



# The Operating Room Global Journal (TORGJ)

<https://torgjournal.org/>

ISSN: 3105-3262



## Predictors of Keloid Recurrence Following Surgical Excision: Clinical, Surgical, and Molecular Determinants

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### ABSTRACT

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#### Declaration:

**Authors' Contribution:** Equal contributions

**Conflict of Interest:** No conflict of interest.

**Funding:** No funding received by the authors.

#### Article History:

Received: 22-02-2026

Accepted: 27-02-2026

Available Online: 28-02-2026

#### QR access this Article



**Background:** Keloids are benign fibroproliferative lesions resulting from abnormal wound healing. Unlike hypertrophic scars, they extend beyond the original injury and rarely regress without treatment. Surgical excision is commonly used for symptomatic or cosmetically unacceptable lesions; however, recurrence rates remain high (45–100%), necessitating structured perioperative strategies to reduce risk.

**Objective:** To synthesize current evidence on predictors of keloid recurrence after surgical excision and propose a risk-stratified framework for operative management.

**Methods:** A narrative review of contemporary literature examining clinical, surgical, and molecular predictors of recurrence was conducted.

**Results:** Younger age, darker Fitzpatrick phototype, family history, and prior recurrence increase risk. Lesion size, chronicity, and location in high-tension areas further contribute to recurrence. Surgical technique significantly influences long-term outcomes. Although persistent profibrotic signaling drives keloid formation, clinically applicable molecular predictive biomarkers remain underdeveloped.

**Conclusion:** Keloid recurrence reflects persistence of a pathological wound microenvironment rather than surgical failure alone. Effective management requires a multifaceted, risk-based approach with ongoing follow-up.

**Keywords:** Keloid; Recurrence; Surgical Excision; Risk Factors; Wound Healing; Adjuvant Therapy

## INTRODUCTION

The Keloids are a type of skin lesion that occurs when the skin does not heal correctly, resulting in a large build-up of collagen and other materials, stretching beyond the area of the wound site. Keloids are growing beyond the margins of the damaged skin area and do not appear to resolve spontaneously, which is different from hypertrophic scars that remain within the area of the wound and will tend to regress over time. The major clinical issues presented by keloids go beyond appearance alone. Patients are also subjected to multiple forms of distress, including itching, discomfort or pain, restricted functioning and/or significant psychological impact on their well-being.

From the surgical perspective, Keloids are one of the most difficult lesions to manage and surgically excising them removes the symptomatic burden for the patient (they relieve the symptoms associated with keloids such as itching and pain) and can provide better aesthetic outcomes for the patient than if they must continue to live with the keloid. However, many of these patients will continue to have trouble with keloids even after having their keloid excised. The estimated rates of recurrence for keloid excision vary widely depending on the location of the keloid and the patient's individual characteristics; however, the overall findings are that excision on its own is insufficient in most instances. Furthermore, the likelihood of having a more aggressive lesion with a greater amount of collagen and resistance to previous methods of treatment increases for those patients who have had a recurrence following surgical excision.

Keloid recurrences occur due to a combination of factors, including surgical technique, inherent patient susceptibility, and mechanical forces on the wound site. Keloids are more commonly found on high-tension areas such as the chest above the sternum, shoulders, and upper back, indicating the importance of mechanical stress in keeping fibroblast activity going via mechanotransduction. Furthermore, there appears to be a genetic and immunological predisposition to keloid formation, suggested by the high level of familial clustering and increased incidence in patients with darker skin. Molecular research has indicated that keloids tend to have continuing activation of abnormally profibrotic signalling (including TGF- $\beta$  mediated pathways) as well as dysregulated immune systems and resistance to apoptosis. Even though this information is becoming clearer, it continues to be challenging to find a clinical way to implement this molecular finding into an actionable predictive tool, limiting the use of predictive biomarkers to make clinical decisions.

Along with high rates of recurrence (when excised alone) and lack of consensus on the best way to manage keloids, there is a need for a systematic approach to developing evidence-based clinical guidance. This narrative-based clinical practice review aims to create a risk-based framework for making perioperative decisions by integrating established clinical predictors, surgical determinants, and new findings from biology. The goal of the review is to help surgeons understand how surgical strategies can correlate with biological understanding, thereby allowing them to rationally approach preventing recurrence.

## METHODS

The information in this Narrative Clinical Practice Review has been compiled to provide an overview of current research available on recurrence predictors related to keloid formation following a surgical excision procedure. This paper will integrate current clinical observations, surgical operating principles, and emerging biological knowledge to develop a framework that can be utilised for making perioperative decisions.

Peer reviewed literature describing operative management and postoperative outcome information was obtained using a structured review of numerous large databases to develop recurrence rate data, the specific techniques used for your surgical intervention, adjunctive therapies and translational biological reports. Most of the studies included would relate directly to clinical outcomes; however, a few have been included to provide an understanding as to how keloids recur and what are the mechanisms involved.

Since this is considered a Narrative Review, formal systematic review methodology was not utilised. Therefore, there were no established inclusion criteria or PRISMA flow diagrams or methodologies for assessing risk of bias based on quantitative data nor was there a grading system for evidence. Therefore, it should be noted that the interpretation of the evidence was descriptive rather than based on formal analysis of each study's design. Additionally, the heterogeneity of the reported recurrence rates and limitations of the existing studies should be noted; therefore, any conclusions drawn from this evidence were based on the best available evidence, and where there is limited high quality Randomised Controlled Trials; these conclusions should be drawn with significant caution in mind.

Artificial intelligence-based language tools were used solely to assist with grammatical refinement, structural organization, and clarity of expression. The authors had complete control over all literary analyses; clinical summaries, conceptual framework and scientific conclusions were independently generated by the authors. The authors take responsibility for the authenticity and accuracy of the final manuscript.

This review aims to define an evidence-based, risk-adaptable surgical management approach for patients with Recurrence. The review does not intend to pool recurrence rates for statistical purposes; its purpose is to translate current literature into a practical and clinically applicable manner.

