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Guideline

German S2k guidelines for the therapy of pathological scars (hypertrophic scars and keloids)

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Preamble

The present guideline was primarily prepared by representatives of the field dermatology and dermatosurgery and is based on the S1 guideline of the German Society of Dermatology from 2004 [1].
Besides the dermatologists many other disciplines are involved in the treatment of keloids. The German Society of Plastic, Reconstructive and Aesthetic Surgeons participated in the review process of this guideline and fundamentally agrees with the content. For further update inclusion of all relevant medical societies already in the initial stage as well as an even more detailed depiction of surgical therapy options are planned.

List of abbreviations used

5-FU, 5-fluorouracil; CI, confidence interval; cw-CO2 laser, continuous-wave CO2 laser; Er:YAG laser, erbium:yttrium-aluminum-garnet laser; FPDL, flashlamp-pumped pulsed dye laser; Gy, gray; HTS, hypertrophic scar; IF, interferon; NaCl, sodium chloride; RR, relative risk; TGF, transforming growth factor; TAC, triamcinolone acetonide

1 Aims/addressees

1.1 Target group

This guideline is targeted at dermatologists in office practice and clinics, who are involved in the treatment of hypertrophic scars and keloids.

1.2 Aims of the guideline

1. Stage-adapted and symptom-oriented selection of therapies to optimize therapy success
2. Avoidance of performing insufficient therapies or of therapies without adequate dosage and corresponding lack of anticipated therapy success
3. Reduction of insecurity in performing rarer therapy forms

1.3 Participating medical societies

German Society of Dermatology (DDG) represented by: Prof. Dr. Sabine Eming, Cologne; Dr. Gerd Gauglitz, Munich; Dr. Silvia Hohenleutner, Regensburg; Prof. Dr. Günther Sebastian, Dresden
Professional Association of German Dermatologists (BVDD) and European Society of Laser Dermatology (ESLD) represented by: Dr. Klaus Fritz, Landau
Austrian Society of Dermatology and Venereology (ÖGDV) and Austrian Society for Dermatosurgery (ÖGDC) represented by: Dr. Josef Koller, Salzburg
German Society for Dermatosurgery (DGDC) and German Society for Dermopharmacy (GD) represented by: PD Dr. Joachim Fluhr, Berlin
Swiss Society of Dermatology and Venereology (SGDV) represented by: Prof. Dr. Renato Panizzon, Lausanne
Participation in the review process: German Society of Plastic, Reconstructive and Aesthetic Surgeons
Project management/methodic coordination: PD Dr. Alexander Nast, Dr. Birte Sporbeck, Division of Evidence-Based Medicine (dEBM), Charité – University Medicine Berlin, Berlin

2 Methods

This guideline is based on the update of the DDG guideline "Keloids and hypertrophic scars" (S1 guideline) developed in 2004 [1].
The guideline was developed according to the methodic stipulations on development and further development of guidelines for diagnostics and therapy

of the Association of the Scientific Medical Societies in Germany (AWMF) and in the three-level concept of the AWMF corresponds to an S2k guideline [2].

The therapy options considered and evaluated are a selection of the guidelines group and in their view represent particularly relevant treatment possibilities. Besides the evaluated therapies further options are available; their evaluation is not subject of the guideline.

All recommendations were approved in a consensus conference employing a formal consensus process (nominal group process). First the state of evidence was presented from the expert viewpoint with subsequent discussion. Each group member made comments on the draft recommendations; divergent proposals were noted. The steps serial discussion, preliminary vote, debate/discussion as well as the final vote followed. In all votes strong consensus (>90 %) could be achieved. The consensus conference took place in Berlin on 7 Nov. 2011. For those interventions for which due to time constraints no consensus was achieved at the consensus conference an online consensus conference was conducted with the same method as in the live conference. If desired, the results of the vote can be obtained from the guidelines group. The moderation of the consensus conference was conducted by Dr. Alexander Nast, who is an AWMF guidelines advisor. All representatives nominated by the medical societies were qualified to vote.

For standardization uniform formulations were employed for the recommendations of the guideline. The following levels are valid:

Strong recommendation	Is recommended
Weak recommendation	Can be recommended
Open recommendation	Can be considered
Recommendation against an intervention	Is not recommended
Absolute recommendation against an intervention	Should not be used

All consensus passages are highlighted in the text with a grey box.

3 Biological aspects of wound healing and scar formation

Sabine Eming

Physiological wound healing of the skin is a complex and cascade-like process biologically with the goal of restoring the integrity of the damaged tissue [3]. Initially there is a marked inflammatory reaction to eliminate defective tissue and pathogens. The formation of new blood vessels, the activation of keratinocytes and fibroblasts at the edge of the wound as well as the synthesis of extracellular matrix components follow. After wound closure through epithelialization the dermal granulation tissue is restructured into a scar and the replacement tissue adapts to biomechanical requirements. In this process the differentiation of fibroblasts into myofibroblasts that are particularly stimulated by *transforming growth factor-β1* (TGF-β1) plays a central role. Myofibroblasts are characterized by contractile actin filaments and a high production of collagen and take on an important function in the contraction and reorganization of the granulation tissue. It is assumed today, that the decrease of myofibroblasts in wound tissue after wound closure is of great significance in limiting scar formation [4].

The dynamics of wound healing is coordinated through a controlled interaction of numerous soluble factors, components of the extracellular matrix and different cells. Scar tissue differs from undamaged skin by the loss of skin appendages, flattening of the rete ridges, altered architecture and composition of the extracellular matrix components and finally by limited mechanical properties. A regeneration of damaged tissue (restitutio ad integrum) is possible only in fetal skin [5]. Even though great advances in the understanding of molecular mechanism of the healing process have been made in the past decades, it still remains unclear why no postnatal regeneration takes place in humans, but that to a varying extent scars always are formed.

3.1 Definition of keloid and hypertrophic scar

Sabine Eming

Keloids and HTS are benign, localized proliferations of connective tissue of the skin and a result of a disturbed interaction of cytokines, cells and the surrounding extracellular matrix involved in the healing process. Keloids and HTS can be differentiated clinically and histologically; their characteristics are contrasted in Table 1 (Table 1). Even though the impact of numerous endogenous and exogenous factors on the extent of scar tissue has been well-illustrated, the molecular basis of pathological scar formation is still poorly understood to date. Pathological scar formation is a reflection of disturbed wound healing with a prolonged and disturbed inflammatory phase and the resulting increased formation and reduced degradation of the extracellular matrix. Experiments on cells isolated from keloid tissue demonstrate numerous alterations on their function such as e.g. in proliferation, apoptosis and/or expression of growth factors and matrix molecules [6]. These observations in part are the basis for the development of new therapy approaches. It is assumed that the disturbed reduction of the myofibroblasts and their prolonged activation in granulation tissue lead to an imbalance in favor of connective tissue synthesis. The effect of mechanical forces on the wound fibroblasts/myofibroblasts is of particular significance and possibly contributes to increased connective tissue synthesis via autocrine stimulation of the cells [4, 7, 8]. This in part explains the effectiveness of operations that relieve tissue tension in the vicinity of the scar. Possibly an altered concentration relationship of different TGF-β isoforms in the activation of the fibroblasts/myofibroblasts also plays a central role [9]. Due to familial tendency to develop keloids, for several years several genetic factors have been discussed (e.g. genes regulating apoptosis, mitogen-activated protein kinase, TGF-β signal cascade, interleukin-6, plasminogen activator inhibitor-1) [10].

