Radiotherapy in Early-Stage Dupuytren's Contracture

Long-Term Results After 13 Years

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Background and Purpose: In early-stage Dupuytren's contracture, radiotherapy is applied to prevent disease progression. Long-term outcome and late toxicity of the treatment were evaluated in a retrospective analysis.

Patients and Methods: Between 12/1982 and 02/2006, 135 patients (208 hands) were irradiated with orthovoltage (120 kV; 20 mA; 4-mm Al filter), in two courses with five daily fractions of 3.0 Gy to a total dose of 30 Gy; separated by a 6- to 8-week interval. The extent of disease was described according to a modified classification of Tubiana et al. Long-term outcome was analyzed at last follow-up between 02/2008 and 05/2008 with a median follow-up of 13 years (range, 2–25 years). Late treatment toxicity and objective reduction of symptoms as change in stage and numbers of nodules and cords were evaluated and used as evidence to assess treatment response.

Results: According to the individual stages, 123 cases (59%) remained stable, 20 (10%) improved, and 65 (31%) progressed. In stage N 87% and in stage N/I 70% remained stable or even regressed. In more advanced stages, the rate of disease progression increased to 62% (stage I) or 86% (stage II). 66% of the patients showed a long-term relief of symptoms (i.e., burning sensations, itching and scratching, pressure and tension). Radiotherapy did not increase the complication rate after surgery in case of disease progression and only minor late toxicity (skin atrophy, dry desquamation) could be observed in 32% of the patients. There was no evidence for a second malignancy induced by radiotherapy.

Conclusion: After a mean follow-up of 13 years radiotherapy is effective in prevention of disease progression and improves patients' symptoms in early-stage Dupuytren's contracture (stage N, N/I). In case of disease progression after radiotherapy, a "salvage" operation is still feasible.

Key Words: Dupuytren's contracture · Benign diseases · Radiotherapy · Long-term results

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Radiotherapie in den Frühstadien des Morbus Dupuytren. Langzeitergebnisse nach 13 Jahren

Hintergrund und Ziel: Im Frühstadium des Morbus Dupuytren wird die perkutane Radiotherapie eingesetzt mit dem Ziel, die weitere Progression der Erkrankung zu verhindern. In einer aktuellen retrospektiven Analyse wurden der Langzeiterfolg sowie die Nebenwirkungen untersucht.

Patienten und Methodik: Im Zeitraum von 12/1982 bis 02/2006 wurden 135 Patienten mit 208 erkrankten Händen am Orthovoltgerät (120 kV; 20 mA; 4-mm-Al-Filter) in zwei Serien (6–8 Wochen Pause) mit je 5 × 3,0 Gy bis zu einer Gesamtdosis von 30 Gy bestrahlt. Die Klassifikation der Erkrankung erfolgte modifiziert nach Tubiana et al. Die Langzeitergebnisse wurden bei einer Nachsorgeuntersuchung zwischen 02/2008 und 05/2008 (mediane Nachbeobachtungszeit 13 Jahre; Spanne 2–25 Jahre) erhoben. Die Spätnebenwirkungen und das Therapieansprechen hinsichtlich der Veränderungen des Erkrankungsstadiums sowie der Anzahl der Knoten und Stränge wurden erfasst.

Ergebnisse: Unter Berücksichtigung des Ausgangsstadiums zeigte sich bei 123 Händen (59%) eine Befundstabilität, 20 Hände (10%) verbesserten sich, während 65 Hände (31%) eine Verschlechterung im Stadium erlitten. Bei Patienten im Stadium N konnte bei 87% der Hände und im Stadium N/I bei 70% eine stabile Situation oder eine Stadienverbesserung erreicht werden. In fortgeschritteneren Stadien stieg das Progressionsrisiko auf 62% (Stadium I) bis 86% (Stadium II). 66% der Patienten berichten über eine anhaltende Symptomrückbildung. Die Radiotherapie führte nicht zu einer erhöhten Komplikationsrate nach einer bei Progression durchgeführten Operation; es zeigten sich nur geringgradige Spätnebenwirkungen (Hautatrophie oder Trockenheit mit Schuppung) bei 32% der Patienten.

