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Radiotherapy is used to treat not only malignant tumors but also benign inflammatory and hypertrophic diseases. Because of concerns about the potential hazards of irradiation, physicians in many countries, especially in North America, ruled radiotherapy out of medical practice for non-malignant diseases. Low-dose radiotherapy modulates the inflammatory response, providing an anti-inflammatory effect. Many researchers have reported low-dose radiotherapy efficacious for degenerative and inflammatory diseases. There are broad potential clinical indications for radiotherapy of non-malignant diseases. The general indications for radiotherapy for non-malignant disorders are acute/chronic painful degenerative diseases, such as chronic or acute painful osteoarthritic diseases of various joints; hypertrophic (hyperproliferative) disorders of soft tissues, such as early stages of Morbus Dupuytren and Ledderhose, keloids and pterygium; functional diseases, such as dysthyroid ophthalmopathy and arteriovenous malformations; and others, such as prophylaxis of heterotopic ossification. Radiotherapy for non-malignant disorders may be safely and effectively used, especially in older patients who suffered from these disorders and those who are reluctant to use other treatment options. (J Rheum Dis 2017;24:74-84)

Key Words. Radiotherapy, Osteoarthritis, Tendinitis, Dupuytren contracture

INTRODUCTION

Ionizing radiation, such as photons (X-rays and gamma rays), electrons, and charged particles, is used to treat benign inflammatory and hypertrophic diseases, as well as malignant tumors. For several decades, irradiation of non-malignant disorders was a common practice. For example, in Leiden in the Netherlands in 1925, 37 patients had radiotherapy for malignant tumors and 143 patients had radiotherapy for non-malignant disorders. In the Rotterdam Radiotherapeutic Institute (Daniel den Hoed Clinic), 3,348 non-malignant disorders were irradiated in 1948 compared with 857 malignant tumors [1]. However, many people and physician are concerned about the potential hazards of tumor or leukemia induction and somatic changes after radiation exposure [2-4]. For that reason, in many countries, especially in North America and Korea, irradiation of non-malignant diseases gradually became less acceptable as a good medical practice and most indications disappeared. Nevertheless, Korean National Health Insurance covers radiotherapy for most non-malignant disorders.

Worldwide, acceptance of radiotherapy for non-malignant diseases varies widely depending on the geographic region and type of non-malignant disease [1]. A few treatment indications are generally accepted, e.g., post-operative prophylaxis of keloids and heterotopic ossification and radiotherapy of dysthyroid ophthalmopathy and desmoids; these indications have a positive approval of over 50% worldwide. In contrast, other indications revealed a divergent acceptance in different regions, e.g., radiotherapy of painful osteoarthrosis (Eastern Europe,
Radiobiological mechanisms

The efficacy of radiotherapy for non-malignant disorders, based on the anti-inflammatory properties of low-dose ionizing radiation, has long been recognized. Low-dose of radiation is known to modulate the inflammatory response, providing an anti-inflammatory effect, while high-dose radiotherapy induces the production of pro-inflammatory cytokines. Many researchers have reported the efficacy of low-dose radiotherapy for the treatment of degenerative and inflammatory diseases. Radiation modulates the function of various inflammatory cells including endothelial cells, polymorphonuclear leukocytes, and macrophages. Even though the current understanding of this process is incomplete, some of these mechanisms have been elucidated.

The objective of this review is to summarize currently proven radiobiological mechanisms in the treatment of non-malignant diseases and to provide information about its clinical applications.

**MAIN SUBJECTS**

Radiobiological mechanisms

The interrelationship between ionizing radiation and the immune system displays a dichotomous character and depends highly on the radiation dose/quality and the immune cell population investigated. In general, X-ray treatments with single doses ≥2 Gy exert proinflammatory effects, while low-dose radiation therapy (single doses <1 Gy) has been shown to modulate a variety of inflammatory processes and clearly shows anti-inflammatory properties [5]. This implies the involvement of complex mechanisms operating differentially at different dose levels.

