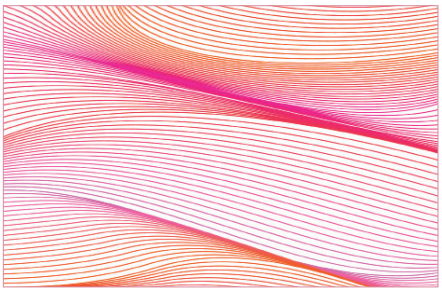

Keloids: A Review of Etiology, Prevention, and Treatment

by UDAYAN BETARBET, MD and TRAVIS W. BLALOCK, MD

Dr. Betarbet is with the Emory University School of Medicine in Atlanta, Georgia and the Division of Plastic Surgery at The University of Texas Medical Branch in Galveston, Texas. Dr. Blalock is with the Department of Dermatology at Emory University School of Medicine in Atlanta, Georgia.

J Clin Aesthet Dermatol. 2020;13(2):33–43

ABSTRACT

Keloids are abnormal scars that cause significant emotional and physical distress in patients when inadequately treated. Keloid formation is theorized to occur as a result of an imbalance between an increased synthesis of collagen and extracellular matrix and decreased degradation of these products. Inflammatory mediators—namely, transforming growth factor beta—have been proposed to influence the dysregulation of collagen remodeling in the scar healing process. Though limited, current knowledge of keloid pathophysiology has guided clinicians to explore novel therapies for keloid prevention and treatment. In addition to conducting research refining the use of common therapies, such as steroids and radiation, clinicians have evaluated the potential of anti-inflammatory and chemotherapeutic molecules to suppress keloid recurrence. Procedural focused therapies, such as cryotherapy and lasers, have also found a role in reducing keloid symptomatology. The purpose of this report is to examine the current literature and review the mechanisms of action, efficacy, and side effects of different keloid therapies. Despite the growing literature investigating reliable methods for keloid management, there are no standardized guidelines or treatment protocols supported by academic governing bodies. Stronger evidence with high-fidelity randomized clinical trials will be needed to determine the optimal therapy regimens for keloids.

KEY WORDS: Collagen, extracellular matrix, keloid, scar

The primary goal in the clinical management of skin wounds, whether unintended or iatrogenic, is to aid the natural dynamic process of wound healing to re-establish baseline skin integrity, function, and aesthetics. Scar formation occurs over distinct phases, including hemostasis, inflammation, proliferation, and remodeling.[1] After injury to the skin, exposed elements in various layers of the skin, in addition to vasoactive and inflammatory chemical mediators, contribute to clot formation for hemostasis and attract inflammatory cells to the site for the inflammatory phase.[2] Key chemical mediators include transforming growth factor beta (TGF-β), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), and vascular growth factor (VEGF).[2] In this phase, neutrophils are the first to be seen active at the injury site to rid the area of debris and possibly infectious material.[1] The inflammatory phase occurs over, on average, three days.[1] Additionally, different subtypes of leukocytes that secrete growth factors, as well as chemotactic proinflammatory cytokines that recruit cell types needed for the proliferative phase, are also present in this phase.[1,2] Endothelial cells, macrophages, and fibroblasts are present to help create granulation tissue, new vasculature, and the extracellular matrix (ECM) that will replace clot in the wound and help migrating cells adhere and function.[2] Within the ECM, Type III collagen is present at this stage of healing. Next, re-epithelization occurs due to the recruitment of keratinocytes.[2] The proliferative phase will occur over subsequent weeks.[1] Then, fibroblasts convert into myofibroblasts, which are responsible for wound contracture.[3] The final healing phase is remodeling. During the remodeling phase, the ECM and granulation tissue degrade via proteases, while mature Type I collagenous matrix and scar tissue form.[3] Furthermore, vascular cells and the myofibroblasts degrade in an organized fashion.[3] The balance of synthesis and the disintegration of cell types is essential to provide optimal wound healing.[1–3] The remodeling phase occurs over months.[1] A deviation in any phase of healing can result in aberrant and sometimes excessive scar formation.[1–3]

KELOIDS AND HYPERTROPHIC SCARS

Keloids and hypertrophic scars are two well-known types of excessive pathologic scarring. These types differ by aesthetics, pathogenesis, histopathology, and treatment, although there are overlapping characteristics. Compared to hypertrophic scars, keloids are characterized as more clinically severe in nature, causing pruritus and pain more frequently in patients.[4] Classically, keloid scars appear slowly over months beyond the initial wound edges, while hypertrophic scars typically develop over a period of weeks and stay within the initial edges.[5] From a histopathologic perspective, keloids include a random organization of Type I and Type III collagen fibers, whereas hypertrophic scars have an organized parallel pattern of Type III collagen.[6,7] Keloids progress to form thick, firm scars that rarely heal spontaneously, unlike hypertrophic scars that can heal unaided over years.[5] Since keloids can

FUNDING: No funding was provided for this study.
DISCLOSURES: The authors have no conflicts of interest relevant to the content of this article.
CORRESPONDENCE: Travis W. Blalock, MD; Email: twblalo@emory.edu

be distressing to patients, there has been great interest in understanding the key aspects of keloid pathogenesis.

KELOID PATHOPHYSIOLOGY

Keloid formation is theorized to be the result of an imbalance of increased synthesis of collagen and ECM and decreased degradation of these products. Increased synthesis of ECM collagen is thought to be related to the overactivation of keloid fibroblasts via the overexpression of inflammatory mediators—namely, TGF-β1.[1] Differential production of isoforms of TGF-β is proposed to be responsible for the excessive collagen production by fibroblasts seen in pathologic scarring.[6] Overexpression of TGF-β1 and TGF-β2 with decreased expression of TGF-β3 production results in increased fibroblast activity and ECM collagen formation.[1,6,8] Keloid fibroblasts are increasingly sensitive to the effects of TGF-β1 due to the receptor's upregulation.[9] In the process of collagen remodeling, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are key mediators that increase degradation and decrease degradation of ECM, respectively.[8] TGF-β1 has been shown to increase TIMP and decrease MMP production, resulting in reduced collagen degradation.[10] Other inflammatory proteins such as VEGF and PDGF have been thought to contribute to the overproduction of collagen as well.[11,12] The activity of these molecules increasing fibroblast activation might be the result of activating mechano-transduction pathways, stimulated by mechanical stress at certain areas of the body, such as the sternum, shoulder, and suprapubic areas.[13–15] Although discovering the cellular processes that mediate keloid formation is still an active area of research, there are a wide variety of therapies that physicians can use to limit keloid formation, progression, recurrence, and symptoms.

PREVENTION AND TREATMENT OPTIONS FOR KELOID MANAGEMENT

Occlusive dressings. Silicone gel sheeting (SGS) is a commonly used occlusive dressing applied to reduce the risk of excessive scar formation. SGS is composed of a semi-occlusive silicone gel sheet combined with a durable silicone membrane.[16] Though the prominent mechanism of action of these dressings is unclear, SGS is theorized to act via hydration and occlusion of the wound bed. Scar tissue has been shown to be more prone to transepidermal water loss, possibly reflecting decreased water barrier function of the stratum corneum.[17] The SGS creates a moisture-retaining environment that prevents dehydration of the stratum corneum, which, in a downstream manner, limits activation of fibroblasts and subsequent collagen production.[18] Several studies have shown that SGS can reduce the incidence of hypertrophic scarring and reduce scar volume.[19–23] The use of SGS requires high levels of patient adherence since protocols often require patients to wear the SGS upwards of 12 hours per day for at least 12 months.[24,25] Efficacy of SGS has primarily been demonstrated when the dressing is used as a preventative measure rather than a method of treatment.[26] The necessary continuous application of SGS in hotter climates might induce a level of humidity that facilitates the formation of bacterial abscesses.[27]

Compressive therapy. Compression therapy is primarily used as an adjunct to surgical excision to prevent recurrence of ear keloids.[28] The mechanisms of pressure therapy are thought to include mechanoreceptor-induced apoptosis of cells in the ECM and/or pressure-induced ischemia that alters fibroblast activity and promotes collagen degradation.[6,29] Compression treatments are wide-ranging, including elastic wrap bandages, custom pressure ear molds, earrings, and magnets.[6,30,31] Studies have shown that ear keloids treated with compression therapy postexcision have a nonrecurrence rate of 70.5 to 95 percent.[32,33] Similar to occlusive dressing therapy, compression therapy has the best results if the pressure device is affixed for at least 12 hours per day for at least six months at a pressure of at least 24mmHg.[32–34] If the pressure exceeds 30mmHg, the compression can potentially cause tissue necrosis.[31,35]

Intralesional steroids. As an accessible and efficacious keloid therapy, intralesional steroids continue to serve as a first-line treatment for many physicians. Typically, triamcinolone is injected at a concentration of either 2.5mg to 20mg for facial keloids or 20mg to 40mg for non-facial keloids.[24] Corticosteroids act by suppressing wound inflammation mediators and fibroblast growth while increasing collagen degradation.[6,36–38] Mechanisms by which triamcinolone alters fibroblast growth include inducing fibroblast hypoactivity by decreasing TGF-β expression and reducing fibroblast density by increasing fibroblast apoptosis.[36,37,39,40] Intralesional triamcinolone as a monotherapy has been shown to reduce keloid recurrence to an average of 50 percent after surgical excision and to reduce scar volume.[41–44] However, the therapeutic response rate of intralesional steroid therapy is highly variable.[41,45] Potential side effects of corticosteroid injection include pain with injection, skin atrophy, alteration in skin pigmentation, and the formation of telangiectasias.[25,45]

Topical imiquimod. Used successfully for the treatment of basal cell carcinoma and human papillomavirus-related warts, imiquimod 5% cream has shown promise as an adjuvant therapy for keloids after excision.[46] Imiquimod is a Toll-like receptor 7 agonist that limits fibroblast production of collagen via increasing local concentrations of interferon alpha (IFN-α).[6,47] IFN-α has been shown to decrease fibroblast activity in a dose-dependent manner, reduce glycosaminoglycan production, and increase collagenase levels.[48,49] The reported recurrence rates of excised keloids with daily topical imiquimod 5% cream have ranged from 0 to 88.9 percent with a follow-up time of 20 to 24 weeks.[47,50–56] The variability of the keloid recurrence rates with imiquimod therapy is likely related to skin tension at the operative site, with ear keloids having lower recurrence rates than shoulder, chest, and back keloids.[57,58] Common side effects of imiquimod include hyperpigmentation, erythema, irritation, and secondary infections that typically resolve upon suspending therapy.[6,47,52]

