INTRODUCTION

Keloids still represent a major challenge in plastic surgery. Many treatment options have been proposed. Thus far, no single one has demonstrated a consistent reliability, given the high recurrence rate reported for all of them.1,2 Radiotherapy was proposed for the treatment of keloids even in the early 20th century, 3,4 but with unsatisfactory results. From the 1940s, the combination of surgical excision and early postoperative radiotherapy allowed for more effective and encouraging results. 5 Thereafter, using electrically charged particles gradually replaced the traditional x-ray irradiation. 6,7 Since the early 2000s, 8 this approach has been the standard treatment for keloids in our unit, too, with a success rate comparable to those of similar protocols reported in the literature. 9

A recent technological innovation, intraoperative radiation therapy (IORT), developed for the treatment of several malignancies, allows for the delivery of radiation directly into the surgical operating field.10

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ABSTRACT

Background: The combination of surgery and postoperative radiotherapy allows for the most effective results with keloids. In this trial, surgery and intraoperative radiation therapy (IORT) technology were used—the hypothesis being that the earlier the application of postoperative radiotherapy, the better the wound healing evolution.

Methods: The study included 16 patients with 21 keloids. The keloids were radically excised and repaired with direct suture or local skin flaps. Collimated electron radiotherapy was applied within 45 minutes of surgery. The outcomes were assessed according to the modified Patient and Observer Scar Assessment Scale; the modified Vancouver Scar Scale; and the modified Common Terminology Criteria for Adverse Events v. 4.0 for skin and subcutaneous tissue disorders.

Results: Recurrences were observed in one out of 16 patients, and in two out of 21 keloids (9.5%). The modified Patient and Observer Scar Assessment Scale demonstrated a statistically significant improvement in pain, itching, color, stiffness, thickness, and irregularity after the treatment. The modified Patient and Observer Scar Assessment Scale displayed a statistically significant improvement in the scar vascularity, pigmentation, thickness, and pliability after the treatment. The modified Vancouver Scar Scale demonstrated a statistically significant improvement in 90.48% of the scars after the treatment. The modified Common Terminology Criteria for Adverse Events v. 4.0 for skin and subcutaneous tissue disorders demonstrated an improvement in erythema multiforme and skin pain across the whole sample, with a temporary hyperpigmentation in 19% of the scars after the treatment.

Conclusion: The combination of surgery and collimated electron radiotherapy with IORT technology demonstrated favorable results in 90.5% of the cases. (Plast Reconstr Surg Glob Open 2021;9:e3738; doi: 10.1097/GOX.0000000000003738; Published online 17 September 2021.)
In our pilot trial, we have used this novel technology of a combined approach involving surgery and immediate postoperative radiotherapy for the treatment of keloids, in order to significantly reduce the time lapse between the surgical excision and the local radiation delivery. Given the hypothesis that the earlier the application of postoperative radiotherapy, the better the evolution of the wound healing process, the aim of this study was the assessment of the outcomes after surgical excision and an immediate, single-dose IORT for keloids.

**MATERIALS AND METHODS**

**Study Design**

A prospective, nonrandomized pilot study was carried out in cooperation between the plastic surgery unit of the University of Pavia (Italy) and the radiotherapy unit of the ICS Maugeri SB SpA IRCCS in Pavia (Italy). The study conformed to the 1975 Declaration of Helsinki; informed written consent was obtained from all of the patients and the trial was approved on March 10, 2014 by the ethics committee of the ICS Maugeri SB SpA IRCCS, Pavia (Italy) (project identification code 925 CE).

The study was carried out over a period of 24 months, from June 2014 to May 2016. A total of 16 patients (10 women, 6 men; age range 18–65 years, mean 34.63 ± 11.74) with 21 keloid scar lesions were enrolled in the study.

The distribution of individuals within the ethnic groups in the sample was: 10 White (62.5%), 3 Hispanic (18.75%), 3 Black (18.75%).

The anatomical topographic distribution of the keloids in the sample was: abdomen 1 (4.76%), neck 2 (9.52%), shoulder 5 (23.82%), earlobe 4 (19.05%), pectoral region 2 (9.52%), scapular region 4 (19.05%), and sternum 3 (14.29%).

