19 Laser-Assisted Photodynamic Therapy

Uwe Paasch

19.1 Introduction

The incidence of non-melanoma skin cancer (non-melanocytic tumors or white or non-melanoma skin cancer, white skin cancer WSC, Fig. 19.1 in the form of actinic keratoses (AK, synonym: squamous cell carcinoma [SCC] in situ of the skin)) and superficial basal cell carcinomas (BCC) in the form of multicentric superficial (BCCms) or solid (BCCsol) is constantly and significantly increasing in the western hemisphere. A major problem here is the frequently encountered area-wide expansion in the sense of field cancerization. For the latter, only a few topics are available, and due to the fact, that large areas are primarily not surgically treatable. The classical photodynamic therapy is not limited in area but has the disadvantage of a high painfulness. While the latter could be minimized by using daylight, the so-called daylight PDT depends on cofactors such as weather, UV radiation, and temperature. As a consequence, artificial "daylight sources" have recently become available, which now make an indoor daylight PDT possible. The increase in the efficiency of PDT through laser assistance, one of the first very successful applications of the concept of laser-assisted drug delivery (LADD), has been successfully combined with these new irradiation concepts. The combination of all these innovations provides us today with new and effective therapeutic options, which are also urgently needed with regard to the epidemiology of light skin cancer.

19.2 Epidemiology of Light Skin Cancer

The causes of the increase in incidence lie in the aging of a large population of people who did not know or underestimate the dangers of chronic UV exposure at work or in private life and who simply did not have access to highly efficient sunscreens used today. With a view to these backgrounds, the recognition of damage to health as a result of job-related UV exposure as an occupational disease (BK 5103) is consistent for certain occupational groups. Overall, it is assumed that the number of these cases will increase fivefold in Germany. Approximately 1.7 million new AKs per year are expected in Germany.

19.3 Supply Options for Light Skin Cancer

In daily patient care and especially in skin cancer screening, it is evident that more and more infiltrative squamous cell carcinomas and basal cell carcinomas are diagnosed as infiltrative scleros-

U. Paasch (✉)
Department of Dermatology, Venerology and Allergology, Universitätsklinikum Leipzig, AöR, Leipzig, Germany
e-mail: uwe.paasch@hautclinicum.de

G. Kautz (ed.), *Energy for the Skin*, https://doi.org/10.1007/978-3-030-90680-1_19

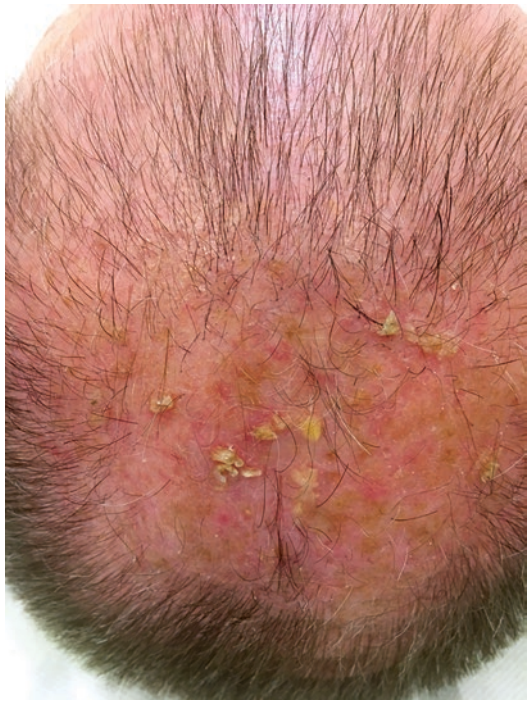


Fig. 19.1 Typical clinical picture of a field cancerization in the area of an alopecia androgenetica

ing or non-sclerosing differentiation (BCCinf) especially in rural areas and must be treated according to guidelines. Already today, basal cell carcinoma is the most common cancer in Germany. From 2007 to 2009 alone, the number of outpatient skin cancer operations rose by 40%, and the number of BCC and SCC requiring inpatient care rose by 11.1% annually. Currently, only about 50% of the eligible persons are aware of their option to skin cancer screening, so that with increasing *public awareness* these numbers will continue to rise.

For both localized and extensive early superficial neoplastic non-melanocytic skin disease (Fig. 19.1), numerous lesion- or field-directed therapies have been established.

Localized AK and BCC are safe and effective using **cryotherapies** and **topicals** addressable. The basic biological course plays an important role here. Thus it usually takes some time until an AK develops into an infiltrative SCC, so that an ordinary AK or a BCC does not have to be rushed into therapeutic maximum measures and the response of basic measures can be waited for. However, about 10% of all patients and about 30% of immunosuppressed patients are expected to transition to invasive SCC after about 2 years.

A BCC never heals on its own and often shows a transition from superficial to infiltrative subtypes with increasing course of the disease.

For this reason, every form of illness of the WSC should be treated by dermatologists.

In particular, the extensive confluent spread of disease in the sense of field cancerization requires an exact diagnostic classification so that the definitive rehabilitation of all forms of WSC growing in this area succeeds as sustainably as possible. The clinician wants a fast, safe, and easy-to-use diagnostic procedure for this purpose. The photodynamic diagnostics to determine at least the area expansion of BCC was evaluated negatively at an early stage. New optical methods such as optical coherence tomography (OCT), confocal reflection microscopy (RCM), and multiphoton spectroscopy (MSP) are currently being introduced into clinical dermatology alongside impedance measurement methods and other methods. The automatic detection of basal cell carcinomas by OCT is already possible today and is used for the optimization of micrographically controlled surgery and experimentally for the optical control of laser ablation of BCC. In practical settings, these methods will help to distinguish localized and planar non-infiltrative or superficial forms of WSC from manifestations with infiltrating growth. This is crucial for the choice of therapy.

The best cure rates for infiltrative SCC and BCC can only be achieved with micrographically controlled surgery. Recurrence rates of approx. 0.5% can be achieved with this method, because even the smallest digitiform tumor proliferates can be reliably detected. For the flat non-infiltrative WSC variants, the operative approach does not make sense and may not be possible for very large areas. In addition to the application of liquid nitrogen or topics, photodynamic therapy (PDT) is also recommended as a selective procedure for the treatment of small

areas. It is exploited that more protoporphyrin IX (PPIX) accumulates in the neoplastic skin when a suitable photosensitizer is applied to the skin. Subsequent inactivation with light of different wavelengths out of the visible range, in the presence of oxygen and sufficient temperature, leads to the formation of radicals that selectively destroy the tumor cells. While the response rates are comparable with the other topical options, the painful nature of photoinactivation in classical PDT (classical PDT, cPDT) limited its clinical use in pronounced planar lesions. A conceptual breakthrough toward less painful PDT protocols was achieved by demonstrating that daylight can also be used for continuous photoinactivation. Thus the so-called daylight PDT was invented (daylight PDT, dPDT). Recently, new topics have been approved for special use in this setting and launched onto the market. In this therapy procedure, a significant part of the oncological therapy, the photoinactivation, is no longer controlled by a physician and is transferred to the responsibility of the patient. This situation and other specific disadvantages of the process, such as the UV component of sunlight, weather, and temperature dependence, led to the development of new radiation sources that emit quasi artificial daylight. The advantage of the established indoor daylight PDT (indoor daylight PDT, artificial daylight PDT, IDL-PDT) lies in the medically controlled photoinactivation. At the same time, developments in the field of fractional lasers led to undreamt of possibilities for increasing the efficiency of PDT by laser-assisted introduction of the photosensitizer into the skin. A new chapter in dermatotherapy, laser-assisted drug delivery, was opened using the example of photodynamic therapy for light skin cancer, the most common skin disease.

19.4 Laser-Assisted Drug Delivery

With the discovery of the almost ideal safety profile of non-ablative fractional lasers (NAFXL) and the subsequent transfer of the concept to ablative lasers (ablative fractional lasers, AFXL), the concept of laser-assisted drug delivery (LADD), i.e., the introduction of substances into the skin after prior microperforation with lasers, was born. Ideas quickly matured into potential areas of application (Table 19.1), but only a few of these were clinically implemented.

The physicochemical and biological properties of the photosensitizers required for PDT in turn enabled the first clinical breakthrough in the sense of a LADD. Laser-assisted or laser-intensified PDT (iPDT) has been able to assert itself in numerous clinical studies with regard to higher efficiency and longer absence of recurrence. Further developments toward laser-assisted daylight PDT and laser-assisted artificial daylight PDT (LA-IDL-PDT) already enrich our therapeutic possibilities. In the following, the concept of LADD in general and in particular will be presented using the example of the different variants of laser-assisted PDT forms.

