Additional Invasive Techniques in Scar Management

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40.1 Background

Soon after the discovery of radiation, radiotherapy was recognized as a treatment technique for tissue overgrowth. Also, hypertrophic scars and keloid disorder were treated both therapeutically and for prevention of recurrent growth following surgery.

Both patients and care providers might hesitate about radiation treatment considering the associated ominous reputation and tissue burden. While radiation treatment represents a significant burden, for the patient as well as financially and logistically, it is also safe and characterized by low recurrence rates, high patient satisfaction, and, in combination with excision, excellent aesthetic results. Therefore, when other techniques fail in preventing keloid disorder recurrence, radiation treatment is a valid option and should be considered.

This chapter will provide an overview of the history of radiation treatment for keloid disorder. The available techniques and suggested dosages, as well as the authors' experiences and vision on indications and biological working mechanisms, are described.

40.2 Introduction

Soon after the discovery of X-ray technology, radiation was recognized as a possible treatment modality for excessive tissue growth. Like malignant tumors, aberrant scars are proliferative tissue overgrowths and were therefore also considered valid targets for treatment with radiation. L. Freund first described the positive effect of roentgen treatment on a hypertrophic scar in 1898. Harris then described the same effect on a keloid disorder in 1901, whereas Wickham recommended radium for the treatment of keloid scars. Already in 1909, Freund combined surgical excision of the keloid with postoperative radiation, where he left the wound open and waited 2–3 days before starting radiation treatment [1]. In the following period, various treatment protocols were described using external radiation with relatively good results. Folke Jacobsson described in 1948 that in 625 cases treated, a total regression of 73.6% was achieved, most of which with radiation alone (*The Treatment of Keloids at Radiumhemmet*, 1921–1941).

External beam radiation therapy uses a radiation source which emits energy onto the target area. The disadvantage of this technique is that it gives a relatively high dose to the adjacent healthy tissue due to the large distance between the radiation source and the target.

Brachytherapy, where the radiation source is placed inside or adjacent to the area requiring treatment, was pioneered in medicine soon after the discovery of radioactivity in 1896 and was widely used in the 1930s to treat

various sorts of tumors. The benefit of brachytherapy over external radiation therapy is the ability to deliver radiation as very localized and enabling a higher dose with fewer side effects and fewer treatments needed for the same effect. Brachytherapy for the treatment of keloid scars is nowadays always combined with excision.

After an enthusiastic start, the usage of brachytherapy declined due to the problematic radiation exposure for staff and patients while handling the radioactive materials. The advent of novel radiation delivery methods and the use of new radioactive sources in the 1950s and 1960s caused a renewed interest in brachytherapy. Current remote afterloading devices provide safety by manually placing a hollow catheter (■ Fig. 40.1b) first and then loading the radioactive source later through the catheter. It was not until 1976 that Malaker et al. introduced this technique for keloid treatment. Current methods focus on excision of the lesion followed by adjuvant radiation therapy. Although this method offers total scar eradication with an optimal aesthetic and low recurrence rates (mean, 10.5%), its use is limited due to significantly higher costs in comparison with other treatment options, as well as availability of the technique in the hospital and the need for more advanced specialist care (e.g., plastic surgeon/dermatologist/radiation oncologist with interest in keloid scar treatment).

40.3 Types of Radiation Therapy

40.3.1 External Beam Radiation Therapy (EBRT)

The classic form of radiation therapy uses a radiation source which emits energy onto the target area. Regular X-ray radiation is probably the most widely available and least expensive radiation option. It does not penetrate too deep, so underlying structures remain undamaged. Due to the inaccuracy of the technique, however, more skin side effects are seen. In superficial radiation therapy (SRT), low-energy X-rays (the same range as diagnostic X-rays) emit photons at 20–150 kV reaching an effective depth of 3.5–16 mm. At higher energy of 200–500 kV, an effective depth of 2 cm is reached (orthovoltage radiation). Electron beam radiotherapy uses a linear accelerator to create β -rays. It reaches a depth of 2–6 cm and can be more accurately delivered.

40.3.2 Brachytherapy (Internal Radiation)

In brachytherapy, a hollow catheter is placed either interstitially during closure or superficially on the desired target area (see ■ Fig. 40.1a–c). After this procedure,

Fig. 40.1 a Keloid of the earlobe. After excision, a hollow catheter is placed before closing the wound b. The catheter is fixed into place to ensure precise radiotherapy delivery c

the catheter is loaded with a radioactive source. The treatment regimen can either be low-dose rate (LDR) or high-dose rate (HDR). In LDR a low-dose-rate radioactive source is used to treat for a longer time frame (20–72 hours). It requires hospitalization in a lightly shielded chamber. In HDR the patient is transferred to a shielded chamber after the excision. Here, a high-dose-rate radioactive source is loaded into the catheter remotely by personnel in a separate area for a short exposure (5–10 minutes). Because of the short treatment duration, HDR can effectively be used as an outpatient treatment option and is therefore preferred over LDR. The main advantage of brachytherapy to external beam radiotherapy is the diminished exposure of surrounding tissue, which also provides the possibility to administer a higher dose in a shorter time frame. Additionally, because the applicator can be shaped to fit the desired area, uneven surfaces will receive the same dose, and deeper structures can be avoided. The most commonly used radioactive source is Iridium-192 which emits γ -rays.

