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RADIOTHERAPY FOR PREVENTION OF DISEASE PROGRESSION IN EARLY-STAGE DUPUYTREN'S CONTRACTURE: INITIAL AND LONG-TERM RESULTS

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Purpose: Radiotherapy (RT) was given to prevent disease progression in early-stage Dupuytren's contracture. Initial response, long-term outcome, and treatment toxicity were evaluated.

Methods: Between 1982 and 1993, 96 patients (142 hands) received orthovoltage RT, which consisted of two courses with daily fractionation of 5×3 Gy (total dose 30 Gy) separated by a 6-week interval. The extent of disease was staged according to the classification of Tubiana *et al.*. Initial evaluation was performed 3 months after completion of RT; long-term outcome was analyzed at last follow-up (i.e., between February and April 1994). The mean follow-up was 6 ± 2 (range 1-12) years. Fifty-seven patients with a minimum follow-up of 5 (median 7.5; mean 9.5-12) years were separately evaluated for long-term outcome (i.e., prevention of disease progression). Acute and late treatment toxicity was assessed using the Radiation Therapy Oncology Group/EORTC criteria.

Results: According to stage, 130 cases (92%) remained stable at 3 months follow-up, 10 improved (7%), and 2 progressed (1%). An objective reduction of symptomatic cords and nodules was achieved in 107 cases (75%) at 3 months follow-up. Moreover, 87% of the patients reported a subjective relief of symptoms. In long-term follow-up, only 16 of 142 cases (11%) had progressed according to stage. In the group with minimum follow-up 5 years ($n = 57$), 44 patients (77%) experienced no disease progression, whereas 13 progressed (23%) inside [8 cases (14%)] or outside [5 cases (9%)] of the RT field. Most failures could have been avoided with appropriate choice of larger safety margins included in the treated portals; however, the failures outside were still amenable for another RT course.

Conclusion: Radiotherapy is effective to prevent disease progression for early-stage Dupuytren's contracture. Thus, it helps to avoid an otherwise necessary surgical procedure which is performed in advanced stages of Dupuytren's contracture. Copyright © 1996 Elsevier Science Inc.

Dupuytren's disease (contracture), Benign diseases, Radiotherapy, Surgery.

INTRODUCTION

Dupuytren's contracture (DC) is a spontaneously occurring connective tissue disorder which involves the palmar fascia of the hand. Generally, a tough induration of the palm and a flexion contraction or extension deficit of the fingers develops which can slowly progress and cause severe functional impairment. In the early stage of the disease, subcutaneous nodules with fixation to the overlying skin occur; later, the formation of tough cords is predominant. The tough cords can progress to the depth of the periosteum of the bone (13, 26, 32). Further disease progression is characterized by retraction of the palmar fascia and contracture of the medial phalangeal (MP) and proximal interphalangeal (PIP) finger joints (preferably the

fourth and fifth fingers). This leads to the typical flexion deformity of the hand and extension deficit of the fingers. The degree of functional loss is the basis of the clinical staging system for DC (26).

Dupuytren's contracture was initially described by the Swiss physician Felix Platter (1614) and Sir Astley Cooper (1824), but it was the French anatomist Baron Guillaume Dupuytren, with his famous lecture in 1831, whose name is associated with the disease (6, 7). More recently, several comprehensive reviews have addressed this disease (25, 28). The nature and demography of DC are not entirely clear. Dupuytren's contracture has a prevalence of 1-3% (37) but varies widely in different parts of the world (34). It mainly affects Caucasians (3, 8) and has its highest reported prevalence of 17% in a small Irish (31)

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and French subpopulation (4). In the reunited Germany, with nearly 80 million inhabitants, the prevalence of DC is estimated between 1.3 and 1.9 million. Dupuytren's contracture occurs in men > 40 years of age and with a male to female ratio of 3:1 (41). Positive family history is more common in women than men (8, 21, 25). Dupuytren's contracture is not coincidental to handedness (18), but two-thirds have a bilateral affliction (25). An increased manifestation occurs in alcoholics, diabetics, and epileptics (3), but the etiology and pathogenesis are still poorly understood.

