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Original research article

Surface brachytherapy in the treatment of keloid scars in Mexico☆

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ABSTRACT

Objective: To demonstrate that superficial high-dose-rate (HDR) brachytherapy by means of Leipzig applicators or moulds with catheters is an adjuvant treatment with impact on local control and low toxicity.
Background: Keloid scars occur in 5–15 % of cases, secondary to an uncontrolled proliferation of fibroblasts and reduction in the inhibition of growth factors.
Material and methods: Retrospective, longitudinal and descriptive study in patients with keloid scars who were treated with superficial HDR brachytherapy in the General Hospital of Mexico between November 2009 and December 2013.
Results: Eighty patients were evaluated, and the mean follow-up was 22.18 months (range 8–48). The anatomic site treated was the ear in 72 patients (90.0 %), anterior thorax in 5 patients, retroauricular region in 2, and abdomen region in 1 patient. The application was performed 24 h after surgery; the dose for 79 patients (99 %) was 1500 cGy/3 fractions, and 1 received 500 cGy in 1 fraction. Adequate healing occurred in 76 patients (95 %), and the local failure was 5 % (95 % CI). Acute toxicity occurred in 15 % (12 patients) with grade 1 radioepithelitis. Chronic toxicity occurred in 22 patients (27.5 %) with grade 1 hypopigmentation and 18 patients (22.5 %) with grade 1 fibrosis. The cosmetic result was good in 72 patients (90 %). During follow-up, 2 patients presented recurrence, and 2 patients persisted.
Conclusions: Treatment with superficial brachytherapy in keloid scars using a mould with catheters or a Leipzig applicator is a therapeutic option that results in 95 % local control and low toxicity.

1. Background

The keloid scar was first described in Smith's Papyrus from 2500 to 3000 BC[1]; in 1817, Albert proposed the word κηλοιδεῖο to differentiate it from benign tumours.[2] Hypertrophic scars and keloids develop via an uncontrolled proliferation of fibroblasts after injury, trauma, infections or perforations in 5–10 % of cases.[1,3]

The treatment of keloids has been very diverse; surgical treatment followed by adjuvant radiotherapy appears to exhibit the best results.[4] With a recurrence rate of 10%–20% and a response rate of 67%–98%,[4,5] this treatment was first described by Sequeira in 1909.[7] The treatment inhibits the cascade of pro-inflammatory cytokines and the excessive production of fibroblasts, induces apoptosis of these cells and limits the toxicity to endothelial cells.[8] Under normal conditions, the fibroblasts have a doubling time of 43.5 h; however, in keloids, it is reduced to 29.5 h. Surgical treatment followed by adjuvant radiotherapy has the best results, with a response rate of 67–98 %. Brachytherapy is the preferred modality of adjuvant radiotherapy, it is not used as the first option of treatment of keloid scars, but it can be given as radical treatment in case of not being able to perform surgery. Therefore, it is important to start radiotherapy at least 24 h after surgery[9,10] with the objective of counteracting the accelerated repopulation induced by growth factors. External radiotherapy uses orthovoltage radiation[4,5,11,12] with Cobalt 602 and electrons,[4,5,13,14] while brachytherapy (Bq),

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which is simple and effective, uses the interstitial and superficial modality.[4,5] High-dose-rate (HDR) Bq is preferred over low dose rate (LDR) Bq because the treatment is ambulatory and is effective in a short time.[4] Interstitial Bq exhibits acceptable results using 12 Gy total (3 Gy per fraction) with the application of 1–2 catheters. The advantage of this technique is that there is less involvement of healthy tissue.[4,15] Several authors have recommended the use of Bq HDR instead of LDR or external radiotherapy[4,16–18]; superficial Bq uses moulds with catheters on irregular surfaces on the skin and produces good results.[19]

In relation to the fractionation scheme, there is no standard because the published series are small, and the hypofractionation schemes used are diverse as indicated below: 20 Gy/5 fractions (Fx), 15−16 Gy/3–4 Fx, dose only 18 Gy.[20–23] In patients in whom surgery is not an option, it can be managed only with radiotherapy at doses of 25–30 Gy (1–2 times a day).[23]

2. Objective

The objective of the present study is to demonstrate that superficial HDR Bq by means of Leipzig applicators and moulds with catheters is an effective adjuvant treatment for keloid scars and that it offers adequate control and a good cosmetic result.

