Is Radiation Therapy for Keloids Acceptable? The Risk of Radiation-Induced Carcinogenesis

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Background: Keloids have been treated by using radiation for over a century, and it is currently suggested that keloids are best treated by a combination of surgery and postoperative radiation therapy, although randomized controlled trials testing this are still lacking. However, plastic surgeons tend to avoid radiation therapy for keloids for fear of inducing malignant tumors. Thus, the authors searched for previous reports of associations between carcinogenesis and keloid radiation therapy, and examined the evidence-based opinions of radiation oncologists regarding the acceptability of using radiation to treat keloids.

Methods: A computerized literature search was carried out using PubMed that included citations from MEDLINE and PubMed Central between 1901 and March of 2009. The following search terms were used: "keloid(s)," "hypertrophic scar(s)," "radiation," "radiation therapy," "radiotherapy," "carcinogenesis," "carcinoma," "cancer," "complications," and "side effects." Moreover, the references for each report were also retrieved.

Results: The authors located five cases of carcinogenesis (i.e., fibrosarcoma, basal cell carcinoma, thyroid carcinoma, and breast carcinoma) that were associated with radiation therapy for keloids. However, it was unclear whether an appropriate dose of radiation was used and whether sufficient protection of surrounding tissues was provided. Moreover, a questionnaire study of radiation oncologists around the world revealed that approximately 80 percent considered radiation to be acceptable for treating keloids.

Conclusions: The authors conclude that the risk of carcinogenesis attributable to keloid radiation therapy is very low when surrounding tissues, including the thyroid and mammary glands, especially in children and infants, are adequately protected, and that radiation therapy is acceptable as a keloid treatment modality. (*Plast. Reconstr. Surg.* 124: 1196, 2009.)

Keloids have been treated by using radiation for over a century. Freund reported in 1898, 3 years after x-rays were first detected by Wilhelm Conrad Röntgen, that hypertrophic scars could be restored to normal skin by roentgen treatment.[1] Subsequently, in 1901, Harris reported that keloids could be treated preoperatively by roentgen exposure. Freund then, in 1909, described the first combination treatment protocol that involved surgery and postoperative roentgen treatment.[1] Thereafter, different radiation protocols were developed for keloid treatment. Some of these involved external irradiation using superficial[2–11] and orthovoltage[12–14] x-rays (photons) and β-rays (electron beams).[11,12,15–21] Others were brachytherapies using β-rays (phosphorus-32[22] or strontium-90/yttrium-90[23,24]) and γ-rays (cobalt-60[25] or iridium-192[26–32]). In addition, radiation therapy has been used as a monotherapy[11,23,29] or in combination with adjuvant therapy delivered preoperatively[33] or postoperatively.[1–10,12–21,23–32] However, it is generally believed that keloids are best treated by a combination of surgery and postoperative radiation therapy, although it should be noted that this notion has not yet been tested by randomized controlled trials. Although it is difficult to determine the effectiveness of irradiation for the

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treatment of keloids because of variations between studies in patient race, age, and sex; keloid area and size; radiation source and dose; result assessment strategies; and follow-up term, the reported postoperative radiation response rates (the rate of recurrences regardless of patient satisfaction) generally fall between 67 and 98 percent.[1–10,12–21,23–32]

Thus, it is currently suggested that keloids can be treated effectively by a combination of surgery and radiation therapy. However, plastic surgeons tend to avoid radiation therapy for keloids for fear of inducing malignant tumors. Thus, we searched for previous reports of carcinogenesis associated with radiation therapy for keloids and examined the evidence-based opinions of radiation oncologists regarding the acceptability of radiation therapy for keloids.

PATIENTS AND METHODS

A computerized literature search was carried out using PubMed, which includes citations from MEDLINE and PubMed Central between 1901 and March of 2009. The following search terms were used: "keloid(s)," "hypertrophic scar(s)," "radiation," "radiation therapy," "radiotherapy," "carcinogenesis," "carcinoma," "cancer," "complications," and "side effects." Moreover, the references of each report were also retrieved.

RESULTS

We located five cases of carcinogenesis (i.e., fibrosarcoma, basal cell carcinoma, thyroid carcinoma, and breast carcinoma) that were associated with radiation therapy for keloids. However, in all cases, it was unclear whether an appropriate dose of radiation was used and whether sufficient protection of surrounding tissues was provided.