Table 19.1 Established and potential applications of topical laser-assisted delivery of active ingredients into the skin

Indication	Potentially applicable active substance
Light-aged skin	Hyaluronic acid, collagen stimulators
Dynamic wrinkles	Argireline
Scars and keloids	Steroids Matrix metalloproteinases Mast cell stabilizers
Melasma	Melanosomin inhibitors
Tattoo	Phagocytosis inhibitors
Photodynamic therapy (PDT)	ALA, MAL
Psoriasis	Vitamin D3 analogs
Vitiligo	Steroids, 5-phosphodiesterase inhibitors, topical immunomodulators
Acne	Retinoids
Hair	5-DHT inhibitors/inductors/PRP
Wounds	Growth factors
Bacteria, fungi, leishmania	Antibiotics, fungicides
Granuloma annulare	Steroids
Vessels	Brimonidine

19.5 Fractional Photothermolysis

After ablative fractional lasers were able to establish themselves extremely quickly in dermatology due to their efficiency and the easily controllable side effect profile. Their indication spectrum has once again multiplied with the concept of laser-assisted drug delivery.

The somewhat less versatile fractional non-ablative lasers are to be distinguished. Such systems emit in the near infrared range and lead to tissue coagulation. They are therefore used, as are other coagulating laser systems. This is especially true for the treatment of wrinkles, but also of redness, scars, acne scars, and dis pigmentation.

In the case of fractional lasers with ablative effects, two basic device classes are available in addition to niche systems and devices that do not work with laser beams and have a fractional ablating or at least perforating effect (radio frequency, heat contact methods [microplasma], needling) (Fig. 19.2). While the Er:YAG laser is easier to adopt for beginners, in the long run a CO_2 laser can be used in a wider range of applications. Today, both systems can handle all common forms of application (cutting, punctiform ablations, scanned ablations, fractionated ablations) and are offered by various companies. It is necessary to evaluate the systems in detail in order to find the most suitable system for the individual use It is important in this consideration that practical experience accumulates with increasing use and that this quickly releases desires for more efficient devices.

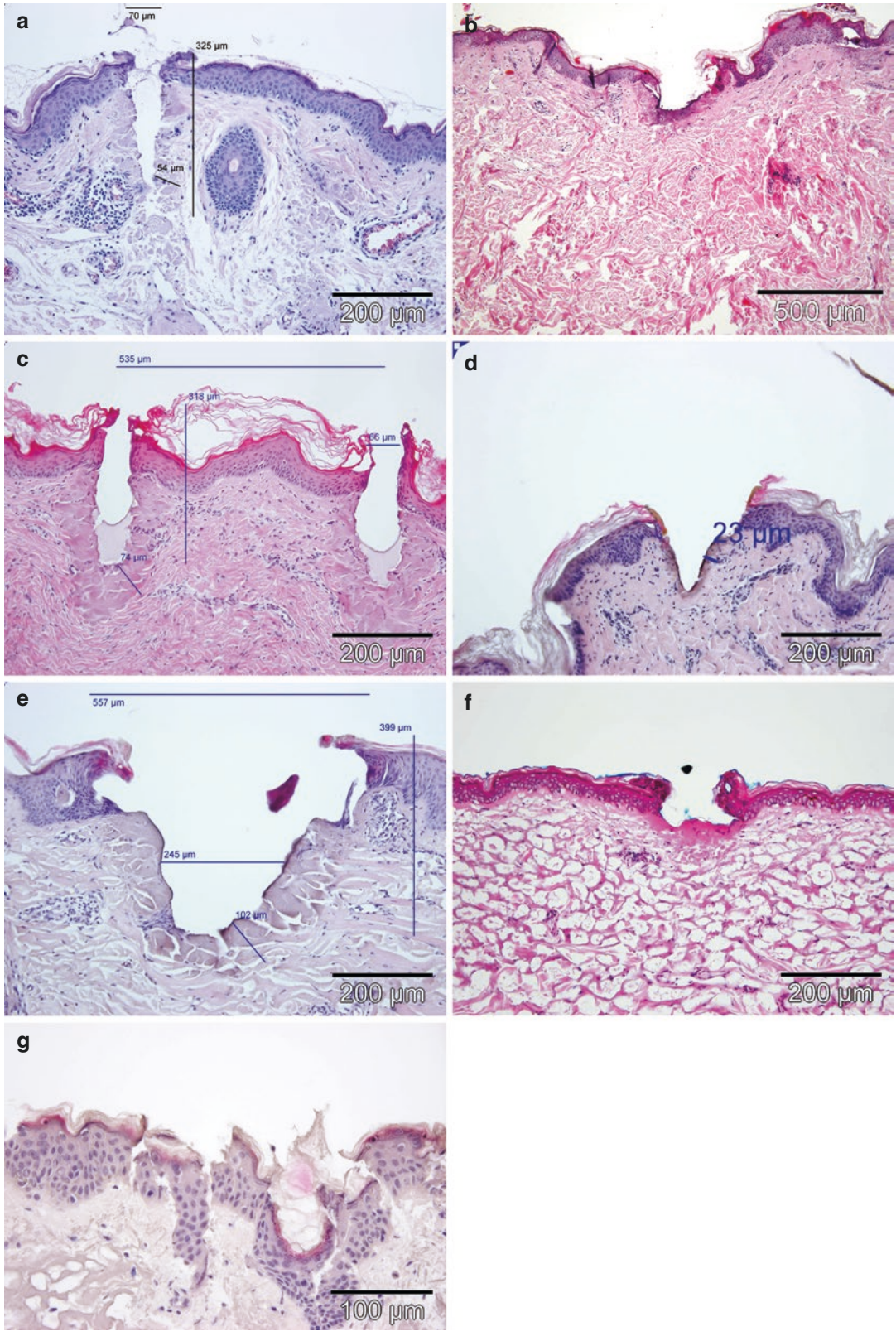
The current technical innovations of the AFXL make it possible to equip fractional Er:YAG lasers with thermal modes, while the latest CO_2 lasers have high power outputs, work extremely fast, and thus unfold less dreaded heat side effects. In addition, systems have been developed which can be located in their biological effect between the two antipodes (Er:YSGG and thulium lasers) due to the wavelengths used. These AFXL alone achieves reproducible, comparable, and promising results in the treatment of sun-damaged and thus potentially neoplastic skin, as well as scars. This becomes possible because large areas of the skin are subjected to a microperforation that heals without scarring if known laser parameter limits are adhered to. They can also be used at WSCs but are usually not curative per se.

Until the healing process is complete, elegantly fitting substances can also be introduced into the skin. This becomes possible because a specific sequence of wound healing takes place after AFXL. The temporary TOR (TOR: temporary opening of the epidermal barrier, Fig. 19.3) to the deep compartments of the skin can thus be opened for a LADD based on published evidence.

19.6 Laser-Assisted Drug Delivery

The quasi uniform ablation pattern of the AFXL early suggested the idea of using the TOR to the skin therapeutically. On the other hand, there is also the danger of sensitization if, for example, sun protection is applied too early. The latter effect can in turn also be intentionally used for vaccination.

Fig. 19.2 (**a**–**g**) Selection of typical shot profiles on human skin. The diameter of the ablation zone is so small that scar-free healing is possible. The depth determines within limits the penetration of the molecule to be applied depending on its physicochemical properties. The coagulation zone serves as a reservoir. (**a**) Ultra-pulsed fractional CO_2 laser (Encore, Lumenis, Israel) Density 5% 10 mJ 120 µm Spot HE4x. (**b**) Chopped fractional CO_2 laser (Exelo$_2$, Alma Lasers GmbH, Germany) 10 W 5 ms 50 mJ Density 200 pts./cm^2 HE 20x. (**c**) Chopped fractional CO_2 laser (Dotscan, GME GmbH, Germany) 5 mJ 0.5 ms 10 W Density 500 pts./cm^2 HE 20x. (**d**) Fractional Er:YAG laser (Burane FX, Alma Lasers, Germany GmbH) FX12 180 mJ ablative 0 J thermal HE 20x. (**e**) Microplasma roller "Legato" (Legato, Alma Lasers GmbH, Germany) atrophic ablative 110 W thermal. (**f**) Thermoablation system (prototype Tixel, Novoxel GmbH, Germany) S-Tip 9 ms HE 4x methylene blue. (**g**) Ablation profiles according to needling (System Dr. Pen, Korea) 1.0 mm HE 40x


a
70 µm
325 µm
54 µm
200 µm
b
500 µm
c
535 µm
318 µm
74 µm
200 µm
d
23 µm
200 µm
e
557 µm
399 µm
245 µm
102 µm
200 µm
f
200 µm
g
100 µm

