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RADIOTHERAPY OPTIMIZATION IN EARLY-STAGE DUPUYTREN'S CONTRACTURE: FIRST RESULTS OF A RANDOMIZED CLINICAL STUDY

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Purpose: Radiotherapy (RT) can prevent progression of Dupuytren's contracture (DC). It is unknown whether there is a dose response and which dose is sufficient. Herein, the 1-year results of a prospective randomized trial are presented which compared two different RT dose concepts with each other.

Methods: 129 patients (67 males; 62 females) were entered in this study: 69 had bilateral and 60 uni-lateral involvement of DC accounting for 198 irradiated hands. According to *Tubiana's classification,* 73 hands had *Stage N* (nodules/cords, no extension deficit = flexion deformity), 61 had *Stage N/I* (≤ 10° deficit), 59 had *Stage I* (11–45° deficit), and 5 had *Stage II* (46–90° deficit) DC. Prophylactic RT was randomly delivered; in Group A, 63 patients (95 hands) received 10 × 3 Gy (total dose, 30 Gy) in 2 series (5 × 3Gy) separated by 8 weeks; in Group B, 66 patients (103 hands) received 7 × 3 Gy (total dose, 21 Gy) in 1 series within 2 weeks. Orthovoltage RT (120 kV) was applied using standard cones and individual shielding of uninvolved areas of the palm. Relevant patient and disease parameters were equally distributed in both groups. Evaluation (toxicity, efficacy) was performed at 3 and 12 months after RT. Subjective (patient's opinion) and objective parameters (palpation, measurements, and comparative photographs) were applied to assess treatment response. Minimum follow-up (FU) was 1 year.

Results: Acute toxicity was minimal, but slightly more pronounced in Group B. Seventy-six (38%) hands developed skin reactions CTC 1° (A, 30; B, 46); and 12 (6%) had skin reactions CTC 2° (A, 4; B, 8). Chronic side effects were limited to dryness, desquamation, skin atrophy, and change of sensation (LENT 1°) in 9 (5%) sites without differences between the two groups. At 3 and 12 months after RT, subjective and objective reduction of symptoms, nodules, and cords occurred in both groups (*p* < 0.01) with no differences between the groups: in Group A, 55 (56%) sites regressed, 35 (37%) remained stable, and 7 (7%) progressed, whereas in Group B, 55 (53%) regressed, 39 (38%) remained stable, and 9 (9%) progressed at 12 months FU (NS). Overall and mean number of nodules, cords, and skin changes decreased at 3 and 12 months. The "treatment failure" rate at 1 year was 16 of 198 (8%), but only 4 (2%) sites required hand surgery for disease progression. Seven of 60 patients with unilateral DC received prophylactic RT for the initially uninvolved, contralateral hand due to progression of DC.

Conclusion: Both prophylactic RT concepts have been well accepted and tolerated by patients. Within the first year, they were equally effective to prevent further disease progression of DC and obtain considerable symptomatic improvement. Although 1-year results suggest similar response rates for both treatment groups, long-term FU of > 5 years has to be awaited for final assessment and recommendation of an optimized RT treatment schedule.   © 2001 Elsevier Science Inc.

Dupuytren's disease (contracture), Radiotherapy of benign diseases, Clinical trials, Orthovoltage radiotherapy, Hand surgery.

INTRODUCTION

Dupuytren's contracture (DC) is a proliferative disorder of the connective tissue, which involves the palmar fascia of the hand. In the early stage, subcutaneous nodules appear, which may be fixed to the overlying skin, later tough cords develop and become predominant in DC. With further progression, the cords reach the periostium of the hand bones and lead to advanced DC, characterized by the contraction

of the palm and the medial phalangeal (MP) and proximal interphalangeal (PIP) joints. This creates the typical flexion deformity of the palm and extension deficit of involved fingers. The clinical staging is based on the extent of the functional loss of the fingers (1–5).

The DC is named after the French anatomist Guillaume Dupuytren, but was initially described by Felix Platter (1614) and Sir Astley Cooper (1824) (6, 7). Its prevalence is 1–3% in Central Europe (2, 8), but varies widely in different parts of the

world (9). Caucasians are mostly affected (10, 11). The highest prevalence is noted in regions of Ireland, Scotland, and France (12, 13). DC starts usually in the 4th decade and peaks in the 5th to 6th decade with a male to female ratio of 3 : 1 (14). Two-thirds develop a bilateral affliction (2, 15). A family history is more pronounced in females than males (2, 11, 16). In the past, DC has been often associated with alcohol or nicotine abuse, diabetes mellitus, and epilepsy (10), but the exact etiology and pathogenesis are still poorly understood.

The clinical course and the typical pathohistologic features of DC are divided into (1) a *proliferative phase* (increased fibroblasts, nodule formation); (2) an *involutional phase* (increased myofibroblasts in diseased fiber bundles) that leads to contracture; and (3) a *residual phase* (collagenous fibers dominate in the connective tissues) (17–19). Unlike desmoids, DC displays no invasion of voluntary muscles (20), but it may slowly progress, stabilize for years, but rarely regresses spontaneously. The reported progression rate without any therapy reaches 50% within 5 years (3). Thus, any successful new treatment strategy requires more than 5 years follow-up (FU) for evaluation.

Drugs (including steroids, allopurinol, DMSO, nonsteroidal anti-inflammatory drugs, enzymes, Vitamin E) have been unable to prevent disease progression in early DC stages (21). Surgery (including local excision, partial or total fasciectomy) is reserved for advanced DC stages when flexion deformity and function-limiting extension deficits are more prominent and disturb daily activities (22). Unfortunately, all surgical results have been impaired by high complication rates of 15–20% (2, 21–23) and a high progression rate of 30–50% despite an initial successful surgical removal of diseased areas (3, 15).

The radiobiologic potential of ionizing radiation is limited to early DC stages, as long as proliferating fibroblasts exist as the predominant radiosensitive target. In addition, excessively expressed growth factors, PDGF and TGF β, may be influenced, as they are responsible for the disturbed growth regulation of the fibroblastic system with increase of myofibroblasts and an aberrant collagen production. The activated monocyte–macrophage system is regarded as another radiosensitive target, which is responsible for and initiates the extensive myofibroblast proliferation (24–28).

