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Adjuvance in refractory keloids using electron beams with a spoiler: Recent results

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ABSTRACT

Aim: To present clinical results of adjuvant irradiation of excised refractory keloid wounds using a novel bolus-free technique developed within our group to irradiate the skin surface with a linear accelerator.

Background: The use of a bolus to increase surface dose over a newly excised keloid presents several problems. Previous solutions are unsatisfactory. Our technique is promising but needs to be evaluated in practice.

Materials and methods: Twenty refractory skin keloids in 19 patients were excised and irradiated in Hospital Plató (Barcelona, Spain) using a 6 MeV electron beam with a 4-mm aluminium spoiler. 15 Gy in fractions of 3 Gy were delivered to the excision site plus a safety margin. All patients were examined during the follow-up (median: 40 months, interval: 12–68 months) and toxicities were recovered.

Results: At the end of the follow-up period, 76% of the cases had not recurred, while the complete response rate amounted to 53%. Residual hypertrophic scars were classified as partial responses. After therapy, itching and pain were observed in 30% of the patients, as well as one telangiectasia and two hyperchromatic scars.

Conclusion: Our technique avoids using a bolus while combining the benefits of electron beam therapy in keloids (fewer secondary effects, and fewer and shorter treatments) with a dose deposition adequate for skin surface treatments. Our results are in line with the most successful therapies evaluated in the literature, as secondary effects are acceptable and recurrence rates are low.

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1. Background

Keloid scars are benign dermal tumours that develop as a result of a skin wound overhealing.¹ The healing of wounds seems to be regulated by a series of cellular growth factors and the equilibrium between matrix degradation and collagen biosynthesis. When a normal healing process occurs, anti-fibrotic factors end up inhibiting fibroblast development and fibroblast synthesis of collagen.² However, when this process fails, the scar keeps growing. This results in a characteristic hard tumour that extends beyond the margins of the wound. Keloids are unattractive and may cause pruritus, dysesthesia and burning.³

Hypertrophic scars (HS) are similar, but must not be confused with keloids. HS stay confined within the bounds of the original wound and tend to regress over time. There are also immunohistochemical differences between both entities.^{2,4–7}

One of the most frequent sites reported for keloid scars are the ear lobes,⁸ while keloids on palms and soles are very rare.⁹ Black and Hispanic populations have a higher incidence ratio compared with Caucasians.^{2,10} In some cases, keloids have been removed from wounds as small as a site from vaccination.¹¹ Moreover, it is common to find them following second or third degree burns. A family history of keloids is often mentioned, although the exact path of inheritance is still unclear.^{2,9} In all cases, keloids represent a serious aesthetic problem, with negative psychosocial consequences, especially for young people.^{4,6,7}

Treatment options are multiple. The initial approach was surgical excision, but it was soon shown to be ineffective¹² because of the high recurrence rate, reported to be at least 50%, and as high as 100% in some studies^{13,14} From then on, several other therapies have been tried, including silicone gel sheeting, intradermal corticosteroids, pressure therapy, cryosurgery, radiotherapy, and laser therapy.

Nowadays, an established treatment in resistant or refractory keloids is surgical excision followed by radiotherapy. Recurrence rates for the first year are as low as 10% in selected cases.^{3,7,15,16} A typical protocol consists of excision followed by the first session of radiotherapy, which will continue through the following days. Dosages and timing differ between teams and institutions.

Various modalities have been proposed and used for the post-excision treatment of keloids, including kilovoltage X-rays, brachytherapy, and megavoltage electrons. Each has its advantages and its disadvantages, although equipment availability is often the most important factor when choosing modality.