### PATHOPHYSIOLOGY OF KELOID FORMATION AND RECURRENCE

Keloids are the result of the dysfunction of normal wound healing processes. The process of normal tissue healing or repair consists of the three separate phases of healing: (1) Inflammation Phase (2) Proliferation Phase and (3) Remodelling Phase. When an individual is susceptible to developing keloids, the normal healing process fails to complete all three phases of injury care, thereby leading keloid formation by continued fibroblast activation, excessive deposition of extracellular matrix, and ultimately the ongoing expansion of the keloid scar tissue beyond its normal boundaries.

Although keloid fibroblasts can proliferate at an increased rate than normal fibroblasts, they demonstrate resistance to programmed cell death (to apoptosis). They are responsible for producing an excess of type I and type III collagen, fibronectin, and proteoglycans, which contribute to the accelerated deposition of collagen and fibronectin in keloid tissues. Also, an increased imbalance exists between matrix metalloproteinases (enzymes that breakdown extracellular matrix) and their tissue inhibitors, thus leading to a failure to breakdown (degrade) the extracellular matrix and accumulation of dense and disorganized bundles of collagen within the keloid tissue. Additionally, myofibroblasts continue to survive in the keloid tissue and contribute to excessive pull, or "contracture," from the keloid tissue, due to their role as contractile cells within the tissue and ongoing extracellular matrix deposition.

The mechanisms that promote fibrosis are closely tied to how cells communicate via signaling pathways. Many of these pathways utilize a class of molecules called "transforming growth factor-betas" (TGF-beta). The TGF-beta class of molecules contains the two prototype isoforms known as TGF-b1 and TGF-b2, both are very powerful and play an important role in the signalling pathways for regulating the growth and differentiation of fibroblasts into myofibroblasts. Activation of the TGF-beta/Smad signaling pathway leads to the production of the extracellular matrix (ECM) and prevents normal ECM remodeling. A number of other pathways exist to provide additional protection to fibroblasts by promoting fibroblast survival and increasing their resistance to programmed cell death (apoptosis). In addition to the TGF-beta pathways that stimulate fibroblast activity, the JAK/STAT pathways, PI3K/Akt/mTOR pathways and MAPK pathways also stimulate fibroblast activity. Although these pathways have been well established and studied, they are not yet available for use in a clinical setting.

Fibroblast activity is also regulated by mechanical forces acting on cells. Fibroblasts respond to mechanical forces such as tension by activating intracellular signalling pathways, including the YAP/TAZ pathways and coordinating transcriptional profiles that enhance the expression of profibrotic genes. This leads us to the sites on the body where

fibroblasts preferentially form keloid scars; high tension areas such as the presternal area of the chest, shoulders and upper back. Surgical excision of keloid scars can result in mechanical stress and additional tissue damage to the keloid scar; a surgical closure that is created under tension can result in re-activation of profibrotic pathways.

### CLINICAL PREDICTORS OF RECURRENCE

It is possible to determine the presence of identifiable clinical factors that can identify the occurrence of keloids prior to surgery that might lead to their occurrence after surgery. Identifying identifiable factors when assessing patient's pre-operative will enable the physician(s) to effectively stratify patients and be able to tailor their peri-operative management according to their recurrence risk.

An individual's age is consistently associated with their propensity to experience a recurrence after surgical excision of keloids. Individuals less than 30 years old have a higher likelihood of recurrence than individuals 30 or older. This is likely because inflammatory responses are typically more robust, and fibroblasts have more ability to replicate themselves at younger ages. As a result, there is an increased chance of developing new collagen and a greater chance that a wound created by surgical intervention will continue to be fibrotically active for a longer period. Although age alone does not determine the outcome from surgery, it does serve as an important modifier of recurrence risk when added to other variables.

Phototype also has a significant impact on an individual's risk of experiencing recurrence following surgical excision of keloids. Individuals with darker Fitzpatrick phototypes are more likely to develop keloids for the first time and to have recurrence after surgical excision. The underlying biological mechanisms behind this have not yet been fully elucidated, but they likely involve differences in inflammatory signaling pathways, fibroblast biology, and cytokine expression. It should be noted that ethnicity does not solely account for biological susceptibility to have keloids; it is more accurately explained through the wound healing properties of the skin associated with the Fitzpatrick phototype than through demographic considerations.

The genetic factors that lead to a person being more likely to have recurrent keloids are a key factor in its recurrence. The fact that there is a familial clustering of keloids lends itself to the theory that a hereditary predisposition exists, which is likely attributed to genetic factors that are involved in fibroblast function, turnover of the extracellular matrix, and modulation of inflammation. There are no genetic markers that have been established for clinical use at this time; however, a positive family history may be indicative of an increased biological risk of developing the disease. Patients with many relatives with keloids usually demonstrate aggressive patterns of recurrence.

The most powerful predictor of subsequent recurrence is a history of previous recurrence. Lesions that are recurrent will have more collagen, more fibroblasts, and less response to standard treatment than a primary lesion. This may mean that the recurrent keloid lesion expresses a more well-established profibrotic phenotype. Therefore, patients who have had lesions excised and then regrown should be classified as high risk and should be treated utilizing a multimodal approach.

The characteristics of a keloid lesion can also be important regarding the likelihood of recurrence. The anatomical location of the keloid lesion is particularly significant. Keloids in high-tension areas such as the presternal area of the chest, along the shoulders, on the upper back, or along the borders of the mandible demonstrate a much higher recurrence rate than a lesion located on the earlobe as it is in a low-tension area. The distribution of keloids in relation to tension illustrates the impact that mechanical stress can have on sustaining fibroblast activation through mechanisms of mechanotransduction. When planning for surgery on keloid lesions, consideration should be given to the mechanical environment surrounding the area of the lesion.

Lesion dimensions provide additional predictive value in terms of prognostic factors. The size of the scar correlates positively with both the number of fibroblasts and the amount of connective tissue that needs to be removed during the excision procedure. This means that larger scars cause larger excisions. The increase in the surface area of the wound may lead to greater amounts of inflammation and mechanical stress after surgery, increasing the chances of developing another keloid. Any lesions greater than five cm in the long axis should be viewed as being at higher risk to recur, particularly if they are located in a location that has mechanical stress on it.

