REVIEW ARTICLE

To remember: Radiotherapy – a successful treatment for early Dupuytren's disease

B. Eberlein,* T. Biedermann

Department of Dermatology and Allergy Biederstein, Technische Universität München, Munich, Germany
*Correspondence: B. Eberlein. E-mail: bernadette.eberlein@tum.de

Abstract

Dupuytren's disease (DD) is a common fibroproliferative condition of the hand which tends to cause progressive digital flexion contracture. Therapeutic strategies to treat the disease include radiotherapy, injections of collagenase clostridium histolyticum, needle fasciotomy and extended surgical intervention dependent on involvement and duration of the disease. We have reviewed the literature with the aim to assess the conditions and effects of radiotherapy in DD. In early stages of the disease, radiotherapy resulted in regression of symptoms/a lack of progression found on average in 40% (range 10–85%)/81% (range 50–100%) of the patients with recurrence rates of only 12–31% after long-term follow-up (>4 years). These results proved to be significantly better than in the untreated patients with natural course of the disease (about 50% progression after a follow-up of 5–6 years). Long-term side-effects (skin dryness) are observed on average in one quarter of the patients, but are well tolerated. Local occurrence of malignancies has not been reported yet. Due to severe functional impairment leading to individual suffering and the high economic burden, treatment of DD in early stages is necessary and radiation therapy represents an effective, safe and economic treatment option.
Received: 17 January 2016; Accepted: 13 April 2016

Conflicts of interest

The authors have no conflict of interest.

Funding sources

The work was not supported by any funding source.

Epidemiology

The prevalence of Dupuytren's disease (DD) varies with age, populations groups and methods of collection. An overall population of 4–6% in the northern Europe are affected by DD[1]. A study in the United States yielded a prevalence estimate of 1% using physician diagnosis and 7% using self-reported features matching the appearance of DD[2]. In the UK population, 3–5% are affected[3]; incidence was estimated to be 3 per 10 000[2]. The incidence increases with age and is 4–6 times more common in males than females. Furthermore, men are affected about 10 years earlier than women and have a more severe disease[4,5]. In a study with over 1000 patients, most commonly, the little finger was involved (49%) followed by the ring finger (32%). Sixty per cent showed a single digit involvement, 17% a bilateral involvement[6].

Pathogenesis

A genetic trait is important for development of DD with a high prevalence in the northern European and Scandinavian population and is rarely seen in African and Asian populations[7]. This benign fibroproliferative disorder of the hand is characterized by the progressive thickening and shortening of the palmar fascia resulting in the formation of cords in early stages and flexion deformities of the digits in later stages[8]. The mechanism of disease progression beginning with a nodule developing to a collagenous disease cord is not well understood. Significant differences in levels of epidermal growth factor (EGF) concentrations between contractured and normal fasciae may suggest the participation of this mediator in the pathogenesis of DD[9]. Gene alterations as well as mitochondrial defects have been found to be associated with DD leading to variations in collagen regulation: It could be shown that a heteroplasmatic mutation located within the mitochondrial 16s RNA region was evident in 90% of patients and absent from all control subjects[10]. A genome-wide association between DD yielded an association with 11 SNPs from nine different loci. Six of these loci contain genes (*WNT4, SFRP4, WNT2, RSPO2, SULF1* and *WNT7B*) which are known to be involved in the Wnt signalling pathway. It is assumed that increased activity of these WNT and R-spondins genes or decreased activity of SFRP could stimulate Wnt signalling and reduce intracellular β-catenin degradation. This mechanism

could trigger fibroblasts to proliferate, leading to the development of Dupuytren's disease[11].

Clinical grading system

The clinical course can generally be divided into three phases: (i) a proliferative phase (increased fibroblasts, nodule formation), (ii) an involutional phase (increased myofibroblasts in fibre bundles) that leads to contracture; and (iii) a residual phase (collagenous fibres dominate in the connective tissues).