Of particular relevance for therapy is the fact that HTS occur without genetic predisposition and can regress spontaneously or through therapy. For keloids the genetic predisposition must be kept in mind and that, for example, after surgical measures or injuries to the skin recurrences must always be expected [11].

4 General recommendations on the treatment of keloids and hypertrophic scars

Alexander Nast

4.1 Necessity of treatment

In principle HTS and keloids are benign skin lesions. The need for treatment

Table 1: Hypertrophic scar and keloid: clinical and histological characteristics.

Characteristics	Hypertrophic scar	Keloid
Incidence	Frequent	Rare, increases with increasing skin pigmentation
Extent	Limited to the original injury	Goes beyond injury
Occurrence	<6 months after injury	>6 months after injury
Regression	Frequent	None
Previous injury	Yes	Yes, but often "minimal trauma" unnoticed by the patient (e.g. folliculitis, scratch or insect bite)
Location	Entire skin surface	Entire skin surface, often ear lobe, sternum, nape
Genetic predisposition	Not known	Yes
Histology	- α-actin positive myofibroblasts - Collagen fibers in wave-like patterns arranged parallel to the epidermis	- Reduced apoptosis - Increased blood vessel development - Thick collagen fibers, in part parallel to the epidermis, in part nodular arranged - Cell-poor center

results from symptoms (e.g. itch/pain), from functional impairment (e.g. contraction/mechanical irritation due to elevation) as well as on aesthetic/cosmetic grounds, that can greatly impact quality of life and cause stigmatization [12]. Bock et al. developed an instrument to assess quality of life specifically for patients with HTS and keloids. In the validation study a severe impairment of quality of life was also observed [13].

4.2 Therapy goals/quality indicators

The therapy goals must be set on an individual basis and be oriented to the complaints of the patient. Depending on the treatment option marked improvement should be achieved after 3–6 treatments or after 3–6 months (e.g. volume reduction by 30–50 %, symptom reduction > 50 % and/or sufficient satisfaction of the patient).

In case of a lack of satisfactory treatment success after 3–6 treatments/ 3–6 months a modification of the treatment strategy (combination/switch/ dose increase) is recommended.

With none of the methods of scar therapy available at present will it succeed in all cases to achieve scar reduction or an improvement of the functional and/or cosmetic situation. The treatment method of first choice cannot be standardized for scars, as too many variables in the development and regression of scars (e.g. location, age and type of scar, genetic disposition etc.) impact the process. Often a combination of different treatment methods is required.

4.3 Classification and evaluation of therapy success

For the clinical routine particularly documentation of size and thickness as well as photo documentation are practical. Further, the satisfaction of the patient and reduction of symptoms are of relevance.
For clinical studies at present particularly the Vancouver Scar Scale (VSS), Patient Scar Assessment Scale (POSAS), Visual Analog Scale (VAS), two-dimensional keloid modeling as well as mid- to high-resolution B-image sonography are employed. Nonetheless, the subjective assessment scales are of only limited suitability for large scars or to evaluate functional impact [14–16].

4.4 Therapy algorithms

The therapy algorithms for the treatment of HTS and keloids are depicted in Figure 1, Figure 2 and Figure 3 (Figure 1–3).

4.5 Exemplary cases

Hypertrophic scar

Background information: A 34-year-old woman, involved in a car accident about three years ago, developed HTS, pruritus and moderate pain. Scars elevated by about 2–3 cm. Patient with a great desire for treatment (Figure 4).

Therapy: Injection of triamcinolone acetonide (TAC) or cryotherapy, in case of persistent redness, use of flashlamp-pumped pulsed dye laser (FPDL) every 4–6 weeks
or
compression and conservative topical therapy, in case of persistent redness use of FPDL every 4–6 weeks
or
with a history of delayed epithelialization (after the accident and deep ulceration) in individual cases: excision and subsequent conservative topical therapy if indicated.

Aesthetically unacceptable hypertrophic scar

Background information: Cord-like HTS in the face after prolonged healing of a traumatic deep abrasion. The patient had no history of a tendency to develop HTS or keloids (Figure 5).
Therapy: Complete (extra-marginal) excision with plastic reconstruction with intracutaneous suture. Aftercare with conservative topical therapy if indicated.

Small keloid

Background information: Spontaneous keloid in a 40-year-old woman, existence since about one year, pruritus and the desire for treatment (Figure 6).
Therapy: Strictly intralesional injection of TAC and/or cryotherapy, in the event of persistent redness use of FPDL every 4–6 weeks, start with about 5–6 J/cm^2.

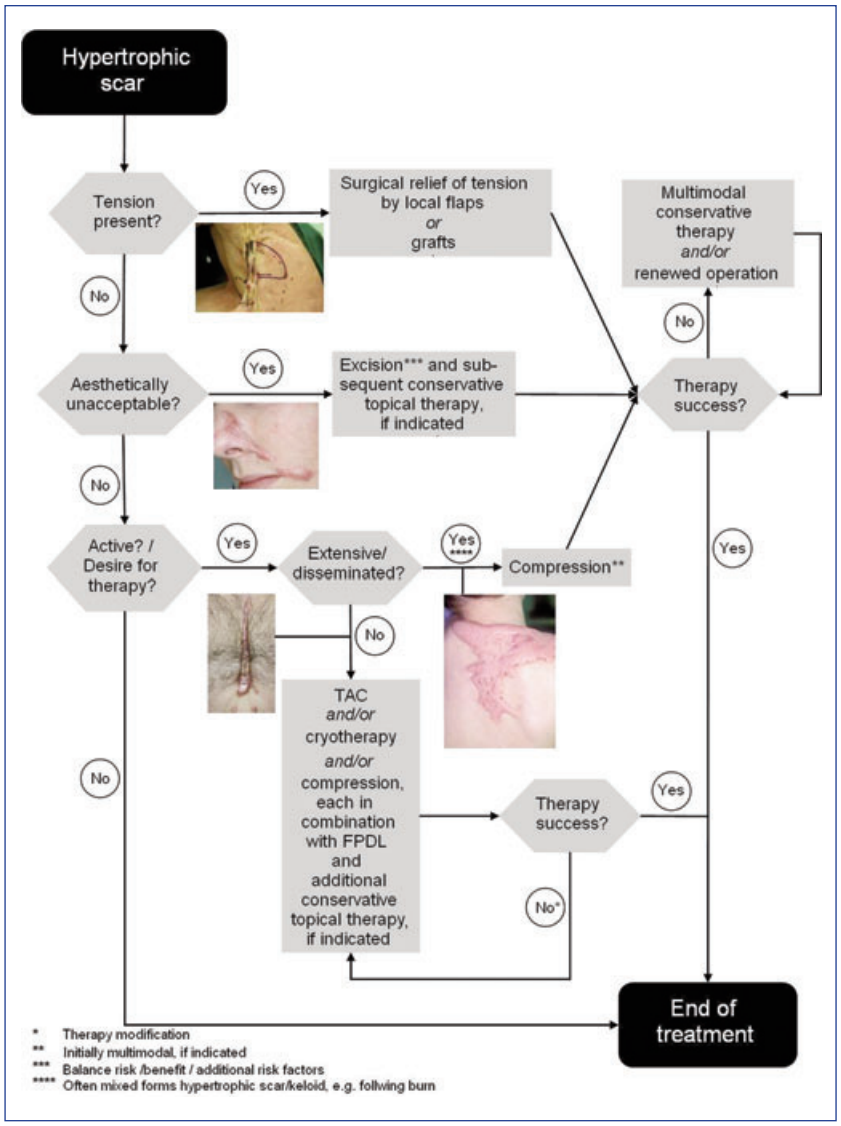

Figure 1: Therapy algorithm hypertrophic scar.

