44 Long-Term Outcome of Radiotherapy for Early Stage Dupuytren's Disease: A Phase III Clinical Study

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44.1 Introduction

Dupuytren's disease (DD) is *a proliferative disorder* of the connective tissue involving the palmar fascia of the hand. In its early stage, *subcutaneous nodules* appear, which may be fixed to the overlying skin. Later, *tough cords* develop and become predominant in what is called Dupuytren's contracture. With further progression, the cords reach the periosteum of the hand bones and lead to advanced DD which is 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 an increasing *extension deficit* of the involved fingers. The clinical staging of DD according to Tubiana et al. (1966) is based on this functional loss of the finger movement (Görlich 1981; McFarlane et al. 1990; Millesi 1981; Moorhead 1956; Schink 1978) (Table 44.1).

DD was initially described by Felix Platter (1614) and Sir Astley Cooper (1822) but is named after the French Guillaume Dupuytren (Dupuytren 1832, 1834). Its prevalence is 1–3% in Central Europe (McFarlane et al. 1990;

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Table 44.1 Classification of Dupuytren's disease (DD) according to Tubiana et al. (1966)

Stage	Clinical symptoms	Extent of extension deficit
Stage N	Nodules, cords, skin retraction and fixation, etc.	None, i.e., no flexion deformity
Stage N/I	As stage N plus deformity of fingers	1–10°[a]
Stage I	As stage N plus flexion deformity of fingers	11–45°
Stage II	As stage N plus flexion deformity of fingers	46–90°
Stage III	As stage N plus flexion deformity of fingers	91–135°
Stage IV	As stage N plus flexion deformity of fingers	>135°

[a]Stage N modified from Keilholz et al. (1996)

Viljanto 1973) but varies widely worldwide (Strickland et al. 1990). Caucasians are believed to be mostly affected (Early 1962; Brenner et al. 1994). Very high prevalence is noted in regions of Ireland, Scotland, and France (Rafter et al. 1980; Brouet 1986) but more recently also in other European countries like Belgium (Degreef and de Smet 2010) and Bosnia (Zerajic and Finsen 2012). DD starts usually in the fourth decade and peaks in the fifth to sixth decade with a male to female ratio of 3:1 (Yost et al 1955). Two-thirds of the patients may develop a bilateral affliction (McFarlane et al. 1990; Hueston 1987). A family background is more pronounced among female than male patients (Early 1962; Ling 1963; McFarlane et al. 1990).

Etiology and pathogenesis are still poorly understood: In the past, DD has been often associated with certain risk factors including alcohol or nicotine abuse, diabetes, and epilepsy (Brenner et al. 1994) but results are still contradictory, and more recently occupation is also being considered as a potential influence of DD onset (Al-Qattan 2006; Descatha 2012).

The clinical course and the typical pathological features of DD are divided in (a) a *proliferative phase* (increased fibroblasts, nodule formation), (b) an *involutional phase* (increased myofibroblasts in diseased fiber bundles) which leads to contracture, and (c) a *residual phase* (collagenous fibers dominate in the connective tissues) (Luck 1959; Tomasek et al. 1987; Mohr and Wessinghage 1994). The different cellular composition especially regarding the low cellularity of proliferating fibroblasts and myofibroblasts in normal tendons and scar tissue and the high cellularity of nodules and cords of the palmar fascia in Dupuytren's disease is shown in Fig. 44.1. This underlines the important role of proliferating fibroblasts and myofibroblasts in the initial disease progression and final transformation into scarring tissue with functional deficit (Dave et al. 2001; Moyer et al. 2002).

Unlike aggressive fibromatosis (desmoids), DD never exhibits an invasion of voluntary muscles (Allen

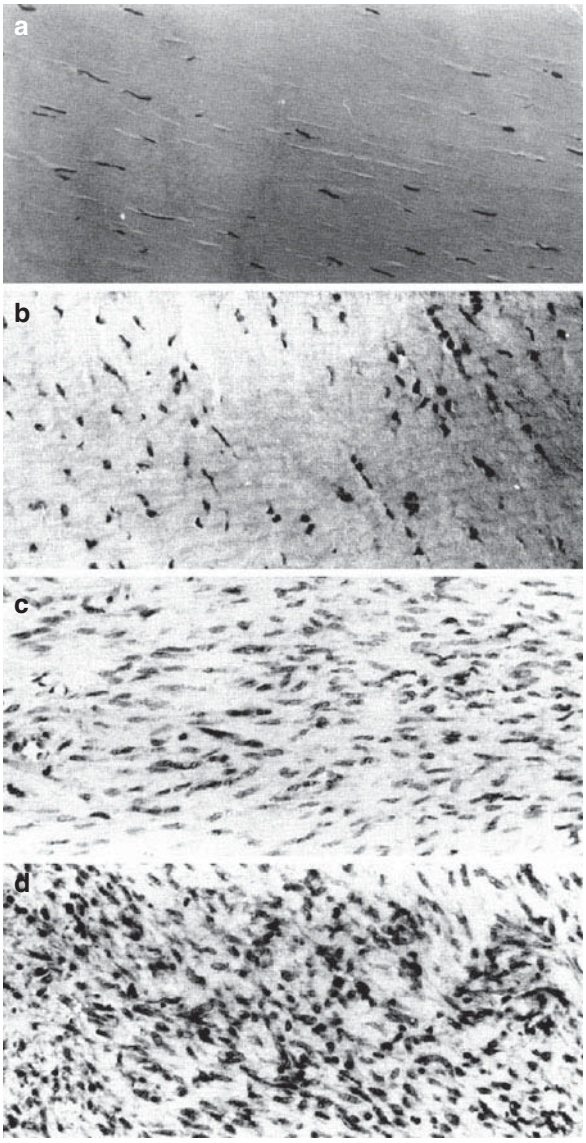

Fig. 44.1 Histopathogenesis of Dupuytren's disease and related tissues. (**a**) Typical tendon tissue with low cellularity. (**b**) Typical scar tissue with low cellularity. (**c**) Typical Dupuytren's cord tissue with increased cellularity. (**d**) Typical Dupuytren's nodular tissue with increased cellularity

1977). DD may progress slowly, sometimes stabilizes for years, but only rarely regresses spontaneously. Without any therapy, DD progresses in about 30–50% within 5 years leading to functional deficiencies and requiring surgical correction (Millesi 1981). Thus, any successful early treatment strategy requires at least 5 years follow-up (FU) for long-term evaluation.

Several noninvasive treatment options have been suggested for prophylaxis of DD progression, but so far no specific drugs (including steroids, allopurinol, DMSO, NSAIDs, enzymes, vitamin E) have been able to prevent the disease progression in the early DD stages (Falter et al. 1991). Injection of corticosteroids did not provide effective long-term results (Ketchum and Donahue 2000). Recently, in more advanced DD stages the injection of collagenase has been examined and found to provide effective release of contracted tissue especially for PIP joints; long-term data over several years are not yet available (Badalamente and Hurst 2012). In addition, minimal invasive surgical techniques like needle fasciotomy have been developed in France and implemented to provide effective release in contracted fingers (Badois et al. 1993). Both minimal invasive techniques provide quick recovery and alleviate repetitive application but with short or uncertain recurrence periods, respectively. Furthermore, both techniques show limited results for PIP joints. Surgery, including fasciotomy and local excision, partial or total fasciectomy, is reserved for advanced *DD stages*, when flexion deformity and function-limiting extension deficits are more prominent and disturb the daily activities. The principal aim is not to cure but to restore normal hand function (Murrell and Francis 1994). Unfortunately, all surgical results are impaired by complication rates in the range of 15–20% and high relapse or progression rates of 30–50% despite successful surgical removal of diseased areas (McFarlane et al. 1990; Falter et al. 1991; Murrell and Francis 1994; Geldmacher 1994; Au-Yong et al. 2005; Loos et al. 2007; Denkler 2010; Becker and Davis 2010). Additional postoperative splinting seems to offer no benefit (Jerosch-Herold et al. 2012). Nevertheless, repeated surgical procedures are required throughout the lifetime (Millesi 1981; Hueston 1987). Moreover, unilateral affliction can develop into bilateral affliction, and additional Ledderhose's disease (LD) may affect previously uninvolved feet.

The *radiobiological potential* of ionizing radiation is clearly limited to the early DD stages, as long as the proliferating fibroblasts exist as predominant radiosensitive target. In addition, the excessively expressed growth factors – platelet-derived growth factor (= PDGF) and tumor growth factor beta (= TGFβ) – can be influenced and downregulated, as they are responsible for the disturbed growth regulation of the fibroblastic system with rapid increase and ongoing stimulation of the myofibroblast proliferation and an aberrant collagen production. Thus, the highly activated monocyte-macrophage system in DD can be regarded as another important radiosensitive target, which is responsible for and initiates the extensive myofibroblast proliferation, at least in the early stages of DD, i.e., during the periods when nodules and cords are developing, but not in the phase of tissue scarring (Lubahn et al. 1984; Terek et al. 1995; Tomasek and Rayan 1995; Rayan et al. 1996; Rubin et al. 1999; Kampinga et al. 2004), Fig. 44.2a, b.

