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Review

Review

# Assessing keloid recurrence following surgical excision and radiation

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## Abstract

Keloids are a fibroproliferative disorder that can result from a cutaneous injury to the reticular dermis. Recurrence rates as high as 100% have been reported following surgical excision alone. Consequently, a variety of post-surgical techniques have been employed to prevent keloid recurrence, including the use of radiation. Although numerous studies have shown post-excisional X-rays, electron beam, lasers and brachytherapy can reduce the rate of keloid recurrence, numerous inconsistencies, including a wide range of definitions for keloid recurrence, make it difficult to compare study outcomes. The review aims to examine the various means for defining keloid recurrence in clinical trials involving the use of radiation therapy. Searches of the Cochrane Library and PubMed were performed to identify the available information for post-surgical keloid recurrence following radiation therapy. Each identified study was reviewed for patient follow-up and criteria used to define keloid recurrence. The search results included clinical studies with external beam radiation, brachytherapy and superficial radiation therapy. Many studies did not include a definition of keloid recurrence, or defined recurrence only as the return of scar tissue. Other studies defined keloid recurrence based on patient self-assessment questionnaires, symptoms and scar elevation and changes in Kyoto Scar Scale, Japan Scar Workshop Scale and Vancouver Scar Scale scores. The results of this review indicate keloidectomy followed by radiation therapy provide satisfactory recurrence rates; however, clinical studies evaluating these treatments do not describe treatment outcomes or use different definitions of keloid recurrence. Consequently, recurrence rates vary widely, making comparisons across studies difficult. Keloid recurrence should be clearly defined using both objective and subjective measures.

**Key words:** Keloid, Keloid scar, Recurrence, External beam radiation, Brachytherapy, Superficial radiation therapy

## Background

Keloids are a fibroproliferative disorder which can occur in genetically susceptible individuals [1]. They may result from a cutaneous injury to the reticular dermis [2], such as surgery or mechanical trauma. Rarely, they may occur spontaneously [3]. Although the mechanism of keloid formation is not known with certainty, they are characterized by increased fibroblasts and collagen formation, new blood vessel growth and the presence of upregulated proinflammatory factors [2, 4]. The negative effects of keloids on quality of life have been well-documented [5, 6].

Surgical excision of keloids as sole therapy is associated with recurrence rates as high as 80% [3], 65–99% [7] and 45–100% [8]. Consequently, a wide range of treatments have

been used to treat keloid scars, including silicon sheeting, topicals, intralesional corticosteroid injections, cryotherapy, lasers and post-keloidectomy radiation therapy [4, 9, 10].

Numerous studies have demonstrated the therapeutic benefits of surgical removal of keloid scars followed by radiation therapy [11–13]. X-ray radiation following surgery appears to prevent keloid recurrence by decreasing fibroblast proliferation, arresting the cell cycle and inducing premature cellular senescence [14]. Similarly, exposure of keloid fibroblast cultures to electron beam radiation downregulates genes involved in cellular and extracellular matrix proliferation and upregulates genes involved in apoptosis and extracellular matrix degradation [15]. Consequently, surgical removal followed by radiation has become the most widely accepted method of treating keloids although there remain differences in radiation type, dose, fraction and interval [12]. Most authors agree that the risk of carcinogenesis in surrounding tissues from radiation therapy for keloids is very low [16–18]. A systematic review of the literature identified five cases of carcinogenesis associated with radiation therapy for keloids consisting of fibrosarcoma, basal cell carcinoma, thyroid carcinoma and breast carcinoma [17]. It was noted that the radiation dose and use of protective shielding was not specified. The results of a survey of radiation oncologists indicated 78% of respondents believed radiation therapy is an acceptable treatment for keloids [19]. Nevertheless, radiation therapy should not be used in children until its safety in this patient population has been established.

One systematic review showed that post-excisional X-ray, electron beam and brachytherapy can reduce the rate of keloid recurrence to 15–23% [20] while another showed the recurrence rate of keloid scars could be <10–20% when surgery was combined with brachytherapy, electron beam therapy or X-ray therapy [21]. Both these reviews applied the linear-quadratic concept to normalize doses to a biologically effective dose (BED) to compare the different doses of radiation used. For keloid scars treated with surgery alone, the rate of recurrence ranged from 50% to 80% while adding radiation therapy following surgery using a BED value >30 Gy reduced the recurrence rate to <10%. The best outcomes were achieved with a BED value of 30 Gy administered within 2 days of surgery [21].