Mid-sized keloid

Background information: Excision of benign skin tumor two years ago, in the further course development of a keloid. Moderate pruritus (Figure 7).

Therapy: Strictly intralesional injection of TAC in combination with cryotherapy.

Small-based keloid

Background information: A 33-year-old women, ear piercing about 15 years ago, development of a keloid, surgery 10 years ago without aftercare resulting in a recurrence (Figure 8).

Therapy: Surgical removal/CO_2 laser ablation, after-treatment with TAC and/or cryotherapy (day 0, depending on findings then about every 4 weeks) and pressure treatment and/or silicone if indicated.

Functionally limiting hypertrophic scars/keloids

Background information: Extensive HTS on the foot with transition into a keloid following a grade IIb burn treated conservatively. This is a 10-year-old boy with rapid growth leading to a contracture of the second to fourth toe with the immediate need for action (Figure 9).

Therapy: Prompt complete excision of the scar with elimination of the scar's pull on the toes. Closure of the defect with a full-thickness graft from the groin region and in part with a split-thickness graft from the scar itself. Subsequently compression and conservative topical therapy.

5 Evaluation of the individual therapy options

5.1 Corticosteroids

Gerd Gauglitz

Mechanism of action

Corticosteroids reduce the excessive growth of the scar by diminishing collagen synthesis as well as glycosaminoglycan synthesis and inhibiting fibroblast proliferation. In addition to the well-known antiinflammatory effect of corticosteroids there is an inhibition of iNOS transcription (iNOS, inducible form of NO synthase [17]) with reduction of collagen production in fibroblasts and inhibition of alpha2-macroglobulin synthesis, an inhibitor of collagenase.

Side effects

The injections are painful. With too deep injection, atrophy of the subcutis may develop; with too superficial injection, telangiectases and disturbed pigmentation can occur. White deposits of the crystal suspension can develop.

Response rate/recurrence rate

The response rate in keloids is about 50–100 %. The recurrence rate is reported to be about 9–50 % [18].

Performance

Most often TAC, 10–40 mg, maximally 5 mg/cm^2, pure or diluted with 0.9 % NaCl or lidocaine 1:2 to 1:4 is injected. The injection is performed with a Luer-Lok syringe strictly intralesionally. A blanching effect signals the endpoint of the infiltration. Further injections are performed as needed at 3-4-week intervals. One study demonstrated that by starting with a low TAC concentration (10 mg/ml) with an increase during the course (20 or 40 mg/ml) the risk of side effects as well as the recurrence rate can be decreased [19]. The performance of superficial cryotherapy immediately before intralesional corticosteroid injection facilitates the subsequent corticosteroid injection through the development of edema [20]. In freshly operated scars TAC treatment can obviously be performed on the day of surgery without disadvantage [21].

Other

As explained by their mechanism of action, corticosteroids are most effective for active lesions, such as erythematous, pruritic or painful scars.

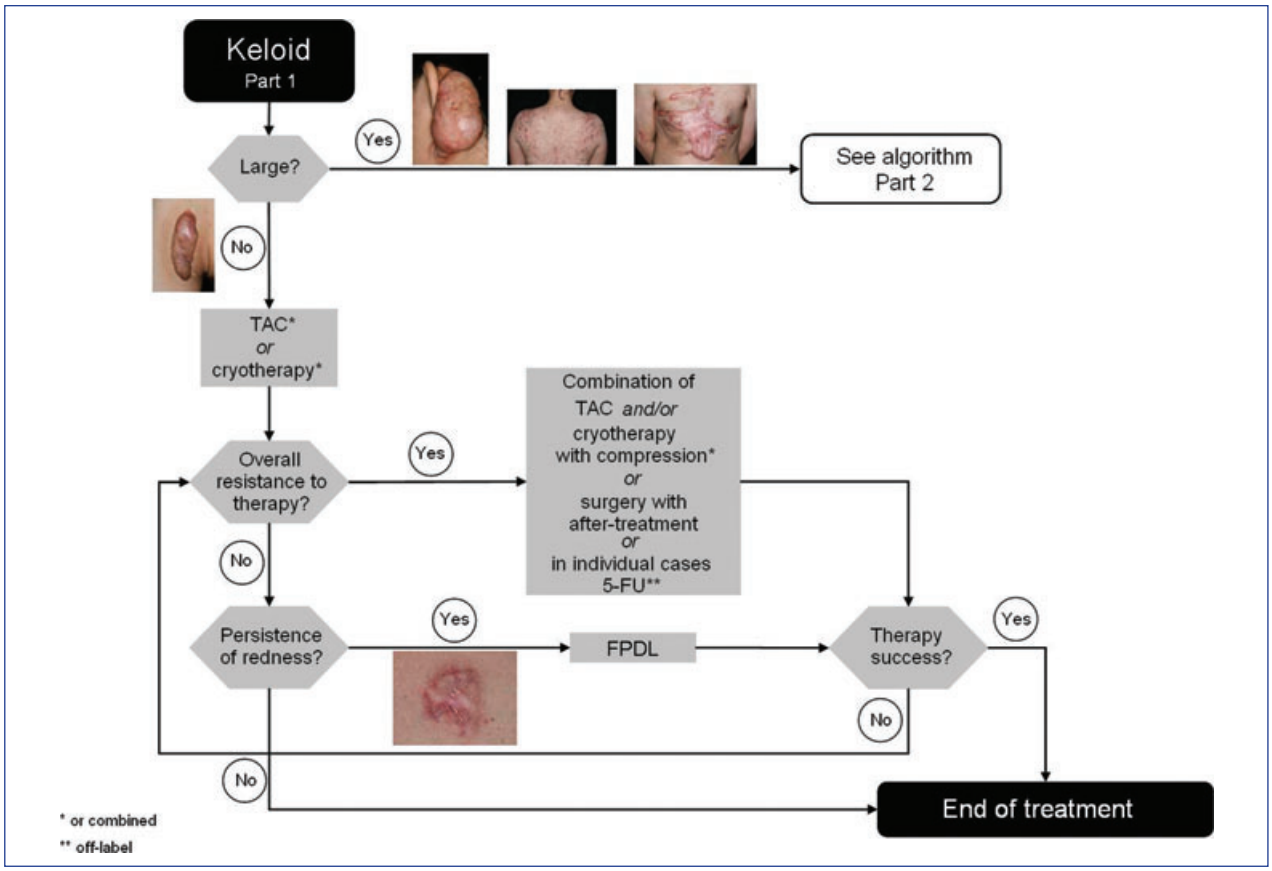

Figure 2: Therapy algorithm keloid (part I).