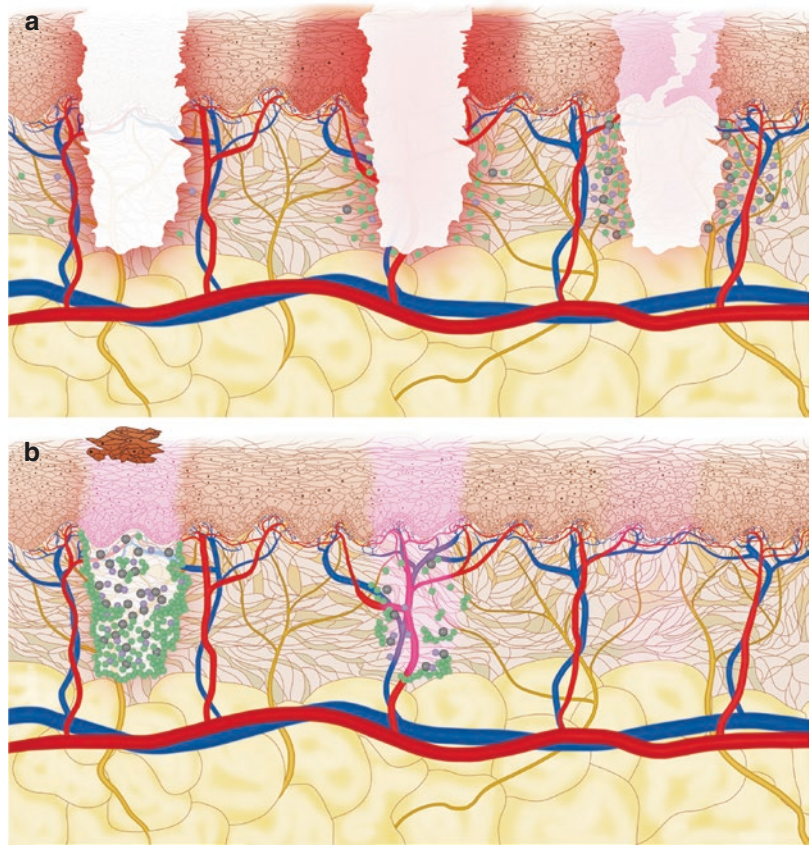


Fig. 19.3 (**a**) Sequence 1. (**b**) Sequence 2

Using histology, optical coherence tomography (OCT), and confocal laser microscopy (RCM) its opening time was determined to be at least 1–6 h. Of the numerous potential therapy options, practical implementations are gradually becoming known (Table 19.2)

It is now known that fractional laser ablation must meet minimum requirements for LADD and that not every laser device is equally suitable. Ideally, you will find a **precise ablation**, in particular of the upper epidermal portions, a **homogeneous columnar dermal ablation channel** which is surrounded by a not too wide coagulation zone. Compared to other methods, such as needling or flat abrasion, the AFXL-PDT is equipped with a powerful CO_2 laser, since this is the only area where a homogeneous PPIX enrichment in area and depth occurs. The coagulation zone is of particular importance. Recent investigations have shown that the same acts like a sponge as a reservoir for introduced molecules. The special influence of the structure of the ablation channels is also confirmed by the biodistribution of MTX and ingenol mebutate. In contrast, however, the density of the ablation channels should be kept rather low.

19.7 The Evolution of PDT

Classical Photodynamic Therapy of the Skin

The cPDT is an effective and widely used therapy for the treatment of AK including its bowenoid variant and the M. Bowen as well as BCC and small solid BCC. Due to the minimally invasive character of PDT, it is particularly suitable for the treatment of multiple lesions and field cancerization, even if the cosmetic result is important.

The mechanism of action of PDT is based on the irradiation of dyes specifically accumulated

Table 19.2 Intensification variants for PDT of the skin

Intensification option	References
Reduction of hyperkeratoses – Peeling/jet peel – Dermabrasion	[1]
Induction of HSP up to 24 before PDT –Diode laser	[2–4] [5]
Warming of the skin – Infrared light –Direct heat	[6–8]
Laser assistance –AFXL using CO_2 laser, ~5% coverage, 20 mJ, <1	[9–13]
Photosensitizer – Preferentially apply ALA immediately up to 1 h after AFXL	[14–16]
Pressure/vacuum	[13]
Incubation – 15–60 min without occlusion	
Photobleaching by means of LED, daylight or artificial daylight	[17, 18]
Pain management – Cooling with cold air blower – Analgesics	
Posttreatment – Steroids short term – Peeling intermittent long term	[19]

in neoplastic cells of the skin, such as the cell's own **protoporphyrin IX (PPIX)** after application of **aminolevulinic acid (ALA)** or their derivatives. PPIX absorbs light of different wavelengths, leading to the formation of reactive oxygen species. The latter destroy vital tumor cell structures and thus lead to the selective elimination of neoplastic transformed skin parts.

Numerous light sources are suitable for inactivating the protoporphyrin IX (PPIX) accumulated in this way, whereby LEDs were able to achieve the best effect in the conventional approach.

Main side effect of the conventionally applied PDT is the **pain**. It is the direct result of the neurotoxic action of the oxygen radicals released during irradiation of the PPIX. The amount of accumulated PPIX depends on several factors: the amount/concentration and type of application added (occlusion, incubation time) as well as the temperature and irradiation intensity. The incubation period is particularly critical. Too long an exposure time should be avoided, as otherwise accumulation would take place in healthy cells and the selectivity would be eliminated.

The **effectiveness** of PDT depends very much on the lesion thickness. The response rates of the cPDT are 75–93% for thin AK, between 64% and 83% for medium AK, and between 39% and 52% for thick AK. The same loss of efficacy can be seen with increasing thickness in basal cell carcinomas. For this reason, it is recommended to repeat the cPDT after 1–2 weeks for thicker lesions.

The loss of effectiveness toward depth is due to the limited penetration depth of the photosensitizer. Effect amplification by means of curettage, peeling, needling, microdermabrasion, NAFXL, and AFXL (Table 19.2), among others, has been the subject of numerous successful studies and was included in the recommendations for carrying out the cPDT.

Daylight PDT

A major disadvantage of the classic PDT was the partly pronounced painfulness, which was largely overcome with the introduction of daylight PDT.

Disadvantages of the use of sunlight are the seasonal limitation (May to October), the extraordinary temperature dependence, and the necessity of additional protection against unwanted UV radiation. In addition, dosimetry cannot usually be guaranteed without additional measuring instruments.

This has led to the development of alternative radiation sources based on LED and other systems, so that a conventional daylight PDT, a laser-assisted daylight PDT, artificial daylight PDT, and a laser-assisted artificial daylight PDT are now available. This combines the advantages of the AFXL-PDT and the daylight PDT. The laser-assisted artificial daylight PDT (indoor daylight PDT) can be used all year round temperature- and dose-controlled.

Laser-Assisted PDT

Extensive studies on laser-assisted drug delivery using ablative fractional lasers in PDT showed

that in particular ALA and its methyl ester (MAL) as well as the hexyl derivative (HAL) are homogeneously and deeply enriched after AFXL and lead to better healing rates with longer recurrence freedom in focal lesions and field-cancerized skin as well as in immunocompromised patients. If such an AFXL-PDT is applied prophylactically, preventive effects can be achieved.

The outstanding clinical effects of AFXL-assisted and thus intensified PDT are explained at the molecular level. Heat shock proteins (HSP, e.g., HSP70) are induced in both postfractional wound healing and PDT, leading to synergistic effects. Heat shock proteins ensure the timely replacement of lethal keratinocytes and the repair of important cell functions in surviving cells. HSP70 can be induced even more intensively if the AFXL is preceded by another thermal stimulus mediated by classical diode lasers. This can be practically implemented up to 24 h before the actual intervention.

In parallel, it could be shown that AFXL is also effective in NMSC, unless there are pronounced hyperkeratoses. Thus, before an AFXL-PDT, a reduction of the hyperkeratoses so typical for the AK and especially for the field cancer is always recommended. In addition to the spa days, more suitable methods for the surface such as peeling, dermabrasion, or jet peeling are also available. It is interesting to note that salicylic acid peeling can suppress tumor development in the mouse model by suppressing p53 expression.