Other inconsistencies when comparing study outcomes include highly variable follow-up periods ranging from months to years [18]. In addition, clinical trials assessing the effectiveness of post-surgical radiation use different definitions of what constitutes a keloid recurrence. Therefore, the objective of the following review is to examine the specific definition of keloid recurrence described in clinical trials using radiation therapy post-keloidectomy.

## Review

### Literature search

Searches of the Cochrane Library and PubMed were performed to identify the available information for post-surgical keloid recurrence following radiation therapy with the limits of 'Human' and 'English Language'. As the subject matter was very broad, numerous searches were performed using combinations of medical subject heading terms, including 'keloids', 'keloid scars', 'treatment', 'therapy', 'radiation therapy', 'superficial radiation therapy', 'superficial X-ray therapy', 'soft X-ray therapy', 'surgery', 'brachytherapy', 'electron beam radiotherapy' and 'clinical trial'. Each identified study was reviewed for patient follow-up and criteria used to define keloid recurrence.

### Radiation treatments for keloids

**Electron beam radiation** Electron beam radiotherapy uses a linear accelerator to deliver energy levels to depths of 2–6 cm without significant damage to deeper structures [22]. When electron beam radiotherapy is applied following surgical removal of keloids, the recurrence rate is dependent on the treatment protocol and keloid location.

In several trials with electron beam radiation therapy, the definition of keloid recurrence was not specified [23–26]. One study defined recurrence as new tissue growth on the surgical scar margin [27], while another study based treatment success on each patient's self-assessment at 18 months post-treatment as follows: Very satisfied, no recurrence, no symptoms; Satisfied, ≤50% recurrence without symptoms; and Unsatisfied, >50% recurrence with symptoms [28] (Table 1). One study classified response to treatment into four groups: Good, no visible scar or small scar in the plane of the skin, no complaints and no recurrence during follow-up; Improved, no itching or other complaints, visible scar partly elevated by no more than 1 mm above the plane of the skin, slight dehiscence and no recurrence during follow-up; Invalid, scar remained and was accompanied by swelling and itching symptoms after treatment and within 3 months; and Relapse, treatment was effective for 3 months but scar became elevated above the plane of the skin, or scar dehiscence and itching and erythema symptoms appeared again after 3 months. Patients achieving levels I and II were defined as well-controlled [29] (Table 1).

**Brachytherapy** Brachytherapy involves placing a radioactive source in or on the target area. High dose–rate brachytherapy can be performed in an outpatient setting and has also been very effective for the post-surgical management of keloids [30].

The definition of recurrence was not defined in many trials with brachytherapy [24, 31–36] while many others simply defined it as keloid or mass reappearance in all or part of the treatment area [30, 37–41] (Table 1). Other definitions included a growing, pruritic, nodular scar [42], growing beyond the boundaries of the original wound [43, 44], elevation of the scar outside the initial wound without itch [45], scars that are not flat [46], any elevation at the treatment site [47] and clinically determined evidence of keloid lesion recurrence utilizing Cosman's criteria [48]. The introduction of immediately administering X-ray therapy following surgical excision of keloids is generally credited to Cosman and

**Table 1.** Keloid recurrence definition assessments

| | |
|---|---|
| **Electron beam radiation** | |
| Patient self-assessment questionnaire [28] | de Oliveira *et al*, 2013 |
| Scar became elevated above the plane of the skin, or scar dehiscence, itching, erythema recurred after 3 months [29] | Shen *et al*, 2015 |
| Japan Scar Workshop Scales [57] | Hseuh *et al*, 2019 |
| Japan Scar Workshop Scales [58] | Ogawa *et al*, 2019 |
| New tissue growth on the surgical scar margin [27] | Carvajal *et al*, 2016 |
| **Brachytherapy** | |
| Keloid or mass reappearance in all or part of the treatment area [37] | Malaker *et al*, 1976 |
| Keloid or mass reappearance in all or part of the treatment area [38] | Arnault *et al*, 2009 |
| Keloid or mass reappearance in all or part of the treatment area [30] | Guix *et al*, 2001 |
| Keloid or mass reappearance in all or part of the treatment area [39] | Fraunholz *et al*, 2005 |
| Keloid or mass reappearance in all or part of the treatment area [40] | Narkwong *et al*, 2006 |
| Keloid or mass reappearance in all or part of the treatment area [41] | Viani *et al*, 2009 |
| Growing pruritic nodular scar [42] | Van Leeuwen *et al*, 2014 |
| Growing beyond boundaries of original wound [43] | Jiang *et al*, 2016 |
| Growing beyond boundaries of original wound [44] | Jiang *et al*, 2018 |
| Elevation of the scar outside the initial wound without itch [45] | Hafkamp *et al*, 2017 |
| Scars that are not flat [46] | Escarmant *et al*, 1993 |
| Any elevation at the treatment site [47] | Kuribayashi *et al*, 2011 |
| Clinically determined evidence of keloid lesion recurrence utilizing Cosman's criteria (48)[a] | Hoang *et al*, 2016 |
| **X-ray therapy** | |
| Elevation of the lesion not confined to the original wound area [51] | Song *et al*, 2014 |
| Signs of extraordinary erythema, induration and hypertrophy of the scar beyond the excision site [52] | Jones *et al*, 2015 |
| Signs of extraordinary erythema, induration and hypertrophy of the scar beyond the excision site [53] | Jones *et al*, 2016 |
| Change in baseline Vancouver Scar Scale scores [60] | Mohammadi *et al*, 2013 |
| Change in baseline Vancouver Scar Scale scores [57] | Hsueh *et al*, 2019 |
| Self-reported patient satisfaction as Excellent, Good, Sufficient and Unsatisfactory [54] | Kim and Lee, 2012 |
| Patient sign and symptom questionnaire [66] | Kim *et al*, 2015 |
| Scar extending beyond the surgical incision [67] | Bennet *et al*, 2017 |
| A >2 mm elevation extending from the initial line of surgery [68] | Emad *et al*, 2010 |