In 1953, Horton et al.[34] reported the case of a 40-year-old woman who received 10.5 Gy of radiation therapy after excision of keloids on her lower lip and chin. Ten years after the radiation treatment, a basal cell carcinoma was detected in her recurred keloids. Although Horton et al.[34] suspected that the basal cell carcinoma was induced by the radiation treatment of the keloids, the radiation source and dose that were used were not precisely detailed. Because this case involved the carcinogenesis of epithelial components, it appears that this may be a case where the surrounding normal tissues underwent carcinogenesis rather than the keloid itself undergoing a malignant change (given that keloids can be considered as a dermal fibroproliferative disorder).

In 1963, Biemans[35] reported the case of a 23-year-old woman who had received 22 Gy of radiation therapy (low-energy 80-kV x-rays) after excision of keloids on her thigh. Three and a half years later, a fibrosarcoma was found on the same region. It is possible that this may be a case where the keloid itself underwent a malignant change, although Biemans[35] made the point that an interval of 3½ years may be too short for the production of malignancy.

In 1982, Hoffman[36] reported the case of an 11-year-old boy who had received 6 Gy of radiation therapy (low-energy, 50-kV x-rays) after excision of keloids and W-plasties on his chin. Eight years later, he developed medullary thyroid carcinoma. Although Hoffman stated in his report[36] that it cannot be excluded that the radiation therapy caused the carcinoma, Botwood et al.[37] subsequently reported that Hoffman, in personal communications, expressed some doubt about whether the treatment had actually caused the disease.

In 1988, Bilbey et al.[38] reported the case of a woman who had received a burn injury at the age of 4 years, after which keloids developed on her chest (these could also have been postburn hypertrophic scars; it should be noted that radiation therapy is no longer recommended for postburn hypertrophic scars). At the age of 13 years, the patient underwent keloid excision and radiation therapy. At the age of 36 years, she was diagnosed with pleural fibrous mesothelioma and ipsilateral infiltrating ductal breast carcinoma. She had no history of asbestos exposure, but her grandmother also had a breast carcinoma. However, because the patient reported experiencing nausea and vomiting as acute complications of the radiation therapy at age 13 and reported growth impairment of her right breast as a late complication, Bilbey et al.[38] speculated that the patient may have been treated with an inappropriate radiation dose that exceeded the dose of 5 to 10 Gy, which was the standard dose in those days.

In 1999, Botwood et al.[37] reported the case of a 57-year-old woman who had received radiation therapy for chest keloids when she was 26 years old. The radiation therapy involved the application of 13 Gy delivered in five fractions (low-energy, 75-kV x-rays). When the patient was 54 years of age, she developed infiltrating ductal breast carcinoma. However, this patient had received hormone replacement therapy for 8 years before this diagnosis. Moreover, her keloids were described as "postburn chest keloids," which suggests that these scars could also have been postburn hypertrophic scars, for which radiation therapy is no longer considered suitable.

In summary, of the five reported cases in which carcinogenesis has been linked to radiation therapy for keloids, only one (the fibrosarcoma case)[35] may have resulted from a malignant change of the keloids. The remaining four cases (basal cell carcinoma,[34] thyroid,[36] and breast carcinoma[37,38]) may have involved carcinogenesis in surrounding normal tissues. However, in the latter four cases, it is unclear whether an appropriate dose of radiation was used and whether sufficient protection of the tissues surrounding the keloids was provided.

DISCUSSION

Attitude of Radiation Oncologists toward Radiation Therapy for Keloids

In 1998, radiation oncologists in facilities located around the world were asked for the first time to complete a questionnaire regarding their views on whether radiation therapy is suitable for the treatment of 28 benign diseases, including keloids.[39] Briefly, a questionnaire was sent out to 1348 institutes. In the first round, answers were obtained from 314 institutes (23.3 percent). After that, the same questionnaire was sent out again to the institutes that had not responded in the first round, which finally led to a total of 508 respondents (37.7 percent) in two rounds. The keloid-specific results of this questionnaire are summarized in Figure 1. In total, 78 percent of the 508 respondents stated that radiation therapy is acceptable for the treatment of keloids[39] (keloid had the top acceptance rate among 28 benign disorders). In particular, of the 77 facilities in the United States and Canada, over 90 percent deemed radiation therapy for keloids to be acceptable.[39] Moreover, of the 99 facilities in central Europe (Austria, Germany, and Switzerland), the 52 facilities in Asia and Oceania (Australia and New Zealand), and the 21 facilities in Africa, the Middle East, and South and Central America, over 80 percent approved of radiation therapy for keloids.[39]

A large-scale survey has not been performed since this study. However, in 2007, Leer et al.[40] stated that there is sufficient support for keloid radiation therapy, from the standpoint of the current clinical evidence of radiotherapy in well-selected nonmalignant disorders. Thus, the general attitude of radiation oncologists seems not to have changed since the survey, although this worldwide survey will need to be updated.