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Schlussfolgerung: Auch nach einer medianen Nachbeobachtungszeit von 13 Jahren erweist sich die Radiotherapie als effektive Maßnahme zur Verhinderung einer weiteren Progression in den Frühstadien der Erkrankung (Stadium N und N/I). Im Fall einer Progression ist eine „Salvage"-Operation ohne erhöhte Nebenwirkungen möglich.

Schlüsselwörter: Morbus Dupuytren · Gutartige Erkrankungen · Radiotherapie · Langzeitresultate

Introduction

Dupuytren's contracture is an inherited proliferative connective tissue disorder which involves the palmar fascia of the hand. In early stage of the disease subcutaneous nodules appear followed by tough cords, both with possible fixation to the overlying skin. Further disease progression is characterized by retraction of the palmar fascia and contracture of the medial phalangeal (MP) and proximal interphalangeal (PIP) finger joints preferably involving the fourth and fifth fingers. This leads to the typical flexion deformity of the hand and an extension deficit of the fingers. The disease is more common in men and patients > 40 years with an estimated 20% of men aged > 60 years are affected [25]. In Germany, about 1.9 million people have Dupuytren's contracture.

The treatment of choice for advanced stages is surgery, if function is impaired or contracture is progressing. At present, typical interventions are a transection of cords (fasciotomy) or an excision of diseased fascial bands (fasciectomy) with or without excision of the overlying skin [32]. Surgery is indicated in symptomatic patients, i.e., if the MP joint contracture reaches 30–40° or if PIP joint contracture exceeds 20°. PIP joint contractures are more likely to cause stiffness and less likely to respond to surgery in advanced stages. The aims of surgery are to reverse digital contractures and to restore hand function [3].

In early stage of Dupuytren's contracture a wait-and-see strategy is preferred, no conservative treatment has been firmly established. In one study an average of 3.2 local injections of glucocorticoids lead to a significant disease regression [13] but also to severe complications like atrophy at the injection site or rupture of the flexor tendon and have no long-term impact on disease progression. Without any therapy, progression is observed in about 50% of patients after a follow-up of 6 years [19].

Radiotherapy has been reported to be effective for prevention of disease progression in early stages with only mild acute or late side effects (RTOG grade 1/2) [1, 11, 12]. The progression of Dupuytren's contracture may be slowly, some cases show stabilization or even spontaneous regression; therefore, a possible therapeutic effect of any treatment should be assessed in long-term follow-up. As hand surgeons still critically discuss the results and side effects of prophylactic radiotherapy, it was necessary to reevaluate the long-term efficacy and late effects of radiotherapy with a median follow-up of 13 years.

Patients and Methods

Patient Characteristics

From 12/1982 to 02/2006, 230 patients with clinically evident and progressive early-stage Dupuytren's contracture were treated at our institute. After clinical examination and counseling with informed consent [28], 178 patients received the prescribed irradiation and were contacted for a follow-up examination; 135 patients completed all examinations, 31 were dead, and twelve refused last follow-up for personal reasons. Because of double-sided affliction in 85% of the patients, a total of 208 hands (sites = cases) were included in this analysis. Last follow-up was performed between 02/2008 and 05/2008.

Pretherapeutic disease symptoms were found in 87/135 patients (64%), eight patients with dysesthesia, 34 with burning/itching, and 45 with pressure/tension.

Predisposition

A structured questionnaire (*Appendix I*) and clinical consultation were used for identifying predisposing factors: a positive family history in 38% of cases (78/208) with 37% males (47/127) and 38% females (31/81), Morbus Ledderhose in 11.5% of cases (24/208), Peyronie's disease in 8.7% of male patients (11/127) and knuckle pads in 2.4% of cases (5/208), diabetes mellitus in 17% of the cases (35/208), and alcoholism in 4%.

The time period from first recognition of typical symptoms until onset of radiotherapy was 1–12, 13–24, 25–36, 37–48, and > 48 months in 28%, 19%, 15%, 14%, and 23% of patients, respectively.

Pretreatment

9/135 patients (6.7%) had received a treatment before irradation: eight patients were sent to radiotherapy with a recurrence of Dupuytren's contracture after surgery and one patient with progressive disease after local corticoid therapy.

Clinical Evaluation

The stage of disease, the number and consistency of palpable nodules and cords were carefully analyzed using a standardized procedure and documentation form (*Appendix II*) to assess the long-term response to radiotherapy at actual follow-up. Functional changes and the total flexion deformity of fingers were measured using a protractor; degrees of flexion deformity of MP, PIP and DIP (distal interphalangeal) joints

were added. The size and number of nodules or cords were directly measured and their consistency palpated. Late toxicities of skin and subcutaneous tissue were scored according to RTOG/EORTC criteria.