Luck (23) divided the clinical course and corresponding histologic features of DC into three phases: (a) the proliferation stage is characterized by an increased presence of fibroblasts; (b) the involution stage is defined by the accumulation of myofibroblasts in the fibrinoid tissue of the diseased fiber bundles, which finally leads to the induction of the typical contracture; (c) in the residual stage, collagenous fibers dominate connective tissues of aponeurosis and neighbouring structures (27, 35). In contrast to the pathologic features of desmoid tumors, DC displays no invasion of the voluntary muscles (1).

The treatment of DC is controversial, because the disease may either slowly progress, stabilize, or spontaneously regress. Without therapy, progression is observed in about 50% after 6 years or more (26). Thus, therapeutic success should be assessed in long-term follow-up. In the early stage of DC, no treatment has been firmly established including surgery or nonoperative methods. Most drugs including steroids, allopurinol, nonsteroidal anti-inflammatory drugs, enzymes, vitamin E, and softening agents have no long-term impact on disease progression (9, 29). Surgery is regarded as the only effective therapy, but is reserved for advanced stages, when flexion deformity and function limiting extension deficit have already developed. Thus, many patients are uncertain about their individual fate and are without a therapeutic option to prevent possible progression. In terms of surgery, a limited fasciectomy is sufficient in most cases; in advanced stages, a total fasciectomy may be necessary (12). Surgical methods are compromised by a complication rate of 15–20% (9, 12, 22, 25). Moreover, disease progression is observed in 30–50% of operated cases (26), either due to incomplete resection of involved connective tissues or to surgically induced scars (18). The rapid progression in the advanced DC stages (26) provides a good rationale for testing alternate methods to prevent disease progression in an early-stage DC.

Ionizing radiation should be tested as a preventive agent, because proliferating fibroblasts provide a good radiosensitive target. A recent textbook (30), which included a national survey on treatment policies for benign diseases in the United States, did not strongly support the use of radiotherapy (RT); another reference (5) and many historical studies (2, 11, 15–17, 19, 20, 24, 38, 39) reported quite favorable results when using RT. Herein, we present a retrospective analysis of initial and long-term outcome

in a consecutive series of patients treated with orthovoltage RT for prevention of disease progression in early stage DC.

PATIENTS AND METHODS

Patients

From 1982 through 1993, 153 patients with clinically evident DC were treated at our institution. Of those, a total of 96 patients (63%) received the prescribed irradiation and had complete follow-up (FU) data. Of the missing 57 patients, 7 were dead and 13 lost to FU; 37 were excluded, as the applied RT protocol deviated in some aspects from the prescribed RT regimen. Patients were contacted and examined in long-term FU between February and April 1994.

Dupuytren's contracture was localized on the right hand in 32, and on the left in 18 patients. Because of double-sided affliction in 46 patients (48%), a total of 142 hands were included in this analysis. The mean age of the 66 men and 30 women was 54 ± 14 years (median 56, range 18–82). A positive family history was reported in 22 men (33%) and 11 women (37%). The patient records revealed 2 evident epileptics, 11 diabetics, and 17 alcoholics. Typical symptoms of DC were reported in 82 cases (58%), including burning and itching sensations and a feeling of pressure and tension in the palm. The mean duration of clinical symptoms before RT was 8 ± 4 years (mean 9, range 1–30). The excluded group of patients had a similar pattern of patient and disease-related parameters.

Clinical evaluation

The stage of disease, size and consistency of palpable nodules and cords, and subjective changes of symptoms (as described by the patient) were carefully analyzed to assess initial (at 3-month FU) and long-term (at actual FU) response to RT. Acute and late toxicity of skin and subcutaneous tissues were scored according to Radiation Therapy Oncology Group/European Organization Research and Treatment of Cancer (EORTC) criteria. Functional changes and flexion deformity of fingers were measured using a protractor. The size of nodules and cords were directly measured and their consistency palpated. Long-term results were analyzed for all cases (Group A, $n = 142$) with a mean FU of 6 ± 2 years (range 1–12), as well as for a subgroup of patients (Group B, $n = 57$), which had a minimum FU of 5 years (mean: 7.5 ± 3).