[a]A growing, pruritic nodular scar. Cosman B, Wolff M. Bilateral earlobe keloids. Plast Reconstr Surg. 1974;**53**:540–3 [10].

Wolff (1974) [10] who used growing, pruritic, nodular scar to define recurrence [47].

**X-ray therapy** Superficial radiation therapy comprises low energy X-rays and is produced by units generally operating in the 50–150 kV range, while orthovoltage X-ray units are defined as those operating in the 150–300 kV range. Both use lower X-ray energy than conventional radiation therapy and are used for treating superficial lesions, such as scars and non-melanoma skin cancers [49].

The definition of recurrence was not defined in a few trials with superficial radiation therapy [11, 18, 50]. Other studies variously defined recurrence as reappearance of keloid or persistent itching and elevation of the lesion not confined to the original wound area [51]; signs of extraordinary erythema, induration and hypertrophy of the scar beyond the site of excision [52, 53]; and self-reported patient satisfaction as Excellent, Good, Sufficient and Unsatisfactory [54] (Table 1).

Three studies used the Kyoto Scar Scale, which rates the objective signs of redness, hardness and elevation on a scale of 0–2, and the subjective symptoms of itching and pain on a scale of 0–1. The resulting total scores (0–8) are then graded as Excellent (0), Good (1–2), Fair (3) and Poor (4–8) [55, 56].

Two studies used the Japan Scar Workshop Scales [57, 58], which uses both a subjective rating of pain and itch and objective ratings of elevation, scar redness and erythema around scars on 3-point scales to create a total score of 0–18 (Table 2). The scale also includes a 12-point pre-treatment scale, including patient race and age, keloid history and subjective and objective characteristics to rate the scar as normal mature, hypertrophic or keloid.

Changes in baseline Vancouver Scar Scale [59] scores were used to assess keloid recurrence in two studies [57, 60] (Table 3). This scale uses subjective and objective ratings of symptoms, pigmentation, vascularity, pliability and height to create a total score.

Most of the studies we reviewed did not define keloid recurrence, or simply defined it as the reappearance of keloid tissue. This likely affected our ability to accurately assess recurrence rates for keloid scars following different radiation therapy modalities, and therefore the most effective treatments and treatment regimen to prevent their recurrence. Ideally, consensus could be reached regarding the use of objective measures for defining keloid scar recurrence for use in clinical research.

The most objective measures of keloid recurrence were the Kyoto Scar Scale [55, 56], the Japan Scar Workshop Scale [57, 58] and the Vancouver Scar Scale [57, 60]. In one large retrospective study, the Vancouver Scar Scale and the