1) Radiation effects on endothelial cells

The development of an inflammatory response is finely regulated by sequential leukocyte-endothelial cell interactions and by the action of inflammatory mediator and adhesion molecules. The adhesion of blood leukocytes to endothelial cells is an essential process during the development of the inflammation. After low-dose irradiation, reduced adhesiveness of blood leukocytes to endothelial cells was observed [6]. Roedel et al. [7] reported that the production of transforming growth factor β1 (TGF-β1) and interleukin-6 (IL-6) was increased at 24 hours after irradiation of murine endothelial cells. In their RNase-protection assays, adhesion of blood mononuclear cells to endothelial cells was at a minimum after exposure to 0.5 Gy of radiation in the range of 0.3 Gy to 3 Gy. TGF-β1 is known to be a key endogenous factor with a potent effect of regulating inflammation. Addition of TGF-β1 to culture medium inhibits leukocyte adhesion in human endothelial cells [8]. In another study regarding the time course, reduced leukocyte adhesiveness to human endothelial cells was observed as biphasic pattern at 4~8 hours and 24~30 hours after irradiation [9]. Another key molecule involved in the anti-inflammatory process of irradiation is NF-κB. Prasad et al. [10] reported that NF-κB showed peak activity at 8 hours and 36 hours following a 0.5 Gy exposure in 244B lymphoblastoid- and B16 melanoma cancer cells. In accordance with an experiment by Prasad et al. [10], an increased NF-κB DNA-binding activity was observed in stimulated human endothelial cells with a maximum at 0.5 Gy. The NF-κB activity was decreased after irradiation at 0.6~0.8 Gy and subsequently increased again at doses of 1 and 3 Gy [11].

2) Radiation effects on leukocytes and macrophages

Neutrophils and their products (e.g., proteases and reactive oxygen species) have been reported to have a relationship with the tissue- and organ-damage associated with inflammation and inflammatory diseases, including rheumatoid arthritis and vasculitis [12,13]. C-C motif chemokine ligand 20 (CCL20) is one of the chemotactic cytokines that neutrophils can produce. After irradiation of endothelial cells and neutrophils, CCL20 secretion is induced by direct contact between neutrophil and endothelial cells. Irradiation with doses between 0.5 Gy and 1 Gy results in a significant reduction of CCL20 secretion. The reduction in CCL20 secretion is correlated with neutrophil adhesion to the endothelial cells [14]. In an experiment by Kern et al. [15], apoptosis of human peripheral blood monocytes was increased dose-dependently. In their experiment, 80% of donors and 47% of samples showed a maximum of apoptosis peaking at a radiation dose between 0.3 and 0.7 Gy. A similar observation was reported by Gaipl et al. [16], in which apoptosis in polymorphonuclear cells was a maximum at 0.3 Gy and a minimum at 0.5 Gy. More recent data further indicate hampered nuclear translocation of the NF-κB/p65 transcription factor, lowered secretion of proinflammatory cy...
tikine IL-1, and increased expression of TGF-β1 by inflammation-stimulated macrophages, concomitant with a significantly reduced migration capability [17]. In conclusion, low-dose X-ray irradiation, most pronounced at a dose of 0.5 Gy, induces an anti-inflammatory cytokine microenvironment for macrophages, which might be accompanied by a resolution of inflammation.

3) In vivo animal models
The efficiency of low-dose radiotherapy has also been proven in several in vivo animal models of inducible arthritis. Some researchers investigated the radiation effect on arthritis using rat models with a variety of arthritis-inducing methods. Hildebrandt et al. [18] induced arthritis in rats by intra-articular injection of inactivated Mycobacterium tuberculosis. They compared an irradiation dose of 1 Gy with 5 fractions and 0.5 Gy with 5 fractions. Prevention of further joint swelling and a reduction in cartilage and bone destruction were observed, but no differences between dose fractionation schedules were found. In another study by the same group, these anti-inflammatory effects seemed to be correlated with reduced inducible nitric oxide synthase (iNOS) activity and increased hemoxygenase 1 (HO-1) levels [19]. Schaue et al. [20] demonstrated that the expression of iNOS was attenuated by radiation concomitant with an increase in the levels of HO-1 and heat shock protein 70 by using a murine carrageenan air pouch model.

