Aesthetic Surgery Journal Advance Access published August 23, 2016

Cosmetic Medicine

Surgical Excision and Adjuvant Brachytherapy vs External Beam Radiation for the Effective Treatment of Keloids: 10-Year Institutional Retrospective Analysis

Aesthetic Surgery Journal
2016, 1–14

DOI: 10.1093/asj/sjw124
www.aestheticsurgeryjournal.com
OXFORD UNIVERSITY PRESS

Don Hoang, MD; Robert Reznik, MD; Matt Orgel, BA; Quanlin Li, MS; Amin Mirhadi, MD; and David A. Kulber, MD

Abstract

Background: Surgically excised keloids reportedly recur at a rate of >45%. Post-excision radiation (RT) has been delivered via external beam radiotherapy (EBRT) or interstitial high dose rate (HDR) brachytherapy. Despite historical data showing 10% to 20% keloid recurrences with post-excision RT, there is a paucity of high-quality evidence comparing keloid recurrences between the two RT modalities.

Objectives: We performed the largest single-institution case-control retrospective study (2004-2014) of keloid recurrence rates and complications between post-excision EBRT and HDR brachytherapy.

Methods: One-hundred and twenty-eight patients, with 264 keloid lesions, were treated by excision alone (n = 28), post-excision EBRT (n = 197), or post-excision HDR brachytherapy (n = 39). Patient and keloid recurrence data were analyzed using mixed effect Cox regression modeling with a statistical threshold of $P < .05$.

Results: Fifty-four percent of keloids recurred after surgical excision alone (9-month median follow up); 19% of keloids recurred with post-excision EBRT (42-month median follow up); 23% of keloids recurred with post-excision brachytherapy (12-month median follow up). Adjuvant EBRT and brachytherapy each showed significant control of keloid recurrence compared to excision alone ($P < .01$). EBRT significantly delayed the time of keloid recurrence over brachytherapy by a mean difference of 2.5 years ($P < .01$).

Conclusions: Post-excision RT shows significant reduction in keloid recurrence compared to excision alone. While the recurrence control rates are not statistically different between EBRT and brachytherapy, keloids treated with EBRT recurred significantly later than those treated by HDR brachytherapy by a mean of 2.5 years. Further workup with a randomized control study will help to refine optimal adjuvant RT treatment.

Level of Evidence: 3

Accepted for publication June 17, 2016.

Keloid scars are benign fibrous dermal growths that extend beyond the borders of their original wound, often developing from even the most minor skin injury (Figure 1). The amount of scar tissue in a keloid scar rarely exhibits any relation to the extent of injury that caused it.[1,2] Keloids are often symptomatic causing major discomfort, pruritus, alloknesis, aching, allodynia, pain, psychological distress, and/or cosmetic disfigurement.[2-5] Keloids develop in 5% to 15% of wounds and occur more commonly in patients with darker pigmented skin (approximately 15:1).[1,6,7] Hypertrophic scars tend to develop more commonly in fair skin than dark skin and should be differentiated from keloids.[2]

Although there are many proposed risk factors for keloid development and/or recurrence, some of the more commonly reported risk factors include dark skin pigmentation, African or Asian ethnic background, family history, genetic

From the Keck School of Medicine, University of Southern California, and Cedars-Sinai Medical Center, Los Angeles, CA.

Corresponding Author:
Dr David A. Kulber, 8635 W. Third St., Suite 990W, Los Angeles, CA 90048, USA.
E-mail: david.kulber@cshs.org