In addition to an extended relapse-free post-therapeutic window, the therapy approach is particularly suitable for immunosuppressed high-risk patients with their considerably higher risk of developing light skin cancer. The preventive effect of PDT in these patients has also been proven.

While initial studies on laser-assisted PDT in basal cell carcinoma were promising, only a non-significant discrete superiority of AFXL-PDT was found in BCC in the high-risk area of the face, the so-called H-zone. Thus, there is a basic risk of an insufficient therapy of deeper neoplasia.

Optimum biodistribution for ALA is already achieved with 5% coverage. The use of external pressure is recommended to ensure that the ablation channels, which are rather sparsely distributed on the skin surface, are filled safely.

With all these modifications, the AFXL-PDT can be further improved and used for the therapy of field cancer even in large areas intensively and safely as well as relatively painlessly. However, it must be accepted that PDT, which has been further developed in this way, cannot be a substitute for surgical restoration and certainly not for micrographically controlled surgery. It remains to be seen whether clinical studies with sufficient follow-up times will be able to evaluate the actual clinical efficiency.

The optimal maintenance therapy is still open. A weekly off-label application of imiquimod 3.75% is recommended in the absence of published evidence. Further fields of application include the female genital tract and onychomycosis, where fractional lasers on the one hand and variants of PDT on the other are already in use.

Laser-Assisted Daylight PDT

The limiting painfulness of the cPDT could be avoided with the introduction of the daylight PDT. The intensification of the conventional PDT by the AFXL-PDT alone also led to a higher painfulness with classical irradiation with 635 nm 37 J/cm^2 over 8 min. Sunlight is also less painful when AFXL-PDT is applied to normal patients as well as to patients at risk for immunosuppression.

Laser-Assisted Artificial Daylight PDT

Sunlight has specific disadvantages: seasonal limitation (May to October), temperature dependence, and carcinogenic UV radiation. The missing dosimetry can be a source of insufficient irradiation.

All these disadvantages can be solved by an alternative indoor radiation source (Fig. 19.4),

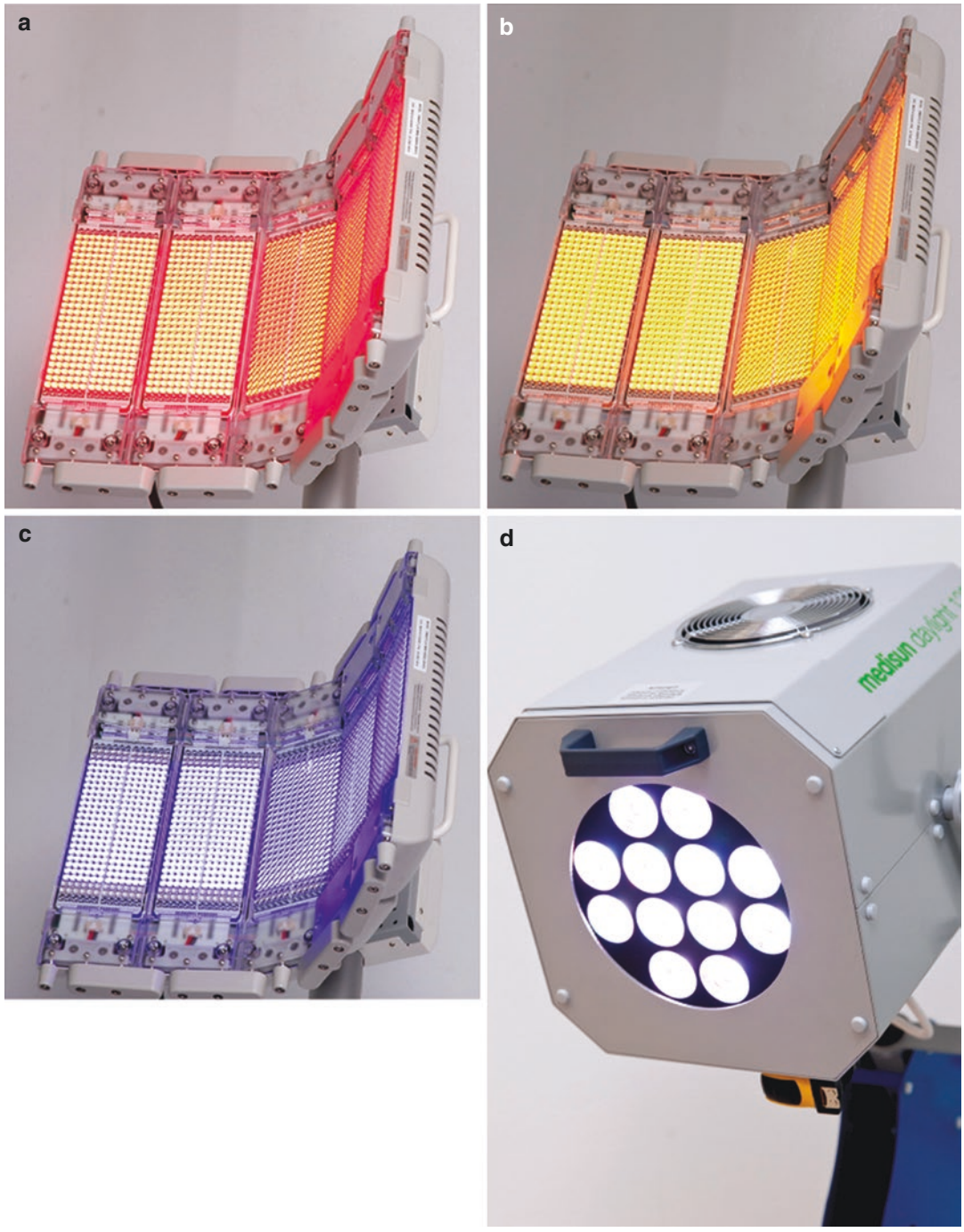


Fig. 19.4 (**a–c**) LED emitting at 415, 535, and 635 nm (Multilight, GME GmbH, Germany). (**d**) Spotlight with white light source

which follows the protocol of daylight therapy. The further development of conventional PDT allows an efficient therapy of field cancerization of large areas with relatively low pain (Fig. 19.5). Further intensification options can also be used (Table 19.2). Infiltrative SCC and thick solid

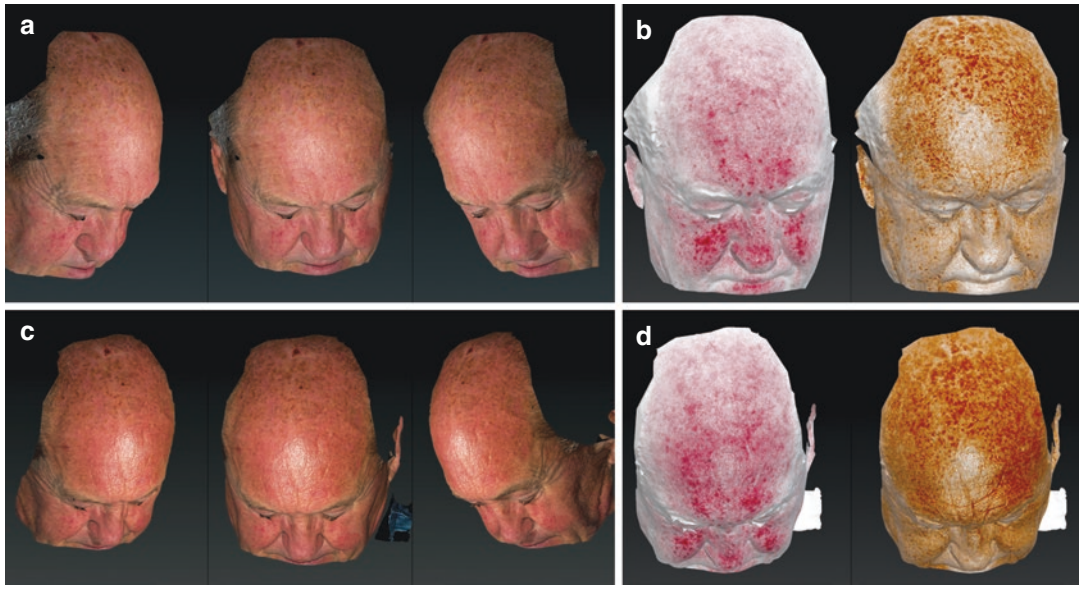


Fig. 19.5 (**a**–**d**) Clinical picture before and after an indoor PDT. (**a**) Clinical picture in front of indoor daylight PDT. (**b**) Representation of vessels and pigments from (**a**) middle before indoor daylight PDT. (**c**) Clinical image after indoor daylight PDT. (**d**) Representation of vessels and pigments from (**c**) center after indoor daylight PDT. The increased blood circulation or vascular reaction becomes clear after the therapy

