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ROLE OF POSTOPERATIVE RADIATION THERAPY IN KELOID TREATMENT TO REDUCE RECURRENCE RATE AFTER SURGERY.

Radiotherapy

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ABSTRACT

Introduction Keloids are dense fibrous tissue arising from an abnormal healing response to an injury that grows beyond the original scar (1-3). This study aimed to evaluate the role of postoperative electron beam radiotherapy in reducing the recurrence rates after surgery, and to analyse the appropriate time of administration of radiation therapy and the most common site of recurrences. **Material And Methods** We retrospectively analysed 34 patients of keloid treated in our institute from January 2011 to January 2019 for the recurrence rates, the appropriate time of administration of radiation therapy and the most common site of recurrences. **Results** Median follow up for all patients was 5years, four patients (11.7%) had recurred within 1 year and the overall local control rate was 88.3%.. All recurrent cases were started treated after 72 hours of surgery. 3 of 4 recurred lesions appeared in high stretch-tension regions (the shoulder, chest wall) and the remaining 1 lesion appeared in low stretch-tension regions (the ear lobe). The acute reactions were observed in 35.29 % (n=12) of the cases, and chronic reactions were observed in 17.64% (n=6) of the cases in our study. **Conclusion** We concluded that postoperative electron beam radiotherapy can be regarded as an effective treatment method for the prevention of keloid recurrence without serious adverse events. However, radiation therapy should be initiated within 72 h after surgical excision to prevent recurrence. Recurred lesions were more common in high stretch-tension regions than in low stretch-tensions.

KEYWORDS

Keloids, Adjuvant Radiation, High tension areas, Recurrence rates

INTRODUCTION

Keloids are defined as dense fibrous tissue arising from an abnormal healing response to a cutaneous injury that grows beyond the original wound scar (1-3). It comprises of atypical fibroblast with excessive deposition of extracellular matrix components (1). Keloids can occur on any part of the body, more commonly occur on the ear lobes, shoulders, chest, and back (2-3). Common causative factors of keloids are piercings, trauma, surgical scars, acne scars, and chickenpox scars (1-3). The incidence of keloids is more common in female compared to male, due to higher frequency of ear lobe piercings in women (2-4). Keloids can occur all skin types but more common in dark skin people. 10% of patients may have a family history (5, 6). Different methods for the treatment of keloids includes intra-lesional steroids, interferon and fluorouracil injections, laser therapy, cryotherapy, silicone gel sheets applications, surgical excision, external radiation therapy, and brachytherapy (1, 4). After surgical excision of keloids, recurrence reported in 50%~80% of patients (1, 7). Adjuvant treatment such as radiation therapy improves therapeutic outcomes after surgery(1, 7, 8). Radiation techniques such as electron beam radiotherapy, and iridium−192 brachytherapy with implants or strontium−90 can be used (7, 8).

This study aimed to evaluate the role of postoperative electron beam radiotherapy in reducing the recurrence rates after surgery, and to analyse the appropriate time of administration of radiation therapy and the most common site of recurrences.

MATERIALS AND METHODS

We retrospectively analysed 34 patients of keloid treated in our institute from January 2011 to January 2019. All patients had undergone surgery and post-operative radiation therapy. None of the patients received intra-lesional steroids. The patients were analysed for the recurrence rates, the appropriate time of administration of radiation therapy and the most common site of recurrences. Patient who could not come to the hospital were telephonically interviewed.

Surgery

All lesions were surgically excised, and the clinical diagnosis of keloids was confirmed histo-pathologically. 28 patients underwent complete excision with grafting and 6 patients underwent intra-lesional excision.

Radiation treatment

Radiation treatment was given using 6-MeV electron beam for 22 patients, 8 patients were treated with 4MeV electrons and 4 patients with 9MeV electrons. To ensure an adequate coverage, a 0.5 or 1-cm thick bolus was applied to the surface of the skin as a tissue compensator. The surrounding normal tissue was shielded with lead (equivalent to 6 mm of lead). Among 34 patients, 26 were treated with 16Gy in 4 fractions (BED-22.4Gy), 4 patients with 20Gy in 5 fraction (BED-28Gy) and 4 patients were treated with 12Gy in 4 fraction (BED-15.6Gy) on daily basis **(as shown in Table 1)**. 24 patients were treated with AP field and 10 patients were treated with oblique fields. Radiation was given within 6 hours of surgery for 2 patients, within 24 hours for 22 patients, within 36 hours for 4 patients, within 48 hours for 2 patients, 2 patients were treated after 72hours and 2 patients were treated after 4days **(as shown in Table 2)**. Because more than 50% of keloid recurrences occur within 6 months of treatment (3, 5, 7), a follow-up period of at least 6 months was necessary and we observed the treated lesions every 3 months after radiotherapy.