The length of time the lesion has been present will influence predictive outcomes. Old and established keloids tend to possess a mature and stable fibrotic architecture, and their molecular dysregulation is often stable over time. In relation to kinesiology/exercise, chronic lesions may become less responsive to single treatment modalities and/or more likely to regrow after they have been excised because they represent a biologically stable fibrotic process.

Most of these clinical predictors will not be found alone - they usually work in a cumulative fashion and are universal in terms of how they represent multiple factors that will contribute to the risk of recurrence. For instance, a young male with an exaggerated lesion located on his presternal area, with dark skin (phototypes 4 to 6) and having previously experienced different size keloids, presents a much higher risk for re-growing than someone with a small first episode keloid on their top lobe. The ability to recognize how these clinical factors relate to each other provides the basis upon which to classify the overall risk of recurrence, and to potentially choose the most appropriate type of treatment for your surgical procedure and adjunctive therapy.

## SURGICAL PREDICTORS AND TECHNIQUE CONSIDERATIONS

Surgical excision is a major way to treat symptomatic or cosmetically significant keloids. However, the recurrence rate after excision is directly impacted by the method used to perform the procedure and the mechanical environment surrounding the wound during recovery. Recurrence rates with excision alone are high because the surgical procedure removes the visible scar tissue but does not repair the underlying dysregulated wound healing process. As such, the surgical approach to keloids must be thought of as not just removing the lesion but also modifying the underlying environment so that it is no longer biologically susceptible to the formation of new lesions.

Treating keloids surgically with excision under mechanical tension during the closure of the wound is one of the most important modifiable risk factors influencing the likelihood of recurrence. Fibroblasts show a strong response to mechanical tension and the application of mechanical tension during closure of the wound allows the fibroblasts to "kick back in" and activate the mechano-transductory pathways of fibroblast phenotypic expression, which result in the stimulation of fibroblasts to produce collagen and provide a long-term means of sustaining fibrous tissue in the area of the surgical excision. The development of mechanical tension during surgery stimulates the production of collagen by fibroblasts and keeps fibroblasts alive, resulting in re-creating the environment under which the original lesion occurred. Thus, important components of the surgical approach to keloids are layering of closure, deep fascial suturing to support the closed wound, adequate undermining before closure of the wound, and avoiding primary closure that is too tight. In addition, the need to eliminate mechanical tension when performing excisional surgery on keloids is critically important in high-tension anatomical regions such as the presternal chest and shoulders.

The length of excision is still a matter for medical professionals. Intralesional excision is where a narrow portion of the keloid will be left behind to help relieve tension on the edges of the wound and decrease the inflammatory response; while the goal of an extralesional excision, is to remove all of the visible pathologic appearance, however, some people have indicated that this can create increased mechanical pressure at the margin of the wound. Current available data does not favour one option over the other, stating that both regimens will have equal results; therefore, it is believed that the use of appropriate adjuncts and tension relieving techniques play a much greater role in determining the results of the

surgery than the extent of the margin. Therefore, the decision on how much tissue to excise should be based on the anatomy of the lesion, size of the lesion and likelihood of recurrence.

Postoperatively how surgical specialists handle the tissue may have an impact on the level of inflammation that occurs following surgery. Any excessive manipulation, length of time performing the case and lack of adequate hemostasis may lead to an increase in the inflammatory response late after the surgery. There is limited direct comparative data to suggest that using gentler techniques and better surgical principles will provide a more positive outcome. Patients known to have a fibroproliferative genetic make-up, should use the principle of gentle handling and adhere to the sexual standards of surgery.

We must also consider the anatomical location of a lesion when considering surgical intervention. For example, a lesion that is dynamically moving or subject to forces over time has specific requirements when repairing the wound. Presternally and shoulder lesions are under constant tensile load as they are involved with respiration and the use of the upper extremity. In these instances, additional techniques may be necessary to redistribute tension to reduce the risk of recurrence.

Surgical management alone is insufficient; it is part of an overall strategy to prevent recurrence. The biomechanical environment created when closing the wound, in conjunction with an individual patient's biological predisposition, dictates whether a postoperative healing process will progress towards normal remodeling or re-activation of fibrotic pathways. The awareness of these factors reinforces the necessity of the planned integration of surgical technique with the postoperative adjuvant therapy for moderate and high-risk patients.

## TREATMENT-RELATED PREDICTORS AND ADJUVANT THERAPIES

There are many factors that influence the recurrence of keloid scars following surgical excision, one of which is the use of adjuvant therapies. While surgical excision removes the established keloid scar volume, it does not directly suppress the biochemical signals that lead to increased fibroblast activity and inflammation, or the processes by which mechanical forces are able to cause collagen deposition (mechanotransduction). For those patients who have identifiable risk factors; combination therapy significantly increases the chances of long-term successful outcome when compared with excisional therapy alone.

### Intralesional Corticosteroids

An adjunct therapy that is frequently used in the postoperative period is intralesional corticosteroids (ICS). Triamcinolone acetonide (TAC) is commonly used because it has been shown in some studies to inhibit fibroblast proliferation, decrease collagen production and suppress the production of inflammatory cytokines by fibroblasts. In addition, corticosteroids will enhance collagen degradation and may promote regression of fibrotic changes early in treatment. When administered in the early postoperative period and subsequently given multiple times, ICS therapy has been shown to decrease the rate of keloid scar recurrence compared with surgical excision alone. However, there are potential side effects associated with the use of ICS such as dermal atrophy, telangiectasia, and changes in pigmentation, especially in areas where cosmetic appearance may be an important issue. Nevertheless, ICS remains the first-line adjuvant therapy for keloid scars in patients at low to moderate risk for recurrence.