Several uncontrolled clinical studies – mostly from Europe and Germany – support the concept of prophylactic RT (Kaplan 1949; Finney 1955; Wasserburger 1956; Dewing 1965; Braun-Falco et al. 1976; Lukacs et al. 1978; Vogt and Hochschau 1980; Hesselkamp et al. 1981; Haase 1982; Köhler 1984; Herbst and Regler 1986; Keilholz et al. 1996, 1997). Long-term analysis has revealed a decreasing response rate with increasing follow-up and increasing stage of DD, but so far RT has not been accepted as a "standard treatment," (Order and Donaldson 1990; Suit and Spiro 1999) although recently some countries have changed their policies regarding the use of RT for early stage DD. For example, the National Institute for Health and Clinical Excellence (NICE) has issued full guidance to the NHS in England, Wales, Scotland, and Northern Ireland on radiation therapy for early Dupuytren's disease (NICE 2010). Nevertheless, the professional awareness for the use of RT and practical skills among radiation therapists and the interdisciplinary cooperation have still to grow in the future (Leer et al. 2007). More important, however, is the fact that treating early stage DD by RT has been increasingly recognized as a means to postpone or even avoid surgery (Dupuytren Society 2011) but is still far from being a generally accepted treatment option.

Although several RT dose concepts have been successfully applied in the past, RT has never been tested in a prospective clinical study against a control group. The first 1-year interim results of our group's prospectively controlled randomized clinical trial were presented (Seegenschmiedt 2001) was designed to establish a dose-response relationship and to optimize the radiotherapeutic treatment management.

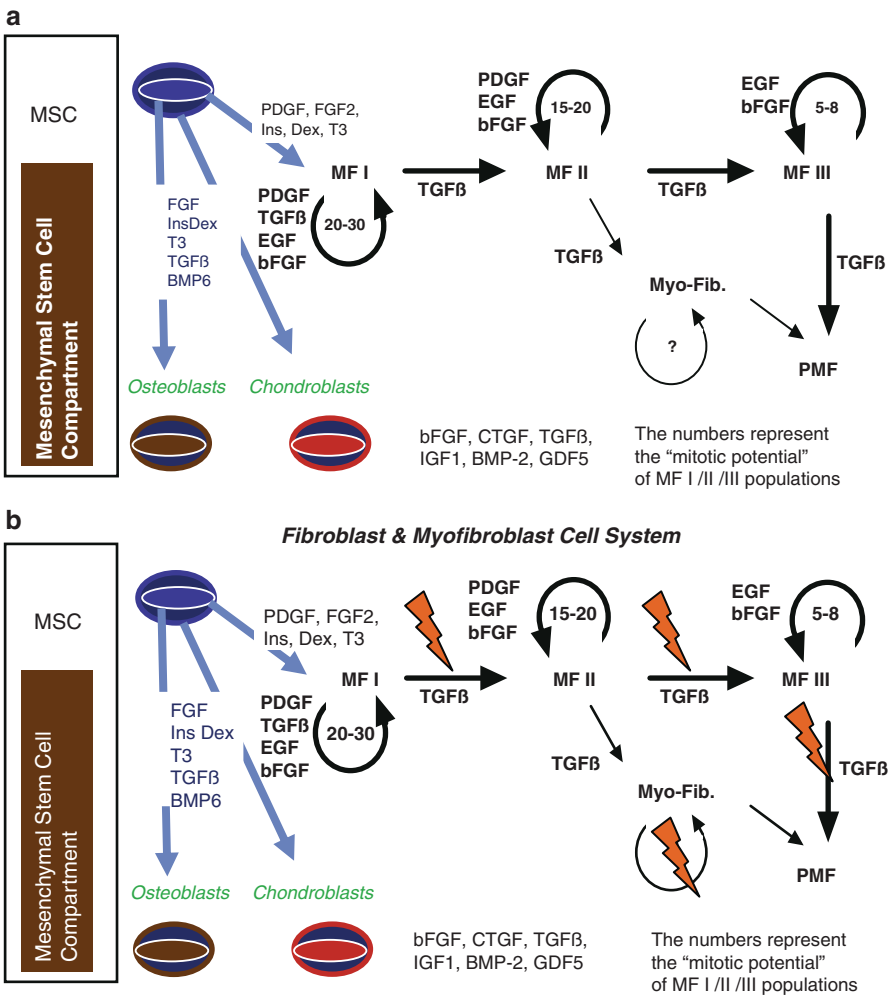

Fig. 44.2 (**a**) Pathomechanism of hyperproliferation in the soft tissue. Fibroblasts like osteoblasts and chondroblasts derive from the unique Mesenchymal Stem Cell Compartment (*MSC*). The proliferation and differentiation of the Fibroblast Cell System (*FCS*) is regulated by multiple growth factors and cytokines including the Platelet-Derived Growth Factor (*PDGF*), the basic Fibroblast Growth Factor (*bFGF*), the Epidermal Growth Factor (*EGF*), and the Tissue Growth Factor *β* (*TGF β*). The PDGF, bFGF, and EGF all act as mitogenetic stimulus for the myofibroblast generations *MF I-*, *MF II-*, and *MF-III*-Fibroblasts derived from the precursor compartment MSC; while PDGF is only weakly mitogenetic for MF-III-Fibroblasts, *TGFβ* induces a rapid mitosis and differentiation of the MF-I-Fibroblasts and their further differentiation into MF-II- and MF-III-Fibroblasts. Simultaneously, *TGFβ* has a leading role for the induction of myofibroblasts and the activation of the collagen synthesis. As seen in the graphic, *TGFβ* supports the shortcut from the proliferative MF II-Fibroblasts to the postmytotic myofibroblasts (*PMF*) via myofibroblasts (*MF*) in an unknown quantity. (**b**) Radiogenic targets to affect the soft tissue hyperproliferation in DD. Ionizing radiation (*RT*) interacts with all generations of myofibroblasts (*MF I, MF II and MF III*) through the Tissue Growth Factor ß (*TGFβ*) leading to a termination of the proliferation and increased transfer into the inactive and postmitotic myofibrocyte population (*PMF*)

44.2 Patients, Materials, and Methods

44.2.1 Patient Characteristics

From January 1997 to December 2009, 624 patients with clinically evident and progressive early stage DD were referred to our clinic for RT or further counseling by orthopedists, surgeons, and family physicians. As of January 2011, a total of 489 patients (198 females; 291 males) had reached a minimum follow-up (FU) of at least 5 years and therefore have been included in our study and were analyzed. The overall mean age was 61.6 ± 10 (median 61, range 29–81) years. Females were older (mean 63.2 ± 9) than males (60.6 ± 11 years). After clinical examination, extensive counseling about the different treatment options including a "wait and see" strategy, 83 patients decided not to receive prophylactic RT for personal or other reasons and served as control group without RT in long-term follow-up. The other 406 patients, who decided to undergo RT were randomized between two different RT concepts: 199 patients received 21 Gy (7 × 3 Gy) ("low-dose RT") total dose, while 207 patients received 30 Gy (10 × 3 Gy) ("high-dose RT") total dose. All patients completed the prescribed RT protocol and all FU evaluations at 3 and 12 months and at last FU after RT in December 2010.

44.2.2 Site Characteristics

A total of 258 (53%) patients presented with unilateral DD, while 230 (47%) had bilateral DD, which resulted in a total of 718 hands (sites) included in this study. A positive family record in the first generation (parents and siblings) was found in 142 (28.5%) patients for DD, in 66 (13.5%) patients for LD, and in 21 (4%) patients for other DD-related conditions such as Garrod's disease (GD) and frozen shoulder syndrome. The time period from first recognition of typical DD symptoms until presentation at our clinic and onset of treatment was 24 ± 12 (range: 62–163) months.