3. Materials and methods

A retrospective, longitudinal and descriptive study was conducted on patients with keloid scars who were treated with HDR Bq in the Radiotherapy Unit of the General Hospital of Mexico, Dr. Ëduardo Liceagaïn the period from November 2009 to December 2013.

The data for the analysis of the present study were obtained from the clinical file and the medical physics file of the Radiotherapy Unit of the General Hospital of Mexico.

Included were patients with a clinical diagnosis of keloid scar who were assessed initially by the Department of Reconstructive Surgery.

The inclusion criteria were the following: patients of any age and sex with clinical diagnosis of keloid scar anywhere on the body, who were initially treated with surgery by the Reconstructive Surgery Service of the General Hospital of Mexico; initiation of Bq treatment 24 h after the surgical procedure and a minimum follow-up of 6 months.

Exclusion criteria: patients treated with surgery outside the General Hospital of Mexico, patients treated exclusively with HDR Bq, surgical event time > 24 h, and follow-up period of less than 6 months.

All of the patients were evaluated before the surgical procedure to identify the site of the scar and its size to define the type of superficial applicator that would be used after the surgical event.

The patients were assessed 24 h after the surgical procedure to start their treatment and were assigned to Bq with a Leipzig applicator or an acrylic mould with catheters, according to the size and location of the surgical wound. We used Nucletron HDR Bq equipment and Iridium 192 as the radiation source using orthogonal plates for dosimetry. The Leipzig applicator was applied in surgical wounds smaller than 2.5 cm in length and generally in the ear lobe; the diameters of these applicators were 1, 2 and 3 cm with a frontal opening (position of the vertical source) and a lateral opening (position of the horizontal source). In surgical wounds greater than 2.5 cm that were located in the helix region of the ear and in other body sites, acrylic moulds with catheters were used (see Fig. 1).

The diameter size of the Leipzig applicator was chosen, allowing for a 5 mm margin of the surgical wound. In the case of acrylic moulds, the determination of the number of catheters was based on the length and shape of the surgical wound with its respective margin of 5 mm.

For the treatment with Leipzig applicators, once the diameter was chosen, it was granted immediately because the dosimetry was previously performed. In the case of the moulds, a plaster negative of the site of the surgical wound was initially made to subsequently make an acrylic mould with the selected number of catheters to cover the treatment site with a margin of 5 mm; the catheters were placed in an equidistant manner (1 cm between each catheter). Subsequently, a simulation was performed with orthogonal plates to identify the position of the catheters in it. Finally, a 2D system planning was performed using optimization with 5 mm source steps to reach coverage with the isodose curve of 95%–100%.

The radiation dose used was 1500 cGy in 3 Fx, 500 cGy/Fx, with BED of 22.5 Gy, the initiation time for treatment with Bq was 24 h after the surgical event for 3 consecutive days.

Acute toxicity was assessed using the RTOG scale (Radiation Treatment Oncology Group) from the initiation of treatment until before 6 months, and chronic toxicity was assessed after 6 months of treatment using the scale of Common Terminology Criteria for Adverse Events (CTCAE v3.0). A specific cosmetic scale was not used to evaluate this result; however, it was considered a good cosmetic result if there was no chronic toxicity or if the changes were reversed in those who presented chronic toxicity.

The statistical analysis consisted of quantitative variables, and measures of central tendency and dispersion were generated for the qualitative variable percentages (descriptive statistics). Nonparametric tests, such as Chi 2, were used and local failure survival curves were included with the Kaplan-Meier technique, with a statistical significance of $p = \leq 0.05$ (95 % CI). The software SPSS V.22 (IBM, Chicago Illinois USA) was used.

4. Results

We analyzed 86 cases of patients with keloid scars; 6 were excluded because they did not comply with the inclusion criteria described. Of the 80 patients included in the study, 54 were women and 26 men; the mean age was 25 years (range 9–74 years). In relation to the etiology, ear piercing with earring was present in 71 patients (89 %); 4 patients (5 %) had undergone reconstructive surgery; and the remaining 5 patients (6 %) presented infection, tattoos, trauma and surgery related to another cause.