Table 1. Radiation dose in 34 keloids patients who received postoperative radiation therapy

Radiation dose	Number of patients (n=34)
16 Gy in 4fr	26 (76.47%)
20Gy in 5fr	4 (11.76%)
12Gy in 4fr	4 (11.76%)

Table 2. Time interval between surgery and initiation of radiation therapy

Within 6 hours	2 (5.88%)
Within 24 hours	22 (64.7%)
Within 36 hours	4 (11.76%)
Within 48 hours	2 (5.88%)
More than 72 hours	2 (5.88%)
More than 4 days	2 (5.88%)

Statistical Analysis

Kaplan Meier curve was generated for time to event analysis for local recurrences using SPSS version 22, where event was defined as first appearance of any recurrence.

RESULTS

Patient characteristics

From January 2011 to January 2019, 34 patients of keloids were treated with postoperative electron beam radiotherapy, out of which 18 were females and 16 were males. 21 patients were below 30 years and 13 patients were above 30 years of age **(as shown in Table 3)**. Among 34 patients 10 cases are recurrent cases and 14 cases are new cases before starting of postoperative electron therapy. 26 patients had single lesion and 8 patients had multiple lesion. The location and causative factors of the lesions for all patients is **as described in Table 4 and 5.**

Table 3. Characteristics of 34 keloid patients who received

postoperative radiation therapy

Characteristic	Number of Patients (n=34)	Percentage
Age (y)		
Range –	14-71years	
Mean	31.38	
Sex		
Male	16 (47.05%)	
Female	18 (52.94%)	
No lesions		
Single	26 (76.47%)	
Multiple	8 (23.52%)	

Table 4. Site of lesions

Site of lesion	No of patients
Chest wall	15 (44.11%)
Abdominal wall	1 (2.94%)
Ear	3 (8.82%)
Shoulder	3 (8.82%)
Scalp	2 (5.88%)
Forearm	1 (2.94%)
Neck	1 (2.94%)
Left shin and foot	1 (2.94%)
Left shoulder and chest wall	1 (2.94%)
Both breast	1 (2.94%)
Left chest wall and flank	1 (2.94%)
Both ear	3 (8.82%)
Abdomen and scapula	1 (2.94%)

Table 5. Causative factors

Causative factors	No. of patients
Piercing	9 (26.47%)
Trauma	7 (20.58%)
Family History	2 (5.88%)
Previous surgical scar	3 (8.82%)
Burns	6 (17.64%)
Unknown	6 (17.64%)
Since childhood	1 (2.94%)

Recurrences

Median follow up for all patients was 5years, four patients (11.7%) had recurred within 1 year and no recurrences were documented in remaining cases. The mean interval of recurrence after surgery was 6.5 months. Out of all the recurrences, 3 were male and 1 was female. The radiation doses administrated in 4 recurred cases 12Gy in 1, 16Gy in 4 fractions in 3 patients. All recurrent cases were started treated after 72 hours of surgery. 3 of 4 recurred lesions appeared in high stretch-tension regions (the shoulder, chest wall) and the remaining 1 lesion appeared in low stretch-tension regions (the ear lobe).

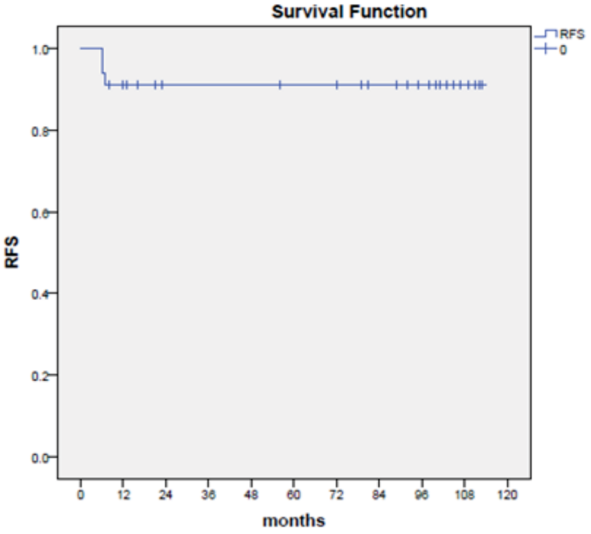

Figure 1. Kaplan Meier curve for Local Recurrence Rate

Radiation Toxicities

During treatment, acute reactions observed were mild skin erythema (grade 1 dermatitis), pain and itching and these symptoms disappeared within a few weeks of treatment. Surgical wound dehiscence did not occur in any patients. During the follow-up period, chronic reactions observed are hyperpigmentation and fibrosis of skin. The acute reactions were observed in 35.29 % (n=12) of the cases, and chronic reactions were observed in 17.64% (n=6) of the cases in our study. Secondary carcinogenesis did not occur during the follow-up period.