Superficial X-rays can deliver very homogeneous doses to the skin surface,¹⁵ but have a high absorption rate to any bone below the irradiated area.¹⁷ Beta radiation can be delivered using dermal 90Sr applicators¹⁸ and Iridium-192 brachytherapy is delivered with a radioactive source attached to a wire that passes through a catheter placed under the suture. Electron beams are delivered using high-energy linac accelerators, with the lowest energy levels (4–6 MeV) being the most appropriate for skin treatments. Dose homogeneity is easily achieved, and treatment can be applied in five minutes per day of treatment. However, entry-surface doses are

too low with electrons and require a bolus in contact with the skin.¹⁹

2. Aim

A new method to increase the surface dose and to reduce the electron penetration range was published by our group as a hygienic alternative to the conventional bolus. The method consists in adding an aluminium spoiler at the end of the electron applicator, which results in an optimal radiation beam for skin irradiation.²⁰

Historically, beam spoilers have been employed in photon therapy to increase the build-up dose near the surface, but their use in conjunction with electron beams in clinical practice after surgery has not been previously evaluated.²⁰ Between 2007 and 2012, our institution treated 20 keloids in 19 patients using this modality.²¹ In what follows, we evaluate our clinical results and discuss them in the light of the existing literature.

3. Materials and methods

Nineteen patients with 20 keloid scars were included in the study according to the following criteria:

1. Keloids had proved resistant to previous treatments. Specifically, all cases had received at least two rounds of corticosteroids. Additionally, four cases underwent surgery before being treated with corticosteroids.
2. The complete extralesional surgical removal could be planned in one session with primary default closure without skin grafts or transposition. Irradiation was planned and started the same day.
3. Physical characteristics of the scar were adequate. Desired depth of treatment was below 1 cm and the irradiated site could be isolated. For instance, flatness was achieved by fixing the surgical ear bed or by using thermoplastic masks with holes in the irradiated site.
4. Three patients had been previously irradiated with electron beam therapy, and the keloid was close to a tumour site for two of them:
 1. One patient received 15 Gy in 5 fractions for a keloid. Afterwards, a squamous carcinoma was diagnosed with a biopsy in the underlying site. An excision with negative margins followed, but the patient developed a new keloid, which was excised and treated at our centre.
 2. Another patient received 60 Gy in 30 fractions at the site of a parotid gland tumour. The keloid appeared in the non-irradiated margin of the excision.
 3. The third patient had an initial keloid dating back to 1998, which was excised and grew back, excised again in 2003 and treated with corticosteroids and 15 Gy in 5 fractions, but proved resistant once again. In 2008 the keloid was excised and treated with our technique.

Average age was 38.5 years (range 16–80). The main sites for treatment were earlobe (10 cases) and thorax (7 cases) (Fig. 1). See Table 1 for the patients' demographics.

Fig. 1 – A refractory ear lobe keloid that received a previous treatment such as corticosteroid i.l. injection therapy, pressure therapy, excision, laser therapy, alone or combined.

All patients included consented to the treatment protocol and to the requirement of coming back for the follow up.

Surgery. Removal of the keloidal tissue was complete in 60% of the cases with 3–5 mm margins. In 40% (8) of the cases a revision showed microscopical residual keloidal tissue. Surgery was performed preferably on Monday so as to schedule irradiation through the week. To avoid excessive skin tension, surgical margins were approximated and primarily closed with absorbable subcutaneous sutures and non-absorbable trans-cutaneous sutures to close the wound. Some areas, such as the ears, required not only the removal of the keloid, but also an immediate reconstruction, because keloids usually invade and destroy healthy tissue causing deformation. All excised keloids passed an independent histological examination. Skin sutures were removed after the therapy finished.

Table 1 – Patient demographics.

N: 19 patients (n: 20 keloid cases)
Females: 11 (one female presented keloids in both ear lobes)
Males: 8
Age (years): median: 33.5; mean 38.5 (range 16–80)
Localization
Ear lobe: 10
Thorax: 7
Anterior: 3
Dorsal: 1
Shoulder: 3
Face: 2
Follow up:
Average: 36 months
Median: 40 months
Lost: 3 cases
Size: range 1–6 cm (median 2)
Results: 13 of 17 followed cases responded (76.5%)
Complete response: 9 (53%)
Partial response: 4 (23.5%)
Recurrences: 4 (23.5%)

Fig. 2 – Scheme of the treatment setup. The vertical shade shows the applicator field. The lead blocks at least 10 mm of this field. The spoiler blocks the light, so it is added after doing the setup, just before the irradiation.