Topical mitomycin C. Shown to reduce scarring after ophthalmologic, tracheal, and laryngeal surgery, mitomycin C can reduce keloid recurrence postexcision.[59–62] Mitomycin C is an anti-neoplastic derivative of *Streptomyces caespitosus* that alkylates and cross-links DNA, inhibiting cell proliferation.[63] Mitomycin C has been shown in *in-vitro* studies of adult dermal fibroblasts to decrease fibroblast proliferation at concentrations of 0.4mg/mL and 0.1mg/mL.[63,64] *In-vitro* studies with mitomycin C demonstrated complete cell death with continuous exposure for one week and cellular growth at three weeks after a single exposure of five minutes.[63,64] Clinical treatment regimens in the literature include application of an absorbent material soaked in 1mg/mL of mitomycin C for 3 to 5 minutes with reapplication at three weeks.[57] Studies that used mitomycin C as the only adjunctive therapy to surgical excision report recurrence rates from

0 to 33 percent at six months, though some studies have demonstrated several patients with nonrecurrence at greater than 12 months.[65–71] Intralesional mitomycin C has been shown to result in wound ulceration.[66] Reported side effects for mitomycin C have included hypopigmentation and posttreatment pain.[66,67]

Intralesional and topical 5-fluorouracil (5-FU). Primarily used as a chemotherapeutic, 5-FU is a pyrimidine analog that irreversibly inhibits thymidine synthase, leading to the disruption of DNA replication and cellular proliferation.[72] 5-FU has been shown *in-vitro* to reduce fibroblast growth, induce fibroblast apoptosis, and decrease TGF-β-driven collagen synthesis.[73,74] When used as a monotherapy for keloids, 5-FU has been reported to have a 21 to 35 percent rate of recurrence at a minimum of three months and maintain keloid volume reduction of keloids for at least six months after the last therapy session in 58 to 65 percent of patients.[28,75–77] Studies have described the successful use of 5-FU as therapy for keloid scars resistant to at least one alternate therapy, with a 19 to 47 percent rate of recurrence after at least six months and resolution of painful and itching scar symptoms.[28,78–80] Specifically for ear keloids postexcision, one study reported 96 percent of female patients had at least a 75-percent scar volume reduction and 3.57 percent rate of recurrence.[28,81] Keloids older than two years might have greater resistance to 5-FU treatment.[75,80] Several studies have consistently noted side effects of pain on injection, wound ulceration, and hyperpigmentation after intralesional 5-FU therapy.[28,75–77,80] Known systemic side effects of 5-FU include anemia, leukopenia, and thrombocytopenia, though none have been observed after intralesional injection.[25] Though topical 5-FU has been used in many dermatologic conditions, no studies have examined the use of topical 5-FU for keloids and hypertrophic scars.[82] However, there has been initial successes in patient satisfaction and keloid symptomatology with the use of 5-FU tattooing.[83] The process of 5-FU tattooing involves dripping of a 50-mg/mL 5-FU solution onto the keloid, followed by multiple keloid punctures with a 27-gauge needle, and finally dripping of 5-FU solution over the keloid again.[83]

Interferons. Interferons compose a group of cytokines that mediate complex cellular interactions, including immunoregulatory, antifibrotic, and antiproliferative functions.[84,85] Interferon alpha-2b and interferon gamma have been evaluated as therapeutic treatment options for keloids. Both interferon alpha-2b and interferon gamma have been shown to suppress collagen synthesis and scar contraction by fibroblasts, although the extent to which interferon action alters TGF-β–induced fibrosis is unclear.[39,48,85–88] There is limited evidence regarding the efficacy of either interferon alpha-2b or interferon gamma compared to placebo. Interferon alpha-2b has been described to be injected at least twice into keloids at dosages of 500,000 to 6 million units.[48,89–92] Though one study reported 18.7 percent keloid recurrence after keloid excision with postoperative interferon at a mean follow-up of 7.9 months, several studies reported either no significant difference in recurrence rates or a significant difference in scar volume compared to placebo.[89–92] There is no consistent regimen of interferon-alpha-2b that was used among published studies. Similarly, studies evaluating interferon gamma treatment of keloids postexcision did not have consistent treatment regimens. Evaluators injected either 0.1mg or 0.01mg at a frequency of 1 to 3 times per week for 3 to 10 weeks.[93–95] Though interferon gamma did consistently demonstrate keloid volume reduction during the treatment period for multiple studies, there is no reliable data for keloid recurrence with this intervention.[93–95] Systemic side effects—namely, influenza-like symptoms of fever and myalgias—were noted in several studies using either form of interferon.[89,91,95,96] Acetaminophen was used with success as prophylaxis for these systemic symptoms.[90,92,94,95]

Bleomycin. Bleomycin is an glycopeptide isolate of *Streptomyces verticillus* that has been predominately used as a chemotherapeutic and secondarily studied as a treatment for keloids and hypertrophic scars.[97] As a chemotherapeutic, bleomycin acts to cleave single-stranded and double-stranded DNA and induce apoptosis.[98,99] Regarding keloid pathology, bleomycin has been shown to suppress collagen synthesis by dermal fibroblasts, increase collagen turnover, and decrease the levels of lysyl-oxidase required for collagen maturation.[100–102] There are multiple methods by which the effectiveness of bleomycin to reduce keloid burden has been studied, including tattooing, dermojet intralesional injection, and intralesional injection plus or minus in combination with electroporation therapy. The bleomycin tattooing protocol has been described as first dripping a bleomycin solution onto the area, then puncturing the treated area multiple times using a 22- to 25-gauge needle.[103–105] The evidence to support the efficacy of bleomycin tattooing is difficult to interpret due to the variability of the bleomycin tattooing protocols studied in the current literature. Studies dripped 1.5IU/mL of bleomycin concentrations of 3IU/cm^2 and 6IU/cm^2 on patient scars followed by 40 punctures per 1cm^2 or 5cm^2.[103–105] In the literature, bleomycin tattooing protocols required the administration of multiple sessions, though each study administered each tattooing session at inconsistent time intervals and recorded follow-up at different periods posttreatment.[103–105] Still, bleomycin tattooing for keloids has shown some success across each tattooing protocol, with 66 to 77 percent of patients experiencing greater than 70-percent scar flattening.[103–105] Recurrence rates after using bleomycin tattooing range from 14 to 28.6 percent at between 10 to 18 months posttreatment.[103–105] Saray et al[106] studied the use of bleomycin intralesional injections to treat steroid-resistant keloids at 0.6IU/cm^2 using a dermojet device (MadaJet XL; Mada Inc., Carlstadt, New Jersey).[106] This group administered treatment at intervals of four weeks until favorable aesthetic results and symptom reduction were achieved.[106] This group reported that 73 percent of patients achieved complete flattening with zero-percent recurrence after at least 16 months, with patients receiving an average of 3.8 sessions per keloid.[106] As a novel alternative treatment regimen for increased drug penetration, Manca et al[107] treated keloids with intralesional bleomycin injections augmented by electroporation therapy. Electroporation therapy utilizes a current across the keloid area to increase cellular permeability.[107] More than half of patients who underwent bleomycin injection therapy were treated with between two and four sessions until adequate improvement was noted.[107] Manca et al reported that 94 percent of patients demonstrated a greater than 50-percent reduction and 83 percent of patients had reduction in erythema, pain, and pruritus at 12 months posttreatment.[107] Regardless of the method of bleomycin delivery, common side effects included hyperpigmentation, pain on injection, and dermal atrophy.[103–107] Saray et al[106] helped patients reduce the side effect of hyperpigmentation with the application of topical tretinoin.

Surgical techniques. Beyond simple surgical excision, surgical management of keloids

encompasses multiple novel reconstructive techniques that have demonstrated reduced rates of recurrence with treatment-resistant keloids. Simple full or shave excision of a keloid is rarely used as a monotherapy, since recurrence rates for surgical excision range from 45 to 100 percent.[6,108] One suggested cause of high recurrence rates with excision has been incomplete surgical margins.[109,110] There are several key principles regarding management of the resultant wound bed that are commonly accepted to reduce keloid recurrence. General recommendations for primary wound closure following complete excision include gentle handling of tissue, avoidance of wound bed tension, eversion of wound edges, meticulous approximation of wound edges, and adequate control of infection and bleeding.[6,108,111] For ear keloid skin reconstruction, bilayered banner transposition flaps and double-crossed skin flaps have been described to reduce wound bed tension.[112,113] As an alternative to primary closure after complete keloid excision, the use of full-thickness skin grafts have been shown to be effective in the literature. Ziccardi et al[114] described the use of a full-thickness skin graft from the excised keloid skin with no recurrence at six months.In larger study, Burm et al[115] studied the use of full-thickness skin grafts for helical rim keloids defects with exposed cartilage. The skin grafts were placed after the wound bed was de-epithelized 2 to 3mm beyond the original keloid border.[115] Burm et al reported no recurrence with no adjunctive therapy for all patients with a follow-up period varying from nine months to six years.[115] All of the patients treated by this group had failed prior excision and/or steroid therapy.[115] In comparison, Nguyen et al[116] described the use of a bilaminar dermal skin replacement system (Integra; Integra LifeSciences Corp., Plainsboro, New Jersey) to create a neodermis with subsequent epidermal skin grafting for treatment-resistant keloids.Without further adjunctive therapy, all of the patients receiving this therapy reported no recurrence at a mean follow-up of 38 to 60 months.[116] For large treatment-resistant keloids, pedicle perforator and free-flap coverage of wound defects have been reported with no recurrence at a minimum of 18 months with the use of adjunctive radiation therapy.[117–119]

