Morbus Dupuytren/Morbus Ledderhose

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Michael Heinrich Seegenschmiedt

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M. H. Seegenschmiedt, MD
Professor, Dept. of Radiation Oncology and Therapeutic Radiology, Alfried Krupp Hospital, Alfried Krupp Straße 21, 45117 Essen, Germany

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9.1 Introduction & Definition

The digitopalmar contracture named after Guillaume Dupuytren (1832, 1834) [36, 37] and the corresponding digito-plantar contracture named after Georg Ledderhose (1897) [91] are fibrous, proliferative hyperplastic disorders of pre-existing connective tissue structures of the fascia of the fingers and palm or the toes and sole, respectively. However, in Morbus Dupuytren (MD) and Morbus Ledderhose (ML), the digitopalmar and digitoplantar changes are not just singular afflictions, but part of a systemic connective tissue disorder [41], which is confirmed by subtle biochemical changes and obvious ectopic fibrous deposits, which are located, for example, above the dorsal proximal interphalangeal joints (= knuckle pads), on the auricular helix, the hand wrist, the elbow and inside the penis (= Morbus Peyronie). These tissue

changes are histologically identical, but all efforts to identify a single cause of this generalized disorder have failed, and numerous hypotheses about the disease onset and progression have been published, but a simple and straightforward explanation is still missing. Economic consequences and individual suffering are enormous because of the functional restrictions of the afflicted hands and feet. Limited manual and walking abilities not only affect professional, but also private life and leisure activities. Thus, prevention of disease progression, stabilization of hand function or painless gait are valuable goals for the early disease stage as are surgical restoration of disabled extremity function as primary strategy for the more advanced disease stages. In the following sections MD and ML are addressed separately only if there are specific and important differences between the two hyperproliferative fibroblastic disorders.

9.2 General Aspects

9.2.1 Historical Background

Before the clinical details of digitopalmar contracture–known as Dupuytren's contracture or Morbus Dupuytren–were described and presented in his famous lecture on 5 December 1831 by the French anatomist and surgeon Guillaume Dupuytren (1777–1835), earlier reports had already mentioned this disorder: in the 12th century in the *Longer Saga of Magnus of Orkney* (Scotland) a crippling contracture of the fingers was described; the cosmopolitan physician of Basel, Switzerland, Felix Platter (1614) [161], mentioned the disease and its most significant feature, the "digiti astrici," but wrongly assumed that this "contraction digitorum" is caused by displaced flexor tendons; in 1777, Henry Cline described in his notebook the flexion deformity of two hands of a corpse that he had dissected [40]; Alexis Boyer, Napoleon's physician, called the disorder "crispertura tendinum" [40], and the English physician Sir Astley Cooper (1824) ascribed the disorder primarily to the palmar fascia [29] 10 years before the French Guillaume Dupuytren.

The typical palmar contracture, extension deficit or flexion deformity was sometimes graphically described as "oath hand," "prayers hand" or "apostle's hand" [73, 61] and certain gestures and actions, e.g., the Episcopal or papal "sign of benediction" have been associated with MD. Some pragmatic ideas and surgical techniques have been influenced by physicians like the surgeon Henry Cline, who performed the first fasciotomy in 1808 [52]; Goyrand (1834) [53] was the first to advocate the total excision of the diseased fascial tissue because of the high relapse rate after local fasciotomy only. Lexer (1931) propagated even more aggressive surgical procedures such as complete aponeurectomy and dermatofasciectomy [94].

In contrast to MD, the plantar type of the disease was much later described in 1897 by the German surgeon Georg Ledderhose. In his quite remarkable paper, Ledderhose summarized 50 individual cases that he had observed or operated on [51], which later caused the coining of the term Morbus Ledderhose (ML). However, up to now neither the true pathogenesis nor any causal therapy for MD and ML has been found.

9.2.2 Epidemiology

The prevalence of MD and ML varies worldwide. Both disorders are most common in the western hemisphere among the Caucasian population, primarily among northern Europeans or their descendants, as long as they stem primarily from the northern European cultural area [145]. The prevalence of MD in the unselected white North American population is about 1–2% [127], while among Norwegians 9.4% of men and 2.8% of women [110, 111] and among English people 5% of men and 3.5% of women are affected. The highest rate of MD has been observed among the Irish population with 17% prevalence [133]. In Germany, nowadays 9.8% of men and 3.3% of women, i.e., 1.3 to 1.9 of the 80 million inhabitants, are affected by MD [17, 19]. MD starts in the 4th decade and peaks in the 5th to 6th decades, with a male to female ratio of 3:1; two-thirds develop a bilateral affliction; a family history is more pronounced in females than males [172, 39, 95, 69, 104].

Prevalence of ML is much rarer than in MD with a ratio of 1:5–1:10. However, the incidence of concomitant MD in ML ranges from 9-65% [4, 9], while knuckle pads occur in up to 42% of patients with ML [149]. With regard to the age at disease onset,

ML starts somewhat earlier than MD in the 3rd to 4th decade; similarly to MD, it affects males more often than females with a ratio of 3:2; bilateral affliction is possible, but occurs less often than in MD (25–35%) [27, 75]. Even children and adolescents can be affected by ML [50, 134]. In contrast to MD, which affects preferentially the 3rd to 5th rays of the hand (lateral = ulnar hand side), digitoplantar fibromatosis mostly occurs at the 1st and 2nd rays of the foot (medial = inner foot side). Proliferation in the plantar aponeurosis may be so aggressive that the overlying skin, the fascia and deep structures of the sole are affected, but unlike desmoids, ML/MD do not invade the voluntary muscles [3, 41].

9.2.3 Etiology

Many studies demonstrate a continuous increase in the prevalence of MD and ML with progressing age [163]. Few cases were reported at the age of 21–30 years among 1 million American soldiers [28]. In Great Britain, MD was found in 18% of males and 9% of females at an age beyond 75 years [39]. In a German study the highest incidence was observed in the middle age group (56.8 years), especially in the 6th decade of life in males (31.3%) and the 7th decade in females (39.4%).

In all races and countries, women are significantly less affected by MD and ML than men. In females the peak manifestation usually occurs 15 years later than in males [23, 111], but the male/female ratio equalizes with increasing age. The hypothesis that gradual differences in estrogen or progesterone receptors of the affected tissue may cause the gender specific difference of MD has not been verified [57].

Interestingly, MD does not correlate with right or left handedness or the dominant hand. In most cases, the typical flexion deformity starts unilaterally, but after sufficiently long-term follow-up the disorder will affect the other hand or foot, respectively. In a large series, Millesi [112] described the bilateral to unilateral ratio as 4:1 and unilateral MD in the right hand in 12% and 7% in the left hand. Lower ratios of handedness have been reported by McFarlane [103] and Brenner et al. [17, 19] with 2:1 and 1.2:1, respectively. Ling [95] described identical frequencies of MD in enzygotic twins that were not affected by different occupations.

9.2.4 Pathogenesis and Risk Factors

Possible links between MD/ML and other disorders are explored to detect identical and reproducible pathways that are consistent with the common etiology of MD and ML. However, even an obvious association between an underlying disorder and MD/ML has to be questioned with regard to whether both disorders have in fact common causes or whether they just influence each other [22, 103]. Often times the coincidence may be affected just by the patient's age. Various other factors between specific disorders and MD/ML have been discussed: a repetitive (chronic) trauma, the occurrence of ectopic fibromatosis, the possible cause of hepatic cirrhosis and the influence of alcohol and nicotine abuse, concomitant epileptic and neurogenic disorders and hereditary factors, etc. It was Hueston [63, 68] who coined the term "Dupuytren diathesis" for patients with MD and the multiple predisposing factors summarized in Table 9.1. In the following sections we address the different aspects and possible risks or coincidental factors for the clinical development and progression of MD and/or ML.

Table 9.1. Dupuytren's diathesis

Strong family history
Onset at an early age
Occurrence of multiple and ectopic fibromatous deposits:
e.g., Morbus Ledderhose, knuckle pads, Peyronie's disease
[56, 102, 161, 168]

9.2.4.1 Trauma

In most countries a link between repetitive (chronic) or acute trauma and MD/ML is being dismissed; both disorders still have not been recognized as occupational disorders. MD has a similar frequency in Australians and North Americans of Celtic-British origin; this reveals that environmental factors such as the type of occupation, various chronic traumata, and climate conditions have no impact on the development and progression of MD/ML [17, 84]. Nevertheless, Brenner et al. [19] showed that the severity of MD according to Tubiana's classification correlates with heavy manual labor. Mikkelsen [111] published a score of 1.9 for intellectual workers as compared to 2.23 for patients engaged in hard physical occupa-

tions. Some authors believe that repetitive "vibrations" in occupational activities induce a connective tissue proliferation [96].

9.2.4.2 Ectopic Fibromatosis

Deposits of connective tissue in other sites parallel to MD/ML are known as ectopic fibromatoses, such as plantar fibromatosis (= ML) [26], knuckle pads on the second to fifth digits [25] or as penile fibromatosis (= Morbus Peyronie) [171]; rarely additional deposits are found on the auricular concha, the tongue, the hand wrist and forearm and the Achilles tendon [146]. The so-called "aggressive polyfibromatosis" is a very rare disorder causing bilateral rigid flexion contractures of the hand and ubiquitous spontaneous keloid scarring without prior trauma all over the body [51]. Hueston [63] argued that knuckle pads are a strong indicator of Dupuytren diathesis; their frequency in MD patients varies between 11–44% [163]. Plantar fibromatosis has a prevalence among MD patients of 1.5–12% [113]. A male predominance of 2:1 has been reported by Donato and Morrison [34]. Although lesions on the foot are identical in pathohistological appearance, ML can hardly be explained by heavy manual or foot work; the hardening of the plantar aponeurosis preferentially occurs in the non-weight bearing instep area of the sole, and contractures of the toes (= hammer toes) are rarely observed even in advanced ML [27]. Penile fibromatosis occurs in only 1% of MD patients [19], but 10% with this disorder have or may develop MD in long-term observation [76]. Nyberg et al. [126] found an autosomal dominant trait in all pedigrees of three families with MD and Morbus Peyronie; most individuals were HLA (histocompatibility antigen)-B-27 positive, which implies a pleiotropic effect of the same gene.