There are different clinical grading systems, e.g. the grading system according to Iselin and Dieckmann[12] or according to Millesi[13], but the one of Tubiana[14] with the modified stage N[15] is the most commonly employed system in the recent years (Table 1).

Treatment – overview

There is no curative treatment for DD. Treatments can be divided into non-invasive and invasive treatments. The most commonly used non-invasive treatment is radiation therapy.

Radiation therapy is performed since more than 90 years and today, we know that it is very useful in the early stages of the disease. The procedure of radiotherapy will be presented below.

Collagenase clostridium histolyticum (CCH) has been available for approximately 5 years and represents a minimally invasive procedure. It is an injectable enzymatic treatment for adults with a palpable cord. CCH is injected locally and reduces the collagen cord by lysis and leads to a spontaneous cord rupture. Alternatively, cord rupture is induced by a standardized finger extension. Clinical success (defined as reduction in contracture to 5° or less) was achieved in up to 77% of the patients depending on the severity of contracture and DD joint localization[16].

Percutaneous needle aponeurotomy or needle fasciotomy (PNF) is a minimally invasive technique performed under local anaesthesia whereby, a small needle is used to weaken and manipulate the cords. With this technique, the cords can be ruptured by means of passive finger extension. Total passive extension deficit improvement (the primary outcome in a 6-week study) improved on average by 63% for PNF[17].

Surgical intervention is usually considered when the metacarpophalangeal (MP) joint contracture is ≥30° or when there is any degree of proximal interphalangeal (PIP) contracture[18,19]. The most widely used surgical procedure is partial, regional or limited fasciectomy (open, partial fasciectomy, OPF). With this method, total passive extension deficit (the primary outcome in a 6-week study) improved on average by 79%[19].

The systematic review by Chen *et al.* reported the rates of recurrence following OPF, PNF and CCH ranging from 12% to 39% (mean follow-up time of 1.5–7.3 years), 50% to 58% (mean follow-up time of 3–5 years), and 10% to 31% (mean follow-up time of 120 days to 4 years) respectively[20] (Table 2). Summarizes the treatments according to the severity of the disease.

Table 1 Tubiana grading system, modified by Keilholz *et al.*[14,15]

Stage	Deformity
0	No lesion
N	Palmar nodules or cords without presence of contracture
N/I	Beginning of contracture (TFD between 1° and 5°)
I	TFD between 6° and 45°
II	TFD between 46° and 90°
III	TFD between 91° and 135°
IV	TFD >135°

TFD, total flexion deformity.

Radiation therapy

Sources and selection criteria

We used PubMed and Medline search engines as well as guidelines for the radiotherapy of non-malignant disorders[21,22], German[23–25] and international text books[26] about radiotherapy of DD (with cited articles) to identify studies for clarifying the impact of radiotherapy on early stages of DD.

History

Radiation therapy for DD has been used since 1902, first reported by Antoine Béclère (mentioned in ref.[27]). Also in 1905, radiotherapy was recommended as one therapeutical option in DD[28]. Since 1923, the possibility of Grenz ray therapy, brachytherapy and therapy with soft X-rays increased the therapeutic options in DD. Accumulated data resulted in the concept from 1949, that radiotherapy is effective in the early stages of DD[29]. First publications in Medline appeared in the year 1953 with a radium-mould technique[30], but studies using radiotherapy for DD, mainly by European authors, remained limited.

Treatment results with an improvement of clinical symptoms in early stages of DD have been described in a German dermatology standard textbook about radiotherapy of skin diseases in 1959 by Schirren *et al.*[31] and consequently, this therapy was especially applied in German speaking countries (Table 3).