In an effort to preserve local viable keloid skin, Lee et al[120] first described the core excision procedure. During core excision, the inner fibrous core of the keloid is removed and the resultant defect replaced with a keloid rind flap composed of epidermis and thin dermis. Lee et al demonstrated histological evidence of the subcapsular plexus supplying blood to the keloid rind flaps.[120] This technique is supported by data suggesting that fibroblasts at the core of the keloid have lower rates of apoptosis relative to a normal rate of fibroblast apoptosis in the keloid rind flap.[121,122] The initial study of keloid core excision reported that 17 percent of patients showed recurrence, with 29 percent of patients suffering from either flap necrosis or congestion.[120] Subsequent studies in the literature have reported a recurrence rate of 0 to 44 percent without adjuvant therapy at 18 months.[108,122,123]

Cryotherapy. Cryotherapy involves the administration of freezing therapy to keloids to reduce scar volume and recurrence. During cryotherapy, the temperature of the keloid scar is lowered below -22°C.[124] Low temperatures have been suggested to induce vascular damage, resulting in cell anoxia, cryonecrosis, and coagulative necrosis.[124,125] Histologic studies after cryotherapy have highlighted several significant changes in scar tissue structure. Posttreatment scar biopsies have demonstrated the reorganization of collagen fibers into a more compact parallel fashion comparable to classic scar and resultant dermal collagen structure.[124–126] Additionally, keloid tissue exposed to cryotherapy has been reported to have reduced myofibroblasts, reduced mast cells, and reduced production of TGF-β by dermal fibroblasts.[126,127] Currently, options for cryotherapy include spray, contact, and intralesional therapy. Compared to spray and contact cryotherapy, intralesional cryotherapy facilitates greater freezing of the abnormal keloid and often requires fewer treatment sessions for a satisfactory scar outcome.[124,128–130] Intralesional cryotherapy is performed by introducing a needle with or without a cryoprobe into the long axis of the keloid scar, which allows for the passage of liquid nitrogen vapor to freeze the tissue.[131] Studies have reported that intralesional cryotherapy can reduce keloid volume by an average of 51.4 to 67.4 percent at 12 months after the last treatment.[124,125,132–134] There is some evidence to suggest greater efficacy of intralesional cryotherapy in individuals with keloids of less than 10cm^2 or with ear keloids.[128,132] Regarding patients who failed prior steroid therapy, Gupta et al[129] reported 58 percent of their patients had greater than 75 percent flattening at least seven months after the last treatment.[129] Recurrence rates from 0 to 24 percent have been reported 6 to 18 months posttreatment.[124,125,133,134] Common side effects from intralesional cryotherapy include temporary lesion blistering, mild-to-moderate postoperative pain, and temporary hypopigmentation.[124,125,130–134] Some studies have noted that patients with Fitzpatrick skin Types IV to VI have a greater rate of persistent hypopigmentation.[133,134]

Radiation therapy. Since the beginning of the 20th century, investigators have evaluated different radiation methods to identify the best protocols to treat keloids.[135] Primarily, radiation therapy has been shown to be most effective as an adjunctive therapy to surgical excision compared to monotherapy.[136,137] Though the mechanism of action of radiation therapy is not known, *in-vitro* studies of radiation therapy have demonstrated increased rates of premature cellular senescence of keloidal fibroblasts and decreased proliferation in a dose-dependent fashion.[138] Currently, there are two primary forms of radiation for keloids: external and internal. X-ray and electron-beam radiation therapy (EBRT) are the two forms of external-beam radiation that have been studied in the literature. Interstitial brachytherapy is a form of internal radiation that uses a hollow catheter placed into the dermis of the keloid scar to deliver localized radiation therapy.[139,140] Interstitial brachytherapy can be administered as a low dose rate (LDR) or high dose rate (HDR).[140] HDR brachytherapy has been heavily studied in comparison with LDR brachytherapy since LDR treatment time ranges from 20 to 72 hours relative to 5 to 10 minutes for HDR treatment.[141,142] Additionally, HDR therapy has been shown to provide better relief of keloid symptoms, such as pain or pruritus, compared to LDR therapy.[143] Radiation therapy can be administered in a single treatment dose or fractionated over a period of time. Fractionation of radiation therapy has been shown to reduce posttreatment skin changes compared to single dose therapy.[144]

The comparison of studies examining radiation therapy is difficult, considering most studies are retrospective reviews that examine variable radiation dosages, variable definitions of recurrence, and variable timing of radiation delivery.[145–147] Moreover, retrospective studies on radiation treatment examine mixed populations of hypertrophic scars and keloids and have variable histologic confirmation of keloid

pathology.[146] Thus, recurrence rates reported in the literature range from 2 to 72 percent.[145–148] Still, shared aspects of effective radiation therapy have been supported. Evidence in the current literature suggests the use of different radiation dosages and fractionation protocols depending on the location of the keloid on the body.[148–150] Regarding the fractionation of radiation therapy, protocols that use higher-dose fractions for shorter treatment schedules have similar efficacy to longer treatment schedules.[149]

Recent studies reporting recurrence rates of different keloid radiation methods have compared the biological effective dose (BED) of different protocols. The BED accounts for the radiation dose per fraction, number of fractions, and overall treatment time in a calculation for the relative biological effectiveness of different radiation therapies.[150] In a meta-analysis of literature published from 1942 to 2014, Mankowski et al[137] used BED calculations to report recurrence rates of 23 percent, 23 percent, and 15 percent for X-ray, ERBT, and brachytherapy protocols, respectively, at an average minimum follow-up of 14.4 months.[137] However, this meta-analysis did not exclude studies on the basis of a lack of histological confirmation of keloids and the definition of recurrence was not standardized. A literature review conducted by van Leeuwen et al. only included studies with excisional biopsy verification of keloid pathology and reported mean recurrence rates of 10.5 and 22.2 percent, respectively, for HDR and external radiation therapy.[140] Though numerous studies have been conducted for radiation treatment of keloids, there is still no consensus regarding overall dosage and fractionation. Any effort made toward reaching this consensus protocol will be difficult since the comparison of varying protocols using BED calculations is still unreliable. Several studies using BED calculations have differed in the α/β ratio used in the equation.[137,149–151] The α/β is a ratio representing an indirect reflection of how the tissue reacts to radiation, with acutely reacting tissues having higher values than late reacting tissues.[150] Future studies evaluating radiation therapy must be more rigorous in excluding nonkeloid scars, propose a standardized definition of recurrence, and use a common α/β ratio for BED comparison. In addition to reporting more accurate long-term recurrence rates, short and long-term side effects of radiation therapy must be stringently recorded.

Patients subjected to radiation therapy are at risk for several skin-related complications. In the short term, patients might experience erythema, desquamation, and transient changes in pigmentation.[137,152] In the long term, patients might experience permanent dyspigmentation, depigmentation, atrophy, telangiectasias, subcutaneous fibrosis, chronic wounds, and possibly a radiation-induced malignancy.[152,153] Risks of skin complications after radiation therapy have been noted to increase with dosage.[145,148] Carcinogenesis is considered a long-term risk of radiation therapy for keloids. In a computerized review of literature published from 1901 to 2009, Ogawa et al[152] found five cases of keloid-related and hypertrophic scar-related carcinogenesis, where the majority of cancers were related to radiation of surrounding tissue. Of note, in this review, two case reports described patients less than 12 years of age and two patients had received radiation of postburn hypertrophic scars, which are no longer candidates for radiation therapy.[152] The risk of carcinogenesis with current radiation therapies, which provide increased precision and smaller margins of treatment, is unclear, as the latency time is greater than 25 years.[154] To reduce the risk of carcinogenesis after keloid radiation therapy, surrounding tissues should be adequately shielded (including radiosensitive breast and thyroid tissue), efforts should be made to identify overall carcinogenic patient risk factors, and radiation therapy should be used with caution in young children.[148,152]

Pulsed-dye laser (PDL). PDL is a form of nonablative laser therapy that targets keloid microvasculature to improve scar appearance. The PDL was initially engineered to treat vascular lesions by adjusting the wavelength of the laser to 585nm to 600nm and specifically targeting hemoglobin and oxyhemoglobin as chromophores.[155] With respect to keloid pathology, PDL is thought to cause microvascular damage that results in local hypoxia and decreased nutrient supply, which serves as a catalyst for several biochemical changes within the scar.[156–158] Many theories, including the disruption of collagen disulfide bonds and increased levels of collagenase, have been suggested but have yet to be proven.[159] Studies have been done on PDL-treated keloid biopsies to elucidate how the laser alters keloid structure. Kuo et al. have reported decreased levels of TGF-β expression, decreased fibroblast proliferation, and increased fibroblast apoptosis from keloid biopsies post-PDL treatment.[160–162] This supported the histological evidence of a reduction in the fibroblast and the production of loose, less coarse collagen fibers from keloid biopsies treated with PDL.[163]

To achieve a therapeutic effect, PDL therapy is typically administered in adjacent nonoverlapping laser pulses over the length of the scar using a laser wavelength of 585nm to 595nm.[128,158,163–168] PDL therapy is offered up to 12 to 18 sessions with 4 to 8 weeks between sessions.[155,158,169,170] Variables can be adjusted for PDL therapy, including fluence (J/cm^2), pulse duration (ms), and spot size (mm).[168] Manuskiatti et al[170] reported that a shorter pulse width of 0.45ms provided greater sternotomy scar reduction relative to 40ms. The effect of fluence on PDL therapy scar outcomes is still uncertain. Using a split-scar study, Manuskiatti et al[165] evaluated several different PDL fluences without noting any significant difference in treatment outcomes, but described faster treatment responses with lower fluences. In contrast, lower fluences (3J/cm^2) have also been demonstrated to increase TGF-β levels and collagen synthesis, while higher fluences (10–18J/cm2) have invoked decreases in TGF-β level.[171,172]