With respect to the treated anatomical site, the frequency was greater in the ear in a total of 72 patients (90.0 %), the anterior thorax in 5 patients, the retroauricular region in 2 patients and the abdomen in 1 patient. The most frequently treated subsite of the ear was the lobe (67 patients), followed by the helix region in 5 patients.

In relation to the number of previous surgeries as part of the keloid scar treatment, it was the first surgery for 68 patients (85 %), second surgery for 7 patients, the third surgery for 3 patients and fourth surgery for 2 patients.

The type of surgery that was performed by the Department of Reconstructive Surgery was local excision in 76 patients (95 %) and excision + graft reconstruction in 4 patients (5 %).

The 80 patients started adjuvant treatment with Bq 24 h after the surgical procedure; 50 patients (63 %) received Bq in a single site, 29 patients (36 %) were treated at 2 sites, and 1 patient was treated at 3 sites (see Table 1).

The prescribed dose of 15 Gy in 3 Fx was administered in 79 patients (99 %) and 5 Gy in 1 Fx in one patient.

The dose prescription was 0.5 cm deep in 61 patients (76 %) and at the surface in 19 patients (24 %); the surface prescription

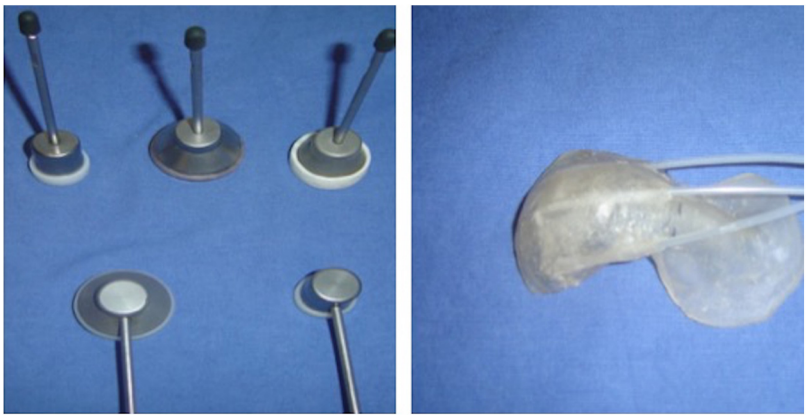

Fig. 1. Leipzig applicator and acrylic mould.

Table 1
Characteristics of the patients.

Characteristics	Patients n (%)
Age, years	
9	1(1)
10–20	28(35)
21-30	30(38)
31-40	13(16)
41-50	7(9)
74	1(1)
Gender	
Female	54 (67.5)
Male	26(32.5)
Etiology	
Earring placement	71(89)
Reconstructive surgical	6 (5)
Others	5 (6)
Previous surgical	
None	68(85)
1	7(9)
2	3(4)
3	2(2)
Localization of keloids	
Ear Lobe	67(84)
Ear Helix	5(6)
Retroauricular	2(3)
Anterior thorax	5(6)
Skin of abdomen	1(1)
Surgical realized	
Excision	76(95)
Excision + graft reconstruction	4(5)
Surgical complication	
None	76(95)
Seroma	2(2.5)
Hematoma	2(2.5)
Treated sites	
1	50(63)
2	29(36)
3	1(1)

Table 2
Statistic analysis of the risk factors.

Etiology		
	Patients	Percent
Piercing by earrings	71	88.8
Reconstructive Surgery	4	5
Tattoos	1	1.3
Infection	2	2.5
Trauma	1	1.3
Surgery for another pathology	1	1.3
Total	80	100

was indicated in patients with an ear-lobe thickness <5 mm and in surgical wounds of the helix.

