Chest keloids: effect of surgical excision and adjuvant radiotherapy on recurrence, a systematic review and meta-analysis
“Chest keloids: effect of surgical excision and adjuvant radiotherapy on recurrence, a systematic review and meta-analysis”

Short running head:
Chest keloids: a meta-analysis

Attached follows the submission of the article, “Chest keloids: effect of surgical excision and adjuvant radiotherapy on recurrence, a systematic review and meta-analysis”. This paper seeks to demonstrate the role of excision and adjuvant radiotherapy in the therapy of chest wall keloids from existing literature. This submission has been assembled as per the current Guide for Authors, and the authors have agreed upon this submission in its current format. This paper is comprised of original material and has not been published elsewhere nor is it currently for submission in other journals.

In this submission should be included:
- Manuscript
- Tables (1 and 2)
- Figures (1, 2 and 3)
- Supplementary materials: PRISMA checklists, MOOSE checklists, GRADE assessments, PROSPERO protocol registration, search strategy, bias assessment.

As the corresponding author, any queries or recommendations from this submission should be directed to Dr Oliver Miles.

Author list: Oliver J. Miles, MD¹; Jieyun Zhou, MBBS²; Sarang Paleri, MD³; Tsien Fua, MBBS⁴; Anand Ramakrishnan, MD⁵.
1. Oliver J Miles, MD. Department of Plastic and Reconstructive Surgery, St Vincent’s Hospital Melbourne


3. Sarang Paleri, MD. Department of Cardiology, St Vincent’s Hospital Melbourne.

4. Tsien Fua, MBBS. Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne.

5. Anand Ramakrishnan, MD. Director of Plastic and Reconstructive Surgery, Royal Melbourne Hospital.

**Corresponding author:**

Oliver J Miles, MD

St Vincent’s Hospital Melbourne

41 Victoria Parade

Fitzroy, VIC 3065 Australia

olivermiles91@gmail.com

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Abstract

Background: Chest keloids are a difficult subgroup of scars to treat, likely secondary to the high wound tension in the area that promotes excessive fibroblast proliferation and collagen deposition. Excision and adjuvant radiotherapy has been demonstrated as an efficacious treatment for keloids in general, but no meta-analysis exists to support the claims for chest keloids. This study aims to identify the rate of recurrence after surgical resection and radiotherapy on patients with chest keloids.

Methods: A search was performed using Embase, MEDLINE, Pubmed and Cochrane database on 22nd December 2018 for terms “radiotherapy”, “keloid” and “chest”. Papers included met a prospectively designed inclusion criteria assessed by multiple investigators.

Results: Twelve studies, including 1 randomised controlled trial, were included for a total of 400 patients with a chest keloid scar managed with surgical excision and adjuvant radiotherapy. Overall pooled-estimate of recurrence rate was 22% (95% CI 12-32%). Meta-regression did not demonstrate a significant effect for method of wound closure, type of radiotherapy, radiotherapy dose (BED<sub>10</sub>) and study type.

Conclusion: Excision and adjuvant radiotherapy represents an effective method of treatment for chest keloids, however sufficient prospective data, including randomised controlled trials, does not yet exist to support these findings. Further studies with sufficient subgroup analysis for keloid location are required to add to the pool of literature that can be added to this meta-analysis.

Keywords: Plastic and Reconstructive Surgery, Cardiothoracic Surgery, Keloid, Radiotherapy
Introduction

Keloids are described as scars that grow outside the original wound margins, due to abnormal wound healing. This phenomenon is postulated to occur secondary to errors in fibroblast proliferation and in collagen deposition. Simple excision of keloid scars is prone to high recurrence, in excess of 50%[1]. Thus, the most appropriate and effective method and treatment for keloids is surgical excision with adjuvant therapy. Options include radiotherapy, corticosteroid injection, pressure bandaging and silicone dressings.

Chest keloids represent a subset of keloids that are prone to higher rates of recurrence, likely related to higher wound tension after excision and closure, with recurrence rates as high as 49% for chest wounds treated with post-excisional radiotherapy[2]. Previous reviews have observed the effect of multimodal therapy on keloids in general and for earlobe keloids[3, 4], however there has yet to be a review focusing solely on chest keloids. The aim of this systematic review is to pool previous studies and highlight the true recurrence of chest keloids following excision and adjuvant radiotherapy for an historically difficult subset of wounds.

