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Hypofractionated electron-beam radiation therapy for keloids: retrospective study of 568 cases with 834 lesions

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ABSTRACT

We aimed to analyze the outcomes of hypofractionated high-energy electron beam radiotherapy for the treatment of keloids. From February 1998 to January 2012, 568 patients with a total of 834 keloids underwent radiotherapy: 826 lesions with postoperative radiotherapy, and 36 with skin-grafting. Lesion size was >5 cm in 335 keloids. An electron-beam of 6 or 7 MeV was used, with a total dose of 18 Gy (two fractions with a 1-week interval) covering the lesion with a 1-cm margin. The time between surgery and radiotherapy was 24–48 h. Skin-grafted patients underwent radiotherapy 10–15 days after the operation. The median follow-up was 40 months (range: 12–160 months). The local control rate was 88.25% (736/834). The relapse rate was 9.59% (80/834), and the time to relapse was 6–28 months (median: 12 months). Univariate analyses showed that gender, age, keloid size, keloid site, skin grafting, and operation-to-irradiation interval influenced the local control rate. Multivariate analysis showed that the relapse rate was correlated with gender ($P = 0.048$), age ($P < 0.01$), operation-to-irradiation interval ($P < 0.01$), keloid site ($P < 0.01$), surgical method ($P = 0.04$) and keloid size ($P < 0.02$). Adverse effects were observed in 9.83% (82/834). No radiation-induced cancers were observed. Hypofractionated high-energy electron beam radiotherapy for keloids yielded excellent outcomes, especially in cases without skin grafting. Early postoperative radiotherapy with limited hypofractionation could be a good choice for keloid treatment.

KEYWORDS: keloids, radiotherapy, electron beam, prognosis, assessment

INTRODUCTION

A keloid is a benign disease characterized by a variable growth of dense fibrous tissue due to an abnormal healing response to a cutaneous injury, sometimes beyond the original borders of the wound. It may cause itching, tenderness and pain, and may be disfiguring. Therefore, treatment is often necessary and may include corticosteroids, surgery, cryosurgery, laser therapy, chemotherapy and/or radiotherapy. The recurrence rate after simple excision is 45–100% [1]. The results from studies on postoperative radiotherapy are controversial, but there is strong evidence suggesting that postoperative radiotherapy is commonly used to suppress the overgrowth of scar tissue [2]. Indeed, the recurrence rate after radiation therapy is ∼20% [3]. A randomized trial of surgery and immediate radiotherapy vs surgery and cryotherapy and intralesional steroid injection have shown that patients undergoing surgery and adjuvant irradiation had less recurrence than cryotherapy and intralesional steroid injection, and had a better safety profile [4]. A study showed that high-energy electron radiotherapy could provide a better dose distribution compared with the use of kilovoltage X-rays for controlling keloids [5]. Furthermore, Flickinger *et al.* [6] have suggested that radiotherapy

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with a limited number of fractions and with a high dose per fraction is the best strategy for the postoperative treatment of keloids. However, the total radiation dose and the number of fractions are still controversial.

In the present study, we assessed our cases of keloids treated with postoperative radiotherapy, and analyzed long-term control under a range of conditions, including keloid size, keloid site, surgical methods, and time interval between surgery and radiotherapy. In addition, we assessed treatment response and adverse effects.

MATERIALS AND METHODS

Patients

This retrospective study was conducted at the Department of Orthopedics and the Department of Radiation Oncology, Peking Union Medical College Hospital in Beijing. From February 1998 to January 2012, 834 keloids in 568 patients were treated with radiotherapy. All patients with keloids treated using surgery and radiotherapy were included, and this is the standard treatment in our center. Patients with a history of previous treatments for keloids were excluded. For patients who underwent multiple lines of treatment, only the first treatment was considered.

Treatment

The external beam was administered with 6 or 7 MeV electrons. In our center, two factors are considered crucial for treatment success, and they are systematically verified at each treatment. First, the scar in a specific radiation field should remain flat and its position confirmed by the clinician. Second, 0.5 cm of wax is used to improve the surface dose. The radiation field includes the entire scar or the entire postoperative scar (including structure/puncture hole), with a margin of 1 cm around the lesion. Non-target areas are shielded using a 0.8-cm customized lead sheet.

A total dose of 18 Gy in two fractions a week apart was prescribed. The required monitor unit and treatment times were calculated manually.