The general cohort’s characteristics are displayed in Table 1.

The unique inclusion criterion was as follows:
- Keloids of any anatomical site present for at least 12 months.

The exclusion criteria were as follows:
- Keloids larger than 8 cm (extending beyond the colimator’s size limits).
- Keloids previously treated with other radiotherapy modalities.
- Pregnant and breastfeeding patients.
- Collagen diseases (scleroderma and lupus).
- Patients already involved in other clinical trials in the 30 days before the start of the study.
- Use of steroids and/or immunosuppressant drugs in the last 6 weeks.

The patients underwent a two-step preoperative radiotherapy consultation: first, to establish the patient’s eligibility for the radiotherapy; then, to finalize the treatment settings.

The patients were enrolled in the trial once both the surgeon and the radiotherapist agreed on the combined treatment. At this stage, the procedure would be scheduled ($T_0$).

### Table 1. Patient Characteristics and Lesions Distribution

| Patient-level Information | No. patients | Gender | Age (y) | Ethnicity |
|---------------------------|--------------|--------|---------|-----------|
| No. lesions               | 21           | Men    | 35 (IQR: 26–43) | White 10 (62.5%) |
| No. lesions by patient    | 1 (1–1.25)   | Women | 35 (26–43) | Hispanic 3 (18.75%) |
| Median (IQR)              | 1–3          |        |         | Black 3 (18.75%) |
| Min – Max                 |              |        |         |            |

Data are described as absolute and relative frequency (%) if not otherwise specified.

### Treatment Protocol

The surgical treatment consisted of the radical excision of the keloid from healthy tissue, and a tension-free wound repair with direct suture or local skin flaps.

Each excised keloid underwent a histological examination to differentiate true keloids from hypertrophic scars.

All of the surgical procedures were performed by the same surgeon.

The setting and staff organization allowed for the application of the IORT within a time frame no longer than 45 minutes after the completion of the surgical procedure and before the wound dressing.

After the suture removal, all of the patients followed the unit’s standard surgical wound care postoperative protocol. This required a gentle, scar longitudinal massage with sulfur mucopolysaccharide enriched moisturizing cream; the localized application of a silicone sheet; and a full sunblock cream for 9 months. The patients, where practicable, were advised to wear compressive elastic garments during this period, also.

### Radiotherapy Treatment Modality

The surgical wounds were irradiated with an intraoperative mobile electron linear accelerator, specifically designed for unshielded operating rooms (LIAC, SIT, Sordinafort Technology S.p.A., Italy). The device is provided with a motor-powered mobile arm-unit that allows for five degrees of freedom, similar to a human limb. The unit is operated by a cable-connected remote-control rack. The accelerator allows for four electron energy output levels: 6, 8, 10, and 12 MeV. Radiotherapy was set at the level of 6 MeV to prevent the maximal dose of electrons going deeper than 5 mm under the skin.

The electrons are collimated by sterile cylindric polymethylmethacrylate applicators (available in different
diameter sizes, ranging from 3 to 10 cm), that are placed in direct contact with the skin. The appropriate diameter of the applicator was determined by including the surgical wound size, plus at least a 1.5 cm distance from the cylinder base circumference, to take into account the beam fringe (Fig. 1).

A 2.2-mm-thick lead compound sheet (density 3.75 g/cm³) was placed on the surrounding healthy skin, to spare underlying organs any risk from unnecessary irradiation. A single dose of 12 Gy was delivered to the entire surgical bed in all of the cases.

The IORT was carried out within an average time of 27 minutes.

**Scar Evaluation Methods**

The outcomes were evaluated with the association of three subjective scar assessment tools:

1. POSAS.
2. Modified Vancouver Scar Scale (VSS).
3. Modified Common Terminology Criteria for Adverse Events v. 4.0 (CTCAE) for skin and subcutaneous tissue disorders.

