Calcifying Tendonitis of the Shoulder Joint

Predictive Value of Pretreatment Sonography for the Response to Low-Dose Radiotherapy

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Background and Purpose: Calcifying tendonitis is a degenerative inflammatory joint disorder. Pain relief can be successfully achieved with low-dose radiotherapy. It is actually unknown which types of calcifying tendonitis respond to radiotherapy and which do not. The authors tried to get predictive objectives for the response to radiotherapy on the basis of different morphological patterns of calcifications evaluated by X-ray and ultrasound.

Patients and Methods: Between August 1999 and September 2002, a total of 102 patients with 115 painful shoulder joints underwent low-dose radiotherapy. At the beginning of radiotherapy, every shoulder joint was examined with a radiograph in two planes. In addition, sonography was performed before and during therapy. This examination was repeated 6 and 18 months after irradiation. Radiotherapy consisted of two series with a total dose of 6.0 Gy. 29 joints with calcifying tendonitis could be further divided using the sonographic and radiographic classification according to Farin and Gärtner, respectively.

Results: Pain relief was achieved in 94/115 joints (82%) at a follow-up of 18 months (median). A different response to radiotherapy was found using the sonographic classification of Farin: calcifying tendonitis type III (n = 18) responded well in contrast to a significantly worse result in type I (n = 11). The radiologic classification did not provide a predictive value.

Conclusion: Sonographic classification of calcifying tendonitis is predictive for the outcome after radiotherapy. Especially patients with Farin type III calcification will benefit from low-dose radiotherapy.

Key Words: Calcifying tendonitis · Low-dose radiotherapy · Sonographic classification

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Tendinosis calcarea des Schultergelenks. Prädiktive Aussage einer prätherapeutischen Sonographie für das Ansprechen nach niedrigdosierter Strahlentherapie

Hintergrund und Ziel: Die Tendinosis calcarea ist eine degenerativ-entzündliche Gelenkerkrankung, bei der zur Schmerzlinderung auch die niedrigdosierte Strahlentherapie erfolgreich eingesetzt wird. Bisher ist nicht bekannt, welche Formen der Tendinosis calcarea auf die Radiotherapie ansprechen. Deshalb versuchten die Autoren, aufgrund der unterschiedlichen morphologischen Verkalkungsmuster im Ultraschall und Röntgenbild eine prädiktive Aussage zum Therapieansprechen zu treffen.

Patienten und Methodik: Von August 1999 bis September 2002 wurden insgesamt 102 Patienten mit 115 symptomatischen Schultergelenken behandelt (Tabelle 1). Neben einer konventionellen Röntgenaufnahme des Schultergelenks in zwei Ebenen wurden alle Schultergelenke vor und unter Radiotherapie sowie 6 und 18 Monate nach Therapieende sonographisch untersucht. Die Strahlentherapie umfasste zwei Behandlungsserien bis zu einer Gesamtdosis von 6,0 Gy. Bei 29 Schultergelenken mit Tendinosis calcarea erfolgte die Subtypisierung hinsichtlich des Verkalkungstyps sonographisch nach Farin sowie röntgenologisch nach Gärtner (Tabelle 4).

Ergebnisse: Insgesamt trat bei 94/115 Schultergelenken (82%) nach 18-monatiger Verlaufskontrolle eine Beschwerdebesserung ein. Bei der sonographischen Klassifizierung fand sich ein unterschiedliches Therapieansprechen: Die Tendinosis calcarea Typ Farin III (n = 18) sprach sehr gut auf die Therapie an (Abbildung 1), Typ Farin I (n = 11) zeigte ein signifikant schlechteres Therapieansprechen (Abbildung 2). Mit der röntgenologischen Subklassifizierung konnte keine prädiktive Aussage getroffen werden (Tabelle 3).

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Schlussfolgerung: Die Subtypisierung der Tendinosis calcarea im Ultraschall nach Farin ermöglicht eine genauere prädiktive Aussage bezüglich des Ansprechens auf eine niedrigdosierte Strahlentherapie. Zukünftig sollten inbesondere Patienten mit einem Verkalkungstyp III einer Strahlentherapie zugeführt werden.

