



Surgical Excision with Adjuvant Irradiation for Treatment of Keloid Scars: A Systematic Review

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Background: Excision followed by adjuvant irradiation is considered safe and most efficacious for treatment of keloid scars. Recently, different authors published successful treatment protocols and recommended the following: (1) the use of high-dose-rate brachytherapy instead of low-dose-rate brachytherapy or external radiation; (2) a short-time interval between operation and irradiation; (3) single fraction instead of multifraction irradiation; and (4) a minimum of 12- to 24-month follow-up post treatment.

Methods: This study evaluates the above recommendations with a systematic review of the English-language literature, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. Both PubMed and EMBASE were searched. Studies were graded according to the American Society of Plastic Surgeons Rating Levels of Evidence.

Results: Thirty-three studies were selected. Six studies were graded as level of evidence type II studies and 27 as type III. High-dose-rate brachytherapy showed lower recurrence rates compared with low-dose-rate brachytherapy and external radiation. A short-time (<7 hours) interval between scar excision and irradiation results in a lower recurrence rate compared with long-time intervals (>24 hours). Single-fraction irradiation showed promising results in terms of recurrence rate and patient convenience. Finally, scar recurrences were seen between 2 and 36 months, with a mean of 15 months.

Conclusions: Based on this systematic review of the literature, the evidence confirms the recommendations stated by authors in the recent years. However, due to the lack of high-quality randomized studies, the quality of this evidence is limited. More randomized studies will generate stronger recommendations. (*Plast Reconstr Surg Glob Open* 2015;3:e440; doi: 10.1097/GOX.0000000000000357; Published online 1 July 2015.)

Keloid scars are a benign fibroproliferative disease impairing the quality of life of patients by causing cosmetic disfigurement and complaints of pain and pruritus.^{1,2} Treatment is difficult with high recurrence rates and even growth stimulus as the main issue.¹ According to the international advisory panel on scar management, surgical excision

with postoperative radiation therapy is considered the most efficacious treatment.³

Radiation therapy for treatment of keloid scars was first described by Sequeira⁴ in 1909. Traditionally,

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it was applied externally by a variety of devices.⁵ Although good results were achieved, external radiation therapy requires a relatively high irradiation dose due to the large distance between the radiation source and the scar. Also, the surrounding healthy skin is unnecessarily exposed to radiation.⁶

To solve these problems, Malaker et al⁶ introduced a technique called “brachytherapy” (also called interstitial or internal radiation) in 1976. Nowadays, it is available as low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy. In both methods, a hollow catheter is incorporated in the surgical lesion after excision of the scar, through which a radioactive source is directed. In this way, irradiation is effectively localized from inside the lesion, only targeting the desired area.⁶ With LDR brachytherapy, a low-dose radioactive source is used and removed after typically 20–72 hours.⁷ In contrast, with HDR brachytherapy, a high radioactive source is applied for a short period of 5–10 minutes.⁸ Due to the short treatment time, HDR brachytherapy is an outpatient procedure enhancing patient convenience, whereas LDR brachytherapy requires hospitalization (Fig. 1).

Recently, different authors described new protocols aiming to reduce keloid recurrence and improve patient convenience.^{7–14} They recommended the following: (1) the use of HDR brachytherapy instead of LDR brachytherapy or external radiation^{8,9}; (2) a short-time interval between operation and irradiation^{7,8}; (3) single fraction instead of multifraction irradiation^{10–13}; and (4) a minimum of a 12- to 24-month follow-up post treatment.^{14,15} This systematic review evaluates these recommendations.

METHODS

Search Strategy

A comprehensive systematic review of the English-language literature was performed, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. PubMed and EMBASE were searched from inception to January 14, 2014, and January 23, 2014, respectively. The following terms were used as index terms or free-text words: “cicatrix” or “scars” (including synonyms and closely related words as hypertrophic scar and keloid scar) and “brachytherapy” or “x-ray therapy” or “surface radiotherapy.”

References of retrieved articles were scanned for additional studies. Inclusion criteria consisted of the following: (1) any English-language randomized controlled trials (RCTs), controlled clinical trials, or prospective or retrospective cohort studies reporting surgical excision (primary closure, no use

of skin grafts) with adjuvant radiotherapy for treatment of keloid scars; (2) a minimum follow-up duration of 1 year for all lesions; (3) studies including solely keloid scars or studies with a clear definitions distinguishing hypertrophic and keloid scars and separate analysis for both lesions; (4) no adjuvant interventions following surgical excision other than radiation therapy; (5) studies measuring recurrence rate as outcome, based on the regrowth of the keloid scars with or without functional complaints⁸; and (6) poster abstracts, case reports, or letters to the editor were not included. In case of duplicate articles, only one was included.

