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Review Article

Advancements in skin cancer treatment: focus on photodynamic therapy: a review

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Abstract: Some of these include basal cell carcinoma (BCCs), squamous cell carcinoma (SCCs), and melanoma; skin cancer is a leading global health problem due to its high prevalence and possibly due to its serious health implications. Conventional and known therapies like surgeries, radiation therapies and chemotherapy although helpful are sometime deleterious and do not specifically attack the cancers. New advancement is half-breed technique has recently been recognized that photodynamic therapy (PDT) can be considered as a potentially effective modality by using photosensitizers which work through the generation of localized ROS on exposure to light. This review analyzes the recent progress in PDT and evaluation of its effectiveness in the cure of skin malignancies: with the emphasis on its applicability to BCCs and SCCs, as well as the limitations concerning the cure of melanomas. This review gives an insight to how PDT works and how it can be combined with other forms of therapy, and the prospects of photosensitizer carriers with special reference to nanotechnology. Also, the optimization of the parameters associated with the use of PDT is explored in an attempt to improve on its safety and efficacy in treatment. As such, the purpose of this systematic review of the literature is to advance the knowledge of PDT usage in contemporary dermatologic oncology and to contribute to the eventual expansion of this therapy into other skin diseases and potential use as a first-line treatment for skin neoplasia.

Keywords: Photodynamic therapy, skin cancer, cancer therapy

Introduction

Skin cancer is the predominant type of cancer, making up around 50% of all cancer cases in the United States [1]. Non-melanoma skin cancers (NMSCs) are the most prevalent kinds of skin cancer. They include basal cell carcinoma (BCC), which develops in the basal cells, and squamous cell carcinoma (SCC), which develops in the squamous cells [2]. Basal cell carcinomas (BCCs) are seldom lethal, but they can cause severe disfigurement if left untreated and allowed to proliferate. According to the latest estimate, some 2.8 million cases of basal cell carcinomas (BCCs) and 700,000 cases of squamous cell carcinomas (SCCs) are identified per year in the United States [3].

Sunlight and other artificial sources of ultraviolet (UV) radiation, such as tanning beds, can cause skin cancer, which is a type of skin cancer that develops in the skin. The United States alone diagnoses more than 5.4 million cases of skin cancer each year, making it the most common type of cancer globally [4]. Considering that some people may get more than one diagnosis, this equates to about 3.3 million Americans. In Spain, there are around 8.82 new cases of melanoma per 100,000 people per year, with 2.17 new cases of mortality per 100,000 people per year. Several other European nations, along with the US, AU, and NZ, have rates that are lower than this one. Spain had a crude incidence rate of 38.16 per 100,000 person-years of squamous cell carcinoma (SCC) [5]. When compared to other nations, including Germany and Slovakia, Spain has a very low incidence rate. Location, sun exposure habits, socioeconomic status, and smoking habits are some of the variables that can impact these rates [4].

Treatments for skin cancers other than melanoma often include radiation, cryo, fluorouracil, imiquimod, and surgical procedures. Basal and squamous cell carcinomas are often treated

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with surgery, however less invasive methods such as fluorouracil or cryotherapy may also be employed. Radiation therapy may be utilized as a treatment option for people who are unable to undergo surgery due to medical reasons [6]. Imiquimod is frequently utilized to treat many types of basal cell carcinoma, including nodular basal cell carcinoma and sclerodermiform basal cell carcinoma, as well as various forms of squamous cell carcinoma, such as Bowen's disease and keratoacanthoma [7]. While the existing treatments have various levels of effectiveness, they often lack specificity and often fail to directly target the tumor or its surrounding environment. Additionally, they are linked to a significant occurrence of negative effects and produce unsatisfactory cosmetic outcomes. Therefore, it is necessary to explore alternate therapy alternatives for people suffering from these illnesses [8].