Clinical end points

The following clinical end points were assessed in short- and long-term FU:

- Stage of disease was classified according to Tubiana *et al.* (36). This classification is based on the total flexion deformity/extension deficit of the involved MP and PIP finger joints: Stage 0 = no (apparent) lesion; Stage N = nodules without flexion deformity; Stage I = 1–45°;

Table 1. Stage distribution and patient characteristics prior to RT

Stage of MD*	Total group (n = 142)		Group with FU >5 years (n = 57)	
	n	(%)	n	(%)
Stage N: nodes without flexion deformity	82	(58)	28	(49)
Stage N/I: nodes with flexion deformity 1–5°	17	(12)	10	(18)
Stage I: nodes with flexion deformity 6–45°	30	(21)	17	(30)
Stage II: nodes with flexion deformity 46–90°	12	(8)	1	(2)
Stage III: nodes with flexion deformity >90°	1	(1)	1	(2)

* Modified classification according to Tubiana, *et al.* (36). The distribution of stages between both groups of patients was not significant.

Stage II = 46–90°; Stage III: 91–135°; Stage IV = >135° flexion deformity. Because Stage I defines a very large range of functional deficit which does not allow differentiation between early and late changes, an intermediate Stage N/I was defined which allows classification of early afflictions with a minimal flexion deformity between 1° and 5°. The specific stage distribution of all 142 cases before RT according to this modified staging system is summarized in Table 1.

- Dimensions and consistency of palpable nodules and cords were independently assessed, measured, and categorized by two examiners (L.K. and M.H.S.). The individual findings were drawn on the skin surface using markers and documented on a photocopy print at a 1:1 scale using the method of Herbst and Regler (16). Palpable indurations were quantified in five different grades: P = progression of flexion deformity or enlargement of the involved area of the palm; 0 = no change of the flexion deformity and the involved area of the palm; R+/+/+/+/+ = regression of nodules and cords in three categories: moderate = reduction of nodule or cord size by 25–50% with some softening; good = reduction of nodule or cord size by 51–75% with major softening; excellent = reduction of nodule or cord size by >75% or complete resolution.

Patients who underwent hand surgery in long-term FU were scored as progression (P).

- Subjective patient complaints and symptoms were documented on the patient's chart, including burning, itch-

ing, tension, and pressure sensations before RT. For all 142 cases, the distribution of the subjective symptoms, palpable cords or nodules, and measurable flexion deformity before RT are summarized in Table 2.

Radiation Therapy

The application of RT was based on the objective findings of each hand and the individual grade and extent of DC. RT was carried out with orthovoltage X rays (Stabilipan: Siemens Company, Erlangen, Germany) using 120-kV photons/20 mA per 2-mm aluminum filter. A 6 × 8-cm cone with a focus skin distance (FSD) of 40 cm was used. Uninvolved areas of the palm were individually shielded by placing 3-mm-thick lead cutouts. Our treatment policy was to irradiate all afflicted areas with a distal and proximal margin of 1 cm and lateral margins of 0.5 cm around all palpable cords and nodules. The RT was prescribed in two separate courses of 5 × 3 Gy each and a total dose of 30 Gy. The interval between the two RT courses was 6 weeks. The RT dose was individually prescribed with the skin surface as the reference dose level. The recommended radiation protection measures (beam direction, patient positioning, lead apron, etc.) were applied.

RESULTS

Initial response

The following findings were noted 3 months after RT:

1. A total of 130 afflicted hands (92%) had no progression of stage according to the classification system. Twelve

Table 2. Distribution of symptoms, nodules, and cords prior to RT

Disease symptoms*	Total group (n = 142)		Subgroup FU >5 years (n = 57)	
	n	(%)	n	(%)
Burning, itching, pressure, and tension	82	(58)	28	(49)
Skin fixation	32	(23)	17	(29)
Palpable nodes	119	(84)	44	(78)
Palpable cords	106	(75)	39	(68)
Objective measurable flexion deformity (≥ 1°)	60	(42)	29	(51)

* Multiple signs and symptoms per case are possible. The distribution of symptoms between both patient groups was not significant.