Procedure of radiation therapy

Radiation therapy by dermatologists is usually carried out with soft X-rays (Dermopan II, Siemens, Germany), using 50-kV photons at 25 mA, a 1-mm aluminium filter and a 2-mm cellon

Table 2 Treatments according to the stage of the disease (modified after ref. 48)

Stage	N	N/I	I	II	III	IV
Radiation therapy	x	x	o			
Needle fasciotomy		o	x	x	o	o
Collagenase injection			x	x	o	o
Surgery			x	x	x	o

x, well suited, usually used; o, occasionally used.

Table 3 Overview of newer different radiotherapy treatments and their outcomes

Protocol with different cumulative doses	Location of radiotherapy	Number of patients (sites) [total/early stages N, N/I, I]	Protocol (Gy per week and interval)	Follow-up	Chronic side-effects (dryness/ atrophy)	Results (no progression/ improvement)
Untreated control						
Seegenschmiedt 2012[41]	Hamburg	122/113	Not irradiated	>5 years	n. p.	48%/n.p.
Use of 20 Gy and 21 Gy						
Köhler 1984[45]	Cottbus	31/31	(3-)5 × 2 Gy, no interval (3-)5 × 2 Gy	Up to 2.5 years	n. p.	82%/21%
Seegenschmiedt 2001[39]	Essen Erlangen	66 (103 sites)/ 101 sites	7 × 3 Gy within 2 weeks	>1 year	4%	91%/53%
Seegenschmiedt 2012[42]	Hamburg	293/288	7 × 3 Gy within 2 weeks	>5 years	16%	78%/n. p.
Use of 30 to 32 Gy						
Lukacs 1978[32]	Munich LMU	36/32	2 × 4 Gy 8 weeks (repeated 4 x)	Up to 5 years	n. p.	100%/81%
Vogt 1980[33]	Munich TU	109/98	2 × 4 Gy 8 weeks (repeated 4 x)	>3 years	n. p.	95%/21%
Herbst 1985[36]	Erlangen	33 (51 sites)/ 46 sites)	5 × 3 Gy 6 weeks 5 × 3 Gy	>1,5 years	0%	98%/85%
Weinzierl 1993[51]	Erlangen	34	5 × 3 Gy 6 weeks 5 × 3 Gy	Median 7 years (6.25–7.5 years)	32%/ n.p.	50%/9%
Keilholz 1997[37]	Erlangen, Essen	96 (142 sites)/ 129 sites	5 × 3 Gy 6 weeks 5 × 3 Gy	Median 6 years (1–12 years)	64%/ 13%	94%/n.p.
Seegenschmiedt 2001[39]	Essen, Erlangen	63 (95 sites)/ 93 sites	5 × 3 Gy 8 weeks 5 × 3 Gy	>1 year	5%	93%/56%
Adamietz 2001[46]	Erlangen, Fürth	99 (176 sites)/ 161 sites	5 × 3 Gy 6–8 weeks 5 × 3 Gy	Median 10 years (7–18 years)	25%/ 8.5%	59%/10%
Betz 2010[38]	Erlangen, Bayreuth	135 (208 sites)/ 198 sites	5 × 3 Gy 6–8 weeks 5 × 3 Gy	Median 13 years (2–25 years)	23%/ 7%	69%/10%
Seegenschmiedt 2012[41]	Hamburg	303/299	5 × 3 Gy 10–12 weeks 5 × 3 Gy	>5 years	11.5%	84%/n.p.
Zirbs 2015[35]	Munich TU	206 (297 sites)	2 × 4 Gy 8 weeks (repeated 4 x)	Median 3.25 years (0.5 – 9.5 years)	20%/ 3%	80%/45%
Use of about 40 Gy						
Hesselkamp 1981[44]	Hamburg	46	2 × 4 Gy 3 months (repeated 3–5 x)	Up to 9 years	63%/ n.p.	93%/52%

n.p., not published.

filter. Radiation is led through a tube (diameter, 4 cm) at a focus skin distance of 15 cm. A total dose of 32 Gy is applied, with an 8-week interval between the four courses of two fractions at two consecutive days with a single dose of 4 Gy[32–35].