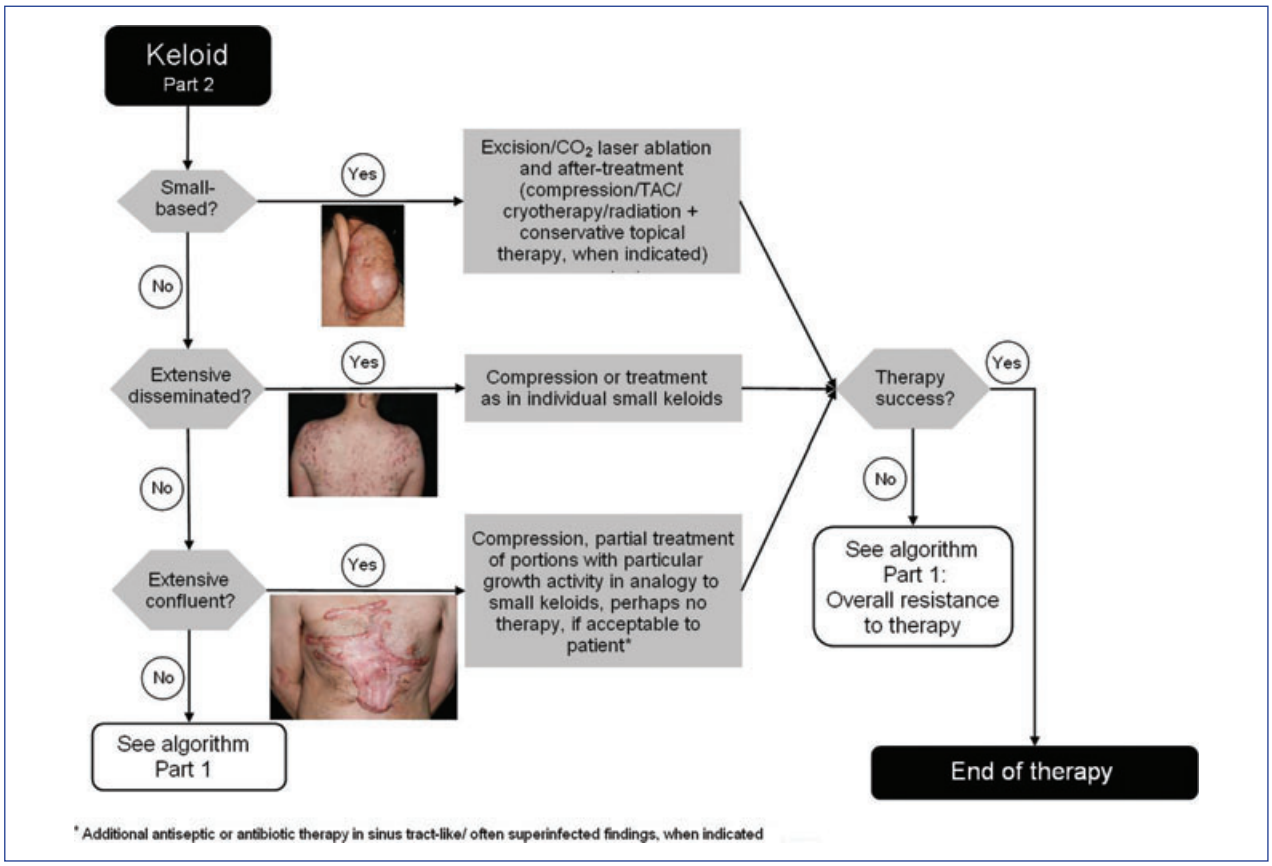

Figure 3: Therapy algorithm keloid (part II).

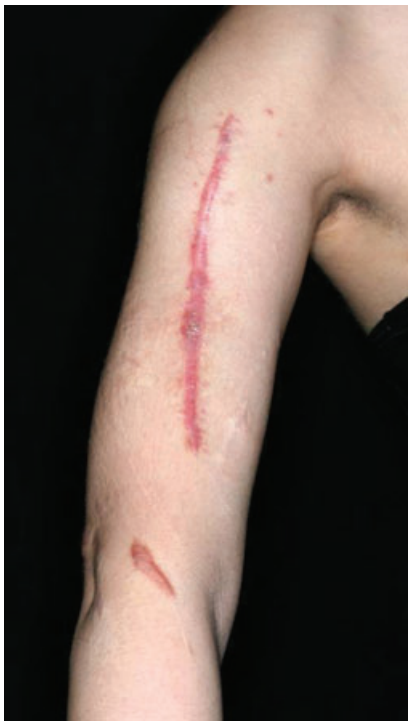

Figure 4: Hypertrophic scar.

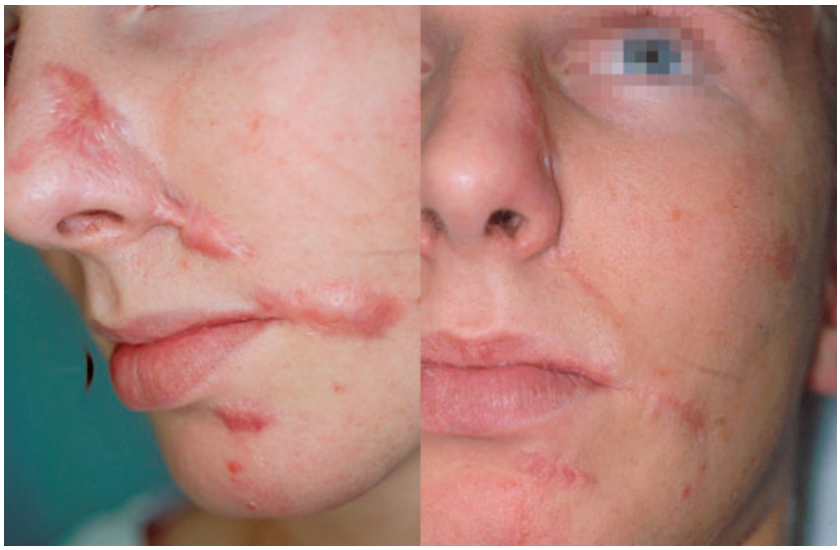

Figure 5: Aesthetic unacceptable hypertrophic scar before and after surgical therapy.

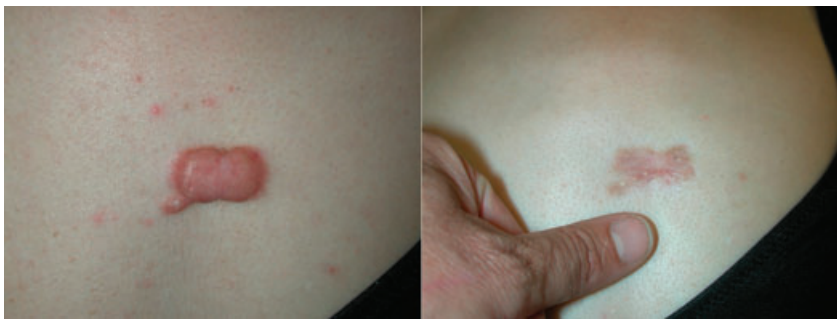

Figure 6: Small keloid before and after therapy.

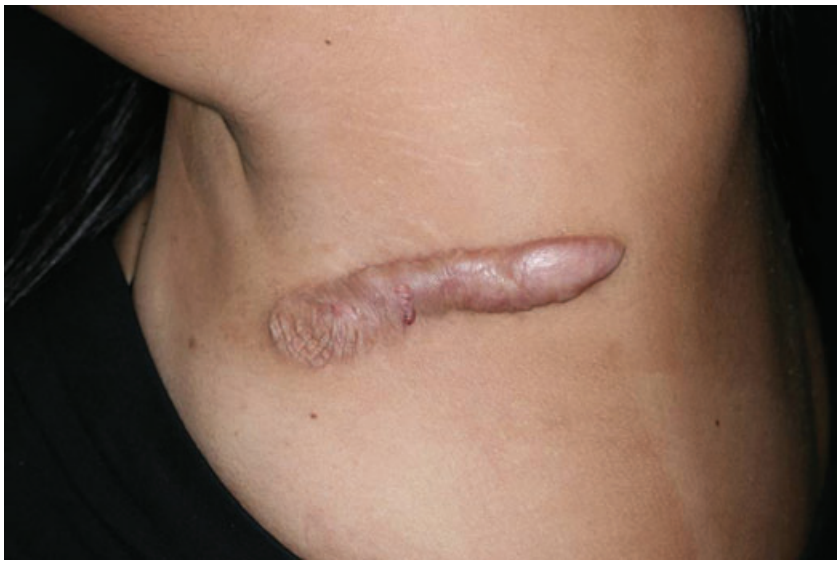

Figure 7: Mid-sized keloid.