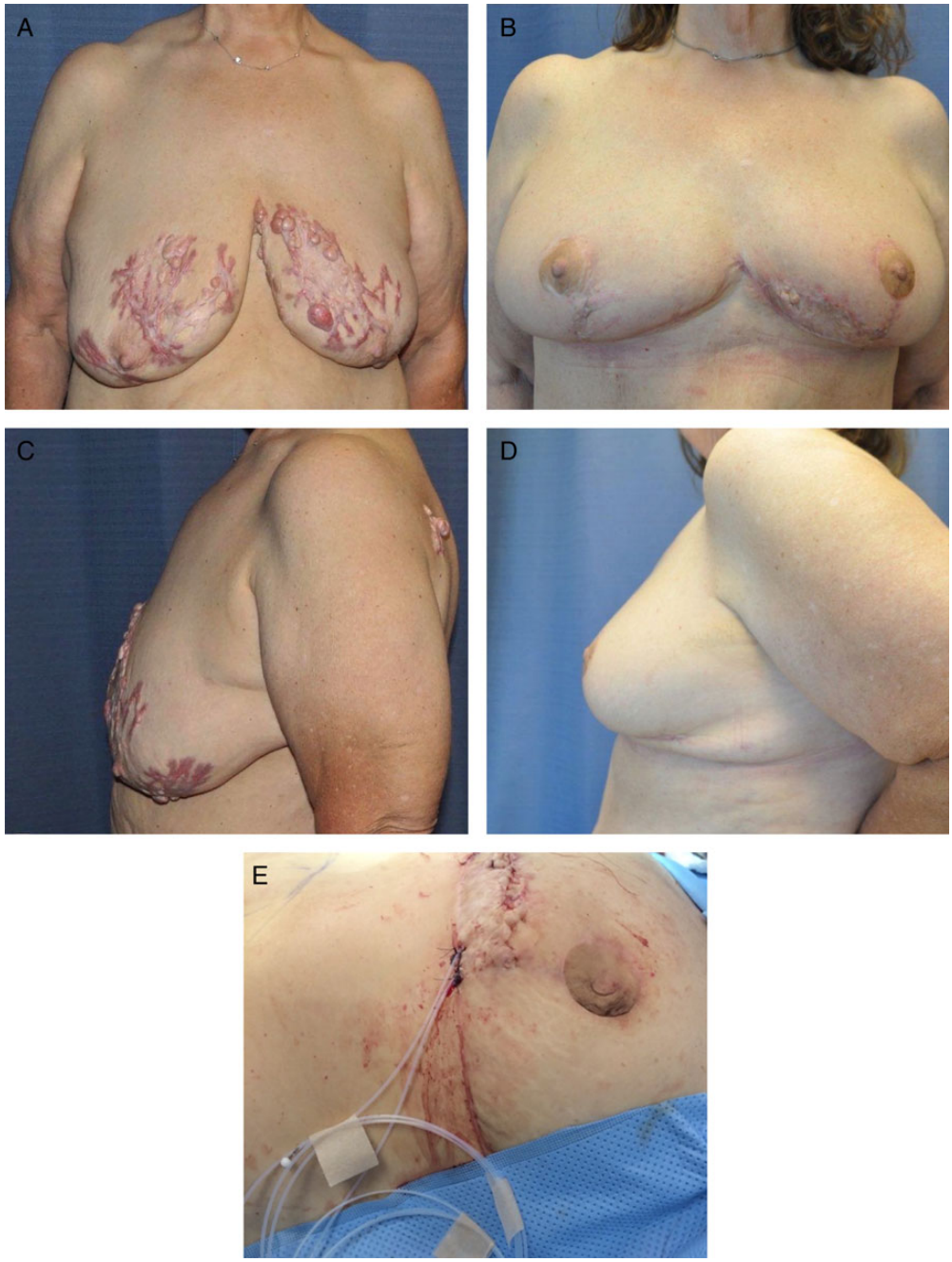

Figure 1. Frontal (A) and lateral (C) views of an otherwise healthy 54-year-old woman who developed keloid scarring from bilateral breast biopsies which caused her major discomfort in the form of relentless pruritus, pain, psychological distress, and cosmetic disfigurement. (B, D) Postoperative photographs taken at 12 months after combined reduction mammoplasty and keloid excision, followed by HDR brachytherapy. (E) The interstitial brachytherapy catheters were placed intraoperatively immediately following surgical excision and prior to completion of primary closure.

predispositions such as the keloid susceptibility loci (chromosomes 2q23 and 7p11), anatomic wound site, wound infections, and chronic wounds.[8-11]

The management of keloids has long been and continues to be difficult due to frequent recurrences and the lack of standard treatment guidelines. The initial management of keloids ranges in practice from conservative measures such as intralesional injections such as with steroids, occlusive dressing, compression therapy, silicone gel or sheeting, laser therapy, to more "aggressive" treatment options of

Table 1. Keloid Treatment Options

Conservative Therapies	Minimally Invasive Therapies	Invasive Therapies
Injections (intralesional vs extralesional) Corticosteroid Fluorouracil (5-FU) Bleomycin Interferon alfa-2b **Dressings** Occlusive Silicone sheets **Topical** Silicone gel Imiquimod Extractum cepae (onion extract)	**Cryotherapy laser** Flashlamp pulse-dye laser (FPDL) Carbon dioxide (CO_2) Argon Neodymium:yttrium-aluminum-garnet (Nd:YAG) Erbium:yttrium-aluminum-garnet (Er:YAG) **Radiotherapy** External beam radiation Megavoltage (MeV) electrons Superficial/kilovoltage (kVp) photons Brachytherapy Interstitial vs. superficial Low-dose rate (LDR) vs High-dose rate (HDR) Radioisotope: Cobalt-60 vs. Iridium-192	**Surgical excision** Intramarginal vs extramarginal +/− Injection +/− radiation

surgical excision with or without the addition of postoperative radiotherapy (Table 1). Rarely, definitive radiotherapy without preceding excision is employed.[4,12-17]

The incidence of keloid recurrence remains unacceptably high with upfront treatment consisting of only conservative therapies or with surgical excision alone. Specifically, the recurrence rate of keloids after surgical excision alone has been reported to range between 45% and 100%.[15,17,18] This recurrence rate is similar to but still slightly lower than the >50% recurrence rate seen with conservative therapy use alone.[9,17,19] On the other hand, the rate of keloid recurrence with the addition of postoperative conservative therapies mentioned earlier such as intralesional corticosteroid or intralesional interferon alfa-2b injections has been described to be an improvement over surgical excision alone, reducing the rate down to <40% (range, 8%-60%).[15,17,20-24]

The advantage of postoperative radiotherapy over other perioperative therapies (specifically postoperative steroid injection) was demonstrated in a small randomized trial published by Sclafani et al in 1996.[25] It has also repeatedly been shown in numerous retrospective studies and systematic reviews that the addition of adjuvant radiation to surgical excision shows lower rates of keloid scar recurrence to approximately 20% (range, 10%-70%) when compared to most other adjuvant treatment options in clinical practice.[8,16,17,26-31] This is particularly the case for keloids that are excised and irradiated as upfront, first-line treatment; in this setting the rate of relapse is less than half of those lesions that are treated with radiotherapy after having failed prior treatments.[27] An international advisory panel on scar management recommended that surgical excision followed by postoperative radiotherapy is the most efficacious treatment regimen, particularly for severe keloids, treatment failures, and/or recalcitrant keloids.[17,31] No recommendations however have been made to support the upfront use of adjuvant radiotherapy following keloid excision instead of reserving its use only for recurrent lesions.

Postoperative radiation can be applied either externally through external beam radiotherapy (EBRT) or internally via brachytherapy. EBRT for keloid irradiation can be delivered by way of a variety of devices, techniques, and modalities, including the use of megavoltage (MeV) electrons and low-energy kilovoltage (kVp) photons (also referred to as orthovoltage or superficial X-ray radiation). Brachytherapy for keloid irradiation has previously been delivered via different delivery techniques (interstitial vs superficial catheter treatment), a variety of different radioisotope sources (Cobalt-60, Iridium-192), and either low-dose rate (LDR) or high-dose rate (HDR) (Table 1).[26,28,29,31,32] Evidence in the radiation oncology literature has shown no significant advantage between MeV electron beam radiotherapy compared with superficial kVp X-ray therapy in the treatment of keloids, but that HDR brachytherapy is better than LDR brachytherapy in reducing keloid recurrence rates.[11,31,33] Despite both external beam and brachytherapy radiation modalities existing and being commonly used for keloids following surgical excision, there is a paucity of high-quality evidence comparing keloid recurrence outcomes between these techniques which makes it difficult to establish standard of care radiotherapy-based treatment guidelines in the management of keloids.[9,31,34]

Thus, we devised the largest single institutute retrospective case series study to critically evaluate keloid control rates between adjuvant post-excision HDR interstitial brachytherapy treatment vs external beam radiotherapy treatment. In addition, we extended our retrospective case series study to evaluate our institutional keloid recurrence rates between those lesions treated with surgical excision alone compared to excision with immediate postoperative radiotherapy treatment.

METHODS

Patient Collection

A retrospective review was performed on 128 consecutive patients with a total of 264 keloid scars that underwent surgical excision at Cedars-Sinai Medical Center over a 10-year period from 2004 to 2014. Patient demographic data were collected for all patients and keloid lesions included in the study. Of these 128 patients, 108 patients (236 keloid lesions) underwent immediate postoperative radiation at our institution over this same 10-year time period, while the remaining 20 patients (28 keloid lesions) underwent surgical excision alone. Notably, some patients had more than a single keloid lesion treated (range, 1-10 lesions per patient), and keloids that occurred at different sites in the same patient were considered to be different lesions. Both adult and pediatric patients were included in our study, with the only exclusion criteria for post-excision radiotherapy being pregnancy or previously documented or suspected radio sensitivity condition/syndrome, neither of which were observed in any of our studied patient population (Table 2).