Plastic surgeons generally tend to avoid radiation therapy for benign tumors such as keloids for fear of inducing malignant tumors. However, the widespread approval of radiation therapy for keloids by radiation oncologists that was described above suggests that this fear may be largely unfounded, and that radiation therapy can be considered to be relatively safe for the treatment of keloids.

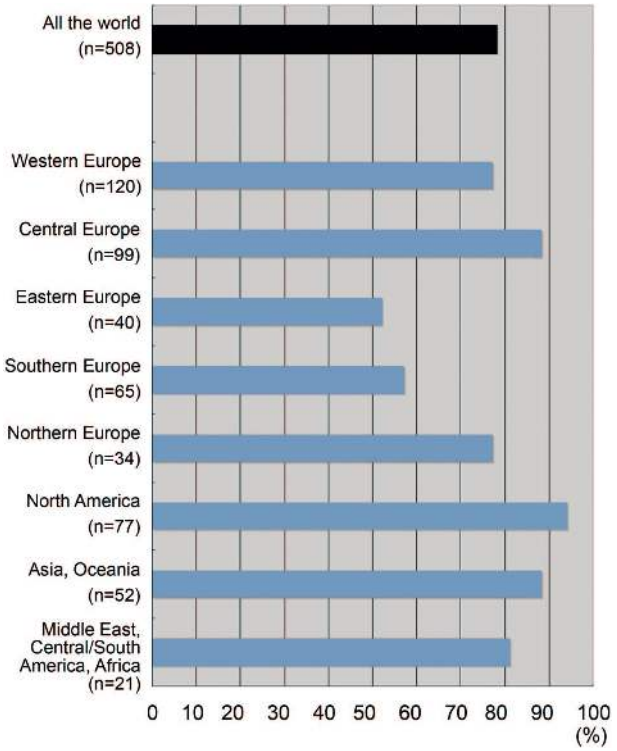

Fig. 1. Summary of the opinions of radiation oncologists globally regarding the acceptability of radiation therapy for keloids (from Leer JW, van Houtte P, Davelaar J. Indications and treatment schedules for irradiation of benign diseases: A survey. *Radiother Oncol.* 1998;48:249–257). Radiation oncologists from 508 facilities around the world participated in a questionnaire survey. Of these respondent facilities, 78 percent stated that radiation therapy is acceptable for the treatment of keloids.

Complications of Radiation Therapy for Keloids

Since the target of radiation therapy for keloids is the skin, especially the dermis, the reaction of the skin to radiation therapy is of primary interest. Acute skin reactions to radiation therapy occur during the first 7 to 10 days after treatment and are characterized initially by erythema that then progresses to pigmentation, epilation, and desquamation, particularly when higher doses are applied.[41] Subacute and late complications occur several weeks after radiation therapy. Scarring, permanent pigmentation, depigmentation, atrophy, telangiectasis, subcutaneous fibrosis, and necrosis can develop and progress

for long periods.[41] Other potential complications of radiation therapy for keloids include wound dehiscence in a postoperative radiation setting and, importantly, carcinogenesis. However, whereas previous reports of radiation therapy of keloids have noted the occurrence of erythema,[18,19,21] pigmentation,[3,4,18,21,29] depigmentation,[7,18,19] and telangiectasia,[19,29] ulceration and wound dehiscence have not been mentioned.

With respect to the complication rate, Speranza[42] reported a survey of 234 patients (European, 53.1 percent; African, 19.8 percent) who received surgery and 15 Gy in three daily 5-Gy fractions of orthovoltage radiation therapy. For acute toxicity outcomes, 54.2 percent reported skin redness (38.5 percent mild, 42.3 percent moderate, and 17.3 percent severe), 24 percent reported skin desquamation, 10.4 percent reported wound dehiscence, and 6.3 percent reported infection. For late toxicity outcomes, 27 percent reported the presence of telangiectasia and 62 percent reported permanent skin color changes (either hypopigmentation or hyperpigmentation). In this survey, on a satisfaction scale ranging from 1 to 10, 60 percent reported a satisfaction level of greater than or equal to 8. Telangiectasia was the most significant predictor of low satisfaction (≤ 3) ($p < 0.005$).