9.2.4.3 Hepatic Cirrhosis and Alcohol Abuse

Attali et al. [8] reported a much higher prevalence of MD in patients with histologically verified cirrhotic or non-cirrhotic alcoholic liver disease as compared to patients with non-alcoholic liver disease (26% versus 6%), but the difference was not significant among alcoholics with and without liver disease. Noble et al. [124] confirmed a higher frequency of MD among heavy drinkers and secondary to liver disease induced by alcohol abuse, but genetic factors seem to have an even higher impact on the etiology. Reduced microcirculation and generation of oxygen free radicals are considered as pathogenetic factors in alcohol toxic MD, but data about alcohol abuse and MD/ML are controversial. Hurst et al. [70] reported a similar proportion of regular alcohol consumers in control versus the MD group (35% versus 39%), while Burge et al. [24] reported a clear difference of weekly alcohol consumption in the MD group (mean 7.3 units per week) as compared to controls (5.4 units per week) based on the World Health Organization (WHO) AUDIT (Alcohol Use Disorder Identification Test). According to Rabinowitz et al. [132] alcohol induces incomplete fatty acid oxidation in location-matched digito-fascial specimens, which is reflected by accumulation of octanoate and short-chain fatty acids responsible for subsequent liver hypoxia. Patients with MD are found to have pathologically high tissue concentrations of methyl esters and free cholesterol, indicators of mild hypoxia. Altered fat also acts as an irritant and stimulates fibroblast proliferation, which induces the development of liver cirrhosis and digitopalmar fibromatosis.

9.2.4.4 Nicotine Abuse

Nicotine abuse can alter the microcirculation and induce tissue hypoxia through similar pathways as for alcohol abuse. Latha et al. [87] explained how nicotine consumption might affect the tissue concentration of various glycosaminglycans (GAG) fractions in various animal models. The GAGs are of great importance in the etiopathogenesis of MD. Burge et al. [24] revealed that the mean lifetime nicotine consumption ("pack years") reached 16.7 pack-years in 22% of MD patients, but only 12.0 pack-years in the control group.

9.2.4.5 Epileptic Disorders

Early [39] reported an increased MD rate in patients with epilepsy, in women 11-fold and in men 5-fold greater than in the normal population. Two hypotheses explain this coincidence: both disorders are hereditary with genetic causes, or digito-palmar fibromatosis is just a side effect of the use of antiepileptic medication. Moreover, there is also an age-related increase in the incidence of MD among patients with epilepsy, and the incidence increases with the duration of epilepsy [70]. Nevertheless, so

far no prospective study has proven a correlation between phenolbarbiturate intake and the development of MD. Thus, a conclusive explanation is still missing as to why the prevalence of MD is significantly increased in epileptics.

9.2.4.6 Neurogenic Causes

The ulnar type of MD dominates and may sometimes be associated with ulnar nerve impairment. Cases of combined median and ulnar nerve impairment have been described in conjunction with MD that were associated with prolonged sensory nerve action potential and simultaneous signs of polyneuropathy [116]. MD can affect areas beyond the fourth and fifth digits, which are supplied by the N. ulnaris, and progressive digitopalmar disease may involve the N. ulnaris over time anyway. From a more practical point of view, the principle of cause and effect may be simply confounded by claiming the onset only by neurogenic causes.

9.2.4.7 Hereditary Factors

MD and ML are assumed to be autosomal dominant disorders with variable penetrance inherited via a single gene (mutant allele) [104]. The gene in question is of dominant type, but only homozygosy induces an aggressive and progressive course of disease with variable ectopic deposits and a widespread disease. Moreover, epidemiological studies show a spontaneous occurrence of MD and/or ML among adolescents. Nevertheless, the spontaneous autosomal dominant mutation at any given genetic locus can be expected in only 1:100,000 newborns. Dal Cin [31] detected a significantly increased rate of clones in patients with MD, e.g., loss of chromosome Y and trisomies of chromosomes +7 and +8. While trisomy 7 is known both from solid tumors and normal brain and kidney tissues, trisomy 8 is always associated with the occurrence of fibrous tumors, e.g., desmoids; it is also a clinical indicator for a higher relapse rate after surgical procedures of MD.

9.2.4.8 Autoimmune Disorders

Autoimmune aggression is induced by false "self-recognition" of tissue and starts a poorly controlled, repetitive reparative response to tissue injury or physiological degradation. Menzel [107] detected serum antibodies to collagen type III in some patients with MD and a low concentration of antibodies to denatured type I collagen in others. Pereira et al. [129] found IgG antibodies to at least one of the collagen types I to IV in 69% of MD patients, but only in 28% blood donor controls. Thus, an increased type III collagen production was postulated; the minimally raised type I and V collagen was explained as non-specific cross-reaction and the elevated type II collagen as an indicator of a connective tissue disorder. Gudmundsson et al. [54] reported a marked increase in DR+ T-lymphocytes compared with healthy controls, and in patients with both MD and ML the proportion of DR+ T-lymphocytes was even higher than with MD alone. All MD patients had a lower proportion of CD+ B-lymphocytes compared with normal controls. These findings support an immunological etiopathogenesis, where activated peripheral T-lymphocytes and possibly B-lymphocytes are important factors in triggering the onset of MD and ML. Patients with an acquired immune deficiency syndrome (AIDS) have an increased prevalence of MD [16]: 36% of HIV-positive patients had concomitant MD, 18% even bilaterally. There is also evidence for an increased activity of oxygen free radicals in HIV patients, suggesting a single induction mechanism for MD/ML and AIDS.

9.2.4.9 Diabetes Mellitus

The incidence of MD among patients with diabetes mellitus reaches 40% [127]. Advanced glycation end products (AGE) develop from non-enzymatic reactions of glucose and proteins (glucation) with structural rearrangement, dehydration and condensation, especially in diabetics with associated MD [124, 138]. AGE attract monocytes and macrophages with high-affinity receptors as binding sites for AGE products. Macrophages are responsible for the release of pro-inflammatory cytokines that support the degradation and removal of cell detritus and stimulate remodeling. AGE protein receptors are found on spindle-shaped fibroblasts, smooth muscle cells and endothelial cells. In conjunction with collagen, AGEs are responsible for cross-linking and fibrillar stability. In-vivo studies show that macro-molecular agglomeration can be blocked by aminoguanidine. Thus, a future therapy could be the implementation of newly developed AGE inhibitors.

9.2.4.10 Vascular Disorders

In MD patients, microvessels are narrowed by thickened endothelial walls; they contain circumferential layers of mononuclear, spindle-shaped cells with lamellar arrangement around the basal lamina [120]. This transformation results in local tissue hypoxia and microvascular occlusion or vice versa, which facilitates the conversion of the primarily fixed (= non-migratory) fibroblasts into the mobile and contractile myofibroblasts [81]. Interestingly, the occluded micro-vessels realign parallel to the tension lines of MD cords. Murrell et al. [119] assumed that adverse conditions such as chronic hypoxia may lead to pericyte necrosis and induce subsequent regeneration within the outer layers of the old basal membrane with a partial or complete capillary occlusion, finally leading to the known fibroblast proliferation as part of the reparative process. This hypothesis explains the trigger mechanism in MD/ML. The microvascular phenomenon opens a unified pathway for the diabetic microangiopathy, chronic hand trauma, cigarette smoking, alcohol abuse, and hepatic cirrhosis to induce digito-palmar and digito-plantar fibrosis [60, 81].

9.2.4.11 Oxygen Free Radicals

So far, it is unknown which agents stimulate the fibroblast growth factor (FGF) from endothelial or perivascular cells leading to the fibroblast proliferation and subsequent transformation to myofibroblasts as part of the angio-genetic reaction. Possible causative factors are oxygen free radicals; their urge to scavenge electrons characterizes them as highly reactive substances. Activated polymorphonuclear leuco- and monocytes and macrophages can produce oxygen free radicals that are physiologically required for the lysis of migrating cells or the increase of endothelial permeability. Radicals induce the release of chemotactical plasma substances. Under hypoxic conditions the energy production is transformed from the efficient oxidative phosphorylization into the less effective glycolysis. Under hypoxic conditions adenosine-tri-phosphate (ATP) breaks down into the purin bases hypoxanthine (HX) and xanthine (X), and the enzyme HX dehydrogenase is converted to X-oxidase, which releases the oxygen free radicals O2• , OH• and H2O2. Murell [118, 120] detected in specimens taken from fascial tissue of MD patients a higher concentration of HX than in normal fascial tissue and found that normal fascial tissue reacting with HX-oxidase produced further free oxygen radicals. The increased HX concentration in patients with MD is almost six-fold. In the palmar aponeurosis of MD patients, HX increases with cell density and is two-fold in nodules compared to cords. According to Murrell et al. [121, 122] endogenously released radicals stimulate the fibroblast proliferation, and fibroblasts themselves generate and release radicals. Oxygen free radicals released into the extracellular matrix can cause tissue damage by lipid peroxidation, disruption of organelle membranes, and degradation of glycosaminglycan hyaluronic acid [169].

In addition to the excessive hyaluronic acid concentrations, which are indicative for repetitive remodeling, the fascial extracellular matrix shows changes in the relation of collagen I to collagen III and of the embedded mobile and stationary cells. The variable myofibroblasts appear to be the decisive and pathognomic cells in MD/ML. Myofibroblasts are specifically sensitive to oxidative stress conditions. Their synthesis and cell surface behavior can influence and modulate the extracellular matrix in which the myofibroblasts themselves occur. The auto- and paracrine cellular stimulation and activity are perpetuated by the expression of fibroblast growth factor (FGF) and transforming growth factor beta (TGF-β) [10].

9.2.4.12 Nutritional Factors

Besides genetic conditions, it seems not unusual that nutritional conditions influence the incidence and course of MD and ML, as both disorders are very rare in geographic regions where large amounts of antioxidizing citrus fruits, native olive oil, and a high proportion of raw food are consumed, e.g., Mediterranean or Asian populations.

9.3 Diagnostic and Clinical Aspects

The clinical course of MD and ML is dependent on the individual disposition [150]. Both disorders may spontaneously regress or progress slowly, sometimes being interrupted by phases of stagnation; in

some cases they can even rapidly progress causing contracture-induced dislocations of digital joints within a short time in MD or walking difficulties in ML. In addition to the usual MD stages, special subtypes have been differentiated in MD because of the subsequent characteristic clinical course: (1) the particularly "mild MD variant" in patients with diabetes mellitus and (2) the "aggressive MD variant" in younger people between an age of 30–40 years that expands bilaterally on the ulnar and radial side of palm [103].