In the current literature, there exists a paucity of studies specifically examining the effect of PDL on keloids. Most studies involve a mixed cohort of patients with either hypertrophic or keloid scars, used subjective evaluation of the scars to assess the effect of PDL therapy, and had a follow-up time of between one and six months after the last treatment.[155,164,170] Regarding hypertrophic and keloid scars, Cannarozzo et al[155] reported 49 percent of patients had at least a 75-percent improvement in overall scar color, height, pliability, and texture after 4 to 6 sessions.[155] Similarly, Al-Mohamady et al[164] described a 55-percent improvement in Vancouver Scar Scale after six treatments, with less improvement seen in older scars. Studies evaluating objective measures have shown PDL therapy to reduce scar volume by 24 to 45 percent after 3 to 6 treatment sessions.[165,170] Additionally, Alster et al[163] demonstrated that PDL therapy relieved keloid symptoms of pain, pruritus, and burning. There is no current data to determine how PDL therapy influences the recurrence of keloid scars, though there is evidence that PDL therapy, in some cases, can cause scar recurrence.[168,173]

Common side effects of PDL therapy for scars include temporary purpura, blistering, crusting, and postinflammatory pigmentary

changes.[155,164,165,170] Side effects are more common in individuals with darker skin tones.[174] Epidermal cooling with PDL treatment has been shown to be a useful adjunct treatment to reduce adverse complications, including purpura, dyspigmentation, and additional scarring.[170,175]

Ablative laser. Though ablative carbon dioxide (CO_2) and erbium doped yttrium aluminium garnet (Er: YAG) lasers have been commonly used for scar revision, there is limited evidence regarding the use of these lasers for keloids. CO_2 and Er:YAG lasers target water molecules to cause local tissue changes, including collagen remodeling, increased levels of basic fibroblast growth factor, and decreased levels of TGF-β. CO_2 and Er:YAG lasers can be used to either superficially ablate keloid tissue or surgically excise keloid scars.[176–178]

There is evidence that multiple ablative CO_2 treatments are necessary for longer-lasting scar improvement. Multiple ablative fractional CO_2 laser treatments have been shown to primarily reduce hypertrophic and keloid scar pliability.[176] Similarly, multiple ablative high-energy CO_2 laser treatments with varying laser frequencies have improved keloid pigmentation, pliability, and scar bulk at six months after the last treatment.[178] Scrimali et al described monthly fractional CO_2 treatments resulting in no recurrence of keloid and hypertrophic scars at one year after 6 to 12 treatments.[179,180] In contrast, Ang et al[181] noted complete earlobe keloid recurrence after a single ablative CO_2 treatment.

Compared to simple scalpel surgical excision of keloids, CO_2 laser excision without adjunctive therapy has similarly high rates of recurrence, ranging from 74 to 100 percent at one year, but decreased blood loss and postoperative pain.[182,183] Adjunctive intralesional steroid therapy and cyanoacrylate glue have been shown to improve scar revision results of CO_2 laser keloid excision.[184,185]

There is a paucity of studies evaluating the effects of ablative Er:YAG laser therapy on keloids. Wagner et al[186] conducted a pilot study using Er:YAG laser therapy to treat a mixed-patient cohort with hypertrophic and keloid scars. Er:YAG laser therapy was able to reduce scar redness, scar elevation, and scar hardness on average by 50 percent.[186]

Side effects of laser therapy of keloids have been infrequently reported in studies but include erythema, edema, and hyperpigmentation.[178] Hypertrophic scarring, notably on the neck, has been described as a possible side effect to ablative CO_2 resurfacing.[187]

Laser-assisted drug delivery (LADD). To increase the bioavailability of topical scar therapies, lasers have been used to increase drug penetration beyond the stratum corneum.[188,189] In LADD, common ablative lasers, such as CO_2 and Er:YAG lasers, are applied to create cylindrically shaped microablation zones into the skin that allow for topical agents to reach the dermis.[190] Though common topical keloid-treating agents, including corticosteroids, 5-FU, and imiquimod have been studied using LADD, there is limited literature investigating the use of LADD for keloid treatment.[190,191]

Cavalie et al[192] studied the use of Er:YAG laser every other week with the twice daily application of topical betamethasone cream until an adequate improvement in keloids was observed. After a median of nine treatments, there was a median overall improvement of 50 percent, with greater improvement seen in acne-induced keloids.[192] After final treatment, 22 percent of patients had recurrence within the first two months.[192] Subsequently, Park et al[193] compared the efficacy of Er:YAG LADD of intralesional triamcinolone acetonide therapy and topical desoxymethasone. This group conducted a split scar study to compare these two therapies and administered each LADD steroid treatment in a total of four sessions with six-week intervals.[193] The group noted significant improvement of the scar halves 12 weeks following the last therapy, though there was some worsening noted at the end of the observation period.[193] Patients rated their satisfaction with their treatment outcome as "moderately satisfied" at the end of the trial.[193]

5-FU and imiquimod with LADD have been shown to increase drug penetration and decrease the required dosage for optimal efficacy in murine and porcine skin models.[194–196] Further studies are necessary to explore the effectiveness of these topical therapies with LADD for keloid treatment.

Platelet-rich plasma (PRP). PRP is concentrated autologous plasma that contains supra-physiologic levels of platelets and alpha granules with growth factors and cytokines, such as vascular endothelial growth factor, platelet-derived growth factor, and TGF-β.[197] PRP has been popularized as an adjunctive treatment to help with a variety of dermatologic conditions, including chronic wounds, alopecia, and scars.[198] Recent studies have focused on the role of PRP in altering keloid pathology. *In-vivo* studies with dermal fibroblasts have demonstrated that PRP increased fibroblast proliferation, expression of collagen, and matrix protein synthesis.[199,200] Increased levels of TGF-β in PRP have been proposed to activate a negative feedback mechanism in the TGF-β signaling pathway.[201] Currently, PRP has been studied as a postsurgical excision therapy that is injected into the wound bed. Hersant et al[202] reported 29 percent keloid recurrence at two years when PRP was used intraoperatively during surgical excision and postoperatively in a monthly regimen for three months.[202] This study suggests the potential of PRP to modify abnormal healing of keloid wounds typically seen after only surgical excision. Jones et al[203] reported that the use of PRP as an adjunct to surgical excision and X-ray radiotherapy for ear keloids reduces the recurrence rate to six percent at two years.[203] Azzam et al[204] reported a recurrence rate of 32 percent when PRP was used as an adjunct to surgical excision and cryotherapy.[204]

CONCLUSION

The breadth of therapies available for the prevention and treatment of keloids is continually expanding, with encouraging recent progress from novel strategies. As clinicians become more familiar with the use of the different injectable treatments and devices described in the literature, reliable data can be gathered regarding their consistent use. Currently, there exist no standardized guidelines for keloid management endorsed by a governing academic body. The present absence of large, high-quality studies evaluating the efficacy different keloid modalities restricts the establishment of standardized guidelines for keloid management. The desire for higher levels of evidence to guide keloid management for all physicians is echoed in the current literature as well as by our study population.[25,205–208]. Currently, there are no high-quality randomized controlled trials (RCTs) and few low-quality RCTs evaluating different keloid treatments.[177,207] Retrospective cohort, prospective cohort, and systematic reviews compose the current evidence for the majority of keloid therapies.[6,25,177,207] Durani and Bayat[207] noted that poor methodological quality was a common reason that decreased the level of evidence provided by several nonrandomized comparative studies. Designing reliable studies to investigate keloid treatments requires a

standardization of experimental methods not currently seen in the literature. There is no consistency among current studies to exclusively study keloids instead of mixed hypertrophic and keloid scar populations or to have consistent means by which to evaluate therapy success. When evaluating keloid therapies, studies should consistently use validated tools for scar assessment, such as the Vancouver Scar Scale and the Patient and Observer Scar Assessment Scale.[177] Additionally, studies should make an effort to include subjective measures of reduction in scar volume. A consistent experimental design is necessary to perform comparative studies between treatment modalities. Keloids continue to be a challenging pathology for clinicians, and future treatment regimens must be based on high-quality studies with replicable improvement in outcomes.