Several uncontrolled clinical studies—mostly from Europe—support the concept of prophylactic RT (29–41), but, so far, RT has not been accepted as a "standard treatment" (42, 43). Although several dose concepts have been successfully applied in the past, RT has never been tested in a prospective clinical study. Herein, the 1-year interim results are presented from our prospectively controlled randomized clinical trial, which was designed for radiotherapeutic treatment optimization (i.e., dose reduction).

PATIENTS, MATERIALS, AND METHODS

Patients characteristics

From June 1997 to December 1998, 168 patients with clinically evident and progressive early-stage DC were re-

ferred for RT by orthopedics, surgeons, and family physicians. The mean age of the 96 men and 72 women was 62 $\pm$ 13 (median, 60; range, 36–76) years. After clinical examination and counseling with informed consent, 26 patients refused or did not qualify for prophylactic RT for personal or other reasons. Three patients did not comply with the RT protocol, and 10 patients were unable to complete all follow-up (FU) visits, in time. In December 1999, 129 of 142 (91%) irradiated patients (67 men; 62 women) had completed the prescribed RT protocol including all FU evaluations.

Case characteristics

A total of 110 (85%) patients had a right hand and 88 (68%) patients a left hand involvement that required prophylactic irradiation; as a consequence, 69 (53%) patients required bilateral and 60 (47%) patients unilateral prophylactic RT. Thus, a total of 198 hands ("sites" = "cases") were irradiated for progressive DC.

Predisposition

Using a structured questionnaire (Appendix I) and clinical consultation, the following predisposing factors were identified: a positive family history in 36 (28%) patients (22 of 62 women, 14 of 67 men); Morbus Ledderhose of the plantar fascia in 19 (15%) patients (11 women, 8 men); knuckle pads in 17 (13%) patients (7 women, 10 men); a history of keloids in 4 (3%) patients (3 women, 1 men); a trauma of the palm in 17 (13%) patients (5 women, 12 men); diabetes mellitus in 22 (17%) patients (12 women, 10 men); epilepsy in 3 (2%) patients (3 men); liver disease/cirrhosis in 29 (15%) patients (10 women, 19 men); peripheral arteriosclerosis in 24 (19%) (8 women 16 men) patients, and/or nicotine abuse in 20 (15%) patients (7 women, 13 men). Alcohol abuse was not specifically asked or systematically analyzed among the patients.

Pretreatment

Sixty-two (48%) patients had received one or more of the following treatments before RT: surgical procedures including local excisions and partial fasciectomy in 25 (19%), topical use of steroids (injections) in 6 (5%), systemic nonsteroidal anti-inflammatory drugs in 13 (11%), Vitamin E in 25 (19%), other drugs in 15 (12%), and/or other therapeutic measures in 12 (9%) patients.

Clinical symptoms

The dimensions and consistency of nodules and cords, skin changes, finger mobility, etc., were assessed by clinical inspection, palpation and measurements (M.H.S./F.G./T.O.) (Appendix II). All findings were directly drawn on the skin and photographed using a photocopy machine (33, 40) (Fig. 1A). Following clinical signs have been identified before the onset of RT: 68 (34%) sites were associated with unpleasant burning or itching sensations or feeling of pressure or tension in the involved palm; a total of 1426 nodules (mean, 7.2 $\pm$ 3.4; range, 2–16 nodules per case) and 788
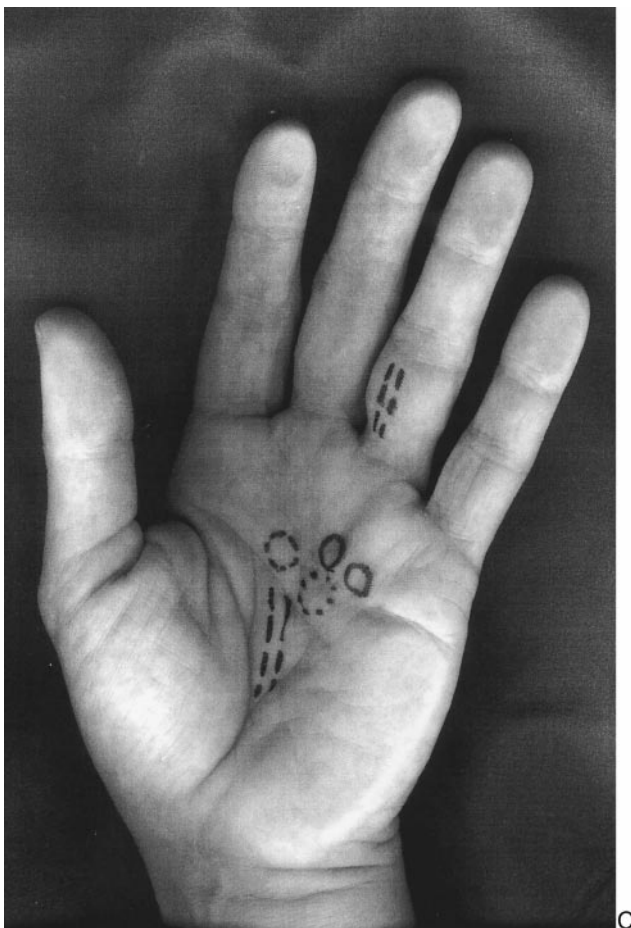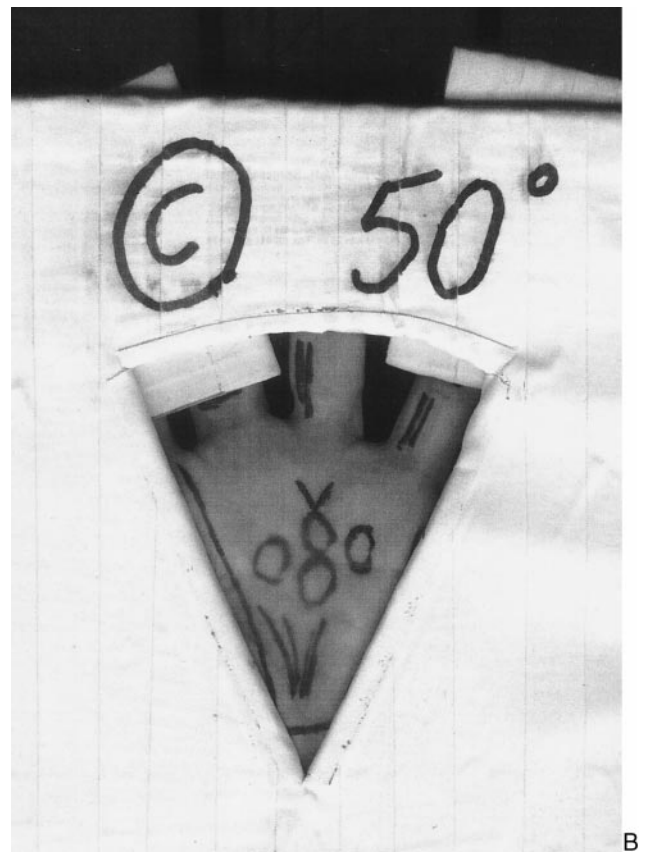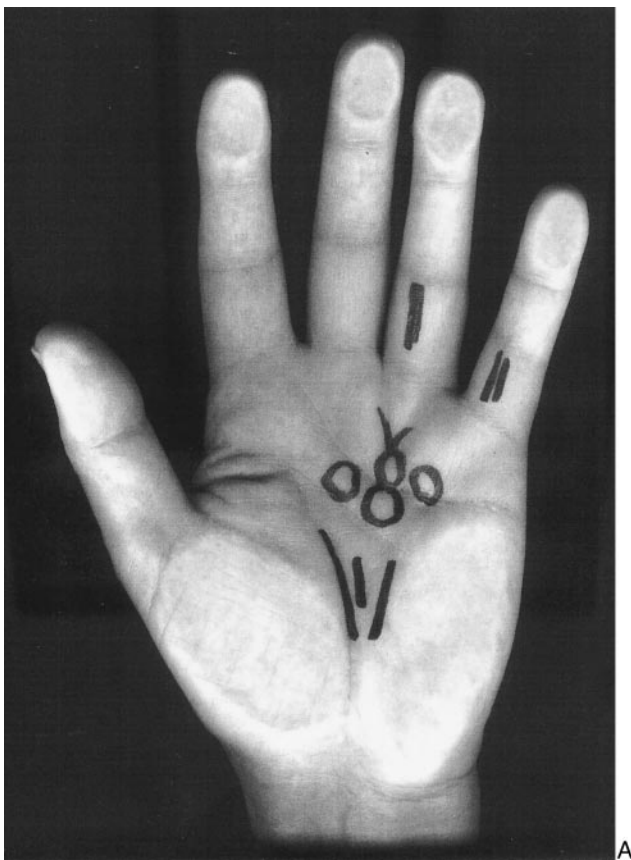
Fig. 1A. Clinical documentation of nodules (circles) and cords (full lines) on the hand of a 64-year-old man presenting with DC stage N/I; the planned RT portal is outlined before the first treatment session for the preparation of individual shielding and dosimetry. B. Orthovoltage treatment setup with individual shielding of uninvolved areas of the palm using 3-mm lead rubber plates. C. Follow-up at 12 months: nodules and cords of equal consistency (full lines) and softer consistency or regressed in size (dashed lines) as compared to the initial status.