**Modified Patient and Observer Scar Assessment Scale**

The modified POSAS Patient Scale is a six-item scar self-assessment scale with a score range of 1–10, where the lower the score, the better the scar feature. The markers assessed are pain, itching, color, stiffness, thickness, and irregularity. The lowest score corresponds to a situation similar to that of the normal skin (ie, normal pigmentation, no itching), whereas the highest one represents the largest difference from normal skin (ie, the worst imaginable scar or sensation). The total score can range from 6 to 60. Unlike in the original POSAS Patient Scale, the “overall opinion” assessment is not included in the sum score. All of the items are easy to understand and the observer provides the essential information, to allow an easy and reliable patient self-assessment, without influencing the patient’s choice.

The original POSAS Observer Scale consists of seven items (vascularity, pigmentation, thickness, relief, pliability, surface area, and overall opinion).

In our study, these seven were reduced to four by excluding the following parameters: “surface area,” “relief” (as these were not considered pertinent to a linear and fresh surgical scar resulting from the keloid excision), and “overall opinion.”

The vascularity was assessed through the intensity of the capillary refill after blanching the scar with a sheet of plexiglass; the same technique allowed for the assessment of the pigmentation after the contribution of vascularity was eliminated; the thickness was assessed with a caliper as the average distance between the epidermal surface of the scar and the epidermal level of the surrounding healthy skin; pliability was measured as the suppleness of the scar assessed by wrinkling the scar between the thumb and index finger. All items were scored on a scale ranging from 1 (like normal skin) to 10 (worst scar imaginable). The sum of the scores of the four items resulted in the POSAS Observer total score. All of the parameters were always compared with those of the normal skin on a comparable anatomic site.

The examiner assessed and scored the scar without being influenced by the patient’s perception.

The total score of both scales was simply calculated by summing up the respective total scores.

**Modified Vancouver Scar Scale**

The VSS is an internationally recognized scale for the evaluation of burn-related scars, and was subsequently modified, by various authors, to better apply to the specific requirements of the different studies.

In our study, we used an original scar assessment scale derived from the original VSS by blending its different items into four descriptive grades of increasing scar severity: normal (grade 1), slightly hypertrophic (grade 2), frankly hypertrophic (grade 3), and keloid (grade 4) (Table 2).

**Modified Common Terminology Criteria for Adverse Events v. 4.0 (CTCAE v.4.0) for Skin and Subcutaneous Tissue Disorders**

The CTCAE v.4.0 for skin and subcutaneous tissue disorders is universally accepted in the field of radiation therapies to specifically evaluate the side effects of the radiotherapy. Within the original CTCAE v. 4.0 for skin and subcutaneous tissue disorders, a selection of 14 of 34 parameters was used in our study: dry skin, erythema multiforme, skin pain, fat atrophy, erythrodema, photosensitivity, pruritus, rash acneiform, skin atrophy, skin hyperpigmentation, telangiectasia, toxic epidermal necrolysis, rash maculo-papular, urticaria. The score range was 0–5, where the lower the score, the better the
Follow-up

Patients were reviewed by the surgeon at day (±2) 5 \(T_5\), 10 \(T_{10}\), 15 \(T_{15}\), 30 \(T_{30}\), 45 \(T_{45}\), 60 \(T_{60}\), 90 \(T_{90}\), 120 \(T_{120}\), 150 \(T_{150}\), and 180 \(T_{180}\) days after treatment \(T_W\).

The radiotherapy follow-up was performed 180 days after treatment \(T_W\).

At each follow-up visit, medical photographs were taken and the rating scales were filled in.

Statistical Analysis

Numeric variable distributions are described by median [75th–25th percentile (interquartile range, IQR)], categorical variable distribution, and absolute and relative (\%) frequency. The presence of statistically significant differences between time points was tested by the Wilcoxon signed rank test for paired samples under the null hypothesis of no variation. The Bonferroni-corrected significance level was set to 0.0045 (\(\alpha = 0.05/\text{number of tests performed} = 11\)). Statistical procedures were performed by the R software tool (http://www.r-project.org/).

RESULTS

All of the variables of the modified POSAS Patient Scale demonstrated an overall improvement after the treatment (pain \(P < 0.05\); all of the remaining variables \(P < 0.0045\)).

