Lesion Site Is the Key Prognostic Factor for Keloid Patients Receiving Surgery With Adjuvant Radiotherapy

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Background: Keloid is a benign tumor with high recurrence rate; accordingly, complete surgical excision with adjuvant radiotherapy is one of the most effective treatments. This study reviewed outcomes of keloid patients receiving surgery and adjuvant radiotherapy in Kaohsiung Medical University Hospital.

Materials and Methods: All patients received radiation dose with 15 Gy, with their first radiotherapy within 24 hours after surgical excision. The end points were recurrence rate and local recurrence-free interval (LRFI), defined clinically as palpable gross tumor over the treatment site and duration from the last day of radiotherapy to disease recurrence.

Results: From May 2017 to July 2020, 32 patients with 40 keloid lesions were included. The mean age for these patients was 37.6 years, and the median follow-up time was 15.3 months. The overall recurrence rate was 52.5%, and the median LRFI was 9.7 months. Recurrence rates for males and females were 46.7% and 56% (P = 0.567), respectively; for head and ear, chest, shoulder, and upper extremities, and abdomen and back were 12.5%, 61.5%, 63.6%, and 62.5% (P = 0.093); for lesions over 20 cm² and below 20 cm² were 62.5% and 50% (P = 0.527); and for megavoltage electron beam and kilovoltage photon beam were 56.7% and 40% (P = 0.361), respectively. Patients were further classified into 2 groups by lesion sites, which showed lower recurrence rate (P = 0.011) and longer LRFI (P = 0.028) with lesions over the head and ear than other sites.

Conclusions: We found that lesion site might be a prognostic factor for keloid recurrence. Adjuvant radiation dose escalation for high-recurrence risk areas (other than the head and ear) might be required.

Key Words: keloid, lesion site, recurrence, radiotherapy, surgery

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To further understand the factors that might affect the local control rate of keloid, keloid patients receiving surgical excision with adjuvant radiotherapy in Kaohsiung Medical University Hospital were reviewed.

**MATERIALS AND METHODS**

The radiation oncology department database was used to include keloid patients receiving surgical excision and postoperative radiotherapy, those having completed a radiotherapy course, received first radiotherapy within 24 hours after surgery, and received radiation dose with 15 Gy in the study. Patients having been followed up for less than 6 months and/or aged less than 18 years were excluded. The primary end point was recurrence rate, and recurrence was defined clinically as palpable gross tumor over the original treatment site, with or without subjective symptoms such as pain or pruritus, with secondary end point set as local recurrence-free interval (LRFI) defined as duration from the last day of radiotherapy to disease recurrence. Patients were evaluated by following up at the outpatient department or by telephone if they were unwilling to visit the department due to the COVID-19 pandemic. Recurrence was determined by same plastic surgeon and radiation oncologist.

Tumor excisions for these patients were performed mainly by plastic surgeons with or without flap reconstruction. Adjuvant radiotherapy was performed with electron beam of 6 or 9 million electron volts by Linear accelerator or bolus or photon beam of 50 kV by Xoft Axxent Electronic Brachytherapy (eBx) System (San Jose, CA). Treatment fields encompassed the keloid surgical suture line with an expansion of the surrounding margin of 1 to 1.5 cm. Radiation dose was 15 Gy in 3 fractions. After treatment, patients were followed up at the plastic surgery outpatient department for wound care.

Two end points were analyzed with multiple variants such as sex, tumor location, tumor size, and treatment modality. In univariate analysis, \( \chi^2 \) test was used for recurrence rate and Kaplan-Meier method for LRFI. In multivariate analysis, logistic regression was used for recurrence rate and Cox regression method for LRFI. Values of \( P < 0.05 \) indicated statistical significance. All statistical analyses were performed by SPSS software for Windows (SPSS version 19; IBM Corp). The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-SV[I]-20210071).