One hundred eleven applications were made, of which 94 were with Leipzig applicators and 17 with acrylic moulds. Of the 94 applications with Leipzig applicators, 43 used applicators of 3 cm diameter, 49 used applicators of 2 cm diameter, and only 2 used applicators of 1 cm diameter; as for the opening of the applicator, 89 applications used horizontal Leipzig applicators and 5 used vertical ones. Of the acrylic moulds, 6 moulds had a single catheter, 4 moulds had 2 catheters, 6 moulds had 3 catheters, and 1 mould had 5 catheters.

The mean follow-up was 22.18 months (range 8–48 months). A month after the end of the Bq, 2 patients presented keloid scarring; therefore, it was considered that they did not respond (residual keloid). Of these patients, one received only 1 fraction of Bq (500 cGy) because she had not completed treatment and the other patient had already undergone 3 previous surgeries in the region of lobe.

The response to treatment was considered adequate in 76 patients (95 %), and the local failure was 5 % (95 % CI), as shown in the Kaplan-Meier curve (see Table 2, Fig. 2).

The cosmetic result was good in 72 patients (90 %), regular in 6 patients and bad in 2 (residual keloid) (see Fig. 3).

We observed that the number of previous surgeries and the total number of fractions, as factors of poor prognosis, were associated with persistence, with statistically significant results ($p < 0.0001$) being obtained for both. Factors associated with recurrence correlated with the type of surgery (excision + graft reconstruction) ($p < 0.003$), but not with the treated anatomical region ($p = 0.08$) or the number of previous surgeries ($p = 0.9$).

Regarding acute toxicity, 84 % (67 patients) exhibited no toxicity, 15 % (12 patients) presented grade 1 radioepithelitis, and 1 % presented Grade 2 radioepithelitis. The presence of acute toxicity was significantly associated with the type of applicator ($p < 0.03$), because the application of the Leipzig applicator was associated more with radioepithelitis, but without significant impact, when correlating with the type of surgery performed or the prescription of doses ($p = 0.9$ and $p = 0.08$, respectively).

Chronic toxicity was assessed 6 months after receiving treatment; 38 patients (47.5 %) did not present toxicity, hypopigmentation grade 1 was observed in 22 patients (27.5 %), and fibrosis grade 1 was expressed as a node at the central portion of the scar in 18 patients (22.5 %). Two patients exhibited the combination of both toxicities.

The factor that showed a statistically significant association with chronic toxicity was the dose 0.5 cm deep ($p = 0.01$), which did not correlate with the fraction size or surgery performed ($p = 0.7$ and 0.2, respectively). Successful complete reversal of the same was

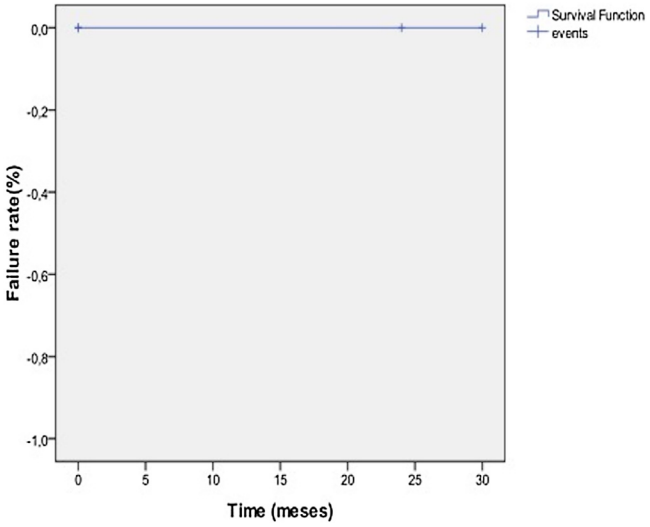

Fig. 2. Kaplan-Meier curve of local failure.