Radiologists prefer orthovoltage units (RT 250, Philips Co., Hamburg, Germany or Stabilipan, Siemens, Germany) with 120 kV at 20 mA and with 2 mm aluminium (6 × 8 cm/ 10 cm × 12 cm cones) at a source skin distance of 40 cm. Two different protocols were compared; the established one with 10 fractions of 3 Gy (total dose 30 Gy) in two series of each 5 × 3 Gy in 1 week separated by 6–8 weeks[36–38] vs. 7 fractions of 3 Gy in 1 series (total treatment time, 2 weeks)[39].

Irradiation with high-speed electrons (4–9 MeV) was also described[36,40].

Uninvolved areas of the palm were shielded by placing 1–3-mm lead rubber plates with a margin to the palpable nodules and cords of 0.5–2 cm.

An overview about radiotherapy protocols is given in the German guidelines for radiotherapy of benign diseases, by Seegenschmiedt *et al.* and in Table 3, showing single doses of 2–4 Gy, cumulative doses of up to 42 Gy and intervals up to 12 weeks[41,42].

Mechanism of action

The predominant radiosensitive targets are proliferating fibroblasts and myofibroblasts. Therefore, the radiobiologic potential of ionizing radiation is limited to early stages of DD. Furthermore, growth factors, PDGF and TGF beta and the activated monocyte – macrophage system may be influenced by radiotherapy[43]. However, experimental analyses on its mode of action in DD are still warranted.

Outcomes

Radiotherapy vs. wait and see Radiotherapy of DD in early stages was shown to be significantly ($P < 0.001$) superior to a 'wait and see' strategy[42]. After a follow-up of at least 5 years (mean 8.5 years), 78% of the irradiated patients showed a remission or a stabilization and 22%, a clinical progress (13.5% surgical intervention) vs. 52% progression (30% surgical intervention) in the unirradiated group. Another author states a disease progression of 150 hands in stage N in about 46.5% without intervention after more than 6 years[13], which is higher than almost all published progression after sufficient irradiation in early stages (Table 3).

Effects dependent on symptom duration The effect of radiotherapy (lack of progression or even regression) seems to be limited to the early stages of DD. This could be convincingly shown by Betz *et al.*[38] showing a regression in 24%/11%/3%/3%/3% or a status idem in 74%/70%/56%/53%/41% of the patients irradiated during the first/second/third/fourth/> fourth year after the beginning of symptoms. Correspondingly progression was seen in 2%/19%/41%/43%/55% of the patients with a median follow-up of 13 years. Another study also revealed a significantly higher improvement in patients with symptom duration of <20 months[35].

As a consequence, irradiation 2 years after symptom appearance in DD is regarded to be less promising.

Choice of cumulative dose Schirren *et al.*[31] never used a total dose exceeding 32 Gy (within 12 months) and even placed a warning for higher total doses (up to 70 Gy). Braun-Falco and Lukacs even recommended a cumulative dose of 24 Gy[25]. On the other hand, total doses below 16 Gy failed to show any effects[31]. More recent publications using a total dose of 21 Gy found improvement or stabilization of symptoms in 91% of the patients vs. 93% in a group of patients irradiated with a total dose of 30 Gy after a follow-up time of 12 months[42]. Using total doses from 30 to 32 Gy for improvement or stabilization of DD was also confirmed in other studies in 98% (follow-up >18 months), 95% (follow-up >3 years), 80% (median follow-up of 4 years and 4 months), 100% (follow-up up to 5 years) and 94% (follow-up with a median of 6 years)[32,33,35–37]of the patients. A study using a cumulative dose of 40 Gy showed an improvement or stabilization in 93% (follow-up up to 9 years)[44] and another with 20 Gy in 82% (follow-up up to 2.5 years)[45]of the patients.

In summary, there is a clear trend for better long-term improvement of DD with higher cumulative doses, but it can be recommended not to exceed 40 Gy. The most commonly used cumulative doses are between 30 and 32 Gy (Table 3).