Evaluation of treatment response and adverse effects

The evaluation standards were proposed by Enhamre and Hammar [7] and by Veen and Kal [8]. The responses to treatment were classified into four levels: Level I (Good), no visible scar or small scar in the plane of the skin, no complaints, and no recurrence during follow-up; Level II (Improved), no itching or other complaints, visible scar partly elevated by no more than 1 mm above the plane of the skin, slight dehiscence, and no recurrence during follow-up; Level III (Invalid), scar remained and was accompanied by swelling and itching symptoms after treatment, within 3 months; and Level IV (Relapse), treatment was effective for 3 months, but scar became elevated above the plane of the skin, or scar dehiscence and itching and erythema symptoms appeared again, all after 3 months. Patients achieving Levels I and II were defined as well controlled.

The initial treatment response was evaluated in all 568 patients (834 lesions) at the first follow-up examination (1–3 months after the end of radiotherapy). In our center, the follow-up policy for keloid patients with radiotherapy consists of a 3-month observation. The end of follow-up was in June 2013, and the median follow-up was 40 (range 12–160) months.

Acute radiotherapy-related complications were: skin ulceration within the radiation field, unhealed wound, and/or grafted skin necrosis after operation. Chronic adverse effects included skin hyperpigmentation and/or telangiectasia with depigmentation (occurring within a year after treatment). Some severe skin hyperpigmentation affected cosmetic appearance.

Statistical analysis

The long-term recurrence rate and radiotherapy-related adverse effect rate were analyzed using the Kaplan–Meier method and the log-rank test. Multivariate analysis was performed, and the Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs). All statistical analyses were performed using the R software, version 3.0.1 GUI 1.61 Snow Leopard builds (6492). *P*-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the patients and lesions

Patient and lesion characteristics are summarized in Tables 1 and 2. There were 103 men and 465 women, aged between 5 and 80 years, most of them being between 21 and 35 years (median age of 29 years). Of the lesions, 331 were in a site with high stretch tension (such as the chest wall, back, shoulder, or lower limbs), and 503 were in a site with low stretch tension (such as ear lobe, face, neck, abdomen or upper limbs). Of the 568 patients with 834 lesions, 8 preoperative radiotherapy patients (each patient with one lesion) received the first fraction before surgery, and the second fraction within 48 h after surgery. So, of the 834 lesions, 690 were treated with postoperative radiotherapy within 48 h of surgery, and 144 lesions were treated >48 h after surgery. Twenty-two patients (36 of the 834 lesions) received radiotherapy 10–15 days after skin graft surgery, to allow for grafted skin-flap survival.

Treatment results

The results of treatments are presented in Table 3. Most lesions (88.25%, 736/834) achieved Level I (539/834) or Level II (197/834) responses. Level III and IV responses occurred in 2.16% (18/834) and 9.59% (80/834) of lesions, respectively. The median time to recurrence was 12 (range 6–28) months.

Among the 18 lesions with a Level III response after treatment, 4 had received skin grafts, 12 were large primary keloids (>5 cm), and 4 received radiotherapy more than 48 h after surgery. Furthermore, 7 of these lesions were in an area with high stretch tension.

Among the 80 lesions with a Level IV response after treatment, 7 had received skin grafts, 41 were large primary keloids (>5 cm) and 35 received radiotherapy more than 48 h after surgery. In addition, 52 of these lesions were in an area with high stretch tension.

Figure 1 and Table 4 show the results from the univariate analyses. Gender, age, lesion size, lesion site, skin grafting, and time interval between surgery and irradiation were significant factors affecting response to treatment. Regarding gender, the control rate was 79.18% in males (median control time of 40 months) and 91.93% in females (median control time of 44 months). With respect to age, the control rate was 87.19% in those ≤29 years (median control time of 41 months) and 91.52% in those >29 years (median control time of 51 months). With respect to lesion size, the control rate was 92.02% in lesions ≤5 cm (median control time of 42 months), compared with

