Review Article

Radiation Therapy in Keloids Treatment: History, Strategy, Effectiveness, and Complication

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Abstract

Objective: Radiation therapy combined with surgical excision was considered as one of the most effective treatment plans for keloid lesions. However, there was no unanimity found over present literatures regarding the issue on optimized treatment strategy for keloids. We here provide a comprehensive review over this issue and emphasize on the influencing factors.

Data Sources: The data analyzed in this review were searched from articles included in PubMed and EMBASE databases.

Study Selection: The original articles and critical reviews discussing the application of radiation therapy in keloids treatment were selected for this review.

Results: The application of radiation therapy has transitioned from simple superficial X-ray irradiation to brachytherapy. Furthermore, several factors including radiation type, dose, fraction, interval, and complications were reviewed, and the results revealed that these factors were significant toward clinical outcome at various levels.

Conclusions: Both past and present evidence support the idea that combination therapy of radiation and surgical therapy is safe and feasible. However, the optimization of treatment strategy was based on different radiation types and should take dose, fractions, interval, and complications into consideration, which will then decrease the rate of recurrence and increase the level of satisfaction.

Key words: Combination Therapy; Keloids; Radiation Therapy

Introduction

Derived from the word in Greek meaning "crab's claw," keloids, continuously annoyed surgeons as one of the major postoperative complications and sequelae of trauma. The prevalence varied both in different areas and races.[1-3] Without known precise incidence and prevalence rate, keloids, whether primary or secondary, tend to occur in individuals with a family history and darker skinned race such as Africans and Asians.[4] Due to the partial understanding of the underlying keloid formation mechanisms, the warranted clinical solutions are still absent. Multiple modality treatment strategies such as combining simple surgical excision to therapeutic approaches were clinically applied; the outcomes were yet promising. Publicly known, surgical excision of keloids alone is considered as an ineffective treatment due to its recurrence rate of 45–100%,[5] which then promotes the need for combination therapy. As one of the adjuvant therapies, local postoperative radiation treatment offers us a potentially better result based on scientific and empiric evidence. Based on a review published in 2006, postoperative radiation followed by surgical excision will result in a control rate of 67–98%.[6] Interestingly, the overall control rate and relapsing rate varied in different literatures due to diversified lesion sites and inadequate histological confirmation. Various literatures recommended other treatments such as intralesional steroid injection, primary subtotal surgical excision, reconstructive surgical techniques, and postoperative irradiation. In the meta-analysis published in 2016, triamcinolone injection and radiation were both considered outstanding treatments for keloids without significant difference.[7] However, some of

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the patients relapsed after triamcinolone injections were then treated with adjuvant radiation therapy. Other methods such as laser treatment, silicone gel, pressure therapy, or 5-FU were either proven ineffective or still lack of strong clinical evidence. Here, we present a comprehensive and thorough review on radiotherapy and keloids, mainly discussing the history, different modalities, and complications.

