NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of radiation therapy for early Dupuytren's disease

In Dupuytren’s disease, connective tissue in the palm of the hands thickens. This causes nodules (small, hard lumps) to form under the skin of the palm. Over time, the nodules can extend and form cords of tissue. These cords can shorten and cause the fingers to bend permanently towards the palm. Radiation therapy for early Dupuytren’s disease involves directing low energy X-rays at the affected tissue with the aim of stopping the disease progressing. Treatment can be repeated in some patients.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in December 2015 and updated in September 2016.

Procedure name

- Radiation therapy for early Dupuytren's disease

Specialist societies

- British Association of Plastic, Reconstructive and Aesthetic Surgeons
- British Orthopaedic Association
- British Society for Surgery of the Hand

- Royal College of Radiologists – Faculty of Clinical Oncology.

Description

Indications and current treatment

Dupuytren's disease is a benign fibroproliferative disorder of the fascia of the hand and fingers. Its aetiology is unknown. It is characterised by connective tissue thickening in the palm of the hand, forming nodules. These nodules are thought to progress to form cords, which cause difficulty in extending the fingers. Symptoms include reduced range of motion, reduced hand function and pain. It most commonly affects the fourth and fifth fingers. Most patients are affected in both hands. There is no formal clinical definition of early disease but the term is generally used for patients with contractures of 30 degrees or less, with or without palmar disease. Not all patients have progressive disease, and the natural history of the disease is not well understood.

Treatments for Dupuytren’s disease aim to restore hand function and prevent progression. These include needle aponeurotomy (percutaneous needle fasciotomy) in earlier disease, and open surgical correction (fasciotomy or fasciectomy) in later disease when secondary changes to tendons and joints have developed. Limited fasciectomy is the most commonly used open surgical treatment. Dermofasciectomy is used for advanced cases. A non-surgical treatment using injectable collagenase clostridium histolyticum is also sometimes used.

What the procedure involves

The aim of this procedure is to prevent or postpone disease progression, and reduce the need for surgical intervention. The mechanism of action of radiation therapy is uncertain, but it is thought to affect the development and growth rate of fibroblasts in the palmar fascia.

Radiation therapy is delivered to the nodules and cords that have formed in the hands. The usual regimen is 30 Gy in 10 fractions, consisting of 2 phases of 15 Gy in 5 fractions with a gap of 6–12 weeks between the 2 phases. Alternatively, 21 Gy may be given in 7 fractions on alternate days over 2 weeks.[6]

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to radiation therapy for early Dupuytren's disease. The following databases were searched, covering the period from their start to 6 September 2016: MEDLINE,

PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with early Dupuytren's disease.
Intervention/test	Radiation therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 925 patients from 1 randomised controlled trial[1], 5 case series[2-6] and 1 systematic review[7].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on radiation therapy for early Dupuytren's disease

Study 1 Seegenschmiedt MH (2001) – *included in 2010 overview*

Details

Study type	**Randomised controlled trial comparing 2 levels of radiation**
Country	Germany
Recruitment period	1997–98
Study population and number	**n=129 (63 group A; 66 group B; 2 different dose regimens), 198 hands**
Age and sex	Mean 62 years; 52% (67/129) male
Patient selection criteria	Patients with clinically evident and progressive early stage Dupuytren's disease.
Technique	Radiation therapy applied at a distance of 40 cm with areas of the palm not involved shielded by lead rubber plates. Group A: 10 fractions of 3 Gy (total dose 30 Gy) in 2 periods of treatment separated by 8 weeks. Group B: 7 fractions of 3 Gy (total 21 Gy) on alternate days.
Follow-up	**1 year minimum**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 3 patients in group A refused the second week of treatment. The analysis is stated as being done on intention-to-treat principle. A total of 129 patients were analysed, but 142 started radiotherapy, of which 3 were non-compliant with radiation therapy (RT) and 10 did not complete follow up. There were 129 who 'had completed the prescribed RT protocol' and were included in analyses, but 9% of the study population were not described in the results. There was no description of which arms of the trial the 10 patients lost to follow-up were from.

Study design issues:

- It is unclear how they defined patients with 'progressive early stage' disease.
- Both groups had RT, there was no placebo
- Safety outcomes are reported overall and not by group.
- Methods of randomisation and blinding not reported.

Study population issues: 53% bilateral treatment needed. Previous treatment included local excision/partial fasciotomy (19%), topical steroid injections (5%), systemic nonsteroidal anti-inflammatory drugs, local vitamin E (19%), other drugs (12%), other therapeutic measures (9%); 34% burning/ itching/pressure or tension. Mean lag from onset of symptoms to radiation therapy treatment 26 months.

Other issues: Dupuytren's disease stage evaluated at baseline but not explicitly reported at follow-up assessment. The primary outcome was patient recall of subjective 'progression', 'stability' or 'regression', which is likely to be subject to recall bias.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **129 (63 group A, 66 group B)**

Dupuytren's disease stage

Subjective symptom assessment at 12 months. By patients treated.

	Group A	Group B
Regression of symptoms	65% (41/63)*	53% (35/66)*
Stable condition	30% (19/63)	41% (27/66)
Progression	5% (3/63)	6% (4/66)

*Statistically significant improvement from baseline in both groups, p<0.01.

Measurement of significance between groups not reported.

Objective symptom assessment (number and consistency of cords, nodules, and extension deficit) at 12 months. By hands treated.

	Group A	Group B
Regressed	56% (53/95)*	53% (55/103)*
Stable	37% (35/95)	38% (39/103)
Progression	7% (7/95)	9% (9/103)

*Statistically significant improvement from baseline in both groups, p<0.01.

No statistically significant differences were found between the groups.

Overall across the 2 groups **treatment failure** (new nodules) was reported in 6% (11/198) of hands, (new cords) in 4% (7/198), and (increased flexion deformity) in 6% (12/198).

3% (4/129) of patients had **corrective hand surgery** within 1 year of follow-up.