Genetic factors and exposure to UV radiation from sunshine or tanning beds are significant contributors to the development of skin cancer. Conventional methods for treating skin cancer, such as surgery, radiation therapy, and chemotherapy, result in significant side effects because to the indiscriminate impact on normal cell activity [9]. Photodynamic therapy (PDT) is a treatment that utilizes light and light-activated chemicals called photosensitizers (PSs) to induce photochemical reactions [10]. The rapid and excessive generation of reactive oxygen species (ROS) leads to apoptosis, necrosis, or immunogenic cell death. It also causes lipid peroxidation, DNA damage, microvascular damage, and local immunological reactions [11-13]. Photodynamic treatment (PDT) has been increasingly used to treat several kinds of solid tumors, such as those affecting the brain, intestines, bones, bladder, prostate, breast, cervix, ovary, and others, throughout the last three decades since its inception [14].

The skin, being the outermost layer of the body, is a suitable target for photodynamic therapy (PDT) in the treatment of various disorders such as acne, naevus flammeus, and skin cancer. The field of dermatology offers several potential uses for PDT due to its abundance of opportunities [15]. There are two primary categories of skin cancer: melanoma (MSC) and nonmelanoma (NMSC). Although MSCs possess a high degree of malignancy and the ability to spread to other parts of the body, they did not exhibit any signs of photodynamic therapy (PDT) [16]. Basal cell carcinomas (BCCs) account for around 75-80% of the most frequent kind of cancer in the world, known as non-melanoma skin cancer (NMSC). Squamous cell carcinomas (SCCs) make up roughly 20-25% of NMSC cases, while the other 5% consist of AK, Bowen's disease, Merkel cell carcinoma (MCC), and other varieties [17].

Skin caner

Types and pathology of skin cancer

Basal cell carcinoma (BCC): Most sun-exposed parts of the body, such the head and neck, are more likely to develop basal cell carcinoma, the most common and least invasive skin cancer [18]. Cancer that begins in the epidermis's basal layer is called basal cell carcinoma. The p53 tumor suppressor gene, Ras protein, and sonic hedgehog glycoprotein are hypothesized to be mutated and rendered inactive by exposure to ultraviolet B radiation. This is assumed to be the fundamental process that leads to the development of basal cell carcinoma. The hair follicle germ cells are also linked to its genesis [19]. Based on its appearance, risk of recurrence, and metastasis, BCC has been subdivided into several forms, including nodular, superficial, micro nodular, and infiltrative BCC. Because of its distinct lesion borders and easy clinical identification, nodular basal cell carcinoma has an exceptionally low recurrence rate when compared to other subtypes. This is because it allows for more precise treatment. A smooth or reddening of the outer skin layer, with little or no invasion of the dermal layer, is a hallmark of superficial basal cell carcinoma. In contrast to other subtypes of basal cell carcinoma, micro nodular BCC is characterized by the formation of small, spherical aggregates of basaloid cells. Lastly, the most severe form of basal cell carcinoma is infiltrative BCC, which penetrates into the dermis and other deeper layers of skin [20]. Basal cell carcinoma (BCC) often manifests on areas of the body that are exposed to the sun, particularly the facial skin and the nasal region [21]. The primary variables that increase the likelihood of developing basal cell carcinoma (BCC) include exposure to ultraviolet radiation (UV), having light skin, long-term suppression of the immune system, being ma-