- hands changed DC stage: 10 (7%) improved and 2 (1%) decreased in their functional status. Improvement was noted in 2 of 82 hands (2%) with Stage N, 5 of 17 with Stage N/I (29%), and 3 of 30 with Stage I (10%). Stage II or III cases did not improve. In addition, there were two progressions from Stage I to Stage II.
- With regard to size and consistency of palpable nodules and cords, 33 hands (23%) remained stable and 107 (75%) achieved a reduction of size and softer consistency: 65 of 82 in Stage N (79%); 15 of 17 in Stage N/I (88%); 22 of 30 in Stage I (73%); and 5 of 13 in Stage II or III (38%). The improvement was significant only with regard to Stage II/III ($p < 0.05$). Two cases with impaired flexion deformity (stage progression) progressed in terms of nodule and cord consistency and DC-related symptoms. This progression started 6 and 9 months after RT. Further details of the results are summarized in Table 3.
 - With regard to complaints and symptoms, 25 remained unchanged (18%); 64 displayed a moderate reduction (45%) and 41 a major reduction (29%), whereas 6 reached a complete relief (4%) of symptoms. Six cases developed worse symptoms, 2 parallel with DC progression and 4 despite DC stabilization.

Long-term results

The following long-term results were found in Group A ($n = 142$ hands):

- In long-term FU, no further downstaging was achieved. Besides two initial progressions, 7 other progressions (5%) were observed within the RT field. Subsequently, 6 of these cases underwent surgery. Thus, 133 cases (94%) remained stable or even improved within the RT field. As 7 progressions (5%) occurred outside the RT field, the total progression rate amounted to 16 cases (11%).
- With regard to size and consistency of palpable nodules and cords, further changes in long-term FU were minimal. Thus, 24 hands (17%) remained stable, 102 (72%) improved in size and consistency, and 16 (11%) showed a progression in terms of nodule and cord size and consistency. Of those, 9 (6%) were located inside and 7 (5%) outside the RT portal.

- Patients' complaints and symptoms in long-term FU were relatively minor, such that 83 of 96 (87%) were satisfied with the long-term outcome.

In Group B ($n = 57$) with 5-year minimum FU, progression according to DC stage was observed in 13 hands (23%), whereas 44 hands (77%) had stable [38 (67%)] or improved [6 (11%)] condition. Eight cases (14%) progressed within the RT field, whereas five (9%) progressed outside. With regard to size and consistency of nodules and cords, 8 cases (14%) remained in stable condition, 41 (72%) improved, and 8 (14%) progressed within the RT field.

In summary, only 13 progressions occurred after a median FU of 5 years. Two reasons were attributed to failures: five progressions occurred at the edge of the RT field owing to an underestimation of the DC extension or to underdosage within the RT field. All progressions outside the RT field were reirradiated without relapse or surgical treatment in long-term FU.

Treatment toxicity

A total of 61 hands (43%) developed acute mild skin reactions (Grade 1), erythema, and dry desquamation. During RT, most patients complained of itching and burning sensations. Fourteen cases (10%) developed radiodermatitis (Grade 2) with pronounced erythema and moderate edema. Grade 3/4 toxicities were not observed. Within the irradiated area, only minor long-term radiogenic skin and subcutaneous changes were found in 110 hands (77%): 91 (64%) had dry skin and increased desquamation, 19 (13%) had mild skin atrophy accompanied by slight fibrosis or occasional teleangiectasia. Chronic Grade 3 or 4 reactions were not observed.

DISCUSSION

Despite a good clinical rationale, the basic mechanisms of ionizing radiation to prevent disease progression in DC are not well understood. Obviously, a high concentration of free radicals can severely damage fibroblasts and may reduce their cell density and impair their proliferative activity (29). Thus, it might be assumed that ionizing radiation produces high concentrations of free radicals in the

Table 3. Change of palpable nodules and cords (according to stage) after 3 months FU

Stage of disease*	Stable condition (O)	Regression of size and consistency			Progression of findings (P)
		R+	R++	R+++	
Stage N ($n = 82$)	17	35	23	7	
Stage N/I ($n = 17$)	2	6	7	2	
Stage I ($n = 30$)	6	6	10	6	2
Stage II/III ($n = 12$)	8	5			
Total	33 (23%)	52 (37%)	40 (28%)	15 (11%)	2 (1%)

* Modified classification system according to Tubiana *et al.* (36). The distribution between the different stages was not significant.