The article screening process was performed as follows: 3 investigators (M.C.E.v.L., S.C.S., and J.C.F.K.) carried out the initial searches and 2 investigators (M.C.E.v.L. and S.C.S.) independently reviewed the studies for eligibility. Investigators were blinded to each other, meeting only to compare findings after completing the extraction process. Decisions about eligibility were resolved by discussion. Seventy potentially relevant studies were identified from the initial searches. Subsequently, 2 authors (M.C.E.v.L. and S.C.S.) independently screened the full-text articles for eligibility using a standardized data abstraction form with inclusion and exclusion criteria. Disagreement was resolved by discussion. This eventually resulted in 33 articles (Fig. 2).

Data Extraction

One reviewer extracted data and a second review author verified the accuracy of the extracted data. Discrepancies in opinion about an article were reviewed, and consensus was achieved through discussion. A standardized data form was used to obtain the following information: (1) study characteristics; (2) study participants (including origin or Fitzpatrick score); (3) study design (prospective/retrospective and follow-up duration); (4) intervention, including type of radiation. Type of radiation was divided into external radiation (all different external devices including the surface applicator), LDR brachytherapy, and HDR brachytherapy. Also, radiation dosage and radiation scheme were extracted; (5) study results, of which the recurrence rate was the main outcome. Thereafter, data were arranged in evidence tables according to type of radiation.

Methodological Quality Assessment

Heterogeneity in study design and outcome measures did not allow for quantitative pooling of data for meta-analysis. The extracted studies were graded according to the American Society of Plastic Surgeons Rating Levels of Evidence.¹⁶ This classification assigns each article to a corresponding level of

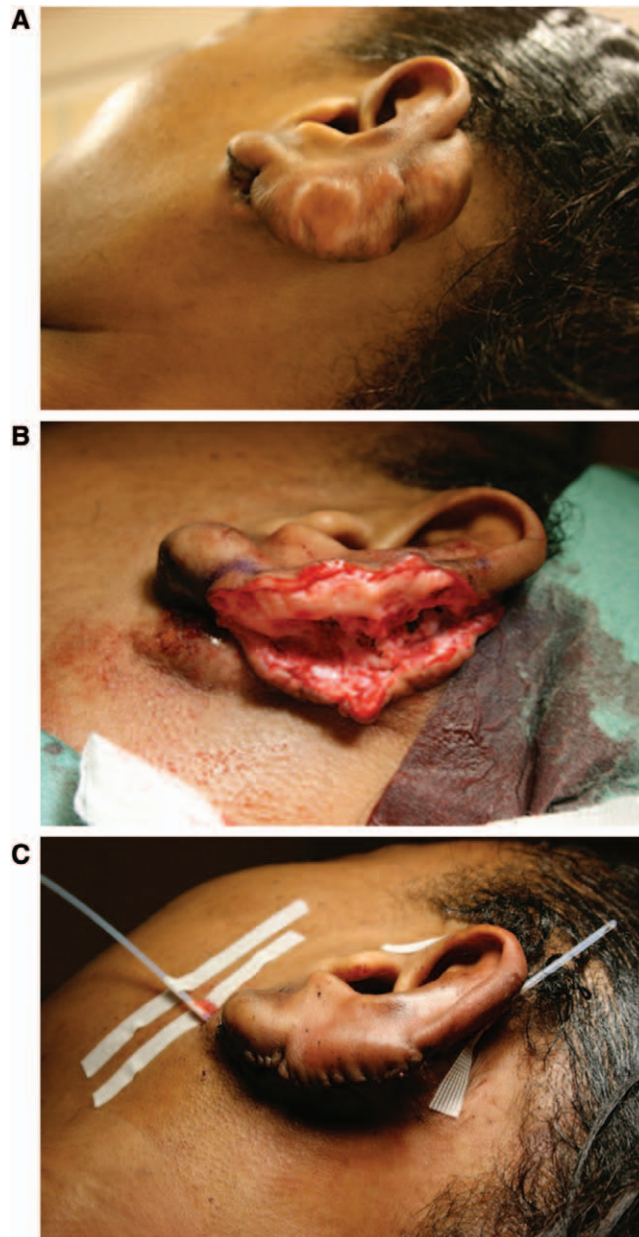


Figure 1. Surgical excision with adjuvant brachytherapy. Example of an auricular keloid scar (A) with surgical excision (B). C, A catheter is positioned between the dermal edges of the wound, below the surface of the skin and extending out of the skin beyond the wound. Postoperatively, the patient will be transferred to the radiation department for the adjuvant high-dose-rate brachytherapy (Source: van Leeuwen MC, Stokmans SC, Bulstra AE, et al. High-dose-rate brachytherapy for the treatment of recalcitrant keloids: a unique, effective treatment protocol. *Plast Reconstr Surg.* 2014;134:527–534).

evidence ranging from I (highest) to V (lowest). We classified a level II study to prospective studies, with a clear definition of keloid scars¹⁷ and recurrence.¹⁸