Total number of nodules

	Group A	Group B
Baseline	694	734
3 months	463	605
12 months	334	295

p <0.01 for both groups compared with baseline

No statistically significant differences were found between the groups.

Total number of cords

	Group A	Group B
Baseline	428	360
3 months	273	201
12 months	208	221

p <0.01 for both groups compared with baseline

No statistically significant differences were found between the groups.

Safety

Complications

Overall acute (to 4-week follow up) toxicity events

Outcome	Rate (198 hands)
Skin dryness/redness	38% (76/198)
Extensive erythema	6% (12/198)
Dry desquamation	5% (10/198)
Wet desquamation	2% (3/198)
Pronounced swelling	2% (3/198)

There was no statistically significant difference in the rate of acute toxic complications between group A (36% [34/95]) and group B (52% [54/103]).

Overall chronic toxicity events (minimum follow-up of 1 year)

	Group A	Group B
3 months	16% (15/95)	11% (11/103)
12 months	4% (4/95)	5% (5/103)

Most of these events were **dryness, increased desquamation, mild skin atrophy, or slight subcutaneous fibrosis requiring ointments. Alteration of heat and pain sensation** occurred in 4% (8/198) of hands.

Study 2 Zirbs M (2015)

Details

Study type	**Retrospective case series**
Country	Germany
Recruitment period	1999–2008
Study population and number	n=**206** patients with Dupuytren's disease
Age and sex	Median 62.9 years; 60% (123/206) male
Patient selection criteria	Patients with Dupuytren's disease who were treated by radiotherapy and who returned the study questionnaire.
Technique	Radiation therapy was done with soft X-rays (Dermopan II, Siemens). A total dose of 32 Gy was applied, with an 8-week interval between the 4 courses of two fractions at two consecutive days with a single dose of 4 Gy.
Follow-up	**6 months to 9.5 years (median 40 months)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Not reported.

Study design issues: There is potential for responder and recall bias as data were collected using questionnaires sent to patients at a median follow-up of 40 months: only those who responded were included in the analysis. Response rate was 58% (206/355).

Study population issues:

- Bimanual involvement was found in 44% of patients (91/206), 56% of patients (115/206) had a unilateral involvement. The right hand was affected in 63% of patients (72/115) and the left hand in 37% (43/115).
- A total of 18% (37/206) of patients had had 1 or more treatments: hand surgery in 9% (18/206) of patients; needle fasciotomy in 4% (8/206) of patients; local steroid injection in 1% (3/206) of patients; in single patient's oral intake of vitamins, shock-wave therapy, magnetic field therapy, massage with homeopathic creams, therapy with systemic non-steroidal anti-inflammatory drugs, hand gymnastics, massage and injections of non-medical practitioners.
- A total of 59% (122/206) of patients showed a "slow progressive activity" of the disease, 11% (23/206) had a "slow progression in batches", 12% (25/206) had a 'rapid progression' and 7% (14/206) a "very rapid disease progression".
- A total of 67% (139/206) of patients (no data 33% (67/206) patients) had a median of 20 months (range was 0–329 months or 27.5 years) as first recognition of Dupuytren's disease and onset of the radiation therapy.

Other issues: Not reported.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 206

Symptom assessment
• Regression of symptoms: 45% (93/206) of patients
• No further disease progression (including patients with regression): 80% (165/206).
• Statistically significantly better improvement in patients with symptom duration of less than 20 months (p<0.05).
• No difference in results was found with regard to symptoms or number of nodules and/or cords nor age of the patients.

Subjective therapeutic effects
Subjective therapeutic effects for 426 nodes and/or cords showed a reduction of 92 nodules and/or cords.

Satisfaction with the therapy (measured with a visual analogue scale, n=198 patients): very good, average score of 7.9 points (SD 2.7 points, median of 9 points)</td><td>Acute toxicity events
<table><tr><td>Toxicity event</td><td>Rate (n=206)</td></tr><tr><td>Dryness of the treated skin</td><td>40% (82/206)</td></tr><tr><td>Erythema of the treated area</td><td>20% (42/206)</td></tr><tr><td>Desquamation</td><td>4% (8/206)</td></tr></table>
Chronic side effects that persisted more than 4 weeks after the end of the treatment
<table><tr><td>Toxicity event</td><td>Rate (n=206)</td></tr><tr><td>Dryness of the treated skin</td><td>20% (41/206)</td></tr><tr><td>Lack of sweating</td><td>4% (8/206)</td></tr><tr><td>Skin atrophy</td><td>3% (7/206)</td></tr><tr><td>Telangiectasia</td><td>3% (6/206)</td></tr><tr><td>Desquamation</td><td>2% (5/206)</td></tr><tr><td>Sensory affection</td><td>2% (4/206)</td></tr></table></td></tr>
<tr><td colspan="2">Abbreviations used: SD, standard deviation.</td></tr>
</table>

Study 3 Betz N (2010) - *included in 2010 overview*

Details

Study type	**Case series**
Country	Germany
Recruitment period	1982–2006
Study population and number	n=**135 (208 hands)** patients with early stage Dupuytren's disease. Bilateral 85%. 23% of patients had a lag from diagnosis to radiation therapy >48 months.
Age and sex	Age: not reported. Sex: not reported
Patient selection criteria	Patients with early stage Dupuytren's disease.
Technique	Radiation therapy applied at a distance of 40 cm with areas of the palm not involved shielded by lead rubber plates. Two course of 5 fractions of 3 Gy (total dose 30 Gy) in 2 periods of treatment separated by 6 weeks.
Follow-up	**Median 13 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Retrospective study, complete follow-up available for 76% (135/178) patients treated. 31 patients had died, 12 lost to follow-up.

Study design issues:

- Treatment aim was prevention of disease progression.
- Method for assessment of subjective efficacy outcomes not described.
- It is not clear whether clinical assessment of functional status was based on the stage score that was measured at baseline. Four hands had worse symptoms while Dupuytren's disease stage remained unchanged.

Study population issues: Excluded patients had a similar clinical and demographic characteristics to those analysed.