DISCUSSION

Keloid is a benign, but a locally aggressive lesion which often grows into big lesions which affects the appearance and quality of life of a person. Because of the lack of clarity on the cause of keloids, the treatment of keloid still remains to be a dilemma. There are multiple modalities of treatment which are tried but there are no organized trials to ascertain the efficacy of these modalities. Surgical excision alone has been found to have a recurrence rate of 65 to 99% (9). A number of adjuvant treatment have been tried in cases of keloid like cryotherapy, pressure treatment and silicone gel sheeting which had a recurrence rate of more than 50% (10). Intra- lesional are currently considered the first line of treatment, but it has a high frequency of side- effects upto 63% (11) and the recurrence rate is very variable ranging from 9-50% (12).

Surgery followed by radiation therapy proved to be most effective with a recurrence rate of 20% (13). Postoperative radiotherapy causes decrease fibroblast proliferation and causing a rapid degranulation of mast cells which are the main secretors of histamine (1, 14, 15). Radiation inhibits histamine release from mast cells, which in turn inhibits the proliferation of fibroblasts. Thus, the mechanism by which radiation inhibits keloids or hypertrophic scars is the suppression of fibroblast proliferation and inhibition of collagen synthesis(14, 16).

However, radiation therapy protocols in keloid cases has not been studied in a uniform manner. There are multiple doses and techniques used, and there is no standard protocol available. Studies have used doses varying from 15-20Gy (11), although few recent reports have shown better outcomes with doses as high as 25-30Gy (21). The timing of treatment post radiation also varies from center to center. Thus, in our study, we have aimed to evaluate the outcomes of the patients treated in our institution with electron therapy and evaluate the recurrence rates. Also we analyzed the effect of the time of start of treatment and the site of the lesion on the outcome.

In our study, we have treated all our patients with electron therapy since they all were superficial lesions and we could achieve proper coverage with electrons. It also had a benefit of rapid dose fall-off which saved the underlying structure from exposure to radiation. The recurrence rate in our study was 11.7% (n=4) and the overall local control rate was 88.3%. Our outcomes were comparable with those of the published literature. Recurrence rates between 15% and 32.7% have been reported in the literature (7, 22). Kovalic and Perez (23) monitored 75 patients with 113 treated scars and found an overall local control rate of 73%. Borok et al (24) reported excellent cosmetic results without recurrence in 92% of cases.

Considering that the proliferation phase occurs 2 or 3 days (48~72 h) after an injury, radiation therapy should be initiated within 72 h after keloid surgery to minimize the recurrences. It has been seen that in the patients where radiation was given 72 hours after surgery, the recurrence rates were high. In our study all 4 recurred lesions were given radiation after 72 hours. Rest of our patients (88.2%) received radiation within 72 hours. The reason for delay in radiation in our hospital are mostly related to logistic issues, unawareness of the treating surgeon to refer the case for radiation and reluctance to take radiation on part of the patients. In Sun Young Lee et al (21) study which included 37 lesions, 7 cases recurred in their study and 6 of the 7 (85.7%) recurred cases were treated after 72hours of surgery.

The mean time interval of recurrence for our study was 6.5 months. Most of the keloid lesions have been shown to recur within one year of treatment. In study done by Klumpar et al, the average time of therapy to recurrence was 7 months (18). However in study done by Sruthi et al, the median time to recur was 13.6 months (19). In the study done by Pontoriero et al, keloids relapse was observed within one year in 8 patients (12.9%) and after the first year and within 24 months in 2 patients (3.2%) (20).

Regarding the location of the keloid impacting the recurrences, in our study, 75% lesions recurred in high stretch-tension regions (the shoulder, chest wall). The reason of higher recurrences here is the excessive proliferation of collagen fibers in keloid scars with high stretch-tension. Repeated hyperextension stimulation leads to

collagen overgrowth at treated keloid sites (14, 15). Sun Young Lee et al (21) reported 5 of the 7 recurrences at sites of high stretch-tension. Contrary to our findings, the study done by Klumpar et al which analyzed 83 patients with 126 lesions, did not show any effect of location of lesion on recurrence on multivariate analysis (18).

The acute side effect of radiation dermatitis was observed in 34.29% (n-12patients) of the cases, and chronic side effects were observed in 17.64% (n-6patients) of the cases in our study. Sun Young Lee et al (21) study reported acute side effect of radiation dermatitis was observed in 21.6% of the cases, and chronic side effects were observed in 8.2% of the cases. Klumpar et al reported side effects of radiation in 42% of their cases in form of hyperpigmentation, pruritus, erythema, paresthesia and pain (18).

We understand the shortcomings of our study. It is a retrospective study with limited number of cases. The dose fractionation in our study is variable. The timing of start of radiation after surgery is also different. The sample size or follow-up of our study was not enough to see rare side-effects like secondary malignancies, which is an area of concern for patients before considering radiation as a treatment. Further prospective studies with large sample size and longer follow-up are required for establishing the standard of care in keloid treatment.

CONCLUSION

We concluded that postoperative electron beam radiotherapy can be regarded as an effective treatment method for the prevention of keloid recurrence without serious adverse events. However, radiation therapy should be initiated within 72 h after surgical excision to prevent recurrence. Recurred lesions were more common in high stretch-tension regions than in low stretch-tensions.

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