Choice of single dose and intervals Intervals between irradiations are necessary in order to reduce side-effects for the skin. Some authors performed serial irradiations (2 or 3 Gy as single doses up to 7 irradiations within 15 days[39,42]); others used intervals from 4 up to 8 weeks (sometimes 12 weeks) after serial irradiations of 3 Gy or after application of 2 × 4 Gy on two consecutive days[32,34,35].

Acute toxicity (redness, dryness or desquamation of the skin within 6 weeks after radiotherapy) occurred more often and more intense (32%) in the groups without intervals compared to a protocol with longer intervals (24%)[42] using 3 Gy as a single dose, but the results were similar to protocols using 4 Gy as single dose (32%)[35].

Also chronic side-effects (dryness, increased desquamation, mild skin atrophy, lack of sweating, angiectasia, sensory disturbance) showed a similar trend (e.g. serial irradiations: 16%, irradiations with intervals: 11.5%) in the same study[42]. Protocols using 4 Gy as single dose on two consecutive days usually apply an interval of at least 8 weeks[25,33–35,44]. Dryness of skin was seen in 20% as a chronic side-effect[35].

2 Gy as a single dose was only used in one study[45], 4 Gy was never exceeded as a single dose. Thus, 3 Gy or 4 Gy are most often used as single doses. For higher single doses (4 Gy), longer intervals (at least 8 weeks) are recommended in order to minimize the side-effects.

Long-term effects Follow-up for a decade or longer (median: 13 years) showed a progression of DD in 22% or 31% of the patients[38,46] respectively; follow-up between 4 and 10 years showed a progression in 12%[42], 23%[37] or 20%[35], and effects depended on the disease stage when patients were treated (see above). In one study, 19% of the patients developed new DD lesions in non-irradiated areas after a median of 10 years[46].

Disease progression or reoccurrence following longer follow-up time with 31% recurrence being the highest rate published after a median follow-up of 13 years[38] is much better compared to surgical treatments with recurrence rates of 39% (OPF) or up to 58% (PNF) after a follow-up of up to 7 years. Effects of CCH after 5 years of application with recurrence rates up to 31% are also less favourable compared to radiotherapy[20].

Risk of skin cancer The risk of developing cancer and other neoplasias is a given fact when applying ionizing radiation to human cells. It has been shown that a cumulative dose of 30 Gy does not increase the risk of neoplasias in radiated areas as shown by Betz *et al.*[38] after 13 years of follow-up. The risk of developing skin cancer is clearly related to the total dose applied, showing that cumulative doses up to 30 Gy have a very low risk for neoplasias[47]. Cases of skin cancer in the treated area after radiotherapy of DD have not been published yet, even though this treatment has been performed since decades. Furthermore, the 'Deutsche Dupuytren Gesellschaft' (German Dupuytren Society) published cancer risk estimations due to radiotherapy of DD[48]. One of these estimation points to a risk dependent on the patient age and gender at the time of irradiation. With a median age of patients with DD of about 50 years[2,] the calculated risk is 0.04–0.05% which is very small and negligible compared to the natural cancer risk[49]. Only younger people up to the age of 30 years may have an increased risk of 0.1–0.2%[42].

Cost-effectiveness Vogt *et al.* calculated that radiotherapy in DD is also a prophylactic treatment and therefore clearly more cost-efficient (11-times) than surgical treatments[33].

Open questions and outlook

This summary of available data confirms the positive effects of radiotherapy in early DD on contractures and therefore recommends its application. However, there is a lack of controlled and international studies with regard to single doses, total doses, optimal intervals and different and newer sources of radiation. Furthermore, there are no studies on possible positive effects (prevention of reoccurrence) of radiotherapy following invasive treatments (PNF, CCH and OP), which could be expected based on suspected mechanisms of action. Radiotherapy is often not applied by surgeons[50,51] and arguments brought forward are lack of efficacy and side-effects in case of later surgical treatments, which apparently is not true. However, in observed cases, preceding radiotherapy had no negative effects on complication rates in surgical treatments of advanced stages of DD[42,44]. Only one author claimed, that two out of 42 patients undergoing a surgical procedure following radiation therapy, showed a delayed wound healing[38]. However, a controlled study is still lacking.