History and Overview: From Superficial X-ray Irradiation to Brachytherapy

De Bearman and Gourgerot have first described the treatment of keloids using superficial X-ray irradiation in 1906, other detailed reports on using X-ray as a treatment method for keloids surfaced around 1920 and 1933.[8,9] Postoperative radiation was first recommended for the prevention of keloids recurrence, and around the 1940s to 1950s, it was described as a proactive approach.[10-14] However, even when radiation therapy has not been proven to be effective in the 1960s, and when treating keloids and hypertrophic scars both remained as a problem, preventive X-ray irradiation has already been widely accepted and practiced.[15] The dose-dependent approach was later disclosed. In one preliminary study in New York, similar modality (100 kVp, 1.0–2.0 mm. target-skin distance) radiation was reported in treating keloids.[16] It turned out to be a predictable keloid behaving manner which demonstrated a 60% (18/30) regrowth at controlling rate and a nonsignificant time-dose relationship at controlling symptoms. However, another study conducted in Melbourne indicated potential dose-dependent results.[17] Furthermore, low-dose superficial X-ray irradiation within 48 h postoperatively has proven to prevent keloid relapse.[18] Gradually, further well-designed studies have supported the comparative effectiveness of combination therapy between surgical keloidectomy and postoperative X-ray irradiation therapy.[19,20] Another consecutive study of 78 keloids from 40 patients with at least 1-year follow-up revealed that immediate postoperative X-ray therapy resulted in a decrease in recurrence rate per lesion compared to surgical excision alone.[21] Furthermore, more long-term retrospective studies on keloids detailed the importance of irradiation postoperatively. Kovalic and Perez, followed 75 patients with 113 keloids for a mean time of 9.75 years, demonstrated an overall control rate of 73%.[22] Many other studies on site-specific keloids or a conglomerate of keloids or hypertrophic scars largely supported the effectiveness of irradiation as an adjuvant therapy. One study presented a total recurrence rate of 2.4% (9/375) out of 393 keloid sites on 250 patients within 50 years.[23] Cosmetic results such as sizes, pigment, margins, and textures were also thoroughly documented in the retrospective study. X-ray irradiation was gradually replaced by the technological advancement of electron beam irradiation. Up to a dose of 15 Gy, irradiation given to the patients after surgical excision of hypertrophic scars successfully prevented hypertrophic scars or keloids formation and recurrence.[24] Relative lower recurrence rate was also reported after technology mainstay transition[25,26] among Asians with keloids. Later, high-dose-rate (HDR) brachytherapy provided us with an alternative external radiation therapy, particularly for patients who are resistant to adjuvant external beam radiation therapy or corticosteroids, which resulted in a recurrence rate ranging from 4.7% to 21%.[27-29] As another salvage treatment for treating resistant keloids, HDR brachytherapy combined with repeated excisions significantly demonstrated a lower recurrence rate of refractory keloids. Excellent cosmetic results earn a satisfactory rate of 86.9%, except for observed skin pigmentation and telangiectasia.[30] Therefore, the results from numerous studies demonstrated a significantly lower recurrence rate (ranging from 12% to 28%), proving the effectiveness of postoperative irradiation therapy.[31]

Different Radiations, Keloids, and Strategies

Different radiation

Rapid progress was made along with universal application of radiation therapy in treating various diseases, boosted by advances in imaging techniques, computerized treatment planning systems, and radiation therapy machines.[32] There has not been any consensus formed in standardized treatment despite the International Clinical Recommendations on Scar Management contrived in 2002.[33] A total of four facilities are currently employing the current radiation therapy, including radioactive isotope carrying α, β, γ, and neutrons particles, generating X-rays at various energy level, electron accelerators, and heavy particle accelerators. Accompanied by initiation of adjuvant therapy in treating scars or keloids in the 1910s, X-ray was considered the exclusive method to deliver energy to the targeted sites for more than 50 years. However, two major methods in delivering ionizing radiation recently (electrically charged particles) comprised external beam radiation and internal radiation or brachytherapy, to deposit energy toward targeted areas. Higher dosage and normal tissue sparing were later achieved by the emergence of advanced linear accelerators, and these techniques were characterized clinically to include different levels of linear energy transfer, higher DNA damage, and normal tissue sparing.

Comparison between different types of radiation therapy can be seen. Effectiveness, unconstraint, feasibility, and safety were all taken into consideration. The concept of biological effective dose enabled this cross-sectional comparison. In actuality, most of the current literature recommendations were based on retrospective studies other than prospective studies. In addition to that, the difficulty in clinical distinction between keloids and hypertrophic scars and the lack of histopathological confirmation decrease the validity of these studies.[34] The absence in keloid histological confirmation might be explained by the near-zero rate of malignancies or dysplasias.[35] Therefore, due to the limitations, there are no preferred treatments of keloids in specific sites. Treatments such as superficial and orthovoltage X-rays (photons) therapy, brachytherapy (β-rays using phosphorus-32[22]/strontium-90, γ-rays using cobalt-60[25]/iridium-192),[30]

and electron beam (β-rays)[36] were all proven to be helpful, even at different levels, suggesting a great improvement in postoperative irradiation protocols happened in last few decades. Effectiveness and complications were both taken into consideration.