Schlüsselwörter: Tendinosis calcarea · Schultergelenkbestrahlung · Sonographische Klassifizierung

Introduction

Calcifying tendonitis is part of a group of degenerative shoulder joint disorders, which leads to painfully limited movement. Treatment options encompass oral antiphlogistics, local injections of steroids, ultrasound, shock-wave, magnetic-field therapy and, finally, low-dose radiotherapy (LD-RT) [1, 10, 11, 15, 25]. DePalma implemented the term of secondary impingement in 1952, which contains the calcifying tendonitis, bursitis subdeltoidea, and partial and total rupture of rotator cuff [4]. Calcifications develop at the insertion of the tendon, i.e., of supraspinatus muscle, and can be detected radiographically and by ultrasound. Three different patterns of calcifications can be differentiated in plane radiographs described by Gärtner & Heyer [7]. Ultrasound also provides a differentiation of calcific deposits in three types [5].

Up to now, there is no clinical consensus of which classification has the most predictive value for the response to LD-RT. We aimed to classify the calcific deposits according to the findings by radiograph and ultrasound and to correlate the results with the clinical response to radiotherapy graduated by an accepted orthopedic score [3].

Patients and Methods

After counseling with informed consent [27], a total of 102 patients with 115 painful shoulder joints underwent LD-RT from August 1999 to September 2002 (male : female 42 : 60, age 57, range 40–79 years). 61 patients had therapy to the right side, 28 to the left side, and 13 bilateral. Every treated shoulder was carefully examined clinically and with ultrasound at the beginning of therapy, during therapy, as well as 6 and 18 months after the end of radiotherapy. In addition, a radiograph in two planes of the shoulder was required before treatment to exclude osseous fractures and bone lesions and to classify the type of impingement.

Ultrasound was performed by an experienced orthopedic examiner (B.A.). Two machines (Sonoline Prima, Sonoline Sienna, Siemens, Erlangen, Germany) were used with a 7.5-MHz linear transducer. The sonographic examination included the assessment of the rotator cuff, detection and classification of calcific deposits (Farin type I–III) and, finally, the tissue focusing bursitis and tendovaginitis. The examination was documented in thermoprint paper and SVHS video.

Farin typifies three different patterns of calcifications [5]. Type I consists of a hyperreflexive lesion with a well-circumscribed dorsal acoustic shadow. The latter is diminished in type II and not detectable in type III. At the beginning of therapy, the calcific deposits were additionally classified radiographically into three different types using the Gärtner Score [7].

29 shoulder joints affected with calcifying tendonitis were opposed to 86 shoulders with different degenerative disorders as shown in Table 1.

Radiotherapy was applied with an orthovolt machine (Stabilipan, Siemens) 250 kV, 15 mAs, 1-mm Cu filter, tubus size 10 × 15 cm, focus-skin distance 40 cm with two opposed fields. The single dose was 0.5 Gy, two to three fractions per week to a total dose of 3.0 Gy. After a break of 6 weeks treatment was continued with a second series of 3.0 Gy. We paid careful attention to the protection of the gonads, thyroid gland, and breast tissue.

Table 1. Different diagnoses of shoulder joint disorders including calcifying tendonitis.

Tabelle 1. Diagnosen der Schultergelenkerkrankungen einschließlich der Tendinosis calcarea.

Disease	Cases	
	(n)	(%)
Calcifying tendonitis	29	26
Bursitis subdeltoidea	16	14
Tendovaginitis of the long head of the biceps tendon	7	6
Partial tear of rotator cuff	14	12
Complete tear of rotator cuff	2	2
Capsulitis adhaesiva	3	3
Omarthrosis	13	11
Labral tear	4	3
Acromion type II/III	0	0
Arthrosis of acromioclavicular joint	19	16
Subacromial spur	8	7
Total	115	100

Table 2. Assessment of Constant Score according to patients' age and sex.

Tabelle 2. Wertung des alters- und geschlechtsadaptierten Constant-Scores.

Assessment of treatment success	Orthopedic Constant Score (%)
Excellent	91–100
Good	81–90
Satisfying	71–80
Adequate	61–70
Bad	≤ 60

The response to therapy was assessed with the orthopedic Constant Score according to patients' age and sex [3] (Table 2). Clinical examination was performed at the beginning of therapy, before the second series, and 6 and 18 months after end of radiotherapy [1]. Clinical results were correlated with the findings in radiographs and ultrasound.

Statistical analysis was performed with SPSS software (SPSS Inc., Chicago, IL, USA). All parametric parameters were checked with χ^2-test according to their significance, the Constant Score additionally with the t-test. The level of significance was $p \leq 0.05$.