Clinical Endpoints

Stage of disease was classified according to Tubiana et al. [34] (*Appendix III*). As stage I comprises a large range of total flexion deformity (1–45°), an intermediate stage was defined [12], which allows a better differentiation between initial stage I disease (defined as stage N/I with 1–5° total flexion deformity) and more advances stage I (5–45° total flexion deformity). Due to stage of disease, treatment outcome was defined as "regression", "stable" or "progression" and was differentiated into in-field or out-field progression or both. According to this modified classification the pretherapeutic distribution of stages are demonstrated in Table 1.

Numbers of nodules or cords were evaluated by palpation (Table 2); an increase in numbers was defined as "progression", a decrease as "regression", and no change in numbers as "stable".

Statistical analysis was performed with SPSS 15.0 software. All parametric variables were checked with the χ^2-test according to their significance. The level of significance was ≤ 0.05.

Table 1. Stage distribution prior to radiotherapie (RT).

Tabelle 1. Stadienverteilung vor Beginn der Radiotherapie (RT).

Stage pre-RT	N	N/I	I	II	III	IV
Cases [n (%)] (total n = 208)	115 (55)	33 (16)	50 (24)	7 (3)	2 (1)	1 (0.5)

Table 2. Distribution of nodules and cords prior to radiotherapy (RT).

Tabelle 2. Verteilung der Knoten und Stränge vor Beginn der Radiotherapie (RT).

Stage pre-RT	N	N/I	I	II	III	IV
Numbers of nodules/cords	311	100	152	45	9	4

Radiotherapy

Radiotherapy was carried out with 120-kV photons, 20 mA, and a 2-mm aluminum filter (Stabilipan; Siemens Co., Erlangen, Germany). A 6 × 8 cm cone with a focus-skin distance of 40 cm was used, and the whole afflicted area with all palpable nodules and cords were included into the irradiation field. Uninvolved areas of the palm were shielded by placing 3-mm lead rubber plates with a margin to the palpable nodules and cords of 1–2 cm distally/proximally and 1 cm laterally. All recommended radiation protection measures were applied especially to minimize cancer risk from radiotherapy [26, 33].

Radiotherapy was prescribed in two separate courses of five daily fractions of 3.0 Gy each to a total dose of 30 Gy. The interval between the two courses was 6 weeks and radiotherapy dose was individually prescribed with the skin surface as the reference dose level.