X-ray

Since radiation therapy was applied for treating keloids, X-ray, as the very important photon radiation, had continuously acted as the special role in treating keloids. To date, X-ray still acts as an adjuvant role in new combination therapies.[37,38] X-ray was generated by an electron-exciting device and customarily delivers superficial low-dose radiation toward the lesions. Originally, radiation therapists use 100–400 keV; however, low-energy X-ray resulted with more acute skin side effects. It gradually became outdated but still within the application for some special cases. Excluding the early time when strict radiation therapy protocol, scar evaluation, and defined complications were absent, especially before 1970, effectiveness was simply evaluated by recurrence rate. Insufficient follow-up time and evaluating items might cause statistical bias. On the other hand, another main concern was the patient's compliance. A total dose of 15 and 20 Gy dose can decrease recurrence rate down to minimum of 8% under relatively thorough review,[18,21,39] regardless of lesion sites. Some studies reported that recurrence rate lower than 5% might be attributed to the lack of histological confirmation and insufficient follow-up duration. As one of the principle complications, hyperpigmentation rate was reported around 30%.[40] The other major postirradiation complications including hypopigmentation, delayed wound healing, chronic swelling, chondritis, dermatitis, and skin ulceration were believed to be infrequent. Historically speaking, lower X-ray-induced acute skin complications reported in early literatures compared with other radiation treatment can be credited to its shorter duration and lower dosage. The majority of studies on X-ray ionizing irradiation treatment in combination with previous treatments on keloids have these primary limitations: various patients' compliance, diversified lesion sites, filtration usage, shorter follow-up duration, and inadequate evaluation items. Moreover, due to homogeneous earlobe sites, 60 kV and 120 kV beams achieved homogeneity of two separated but close lesions treatment, with the satisfaction rating of 4.7/5.[41]

Electron beams

Keloids, benign superficial skin lesions, can thus be treated with superficial ionizing irradiation and displace the traditional X-ray treatment. Narrower and more concentrated radiation depositions became more appropriate for treating local superficial lesions such as keloids. Organized dose distribution curve demonstrated that the steeper the dose fall-off is, the more condensed radiation deposition and less damaged normal tissue.[42] After the radiation therapy, the bowel irradiation dose detected was quite higher when using kilo-voltage superficial X-ray and photons compared with 6-MeV electron, which is currently used as the primary radiation therapy treatment universally, particularly in superficial skin tumors. As one of the particle radiations, external beam radiation became the main therapy treatment for keloids since the early 1990s, accompanied by progress of radiation therapy. The overall recurrence rate reported in literatures varied from 8% to 29.3%, due to different composition of keloids sites and chronological reasons,[31,43,44] with the total dose of 15–20 Gy within 3 fractions. Additionally, if the surgeons use improved tension-decrease suturing methods, the relapse rate can reach as low as 2.2% in treating smaller (<3 cm) chest keloids.[45] Electron beam treatment does not always cause severe acute skin complications and induce adverse effects <10%[36,46] when compared to X-rays. Electron beam was thought to be appropriate for treating flat and bulky lesions due to its radiation coverage surface.[47] With the help of a bolus, reduced irradiation dose could achieve excellent clinical outcome. Another study which replaced the spoiler with the bolus had also proved to be feasible and safe.[48] Worth mentioning, linear accelerator had achieved better clinical outcomes due to its improved surgical skills and postoperative wound care, such as superficial subcutaneous suture.

