Original Article

Comparative study between the radiotherapy treatment with electrons and beta-therapy after keloid surgery

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(We declare no conflict of interest).

ABSTRACT

Introduction: The surgery of keloids as an individual therapy has high rates of recurrence and needs adjuvant therapies as a complement. Recent keloids are rich in fibroblasts, which are highly radiosensitive, wich explains the good results of percutaneous radiotherapy after surgery. **Objective:** To compare the beta-therapy results with the electron-beam technique in newly operated keloids. **Patients and methods:** A prospective, comparative, randomized study was outlined including patients in the immediate postoperative period of surgical excision of keloids. Divided into groups G1 and G2 respectively, they received treatment with Sr90 plates or electrons from the linear accelerator. The patients were followed for 10 years. The results were performed using information from patients, photograph parameters, observation and measurement of injuries, according to the criteria: Unchanged, Regular, Good and Excellent. **Results:** There were 26 patients, 13 in each group. In G1, 54% presented regular and unchanged improvement criteria, and 46% had good or excellent criteria. In G2, the results were respectively 23% and 77%. **Conclusion:** Irradiation with electron-beam has better results than beta-therapy for the treatment of surgically removed keloids, due to better distribution in the tissue. No radio-induced tumors were observed.
Keywords: keloid, electrons, strontium.

INTRODUCTION

Keloids are benign lesions consisting of marked hyperplasia of the specialized tissue of the dermis, that can originate after trauma or other skin lesions. The balance between formation and degradation in the collagen production is essential for the normal healing process, and keloid is the result of excessive deposition of collagen in the extracellular matrix during healing.[1,2,3]

Keloids are morphologically characterized by cell hyperplasia, due to the presence of polyclonal fibroblasts, which are intrinsically normal and respond to abnormal extracellular signal.[4,5] It can be induced by surgery, lacerations, tattoos, burns, injections, bites and vaccinations, as well as dermatosis (Hidradenitis Suppurativa, acne) or a reaction to a foreign body. In literature, the vaccine reported as the one that produces most keloids is BCG (bacillus of Calvet Guerin).[6,7] The pathology incidence varies from 0.09% in England to 16% in Congo.[8]

The keloid pathogenesis remains unknown; however family tendency and high frequency in individuals with dark skin demonstrate a genetic component.[9,10]

For patients, keloids are not only an aesthetic problem. Symptoms like itching, pain, burning sensation and intolerance to contact with some cloth are often more important than the aesthetics issue, collaborating with life quality worsening.[11,12]

The surgery alone has a recurrence rate of 50-80%, which led to the use of a wide variety of adjuvant therapies to reduce it.[13] Through meta-analysis and review of the literature in 2006, Leventhal et al.[14], by analyzing 70 sets of treatment of keloids, concluded that the highest percentage of improvement was around 60%, and the result of most of the treatments described does not approach this value.

The most frequently adjuvant therapies used are cryotherapy, laser therapy, compression and intralesional injection of steroid, with varying results.[15-17] New treatments have been introduced more recently, including intralesional injection of 5-fluorouracil, topical mitomycin C, interferon alpha, imiquimod 5% topical and intralesional bleomycin.[18] In 2005, Sanders et al.[19] published that the use of topical mitomycin C is not involved in preventing the recurrence of surgically removed keloids. At the same year, Davison et al.[20] stated that the use of interferon alpha-2b is not effective in the clinical management of such lesions. Even with the use of intralesional glucocorticoid injections for treating multiple keloids, there are reports of Cushing's syndrome and skin atrophy.[21,22]

The modality of treatment that reached the lowest rate of relapse was the post-operative percutaneous radiotherapy,[23] with rates of 2-36%. An important concept is that once the keloid is formed it is not radiosensitive, since the fibrous tissue under these circumstances suffers little or no change with irradiation. However, the scars of recent fibroblasts are highly radiosensitive. Since recent keloids are rich in fibroblasts,[24] Trott[25] has proposed that the mode of action of the connective tissue irradiation with cellular hyperplasia, at the expense of fibroblasts, is based on the inhibition of proliferation and on the stimulation of these cells differentiation.

In reviewing the literature, we found that until the 70's low-energy photon beams of conventional X-rays were employed in schemes with single or multiple doses. In our environment, Sr90 plates have been used up to date (Strontium 90 – radioisotope) in approximate doses of 30 Gy (gray = unit of absorbed dose), known as beta-therapy,[26,27] with disappointing results in the long term. Based on this fact, some authors began to use low-energy electron beams, with encouraging results and less complication rate. In 1990, Lo et al.[28] reported the use of electron beam in a single dose with good results. In the 70's, Malakar et al.[29] and Guix et al.[30] published their work using Iridium following keloid surgery, while De Lorenzi et al.[31] used the brachytherapy with excellent results (79, 1%). In 2003, Ogawa et al.[32] conducted a retrospective study of 147 cases followed for more than 18 months, treated with postoperative irradiation with electron beam, with doses of 15 Gy. Their results showed success in 73 and 92%, and this variation was a consequence of the different locations of the lesions; the rate of recurrence is higher when they are located in the chest wall, followed by the scapular region.