Table 1. Demographics of 568 patients

	Number of patients (%)
Gender	
Males	103 (18.1)
Females	465 (81.9)
Age (years)	
<10	2 (0.4)
10–19	56 (9.9)
20–29	228 (40.1)
30–39	123 (21.7)
40–49	71 (12.5)
50–59	49 (8.6)
60–70	23 (4.0)
>70	16 (2.8)
Median (range)	29 (5–80)
Keloid lesions	
1	385 (67.6)
2	135 (23.8)
3	29 (5.1)
4	14 (2.5)
5	2 (0.4)
6	1 (0.2)
7	1 (0.2)
8	1 (0.2)
Median (range)	1 (1–8)
Total	568

Table 2. Characteristics of 834 lesions

	Number of lesions (%)
Longest axis (cm)	
≤5	499 (59.8)
>5	335 (40.2)
Site	
With high stretch tension	
Chest wall	206 (24.7)
Back	36 (4.3)
Shoulder	56 (6.7)
Lower limbs	33 (4.0)
With low stretch tension	
Ear lobe	239 (28.6)
Face	19 (2.3)
Neck	57 (6.8)
Abdomen	120 (14.4)
Upper limbs	68 (8.2)
Treatment method	
Radiotherapy before surgery	8 (1.0)
Radiotherapy after surgery	826 (99.0)
Surgery method	
With skin grafting	36 (4.3)
Without skin grafting	798 (95.7)
Interval time from surgery to radiotherapy (h)	
≤24	641 (76.8)
≤48	49 (5.9)
>48	144 (17.3)

85.81% in large lesions (>5 cm, median control time of 38 months). With respect to lesion site, the control rate was 93.68% in low-tension stretch sites (median control time of 50 months), compared with 83.24% in high-stretch tension sites (median control time of 36 months). With respect to the surgical approach, the control rate of surgery with skin grafting was 76.32% (median control time of 34 months), compared with 90.09% with surgery alone (median control time of 48 months). With respect to the time interval between surgery and radiotherapy, the control rate was 91.48% when the time interval was ≤24 h (median control time of 51 months), compared with 86.04% for >24 h and ≤48 h (median control time of 41 months), and with 81.25% for >48 h (median control time of 36 months).

Table 4 presents the multivariate analysis. Gender, age, lesion size, lesion site, skin grafting, and time interval between surgery and irradiation remained statistically significant. Females displayed a decreased relapse rate compared with male (HR = 0.63, 95% CI: 0.41–0.99, $P = 0.048$). Patients ages >29 years displayed a decreased relapse rate compared with those ≤29 years (HR = 0.42, 95% CI: 0.27–0.65, $P < 0.01$). Keloids >5 cm displayed an increased relapse rate compared with keloids ≤5 cm (HR = 2.05, 95% CI: 1.34–3.15, $P < 0.01$). Keloids in sites with high stretch tension displayed an increased relapse rate compared with keloids in sites with low stretch tension (HR = 1.91, 95% CI: 1.26–2.89, $P < 0.01$). Surgery without skin grafting displayed a decreased relapse rate compared with surgery with skin grafting (HR = 0.51, 95% CI: 0.25–0.97, $P < 0.01$). Time intervals of >24 h but ≤48 h between surgery and radiotherapy (HR = 1.52, 95% CI: 1.33–1.82, $P < 0.02$) and of >48 h (HR = 1.77, 95% CI: 1.32–1.89, $P < 0.02$) showed an increased relapse rate compared with the time interval of ≤24 h.

Table 3. Response to treatment according to various factors

Factor	Category (*n*)	Result of treatment response (*n*)				Well controlled (%)	*P*-value
		Level I	Level II	Level III	Level IV		
Longest axis (cm)	≤5 (499)	359	95	6	39	90.98	<0.01
	>5 (335)	180	102	12	41	84.18	
Site	Ear lobe (239)	195	36	5	3	96.65	<0.01
	Chest wall (206)	111	59	5	31	82.52	
	Abdomen (120)	76	35	0	9	92.50	
	Upper limbs (68)	36	16	1	15	76.47	
	Neck (57)	31	21	4	1	91.23	
	Shoulder (56)	27	13	1	15	71.43	
	Back (36)	23	9	0	4	88.89	
	Lower limbs (33)	24	6	1	2	90.91	
	Face (19)	11	7	1	0	94.74	
Surgery method	With skin grafting (36)	18	8	3	7	72.22	<0.01
	Without skin grafting (798)	521	189	15	73	88.97	
Interval time from surgery to radiotherapy (h)	≤24 (641)	426	168	8	39	92.67	<0.01
	≤48 (49)	26	11	6	6	75.51	
	>48 (144)	85	20	4	35	72.92	