Treatment Selection

The decision between post-excision external beam radiation and post-excision brachytherapy was made jointly between the plastic surgeon and treating radiation oncologist, accounting for such factors as the number of keloid lesions treated, the resulting width, linearity, and depth of the keloid excision site, ability to surgically place interstitial brachytherapy catheter, as well as patient preference with respect to a fractionated vs single fraction radiotherapy regimen.

Surgical Excision

Most previous studies evaluating radiation and excision treatment modalities use an extralesional or extramarginal

Table 2. Characteristics of 128 Patients Undergoing Keloid Treatment

	Number of Patients (%)			
	Brachytherapy ($n = 24$)	EBRT ($n = 84$)	Surgery alone ($n = 20$)	Total ($n = 128$)
Sex				
Female	21 (87%)	60 (71%)	17 (85%)	98 (77%)
Male	3 (13%)	24 (29%)	3 (15%)	30 (23%)
Age (years)				
<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)
10-19	0 (0%)	6 (7%)	0 (0%)	6 (5%)
20-39	6 (25%)	27 (32%)	5 (25%)	38 (30%)
40-69	17 (71%)	46 (55%)	14 (70%)	77 (60%)
>69	1 (4%)	5 (6%)	1 (5%)	7 (5%)
Keloid lesions				
1	14 (83%)	40 (48%)	14 (70%)	68 (53%)
2	9 (17%)	21 (25%)	5 (25%)	35 (27%)
3	0 (0%)	8 (10%)	1 (5%)	9 (7%)
4	0 (0%)	6 (7%)	0 (0%)	6 (5%)
>5	1 (0%)	9 (11%)	0 (0%)	10 (8%)
Total	39	197	28	264
Ethnicity				
African American	12 (50%)	43 (51%)	9 (45%)	64 (50%)
Caucasian	5 (21%)	18 (21%)	9 (45%)	32 (25%)
Asian	5 (21%)	12 (14%)	0 (0%)	17 (13%)
Hispanic	2 (8%)	11 (13%)	2 (10%)	15 (11%)

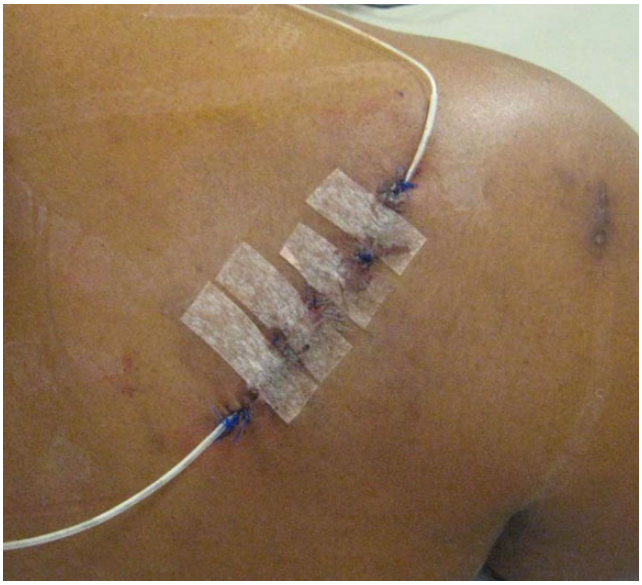

Figure 2. A 27-year-old otherwise healthy woman who developed a keloid after a back lipoma excision is shown 10 hours after surgery with an interstitial brachytherapy catheter in place immediately prior to delivery of radiation.

keloid excision approach. Only one study in a recent review article was found to use intralesional excision.[31] All patients in this study similarly underwent complete extramarginal excision of their keloid scars in order to remain consistent with popular and standard treatment for excision currently reported in practice. The resulting wound was sutured with absorbable sutures and closed in layers to achieve a minimal tension primary repair. For those lesions treated with postoperative brachytherapy, the interstitial brachytherapy catheters were placed intraoperatively immediately following surgical excision and prior to completion of primary closure. Specifically, this process entailed insertion of a Varian (Varian Medical Systems, Palo Alto, CA) 6-French flexible single lumen interstitial HDR brachytherapy catheter under the dermis, which was then sutured in place to the soft tissue (Figures 1E and 2). The surgical technique utilized was similar to the technique described by Veen and Kal.[35] Closed wounds were subsequently dressed with xeroform over the incision and an occlusive Tegaderm dressing (3M, St. Paul, MN) to maintain a moist wound healing environment. The patients were then transported down to the radiation oncology department for CT simulation scan and subsequent treatment planning.

Radiation Therapy

With respect to those lesions that were treated with postoperative radiotherapy, 39 keloid lesions were treated with immediate postoperative HDR single lumen interstitial brachytherapy, and 197 keloid lesions were treated with adjuvant EBRT (Table 2). All patients that received radiotherapy were informed about the possible harmful effects of radiotherapy, including rare risk of late carcinogenesis, and signed informed consent forms were obtained prior to the start of radiotherapy.

The brachytherapy treatment was delivered utilizing an Iridium-192 (Ir-192) radioisotope source using a VariSource iX afterloader (Varian Medical Systems, Palo Alto, CA). Following the completion of brachytherapy treatment, the securing sutures and interstitial brachytherapy catheter were removed by the radiation oncologist without disturbing the primary wound closure sutures, as previously described. The HDR brachytherapy treatments were prescribed to deliver 8 to 12 units of gray (Gy) over a single fraction to a 5 mm distance from the source. The superficial radiation treatments were all planned and delivered using a Pantak Therapax-150 superficial X-ray treatment machine (Pantak Inc, East Haven, CT) using a clinical setup. All treatment planning, regardless of brachytherapy or EBRT, was performed using Eclipse Treatment Planning System (Varian Medical Systems, Palo Alto, CA).