Table 1. Classification of Duputren's contracture (DC) according to Tubiana, Michon, and Thomine (1966) [see Ref. 44]

Stage	Clinical symptoms	Extent of extension deficit (=flexion deformity)
Stage N	Clinical Symptoms, i.e., Nodules, cords, skin retraction, and fixation, etc.	None
Stage N/I*	Clinical symptoms plus flexion deformity of fingers	1–10°
Stage I	Clinical symptoms plus flexion deformity of fingers	11–45°
Stage II	Clinical symptoms plus flexion deformity of fingers	46–90°
Stage III	Clinical symptoms plus flexion deformity of fingers	91–135°
STage IV	Clinical symptoms plus flexion deformity of fingrs	>135°

*Modified from Keilholz, Seegenschmiedt, and Sauer (1996) [see Ref. 40].

cords (mean, 4.0 ± 2.1; range, 1–8 cords per case) were observed; a clearly visible deep skin retraction was seen in 169 sites (mean, 0.9 ± 0.5; range, 0–5 per case) and a palpable skin fixation assessed in 136 sites (mean, 0.7 ± 0.3; range, 0–4 per case). The mean observed time period from first recognition of typical DC symptoms until onset of RT was 26 ± 8 (range, 4–78) months.

Stage of DC

Staging of DC was conducted according to Tubiana *et al.* (44); it is based on the measurable total flexion deformity of palm and involved MP/PIP/DIP finger joints (Table 1). As Stage I comprises a large range of functional loss (1–45°), which allows no differentiation between initial and late changes, an intermediate Stage N/I was defined for minor

extension deficits of 1–10° (40, 41). According to this modified classification, Stage N was observed in 73 (37%) sites, Stage N/I in 61 (31%), Stage I in 59 (30%), and Stage II in 5 (3%) sites. According to the patients' statements, all involved sites had experienced progressive symptoms at least within the last 6 months before RT.

Radiotherapy

Radiotherapy was applied depending on the individual grade and extent of DC.

An orthovoltage unit (RT 250, Philips Co., Hamburg, Germany) was used (120 kV/20 mAs/2 mm Al, 6 × 8 cm/10 cm × 12 cm cones) at a source skin distance (SSD) of 40 cm. All areas of the palm that were not involved in the portal were individually shielded with 3-mm thick lead rubber plates. (Fig. 1B). It was common policy in our department to treat the whole afflicted area of the palm (all palpable and visible cords and nodules) with sufficient distal, proximal (1–2 cm), and lateral margins (0.5–1 cm). All recommended radiation protection measures (appropriate beam direction, patient positioning, use of lead apron, etc.) were applied.

After informed consent, patients were randomized to receive one of the following two RT schedules:

1. Group A (63 patients/95 hands) received 10 fractions of 3 Gy (total dose, 30 Gy) in 2 series of each 5 × 3Gy in 1 week separated by 8 weeks (total treatment time, 10 weeks);

2. Group B (66 patients/103 hands) received 7 fractions of 3 Gy every other day (total dose, 21 Gy) in 1 series (total treatment time, 2 weeks).