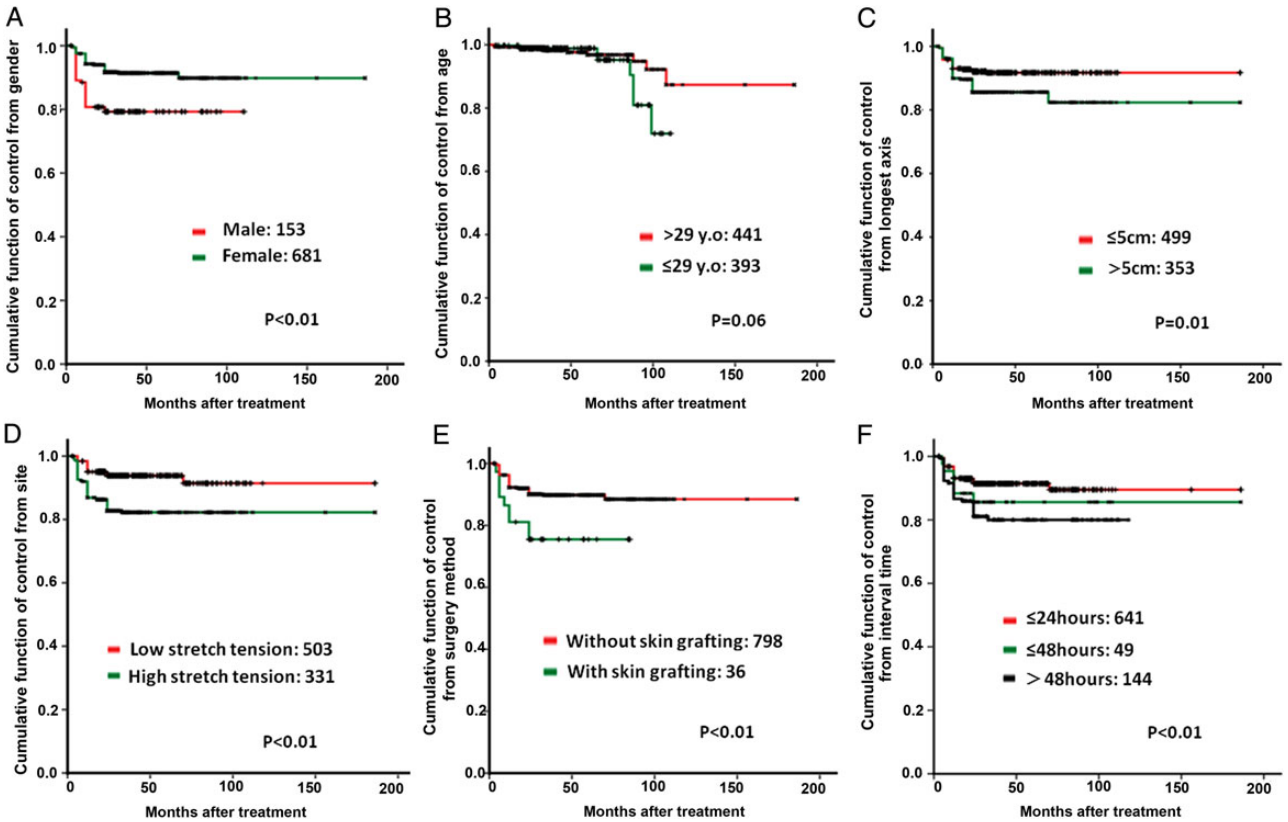

Figure 1. Univariate analyses of control rate. (A) Gender, female vs male. (B) Age, ≤29 vs >29 years. (C) Keloid size, ≤5 cm vs >5 cm. (D) Keloid site, low stretch tension vs high stretch tension. (E) Surgical approach, without skin grafting vs with skin grafting. (F) Time interval between surgery and radiotherapy, ≤24 h vs 48 h vs >48 h.