### Antimetabolites

Antimetabolites (such as 5-fluorouracil) have shown further reduction of recurrence. In fibroblasts that rapidly proliferate, 5-fluorouracil induces cell death and affects fibrosis-related signaling pathways (e.g., by inhibiting TGF-beta signaling). Utilizing both steroids and 5-fluorouracil may improve therapeutic response while decreasing the total amount of steroid needed to achieve a response, and this combination is especially key in the treatment of moderate or very aggressive lesions, as well as those with a previous recurrence.

**Post Operative Radiation therapy**

Administering postoperative radiation soon after surgical excision (typically one to four days) reduces recurrences, particularly among lesions in high-risk anatomic locations and those with a prior recurrence. Radiation therapy also slows down the proliferation of fibroblasts, inhibits blood vessel creation, and destroys the ability of actively replicating cells to replicate their genetic information. Early radiation appears to provide greater benefit than delayed radiation treatment. While newer radiation treatments are low-dose and reduce the risk of long-term complications, careful selection of patients, especially young patients where the theoretical carcinogenic risk is more significant, remains critical to safe and effective treatment.

**Non-surgical treatment of keloids**

Non-invasive techniques, such as silicone and pressure therapy, are considered useful adjunct methods for scar management. Their effects are thought to be related to increasing scar hydration; providing changes to oxygen tension; and changing how collagen fibers are organized. While they cannot be used alone to treat high-risk lesions, they fit into more comprehensive post-operative management programs, especially when combined with pharmaceuticals.

**Lasers and other energy-based treatments for keloids**

Laser-based treatments, such as pulsed dye and fractional ablative lasers, can help diminish blood flow into the scar tissue; increase flexibility of the scar tissue; and increase the ability of drugs injected into the scar to enter and distribute homogeneously throughout the tissue. While there are many opportunities for laser therapies, these therapies should typically not be used alone or as first-line treatment options due to their variable long-term effects with regards to recurrence, depending on the study.

**Timing**

Timing of adjunctive therapy has significant implications. Ideally, primary therapy (e.g., surgical excision) with adjuvant therapy should be initiated prior to observing clinical signs of regrowth and can disrupt the initiation of profibrotic signals. Delayed treatment or intervention may develop a new fibrotic microenvironment which will become progressively more difficult to treat with adjunctive therapies.

**Multimodal Treatment Approach**

Current literature supports the use of a multimodal treatment approach, where the intensity of adjunctive therapies is related to pre-operative recurrence risk. For instance, surgical excision alone is rarely adequate for patients with multiple pre-operative risk factors; therefore, the best approach to reduce recurrences is to incorporate a tension-reducing surgical technique; early pharmacological modulation; selective radiotherapy for high-risk patients; and appropriate monitoring.

**RISK STRATIFICATION FRAMEWORK AND CLINICAL MANAGEMENT MODEL**

To effectively prevent keloids from returning, it is best to start with a structured preoperative assessment of the patient's likelihood of recurrence. The likelihood of keloid recurrence cannot be established by one specific factor, but by the summation of the interaction of a few patient-specific variables that include: biological predisposition, characteristics of the lesion, anatomical biomechanics and operative factors. Thus, the creation of a clinical framework would require the integration of the above-mentioned factors to form a clear strategy for how one will manage the risk of keloid recurrence.

This paper will develop a model that synthesizes the most common clinical predictors of recurrence and will serve as an example of a structured framework for predicting recurrence risk and how it may influence perioperative decision making. It should be noted that this model is a conceptual model and will not have been prospectively validated.

Table 1. Proposed Clinical Risk Stratification Model for Keloid Recurrence

Risk Factor	Clinical Feature	Assigned Weight
Age	Younger than 30 years	1
Fitzpatrick phototype	Type III–VI	1
Family history	Positive	1
Prior recurrence	Present	2
Anatomical site	Presternal, shoulder, upper back	2
Lesion size	Greater than 5 cm	1
Multiple lesions	Present	1

### METHODOLOGICAL RATIONALE FOR WEIGHT ALLOCATION

Here's the proposal weighting system uses a structured synthesis of three areas to determine the weight they presume (the association of predictors). The three areas include (1) consistency of the published cohort and observational studies to demonstrate that the predictor is associated with recurrence; (2) trends in recurrence risk magnitude; and (3) biological plausibility based on the mechanistic understanding of fibroproliferative activity. No quantitative meta-analysis was conducted in this review; therefore, weights are not derived from pooled statistical modeling, but from the officer's integration of the qualitative evidence.

Predictors that are assigned a weight of 2 (e.g., prior recurrence and high-tension) were selected because they have consistently been identified in the clinical literature as strong recurrence predictors and have a clear biological basis for recurrence. Prior recurrence indicates a biologically based, positively profibrotic, phenotype (characterized by increased collagen deposition, increased apoptosis resistance, and increased epigenetic persistence). Additionally, high-tension areas (presteral chest, shoulders and upper back) have shown not only higher rates of recurrence as observed in surgical outcomes but also have clearly demonstrated mechanotransduction (fibroblast activation via applied mechanical tension), warranting the assignment of a higher weight on the basis of biological plausibility.

Predictors assigned a weight of 1 (age <30 years, Fitzpatrick skin type III - VI, positive family history, lesion size >5 cm, multiplicity) provide statistically reproducible but lower than average evidence of association for recurrence. Predictors assigned a weight of one have an impact on biological and wound healing. However, when comparing the magnitude of independent associated recurrence for each of these predictors is lower or more imprecise when compared to that of prior recurrence or high-tension anatomical predictors.

As such, the weights reflect the strength of association trends and mechanistic backing rather than statistical models. The score is designed to offer structured clinical guidance, not to serve as a validated predictive tool. Prior to employing this in a clinical setting, it will require prospective validation studies.