Methods

Literature search

Eligible articles were identified in accordance with a prospectively designed protocol (PROSPERO, Supplementary material 1) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplementary material2-4) criteria using the databases: PubMed, MEDLINE, Embase, Web of Science, Cochrane Reviews Database and review of references of key articles. The ‘Epub Ahead of Print, In-Process and Other Non-Indexed Citations’ function on MEDLINE was used to limit publication bias. The aim of the search was to identify all studies prior to December 2018 that commented on recurrence post surgical excision and radiotherapy of chest wall keloids. Search terms
included “radiotherap*”, “radiation therapy”, “keloid”, “chest”, “thorax”, “breast”, “pre-ternal” and “stern*” as discussed with a trained librarian (Supplementary material 5).

Selection criteria

Studies were included according to the pre-defined criteria if they 1) were available in full length text, 2) commented on keloids occurring on the chest wall, 3) contained sufficient treatment modality information and detail including surgical excision and radiotherapy regimen and 4) were either a retrospective/prospective trial, a cohort study or consecutive case series with minimum ten patients. Studies were excluded if 1) authors were not specified, 2) the article was not published in the English language, 3) recurrence rates for chest keloids were not specified, 4) they contained incomplete data regarding recurrence, 5) the article commented on fewer than ten cases (n<10) or 6) the article was a review article.

Selection of relevant studies

Two authors (O.M and J.Z) independently reviewed and evaluated study validity according to the described selection criteria, and were critically appraised for quality of data and bias (selection bias, allocation concealment, blinding of patients and assessors). Review of abstracts was performed and then full text articles were reviewed, with studies excluded at each time according to the exclusion criteria listed. Full text articles were only selected if the inclusion criteria were met. Discrepancy in study selection between O.M and J.Z was resolved by 3rd author review (S.P). All three authors are formally trained in literature searching.

Data extraction

Two authors (O.M and J.Z) independently extracted predetermined outcomes from included studies. The primary outcome variable assessed was recurrence after surgical excision of keloid and adjuvant therapy, with predictor variables including type of radiotherapy. Recurrence was determined as the
percentage of patients who developed keloid recurrence after treatment. Where recurrence of keloid and hypertrophic scarring was recorded, both were included as recurrence. Data, where available, commenting on complication rate, type and radiotherapy dose (Gy/BED10) was also compiled. Studies with incomplete reporting of data were excluded from subgroup analysis and meta-regression.

Statistical analysis

Stata 13.0 statistical software was used for this meta-analysis. Recurrence for each study was collected as a percentage for the given population and pooled binomial meta-analyses were performed. The pooled studies were assessed for heterogeneity using the $I^2$ test, which assessed the hypothesis that variation of method across studies may impact effect size. Significance was set at a $p$ value of <0.05 and a random effects model was used to establish the pooled rate of recurrence and 95% confidence interval. A forest plot was established from the pooled data to indicate the proposed rate of recurrence and its 95% confidence interval.

Results

Study identification

Eligible studies were identified as indicated in Figure 1. Database searches identified 281 papers, with one other paper added from other resources. 165 papers remained after duplicate removal. Review of abstracts and titles revealed 32 full text articles for review. Ten papers were excluded as they were review articles/letters. Four papers were excluded as they did not specify a recurrence rate, another four papers were excluded as the specific rate of recurrence was not available for applicable locations. Two papers were excluded as they reported outcomes for less than ten keloids. Twelve final papers were included in the final analysis[5-16].
Characteristics of studies included

Twelve final studies were included for a total of 400 patients with a chest wall keloid treated with surgical excision and adjuvant radiotherapy. Clinical data is illustrated in Tables 1 and 2. Nine of the twelve studies were retrospective cohort studies, with just one being a randomized controlled trial, increasing risk of selection bias and lack of blinding. Where available, information regarding type of radiotherapy and most common complication are listed. Three of the twelve studies were in countries with predominantly Caucasian populations. Ethnicity within studies was unable to be extrapolated, so was not a considered variable in this meta-analysis. Study region was used as a surrogate for ethnicity in meta-regression, however was non-significant in predicting recurrence. Consistency of effects of the studies included was low ($I^2 = 87.6\%$), with p statistic $<0.001$, indicating a high degree of heterogeneity between studies. A random effects model was employed for meta-analysis in keeping with the rejected hypothesis for study homogeneity.

Treatment efficacy

All studies included had recurrence for chest keloids post treatment recorded as a percentage/recurrence rate over the duration of follow-up. The pooled estimate of keloid recurrence was 22% (95% CI 12-32%, p<0.001) as indicated in the Forest Plot in Figure 2. Meta-regression was performed accounting for radiotherapy dose (BED10), radiotherapy type, study type, study region and method of closure, all of which were non-significant (p values of 0.77, 0.59, 0.80, 0.76 and 0.53 respectively).