Table 4. Long-term control of 834 lesions

Factor	Category	Control rate (%)	Univariate analysis		Multivariate analysis	
			Median control time and Confidence Interval (months)	*P*-value	Hazard ratio and Confidence Interval	*P*-value
Gender	Male	79.18	40 (38.78–44.47)	<0.01	1	0.048
	Female	91.93	44 (36.92–48.88)		0.63 (0.41–0.99)	
Age	≤29 years	87.19	41 (38.51–43.32)	<0.01	1	
	>29 years	91.52	51 (48.16–54.73)		0.42 (0.27–0.65)	<0.01
Longest axis	≤5cm	92.02	42 (38.13–48.81)	0.01	1	<0.01
	>5cm	85.81	38 (34.23–41.61)		2.05 (1.34–3.15)	
Site	With low stretch tension	93.68	50 (47.91–56.49)	<0.01	1	<0.01
	With high stretch tension	83.24	36 (34.27–38.78)		1.91 (1.26–2.89)	
Surgery method	With skin grafting	76.32	34 (32.71–36.27)	<0.01	1	0.04
	Without skin grafting	90.09	48 (42.49–51.05)		0.51 (0.25–0.97)	
Interval time from surgery to radiotherapy (h)	≤24	91.48	51 (48.96–59.69)	<0.01	1	0.017
	≤48	86.04	41 (36.42–47.56)		1.52 (1.33–1.82)	
	>48	81.25	36 (34.07–37.22)		1.77 (1.32–1.89)	

No acute radiotherapy-related adverse effect was observed. The chronic adverse effect rate was 9.83% (82/834). Pigmentation was the most common adverse effect, and it occurred during the year after radiotherapy. No cases of treatment-related cancers occurred during follow-up.

DISCUSSION

Keloids are benign lesions caused by abnormal wound responses in predisposed individuals, and are an excessive connective tissue response to trauma, inflammation, surgery or burns [9]. In keloids, collagen synthesis is ~20 times greater than in normal unscarred skin, and three times greater than in hypertrophic scars [10]. This collagen overproduction can be attributed to a stronger proliferating activity of keloid fibroblasts [11]. *In vitro*, inhibition of proliferation of fibroblasts by repeated irradiations with cumulative doses of up to 10 Gy yielded similar effects to single irradiations [12]. The results of the present study suggest that the treatment of keloids with surgery and immediate hypofractionated high-dose radiotherapy was efficient and safe, especially for keloids in the face and neck. In addition, no radiation-associated severe early or late toxicity was observed during follow-up, and no radiation-induced secondary malignancy was observed during follow-up.

It has been demonstrated that keloids can be prevented from growing using immediate postsurgical radiotherapy [13, 14]. In a review of studies about postoperative keloid radiotherapy, Kal and Veen [15] recommended a relatively high biological effective dose (BED) of 30–40 Gy. In the present study, we used 18 Gy/2 fr, which corresponds to a dose of 28.8–34.2 Gy, and we obtained a good control rate. In addition, the incidence of adverse reactions was very low. A systematic review by Flickinger *et al.* [6] of all studies reporting results about postoperative external beam radiotherapy for keloids concluded that deeper-penetrating radiotherapy with an electron beam or ^{60}Co led to significantly lower recurrence rates after keloid resection compared with other radiotherapy techniques. In the present study, our results confirmed that high BED should be used in postoperative radiation using a linear particle accelerator (LINAC) electron beam. Disorganized collagen leading to a keloid is laid down by fibroblasts that have migrated into the wound 2–10 days after injury [16]. Therefore, early intervention with radiotherapy should be the best timing for the treatment of keloids. Studies have reported that the threshold dose should be 12–14 Gy in a single fraction for reliable control by X-rays in a postoperative setting, and that radiotherapy should be given immediately after excision [7, 17–19]. Enhamre and Hammar [7] observed no association between treatment outcomes and the time interval between excision and radiation. Sakamoto *et al.* [20] stated that the time interval from operation did not affect the local control and adverse effects after radiotherapy. In the present study, the time interval after surgery significantly affected treatment efficacy. Indeed, patients who received radiotherapy within two days after operation had a better prognosis than patients who received radiotherapy more than two days after surgery. Therefore, we recommend that undergoing radiotherapy within 24 h after surgery may be the best timing for the control of keloids. However, differences in treatment regimens could have introduced some

confusion, resulting in conflicting results. Indeed, Sakamoto *et al.* used regimens ranging from 16 Gy/8 fr to 40 Gy/8 fr, whereas we used 18 Gy/2 fr. Further randomized prospective trials should be designed to address this issue.