#### Table 2. Justification Framework for Risk Weight Assignment

Predictor	Evidence Consistency Across Cohorts	Biological/Clinical Rationale	Assigned Weight Justification
Prior recurrence	Consistently strongest predictor in observational studies	Established profibrotic phenotype, apoptosis resistance	Strong magnitude + mechanistic support → Weight 2
High-tension anatomical site	Frequently associated with higher recurrence rates	Mechanotransduction (YAP/TAZ activation) sustains fibroblast activity	Strong clinical + biological link → Weight 2
Age <30 years	Moderate association	Robust inflammatory response and fibroblast proliferation	Moderate association → Weight 1
Fitzpatrick III–VI	Increased susceptibility, variable recurrence magnitude	Cytokine profile and fibroblast biology differences	Moderate biological predisposition → Weight 1
Family history	Familial clustering observed	Genetic predisposition affecting ECM regulation	Susceptibility factor → Weight 1
Lesion size >5 cm	Larger excision surface, greater inflammation	Increased fibroblast burden and wound stress	Moderate magnitude effect → Weight 1
Multiple lesions	Associated with aggressive phenotype	Suggests systemic fibroproliferative tendency	Risk modifier → Weight 1

Total cumulative scores will have the following interpretations: A score of 0 to 2 indicates low risk; a score of 3 to 4 means moderate risk; a score of 5 to 6 represents high risk; and a score of 7 or more indicates very high risk for recurrence after excision. Small primary lesions in areas of low-tension anatomy (not including family history or prior recurrences) typically represent low risk status. For these patients, early excision and intralesional corticosteroid injection, along with routine post-operative surveillance, may suffice for treatment.

Generally, patients in the moderate-risk category will have evidence of modifying factors (example: younger patient, darker phototype, larger lesion size) in addition to location of the lesion being in areas of mechanical stress. For these patients, excision should be performed with the goal of minimizing tension and early initiation of adjuvant pharmacological therapy.

Patients at high risk of recurrence typically have a set of cumulative predictor variables including prior recurrence, size of lesion, family history, and anatomical location that involves high tension. These patients require more than just excision as their surgical management; a surgical plan that attempts to minimize the tension during the closure is essential. Depending upon the benefit and risk of early postoperative radiation therapy, a decision about use could be made. The administration of serial intralesional pharmacotherapy should be considered for high-risk patients as a proactive rather than reactive treatment.

Very high-risk patients are particularly difficult to manage as a result of recurrent lesions that have returned multiple times or lesions that regrow rapidly. Therefore, a comprehensive multimodal approach to the treatment plan should be utilized to modulate the wound microenvironment during its early remodeling phase. Patients who fall into the very high-risk category should have close monitoring for one year after their surgery.

The importance of structured postoperative follow-up for all patients cannot be overstated; the presence of early clinical signs (e.g., itchiness, localized firmness, redness, progressive thickening of the incision) may signal the reactivation of

fibroproliferative pathways. If possible, initiation or intensification of intralesional therapy should take place at the earliest signs of recurrence in order to prevent developing established recurrences.

This risk-adapted approach to surgical management turns biological scientific knowledge into the surgical management of high-risk patients. Although no formal validation studies exist to date for this approach, structured preoperative cumulative risk factor assessments provide a rationale and clinical foundation for reducing recurrence rates.

### Stepwise Risk-Adapted Clinical Decision Algorithm

The structured risk stratification model has been converted into a reproducible clinical practice through a stepwise decision pathway. Each element of the algorithm, from cumulative risk score to operative plan, adjuvant therapy selection, timing of interventions and follow-up escalation, are linked together.

#### Step 1: Preoperative Risk Assessment

The first step is to complete a cumulative risk score for all patients being considered for surgical excision, prior to surgery, using the structured risk framework outlined in Table 1. The risk score categories are defined as follows:

0-2 = Low risk

3-4 = Moderate risk

5-6 = High risk

≥7 = Very High risk

The pre-operative assessment of the patient's cumulative risk will assist in the operative plan.

#### Step 2: Treatment Selection According to Risk Category

The second step is to select a treatment based on the risk category of the patient.

Low Risk (Score 0–2):

For a patient classified as a low risk (0-2), the following treatment options should be selected:

- Surgical excision with careful, layered closure to reduce tension.
- Postoperative silicone or pressure therapy.
- If symptoms indicative of early inflammation are noted during the postoperative period, consider an early intralesional corticosteroid injection.

#### Moderate Risk (Score 3–4):

For a patient classified as moderate risk (3-4), the following treatment options should be selected:

- Surgical excision using an aggressive technique to minimize tension (deep fascial sutures, maximally undermined).
- Initiate serial intralesional corticosteroid injections within 2-3 weeks postoperatively.
- Silicone therapy during the remodeling phase.

#### High Risk (Score 5–6):

For a patient classified as a high risk (5-6), the following treatment options should be selected:

- Surgical excision that reduces tension.
- Pharmacological manipulation of surgery (corticosteroids intralesionally (though can use 5-FU intralesionally)) early on after surgery.
- Radiotherapy was considered postoperative (within 24–72 hrs) if done in regions of high anatomy tension or in patients that have previously had a recurrence.
- Routine follow-up appointments were scheduled every 4 to 6 weeks for the initial 6 months.
- All treatments should be done as part of a single treatment program.

#### Very High Risk (Score ≥7):

For a patient classified as a Very High Risk (Score  $\geq 7$ ), the following treatment options should be selected:

- Multimodal strategy planned preoperatively
- Surgical excision with maximal biomechanical optimization
- Early postoperative radiotherapy (ideally within 24–72 hours) unless contraindicated
- Scheduled serial intralesional pharmacotherapy beginning in early remodeling phase
- Close monitoring at 4-week intervals for first 12 months

### Step 3: Timing of Adjunctive Therapy

It is important to begin adjunctive therapies prior to their necessity as opposed to afterwards.

Radiation therapy has a more significant response when given within the early proliferative phase (generally 1-4 days after excision). Intralesional corticosteroids should be used once the epithelialization has occurred, but prior to the appearance of clinical recurrence (usually within 2-3 weeks). If there is a visible recurrence before treatment, the effectiveness of treatment may be compromised due to the formation of a new fibrotic microenvironment.