9.3.1 Laboratory Testing

Based on the plasma distribution patterns of sulfated and non-sulfated glycosaminoglycans, MD and ML can be diagnosed with a probability of over 90% by laboratory methods alone, and without the knowledge of the individual and the connective tissue disorder. Thus, glycosaminoglycan determination will become a standard diagnostic tool as the rheumatoid factor test with respect to other connective tissue disorders.

9.3.2 Precursor Signs

Specific precursors of the actual onset of MD or ML are a burning sensation, itching, pressure and tension in the affected palm or sole. Patients may also complain about some localized nerve irritation, an impaired fitness for the daily use of the hand or foot and the inability to perform specific manual work (in MD) or development of some walking difficulties (in ML). The beginning contracture of the fingers may cause functional problems, e.g., when donning gloves, putting the hands in the pockets or shaking or squeezing hands. Patients with MD may also report that they unintentionally poke themselves in the eye with the contracted fingers when washing or shaving their face.

9.3.3 Clinical Symptoms

The typical course and clinical symptoms of MD/ML are divided into three different clinical phases: (1) the proliferative phase (characterized by an increased number of fibroblasts, nodules and early cord formation); (2) the involutional phase (characterized by an increased number of myofibroblasts in diseased fiber bundles) leading to contracture and (3) the residual phase (the collagenous fibers dominate in connective tissue). Unlike desmoids, no invasion of the voluntary muscles occurs [3]. The disease may slowly progress, stabilize for years or rarely regresses spontaneously. The average progression rate of patients without any therapy is about 50% within 5 years [113]. The typical chronology of the development of MD is summarized in Table 9.2.

Table 9.2. Clinical symptoms and chronological development of Morbus Dupuytren

Disease onset	Precursor symptoms: itching, burning, tension, etc., and beginning changes of the skin relief with distally open U-shaped deformation; disturbances over proximal or distal palmar crease (Hugh Johnson sign)
Nodular stage	Soft nodules (and beginning cords) mostly affecting fingers D3 – D5 (ulnar type), rarely D1–D2 (radial type) with unrestricted motion: i.e., full 180° extension of all fingers, full abduction of the thumb
Cord formation	Increasing number of hard confluent nodules and early cord formation with puckered palmar skin and beginning flexion contracture (= extension deficit): ≦10°
Contraction stage	Progressing cord formation with flexion contracture of fingers: the total sum of the extension deficit defines the actual MD stage: stage I=11–45°/stage II=46–90°/stage III=91–135°/stage IV=>135° (degree in ° = total contracture angle in degrees) (Tubiana's classification)
Special disease signs	Hyperextension of the distal interphalangeal joints (DIP) ; V-shaped deformation of interdigital space

In ML the slowly growing nodules are initially not detected by the affected individual unless first functional disorders such as walking difficulties or distressing symptoms including pain, tension or pressure sensation cause the attention of the affected individual and lead to a first medical exam [27]. Concomitant MD, knuckle pads of one or both hands and Morbus Peyronie in males may support the clinical diagnosis of ML. In contrast to MD, ML rarely displays a contracture of the foot or single toes [34].

Figure 9.1 shows a 46-year-old male patient with a positive family history and bilateral involvement of MD and ML on the left foot. Because of functional problems, his right hand and left foot were irradiated to prevent disease progression.

9.3.4 Classification of Morbus Dupuytren

The classification of MD allows the definition of treatment indications and the analysis of long-term outcome. For practical reasons the grading system by Tubiana et al. [158-160] is mostly applied in the literature; it assesses the extension deficit in the five digitopalmar segments of D1 (thumb) to D5 (little finger); thereby, the first interdigital space is defined as a part of the D1 segment. In each segment, the palmar and the digital lesions are assigned to a particular stage, and the score of that particular longitudinal segment also reflects the clinical stage. Each stage corresponds to a step change or an extension deficit of 45 degrees of a specific finger or digital segment (see also Table 9.2). The deformity score of each finger is determined as the total extension deficit of all digital joints, i.e., the metacarpophalangeal joint (MCP), proximal and distal interphalangeal joints (PIP/DIP); the possible hyperextension (0–20°) of the DIP joint is added to the total sum of contracture. Thus, the lack of extension for individual fingers can range from 0–200°. For the thumb (D1) with only two joints the deformity can reach 0–160°. The adduction contracture of the D1 web space corresponds to a gradual abduction loss of 15° (Table 9.3).

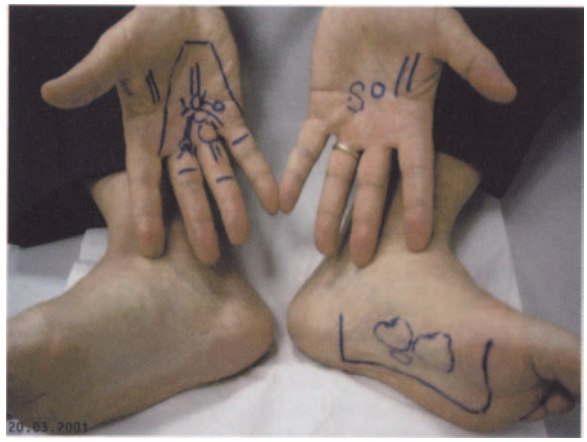

Fig. 9.1. A 46-year old patient with bilateral MD and ML of the left foot

In contrast to MD, ML rarely displays a contracture of the foot or single toes, but the walking difficulties are often apparent [34]. Thus, so far no classification system has been established.

Specific abbreviations are used for the clarification of important details: the letter "D" indicates the spread of the lesion primarily onto the fingers; the letter "H" indicates that the distal phalanx is hyperextended; the letter "A" stands for finger amputation; the letter "F" is used for ankylosis or fusion, the letter "L" for limited extension or flexion deficit and the letter "R" for relapse after surgery. Woodruff et al. [170] conceived a system that helps to predict the expected time point of the required operation. How-

Table 9.3. Classification of MD according to Tubiana et al. [158, 159, 160]

Stage	D1 (thumb)	D2–D5 (other fingers)	Points
Stage 0	Neither nodule nor loss of abduction	No extension deficit No nodular or cord lesion	=0
Stage N	Nodule without loss of abduction	Nodule without flexion contracture	=0.5
Stage I	Abduction angle; range 45–30°	Extension deficit of all finger joints is equivalent or less than 45°	=1
Stage II	Abduction angle; range 29–15°	Extension deficit of all finger joints reaches 46–90°	=2
Stage III	Abduction angle; range 14–0°	Extension deficit of all finger joints reaches 91–135°	=3
Stage IV	n.a.	Extension deficit of all finger joints reaches more than 135°	=4
Tubiana Point Score	**Maximum: 3 points**	**Maximum: 5×4 points**	**=23**

ever, no universal grading system can encompass the multiple expressions and variations of MD.

9.3.5 Imaging Techniques

Due to the obvious clinical findings and clinical course of MD/ML, specific imaging techniques are less often required for diagnostic confirmation than in other disorders. The table top test and photographic documentation are sufficient in most cases. We recommend outlining all visible and palpable skin changes (nodules, cords, skin fixation; possibly scars) with a marker pen and take a photograph or photocopy on a 1:1 scale on a regular basis to compare all possible changes in long-term follow-up. In addition, ultrasound and magnetic resonance (T2-weighted) imaging allow the exact assessment of lesion diameter and depth of „key nodules"; they can detect possible infiltration of the skin and nerve structures and support the differential diagnosis including benign fibroma, desmoids (= aggressive fibromatosis) and low grade soft tissue sarcoma [15]. Nevertheless, any unclear findings should be confirmed by needle biopsy and pathohistologic examination. Radiographs in two projections (dorso-palmar and lateral or oblique 45° neutral projections) are obtained prior to surgery to rule out primary joint processes. These radiographs should document any articular changes. Prior to any re-operation, the clinical examination should be supplemented by an exam of the digital perfusion by Doppler ultrasound or angiography to rule out possible preoperative risks and postoperative complications (e.g., wound necrosis).

9.4 Documentation and Evaluation

The detailed documentation of the loco-regional status of both hands is essential prior to any treatment and as a baseline assessment during the "watchful waiting" period. We have developed a specific documentation set that consists of three basic forms: (1) the baseline documentation (including patient parameters, risk factors, family and disease history, pre-treatment(s); (2) the pre-treatment assessment (including distribution of nodules and cords, skin changes, contractures, symptoms, etc.); (3) the post-treatment assessment (at 3 months, 1 year and at any time in the long-term follow-up). These forms are included as Appendices I – III at the end of this chapter. It is important for the long-term evaluation to define the specific disease status with regard to the actual disease stage, the range of motion (ROM) of all joints and possible functional disorders and clinical symptoms.

9.4.1 Disease Stage

The most appropriate evaluation is the documented disease stage according to the classification of Tubiana et al. [158-160]. The spontaneous regression of nodules and cords is much less likely than the stabilization of the disease stage. Thus, any increase of nodules and cords in their number or individual size, any progression of the clinical stage, or the increase of clinical symptoms and any required surgical intervention can be regarded as a "negative endpoint" in prospectively controlled clinical series. With the implementation of non-invasive methods like collagenase injections and needle fasciotomy or hand surgery, dramatic improvements with regard to the disease stage, range of motion and reduction of clinical symptoms are possible, especially in the more advanced MD stages II to IV; any decrease of nodules and cords and clinical symptoms and the stage reduction can be used as a "positive endpoint" in clinical series including the avoidance of surgical intervention.

9.4.2 Range of Motion (ROM)

A more refined clinical evaluation especially in more advanced stage MD takes the exact change of the range of motion (ROM) of each finger segment into account. This allows comparing the total Tubiana score or measuring the change of the ROM of all involved fingers or the maximum finger extension deficit before, after and in long-term follow-up after a specific therapeutic intervention. Thus, progression or regression of the disease can be defined as an increasing or decreasing extension deficit of at least 10° at any involved finger or digital segment. This is important as many prospective studies lack a clear definition of "recurrence."