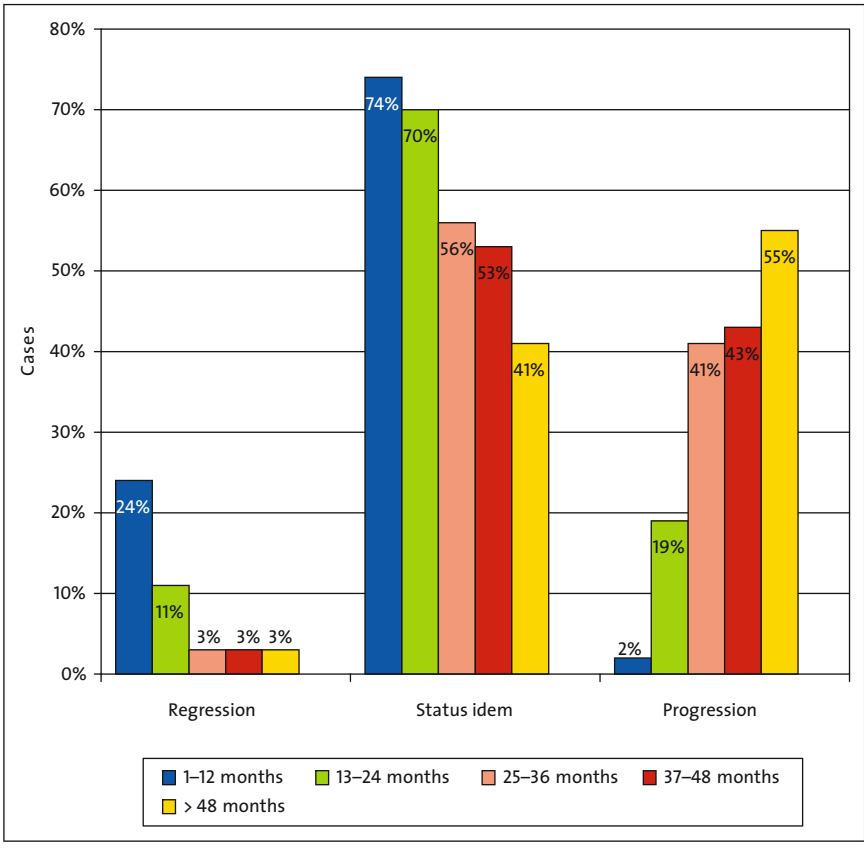

Figure 1. Influence of duration of symptoms on long-term effects of radiotherapy.

Abbildung 1. Einfluss der Anamnesedauer auf den Langzeiteffekt der Radiotherapie.

Results

Long-Term Results with Regard to Stage

A total of 143/208 afflicted hands (69%) had no progression of stage according to the classification system after a median follow-up of 13 years. 123 cases (59%) remained stable, and in 20 cases (10%) a regression was observed. In 65 cases (31%) a progression was demonstrated with 14%, 3%, and 14% of cases in-field only, out-field only, and in- and out-field, respectively. With respect to

the initial stage of the disease the changes in stage are summarized in Table 3.

The time period from first recognition of typical symptoms until onset of radiotherapy significantly influenced long-term effects of radiotherapy: patients with progressive disease irradiated within the 1st year of diagnosis showed significant better long-term results compared to those treated after 48 months ($p < 0.001$; Figure 1).

Long-Term Results with Regard to Number of Nodules and Cords

A total of 88/208 hands (42%) progressed in terms of the number of nodules and cords, the new nodules or cords were localized in-field only in 16%, out-field only in 10%, and in- and out-field in 16% of cases. With respect to the preradiotherapy evaluation the changes of numbers of nodules and cords are demonstrated in Table 4.

Table 3. Clinical course according to stage after a median follow-up of 13 years; in initial stage N, seven cases demonstrated a clinically complete response after radiotherapy (RT).

Tabelle 3. Stadienabhängiger Krankheitsverlauf nach einer medianen Nachbeobachtungszeit von 13 Jahren; im primären Stadium N zeigten sieben Hände eine komplette Remission nach Radiotherapie (RT).

Stage pre-RT	Regression n (%)	Stable disease n (%)	Progression in-field n (%)	Progression out-field n (%)	Progression in + out n (%)
N (n = 115)	7 (6)	93 (81)	9 (8)	0	6 (5)
N/I (n = 33)	10 (30)	13 (40)	8 (24)	2 (6)	0
I (n = 50)	3 (6)	16 (32)	12 (24)	4 (8)	15 (30)
II (n = 7)	0	1 (14)	0	0	6 (86)
III (n = 2)	0	0	0	0	2 (100)
IV (n = 1)	0	0	0	0	1 (100)
Total (n = 208)	20 (10)	123 (59)	29 (14)	6 (3)	30 (14)

Table 4. Change in numbers of nodules and cords after a median follow-up of 13 years. RT: radiotherapy.

Tabelle 4. Veränderungen der Anzahl der Knoten und Stränge nach einer medianen Nachbeobachtungsdauer von 13 Jahren. RT: Radiotherapie.

Stage pre-RT	Regression n (%)	Stable disease n (%)	Progression in-field n (%)	Progression out-field n (%)	Progression in + out n (%)
N (n = 115)	42 (37)	36 (31)	17 (15)	11 (10)	9 (8)
N/I (n = 33)	6 (18)	16 (48)	5 (15)	6 (18)	0
I (n = 50)	2 (4)	18 (36)	11 (22)	4 (8)	15 (30)
II (n = 7)	0	0	0	0	7 (100)
III (n = 2)	0	0	0	0	2 (100)
IV (n = 1)	0	0	0	0	1 (100)
Total (n = 208)	50 (24)	70 (34)	33 (16)	21 (10)	34 (16)

Table 5. Long-term results with regard to relief of symptoms. RT: radiotherapy.

Tabelle 5. Langzeitergebnisse hinsichtlich der Beschwerdebesserungen (Dysästhesie, Brennen/Stechen; Druck-/Spannungsgefühl). RT: Radiotherapie.