44.2.3 Disease Predisposition

By using a structured questionnaire (Appendix) and careful interview, the following predisposing factors for DD were identified in the patients' record: A *positive family history* was found in 165 (34%) patients (92 of 198 (46%) females, 73 of 291 (25%) males); *Morbus Ledderhose* of the plantar fascia was found in 92 (19%) patients (51 females; 41 males); *Garrod's disease (knuckle pads)* was observed in 13 (3%) patients (7 females; 6 males); a *history of keloids/hypertrophic scar* after trauma or surgery was reported by 19 (4%) patients (11 females; 8 males); a *trauma* of the upper extremity and hand was documented in 39 (8%) patients (14 females; 25 males); *diabetes mellitus* was actually present in 36 (7%) patients (16 females; 20 males); an *epileptic disorder* was reported by 10 (2%) patients (3 females; 7 males); *liver disease/cirrhosis* in 28 (6%) was known in 28 (6%) patients (9 females; 19 males); the regular use of *nicotine* was stated by 22% patients (43 females; 65 males); regular *alcohol consumption* was reported by 62 (13%) patients (24 females; 38 males); combined use of regular alcohol and nicotine intake was stated by 47 (10%) of all patients, but these later figures regarding alcohol have to be taken with some uncertainty.

44.2.4 Pretreatment

One hundred and thirty-two (27%) patients underwent one or more of the following treatments prior to the use of RT: surgical procedures including local excisions and partial fasciectomy in 65 (13%) patients, topical use of steroids (injections) in 36 (7%), systemic NSAID in 28 (6%), vitamin E in 45 (9%) or other drugs in 14 (3%) patients, and other unspecified therapeutic measures in 16 (3%) patients.

44.2.5 Stage of Disease

Staging was conducted according to Tubiana et al. (1966), which is based on the measurable total flexion deformity of palm and involved MP/PIP/DIP finger joints (Table 44.1). As *stage I* comprises a very large range of function loss (1–45°) allowing no differentiation between initial and later changes, an *intermediate stage N/I* was defined for angle deficits of 1–10° (Keilholz et al. 1996, 1997). According to this modified classification, stage N occurred in 470 (65.5%) sites, stage N/I in 124 (17%), stage I in 106 (15%), and stage II in 18 (2.5%) sites. According to the patient's record, all involved sites had experienced progressive symptoms at least within the last 6–12 months before RT.

44.2.6 Objective Signs

The dimensions and consistency of nodules, cords, skin changes, and finger mobility were assessed by clinical inspection, palpation, and measurements with a linear ruler. All findings were drawn onto the skin and photographed or photocopied (Herbst and Regler 1986; Keilholz et al. 1996). An example is given in Fig. 44.3.

A total of 2,849 nodules were diagnosed in almost all patients and sites, i.e., 712 (99%) hands exposed a mean number of 4 nodules and a mean size of 1.1 cm in diameter for the respective largest nodule. In addition, 866 cords were diagnosed in 360 (50%) hands with a mean number of 2.4 and a mean length of 2.0 cm. Typical skin retractions or pits were found in 251 (31%) sites. An extension of the DD from the palmar region into the fingers (digital involvement) was found in 233 (32%) hands; an objective angle deficit was measured in 248 (34.5%) hands. The overall mean angle deficit of the most involved digit was 17.3°.

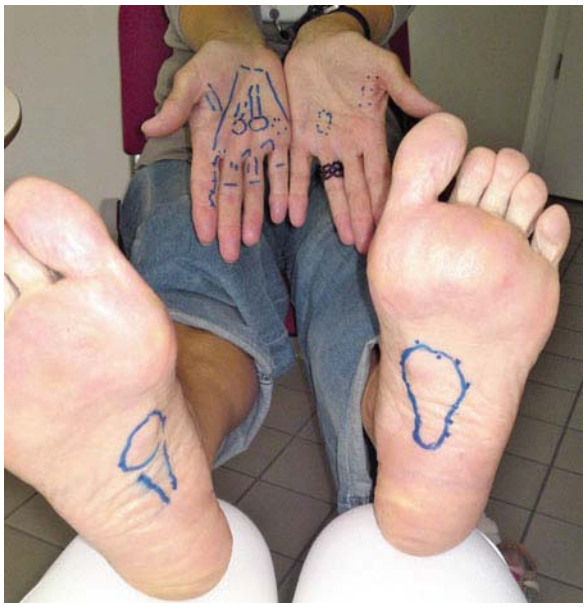

Fig. 44.3 A 49-year old female with typical distribution of nodes and cords in the right hand and two large nodes in both feet (combined Dupuytren and Ledderhose's disease). Stage N Dupuytren's disease in the right-hand palm plus early signs in the left-hand palm; stage I Ledderhose's disease in the right and stage II Ledderhose's in the left foot sole

44.2.7 Subjective Symptoms

The following subjective symptoms were reported prior to the onset of RT: Patients complained about *pressure* in the palm in 75 (10%) sites, *tension* in the palm or in the fingers in 140 (19.5%) sites, *pain sensation* in 29 (4%) sites, and *burning or itching sensations* in 45 (6%) sites. Regarding hand dysfunction in daily life, 152 (21%) sites were affected, and 89 (12%) sites were affected for special functions during profession (e.g., musician, crafts work, etc.) or sports activities. Patients scored their symptoms on a 10-scale linear analogue scale (LAS). Overall, the symptom score for all patients at the time of first presentation and before onset of any treatment was 3.1 ± 1.7.

44.2.8 Radiotherapy

Local RT was applied depending on the individual grade and extent of DD. It was common policy in our clinic to treat the whole afflicted area of the palm including all palpable and visible nodes and cords with sufficient distal and proximal (1–2 cm) and lateral margins (1 cm) (Fig. 44.4). An orthovoltage unit[1] was used with 120 kV X-rays (20 mAs/2 mm Al filter) and two cones of 6 × 8 cm and 10 × 12 cm with a source to skin distance (SSD) of 40 cm. All uninvolved areas of the palm and digits were individually shielded using 3-mm-thick lead rubber plates (Fig. 44.5). In addition, all other recommended radiation protection measures (appropriate beam direction, patient positioning, use of lead apron, etc.) were applied to minimize radiation exposure to the patient.

44.2.9 Randomization

After full informed consent about the typical disease progression and all possible treatment options including RT, patients could decide between observation only and radiotherapy:

(a) *Eighty-three patients* (166 hands) decided to be observed and were regarded as "control group" (group A).

Those who decided to be treated were randomized to receive one of the following two RT schedules:

(b) *One hundred and ninety-nine patients* (293 hands) received 7 fractions of 3 Gy every other day (total dose: 21 Gy) in *one RT series* (total treatment time: 15 days or 2 weeks) (group B).

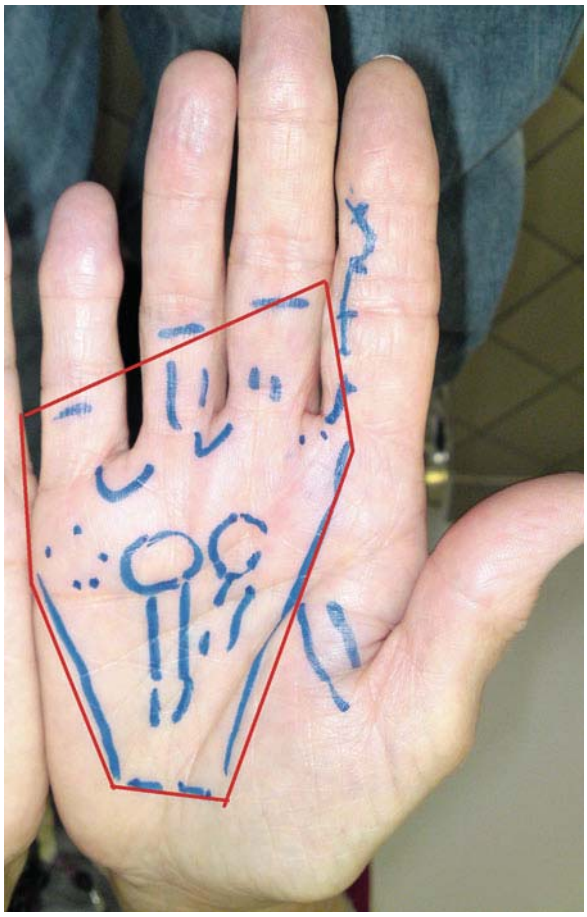

Fig. 44.4 A 49-nine year-old-female with DD and palmar and digital involvement in stage N. Nodules are marked as *circles*, cords with *double-lines*; scar between DIP and PIP joint of D2 from a previous operation; red outline of the RT portal with a 1–2 cm margin around the palpable lesions which extend from the lower palm into the digits D3–D5

(c) *Two hundred and seven patients* (404 hands) received a total of 10 fractions of 3 Gy (total dose: 30 Gy) in 2 *series* of each 5×3 Gy in 1 week separated by 10–12 weeks (total treatment time: 12–16 weeks) (group C).

Most of the relevant patient and site characteristics were equally distributed between control and RT and between both RT groups (Tables 44.2 and 44.3). Minor differences were only observed between males and females; recurrent disease and DD stage II–IV disease was slightly more frequent in the control group (each 9%) as compared to the RT groups. All other differences were not statistically significant between the three groups.