Adverse events

Complications post radiotherapy were poorly documented throughout most papers. Excluding transient erythema, reported to occur in almost all cases, most commonly reported complications were transient pigmentation (hypopigmentation or hyperpigmentation) changes and superficial
wound dehiscence, as outlined in Table 2. There were no post-operative tumours noted. Radiotherapy was generally reported as well tolerated.

Discussion

Chest keloids are notoriously difficult to treat, due to the high wound tension and possibly the high sebaceous gland concentration, which stimulates T cell mediated inflammation that causes keloid development[1]. A previous meta-analysis [3] reported a recurrence rate for chest and trunk keloids of 34% (95% CI 23-47%) and an OR of 4.47 (p=0.003) for predicting recurrence when compared to ear keloids treated with post-excisional adjuvant radiotherapy (Figure 3[5]). Our study reports a lower recurrence rate of 22% (95% CI 12-32%), and to this date pools the largest number of chest keloids studied (400 keloids from twelve studies). Van der Kar et al[17] reported a 100% recurrence rate for chest keloids managed with excision and adjuvant radiotherapy, however this study did not meet inclusion criteria for our series (n=4). This contrasts greatly with our series, where three studies quoted recurrence rates below 10% and all studies below 50%, highlighting the heterogeneity of studies looking at chest keloids, indicating the need for more focused and prospective literature examining the question at hand.

Radiotherapy

Post-excisional radiotherapy has been established as superior to radiation monotherapy for the treatment of keloids, with recurrence of 22% compared to 37-43% for monotherapy[3, 18]. Adjuvant radiotherapy has optimum impact on recurrence when performed within one to three days post-excision[19]. Delay is necessary when wound closure is achieved by grafting as the wound bed requires time to allow revascularisation, however this was not noted to worsen recurrence in our observed studies with a recurrence of 9.1-38%[13, 15]. Brachytherapy and electron beam therapy have been shown to be superior to X-ray beam radiotherapy for all keloids[3], however we were not able to comment on this in our series as no
studies identified used X-ray radiotherapy. There was no demonstrable difference between
brachytherapy and electron beam radiotherapy on meta-regression. Brachytherapy has the
advantage of being a topical therapy and an easier to administer treatment, with more effective
methods of local shielding. Areas of high tension such as the chest may require higher radiation
dosing, with a suggested regimen of 20Gy delivered in four fractions over four days being optimal[8],
however our study was not able to substantiate this finding or suggest an ideal dosing regimen.
Adverse effects of radiotherapy are a known drawback, with rates of temporary pigmentation ranging
between 11-46%[2, 9], however adverse effects were poorly documented in most studies observed.
The concern of carcinogenicity from radiotherapy has a very low incidence, with only five cases being
previously documented[20], representing a near negligible risk.

Method of closure

Closure method is predominantly dictated by the size of the chest wall defect, with smaller defects
lending themselves to direct closure and larger defects requiring either grafting or flap closure. Graft
harvest and inset is simpler and has less donor site morbidity than flap closure, however grafts may
yield a lesser cosmetic outcome and delay the time to adjuvant radiotherapy, usually by seven to ten
days, as the graft has to establish revascularization prior to radiotherapy. There is the concern of
keloid recurrence at the edges of the graft, however pre-excisional radiotherapy before excision and
grafting has been a useful method to combat the delay to radiotherapy and peri-lesional keloid
development[13, 21].

Flaps are the best method for reducing tension at the site of previous keloid, and may offer skin
matched in color and thickness to the recipient site[22, 23], but yields another potential wound for
keloid formation at the donor site, often requiring adjuvant irradiation[24]. Current flaps include
propellered internal mammary perforator flaps, superior epigastric artery perforator flaps,
parasternal intercostal perforator flaps or superficial circumflex iliac perforator free flaps[6, 22, 24,
25]. The theory that direct closure may produce the greatest wound tension and induce keloid
recurrence was not supported in this series, with meta-regression yielding a non-significant result
when comparing method of wound closure.
Limitations

In light of the relatively poor sub-group analysis commented on in the literature for keloid management, very few studies met the inclusion criteria and limited the capacity of this review to compare between different treatment regimens for chest keloids. This review included relatively heterogenous studies, with a variety of methods used for surgical closure and radiotherapy regimens that makes specific comment on treatment protocols difficult. The retrospective nature of most of the studies likely will result on under-reporting of negative outcomes, increasing the risk of selection bias. There was no standardized validated method of assessing scars used between studies, meaning reported outcomes are subjective. The quality of evidence was however ‘very low’ according to GRADE (Supplementary material 6,7).