Arenas et al. [21] showed that radiation with doses of 0.1, 0.3, or 0.6 Gy reduced leukocyte adhesion to intestinal venules in mice, and that the maximum effect was achieved at doses of 0.3 Gy. This study showed that low-dose radiotherapy has significant anti-inflammatory effects, inhibiting leukocyte recruitment and increasing circulating levels of TGF-β1.

The optimal timing of radiotherapy during inflammatory processes was evaluated by the following two studies, and both studies suggested that irradiation during the early inflammatory phase was more efficient. Frey et al. [22] used a human tumor necrosis factor (TNF-) transgenic mouse model that expressed the human cytokine TNF-α and that develop chronic polyarthritis at an age of 4~6 weeks. Symptoms of polyarthritis of mice were significantly improved by irradiation with 2.5 Gy in 5 fractions during the beginning of the disease. In the study by Liebmann et al. [23], 5 Gy in 5 fractions and 2.5 Gy in 5 fractions with various treatment schedules were tested on inducible arthritis models in rats. The most pronounced treatment effect was observed after two daily fractionated series of 2.5 Gy in 5 fractions with an early treatment onset and repetition interval.

Clinical application of low-dose radiotherapy
The potential clinical indications for radiotherapy of non-malignant diseases are various, and an interdisciplinary agreement has not always been achieved. According to the German Working Group on Radiotherapy of Benign Diseases, the general indications for radiotherapy in German-speaking countries and in central and Eastern European region are as follows [24]:

1. Acute/chronic inflammatory disorders, e.g., axillary sweat gland abscess, furuncula, carbuncula, paranthrium, and other infections not responding to antibiotics

2. Acute/chronic painful degenerative diseases, e.g., insertion tendinitis and chronic or acute painful osteoarthritic diseases of various joints (e.g., hip and knee)

3. Hypertrophic (hyperproliferative) disorders of soft tissues, e.g., prophylactic radiotherapy in early stages of Morbus Dupuytren and Ledderhose, and Morbus Peyronie (induratio penis plastica), and postoperative prophylaxis of recurrence for keloids and pterygium

4. Functional diseases, such as dysthyroid ophthalmopathy, arteriovenous malformations, age-related macular degeneration, persisting lymphatic fistula

5. Other indications, such as prophylaxis of heterotopic ossification at various joints, prophylaxis of neointimal hyperplasia, e.g., after arterial dilatation or stent implantation, obstruction of hemangiomas and other vascular disorders of various organs

6. Dermatologic diseases, e.g., pruritus due to itching dermatoses and eczemas, inaccessible psoriatic focuses (e.g., subungual focuses), basaloma

After a patient and his/her physician decide to receive radiotherapy, these steps are generally followed (Figure 1A): At first, a consultation with a radiation oncologist will be conducted to discuss the role and possible side effects of radiotherapy and to determine the type and dose of radiotherapy to be used. During the simulation process, the patient’s computed tomography (CT) images are obtained. Sometimes, specific areas of the body need to be immobilized by a thermoplastic mask and/or an evacuated cushion (Figure 1B) to prevent movement during radiotherapy. Once the simulation process is completed, the scanned images are sent to the treatment planning system. The radiation oncologist contours the target volume and normal organs at risk. A medical physicist gen-
erates treatment planning using sophisticated computer software, a process that can take several days. After the completion of the treatment planning process, the radiation oncologist then determines the total area that will be irradiated, the total dose that will be delivered to the target volume, and the radiation dose that will be delivered to the normal organs around the tumor. After the radiation oncologist approves the radiotherapy plan, the patient can start treatment.

On the first day of the treatment and usually at least once per week, simple radiography or cone beam CT images are taken to check the accuracy of the patient setup during radiotherapy. The patient meets with the radiation oncologist at least once per week to discuss the treatment progress and any radiation side effects.