Relevant patient and case characteristics were equally distributed between both treatment groups, including gender, age, subjective symptoms, DC stage (all Table 2) as well as predisposition, disease location, and prior treatment. In addition, the overall distributions of nodules (Fig. 2A),

Table 2. Patient and disease characteristics according to treatment group

Parameter	Group A (30Gy)	Group B (21Gy)	Total group
Patients	$n = 63$	$n = 66$	$n = 129$
Gender (F/M)	30 F/33 M	32 F/34 M	62 F/67 M
Age (mean ± SD)	65 ± 11 years	61 ± 14 years	62 ± 13 years
Subjective symptoms	$n = 95$	$n = 103$	$n = 198$
	n (mean/range)	n (mean/range)	n (mean/range)
Nodules	694 (7.3/2–16)	732 (7.1/2–14)	1.426 (7.2/2–16)
Cords	428 (4.5/1–7)	360 (3.5/1–8)	788 (4.0/1–8)
Skin retraction	101 (1.1/0–5)	68 (0.7/0–4)	169 (0.9/0–5)
Skin fixation	79 (0.8/0–4)	57 (0.6/0–3)	136 (0.7/0–4)
Disease stage*	n (%)	n (%)	n (%)
Stage N	32 (34%)	41 (40%)	73 (37%)
Stage N/I	31 (33%)	30 (29%)	61 (31%)
Stage I	29 (31%)	30 (29%)	59 (30%)
Stage II	3 (3%)	2 (2%)	5 (3%)

*Modified according to Tubiana *et al.* (1966) [44] and Keilholz *et al.* (1996) [Ref. 40]; there were no statistically significant differences between the different subgroups of group A and group B (all $P > 0.05$).

Distribution of Nodules

Concept A

100%
86%
71%
14%
7%

N = 95

D1 D2 D3 D4 D5

A

Concept B

100%
72%
69%
17%
6%

N = 103

D5 D4 D3 D2 D1

Distribution of Cords

Concept A

93%
71%
44%
46%
11%

N = 95

B

D1 D2 D3 D4 D5

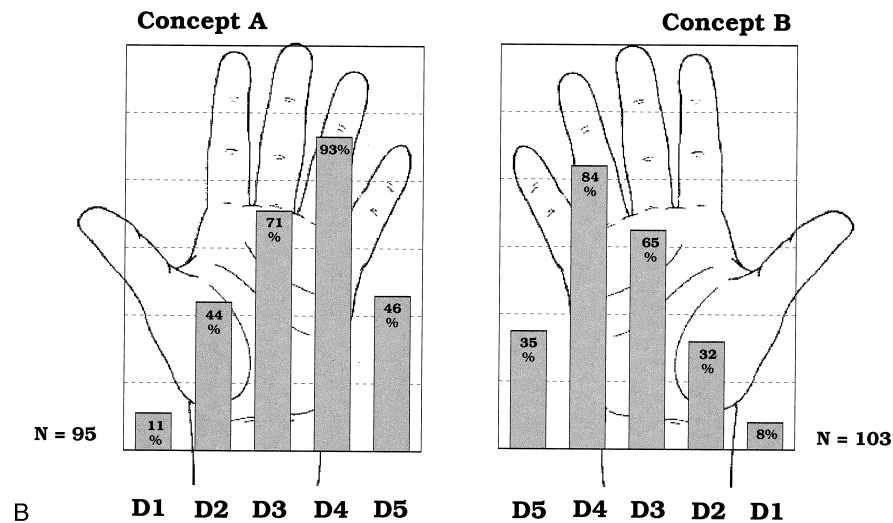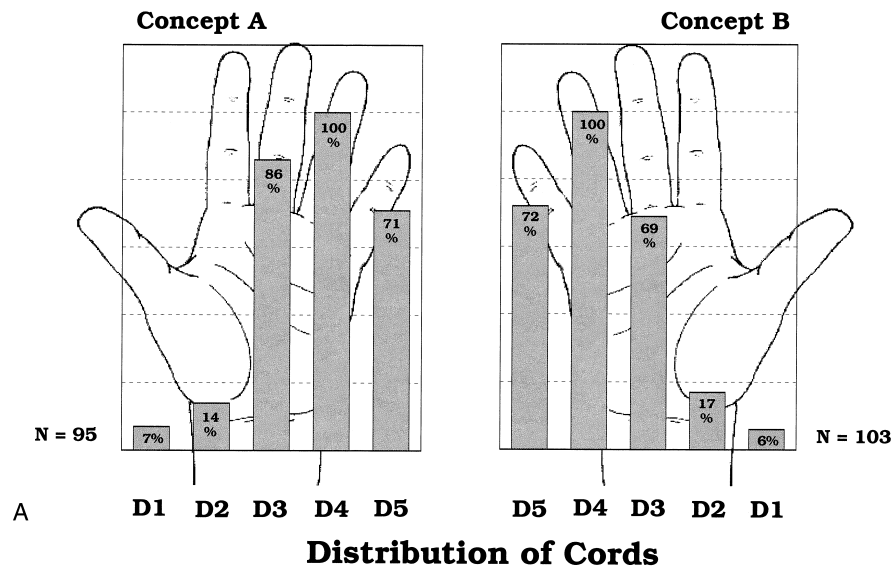**Concept B**

84%
65%
35%
32%
8%

N = 103

D5 D4 D3 D2 D1

Fig. 2A. Overall distribution of 1426 nodules before RT according to treatment group and handiness: the 3rd and 4th fingers were most oftenly involved. B. Overall distribution of 788 cords before RT according to treatment group and handiness: the 3rd and 4th fingers were most oftenly involved. C. Overall distribution of treatment stage according to treatment Group A (*n* = 95) and treatment Group B (*n* = 103).

cords (Fig. 2B), and DC stage (Fig. 2C) were similar in both treatment groups.

Evaluation

Subjective response, DC stage, number, size, and consistency of nodules and cords, and finger mobility were assessed at 3 and 12 months FU. Subjective response was stated by the patient either as "progression," "stable condition," or "regression of symptoms." Regression was assessed as relative value (in %) comparing FU findings to RT onset. Objective findings (palpable nodules, cords) or visible signs were assessed by physicians (MHS, TO,

FG), marked on the skin, and photocopied (Fig. 1C) to compare the actual and initial DC status (40, 41). Functional changes (flexion deformity of the palm, extension deficit of fingers) were measured with a protractor. Acute and chronic toxicity was scored according to CTC- and LENT-SOMA criteria. All 129 patients reached a minimum FU of 1 year.