### Step 4: Follow up and criteria for escalation

A structured follow-up will be required for all patients for a minimum of twelve months following surgery. Signs to look for when determining if a recurrence will occur include:

- Persistent itching
- Localised hardened area (induration)
- Erythema beyond incision borders
- Progressive thickening of scar

If any of these signs are present early on in the evaluation, intralesional therapy or another type of pharmacologic intervention should be added or the response escalated, regardless of whether a clear clinical recurrence has occurred.

## MOLECULAR DETERMINANTS OF RECURRENCE AND THEIR CLINICAL IMPLICATIONS

Molecular biology advances reveal that keloids can recur due to the ongoing stimulation of a malfunctioning microenvironment; they are not just due to a missed technical failure during the surgical excision process. Multiple factors such as continuous stimulation of fibroblasts (connective tissue cells), inability of cells to undergo programmed cell death (apoptosis), changes to immune-mediated signaling pathways, and issues with mechanotransduction work together to produce a fibrotic expansion. Although there are no molecular markers available for clinical use presently, understanding the mechanisms involved provides biologic rationale for the management process described in this review.

### Biological Rationale for Tension-Reducing Surgical Closure

There is a marked responsiveness of fibroblasts to mechanical stimuli. The mechanical tension created in the surgical closure will activate various intracellular pathways such as the YAP and TAZ signaling pathways and associated transcriptional programs that ultimately will result in increased collagen production and extracellular matrix deposition. Fibroblasts remain activated in high-tension parts of the body because they are exposed to constant mechanical loading even after surgical excision.

The biologic mechanisms described above provide specific biologic rationale for employing carefully executed tension-reducing techniques in surgical repairs. For example, performing a layered closure (closure of skin), deep fascial support, adequate undermining, and avoiding excessive tension during primary closure are not only technical refinements; they are also biologically justified attempts to minimize the reactivation of profibrogenic signaling pathways due to mechanotransduction.

### Mechanistic Basis for Early Postoperative Radiotherapy

The proliferative phase of wound healing is dependent upon the proliferation of fibroblasts and deposition of new extracellular matrix. The primary mechanism that contributes to the antifibrotic effect of radiation therapy is the inhibition of the proliferation of fibroblasts in the actively dividing state, as well as inducing apoptosis in those cells that are cycling rapidly.

Delivering radiotherapy within the early postoperative period (generally 24 to 72 hours) is designed to affect fibroblasts in their most vulnerable, rapidly dividing state. By delaying the delivery of radiation, a stable fibroproliferative microenvironment can develop, so that the fibroblasts have decreased response to interventions. Therefore, the biological basis for the recommended timing of this algorithm is established based on the dynamics of wound healing.

### Molecular Basis for Aggressive Behavior in Recurrent Lesions

The recurrent keloids generally consist of high levels of collagen, resistance to apoptosis, and have persistent activation of profibrotic pathways such as TGF- $\beta$ /Smad, JAK/STAT, and PI3K/Akt/mTOR. Epigenetic modifications such as modification to DNA methylation and histone acetylation patterns contribute to a sustained "fibrotic memory" that may explain the aggressive behavior of the recurrent lesions in comparison to primary lesions.

This molecular profile is a justification for multimodal therapy for the patient who has experienced a prior recurrence. The recurrent lesion represents biologically established fibroproliferative states and therefore surgical excision is not justifiable, but early pharmacologic modulation and selective radiation are biologically justifiable.

### Translational Limitations and Future Integration

There are advancements in genomic profiling, transcriptomics, and the identification of single nucleotide polymorphisms related to fibroproliferative susceptibility; however, there currently is no molecular biomarker that has clinical validation for everyday use in perioperative decision-making. While several machine learning models combining molecular and clinical predictors have been developed and/or are in development, these models are still in the early stages of validation and demonstration of additional clinical benefit before they can be implemented.

Currently, robust and structured clinical assessment of risk remains the most actionable basis for recurrence prevention, while molecular knowledge provides biological justification for surgical and adjuvant treatment strategies.

## CHALLENGES AND CONTROVERSIES

Despite a growing knowledge of keloid behavior and patterns of recurrence, a variety of both methodological and clinical challenges limit the implementation of standardized management protocols. One of the most significant problems with the current literature is that there is marked heterogeneity among the currently published studies. Variability of reported rates of recurrence are attributable to differences in patient populations, differing anatomical locations, differing techniques used for surgical excision, differing types of adjuvant treatment used and different lengths of follow-up in the studies being published. Additionally, the various definitions of recurrence (e.g. whether the keloid has visibly extended beyond the incision margin, recurrence based on symptoms, need for re-excision, etc.) present additional variables making comparisons between studies difficult and impede the development of global treatment algorithms.

Even if all of the studies above used standardized measures, interpretation of the overall quality of evidence still presents barriers for the clinician. Currently, almost all available literature consists of retrospective cohort studies and either small single-institution or small, multi-institutional prospective studies. There are very few randomized controlled trials that have compared various multimodal strategies. Reasons for the lack of high-quality comparative data include ethical issues, precision in patient selection for long follow-up and difficulty in standardizing procedures across the differences in anatomical sites where patients have keloids. Therefore, many of the recommendations made by individual providers

rely on the aggregate experience of that provider and the judgement of expert opinion, rather than based on a pre-determined level of evidence.

There is disagreement among professionals about the best way to do surgeries and use medicine after surgery. There are two different philosophies on how to do surgery (take out the tumor entirely or remove as much as possible) as well as how to give radiation (over what period of time/how many times) and how often to give medications after surgery. Because there is inconsistency in the way institutions run their practices, doctors may have different experiences when treating patients and determining if the patient recurs.

Caution is necessary when evaluating research studies that involve molecular biology. Although there are many possible targets for therapy in the future, few clinical applications have come from this research to date. There is a danger in applying scientific results to clinical settings prematurely because the evidence is limited. If molecular markers are going to be incorporated into surgical decision-making processes, they will need to be validated and shown to provide additional predictive information compared to clinical parameters.

The possible effects of using radiation therapy after surgery is ethically debatable, particularly for patients who are younger. Although recent low-dose radiation usage has improved safety compared to previous types of radiation, there is a concern for long-term cancer risk with use of radiation. When making the decision about whether or not to use radiation after surgery, the patient should have an open dialogue with their provider about these possible risks and consider the risks/benefits for the individual patient.