The electron beams used in radiotherapy treatments are produced by linear accelerators. They are monoenergetic in the wave guide output, with a diameter of approximately 3 to 4 mm, and then they are deflected by magnetic fields and directed to the spreader filter, where there is homogenization of the dose. Then, they pass through ionization chambers for dose monitoring.

When the electron beam interacts with the tissues from the skin, there is a continuous loss of energy through the linear energy transfer (LET), whose value during the range of 4 to 20 MeV (million electron volt = unit of energy for electron beams) is 2 MeV per cm. A beam of 10 MeV reaches approximately 5 cm in water. Therefore, the electrons are used for treating superficial or semi-deep lesions without irradiating tissues beyond the target. By comparing the depth of dose distribution between the Sr90 plate and the 5-MeV electron beam, we can see that electrons show a better distribution (Graph 1). The observation over years of personal experience with electrons showed that such treatment could be effective as adjunctive therapy in the therapeutic approach of keloids.

The proposal of this study was to compare the response of keloids after surgery to radiotherapy treatment using linear accelerator electrons or Sr90 plates, assessing the risk of developing radiation malignancies,[33] side effects and long-term results.

PATIENTS AND METHODS

This was a prospective, comparative, randomized study including patients of both genders in the immediate postoperative period (24 to 72 hours) that were subjected to the following excisional surgical technique for keloid treatment:

a) bright green marking of the lesion limits with a safety margin of 1 mm;
b) incision and excision of the keloid until the subcutaneous tissue;
c) hemostasis with monopolar electrocoagulatory (Wavetronic® device);
d) edge-to-edge primary suture in monoblock using a nylon thread;
e) dressing with a grid of Micropore adhesive plaster.

The patients were randomly divided into two groups: group 1 (G1) was treated with plates of Sr90, with daily sessions (a total of 8 sessions, 300 cGy per session) 5 days a week, while group 2 (G2) was treated with electrons from the linear accelerator and energy of 6 MeV, with the same protocol used in G1.

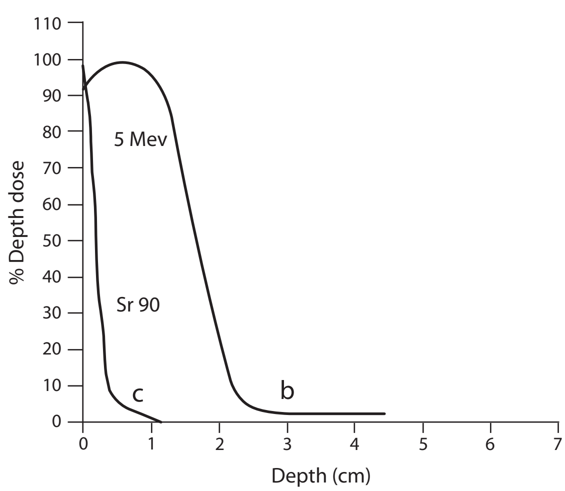
The patients were recruited after surgery during a period of 3 years (1994 to 1997) and were evaluated after 30 days, 6 and 18 months, and annually for up to 10 years. The exclusion criteria were: referral to post-surgical period for more than 03 days, prior laser or cryotherapy treatment, presence of compressive dressing with a volume that could produce significant absorption of the beam radiation, partial surgical removal with graft, absence of sutures for wound healing by second intention, and tension suture on the edges which can lead to dehiscence.

All patients were informed about the participation in a comparative study through an informed consent form, and the research project was approved by the Medical Ethics Committee of the Hospital das Clínicas, Faculdade de Medicina de Botucatu, June 30, 1994 (Of. N. 022/94-CEM).

The evaluation of results was performed using the patients' information related to aesthetic and symptomatic aspects for 18 months. Photographic parameters, observation and measurement of lesions were also used, considering the following criteria:

Unchanged: > 75% recurrence/**Regular**: 50 to 75% recurrence without symptoms/**Good**: ≤ 50% recurrence without symptoms/**Excellent**: no recurrence and no symptoms.

The first patients included were followed for 13 years and the last ones for 10 years.



Graph 1 – Comparison of depth dose percentage related to the depth function in cm, between a beam of 5 MeV and Sr90.

RESULTS

The study included 26 patients, 8 men and 18 women, aged between 9 and 79 years, divided into groups G1 and G2, with 13 patients each. Results are shown in Chart 1 and 2. In G1 54% presented unchanged and irregular improvement criteria and 46% had good or excellent criteria. In G2, results were 23% and 77%, respectively (23% good and 54% excellent).