REFERENCES

1. Wang PH, Huang BS, Horng HC, et al. Wound healing. *J Chin Med Assoc.* 2018;81(2):94–101.
2. Eming SA. Biology of wound healing. In: Bolognia JL, Schaffer JV, Cerroni L, ed. *Dermatology.* 4th ed. Philadelphia, PA: Elsevier; 2018: 2413–2424.
3. Chu EA, Byrne PJ, Odland RM, Goding, Jr. GS. Skin flap physiology and wound healing. In: Flint PW, Haughey BH, Lund V, et al. *Cummings Otolaryngology.* Philadelphia, PA: W. B. Saunders; 2015: 1124–1136.
4. Ghazawi FM, Zargham R, Gilardino MS, et al. Insights into the pathophysiology of hypertrophic scars and keloids: how do they differ? *Adv Skin Wound Care.* 2018;31(1):582–595.
5. Hu MS, Zielins ER, Longaker MT, Lorenz HP. Scar prevention, treatment, and revision. In: Gurtner GC, Neligan PC, ed. *Plastic Surgery.* Philadelphia, PA: Elsevier; 2018: 196–213.
6. Berman B, Maderal A, Raphael B. Keloids and hypertrophic Scars: pathophysiology, classification, and treatment. *Dermatol Surg.* 2017;43 Suppl 1:S3–S18.
7. Leong M, Murphy KD, Phillips LG. Wound healing. In: Townsend CM Jr., Beauchamp, RD, Evers BM, Mattox KL, ed. *Sabiston Textbook of Surgery.* Philadelphia, PA: Elsevier; 2017: 130–162.
8. Lee HJ, Jang YJ. Recent understandings of biology, prophylaxis and treatment strategies for hypertrophic scars and keloids. *Int J Mol Sci.* 2018;19(3). pii: E711.
9. Su CW, Alizadeh K, Boddie A, Lee RC. The problem scar. *Clin Plast Surg.* 1998;25(3):451–465.
10. Lin PS, Chang HH, Yeh CY, et al. Transforming growth factor beta 1 increases collagen content, and stimulates procollagen I and tissue inhibitor of metalloproteinase-1 production of dental pulp cells: Role of MEK/ERK and activin receptor-like kinase-5/Smad signaling. *J Formos Med Assoc.* 2017;116(5):351–358.
11. Haisa M, Okochi H, Grotendorst GR. Elevated levels of PDGF α receptors in keloid fibroblasts contribute to an enhanced response to PDGF. *J Invest Dermatol.* 1994;103(4):560–563.
12. Le AD, Zhang Q, Wu Y, et al. Elevated vascular endothelial growth factor in keloids: relevance to tissue fibrosis. *Cells Tissues Organs.* 2004;176 (1–3):87–94.
13. Harn HI, Ogawa R, Hsu CK, et al. The tension biology of wound healing. *Exp Dermatol.* 2017;28(4): 464–471.
14. Hsu CK, Lin HH, Harn HI, et al. Caveolin-1 controls hyperresponsiveness to mechanical stimuli and fibrogenesis-associated RUNX2 activation in keloid fibroblasts. *J Invest Dermatol.* 2018;138(1):208–218.
15. Suarez E, Syed F, Alonso-Rasgado T, Bayat A. Identification of biomarkers involved in differential profiling of hypertrophic and keloid scars versus normal skin. *Arch Dermatol Res.* 2015;307(2): 115–133.
16. Monstrey S, Middelkoop E, Vranckx JJ, et al. Updated scar management practical guidelines: non-invasive and invasive measures. *J Plast Reconstr Aesthet Surg.* 2014;67(8):1017–1025.
17. Suetake T, Sasai S, Zhen YX, et al. Functional analyses of the stratum corneum in scars. Sequential studies after injury and comparison among keloids, hypertrophic scars, and atrophic scars. *Arch Dermatol.* 1996;132(12):1453–1458.
18. Tandara AA, Mustoe TA. The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel. *J Plast Reconstr Aesthet Surg.* 2008;61(10):1219–1225.
19. Berman B, Flores F. Comparison of a silicone gel-filled cushion and silicon gel sheeting for the treatment of hypertrophic or keloid scars. *Dermatol Surg.* 1999;25(6):484-486.
20. Cruz-Korchin NI. Effectiveness of silicone sheets in the prevention of hypertrophic breast scars. *Ann Plast Surg.* 1996;37(4):345–348.
21. Gold MH, Foster TD, Adair MA, et al. Prevention of hypertrophic scars and keloids by the prophylactic use of topical silicone gel sheets following a surgical procedure in an office setting. *Dermatol Surg.* 2001;27(7):641–644.
22. Kim JS, Hong JP, t al. The efficacy of a silicone sheet in postoperative scar management. *Adv Skin Wound Care.* 2016;29(9):414–420.
23. O'Brien L, Jones DJ. Silicone gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev.* 2013;(9):CD003826.
24. Gold MH, McGuire M, Mustoe TA, et al. Updated international clinical recommendations on scar management: part 2—algorithms for scar prevention and treatment. *Dermatol Surg.* 2014;40(8):825–831.
25. Heppt MV, Breuninger H, Reinholz M, et al. Current strategies in the treatment of scars and keloids. *Facial Plast Surg.* 2015;31(4):386–395.
26. Berman B, Perez OA, Konda S, et al. A review of the biologic effects, clinical efficacy, and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. *Dermatol Surg.* 2007;33(11):1291–1302; discussion 302–303.
27. Tang HL, Lau KK, Sam R, Ing TS. Chest wall abscesses due to continuous application of silicone gel sheets for keloid management. *BMJ Case Rep.* 2015;2015. pii: bcr2014206777.
28. Al-Attar A, Mess S, Thomassen JM, et al. Keloid pathogenesis and treatment. *Plast Reconstr Surg.* 2006;117(1):286–300.
29. Reno F, Grazianetti P, Cannas M. Effects of mechanical compression on hypertrophic scars: prostaglandin E2 release. *Burns.* 2001;27(3): 215–218.
30. Sand M, Sand D, Boorboor P, et al. Combination of surgical excision and custom designed silicon pressure splint therapy for keloids on the helical rim. *Head Face Med.* 2007;3:14.
31. Park TH, Seo SW, Kim JK, Chang CH. Outcomes of surgical excision with pressure therapy using magnets and identification of risk factors for recurrent keloids. *Plast Reconstr Surg.* 2011;128(2):431–439.
32. Park TH, Rah DK. Successful eradication of helical rim keloids with surgical excision followed by pressure therapy using a combination of magnets and silicone gel sheeting. *Int Wound J.* 2017;14(2):302–306.
33. Tanaydin V, Beugels J, Piatkowski A, et al. Efficacy of custom-made pressure clips for ear keloid treatment after surgical excision. *J Plast Reconstr Aesthet Surg.* 2016;69:115–121.
34. Chrisostomidis C, Konofaos P, Chrisostomidis G, et al. Management of external ear keloids using form-pressure therapy. *Clin Exp Dermatol.* 2008;33(3):273–275.
35. Niessen FB, Spauwen PH, Schalkwijk J, Kon M. On the nature of hypertrophic scars and keloids: a review. *Plast Reconstr Surg.* 1999;104(5):1435–1458.
36. Wu WS, Wang FS, Yang KD, et al. Dexamethasone induction of keloid regression through effective suppression of VEGF expression and keloid fibroblast proliferation. *J Invest Dermatol.* 2006;126(6): 1264–1271.
37. Boyadjiev C, Popchristova E, Mazgalova J. Histomorphologic changes in keloids treated with Kenacort. *J Trauma.* 1995;38(2):299–302.
38. McCoy BJ, Diegelmann RF, Cohen IK. *In vitro* inhibition of cell growth, collagen synthesis, and prolyl hydroxylase activity by triamcinolone acetonide. *Proc Soc Exp Biol Med.* 1980;163(2): 216–222.
39. Xu SJ, Teng JY, Xie J, et al. [Comparison of the mechanisms of intralesional steroid, interferon or verapamil injection in the treatment of proliferative scars]. *Zhonghua Zheng Xing Wai Ke Za Zhi.* 2009;25(1):37–40. Article in Chinese.