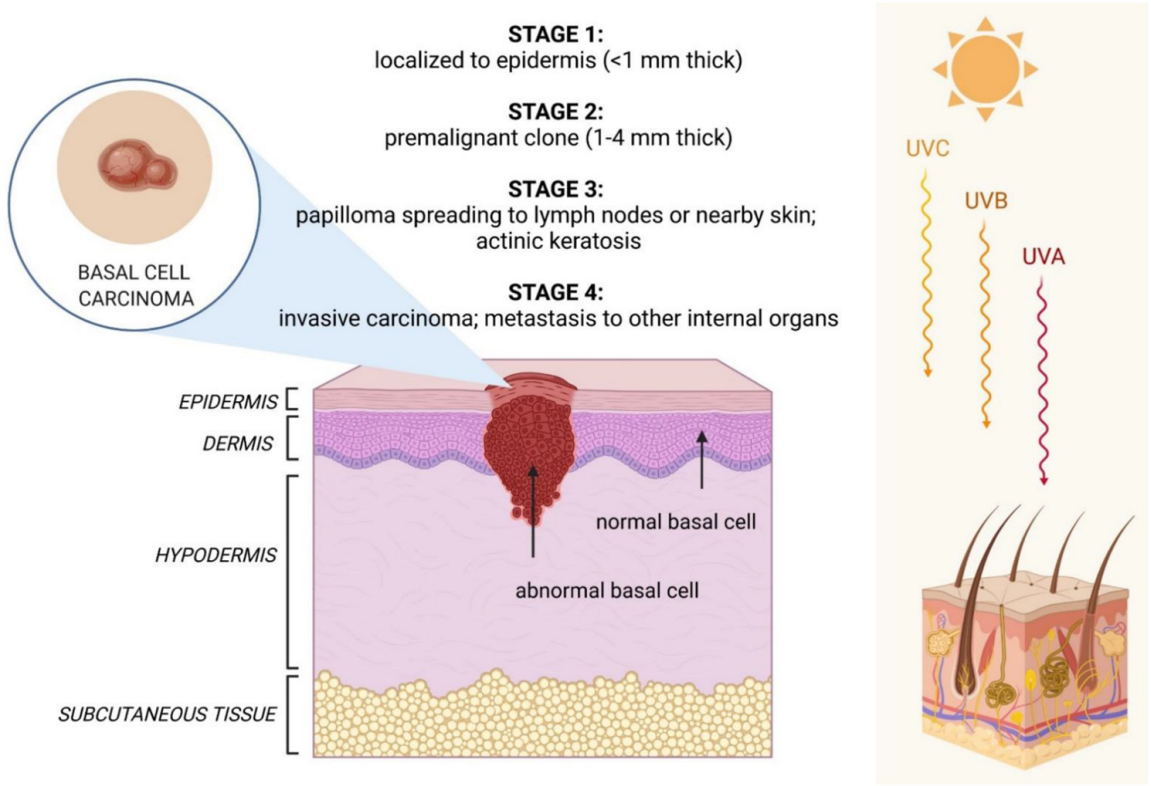

Figure 1. Four stages of BCC development under sunlight exposure [138].

le, being of advanced age, and having certain genodermatoses [22]. **Figure 1** illustrates the several phases of basal cell carcinoma (BCC) development that are linked to exposure to sunlight. Factors that increase the likelihood of developing basal cell carcinoma include heredity (e.g., Gorlin-Goltz syndrome), chronological age, gender, immunosuppression, sun exposure, and Fitzpatrick skin types I and II [23].

Squamous cell carcinoma: Among skin cancers, squamous cell carcinoma ranks second with a prevalence of 25%. Comparatively, basal cell carcinoma is less intrusive [24]. Squamous cell carcinoma is more likely to occur in the cervicofacial regions, such as the lower lip and ears, than basal cell carcinoma. In SCC, Ras protein is pivotal, in contrast to BCC, which develops from a mix of E-cadherin protein inactivation and p53 tumour suppressor gene mutation. An aberrant proliferation of invasive squamous cells with metastasis potential is the hallmark of squamous cell carcinoma [25]. Lesion location, depth, size, and distinctiveness all have a role in SCC severity. Lesions with dimensions larger than 2 cm in diameter and 4 mm in depth are more prone to recurrence and metastasis. When it comes to differentiation, a fully-formed SCC is marked by distinct cell structural variations, uneven dermal neoplastic keratinocyte infiltration, and varying degrees of inflammation and fibrosis underneath the tumor. Moderate SCC, on the other hand, invades blood vessels and has increased mitotic activity and a more widespread invasion. Squamous cell carcinoma with poor differentiation often invades the dermis and lacks keratinization. Overexposure to UV radiation is a major cause of SCC and BCC (**Figure 2**). Nevertheless, SCC is thought to be caused by other factors as well, including chemical carcinogens, genodermatoses, inflammatory conditions, and medications (tumor necrosis factor α inhibitors) [26, 27].