Results

A total of 82% of all shoulders (94/115) responded to radiotherapy with pain relief after a follow-up of 18 months.

Focused on the calcifying tendonitis, we found a different clinical response according to the Constant Score. There was a significant difference in the sonographic scoring of calcific deposits in contrast to the findings in plane radiographs. All patients with Farin type III calcifying tendonitis (n = 18) experienced complete pain relief with an increasing mobility in the shoulder joint after completion of therapy (Table 3, Figure 1).

In type I calcifying tendonitis, an excellent result could be achieved in five of eleven cases (Table 3, Figure 2). Three patients had a good response, further three patients did not respond to therapy.

The excellent results in Farin type III calcifying tendonitis were stable during the observation period after 6 weeks and 18 months. No calcific deposits were visible in ultrasound at the last follow-up. Type I calcifications did not show any change in sonographic morphology except for one case. Table 4 outlines the frequency of different types of calcifications including the classification of Gärtner [7] and Farin [5].

The radiographic classification of the calcific deposits according to Gärtner did not provide a significant difference in the response to therapy.

Figure 1. Calcifying tendonitis Farin type III, sonography of the shoulder joint. The calcification (between two cross marks) is typically not accompanied by a dorsal acoustic shadow.

Abbildung 1. Tendinitis calcarea Farin-Typ III, Ultraschallbild des Schultergelenks. Die Verkalkung (zwischen zwei Kreuzmarkierungen) stellt sich ohne dorsalen Schallschatten dar, typisch für eine Verkalkung Typ III nach Farin.

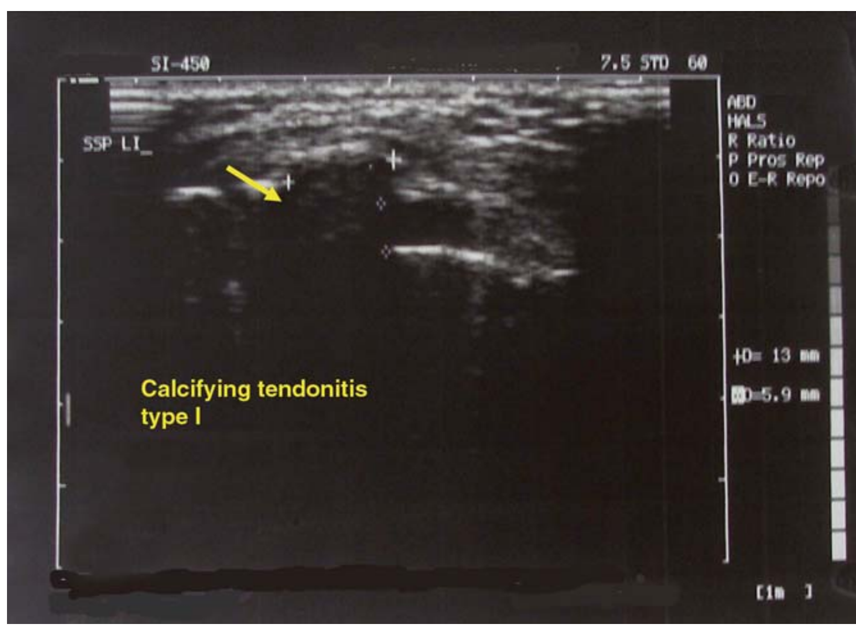

Figure 2. Calcifying tendonitis Farin type I, sonography of the shoulder joint. The calcification (between two cross marks) with hyperreflexion shows a dorsal acoustic shadow (arrow). This finding represents a type I according to Farin.

Abbildung 2. Tendinitis calcarea Farin-Typ I, Ultraschallbild des Schultergelenks. Die Verkalkung (zwischen zwei Kreuzmarkierungen) zeigt einen dorsalen Schallschatten (Pfeil), typisch für eine Verkalkung Typ I nach Farin.

Table 3. Response (pain relief) to radiotherapy (RT) according to sonographic Farin type; significant difference between Farin type I and III ($p = 0.01$).

Tabelle 3. Ansprechen (Schmerzlinderung) auf die Radiotherapie (RT) in Abhängigkeit vom sonographischen Typ nach Farin. Signifikanter Unterschied zwischen Farin-Typ I und III ($p = 0,01$).