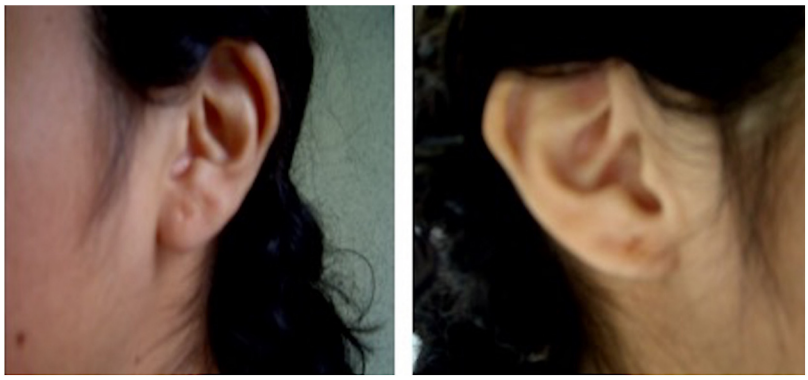

Fig. 3. Cosmetic result after 3 years in 2 different patients.

obtained at 24 months in 36 patients (45 %), and the remaining 6 patients did not show changes.

During follow-up, 2 patients exhibited recurrence: one patient at 24 months in the helix region and the other patient in the thorax region before 30 months (see Fig. 4).

Follow-up was completed in 65 patients (81 %). The remaining patients (14 %) were lost to follow-up after 2 years; therefore, they had to perform communication via telephone to verify that they were in control. Patients with persistence and recurrence were sent to reconstructive surgery to evaluate a new surgery or to evaluate another management alternative.

5. Discussion

The keloid scar is a benign entity that occurs with greater frequency in the region of the sternum, shoulders, hip, and neck; recently, increased incidence has been observed in the lobe of the ear due to the practice of perforation.[1] The uncontrolled proliferation of fibroblasts determines the appearance of keloid scars; in normal conditions, the healing is mediated by a process of apoptosis that removes the injured cells which are replaced by new tissue and the same scar. When this equilibrium is lost, alteration occurs in the cytokines that regulate this process and generates a reduction in the inhibition of growth factors (e.g., epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (DPGF), interferon, and tumour necrosis factor (TNF)), which leads to an incomplete scar, with fibrous tissue, collagen,

Fig. 4. Recurrence in the helix region (24 months).

fibronectin and increased proteoglycans, as well as microvasculature and sensory endings, causing scarring keloids.[1] In the same way, these scars have a high percentage of recurrence; a meta-analysis showed that the probability of recurrence is approximately

37 % with surgery alone.[4,22,26,27] Surgical treatment plus adjuvant radiotherapy offers the best results, with a control rate of up to 80 % in some series.[4,5] Bq is the preferred modality of adjuvant radiotherapy; it is not used as the first option in treatment of keloid scars.

Other treatments are plesiotherapy, injection of steroids, application of laser with carbon dioxide, cryotherapy, patches with silicone gel, retinoic acid, injection of triamcinolone acetonide, patches of silica and radiofrequency.[4–6]

In relation to radiotherapy treatment, Bq is a highly recommended modality, and the type of superficial Bq has gained popularity with a probability of recurrence of 15 % compared to 23 % for external radiotherapy.[5,15–19,22] In our review, referring to the published literature, the female sex is more affected due to the association with the etiology of ear piercing (88.8 %) and the use of earrings; with respect to age, a 9-year-old patient was included, who had undergone a reconstructive surgery in the lobe of the ear due to anatomical defect, and the treatment was granted because no risk of radio-induced neoplasia with HDR Bq was demonstrated.[6,15] Of our patients, 15 % underwent previous surgeries before the study, which shows that treatment with surgery alone for the keloid scar has a high percentage of recurrence (> 50 %).[4]

It has been determined that the keloid scar belongs to the group of acute response tissues with an α / β of 10 Gy, as reported in the study by Kal and Veen.[24] However, Flickinger et al. show that the control is found to be a function of radiobiological dose-response; it is known that postoperative radiotherapy for keloids has a low α / β (average of 2.8 Gy).[25] Therefore, high doses per fraction in a short time are effective for the treatment of these scars; it has been described that a dose per fraction of 5 Gy can induce radiolysis of fibroblasts.[1] The total doses that are proposed to result in adequate control are more than 12 Gy and, ideally, doses of 15–20 Gy are suggested; several studies indicate that the effective biological dose (BED) should reach 25 Gy (ideally 30 Gy), since the recurrence rate is 10 %.[1,15]