The main endpoint of the study was "reduction of symptoms" (patient related) and "stabilization" or "reduction of findings" including nodules, cords, and skin changes (physician related). Subjective or objective progression of symptoms or any finding was regarded as "treatment failure."
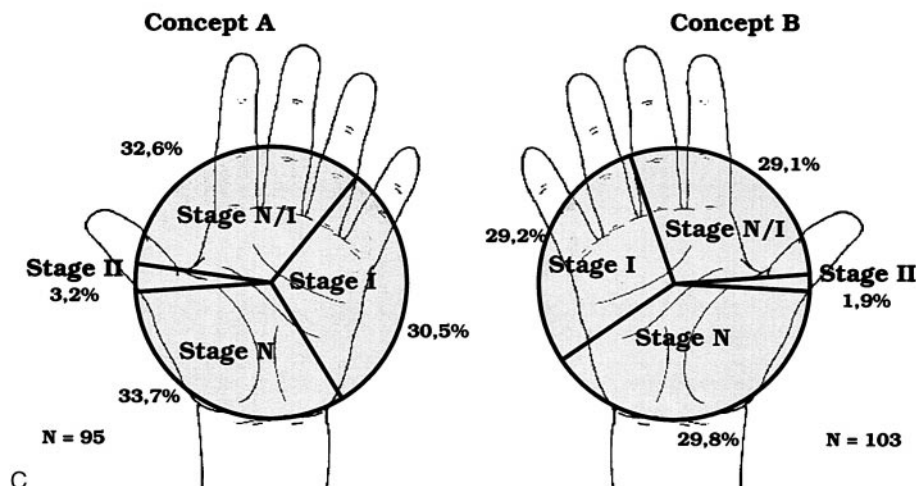
Stage Distribution

Fig. 2. (*Cont'd*)

RESULTS

Compliance

A total of 3 (3%) patients in Group A refused the second RT series after completion of the first series (15 Gy). They will be followed according to the "intention-to-treat" concept in Group A for evaluation of long-term response. All Group B patients completed RT.

Toxicity

Acute toxicity within 4 weeks after RT was observed in 76 (38%) sites as redness or dryness of the skin (CTC 1°); 12 (6%) sites developed extensive erythema (12 sites), dry (10 sites) or moist desquamation (3 sites), or pronounced swelling (3 sites) (CTC 2°). Most reactions were limited to the RT portal; they occurred more often and intensively in Group B (46 CTC 1°/8 CTC 2° = 52%) as compared to Group A (30 CTC 1°/4 CTC 2° = 36%), but without statistical significance.

Chronic side effects were observed in 26 (13%) sites at 3 months FU (Group A, 15; Group B, 11) and in 9 (5%) sites at 12 months FU (A: 4; B: 5). Most of these patients complained of dryness, increased desquamation, or mild skin atrophy accompanied by slight subcutaneous fibrosis that required an occasional or daily use of ointments (LENT Grade 1°/2°); in 8 sites, alteration of heat and pain sensation occurred. Overall, no significant toxicity differences were observed between the two treatment groups.

Treatment results

At 12 months FU, a significant subjective and objective reduction of symptoms, nodules and cords was observed in both treatment groups (all *p* < 0.01): regarding subjective response, 76 (59%) patients (Group A, 41; Group B, 35) stated "regression of DC symptoms" in 120 (61%) sites (A, 60; B, 60); the range of regression was equal for both treatment groups: < 25% regression for 74 of 120 (62%) sites (A, 35; B, 39), 25–50% regression for 37 (31%) sites (A, 18; B, 19), 51–75% regression in 7 (6%) sites (A, 5; B, 2), and > 75% regression in 2 (2%) sites (all in Group A); in addition, 46 (36%) patients (A, 19; B, 27) had "stable condition" in 65 (33%) sites (A, 30; B, 35), whereas 7 (5%) patients (A, 3; B, 4) suffered "progression of DC symptoms" in 13 (7%) sites (A, 5; B, 8). The patient's view about "disease progression" correlated well with objective findings: additional nodules (6 patients/11 sites) and cords (5 patients/7 sites) or an increased extension deficit (7 patients/12 sites).

According to objective criteria (i.e., reduced number and consistency of cords and nodules, reduction of extension deficit), a total of 108 (54%) sites regressed (Group A, 53; Group B, 55), 74 (37%) remained stable (A, 35; B, 39), and 16 (8%) sites progressed (A, 7; B, 9) at 12 months FU. When compared with the initial status prior to RT, both treatment groups improved significantly (*p* < 0.01) at 3 and 12 months FU, but, when compared with each other, no differences were found between group A and group B for all objective findings (Figs. 3A–3C). Sixteen sites developed "treatment failure" either as new nodules (11 sites), new cords (7 sites), or increased flexion deformity of palm or any finger (12 sites) in the range of 10–50°. 4 (3%) patients (4 [2%] sites) required (or decided on their own) to undergo corrective hand surgery within the first year.

Overall, the initially observed 1426 nodules were reduced by 360 nodules at 3 months (Group A, minus 231; Group B, minus 129) and by 799 nodules (A, minus 360; B, minus 439) at 12 months FU (*p* < 0.01). Similarly, the 788 cords decreased by 299 (A, minus 155; B, minus 144) at 3 months and by 359 (A, minus 220; B, minus 139) at 12 months FU (*p* < 0.01). The observed 405 skin changes were reduced by 42 (A, minus 24; B, minus 18) at 3 months