RESULTS

Study Characteristics

Initial database searches identified 3546 articles. A flow diagram of the search and selection process

is shown in Figure 2; 3339 articles were eliminated based on the title of the article because there was no relation between radiation therapy and keloid scars. Next, 207 abstracts were screened, of which 137 were excluded for not meeting with the selection criteria. Thus, 70 full-text articles were analyzed. Sixteen studies were excluded because they did not have a minimum of a 1-year follow-up, 10 studies were not prospective or retrospective, 5 were not in English, 5 had no specific outcome measures, and there was 1

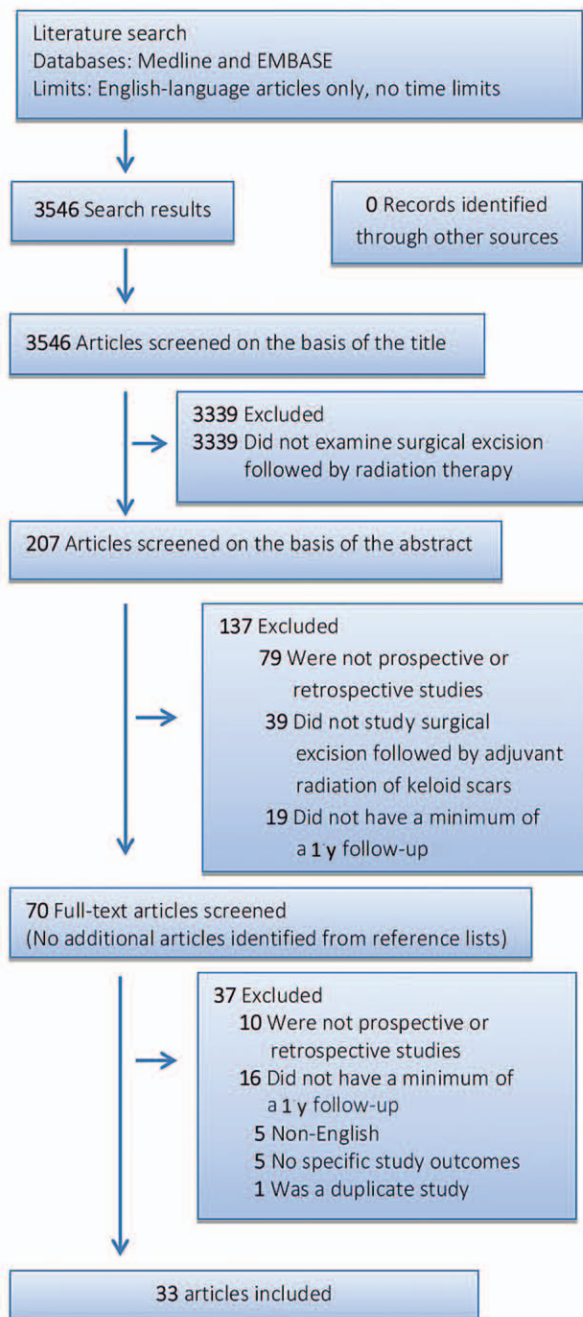


Figure 2. Flow diagram of the search and selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

duplicate study. Finally, 33 articles met all inclusion criteria (Fig. 2).

A summary of the characteristics of the included studies is given in Table 1. Of the included articles, 10 were from the United States, 4 from Japan, and 4 from India. The remaining 15 studies were from 9 different countries. Twenty-five studies used external radiation, 5 used HDR brachytherapy, and 3 used

LDR brachytherapy. The mean publication date was most recent for studies using HDR brachytherapy (HDR: 2005, range, 2001–2008; external: 1996, range, 1970–2013; LDR: 1992, range, 1976–2009).

Methodological Quality

We classified 6 studies with level of evidence type II and 27 studies with level of evidence type III. There were 2 RCT studies, randomizing different keloid treatment options, of which radiation was one. Twelve studies were prospective and 19 retrospective (Table 1).

Patient Characteristics

The sample size of the included studies ranged from 12 to 501 patients (mean, 97.8 ± 18.8) with a total of 17–570 scars (mean, 111.9 ± 22.4). In total, 3130 patients with 3470 keloid scars were treated. The follow-up ranged from 12 to 239 months (mean, 49 ± 9.5 months). Although all included studies mentioned a minimum of a 1-year follow-up, 42% did not describe the range of the follow-up completely. Patients' origin was noted in 57.6% of the studies: the majority treated a mixed population (74%), although origin or skin type was not always specified. Others treated solely white (5%), Asian (10.5%), or Afro-American patients (10.5%). The location of the keloid scars was mixed in 67% of the studies. In 18% of the studies, only keloid scars located on the earlobes were treated and 15% of the studies did not specify scar location. The mean age of the patients was 28.7 ± 1.3 years (range, 2–82 years). In 35% of the studies, age was not described.

Excision and Radiation Type

Most studies used an extralesional approach to excise the scar ($n = 12$), only one study¹⁹ excised the scar intralesionally. Other studies did not specify their excision approach.