9.4.3 Evaluation Period

As MD and ML are systemic disorders with an intrinsic capacity to develop a further disease progression or secondary recurrences after surgical procedures, long-term observation and evaluation are required. As a rule of thumb, without any treatment a 50% progression rate can be expected within a 5-year observation period. Thus, any direct comparison of different and/or competing treatment concepts has to reach at least a minimum follow-up of 5 years to allow a meaningful comparison not only among each other, but also with the natural course of the disease without any treatment. Our recommendation for follow-up is as follows: within the first year of watchful waiting or after implementation of therapeutic measures, clinical assessment should be performed at 3, 6 and 12 months follow-up, and thereafter every year up to 10 years, which unfortunately most reported clinical series have never achieved in the past. By using this approach, any disease progression and occurrence of relapses can be analyzed and graphically plotted using the Kaplan-Meier actuarial method.

9.5 Treatment Strategies

Due to the unknown cause of MD and ML obviously many different and conflicting suggestions for therapeutic management have been made in the past, but none of them is of causal nature. The mainstay of treatment is still watchful waiting during early and stable disease phases. In the context of this chapter, we will restrict ourselves to the presentation and discussion of medication, surgical management and radiotherapy.

9.5.1 Medical Treatment

Hueston [65, 66] applied "enzymatic fasciotomy" using local injections of trypsine, hyaluronidase and local anesthetic, but could not achieve long-term improvement of digital contractures. Badalamente and Hurst [11] continued this research and in a phase II study tested increasing doses of 300–10,000 units of the enzyme collagenase, which is derived from clostridia; in dose-escalation studies they found that only doses of 10,000 units would improve the MCP and PIP flexion contractures to some extent, but temporary side effects such as dysesthesia, hematoma and hand edema occurred in many patients; moreover, the 2-year relapse rate was 25%. Other disadvantages included tendon rupture due to enzymolysis, neurovascular traumata, etc., which could be avoided by using sonographic control for the repeated local injections.

The intralesional application of antioxidant-eliminating radicals, so-called "scavengers," such as orgotein, has been examined only with slight success rates, but the agent has now been delisted by health authorities. The xanthin-oxydase/-dehydrogenase inhibitor allopurinol has been suggested by Joyce [77], and Murrell et al. [117] showed a significant ROM improvement of up to 10 degrees after daily administration of 300 mg allopurinol for 3 months; there have also been claims of achieving complete finger extension after a 2-year medication period, but a large clinical series is missing.

Other researchers have suggested cytotoxic drugs like colchicine and vinblastine [33] or the fibroblast growth factor saporin, which can be derived from the plant common soapwort (Saponaria officinalis, which occurs in approximately 30 different species in the Mediterranean region and Eurasia) [86, 151]; this protein has ribosome-inactivating properties and has been successfully applied in patients with AIDS, tumors, and graft versus host reactions. Selenium, a typical receptor blocker and inhibitor of the interaction between cell and matrix (calcium blockers or integrins), is also thought to be beneficial in preventing disease progression. Other drugs (including steroids, DMSO, NSAIDs and vitamin E) have been unable to prevent disease progression in early MD stages [42]. For early stage ML, a few conservative options are available, including foot orthosis or steroid injections [128].

None of the above-mentioned methods has produced long-term results in controlled clinical trials, and they are therefore not approved as evidence-based treatment methods in MD and ML. In the future, scavengers, inhibitors of cell-matrix interaction, and even somatic gene therapy may offer some useful therapy options besides radiotherapy for early prevention and surgery for function recovery or disease stabilization both in MD and ML.

9.5.2 Surgical Management

Hand surgery has evolved over the past decades as the main treatment option in MD and ML, but is reserved for the later stages of the disease. A surgical intervention in MD and ML is required whenever the hand or foot function is severely disabled, and clinical symptoms compromise the quality of life. Nowadays, various surgical approaches–very limited to radical–are available for different clinical stages and therapeutic indications. The aim of all forms of local to radical surgery is to improve the hand function by minimizing the extension deficit of the fingers and the abduction loss of the thumb in both the ulnar and radial type of MD and, respectively, to improve the foot function and gait in ML. In addition, specific symptoms like par- and dysesthesia due to nerve compression may be improved by the local excision of the connective tissue tumor. The open surgical procedures aim to remove the macroscopically altered tissue of the digito-palmar fascia, to correct the contracture of all affected finger joints, and to preserve the neurovascular bundle and the soft tissue coverage [71]. However, the risk of further progression or relapse is always present, and despite the best surgical intervention a desired "restitution ad integrum" cannot be expected at any stage of MD and ML. Moreover, so far any adjuvant therapies after primary or relapse surgery have not been established.

9.5.2.1 Surgical Indications

Prior to any surgical intervention the long-term goals have to be defined both by the patient and the surgeon. Usually an early surgical intervention is not appropriate, as MD and ML are benign conditions that can reach a state of temporary or permanent standstill at any disease stage. Surgical interventions may even lead to more rapid progression than without any treatment. In general, surgery is indicated if daily activities are hindered, which is usually the case if MD reaches Tubiana's stage III (>90°) or if pain and walking difficulties occur in ML, respectively. Subjective complaints such as insecure grip or dysesthesia only serve as relative indications for hand surgery. Always the potential surgical complications have to be weighed against the possible functional recovery, and it has to be kept in mind that MD and ML are systemic connective tissue disorders, which in principle are not curable and amenable to a local surgical intervention, as the surgical measures never treat the underlying factors of the idiopathic, genetic disorder [19].

Hueston's table-top test [67] is most useful to determine the optimal time of surgical intervention: it is considered "positive" if the total contraction of all finger joints exceeds more than 30° [13, 71]. In contrast, if the adequate surgical procedure comes too late, postoperatively an extension deficit (i.e., secondary contractures) may persist, as some joint capsules (MCP, PIP, DIP) may already be contracted. The best choice of surgery is to operate in order to relieve specific symptoms or improve disabled functions.

9.5.2.2 Surgical Techniques

According to Brenner [19] the following types of surgery have been established for MD: (1) nodulectomy, (2) palliative fasciotomy, (3) subcutaneous needle fasciotomy, (4) segmental aponeurectomy (= limited excision), (5) subtotal fasciectomy, (6) total or radical aponeurectomy and (7) dermatofasciectomy. These surgical procedures are not competing techniques, as each one has a specific indication.

Nodulectomy and fasciotomy are simple surgical procedures either performed as a subcutaneous minimally invasive approach or as a locoregional type; they aim to improve the finger and hand function by a simple excision of the disturbing nodule or by division of the contracting cord. As a palliative procedure it is mainly indicated in the elderly with generally poor health conditions, while in younger patients it is performed whenever a more invasive fasciectomy is not indicated.

Subcutaneous needle fasciectomy is a minimally invasive procedure usually performed under local anesthesia on patients with multiple associated disorders. It is mainly applied in Francophone regions as the first surgical step in an otherwise escalating sequence of surgical procedures [93]. It provides an immediate visible success both for the patient and the physician, but has a relapse rate of almost 50% in 2 years. Nevertheless, it can be repeated several times on one or more digital segments.

Partial fasciectomy is reserved for the more advanced MD stages with extension deficits of >90° and severely impaired finger function; it is suitable for patients of any age with localized involvement

(e.g., fourth and fifth fingers) and of any degree of contracture; it is also suitable for relapses.

Segmental aponeurectomy is a piece-wise cord resection via a small approach; it is performed in patients of any age and aims to improve the extension deficit by a programmed resection of diffuse cord formations over relatively short segments [114, 115].

The so-called "open palm technique" particularly aims for a good release of the metacarpo-phalangeal (MCP) contracture; it is indicated in multidigital MD stage 3 to 4, and especially in MCP retraction; it can also be applied in the elderly and in patients in whom skin grafts or flaps should be avoided [98, 99].

Total fasciectomy (= radical fasciectomy) is a very aggressive surgical approach and was initially proposed to "cure" the disease [147], but nowadays it is applied only in patients with widespread disease, but good general and local conditions and with contractures of the most affected fingers not exceeding 45–90° (Tubiana stage II). Nowadays, only about 20% of all surgical patients may undergo total fasciectomy.

Dermato-fasciectomy is mostly advised in young adults with digitopalmar fibromatosis infiltrating the skin, in cases of very aggressive progression, Dupuytren's diathesis, or after multiple surgical relapses. Nowadays about 15% of all surgical patients may require dermato-fasciectomy.

Other surgical procedures include selective arthrolysis, arthroplasty, and arthrodesis of the PIP joint during the initial intervention, if the flexion contracture exceeds 90 degrees; the latter is also indicated in most recurrent contractures. The continuous elongation technique (T.E.C.) introduced and described by Messina et al. [108] aims to straighten the fingers by applying a skeletal traction device (i.e., a modified external fixateur). Simultaneous surgical interventions, such as prophylactic surgery of carpal tunnel syndrome (CTS), are not recommended due to a higher perioperative complication rate.

9.5.2.3 Contraindications for Surgery

Non-compliant patients and those with poor general health conditions are not candidates for surgery, including those with progressive cerebrovascular disorders and Parkinson's disease. Local infection and chronic eczema of the palm or sole are also contraindications for hand or foot surgery. Hueston [63] considers patients with a strong Dupuytren's diathesis poor candidates for surgery, i.e., young people with both hands affected, a positive family history and multiple ectopic connective tissue deposits (knuckle pads, ML, Morbus Peyronie).

9.5.2.4 Results of Surgery in Morbus Dupuytren

Surgery aims to improve preoperatively unacceptable functional conditions. Thus, any relapse of nodules and cords or further loss of range of motion (ROM) in an operated segment and secondary surgical procedures can be regarded as "treatment failure." Opinions vary with respect to the point in time that allows a reliable prediction of relapse: Hueston [64] reported that 87% of all relapses occur during the first 2 postoperative years, while Millesi [112] found only 48% of the relapses to occur more than 3 years after the initial surgery. Tubiana and Leclercq [160] stated a 34% relapse rate within the first 3 years, while after 5 and 10 years the relapse rate increased to 50% and 65% of their patients. Norotte et al. [125] summarized the most important poor prognostic factors for relapse after hand surgery (in descending order of importance): (1) age less than 50 years; (2) advanced stages 3 and 4 at the time of initial surgery; (3) additional factors like epilepsy, misuse of alcohol or a familial diathesis. However, some part of the relapse rates may also depend on the surgeon's skills and the applied surgical method (Table 9.4).