**RESULT**

From May 2017 to July 2020, 32 patients with 40 keloid lesions were included from our radiation oncology database (Table 1). The mean age for these patients was 37.6 years (range, 18–64 years), and the median follow-up time was 15.3 months (range, 6.57–43.57 months). The overall recurrence rate for these 40 lesions was 52.5% (21/40). The univariate analysis revealed that lesion site was a significant factor affecting recurrence rate (Table 2). The lesions on the head and ear had a lower recurrence rate than those on other sites. In univariate analysis for LRFI, lesion site was also a significant factor, with the longest recurrence-free interval occurring in lesions on the head and ear (Table 3). The lesion site had a significant impact on the duration of LRFI.

| Characteristic                        | No Recurrence, \( n \) (%) | Recurrence, \( n \) (%) | \( P \) |
|---------------------------------------|-----------------------------|-------------------------|-------|
| Sex, lesions                          |                             |                         | 0.567 |
| Male                                  | 8 (53.3)                    | 7 (46.7)                |       |
| Female                                | 11 (44)                     | 14 (56)                 |       |
| Lesion site, lesions                  |                             |                         | 0.093 |
| Head and ear                          | 7 (87.5)                    | 1 (12.5)                |       |
| Chest                                 | 5 (38.5)                    | 8 (61.5)                |       |
| Shoulder and upper extremities        | 4 (36.4)                    | 7 (63.6)                |       |
| Back and abdomen                      | 3 (37.5)                    | 5 (62.5)                |       |
| Lesion site, lesions                  |                             |                         | 0.011 |
| Head and ear                          | 7 (87.5)                    | 1 (12.5)                |       |
| Others                                | 12 (37.5)                   | 20 (62.5)               |       |
| Size, lesions                         |                             |                         | 0.527 |
| Over 20 cm\(^2\)                      | 3 (37.5)                    | 5 (62.5)                |       |
| Under 20 cm\(^2\)                     | 16 (50)                     | 16 (50)                 |       |
| Radiotherapy modality, lesions        |                             |                         | 0.361 |
| Electron beam                         | 13 (43.3)                   | 17 (56.7)               |       |
| 50 kV photon                           | 6 (60)                      | 4 (40)                  |       |

**TABLE 1. Patient Characteristics**

| Characteristic                        | \( n \) (% ) |
|---------------------------------------|--------------|
| Age, mean ± SD, y                     | 37.6 ± 12.6  |
| Median (range) follow-up, mo          | 15.3 (6.57–43.57) |
| Sex, lesions                          |              |
| Male                                  | 15 (40)      |
| Female                                | 25 (60)      |
| Lesion site, lesions                  |              |
| Head                                  | 2 (5)        |
| Ear                                   | 6 (15)       |
| Shoulder                              | 4 (10)       |
| Chest                                 | 13 (32.5)    |
| Back                                  | 4 (10)       |
| Abdomen                               | 4 (10)       |
| Upper extremities                     | 7 (17.5)     |
| Size, lesions                         |              |
| Over 20 cm\(^2\)                      | 7 (17.5)     |
| Under 20 cm\(^2\)                     | 33 (82.5)    |
| Radiotherapy modality, lesions        |              |
| Electron beam                         | 30 (75)      |
| 50 kV photon                           | 10 (25)      |
| Recurrence                            |              |
| Yes                                   | 21 (52.5)    |
| No                                    | 19 (47.5)    |

**TABLE 2. Univariate Analysis for Recurrence Rate**

| Characteristic                        | Average LRFI, mo | \( P \) |
|---------------------------------------|------------------|-------|
| Sex, lesions                          |                  |       |
| Male                                  | 25.4             |       |
| Female                                | 14.9             |       |
| Lesion site, lesions                  |                  |       |
| Head and ear                          | 37.3             | 0.181 |
| Chest                                 | 11.8             |       |
| Shoulder and upper extremities        | 13.7             |       |
| Back and abdomen                      | 13.9             |       |
| Radiotherapy modality, lesions        |                  |       |
| Electron beam                         | 20.3             |       |
| 50 kV photon                           | 16.2             |       |

**TABLE 3. Univariate Analysis for Local Recurrence-Free Interval**

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52.5%, and the median LRFI was 9.7 months. Because of the small number for lesions from different body locations, we grouped these lesions into head and ear (n = 8), chest (n = 13), shoulder and upper extremities (n = 11), and abdomen and back (n = 8).

Recurrence rates for males and females, respectively, were 46.7% and 56% (P = 0.567); for head and ear, chest, shoulder and upper extremities, and abdomen and back were 12.5%, 61.5%, 63.6%, and 62.5% (P = 0.093); for lesions over 20 cm² and below 20 cm² were 62.5% and 50% (P = 0.527); and for megavoltage electron beam and kilovoltage photon beam were 56.7% and 40% (P = 0.361) (Table 2).