Response to RT	Complete pain relief (n)	Partial pain relief (n)	No response (n)
Farin type I (n = 11)	5	3	3
Farin type III (n = 18)	18	0	0

Table 4. Frequency of different types of calcifications classified sonographically (Farin) and radiographically (Gärtner).

Tabelle 4. Anzahl der unterschiedlichen Verkalkungstypen, sonographisch nach Farin und radiographisch nach Gärtner klassifiziert.

Classification of calcifications	Gärtner		
Farin	Type 1	Type 2	Type 3
Type I (n = 11)	4	4	3
Type III (n = 18)	6	8	4

By contrast, the sonographic pattern of Farin type I and III demonstrated significant differences regarding the response to radiotherapy ($p = 0.01$).

Discussion

LD-RT of inflammatory and degenerative joint disorders is a well-accepted therapy option to achieve good to excellent pain relief, reported by many authors [1, 10–12, 14–16, 18, 25, 26, 28, 31, 33]. Up to now, in most publications on LD-RT of painful shoulder diseases, the terms periarthritis humeroscapularis and supraspinatus syndrome are used. Both terms summarize different disorders but lack further differentiation of the etiopathologic cause of the disorder and do not provide a prediction of response to therapy.

A more recent publication of our study group demonstrated an etiologic assignment of different diseases to the primary, secondary and non-impingement, based on the exact diagnosis of shoulder pain [1]. We concluded that this assignment provides a better prediction of response to therapy. LD-RT resulted in excellent pain relief in shoulders with secondary impingement. Focusing on the calcifying tendonitis, no predictive reliable parameter was found to evaluate a potential response to therapy. To find out types of calcification predictive for a success of treatment, different scoring systems of calcification had to be proven in terms of a predictive value.

There was no significant correlation between the radiologic classification of the calcification according to Gärtner and treatment outcome. By contrast, the sonographic differentiation in type I and III according to Farin provided a significant correlation to the clinical results according to the Constant Score ($p = 0.01$).

Farin described three types of calcifications. Type I shows a hyperreflexive lesion with an accompanying acoustic dorsal shadow. The latter is reduced in type II and not visible in type III. We primarily differentiated all calcifications into three types, but significant differences were found between type I/II and III only.

Calcifying tendonitis affects the tendon of supraspinatus in 80% of all cases, followed by the tendon of infraspinatus (15%), and tendon of subscapularis (5%). Most patients are aged between 30 and 50 years [25].

The course of calcifying tendonitis can be divided pathologically into three different stages: precalcification, calcification, and postcalcification [29]. A chondrogenic metaplasia of the tendon should be activated by a hypoxia in the stage of precalcification. Chondrocytes build proteoglycans, which develop to fibrocartilage. Transformed tenocytes produce hydroxide crystal in the stage of calcification. The latter are deposited in the intercellular substance and pass into a phase of rest. Small vessels grow from the periphery into the tendon, followed by an invasion of macrophages and giant cells (phase of formation). At the end of this degenerative process, calcifications are removed by phagocytosis. The annual quote of natural absorption accounts for 6.4% [32].

We demonstrate that a complete absorption of calcifications can be achieved only in cases of Farin type III calcification with an increase of absorption from 6.4% to 100% after radiotherapy. The radiographic findings could not be assigned to the different stages of calcifying tendonitis [5, 9]. Our results show that the radiographic findings have no predictable value to assess the response to LD-RT. By contrast, the sonographic pattern is influenced by the physical property of calcifications. Density and the quota of liquid represent important parameters. Farin demonstrated a good correlation between the sonographic pattern and the consistency of calcifications [5]. Hyperreflexive echo texture accompanied by a dorsal shadow could correspond to the phase of formation and rest. The latter should match with the sonographic type I according to Farin and demonstrated no changes during and after radiotherapy with one exception. Absorptive phase is reflected in a hyperreflexive echo without a dorsal shadow. Those calcifications could correlate with type III according to Farin with an absorption quote of 100% after LD-RT.