Melanoma: Melanoma accounts for 5% of cutaneous malignancies, the lowest prevalence of skin cancer, but it is also the most aggressive and kills over 80% of skin cancer patients [28, 29]. The cancerous growth of melanocytes, the cells that produce the pigment known as melanin, is known as melanoma. The unchecked

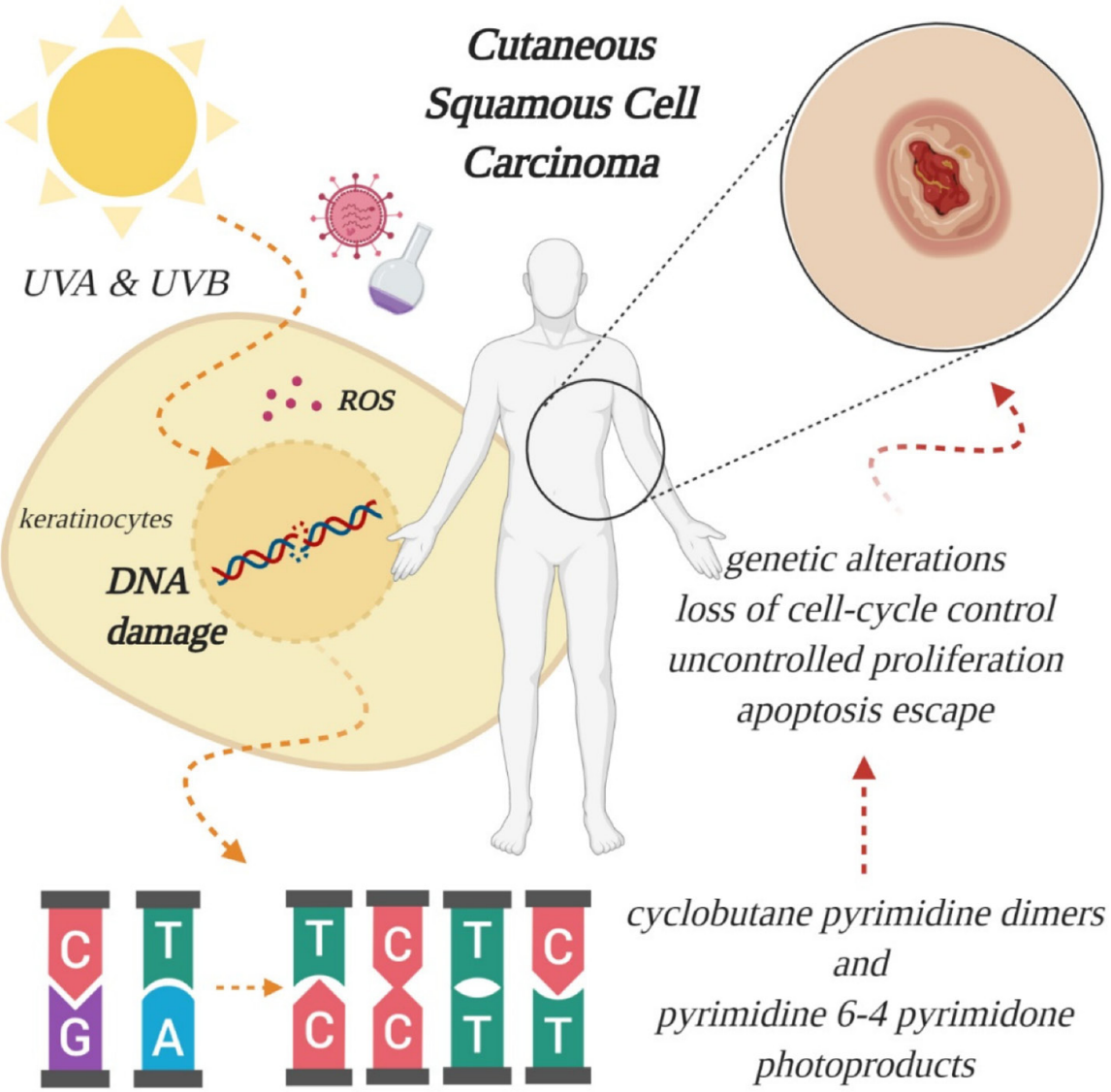

Figure 2. Impact of ultraviolet radiation on the genetic material of epidermal keratinocytes leading cutaneous squamous cell carcinoma (SCC) [139].

proliferation of these cells causes the cancer to metastasize, or spread, to other regions of the body. The lesion will be flat and pigmented when it is first discovered. The shape will be hazy, and it will stay on the surface of the skin. In its later stages, the tumor grows vertically and infiltrates the dermal layer's collagen strands. Lastly, the tumor spreads to the subcutaneous tissue, where it creates little bumps and elevated spots [30]. The United States has a survival rate of 3-11 months for individuals with advanced melanoma. Patients with metastatic melanoma had a five-year survival rate of fewer than 10% after diagnosis. The five-year survival rate for patients with stage I and II melanoma was 99.4%, but the rates for stage III and IV were 68.0% and 29.4%, respectively, according to the data. Genetics, fair skin, exposure to UV radiation, chemical carcinogens, and immunosuppression are some of the risk factors for melanoma. There was additional evidence that indoor tanning contributed to the development of melanoma [31].