With respect to the EBRT treatment details, the electron EBRT treatments were delivered using 6- or 9-MeV electrons delivered via linear accelerator, prescribed to the 90% isodose line, with overlying 0.5 to 1 cm tissue-equivalent silicone bolus in place. The treatment field was confined to the keloid region (postoperative excision site and any suture/puncture holes) plus adequate surrounding margin (3-5 mm) to allow for setup margin, horizontal nature of the target, and account for electron beam penumbra (electron scattering) and electron block selection. The superficial photon treatments were delivered using 80- or 100-kVp superficial X-rays at 15 to 25 cm target-to-skin distance, prescribed to depth of dose maximum, which is at the skin surface for these superficial energy X-ray therapies (Figure 3). The 90% isodose target area of the superficial X-ray treatments encompassed the same keloid region as described above for the electron EBRT treatments, with an approximate 0.5 to 1.0 cm horizontal margin around the target region to account for setup uncertainties, horizontal nature of the target, and penumbra of the low-voltage (superficial energy) beams. The treatment fields for the superficial treatments were bound laterally by 1 to 2 mm lead alloy blocks to shield the surrounding non-target areas. The range of doses delivered with the adjuvant EBRT treatments ranged from 9 to 30 Gy delivered over one to 10 daily fractions to the applied dose point.

All patients in the study that received radiation received their first dose within 36 hours of the keloid excision, other than one patient who was treated to three keloid lesions 137 days after surgery. In addition, the overall treatment time, defined as the time period between surgery and the last radiation dose, was ≤7 days for all patients except for the above noted patient treated 137 days following surgery,

and one other patient whose overall treatment time for four keloid lesions spanned a total of 8 days. The biologic effective dose for each radiation modality was calculated to be similar and is presented in Table 3. Banana equivalent dose (BED) correction using the time correction factor shown in Table 3 was necessary in this second patient in order to account for the radiobiologic potential for accelerated keloid tissue proliferation in treatment courses extending beyond 7 days.[18,33]

Keloid characteristics were collected for all patients and keloid lesions included in the study. This included inciting event (etiology) of scar (surgery, trauma, unknown), keloid size at time of resection based on pathologist review of resection specimen, location of keloid scar (classified into four categories: abdomen; breasts/back/chest; upper extremities; head and neck), history of previous excision, and post-excision follow-up time. In addition, any radiotherapy treatment-related complication was recorded as well (Table 4).

The primary outcome being evaluated in both study questions (excision alone vs excision and immediate adjuvant radiotherapy; adjuvant HDR interstitial brachytherapy vs adjuvant EBRT) was keloid recurrence rate. Recurrence rate and time to recurrence was determined by review of plastic surgery and/or radiation oncology clinic follow-up notes. Recurrence was defined as clinically-determined evidence of keloid lesion recurrence (utilizing Cosman's criteria[36]) by either the plastic surgeon or radiation oncologist. The time to recurrence was calculated from time from completion of therapy, either adjuvant radiotherapy treatment for those that underwent this therapy or time from surgical excision for those that underwent surgical excision alone. Our study protocol was approved by the institutional review board of Cedars-Sinai Medical Center.

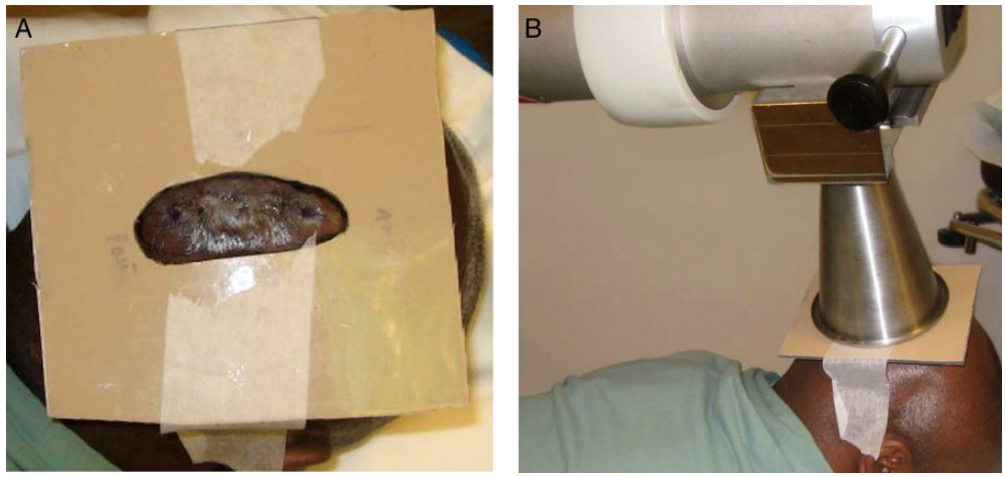

Figure 3. (A) A 48-year-old male who developed a keloid on his posterior scalp after a traumatic laceration is shown 12 hours after surgery for superficial X-ray radiation. The treatment field was confined to the keloid region, which includes the postoperative excision site plus and any suture/puncture holes with an approximate 0.5-1.0 cm horizontal margin to allow for setup uncertainties, horizontal nature of the target, and superficial x-ray penumbra. (B) The patient shown receiving his first fraction of superficial X-ray radiation 12 hours after surgery.

Table 3. Biologic Effective Dose Calculations for Radiation Modalities Employed Post-Excision

	BED, $Gy_{2.08}$ (α/β[33]: 2.08)	BED, $Gy_{10.0}$ (α/β[18]: 10.0)
EBRT - MeV electrons	22.0-58.5	11.7-28.0
EBRT - 80-kVP superficial X-rays	28.3-67.0	14.2-27.8
EBRT - 100-kVP superficial X-rays	43.0-71.7[a]	19.7-32.8[a]
HDR brachytherapy (Iridium-192)	38.8-81.2	14.4-26.4

RBE value (Ir-192 γ-rays (brachytherapy) and megavoltage (MeV) electrons)[18,33]: 1.0; RBE value (100 kVp superficial photons)[18,33]: 1.13; RBE value (80 kVp superficial photons)[18,33]: 1.17; k: BED time correction (T-7) factor[18,33]: −1.34 Gy/day for treatment extending beyond 7 days (applicable to one patient). α/β, alpha/beta ratio; BED, biologic effective dose (BED = RBE*D[1 + RBE*d/(α/β)]-k*t); d, dose per fraction; D: total dose; HDR, high-dose rate; k, repair per day (after 7 days); RBE, relative biologic effectiveness; t: overall treatment time. [a] Excluding the data from the single patient treated with 100-kVp superficial EBRT to three lesions following an extended interval time (137 days) following surgery.