Table 4. Literature Review: Clinical Results of Radiotherapy (RT) for Dupuytren's Contracture

Study	Patients (n)	Cases (n)	RT prescription		Follow-up [years (%)]	Clinical outcome		
			Fractionation	RT dose		Improvement	Stable	Progression
Finney (11)	43		1-3 RT palmar mold r.	1000-3000 r surface dose	Not specified 25 cases (58%)	15/25 (60%) good functional results		
Wasserburger (39)	213		1-3 RT: 400 mg RaE1	1000-3000 r surface dose	Long period: 146 patients (69%)	Stage I: 62/69 (90%); II: 26/46 (57%); III: 10/31 (32%)	Long-term cure:	
Lukaacs <i>et al.</i> (24)	106	(158) I 140 II/III 18	RT day 1 + 2 8 wk break 4 RT courses	4 Gy SD 32 Gy TD	Not specified 36 cases (23%)	Overall: 29 (81%) I 26/32 (81%) II 3/ 4 (75%)	Overall: 7 (19%) I: 6/32 (19%)	none
Vogt and Hochschau (38)	109 1 98 II 4 III/IV 7	(154)	RT day 1 + 2 8 wk break 4 RT courses	4 Gy SD 32 Gy SD	>3 years: 109 patients (63%)	Overall: 22 (20%) 21/98 (21%) II 1/ 4 (25%) III/IV	Overall: 81 (74%) I 73/98 (74%) II 2/4 (50%) III 6/7 (86%)	6 (6%); 1 4/98 (4%) II 1/4 (25%) III 1/5 (20%)
Hesselkamp <i>et al.</i> (17)	46 Stage I	(65)	RT day 1 + 2 3 mo break 5 RT courses	4 Gy SD 40 Gy TD	1-9 years: 46 patients (53%)	Overall: 24 (52%)	Overall: 19 (41%)	3 (7%);
Köhler (20)	31 Stage I	(38)	RT 3-5 X/wk 1 RT course	2 Gy SD 20 Gy TD	1-3 years: 33 cases (87%)	Overall: 7 (21%)	Overall: 20 (61%)	6 (18%)
Herbst und Regler (16)	33	(46)	RT: 5 X/wk 4- 12 wk break 1-2 RT courses	3 Gy SD 9-42 Gy TD	>1.5 years: 46 cases (100%)	None	Overall: 45 (98%)	1 (2%)
Erlangen	96	(142) I 129 II 12 III 1	RT: 5 X/wk 6 wk break 2 RT courses	3 Gy/30 Gy	1-12 years, median 6 years: 96/153 (63%)	Overall: 102 (72%) symptoms; stage: 10 (7%)	Overall: 24 (17%) symptoms; stage: 116 (82%)	16 (11%) symptoms; 16 (11%) range

SD, TD = single, total dose; I, II, III, IV = Dupuytren's contracture stages according the classification system of Tubiana *et al.* (36).

connective tissue of the palmar aponeurosis, which reduces the accumulated fibroblasts and induces a transition from a proliferative to a residual stage of Dupuytren's disease.

The results of our study are well confirmed in the literature (11, 16, 17, 20, 24, 38, 39) (Table 4). In all studies RT was preferably applied for early stages of DC. Nevertheless, the available data are heterogeneous with regard to (a) the reported patient population (different stages, proportion of patients followed in long-term FU); (b) the chosen RT prescription (fractionation, courses, single and total RT dose); (c) the assessed treatment end points; and (d) the reported FU. Thus, a direct comparison among these studies and with ours is not easy.

The potential of RT to stabilize the disease process was shown in several studies: Lukacs *et al.* (24) observed no progression in 36 cases, but presented only 23% of the originally treated patients and did not state the FU period. Hesselkamp *et al.* (17) studied 46 patients with a minimum FU of 2 years, who achieved improved or stable conditions in 93%. Nearly identical results were reported by Vogt and Hochschau (38), who followed 109 of 172 patients (63%) for more than 3 years: 81 cases (74%) remained stable in Stage I, whereas 22 (20%) improved. Köhler (20) observed 33 patients for 1–3 years; 7 cases (21%) improved, 20 (61%) remained stable, and 6 (18%) progressed. In the initial clinical experience of our institution, which was summarized by Herbst and Regler (16), 45 of 46 cases (98%) remained stable after a short median FU of 1.5 years.