Radiotherapy. Postoperative adjuvant radiotherapy was initiated in all patients straightaway with a maximum of 4 h after surgical removal. The standardized total dose was of 15 Gy, administered in five fractions of 300 cGy over the subsequent postoperative week. Treatment was delivered using a 6 MeV beam with a 4-mm thick aluminium spoiler covering the end of the electron applicator. The area to be irradiated was delimited by a thin (2-mm) lead cover, reducing the visual field from the linear accelerator by at least 1 cm in all directions. This is necessary to reduce the penumbra of the degenerated electron field to an acceptable level for medical practice, see [20] for a detailed explanation. The irradiated area included a 5 mm margin. Fig. 2 shows a standard scheme of treatment, and an example is shown in Fig. 3. Except in 3 cases, all surgical scars were shorter than 4 cm.

Note that the spoiler changes greatly the cGy/MU ratio, with factors in the order of 2× for typical field sizes. The physicians must be aware that the standard “treatment tables” that are

Fig. 3 – Example of a treatment. The lead is covered with gauze for patient comfort.

Fig. 4 – From left to right: a left ear lobe keloid in a young patient; the treatment field marked on the skin just after excision; and the result of treatment after two years.

sometimes available for emergency or fast calculations are not valid when a spoiler is added to the beam.

Follow up. The evaluation of results and collateral effects was conducted before the surgery, every 4–6 months during the first year after the surgery, and every 12 months during the rest of the follow-up period (median: 40 months, interval: 12–68 months).

Recurrence was defined as the elevation of the scar that extends beyond the original surgical field. Alternatively, a scar without any signs of lifting and extending was considered a non-recurrence. Slight hypertrophic scars were classified as non-recurrences and as partial responses, consistent with a pattern in which the uncontrolled growth of the keloid is the main characteristic of the disease. However, a complete response would have yielded a satisfactory aesthetic result.

Clinical evaluation was performed aided by pictures to compare with previous visits in terms of vascularization, pigmentation, thickness, relief, flexibility in the treated skin as well as the extent of the surface area. All patients were asked to do a self-assessment of the treatment and of the aesthetic result, which was also evaluated independently by the physician.

In secondary effects, pain, pruritus, stiffness and irregularity were considered in the follow-up as well as secondary effects from the radiation.

Some information had to be gathered through phone calls, especially for the patients for whom the follow up took place later. Because of that, a standardized questionnaire²² was discussed but finally rejected.

4. Results

Seventeen cases were followed up for more than 12 months (median follow-up 40 months) and are included in the

statistical analysis. Three cases were lost after the first control and were therefore excluded.

The overall response was 76.5% (13 cases), with a 59% (10 cases) complete response rate (see Fig. 4). The remaining 17.5% (3 cases) had a hypertrophic scar on the keloid site, which is considered as no recurrence, but from the pathological point of view is not a complete response. One of the HS was successfully rescued using steroids (see Fig. 5). The recurrence-free rate at 24 months amounted to 75.8% using actuarial estimates.

Patients generally showed local pain and/or pruritus before treatment. In 5 cases, this continued after treatment. Of these 5 patients, 3 relapsed later on, one was left with a wide residual scar with telangiectasias (grade 1) and the last one had a wild hypertrophic scar.

Relapses were observed at 5, 10, 12 and 20 months after treatment (mean: 12 months). Histological analysis showed that one case had positive margins and should be considered persistent rather than recurrent. A thorax case resulted in an explosive recurrence after 20 months. Finally, two ear-lobe cases relapsed within one year. On a side note, one of the recurrences showed some reduction in size after treatment.

In eleven cases (65%), the patients considered the result of the treatment “good” or “very good”, while this was true only for ten cases (59%) according to the physician. Two patients (12%) showed hyperchromasia in the follow-up, and one (6%) of them also had a telangiectasia.

For the three patients previously irradiated with electron beam therapy, the only observed secondary effect was a mild pigmentation, which disappeared before the first control.