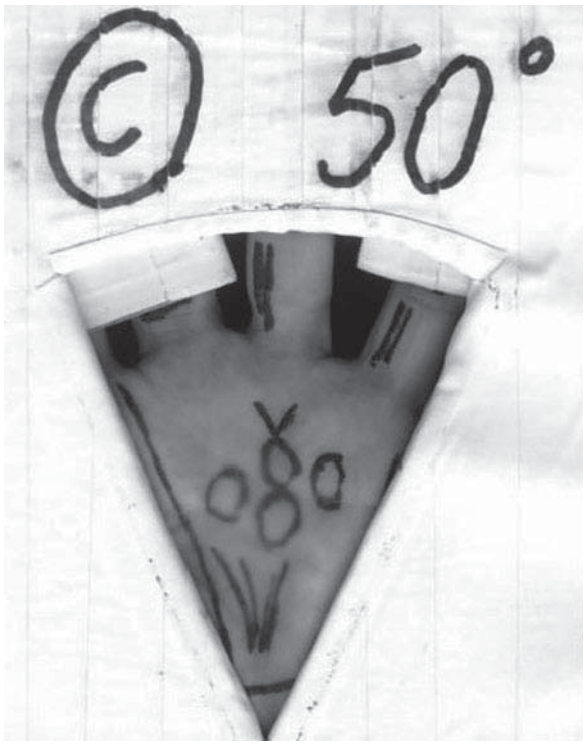

Fig. 44.5 Individual shielding of uninvolved areas by 3-mm-thick lead rubber plate

44.2.10 Evaluation and Statistics

All patients in this study completed at least 5 years follow-up (FU). Mean FU was 102 months and median FU 104 months. The clinical evaluation (treatment side effect and efficacy) was performed at 3 and 12 months and at last follow-up (FU) after RT. Final evaluation was in December 2010. Acute and chronic radiogenic toxicity was scored according to the Common Toxicity Criteria (CTC) (Trotti et al. 2000, 2003) and the Late Effects Normal Tissue (LENT) criteria (Pavy et al. 1995; Rubin et al. 1995; Seegenschmiedt 1998), each with 4 grades of severity. The *primary endpoints* of the study were *objective clinical signs of progression* and *necessity of surgery* or *salvage surgery*. Secondary endpoints were treatment of side effects and specific objective disease parameters (number and size of nodules, cords, flexion deformity of the palm, extension deficit of fingers) and subjective criteria (symptoms and function) and patient's subjective satisfaction using the 10-scale LAS.

The statistical analysis was performed with the software program SPSS (Chicago, IL). For categorical

Table 44.2 Patient characteristics

	A: control	B: RT 21 Gy	C: RT 30 Gy	All
Patients	83	199	207	489
– Females	34 (41%)	83 (42%)	81 (39%)	198 (40%)
– Males	49 (59%)	116 (58%)	126 (61%)	291 (60%)
Age (years) @ 1st Exam				
– Mean	61.3 + 11	62.1 + 13	62.6 + 9	61.6 + 10
– Median	61	63	62	62
– Range	29–74	34–79	33–81	29–81
Affected hands	122 (73%)	293 (74%)	303 (73%)	718 (73%)
# Hands (# pts × 2)	166	398	414	978
– Uninvolved	44 (27%)	105 (26%)	109 (26%)	258 (26%)
– Unilateral	44	105	109	258
– Bilateral	39	94	97	230
Positive family record (first degree)				
– Dupuytren's disease	27 (31%)	56 (28%)	59 (28.5%)	142 (28.5%)
– Ledderhose's disease	13 (16%)	27 (13.5%)	26 (12.5%)	66 (13.5%)
– Others (GD, FS etc.)	3 (3%)	8 (4%)	10 (5%)	21 (4%)
Comorbidity				
– Ledderhose's disease	17 (20.5%)	38 (19%)	37 (18%)	92 (19%)
– Garrod's disease (GD)	3 (4%)	6 (3%)	4 (2%)	13 (3%)
– Peyronie's disease (M)	3 (6%)	5 (4%)	4 (3%)	12 (3%)
– Frozen shoulder (FS)	6 (7%)	9 (4.5%)	8 (4%)	23 (5%)
– Keloid/Hypertr. Scar	4 (5%)	8 (4%)	7 (3%)	19 (4%)
– Any "Hand Trauma"	9 (11%)	14 (7%)	16 (8%)	39 (8%)
– Diabetes mellitus	7 (8%)	14 (7%)	15 (7%)	36 (7%)
– Any liver disease	5 (6%)	11 (5.5%)	12 (6%)	28 (6%)
– Epileptic disorder	2 (2%)	4 (2%)	4 (1.5%)	10 (2%)
Risk factors				
– Nicotine abuse (NA)	18 (22%)	46 (23%)	44 (21%)	108 (22%)
– Alcohol abuse (AA)	13 (16%)	26 (13%)	23 (11%)	62 (13%)
– Combined NA + AA	10 (12%)	19 (10%)	18 (9%)	47 (10%)
First symptoms (months) before RT				
– Mean	26 ± 12	23 ± 11	24 ± 13	24 ± 12
– Median	22	21	21	21
– Range	6–240	12–264	9–248	6–264
Follow-up (months)				
– Minimum	60	61	62	61
– Mean	102 ± 18	103 ± 19	102 ± 21	102 ± 20
– Median	104	105	104	104
– Range	60–160	61–162	62–163	62–163

DD Dupuytren's disease, *LD* Ledderhose's disease, *GD* Garrod's disease (knuckle pads), *FS* frozen shoulder, *NA* nicotine abuse, *AA* alcohol abuse

None of the above parameters were statistically significantly different between the treatment groups ($p < 0.05$)

Table 44.3 Treatment site characteristics

	A: control	B: RT 21 Gy	C: RT 30 Gy	All
Patients (Table 44.1)	83	199	207	489
Overall # hands	166	398	414	978
Affected hands	122 (73%)	293 (74%)	303 (73%)	718 (73%)
– Uninvolved	44 (27%)	105 (26%)	109 (27%)	258 (27%)
– Right hand (RH)	(23)	(54)	(52)	129
– Left hand (LH)	(21)	(51)	(57)	129
– Bilateral (RH+LH)	39 (47%)	94 (47%)	97 (47%)	230 (47%)
– Primary disease	113 (91%)	290 (99%)	299 (99%)	702 (98%)
– Recurrent (post Sx)	9 (9%)	3 (1%)	4 (1%)	16 (2%)
Nodes				
– Present (yes)	120 (98%)	291 (99%)	301 (99%)	712 (99%)
– Mean #	4.0 ± 2.3	4.1 ± 2.4	3.8 ± 2.0	4.0 ± 2.4
– Mean size (cm²)	1.0 ± 0.8	1.1 ± 0.9	1.2 ± 0.8	1.1 ± 0.9
Cords				
– Present (yes)	59 (48%)	146 (50%)	155 (51%)	360 (50%)
– Mean #	2.1 ± 1.3	2.4 ± 1.5	2.4 ± 1.5	2.4 ± 1.5
– Mean length (cm)	1.8 ± 1.2	2.1 ± 1.3	1.9 ± 1.1	2.0 ± 1.2
Pits				
– Present (yes)	46 (38%)	102 (35%)	103 (34%)	251 (35%)
Classification				
– Stage N	76 (62%)	195 (67%)	199 (66%)	470 (65,5%)
– Stage N/I	21 (21%)	50 (17%)	53 (17%)	124 (17%)
– Stage I	16 (16%)	43 (14,5%)	47 (16%)	106 (15%)
– Stage II–IV*	9 (9%)	5 (2%)	4 (1%)	18 (2.5%)
Clinical symptoms				
Digital involvement	41 (34%)	92 (31%)	100 (33%)	233 (32%)
Extension deficit	46 (38%)	98 (33%)	104 (34%)	248 (34.5%)
Mean deficit (°)*	26.6 ± 14.3	19.2 ± 6.9	15.0 ± 5.9	17.3 ± 9.1
– Pressure	14 (11.5%)	30 (10%)	31 (10%)	75 (10%)
– Tension	23 (19%)	56 (19%)	61 (20%)	140 (19.5%)
– Pain	6 (5%)	11 (4%)	12 (4%)	29 (4%)
– Itching & Other S.	8 (6.5%)	16 (5.5%)	21 (7%)	45 (6%)
Symptom score	3.3 ± 1.8	3.1 ± 1.6	3.0 ± 1.5	3.1 ± 1.7
Functional impairment				
– Any dysfunction	29 (24%)	62 (23%)	61 (20%)	152 (21%)
– Special functions (sports, hobbies)	18 (15%)	36 (12%)	35 (11.5%)	89 (12%)

DD Dupuytren's disease, *LD* Ledderhose's disease, *GD* Garrod's disease (knuckle pads), *FS* frozen shoulder, *NA* nicotine abuse, *AA* alcohol abuse, *n.a* not available
*$p < 0.05$

variable numbers and percentage values and for continuous variable median, mean and range values were calculated. Statistical testing for independence of categorical and continuous variables between different groups, time points, and study endpoints included the Student-t, the Cochran-Mantel-Haenszel, and the Wilcoxon test. Univariate and multivariate analyses were performed using the logistic regression analysis. P-values lower than 0.05 were defined as statistical significant for two-sided tests.