1) Painful degenerative disorders including osteoarthritis and tendinitis

Painful degenerative joint disorders are the most common indications for radiotherapy of non-malignant diseases. In this category, painful osteoarthritis and tendinitis involving various joints have been successfully treated with radiotherapy (Table 1). Osteoarthritis is a degenerative disorder of articular cartilage and tendinitis is a soft tissue disorder involving the attachment site of a tendon or ligament to a bone. Although little is known about the accurate biologic mechanism of the radiation effect on osteoarthritis, clinical data suggest that low-dose radiotherapy is effective for the treatment of painful osteoarthritis [25-28].

Trott and Kamprad [29] raised the possibility that the synovial membrane may be the critical target of radiotherapy for osteoarthritis, on the basis of the results from previous animal model experiments. They also hypothesized that the effect of radiation in relieving symptoms of tendinitis may be related to decreased activity of iNOS pathways and NO production.

Seegenschmiedt and Keilholz [30] reported the results of 200 patients with epicondylopathia humeri (n=104) and peritendiniti humeroscapularis (n=96) treated with radiotherapy. Complete pain relief and partial pain relief was achieved in 50% and 21% for elbow patients and 48% and 26% for shoulder patients, respectively. Niewald et al. [31] reported similar findings in 140 patients with shoulder periarthritis in which pain relief and improvement of motility was 59% and 89%, respectively, at a median 4.5 months after radiotherapy. Both studies used a low radiation dose of 6 Gy in 6 fractions, 6 Gy in 12 fractions, or 3 Gy in 6 fractions.

Plantar fasciitis, also known as painful heel spurs, has
Table 1. Summary of the studies of radiotherapy for painful degenerative diseases

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Year</th>
<th>Patient, n</th>
<th>Response rate</th>
<th>Daily dose (Gy) × fraction</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seegenschmiedt et al. [30]</td>
<td>Epicondylopathia humeri (EPH)/peritendinitis humeroscapularis (PHS)</td>
<td>1998</td>
<td>200</td>
<td>Complete response: EPH 51%, PHS 48%</td>
<td>1.0×6</td>
<td>No side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial response: EPH 20%, PHS 26%</td>
<td>0.5×12</td>
<td>No secondary malignancy</td>
</tr>
<tr>
<td>Niewald et al. [31]</td>
<td>Periarthritis of the shoulder</td>
<td>2007</td>
<td>141</td>
<td>Pain relief: 69%</td>
<td>1.0×6</td>
<td>No side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Motility improvement: 89%</td>
<td>(mostly)</td>
<td>NA</td>
</tr>
<tr>
<td>Ott et al. [25]*</td>
<td>Painful elbow syndrome</td>
<td>2012</td>
<td>199</td>
<td>Early response: 80%</td>
<td>0.5×6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Delayed response: 91%</td>
<td>1×6</td>
<td>NA</td>
</tr>
<tr>
<td>Hermann et al. [34]</td>
<td>Plantar fasciitis</td>
<td>2013</td>
<td>250</td>
<td>Complete response: 38%</td>
<td>0.5×6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial response: 32%</td>
<td>1×6</td>
<td>NA</td>
</tr>
<tr>
<td>Badakhshi et al. [33]</td>
<td>Plantar fasciitis</td>
<td>2014</td>
<td>171</td>
<td>Pain relief rate: 61.4%</td>
<td>0.5×6</td>
<td>NA</td>
</tr>
<tr>
<td>Ott et al. [26]*</td>
<td>Painful shoulder syndrome</td>
<td>2014</td>
<td>312</td>
<td>Early, delayed, and long-term response: 83%, 85%, and 82%, respectively</td>
<td>0.5×6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1×6</td>
<td>NA</td>
</tr>
<tr>
<td>Ott et al. [28]*</td>
<td>Achillodynia</td>
<td>2015</td>
<td>112</td>
<td>Early, delayed, and long-term response: 84%, 88%, and 95%, respectively</td>
<td>0.5×6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1×6</td>
<td>NA</td>
</tr>
<tr>
<td>Micke et al. [27]</td>
<td>Calcaneodynia, achillodynia, painful gonarthrosis, painful bursitis trochanterica</td>
<td>2016</td>
<td>166</td>
<td>Good response: 37.3%</td>
<td>0.5~1.0×1</td>
<td>No side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1×6</td>
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</table>