**Table 2.** Japan Scar Workshop Scale

**Japan Scar Scale 2015 (Classification and Evaluation of Keloids and Hypertrophic Scars)**

**Classification** (For grading and selection of appropriate treatment methods)

| | | |
|---|---|---|
| **Risk factors** | | |
| 1. Human race | Africans | 2 |
| | Others | 1 |
| | Caucasians | 0 |
| 2. Familial tendency | Clearly exists | 1 |
| | Not clearly | 0 |
| 3. Number | Multiple | 2 |
| | Solitary | 0 |
| 4. Region | Anterior chest, Scapular-Shoulder, Suprapubic | 2 |
| | Others | 0 |
| 5. Age at onset | 0—30 y/o | 2 |
| | 31—60 y/o | 1 |
| | 60— y/o | 0 |
| 6. Causes | Unknown or minute | 3 |
| | Specific wound type such as surgery | 0 |
| **Present symptoms** | | |
| 7. Size ($cm^2$) | Over 20$cm^2$ | 1 |
| | Under 20$cm^2$ | 0 |
| 8. Vertical growth (Elevation) | Clearly exists | 2 |
| | Not clearly | 0 |
| 9. Horizontal growth | Clearly exists | 3 |
| | Not clearly | 0 |
| 10. Shape | Characteristic shape | 3 |
| | Others | 0 |
| 11. Erythema around scars | Clearly present | 2 |
| | Not present | 0 |
| 12. Subjective symptoms | Always exist | 2 |
| | Intermittent | 1 |
| | None | 0 |
| | | Total 0—25 |

Remarks

| | | |
|---|---|---|
| 0—5 | Character like matured scars | (intractability : low risk) |
| 6—15 | Character like hypertrophic scars | (intractability : middle risk) |
| 16—25 | Character like keloids | (intractability : high risk) |

**Evaluation** (For judging treatment results and for following-up)

| | | | |
|---|---|---|---|
| 1. Induration | | | |
| 0 : None | 1 : Weak | 2 : Mild | 3 : Strong |
| 2. Elevation | | | |
| 0 : None | 1 : Weak | 2 : Mild | 3 : Strong |
| 3. Redness of scars | | | |
| 0 : None | 1 : Weak | 2 : Mild | 3 : Strong |
| 4. Erythema around scars | | | |
| 0 : None | 1 : Weak | 2 : Mild | 3 : Strong |
| 5. Spontaneous and pressing pain | | | |
| 0 : None | 1 : Weak | 2 : Mild | 3 : Strong |
| 6. Itch | | | |
| 0 : None | 1 : Weak | 2 : Mild | 3 : Strong |

Total 0-18

Remarks

Weak: symptoms exist in less than 1/3 of the area, or are intermittently

Strong: symptoms exist in the entire region, or are continuous

Mild: between weak and strong

Ogawa R, Akaishi S, Akita S, Okabe K, Shimizu T, Sunaga A, et al. JSW Scar Scale Working Group. Japan Scar Workshop ( JSW) Scar Scale 2015. Available online at: http://www.scar-keloid.com/en/index.html

**Table 3.** Vancouver Scar Scale

| Scar Trait | Rating Scale |
|---|---|
| Symptoms | None (0) Mild itch/burn (1) Moderate itch/burn (2) Severe itch/burn (3) |
| Pigmentation | Color same as surrounding skin (0) Hypopigmentation (1) Hyperpigmentation (2) |
| Vascularity | Normal (0) Pink (1) Red (2) Purple (3) |
| Pliability | Normal (0) Supple, flexible with minimal resistance (1) Yielding, giving way to pressure with moderate resistance (2) Firm, solid, resistant to pressure (3) Banding, rope-like tissue (4) Contracture, permanent shortening of scar-producing deformity (5) |
| Height | Normal (0) <2 mm (1) 2–5 mm (2) >5 mm (3) |

Japan Scar Workshop Scar Scale showed good correlation with keloid recurrence [57].

Recent studies have demonstrated the value of imaging devices for establishing keloid recurrence following other treatment modalities. One study used a three-dimensional stereoscopic optical system was shown to be a valid, accurate and objective means for measuring long-term changes in scar volume and assessing treatment response in two patients [61]. A similar assessment in a larger population of patients with keloids and hypertrophic scars (n = 22) revealed good intra- and inter-rater reliability [62]. Other studies have validated the precision and reliability of measuring keloid volume by

making three-dimensional impressions [63, 64]. Ultrasound imaging has also been used for measuring scar height and depth of penetration [65].

## Conclusion

The results of this review indicate keloidectomy followed by radiation therapy provide satisfactory recurrence rates; however, clinical studies evaluating these treatments do not describe treatment outcomes or use different definitions of keloid recurrence. Consequently, recurrence rates vary widely, making comparisons across studies difficult. Keloid recurrence should be clearly defined, taking into account both objective and subjective measures.

## Abbreviations

BED: biologically effective dose

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## Authors' contributions

MG, BB, MS and DG participated in the collection and interpretation of review articles. All authors read and approved the final manuscript.

## Conflicts of interest

The authors declare that they have no competing interests.

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