Studies using external radiation, HDR brachytherapy, or LDR brachytherapy were compared on study characteristics and study outcomes (Table 2). When analyzing the patient populations per radiation type group, no major differences in patient characteristics were seen.

The mean total radiation dose for studies investigating external radiation and HDR brachytherapy was the same. Studies using LDR brachytherapy applied a higher radiation dose (external, 13.5 ± 3.3 ; HDR, 13.7 ± 2.6 ; LDR, 19.3 ± 1.2).

HDR brachytherapy was associated with the lowest mean recurrence rate, followed by LDR brachytherapy and external radiation therapy (HDR, 10.5 ± 15 ; range, 0–44; LDR, 21.3 ± 2.1 ; range, 19.4–23.6; external, 22.2 ± 16 ; range, 0–72). When looking only at

level of evidence type II studies, HDR brachytherapy showed the lowest recurrence rate as well.

Only one study used a device to measure scar quality: Akita et al²⁰ described the use of a Durometer to measure scar hardness, which improved with 50% posttreatment compared with pretreatment. No other studies used objective devices measuring scar elasticity, scar volume, or scar color.

Three studies^{5,8,20} used standardized assessment methods as the Patient and Observer Scar Assessment Scale (POSAS)^{21,22} or the Vancouver Scar Scale.²³ Kreulen and Van de Kar et al⁵ reported high POSAS scores (the higher the score, the less the scar resembles normal skin) after treatment using external radiation. In contrast, van Leeuwen et al⁸ reported low POSAS scores after treatment using HDR brachytherapy.

Akita et al²⁰ reported a significantly better improvement after external radiotherapy on all categories using the Vancouver Scar Scale compared with pretreatment. Other studies used different, nonvalidated, assessment tools.²⁴

Short Interval

Many authors used a time interval of less than 24 hours between excision and irradiation.^{8,25,26} Especially with the use of brachytherapy, authors described an immediate transfer to the radiation department after surgery, resulting in an interval of less than 7 hours.^{7,8}

Table 3 shows the differences in recurrence rate for radiation following excision within 7 hours,^{7,8,12,19,24,27,28} within 24 hours,^{5,9,10,14,15,29-34} or a longer period between excision and radiation.

In the external radiation group of studies, the rate of recurrence of keloid scars decreased when radiation was applied within 7 hours, compared with 24 hours or longer (external radiotherapy: <7 hours, 17 ± 4; 7–24 hours, 28 ± 7; >24 hours, 21 ± 2). With HDR brachytherapy, radiation within 7 hours showed no difference in recurrence rate compared with HDR brachytherapy applied within 24 hours. Within the LDR brachytherapy group, comparison was not possible because of the low number of included studies.

Single Fraction

Of the included studies, Ragoowansi et al^{10,15} and Sclafani et al¹² promoted a single-fraction radiation therapy using external radiation. When looking at the mean recurrence rate for these single-fraction protocols, a lower recurrence rate (12 ± 8.8) was seen compared with the mean recurrence rate within the total external radiation group (22.2 ± 16). In addition, no complications were described, and

good results were achieved in terms of scar quality and patient's satisfaction.

Recurrence

Ten studies (30%) provided information about the incidence of recurrence. The mean time for the incidence of recurrence after treatment was 14.8 ± 6.7 months with a range of 2–36 months (Table 4). Twelve studies described a definition for recurrence. Authors defined recurrence as any regrowth of tissue^{8,12,24,35,36}, mild or failure relapse³⁸; a symptomatic reappearance²⁸; a regrowth extending beyond the original surgical field⁹; pain, itch from the scar, clinical evidence of a mass; obvious return of the lesion^{10,15}; or just as impairment.³⁴

Complications

In all selected studies, no relation between scar radiation and malignancies was found. This is in accordance with other literature.³⁸⁻⁴⁰

DISCUSSION

The use of excision followed by adjuvant irradiation for the treatment of keloid scars is mostly based on research performed in the 1960s by Van den Brenk and Minty²⁵ and Cosman et al.²⁷ They were the first to compare different radiation protocols for the treatment of keloid scars.^{25,26}

In their studies, the treatment options were divided in 2 categories: (1) primary irradiation without surgery and (2) lesions treated by excision combined with planned early and late prophylactic irradiation. Both authors draw comparative conclusions stating that (1) primary irradiation without surgery may relieve symptoms but fails to cause resolution of the actual lesion. (2) Late postoperative radiation is associated with higher recurrence rates compared with early postoperative radiation.^{25,26}

In 1967, Nicoletis and Chassagne⁴¹ were the first to introduce interstitial (or internal) radiation, also called brachytherapy. Hereby, radiation is effectively localized inside the scar lesion, only targeting the area which is desired to irradiate. This in contrast to external radiotherapy in which considerable radiation of adjacent tissue is inevitable. This is undesirable, as exposure to radiation should be minimized in this often young population suffering from a benign disease which only needs radiation in a small area.