Our study provides much longer FU data than others, which allows analysis of long-term effects of RT. After a median FU of 6 years for the whole group, only 16 cases (11%) had progressed. However, taking into account only cases which progressed within the RT field, the progression rate was even lower [i.e., 8 of 142 (6%)]. When considering the group with at least 5 years FU (median FU 7.5), 44 cases (77%) remained stable or improved. This confirms the efficacy of RT to prevent disease progression in long-term FU. Moreover, most cases [41 (72%)] had reduced symptoms (i.e., an involution of nodules, cords, and strands). Of 13 failures, only 8 of 57 (14%) progressed within the RT field and 5 (9%) outside the RT field. This total progression rate of 23% is considerably lower than the reported 50% progression rate of untreated patients or patients who undergo surgery in the more advanced stages of DC (26).

Among surgeons, RT is not well accepted for various reasons (40). We agree that advanced Stages II–IV do not benefit from prophylactic or therapeutic RT. This has been observed in our study as well as in the literature (Table 4). Thus, all advanced cases should be transferred to a hand surgeon. The rationale for RT applies only to early Stages N and N/I, in which the symptoms and the functional deficit are still minor, as about 50% of all cases will progress and suffer functional loss in later times. Moreover, if patients with Stage I disease refuse surgery, they may also gain long-term stabilization using RT as preven-

tive measure. Interestingly, our patient accrual originated more from general practitioners and orthopedics than from hand surgeons.

There is no clear-cut dose–response relationship for DC. Some data (20) suggest that single doses of ≥ 2 Gy and total doses of ≥ 20 Gy are required to keep the progression rate low. Similar responses were reported by Vogt and Hochschau (38) when using 4 Gy twice weekly every 8 weeks up to a total dose of 32 Gy. Similarly, Hesselkamp *et al.* (17) used the same single dose of 4 Gy, but an interval of 3 months between different RT courses; they escalated the total dose to 40 Gy depending on the individual clinical findings. Large single doses of 1000 r/session every 3–6 months and up to 3000 Roentgen total dose were applied in early studies (11, 39).

In our study, a single dose of 3 Gy and a total dose of 30 Gy were very effective. With this schedule, side effects were still minor. Generally, the total RT dose should not compromise surgical procedures after RT in case of treatment failure (9). However, none of our patients who underwent surgery for progression experienced severe perioperative complications.

The size of the RT field appears to be very critical for treatment outcome. Whereas Hesselkamp *et al.* (17) irradiated the whole palm, Vogt and Hochschau (38) included only the diseased areas. Both studies recorded a low progression rate of 6–7%. In our study, 8 in-field relapses and 5 progressions outside the RT field were observed after a mean FU of 5 years. As some failures occur owing to an underestimation of the longitudinal and lateral extension of DC, larger safety margins (2 cm longitudinal, 1 cm lateral) around all visible and palpable lesions may reduce the relapse rate by $>50\%$. Fortunately, any later disease progression is amenable to a second RT course, as long as there is no overlap with the original RT portal. In summary, we would not support Köhler's suggestion (20) to treat the entire palmar aponeurosis; instead, we prefer to deliver supplemental RT treatment if progression occurs anywhere outside the treated RT field.

The applied RT techniques have varied widely. Early studies used radium grip cylinders or palmar molds (11, 39). Some groups recommended 50 kV radiation with a tissue half-value layer (HVL) of 14 mm (14, 17, 38). However, in our opinion, this HVL is too small to treat pronounced nodules and cords reaching down to the periosmium. Similar to other groups (5, 11, 19), we prefer 120 kV/20 mA orthovoltage radiation with an HVL of 33 mm to reach all structures of the aponeurosis (5, 11, 19). Contact radium therapy has been also successfully applied (11, 39), but inappropriate dosage may lead to poor results (33). Finck (10) observed no relapse of disease when using 70–100 mg radium element hours per treatment and two to five treatments at intervals of 4–8 weeks. Generally, careful dosimetry, precise dose prescription to the appropriate target volume, and diligent treatment application to all involved areas of DC are the most important requirements to achieve favorable long-

term results, and to prevent further disease progression in DC.

CONCLUSION

Radiotherapy for early-stage DC was very effective in long-term FU to prevent disease progression in about 75%

of treated cases. The observed acute and late toxicities were acceptable. RT did not increase the complication rate when surgery became necessary at a later point in the course of the disease. Thus, RT appears to be the treatment of choice in early-stage DC. Prospective multicenter studies are warranted.

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