44.3 Results

44.3.1 Treatment Compliance

A total of 2 (1%) patients in group B (21 Gy total dose) received only 15 Gy, and 7 (3%) patients in group C (30 Gy total dose) did not receive the second RT series after completion of the first series (15 Gy) for various reasons. All patients were followed and evaluated according to the "intention-to-treat" concept in their specific treatment groups.

44.3.2 Treatment Toxicity

Acute toxicity within 6 weeks after RT was observed in 166 of 596 (28%) irradiated sites, in 151 (25%) cases presenting as redness or dryness of the skin (CTC grade 1), and in only 16 (2%) cases as an extensive erythema, moist desquamation, or with pronounced local swelling (CTC 2°). Most of these reactions were limited to the RT portal. Acute toxicity occurred more often and intensively after 7 fractions of 3 Gy (group B) than after each of the two RT series with each 5 fractions of 3 Gy (group C) (93/293 = 32% versus 74/303 = 24%, $p = 0.046$).

Chronic side effects at last FU occurred in 83 (14%) sites, either as *dryness*, *increased desquamation*, or *mild skin atrophy* accompanied by *slight subcutaneous fibrosis* which required occasionally to daily use moist ointments (LENT grade 1); in a few sites, alteration of heat and pain sensation occurred. In addition, the incidence of late effects was higher in the 21 Gy group (48 of 293 = 16%) as compared to the 30 Gy group (35 of 303 = 11.5%) ($p = 0.088$, n.s.), with a statistical trend in favor of the 30 Gy group.

44.3.3 Primary Study Endpoints

At last FU, an overall *DD stage progression* was observed in 176 of 718 (24.5%) sites. The differences in the DD stage progression between the control group with 63 of 122 hands progressing (52%) and the 21 Gy group with 64 of 293 hands (22%) ($p < 0.001$) and the 30 Gy group with 49 of 303 (16%) progressing ($p < 0.001$) were highly significant; however, the difference between the two RT groups showed only a statistical trend ($p = 0.077$). When *all clinical signs of progression* were included in the analysis, the progression rate of the control group was 76 of 122 (62%) versus 71 of 293 (24%) in the 21 Gy group and 59 of 303 (19.5%) in the 30 Gy group ($p < 0.001$); again, the difference between the RT groups was not statistically significant but with a statistical trend in favor of the 30 Gy group ($p = 0.106$). Similarly, when considering the number of sites which required surgery due to ongoing progression of the disease, the differences between the control group (37 of 122 = 30%) and the 21 Gy group (35 of 293 = 12%) and the 30 Gy group (25 of 303 = 8%) were highly statistically significant ($p < 0.001$), while the differences between the RT groups were not significant ($p = 0.134$).

44.3.4 Secondary Study Endpoints

Similar, several other details in treatment outcome showed a clear advantage of the two RT groups (21 and 30 Gy) versus the control group:

(a) The mean *number of nodes per site* increased in the control group (plus 1.2–5.2 nodes), while it was reduced in the 21 Gy (–0.4 to 3.7 nodes) and 30 Gy group (–0.6 to 3.6 nodes) (both $p < 0.001$).
(b) The mean *number of cords per site* increased in the control group (plus 1.1–3.2 cords), while it was reduced in the 21 Gy (– 0.4 to 2.0 cords) and 30 Gy group (–0.3 to 2.1 cords) (both $p < 0.001$).
(c) The *digital involvement* at last FU increased in the control group in 37 of 122 (30%) sites as compared to the 21 Gy group with 16 of 293 (5.5%) and the 30 Gy group with 9 of 303 (3%) (both $p < 0.001$).
(d) The *extension deficit* at last FU increased in the control group in 43 of 122 (35%) sites as compared to the 21 Gy group with 21 of 293 (7%) and the 30 Gy group with 13 of 303 (4%) (both $p < 0.001$).

(e) The *mean angle of the extension deficit* at last FU increased in the control group by an average of 13.2° as compared to 2.2° (21 Gy group) and 0.9° (30 Gy group) (both $p<0.05$).
(f) The *mean symptom score* at last FU increased in the control group by an average of 1.4–4.7 points as compared to a reduction of 0.5 points to 2.6 points in the 21 Gy group and of 0.7 points to 2.3 points in the 30 Gy group (both $p<0.05$). Symptom relief occurred in 4 of 51 (8%) affected sites in the control group as compared to 24 of 113 (21%) in the 21 Gy group and 32 of 125 (26%) in the 30 Gy group (both $p<0.001$).
(g) The *overall satisfaction with the disease status* at last FU was 12 of 122 (10%) in the control group and 141 of 293 (48%) in the 21 Gy group and 155 of 303 (51%) in the 30 Gy group (both $p<0.001$).

44.3.5 Overall Relapse/Progression

At last FU 63 of 122 sites in the control group revealed disease progression in the "potential RT portal," i.e., within an initially suggested RT area. In contrast, progression or relapse within an irradiated area was only present in 28 of 293 (9.5%) sites of the 21 Gy groups and in 22 of 303 (7%) sites of the 30 Gy group (both $p<0.001$). However, additional progression outside the irradiated area occurred in 63 of 293 (21.5%) hands of the 21 Gy group and in 51 of 303 (17%) hands of the 30 Gy group. This indicates, that sometimes RT portals may have been chosen too small, or ongoing trigger mechanisms have initiated further disease in untreated areas as compared to treated areas. Salvage treatments included surgery (as mentioned above) and salvage RT in 24 of 122 (20%) of the control group and in 16 of 293 (5.5%) hands in the 21 Gy group and in 18 of 303 (6%) hands in the 30 Gy group (both $p<0.001$).

44.3.6 Prognostic Parameters

Differences in treatment outcome were analyzed for the two endpoints "progression of disease" and "surgery required" at last FU. As already shown, the use of RT treatment with either 21 Gy or 30 Gy was far superior to avoid disease progression than with observation only, while the differences between the two RT groups were not significant but revealed a statistical trend in favor of the 30 Gy group over the 21 Gy group with regard to DD stage progression ($p=0.077$) and overall signs of progression ($p=0.106$).

Several *patient-related parameters* were analyzed: With regard to *gender*, 68 of 198 (34%) females and 108 of 291 (37%) males experienced progression (n.s.); with regard to *age*, 85 of 263 (32%) patients older than 60 years had progression as compared to 91 of 225 (40%) patients younger than 60 years. Regarding the *use of nicotine*, 49 of 108 (45%) smokers experienced progression as compared to 129 of 381 (33%) non-smokers ($p=0.028$); regarding the *use of alcohol*, 29 of 62 (47%) patients with regular alcohol intake experienced progression as compared to 147 of 427 (34%) abstinent patients ($p=0.028$).

Patients with a longer *symptom duration* prior to RT had a higher rate of progression than those with a shorter interval. Using a cutoff value of 24 months, 98 of 231 (42%) with longer duration of symptoms developed progression as compared to 78 of 258 (30%) with shorter duration.

The *DD stage prior to RT* was the most important prognostic factor for treatment outcome independent from the treatment group. Forty-seven of 470 (10%) sites with stage N, 51 of 124 (41%) sites with stage N/I, 62 of 106 (58%) sites with stage I, and 16 of 18 (89%) sites with stages II, III, and IV progressed in long-term FU. In summary, patients with a higher DD stage developed higher progression rates ($p<0.0001$) (Table 44.4).

The relevant prognostic parameters from the univariate analysis were also used for the final multivariate analysis using a logistic regression process. Table 44.5 summarizes the result: Only symptom duration >24 months, advanced stage of disease (N versus N/I and more), digital involvement, and the use of RT were statistically significant parameters; use of smoking showed a statistical trend. In addition, the difference between the two dose groups showed a statistical trend in favor of the 30 Gy group.