The conclusions of Van den Brenk and Minty²⁵ and Cosman et al²⁶ combined with the introduction of brachytherapy led to several recent publications in which protocols were described resulting in low recurrence rates and enhanced patient

Table 1. Characteristics

| Study | Study Type | Number (patient/lesion) | Scar Location | Fitzpatrick | Follow-up, Mean (Range)(mo) | Radiation (Fraction/Dose) |
|-------------------------------------|------------|-------------------------|---------------|--------------|-----------------------------|--|
| External radiotherapy | | | | | | |
| Ogawa et al ⁴² | R | 145/174 | Ear | NA | 18M (NA) | 2/10 Gy 2/15 Gy |
| Kim and Lee ³¹ | P | 26/26 | Abd | NA | 27 (19–36) | 3/12–15 Gy |
| Emad et al ³⁷ | P | 26/76 | Var | NA | 19 (12–24) | 3/12 Gy |
| Sakamoto et al ³⁵ | R | 119/194 | Var | F3–4; Asian | 36 (12–164) | 8/16–40 Gy |
| Kar et al ⁴³ | R | 21/32 | Var | F1–6 | 19 (12–35) | 3–4/12 Gy |
| Akita et al ²⁰ | R | 32/38 | Var | NA | 50 (12–108) | 4–11/12 Gy |
| Ragoowansi et al ¹⁰ | R | 80/80 | Var | F1–6 | NA (12–60) | 1/10 Gy |
| Ogawa et al ³⁶ | R | 129/147 | Var | NA | 24 (18–128) | 3/15 Gy |
| Maarouf et al ⁴⁴ | R | 36/50 | Var | NA | 84 (36–126) | 3–5/9–15 Gy |
| Perez et al ¹⁴ | R | 110/163 | Var | F1–6 | 81 (24–239) | 3/12 Gy |
| Ragoowansi et al ¹⁵ | P | 35/35 | Ear | F1–6 | NA (12–60) | 1/10 Gy |
| Wagner et al ⁴⁵ | R | 139/166 | Var | NA | 240 (1–NA) | 14 Gy (range, 7.5–28.5 Gy) |
| Sclafani et al ¹² | RCT | 42/50 | Ear | F1–6 | 18 (12–NA) | I: 1/10 Gy II: 1/7 Gy |
| Norris ³³ | R | 24/24 | NA | F5–6 | 24 (NA) | 3/1200 rad |
| Duronsinmi-Etti et al ⁴⁶ | P | 244/454 | Var | F5–6 | 24 (NA) | 1–3/5–15 Gy |
| Chaudhry et al ²⁹ | R | 36/36 | Ear | F3–6 | 67 (24–130) | 3/18 Gy |
| Darzi et al ⁴⁷ | RCT | 100/58 | NA | NA | 24 (NA) | I: Pre + post: 16 Gy II: Post: 2/16 Gy |
| Supé et al ⁴⁸ | P | 64/64 | Var | F3–4; Indian | 12 (NA) | 4/20 Gy |
| Doornbos et al ⁴⁹ | R | 200/278 | NA | NA | NA (12–24) | 2–4/15 Gy |
| Kovalic and Perez ³² | R | 76/76 | Ear | F1–6 | 117 (13–239) | 3/12 Gy |
| Sällström et al ³⁴ | P | 124/124 | Var | F1–6 | 24 (NA) | 3/1800 rad |
| Deka et al ⁵⁰ | P | 86/86 | Var | NA | 12 (NA) | 4/20 Gy |
| Ollstein et al ¹⁹ | P | 40/86 | Var | F1–6 | 24 (12–NA) | 3/1500 rad |
| Inalsingh ⁵¹ | R | 501/NA | Var | F1–6 | 24 (NA) | 4 Gy monthly |
| King ⁵² | R | 32/32 | Var | F1–6 | 180 (NA) | 1–2/1000–3000 rad |
| High-dose-rate brachytherapy | | | | | | |
| van Leeuwen et al ⁸ | P | 43/67 | Var | F1–6 | 33 (24–96) | 2/12 Gy |
| Arneja et al ⁹ | R | 25/25 | Ear | F1–6 | 36 (12–60) | 3/15 Gy |
| Veen and Kal ²⁸ | P | 35/54 | Var | NA | 12 (NA) | I: 4 Gy + 2×3 Gy II: 6 Gy + 2×4 Gy III: 3×6 Gy |
| Garg et al ³⁰ | R | 12/17 | Var | NA | 26 (12–71) | 3/15 Gy |
| Guix et al ²⁴ | P | 169/169 | Var | F1–2 | 37 (13–85) | 4/12 Gy |
| Low-dose-rate brachytherapy | | | | | | |
| Arnault et al ²⁷ | R | 31/55 | Var | F1–6 | 84 (24–192) | 17.9 Gy at 5 mm |
| Escarmant et al ⁷ | R | 361/570 | Var | NA | 82 (15–156) | 20 Gy at 5 mm |
| Malaker et al ⁶ | P | 30/31 | Var | NA | 24 (NA) | 2000 rad at 2.5 mm |