NA: not available. *Prospective trial.

been widely treated with radiotherapy in Germany [32]. Badakhshi and Buadch [33] analyzed 171 patients older than 65 years with painful plantar fasciitis who were treated with radiotherapy (3 Gy in 6 fractions) in their institution. They showed a pain relief rate of 67.3% and 61.4% at 3 months and 54 months after radiotherapy, respectively. Hermann et al. [34] reported an interesting result with regard to the factors associated with the response rate of radiation outcome in plantar fasciitis. In their analysis of 250 patients (285 heels), an age older than 53 years, length of heel spur ≤6.5 mm, and onset of pain <12 months were associated with a positive radiotherapy response.

An analgesic effect of radiotherapy has been demonstrated in the treatment of painful knee osteoarthritis. In a German pattern-of-care study performed by Mücke et al. [35], median pain reduction for at least 3 months was reported in 60% of 5,069 evaluated cases. The median total dose and daily dose were 6 Gy and 1 Gy, respectively. Keller et al. [36] also demonstrated that 79.3% of the 1,037 patients experienced relief of their pain with low-dose radiotherapy.

Overall, low-dose radiotherapy has been found to be an effective treatment option for painful degenerative disorders, with a low toxicity rate. According to the German Society of Radiation Therapy and Oncology (DEGRO) guidelines, total doses of 3~6 Gy with daily doses of 0.5~1 Gy in 2~3 weekly fractions are recommended for painful degenerative disorders [37] (Table 2). Minten et al. [38] reviewed the effectiveness and safety of low-dose radiotherapy in the treatment of osteoarthritis. They found that in 25%~90% and 29%~71% of cases patients’ pain and function improved, respectively. However, they concluded that there was still insufficient evidence for a positive effect of low-dose radiotherapy on pain and functioning in patients with osteoarthritis, due to the absence of high-quality studies.

2) Hyperproliferative disorders

1) Dupuytren’s contracture

Dupuytren’s contracture, also known as Morbus Dupuytren and Morbus Ledderhose, are hyperproliferative disorders of the palmar fascia and plantar fascia, respectively. In the early stages, they usually present with
Table 2. Specific treatment recommendations regarding radiation doses and indications by the German Working Group on Radiotherapy of Benign Diseases [24]

<table>
<thead>
<tr>
<th>Disease</th>
<th>Indication</th>
<th>Single dose (Gy)</th>
<th>Fractionation</th>
<th>Total dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative disease</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insertion tendinitis</td>
<td>Painful periarthropathia humeroscapularis, epicondylopathy humeri radialis or ulnaris, calcaneodynia = plantar or dorsal calcaneal spur, refractory to conventional and drug treatment</td>
<td>0.5 ~ 1.0</td>
<td>2 ~ 3 fx/wk</td>
<td>3 ~ 12</td>
</tr>
<tr>
<td>Painful osteoarthritis</td>
<td>Acute exacerbated painful osteoarthrosis of the hip, of the knee, the shoulder, the finger joints and of the thumb joint as well as arthrosis of other joints, refractory to conventional and drug treatment</td>
<td>0.5 ~ 1.0</td>
<td>2 ~ 3 fx/wk</td>
<td>3 ~ 10</td>
</tr>
<tr>
<td>Hyperproliferative disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbus Dupuytren, Morbus Ledderhose</td>
<td>In the early stage (with progressive node or strand formation without extension deficit and symptoms) for the prevention of surgery in more advanced stages</td>
<td>2.0 ~ 4.0</td>
<td>2 ~ 5 fx/wk</td>
<td>20 ~ 40</td>
</tr>
<tr>
<td>Keloid</td>
<td>Postoperative prophylaxis of a recurrence</td>
<td>2.0 ~ 3.0</td>
<td>3 ~ 5 fx/wk</td>
<td>12 ~ 20</td>
</tr>
<tr>
<td>Functional diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterotopic ossification</td>
<td>Prophylaxis of heterotopic ossifications after trauma or surgery of large joints (hip, knee, shoulder, elbow, other joints), after severe polytrauma with CNS involvement and for prophylaxis of recurrence after surgical removal of scar bones (thoracic and abdominal wall)</td>
<td>2.0 ~ 4.0</td>
<td>3 ~ 5 times after surgery</td>
<td>8.0 ~ 12.0</td>
</tr>
<tr>
<td>Dysthyroid ophthalmopathy</td>
<td>Progressive ocular symptoms with or without autoimmune thyropathy or other thyroid disease</td>
<td>1.5 ~ 2.0</td>
<td>4 ~ 5 fx/wk before/after surgery</td>
<td>10 ~ 20</td>
</tr>
</tbody>
</table>