44.4 Discussion

This clinical study is the first to document the long-term outcome of untreated DD versus DD treated with RT applied in two different dose levels. The distribution

Table 44.4 Stage of DD prior to RT and DD stage progression at last FU

	A: control	B: RT 21 Gy	C: RT 30 Gy	All
Progression	$n=122$	$n=293$	$N=303$	$N=718$
DD stage				
Stage N	26 of 76 (34%)	14 of 195 (7%)	7 of 199 (3.5%)	47 of 470 (10%)
Stage N/I	14 of 21 (67%)	21 of 50 (42%)	16 of 53 (30%)	51 of 124 (41%)
Stage I	14 of 16 (87.5%)	25 of 43 (58%)	23 of 47 (49%)	62 of 106 (58%)
Stage II–IV	9 of 9 (100%)	4 of 5 (80%)	3 of 4 (75%)	16 of 18 (89%)
DD stage progression	63 of 122 (52%)	64 of 293 (22%)	49 of 303 (16%)	176 of 718 (24,5%)

Statistical analysis with 8 degrees of freedom: $p<0.0001$

Table 44.5 Prognostic parameters for disease progression in multivariate analysis

Parameter	Partition (favorable first)	*p*-value	Odds ratio
Patient			
Gender	Female vs. male	= 0.26, n.s.	1.29
Age	≥60 vs. <60 years	= 0.18, n.s.	1.43
Smoking	Non-smoking vs. smoking	= 0.08	1.58
Alcohol	Non-alcohol vs. alcohol	= 0.12, n.s.	1.36
Disease			
Symptom duration	<24 vs. ≥24 months	= 0.007	1.86
Stage of disease	Stage N vs. N/I–IV	<0.001	3.41
Extension deficit	0–5° vs. >6° to >90°	<0.001	2.67
Digital involvement	No involvement vs. involvement	<0.01	1.78
Treatment			
RT vs. No RT	RT (21 & 30) vs. control	<0.0001	6.32
RT dose	RT 21 vs. 30 Gy	=0.08	1.61

of all relevant data regarding the patient and site-specific characteristics enable a direct comparison of outcomes. Thus, it is necessary to understand the basic rationale for the use of ionizing radiation in the early stages of DD, as only the early stages of DD seem to be most responsive to the use of ionizing radiation.

44.4.1 Rationale of Radiotherapy

Early stages of DD are characterized by *proliferation of fibrous tissue* in the form of nodules or cords; they have several features in common with benign neoplastic fibromatosis (McFarlane et al. 1990; Luck 1959). The evolution of DD acts similar to the *wound healing* through contraction and maturation of fibrous tissue (Rodemann and Bamberg 1995; Mutsaers et al. 1997). The fibro-fatty tissue between the skin and palmar aponeurosis is regarded as primary site of disease onset. The abnormal fibrous tissue develops around ligamentous cords that have a predominantly longitudinal orientation and follow the tension lines of the palm. *Pathological forces* and *mechanical stress* play an important role in the pathogenesis and development of DD (Flint 1990a). From a radiobiological view, the *proliferation process* is the most important component of DD. It is driven by *immature fibroblast and myofibroblasts* (Gabbiani et al. 1971; Rudolph and Vande Berg 1991), which produce the extracellular matrix consisting of fibronectin, laminin, collagen type IV, and tenascin (Berndt et al. 1994). Myofibroblast phenotypes and growth factor gene synthesis are present in active proliferating nodules of DD (Berndt et al. 1994). Similar to the wound healing process in DD, increased *growth factor* levels are found including the messenger-RNA for interleukin-1, basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-beta), platelet-derived growth factor (PDGF) (Terek et al. 1995; Tomasek and Rayan 1995; Kampinga et al. 2004), epidermal growth factor (EGF), and connective tissue growth factor (CTGF) which stimulate the fibroblast proliferation (Baird et al. 1993; Brenner et al. 1996; Igarashi et al. 1996).

It has been suggested that in DD, local ischemia is induced by microvessel narrowing, which produce free radicals and damage the surrounding stroma and stimulate perivascular fibroblast proliferation; repeated pericyte damage, fibroblast proliferation, and collagen deposition further enhance microvessel ischemia, thereby self-propagating the pathogenetic process (Gabbiani et al. 1971; Kischer and Speer 1986; Murrell et al. 1989, 1990). However, so far there is not a clear concept of what really initiates the pathological proliferation in DD: a *traumatic process*, i.e., rupture of fascial fibers (Skoog 1948; Flint 1990b; Rodemann and Bamberg 1995) or an *inflammatory process* with adhesions between ligamentous structures (Andrew et al. 1991; McGrouther 1982). In the latter situation, additional radiosensitive targets are available.

In summary, the pathogenesis of DD provides a good rationale for using ionizing radiation in early DD stages: (a) *Proliferating fibroblasts and myofibroblasts* are radiosensitive target cells; (b) the radiogenic induction of free radicals damages fibroblasts, impairs their proliferative activity, and thereby may reduce cell density (Murrell and Francis 1994); (c) RT interferes with the over-expressed growth factors, especially PDGF and TGF beta (Terek et al. 1995; Tomasek and Rayan 1995; Rayan et al. 1996; Kampinga et al. 2004); (d) *activated monocytes and macrophages* are very radiosensitive target cells which interact with the inflammatory and reparative processes and the onset and extent of myofibroblast proliferation (Rubin et al. 1999). In the past, similar pathogenetic pathways and radiosensitive target cells have been identified for the prophylactic effects of intravascular RT to inhibit arterial restenosis (Crocker 1999; Tripuraneni et al. 1999) or for use of external beam RT to avoid relapses after resection of keloids (Suit and Spiro 1999) or pterygium of the eye (Smitt and Donaldson 1999) or to influence progression Morbus Ledderhose (Seegenschmiedt & Attassi, 2003) and in Peyronie's disease (Incrocci et al. 2008). Moreover, in the radiotherapy community the awareness and skills about the use of RT for benign conditions has clearly increased over the past decade (Leer et al. 2007).

44.4.2 Clinical Results of Radiotherapy

Besides our present study, the efficacy of local RT to impact on the early stages of DD has been shown in many clinical trials since the early 1950s of the last century (Finney 1955; Wasserburger 1956; Lukacs et al. 1978; Vogt and Hochschau 1980; Hesselkamp et al. 1981; Haase 1982; Köhler 1984; Herbst and Regler 1986; Keilholz et al. 1996, 1997) (Table 44.6). However, the first clinical studies were limited by short FU: Lukacs et al. (1978) observed "no disease progression" in 36 sites at 1 year. Hesselkamp et al. (1981) reached "improved or stable conditions" for over 2 years in 93% of 46 sites. Vogt and Hochschau (1980) found 94% of 109 irradiated sites "stable" or "improved" after more than 3 years. Köhler (1984) reported 82% of 33 sites "improved or stable," and 6 "progressed" after 3 years. Herbst and Regler (1986) observed all 45 sites "stable or improved" after a median of 1.5 years.

It was the group in Erlangen (Germany) which reported the first 5-year results which could be compared with the reported outcome in published surgical series: Keilholz et al. (1996, 1997) found 72% of 142 sites with "regression of nodules and cords" at last FU; of 57 sites with a minimum FU of 5 years, only 5 (9%) sites progressed outside and 8 (14%) inside the RT portal; thus the overall local control was 77%. Adamietz et al. (2001) conducted an extended analysis of the same study population, but with a longer median FU of 10 years, and confirmed the results from the pilot study. They also identified a DD stage-dependent response pattern, with better outcome in early DD stages as compared to more advanced DD stages: In stage N 84% and stage N/I 67% of cases remained stable, while 65% of stage I and 83% in stage II had progressive nodules and cords. In case of DD progression, no complications occurred after a further RT series or after salvage surgery. Recently, Betz et al. (2010) increased the median FU of the same study population to 13 years and confirmed the stage-dependent outcome which corresponds well with the stage-dependent outcome in our own study.