Table 4. Characteristics of 264 Keloids

	Keloid Lesions (%)			
	Brachytherapy	EBRT	Surgery Alone	Total
Keloid lesions	39 (15%)	197 (75%)	28 (11%)	264
Etiology				
Surgery	27 (69%)	100 (51%)	27 (96%)	154 (58%)
Trauma	4 (10%)	35 (18%)	1 (4%)	40 (15%)
Unknown	8 (21%)	62 (31%)	0 (0%)	70 (27%)
Location				
Abdomen	11 (28%)	40 (20%)	3 (11%)	54 (20%)
Breasts/chest/back	21 (54%)	59 (30%)	22 (79%)	102 (39%)
Upper extremities	3 (8%)	39 (20%)	1 (4%)	43 (16%)
Head and neck	4 (10%)	54 (27%)	2 (7%)	60 (23%)
Unknown	0 (0%)	5 (3%)	0 (0%)	5 (2%)
Size				
>8 cm	21 (54%)	66 (34%)	11 (40%)	98 (37%)
<8 cm	18 (46%)	131 (66%)	17 (60%)	166 (63%)
Previous excisions				
Yes	18 (46%)	89 (45%)	3 (11%)	65 (25%)
No	21 (54%)	108 (55%)	25 (89%)	124 (47%)
Unknown	0 (0%)	0 (0%)	0 (0%)	75 (28%)
Recurrence				
Yes	9 (23%)	37 (19%)	15 (54%)	61 (23%)
No	30 (77%)	160 (81%)	13 (46%)	203 (77%)
Abdomen	4 (44%)	13 (35%)	1 (7%)	18 (30%)
Breasts/chest/back	3 (33%)	6 (16%)	13 (87%)	22 (36%)
Upper extremities	0 (0%)	7 (19%)	1 (7%)	8 (13%)
Head and Neck	2 (22%)	11 (30%)	0 (0%)	13 (21%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Radiotherapy-related complications				
Erythema	1 (3%)	2 (1%)	-	3 (1%)
Hyperpigmentation	2 (5%)	2 (1%)	-	4 (2%)
Surgical Site Infection/dehiscence	3 (8%)	0 (0%)	-	3 (1%)
None	33 (85%)	193 (98%)	-	226 (96%)
Mean [median] Post-excision follow up (months)	16.5 [12]	53.4 [42]	12.8 [9]	27.6 [21]

Statistical Analysis

Recurrence data were analyzed using mixed effect Cox regression modeling.[37] All *P*-values were two-tailed, and a value of <0.05 was determined to be a statistically significant difference. All statistical analysis was performed using Stata.

RESULTS

The demographics of the 128 patients are shown in Table 2. The patients ranged in age from 14 to 83 years (mean ages, 49 years for brachytherapy; 43 years for EBRT; and 50 years for surgery alone). There was a greater number of female patients treated (98, 77%), compared to males (30, 23%), which was similar within each treatment group. The characteristics of the individual keloid lesions classified by delivered treatment modality are shown in Table 4. The etiology of the keloid scars was predominantly related to previous surgical intervention, representing 69% of the keloids treated with adjuvant brachytherapy, 51% of the keloids treated with adjuvant EBRT, and 96% of the surgery alone treated keloids. The majority of the lesions treated by brachytherapy were on the breasts, chest, or back (54%), while the remainder of the lesions were located on the abdomen (28%), head and neck (10%), and upper extremities (8%). The distribution across keloid location in the EBRT treated group was more evenly spread between breast, chest, or back, head and neck, abdomen, and upper extremities, with percentages ranging between 20% to 30% for all four anatomic locations. In the surgery alone group, 79% of the excised keloids were on the breasts, chest, or back, while only 11% were on the abdomen, and the remainder on the head and neck and upper extremities. Brachytherapy keloid lesions were measured to be >8 cm in length 54% of the time, while only 34% of EBRT treated lesions were at least as large. Surgery alone lesions were of similar size 40% of cases. The vast majority of the surgery alone patients had not undergone previous excision (89%), consistent with expected clinical practice of proceeding with surgical excision alone upfront and reserving the addition of adjuvant post-excision radiation (RT) for recurrent keloid lesions. Also consistent with clinical practice, among the brachytherapy and EBRT groups only 54% and 55%, respectively, had not undergone previous surgical excisions (Table 4).

Recurrence rates varied between treatment groups with the surgery alone group showing a 54% ($n = 15$) keloid recurrence rate at a median follow up of 9 months (mean, 12.8 months; range, 6-32 months). The brachytherapy treated group showed a 23% ($n = 9$) keloid recurrence rate at a median follow up of 12 months (mean, 16.5 months; range, 8-70 months), and the EBRT treated group showed a 19% ($n = 37$) keloid recurrence rate at a median follow up of 42 months (mean, 53.4 months; range, 10-136 months). Recurrence rate by anatomic location inclusive of all three treatment-groups was 36% ($n = 22$) for the breasts (Figure 1), chest, or back region; 30% ($n = 18$) for the abdomen region; 13% ($n = 8$) for the upper extremities; 21% ($n = 13$) for the head and neck (Table 4).

The radiotherapy-related complications were separated into acute and long-term side effects. The incidence of acute radiation-related side effects was minimal among our study patients, with no grade 2 or higher acute or long-term adverse events per Common Terminology Criteria for Adverse Events v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). Of the brachytherapy treated keloid lesions, one developed a grade 1 surgical site (skin) infection, two developed grade 1 wound dehiscence complication, one developed acute transient grade 1 treatment-site erythema, and two developed grade 1 treatment-site hyperpigmentation (Table 4). Of the EBRT treated keloid lesions, two developed acute transient grade 1 treatment-site erythema and two developed grade 1 treatment-site hyperpigmentation (Table 4). Of note, there was no observed treatment-related hypopigmentation, and there were no reports of long-term complications or identified development of malignancy in our study population during the 10-year study time period.

Table 5. Univariate Analysis: Variables Associated with Keloid Recurrence

Variable	Univariate Analysis
	P Value
Age	.21
Sex	.61
Ethnicity (African American)	.31
Ethnicity (Asian)	.30
Ethnicity (Hispanic)	.31
Lesion size	.84
Lesion location (abdomen)	.24
Lesion location (breasts/chest/back)	.44
Lesion location (upper extremity)	.26
Lesion location (head and neck)	**.01**
Lesion etiology	.09
Previous excision	.29
Radiation dose	.46
Adjuvant brachytherapy	**<.01**
Adjuvant EBRT	**<.01**

P < .05: statistically significant. EBRT, external beam radiotherapy.