40. Hochman B, Locali RF, Matsuoka PK, Ferreira LM. Intralesional triamcinolone acetonide for keloid treatment: a systematic review. *Aesthetic Plast Surg.* 2008;32(4):705–709.
41. Trisliana Perdanasari A, Lazzeri D, Su W, et al. Recent developments in the use of intralesional injections keloid treatment. *Arch Plast Surg.* 2014;41(6): 620–629.
42. Muneuchi G, Suzuki S, Onodera M, et al. Long-term outcome of intralesional injection of triamcinolone acetonide for the treatment of keloid scars in Asian patients. *Scand J Plast Reconstr Surg Hand Surg.* 2006;40(2):111–116.
43. Park TH, Seo SW, Kim JK, Chang CH. Clinical characteristics of facial keloids treated with surgical excision followed by intra- and postoperative intralesional steroid injections. *Aesthetic Plast Surg.* 2012;36(1):169–173.
44. Anthony ET, Lemonas P, Navsaria HA, Moir GC. The cost effectiveness of intralesional steroid therapy for keloids. *Dermatol Surg.* 2010;36(10):1624–1626.
45. Ledon JA, Savas J, Franca K, et al. Intralesional treatment for keloids and hypertrophic scars: a review. *Dermatol Surg.* 2013;39(12):1745–1757.
46. Berman B. Imiquimod: a new immune response modifier for the treatment of external genital warts and other diseases in dermatology. *Int J Dermatol.* 2002;41 Suppl 1:7–11.
47. Berman B, Kaufman J. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. *J Am Acad Dermatol.* 2002;47(4 Suppl):S209–S11.
48. Berman B, Duncan MR. Short-term keloid treatment in vivo with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan, and collagenase production in vitro. *J Am Acad Dermatol.* 1989;21(4 Pt 1):694–702.
49. Jimenez SA, Freundlich B, Rosenbloom J. Selective inhibition of human diploid fibroblast collagen synthesis by interferons. *J Clin Invest.* 1984;74(3):1112–1116.
50. Stashower ME. Successful treatment of earlobe keloids with imiquimod after tangential shave excision. *Dermatol Surg.* 2006;32(3):380–386.
51. Martin-Garcia R, Busquets A. Postsurgical use of imiquimod 5% cream in the prevention of earlobe keloid recurrences: results of an open-label, pilot study. *Dermatol Surg.* 2005; 31(11 Pt 1):1394–1398.
52. Patel PJ, Skinner RB, Jr. Experience with keloids after excision and application of 5% imiquimod cream. *Dermatol Surg.* 2006;32(3):462.
53. Malhotra AK, Gupta S, Khaitan BK, Sharma VK. Imiquimod 5% cream for the prevention of recurrence after excision of presternal keloids. *Dermatology.* 2007;215(1):63–65.
54. Chuangsuwanich A, Gunjittisomram S. The efficacy of 5% imiquimod cream in the prevention of recurrence of excised keloids. *J Med Assoc Thai.* 2007;90(7):1363–1367.
55. Cacao F, Tanaka V, Messina M. Failure of imiquimod 5% cream to prevent recurrence of surgically excised trunk keloids. *Dermatol Surg.* 2009;35(4):629–633.
56. Berman B, Harrison-Balestra C, Perez O, et al. Treatment of keloid scars post-shave excision with imiquimod 5% cream: a prospective, double-blind, placebo-controlled pilot study. *J Drugs Dermatol.* 2009;8(5):455–458.
57. Shin JY, Yun SK, Roh SG, et al. Efficacy of 2 representative topical agents to prevent keloid recurrence after surgical excision. *J Oral Maxillofac Surg.* 2017;75(2):401.e1–e6.
58. Sidgwick GP, McGeorge D, Bayat A. A comprehensive evidence-based review on the role of topicals and dressings in the management of skin scarring. *Arch Dermatol Res.* 2015;307(6):461–477.
59. Chan HHL, Kong YXG. Glaucoma surgery and induced astigmatism: a systematic review. *Eye Vis (Lond).* 2017;4:27.
60. Gnagi SH, White DR. Beyond dilation: current concepts in endoscopic airway stenting and reconstruction. *Curr Opin Otolaryngol Head Neck Surg.* 2016;24(6):516–521.
61. Perepelitsyn I, Shapshay SM. Endoscopic treatment of laryngeal and tracheal stenosis-has mitomycin C improved the outcome? *Otolaryngol Head Neck Surg.* 2004;131(1):16–20.
62. Seiler T, Schnelle B, Wollensak J. Pterygium excision using 193-nm excimer laser smoothing and topical mitomycin C. *Ger J Ophthalmol.*1992;1(6):429–431.
63. Chen T, Kunnavatana SS, Koch RJ. Effects of mitomycin-C on normal dermal fibroblasts. *Laryngoscope.* 2006;116(4):514–517.
64. Simmian R, Alani H, Williams F. Effect of mitomycin C on keloid fibroblasts: an in vitro study. *Ann Plast Surg.* 2003;50(1):71–76.
65. Sanni A, Ikponmwosa S, Golio D, Tehrani K. The use of mitomycin C and keloid scar recurrence. *Plast Reconstr Surg.* 2010;126:3.
66. Seo SH, Sung HW. Treatment of keloids and hypertrophic scars using topical and intralesional mitomycin C. *J Eur Acad Dermatol Venereol.* 2012;26(5):634–638.
67. Chi SG, Kim JY, Lee WJ, et al. Ear keloids as a primary candidate for the application of mitomycin C after shave excision: in vivo and in vitro study. *Dermatol Surg.* 2011;37(2):168–175.
68. Gupta M, Narang T. Role of mitomycin C in reducing keloid recurrence: patient series and literature review. *J Laryngol Otol.* 2010;125(3):297–300.
69. Bailey J, Waite A, Clayton W, Rustin M. Application of topical mitomycin C to the base of shave-removed keloid scars to prevent their recurrence. *Br J Dermatol.* 2007;156(4):682–686.
70. Stewart C, Kim J. Application of mitomycin-C for head and neck keloids. *Otolaryngol Head Neck Surg.* 2006;135(6):946–950.
71. Talmi Y, Orenstein A, Wolf M, Kronenberg J. Use of mitomycin C for treatment of keloid: a preliminary report. *Otolaryngol Head Neck Surg.* 2005;132(4):598–601.
72. Parker WB, Cheng YC. Metabolism and mechanism of action of 5-fluorouracil. *Pharmacol Ther.* 1990;48(3):381–395.
73. Huang L, Wong YP, Cai YJ, et al. Low-dose 5-fluorouracil induces cell cycle G2 arrest and apoptosis in keloid fibroblasts. *Br J Dermatol.* 2010;163(6):1181–1195.
74. Wendling J, Marchand A, Mauviel A, Verrecchia F. 5-fluorouracil blocks transforming growth factor-beta-induced alpha 2 type I collagen gene (COL1A2) expression in human fibroblasts via c-Jun NH2-terminal kinase/activator protein-1 activation. *Mol Pharmacol.* 2003;64(3):707–713.
75. Gupta S, Kalra A. Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. *Dermatology.* 2002;204(2):130–132.
76. Prabhu A, Sreekar H, Powar R, Uppin V. A randomized controlled trial comparing the efficacy of intralesional 5-fluorouracil versus triamcinolone acetonide in the treatment of keloids. *Journal of the Scientific Society.* 2012;39(1):19–25.
77. Saha AK, Mukhopadhyay M. A comparative clinical study on role of 5-flurouracil versus triamcinolone in the treatment of keloids. *Indian J Surg.* 2012;74(4):326–329.
78. Goldan O, Weissman O, Regev E, et al. Treatment of postdermabrasion facial hypertrophic and keloid scars with intralesional 5-Fluorouracil injections. *Aesthetic Plast Surg.* 2008;32(2):389–392.
79. Haurani MJ, Foreman K, Yang JJ, Siddiqui A. 5-Fluorouracil treatment of problematic scars. *Plast Reconstr Surg.* 2009;123(1):139–148; discussion 49–51.
80. Kontochristopoulos G, Stefanaki C, Panagiotopoulos A, et al. Intralesional 5-fluorouracil in the treatment of keloids: an open clinical and histopathologic study. *J Am Acad Dermatol.* 2005;52(3 Pt 1):474–479.
81. Khare N, Patil SB. A novel approach for management of ear keloids: results of excision combined with 5-fluorouracil injection. *J Plast Reconstr Aesthet Surg.* 2012;65(11):e315–e317.
82. Prince G, Cameron M, Fathi R, Alkousakis T. Topical 5-fluorouracil in dermatologic disease. *Int J Dermatol.* 2018;57(10):1259–1264.
83. Sadeghinia A, Sadeghinia S. Comparison of the efficacy of intralesional triamcinolone acetonide and 5-fluorouracil tattooing for the treatment of keloids. *Dermatol Surg.* 2012;38(1):104–109.
84. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist.* 2001;6(1):34–55.
85. Granstein R, Flotte T, Amento E. Interferons and collagen production. *J Invest Dermatol.* 1990;95(6 Suppl):75S–80S.
86. Liu JQ, Hu DH, Zhang ZF, et al. [Effects of interferon-

gamma on the transforming growth factor beta/Smad pathway in keloid-derived fibroblasts]. *Zhonghua Shao Shang Za Zhi.* 2009;25(6):454–459.
87. Hasegawa T, Nakao A, Sumiyoshi K, et al. IFN-gamma fails to antagonize fibrotic effect of TGF-beta on keloid-derived dermal fibroblasts. *J Dermatol Sci.* 2003;32(1):19–24.
88. Sahara K, Kucukcelebi A, Ko F, et al. Suppression of in vitro proliferative scar fibroblast contraction by interferon alfa-2b. *Wound Repair Regen.* 1993;1(1):22–27.
89. Davison SP, Mess S, Kauffman LC, Al-Attar A. Ineffective treatment of keloids with interferon alpha-2b. *Plast Reconstr Surg.* 2006;117(1):247–252.
90. Berman B, Flores F. Recurrence rates of excised keloids treated with postoperative triamcinolone acetonide injections or interferon alfa-2b injections. *J Am Acad Dermatol.* 1997;37(5 Pt 1):755–757.
91. al-Khawajah MM. Failure of interferon-alpha 2b in the treatment of mature keloids. *Int J Dermatol.* 1996;35(7):515–517.
92. Wong TW, Chiu HC, Yip KM. Intralesional interferon alpha-2b has no effect in the treatment of keloids. *Br J Dermatol.* 1994;130(5):683–685.
93. Broker BJ, Rosen D, Amsberry J, et al. Keloid excision and recurrence prophylaxis via intradermal interferon-gamma injections: a pilot study. *Laryngoscope.* 1996;106(12 Pt 1):1497–501.
94. Granstein RD, Rook A, Flotte TJ, et al. A controlled trial of intralesional recombinant interferon-gamma in the treatment of keloidal scarring. Clinical and histologic findings. *Arch Dermatol.* 1990;126(10):1295–1302.
95. Larrabee WF, Jr., East CA, Jaffe HS, et al. Intralesional interferon gamma treatment for keloids and hypertrophic scars. *Arch Otolaryngol Head Neck Surg.* 1990;116(10):1159–1162.
96. Lee JH, Kim SE, Lee AY. Effects of interferon-alpha2b on keloid treatment with triamcinolone acetonide intralesional injection. *Int J Dermatol.* 2008;47(2):183–186.
97. Yamamoto T. Bleomycin and the skin. *Br J Dermatol.* 2006;155(5):869–875.
98. Takeuchi T. Antitumor antibiotics discovered and studied at the Institute of Microbial Chemistry. *J Cancer Res Clin Oncol.* 1995;121(9–10):505–510.
99. Tounekti O, Pron G, Belehradek J, Jr., Mir LM. Bleomycin, an apoptosis-mimetic drug that induces two types of cell death depending on the number of molecules internalized. *Cancer Res.* 1993;53(22):5462–5469.
100. Hendricks T, Martens MF, Huyben CM, Wobbes T. Inhibition of basal and TGF beta-induced fibroblast collagen synthesis by antineoplastic agents. Implications for wound healing. *Br J Cancer.* 1993;67(3):545–550.
101. Sterling KM, Jr., DiPetrillo TA, Kotch JP, Cutroneo KR. Bleomycin-induced increase of collagen turnover in IMR-90 fibroblasts: an in vitro model of connective tissue restructuring during lung fibrosis. *Cancer Res.* 1982;42(9):3502–3506.
102. Yeowell HN, Marshall MK, Walker LC, et al. Regulation of lysyl oxidase mRNA in dermal fibroblasts from normal donors and patients with inherited connective tissue disorders. *Arch Biochem Biophys.* 1994;308(1):299–305.
103. Aggarwal H, Saxena A, Lubana PS, et al. Treatment of keloids and hypertrophic scars using bleom. *J Cosmet Dermatol.* 2008;7(1):43–49.
104. Espana A, Solano T, Quintanilla E. Bleomycin in the treatment of keloids and hypertrophic scars by multiple needle punctures. *Dermatol Surg.* 2001;27(1):23–27.
105. Naeini FF, Najafian J, Ahmadpour K. Bleomycin tattooing as a promising therapeutic modality in large keloids and hypertrophic scars. *Dermatol Surg.* 2006;32(8):1023–1029; discussion 9–30.
106. Saray Y, Gulec AT. Treatment of keloids and hypertrophic scars with dermojet injections of bleomycin: a preliminary study. *Int J Dermatol.* 2005;44(9):777–784.
107. Manca G, Pandolfi P, Gregorelli C, et al. Treatment of keloids and hypertrophic scars with bleomycin and electroporation. *Plast Reconstr Surg.* 2013;132(4):621e–630e.
108. Kim DY, Kim ES, Eo SR, et al. A surgical approach for earlobe keloid: keloid fillet flap. *Plast Reconstr Surg.* 2004;113(6):1668–1674.
109. Syed F, Ahmadi E, Iqbal SA, et al. Fibroblasts from the growing margin of keloid scars produce higher levels of collagen I and III compared with intralesional and extralesional sites: clinical implications for lesional site-directed therapy. *Br J Dermatol.* 2011;164(1):83–96.
110. Tan KT, Shah N, Pritchard SA, et al. The influence of surgical excision margins on keloid prognosis. *Ann Plast Surg.* 2010;64(1):55–58.
111. Balaraman B, Geddes ER, Friedman PM. Best reconstructive techniques: improving the final scar. *Dermatol Surg.* 2015;41 Suppl 10:S265–S275.
112. Sleilati F. Immediate earlobe reconstruction with double-crossed skin flaps. *J Plast Reconstr Aesthet Surg.* 2006;59(9):1003–1005.
113. Tannir D, Leshin B. Utility of a bilayered banner transposition flap in reconstruction of the lower third of the pinna. *Dermatol Surg.* 2000;26(7): 687–689.
114. Ziccardi VB, Lamphier J. Use of keloid skin as an autograft for earlobe reconstruction after excision. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;89(6):674–675.
115. Burm JS, Hansen JE. Full-thickness skin grafting with marginal deepithelialization of the defect for reconstruction of helical rim keloids. *Ann Plast Surg.* 2010;65(2):193–196.
116. Nguyen KT, Shikowitz L, Kasabian AK, Bastidas N. A novel approach to keloid reconstruction with bilaminar dermal substitute and epidermal skin grafting. *Plast Reconstr Surg.* 2016;138(1):235–239.
117. Chen Y, Chhabra N, Liu YC, Zender CA. Lateral arm microvascular free tissue reconstruction of a large neck keloid. *Am J Otolaryngol.* 2014;35(4):514–516.
118. Wang J, Min P, Grassetti L, et al. Preliminary outcomes of distal IMAP and SEAP flaps for the treatment of unstable keloids subject to recurrent inflammation and infections in the lower sternal and upper abdominal areas. *J Reconstr Microsurg.* 2015;31(9):621–630.
119. Xue D, Qian H. Surgical management for large chest keloids with internal mammary artery perforator flap. *An Bras Dermatol.* 2016;91(1):103–105.
120. Lee Y, Minn KW, Baek RM, Hong JJ. A new surgical treatment of keloid: keloid core excision. *Ann Plast Surg.* 2001;46(2):135–140.
121. Luo S, Benathan M, Raffoul W, et al. Abnormal balance between proliferation and apoptotic cell death in fibroblasts derived from keloid lesions. *Plast Reconstr Surg.* 2001;107(1):87–96.
122. Wong MS. Intralesional excision of keloids. *Plast Reconstr Surg.* 2005;116(2):675.
123. Ogawa R, Akaishi S, Dohi T, et al. Analysis of the surgical treatments of 63 keloids on the cartilaginous part of the auricle: effectiveness of the core excision method. *Plast Reconstr Surg.* 2015;135(3):868–875.
124. Har-Shai Y, Amar M, Sabo E. Intralesional cryotherapy for enhancing the involution of hypertrophic scars and keloids. *Plast Reconstr Surg.* 2003;111(6):1841–1852.
125. Har-Shai Y, Sabo E, Rohde E, et al. Intralesional cryosurgery enhances the involution of recalcitrant auricular keloids: a new clinical approach supported by experimental studies. *Wound Repair Regen.* 2006;14(1):18–27.
126. Har-Shai Y, Mettanes I, Zilberstein Y, et al. Keloid histopathology after intralesional cryosurgery treatment. *J Eur Acad Dermatol Venereol.* 2011;25(9):1027–1036.
127. Awad SM, Ismail SA, Sayed DS, et al. Suppression of transforming growth factor-beta1 expression in keloids after cryosurgery. *Cryobiology.* 2017;75: 151–153.
128. Abdel-Meguid AM, Weshahy AH, Sayed DS, et al. Intralesional vs. contact cryosurgery in treatment of keloids: a clinical and immunohistochemical study. *Int J Dermatol.* 2015;54(4):468–475.
129. Gupta S, Kumar B. Intralesional cryosurgery using lumbar puncture and/or hypodermic needles for large, bulky, recalcitrant keloids. *Int J Dermatol.* 2001;40(5):349–353.
130. Mourad B, Elfar N, Elsheikh S. Spray versus intralesional cryotherapy for keloids. *J Dermatolog Treat.* 2016;27(3):264–269.
131. O'Boyle CP, Shayan-Arani H, Hamada MW. Intralesional cryotherapy for hypertrophic scars and keloids: a review. *Scars Burn Heal.* 2017;3:2059513117702162.
132. Chopinaud M, Pham AD, Labbe D, et al. Intralesional cryosurgery to treat keloid scars: results from a