The debate continues on how we define recurrence in soft tissue reconstruction surgery and its causes; incomplete excision is one possible cause for recurrence according to some authors while intrinsic biology and the mechanical environment may be more significant causes according to other authors. Most studies to date support the hypothesis that recurrence results from the reactivation of a dysregulated wound-healing microenvironment (as opposed to being the result of purely technical surgical failure).

The challenges posed by these differing views will require standardized definitions, multicenter, prospective trials with long-term follow-up, and the incorporation of translational research into the development of clinical protocols. Until such time, the most reasonable management plan would be a multimodal risk-adapted approach; based on the currently available cumulative clinical evidence.

## FUTURE DIRECTIONS

### **Antifibrotic Therapy Targeted to Specific Pathways**

Recent advancements in research concerning molecular devices have led to the identification of numerous different signalling mechanisms that are responsible for maintaining fibroblast activation for long periods of time, including the TGF-beta/Smad pathway, JAK/STAT signalling pathway, and PI3K/Akt/mTOR signalling pathway. Therapies being developed in the future will most likely include the selective inhibition of these pathways or pathways to prevent collagen overproduction at its source. Initial studies on modulating TGF-beta receptor activity, inhibiting lysyl oxidase to limit cross-linking of collagen, and selectively inhibiting signalling pathways found potential. These areas, however, remain experimental and need to be verified in a clinical setting before being considered for routine clinical use in surgical settings.

### **Modulating Epigenetic Changes & RNA-Based Targeting of Fibrosis**

Recent evidence suggests that the persistence of the profibrotic cellular phenotype resulting from epigenetic changes plays a significant role in the development of new lesions after previous lesions have healed. Modulating DNA methylation, histone acetylation, or the expression of non-coding RNAs may be a possible way to reverse the fibrotic

memory left after lesion healing. Current research is being conducted to determine if RNA interference can be used to inhibit the expression of specific profibrotic genes. These methods currently remain in preclinical studies and have not yet proven to be clinically safe or efficacious through large clinical studies.

### **Optimization of Multimodal Protocols**

In the short term, refining the use of multimodal clinical protocols may have the greatest impact on the provision of novel molecular therapies. Future research should include examining the standardization of postoperative radiotherapy timing, optimizing pharmaceutical regimens for intralesional treatments, and identifying the ideal frequency of surveillance. Evidence-based recommendations for the use of tension-reducing surgical techniques in conjunction with structured adjuvant therapies could be strengthened through comparative, prospective studies. The development of consensus-driven perioperative pathways may provide for the improved reproducibility of clinical pathways among institutions.

### **Predictive Modeling and Personalized Risk Assessment**

Combining clinical variables and biological markers into predictive models represents an important area of future investigation. Recent exploratory studies utilizing machine-learning approaches have assessed the ability of combined data sets to predict the likelihood of recurrence. While initial results are encouraging, these models will require further validation using an external database, transparent methodology, and validated clinical utility prior to being introduced into practice. Future predictive models will require that they demonstrate improved patient outcomes above and beyond what has been achieved through the use of structured clinical risk assessment methods.

### **Translational Integration into Surgical Practice**

As we move forward, an important challenge will be to help bridge the gap between biological discovery and operative application. The goal of translational research should be to develop and validate biological markers that can significantly influence perioperative decision-making. Prospective studies to link molecular characteristics with standardized recurrence outcomes will help to identify which biological markers have true predictive power. Until then, clinical management will continue to depend primarily on the use of structured clinical assessment of known risk factors.

## **CLINICAL IMPLICATIONS**

The identification of predictors of recurrence should change the way that surgeons approach keloid management. The high recurrence rates seen after only excision demonstrate that surgical intervention will not be able to eliminate a keloid in most patients. As such, the planning of the surgical procedure must consider biological and mechanical risks in addition to just the excision.

The evaluation of patients preoperatively should include their age, skin type, family history, history of previous recurrences, size of lesion, and location of lesion. If the patient has multiple risk factors, they should be counseled about their increased chance of recurrence and the potential need for additional treatment options. The importance of shared decision-making is greatest when deciding whether to proceed with radiation therapy or repeat injections into the lesion. The surgical approach should be adjusted according to the recurrence risk. In areas where there is high tension on the closure, a careful layered closure and strategies to reduce the tension and stress from the closure are necessary. The setting of the closure and stress from the closure may determine if the healing process following the operation will progress towards normal healing or reactivate the fibroblastic pathways. Therefore, caring for the tissue and minimizing tension is not just a technical refinement but also has a biological rationale.

In moderate to high-risk patients, the adoption of proactive treatment versus reactive treatment of adjuvant therapy is critical. Within this context, the early use of intralesional corticosteroids, the use of combinations of different medications when appropriate and the strategically selective use of postoperative radiation may provide a therapeutic method to halt or limit fibroblast activity prior to the recognition of clinical recurrence. The act of waiting to observe a recurrence may

lead to the establishment of a new fibrotic microenvironment that would establish an increased level of resistance to treatment.

The need for structured postoperative monitoring is equally critical. The period of wound healing through the remodeling phase is a period of vulnerability to the establishment of clinically reoccurring events, which may generally be identified as evidence of symptom manifestations such as itching, thickening of skin, and redness. Prompt detection of potential symptoms allows for timely therapeutic intervention. Structured postoperative follow-up visits (for at least the first year following surgery) allow for the assessment of early clinical recurrence and the initiation of treatment prior to the establishment of growth in the lesion.

The recent evolution of molecular insight into recurrence has allowed for better insight into the mechanisms of recurrence; however, molecular insights have not replaced the need for the use of clinical judgment when determining new and/or the prevention of recurrence. There are currently no validly validated biomarkers available for the prevention of recurrence; hence, the basis for the prevention of recurrence must be the application of structured clinical evaluations in conjunction with disciplined multimodal treatment. Integrating risk stratification into routine surgical practice is a concrete first step toward reducing recurrence and improving long-term functional and aesthetic outcomes.

