99)
Age ≥70 y	158 (60.3%)	208 (37.8%)
Male sex	81 (35.8%)	94 (19.8%)
Body mass index*	27.6 (16.91-46.08)	28.28 (17.9-55.74)
Body mass index ≥25.0 kg/m^2	155 (64.58%)	385 (72.64%)
Right hip	134 (51.1%)	269 (49%)
Diagnosis confirmation by MRI	22 (8.4%)	152 (27.7%)
Hip prosthesis	—	88 (16%)
Knee prosthesis	8 (3.1%)	10 (1.8%)
VAS†	7 (2-10)	8 (3-10)
Stress pain	257 (98.1%)	520 (94.7%)
Rest pain	103 (39.3%)	173 (31.5%)
Night pain	75 (28.6%)	228 (41.5%)
Symptom duration <6 mo	48 (18.3%)	98 (17.9%)
Symptom duration 6-12 mo	69 (26.3%)	161 (29.3%)
Symptom duration >12 mo	133 (50.8%)	280 (51%)
Prior therapies:		
Pain therapy		
- WHO-level I	190 (72.5%)	411 (74.9%)
- WHO-level II	18 (6.9%)	45 (8.2%)
- WHO-level III	12 (4.6%)	15 (2.7%)
Physiotherapy before LD-EBRT	138 (52.7%)	311 (56.6%)
Injections before LD-EBRT	79 (30.2%)	286 (52.1%)
Corticosteroids orally before LD-EBRT	23 (8.8%)	52 (9.5%)
Acupuncture	7 (2.7%)	18 (3.3%)
Warm/cold	4 (1.5%)	8 (1.5%)
Laser therapy	1 (0.5%)	1 (0.2%)
Kellgren-Lawrence score†	2 (1-4)	1 (0-4)
Specifications of LD-EBRT:		
Duration of LD-EBRT > 3 wk	88 (33.6%)	217 (39.5%)
Target volume LD-EBRT - peripheral	7 (2.7%)	317 (57.7%)
Target volume - femoral head	98 (37.7%)	3 (0.5%)
Target volume - peripheral and femoral head	157 (59.9%)	229 (41.7%)
PTV volume*	603.95 (113-2029)	859.7 (129-2495)
PTV volume > mean	106 (40.5%)	239 (43.5%)
Distance between the superior field border and the greater trochanter (cm)*	4.52 (1.5-14)	5.31 (1-13)
Distance between the inferior field border and the minor trochanter (cm)*	−0.8 (−13 to11)	1.32 (−5 to13)
Season of LD-EBRT		
- Spring	58 (22.1%)	122 (22.2%)
- Summer	72 (27.5%)	146 (26.6%)
- Autumn	78 (29.8%)	136 (24.8%)
- Winter	54 (20.6%)	145 (26.4%)
Efficacy of LD-EBRT		
Number of cycles of LD-EBRT*	1.27 (1-3)	1.35 (1-3)
Follow-up time in months*	3.07 (0-55)	6.79 (0-129)
Initial increase in pain during LD-EBRT	36 (13.74%)	76 (13.8%)
Response directly after LD-EBRT	143 (54.6%)	303 (55.2%)
Response at the end of follow-up	152 (58.02%)	348 (63.39%)

Abbreviations: GTPS = greater trochanteric pain syndrome; LD-EBRT = low-dose external beam radiation therapy; MRI = magnetic resonance imaging; PTV = planning target volume; VAS = Visual Analog Scale.

[a] * Mean (range).

† Median (range).

symptoms initially reported a median score of 8 of 10. These patients were also treated significantly more frequently with a WHO-level II analgesic than those who reported a response after LD-EBRT. Accordingly, it may be postulated that the LD-EBRT should be considered after failure of treatment with an analgesic of WHO-level I and therefore before use of an analgesic of WHO-level II.

Overall, patients with initially more severe pain in GTPS had a lower treatment success after LD-EBRT. The pathogenesis of tendinopathy may explain this finding. Using Achilles tendinopathy as an example, it has been demonstrated that the formation of scar tissue is accompanied by

Table 3. Multivariate logistic regression with backward selection (Wald)

	Multivariate logistic regression with backward selection (Wald)	
	P value	OR (95% CI)
GTPS		
Symptom duration >12 mo	*.0007*	1.943 (1.326-2.848)
Increase in pain	*.005*	2.091 (1.245-3.514)
Prior hip prosthesis	*.016*	1.864 (1.125-3.090)
VAS	.087	1.119 (0.984-1.272)
Coxarthrosis		
Increase in pain	*.008*	2.928 (1.332-6.436)
Kellgren-Lawrence score 3	.58	1.722 (0.982-3.019)
Body mass index ≥25.0 kg/m^2	*.013*	2.091 (1.168-3.744)
Age ≥70 y	*.004*	2.411 (1.330-4.368)

Abbreviations: GTPS = greater trochanteric pain syndrome; OR = odds ratio.

neovascularization and the ingrowth of nerve fibers into the tendon. In the subsequent chronification, the vessels regress, whereas the nerve fibers remain. An increased concentration of glutamate and substance P, in addition to the retention of the nerve fibers, leads to increased nociception.[37] Hence, it is hypothesized that patients in the acute stage of the disease experience less pain with higher inflammation than those in the chronic stage, which is why LD-EBRT can often be more effective in these patients.