retrospective study. *Dermatology.* 2014;229(3): 263–270.
133. van Leeuwen MC, Bulstra AE, van Leeuwen PA, Niessen FB. A new argon gas-based device for the treatment of keloid scars with the use of intralesional cryotherapy. *J Plast Reconstr Aesthet Surg.* 2014;67(12):1703–1710.
134. van Leeuwen MC, van der Wal MB, Bulstra AE, et al. Intralesional cryotherapy for treatment of keloid scars: a prospective study. *Plast Reconstr Surg.* 2015;135(2):580–589.
135. Xu J, Yang E, Yu NZ, Long X. Radiation therapy in keloids treatment: history, strategy, effectiveness, and complication. *Chin Med J (Engl).* 2017;130(14):1715–1721.
136. Guix B, Henriquez I, Andres A, et al. Treatment of keloids by high-dose-rate brachytherapy: a seven-year study. *Int J Radiat Oncol Biol Phys.* 2001;50(1):167–172.
137. Mankowski P, Kanevsky J, Tomlinson J, et al. Optimizing radiotherapy for keloids: a meta-analysis systematic review comparing recurrence rates between different radiation modalities. *Ann Plast Surg.* 2017;78(4):403–411.
138. Ji J, Tian Y, Zhu YQ, et al. Ionizing irradiation inhibits keloid fibroblast cell proliferation and induces premature cellular senescence. *J Dermatol.* 2015;42(1):56–63.
139. Goutos I, Ogawa R. Brachytherapy in the adjuvant management of keloid scars: literature review. *Scars Burn Heal.* 2017;3:2059513117735483.
140. van Leeuwen MC, Stokmans SC, Bulstra AE, et al. Surgical excision with adjuvant irradiation for treatment of keloid scars: a systematic review. *Plast Reconstr Surg Glob Open.* 2015;3(7):e440.
141. Escarmant P, Zimmermann S, Amar A, et al. The treatment of 783 keloid scars by iridium 192 interstitial irradiation after surgical excision. *Int J Radiat Oncol Biol Phys.* 1993;26(2):245–251.
142. van Leeuwen MC, Stokmans SC, Bulstra AE, et al. High-dose-rate brachytherapy for the treatment of recalcitrant keloids: a unique, effective treatment protocol. *Plast Reconstr Surg.* 2014;134(3):527–534.
143. De Cicco L, Vischioni B, Vavassori A, et al. Postoperative management of keloids: low-dose-rate and high-dose-rate brachytherapy. *Brachytherapy.* 2014;13(5):508–513.
144. Van Den Brenk HA, Minty CC. Radiation in the management of keloids and hypertrophic scars. *Br J. Surg.* 1960;47:595–605.
145. Sakamoto T, Oya N, Shibuya K, Nagata Y, Hiraoka M. Dose-response relationship and dose optimization in radiotherapy of postoperative keloids. *Radiother Oncol.* 2009;91(2):271–276.
146. van de Kar AL, Kreulen M, van Zuijlen PP, Oldenburger F. The results of surgical excision and adjuvant irradiation for therapy-resistant keloids: a prospective clinical outcome study. *Plast Reconstr Surg.* 2007;119(7):2248–2254.
147. Berman B, Nestor MS, Gold MH, et al. Low rate of keloid recurrences following treatment of keloidectomy sites with a biologically effective dose 30 of superficial radiation. *The Journal of Cutaneous Medicine.* 2018;2(6):402–403.
148. Ogawa R, Miyashita T, Hyakusoku H, et al. Postoperative radiation protocol for keloids and hypertrophic scars: statistical analysis of 370 sites followed for over 18 months. *Ann Plast Surg.* 2007;59(6):688–691.
149. Flickinger JC. A radiobiological analysis of multicenter data for postoperative keloid radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;79(4):1164–1170.
150. Kal HB, Veen RE. Biologically effective doses of postoperative radiotherapy in the prevention of keloids. Dose-effect relationship. *Strahlenther Onkol.* 2005;181(11):717–723.
151. Renz P, Hasan S, Gresswell S, et al. Dose effect in adjuvant radiation therapy for the treatment of resected keloids. *Int J Radiat Oncol Biol Phys.* 2018;102(1):149–154.
152. Ogawa R, Yoshitatsu S, Yoshida K, Miyashita T. Is radiation therapy for keloids acceptable? The risk of radiation-induced carcinogenesis. *Plast Reconstr Surg.* 2009;124(4):1196–1201.
153. Bijlard E, Verduijn GM, Harmeling JX, et al. Optimal high-dose-rate brachytherapy fractionation scheme after keloid excision: a retrospective multicenter comparison of recurrence rates and complications. *Int J Radiat Oncol Biol Phys.* 2018;100(3):679–686.
154. McKeown SR, Hatfield P, Prestwich RJ, et al. Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. *Br J Radiol.* 2015;88(1056):20150405.
155. Cannarozzo G, Sannino M, Tamburi F, et al. Flash-lamp pulsed-dye laser treatment of keloids: results of an observational study. *Photomed Laser Surg.* 2015;33(5):274–277.
156. Hultman CS, Edkins RE, Lee CN, et al. Shine on: review of laser- and light-based therapies for the treatment of burn scars. *Dermatol Res Pract.* 2012;2012:243651.
157. Reiken SR, Wolfort SF, Berthiaume F, et al. Control of hypertrophic scar growth using selective photothermolysis. *Lasers Surg Med.* 1997;21(1): 7–12.
158. Stephanides S, Rai S, August P, et al. Treatment of refractory keloids with pulsed dye laser alone and with rotational pulsed dye laser and intralesional corticosteroids: a retrospective case series. *Laser Ther.* 2011;20(4):279–286.
159. Dierickx C, Goldman MP, Fitzpatrick RE. Laser treatment of erythematous/hypertrophic and pigmented scars in 26 patients. *Plast Reconstr Surg.* 1995;95(1):84–90; discussion 1–2.
160. Kuo YR, Jeng SF, Wang FS, et al. Flashlamp pulsed dye laser (PDL) suppression of keloid proliferation through down-regulation of TGF-beta1 expression and extracellular matrix expression. *Lasers Surg Med.* 2004;34(2):104–108.
161. Kuo YR, Wu WS, Jeng SF, et al. Activation of ERK and p38 kinase mediated keloid fibroblast apoptosis after flashlamp pulsed-dye laser treatment. *Lasers Surg Med.* 2005;36(1):31–37.
162. Kuo YR, Wu WS, Wang FS. Flashlamp pulsed-dye laser suppressed TGF-beta1 expression and proliferation in cultured keloid fibroblasts is mediated by MAPK pathway. *Lasers Surg Med.* 2007;39(4):358–364.
163. Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. *Lancet.* 1995;345(8959): 1198–1200.
164. Al-Mohamady Ael S, Ibrahim SM, Muhammad MM. Pulsed dye laser versus long-pulsed Nd:YAG laser in the treatment of hypertrophic scars and keloid: a comparative randomized split-scar trial. *J Cosmet Laser Ther.* 2016;18(4):208–212.
165. Manuskiatti W, Fitzpatrick RE, Goldman MP. Energy density and numbers of treatment affect response of keloidal and hypertrophic sternotomy scars to the 585-nm flashlamp-pumped pulsed-dye laser. *J Am Acad Dermatol.* 2001;45(4):557–565.
166. Nouri K, Elsaie ML, Vejjabhinanta V, et al. Comparison of the effects of short- and long-pulse durations when using a 585-nm pulsed dye laser in the treatment of new surgical scars. *Lasers Med Sci.* 2010;25(1):121–126.
167. Paquet P, Hermanns JF, Pierard GE. Effect of the 585 nm flashlamp-pumped pulsed dye laser for the treatment of keloids. *Dermatol Surg.* 2001;27(2):171–174.
168. Shih PY, Chen HH, Chen CH, et al. Rapid recurrence of keloid after pulse dye laser treatment. *Dermatol Surg.* 2008;34(8):1124–1127.
169. de las Alas JM, Siripunvarapon AH, Dofitas BL. Pulsed dye laser for the treatment of keloid and hypertrophic scars: a systematic review. *Expert Rev Med Devices.* 2012;9(6):641–650.
170. Manuskiatti W, Wanitphakdeedecha R, Fitzpatrick RE. Effect of pulse width of a 595-nm flashlamp-pumped pulsed dye laser on the treatment response of keloidal and hypertrophic sternotomy scars. *Dermatol Surg.* 2007;33(2):152–161.
171. Kuo YR, Wu WS, Jeng SF, et al. Suppressed TGF-beta1 expression is correlated with up-regulation of matrix metalloproteinase-13 in keloid regression after flashlamp pulsed-dye laser treatment. *Lasers Surg Med.* 2005;36(1):38–42.
172. Yu HY, Chen DF, Wang Q, Cheng H. Effects of lower fluence pulsed dye laser irradiation on production of collagen and the mRNA expression of collagen relative gene in cultured fibroblasts in vitro. Chinese medical journal 2006;119(18):1543–1547.
173. Swinehart JM. Hypertrophic scarring resulting from flashlamp-pumped pulsed dye laser surgery. *J Am Acad*