Regarding levels of pain recorded, the absence of pain was demonstrated in about half of the sample at the preoperative time. The remaining half of the patients reported a pain score ranging from 4 to 8, with a prevalence of the score 6. In the early postoperative period, a trend of a progressive decrease in pain was observed, and a reasonable wellness status was reported around 2–4 weeks postoperatively in the whole sample. At 45 days after the treatment, although the number of patients with reduced pain increased, some individuals reported a progressive increase of pain. Such a trend settled within 2–3 months postoperatively, yielding a stable absence of pain at 6 months, in 87.5% of cases. Only two scars, in the same patient, displayed a recurrence of pain, whose intensity was recorded as moderate.

Twelve patients (75%) recorded a degree of relatively severe itching before the treatment. In the immediate postoperative period, all of these 12 patients noted a substantial reduction or disappearance of itching. Across the whole sample (16 patients in total), the most satisfactory wellness status was reported around 2 months postoperatively. At 6 months, although 14 of 16 (87.5%) patients had a stable remission of itching, in the remaining two (12.5%), the symptom recurred with a lesser intensity versus the preoperative condition.

During the immediate postoperative period, as expected, a dramatic decrease of the scar thickness was observed in all cases. Following this, a slight thickening was observed, and this figure remained stable till the end of the study in 16 of 21 (76.2%) scars. Five (23.8%) scars displayed a more substantial increase of thickness starting 2 months after the treatment. Similarly, at the 2 month mark, this trend was noted with regard to both stiffness and irregularity measurements.

All of the scars displayed color anomalies at the preoperative time. All of them settled back almost to normal at the immediate postoperative time. A progressive moderate worsening of the scar color was reported between 2 and 4 weeks postoperatively, with a peak at 30 days after the treatment. Then, a progressive improvement was observed till the end of the study, when the color settled back almost to normal in 17 of 21 scars (80.9%).

The modified POSAS Observer Scale displayed a statistically significant overall improvement in all of the variables \((P < 0.0045)\) after the treatment.

Both vascularization and pigmentation scores substantially matched the color ones in the POSAS Patient Scale. At the end of the study, both items featured much better scores versus the preoperative condition, with the scars showing a color almost similar to that of the normal skin. The scores for thickness and pliability in the POSAS Observer Scale substantially overlapped the same categories in the POSAS Patient Scale, too.

The modified VSS demonstrated a statistically significant overall improvement in 19 of 21 scars (90.4%) after the treatment \((P < 0.0045)\). The scores, after an early postoperative improvement, demonstrated a progressive onset of a pathological scar trait between 45 and 60 days after the treatment. Nevertheless, at the end of the study, a favorable settling was observed in the majority of the cases. In detail, 15 of 16 patients (93.7%), corresponding to 19 of 21 keloids (90.48%), demonstrated an improvement after the treatment, whereas the remaining patient (6.2%) with two keloids (9.5%) experienced a recurrence with the same score as the pretreatment condition.

The results in the modified POSAS and VSS scales are summarized in Table 3 and Supplemental Digital Contents 1–3. (See figure, Supplemental Digital Content 1, which displays bubble plots describing the modified...
POSAS scales distribution at different time points. The diameter of each dot and color shade is proportional to the number of patients by time and value. The average value of lesions by patient was the unit of the analysis. See figure, Supplemental Digital Content 2, which displays bubble plots describing the modified POSAS Observer scales distribution at different time points. The diameter of each dot and color shade is proportional to the number of patients by time and value. The average value of lesions by patient rounded to the closest integer was the unit of the analysis.

Within the modified CTCAE v.4.0 for skin and subcutaneous tissue disorders, only 3 variables (erythema multiforme, pain of skin, skin hyperpigmentation) displayed statistically significant results (\(P < 0.05\)). An improvement in erythema multiforme and pain of skin was reported in all of the cases after the treatment. However, a light, circle-shaped skin hyperpigmentation was observed in 4 of the 21 (19%) keloids treated, in three of 16 patients (18.7%). The latter adverse effect was likely to have been related to the size and shape of the collimator used, and this effect regressed in all of the cases within 5 months.

The results in the modified CTCAE v.4.0 for skin and subcutaneous tissue disorders are summarized in Table 4.