40.4 Excision and Radiation Type

Radiotherapy should be reserved for recurrent keloid scars because of its invasive characteristic and significant cost. It should be noted that both excision-only and radiation-only have higher recurrence rates compared to excision followed by radiation [2]. The keloid is preferably excised in an extrasional fashion [2] and closed primarily. If this is not an option due to the size of the scar or high tension on the wound edges, skin grafts can be used, or excision of the core of the keloid can be performed.

Close cooperation with the local radiotherapy department is necessary to facilitate radiation therapy for keloids. Radiation equipment usually represents a significant cost to any hospital, and keloid treatment with radiation therapy will most likely only be performed in a small fraction of treatments. This means physicians will probably be bound to techniques that are already available in their hospital. Usually, a form of

external radiation will be available, while brachytherapy may be more common in larger medical centers in developed countries.

When planning the procedure, two main considerations should be timing and adequate dosage of the radiation therapy. The first dose should be administered as soon as possible after excision. A clear decrease in recurrence rate was seen in external radiation if treated within 7 hours as opposed to the first 24 hours. HDR brachytherapy should be administered in the first 24 hours after surgery and is also likely more effective in the first 7 hours [3]. Many protocols, therefore, opt to transfer the patient to the radiation department immediately after excision [2]. Choosing the right dosage is important and there is no “gold standard” (yet). The concept of biological effective dose (BED) is important in the radiation regimen to be formed. BED is the measure used to quantitatively indicate the biological effect of any radiotherapy treatment. Because it corrects for the dose per fraction given and the fraction number, it will allow comparison of all kinds of treatments and modalities. In keloid treatment, it would appear that administering less than a BED of 10–12 Gy is correlated with a higher recurrence rate [2]. Literature suggests there seems to be a strict threshold because doses of less than 10 Gy repeatedly report higher recurrence rates. This would also mean that a single fraction could be enough, possibly preventing an overnight stay and/or additional hospital visits. At present, there are not enough studies yet in support of this, and a recent study even found a higher recurrence rate in a 13 Gy single-fraction protocol [4]. In a multicenter comparison of HDR brachytherapy, 2×6 Gy (BED of 19) treatment gave an equally low recurrence and lower complication rates than using 2×9 and 3×6 Gy [4]. Administering more than a BED of 20 Gy seems unnecessary in HDR brachytherapy [4]. In the treatment of earlobe keloids with EBRT, a BED of 15–22.5 over two fractions (2×10 Gy) was found to be sufficient [5]. In a recent systematic review, HDR brachytherapy achieved the lowest mean recurrence rate, followed by LDR

brachytherapy and external radiation therapy (HDR, $10.5 \pm 15\%$; range, 0–44; LDR, $21.3 \pm 2.1\%$; range, 19.4–23.6; external, $22.2 \pm 16\%$; range, 0–72) [2].

40.5 Recurrence

When reviewing the literature, it should be kept in mind that recurrence is often defined differently. It can be described as any regrowth of tissue, mild or total relapse, or even regrowth extending beyond the borders of the original lesion. Symptoms like pain or itching or any other complaint in the operated area not related to radiation may be counted as recurrence. With respect to radiation therapy, recurrence is usually correlated to the administered BED; the higher the BED, the lower the recurrence and vice versa. Since the opposite can be said of complications, a balanced approach should be made toward BED. Recurrence rate is also influenced by location; in a recent meta-analysis, Mankowski et al. found the chest and trunk to have higher recurrence rates (34%) as opposed to the ears (12%) [5]. Furthermore, to properly assess recurrence, a follow-up of at least 1 or 2 years posttreatment should be considered to avoid bias by missing recurrences.