Factors associated with keloid control are the following: the size of the scar (lesions> 6 cm have poor control); a surgical margin $\leq$ 2 mm around the scar is insufficient (ideally, it should be 4–5 mm); the time to start treatment with radiotherapy should be <5 days post-surgery (ideal <2 days); when the BED is below 20–25 Gy, the cosmetic result is poor and the recurrence rate increases by 14 %; therefore, low doses have a greater risk of recurrence.[1]

Hafkamp et al. evaluated 13 Gy in 1 Fx and reported a recurrence rate close to 25 %.[23]

The treatment schemes recommended in multifractions are 15 Gy in 3 Fx or 20 Gy in 4 Fx; the latter is recommended in specific areas, such as the anterior chest wall, the scapular region, the lower jaw and the suprapubic region.[28]

In our study, all patients started Bq treatment 24 h later, as reported in most series[9,10] and the programmed dose was 1500 cGy in 3 Fx, as recommended in the international literature[5,15,20–23] that corresponds to a BED of 22.5 Gy. Although it is slightly below that suggested in the reviews to achieve an adequate response,[1–15] it was granted with results comparable to the results of other series; however, current studies have suggested that with a BED above 20 Gy, adequate local control is obtained.[5,26] The modality of superficial Bq with acrylic moulds and catheters has increased. However, in our study, only 17 were applied, and Leipzig applicators were used more frequently (94 applications); the latter are easy to place and are used when the keloid diameter is less than 2.5 cm. In total, 111 applications were made, because in 30 patients, more than 1 site was treated and in 50 patients, only one site was treated.

Our study demonstrated that when there are previous surgeries, the possibility of no control is increased, and the result is a residual keloid. A similar result is observed when the dose and the number of fractions are incomplete. Etiology, anatomical region, or the type of surgery performed were found to be insignificant for residual keloids ($p = 0.9$, 0.9 and 0.7, respectively); however, these factors may contribute to less control according to the literature.[1,6] Of the 2 recurrences in our study, the one in the anterior thorax underwent excision and reconstruction with graft, and the etiology of its keloid was reconstructive surgery; the recurrence in the helix region was not associated with previous surgeries, and only excision was performed. According to the analysis, the type of surgery prior to radiation, but not the anatomical site, was significant, as described in other studies.[1,6] These studies report that sites of greater tension of the skin have less control, the sites of greater tension are the thorax, scapula, auricular pavilion, suprapubic region, and those with the least tension are the lobe and neck[6]; therefore, the dose for sites of greater tension would have to be higher to result in control. Although there were other cases of thorax keloids in our study, the patient underwent surgery and reconstruction before radiation, which increased the possibility of recurrence in addition to the dose given.

In our study, 16 % of the patients presented grade 1 acute toxicity, which was lower than that reported in the literature.[6,8,15,16] Although the type of applicator was significant, it is related because the Leipzig applicator was the most used; this result is contradictory to reports from the literature, which state that that interstitial or superficial Bq with moulds are used more frequently.[16–19] Chronic toxicity occurred in 52.5 % of the cases, with hypopigmentation and fibrosis being predominant, and the prescription of doses at 0.5 cm depth was the significant factor for its occurrence; after 2 years, this toxicity was reversed in 45 % of the patients, and only 6 patients exhibited no changes. Compared with reports from the literature, the chronic toxicity of the present study is lower.[6,8,16] Although in the study, the dose per fraction was not significant, it is important to remember that total doses> 20 Gy are associated with greater chronic toxicity. Unlike acute toxicity, for chronic toxicity, the type of applicator used did not have any significance.

The control achieved with our treatment scheme (15 Gy/3Fx) was adequate; 95 % of the patients exhibited control, and the local failure was 5 %, which is lower than the results from other reviews that report up to 12 % of recurrence.[4,5] Although the follow-up is relatively short, the result is good, and this is due to the time of treatment initiation, which was 24 h after the surgical event. It is important to increase the dose in regions with greater risk of poor control (higher stress sites).

6. Conclusions

Superficial Bq in keloid scars is simple and effective by means of Leipzig applicators and moulds with catheters according to the characteristics of the patient is an option that offers adequate results with respect to both control and cosmetic outcome.

Financial disclosure

None declared.

Conflict of interest

None declared.

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