The association between parameter variations and demographic characteristics (age, gender, ethnicity) was also evaluated, and no statistically significant associations were reported.

The follow-up period for the sample as a whole, was 6 months. Although a few of the patients were monitored for longer, no additional changes in their 6-month outcome were observed.

### Table 3. Scales Variation between T₀ and T₁₀ Time Points

| Scale | Median (IQR) | T₀       | T₁₀      | T₁₀ – T₀    | P    |
|-------|--------------|----------|----------|-------------|------|
| Patient |              |          |          |             |      |
| POSAS pain | 3 (1:6)     | 1 (1:1)  | –1 (–4:0)| 0.0037*    |
| POSAS itching | 7 (6:9)   | 1 (1:3)  | –5 (–7:4)| 0.0004*    |
| POSAS color | 8 (5:9)    | 2 (1:2)  | –6 (–7:5)| 0.0005*    |
| POSAS stiffness | 8 (7:9)   | 2 (1:2)  | –7 (–8:6)| 0.0017*    |
| POSAS thickness | 7 (6:9)   | 1 (1:2)  | –5 (–8:4)| 0.0001*    |
| POSAS irregularity | 9 (7:10) | 2 (1:2)  | –7 (–8:4)| <0.0001*   |
| Observer |              |          |          |             |      |
| POSAS vascularity | 6 (5:7)   | 2 (1:3)  | –4 (–5:2)| 0.0002*    |
| POSAS pigmentation | 6 (4:7)  | 2 (2:2)  | –3 (–4:2)| <0.0001*   |
| POSAS (obs) thickness | 6 (5:8)  | 2 (1:3)  | –4 (–6:2)| <0.0001*   |
| POSAS pliability | 6 (5:8)   | 1 (1:2)  | –4 (–6:5)| <0.0001*   |
| Modified Vancouver scar scale | 4 (4:4)  | 1 (1:3)  | –2 (–3:1)| 0.0001*    |

*\(P < 0.0045\), based on the Bonferroni correction for multiple testing (11 tests were performed).

Scale = analyzed scale; \(T₀\) = scales distribution at \(T₀\) described by median value (25\% – 75\% percentile, IQR); \(T₁₀\) = scales distribution at \(T₁₀\) described by median value (IQR); \(T₁₀ – T₀\) = scales variation between \(T₀\) and \(T₁₀\) described by median value (IQR). Lesions were the unit of the analyses.

### Table 4. Scale Variations in the Modified CTCAE v.4.0 for Skin and Subcutaneous Tissue Disorders between T₀ and T₁₀ Time Points

| Variable | Median (IQR) | T₀       | T₁       | T₁ – T₀    | P    |
|----------|--------------|----------|----------|------------|------|
| Dry skin | 0 (0)        | 0 (0)    | 0 (0)    | 1          |      |
| Erythema multiforme | 0 (1)      | 0 (0)    | –0.5 (1) | 0.024*     |
| Fat atrophy | 0 (0)      | 0 (0)    | 0 (0)    | N.V.       |
| Skin pain | 1 (0.12)    | 0 (0.12) | –1 (1)   | 0.010*     |
| photosensitivity | 0 (0)     | 0 (0.25) | 0 (0.25) | 0.149      |
| Pruritus | 1 (1)        | 1 (1)    | 0 (0)    | 1.000      |
| Erythroderma | 0 (0)      | 0 (0)    | 0 (0)    | N.V.       |
| Rash–acneiform | 0 (0)     | 0 (0)    | 0 (0)    | N.V.       |
| Rash–maculopapular | 0 (0)    | 0 (0)    | 0 (0)    | N.V.       |
| Skin atrophy | 0 (0)      | 0 (0)    | 0 (0)    | N.V.       |
| Skin hyperpigmentation | 0 (0.25) | 1 (1.12) | 0.5 (1)  | 0.012*     |
| Toxic epidermal necrolysis | 0 (0)   | 0 (0)    | 0 (0)    | 1          |
| Telangectasia | 0 (0)      | 0 (0)    | 0 (0)    | N.V.       |
| Urticarial | 0 (0)       | 0 (0)    | 0 (0)    | N.V.       |

*\(P < 0.05\), based on the Bonferroni correction for multiple testing (18 tests were performed).