Recommendation corticosteroids
Therapy of HTS and keloids with strictly intralesional injection of corticosteroids is recommended.
In HTS and keloids a combination with cryotherapy is recommended.
Purely topical use in the form of creams or ointments is not recommended.
The use of corticosteroid injections after surgical therapy of keloids is recommended.
The use of corticosteroid injections postoperatively for prevention of de novo development of HTS or keloids in patients at risk/with a predisposition can be considered.

5.2 Cryotherapy

Gerd Gauglitz

Mechanism of action

The effects are based especially on changes in microcirculation with cold-induced alteration, thrombosis and consecutive ischemic cell death.

Side effects

Protracted healing time of about four weeks and frequent (reversible) depigmentation due to destruction of the cold-sensitive melanocytes.

Response rate/recurrence rate

Zouboulis et al. report of "excellent response" or "good response" in 62.5 % of patients with keloids and HTS, with HTS responding more rapidly than keloids (in 53 % of HTS patients <3 treatments being required, in 16 % of keloid patients <3 treatments necessary)

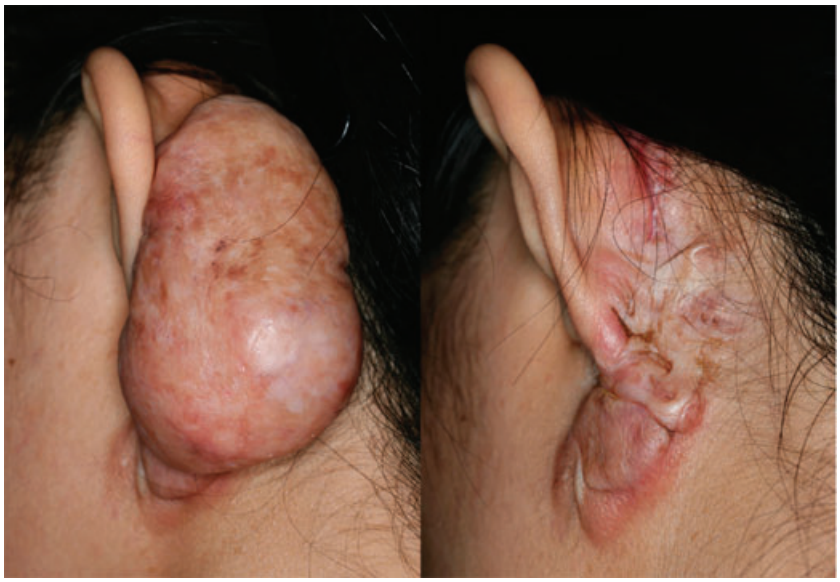

Figure 8: Small-based keloid.

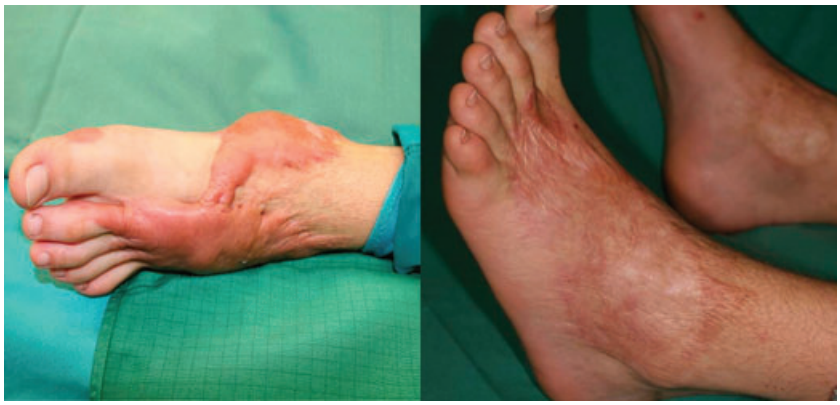

Figure 9: Large hypertrophic scar before and after combined therapy.

[22]. Ernst et al. [23] report a response rate of 82 % in HTS and 64 % in keloids.

Performance
Fundamentally, different approaches can be distinguished:

1. Short cryotherapy especially in combination with TAC to facilitate the injection of TAC.
2. Intensive cryotherapy with complete freezing of the tissue.

Spray and contact as well as intralesional cryotherapy can be performed.
Repetition of the procedure in 4–6-week intervals until the lesion is completely flattened is usually necessary.

Other
The patient should be warned to expect a blister progressing to a weeping wound and treated with antiseptics if indicated. The next treatment should take place only after healing of the defect caused by the previous treatment.

Recommendation cryotherapy
Therapy of HTS (small) as well as keloids with cryotherapy is recommended.
Therapy of keloids with cryotherapy in combination with triamcinolone is recommended.
The use of cryotherapy after surgical therapy of keloids can be recommended in individual cases.
The use of cryotherapy postoperatively as prophylaxis of de novo development of HTS or keloids in patients at risk/with a predisposition is not recommended.

5.3 Pressure therapy

Joachim Fluhr

Mechanism of action
Topical pressure reduces capillary perfusion, accelerates maturation of collagen and thereby flattening of the scar.

Side effects
Unpleasant sensations due to heat, sweating and swelling of the limbs, dermatitis, pressure erosions and ulcerations.

Response rate/recurrence rate
No clear positive effect of compression garments was found in a meta-analysis [24]. By use of specific pressure instruments (e.g. magnetic buttons, stents, oyster-shell sculptures) good response rates particularly on the ear have been reported [25, 26]. The use of 20–25 mmHg was significantly superior to treatment of HTS with 10–15 mmHg [27]. A definite statement on the recurrence rate cannot be made, as the follow-up period in most studies was only several months.

Performance
Pressure therapy usually using elastic materials should be started as early as possible (i.e. with conclusion of re-epithelialization), when a tendency for development of pathological scars is known even preventively. The required pressure is 20–30 mmHg (corresponds to compression class II) and should be continued the whole day, i.e. 24 hours. Pressure therapy is usually performed with pressure suits or bandages, sometimes with transparent plastic masks or pressure buttons in special locations. With compression bandages made out of the to be favored long stretch material, slight differences in circumference (e.g. edema) has less of an impact than with short stretch material, so that the still tolerable maximum pressure is reached distinctly later, while on the other hand the still effective minimum pressure is less likely to be fallen short of. In the individually made pressure bandages the applied pressure declines after about six months due to the material. A slow reduction of the pressure over the course of the treatment period of 6–24 months can be done. In postoperative prophylaxis the treatment period should last at least 6–24 months.

Other
The therapy is time-consuming for the patient and places high demands on

patient and physician with respect to adherence.
The therapy is in part associated with high costs, so that documentation of the initial findings and course should particularly be considered.

Recommendation pressure therapy
Therapy of HTS and keloids with pressure can especially be recommended for extensive scars and keloids or in special locations (e.g. on the ear).
Particularly when there is a known tendency to HTS and keloids postoperatively as well as after surgical removal of preexisting HTS and keloids pressure treatment can be recommended in suitable locations.