Development of Nodules
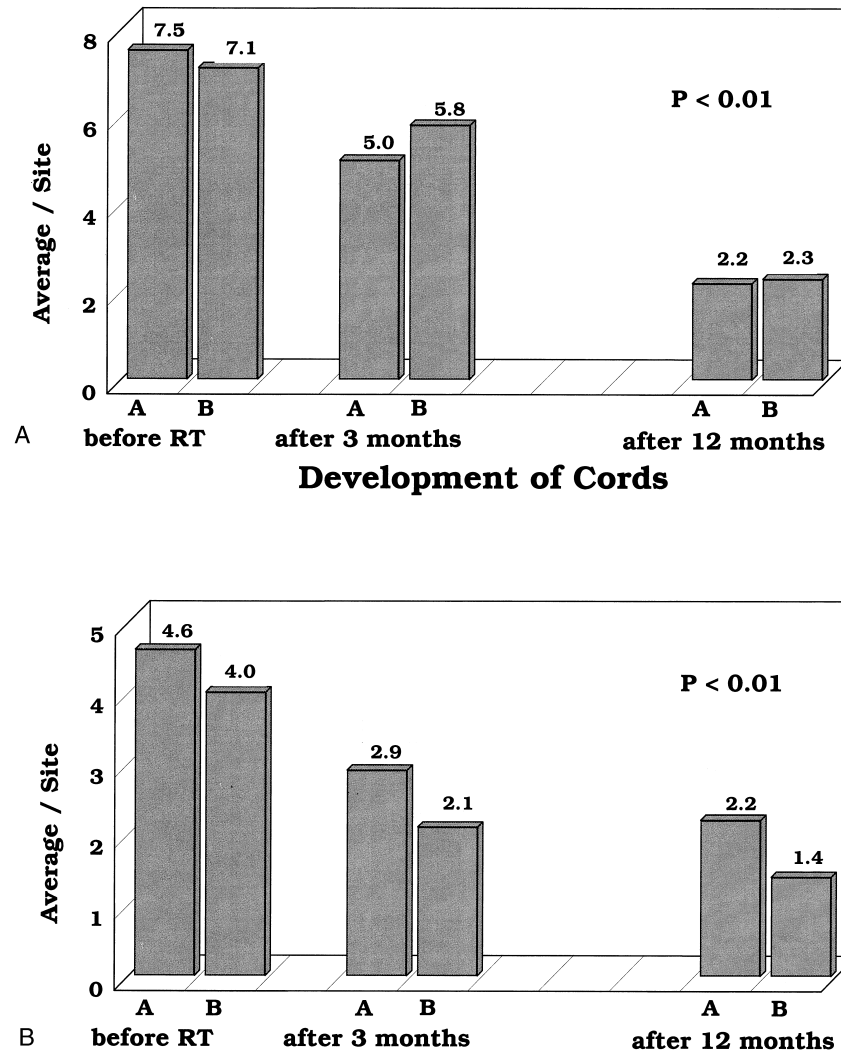

A

Development of Cords

B

Fig. 3A. Development of nodules before RT, and at 3 months and 12 months follow-up. B. Development of cords before RT, and at 3 months and 12 months follow-up. C. Development of skin changes before RT, and at 3 months and 12 months follow-up.

FU and by 66 (A, minus 31; B, minus 25) at 12 months FU, respectively ($p < 0.01$). Accordingly, the mean number of nodules (7.2 per case), cords (4.0 per case), and sites with skin fixation decreased at 3 and 12 months FU ($p < 0.01$, all groups) (Figs. 3A–C). For all aspects of objective response, no statistically significant difference was observed between the groups.

Most interestingly, within the first year of FU, 7 of 60 (12%) patients with unilateral DC disease required further prophylactic RT for the initially uninvolved contralateral hand due to an obvious progression of DC within this time period. During the same time period, however, the irradiated hand remained in remission (4 hands) or stable condition (3 hands).

DISCUSSION

DC is a characterized by proliferation of fibrous tissue in form of nodules or cords (17). It has features in common with benign neoplastic fibromatosis (2) and undergoes an evolution, through contraction and maturation of fibrous tissue, which is similar to wound healing or radiation fibrosis (45, 46). Digital contracture is preceded by appearance of nodules and cords in the palm and the fingers. The fibro-fatty tissue layer between the skin and the deep structures of the palmar aponeurosis is regarded as the primary site of the disease onset. The abnormal fibrous tissue develops within and all around the ligamentous strands that have a predominantly longitudinal orientation and follow longi-

Development of Skin Changes
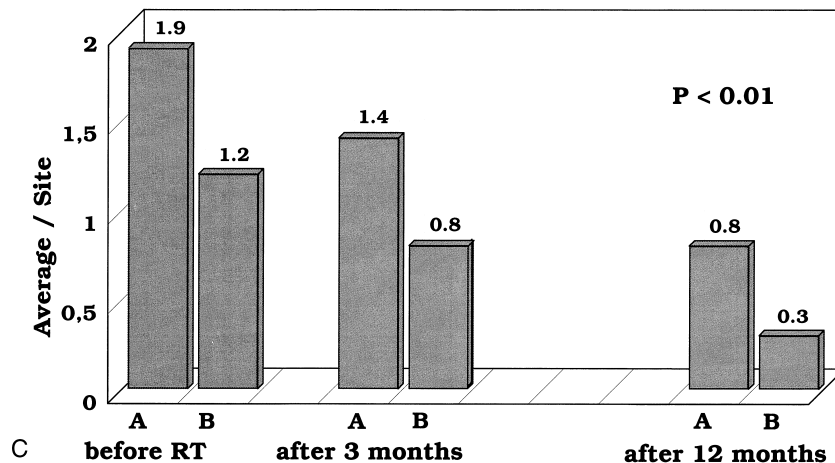
(Retraction, Fixation)

Fig. 3. (*Cont'd*)

tudinal tension lines of the palm. Thus, some pathologic forces and enhanced mechanical stress may play an important role in the pathogenesis and development of DC (47).

From a radiobiological view, the proliferation process is the most interesting component of DC. It is driven by immature fibroblasts, mostly myofibroblasts (48, 49), which produce an extracellular matrix with fibronectin, laminin, collagen Type IV, and tenascin as constituents (50). Myofibroblast phenotype and growth factor synthesis have been exclusively localized in active proliferative nodules (50). Similar to DC, initial events in wound healing and fibrosis are mediated by growth factors produced by platelets and macrophages (51). There is also good evidence for raised growth factor levels in DC, e.g., messenger-RNA for interleukin-1, basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-beta), which are known to stimulate fibroblasts (52). The platelet-derived growth factor (PDGF) B gene has been found to be expressed in DC specimens (25, 26); in addition, the epidermal growth factor (EGF) and the connective tissue growth factor (CTGF) have been suggested to play a pathogenetic role in DC (53).

As cell of origin for the masses of proliferation, the vascular pericyte has been suggested (54). It has been also hypothesized that microvessel narrowing causes local ischemia and generates free radicals that damage the surrounding stroma and stimulate perivascular fibroblast proliferation. Continued pericyte damage, fibroblast proliferation, and collagen deposition further encourage a microvessel ischemia, thereby self-propagating the pathogenetic process (55, 56). There is also not a clear concept of what really initiates the pathologic proliferation: a traumatic process, i.e., rupture of fascial fibers (46, 57, 58) or an inflammatory process with adhesions between ligamentous structures (59, 60).