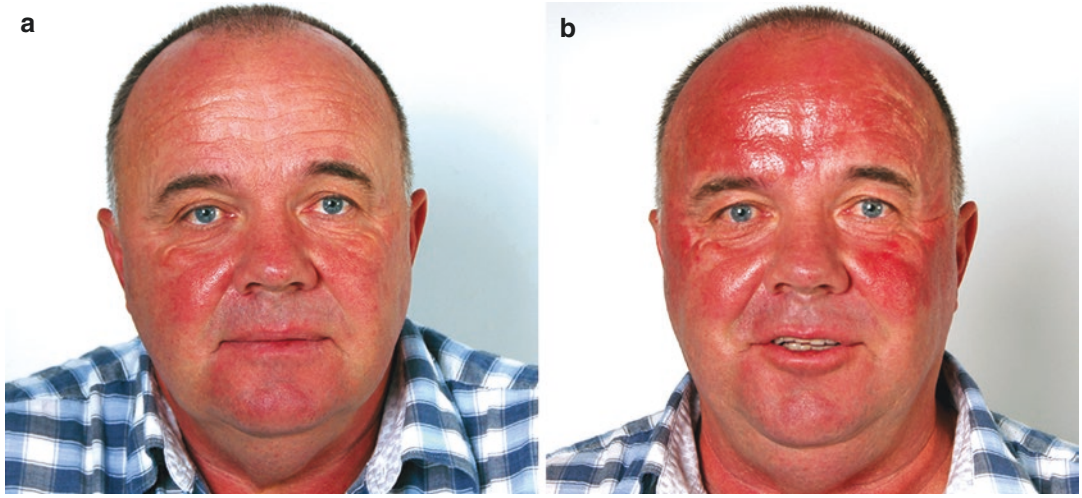


Fig. 19.6 (**a**, **b**) Clinical course spectrum after indoor PDT. (**a**) Clinical picture in front of indoor PDT. (**b**) Clinical picture 1 week after indoor PDT

and infiltrative BCC, however, remain reserved for micrographically controlled surgical sanitation. Depending on the tumor load, the clinical reactions can be moderate to intense (Fig. 19.6). In addition to the use of a suitable laser and photosensitizer, the intensification option of the LADD should be considered (Table 19.2). A standardized protocol is required to ensure the efficacy of the therapy with minimal side effects (Fig. 19.7).

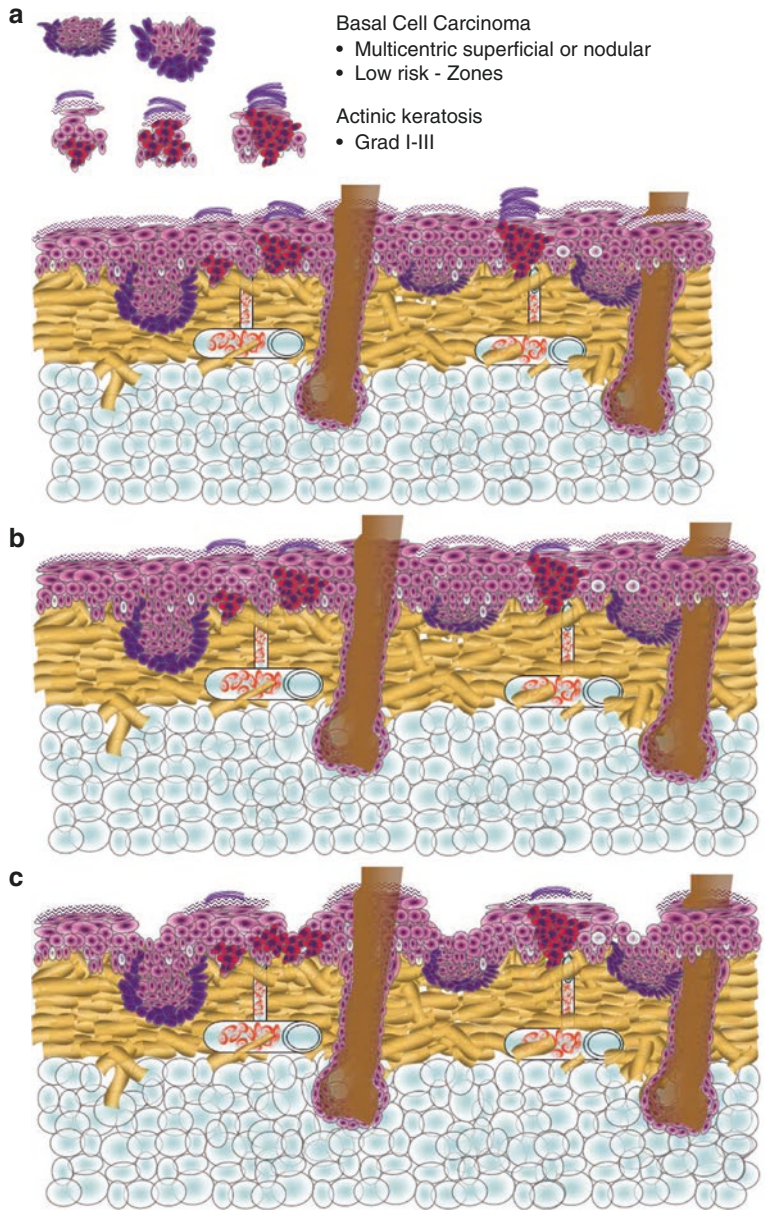


Fig. 19.7 Protocol of indoor PDT (laser-assisted artificial daylight PDT). (**a**) Schematic representation of superficial light skin cancer (non-melanocytic tumors or white or non-melanoma skin cancer, light skin cancer WSC) in the form of actinic keratoses (AK, synonym: squamous cell carcinoma [SCC] in situ of the skin) and superficial basal cell carcinomas (BCC) in the form of multicentrally superficially differentiated (BCCms) or solid (BCCsol) differentiated (BCCsol) superficially. (**b**) The first step in the preparation of PDT in all its variations is the elimination of superficial cornifications and tumor parts using suitable procedures such as peeling, jet peeling, abrasion (med. Sandpaper, microdermabrasion), curettage, or shave excision. (**c**) Second step in the intensification of cPDT: microperforations of the skin are introduced using suitable methods such as AFXL, fractional radiofrequency, or needling. A relatively low coverage of <5% is to be used for optimal biosdistribution. (**d**) Third step of intensified PDT: application of a suitable photosensitizer. (**e**) Fourth step of the intensified PDT: improvement of the biodistribution by applying pressure from the outside and then incubation and construction of the PPIX in the neoplastic transformed cells. (**f**) Fifth step of intensified PDT: photodeactivation of PPIX in the presence of oxygen leads to the destruction of neoplastic cells. The classic red LED 36 J/cm^2 can be used as a light source. The light can also be blue (North America preferred) and a combination of both with and without additional yellow light, daylight, and artificial daylight. (**g**) Sixth and final step of intensified PDT: cure