5.4 Surgical aspects of the treatment of keloids and hypertrophic scars

Josef Koller

Mechanism of action

Depending on the individual initial situation and pathogenesis of the scar formation three important mechanisms of action come in to be useful in surgical wound treatment:

1. The increased tension represents a central aspect in the development of a HTS. The successful removal of the scar tract can be achieved with Z- or W-plasty or by use of grafts or local skin flaps. All methods mentioned in the end effect lengthen the scar and interrupt the vicious circle between scar tension and consecutive further thickening of the scar due to permanently stimulated collagen production.
2. HTS and keloids that developed on the basis of delayed wound healing (e.g. deep dermal burn or wound infection) are transformed by surgery (excision with suture or graft) into a wound with a short healing time.
3. Through the surgical removal of scar tissue a situation corresponding to a fresh wound still without fibrosis is achieved, in which renewed excessive scarring can be reduced by adjuvant conservative therapy.

Side effects

In the event of wound infections, necrosis of skin flaps and graft rejection delayed wound healing can again result in the development of a possibly even larger scar than preoperatively. In addition, particularly when a respective disposition is present a recurrence occurs when surgical after-treatment does not eliminate the most important pathogenetic factors, namely the increased tension on the scar.

Response rate/recurrence rate

Hardly any studies with sufficient methodic quality exist for surgery of scars [28]. Among others, this may be due to the fact that in part HTS are not differentiated from keloids (which at times may be difficult) or follow-up times were too short. The recurrence rates following simple surgical excision therefore fluctuates between 45 to 100 % [29]. Keloid excisions can be performed intra- or extra-marginally. In a recent study on 75 patients with intra- vs. extra-marginal excision a significantly lower recurrence rate was seen in completely excised keloids in comparison to those not completely removed at the edge or the wound base [30]. A modification of the intramarginal excision method has been reported by Lee [32] and by Kim [32]. The skin above the keloid is lifted as a pedicled flap; subsequently the underlying scar tissue is excised. The previously formed skin flap is used for closure of the defect. Lee reported that in the observation period no recurrence was seen in any keloid that healed without complications and was not treated in an adjuvant manner. Kim et al. [32] observed a recurrence in four of nine cases (all without adjuvant concomitant therapy).
Most studies, nonetheless, evaluate combination techniques with surgical excision and adjuvant radiotherapy, pressure therapy, intralesional corticosteroids and silicone dressings [33].
The combination of excision and postoperative intralesional corticosteroid injection (40 mg triamcinolone monthly over at least three months) resulted in no recurrence in twelve patients with earlobe keloids with a follow-up between three and 16 months [34]. Using a similar regimen Rosen et al. [35] observed a keloid recurrence in 23 % of the patients.
The combination of excision and pressure therapy with magnetic buttons in more than 1,400 ear keloids resulted in a recurrence-free rate of almost 90 % with 18 months of follow-up [36]; Hassel et al. [37] achieved a similar result with an "oyster splinter" technique.
The combination of excision with subsequent postoperative radiotherapy resulted in freedom from recurrence in 84 % after five years with only slight differences between the individual locations (earlobe, presternal, etc.) [38]. Nevertheless, van de Kar in a prospective study on previously successfully surgically and/or conservatively treated patients a recurrence rate of 72 % after extra-marginal excision and postoperative radiation therapy [39].
Excision and silicone gel dressings: The studies on this subject are contradictory. In a Cochrane Database Review the authors conclude that only weak evidence exists for an advantage of silicone gel films in the prevention of HTS and keloids following excision [40].
Excision and imiquimod in keloids on the trunk: After positive initial reports Cação et al. [41] and Malhotra [42] found no efficacy of imiquimod 5 % cream in keloids on the trunk after surgical excision.

Performance

For surgical correction of uncomplicated HTS there exists a fundamental recommendation to perform this at the earliest one year after the development of the scar due to the frequent spontaneous regression. Excluded from this are contractures causing functional impairment (e.g. limited opening of the mouth, lifting the head, extending the fingers, etc.) or a disfiguring scar in a cosmetically important location.
The waiting period usually does not apply to keloids, as surgery is usually performed only after the failure of conservative treatment option. In keloids, surgery is combined with adjuvant treatment; in HTS (particularly in recurrences) adjuvant treatment can be employed.

The surgical techniques for the two scar types are in principle the same. Z- and W-plasty are, nonetheless, employed almost exclusively for HTS.
With excision and primary wound closure, among others, small HTS that developed on the basis of disturbed wound healing with delayed healing as well as small keloids can be treated [43]. Z- and W-plasty displace the tension on the HTS by up to 90 % and lengthen the scar. The resulting relief of tension can affect a lack of recurrence.
Split- and full-thickness skin grafts are suited primarily for covering larger, extensive scars that developed on the basis

of a wound healing disturbance (e.g. deep dermal burn). Local flaps, distant flaps and the tissue expander are occasionally employed particularly for broad scar strands.
Because of the underlying genetic predisposition, following surgical removal of keloids, a recurrence must be expected.

Recommendation surgical therapy
Surgical therapy of HTS without tension and without cosmetic disfigurement with an age of less than one year is not recommended.
HTS under tension should be relieved of the strain primarily surgically in a timely manner (Z- or W-plasty, grafts or flaps) particularly when contractures with functional limitations have already developed.
The excision of small, cosmetically distressing HTS that developed on the basis of disturbed wound healing can be recommended.
For small-based larger keloids primary surgical therapy can be recommended.
For all other keloids surgical therapy is recommended only after the failure of conservative therapy.
No final judgment can be made, if intra- or extra-marginal excision is to be favored.
The combination of surgical keloid therapy with an after-therapy (e.g. intralesional corticosteroid, pressure therapy, radiation, cryotherapy) is recommended in principle.
No final judgment can be made on which after-therapy achieves the best results.

5.5 Ablative laser therapy

Silvia Hohenleutner

Laser devices

Continual-wave CO_2 laser (cw-CO_2 laser), pulsed erbium:yttrium-aluminum-garnet laser (Er:YAG laser)

Mechanism of action

Due to the high absorption of laser light in water vaporization (CO_2 laser) or explosion-like ablation (Er:YAG laser) of tissue occurs. The aim of ablative laser treatment in keloids or HTS is flattening of the exophytic scar tissue.

Side effects

Erosions, weeping, crusting and erythema of longer persistence are obligatory in ablative laser therapy. De- and hyperpigmentation are more marked and persist longer after CO_2 laser therapy than after the Er:YAG laser which ablates almost without heat. Viral or bacterial superinfections are further possible complications.

Response rate

Some reviews suggest a recurrence rate for HTS after CO_2 laser treatment of up to 92% , often citing Apfelberg et al. [44]. In the cited study, however, only keloids were treated. A differentiation between proliferating keloids and HTS with tendency for spontaneous regression is of great importance in determining the indication.
No longer active, "burned out" HTS (e.g. burn scars with bridges or contracture formation, incompletely regressed surgical or trauma scars after a "wait-and-see strategy", step formation after inaccurate adaptation of surgical wound edges or after bites) can often be exactly flattened by ablative laser techniques and in a bloodless manner in comparison to scalpel excision through the possibility of ablation in layers.
In keloids, due to the above-mentioned tendency to recur, ablative laser therapy just as excision as monotherapy is usually contraindicated. Particularly in large exophytic keloids, where therapy with other methods alone does not appear promising, a CO_2 laser removal of the exophytic portion in the sense of debulking can be attempted. To avoid a recurrence this must definitely be combined with other procedures such as intralesional corticosteroid injections, cryotherapy, pressure therapy or radiation therapy. In broad-based ear keloids, for example, good results can be achieved by ablation followed by compression therapy with specially constructed ear clips [45].