Other issues: 7% (9/135) of patients had had previous treatment either surgery or local steroids.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 135 (208 hands)

Dupuytren’s disease stage

Clinical assessment at median 13-year follow-up
<table>
<tr><td>Disease regression</td><td>10% (20/208)</td></tr>
<tr><td>Stable disease</td><td>59% (123/208)</td></tr>
<tr><td>Progression</td><td>31% (65/208)</td></tr>
</table>
Patients with progressive disease treated within 1 year of diagnosis showed statistically significant better long-term results than those treated after 48 months (p<0.001).

Symptoms at median 13-year follow-up (n = 87 patients)
<table>
<tr><td>Progression</td><td>20% (17/87)</td></tr>
<tr><td>Complete relief</td><td>16% (14/87)</td></tr>
<tr><td>Good relief</td><td>18% (16/87)</td></tr>
<tr><td>Minor relief</td><td>32% (28/87)</td></tr>
<tr><td>Unchanged</td><td>14% (12/87)</td></tr>
</table>
Need for further treatment
20% (42/208) of hands needed subsequent surgery.
</td><td>
Treatment toxicity was evaluated using the European Organisation Research and Treatment of Cancer criteria. Outcomes reported within the treated area only.
<table>
<tr><th>Long-term outcome</th><th>Rate (%, n=208 hands)</th></tr>
<tr><td>All minor long-term changes</td><td>32% (66/208)</td></tr>
<tr><td>Dry skin and increased desquamation</td><td>23% (47/208))</td></tr>
<tr><td>Mild skin atrophy with occasional telangiectasia</td><td>7% (14/208)</td></tr>
<tr><td>Erythema at up to 1 year</td><td>2% (5/208)</td></tr>
</table>
Most patients complained of itching and burning during treatment.

No chronic grade 3 or 4 reactions were observed.

There was no induction of cancer at final follow-up.
</td></tr>
</table>

Study 4 Schuster J (2015)

Details

Study type	**Case series**
Country	US
Recruitment period	2008–13
Study population and number	n=**33** patients with early stage palmar and plantar fibromatosis treated by 66 radiation therapy treatments (45 hands,15 feet and 6 reirradiations) at 60 different sites
Age and sex	Age not reported; 52% (17/33) male
Patient selection criteria	Patients with early stage palmar and plantar fibromatosis who completed a survey either in person or by telephone.
Technique	21 Gy (3 Gy in 7 fractions): 26% (17/66) of treatments 30 Gy (3 Gy in 10 fractions with 6- to 8-week breaks after 15 Gy): 65% (43/66) of treatments Reirradiation dose: 21 Gy: 6% (4/66) of treatments 20 Gy: 3% (2/66) of treatments
Follow-up	**1 to 61 months (median 31 months)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- No formal clinical follow-up was scheduled because most of the patients lived far away from the clinic. All previously treated patients with early stage palmar and plantar fibromatosis were invited to participate in a survey.
- The survey was conducted by a radiation oncology physician via phone or in person.

Study design issues:

- No distinction in the results between the patients treated for palmar or plantar fibromatosis.
- Twenty-four patients completed 1 treatment course, 7 completed 2 treatment courses and 2 completed 3 treatment courses.

Study population issues:

- The affected sites were the right hand in 48% (32/66) of treatments, the left hand in 29% (19/66), the right foot in 12% (8/66) and the left foot in 11% (7/66).
- The median number of cords was 2 (range 0 to 6) and the median number of nodules was 3 (range 1 to 15).
- Before radiation therapy, reported symptoms included itch/paraesthesia at 35% (21/60) of sites, palmar or plantar pressure sensation at 70% (42/60) of sites and skin changes at 17% (10/60) of sites. Limitation of finger mobility was described at 18% (11/60) of sites.
- All palmar fibromatosis patients were staged as either N (disease with no contracture) or N/I (disease with up to10 degrees of contracture).
- 18% (6/33) of patients had been treated previously before radiation oncology consultation: 4 by surgery and 2 by steroid injections.

Other issues: Not reported.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 33

Disease progression: 61% (20/33) – Any location
• Multiple locations: 30% (10/33)
• Border only (outside the radiation therapy field but near previously treated site): 1 patient
• Outside only (at a different distal extremity): 15% (5/33)
• In-field only (within radiation therapy field): 12% (4/33)
• Final in-field disease progression (includes reirradiation): 21% (7/33)
• In-field disease progression:
23% (14/60) of sites before reirradiation
17% (10/60) of sites after reirradiation
• In-field disease progression was not statistically different between 21-Gy and 30-Gy treatment doses (35% versus 16%, X^2=0.11)

Need for further treatment
• Invasive surgery: 6% (2/33)
• Five additional treatments were done by 3 patients after completing radiation therapy: Xiaflex (n=1), needle aponeurotomy (n=2), reirradiation by outside radiation oncologist (n=1) and massage (n=1).

Symptoms control
<table>
<tr><th></th><th>% sites</th></tr>
<tr><td>Improvement of pain with strain</td><td>81% (30/37)</td></tr>
<tr><td>Improvement of pain at rest</td><td>70% (19/27)</td></tr>
<tr><td>Relief from itch/burn sensation</td><td>81% (17/21)</td></tr>
<tr><td>Plantar or palmar site pressure sensation stabilised or improved</td><td>95% (40/42)</td></tr>
<tr><td>Limited mobility of the hand improved or stabilised</td><td>64% (7/11)</td></tr>
<tr><td>Overall rate of improvement or stability</td><td>93%</td></tr>
</table>
No statistical differences between sites receiving 21 Gy versus 30 Gy for symptom improvement or stability (95% versus 92%, X^2=0.50).

Reirradiation
• 12 % (4/33) of patients completed reirradiation for in-field disease progression at 10% (6/60) of sites.
• In-field disease control was achieved at 67% (4/6) of sites.

Patient satisfaction: 94% (31/33) of patients considered radiation therapy successful.
</td><td>
Acute toxicity: 39% (13/33) of patients
Some patients reported more than 1 acute toxicity.