Nowadays, it is well accepted that early perioperative radiotherapy after surgical excision is an effective management therapy for resistant keloids. It is also the most common referral for benign conditions in radiotherapy departments,²³ although not the only one.²⁴ A retrospective analysis of $n = 80$

Fig. 5 – Hypertrophic scar as a result from treatment, treated with corticoids as a rescue strategy. The image on the left shows the lesion before rescue and the right image shows the lesion after the first i.l. injection.

cases²⁵ suggested that the majority of keloid scars can be controlled by a single operation with immediate adjuvant single fraction radiotherapy. The recurrence after one year was below 10%, although the recommendation for these cases is at least two years of follow-up. In our case, three of the four recurrences occurred at least ten months after the treatment, and one of them happened after 20 months.

There is no consensus regarding the optimal fraction dose or schedule. In other studies, doses delivered have ranged from 3 to 40 Gy in either single or multiple fractions. Some investigators believe that the total dose of irradiation is more important than the timing²⁶ or fraction size.²⁷ Fred Doornbos et al.²⁷ reported a trend towards a dose-related response between 9 and 15 Gy, with higher doses being more effective in terms of recurrence rate. A meta-analysis by Kal et al.²⁸ concluded that most doses are too low to prevent recurrence, recommended a biologically effective dose (BED) ranging between 30 and 40 Gy, and advocated for a single fraction of 13–15 Gy the same day of the excision.

In our case, treatment was delivered in five fractions of 3 Gy during the week following the excision, for a total BED of 19.5 Gy using the model in Kal et al. In retrospect, we could conclude that from the point of view of local control this is a sub-optimal dose, with an estimated recurrence rate above 20%. Our results are in line with the conclusions of Kal et al., given that our recurrence rate is 4 cases in 17 (23.5%).

Morbidity, however, is well above acceptable levels in our study, probably because of the adjusted BED delivered. On the other hand, BED models widely vary across authors: Flickinger²⁹ performed a multivariate logistic regression which calculated values of $\alpha/\beta \sim 2$, while Kal used $\alpha/\beta = 10$ instead. Interestingly, the results of both studies are compatible regarding treatment schemes, with Flickinger suggesting

a 3-day treatment totalling 19 Gy for earlobes and 24 Gy for all other sites to control 95% of cases. This would yield 43.5 Gy BED using the model advocated by Kal et al. Our evidence suggests that Flickinger's model might not be totally accurate as far as the calculation of α/β values is concerned. However, as we have shown, this is not critical, because almost all treatments are delivered in five fractions (in contrast with standard radiotherapy, in which some treatments consist of 40 fractions or more). Sakamoto et al.³⁰ use Kal et al. as a benchmark and conclude that 20 Gy in five fractions is the preferred treatment scheme, balancing low morbidity with an expected high control rate.

Regarding the technique used to deliver the radiation, perhaps the most traditional approach still in use today is orthovoltage X-rays^{15,31} but, as stated above, dose absorption to bone structures directly below the wound is an important factor to be taken into account. Ear-lobe keloids are an ideal site for the relatively small fields available for orthovoltage X-ray equipment, and are also the type of keloid most often reported.

A study using 90Sr beta radiation therapy, treating 20 Gy in 4 daily fractions¹⁸ found 36% relapses in 41 patients with a follow-up of 71 months. 90Sr decays into 90Y which emits β radiation with very low penetration: 10% or less of the prescribed dose penetrates to depths beyond 5 mm. Brachytherapy Strontium-90 applicators are very similar to electron beams in this sense. Highest doses are delivered to the superficial layers of the dermis, which combined with the single-dose treatment cause late side effects on the skin. The same study reports 63% of hypopigmentation, 48% of telangiectasias, and 42% hyperpigmentation for the non-relapse patients.

Brachytherapy reports very good results. Garg et al.¹⁶ show only a 12% recurrence rate, and Rio et al.³² mention an 83%

response after a total dose of 20 Gy. Another study by Bisbal et al.⁷ claims recurrence rates as low as 4% using a similar scheme. Secondary effects, however, are high, with 70% hyperchromasia or telangiectasias in [32]. Radioactive sources deliver high doses to any tissue in contact with the catheter, which explains the excess secondary effects when using brachytherapy. With brachytherapy, complex irradiations, like a homogeneous dose along a suture, can be achieved.¹⁶ Indeed, brachytherapy is the optimal irradiation technique to treat a skin fold under the breast or a keloid that wraps around an arm or leg. On the other hand, the catheter poses an additional burden for the patient if treatment is delivered in more than one fraction.