Table 6. Multivariate Analysis of Keloid Recurrence

Multivariate Analysis		
Variable (reference level: surgical excision alone)	Hazard Ratio	*P* Value
Lesion location (abdomen)	0.91	.89
Lesion location (breasts/chest/back)	0.87	.89
Lesion location (upper extremity)	0.90	.89
Lesion location (head and neck)	0.43	.46
Adjuvant brachytherapy	0.08	.04
Adjuvant EBRT	<0.01	<.01
Variable (reference level: adjuvant EBRT)	**Hazard Ratio**	***P* Value**
Adjuvant brachytherapy	54.2	<.01
Surgical excision alone	716.1	<.01

EBRT, external beam radiotherapy.

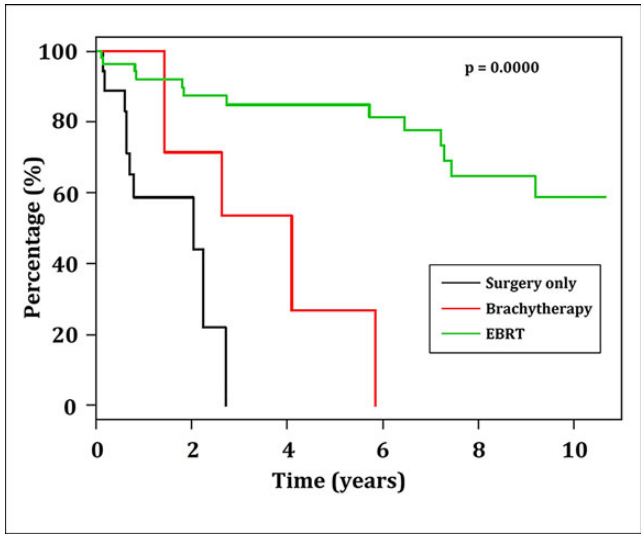

Figure 4. Kaplan-Meier estimations predicted a mean rate of keloid recurrence for post-excision brachytherapy of one year vs 3.5 years for external beam treatment. EBRT, external beam radiotherapy.

In looking at the relationship between the various patient and keloid characteristics with the observed keloid recurrence rates, univariate analysis was performed examining the effects of age, sex, ethnicity, lesion size, lesion location, lesion etiology, previous excision, radiation dose, adjuvant brachytherapy, and adjuvant EBRT on rate of recurrence. Only the addition of adjuvant radiotherapy, specifically adjuvant brachytherapy ($P < .01$) and adjuvant EBRT ($P < .01$), and head and neck lesion location were found to be statistically significant in favor of decreased keloid recurrence (hazard ratio (HR): 0.65, $P = .01$). The remainder of the variables, including delivered radiation dose, which was examined as a continuous variable, showed no significance ($P = .46$) (Table 5). Multivariate analysis was also performed, with head and neck location no longer found to be statistically significant ($P = .46$) for recurrence, however adjuvant brachytherapy (HR: 0.08; $P = .04$) and adjuvant EBRT (HR: < 0.01; $P < .01$) continued to show significantly decreased keloid recurrence risk compared to surgical excision alone. In comparing the rate of recurrence between the adjuvant radiotherapy modalities, there was no statistically significant difference between recurrence rates of brachytherapy vs EBRT ($P > .05$). However, when comparing the time to recurrence between the brachytherapy and EBRT treatment groups, there was a statistically significant shorter time to recurrence with adjuvant brachytherapy compared to adjuvant EBRT (HR: 54.2; $P < .01$) (Table 6). Kaplan-Meier estimations predicted a mean rate of recurrence for brachytherapy of one year vs 3.5 years for external beam treatment as illustrated in Figure 4. Comparing the hazard ratios of time to keloid recurrence of surgery alone vs the other modalities, surgical excision alone had the highest risk of mean recurrence at the shortest interval of time at 9 months.

DISCUSSION

Keloids continue to remain a difficult problem in plastic surgery, given their high recurrence rate with utilization of conservative therapies or surgical excision alone.

Our study showed a recurrence rate of 19% (46/236) after keloid excision followed by immediate postoperative radiation, consistent with recurrence rates in the literature of approximately 20%. The 19% rate of recurrence was significantly better than the 54% (15/28) recurrence rate observed in the surgical excision alone group in our study, which is also consistent with that of the literature.[8,16,17,26-30]

The keloid control rates observed in our study though are lower than the 90% to 95% control rates predicted by the Flickinger study and some other previous literature.[31,33] This difference may be attributed to at least two factors present in our study. One such difference lies in the BED of the doses utilized in our study that are lower than those suggested in the Flickinger study. The Flickinger data suggest a dose of 21.5 to 22.2 Gy delivered over 3 fractions to achieve 90% control for non-earlobe keloid sites, which utilizing an α/β ratio of 2.08, is a BED range of 95.6 to 101.2 $Gy_{2.08}$. Kal and Veen in 2005[18] as previously discussed, recommended that for successful prevention of keloid recurrence (< 10% recurrence), a relatively high-dose of radiation, with a BED of at least 30 Gy_{10}, must be used. Of importance though is that

the Kal and Veen BED recommendations are based on using an α/β ratio of 10 based on those authors' classification of keloid tissue as an early responding tissue.[18] However, in order to compare the Flickinger recommended BED values to those of Kal and Veen and compare those BED values to those in our study, the same α/β ratio must be used. Using an α/β ratio of 2.08, the recommended dose regimens in the Kal and Veen 2005 paper (ie, single acute dose of 13 Gy, two fractions of 8 Gy, three fractions of 6 Gy, or single dose of 27 Gy with LDR), range from 70.0 to 94.3 $Gy_{2.08}$. The highest BED calculated in our study was 81.2 $Gy_{2.08}$ based on a single fraction 12 Gy HDR brachytherapy treatment regimen while the remainder were close to or less than the recommended BED values of either Kal and Veen or Flickinger (Table 3).[12,18,33]

An additional factor that may have contributed to the lower than expected control rate seen in our study compared to some of the prior literature may have our interval time between surgery and postoperative radiotherapy. As previously mentioned, all but one patient that received adjuvant radiation in our study received their first dose within 36 hours of keloid excision. Various reports in the literature have shown a correlation between favorable treatment responses and short interval time between surgery and radiotherapy.[31] Earlier studies have reported that the most effective time to give adjuvant radiation is within the first 1 to 2 weeks after excision, although others have shortened this window for postoperative therapy to 72 hours (3 days).[5] More recently an increasing number of studies have advocated for an even shorter interval time between surgery and commencement of radiotherapy, with postoperative radiotherapy recommended to be delivered ideally within 24 to 48 hours.[12,16,18,38] A recent systemic review, recognized that an even shorter time interval of <7 hours between keloid excision and EBRT was associated with lower recurrence rates compared to longer time intervals. This finding was also true for adjuvant HDR brachytherapy.[31]

In specifically looking at postoperative brachytherapy studies, review of the literature reveals several key studies, which when compared to our study reveal some significant differences in technique, follow up, and prescribed dose.[8,29,39,40] These differences between each of these studies and our study could be expected to significantly contribute to the differences in the findings between those studies and our study.