<table>
<tr><th>Acute toxicities</th><th>Sites (n=60)</th></tr>
<tr><td>Erythema</td><td>20% (12/60)</td></tr>
<tr><td>Dryness</td><td>13% (8/60)</td></tr>
<tr><td>Dry desquamation</td><td>5% (3/60)</td></tr>
<tr><td>Oedema</td><td>5% (3/60)</td></tr>
<tr><td>Tenderness</td><td>3% (2/60)</td></tr>
<tr><td>Fatigue</td><td>2% (1/60)</td></tr>
</table>
Late toxicity: 30% (10/33) of patients
<table>
<tr><th>Late toxicities</th><th>Sites (n=60)</th></tr>
<tr><td>Dryness</td><td>25% (15/60)</td></tr>
<tr><td>Weakness (subjective 10–20% reduction in strength)</td><td>3% (2/60)</td></tr>
<tr><td>Reduced nail health</td><td>3% (2/60)</td></tr>
<tr><td>Hyperpigmentation</td><td>3% (2/60)</td></tr>
</table>
No grade ≥2 late Common Terminology Criteria for Adverse Events, version 4, toxicities were reported.
Acute and late side effects were not statistically different between sites receiving 21Gy versus 30 Gy (37% versus 28%, χ^2=0.48 for acute and 12% versus 35%, χ^2=0.07 for late side effects).

Reirradiation (6 sites)
Median follow-up: 35 months (range 18 to 36 months).
Acute toxicities: erythema (5/6 sites), oedema (1/6 site) and dryness (2/6 sites).
Late toxicity was not reported.
</td></tr>
</table>

Study 5 Grenfell S (2014)

Details

Study type	**Case series**
Country	Australia
Recruitment period	2008-2011
Study population and number	n=**6** consecutive patients (9 sites) with early stage fascial fibromatosis (3 palmar and 3 plantar)
Age and sex	Mean 54 years; 67% (4/6) male
Patient selection criteria	Not reported.
Technique	Radiotherapy was delivered in 2 phases. First, 15 Gy in 5 fractions at 3 Gy using a single direct 6-MeV or 9-MeV electron field, with each field treated daily, Monday to Friday, for 1 week, followed by a 6-week break. Then, the first phase was repeated.
Follow-up	**Median 38.5 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Not reported.

Study design issues: Retrospective study.

Study population issues: Symptoms duration from 6 weeks to 15 years. 33% (2/6) of patients had been treated by surgery before being treated by radiotherapy.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **6** **Disease progression**: • None during median follow-up of 38.5 months. All patients showed disease regression or a reduction of symptoms.	**Acute toxicity** **Minimal fatigue, mild local oedema and erythema**.

Study 6 Smith M L (2015) [Conference abstract only]

Details

Study type	**Case series**
Country	USA
Recruitment period	Not reported
Study population and number	n=**17** patients (40 sites) with Dupuytren's contracture and Morbus Ledderhose (28 hands and 12 feet)
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	Radiation therapy was delivered with 6-12 MeV electron therapy with customised blocking and bolus. Treatment was 3Gy per fraction x7 fractions in 5 days to a total dose of 21Gy.
Follow-up	**Mean 35 months (8-67 months)**
Conflict of interest/source of funding	None

Analysis
Follow-up issues: Not reported.
Study design issues:

- Retrospective study.
- There is potential for responder and recall bias as data were collected using questionnaires sent to patients; only those who responded were included in the analysis. Response rate was 55% (17/30).

Study population issues:

- 53% (9/17) of patients had bilateral palm involvement, 29% (5/17) had bilateral feet involvement, and 23% (4/17) had both bilateral palm and either single or bilateral feet involvement.
- 12% of patients returned 5 months and 21 months after initial treatment for a second treatment.
- 18 hands had stage N, 5 hands had stage 1 and 2 hands had stage 2 Dupuytren's disease (classification using the revised Tubiana's Staging System).
- 53% (9/17) of patients had symptoms present for 3-9 months before diagnosis; 24% (4/17) reported symptoms for 1-2 years and 12% (2/17) reported symptoms present for 10 years.

Other issues: Not reported.

Key efficacy and safety findings

Efficacy	Safety
Efficacy findings from conference abstracts are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview.	**Acute toxicity:** 50% (n=8) Mild symptoms in 7 patients and moderate symptoms in 1 patients. **Skin tenderness, redness, peeling, or mild pain**. **Chronic side effects**: 31% (n=5) **Mild tightness of skin, dryness, skin thickening, mild swelling, decreased sensation.**

Study 7 Ball C (2016)

Details

Study type	**Systematic review**
Country	UK (2), Germany (6), Italy (1), Australia (1)
Recruitment period	Search up to October 2015
Study population and number	n= **405 patients with early Dupuytren's disease from 10 case series treated by radiotherapy**
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: studies evaluating non-surgical treatment of adults with early disease where outcomes were monitored using patient reported outcome measures, physical measures, clinical assessment and clinical observation were included. Randomised and non-randomised controlled clinical trials, prospective and retrospective case series, case studies, conference abstracts and letters were eligible for inclusion. In the absence of a definition of early disease studies were included if early Dupuytren's disease was described clinically, with digital contractures not exceeding 30°, Tubiana grades N to 1, and which reported identifiable data. Exclusion criteria: Studies involving 2 or more digits on 1 hand were excluded if any digital contracture exceeded 30°. Studies reporting treatment of later stage disease, recurrent Dupuytren's disease or postoperative Dupuytren's disease were excluded. Patients within studies who had received treatment previously for Dupuytren's disease in the pertinent hand were excluded. There was no language restriction for eligibility for inclusion. There was no restriction regarding duration of post intervention monitoring.
Technique	Radiotherapy regimen varied across studies
Follow-up	**Follow-up varied across studies**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- A number of publications reporting radiotherapy treatment for early Dupuytren's disease could not be included for review as the authors only extracted the results for patients who met their definition of 'early disease' with no previous treatment.
- 4/10 case series described results for less than 10 patients and are unlikely to have been adequately powered to permit conclusions.