Concerning electron beam therapy, several studies^{33,34} report very good results, with little or no side effects when using electron beam therapy, although recurrence rates vary.

The use of electron beam therapy seems to maximize treatment benefits while minimizing the burden imposed on the patient and the side effects, being the recommended technique when the aesthetic outcome is critical.¹⁸

The main disadvantage of electron beams is the entry dose. While other techniques cause secondary effects, entry-surface dose with electrons is reduced to as much as 60% of the maximum dose. The solution until now has been to use a bolus.¹⁹ Our group introduced a novelty in electron beam therapy by using a spoiler. A spoiler blocks the electron beam, forcing electrons to interact with it, lowering their energy and broadening their spectrum. The resulting beam includes electrons with low energy which deliver dose to the surface, and also some electrons with higher energy which deliver dose as a normal electron beam would do, enabling us to treat the skin without a bolus but with all the advantages of electron beam therapy.

Consistent with this, the side effects experienced by our patients are very few and relatively mild: considering the ten patients followed for more than 2 years that had no recurrence, our rates of side effects from treatment are 20% (hyperchromasia) and 10% (telangiectasia).

Regarding prognosis, Viani et al.³⁵ found that keloids with size ≥ 5 cm, localized in the thorax region, derived from a burn scar or being a recurrence from a previous keloid where all factors that increased the odds of a bad outcome. In our study, there were no keloids with a burn aetiology, and all cases were recurrences, so only size and region could be analyzed. Three recurrences were reported in the auricular region out of 10 cases (30%), while only one patient had a recurrence in the thorax region out of 7 cases (14%). In our study only two keloids were bigger than 5 cm, and they did not recur. If we consider all the keloids that were bigger than the median size (2 cm) we find only one recurrence out of 4 cases. We find, therefore, no correlation with Viani et al. but this is probably a consequence of our small sample. The high recurrence rate in the auricular region deserves a second look in the future. Irrespective of these prognostic factors, the worst recurrence in our study was suffered by a patient who had a 3-day gap during treatment, a fact that greatly decreases BED and that might have been the cause of the recurrence.

An International Advisory Panel¹³ conducted a thorough bibliographical search and discussed the evidence presented by the wide spectrum of trials conducted on keloid scars. Their

final recommendations are restricted to silicone gel sheeting and pressure therapy as preventive measures after surgery, and corticosteroids as first line therapy (alone or as adjuvant therapy). For other therapies, the Panel pointed to the lack of evidence in the form of randomized, prospective studies, long term follow-ups and surveillance of side effects. For example, cryotherapy alone has good results, but it often causes hypopigmentation, making it unsuitable for large scars; current laser therapy shows good results, but in the past it was associated with high levels of recurrence; and radiation therapy (adjuvant to surgical excision) is generally agreed as the most effective treatment in severe cases of keloids, but there are concerns associated with radiation and its carcinogenic effects.³⁶ For this reason, the use of radiation therapy for benign diseases has decreased in recent years.^{4,6}

However, data from combined studies that followed thousands of patients show low carcinogenic rates and small excess risk of cancer after employing radiation at different locations.^{6,36} Finally, Leer et al.³⁷ consider that there is sufficient evidence concerning keloid treatment using radiation to use it routinely for treatment.

5. Conclusions

Our results are in line with the most successful therapies evaluated in the literature, as secondary effects are acceptable and recurrence rates are low. In this regard, we consider that the proposed technique yields positive results. We also consider post excision radiotherapy for refractory keloids a valid option with results comparable or better than other means evaluated in the literature. Our technique combines the benefits of electron beam therapy in keloids (fewer secondary effects, and fewer and shorter treatments) with a dose deposition adequate for skin surface treatment but without the problems associated with placing a non-sterile bolus over a newly excised keloid wound. The evidence presented suggests that our bolus-free technique is a feasible and effective option to irradiate keloids that have proven resistant to other treatments while keeping aesthetic considerations in mind.

Conflict of interest

None declared.

Financial disclosure

None declared.

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