40.5.1 Complications

Complications following radiotherapy of the skin are scored with the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) [6]; see ■ Table 40.1. Since radiotherapy influences wound healing, wound-related complications like wound dehiscence, infection, and the failure of the wound to close (chronic wound) are additional entities to consider. The most commonly seen complications are erythema, temporary and permanent pigmentation disturbances, and telangiectasia. Wound-related complications are rarely seen when administering doses as

■ **Table 40.1** Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) [6]

Grade	1	2	3	4
Acute	Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Late	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration

discussed earlier. Reported recurrence and complication rates vary. A recent retrospective study comparing 2×9 Gy, 3×6 Gy, and 2×6 Gy reported minor complications in 57%, 40%, and 33.7%, respectively, and 18.6%, 13.8%, and 3.3% major complications, respectively. Recurrence was the same for all groups (25%) [4]. Pigmentation complications are more commonly seen in people with a darker skin (Fitzpatrick V–VI) who seem to benefit from brachytherapy in which the irradiated area is greatly reduced [7]. It should be noted that pigmentation differences are less prevalent in brachytherapy in comparison with cryotherapy [8]. Furthermore, HDR brachytherapy yields good results in patient-reported outcomes such as the Patient and Observer Scar Assessment Scale [7].

40.6 Safety Concerns

When administering radiotherapy for benign diseases, concerns will arise about the risk of inducing secondary malignancy in the treated area. As of now, only a few cases have been described in external radiotherapy, and Ogawa et al. found the risk to be very low, with an estimated incidence of 0.1–0.0335% [3]. No cases of late malignancy have been described while using brachytherapy. Of course, the possibility should be mentioned when discussing therapeutic options with the patient [3].

40.7 Additional Thoughts on the Biomechanisms of Radiotherapy in Keloid Treatment

The working mechanism of radiation therapy to prevent the recurrence of the keloid scar is still the subject of research. Initially, the application was based on the principle that radiation inhibits tissue growth, and since both keloid disorder and hypertrophic scars are considered tissue overgrowth reactions, they were treated as such. Early irradiation, within 7 hours of surgery, has been shown to result in lower recurrence rates as opposed to a later moment [2]. This suggests that interfering in the early stages of wound healing is paramount in preventing recurrence of the disorder. Radiation is especially harmful to dividing cells; the fact that particularly the most proliferative cells are vulnerable explains its effectiveness in treating cell overgrowth.

Fibroblasts have been linked to keloid disorder for a long time, and ionizing radiation has been proven to influence keloid fibroblast proliferation [9]. Current theories consider keloids to be an immunological problem where endothelial cells and neovascularization may play a pivotal role as well [10]. During surgery or trauma, the

tissue is damaged, and blood vessels are severed. To provide the upcoming immune cells and fibroblasts with enough nutrients and oxygen, new blood vessels are formed along the wound edges, while the surroundings of the wound show redness as a sign of vasodilation. This process starts during the first hours following wounding [11]. Endothelial dysfunction has been linked to abnormal wound healing [10, 12, 13], so by suppressing endothelial cells and therefore angiogenesis due to radiation, the formation of dysfunctional blood vessels could be prevented and inflammation decreased, ultimately potentially suppressing keloid formation and preventing recurrence [1, 10].

In the classic definition, hypertrophic scarring is confined within the boundaries of the original lesion, whereas a keloid scar grows beyond its boundaries. However, in close visual inspection of hypertrophic scars, we see that they also can extend beyond the borders of the original lesion. The extension beyond the scar borders is less compared to keloid disorder, and the ongoing process of scar formation stops earlier. In the case of keloid disorder, the vascularity is the highest just around the keloid as may be observed clinically during excision (■ Fig. 40.2).

40.8 Conclusions

Radiotherapy is a last resort option for recurrent and therapy-resistant keloids and hypertrophic scars. It represents a significant burden, both financially and logistically as well as to the patient. On the other hand, it is a very efficacious treatment option (in preventing recurrence) while obtaining the most optimal esthetic result. It is a safe procedure and most patients experience no or minor side effects. The therapeutic goal should be to try and excise the entire keloid (extralesionally) and start radiation treatment as soon as possible, preferably within 7 hours. Between external radiation and LDR and HDR brachytherapy, the most preferable option is high-dose-rate (HDR) brachytherapy because of the

- Ability to customize the device per treatment area, therefore only radiating the target area while minimizing radiation damage to the healthy surrounding tissue
- Lower total BED compared to external radiation to achieve the same effect
- Ability to deliver the desired BED in a short period of time, allowing an outpatient setting

The optimal dose appears to be around a BED of 20–30 Gy; however, more research works are needed to determine treatment protocols. Physicians should adjust their therapies on the merit of experience and existing

Fig. 40.2 **a** Hypertrophic scar on the shoulder (age 18 months) with apparent vascular involvement. **b** Hypertrophic scar after cesarean section (age 5 years) extending beyond its borders. **c** Hypertrophic

scar after breast reduction surgery (age 2 years) extending beyond its borders

literature in collaboration with the local radiotherapy department and in accordance with the wishes of the patient.

Take Home Message

- Consider excision and radiotherapy as a last resort for therapy-resistant keloids.
- HDR brachytherapy started <7 hours after surgery and a BED of ± 20 is recommended.
- The chance of secondary malignancy seems very low.

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