Treatment of DD in early active stages (N and N/I) is very promising and radiation therapy represents an effective, safe and economic treatment of DD. This type of treatment is not offered to many patients with early DD and 'spreading the words' among dermatologists is one of the important measures to improve DD outcome.

References

1 Ross DC. Epidemiology of Dupuytren′s disease. *Hand Clin* 1999; **15**: 53–62.
2 Di Benedetti DB, Nguyen D, Zografos L *et al.* Prevalence, incidence and treatments of Dupuytren′s disease in the United States: results from a population-based study. *HAND* 2011; **6**: 149–158.
3 Gerber RA, Perry R, Thompson R, Bainbridge C. Dupuytren's contracture: a retrospective database analysis to assess clinical management and costs in England. *BMC Musculoskelet Disord* 2011; **12**: 73.
4 Hindocha S, Stanley JK, Watson S, Bayat A. Dupuytren′s diathesis revisited: evaluation of prognostic indicators for risk of disease recurrence. *J Hand Surg (Am)* 2006; **31**: 1626–1634.
5 Wilbrand S, Ekborn A, Gerdin B. The sex ratio and rate of reoperation for Dupuytren's contracture in men and women. *J Hand Surg (Br)* 1999; **24**: 456–459.
6 Dias JJ, Braybrooke J. Dupuytren's contracture: an audit of the outcomes of surgery. *J Hand Surg (Br)* 2006; **31**: 514–521.
7 Hindocha S, John S, Stanley JK *et al.* The heritability of Dupuytren's disease: familial aggregation and its clinical significance. *J Hand Surg (Am)* 2006; **31**: 204–210.
8 Rayan GM. Dupuytren's disease: anatomy, pathology and presentation. In: Seegenschmiedt H, Bayat A, Gabbiani G, Werker P, Wach W, eds. Dupuytren's Disease and Related Hyperproliferative Disorders (Eaton C. Springer, Berlin, Heidelberg, 2012: 3–10.
9 Augoff K, Kula J, Gosk J, Rutowski R. Epidermal growth factor in Dupuytren's disease. *Plast Reconstr Surg* 2005; **115**: 128–133.
10 Bayat A, Walter J, Helen M. Identification of a novel mitochondrial mutation in Dupuytren's disease using multiplex DHPLC. *Plast Reconstr Surg* 2005; **115**: 134–141.
11 Dolmans GH, Werker PM, Hennies HC *et al.* for the Dutch Dupuytren Study Group, the German Dupuytren Study Group, the LifeLines Cohort Study, and the BSSH-GODD Consortium. Wnt Signaling and Dupuytren's Disease. *N Eng J Med* 2011; **365**: 307–317.
12 Iselin M, Dieckmann G. Notre expérience de traitement de la maladie de Dupuytren. *Mem Acad Chir* 1951; **77**: 251–255.
13 Millesi H. Dupuytren Kontraktur. In: Nigst H, Buck-Gramcko D, Millesi H, eds. Handchirurgie. Georg Thieme Verlag, Stuttgart, 1981: 15.1–15.57.
14 Tubiana R, Michon J, Thomine JM. Evaluation chiffrée des deformations dans la maladie de Dupuytren. In: Tubiana R, Heuston JT, eds. Maladie du Dupuytren. Monographie de G.E.M. Expansion Scientific Francaise, Paris, 1966.
15 Keilholz L, Seegenschmiedt H, Sauer R. Radiotherapy for prevention of disease progression in early-stage Dupuytren's contracture. *Int J Rad Oncol Biol Phys* 1996; **36**: 891–897.
16 Schulze SM, Tursi JP. Postapproval clinical experience in the treatment of Dupuytren's contracture with collagenase clostridium histolyticum (CCH): the first 1000 days. *HAND (NY)* 2014; **9**: 447–458.
17 Canadian Agency for Drugs and Technologies in Health, author. 2013. Needle or open fasciotomy for Dupuytren's Contracture: A review of the comparative efficacy, safety, and cost-effectiveness – an update. URL: https://www.cadth.ca/needle-or-open-fasciotomy-dupuytren (last accessed 17 January 2016).
18 Townley WA, Baker R, Sheppard N, Grobbelaar AO. Dupuytren's contracture unfolded. *BMJ* 2006; **332**: 397–400.
19 Trojian TH, Chu SM. Dupuytren's disease diagnosis and treatment. *Am Fam Physician* 2007; **76**: 86–89.
20 Chen NC, Srinivasan RC, Shauver MJ, Chung KC. A systematic review of outcomes of fasciotomy, aponeurotomy, and collagenase treatments for Dupuytren's contracture. *Hand (NY)* 2011; **6**: 250–255.