Study population issues: There were inconsistencies in the definition of early disease in studies reporting the efficacy of radiotherapy.

Other issues: The Grenfell (2014) is also included in Table 2 as a single study.

Key efficacy and safety findings

Efficacy and Safety

Number of patients analysed: **405 patients from 10 case series**

Summary of results of RT treatment

Author (year) Treatment n patients (hands) with early DD	Outcome measure	Results			Recurrence	Adverse events
		Improved	No change	Deteriorated		
Keilholz (1996) Radiotherapy (129 hands)	Clinical assessment of consistency and size of nodule	79% (102/129)	19% (25/129)	2% (2/129)	NR	**EORTC Grade 1 and 2 toxicity** for total cohort (n=142 hands).
Lukacs (1978) Radiotherapy n=32	Clinical assessment of softening of nodules, contracture improvement	81% (26/32)	19% (6/32)	0	NR	NR
Hesselkamp (1981) Radiotherapy n=46	Clinical assessment of softening of nodules and cords	52% (24/46)	41% (19/46)	7% (3/46)	NR	63 % **dry skin with desquamation** 24 % **skin atrophy, pigmentation and telangiectasia**
Adamietz (2001) Radiotherapy (156 hands)	Tubiana grade	11% (18/156)	51% (79/156)	38% (59/156) (27 within and 32 outside RT field)	At 10 years • Stage N: >20 % (n = 13) • Stage N/1: >20 % (n = 13) • Stage 1: 65 % (n = 30).	For total cohort of 176 hands at median 10 years, 25% (44) reported **strong desquamation** and 9% (15) **cutaneous telangiectasia with subcutaneous atrophy**
Kohler (1984) Radiotherapy n=29 (33 hands)	Clinical assessment of softening of DD tissue	21% (7/33)	61% (20/33)	18% (6/33)	1 outside the radiotherapy area	NR
Weinzierl (1993) Radiotherapy n=34 Injection Superoxide dismutase n = 22	Clinical assessment of consistency and size of nodules	9% (3/34) 32% (7/22)	41% (14/34) 41% (9/22)	50% (17/34) 27% (6/22)	NR NR	32 % had small but ongoing **skin change (dry skin**). No local or systemic adverse effects
Corsi (1966) Radiotherapy, plesiotherapy plus vitamin E n=10 (11 hands)	Clinical assessment of skin consistency, nodule size and digital extension	73% (8/11)	27% (3/11)	0	NR	**Temporary skin rash and epidermolysis** noted at end of treatment (number affected not given).
Grenfell (2014) Radiotherapy n= 3 (4 hands)	Clinical assessment whether nodule size and hardness	100% (4/4)	0	0	None at 34–42 months	Acute side effects: **minimal fatigue, mild local oedema and erythema for total cohort**. Number affected and duration not given.
Finney (1953) Radiotherapy n=7	Clinical assessment of functional	86% (6/7)	14% (1/7)	0	None at 2–10 years	1st degree reaction: **skin dryness, slight erythema** for

	improvement					total cohort. Number affected not given
Finney (1955) Radiotherapy n=3	Clinical assessment of functional improvement	100% (3/3)	0	0	NR	2nd degree reaction: **skin dryness, persistent paraesthesia** for total cohort. Number affected not given. Paraesthesia persisting up to 12 months in 2 cases.

Abbreviations used: DD, Dupuytren's disease; EORTC, European Organization for Research and Treatment of Cancer; NR, not reported; RT, radiotherapy.

Efficacy

Symptomatic improvement

In a randomised controlled trial (RCT) of 129 patients (198 hands), in which both groups had radiation therapy, objective symptom assessment (number and consistency of cords and nodules, and degree of extension deficit) showed regression of Dupuytren's disease at 1-year follow-up in 56% (53/95) of hands treated with 30 Gy of radiation and in 53% (55/103) of hands treated with 21 Gy ($p<0.01$ for the before-after change in both groups; no statistically significant difference between groups). The symptoms remained stable in a further 37% (35/95) of hands treated with 30 Gy of radiation and a further 38% (39/103) of hands treated with 21 Gy (no statistically significant difference between groups). Overall disease progression rate at 1 year was 8% (16/198). New nodules were reported in 6% (11/198) of hands, new cords in 4% (7/198) and increased flexion deformity in 6% (12/198).The same trial reported that subjective symptom assessment (not otherwise defined) showed statistically significant regression of Dupuytren's disease at 1-year follow-up in 65% (41/63) of patients in the group treated with 30 Gy of radiation, and 53% (35/66) of patients treated with 21 Gy ($p<0.01$ for the within group change; level of statistical significance between groups not reported). The condition remained stable in a further 30% (19/63) of patients in the 30-Gy group and a further 41% (27/66) of patients in the 21-Gy group (level of statistical significance between groups not reported).[1]

In a case series of 206 patients treated with 32 Gy of radiation, which collected self-reported questionnaire data at a median follow-up of 40 months, symptoms regressed in 45% (93/206) of patients and there was no further disease progression (including patients with regression) in 80% (165/206) of patients.[2]

In a case series of 135 patients (208 hands) treated with 30 Gy of radiation, clinical evaluation after a median follow-up of 13 years showed complete relief of symptoms in 16% (14/87) of patients, good relief in symptoms in 18% (16/87), minor relief in 32% (28/87), unchanged symptoms in 14% (12/87) and progression of symptoms in 20% (17/87). In the same case series, clinical evaluation after a median follow-up of 13 years showed regression of the disease in 10% (20/208) of hands, stable disease in 59% (123/208) of hands and progression in 31% (65/208) of hands.[3]

In a case series of 33 patients (60 treated sites), which collected self-reported survey data after a median follow-up of 31 months, the disease progressed at any location within or outside the radiation therapy treatment field in 61% (20/33) of patients. In-field progression occurred in 23% (14/60) of sites but 4 sites were successfully re-irradiated with final local control in 83% (50/60) of sites. In the same study, the symptoms improved or remained stable in 93% of sites (relative numbers not given).[4]