Symptom	Patients pre-RT n (%)	Status idem n (%)	Minor relief n (%)	Good relief n (%)	Complete relief n (%)	Progression n (%)
Dysesthesia	8 (9)	2 (2)	3 (3)	1 (1)	0	2 (2)
Burning/itching	34 (39)	4 (5)	12 (14)	5 (6)	6 (7)	7 (8)
Pressure/tension	45 (52)	6 (7)	13 (15)	10 (11)	8 (9)	8 (9)
Total	87	12 (14)	28 (32)	16 (18)	14 (16)	17 (20)

Patients' Complaints and Symptoms

Patients' complaints and symptoms were relatively minor, such that 58/87 patients (66%) experienced a partial or complete relief of symptoms (Table 5).

Treatment Toxicity – Late Effects

Within the irradiated area only minor long-term radiogenic skin and subcutaneous changes were found in 66/208 cases (32%); 47 cases (23%) had dry skin and increased desquamation (grade 1/2), 14 cases (7%) skin atrophy with occasional telangiectasia (grade 2) and five cases (2%) with an erythema up to 1 year. Chronic grade 3 or 4 reactions were not observed. No induction of cancer could be detected at last follow-up.

Due to progression of disease 39/65 patients (42 cases) experienced a surgical procedure; in two cases (5%) a delayed wound healing was observed. 20 cases demonstrated a stable disease postoperatively, 22 cases were progressive with increasing flexion deformity.

Discussion

Dupuytren's contracture is characterized by the appearance of nodules of hyperproliferative cells, i.e., fibroblasts and myofibroblasts, within the palmar fascia. During the course of the disease large bands of contracted and collagen-rich fibrotic tissue arise with an increasing flexion deformity of the affected fingers, if left untreated.

Fibroblasts are believed to play an important role in the genesis of Dupuytren's contracture, and the proliferation process of fibroblasts is one of the hallmarks of the disorder [4, 20]. Fibroblasts and myofibroblasts (primarily derived from fibroblasts) actively

Table 6. Long-term effect of radiotherapy (RT) with regard to stage dependent on follow-up period (FU).

Tabelle 6. Langzeiteffekt der Radiotherapie im Bezug auf das Stadium abhängig von der Nachbeobachtungsdauer (FU).

Stage Study	N n (%) progression-free	N/I n (%) progression-free	I n (%) progression-free	II–IV n (%) progression-free	Total n (%) progression-free
Keilholz et al., 1997 [11] FU 6 years	81/82 (99)	15/17 (88)	23/30 (77)	7/13 (54)	126/142 (89)
Adamietz et al., 2001 [1] FU 10 years	69/81 (85)	10/15 (67)	23/65 (35)	2/15 (13)	104/176 (60)
Actual study FU 13 years	100/115 (87)	23/33 (70)	19/50 (38)	1/10 (10)	143/208 (69)

control both extracellular matrix remodeling and scar deposition, important processes regulating wound healing, which may be dysregulated in Dupuytren's contracture. Satish et al. [27] compared the gene expression profiles of fibroblasts from patients and controls to find key genes whose regulation might be significantly altered. They found a downregulation of three genes, encoding for components of the extracellular matrix (proteoglycan 4, fibulin-I transcript variant D, and collagen α I type XV). These "candidate genes" were analyzed in order to find molecular targets for alternative therapies in the future.

The treatment of choice in symptomatic stage is surgery, but no specific surgical approach has proven to be consistently more effective than others. Recurrence due to the trauma associated with surgery is common in up to 60% of the cases with a progressive scar contracture and, additionally, a complication rate of about 19% in the early postoperative period [32]. In more recent studies, surgical approaches with prolonged low-load tension postoperatively were evaluated [15] without a significant improvement of final extension deficit. Hence there is a rationale for radiotherapy in early stage to prevent disease progression and a functional deficit in later times even after surgery.

Radiotherapy is a well-accepted therapy option in different hyperproliferative [8, 16, 22, 29] or inflammatory [2, 7, 9, 31] benign diseases, but the underlying radiobiological mechanism cannot easily be explained. Radiotherapy does not work via one single mechanism but rather through a complex interaction of different effects of many cell types [10, 23, 24]. One of the key players in the pathogenesis of Dupuytren's contracture are immature fibroblasts, mostly myofibroblasts, and therefore a possible target for radiotherapy. Proliferating fibroblasts/myofibroblasts are radiosensitive cells and the induction of free radicals by radiotherapy impairs their proliferative activity and thereby reduces the cell density [21].