NA, not available; R, retrospective; P, prospective; Abd, abdomen; Var, various; Def R/K, application of preset definitions for recurrence (R) and keloid scars (K).

| Reference | <24 H | Histological Confirmation | Def R/K | Outcome Measures | Recurrence | Level of Evidence |
|------------|-------|---------------------------|---------|--|-------------------------|-------------------|
| 4 Mev | No | No | -/- | Advise to treat earlobes with 10 Gy divided over 2 fractions | 10 Gy: 4.6% | III |
| 6 Mev | Yes | No | -/- | 96% of patients satisfied | 15 Gy: 4.9% | III |
| 120 Kv | No | No | +/+ | Complaints of pain and itching improved in all lesions | 23% | II |
| 55–100 KvP | No | No | +/- | Advice for 20 Gy in 5 fractions | 33% | III |
| 250 Kv | Yes | Yes | +/+ | 48% judges their keloid recurrence as worse than pretreatment | 71.9% | III |
| 9 Mev | No | No | -/- | Vancouver Scar Scale: improvement | 21% | III |
| 60 Kv | Yes | No | +/+ | Durometer: softer scars | 16% | III |
| 4 MeV | No | No | +/- | Early, single, postoperative radiation is simple and effective | 32.7% | III |
| 5–6 Mev | No | No | -/- | Significant more recurrence at high tension locations | 16% | III |
| 4 Mv | Yes | No | -/- | 83% of the patients were very satisfied | 33% | III |
| 100 Kv | Yes | No | +/- | Advice minimum of 2-y follow-up | 20.60% | III |
| NA | No | No | -/- | Advice minimum of 2- to 3-y follow-up | Mean, 20% (range, 8–33) | III |
| 100 Kv | Yes | No | +/+ | A low dose of 8-10 Gy may be sufficient | I: 12.5% | II |
| 100 Kv | Yes | Yes | -/+ | Radiotherapy appears more effective than steroid inject | II: 0% | III |
| 50 Kv | No | No | -/- | Transitory hyperpigmentation | 53% | III |
| 100 Kv | Yes | Yes | -/+ | A short course for postoperative radiotherapy benefits the patient | 7% | III |
| NA | No | Yes | -/+ | Satisfactory results in 97.2% | 2.8% | III |
| NA | No | No | -/- | Failure rate: early (19%) vs late postsurgery radiation (43%) | I: 34% | III |
| 120 Kv | No | No | -/- | Fraction given weekly and biweekly | II: 27% | III |
| 4 Mv | Yes | No | -/- | Irradiation of a regrowing lesion following excision prevents recurrence | Weekly, 20% | III |
| 50 Kw | Yes | Yes | +/+ | Size: ≤ 2 cm, 85% success; ≥ 2 cm, 47% success | Biweekly, 35% | III |
| 16.65 GBq | No | No | -/- | Slight hyperpigmentation in 31% of the patients | 14.8% | III |
| 100 KvP | Yes | Yes | -/+ | 5 Gy given biweekly most appropriate | 27% | III |
| 60–90 KvP | No | No | -/- | No difference between white and nonwhite | 8% | II |
| 1–3 Mv | No | No | -/- | If skin graft was needed -> preoperation radiation | 30% | III |
| 5 mm | Yes | No | +/+ | Patients were treated on a monthly base, starting the 18th day postsurgery | 21% | III |
| 3–6 mm | Yes | No | -/- | Symptomatic relief in 52.6% | 23.5% | III |
| 5 mm | Yes | No | +/+ | First radiation within 6 h | 25.8% | III |
| 10 mm | Yes | No | -/- | Pigmentation problems in F5–6 patients | 3.1% | II |
| 10 mm | Yes | No | +/+ | 92% had successful treatment | 8% | III |
| 5 mm | Yes | Yes | +/+ | Advice 3×6 Gy | I: 44% | II |
| 2.5 mm | Yes | No | -/- | Better cosmetic results with higher dose schemes | II: 3% | III |
| | | | | HDR brachytherapy can be effective after earlier failure with external radiation | III: 0% | III |
| | | | | 4 fractions within 24 h | 12% | III |
| | | | | 96%: excellent result | 3.4% | II |
| | | | | F5–6: high risk of recurrence | 23.6% | III |
| | | | | 79% itching ↓ | 21% | III |
| | | | | 87.5% pain ↓ | 19.4% | III |
| | | | | Cosmetic appearance ↑75% | | |
| | | | | Recurring keloids had received a larger dose | | |
| | | | | Only linear scars could be treated | | |