In a case series of 6 patients treated with 30 Gy of radiation, clinical assessment after a median follow-up of 38.5 months showed no disease progression; all patients showed disease regression or a reduction of symptoms.[5]

Avoidance of surgery

In the RCT of 129 patients (198 hands) treated with 30 Gy or 21 Gy of radiation, 3% (4/129) of patients needed hand surgery for disease progression within 1 year of follow-up.[1]

In the case series of 135 patients (208 hands), 20% (42/208) of hands needed surgery within a median follow-up of 13 years.[3]

In the case series of 33 patients, 6% (2/33) of patients needed surgery within a median follow-up of 31 months.[4]

Patient satisfaction

In the case series of 206 patients, the mean (± standard deviation) score for satisfaction with the therapy (measured with a visual analogue scale from 0 [not satisfied] to 10 [extremely satisfied]) was 7.9±2.7 points (n=198 patients) at a median follow-up of 40 months.[2]

In the case series of 33 patients, 94% (31/33) of patients considered radiation therapy successful (defined by patient report indicating whether patients felt that radiation therapy had been successful or not) at a median follow-up of 31 months.[4]

Safety

Acute toxicity

Overall, acute toxicity including skin tenderness, redness, peeling, or mild pain was reported in 50% (n=8, denominator not stated) of patients in a case series of 17 patients (treated with 21 Gy of radiation) that collected self-report questionnaire data.[6]

Dry skin

Dry skin or redness was reported in 38% (76/198) of hands in a randomised controlled trial (RCT) of 129 patients treated with 30 Gy or 21 Gy of radiation within a 4-week follow-up.[1]

Dry skin was reported in 40% (82/206) of patients within 4-week follow-up in a case series of 206 patients treated with 32 Gy of radiation, which collected self-report questionnaire data.[2]

Dry skin was reported in 13% (8/60) of sites in a case series of 33 patients (60 sites), which collected self-report survey data after a median follow-up of 31 months.[4]

Desquamation

Dry desquamation was reported in 5% (10/198) of hands and wet desquamation in 2% (3/198) of hands in the RCT of 129 patients treated with 30 Gy or 21 Gy of radiation within a 4-week follow-up.[1]

Desquamation was reported in 4% (8/206) of patients in the case series of 206 patients treated with 32 Gy of radiation, within 4-week follow-up.[2]

Dry desquamation was reported in 5% (3/60) of sites in the case series of 33 patients (60 sites).[4]

Erythema

Extensive erythema was reported in 6% (12/198) of hands in the RCT of 129 patients treated with 30 Gy or 21 Gy of radiation within a 4-week follow-up.[1]

Erythema was reported in 20% (42/206) of patients in the case series of 206 patients treated with 32 Gy of radiation, within a 4-week follow-up.[2]

Erythema was reported in 20% (12/60) of sites in the case series of 33 patients (60 sites).[4]

Swelling

Pronounced swelling was reported in 2% (3/198) of hands in the RCT of 129 patients treated with 30 Gy or 21 Gy of radiation within a 4-week follow-up.[1]

Oedema was reported in 5% (3/60) of sites in the case series of 33 patients (60 sites).[4]

Tenderness

Tenderness was reported in 3% (2/60) of sites in the case series of 33 patients.[4]

Fatigue

Fatigue was reported in 1 patient in the case series of 33 patients (60 sites).[4]

Chronic toxicity

Overall, chronic toxicity events occurred in 16% (15/95) of hands treated with 30 Gy of radiation and in 11% (11/103) of hands treated with 21 Gy within 3 months and in 4% (4/95), and 5% (5/103) of hands treated with 30 Gy or 21 Gy respectively within 12 months of radiation therapy, in the RCT of 129 patients. Most of these events were skin dryness, increased desquamation, mild skin atrophy, or slight subcutaneous fibrosis needing topical treatment (type of treatment not stated).[1]

Overall, chronic toxicity including mild tightness of the skin, dryness, skin thickening, mild swelling and decreased sensation was reported in 31% (n=5, denominator not stated) of patients in the case series of 17 patients, with a mean follow-up of 35 months.[6]

Dry skin/ Desquamation

Dry skin was reported in 20% (41/206) of patients in the case series of 206 patients treated with 32 Gy of radiation, in more than 4 weeks of follow-up. Desquamation was reported in 2% (5/206) of patients in the same case series of 206 patients.[2]

Dry skin and increased desquamation were reported in 23% (47/208) of hands in a case series of 135 patients within a median follow-up of 13 years.[3]

Dry skin was reported in 25% (15/60) of sites in the case series of 33 patients (60 sites) within a median follow-up of 31 months.[4]

Lack of sweating

Lack of sweating was reported in 4% (8/206) of patients in the case series of 206 patients treated with 32 Gy of radiation within a median follow-up of 40 months.[2]

Skin atrophy/ telangiectasia

Skin atrophy was reported in 3% (7/206) of patients in the case series of 206 patients treated with 32 Gy of radiation, in more than 4 weeks of follow-up. In the same study, telangiectasia was reported in 3% (6/206) of patients, in more than 4 weeks of follow-up.[2]

Mild skin atrophy with occasional telangiectasia was reported in 7% (14/208) of hands in the case series of 135 patients within a median follow-up of 13 years. [3]

Sensory affection

Alteration of heat and pain sensation was reported in 4% (8/198) of hands in the RCT of 129 patients treated with 30 Gy or 21 Gy (minimum follow-up of 1 year).[1]

Sensory affection was reported in 2% (4/206) of patients in the case series of 206 patients treated with 32 Gy of radiation, in more than 4 weeks of follow-up.[2]

Erythema

Erythema was reported in 2% (5/208) of patients in the case series of 135 patients at up to 1 year.[3]

Weakness

Weakness (subjective 10–20% reduction in strength) was reported in 3% (2/60) of sites in the case series of 33 patients within a median follow-up of 31 months.[4]

Reduced nail health

Reduced nail health was reported in 3% (2/60) of sites in the case series of 33 patients within a median follow-up of 31 months.[4]

Hyperpigmentation

Hyperpigmentation was reported in 3% (2/60) of sites in the case series of 33 patients within a median follow-up of 31 months.[4]

Validity and generalisability of the studies

- Radiation technique, dose and fractionation vary between studies.
- Two of the studies include patients with palmar and plantar fibromatosis.[4,5]
- There is little systematic evaluation of safety outcomes such as long term complications relating to irradiation.
- Different classifications for assessing Dupuytren's disease have been used in the studies included.
- Efficacy outcomes are largely subjective.