21 Seegenschmiedt MH, Micke O, Mücke R; German Cooperative Group on Radiotherapy for Non-malignant Diseases (GCG-BD). Radiotherapy for non-malignant disorders: state of the art and update of the evidence-based practice guidelines. *Br J Radiol* 2015; **88**:20150080.
22 Seegenschmiedt MH, Micke O, Niewald M *et al.* German Cooperative Group on Radiotherapy of Benign Diseases (GCG-BD). *Strahlenther Onkol* 2015; **191**: 541–548.
23 Marchionini A, Schirren CG. Strahlentherapie von Hautkrankheiten. Springer, Berlin, Göttingen, Heidelberg, 1959.
24 Peter RU, Plewig G. Strahlentherapie Dermatologischer Erkrankungen. Blackwell, Berlin, Wien, 1996.
25 Braun-Falco O, Lukacs S. Dermatologische Röntgentherapie: Ein Leitfaden für die Praxis. Springer, Berlin, Heidelberg, 1973.
26 Eaton C, Seegenschmiedt MH, Bayat A *et al.* Dupuytren's Disease and Related Hyperproliferative Disorders. Springer, Berlin, Heidelberg, 2012.
27 Solomon, Bisson, Gibert. Le traitment roentgentherapique de la maladie de dupuytren. *Compte rendu de la 49e session Grenoble* 1923; 1926; 582–583.
28 Herdman WJ. Contraction Dupuytren; indication pour son traitement. *Revue internationale d'électrothérapie* 1905; **14**: 257–263.
29 Reisner A. Behandlung der Hautgeschwülste. *Strahlentherapie* 1949; **79**: 373.
30 Finney R. Dupuytren's contracture – a radiotherapeutic approach. *Lancet* 1953; **265**: 1064–1666.
31 Schirren CG. Röntgentherapie gutartiger Geschwülste der Haut. Dupuytrensche Kontraktur. In: Jadassohn J, ed. Handbuch der Haut- und Geschlechtskrankheiten Ergänzungswerk Bd.. V/2 Strahlentherapie von Hautkrankheiten, Springer Berlin, Göttingen, Heidelberg, 1959; 329–330.
32 Lukacs S, Braun-Falco O, Goldschmidt H. Radiotherapy of benign dermatosis: Indications, practice and results. *J Dermatol Surg Oncol* 1978; **4**: 620–625.
33 Vogt HJ, Hochschau L. Behandlung der Dupuytrenschen Kontraktur. *MMW Münchn Med Wochenschr* 1980; **122**(4): 125–130.
34 Vogt HJ. Strahlentherapie fibrosierender Hauterkrankungen. In: Plewig G, Peter RU, eds. Strahlentherapie dermatologischer Erkrankungen. Blackwell, Berlin, Wien, 1996: 143–160.
35 Zirbs M, Anzeneder T, Bruckbauer H *et al.* Radiotherapy with soft X-rays in Dupuytren's disease – successful, well-tolerated and satisfying. *J Eur Acad Dermatol Venereol* 2015; **29**: 904–911.
36 Herbst M, Regler B. Dupuytren Kontrakur. Radiotherapie der Frühstadien. *Strahlenther* 1985; **161**: 143–147.
37 Keilholz L, Seegenschmiedt MH, Born AD. Radiotherapie im frühen Stadium des Morbus Dupuytren. Indikation, Technik und Langzeitergebnisse. *Strahlenther Onkol* 1997; **173**: 27–35.