9.5.2.5 Complications of Surgery in Morbus Dupuytren

Surgery is an invasive treatment that can induce complications such as hematoma, edema, local infection, iatrogenic neurovascular injury, wound necrosis or other healing problems and/or reflex sympathetic dystrophy (= algodystrophy). Even in early stages, surgical complications can occur. Thus, a pure "removal of nodules" is never indicated nor is surgery during Tubiana stage I and II, unless the table top test is positive. Fasciectomy during the early nodular stage and early cord formation needs to be avoided as it may lead to an exacerbation of the disease. For MD recurrences appropriate surgery is only indicated in the presence of functional impairment. Geldmacher [49] reported on an overall complication rate of about 15% in 2,160 fasciectomies, among them 91% partial fasciectomies; the complications included 61 (2.8%)

Table 9.4. Progression and relapse rates after surgery in Morbus Dupuytren

Study	Surgical method	Cases (n)	Follow-up	Progression/relapse
Luck [100]	FT	n.a.	n.a.	n.a./71%
Millesi [112]	FT	9	3–5 years	n.a./78%
Lermusiaux [93]	Needle FT	736 (rays)	n.a.	50%
Moermans [115]	Segmental ANE	141/240	2.9 years	16%/23%
Hueston [62]	Partial FE	96	2 years	28.1%/12.5%
Millesi [112, 113]	Partial & total FE	577	> 5 years	Jointly: 39%
Leclercq [89]	Partial FE	50/89	10 years	n.a./66%
Norotte [125]	Partial FE	58	10 years	n.a./71%
De Maglio [32]	Partial FE	124	33 months	26.2%/24.1%
McGrouther [106]	Partial FE	100	5 years	n.a./50%
Sennwald [145]	Total FE	103/256	3–6 months	n.a./21.4%
Brenner [17, 19]	Total FE	48/239	4 years	Jointly: 39.7%
Allieu [5]	Open palm technique	77/164	3 years	19.4%/29.7%
Foucher [47]	Open palm technique	107/140	>5 years	39.0%/40.6%
Tonkin [156]	Dermato-fasciectomy	41/100	3 years	n.a./4% (underneath skin graft); 33–42% (under original skin)
Ketchum [80]	Dermato-fasciectomy	24/36	3.9 years	8%/0%
Brotherston [21]	Dermato-fasciectomy	n.a.	100 months	n.a./0%
Hall [56]	Dermato-fasciectomy	67/90	4 years	n.a./8%

Legend: n.a. = not available
FT = fasciotomy; FE = fasciectomy; ANE = aponeurectomy

nerve lesions, 28 (1.3%) secondary amputations as a result of malperfusion, 5 (0.23%) tendon injuries, 25 (1.2%) secondary hemorrhages, 61 (2.8%) reflex sympathetic dystrophy, 58 (2.7%) local infections and 102 (4.7%) skin necrosis. Other series have addressed the differences in surgical techniques and their relative complication rates. Overall, the following figures and ranges have been reported in the literature (Table 9.5)

9.5.2.6 Results of Surgery in Morbus Ledderhose

Due to a much lower incidence clinical data and reports about surgery of ML are less evolved: the case numbers are much lower and the follow-up limited, but principally similar surgical techniques are applied for ML and MD, i.e.: (1) local fasiectomy (= local excision; LEX); (2) partial to subtotal fasciectomy (= wide excision; WEX); (3) total plantar fasciectomy (PFE) partially performed with skin grafts.

In general, foot surgery has to be carefully indicated and performed only by experienced podiatrists, who monitor patients for long periods. Asymptomatic patients with small lesions should not be operated on; by applying surgery the disease may be triggered to an even more aggressive behavior inducing rapid growth of nodules in formerly uninvolved areas of the foot. The surgical indication is especially difficult in children and adolescents.

Foot surgery should remain the "last option" for advanced ML with rapid progression and unbearable symptoms or complete walking disability after failing all conservative therapies like insoles, local injections and systemic medication (e.g., vitamin E). The aggressive growth of nodules or cords can lead to swelling, severe pain due to nerve entrapment and various other functional deficits. Unfortunately, high relapse and complication rates are well known for primary and secondary foot surgery of ML [4, 7, 9, 38, 55, 92, 130, 165].

In earlier stages of ML, the surgical procedure may involve only a local excision (LEX) of nodules and cords; in more advanced stages or in recurrent disease, partial to subtotal excision (WEX) of the plantar aponeurosis is commonly chosen. In the most advanced stages of ML and after repeated recurrences, total plantar fasciectomy (PFE) is chosen,

Table 9.5. Complications of surgery in Morbus Dupuytren

Type of surgical complication	Needle fasciectomy	Segmental resection	Partial fasciectomy	Open palm technique	Dermato-fasciectomy
No. of studies	2	2	7	3	1
Hematoma	0.8–2.0%	2.3–3.2%.	3.3–7.7%	0%/n.a. (2x)	n.a.
Neurovascular bundle injury	2.0–5.2%	1.1/n.a.	1.4–9.7%	4–18.8%	1.5%
Local infection	n.a./16%	n.a./0%	0.5–2.7%	0–6.3%	n.a.
Local necrosis	n.a. (2×)	n.a./0.6%	1.0–25.8%	0–5%	1.5% 1.5% amputation
Reflex sympatheticdystrophy	1.8%/n.a.	1.1–3.3%	2.2–17.5%	4–12%	0%
Overall	5–20%	5–9%	9–30%	8–35%	(4.5%)

Legend: n.a. = not available;

which is often combined with a free skin (= total skin graft) or fat tissue transplant (= dermal fat graft) to overcome the burden and side effects of tissue loss on the foot sole [88].

The LEX procedure leads to a much higher relapse rate than the WEX or PFE procedures. However, the latter surgical options are compromised by higher complication rates, e.g., local infections, wound necrosis and healing problems, thrombosis, nerve injury and reflex sympathetic dystrophy (RSD). Patients with surgical relapse after LEX, development of hypertrophic scars and/or contracture of the plantar aponeurosis will require more extensive surgical procedures (WEX or PFE). The prognosis of relapses is usually worse than that of the primary lesion. Allen et al. [4] reported a 70% relapse rate after LEX, while after WEX or PFE the relapse rates were much lower [55, 85, 130, 165].

The typical surgical problems are obvious in a recent clinical series by Dürr et al. [38] reporting on 13 feet and 24 (13 primary, 11 secondary) surgical procedures: 7×LEX, 9×WEX, 8×PFE. In long-term FU, only 4 of the 13 (36%) patients with primary lesions did not relapse or progress. Two patients had three operations to achieve a long-term control; in total, 16 of the 24 (67%) surgical procedures lead to a relapse. Therefore, the authors concluded that only primary aggressive surgery could reduce the relapse rate. Similar data exist from Aluisio et al. [7] for 33 cases with over 2 years of follow-up: 7 of the treated 17 patients relapsed, 4 of 10 after a LEX procedure, 1 of 3 after WEX and 2 of 4 after combined WEX/PFE procedures partially involving skin grafting; moreover, 6 of 16 relapses developed a second relapse, mostly after LEX or WEX. In summary, relapses occur more often after local surgery and in patients with multiple nodules, bilateral affliction and positive family history. The recent surgical series regarding outcome of surgery in ML are compiled in Table 9.6

9.5.3 Radiotherapeutic Management

The aim of radiotherapy for MD and ML is not to improve the range of motion or to avoid any functional surgery in the advanced stages, but to pre-

Table 9.6. Results of surgery in Morbus Ledderhose

Study (year)	Pats (N)	Feet (N)	Type of Sx	Relapse (%)	Complication rate (%)/type
Aluisio et al. (1996) [7]	30	33	LEX, WEX, PFE	13 (39%)	9 (27%): 4 wound healing, 2 nerve lesions; 2 chronic pain 1 deep vein thrombosis
Dürr et al. (1989) [38]	11	13	LEX, WEX, PFE	8 (73%)	4 (31%): 4 wound healing
Sammarco (2000) [142]	16	21	WEX	2 (13%)	12 (57%): 11 wound healing, 1 neurinoma

Legend: LEX = local fasiectomy ; WEX = partial/subtotal fasciectomy; PFE = total plantar fasciectomy

vent any further disease progression in the early stages of MD and ML. This preventive or prophylactic strategy aims to protect the patient from any future functional impairment and eventually necessary surgical procedures. However, radiotherapy is not required when the disease is at a standstill for more than a year, as the possible radiosensitive targets, fibroblasts or mediating CD+ T-lymphocytes, or radiosensitive mechanisms, expression of growth factors or stimulation of proliferation may not (anymore) be active. Similarly, on the other end of disease development, in the later stages of MD and ML with fully developed cord formation and contractures of palm and fingers, irradiation appears to have no radiobiological basis because of lacking radiosensitive target cells or mechanisms. Radiotherapy can only fill the therapeutic gap between watchful waiting and necessary functional correction by surgical means.

It is important to note that the effect of ionizing radiation on scarring tissue is not a dissolution or softening, but rather an increase of the fibrotic reaction. Therefore, the scarring process during cord formation and contracture development are not suitable for any radiotherapeutic intervention at all, rather the nodular stage and early cord formation due to the presence of the fibroblasts as radiosensitive target cells. So far, the adjuvant use of radiotherapy, e.g., after surgery of relapses, is unexplored as the invasive procedure may again stimulate the expression of growth factors like fibroblastic growth factor (FGF) and tissue growth factor beta (TGF β), which subsequently trigger renewed proliferation of fibroblasts and stimulate pathological processes and cascades that induced recurrence.