Existing assessments of this procedure

A review of the use of radiotherapy in the UK for the treatment of benign clinical conditions and benign tumours was published in February 2015 by the Royal College of Radiologists[8]. It stated:

- RT is effective in the early stages of Dupuytren's disease, where there is no contracture (stage N) or a contracture of up to 10 degrees (N/I) (grade B). Patients with more advanced disease should not be treated with RT, and may be offered surgical release (grade C).
- Due to the variable progression of this disease, only patients whose disease has progressed within the last 6–12 months should be treated (grade C).
- The aim is to treat nodules and cords to the periosteum of the hand bones, for a depth of 5–15 mm. Therefore, 120–150 kV photons, or up to 6 mega-electron volts (MeV) electrons with appropriate bolus would be reasonable. Proximal and distal margins of 1–2 cm on palpable nodules and cords, with 0.5–1 cm lateral margins should be used (grade D).
- RT dose: the regimen of choice is 30 Gy in ten fractions, consisting of 2 phases of 15 Gy in 5 fractions with a gap of 6–12 weeks between the 2 phases. An alternative fractionation is 21 Gy in 7 fractions on alternate days over 2 weeks (grade B).
- The types of evidence and the grading of recommendations used within this review are based on those proposed by the Scottish Intercollegiate Guidelines Network (SIGN) (appendix 2).

DEGRO guidelines for the radiotherapy of non-malignant disorders were published in March 2015 by the German Cooperative Group on Radiotherapy of Benign Diseases (GCG-BD)[9]. It stated: "Radiotherapy of Morbus Dupuytren should be performed in the earlier nodular stages N and N/I. Level of evidence: 2c; grade of recommendation: B."

A Clinical Knowledge Summary (CKS) was produced by NICE in November 2015[10]. The NICE CKS service provides primary care practitioners with a readily accessible summary of the current evidence base and practical guidance on best practice in respect of over 350 common and/or significant primary care presentations. It stated:

'How should I manage Dupuytren's disease in primary care?

- For people with Dupuytren's contracture and/or significant loss of function.
    - Refer to a hand surgeon, or a specialist in plastic or orthopaedic surgery, for surgical management
- For people with Dupuytren's disease who do not have contracture or any significant loss of function:
    - No treatment is necessary at this stage.
    - Provide an explanation of the condition and reassure the person that any painful nodules should improve with time.
    - Advise the person to return for review if a contracture develops, as referral is then recommended.
    - Corticosteroid injections are not recommended'.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Needle fasciotomy for Dupuytren's contracture. NICE interventional procedure guidance 43 (2004). Available from https://www.nice.org.uk/guidance/ipg43

Technology appraisals

- Dupuytren's contracture – collagenase clostridium histolyticum. NICE technology appraisal guidance ID621 (in development). For more information see http://www.nice.org.uk/guidance/indevelopment/gid-tag364

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Four Specialist Advisor Questionnaires for radiation therapy for early Dupuytren's disease were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme sent 50 questionnaires to 3 NHS trusts for distribution to patients who had the procedure (or their carers). NICE received 34 completed questionnaires.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

- Several papers on this procedure were published in German. NICE interventional procedures methods exclude non-English-language studies from consideration. For completeness they are listed in appendix A.
- No ongoing studies.

References

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9. Seegenschmiedt MH, Micke O, Niewald M et al. ;German Cooperative Group on Radiotherapy of Benign Diseases (GCG-BD) (2015) DEGRO guidelines for the radiotherapy of non-malignant disorders : part III: hyperproliferative disorders. Strahlenther Onkol. 191(7):541-8. doi: 10.1007/s00066-015-0818-2.
10. NICE Clinical Knowledge Summary on Dupuytren's disease (2015). http://cks.nice.org.uk/dupuytrens-disease

Appendix A: Additional papers on radiation therapy for early Dupuytren's disease

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Adamietz B, Keilholz L, Grunert J et al. (2001). Radiotherapy of early stage Dupuytren disease. Long-term results after a median follow-up period of 10 years. Strahlenther Onkol 177(11): 604-610.	Case series N=99 patients (176 hands) FU=median 10 years	In Stage N 84% and Stage N/I 67% of hands remained stable. 65% of the hands in Stage I and 83% in Stage II showed progressive nodules and cords. In case of progression there were no complications after a second radiotherapy or salvage operation.	Article in German.
Eberlein B and Biedermann T. (2016) To remember: Radiotherapy - a successful treatment for early Dupuytren's disease. Journal of the European Academy of Dermatology and Venereology. DOI: 10.1111/jdv.13773	Systematic review n=13 studies	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.	A narrative review of published studies. Another systematic review from 2016 is already included in Table 2.
Finney R. (1953) Dupuytren's Contracture. A radiotherapeutic approach. The Lancet 2: 1064–6	Case series n=25 FU=2 to 10 years	76% (19/25) improved (32% full functional recovery).	Was included in 2010 overview. Study from 1953. No new safety events reported.
Herbst M and Regler G (1985). Dupuytren's contracture. Radiotherapy in the early stages. Strahlentherapie. 161(3):143-7	Case series n= 33 patients (46 hands) FU=18 months	98% stable. 2% progression	Article in German.