Local recurrence-free intervals (months) for male and female were 25.4 and 14.9 (P = 0.623); for head and ear, chest, shoulder and upper extremities, and abdomen and back were 37.3, 11.8, 13.7, and 13.9 (P = 0.181); for lesions over 20 cm² and below 20 cm² were 13.9 and 22.4 (P = 0.642); and for megavoltage electron beam and kilovoltage photon beam were 20.3 and 16.2 (P = 0.886) (Table 3).

Univariate analysis showed no significant difference for recurrence rate and LRFI, but there was a trend in lesion site where the head and ear had lower recurrence rate than other locations. According to this result, lesions were further classified into 2 groups with head and ear and others, which showed lower recurrence rate (P = 0.011) and longer LRFI (P = 0.028) with lesions over the head and ear than other locations (Table 2, Table 3, Fig. 1).

Multivariate analysis showed that keloid location was a significant prognostic factor in these 4 variants for recurrence rate (P = 0.042) when lesions were classified into 2 groups according to univariate analysis results (Table 4), but not for LRFI (Table 5).

**DISCUSSION**

Surgical excision with adjuvant radiotherapy has been used for treating keloid for decades. Radiotherapy mainly targets proliferating fibroblasts thereby inducing cell apoptosis, senescence, and cell cycle arrest,15 which decreases the amount of keloid fibroblast within normal limits16 and lowers the recurrence rate of keloid. Mankowski et al17 reviewed 72 articles, and they found that adjuvant radiotherapy offered an

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**TABLE 4. Multivariate Analysis for Recurrence Rate**

| Characteristic        | 95% Confidence Interval | P   |
|-----------------------|-------------------------|-----|
| Sex                   | 0.139–3.058             | 0.588|
| Lesion site (2 groups*)| 0.010–0.923             | 0.042|
| Lesion size           | 0.200–5.764             | 0.934|
| Radiotherapy modality | 0.345–11.548            | 0.440|

*Two groups: head and ear, others.

**TABLE 5. Multivariate Analysis for Local Recurrence-Free Interval**

| Characteristic        | 95% Confidence Interval | P   |
|-----------------------|-------------------------|-----|
| Sex                   | 0.357–2.475             | 0.899|
| Lesion site (2 groups*)| 0.017–1.042             | 0.055|
| Lesion size           | 0.373–2.966             | 0.923|
| Radiotherapy modality | 0.211–2.456             | 0.600|

*Two groups: head and ear, others.
additional 15% control rate compared with surgery alone, whereas other studies also showed better local control with surgery and adjuvant radiotherapy for keloid patients. According to Japanese treatment guidelines for keloid by Ogawa et al, recurrence rate has no dose-dependent relationship when biologically equivalent dose (with α/β ratio of 10) over 30 Gy is used, so most facilities use adjuvant radiotherapy for keloid with 15 Gy in 3 fractions.

This study analyzed 40 keloid lesions treated by surgical excision and adjuvant radiotherapy with variants of sex, tumor location, tumor size, and treatment modality. For sex, some studies have shown that males have higher recurrence rate and less improvement after treatment, but no difference for recurrence rate between males and females was found in this study. For tumor size, lesions were separated into larger and smaller ones with the cut point of 20 cm² according to the Japan Scar Workshop Scar Scale, which is similar to previous data. Our study showed that superficial x-ray had higher recurrence rate without significant difference (P = 0.527). For treatment modality, a previous study showed the same recurrence rate for electron and superficial x-ray, and our study also showed no significance difference for recurrence rate (P = 0.361) and LRFI (P = 0.886) between these 2 treatment modalities, which is similar to previous data. Our study showed that superficial x-ray had a trend of lower recurrence rate, but this might be due to selection bias for more head and ear lesions in the superficial x-ray group. Mankowski et al found that brachytherapy had the lowest recurrence rate (15%) compared with electron and x-ray radiotherapy (23%), but brachytherapy is performed intermittently mostly, which is more invasive for patients, and medical staff are more easily exposed to radiation. For lesion site, a previous study showed higher recurrence rate at the anterior chest wall, scapular and suprapubic regions, and lower recurrence rate over the ear lobe and other sites. Ogawa et al presented the recurrence rate of 38.3% in high-tension areas with adjuvant electron beam radiotherapy and 5.7% to 17.3% in other areas, which also provides clinical evidence that tension might play a role in diversity of recurrence. Second, different thicknesses of reticular dermis over different locations might affect keloid recurrence, because reticular dermis is where keloid-genic inflammatory cellular activities take place, and different thicknesses of reticular dermis might contain different amounts of keloid fibroblasts. Third, different properties of ECM or inflammation cells might have some impact on keloid recurrence. According to a study by Butzelaar et al, mechanical properties of skin vary with anatomic location and depend largely on composition of ECM. These differences are also found in vascularization and resident immune cell populations, and site-specific variations in ECM properties as well as macrophage numbers exist. They also found that predilection sites for keloid formation contain larger amounts of collagen compared with nonpredilection sites.