The difference between the recurrence rate in our study and that seen in the adjuvant HDR brachytherapy patients in the De Cicco study (38% recurrence rate at a median follow up of 28 months) may be related to the difference in follow up between the two studies.[39] This stems from the concept that local control of keloids is usually defined by control at 24 months,[11,27] given that $>90\%$ of keloid recurrences occur within the first 24 months post-treatment[17,41] and $>50\%$ recur within the first 6 months after treatment.[5] Thus, many studies have advocated for follow up of at least 24 months following adjuvant treatment.[11,27] Furthermore, these recommendations coincide with those of a recent systematic review, in which the authors recommended at least 15 but preferably 24 to 36 months of follow up after postoperative radiotherapy to evaluate for keloid recurrence.[31] When comparing our study to the Arneja or Guix studies,[8,29] these studies had lower rates of recurrence than our study despite their longer period of follow up than our study, and thus is likely attributed to differences between studies of the anatomic location of the keloids studied, as discussed below.

When comparing the BED of the median delivered HDR brachytherapy dose at 5 mm in our study (single 8-12 Gy fraction; BED_{10}: 14.4-26.4 Gy) to that of the De Cicco study, our study showed a greater BED (7.68 Gy_{10} total delivered over four twice-daily (BID) fractions of 1.92 Gy; BED: 9.1 Gy_{10}). Thus the higher BED of the median delivered dose in our study would be expected to show less recurrence, and thus may be the reason for the different study results. However, comparing the recurrence rates and BED utilized in the Arneja et al and Guix et al studies (8% recurrence at a mean follow up of 35 months and 3.4% recurrence at a median follow up of 37 months, respectively),[8,29] suggests that the divergent outcomes more likely reflect differences in patient selection and keloid location.

Both the Arneja and Guix studies had a large number of head and neck keloid lesions treated in each of these studies, with 46% of the lesions in the Guix study located in the head and neck region and 100% of the lesions in the Arneja study located on the earlobe. This is of significance given that keloids located in the head and neck region have been shown in previous studies to show lower keloid formation and recurrence rates compared to other keloid sites such as the anterior chest wall, which have relatively higher wound tension and traction than head and neck locations. This has been shown to remain true even at lower adjuvant radiotherapy doses.[4,18,33,42] This is particularly the case in the setting of earlobe keloids, which have minimal overlying wound tension and mechanical force in the absence of repeat piercings or earrings.[8,9] In our series, head and neck keloid lesions were found not to significantly differ in recurrence rate compared to other areas on multivariate analysis (Table 6).

In review of the literature, our study appears to be the only retrospective study with separate surgery alone, adjuvant EBRT, and adjuvant brachytherapy treatment groups. This is of great significance in that it allows for direct comparison of outcomes between these treatment groups in our study. This differs from previous studies in which outcomes of an excision alone treatment group to either an adjuvant EBRT or adjuvant brachytherapy (LDR or HDR) treatment group have been compared. Thus previous studies have had to rely on historical recurrence rate figures for the

non-studied adjuvant radiotherapy modality for comparison to the studied treatment modalities. The closest study in terms of allowing for comparison between all three treatment groups was a recently published systematic review of 33 retrospective and prospective keloid treatment studies, in which the mean recurrence rate data for each radiotherapy treatment modality were obtained. In this systematic review, HDR brachytherapy showed the lowest mean recurrence rate (10.5%) compared to LDR brachytherapy or EBRT. LDR brachytherapy showed the next lowest mean recurrence rate (21.3%), followed by EBRT (22.2%). In this review, the findings of improved recurrence rate outcomes with HDR brachytherapy over LDR brachytherapy were attributed to the shorter interval and overall treatment time (both < 24 hours) following surgery of HDR brachytherapy. In comparison, LDR's lower dose rate of irradiation by definition results in the treatment time spread out over 20 to 72 hours. The authors also noted that HDR brachytherapy delivers a more focused and efficient radiation of the targeted area compared to EBRT, thereby irradiating less surrounding healthy tissue, requiring a lower dose to achieve the same therapeutic effect, and reducing radionecrosis.[31] In our study, we found that there was no significant difference in recurrence rates between EBRT and HDR brachytherapy. In fact, we found that keloids recurred faster after surgery in the brachytherapy treated group than the EBRT group, if they were to recur.

In addition, only two recent studies have directly compared recurrence rates of adjuvant electron beam radiation to brachytherapy within the same study, although neither of these studies included a surgical excision alone group.[32,43] These two studies required comparison of their recurrence rate data from the two radiotherapy treatment modalities with historical surgery alone recurrence data. The results of our study differ from the results of the above two international studies, in that in our study the EBRT group (which consisted of superficial X-rays or MeV electrons) showed significantly improved keloid control rates compared to HDR brachytherapy. One of these studies, published by a Chinese group, was a single-institutional retrospective analysis of control rate and toxicity of postoperative HDR brachytherapy compared to electron beam irradiation in 116 keloid patients.[32] Similar to our study, the patients were treated over a 10-year period and several different radiotherapy and fractionation schedules were performed in that study. In contrast to our study though, all patients in their study were treated with fractionated regimens in both the HDR brachytherapy and electron beam radiotherapy groups. There was no significant difference in the rate of keloid control between treatment groups with respect to treatment modality (electrons vs HDR brachytherapy), however as seen in Flickinger's literature review,[33] keloid control rate was significantly improved for those patients that received hypo-fractionated regimens (defined as > 2 Gy/fraction in the Duan et al study) compared to conventionally fractionated radiotherapy regimens of 2 Gy/fraction.[32]

The second study was a single institutional retrospective review from a French group in which electron beam radiotherapy was compared with Ir-192 LDR brachytherapy in postoperative keloid irradiation.[43] This French study had a similar proportion of lesions treated with EBRT (116 lesions) compared to brachytherapy (26 lesions) as our study. The total dose and fractionation of both the electron beam and brachytherapy treatment regimens, however differed from our study, with > 95% of the electron beam radiotherapy regimens prescribed to 15 Gy over 5 fractions, while for the LDR brachytherapy treatments, the median dose delivered at 5 mm from the source was 20 Gy. Opposite to the findings of our study, Yossi et al found that there was a non-significant trend to better local control with brachytherapy over electron beam radiation.