Brachytherapy with iridium-192

The estimated recurrence rate of 20% after X-ray or electron beams had bothered the surgeons,[40,49] while brachytherapy with iridium-192 provided physicians an alternative with more concentrated irradiation toward the lesions. Increased sparing of normal tissues from radiation therapy has made brachytherapy the choice of treatment. Alternatively, low-dose-rate (LDR) and HDR were both considered as tolerable and effective when compared to previously mentioned therapy methods. The rate of recurrence after treated by brachytherapy with iridium-192 on average was lower than 13% after the year 2000.[29,50] On the contrary, some literatures which have reported recurrence rate over 20% might be due to rigorous exclusion criteria such as necessitating histological confirmation or ruling out hypertrophic scars.[51] In addition, the lower radiation volume possibly explains the superiority of brachytherapy over external beam when controlling adverse effects. HDR brachytherapy achieved the lowest mean recurrence rate, better than LDR brachytherapy, which might be explained by shorter interval between surgery and HDR brachytherapy (usually within 24 h, shorter than over 20–72 h).[52] HDR brachytherapy was tolerable and patients do no need to be hospitalized, which is necessary for LDR brachytherapy due to lead-coated facilities. To decrease unnecessary damage to normal tissues, dosimetry was recommended. The economic issue was the major concern when decisions had to be made between brachytherapy and other traditional radiation therapy. A custom-made mold guarantees a uniform dose to homogenize the dose distribution, generating a recurrence rate of 99% for primary keloids.[53]

Different interval

Several literatures reported that the postoperative interval between surgery and radiation therapy negatively correlates

with clinical outcome.[54-57] The suggestions from studies conducted in Germany indicated that shorter postoperative interval managed lower rate of relapses.[58,59] Irradiation within 24 h after surgery was widely employed. Doubling the duration of interval from 25.9 h to 43.5 h might produce significant diminution of apoptotic cells and reduced keloid fibroblasts number decrease.[60] The discordant results revealed that the irrelevance of results and postoperative interval was mostly due to relative longer duration between 3 and 14 days, exceeding the cutoff value.[22,61] Most of these studies conducted before the 1990s; the shift of radiation technique from superficial to iridium brachytherapy might cause significant bias. What's more, "the sandwich" protocol composed of preoperative radiation, extralesional excision, and postoperative radiotherapy was considered successful with lower rate of complication and recurrence, with favorable clinical outcome.

Different fractions

Fractionation enabled normal skin cells recovering and keloid fibroblasts transition from radioresistant phase into radiosensitive phase. Conventionally, 3 fractions were considered more reliable than single-high-dose scheme,[43] becoming the standard scheme widely. However, hypofractionated radiation therapy control rate was gradually reported surpassing the traditional fraction significantly.[44] Single-fraction electron beam irradiation of a total dose of 10 Gy was performed in UK, US, and Asia on patients who were refractory to other treatment modalities except for radiotherapy, demonstrating no recurrence and well tolerance.[24,46,62] As an experienced single-center treating keloids with postoperative radiation therapy, a total dose of 18 Gy given a week apart in 2 fractions was considered feasible and safe with only <10% chronic adverse effects. Therefore, at a given dose, relative fewer fractions were more suitable for keloid lesions.

Different doses

Notably, first reported in 2005, biological effective dose is the crucial concept in comparison between different radiation type and facilities. Achieving cross-talk between different radiation therapies, biological effective dose enabled the radiation therapist setting up dose-response models and assessing the consecutive radiation efficacy even radiation therapy type or schedules have changed. A modified probit model setup later which found that lower radiation dose could control the keloids in various sites.[43] It seemed easy for us to understand the very simple principle: higher the doses, better the results.[63,64] Before the year 2000, 15 Gy in total was considered as optimal dose with minimal adverse effect.[31] However, even due to enhanced skin pigmentation, itching and pain relief have encouraged escalation of doses. Biological effective doses for postoperative radiotherapy were crucial for setting up therapeutic regimens and schedules. A total dose >10 Gy can accordingly reduce the recurrence rate, while a total dose >30 Gy will limit the recurrence rate down to <10%. An optimal schedule should at least include a total dose over 30 Gy less than 3 fractions within 48 h postoperatively reported by Kal and Veen.[44,60] However, the more accurate normalization method drew very different summaries. Less than 19.2 postoperative electron beam irradiation could achieve 90–95% favorable control in earlobe sites.