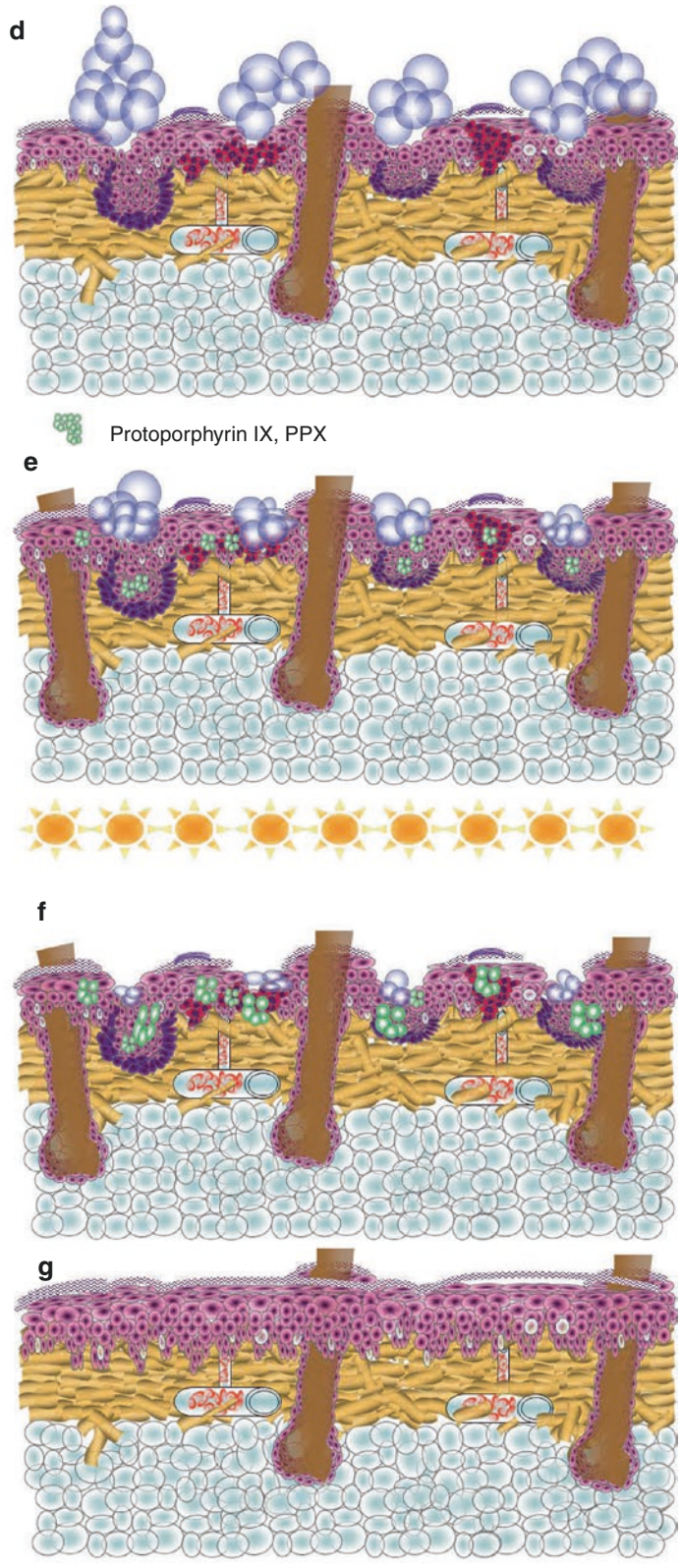


Fig. 19.7 (continued)

Onychomycosis, Nail Psoriasis, and Nail Dystrophy

After initial euphoria about a potentially new principle of action, the **onychomycosis** It has meanwhile been pointed out that lasers as monotherapy cannot control the problem but are more effective in combination with topical agents (also in comparison with topical agent monotherapy). Reinfections in particular must be prevented. The combination with systemic antimycotics was also described as more effective compared to the respective monotherapies. The FDA's approval criteria were revised accordingly. Nevertheless, lasers are regarded as helpful if a system medication is prohibited or could at least be shortened in duration and used for the therapy of the **psoriasis of the nail**. It is interesting to note that even with an idiopathic **onychodystrophy**, therapy options may exist. Not to be neglected, however, are sometimes serious complications after application of lasers to the nail organ, especially in connection with conduction anesthesia and in the presence of neuropathies.

Numerous systems are used that emit light in the area of the skin's optical window, although it is not yet clear exactly which mechanism could be effective.

Diode lasers, which emit in the range of 755–980 nm and have been tested with classical hair removal parameters, are able to heat circumscribed nail areas for a short time far above 60 °C, which also applies to long and short pulsed Nd:YAG lasers and leads to changes in the nail keratin composition. Q-switched 1064 nm Nd:YAG lasers are also described as effective, although the mechanism of action has not been clarified. AFXL is also used in combination with common antifungal drugs.

19.8 Conclusion

Laser dermatology has developed dramatically in the last 5 years. This is reflected not least in almost 3500 new publications on the subject.

The development of fractional lasers has greatly expanded the options of dermatological laser therapy. Today, essential indications are treated with these systems as standard. In addition, the AFXL have made the field of laser-assisted introduction of molecules into the skin practicable. Translatable research results flowed into the further development of PDT and led to the concept of laser-assisted PDT. The superiority of the latter over the classic PDT has already been proven for some applications. Numerous options for further refining treatment protocols using other lasers, radiation sources, devices, and interventions have been identified. In addition, other topics and systemically applicable drugs were used to show that there is still considerable potential for further development of the methodology.

References

1. Togsverd-Bo K, Paasch U, Haak CS, Haedersdal M. Lesion dimensions following ablative fractional laser treatment in non-melanoma skin cancer and premalignant lesions. Lasers Med Sci. 2012;27(3):675–9.
2. Helbig D, Moebius A, Simon JC, Paasch U. Nonablative skin rejuvenation devices and the role of heat shock protein 70: results of a human skin explant model. J Biomed Opt. 2010;15:038002.
3. Helbig D, Paasch U. Molecular changes during skin aging and wound healing after fractional ablative photothermolysis. Skin Res Technol. 2011;17:19–128.
4. Helbig D, Simon JC, Paasch U. Epidermal and dermal changes in response to various skin rejuvenation methods. Int J Cosmet Sci. 2010;32:458–69.
5. Paasch U, Sonja G, Haedersdal M. Synergistic skin heat shock protein expression in response to combined laser treatment with a diode laser and ablative fractional lasers. Int J Hyperthermia. 2014;30:245–9.
6. Ramstad S, Le Anh-Vu N, Johnsson A. The temperature dependence of porphyrin production in Propionibacterium acnes after incubation with 5-aminolevulinic acid (ALA) and its methyl ester (m-ALA). Photochem Photobiol Sci. 2006;5:66–72.
7. Mamalis A, Koo E, Sckisel GD, et al. Temperature-dependent impact of thermal aminolaevulinic acid photodynamic therapy on apoptosis and reactive oxygen species generation in human dermal fibroblasts. Br J Dermatol. 2016;175:512–9.
8. Willey A, Anderson RR, Sakamoto FH. Temperature-modulated photodynamic therapy for the treatment of actinic keratosis on the extremities: a one-year follow-up study. Dermatol Surg. 2015;41:1290–5.
9. Skovbolling HC, Illes M, Paasch U, Haedersdal M. Histological evaluation of vertical laser channels

from ablative fractional resurfacing: an ex vivo pig skin model. Lasers Med Sci. 2010;26:465–71.
10. Taudorf EH, Lerche CM, Erlendsson AM, et al. Fractional laser-assisted drug delivery: laser channel depth influences biodistribution and skin deposition of methotrexate. Lasers Surg Med. 2016;48:519–29.
11. Erlendsson AM, Taudorf EH, Eriksson AH, et al. Ablative fractional laser alters biodistribution of ingenol mebutate in the skin. Arch Dermatol Res. 2015;307:515–22.
12. Haak CS, Christiansen K, Erlendsson AM, et al. Ablative fractional laser enhances MAL-induced PpIX accumulation: impact of laser channel density, incubation time and drug concentration. J Photochem Photobiol B. 2016;159:42–8.
13. Erlendsson AM, Doukas AG, Farinelli WA, et al. Fractional laser-assisted drug delivery: active filling of laser channels with pressure and vacuum alteration. Lasers Surg Med. 2016;48:116–24.
14. Banzhaf CA, Wind BS, Mogensen M, et al. Spatiotemporal closure of fractional laser-ablated channels imaged by optical coherence tomography and reflectance confocal microscopy. Lasers Surg Med. 2016;48:157–65.
15. Haedersdal M, Sakamoto FH, Farinelli WA, et al. Pretreatment with ablative fractional laser changes kinetics and biodistribution of topical 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). Lasers Surg Med. 2014;46:462–9.
16. Haedersdal M, Katsnelson J, Sakamoto FH, et al. Enhanced uptake and photoactivation of topical methyl aminolevulinate after fractional CO_2 laser pretreatment. Lasers Surg Med. 2011;43:804–13.
17. Togsverd-Bo K, Idorn LW, Philipsen PA, et al. Protoporphyrin IX formation and photobleaching in different layers of normal human skin: methyl- and hexylaminolevulinate and different light sources. Exp Dermatol. 2012;21(10):745–50.
18. Wiegell SR, Fabricius S, Stender IM, et al. A randomized, multicentre study of directed daylight exposure times of 1(1/2) vs. 2(1/2) h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol. 2011;164:1083–90.
19. Dainichi T, Ueda S, Furue M, Hashimoto T. By the grace of peeling: the brace function of the stratum corneum in the protection from photo-induced keratinocyte carcinogenesis. Arch Dermatol Res. 2008;300(Suppl 1):S31–8.