Conclusion

Chest keloids remain a difficult subset of wounds for management. This is the largest meta-analysis that focuses on chest keloids and their response to excision and adjuvant radiotherapy. More literature is required on the topic, particularly prospective data with well documented sub-group analysis focusing on specific treatment protocol, ethnicity and anatomical location.
References


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<th>Reference</th>
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Figure legend

Figure 1. PRISMA flow diagram of literature search

Figure 2. Forest-plot of chest keloid recurrence after excision and adjuvant radiotherapy

Figure 3. Photographs of a 28-year-old woman with chest keloid: (A) preoperative; (B) after irradiation, before suture removal; (C) 6 months postoperative; and (D) 24 months postoperative. (Published with permission from Dr B Chen, originally published in Forty-Five Cases of Chest Keloids Treated With Subcutaneous Super-Tension-Reduction Suture Combined With Postoperative Electron-Beam Irradiation Dermatol Surg 2014;40:1378–138)
Figure 1. PRISMA flow diagram of literature search

Studies identified through literature search
- MEDLINE (40)
- Pubmed (42)
- Embase (92)
- Web of Science (84)
- Cochrane (23)

External records identified (1)

Records after duplicates removed (165)

Records screened (165)

Excluded post abstract or title review (133)

Full-text articles assessed for eligibility (32)

Full-text articles excluded
- Review article/letter (10)
- Location not specified (4)
- Recurrence rate absent (4)
- Sample <10 keloids (2)

Studies included in qualitative synthesis (12)
Figure 2. Forest-plot of chest keloid recurrence after excision and adjuvant radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Recurrence (%)</th>
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<tbody>
<tr>
<td>Wang et al (2014)</td>
<td>2.2%, 0-6.5%</td>
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<tr>
<td>Song et al (2018)</td>
<td>11.4%, 1-22%</td>
</tr>
<tr>
<td>Sruthi et al (2018)</td>
<td>17.6%, 0-36%</td>
</tr>
<tr>
<td>Ogawa et al (2007)</td>
<td>14.2%, 3-26%</td>
</tr>
<tr>
<td>Ogawa et al (2003)</td>
<td>43.1%, 7-30%</td>
</tr>
<tr>
<td>Ahmad et al (2018)</td>
<td>30.7%, 6-56%</td>
</tr>
<tr>
<td>De Cicco et al (2014)</td>
<td>25.3%, 15-36%</td>
</tr>
<tr>
<td>Kuribayashi et al (2011)</td>
<td>18.6%, 0-38%</td>
</tr>
<tr>
<td>Li et al (2014)</td>
<td>37.7%, 25-51%</td>
</tr>
<tr>
<td>Wagner et al (1999)</td>
<td>48.8%, 34-63%</td>
</tr>
<tr>
<td>Ship et al (1993)</td>
<td>9.1%, 0-26%</td>
</tr>
<tr>
<td>Zeng et al (2017)</td>
<td>8.3%, 0-24%</td>
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<tr>
<td>Estimate statistic</td>
<td>22%, 12-32%</td>
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Random effects model, $i^2=87.6\%$, $p=0.000$
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<th>Med. f/up (mo.)</th>
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<tr>
<td>Wang et al (2014)</td>
<td>China</td>
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<td>Electron beam</td>
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<td>Prospective</td>
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<td>Electron beam</td>
<td>32.6</td>
<td>Retrospective</td>
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<td>72</td>
<td>Retrospective</td>
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Table legend. 1° = direct closure; SSG = split thickness skin graft; FTSG = full thickness skin graft; RCT = randomized control trial
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<th>Complication (%)</th>
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<td>Wang et al (2014)</td>
<td>45</td>
<td>1 (2.2%)</td>
<td>Pigmentation change (18%), blistering (2.2%)</td>
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<td>Song et al (2018)</td>
<td>35</td>
<td>4 (11.4%)</td>
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<td>Sruthi et al (2018)</td>
<td>17</td>
<td>3 (17.6%)</td>
<td>Dehiscence (8%)</td>
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<td>35</td>
<td>5 (14.2%)</td>
<td>Pigmentation change (37%)</td>
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<td>51</td>
<td>22 (43.1%)</td>
<td>Pigmentation change (46%), dehiscence (6%)</td>
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<td>13</td>
<td>4 (30.7%)</td>
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<td>67</td>
<td>17 (25.3%)</td>
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<td>Dehiscence (6%)</td>
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<td>1 (9.1%)</td>
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<td>Zeng et al (2017)</td>
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<td>1 (8.3%)</td>
<td>Pigmentation change (33%)</td>
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Author/s:
Miles, OJ; Zhou, J; Paleri, S; Fua, T; Ramakrishnan, A

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