9.5.3.1 Radiobiological Rationale

MD and ML are characterized by proliferation of fibrous tissue in the form of nodules and cords that have features in common with benign neoplastic fibromatosis [100, 103]. The diseases develop like wound healing through contraction and maturation of fibrous tissue [123, 136, 137]. The pathologic ligamentous strands have a predominantly longitudinal orientation and follow the longitudinal tension lines of the palm [45, 46]. With regard to radiobiology and possible radiosensitive target cells and mechanisms, the proliferation process is most relevant, as it is driven by the radiosensitive immature mitogenic fibroblasts and myofibroblasts prior to the formation of the scarring contracture [48, 141]. Moreover, the myofibroblast phenotypes and growth factor synthesis predominantly occur in proliferative nodules, i.e., the early stage of the disease [14]. Similarly to wound healing and fibrosis, several raised levels of growth factors produced by platelets and macrophages can be found in MD specimens [18], including the fibroblast growth factor (FGF), transforming growth factor beta (TGF-β, known to stimulate fibroblasts), platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and connective tissue growth factor (CTGF), which all play a key pathogenetic role in MD/ML [6, 10, 12, 72, 153-155]. Induced by free radicals and local ischemia, damaged vascular pericytes are activated and a reparative process is initiated resulting in perivascular fibroblast proliferation [82, 162]. Interestingly, the continued pericyte damage, rapid fibroblast proliferation and collagen deposition further increase the microvessel ischemia, thereby self-propagating the initial pathogenetic process [119, 120]. This multistep pathogenesis and the involved cells and mechanisms provide a good rationale for using ionizing radiation especially in the early stages of MD/ML (Table 9.7).

Similarly to the use in early stage MD/ML, radiotherapy has been successfully implemented in other hyperproliferative disorders, such as prophylaxis of intravascular hyperproliferation after arterial stenting [30, 157], prophylaxis of keloid relapses after surgical excision (see Chap. 11) [152] and avoidance of relapses after resection of recurrent pterygium

Table 9.7. Radiobiological rationale: radiosensitive targets and mechanisms

(1)	Proliferating mitogenic fibroblasts and myofibroblasts are radiosensitive target cells [136, 137, 140]
(2)	Induced free radicals impair proliferative activity of fibroblasts [122]
(3)	Interference with growth factors, especially PDGF and TGF-beta [135, 153, 155]
(4)	Reduction of activated monocytes and macrophages interacting with the inflammatory process and myofibroblast proliferation [140]
(5)	Similar radiosensitive target cells/mechanisms are found for prophylactic radiotherapy:
	in intravascular hyperproliferation after arterial stenting [30, 157]
	in keloid relapses after surgical excision [152]
	in relapses of recurrent pterygium [148]

[148]. In all these instances, relatively low doses of ionizing radiation have been shown to prevent the hyperproliferation of fibrous tissues responsible for the basic pathogenetic process, which matches in-vitro and in-vivo studies [140].

9.5.3.2 Radiotherapy Technique

Careful RT planning has to precede the actual treatment: this involves the outline of the clinical target volume (CTV) on the skin surface, which includes all treatable nodules and cord formation, plus a sufficient safety margin of at least 1 cm laterally and 2 cm in the proximal and distal extension of the outlined disease manifestation (Fig. 9.2). RT for MD and ML is applied using direct palmar or plantar en-face portals. Low-energy electrons of up to 5 Megavolt (MeV) from linac accelerators combined with 5-mm bolus material or low-energy photons of 100–125 Kilovolt (kV) from orthovoltage units without bolus due to rapid dose fall-off at this energy level are implemented. The dose reference point is selected individually between 0–10-mm depth depending on the thickness of the skin and subcutis and the extension of the lesions on the hand and foot, respectively. The calculated and tabulated monitor units account for energy differences, tube size, target depth and reduction of portal size due to shielding of some portions of the portal. The target volume can be individually shaped by using 1-cm-thick lead cutouts (for electrons) or 3-mm lead rubber plates (for

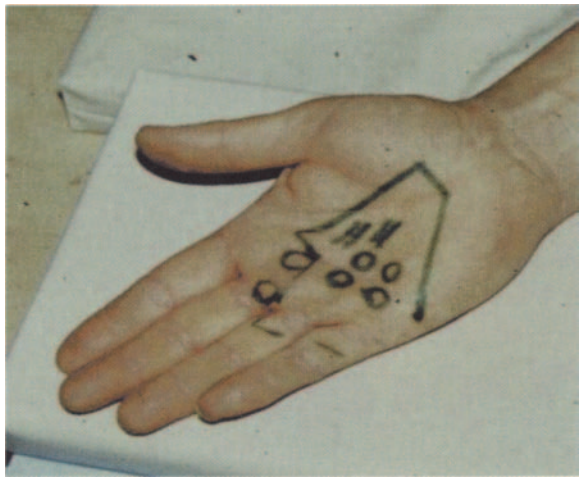

Fig. 9.2. Treatment setup for Morbus Dupuytren: Outline of nodules and cords and clinical target volume on skin surface

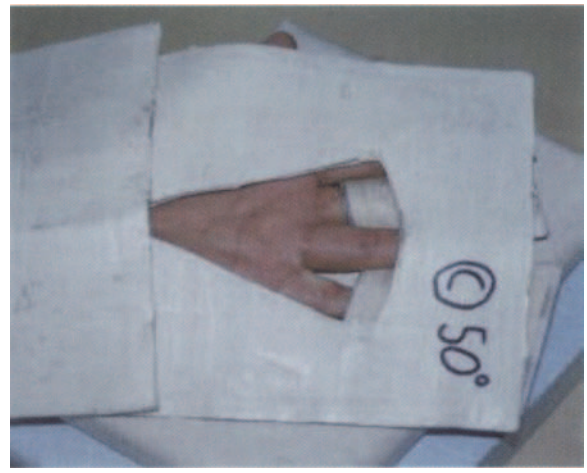

Fig. 9.3. Radiation protection for uninvolved areas of the palm. Coverage of the uninvolved areas of the palm prior to radiotherapy using lead rubber plates (about 3 mm thickness)

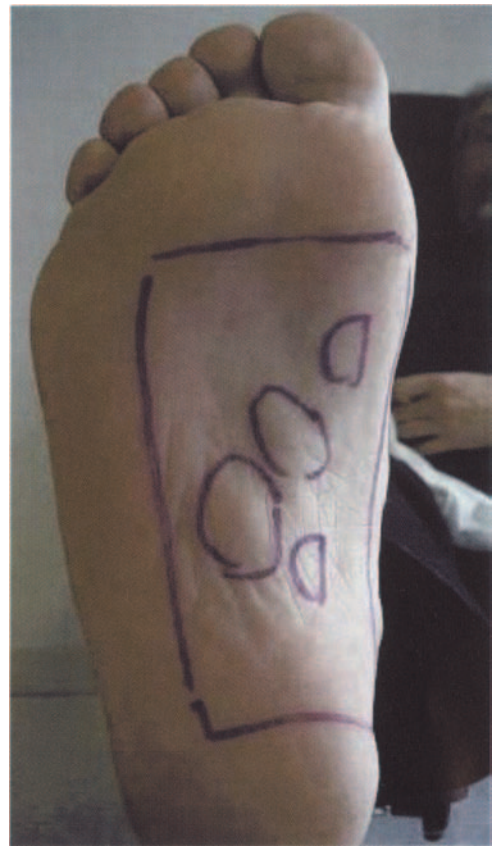

Fig. 9.4. Treatment setup for Morbus Ledderhose. Radiotherapy portal at the medial concavity of the right foot using 2 cm safety margin in proximal/distal and 1 cm in medial/lateral direction

low-energy photons) depending upon the applied RT technique. At our own institution, we use four preformed standard templates with cut-out angles of 30°–60° and 12-cm length; with additional plates we can reduce the open area from a 12-cm radius to any desired length. Examples of treatment set-ups for MD and ML are shown (Figs. 9.3, 9.4).

For an actual treatment session of MD, the patient is seated on a chair close to the treatment table; the back of the affected hand is placed on the treatment table bent about 90° and 0.5 m away from the body, which allows the radiation beam to enter from the open palm. For the treatment of ML, the patient lays prone on the treatment table with the affected foot plantar-flexed, which allows the radiation beam to enter from the open sole. Any radiation beam direction towards the body or pelvic region is to be avoided. Nevertheless, for radiation protection a lead apron is applied in any case, so that no stray irradiation can occur in the pelvic region.

9.5.3.3 Results of Radiotherapy in Morbus Dupuytren

Several clinical studies mostly conducted in Central Europe support the concept of using RT in early MD stages, but so far RT has not been accepted as "standard treatment." Various dose concepts have been successfully applied, but never tested in a prospective clinical study. Therefore, our own group has set up a prospective randomized study and reported interim results of two RT arms (7×3 Gy versus 10×3 Gy), which are to be compared in long-term evaluation with an observation arm only [143].

Table 9.8. Clinical results of radiotherapy in Morbus Dupuytren (historical order)

Study (year)	RT concept		Follow-up	Clinical outcome according to stage [N (%)]		
	Single/total	Dose	(Years)	Regression	Stable condition	Progression
Finney (1955) [44]	1–3× 1.000 rad Ra-Moulage	1.000–3.000 rad	n.a.	Overall: 60% good functional result		
Wasserburger (1956) [166]	1–3× 1.000 rad Ra-Moulage	1.000–3.000 rad	Long-term	Long-term cure: stage I: 90%; stage II: 57%; stage III: 32%		
Lukacs et al. (1978) [101]	(2×4 Gy) ×4 every 2 months	32 Gy	n.a.	I: 81% II: 75%	I: 19%	None
Vogt and Hochschau (1980) [164]	(2×4 Gy) ×4 every 2 months	32 Gy	>3 years	I: 21% II: 25% III: --	I: 74% II: 50% III: 80%	I: 4% II: 25% III: 20%
Hesselkamp et al. (1981) [59]	(2×4 Gy) ×4 every 2 months	40 Gy	1–9 years	Total: 52%	Total: 41%	Total: 7%
Köhler (1984) [83]	10×2 Gy 3–5×/week	20 Gy	1–3 years	Total: 21%	Total: 61%	Total: 18%
Herbst et al. (1985) [58]	3–14×3 Gy 5×/week; 2 RT series	15 (30)–42 Gy	>1.5 years	None	Total: 98%	Total: 2%
Keilholz et al. (1996/1997) [78, 79]	10×3 Gy 5×/week; 2 RT series	30 Gy	1–12 years; median: 6 years	72% symptoms 7% MD stage	17% symptoms 82% MD stage	11% symptoms 11% MD stage
Seegenschmiedt et al. (2000) (randomized) [144]	10×3 Gy vs. 7x×3 Gy vs observation	30 Gy 21 Gy	1–7 years; >1 year in all pts	56% symptoms 53% symptoms	37% symptoms 38% symptoms	7% symptoms 9% symptoms
Adamietz et al. (2000/2001) [2]	1×3 Gy 5×/week; 2 RT series	30 Gy	5–19 years; median: 12 years	Total: 11% only stage N	Total: 60%	Total: 29% only stage I–III

Legend: n.a. = not available; RT = radiotherapy; Gy = Gray;
I, II, III = different stages of Dupuytren's disease according to Tubiana's classification (1961; 1966; 1986)

The clinical results of the different published RT series are compiled in Table 9.8. The data of these studies are often incomplete or not precise with regard to follow-up period and definition of treatment response; moreover, important endpoints like regression or progression have not been substantiated by changes of the disease stage or range of motion achieved; moreover, often the salvage procedures in progressive cases including surgery were not given in detail.