Suggested Reading

Augustin J, Schafer I, Thiess P, et al. [Regional differences in the health care of basal cell carcinoma]. Hautarzt. 2016a;67:822–8.
Augustin M, Anastasiadou Z, Schaarschmidt ML, et al. [Care for skin cancer in Germany: provision and providers]. Hautarzt. 2016b;67:544–8.
Banzhaf CA, Wind BS, Mogensen M, et al. Spatiotemporal closure of fractional laser-ablated channels imaged by optical coherence tomography and reflectance confocal microscopy. Lasers Surg Med. 2016;48:157–65.
Banzhaf CA, Thaysen-Petersen D, Bay C, et al. Fractional laser-assisted drug uptake: impact of time-related topical application to achieve enhanced delivery. Lasers Surg Med. 2017;49(4):348–54.
Bhatta AK, Keyal U, Huang X, Zhao JJ. Fractional carbon-dioxide (CO2) laser-assisted topical therapy for the treatment of onychomycosis. J Am Acad Dermatol. 2016;74:916–23.
Boonchai W, Sathaworawong A, Wongpraparut C, Wanitphakdeedecha R. The sensitization potential of sunscreen after ablative fractional skin resurfacing using modified human repeated insult patch test. J Dermatol Treat. 2015;26:485–8.
Chen X, Shah D, Kositratna G, et al. Facilitation of transcutaneous drug delivery and vaccine immunization by a safe laser technology. J Control Release. 2012;159:43–51.
Choi MC, Kim MS, Lee GH, et al. Photodynamic therapy for premalignant lesions of the vulva and vagina: a long-term follow-up study. Lasers Surg Med. 2015;47(7):566–70.
Dainichi T, Ueda S, Furue M, Hashimoto T. By the grace of peeling: the brace function of the stratum corneum in the protection from photo-induced keratinocyte carcinogenesis. Arch Dermatol Res. 2008;300(Suppl 1):S31–8.
de Oliveira GB, Antonio JR, Antonio CR, Tome FA. The association of fractional CO_2 laser 10.600nm and photodynamic therapy in the treatment of onychomycosis. An Bras Dermatol. 2015;90:68–471.
Duan L, Marvdashti T, Lee A, et al. Automated identification of basal cell carcinoma by polarization-sensitive optical coherence tomography. Biomed Opt Express. 2014;5:3717–29.
Eissing L, Schafer I, Stromer K, et al. [Perception of statutory skin cancer screening in the general population: current findings on participation, knowledge and evaluation]. Hautarzt. 2017;68:371–6.
El-Tatawy RA, Abd El-Naby NM, El-Hawary EE, Talaat RA. A comparative clinical and mycological study of Nd-YAG laser versus topical terbinafine in the treatment of onychomycosis. J Dermatol Treat. 2015;26:461–4.
Erlendsson AM, Taudorf EH, Eriksson AH, et al. Ablative fractional laser alters biodistribution of ingenol mebutate in the skin. Arch Dermatol Res. 2015;307:515–22.
Erlendsson AM, Doukas AG, Farinelli WA, et al. Fractional laser-assisted drug delivery: active filling of laser channels with pressure and vacuum alteration. Lasers Surg Med. 2016;48:116–24.
Fotinos N, Campo MA, Popowycz F, et al. 5-Aminolevulinic acid derivatives in photomedicine: characteristics, application and perspectives. Photochem Photobiol. 2006;82:994–1015.
Francuzik W, Fritz K, Salavastru C. Laser therapies for onychomycosis—critical evaluation of methods

and effectiveness. J Eur Acad Dermatol Venereol. 2016;30:36–942.
Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. Dermatol Surg. 2007;33:1099–101.
Galvan Garcia HR. Onychomycosis: 1064-nm Nd:YAG q-switch laser treatment. J Cosmet Dermatol. 2014;13:32–235.
Gerritsen MJ, Smits T, Kleinpenning MM, et al. Pretreatment to enhance protoporphyrin IX accumulation in photodynamic therapy. Dermatology. 2009;218:193–202.
Glogau RG. The risk of progression to invasive disease. J Am Acad Dermatol. 2000;42:23–4.
Grunewald S, Bodendorf MO, Simon JC, Paasch U. Update dermatologic laser therapy. J Dtsch Dermatol Ges. 2010;9:146–59.
Grunewald S, Bodendorf M, Illes M, et al. In vivo wound healing and dermal matrix remodelling in response to fractional CO(2) laser intervention: clinicopathological correlation in non-facial skin. Int J Hyperthermia. 2011;27:811–8.
Gupta AK, Foley KA, Daigle D. Clinical trials of lasers for toenail onychomycosis: the implications of new regulatory guidance. J Dermatol Treat. 2017;28(3):264–70.
Haak CS, Togsverd-Bo K, Thaysen-Petersen D, et al. Fractional laser-mediated photodynamic therapy of high-risk basal cell carcinomas—a randomized clinical trial. Br J Dermatol. 2015;172:215–22.
Haak CS, Christiansen K, Erlendsson AM, et al. Ablative fractional laser enhances MAL-induced PpIX accumulation: impact of laser channel density, incubation time and drug concentration. J Photochem Photobiol B. 2016;159:42–8.
Haak CS, Hannibal J, Paasch U, et al. Laser-induced thermal coagulation enhances skin uptake of topically applied compounds. Lasers Surg Med. 2017;49(6):582–91.
Haedersdal M, Sakamoto FH, Farinelli WA, et al. Fractional CO(2) laser-assisted drug delivery. Lasers Surg Med. 2010;42:113–22.
Haedersdal M, Katsnelson J, Sakamoto FH, et al. Enhanced uptake and photoactivation of topical methyl aminolevulinate after fractional CO_2 laser pretreatment. Lasers Surg Med. 2011;43:804–13.
Haedersdal M, Togsverd-Bo K, Paasch U. Case reports on the potential of fractional laser-assisted photodynamic therapy for basal cell carcinomas. Lasers Med Sci. 2012;27(5):1091–3.
Haedersdal M, Sakamoto FH, Farinelli WA, et al. Pretreatment with ablative fractional laser changes kinetics and biodistribution of topical 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). Lasers Surg Med. 2014;46:462–9.
Haedersdal M, Erlendsson AM, Paasch U, Anderson RR. Translational medicine in the field of ablative fractional laser (AFXL)-assisted drug delivery: a critical review from basics to current clinical status. J Am Acad Dermatol. 2016;74:981–1004.
Helbig D, Paasch U. Molecular changes during skin aging and wound healing after fractional ablative photothermolysis. Skin Res Technol. 2011;17:19–128.
Helbig D, Moebius A, Simon JC, Paasch U. Nonablative skin rejuvenation devices and the role of heat shock protein 70: results of a human skin explant model. J Biomed Opt. 2010a;15:038002.
Helbig D, Simon JC, Paasch U. Epidermal and dermal changes in response to various skin rejuvenation methods. Int J Cosmet Sci. 2010b;32:458–69.
Helbig D, Simon JC, Paasch U. Photodynamic therapy and the role of heat shock protein 70. Int J Hyperthermia. 2011;27:802–10.
Helou J, Korkomaz J, Haber R, et al. Laser treatment of onychomycosis: beware of ring block anesthesia! Lasers Med Sci. 2015;30:399–2400.
Helou J, Maatouk I, Hajjar MA, Moutran R. Evaluation of Nd:YAG laser device efficacy on onychomycosis: a case series of 30 patients. Mycoses. 2016;59:11.
Helsing P, Togsverd-Bo K, Veierod MB, et al. Intensified fractional CO laser-assisted photodynamic therapy versus laser alone for organ transplant recipients with multiple actinic keratoses and wart-like lesions: a randomized half-side comparative trial on dorsal hands. Br J Dermatol. 2013;169:1087–92.
Hibler BP, Sierra H, Cordova M, et al. Carbon dioxide laser ablation of basal cell carcinoma with visual guidance by reflectance confocal microscopy: a proof-of-principle pilot study. Br J Dermatol. 2016;174:1359–64.
Hollmig ST, Rahman Z, Henderson MT, et al. Lack of efficacy with 1064-nm neodymium:yttrium-aluminum-garnet laser for the treatment of onychomycosis: a randomized, controlled trial. J Am Acad Dermatol. 2014;70:911–7.
John SM, Trakatelli M, Gehring R, et al. CONSENSUS REPORT: recognizing non-melanoma skin cancer, including actinic keratosis, as an occupational disease - A Call to Action. J Eur Acad Dermatol Venereol. 2016;30(Suppl 3):38–45.
Karsai S, Jager M, Oesterhelt A, et al. Treating onychomycosis with the short-pulsed 1064-nm-Nd:YAG laser: results of a prospective randomized controlled trial. J Eur Acad Dermatol Venereol. 2017;31(1):175–80.
Kim TI, Shin MK, Jeong KH, et al. A randomised comparative study of 1064 nm neodymium-doped yttrium aluminium garnet (Nd:YAG) laser and topical antifungal treatment of onychomycosis. Mycoses. 2016;59(12):803–10.
Li Y, Xu J, Zhao JY, Zhuo FL. Self-controlled study of onychomycosis treated with long-pulsed Nd:YAG 1064-nm laser combined with itraconazole. Chin Med J (Engl). 2016;129:929–1934.
Lim EH, Kim HR, Park YO, et al. Toenail onychomycosis treated with a fractional carbon-dioxide laser and topical antifungal cream. J Am Acad Dermatol. 2014;70:918–23.
Mamalis A, Koo E, Sckisel GD, et al. Temperature-dependent impact of thermal aminolaevulinic acid photodynamic therapy on apoptosis and reactive oxy-