According to Flickinger *et al.* [6], BEDs of the various irradiation regimens were recalculated using the linear–quadratic (LQ) method. The dose–response function for keloids has a low α/β ratio, similar to that of late radiation injury reactions. Thus, short treatment regimens with few fractions and high doses should work well and have similar adverse effects compared with regimens with more fractions. Kal *et al.* [21] performed a meta-analysis of postoperative scar radiotherapy using 27 published studies, and the various dose fractionations were converted into BED using the LQ method. The resulting dose–effect relationship suggested that for a BED of <30 Gy, the radiation dose was suboptimal. For a BED of ≥30 Gy, the incidence of keloid recurrence was <10%. In the present study, the dose fractionation was 18 Gy in two fractions, with a BED equivalent of 34.2 Gy. Therefore, it was sufficient for keloid control with a low incidence of adverse effects.

In previous studies, the recurrence rate in patients who received immediate postsurgical radiotherapy was dependent upon higher skin stretch, but not upon lesion size [13, 14]. Ogawa *et al.* [3] reported that keloids in high-tension sites (such as the chest wall, shoulder and supraclavicular) should receive higher doses than keloids in low-tension sites (such as the earlobes, neck and upper extremities). Results of the present study showed that keloids occurring in the neck, face and torso displayed better responses than those in the limbs and shoulders. However, these results suggest that lesion size also influenced the recurrence rate. Therefore, the radiation dose distribution cannot be perfect, and the relapse still occurred. On the other hand, small keloids in low-tension areas, such as on the head, face and neck, achieved good outcomes.

Keloids can be treated surgically, either by resection or by radical mass reduction [22]. In a study by Ogawa *et al.* [23], patients with huge keloids who were treated using flaps and postoperative radiotherapy displayed an uneventful follow-up, and keloid recurrence was not observed. In the present study, patients who underwent radiotherapy after skin grafting had a higher relapse rate than those without skin grafting. We propose two reasons for the poorer control rate. Keloids with skin grafting surgery not only suffered from a long time interval between excision and radiation, but also suffered from a larger wound surface size. The recurrence rate in our study was 11.75% (98/834). Furthermore, in this study, most of these lesions were on the trunk and limbs. However, skin grafting is sometimes used to treat keloids, and we think that determining how these patients react to radiation therapy is important. We have included a Supplemental Table 1 (below) that shows the same analyses but without including the 36 lesions treated with skin grafting. The results are similar to those obtained for the whole study, so postoperative radiotherapy is still recommended for skin graft patients.

Our study examined early and late radiotherapy toxicities. The most frequent early toxicity was skin erythema (in more than half the lesions), as reported by Speranza *et al.* [24]. Bischof *et al.* [13] achieved good to excellent self-satisfaction ratings (62%) with radiation therapy, reporting that subjective assessments did not always fully correlate with clinical examination or incidence of recurrence. Kim and Lee [25] presented 26 postpartum patients with confirmed keloids resulting from previous Cesarean sections: most patients (96%) were satisfied with treatment outcomes. In the present study, despite experiencing some degrees of local recurrence, most subjects remained satisfied with their treatment results. For the late toxicities, Speranza *et al.* [24] reported that the rate of telangiectasia occurrence was 27%. Ogawa *et al.* [3] reported that the rate of late adverse effects was 45.6% 6 months after treatment. The present study showed that the most common treatment-related adverse effect was pigmentation occurring during the year following radiotherapy. No radiotherapy-related secondary malignancies occurred in patients with keloids after long-term follow-up, as previously reported [20, 26].

The present study is not without limitations. Despite the high number of patients, all patients were from the same center, which could introduce center bias. In addition, the follow-up duration was sufficient for observing the recurrence of keloids, but might be not long enough to observe some late toxicities, especially secondary malignancies. This cohort of patients will be followed up, and an update will be presented in a few years. Finally, there was a discrepancy in the gender distribution, and we had no data that could explain the reason for this discrepancy.

In conclusion, the results of the present study indicated that surgery and immediate postoperative (within 48 h) radiotherapy (with 6–7 MeV LINAC electron beam) was an effective and relatively safe choice for the treatment of keloids. More economical and convenient short treatment regimens with high doses and hypofractionation (18 Gy in 2 fractions with a 1-week interval) worked well. Skin-grafted keloids have higher recurrence rates than those without skin grafting. Stretch tension should be taken into account when planning treatment.

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