Dermatol. 1991;25(5 Pt 1):845–846.
174. Jin R, Huang X, Li H, et al. Laser therapy for prevention and treatment of pathologic excessive scars. *Plast Reconstr Surg.* 2013;132(6):1747–1758.
175. Chiu CH, Chan HH, Ho WS, et al. Prospective study of pulsed dye laser in conjunction with cryogen spray cooling for treatment of port wine stains in Chinese patients. *Dermatol Surg.* 2003;29(9):909–915; discussion 15.
176. Azzam OA, Bassiouny DA, El-Hawary MS, et al. Treatment of hypertrophic scars and keloids by fractional carbon dioxide laser: a clinical, histological, and immunohistochemical study. *Lasers Med Sci.* 2016;31(1):9–18.
177. Khansa I, Harrison B, Janis JE. Evidence-based scar management: how to improve results with technique and technology. *Plast Reconstr Surg.* 2016;138(3 Suppl):165s–78s.
178. Nicoletti G, De Francesco F, Mele CM, et al. Clinical and histologic effects from CO2 laser treatment of keloids. *Lasers Med Sci.* 2013;28(3):957–964.
179. Scrimali L, Lomeo G, Nolfo C, et al. Treatment of hypertrophic scars and keloids with a fractional CO2 laser: a personal experience. *J Cosmet Laser Ther.* 2010;12(5):218–221.
180. Scrimali L, Lomeo G, Tamburino S, et al. Laser CO2 versus radiotherapy in treatment of keloid scars. *J Cosmet Laser Ther.* 2012;14(2):94–97.
181. Ang CC, Tay YK, Kwok C. Retrospective analysis of earlobe keloids treated with the carbon dioxide laser ablation or cold steel debulking surgery. *J Cosmet Laser Ther.* 2013;15(5):271–273.
182. Norris JE. The effect of carbon dioxide laser surgery on the recurrence of keloids. *Plast Reconstr Surg.* 1991;87(1):44–49; discussion 50–53.
183. Stern JC, Lucente FE. Carbon dioxide laser excision of earlobe keloids. A prospective study and critical analysis of existing data. *Arch Otolaryngol Head Neck Surg.* 1989;115(9):1107–1111.
184. Driscoll B. Treating keloids with carbon dioxide lasers. *Arch Otolaryngol Head Neck Surg.* 2001;127(9):1145.
185. Tenna S, Aveta A, Filoni A, Persichetti P. A new carbon dioxide laser combined with cyanoacrylate glue to treat earlobe keloids. *Plast Reconstr Surg.* 2012;129(5):843e–844e; author reply 4e–6e.
186. Wagner JA, Paasch U, Bodendorf MO, et al. Treatment of keloids and hypertrophic scars with the triple-mode Er:YAG laser: a pilot study. *Med Laser Appl.* 2011;26(1):10–15.
187. Avram MM, Tope WD, Yu T, Szachowicz E, Nelson JS. Hypertrophic scarring of the neck following ablative fractional carbon dioxide laser resurfacing. *Lasers Surg Med.* 2009;41(3):185–188.
188. Ali FR, Al-Niaimi F. Treatment of nonmelanoma skin cancers using laser-assisted drug delivery. *Dermatol Surg.* 2018;44(2):310.
189. Nino M, Calabro G, Santoianni P. Topical delivery of active principles: the field of dermatological research. *Dermatol Online J.* 2010;16(1):4.
190. Braun SA, Schrumpf H, Buhren BA, et al. Laser-assisted drug delivery: mode of action and use in daily clinical practice. *J Dtsch Dermatol Ges.* 2016;14(5):480–488.
191. Zaleski-Larsen LA, Fabi SG. Laser-assisted drug delivery. *Dermatol Surg.* 2016;42(8):919–931.
192. Cavalie M, Sillard L, Montaudie H, et al. Treatment of keloids with laser-assisted topical steroid delivery: a retrospective study of 23 cases. *Dermatol Ther.* 2015;28(2):74–78.
193. Park JH, Chun JY, Lee JH. Laser-assisted topical corticosteroid delivery for the treatment of keloids. *Lasers Med Sci.* 2017;32(3):601–608.
194. Lee WR, Shen SC, Al-Suwayeh SA, et al. Laser-assisted topical drug delivery by using a low-fluence fractional laser: imiquimod and macromolecules. *J Control Release.* 2011;153(3):240–248.
195. Lee WR, Shen SC, Wang KH, et al. The effect of laser treatment on skin to enhance and control transdermal delivery of 5-fluorouracil. *J Pharm Sci.* 2002;91(7):1613–1626.
196. Wenande E, Olesen UH, Nielsen MM, et al. Fractional laser-assisted topical delivery leads to enhanced, accelerated and deeper cutaneous 5-fluorouracil uptake. *Expert Opin Drug Deliv.* 2017;14(3):307–317.
197. Amable PR, Carias RB, Teixeira MV, et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. *Stem Cell Res Ther.* 2013;4(3):67.
198. Lynch MD, Bashir S. Applications of platelet-rich plasma in dermatology: a critical appraisal of the literature. *J Dermatolog Treat.* 2016;27(3):285–289.
199. Cho JW, Kim SA, Lee KS. Platelet-rich plasma induces increased expression of G1 cell cycle regulators, type I collagen, and matrix metalloproteinase-1 in human skin fibroblasts. *Int J Mol Med.* 2012;29(1):32–36.
200. Kim DH, Je YJ, Kim CD, et al. Can platelet-rich plasma be used for skin rejuvenation? Evaluation of effects of platelet-rich plasma on human dermal fibroblast. *Ann Dermatol.* 2011;23(4):424–431.
201. Nam SM, Kim YB. The effects of platelet-rich plasma on hypertrophic scars fibroblasts. *Int Wound J.* 2018;15(4):547–554.
202. Hersant B, SidAhmed-Mezi M, Picard F, et al. Efficacy of autologous platelet concentrates as adjuvant therapy to surgical excision in the treatment of keloid scars refractory to conventional treatments: a pilot prospective study. *Ann Plast Surg.* 2018;81(2):170–175.
203. Jones ME, McLane J, Adenegan R, et al. Advancing keloid treatment: a novel multimodal approach to ear keloids. *Dermatol Surg.* 2017;43(9):1164–1169.
204. Azzam EZ, Omar SS. Treatment of auricular keloids by triple combination therapy: Surgical excision, platelet-rich plasma, and cryosurgery. *J Cosmet Dermatol.* 2018;17(3):502–510.
205. Davis SA, Feldman SR, McMichael AJ. Management of keloids in the United States, 1990–2009: an analysis of the National Ambulatory Medical Care Survey. *Dermatol Surg.* 2013;39(7):988–994.
206. Del Toro D, Dedhia R, Tollefson TT. Advances in scar management: prevention and management of hypertrophic scars and keloids. *Curr Opin Otolaryngol Head Neck Surg.* 2016;24(4):322–329.
207. Durani P, Bayat A. Levels of evidence for the treatment of keloid disease. *J Plast Reconstr Aesthet Surg.* 2008;61(1):4–17.
208. Forbat E, Ali FR, Al-Niaimi F. Treatment of keloid scars using light-, laser- and energy-based devices: a contemporary review of the literature. *Lasers Med Sci.* 2017;32(9):2145–2154. JCAD