Different sites

The application of radiation therapy in different localizations of keloids extended from earlobe keloids to sternal keloids, most of which demonstrating relative reduction in recurrence rate.[65] We truly have obtained conflicting data even when different kinds of radiation regimen modalities were normalized. Due to fewer tensions, keloids on earlobes, head, and neck were generally considered easier to treat compared to other sites such as trunk (especially chest) and limbs. A dose-response analysis verified the fact that earlobe keloids have significantly lower risk of recurrence after similar radiation therapy.[43] Radiation therapists also decreased earlobe controlling dose from 15 Gy 3 fractions down to 10 Gy 2 fractions. The diminution of radiation dose might also explain the reason why no prominent adverse effects were observed in next 6 years as expected.[66] It might be due to the similarity of growth pattern of fibroblasts in different anatomical sites.[60] In many cases on chest and trunk, we still observe a low rate of relapse or recurrence at relative high doses,[45,57,62] which indicated that higher doses or shorter postoperative interval outweigh anatomical sites distinction in postoperative radiation therapy. Reduced surgical tension might be an another contributing factor.[45]

Effectiveness and Satisfaction

Problematic keloids not only cause function disturbance but also esthetic flaw and keloid-associated symptoms such as itching and pain. Pain and itching were 91% and 96% relieved, respectively, after combination therapy, summarized by Sakamoto *et al*.[67] Elimination of keloid lesion usually eliminates symptoms. Some studies have mentioned that only half of the cases relapsed within 6 months postoperatively, 88 cases relapsed within 24 months, which indicated that 48-month follow-up is a necessary duration for a thorough review on effectiveness and satisfaction.[23,51] Even though there was a lack of follow-up duration, endpoint of these studies was always local recurrence, ranging from 4% to 40% as mentioned before. However, we have noticed that the objective findings in the follow-up examination override satisfaction with treatment results evaluated by patients. Notably, in one study utilizing electron beam radiotherapy treating postoperative keloids, 12 patients demonstrated unsatisfactory feelings about the clinical outcome, of which only two had relapsed.[54] On the other hand, 33% of patients with relapses in this study achieved fulfillment due to symptom relief. As for postradiation complications, telangiectasia was the most common significant predictor of low satisfaction as reported by Speranza *et al*.[68] More studies described the gap between objective assessment and subjective assessment based on esthetic aspects.[69] Therefore, overestimation of cosmetic

clinical outcome should be emphasized before performing the serial treatments. Another study had underlined the symptom relief (often >90%) superior to recurrence or esthetic disfigurement, which explained that why patients with recurrence still displayed satisfaction.[70] Quality of life and social discomfort have greater impact on patients' satisfaction.

Complications

Complications or adverse effects of postoperative radiation therapy could be divided into two categories: acute skin reactions and late complications. In the thorough review offered by Sakamoto *et al*., the overall positive adverse effect rate was accordingly 19% and apparently dose related.[67] Besides, age and etiology were considered having significant impact on positive adverse rate.[67] With respect to the complication rate, various factors were taken into consideration, including different sites, doses, and patients' susceptibility. However, even some distinctions were identified in some literatures, evidence-based predisposing factors for complications were not determined. Normal tissue shielding is pivotal to avoiding carcinogenesis and preventing other skin complications, functionally and cosmetically.