Hesselkamp J, Schulmeyer M, and Wiskemann A (1981). Ro¨ntgentherapie der Dupuytrenschen Kontraktur im Stadium I. Therapiewoche 31:6337–6338.	Case series n= 46 patients (65 sites) FU= 1-9 years	• Regression: 52% (24/46) of patients • Stable condition: 41% (19/46) of patients • Progression: 7% (3/46) of patients.	Article in German.
Keilholz L, Seegenschmiedt MH, Sauer R. (1996). Radiotherapy for prevention of disease progression in early-stage Dupuytren's contracture: initial and long-term results. Int J Radiat Oncol Biol Phys. 1;36(4):891-7.	Case series n=96 patients (142 hands) FU=1 to 12 years	At 3 months: 92% (130/142) stable, 7% (10/142) improved and 1% (2/142) progressed . An objective reduction of symptomatic cords and nodules was achieved in 107 cases (75%) at 3 months follow-up. 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.	Same patient population as in Betz (2010) paper but with a shorter follow-up.
Köhler AH (1984). [Radiotherapy of Dupuytren's contracture]. Radiobiol Radiother. 25(6):851-3.	Case series n= 31 patients (38 sites) FU= 1-3 years (33 sites)	• Regression: 21% (7/33) of sites • Stable condition: 61% (20/33) of sites • Progression: 18% (6/33) of sites.	Article in German.
Seegenschmiedt MH, Keilholz L, Wielputz et al. (2012). Long-term outcome of radiotherapy for early stage Dupuytren's disease: a phase III clinical study. In Dupuytren's Disease and Related Hyperproliferative Disorders. Springer Berlin Heidelberg. pp 349-371	RCT (only the treated patients were randomised) n=489 patients Group A: 83 control Group B: 199 'low-dose radiotherapy' (7x3Gy) Group C: 207 'high-dose radiotherapy' (10x3Gy) FU= mean 8.5 years (5 years minimum)	• Acute toxicity: 25% (151/596) of irradiated sites CTC grade 1 and 2% (16/596) CTC grade 2. • Chronic side effects: 14% LENT grade 1; no secondary cancer was observed in the long-term follow-up. • The progression rate in the control group (any progression 62%, surgery 30%) as compared to RT groups (21 Gy: 24%/surgery 12%; 30 Gy: 19%/surgery 8%) was statistically significantly higher ($p < 0.0001$). • The overall and mean number of nodules, cords, and other changes decreased in the RT groups as compared to the progression in the control group ($p < 0.01$). • There were 8% (50/596) of relapses inside and 19% (114/596) outside the RT field in the RT group as compared to 52% and 28% potential relapses in the control group. • Symptomatic relief in 8% (4/51) of sites in the control group versus 21% (24/113) and 26% (32/125) of sites in the 21 and 30 Gy group, respectively (both $p<0.001$). • Overall satisfaction with the disease status at last FU: 10% (10/122) control versus 48% (141/293) 21 Gy versus 51% (155/303) 30 Gy (both $p<0.001$).	This study was published as part of a book chapter. This is not a peer-reviewed publication .

Wasserburger K (1956). Therapie der Dupuytrenschen Kontraktur. Strahlenther 100:546–560.	Case series n= 213 patients FU= 'long-term' (146 patients)	'Long-term cure': • Stage I: 90% (62/69) of patients • Stage II: 57% (26/46) of patients • Stage III: 32% (10/31) of patients.	Article in German.

Appendix B: Related NICE guidance for radiation therapy for early Dupuytren's disease

Guidance	Recommendations
Interventional procedures	**Needle fasciotomy for Dupuytren's contracture. NICE interventional procedure guidance 43 (2004).** 1.1 Current evidence on the safety and efficacy of needle fasciotomy for Dupuytren's contracture appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance.
Technology appraisals	**Dupuytren's contracture - collagenase clostridium histolyticum. NICE technology appraisal 364 (in development)**

Appendix C: Literature search for radiation therapy for early Dupuytren's disease

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	06/09/2016	Issue 9 of 12, September 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	06/09/2016	Issue 8 of 12, August 2016
HTA database (Cochrane Library)	06/09/2016	Issue 3 of 4, July 2016
MEDLINE (Ovid)	06/09/2016	1946 to August Week 4 2016
MEDLINE In-Process (Ovid)	06/09/2016	September 02, 2016
EMBASE (Ovid)	06/09/2016	1974 to 2016 week 36
PubMed	06/09/2016	n/a
JournalTOCS	06/09/2016	n/a

Trial sources searched on 15/12/2015

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 15/12/2015

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Radiation Dosage/ (42012)

2 (Radi* adj4 (Therap* or Dos* or Treat*)).tw. (183703)

3 Radiotherapy/ (38586)

4 Radiotherap*.tw. (123052)

5 Radiation, Ionizing/ (8784)

6 ((Ionizin* or Ionisin*) adj4 Radi*).tw. (25813)

7 X-Rays/ (26729)

8 (X ray* adj4 (therap* or treat*)).tw. (4442)

9 X radiation*.tw. (1498)

10 radiotherapy, high-energy/ (10189)

11 (high* adj4 energ* adj4 ((radio adj4 therap*) or radiotherap*)).tw. (242)

12 (electron* adj4 beam* adj4 (treat* or therap*)).tw. (933)

13 or/1-12 (345304)

14 Fibroblasts/ (107334)

15 Fascia/ (8963)

16 or/14-15 (116147)

17 Hand/ (37808)

18 (Hand* or Palm* or Finger*).tw. (566729)

19 or/17-18 (576568)

20 16 and 19 (3459)

21 Dupuytren's Contracture/ (2463)

22 ((Dupuytren* or Palmar*) adj4 (Contracture* or Disease* or Morbus* or aponeuros*)).tw. (2333)

23 ((Hand* or Palm* or Finger* or digit*) adj4 (Fibro* or Myxofibro* or Fascia*)).tw. (1574)

24 (Flexion* adj4 Deformit* adj4 (Hand* or Palm* or Finger*)).tw. (84)

25 or/20-24 (7021)

26 13 and 25 (123)

27 Animals/ not Humans/ (4271459)

28 26 not 27 (110)

29 limit 28 to ed=20151215-20160930 (4)