gen species generation in human dermal fibroblasts. Br J Dermatol. 2016;175:512–9.
Manstein D, Herron GS, Sink RK, et al. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. Lasers Surg Med. 2004;34:426–38.
Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications—actinic keratoses, Bowen's disease, basal cell carcinoma. J Eur Acad Dermatol Venereol. 2013a;27:536–44.
Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 2: emerging indications—field cancerization, photorejuvenation and inflammatory/infective dermatoses. J Eur Acad Dermatol Venereol. 2013b;27:672–9.
Moutran R, Maatouk I, Helou J. Diabetic neuropathy and Nd-YAG (1064 nm) laser for onychomycosis: be careful. J Eur Acad Dermatol Venereol. 2015;29:239–1240.
Paasch U. Fraktionale Laser: Wunsch und Wirklichkeit. Akt Dermatol. 2013:257–62.
Paasch U. The future of fractional lasers. Facial Plast Surg. 2016;32:261–8.
Paasch U, Haedersdal M. Laser systems for ablative fractional resurfacing. Expert Rev Med Devices. 2011;8:67–83.
Paasch U, Bodendorf MO, Grunewald S. Dermatologische Lasertherapie: Fraktionale Laser. Berlin: KVM Verlag; 2011.
Paasch U, Sonja G, Haedersdal M. Synergistic skin heat shock protein expression in response to combined laser treatment with a diode laser and ablative fractional lasers. Int J Hyperthermia. 2014a; 30:245–9.
Paasch U, Nenoff P, Seitz AT, et al. Heat profiles of laser-irradiated nails. J Biomed Opt. 2014b;19:8001.
Poetzsch ORF. Bevölkerung Deutschlands bis 2060 - 13. koordinierte Bevölkerungsvorausberechnung. 2015. Statistisches Bundesamt.
Ramstad S, Le Anh-Vu N, Johnsson A. The temperature dependence of porphyrin production in Propionibacterium acnes after incubation with 5-aminolevulinic acid (ALA) and its methyl ester (m-ALA). Photochem Photobiol Sci. 2006;5:66–72.
Rogalski C, Thieme C, Sticherling M, Paasch U. Health economic aspects in the operative treatment of basal cell carcinoma. JEADV. 2003;17:199–200.
Schaefer I, Augustin M, Spehr C, et al. Prevalence and risk factors of actinic keratoses in Germany—analysis of multisource data. J Eur Acad Dermatol Venereol. 2014;28:309–13.
Scheibe P, Braumann UD, Kuska JP, et al. Image-processing chain for a three-dimensional reconstruction of basal cell carcinomas. Exp Dermatol. 2010;19:689–91.
Schmitt J, Haufe E, Trautmann F, et al. Is UV-exposure acquired at work the most important risk factor for cutaneous squamous cell carcinoma? Results of the population-based case-control study FB-181. Br J Dermatol. 2018;178(2):462–72.
Shin MK, Kim TI, Kim WS, et al. Changes in nail keratin observed by Raman spectroscopy after Nd:YAG laser treatment. Microsc Res Tech. 2017;80(4):338–43.
Sierra H, Damanpour S, Hibler B, et al. Confocal imaging of carbon dioxide laser-ablated basal cell carcinomas: an ex-vivo study on the uptake of contrast agent and ablation parameters. Lasers Surg Med. 2016;48:133–9.
Skovbolling HC, Illes M, Paasch U, Haedersdal M. Histological evaluation of vertical laser channels from ablative fractional resurfacing: an ex vivo pig skin model. Lasers Med Sci. 2010;26:465–71.
Skovbolling HC, Illes M, Paasch U, Haedersdal M. Histological evaluation of vertical laser channels from ablative fractional resurfacing: an ex vivo pig skin model. Lasers Med Sci. 2011;26:465–71.
Stockfleth E, Ulrich C, Meyer T, Christophers E. Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. Recent Results Cancer Res. 2002;160:251–8.
Taudorf EH, Lerche CM, Erlendsson AM, et al. Fractional laser-assisted drug delivery: laser channel depth influences biodistribution and skin deposition of methotrexate. Lasers Surg Med. 2016;48:519–29.
Togsverd-Bo K, Idorn LW, Philipsen PA, et al. Protoporphyrin IX formation and photobleaching in different layers of normal human skin: methyl- and hexylaminolevulinate and different light sources. Exp Dermatol. 2012a;21(10):745–50.
Togsverd-Bo K, Haak CS, Thaysen-Petersen D, et al. Intensified photodynamic therapy of actinic keratoses with fractional CO(2) laser—a randomized clinical trial. Br J Dermatol. 2012b;166:1262–9.
Togsverd-Bo K, Paasch U, Haak CS, Haedersdal M. Lesion dimensions following ablative fractional laser treatment in non-melanoma skin cancer and premalignant lesions. Lasers Med Sci. 2012c; 27(3):675–9.
Togsverd-Bo K, Omland SH, Wulf HC, et al. Primary prevention of skin dysplasia in renal transplant recipients with photodynamic therapy: a randomized controlled trial. Am J Transplant. 2015a;15:2986–90.
Togsverd-Bo K, Lei U, Erlendsson AM, et al. Combination of ablative fractional laser and daylight-mediated photodynamic therapy for actinic keratosis in organ transplant recipients—a randomized controlled trial. Br J Dermatol. 2015b;172:467–74.
Togsverd-Bo K, Halldin C, Sandberg C, et al. Photodynamic therapy is more effective than imiquimod for actinic keratosis in organ transplant recipients—a randomized intra-individual controlled trial. Br J Dermatol. 2018;178(4):903–9.
Wang KX, Meekings A, Fluhr JW, et al. Optical coherence tomography-based optimization of mohs micrographic surgery of Basal cell carcinoma: a pilot study. Dermatol Surg. 2013;39:627–33.
Wetzig T, Kendler M, Maschke J, et al. No clinical benefit of preoperative fluorescence diagnosis of basal cell

carcinoma localized in the H-zone of the face. Br J Dermatol. 2010a;162:370–1376.

Wetzig T, Woitek M, Eichhorn K, et al. Surgical excision of basal cell carcinoma with complete margin control: outcome at 5-year follow-up. Dermatology. 2010b;220:363–9.

Wiegell SR, Fabricius S, Stender IM, et al. A randomized, multicentre study of directed daylight exposure times of 1(1/2) vs. 2(1/2) h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. Br J Dermatol. 2011;164:1083–90.

Willey A, Anderson RR, Sakamoto FH. Temperature-modulated photodynamic therapy for the treatment of actinic keratosis on the extremities: a one-year follow-up study. Dermatol Surg. 2015;41:1290–5.

Wiznia LE, Quatrano NA, Mu EW, Rieder EA. A clinical review of laser and light therapy for nail psoriasis and onychomycosis. Dermatol Surg. 2017;43(2):161–72.

Xu Y, Miao X, Zhou B, Luo D. Combined oral terbinafine and long-pulsed 1,064-nm Nd: YAG laser treatment is more effective for onychomycosis than either treatment alone. Dermatol Surg. 2014;40:201–1207.

Zhang J, Lu S, Huang H, et al. Combination therapy for onychomycosis using a fractional 2940-nm Er:YAG laser and 5 % amorolfine lacquer. Lasers Med Sci. 2016;31:1391–6.