Table 2. Study Characteristics Analyzed between External Radiation and HDR and LDR Brachytherapy

| | External Radiation | HDR Brachytherapy | LDR Brachytherapy |
|----------------|--------------------|-------------------|-------------------|
| Patients | 98.68±102 | 60±73 | 140±190 |
| Lesions | 106.21±99 | 66±70 | 218±304 |
| Location | | | 100 |
| lesion | | | |
| Mixed | 53 | 38 | |
| Ear | 17 | 13 | |
| Nonspecified | 30 | 49 | |
| Fitzpatrick | | | |
| 1-6 | 40 | 40 | 33.3 |
| 1-2 | — | 20 | — |
| 3-4 | 8 | — | — |
| 5-6 | 12 | — | — |
| Nonspecified | 40 | 40 | 66.7 |
| Radiation (Gy) | 13.5±3.3 | 13.7±2.6 | 19.3±1.2 |

Table 3. Recurrence Rate of the Different Radiation Types Related to the Time Interval between Surgery and Adjuvant Radiotherapy

| | Hours | | |
|-------------------|----------|----------|----------|
| | >24 | 7-24 | <7 |
| External | 21.5±2.3 | 28.4±7.3 | 16.8±4.3 |
| Brachytherapy HDR | — | 10±2 | 10.7±8.3 |
| Brachytherapy LDR | — | 19.4* | 22.3±1.3 |
| Total | 21.5±2.3 | 25±6 | 14±4 |

Time interval between surgery and radiotherapy of more than 24 hours, less than 24 hours, and within 7 hours.

*Only one study.

convenience.^{9,13,23,28,53} These protocols used HDR brachytherapy in one or more fractions, applied immediately after excision. We evaluated these results and recommendations with a comprehensive review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Radiation Modality

External radiation resulted in a higher recurrence percentage compared with HDR and LDR brachytherapy. This can be explained by the fact that brachytherapy, in contrast to external radiation: (1) has more focused and efficient radiation of the targeted area; (2) requires a lower dose of radiation to achieve the same therapeutic effect, thereby reducing radionecrosis; and (3) provides less irradiation to surrounding healthy tissue.

When looking at brachytherapy, HDR brachytherapy scored lower recurrence rates compared with LDR brachytherapy. Although both techniques are considered brachytherapy, with HDR brachytherapy the total radiation is given in several minutes and ends shortly (<24 hours) following the operation.

Table 4. Recurrence Percentages in Months

| Study | Recurrences | Months |
|---------------------------------|------------------------------|--------|
| Arnault et al ²⁷ | 84% | 24 |
| | 16% | 36 |
| | Mean | 26 |
| Darzi et al ⁴⁷ | 67% | 6 |
| | 22% | 12 |
| | 11% | 24 |
| | Mean | 9 |
| Doornbos et al ⁴⁹ | 70% | 6 |
| | 19% | 12 |
| | 9% | 24 |
| | Mean | 9 |
| Escarmant et al ⁷ | 90.8% | 12 |
| | Ollstein et al ¹⁹ | 75% |
| | 12.5% | 24 |
| | 12.5% | 36 |
| | Mean | 16 |
| | Mean | 12 |
| Perez et al ¹⁴ | Mean | 17 |
| Sclafani et al ¹² | Mean | 17 |
| Wagner et al ⁴⁵ | 15% | 2 |
| | 45% | 6 |
| | 16% | 12 |
| | 24% | 24 |
| | Mean | 11 |
| | Mean | 18 |
| Kovalic and Perez ³² | Range | 12-60 |
| Ragoowansi et al ¹⁰ | | |

With LDR brachytherapy, however, this dose is spread out over 20–72 hours, which is actually a delayed treatment. In addition, HDR brachytherapy is an outpatient procedure enhancing patient convenience, whereas LDR brachytherapy requires hospitalization in lead-coated radioprotection chambers.

Short Interval

Van den Brenk and Minty²⁵ and Cosman et al²⁶ showed that early irradiation, within 24 hours, results in lower recurrence rates, compared with a more delayed irradiation. Other authors, however, hypothesized that early radiation within 7 hours could lower the recurrence rate even further.⁸ As Table 3 shows, this hypothesis was confirmed with the external radiation group of studies.

Surprisingly, this hypothesis was not confirmed in the HDR brachytherapy group. Notably, this discrepancy was caused by one study, which showed a very high recurrence percentage.²⁸ When analyzing this RCT study by Veen and Kal,²⁸ there were 3 groups receiving different radiation doses within 6 hours. The group receiving the smallest amount of gray (10 Gy) scored a high recurrence percentage of 44%. The other 2 groups in this study receiving 14 and 18 Gy showed a 3% and 0% recurrence rate, respectively. The authors hypothesized that this high recurrence rate was due to the low radiation dose of 10 Gy. This is in accordance with other HDR brachytherapy studies, which all applied a dose of 12 Gy or more. Thus, when excluding this deviant rate, an average

recurrence rate of 2.3% was seen in with studies applying brachytherapy within 7 hours. This confirms the trend already seen in the external radiation group toward a low recurrence rate when irradiation is applied within 7 hours. Also, it may show that a minimum of 12-Gy irradiation is required.