The anti-inflammatory effect of LD-RT on calcifying tendonitis is accompanied by a good pain relief but has no simple explanation on a cellular or molecular level. Arenas et al. [2] reported about effects of LD-RT in an animal model of systemic inflammation with a significantly attenuated adhesion of leukocytes in murine intestinal venules, which was correlated with increased levels of circulating transforming growth factor-(TGF-)β_1, as neutralization of TGF-β_1 partially restored the adhesion induced by lipopolysaccharides. More recent experiments in human tumor necrosis factor-transgenic (hTNF-tg) mice [6] demonstrated a significant temporal improvement of the clinical progression of beginning polyarthritis after whole-body LD-RT with single doses of 0.5 Gy. As hTNF-tg mouse represents a model which is very close to the chronic autoimmune situation in humans, these in vivo data confirm anti-inflammatory effects of LD-RT even under conditions of a permanent TNF-α overexpression.

In vitro assays supported in vivo experimental research evaluating the different steps of the inflammatory cascade. LD-RT reduced the adhesion of peripheral blood mononuclear cells (PBMC) to human or murine endothelial cells demonstrating a biphasic kinetics of adhesion [13, 23, 24]. Additionally, the cytokine profile of stimulated endothelial cells was investigated with expression of TGF-β_1 by endothelial cells being increased both on the level of mRNA and protein with the highest effect after 0.5 Gy. Anti-TGF-β_1 antibody treatment restored adhesion of PBMC to irradiated endothelial cells and, furthermore, a biphasic course of TGF-β_1 secretion functionally coincided with the biphasic kinetics of adhesion. So TGF-β_1 is suggested to play a major role in mediating the decreased leukocyte adhesion following LD-RT [23, 24]. With respect to the effects of LD-RT on mononuclear cells, a discontinuous dependence of induction of apoptosis with a relative maximum at 0.3 and 0.7 Gy and a minimum at 0.5 Gy could be observed [17]. The profile of secreted cytokines revealed a reduction of TNF-α and an increase of interleukin-10 expression [22] and may suggest a similar anti-inflammatory mechanism as described by Voll et al. [30]. Gaipl et al. [8] described a biphasic appearance of cell death in irradiated human neutrophil granulocytes (PMN), displaying a relative maximum at 0.3 Gy and minimum at 0.5 Gy, respectively. This biphasic course of cell death was coincident with the protein level of total cellular Akt. Again, a biphasic effect in apoptosis and total Akt levels suggest a biphasic dose effect of LD-RT by initiating a downregulation of inflammation.

In the last few years, an increasing number of in vitro experiments were performed to look for molecular mechanisms underlying the anti-inflammatory efficacy of LD-RT. Various transcription factors such as nuclear factor (NF) κB, c-fos and c-jun that collectively form homo- or heterodimeric activator protein-(AP-)1 transcription factor complex are of crucial importance for the expression of various immune system effector molecules like cytokines or adhesion molecules. After radiotherapy, a biphasic NF-κB DNA-binding and transcriptional activity with relative maxima at 0.5 Gy (LD-RT level) and 3 Gy (above LD-RT level) were observed. To gain further insight into the transcriptional regulation underlying anti-inflammatory effects of LD-RT, Rödel et al. [21] investigated AP-1 activation in endothelial cells after LD-RT with a biphasic DNA-binding activity and a relative maximum at 0.3 Gy.

The anti-inflammatory effects of LD-RT include a variety of cellular and molecular components [19, 20], but all described pathways display a similar dose dependence and a discontinuous dose-effect relation after LD-RT with a maximum efficacy in the dose range between 0.3–0.7 Gy, single doses which are used in clinical practice with excellent results.

A successful response of calcifying tendonitis to LD-RT is not only dependent on the type of calcification but also on the duration of disease. Zwicker et al. could demonstrate that irradiation of chronic calcifying tendonitis did not improve the mobility of the shoulder or intensity of pain [33]. Radiotherapy in patients with acute tendonitis achieved good results: 33% of all patients experienced pain relief after 1 month, 35% had a significant improvement, 21% a slight improvement, and 12% no improvement. The clinical results of Zwicker et al. could be reconfirmed by our findings [1]. Patients with acute inflammatory disorders (bursitis subdeltoidea, tendinosis of the long tendon of biceps) and calcification type III according to Farin achieved a good response to therapy. Patients with calcifying tendonitis type I have a more chronic inflammatory process and demonstrate a worse response to LD-RT.

Conclusion

The subclassification of calcifying tendonitis according to the sonographic pattern described by Farin provides a significant prediction of response to LD-RT. Therefore, sonographic classification of calcifying tendonitis is an appreciable tool to indicate radiotherapy carefully: especially patients with Farin type III calcification will benefit from LD-RT.

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