Secondary tumors and radiation therapy

As a local control therapy, radiation therapy for keloid treatment is well-tolerated with several acute or chronic side effects.[71] As one of the major concerns which patients might have, many authors have addressed this issue forming inconclusive partial consensus. In X-ray epoch, null carcinogenicity rate was mentioned in previous studies before 1990,[23] providing supportive evidence for potential continual application and larger dosage. Skin cancers arising from keloid sties were rarely reported and sometimes corrected by second communication with the authors.[72,73] Ogawa *et al.* have published a paper as an exhaustive review regarding this issue.[74] Most of these singular anecdotal case reports indicated suspicion, the relationship between radiation therapy and carcinogenesis over 10 years later, early in the 20th century. Only one case reported by Biemans,[75] which is a patient having fibrosarcoma derived on the same sites of excised keloid tissue might indicated over irradiation-related carcinogenesis. Other cases were considered having other risk factors outweighing the radiation therapy history, which involved like previous symptoms and over-extended radiation fields.[76,77] In 2007, Leer *et al*. reported a conclusive statement that radiotherapy for keloids was a nonmalignant disorder.[78] Another study even offered us an effective way to calculate the risk generating secondary malignancy to explain the extremely low rate of its occurrence.[64] Notably, contradictory results might be due to the lack of long-term follow-up, including response rate and recalling bias. However, even for some cases within follow-up over 10 years, no secondary malignancies were observed[31,58,79] in recent studies. Even no recent reports demonstrating the so-called carcinogenetic risk, radiation oncologists were still very cautious in treating benign tissues such as keloids.[80] To prevent the emergence of keloid scars after repeated cesarean section, which would cause function disturbance and cosmetic disfiguration, postoperative electron beam radiotherapy was considered safe and feasible, with only tiny fraction of radiation reached the ovaries, while satisfactory rate reached 96% and relative good control rate was achieved.[81] In our more than 10 years of clinical experience utilizing combination therapy as treatments for keloids, no single malignant transformation was observed. Normal tissue shielding should emphasize in various ways, which would be discussed later. Besides, especially for brachytherapy irradiation, some pigmentation like hypopigmentation might be largely avoided by strict intradermal positioning of wire, diminishing the irradiation.[70]

Other complications

Except for radiation-induced carcinogenesis, several postirradiated complications were reported in many retrospective literatures. Ionizing irradiation varies in different studies in radiation type, dosage, and intensity. As local, low-dose, and superficial treatment, systemic radiation therapy produces severe complications such as nausea and vomiting, gastrointestinal disturbance, infertility, fibrosis, lymphedema, and heart disease. Therefore, chronological complications can be divided into two categories: early or late complications. Early toxic outcome or complications cover skin redness, skin peeling, wound dehiscence, and infection. However, late complications include permanent color change (previously hyper- or hypo-pigmentation), telangiectasia, and the presence of scar after treatment. Chronic radiodermatitis aspect was another major concern. Studies indicated that overall irradiation more than 21 Gy might raise the possibility of skin color change.[64] Therefore, some surgeons chose dose lower than 20 Gy to avoid this issue, which still remained controversial.[67] ^{90}Sr beta radiation therapy probably bought more adverse effect rate than other irradiation.[69] Skin redness was considered the primary acute skin adverse effects of various severities in over 50% of patients, which was mentioned in other literatures.[68,74] As for late-onset complications, 62% of color permanent change and 27% telangiectasia in the same study also indicate esthetic discontentment. To be noted, telangiectasia rate varied extensively among different studies with different schemes from 0% to over 20%.

Conclusions

Deemed as the last resort for keloid treatment, combination therapy of surgical excision and adjuvant radiation therapy has proven to be safe and feasible. The relatively low α/β ratio of lower fractions and higher doses was presumed as the choice of treatment. The long history of application of radiation therapy combined with surgical excision in treating keloids has proven its feasibility and safety to a very large extent. The more precise lesion-targeted irradiation with more normal tissue sparing and more esthetic improvement will ensure better patient satisfaction and clinical outcome. Finally, as an experienced single-center treating keloids consistently over 20 years,[36] we recommend that smaller

lesions and fewer skin tensions might achieve smaller relapse or recurrence rate. Meanwhile, regardless of different sites, sizes, and skin tensions, high biological effective dose was accomplished through a linear particle accelerator, as known as electron beam. Early radiation intervention should be applied within 48 h after the surgery, ideally within 24 h. The dose in one single fraction should be >12 Gy to end with reliable clinical outcome, but <20 Gy might cause more adverse effects. As for controversial debate over the interval duration, in contrast to Sakamoto *et al.*,[67] we do recommend two fraction within 1 week as a standardized method to guarantee lower recurrence rate and less adverse effects.

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Conflicts of interest

There are no conflicts of interest

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