Nevertheless, these pathogenetic aspects provide a good

rationale for using ionizing radiation in the early DC stage: (*1*) proliferating fibroblasts and myofibroblasts are radiosensitive target cells; (*2*) the radiogenic induction of free radicals damages fibroblasts, impairs the proliferative activity, and, thereby, reduces the cell density (22); (*3*) the radiogenic interference with the overexpressed growth factors, especially PDGF and TGF β (25–27); and (*4*) the activated monocytes and macrophages are very radiosensitive target cells, and their interaction with the inflammatory process plays a key role for the onset and extent of myofibroblast proliferation (28). Similar pathogenetic pathways and radiosensitive target cells have been identified for prophylaxis of intravascular RT to inhibit arterial restenosis (61, 62) or for external beam RT to avoid relapses after resection of keloids (43) or pterygium of the eye (63).

Efficacy of RT to impact on early-stage DC has been shown in many clinical trials (31, 33, 34, 36–41) (Table 3). Lukacs *et al.* (37) observed "no disease progression" in 36 sites. Hesselkamp *et al.* (34) reached "improved or stable conditions" for over 2 years in 93% of 46 sites. Vogt and Hochschau (38) found 94% of 109 irradiated sites "stable" or "improved" after more than 3 years. Köhler (36) reported 82% of 33 sites "improved or stable," and 6 "progressed" after 3 years. Herbst and Regler (33) observed all 45 sites "stable or improved" after a median of 1.5 years. Keilholz *et al.* (40, 41) found 72% of 142 sites with "regression of nodules and cords," and 57 sites with a minimum FU of 5 years; 5 (9%) progressed outside and 8 (14%) inside the RT portal. All together, these clinical data demonstrate that the observed progression rate after irradiation is much lower than the expected 50% progression rate for untreated patients or for patients who have to undergo surgery in advanced DC stages (3). However, all clinical studies using prophylactic or therapeutic RT of DC are retrospective. Moreover, they have differences in patient, disease, or treat-

Table 3. Radiation concepts and outcome of radiotherapy for Dupuytren's contracture

Study (year)	RT Concept		Follow-up	Clinical outcome according to stage *n* (%)		
	Fractionation	Dose		Regression	Stable Condition	Progression
Finney (1955)	1–3 × 1.000 r Ra-Moulage	1.000–3.000r	NA	Overall: 60% "good functional result"		
Wasserburger (1956)	1–3 × 1000 r Ra-Moulage	1.000–3.000r	long-term	"long-term cure": Stage I: 90%; Stage II: 57%; Stage III: 32%		
Lukacs *et al.* (1978)	2 × 4 Gy (day 1+2) every 2 mos	32 Gy	NA	I: 81% II: 75%	I: 19%	None
Vogt & Hochschau (1980)	2 × 4 Gy (day 1 + 2) every 2 mos	32 Gy	>3 years	I: 21% II: 25% III: —	I: 74% II: 50% III: 86%	I: 4% II: 25% III: 20%
Hesselkemp *et al.* (1981)	2 × 4 Gy (day 1 + 2) every 2 mos	40 Gy	1–9 years	total: 52%	total: 41%	total: 7%;
Köhler (1984)	10 × 2 Gy 3–5 × /week	20 Gy	1–3 years	total: 21%	total: 61%	total: 18%
Herbst *et al.* (1985)	3–14 × 3 Gy 5 × / week; 2 RT series	<42 Gy	>1.5 years	None	total: 98%	total: 2%
Keilholz *et al.* (1996)	10 × 3 Gy 5 × /week; 2 RT series	30 Gy	1–12 years; med.: 6 years	72% symptoms 7% DC stage	17% symptoms 82% DC stage	11% symptoms 11% DC stage
Essen (2000) randomized	10 × 3 Gy 7 × 3 Gy	30 Gy 21 Gy	> 1 year in all patients	56% symptoms 53% symptoms	37% symptoms 38% symptoms	7% symptoms 9% symptoms

Abbreviations: NA = not available; RT = radiotherapy; mos = months; yrs = years; Gy = Gray.
I, II, III = stage of Dupuytren's Contracture according to Tubiana [see Refs. 40, 41, 44].

ment parameters (fractionation, single and total RT dose, treatment time), endpoints, and follow-up periods. Thus, it is difficult to draw any conclusions from these studies. Additionally the question of what minimum dose is effective to reach a sufficient prophylactic or therapeutic potential, remains unanswered. Thus, prospective studies are required to define the lowest possible dose to achieve the best prophylactic or therapeutic effect.

Köhler (36) suggested at least 20 Gy (10 × 2 Gy) total dose to avoid DC progression effectively. Others reported better results with 32–40 Gy (4-Gy single dose) (34, 38). In former times, single doses of 1000 r every 3–6 months up to a total dose of 3000 r have been successfully applied (31, 39, 64). In a careful study, Keilholz *et al.* (40, 41) obtained good long-term outcome using a 30-Gy total dose in 2 RT series of each 5 × 3 Gy. Thus, our trial was set up to compare this proven effective dose of 30 Gy with a lower dose of 21 Gy using the same single doses (3 Gy). Nevertheless, treatment time was much longer in Group A (medium dose, 30 Gy) compared to Group B (low dose, 21 Gy), which was similar to Köhler' series (10 × 2 Gy) (36) of 2 weeks. Thus, both dose- and time-dependent effects can be responsible for any observed differences in long-term outcome. At 3 and 12 months FU, 21 Gy was as effective as 30 Gy, although acute toxicity was more pronounced in the lower dose group and chronic side effects were similar in both groups.

Appropriate RT technique is important for treatment outcome: some studies recommend whole palm irradiation (34,

36), whereas others, including this study, recommend treatment of the diseased areas only (38, 40, 41). We apply individual shielding of uninvolved parts of the palm similar to the methods of Keilholz *et al.* (40, 41), but this may allow DC progression outside the RT portal, if the longitudinal and lateral extension of the disease is underestimated. Large safety margins around visible and palpable lesions should avoid this problem. We do not apply total palm irradiation, to prevent unnecessary side effects. Out-field DC progression is easily amenable to a second RT series, as long as no major overlap with primary RT portals exist; in-field progression may require surgery only for functional deficits and quality of life. Orthovoltage photons (120–150 kV) or linac electrons (3–6 MeV) are required to reach all nodules and cords, which can extend 5- to 15-mm down to the periostium of the hand bones: 120 kV/20 mAs orthovoltage radiation with half-value-layer of 33 mm is sufficient to reach this depth (30, 31, 35, 64). Historic studies used radium grip cylinder or molds (31, 39). Careful dosimetry and dose prescription according to ICRU 50 and diligent treatment application to all involved areas of DC are important requirements to achieve a favorable long-term outcome in DC and avoid possible side effects.