Performance

Tissue removal in fine HTS, step or contracture formation can be performed athermically with little damage to surrounding tissue with the Er:YAG laser. In larger scar volumes and hard scar tissue the cw-CO_2 laser is superior due to the better hemostasis and its greater efficacy in tissue removal.
After CO_2 laser removal of keloids corticosteroid injections or cryotherapy may be started immediately postoperatively and be repeated at intervals of three to four weeks over a longer period of time.
The patient should always be informed that due to the genetic predisposition that even with laser surgical removal of keloids a recurrence must be expected.

Other

Due to a lack of controlled studies, no statement can yet be made on the use of the fractional CO_2 laser in HTS [46, 47]. Likewise individual reports on therapy with the Er:YAG laser in a thermal (non-ablative) mode still require evaluation in controlled, randomized studies [48].

Recommendation ablative laser treatment
A treatment with the CO_2 and Er:YAG laser can be recommended for no longer active HTS with niveau differences, bridge or contracture formation.
CO_2 laser removal of keloids as monotherapy is not recommended.
In certain cases (small-based large keloids/debulking) CO_2 laser removal can be combined with other measures such as corticosteroid injection, cryotherapy, pressure therapy or radiation therapy.

5.6 Non-ablative laser treatment

Silvia Hohenleutner

Laser devices

FPDL (585 or 595 nm)

Mechanism of action

The selective destruction of microvascularization in scar tissue is postulated as the main mechanism of action. Due to the wavelength-dependent selective photothermolysis with the target chromophore oxyhemoglobin coagulation necrosis of the blood vessels develops, that via hypoperfusion and hypoxia is supposed to lead to the regression of pathological scars Further, a reduction of TGF-β1 expression and fibroblast proliferation, up-regulation of MMP-13 (collagenase 3), induction of fibroblast apoptosis and up-regulation of ERK (extracelluar signal-regulated kinase) and p38 MAP kinase activity after the use of FPDL have been reported [49, 50].

Side effects

Purpura persisting for seven to 14 days is obligatory. Depending on the energy density employed and the pigmentation

of the skin vesicles and crusts may occur. Longer persisting hyperpigmentation occurs particularly in darker skin types and are less frequent with use of the wavelength 595 nm than with 585 nm.

Response rate/recurrence rate
Alster and Williams [51] report – with a follow-up period of six months and a relatively small patient collective – a significant improvement of sternotomy scars with respect to erythema, scar thickness, texture and pruritus in comparison to an untreated control area. These results could not be reproduced in several subsequent studies [52]; particularly the results in some case-control studies did not differ from the untreated control groups after longer follow-up observation periods [53, 54].
Due to the lack of untreated controls, too small case numbers, too short follow-up periods, lack of differentiation between HTS and keloids or lack of information on the age and activity of the scars, the majority of published studies do not possess sufficient evidence [28, 55].
There is no comparability of the studies because of differing laser parameters, treatment intervals or follow-up periods and differing target criteria (elevation, redness, pigmentation, pruritus, consistency of the scar) [43]. In summary, the improvement of 50 to 80 % after two treatments with the FPDL stated in individual publications [56] does not appear realistic after reviewing study data or in light of experience in the clinical routine. A subjective improvement of pruritus of active HTS as well as a diminishment of redness can occasionally be observed during the course of treatment. The evidence of existing care, nonetheless, cannot confirm true efficacy with respect to these parameters as opposed to the spontaneous course of HTS.

Performance
Treatment with the 585 nm FPDL is performed depending on the degree of pigmentation of the skin usually with energy density of about 5.5–7,5 J/cm^2 with a spot diameter of 5–7 mm or with about 4.5–5.5 J/cm^2 with a spot size of 10 mm. At least a two-time treatment at an interval of about six to eight weeks is recommended.

Other
Haedersdal [57] reports in a randomized, controlled study of improvement of scar texture in burn scars or mesh grafts after burn injuries with a non-ablative fractional Er:glass laser. Sufficient experience does not yet exist for HTS.

Recommendation non-ablative laser treatment
Treatment with FPDL can be recommended especially for reduction of erythema, e.g. in fresh, highly vascularized, red scars.
Treatment with FPDL can be considered to alleviate severe pruritus.

5.7 Radiation therapy
Renato G. Panizzon
Mechanism of action
Ionizing radiation has two effects on pathological scars: 1) an antiproliferative effect due to inhibition of new cell formation by delay of mitosis or the mitosis-induced cell death. Dose effects, the impact of fractionating, the oxygen effect and the biological activity of different qualities of radiation are also involved. 2) an antiinflammatory effect due to lymphocyte apoptosis, induction of differentiation of fibroblasts/fibrocytes, the effects on the cell membrane, endothelial cells or macrophages/monocytes as well as the effect on leukocyte adhesion (ICAM) and the oligonucleotides (NFκB). The result is a hypocellular, poorly vascularized and hypoxic tissue with less excessive new formation of fibroblasts and finally inhibition of keloid development. An adequate radiation dose restores the balance between scar formation and excessive cell growth without delaying wound healing.

Side effects
Erythema and scaling are seen as an acute side effect for several weeks in the irradiated field; these regress during the further course. In this phase hydrating creams and sun protection are recommended as topical measures. At total doses between 10 and 20 Gy local pigmentation will develop up to one year after irradiation (therefore sun protection!) that does, however, regress. Chronic effects are hyper- and depigmentation, dryness of the skin and telangiectases, that are rare at total doses less than 12 Gy (which is why dermatologists recommend a total dose not over 12 Gy!).

Response rate/recurrence rate
Through postoperative radiation of keloids with total doses between eight and 30 Gy freedom from recurrence after 12–24 months from 79 to 92 % could be achieved [58–60]. In exclusive irradiation of 15 keloids with 9–18 Gy, Doornbos et al. [61] report freedom from recurrence after 12 months in 73 % of cases.

Performance
Postoperative radiation therapy after excision of a keloid should commence within 24 hours. A total dose of usually 12 Gy in six or ten fractions of 2 Gy applied daily or every second day is recommended. The selection of radiation type, i.e. a conventional radiotherapy (RT), brachytherapy or electron therapy or fractionating should be made individually by the treating radiation therapist.

Other
Treatment should preferentially be performed in specialized clinics with interdisciplinary consultation (dermatology, surgery, nuclear medicine).

Recommendation radiation therapy
Therapy of HTS with irradiation is not recommended.
Therapy of keloids with irradiation can be recommended as monotherapy in individual cases.
Irradiation following surgical therapy of keloids can be recommended.
Postoperative irradiation as prevention of the de novo development of HTS or keloids is not recommended.

5.8 Silicone sheets and silicone gel
Klaus Fritz
Mechanism of action
The mechanism of action of silicone gels has not been definitely clarified. Occlusion and the resulting increased moisture especially of the stratum corneum is presumed to have a signal effect on fibroblasts through cytokine release by keratinocytes [62]. Under application after 24 weeks a reduction of mast cells and decreased expression of the Fas antigen in intralesional fibroblasts are seen [63].

Side effects
Foils and cushions can be annoying to use. Gels and creams are usually well-tolerated.

Response rate/recurrence rate
In a Cochrane Review the benefit of silicone use in scar prevention in patients

with a predisposition to developing keloids after surgery was confirmed (RR 0.46, 95 % CI 0.21 to 0.98). In the treatment of scars with silicone sheets elasticity could be significantly improved (RR 8.60, 95 % CI 2.55 to 29.02). The study quality in all studies was unfortunately very low [40].