The mechanism behind immediate irradiation following scar excision remains unclear. Many studies explain the effect of irradiation by the prevention of keloidal fibroblasts to repopulate.^{54,55} This seems illogical, as extralesional scar excision already removed all keloid fibroblasts. Another explanation could be that surgical scar excision will attract local fibroblasts. Stimulated by humoral or cellular factors, these local fibroblasts lead to a disturbed proliferation homeostasis, which eventually can lead to recurring of the scar. Irradiation may modulate these humoral or cellular factors, leading to a disruption of this cascade, thereby preventing scar recurrence. As this process starts directly after the operation, it is important to start the irradiation as quickly as possible, that is, transferring the patient immediately after surgery to the radiation department.

Single Fraction

Surgical excision followed by a single-fraction radiation dose would prevent repeated (outpatient) consultations, thereby increasing the patient convenience and therapy adherence. Moreover, Van Den Brenk and Minty²⁵ stated that there is no place for the use of fractionated small doses of radiation to attain a larger cumulative dose. They state that the dose-effect relationship is strictly threshold and that doses of less than 10 Gy substantially fail to inhibit the growth of regeneration of the scar.²⁵ Out of the studies in this review, 3 studies administered a single-fraction dose with external radiation. They showed low recurrence percentages with good results in terms of scar quality and patient's satisfaction. Importantly, no complications were noted.^{10,12} In our opinion, these results are promising. However, a RCT is required to confirm these results and prove the safety and efficacy of a single-fraction radiation therapy.

Study Protocol

A large part of the initially selected studies were excluded because they did not describe the minimum follow-up of the study. This review reports a mean scar recurrence after a mean of 15 months posttreatment with a maximum range of 36 months. Therefore, we recommend a minimum of 15-month follow-up, but preferably a period of 2 or even 3 years.

In addition, most studies did not clearly define keloid characteristics, keloid recurrence, and study

outcomes. Defining keloid characteristics prevents inclusion of nonkeloid scars, such as hypertrophic scars. This is relevant as hypertrophic scars have better prognostic factors than keloid scars. We advise to use the following definition for inclusion of keloid scars as stated by Ogawa¹⁸: "A fibroproliferative disorder of the skin that grows beyond the boundaries of the original wound or has an unrecognized origin." Also, posttreatment histology of the excised lesion may be used to confirm the nature of the scar.

As described in the result sections, only 12 studies (36%) defined keloid scar recurrence. Most studies, evaluating scar recurrences, use the definition as stated by Cosman and Wolff¹⁸ in 1974: "A growing, pruritic, nodular scar constituted a recurrence; a flat, nonpruritic scar was considered a good result." Furthermore, to define the (residual) scar quality, validated measurement devices can be used. Examples are the Cutometer for scar elasticity,⁵⁶ the Dermaspectrometer for scar color,⁵⁷ and the POSAS for general scar assessment.^{21,22} Finally, inclusion of a variety of Fitzpatrick (F1–6)⁵⁸ score patients is preferable as Afro-American patients (F5+6) are more prone to pigmentation disorders^{59,60} and scar recurrence²⁷ compared with white patients (F1–3).

Primary Closure

The recommendations in this article are based on the included studies, which included all keloid subtypes that could be closed primarily after excision. In the case of large or high-tension keloid scars, which cannot be closed primarily, we advise to use skin grafts as described by Li et al.⁶¹

Comparison with Other Treatment Modalities

As demonstrated in this systematic review, excision with adjuvant HDR brachytherapy offers total scar eradication with low recurrence rates (mean, 10.5%). Other treatment modalities will not always result in a complete volume reduction and demonstrated higher recurrence rates, corticosteroid injections monotherapy (>50%¹⁷), surgery with corticosteroid injections (<50%³), and intralesional cryotherapy (24%⁶²). On the other hand, surgical excision with irradiation is not always possible due to the patient characteristics (pregnant or age, <12 years) or the location of the keloid scar (radiosensitive locations such as the thyroid gland). Finally, it should be mentioned that the costs of excision with irradiation exceed the costs of other treatments significantly. Therefore, excision with adjuvant radiation therapy should be regarded as a "last resort" for (recalcitrant) large keloid scars, when other nonsurgical treatments have failed.

CONCLUSIONS

Based on this systematic review of the literature, the use of HDR brachytherapy following scar excision, preferably applied within 7 hours, results in a low recurrence rate. Also, single-fraction irradiation appears safe and enhances patient convenience. However, the quality of this evidence is limited. There is a paucity of high-quality studies with clearly defined methods and study outcomes. More randomized studies comparing different radiation protocols will generate stronger recommendations.

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