The potential of radiotherapy to stabilize progression of disease was shown in several studies [5, 6, 14, 18, 35], but most of them had a follow-up of only a few years. Our actual study provides a median follow-up of 13 years and allows an analysis of long-term effects and late toxicity. This is important because surgeons are discussing radiotherapy very critically for different reasons, i.e., long-term inefficacy [17, 36] or possible complicated surgery after radiotherapy [5].

After 13-year follow-up, 69% of the cases showed no progression of stage and demonstrate the long-term efficacy of radiotherapy compared to the expected 50% progression rate for untreated patients or patients operated for advanced stages (Table 6). Especially patients with stage N or N/I will profit from radiotherapy with long-term stability of disease.

The question of optimal dose remains still unanswered. Differences in patient selection, disease stage, treatment parameters or follow-up periods are the reasons why previous studies are not comparable. Seegenschmiedt et al. [30] performed a prospective randomized study to find out the lowest possible dose to achieve the best therapeutic effect. Comparing 10×3.0 Gy in two series to 7×3.0 Gy in one, no significant difference in subjective or objective long-term improvement was observed. Acute toxicity was slightly more enhanced in the 7×3.0 Gy group with both regimens having been well accepted and tolerated in both groups. Nevertheless, the follow-up was only 12 months and long-term follow-up is warranted to demonstrate long-term stability for the low-dose group.

In our study, we could show that patients with progressive disease irradiated within the 1st year of diagnosis showed significantly better long-term results; nonetheless, radiotherapy should be performed only in case of progressive disease over a follow-up period of at least 6 months and when the extent of the disease can be estimated more reliably for target volume definition.

Conclusion

Radiotherapy for early-stage Dupuytren's contracture is effective in long-term follow-up with acceptable late toxicity. Radiotherapy does not increase the complication rate when surgery becomes necessary and should be offered within the first 2 years after diagnosis when progression is confirmed after a follow-up period of at least 6 months.

Appendix I

Name:	Vorname:	Geburtsdatum:	Untersuchungs-datum:	Fall-Nr.:

Handseite		Rechts	Links
Erkrankungsbeginn			
Händigkeit			
Belastung der Hände	Normal, erhöht		
Verlauf der Erkrankung	Langsam, in Schüben, rasch, sehr rasch		
Behandlung	Keine		
	Bestrahlung		
	Operation		
	Sonstige		
Verlauf seit Bestrahlung	Status idem		
	Progression (in/out) +/++		
	Regression +/++		
Subjektive Bewertung funktionelle Einschränkung			
Zweiterkrankungen	Morbus Ledderhose		
	Z.n. Unfall		
	Induratio penis plastica		
	Lebererkrankungen		
	Stoffwechselerkrankungen		
	Chronische Polyarthritis		
	Epilepsie		
	Fingerknöchelpolster		
Familiäre Belastung			

Appendix II

	Rechte Hand					Linke Hand				
Fingerstrahl	D I	D II	D III	D IV	D V	D I	D II	D III	D IV	D V
Streckdefizit DIP										
Streckdefizit PIP										
Streckdefizit MP										
Summe des Streckdefizits										
Gesamtbeurteilung/ Stadieneinteilung										
Hyperextension										
Ankylose										
Hautfixation										
Einziehungen										
Knoten (K)										
Stränge (S)										
Konsistenz (K + S) Weich: -, --, --- Derb: +, ++, +++										
Spättoxizität										
Zufriedenheit mit Bestrahlung	1 = sehr zufrieden 2 = zufrieden 3 = unzufrieden									
Auffälligkeiten/ Begleitsymptome										

Appendix III

Classification of Dupuytren's contracture according to Tubiana et al. [34]

Stage	Clinical symptoms	Extent of total extension deficit
I	I.e., nodules, cords, skin retraction/fixation No extension deficit/flexion deformity	None
N/I[a]	Clinical symptoms plus minor extension deficit	1–5°
I	Clinical symptoms plus extension deficit	6–45°
II	Clinical symptoms plus extension deficit	46–90°
III	Clinical symptoms plus extension deficit	91–135°
IV	Clinical symptoms plus extension deficit	> 135°

[a]modified by Keilholz et al. [12]

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