Fx: fraction. Data from the article of Micke et al. (Int J Radiat Oncol Biol Phys 2002;52:496-513) [24].

A painless single palmar or plantar nodule and may spread to adjacent limbs. As it progresses further, cords develop and become predominant. Finally, the cords reach the periosteum of the bones and may result in palmar or plantar contraction in the advanced stages. Their pathogenesis may be divided into three stages: (1) the early stage is characterized by an increase of fibroblasts and the formation of nodules and cords; (2) during the involutional stage, differentiation into myofibroblasts occurs; and (3) in the advanced stage, collagenous fibers are dominant histologically. Radiotherapy for Dupuytren’s contracture is most effective when patients are in the early stages of disease, because the target cells of radiation are proliferating fibroblasts and inflammatory cells (Figure 2).

Previous published studies showed the effectiveness of radiotherapy for preventing progression and for relieving symptoms in early-stage Dupuytren’s contracture (Table 3) [39-42]. In the study by Keilholz et al. [39], 96 patients (142 hands) received two courses of 15 Gy in 5 fractions (total dose 30 Gy) separated by 6 weeks. The authors reported excellent outcomes with 99% of cases remaining stable or improved. The overall rate of symptom relief was 87%. Similarly, Betz et al. [40] analyzed the results of 135 patients (208 hands) with Dupuytren’s contracture...
treated with radiotherapy. With the same dose used by Keilholz et al. [39], 87% of the patients in the early stage remained stable or regressed and 66% of all patients achieved long-term relief of symptoms.

A randomized clinical study to identify the optimal radiation dose in the treatment of Dupuytren’s contracture was conducted by Seegenschmiedt et al. [42]. They compared the results of 489 patients (718 hands) treated with two courses of 15 Gy in 5 fractions (total dose 30 Gy) separated by 12 weeks, one course of 21 Gy in 7 fractions within 2 weeks, and no radiotherapy group. After a mean follow-up of 8.5 years, the progression rates were 19.5%, 24%, and 62% in the 30 Gy group, 21 Gy group, and no radiotherapy group, respectively, and the radiotherapy groups had a significantly lower progression rate.

Therefore, radiotherapy is effective and well tolerated in the prevention of Dupuytren’s contracture when applied in the early nodular stage. Two courses of 15 Gy in 5 fractions (total dose 30 Gy) separated by 6~12 weeks and a single course of 21 Gy in 7 fractions are both recommended [43] (Table 2).

(2) Keloids

Keloids are excessive mesenchymal tissue proliferation in regions of skin injuries that occur as a result of an abnormal wound healing process. Unlike normal scars, they do not regress spontaneously. Surgical excision alone of keloids results in a high recurrence rate of 45%~100% [44]. Radiotherapy has been shown to be effective for reducing the recurrence rate to 10%~20% after surgical excision [45,46]. The target cells of radiotherapy are keloid fibroblasts. In vitro experiments demonstrated that radiation induced apoptosis of fibroblasts and could return tissue to a normal cell population equilibrium [47]. Of note, radiotherapy is most effective during the early stage of keloids, in which proliferating fibroblasts are abundant [48]. Generally, it is recommended that radiotherapy be initiated within 24 hours after surgical excision. Total doses of 16~20 Gy with daily doses of 2~5 Gy in 5 fractions per week are recommended.