The keloid control rates for the electron beam group in our study was 81%, similar to the electron beam group control rate of 85% in the higher dose group of the Duan study; while the control rates of the brachytherapy group in our study were slightly lower than the lower dose group in the Duan study (77% vs 86.4%). The lower control rate of the brachytherapy group and similar control rate of the EBRT group in our study compared to the Duan study, may have contributed to the opposite findings between our study and the Duan study with respect to improved keloid control of postoperative EBRT compared with brachytherapy. On the other hand, the control rate observed in our study for EBRT was higher than that seen in the Yossi study (81% vs 69%), while the control rate for the brachytherapy treatment group was less in our study (77%) than the Yossi study (85%). Once again, in addition to the differences in treatment doses, fractionation, and treatment techniques (HDR vs LDR brachytherapy) between our study and the Yossi study, the higher control rate of the EBRT group and lower control rate of the brachytherapy group in our study compared to the French study, may have contributed to the contrary findings between studies with respect to which postoperative radiotherapy modality had better control of keloid recurrence. The inconsistent design, results, and findings between these three retrospective studies (our study, Duan et al, and Yossi et al) further demonstrate the need for well-designed prospective randomized studies exploring the various aspects of adjuvant keloid radiotherapy to help determine the optimal dose, technique, and modality to be used to minimize keloid recurrence risk.

Some of the limitations of our study include the retrospective nature of the study. Only the EBRT group had median follow up beyond the recommended 3 years of follow up.[12,16,18,33] Patient enrollment and logistics of when patients underwent treatment was the biggest factor in determining the time of follow up. Patients that underwent surgical excision alone received treatment on average at a

more recent date compared to the other two modalities of treatment. We do not believe that with inclusion of more patients into the surgical excision only group (including patients that later underwent external beam or brachytherapy group) would change the recurrence rates observed; they are nearly identical to that published in the literature. Furthermore, based on our Kaplan Meier analysis, we specifically looked at the rate of recurrence based on time, and have shown a significance difference. The shortest follow up occurred within our surgical excision along group. By 9 months median follow up, we appreciated over 50% keloid recurrence rate. With a longer follow-up time, perhaps a higher recurrence rate may be observed, but would not influence our findings that there is a significant difference in time and rate of keloid recurrence when comparing between the treatment modalities. A greater time of follow up would not result in a lower recurrence rate than what we observed.

Another limitation was that our study included patients who were treated by multiple surgeons and radiation oncologists, and thus differences in both surgical techniques and radiotherapy techniques cannot be excluded and thus may have contributed to the study outcomes. This heterogeneity in treatment technique however has previously been seen in many of the prior adjuvant keloid irradiation studies.[28]

Yet another limitation of our study was heterogeneity between patients as well as the inclusion of patients with recurrent disease (ie, those that had undergone previous keloid excisions). It is known that keloids that have failed previous treatments are half as likely to remain controlled compared to those treated with combined surgery and radiotherapy upfront.[27,28] Despite the presence of both of these factors, our recurrence rate of 19% in the combined postoperative radiation group (both EBRT and brachytherapy treated lesions) remained consistent with recurrence rates in the postoperative radiotherapy literature of approximately 20%.[8,16,17,26-30]

Combining the results of treatment of keloids from different anatomic sites would be expected to introduce a possible confounding variable into our study, although review of the literature shows that this variable has been present in many older and even more recent keloid radiotherapy treatment studies.[28,31] Selection bias, which is seen in many retrospective keloid series, was felt to not be present given that the patients in our study were consecutively selected patients from a list of all keloid patients at our institution treated with postoperative radiotherapy and/or surgical excision over the 10-year studied time period.

As mentioned previously, there were no malignancies identified in the patients included in our study, with the probability of tumor induction expected to be exceedingly small given the extremely small treatment volumes and relatively rapid fall-off of the radiotherapy techniques utilized in our study. Despite this, further observation and longer follow up of our patients is essential, particularly given the delay associated with radiation-induced malignancies following radiation exposure.[16,26,27]

CONCLUSION

Despite the above study limitations, our results are felt to be generalizable to keloid patients across most treatment areas/sites. This is particularly the case given that the number of keloid lesions included in our study (264) is significantly greater than most other retrospective and all prospective studies of adjuvant keloid irradiation.[28,31] As mentioned previously, only systematic reviews, in which the number of lesions studied is combined across many studies, would consistently include a greater number of studied lesions than our single institutional study.

The need for well-designed prospective studies in order to determine the optimal treatment strategy and establish standard of care treatment guidelines in the management of keloids is illustrated by the limitations of our study and the limitations seen across the dozens of previous retrospective studies evaluating the treatment of keloids. In particular, only well-designed prospective studies will provide the level of evidence for determination of the optimal radiation dose, fractionation, and modality of radiotherapy (brachytherapy or EBRT) in the postoperative management of keloids. A well-designed prospective study would ideally involve a three-arm study design of surgery alone vs postoperative EBRT vs postoperative brachytherapy, although due to the nature of the treatments (HDR afterloader vs linear accelerator, need for catheter placement for brachytherapy) and excision site characteristics (eg, width, lack of linearity) limiting the dose-distribution with interstitial brachytherapy, blinding or randomization between the postoperative radiotherapy arms would not be possible. Thus, instead randomization between the three arms of surgery alone vs postoperative superficial X-ray radiation vs postoperative electron beam radiotherapy could be performed. Similarly, a prospective trial randomizing treatment between excision alone vs postoperative superficial brachytherapy vs postoperative interstitial brachytherapy would help determine the optimal postoperative keloid radiotherapy modality and delivery technique. In the absence of such studies, treatment guidelines will have to continue to rely on individual retrospective studies in addition to systematic reviews that combine the results of these individual retrospective studies.

In conclusion, postoperative radiotherapy continues to demonstrate significant improvement in keloid recurrence over surgical excision alone. Furthermore, adjuvant EBRT shows improved control rates over brachytherapy. Per review of the literature, adjuvant radiotherapy should be started soon after surgical excision in order to maximize the control rate. Our findings, along with those of other studies, warrant further evaluation with a well-designed prospective study to help determine the optimal adjuvant RT treatment

modality and overall keloid treatment strategy. We aim for our study to provide retrospective data upon which a well-designed prospective study could be created in order to help determine and elucidate the optimal adjuvant keloid radiotherapy modality and treatment paradigm.

Disclosures

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

Funding

The authors received no financial support for the research, authorship, and publication of this article.

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