In our analysis, an initial increase in pain during LD-EBRT was a negative predictor of treatment success. There are contradictory findings in the literature on this effect. Although in LD-EBRT for peritendinitis humeroscapularis, an initial increase in pain correlated with a positive outcome,[38] treatment failures occurred more frequently with LD-EBRT of thumb carpometacarpal osteoarthritis than with GTPS.[13,39]

In patients with GTPS, we did not demonstrate a statistically significant correlation between treatment success and the Kellgren-Lawrence score. This result is particularly important when considering the patient group in which the planning CT scan revealed grade "1" or higher coxarthrosis as an incidental finding (GTPS∩Cox). This group exhibited the same treatment outcome as the overall GTPS group, regardless of any other predictive factors. Ultimately, this result implies that the clinical diagnosis "GTPS" guides the therapy, that is, incidental imaging findings do not need to be included in the target volumes and do not alter the therapy outcome. The close anatomic relationship between GTPS and coxarthrosis might explain this finding. LD-EBRT of the GTPS target volume inevitably results in a significant scattered irradiation dose in the neighboring hip joint. From a radiation protection perspective, it is justifiable to define the PTV as small as possible, particularly to minimize scattered radiation to intrapelvic structures. Because in LD-EBRT of the hip a relatively large amount of bone marrow is exposed to radiation (in contrast to the heel, eg), an increased risk of leukemia cannot be ruled out. This results in a defensive indication, particularly in patients aged <50 years.[8,40,41]

Interestingly, a hip prosthesis was associated with poorer therapeutic outcomes after LD-EBRT in GTPS. This finding is most likely because of the continuous reactivation of the tendinopathy by the foreign body.

Furthermore, none of the LD-EBRT planning parameters were significantly correlated with treatment outcome. This finding is surprising for GTPS. In this case, the superficial and deep bursae of the gluteus maximus muscle and the gluteofemoral bursa should be irradiated.[8] In particular, the center of the gluteofemoral bursa is located approximately 6 cm below the apex of the major trochanter; its caudal edge may lie approximately 3 to 4 cm further distally.[42,43] Therefore, our finding that a more caudal lower field border did not influence treatment results is surprising, as is the PTV size.

Limitations of the study

Because of its retrospective design, unequal distributions of potential influencing factors affecting the therapy results could not be avoided.

Although the VAS, ranging from 0 to 10, was used to record pain before starting LD-EBRT, our retrospective follow-up analysis classified symptoms according to "von Pannewitz." However, von Pannewitz's[20] study from 1933 showed that the patient's assessment of the degree of improvement in several categories of LD-EBRT is feasible for assessing the outcome in benign diseases.

Because of the retrospective study design, we cannot draw any conclusions about a placebo effect of LD-EBRT, particularly in coxarthrosis. Randomized studies with various indications have so far been unable to demonstrate an impact of LD-EBRT but are subject to criticism because of their design, inclusion criteria, and therapies.[8,44-47] A recent

review found no evidence of harm from LD-EBRT based on the available data.[48]

Furthermore, the retrospective design resulted in varying follow-up times, potentially affecting ORRs in unexpected ways.

Conclusions

LD-EBRT appears to be effective for the important causes of hip pain, "coxarthrosis" and "GTPS." It is notable that in both diagnoses, an initial increase of pain after the beginning of LD-EBRT correlated with significantly worse ORR. However, an advanced Kellgren-Lawrence score, an age ≥70 years, and a BMI ≥25.0 kg/m^2 represented negative prognostic factors in coxarthrosis. Early coxarthrosis detected incidentally by imaging apparently had no prognostic significance in GTPS.

The outcome was independent of the LD-EBRT season and the target volume definition.

Although the outcome of coxarthrosis was independent of the prior duration of symptoms, early LD-EBRT was prognostically more effective in GTPS, whereas LD-EBRT after more than 12 months of symptoms was prognostically negative.

In summary, we conclude that LD-EBRT can be an effective treatment option for both indications, GTPS and coxarthrosis. Early use of this treatment option appears to alleviate symptoms, regardless of the time of year or target volume definition.

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