Among hand surgeons, prophylactic RT is poorly known or critically disputed for various reasons, e.g., long-term inefficacy (65), complicated surgery after prior RT (65, 66), or observed side effects (66). Although we doubt the latter observation, we agree that advanced DC Stage II–IV may not benefit much from RT due to the loss of appropriate

target cells (the actively proliferating fibroblast) (38, 39). In our study, 13 sites had progression at 12 months FU; 2 had Stage II DC (2 of 5 sites = 40%), 9 had Stage I DC (9 of 59 sites = 15%), and 2 had Stage N/I DC (2 of 61 sites = 3%), while none of the 73 sites with DC Stage N progressed within the first 12 months. From this preliminary analysis, our advice is to transfer patients with advanced Stages II–IV and/or recurrent lesions primarily to hand surgeons. Close cooperation with hand surgeons is important. Prophylactic RT should not impair good surgical results. Thus, in the long-term perspective, reducing total RT dose is meaningful. This is the main idea of the prospective clinical study presented herein. So far, only 4 (2%) sites have required hand surgery due to DC progression after prophylactic RT, and none of these had surgical complications or enhanced perioperative morbidity.

In summary, the rationale for prophylactic RT applies to early DC stages, because, at these stages, clinical symptoms and functional deficits are still limited. Without RT, more than 50% of patients will progress and suffer functional loss, and will require hand surgery within the next 5 years. Additional clinical studies are required, especially in patients with bilateral DC Stage N and Stage N/I, which would be amenable to a "matched pair" analysis comparing observation (as control) vs. prophylactic irradiation.

CONCLUSIONS

Both tested RT regimens have been well accepted and tolerated by patients. Acute toxicity was slightly more enhanced in the low-dose group (21 Gy) than in the medium-dose group (30 Gy), probably due to the dose-time factor. Significant subjective and objective long-term improvement was achieved in both groups in more than 50% of all sites for several symptom categories (nodules, cords, and skin changes). So far, the overall progression rate at 12 months was only 8%, with no difference between the two groups. Although the 1-year results suggest a similar response for both RT schedules, long-term FU data of at least 5 years are needed for the final assessment of both treatment schedules.

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Appendix I - Morbus Dupuytren - Documentation

Date of 1st Assessment ⌊ ⌋⌊ ⌋⌊ ⌋

Family Name .... **Surname**..................... **Date of Birth** ⌊ ⌋⌊ ⌋⌊ ⌋

General Data :   **No = N;   Yes = Y**

Any Relatives with M. Dupuytren ?   ⌊ ⌋ N   ⌊ ⌋ Y, Who ? ....

Similar Disorders present ?   ⌊ ⌋ Morbus Peyronie   ⌊ ⌋ Morbus Ledderhose

....   ⌊ ⌋ Knuckle Pads   ⌊ ⌋ Keloid(s)

Other Disorders present ?   ⌊ ⌋ Diabetes mellitus   ⌊ ⌋ Epileptic Disorder

....   ⌊ ⌋ Liver Disease, Which ? ....

....   ⌊ ⌋ Perfusion Disorder ? Which ? ....

Trauma of the Hand / Palm ?   ⌊ ⌋ Which ? / When ? ....

Type of Professional / Daily Activities ? ⌊ ⌋ Coarse ⌊ ⌋ Fine Hand Movements ?

Which Profession practiced ?   ....

Smoking ⌊ ⌋ N ⌊ ⌋ Y, ... ⌊ ⌋ Right- ⌊ ⌋ Left-Hander ?

First Onset of Clinical Signs ? .... (estimate in months)

Which Clinical Signs ?		Right Hand		Left Hand
		When ?		**When ?**
Iching / Burning Sensation ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
Increased Palm Tension ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
Increased Pressure at Grip ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
Pain at Rest ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
Pain at Strain ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
First Skin Changes ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
First Palpable Nodules ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
First Palpable Cords ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
First Flexion Deformity ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y
Any Other Complaints ?	⌊ ⌋N	⌊ ⌋Y	⌊ ⌋N	⌊ ⌋Y

Did any of the clinical signs increase during the last time ?

L ⌋N   L ⌋Y,   within L ⌋the last 4 weeks :   ....

L ⌋the last 3 months :   ....

L ⌋the last 12 months :   ....

L ⌋the last L ⌋years :   ....

Was there any „regression" ?   L ⌋N   L ⌋Y, How long ? .:................................

Which physicians did you have counseled ?

L ⌋Family Physician   L ⌋Medical Specialist : ....

Which treatment has been conducted so far for one hand / both hands ?

Treatment :		Right Hand	Left Hand
Medication	L ⌋N		
Steroids	L ⌋N		
Antiphlogistic Drugs	L ⌋N		
Allopurinol	L ⌋N		
Vitamines	L ⌋N		
„Enzymes"	L ⌋N		
„Softening Agents"	L ⌋N		
Others, specify :			
Hand Surgery : (Year, Type)	L ⌋N		
Lokal Injections	L ⌋N		
Lokal Ointments	L ⌋N		
Radiation Therapy	L ⌋N		
Others:			

Appendix II - Morbus Dupuytren – Clinical Examination

Date of Assessment⌊   ⌋⌊   ⌋⌊   ⌋ / .... **Months after Radiotherapy**

Clinical Findings	Right Hand					Left Hand				
Digit / Ray:	D 1	D 2	D 3	D 4	D 5	D 5	D 4	D 3	D 2	D 1
Skin Fixation (F)										
Skin Retraction (R)										
Nodules (N) [cm]										
Cords (C) [cm]										
Extension Deficit										
- DIP-Joint (°)	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
- PIP-Joint (°)	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
- MP-Joint (°)	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
Total Deficit (°):										
Hyperextension (H)										
Ankylosis (A)										
Other Findings, e.g. Surgical scars										
Total Score Stage										

Findings in the Palm (palmar) = P; Findings on Fingers (digital) = D; combined = PD

At any FU Photo Documentation of marked Findings and outlined Treatment portal !

Remission Status: ⌊   ⌋ **Progression :**   .... ⌊   ⌋ **Progression**
                        ⌊   ⌋ **No Change :**   .... ⌊   ⌋ **No Change**
                        ⌊   ⌋ **Regression (%)**   .... ⌊   ⌋ **Regression (%):** ....

Date / Signature: ....●...●..