3) Symptomatic functional disorders

(1) Heterotopic ossifications

Heterotopic ossifications are abnormal bone formations in soft tissues. They occur frequently after musculoskeletal trauma and surgical procedures. Although the etiology is not completely known, the hypothesis is that an inflammatory stimulus by trauma leads to the release of growth factors, causing a differentiation from pluripotent mesenchymal stem cells to osteoblasts. Heterotopic ossifications are mostly asymptomatic. However, it is sometimes painful and may cause decreased range of motion at the joint. For patients who have symptomatic heterotopic ossifications, surgical excision may be performed. After surgery, prophylactic treatment needs to be administered if patients have a high risk of recurrence. Radiotherapy and nonsteroidal anti-inflammatory drugs (NSAIDs) are the two main prophylactic modalities. In a meta-analysis of randomized trials, both treatments showed effective-

### Table 3. Summary of the studies of radiotherapy for Dupuytren’s contracture

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Year</th>
<th>Patient, n</th>
<th>Response rate</th>
<th>Daily dose (Gy) × fraction</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keilholz et al.</td>
<td>Morbus Dupuytren</td>
<td>1996</td>
<td>96</td>
<td>Stable: 92% Improved: 7% Progressed: 1%</td>
<td>3 × 10 NA</td>
<td>NA</td>
</tr>
<tr>
<td>Betz et al.</td>
<td>Morbus Dupuytren</td>
<td>2010</td>
<td>135</td>
<td>Long-term symptom relief: 66%</td>
<td>3 × 10 Minor late skin toxicity: 32% No secondary malignancy</td>
<td>No RTOG grade &gt; 2 toxicity</td>
</tr>
<tr>
<td>Heyd et al.</td>
<td>Morbus Ledderhose</td>
<td>2010</td>
<td>24</td>
<td>Complete remission of cords: 33% Reduced number: 54% Pain relief: 68.4%</td>
<td>3 × 10 4 × 8</td>
<td>No RTOG grade &gt; 2 toxicity</td>
</tr>
<tr>
<td>Seegenschmiedt et al.</td>
<td>Morbus Dupuytren</td>
<td>2012</td>
<td>489</td>
<td>Progression rate: 3 Gy × 10, 19.5%, 3 Gy × 7, 24%, No RT: 62%</td>
<td>3 × 10 CTC grade 1: 26.5% CTC grade 2: 2.5% No secondary cancer</td>
<td>No RTOG grade &gt; 2 toxicity</td>
</tr>
</tbody>
</table>

ness, although radiotherapy tended to be more effective than NSAIDs in preventing severe heterotopic ossifications [49]. The rationale for the use of radiotherapy in heterotopic ossification prophylaxis is that the pluripotent mesenchymal stem cells can be arrested by irradiation before entering the differentiation phase. Thus, the timing of radiotherapy is important and it is recommended that radiotherapy be delivered either at 4 hours preoperatively or up to 72 hours postoperatively. A delivery of 7 ∼ 8 Gy single fractions has been reported to have a good prophylaxis rate, both preoperatively and postoperatively [50].

(2) Dysthyroid ophthalmopathy
Dysthyroid ophthalmopathy is an autoimmune disorder affecting the extraocular muscles and in many cases, it is associated with hyperthyroidism. In mild cases, supportive managements such as lubricants and sunglasses are sufficient while awaiting spontaneous recovery. In severe cases, however, proptosis, periorbital edema, conjunctival erythema, and visual impairment may occur. Therefore, the quality of life of patients can decrease and active treatment is necessary.