Ten years ago, our pilot study (Seegenschmiedt et al. 2001) was the first to analyze the impact of different RT dose regimens on treatment outcome. In the actual update of this study, the long-term analysis, not only a DD stage-dependent response pattern can be confirmed but also a superiority of RT versus observation only. All together, our clinical data demonstrate and confirm that the observed progression rate in early DD stages is much lower after irradiation than the expected 50% progression rate within 5 years for untreated patients or for patients who have to undergo

Table 44.6 Clinical results of radiotherapy for Dupuytren's contracture (literature review)

Study (year)	Patients (sites) (Stage)	(*N*)	RT concept Fractioning	RT dose	Follow-up *N* (%)	Clinical outcome [*N* (%)] *"Regression"*	*"No change"*	*"Progression"*
Finney (1955)	43	NA	1–3 × RT Ra-Moulage	1–3.000 r	FU: NA 25 (58%) sites	15/25 (60%) "Good functional result"		
Wasserburger (1956)	213	NA	1–3 × RT Ra-Moulage	1–3.000 r	"Long–term" 146 (69%) pts	"Long-term cure" stage I: 62 of 69 (90%); Stage II: 26 of 46 (57%); stage III: 10 of 31 (32%)		
Lukacs et al. (1978)	106	(I: 140) (II: 18)	RT day 1 + 2 4 series á 2 mos	4 Gy SD 32 Gy TD	FU: NA 36 (23%) sites	I: 26 of 32 (81%) II: 3 of 4 (75%)	I: 6 of 32 (19%)	None
Vogt and Hochschau (1980)	(I: 98) (II: 4) (III: 7)	(154)	RT day 1 + 2 5 series á 2 mos	4 Gy SD 32 Gy TD	FU > 3 years 109 (63%) pts	I: 21 of 98 (21%) II: 1 of 4 (25%) III: --	I: 73 of 98 (74%) II: 2 of 4 (50%) III: 6 of 7 (86%)	I: 4 of 98 (4%) II: 1 of 4 (25%) III: 1 of 5 (20%)
Hesselkamp et al. (1981)	46	(65)	RT day 1 + 2 5 series á 3 mos	4 Gy SD 40 Gy TD	FU 1–9 years 46 (53%) pts	Total: 24 (52%)	Total: 19 (41%)	Total: 3 (7%);
Köhler (1984)	31	(38)	RT 3–5×/week 1 series	2 Gy SD 20 Gy TD	FU 1–3 years 33 (87%) sites	Total: 7 (21%)	Total: 20 (61%)	Total: 6 (18%)
Herbst et al. 1986	33	(46)	RT 5×/week 2 series á 1–3 mos	3 Gy SD <42 Gy TD	FU > 1,5 years 46 (100%) sites	None	Total: 45 (98%)	Total: 1 (2%)
Keilholz et al. (1997)	96 pts 142 hands	(N: 82) (N/I: 17) (I: 30) (II: 13)	RT 5×/week 6 weeks break 2 series á 2 mos	3 Gy SD 30 Gy TD	FU 1–12 years; median: 6 years	10(7%) improved @ 3 months,, 130 (92%) stable, 2 (1%) progressed Stages N: 99%, N/I: 88%, I: 77%, II–IV: 54% progression-free 13 (23%) progression inside (8 cases) or outside (5 cases) of RT field.		
Adamietz et al. (2001)	99 pts 176 hands	(N: 81) (N/I: 15) (I: 65) (II: 15)	Same RT concept	3 Gy SD 30 Gy TD	FU 7–18 years; median: 10 years	Stages N: 84%, N/I: 67%, I: 35%, II–IV: 17% remain progression-free		
Betz et al. (2010)	135 pts 208 hands	(N: 115) (N/I: 33) (I: 50) (II: 10)	Same RT concept	3 Gy SD 30 Gy TD	FU 2–25 years; median: 13 years	20 (10%) improved, 123 (59%) remained stable, 65 (31%) progressed Stages N 87%, N/I: 70%, I: 38%, II–IV: 14% progression-free		
Seegenschmiedt et al. (2001)	2 arms			3 Gy SD		Subjective/Objective	Subjective/ Objective	Subjective/Objective
	A: 63	(95)	RT 5×/week (×2)	30 Gy TD	FU > 1 year all (100%) pts	55 (56%) symptoms	35 (37%) symptoms	7 (7%) symptoms
	B: 66	(103)	RT 3×/week	21 Gy TD		55 (53%) symptoms	39 (38%) symptoms	9 (9%) symptoms

surgery in advanced DD stages (Millesi 1981). In the more advanced DD stages, stage I to stage IV, however, RT appears not to be as effective, which corresponds well with a relatively presence of proliferating fibroblast and myofibroblasts in these DD stages.

Moreover, our actual clinical study has been conducted in a controlled prospective design which overcomes the previous criticism of using only a retrospective analysis. Thus, our study is the first clear proof of a "therapeutic window" for RT in the early stage of DD. Although the differences between the two RT groups were not yet statistically significant, there is a statistical trend in favor of the higher RT dose of 30 Gy applied in a protracted regimen over 3 months as compared to the lower dose of 21 Gy applied over 2 weeks. With higher numbers for patients and sites, this difference in efficacy and probably less acute side-effects may become statistically significant. Nevertheless, multicenter clinical data are required to confirm these monocentric results.

44.4.3 Prognostic Factors

Köhler (1984) suggested a total dose of at least 20 Gy (10×2 Gy) to avoid DD progression, but his regimen was less successful than most other studies using higher total RT doses, such as 32–40 Gy (4 Gy single dose) (Vogt and Hochschau 1980; Hesselkamp et al. 1981). In the first clinical studies, single doses of 1,000r (corresponding to 10 Gy) every 3–6 months up to a total dose of 3,000r (30 Gy) had been successfully applied (Finney 1955; Finck 1955; Wasserburger 1956). The three clinical studies from Erlangen obtained good long-term outcome using 30 Gy total dose in two RT series of each 5×3 Gy. Our study confirms that a total dose of 30 Gy seems to be more effective than a lower dose of 21 Gy despite using the same single doses (3 Gy). Both dose- and time-dependent effects can be responsible for observed differences in long-term outcome. It is interesting to note that the 21 Gy group developed more acute side effects than the 30 Gy group, while the chronic side effects were similar in both groups.

Using an appropriate RT technique seems to be another important factor for treatment outcome: While some groups have recommended the "whole palm irradiation" (Köhler 1984; Hesselkamp et al. 1981), which is far more than we would recommend, others including ourselves have treated the diseased areas only but with sufficient safety margin (Vogt and Hochschau 1980; Keilholz et al. 1996, 1997). We usually apply an individual shielding of all uninvolved parts of the palm similar to the procedures proposed by Keilholz et al. (1996, 1997); however, this may allow DD progression outside the RT portal if the longitudinal and lateral extension of the disease have been underestimated. Thus, large safety margins of at least 1–2 cm around all visible and palpable lesions should avoid this problem. We do not apply total palm irradiation to avoid unnecessary side effects. We believe that out-field DD progression occurs not very often is then to a second RT series, as long as no major overlap with the primary RT portals exist; in contrast, in-field progression may require surgery. With regard to RT technique, there appears to be no difference between orthovoltage photons (120–150 kV) or linac electrons (3–6 MeV) as long as all nodes and cords are sufficiently covered; this may require a penetration depth of 5–15 mm down to the periosteum of the hand bones. The use of 120 kV/20mAs orthovoltage RT with a half-value layer of 33 mm is sufficient to reach this depth (Kaplan 1949; Finney 1955; Finck 1955; Dewing 1965). Historic RT studies have implemented the radium grip cylinder or radium molds (Wasserburger 1956; Dewing 1965). Nowadays, careful dosimetry and RT dose prescription according to the ICRU 50/62 and diligent RT application to all involved areas of DD are important requirements to achieve a favorable long-term outcome in DD and avoid possible relapses and unnecessary side effects.

44.4.4 Potential Side Effects of Radiotherapy

Ionizing radiation of 30 Gy induced only mild early or late radiogenic toxicity including minor effects like dryness of the skin; major fibrosis has been observed only in few patients, especially in previously operated sites. Simple skin care using moisture and greasy ointments is used to deal with these minor radiogenic sequelae. Late adverse side effects of grade 2 and more have never occurred in long-term FU. Our observations have been confirmed by others in long-term FU (Adamietz et al. 2001; Betz et al. 2010; Heyd et al. 2010). So single neoplasm was similar to the Erlangen study with long-term outcome

(Betz 2010) doses used for DD and LD are associated with a theoretical risk for induction of soft tissue sarcoma or skin cancer in the RT portals estimated to be in the range of 0.5–1% after latency periods of 8–30 years (Jansen et al. 2005; Trott and Kamprad 2006; Seegenschmiedt 2008), but only children and younger adults up to the age of 30 years may have an increased risk. Thus, critical indication after individual risk and benefit assessment and careful RT technique is required for this age group. However, at the present time, no single case of cancer induction has ever been reported after the use of RT for treatment of LD, DD, keloids, hypertrophic scars, or other benign hyperproliferative disorders.