### EVIDENCE STRENGTH CLASSIFICATION OF KEY RECOMMENDATIONS

The classifications of key recommendations made for clinical practice reflect the strength of evidence that supports them in order to provide transparency and clarify the differential level of support provided by the various proposed management strategies. Since this review is a narrative procedure and there is no formal grading of evidence, the classifications reflect the type and consistency with which the literature has demonstrated support for each recommendation (i.e., randomized controlled trials, systematic reviews, cohort studies or expert opinions).

**Table 3. Evidence Classification of Major Clinical Recommendations**

Clinical Recommendation	Evidence Level	Basis of Classification
Surgical excision alone is associated with high recurrence rates	High-quality evidence	Multiple cohort studies and systematic reviews consistently reporting high recurrence rates
Tension-reducing layered closure is recommended	Moderate evidence	Strong biological rationale + consistent observational surgical data
Intralesional corticosteroids as first-line adjuvant therapy	Moderate-quality evidence	Systematic reviews and small randomized trials
Combination therapy (corticosteroids + 5-FU) for aggressive lesions	Moderate evidence	Randomized controlled trials and meta-analyses
Early postoperative radiotherapy reduces recurrence	Moderate evidence	Systematic reviews and long-term institutional series
Silicone and pressure therapy as adjunctive measures	Low-to-moderate evidence	Heterogeneous studies with variable long-term outcomes
Multimodal therapy for high-risk patients	Consensus-based recommendation supported by moderate evidence	Integrated interpretation of recurrence data and biological rationale

Clinical Recommendation	Evidence Level	Basis of Classification
Molecular biomarkers for recurrence prediction	Experimental evidence	Translational research without validated clinical application

### EVIDENCE LEVEL DEFINITIONS

**High Level Evidence:** Multiple cohort studies, systematic reviews, or meta-analyses demonstrate consistent results across many sites.

**Medium Level Evidence:** Results are supported by small randomised trials (where carried out), other well-designed observational studies, or strong biological plausibility.

**Low Level Evidence:** Limited or heterogeneous clinical data available.

**Consensus Recommendation:** Evidence took into account an assessment of the best available evidence and expert interpretation based on low quality study design rather than high-quality but not yet existing trial.

**Experimental Evidence:** Preclinical or Translational work (within the confinement of experimental environments) that currently has no clinical validation.

### CONCLUSION

Keloids can be difficult to manage because of their tendency to return after being removed surgically. Researchers have found that the re-occurrence of keloids is not simply due to a surgeon's poor technique but may also be due in part to a patient having a biological disposition towards forming keloids, as well as the way surgery is performed, the type of care a patient receives after surgery, the characteristics of the keloid and anatomical tension available on the keloid. Therefore, an individual's vulnerability, the characteristics of the keloid itself, anatomical tension, and the way in which the individual is managed peri-operatively all contribute to the ultimate outcome.

Excision of a keloid will result in a high instance (by most standards) that the keloid will return, therefore an individualized, structured, risk assessment-based, multimodal approach to keloid management is essential to provide positive outcomes. Tension-reducing surgical technique, additional pharmacologic manipulations early on in the post-operative process, selective use of radiotherapy in appropriate cases and planned continual post-operative follow up are all recommended components of a rational approach to keloid recurrence prevention.

Recent advances in molecular/genomic research have improved our understanding of the regulatory pathways of fibroblast proliferation; however, these pathways remain largely investigational for the time being and not ready for routine application in the peri-operative area. Future development of improved keloid management techniques will depend upon the creation and validation of risk-adapted treatment algorithms and standardization of keloid treatment protocols, and the accurate incorporation of recently developed biological markers into the standard of care for patients with keloids.

Moving away from a standard treatment approach towards an individual risk-based approach is the likely best means to obtain long-lasting control of keloids. By using biological knowledge about keloids and applying good surgical technique along with planned post-operative follow up for patients who develop keloids, surgeons will likely be able to reduce significantly recurrence rates and therefore significantly improve patient's long-term functional and cosmetic results

### CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## FUNDING STATEMENT

All authors have declared that no financial support was received from any organization for the submitted work.

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**CITE THIS ARTICLE:**

- **APA (7th edition):** Bakshi, I., Pattnaik, D., Sookrah, P., Rawat, H. S., & Choudhary, S. (2026, February 28). *Predictors of keloid recurrence following surgical excision: Clinical, surgical, and molecular determinants. The Operating Room Global Journal (TORGJ)*, 2(1). <https://doi.org/10.64573/torgj2602004>
- **Harvard:** Bakshi, I., Pattnaik, D., Sookrah, P., Rawat, H.S. and Choudhary, S., 2026. *Predictors of keloid recurrence following surgical excision: Clinical, surgical, and molecular determinants. The Operating Room Global Journal (TORGJ)*, 2(1). Published 28 February. Available at: <https://doi.org/10.64573/torgj2602004>
- **Vancouver:** Bakshi I, Pattnaik D, Sookrah P, Rawat HS, Choudhary S. Predictors of keloid recurrence following surgical excision: Clinical, surgical, and molecular determinants. *The Operating Room Global Journal (TORGJ)*. 2026 Feb 28;2(1). <https://doi.org/10.64573/torgj2602004>
- **MLA (9th edition):** Bakshi, Ishaan, et al. "Predictors of Keloid Recurrence Following Surgical Excision: Clinical, Surgical, and Molecular Determinants." *The Operating Room Global Journal (TORGJ)*, vol. 2, no. 1, 28 Feb. 2026, <https://doi.org/10.64573/torgj2602004>
- **Chicago (Author-Date):** Bakshi, Ishaan, Debshree Pattnaik, Parikshita Sookrah, Hriday Singh Rawat, and Savant Choudhary. 2026. "Predictors of Keloid Recurrence Following Surgical Excision: Clinical, Surgical, and Molecular Determinants." *The Operating Room Global Journal (TORGJ)* 2 (1), February 28. <https://doi.org/10.64573/torgj2602004>