\(\text{Median} \pm \text{IQR}\) of each variable’s distribution at T₀, T₁, of the absolute difference between T₁ and T₀; \(P\) value = \(P\) value from the Wilcoxon signed rank test.
DISCUSSION

Keloids are dermal fibroproliferative disorders characterized by an overproduction of extracellular matrix and excessive deposition of collagen, of which the fine mechanisms of formation and progression are still unclear and poorly understood. They occur after dermal injury in genetically susceptible individuals, do not regress spontaneously, and tend to recur after surgical excision. Furthermore, they cause both relevant physical and psychological distress in the affected individuals. Different approaches have been reported in the literature for the treatment of keloids, with extremely variable success rates, according to individual studies. The practice of treating keloids using radiotherapy has been in existence since the early 20th century. The rationale behind the treatment is based upon the cell DNA damage, which occurs following the ionization of a tissue’s molecular structure. The radiant energy directly targets certain key cellular structures, such as DNA, cell membranes, and intracellular organs, and also indirectly harms the cell by producing highly reactive free radicals in the water cytosol. An adequate combination of the radiation dose and exposure time in keloids was demonstrated to induce the fibroblast senescence following the stop of the cell cycle.

Given the high recurrence rate following separate, individual surgical and radiotherapy treatments, the idea of potentially combining the two approaches was, in the 1940s and 1950s, seen as a proactive strategy. Technological innovations in radiotherapy have made electron beam irradiation and brachytherapy available, as a means to minimize posttreatment side effects.

Our study demonstrated that the combination of surgery and radiotherapy with IORT allowed for favorable results in 15 of 16 patients (93.7%) and in 19 of 21 keloids (90.5%) (Figs. 2, 3). No significant influence related to the demographic characteristics of the analyzed patients (age, gender, ethnicity) was observed. The only two relapses observed were in the same White patient, suggesting a strong individual predisposition for keloid recurrence, independent of ethnicity (Figs. 4, 5).

In our sample, a statistically significant improvement was demonstrated after the combined treatment, in all of the variables in the modified POSAS Patient and Observer scales and in the modified VSS scale. No major complications such as desquamation, ulceration, fibrosis, or atrophy were reported during the trial. The only adverse effect was observed in five treated sites of three patients and consisted of a circular area of light hyperpigmentation that was correlated to the shape and size of the collimator that was used. Such hyperpigmentation spontaneously regressed within 5 months. All the patients considered this treatment option favorably as the entire procedure was completed in one single session.

Fig. 2. Keloid in the upper sternal region. A, Pre-treatment view. B, Posttreatment view.
Undoubtedly, this treatment has some downsides, too. Not every institution can afford the cost of the mobile linear accelerator and its maintenance. Also, the procedure itself is time-consuming in the operating theatre and requires the close interaction of trained surgical and radiotherapy staff, with a further increase in the overall cost.

Keloids remain a difficult-to-treat disorder due to their multi-factorial etio-pathogenesis. The favorable outcomes in our study might confirm the relevant role of the early bio-humoral cascade after tissue injury, and encourage further investigation along this research line with larger samples.

Nevertheless, all of the data in our study consistently confirm that the critical time for the development of a pathological trait in the wound-healing process is around 2 months after the trauma. The local delivery of radiation is likely to interfere with the cell phase of the immediate wound healing process, while the onset of pathological scarring might be related to a later molecular mechanism. Due to the pilot nature of the trial, several limitations affected the study, such as the small sample size; the absence of a randomization or a control sample comparison; the changes and adaptations of the validated scales, and the lack of objectively measurable assessments.
CONCLUSIONS

The combination of surgery and immediate post-operative collimated electron radiotherapy with IORT demonstrated favorable results in 90.5% of the cases. Consequently, we feel the early time-related, favorable effects of postoperative radiotherapy on keloids merit further investigation with emphasis on the early cellular phase of the wound healing process. This could allow us to better define the mechanisms of keloid formation in predisposed individuals.

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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