Lukacs et al. [101] reported "no disease progression" in 36 hands following RT. Hesselkamp et al. [59] reached "improved or stable conditions" for over 2 years in 93% of 46 irradiated hands. Vogt and Hochschau [164] found 94% of 109 irradiated sites "stable or improved" after more than 3 years. Köhler [83] reported 82% of 33 treated hands to be "improved or stable" and 6 "progressed" after 3 years of follow-up. Herbst and Regler [58] observed all 45 treated hands as "stable or improved" after a median follow-up of 1.5 years. Keilholz et al. [78, 79] found 72% of 142 treated hands with "regression of nodules and cords;" of the 57 hands followed for a minimum of 5 years, 5 had progressed outside and 8 inside the RT portal. Adamietz et al. [1, 2] reported long-term data with a median of 12 (range 5–19) years of follow-up: 123 (60%) of 205 irradiated hands remained in stable condition; 22 (11%) were improved and 60 (29%) had progressed, mostly cases with the more advanced MD stages I-III. All together, these clinical data demonstrate a lower progression rate after irradiation in the early MD stages than after surgery in more advanced stages. Irradiation seems to produce better long-term results than the expected 50% progression rate for untreated patients.

Unfortunately, all clinical studies using prophylactic or therapeutic RT for MD are retrospective, and as they have differences in patient, disease or treatment parameters (fractionation, single and total RT dose, treatment time), primary endpoints and variable follow-up periods, nowadays no strong comparisons and conclusions can be drawn. The question what minimum dose is effective to reach a sufficient therapeutic potential still remains unanswered. Therefore, prospective studies are still required to define the lowest possible dose for the best therapeutic effect.

Köhler [83] suggested a total RT dose of at least 20 Gy applied in ten fractions of 2 Gy to avoid any disease progression; other authors reported somewhat better clinical outcome with a total dose of 32–40 Gy (8×4 Gy single dose) [59, 164]. In addition, even large single doses of 1,000 rad applied every 3–6 months up to a total dose of 3,000–4,000 rad have been successfully applied [43, 44, 166]. Keilholz et al. [78, 79] obtained good long-term outcomes with 30-Gy total doses, which were applied in two RT series of each 5×3 Gy, which were separated by 3 months. In summary, both the RT dose and the time-dependent effects can be responsible for any difference in the long-term outcome after RT of MD and ML. Thus, prospective dose-finding trials are still required. However, prophylactic RT should not impair possible good surgical results. Thus, it is favorable to reduce the total RT dose without compromising the efficacy, which is the main idea of our own prospective clinical study.

The appropriate RT technique is an important aspect to achieve favorable results: some studies applied whole palm irradiation [59, 83], while others including ourselves treat the diseased areas only [78, 79, 164]. We never apply whole palm irradiation to prevent unnecessary side effects; instead, we always apply individual shielding of uninvolved areas of the palm and use bolus material to compensate for air pockets, for example, along the radial side of the hand or between fingers [143]. This approach may allow disease progression outside the treatment portal, especially if the longitudinal and lateral extension of the disease process is underestimated, but large safety margins around the visible and palpable lesions are to be employed to avoid this potential failure. Careful radiation dosimetry and dose prescription according to the ICRU 50/62 recommendations and diligent treatment application are important requirements to achieve a favorable long-term outcome including no side effects. After local RT out-field disease progression is possible, but still amenable to a second RT series, as long as no overlap with the primary RT portals exists; in-field progression should not be treated with RT due to possible risks of higher radiation exposure; in these cases salvage hand surgery is required for any severe functional deficits.

9.5.3.4 Possible Risks of Radiotherapy

Among hand and foot surgeons, the principle rationale and goals of radiotherapy for MD/ML are still poorly understood and often critically dis-

puted for various reasons: (1) generally, therapy of "early stage" MD or ML is not accepted because of the option of spontaneous disease regression; (2) long-term side effects of radiotherapy are feared including possible carcinogenesis; frightening case reports on radiation necrosis are shown in textbooks, e.g., deep skin ulcers (but detailed data regarding dose and treatment portals are missing) [20, 42]; (3) long-term inefficacy of RT is reported on some irradiated cases in which salvage surgery was performed (but without a control group) [167]; (4) hand surgery is considered more complicated or even impossible following prior RT (but without a control group) [42, 167]; (5) RT for more advanced stages of MD/ML was shown to be not successful, but radiosensitive target cells/mechanisms are missing in this stage of disease [1, 2]; (6) controlled randomized trials defining the optimal dose or comparing observation versus RT in long-term follow-up are still missing .

Nevertheless, in summary most RT series have shown long-term efficacy in the early, but not in the advanced stages of MD [1, 2]. None of the RT series using single doses as high as 10 Gy or total doses up to 42 Gy have reported long-term severe radiogenic side effects or tumor induction within the treatment portal; the applied doses are much too low to reach dose levels that may possibly induce severe fibrosis, lymphatic occlusion, actinic nerve lesions, radiodermatitis or radiogenic ulcers, as mentioned by Brenner and Rayan [20]; these latter effects would require RT doses at least over 60 Gy [139]. Carcinogenesis is another concern that has to be addressed in the informed consent prior to RT, but usually risks are exaggerated and not justified, especially when dealing with the elderly population at risk for MD (50–70 years) [74]; only 1% of secondary sarcomas have occurred within treatment portals 8–30 years following radiation doses of 30 Gy or higher; induction of skin cancer is slightly increased with low doses (1–2%) [97]; higher incidences require much higher doses above 70 Gy [35]. Thus, it is very important to use the appropriate indication window for prophylactic RT (in stage N/I disease) and to spare patients from any excessive or unnecessary high radiation, e.g., in the quiescent early disease stage or when it is regarded as being ineffective (in stage II–IV disease); always the lowest effective dose should be applied [109].

9.5.3.5 Own Clinical Results in Morbus Dupuytren

Since 1997, we have started a prospective randomized clinical trial at our institution to compare two different dose concepts in patients with early stage MD (dose optimization study); concomitantly, a group of patients has chosen clinical observation only after consultation for radiotherapy and is since then followed closely. An interim analysis was performed in the year 2000 to rule out any imbalances and unexpected differences between the two radiation groups: at that time, 129 patients (67 males, 62 females) had received radiation: 69 had bilateral and 60 unilateral MD affliction accounting for a total of 198 irradiated hands. According to the modified Tubiana classification, 73 hands had MD stage N, 61 stage N/I (≤10° deficit), 59 stage I (11–45° deficit) and 5 MD stage II (46–90° deficit). Radiotherapy was randomly assigned in two RT dose groups: patients in group A (63 patients, 95 hands) received a total of ten fractions of 3 Gy (total dose: 30 Gy) in two series of each 5×3 Gy, which were separated by 8–12 weeks break; patients in group B (66 patients, 103 hands) received seven fractions of 3 Gy (total dose: 21 Gy) in only one RT series applied 2–3× per week within 2 weeks. An orthovoltage RT unit with 120-kV photons was used in all cases; standard cones (8×10 cm or 10×15 cm) and individual shielding of uninvolved areas of the palm were applied. Patient and disease parameters were equally distributed in both groups. Treatment outcome (toxicity, efficacy) was analyzed 3 and 12 months after RT. Subjective (patient) and objective parameters (palpation, measurements, comparative photographs) were applied to assess the clinical response at a minimum follow-up of 1 year.

Acute toxicity was slightly more pronounced in group B (21 Gy): 76 (38%) hands had short-term skin reactions CTC grade 1 (A: 30; B: 46); only 12 (6%) hands developed skin reactions CTC grade 2 (A: 4; B: 8); chronic side effects (dryness, slight desquamation, skin atrophy, change of sensation) LENT 1° were noted in 9 (5%) hands, but without differences between the RT groups.

Three and 12 months after RT, a subjective and objective reduction of symptoms, including nodules and cords, was observed in comparison with

the treatment onset (P<0.01), but no significant differences were observed between the RT groups: at 12 months, in group A 55 (56%) hands showed regression of clinical signs, 35 (37%) remained stable and 7 (7%) progressed, while in group B 55 (53%) hands regressed, 39 (38%) remained stable and 9 (9%) progressed (n.s.). The overall and mean numbers of palpable nodules, cords and associated skin changes decreased significantly at 3 and 12 months (P<0.05). The treatment failure rate (progression of symptoms and findings) at 1 year was 16 out of 198 (8%) hands, but only 4 (2%) hands required surgery because of increasing symptoms or functional deficit. Most interestingly, 7 of 60 patients with previous unilateral MD had disease progression in the initially uninvolved and untreated contralateral hand without progression of the irradiated hand.

In conclusion, both RT concepts have been accepted and well tolerated by the patients. Within the first year they were equally effective to prevent further disease progression of MD and even obtain symptomatic improvement. The 1-year results suggest similar response rates for both treatment groups; however, long-term FU of at least 5 years has to be awaited for final the assessment and comparison with the group of patients that chose observation only.

9.5.3.6 Own Clinical Results in Morbus Ledderhose

So far, no clinical data are available in the literature with regard to the use of RT for the treatment of ML. Our group was the first worldwide to initiate a prospective phase II study to examine whether ionizing radiation could change the disease progression and avoid surgery in symptomatic and progressive ML [144].