Performance
Silicones are available as gels, creams, cushions, sheets and foils. They are usually employed 12–24 h/day over 12–24 weeks.

Other
Silicone products offer the advantage of painless treatment and are usually easy to use

Recommendation silicone sheets and silicone gel
Treatment with silicone products can particularly be considered as additional therapy in active HTS.
The use of silicone products postoperatively for prevention of de novo development of HTS or keloids in patients at risk/with a predisposition as well as after surgical therapy of HTS and/or keloids can be recommended.

5.9 Extractum cepae (onion extract)
Gerd Gauglitz
Mechanism of action
Extractum cepae acts in an antiinflammatory manner, is bactericidal and inhibits fibroblast proliferation. As possible mechanisms the induction of matrix metalloproteinase I (MMP-I) [64] as well as an inhibition of the TGF-β/Smad signaling pathway [65] are discussed.

Side effects
Side effects of scar gels containing onion extract are rare. In the event of intolerance of ingredients of the ointment allergic contact dermatitis can develop.

Response rate/recurrence rate
Study data on the efficacy of extractum cepae for prevention and treatment of HTS or keloids is inconsistent and the quality of the studies is poor overall.
For prevention of HTS and keloids a prospective, randomized, controlled, non-blinded study on children with surgery on the thorax after 6-month use of a scar gel containing an onion extract a less frequent development of excessive scars than in the untreated comparison group was observed [66]. The therapy in the comparative group remains largely unclear with the statement "normal wound therapy". This is of particular significance, as in a further comparative study on improving scar quality (erythema, pruritus, burning, pain, hypertrophy) between scar gels containing onion extract and a topical agent based on petrolatum a specific effect of the ingredients could not be proven [67].
It must be considered, however, that the patient number in this study was low on the whole, the operations were not on specific predilection sites such as e.g. the thorax, and thus statistically significant results could have been expected only with very high patient numbers.
For treatment of HTS and keloids the benefit of a combination of intralesional triamcinolone and an onion extract gel was reported as positive, with both monotherapy with triamcinolone alone as well as the combination with an additional topical agent containing onion skin extract resulted in statistically significant improvement. A calculation of statistical significance with respect to the differences of the therapy concepts was, nonetheless, not done in the study [68].

Performance
Topical application should usually be performed several times daily with mild massage of the scar tissue. In hard, old scars use under occlusion can also be considered. In prophylactic postoperative use, treatment can be started shortly after removal of sutures. In the treatment of open wounds prophylaxis should be delayed until complete epithelialization of the wound. Treatment usually continues over several weeks to months.

Other
The use offers the advantage of a painless treatment and is usually easy to use. The preparations with extractum cepae usually contain other ingredients.

Recommendation extractum cepae (onion extract)
Therapy of active HTS with combination preparations containing extractum cepae (onion extract) can be considered as an additional therapy.
The use of combination preparations containing extractum cepae (onion extract) for postoperative prophylaxis of de novo development of HTS or keloids as well as for prevention of recurrence after surgical therapy of a HTS/a keloid can be considered.

5.10 5-fluorouracil
Gerd Gauglitz
Mechanism of action
Since 1989 5-fluorouracil (5-FU) has been used particularly in the USA for treatment of keloids. The agent 5-FU inhibits the proliferation of fibroblasts as a pyrimidine analog.

Side effects
Pain at injection, hyperpigmentation, skin irritation and ulceration. Listed contraindications are among others anemia, leukopenia, thrombocytopenia, pregnancy, bone marrow depression and infection. Systemic side effects have not been observed to date

Efficacy
The response rate in keloids is about 50 % [69]. Recent studies have demonstrated that even lower concentrations of 5-FU in combination with intralesional corticosteroids can effectively reduce the recurrence rate after surgical removal of ear keloids [70]. In a prospective, randomized study with 10 patients with untreated hypertrophic or keloidal sternotomy scars all four different treatment regimens (dye laser, intralesional triamcinolone, intralesional 5-FU and combination) resulted in significant improvement of the scar. Significant differences in efficacy between the individual therapy approaches were not found, with the triamcinolone group having side effects of longer persistence [71]. Strictly intralesional injection of a combination of 5-FU (50 mg/ml) and triamcinolone acetonide (TAC) (40 mg/ml) (1:3) for the treatment keloids was examined in a retrospective study with either 5-FU/ TAC/excision or TAC/excision in a total of 102 patients, with the combination of 5-FU/ TAC/excision proving superior to the combination TAC/excision [72]. In a prospective study with a total of 69 patients the combination of TAC (40 mg/ml):5-FU 50 mg/ml) (1:9) once weekly for two months injected strictly intralesionally and in part additional use of a dye laser was shown to be superior to exclusive weekly injection of TAC

40 mg/ml [73]. In a further double-blind, prospective study on 40 patients with keloids and HTS better results with respect to reduction of size and redness were seen with the combination TAC (40 mg/ml):5-FU (50 mg/ml) (1:9) in comparison to the injection of TAC 40 mg/ml alone [74].

Performance
At the start of treatment as well as after four injections a blood count should be done. Injections are done once weekly in a concentration of 50 mg/ml and a total dose of maximally 50–150 mg per treatment. Up to 16 injections can be performed [75].

Other
The treatment is off-label.

Recommendation 5-fluorouracil
Treatment of HTS with 5-FU is not recommended.
Treatment of therapy-refractory keloids with 5-FU can be considered.
For prevention of de novo development of recurrence after surgical therapy treatment with 5-FU is not recommended.

6 Further therapy approaches

6.1 Interferon

Joachim Fluhr

Mechanism of action
Interferon-alpha (IF-α) and interferon-gamma (IF-γ) reduce the overproduction of type I/III collagen synthesis as well as the production of glycosaminoglycans in the scar-forming fibroblasts. IF-α2b in addition to this increases the activity of collagenase and reduces angiogenesis.

Side effects
IF can easily induce flu-like symptoms, mild pain as well as inflammatory reactions at the injection site.

Response rate/recurrence rate
The response rate of intralesional monotherapy with IF-α and IF-γ lies between about 20 to 68 % as well as abut 80 % in combination with TAC. In controlled, prospective studies the efficacy of the injections was not always significant. Study data do not allow for definitive evaluation for the treatment of HTS and keloids [76].

Performance
The injection of IF-α2b is intralesional usually with a two-time procedure at an interval of four to seven days. As prevention of a recurrence the injection can be made on the day of surgery. In a combination study with TAC 0.5 million units of IF-α2b per cm^2 were injected in combination with TAC twice weekly [77].

Other
Interferon has no license for the treatment of keloids in Germany/Austria (off-label use). The therapy is costly.

Recommendation interferon
Treatment of HTS and keloids with interferons as monotherapy cannot be recommended at present.
Treatment of keloids and HTS with interferons in combination with TAC can be considered in individual cases in which other therapy options were not sufficiently successful.

6.2 Calcium channel blockers, imiquimod, bleomycin

Recommendation calcium channel blockers, imiquimod, bleomycin
A recommendation for or against the use of calcium channel blockers, imiquimod or bleomycin cannot be made at present due to the small amount of as well as often contradictory data.

7 Authors/validity

The current version of the guideline is an update of the guideline of 2004.
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Level: 2k
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7.1 Declarations on conflicts of interest

See exhaustive account under keloid guideline (Keloidleitlinie): *www.awmf.org*

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