All the aforementioned reasons might play a role in the mechanism of keloid formation. Finally, different activity of fibroblasts from different body sites might affect keloid recurrence. Previous studies have shown that keloid fibroblast is more sensitive to inflammatory factors than normal skin fibroblast. To find whether different activity of fibroblasts from different body sites exists, we compared cell survival of keloid fibroblasts from our patients with normal fibroblast by the MTT method after irradiation to culture medium, which showed higher survival rate for keloid fibroblasts. Keloid fibroblasts were found to be more radiosensitive than normal fibroblasts, indicating that difference of radiosensitivity exists between fibroblasts. The authors are now collecting keloid fibroblasts from different body sites in an attempt to determine whether fibroblasts from different body sites play a role in keloid recurrence while also trying to find the specific proper radiation dose for keloid over different body sites.

There are some advantages in our study. Enrolled patients all received the same radiation dose, having the first radiotherapy within 24 hours after surgery as per the suggestion of previous studies. Local recurrence-free interval was also analyzed as our end point, which provided more information than previous studies. Unfortunately, the limitations in our study include a small sample of only 40 lesions with relatively short follow-up time, as well as limited record of adverse effects able to be accessed. Patients showed higher recurrence rates than other studies, especially for lesions over sites other than the head and ear (Table 6), and we assume this might be due to other studies excluding patients with high risk factors such as multiple lesions or family history.

### TABLE 6. Literature Review of Keloid Patients Receiving Surgery and Adjuvant Radiotherapy

| Year, Author | Radiation Dose (Gray) | Results |
|--------------|-----------------------|---------|
| 2006, Slemp and Kirschner | 15–20 | Control rate 65%–99% |
| 2009, Ogawa et al | Not mentioned | Response rate 67%–98% |
| 2015, Lee and Park | 12–18 | Nonrecurrence rate 81.1% |
| 2015, Shen et al | 18 | Nonrecurrence rate 90.4% |
| 2018, Renz et al | 12–20 | Nonrecurrence rate 94.4% |
| 2019, Petrou et al | 15 | Nonrecurrence rate 94% |
| 2019, Ogawa et al | 15 for ear, 15 for neck, 15 for chest wall, 15 for scapula, 10–15 for ear, 20 for chest wall, 20 for scapula | Nonrecurrence rate 85% |
| 2019, Hsueh et al | 20 for high tension area, 12 for other area | Nonrecurrence rate 83% |

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and so on. Other than this, some patients did not receive regular follow-up for proper postoperative treatment and follow-up care because keloid is a benign disease, especially while the hospital was under the pandemic of COVID-19, which might possibly have increased the risk of recurrence. Last, because this is a retrospective study, some data are missing. Bias might also exist, especially when determining recurrence and LRFI.

Recently, studies have found lower recurrence rate with radiation total dose over 20 Gy or biologically equivalent dose (with α/β ratio of 2) over 60 Gy, especially for lesions over the anterior chest, scapula, and suprapubic areas. Higher doses can provide better local control, but might carry high risk of acute and delayed adverse effects, including secondary malignancy. We are now modifying our adjuvant radiation dose to keloid lesions over different body sites in order to determine site-specific dosages for keloid patients by clinical and basic research.

To conclude, in the retrospective review, it was found that lesion sites might be a prognostic factor for keloid recurrence. Keloid tumors over the head and ear area achieved good local control rate (87.5%) with adjuvant radiotherapy with 15 Gy. Adjuvant radiation dose escalation for high-recurrence risk areas (other than head and ear) might be required.

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