Since 1996, 35 patients have been referred to our institution to obtain radiation treatment of their ML on one or both feet. As not all feet showed progressive disease, ten patients were advised for a watchful waiting policy only. Thus, in 2002, 12 female and 13 male patients (median age: 56 years) who had been irradiated for progressive ML and were followed for at least 1 year were evaluated. As 11 patients had bilateral ML, a total of 36 feet were treated and analyzed. Prior to RT, a total of 63 nodules were found on all feet, and 20 cords on 13 feet. Most patients had additional clinical symptoms including pain (n=15), pressure or tension sensation (12) and walking difficulties (8).

In all patients low-energy orthovoltage photons (150 kV) were applied to cover the plantar aponeurosis including all palpable nodules and cords plus a sufficiently large safety margin. Usually two RT series were applied (each 5×3 Gy) that were separated by 8–12 weeks up to a total dose of 30 Gy. The clinical evaluation was performed after each RT series at 3 and 12 months and at last follow-up. The primary endpoint was the prevention of any disease progression (any symptoms) and the avoidance of foot surgery. Secondary endpoints were the reduction of objective morphological (size) and functional parameters (gait) and patient satisfaction (visual analogue scale).

After a median FU of 38 (12–67) months, no progression of disease was found in all feet and none of them had to undergo surgery. Eleven feet had a reduced number (minus 16) or size of nodules; 7 of 13 feet had a reduced number (minus 9) or length of cords; the gait was improved in 6 of 12 involved feet; pain reduction or complete resolution occurred in 9 of 15 afflicted feet; other symptoms resolved in 8 of 18 affected feet. Twenty of 25 patients regarded a total of 28 feet as "improved," and 8 feet were in "stable condition." The median subjective improvement stated by the patients was 50% (0–100%). Radiogenic side effects were minimal: within 3 months after RT a slight erythema (CTC 1°) was noted at the RT portal in five feet and dry skin changes were observed in three feet in long-term FU of at least 12 months.

In conclusion, RT appears to be a very effective treatment in progressive ML; with appropriate early application it may even prevent an otherwise necessary surgical intervention in a long-term perspective. Obviously, not only nodules, but also cords and clinical symptoms can regress. However, a minimum FU of more than 5 years is required for final analysis and comparison with the observation group. Moreover, multicenter prospective phase III studies (including sham versus RT or comparison of different RT schedules) are required to confirm these results.

9.6 Comprehensive Discussion

Both Morbus Dupuytren (MD) and Morbus Ledderhose (ML) have many disease aspects in common including the hereditary background and risk factors. Their economic and personal impact should not be underestimated. The almost certain hereditary background provides a specific challenge for counseling the descendants with regard to additional risks and possible actions to prevent an early disease onset, e.g., avoid alcohol and nicotine consumption.

Watchful waiting is the appropriate measure for the early and/or quiescent stages of MD and ML. A regular exam and photographic documentation are advised to follow the suspected and manifest clinical changes parallel to the reported individual's subjective symptoms.

Prior to any conservative or invasive treatment, patients should be advised about the fact that the disease can take an unpredictable course, i.e., come to a standstill at any time without treatment or become even more active after an invasive procedure planned for functional or symptomatic improvement. The high expectations of patients prior to any treatment have to be mitigated, as a complete "restitutio ad integrum" can never be achieved.

The implementation of external radiotherapy is not commonly accepted, but supported by a strong radiobiological rationale addressing both sensitive target cells and mechanisms that are important in the pathogenesis of MD and ML. So far, ionizing radiation appears to be the only effective means to interact with the early disease phase of MD and ML. However, it should be only applied during the proliferative phase, which is characterized by the formation of nodules and soft cords and first disturbing symptoms; this approach provides the best chance to actually interfere with the mitogenic proliferative fibroblast and myofibroblast population that dominates the early disease process. Progressive symptoms should be present for at least 6 months; otherwise close observation with an appropriate follow-up period should be awaited to document any disease progress prior to the treatment onset.

The first clinical data support the concept of radiotherapy in early stage disease; however, prospective controlled trials are still required to affirm the good results in long-term follow-up for at least 5 years. Concerns of other disciplines including hand surgeons regarding late sequelae or compromised surgery should be taken seriously, and long-term observation beyond 10 years should be planned for any prospective trial. So far, no increased radiogenic acute or late side effects have been reported systematically.

Obviously, there is no place for RT in the later stages of MD characterized by increased cord formation and contracture of the palm and fingers, as fibroblasts as radiosensitive target cells are not available anymore. These stages are primarily reserved for surgical intervention to improve functional problems and alleviate clinical symptoms.

Secondary relapses and disease progression in uninvolved areas can be expected in up to 50% within 5 years after surgery. So far, no clinical experiences and outcome data are available for the use of adjuvant RT in recurrent cases. At that stage, several surgical procedures are available that have their specific indications and success and complication rates. Only well-experienced specialists (hand surgeons and podiatrists) should perform these procedures, and they warrant long-term observation. Any incident or even iatrogenic treatment complication should be precisely documented and openly discussed with the individual patient. Long-term observation and cooperation with those patients affected are mandatory.

Bullet Points

- Morbus Dupuytren (MD) and Ledderhose (ML) are most likely autosomal dominant disorders with variable penetrance inherited via a single gene (mutant allele); Caucasians are almost exclusively affected with a male to female predominance; both disorders are characterized by proliferation of fibrous tissue (nodules and cords) in the digitopalmar (MD) and digitoplantar aponeurosis (ML).
- The pathogenetic mechanisms have not been found, but several risk factors have been identified: ectopic fibromatosis (knuckle pads, M. Peyronie), hepatic cirrhosis, alcohol and nicotine abuse, epileptic disorders, neurogenic causes, hereditary factors (including Dupuytren diathesis), autoimmune disorders (including AIDS), diabetes mellitus, vascular disorders, presence of hypoxia and oxygen free radicals, and nutritional factors.
- Diagnosis of MD and ML is simple (clinical observation and manual examination); however, ultrasound and MRI are helpful to differentiate the "nodular tumors" from benign soft tissue tumors, desmoids or sarcomas. Prior to any surgery orthogonal X-rays of the hand or foot serve as a basic assessment for long-term analysis. Clinical documentation of typical nodules and cords via direct photography or photocopy is recommended.
- Both disorders can spontaneously come to a standstill, may slowly progress over years or exacerbate rapidly to cause severe symptoms or functional impairment: manual malfunction through palmar or digital contracture with extension deficit of fingers and abduction loss of thumb (MD) or pain and walking difficulties (ML).
- Watchful waiting is the appropriate measure for non-proliferating disease; no conservative treatment methods (medication, gymnastics, nutrients, etc.) have been established, which can successfully prevent the disease progression in long-term follow-up.
- Surgery is the required measure for advanced stages of MD and ML, but "restitutio ad integrum" is not achievable; symptomatic relief and functional improvement (manual and walking abilities) are the main objectives. For the different indications various methods locally confined to radical surgery are available. Hand surgery has a 5-year progression rate of almost 50% and an overall complication rate of 15%.
- Radiotherapy is not an established treatment method so far, but the radiobiological rationale and first clinical results are very convincing with regard to prevention of disease progression in early stages of MD and ML: besides regression of nodules, cords and symptoms, most cases can be stabilized; the overall progression rate in stage N and N/I disease (MD) reaches about 20%, but is much higher in more advanced stages, where radiotherapy is not indicated; acute and chronic treatment side effects of radiotherapy are minimal.
- The recommended RT dose concepts are: 3-Gy single dose and 20–30 Gy total dose; a protracted application (two to three fractions per week or two radiation series) appear to be favorable. However, multicenter prospective controlled clinical trials are still required to establish the role of RT and the optimal dose concept for early stage progressive MD and ML.

Appendix 9.1

Morbus Dupuytren–basic documentation

Date of 1st contact: D _____ M _____ Y_____

Name: _____ Date of Birth: D _____ M _____ Y_____

General data: No = N; Yes = Y

Dupuytren in family history? ☐ No; ☐ Yes, who ? _____

Related diseases existing? ☐ Morbus Peyronie ☐ Morbus Ledderhose
☐ Knuckle pads ☐ Keloid / Hypertr. scar

Other diseases existing? ☐ Diabetes mellitus ☐ Epileptic disorder
☐ Liver disease, which: _____
☐ Arteriosclerosis, where: _____

Trauma involving the hands? ☐ which : _____

Smoking ☐ No ☐ Yes ☐ Right handed ☐ Left handed

Professional/leisure hand activities ☐ Rough activities ☐ Fine activities

Which profession/leisure activity? _____

1st clinical symptoms recognized since (estimation in months)_____

Clinical symptoms Which?	Right hand / digits If yes, when?	Left hand / digits If yes, 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 _____

Appendix 9.2

Morbus Dupuytren–pre-treatment assessment

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 stabilization ? ☐ no; ☐ yes, how long: _____

Which physicians did you consult?

☐ General practitioner ☐ Specialist/name: _____

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

Therapy	Right hand / digits	Left hand / digits
Medication		
Steroids		
Allopurinol		
Antirheumatics/antiphlogistics		
Vitamins		
Enzymes		
Tissue-softening agents		
Others:		
Surgical procedures		
(Date, Sx type)		
Radiotherapy:		
(Date, RT dose)		
Local injections		
Date, drug		
Local Ointments		
Other therapies		

Appendix 9.3

Morbus Dupuytren–pre-treatment examination

Physical findings prior to Tx start Date: D _____ M _____ Y _____

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 in cm]										
Cords (C) [largest size in 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.										
Disease stage										

Abbreviations: finding at palm (= palmar) = P; findings at digits (= digital) = D; combined = PD

RT indication given for the ☐ Right hand ☐ Left hand

Obtain photograph/photocopy of drawn findings and planned RT treatment portal!

Date, signature (physician): _____

Appendix 9.4

Morbus Dupuytren–post-treatment examination at 3 / 6 / 12 months after Tx

Physical findings Date: D _____ M _____ Y _____ (at ___ months/years after Tx)

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 in cm]										
Cords (C) [largest size in 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.										
Disease stage										

Abbreviations: finding at the palm (= palmar) = P; findings at digits (= digital) = D; combined = PD
Changes after RT: improvement (↑), +++ / ++ / + ; stable =; worsening ↓ - / -- / ---

Clinical status:

☐ Progression
☐ Stability
☐ Remission (%): _____

☐ Progression
☐ Stability
☐ Remission (%): _____

Date, signature (physician): _____

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