STATISTICAL ANALYSIS

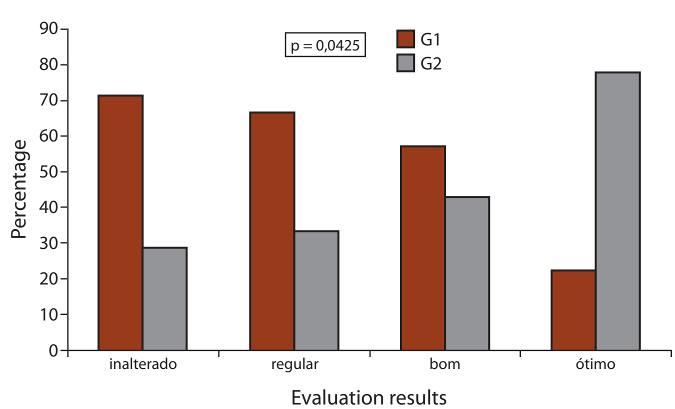
The number of observations in most evaluation results (unchanged, regular, good, excellent) per group was small (< 5), preventing the use of chi-square distribution. Fisher's exact test was used in order to determine the association between the group and the evaluation results. Fisher's test for group *versus* evaluation result resulted in a critical value (p) of 0.0425, i.e., a significant association between the groups (G1 and G2) and the evaluation results. This association can be easily seen in Graphic 2. Note that in G1 unchanged and regular results prevail, and in group G2 good and excellent results prevail (Graphic 2). The following iconographic sequence indicates the results: Pictures 1 to 6.

DISCUSSION

There are several types of treatment for keloids, however none is effective alone. The most commonly used are: surgery, cryotherapy, intralesional steroid injection, laser, compressive treatment and radiation, but all with little effectiveness.

Surgery was the one most used alone, but with high recurrence rates: 50-80%.[13] The keloid, once formed, is not radiosensitizing, and the radiotherapy, as a single modality of treatment, is not used. However, radiotherapy has shown low recurrence rates (12-28%) as an adjuvant therapy to surgery when compared with results of other techniques. In a meta-analysis and literature review analyzing 70 sets of treatment

Figure 1 – A) Pre-treatment (G2 Group - electrons).
B) Post-treatment (G2 Group - electrons).



Graph 2 – Pattern of results between groups G1 and G2.

Chart 1 – Results of treatment with Sr90 plates in G1

G1	Results			
	Unchanged	Regular	Good	Excellent
1	x			
2	x			
3	x			
4			x	
5			x	
6		x		
7			x	
8			x	
9	x			
10				x
11				x
12	x			
13		x		

Chart 2 – Results of the treatments with electrons in G2

G2	Results			
	Unchanged	Regular	Good	Excellent
1				x
2	x			
3				x
4				x
5		x		
6				x
7				x
8			x	
9				x
10			x	
11				x
12	x			
13			x	

for keloids, Leventhal et al.[14] concluded that the higher improvement rate was 60%. In our study, good and excellent results totaled 77% when using electron beam in the immediate postoperative period of surgically removed keloids.

In this series of cases, we observed one withdrawal at the start of radiotherapy, due to dehiscence resulting from tension in the suture line. Patient G1 – 2 and G2 – 3, which appear in both groups, was treated initially with beta-therapy, and later with electrons, with good results. One patient was excluded from the series after 3 applications because she had developed infection in the scar by the 4th postoperative day. The only side effect observed in all cases was hyperpigmentation of the irradiated area, which varies from patient to patient, disappearing after 3 months. It should be noted that this adverse effect is minimal when compared to pain during freezing and to permanent hypopigmentation from cryosurgery, as well as atrophy, hypopigmentation and an inhibition of the healing process from intralesional steroid injection. When combining surgery and radiation in many therapeutic modalities, except for electron beam, the distribution dose in depth is not uniform, which probably justifies the poor results for this combination.

When using electron beams of linear accelerators in radiotherapy treatment, it is possible to optimize the dose distribution of the tissue, choosing the most appropriate energy for each thickness to be irradiated. No cases of tumor radiation were revealed following 10 years of this series. These data are in agreement with the literature. The most likely explanation is the low dose used, much lower than those employed in the publications of Spagnolo et al.,[33] where photons were used with much more irradiated bodies and bigger radiation scattered in depth. The authors believe that

Figure 2 – A) Pre-treatment (G2 Group - electrons).
B) Post-treatment (G2 Group - electrons).

Figure 3 – A) Pre-treatment (G2 Group - electrons).
B) Post-treatment (G2 Group - electrons).

the good and excellent results are a true consequence of the proposed method, since it remained unchanged for 10 years, and they recommend it as keloid proposal therapy.

CONCLUSIONS

The combination of surgery and radiotherapy with electrons, adjuvant in the immediate postoperative period is the best tolerated modality of treatment with minimal side effects and lower rates of relapse in the scheme of 300 cGy/ day in 8 sessions. No malignancy cases were observed. The radiotherapy with electrons is more effective than the beta-therapy for the treatment of keloids, due to a better dose distribution in the tissue. S&CD

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