Evidence-Based Opinions Regarding Carcinogenesis Associated with Radiation Therapy for Keloids

The International Commission on Radiological Protection in 2007 recommended that radiation-sensitive tissues, such as the mammary gland and thyroid, should be protected as much as possible to prevent the development of radiation-induced breast and thyroid carcinomas.[43] However, the cutaneous malignant changes that could potentially arise from radiation therapy, such as the basal cell carcinoma reported by Horton et al.,[34] can be detected early and consequently rapidly cured. This suggests that, when surrounding tissues are adequately protected, the risk of radiation-induced carcinogenesis is low. Indeed, Leer et al.[40] have stated that "the risk of the induction of secondary tumors had been overestimated in the past." However, they also commented that it is important that radiation therapy should be performed with an appropriate source, dose, and irradiation field, and only after the patient is informed according to the "standard opinion of radiotherapy of nonmalignant disorders" and consents to the treatment.[40] There is sufficient evidence that radiotherapy is effective for keloids and that there should be no age limit on this treatment, provided alternatives are not effective.[40]

However, we should not deny the possibility that radiation therapy for keloids could induce secondary tumors, and patients should not be forced to receive radiation therapy. Moreover, additional caution is still required with regard to the radiation treatment of young patients, and children should only be treated in emergency situations where no other therapeutic solutions seem possible.[40] Supporting this position are the studies by Lundell et al.,[44,45] who showed that people irradiated as infants suffer an increased relative risk of radiation-induced carcinogenesis in the thyroid and mammary gland. This was determined by two cohort studies, one examining thyroid cancer rates in 14,351 patients who were irradiated as infants[44] and the other measuring breast cancer rates in 9675 individuals who were irradiated as infants.[45] It was observed that for thyroid cancer, the increased relative risk per gray was 4.92 (95 percent confidence interval, 1.26 to 10.2) per person-year gray; this effect lasted for at least 40 years after the irradiation.[44] In addition, for breast cancer, the increased relative risk increased significantly over time after exposure, with the increased relative risk at 1 Gy at 50 or more years after exposure being 2.25 (95 percent confidence interval, 0.59 to 5.62).[45] These observations indicate that X Gy irradiation to Y percent area of the thyroid and mammary gland in infancy results in a $1 + 4.92*X*0.01*Y*$ and $1 + 2.25*X*0.01*Y*$ fold increase in risk of radiation-induced carcinogenesis, respectively. Thus, for example, 20 Gy of irradiation to 5 percent of the thyroid or mammary gland results in a 5.92- and 3.25-fold increased risk of thyroid and breast carcinogenesis, respectively. Thus, it is essential that the thyroid and mammary gland should be protected when children are to be irradiated, and that radiation therapy for keloids should not be used in infancy when it is likely that these organs will be exposed to radiation.

Optimal Dose for Radiation Therapy for Keloids

From our review of the literature,[2–32] it appears that for maximal efficacy and safety, postoperative radiation therapy for keloids in adults should involve the application of 10 to 20 Gy delivered as 5 Gy per fraction. When Kal and Veen[46] calculated the biologically effective doses of various radiation regimens for keloid therapy by using the linear-

quadratic concept, they observed that for biologically effective dose values of less than 10 Gy, the recurrence rate decreased as a function of biologically effective dose, whereas for biologically effective dose values exceeding 30 Gy, the recurrence rate was less than 10 percent.[46] A biologically effective dose value of 30 Gy can be obtained with, for instance, a single fraction dose of 13 Gy, two fractions of 8 Gy, three fractions of 6 Gy, or a single dose of 27 Gy administered at low dose rate.[46] Kal and Veen also concluded that the radiation treatment should be administered within 2 days after surgery.

In fact, a total dose of 15 Gy has been used the most frequently according to the survey by Leer et al.[39] Moreover, it has also been recommended in the literature that site-dependent dose protocols should be made available for the treatment of keloids, as these protocols may adjust the total dose of radiation that should be delivered. This concept is based on the analysis of the therapeutic outcomes showing that the recurrence rates in the sites with high stretch tension, such as the chest wall, and the scapular and suprapubic regions were statistically higher than in sites without high tension.[18] For example,[21] the following radiation doses and procedures were suggested as useful: (1) for the anterior chest wall, shoulder-scapular region, and suprapubic region, 20 Gy in four fractions over 4 days; (2) for the ear lobe, 10 Gy in two fractions over 2 days; and (3) for other sites, 15 Gy in three fractions over 3 days. However, these protocols should be optimized according to the race of the patient.

CONCLUSIONS

We conclude that the risk of carcinogenesis from keloid radiation therapy is very low when performed with adequate doses and under conditions that provide adequate protection of surrounding tissues, including the thyroid and mammary glands, especially in children and infants, and that radiation therapy is acceptable as a keloid treatment modality. However, randomized controlled trials of radiation therapy will be necessary to determine the influence of such factors as the patient's race, age, and sex; keloid area and size; radiation source and dose; result assessment strategies and follow-up term; and response rates, recurrence rate, and patient satisfaction.

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