The etiology of dysthyroid ophthalmopathy is that activated T-lymphocytes lead to inflammatory reactions and consequent fibrosis. The rationale for the use of radiotherapy for dysthyroid ophthalmopathy is that radiation could arrest the immune process and could induce a remission of the inflammatory and fibrotic changes. In multiple randomized prospective and retrospective trials, radiotherapy achieved relief of eye symptoms in 65% to 75% of cases [51-55]. According to the DERGO guideline, in the early inflammatory phase, total doses of 2.4 ∼ 16 Gy in 8 fractions and in the advanced inflammatory phase, total doses of 16 ∼ 20 Gy in 8 ∼ 10 fractions are recommended [50]. A representative of dose distributions is shown in Figure 3.

Radiation risk
Generally, for non-malignant diseases, radiotherapy is considered when non-radiotherapeutic treatment options fail. The risks of radiation exposure always have to be weighed against the therapeutic benefit. For patients with non-malignant disorders who were treated with low to intermediate radiation dose, most normal tissue side effects have been reported as rare or minimal as shown in Tables 1 and 3.

The major reason why clinicians hesitate to apply radiotherapy for their patients, despite its known efficacy, may be concerns about the potential risk of secondary malignancy [2-4]. However, the evidence of cancer risk comes from disparate sources and was extracted from data using outdated radiotherapeutic techniques. The primary sources of data were from Hiroshima and Nagasaki, although this radiation exposure was evenly distributed throughout the body. Therefore, some authors believe that cancer risks estimated by the effective dose method may overestimate the true risks of low-dose radiotherapy of small body parts [56].

In the last two decades, radiotherapy techniques have substantially improved. The delivery of radiation while minimizing the dose to the normal tissues is more feasible than before, using various techniques including three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, and charged particle therapy. Also, there are many methods for radiation protection, including the following: selection of the smallest effective dose; use of several portals or the smallest effective field size for a given target volume; orientation of the radiation beam’s direction of entry away from the body stem or radiosensitive organs (e.g., thyroid, gonads, eye lens); application of shielding (individualized and/or standardized lead absorbers) in radiation portals; and use of a lead capsule (for the male gonads), lead collar (in the neck area), or lead apron (in the pelvic area).
Recently, McKeown et al. [57] reviewed the available evidence that informs the risk following exposure to low to intermediate dose radiotherapy. The authors demonstrated that the risk of secondary malignancy was very small and reduces further with increasing age. In a prospective, randomized study for patients with painful heel spur, good analgesic effects of radiotherapy was shown without any acute side effects [58]. There were also concerns about the potential hazards of tumor and leukemia induction and somatic changes after radiotherapy exposure for non-malignant disorders [3,4]. However, Broerse et al. [59] found very little increase in the risk of tumor induction calculated with mathematical models, but the overall contribution to a patient’s general lifetime risk remains unclear. They stated that after the fourth decade of life, the attributable lifetime risk may be lower than that for the general population. Irradiation of patients younger than 40 years old requires caution and the balance of risk versus benefit needs to be considered.

There is another group of patients who may be at greater risk of radiation toxicity. Patients with collagen vascular diseases (CVD) have shown increased radiation toxicity and many physicians believe that collagen vascular disease is a relative contraindication to radiotherapy. Some researchers reported that severe late toxicity increased in patients with CVD other than rheumatoid arthritis [60,61]. Other researchers reported that patients with scleroderma or systemic lupus erythematosus had more severe radiation toxicity [62,63]. Therefore, a particular attention is required when we irradiate patients with high risk CVD (e.g., scleroderma, systemic lupus erythematosus).

**CONCLUSION**

This review summarizes the radiobiological mechanisms and clinical results from previously published studies with respect to the use of radiotherapy for non-malignant disorders. The anti-inflammatory effect of low-dose radiotherapy has been shown in a variety of in vitro and in vivo studies. Furthermore, a number of clinical trials have demonstrated the efficacy of radiotherapy in patients with non-malignant disorders.

Radiotherapy for non-malignant disorders may be safely and effectively used, especially in older patients who suffered from these disorders and those who are reluctant to use other non-radiotherapeutic treatment options.

**CONFLICT OF INTEREST**

No potential conflicts of interest relevant to this article were reported.

**REFERENCES**


43. Seegenschmiedt MH, Micke O, Niewald M, Bücker R, Eich...