38 Betz N, Ott OL, Adamietz B *et al.* Radiotherapy in early-stage Dupuytren's Contracture. *Strahlenther Onkol* 2010; **86**: 82–90.
39 Seegenschmiedt MH, Olschewski T, Guntrum F. Radiotherapy optimization in early-stage Dupuytren's contracture: first results of a randomized clinical study. *Int J Radiat Oncol Biol Phys* 2001; **49**: 785–798.
40 Grenfell S, Borg M. Radiotherapy in fascial fibromatosis: a case series, literature review and considerations for treatment of early-stage disease. *J Med Imag Rad Oncol* 2014; **58**: 641–647.
41 Micke O, Mücke R, Seegenschmiedt MH. 2013. Fachgruppenspezifische evidenzbasierte S2e-Leitlinie der Deutschen Gesellschaft für Radioonkologie (DEGRO). Version 1.0 vom 14.11.2013: 55 – 69. URL: www.degro.org/dav/html/leitlinien/GutartigeErkrankungen.pdf (last accessed 17 January 2016).
42 Seegenschmiedt MH, Keilholz L, Wielpütz M *et al.* Long-term outcome of radiotherapy for early stage dupuytren's disease: a phase iii clinical study (chapter 44). In: Seegenschmiedt MH, Bayat A *et al.*, eds. Dupuytren's Disease and Related Hyperproliferative Disorders (Eaton C. Springer, Berlin, Heidelberg, 2012: 409–427.
43 Rubin P, Soni A, Williams JP. The molecular and cellular biologic basis for radiation treatment of benign proliferative diseases. *Semin Radiat Oncol* 1999; **9**: 203–214.
44 Hesselkamp J, Schulmeyer M, Wiskemann A. Röntgentherapie der Dupuytrenschen Kontraktur im Stadium I. *Therapiewoche* 1981; **31**: 6337–6338.
45 Köhler AH. Die Strahlentherapie der Dupuytrenschen Kontraktur. *Radiobiol Radiother* 1984; **25**: 851–853.
46 Adamietz B, Keilholz L, Grünert J, Sauer R. Die Radiotherapie des Morbus Dupuytren im Frühstadium. *Strahlenther Onkol* 2001; **177**: 604–610.
47 Landthaler M, Hagspiel HJ, Braun-Falco O. Late irradiation damage to the skin caused by soft X-ray radiation therapy of cutaneous tumors. *Arch Dermatol* 1995; **131**: 182–186.
48 Deutsche Dupuytren Gesellschaft. URL: www.dupuytren-online.malade (last accessed 17 January 2016).
49 Jansen J, Boerse J, Zoetelief J *et al.* Estimation of the carcinogenic risk of radiotherapy of benign diseases from shoulder to heel. *Radiother Oncol* 2005; **76**: 270–277.
50 Falter E, Herndl E, Mühlbauer W. Dupuytrensche Kontraktur. Wann operieren? Konservative Behandlung? *Fortsch Med* 1991; **10**: 223–226.
51 Weinzierl G, Flügel M, Geldmacher J. Fehlen der Effektivität der alternativ nichtchirurgischen Behandlungsverfahren bei Morbus Dupuytren. *Chirurg* 1993; **64**: 294–492.