44.4.5 Radiotherapy and Surgery

Among most hand surgeons, prophylactic RT is not only poorly known but also criticized for various reasons, e.g., long-term inefficacy (Finck 1955), surgery complications after application of RT (Falter et al. 1991; Weinzierl et al. 1993), or observed side effects (Falter et al. 1991). Although we doubt the latter observations as they lack controlled published data, we agree that advanced DD stage II–IV may not benefit from RT due to the loss of appropriate target cells, the actively proliferating fibroblast (Wasserburger 1956; Vogt and Hochschau 1980). In our study, DD stage I to stage IV were insufficiently treated with RT; even in DD stage N/I, only 58% in the 21 Gy group and 70% in the 30 Gy group were controlled in long-term FU without progression, which is still much better than the 33% in the control group. However, the best long-term results were achieved in DD stage N with over 90% of the irradiated sites remaining in a stable or even slightly improved condition. From this analysis, our advice is to transfer patients with advanced stages I–IV and/or recurrent lesions primarily to the hand surgeons. Close cooperation with hand surgeons is always important, as prophylactic RT should not impair possible good surgical results. In our study all those sites, which required hand surgery due to DD progression after prophylactic RT in long-term FU, were operated without surgical complications or enhanced perioperative morbidity.

In summary, the rationale for prophylactic RT applies to the early DD stage N and stage N/I with a maximum extension deficit of 10° because in this stage the clinical symptoms and functional deficits are still limited, and radiosensitive target cells and target mechanisms are still active. Otherwise, in the more advanced DD stages I to IV, more than 50% of patients will progress and suffer functional loss; at least 30% will require hand surgery within the next 5 years. It will be of great interest for the medical community if there might be a further role for RT in case of an early relapse after surgery, as this relapse may be driven by renewed fibroblast and myofibroblast proliferation. However, this question can only be answered in a prospective clinical study and in close cooperation with the hand surgeons.

44.5 Conclusions

The use of RT in early stage DD is superior to observation only. In long-term FU, the stage N and to some extent also stage N/I patients and sites clearly benefit from the prophylactic irradiation.

Both tested RT regimens (21 and 30 Gy) have been well accepted and tolerated by the patients. Acute toxicity was slightly enhanced in the low-dose group (21 Gy) compared with the medium-dose group (30 Gy), probably due to the time factor of a higher total dose within one RT series. Response to RT or avoidance of DD progression or surgery was slightly better in the 30 Gy group as compared to the 21 Gy group (statistical trend).

Important prognostic factors in univariate analysis were gender, age, alcohol and nicotine consumption, time interval of first symptoms to first treatment, DD stage, and DD stage-dependent parameters such as involvement of fingers and amount of extension deficit. The most important independent prognostic factor in multivariate analysis was DD stage and use of RT as compared to observation only.

Additional potential for RT may be relevant for those patients who develop a rapid progression or early relapse after surgery assuming that myofibroblasts and proliferating fibroblasts are also active in these situations; further prospective clinical trials and prognostic testing are required.

Appendix A

Morbus Dupuytren - Documentation

Date of 1st Contact ⌊ ⌋D⌊ ⌋M⌊ ⌋Y

Name ..... **Birth Date** ⌊ ⌋D⌊ ⌋M⌊ ⌋Y

General Data :	⌊ ⌋**Right Handed**	⌊ ⌋**Left Handed**
Dupuytren in Family History?	⌊ ⌋No; ⌊ ⌋Yes, who?	
Related Diseases Existing?	⌊ ⌋M. Peyronie	⌊ ⌋M. Ledderhose
.....	⌊ ⌋Knuckle Pads	⌊ ⌋Keloid
Other Diseases Existing?	⌊ ⌋Diabetes mellitus	⌊ ⌋Epilepsy
Alcohol Intake ⌊ ⌋No ⌊ ⌋Yes	⌊ ⌋Liver Disease, which:	
Smoking ⌊ ⌋No ⌊ ⌋Yes	⌊ ⌋Artheriosclerosis, where:	
Trauma involving Hands?	⌊ ⌋which :	
Professional / Leisure Hand Activities	⌊ ⌋Rough Activities	⌊ ⌋Fine Activities
Which Professional / Leisure Activity?	.....	

1st Clinical Symptoms recognized since ..... (months/years)

Clinical Symptoms		**Right Hand**		**Left Hand**
Which?		**when?**		**when?**
Itching and Burning?	⌊ ⌋**N**	⌊ ⌋**Y**	⌊ ⌋**N**	⌊ ⌋**Y**
Tension Feeling?	⌊ ⌋**N**	⌊ ⌋**Y**	⌊ ⌋**N**	⌊ ⌋**Y**
Pressure Feeling?	⌊ ⌋**N**	⌊ ⌋**Y**	⌊ ⌋**N**	⌊ ⌋**Y**
Pain at Rest?	⌊ ⌋**N**	⌊ ⌋**Y**	⌊ ⌋**N**	⌊ ⌋**Y**
Pain during Motion?	⌊ ⌋**N**	⌊ ⌋**Y**	⌊ ⌋**N**	⌊ ⌋**Y**
Skin Retraction? / when?	⌊ ⌋**N**	⌊ ⌋**Y /**	⌊ ⌋**N**	⌊ ⌋**Y /**
Palpable Nodules? / when?	⌊ ⌋**N**	⌊ ⌋**Y /**	⌊ ⌋**N**	⌊ ⌋**Y /**
Palpable Cords? / when?	⌊ ⌋**N**	⌊ ⌋**Y /**	⌊ ⌋**N**	⌊ ⌋**Y /**
Flexion Deformity? / when?	⌊ ⌋**N**	⌊ ⌋**Y /**	⌊ ⌋**N**	⌊ ⌋**Y /**
Other Symptoms? / which?	⌊ ⌋**N**	⌊ ⌋**Y /**	⌊ ⌋**N**	⌊ ⌋**Y /**

Free Text (Disease Development)

Have clinical symptoms increased within the past period? ⌊ ⌋No; ⌊ ⌋Yes,

within ⌊ ⌋the past 4 weeks: ..... ⌊ ⌋the past 3 months: .....

⌊ ⌋the past 12 months: ..... ⌊ ⌋the past ⌊ ⌋ years : .....

Intercurrent stabilisation? ⌊ ⌋no; ⌊ ⌋ yes, ...

Which physicians did you consult ?

⌊ ⌋General Practitioner ⌊ ⌋Specialist/Name : .....

Which treatment(s) has (have) been performed for the involved hand(s)?

Therapy :	**Right Hand**	**Left Hand**
Medication Steroids Allopurinol Antirheumatics/Antiphlogistics Vitamines Enzymes Tissue softening agents Others:		
Surgical Procedures (Date, Sx Type)		
Radiotherapy: (Date, RT Dose)		
Local Injections Date, Drug		
Lokal Ointments		
Other Therapies		

Basic Findings **Date** ⌊ ⌋D⌊ ⌋M⌊ ⌋Y **(prior to RT Start)**

Findings	**Right Hand**					**Left Hand**				
Digits	**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) [largest size [cm]										
Cords (C) [largest size [cm]										
Flexion Deformity [angle in degree "°"]										
– DIP joints < °	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
– PIP joints < °	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
– MP joints < °	------	------	------	------	------	------	------	------	------	------
Total Deficit : < °	____	____	____	____	____	____	____	____	____	____
Hyperextension (H)										
Ankylosis (A)										
Other Findings: e.g. Surgical Scars etc.										
Symptom Score (LAS - scale 0–10)										
Disease Stage										

Abbreviations: finding at the palm (palmar) = **P**; findings at the fingers (digital) = **D**; combined = **PD**
Notes:

RT indication for ⌊ ⌋**Right Hand / D** ..... ⌊ ⌋**Left Hand** .....

Obtain photo or photocopy of drawn findings and the planned RT treatment portal !

Date, Signature (Physician): .....

Follow-Up Findings **Date** ⌊ ⌋D⌊ ⌋M⌊ ⌋Y **(at ..... months after RT)**

Findings	**Right Hand**					**Left Hand**				
Digits	**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) [largest size [cm]										
Cords (C) [largest size [cm]										
Flexion Deformity [angle in degree "°"]										
– DIP joints < °	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
– PIP joints < °	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------
– MP joints < °	------	------	------	------	------	------	------	------	------	------
Total Deficit : < °	____	____	____	____	____	____	____	____	____	____
Hyperextension (H)										
Ankylosis (A)										
Other Findings: e.g. Surgical Scars etc.										
Symptom Score (LAS-scale 0–10)										
Disease Stage										

Abbreviations: finding at the palm (palmar) = **P**; findings at the fingers (digital) = **D**; combined = **PD**
Change after RT: Improved (🡅)"**+++ 100% / ++ > 50% / + > 25%**"; Stable"**=**"; Worsened (🡇)"**–/ – / –**";

Notes:

Clinical Status:

⌊ ⌋ **Progression**	⌊ ⌋ **Progression**
⌊ ⌋ **Stable Disease**	⌊ ⌋ **Stable Disease**
⌊ ⌋ **Remission (%) : .....**	⌊ ⌋ **Remission (%): .....**

Date, Signature (Physician): .....

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