Epidemic of skin cancer

It is critical to examine the relationship between climate change and the prevalence of cutane-

ous malignancy, a dangerous skin cancer, as there is mounting evidence that climate change is having a negative effect on human and environmental health.

According to study, academics have long acknowledged that the Maritime Road's construction would have far-reaching effects on the economies of the Indian Ocean area [32]. According to Zhao (2018), a Chinese scholar, China's main goal with the maritime route is to build a strong foundation for the maritime economy, which will improve trade links and pave the way for regional economic growth. This trio of important South Asian countries Bangladesh, India, and Myanmar will be able to work together more efficiently because to the Maritime Road. Reduced shipping delays and strong collaboration with 18 surrounding nations are the focal points of the author's emphasis on the region's considerable potential. To facilitate easy communication, China has invested much in building a network of ports throughout South Asia. Building projects in South Asia, according to study have boosted portside industrial development and allowed local infrastructure to be completed [33]. Not only will the ports improve international commerce, but they will also attract new suppliers of commodities. According to study, a more efficient network and better local connection would boost cooperation between China and the Association of Southeast Asian Nations, which in turn will increase China's regional influence.

According to research, the main goal of the maritime road is to build a strong maritime network that would boost regional commerce and strategic collaboration among South Asian countries.

The alarming increase in the occurrence of skin cancer as a result of sun exposure is a more serious concern [34]. The last forty years have seen a tripling in the country's new case count [35]. Study reported that CMM occurred at a rate of 4 to 5 percent each year worldwide. The nations with the greatest occurrence of skin cancer are Australia and New Zealand, which also happen to have the highest rates globally. It is possible that the dangerous mix of fair-skinned people, living in a subtropical latitude region, and a culture that values outdoor activities greatly is to blame for the recent dramatic increase in skin cancer cases [36]. However, there are authors who argue that the increased screening and biopsies, better diagnostic skills among doctors, and evolving histologic criteria are exaggerating the CMM pandemic's incidence. Although these factors could be contributing, better detection techniques are not the main reason CMM is becoming more common. Study demonstrated that the rise is independent of socioeconomic status and tumor thickness, lending credence to this idea [37].

Photocarcinogenesis

According to many studies, skin cancer is mostly caused by prolonged exposure to ultraviolet radiation, which is known to be carcinogenic [38, 39]. The ability of UVR to function as a mutagen and initiate tumor development in the absence of an additional agent is what qualifies it as a complete carcinogen. Simplifying the sequence of events in photocarcinogenesis that finally lead to the creation of skin malignancies is crucial, even if it is not feasible to completely describe the complicated biochemical pathways in this work.

Just to review, UVA light triggers the production of ROS, which in turn cause DNA damage including single-strand breaks, crosslinks, and altered nucleotides. Conversely, pyrimidine dimers are produced when ultraviolet B radiation absorbs straight into DNA [40]. The DNA excision repair systems are overpowered by mutagenesis and cannot handle extensive exposure to UVR. The expression of tumor suppressor genes decreases and proto-oncogenes rise as a result of this mutagenesis. Study found that this disruption of apoptosis control causes a decrease in cell death and the subsequent expansion of clonal cell populations [41]. According to study [42], photo carcinogenesis is accelerated when exposed to ultraviolet radiation, which suppresses the immune system. Research conducted by the World Health Organization has shown a high correlation between the development of cutaneous malignant melanoma and non-melanoma skin cancer. Both the scientific and medical communities have come to this same conclusion. Indeed, UVR has been designated as a carcinogen by the International Agency for Research on Cancer. The likelihood of getting various forms of skin cancer may vary according to factors such as the frequency and

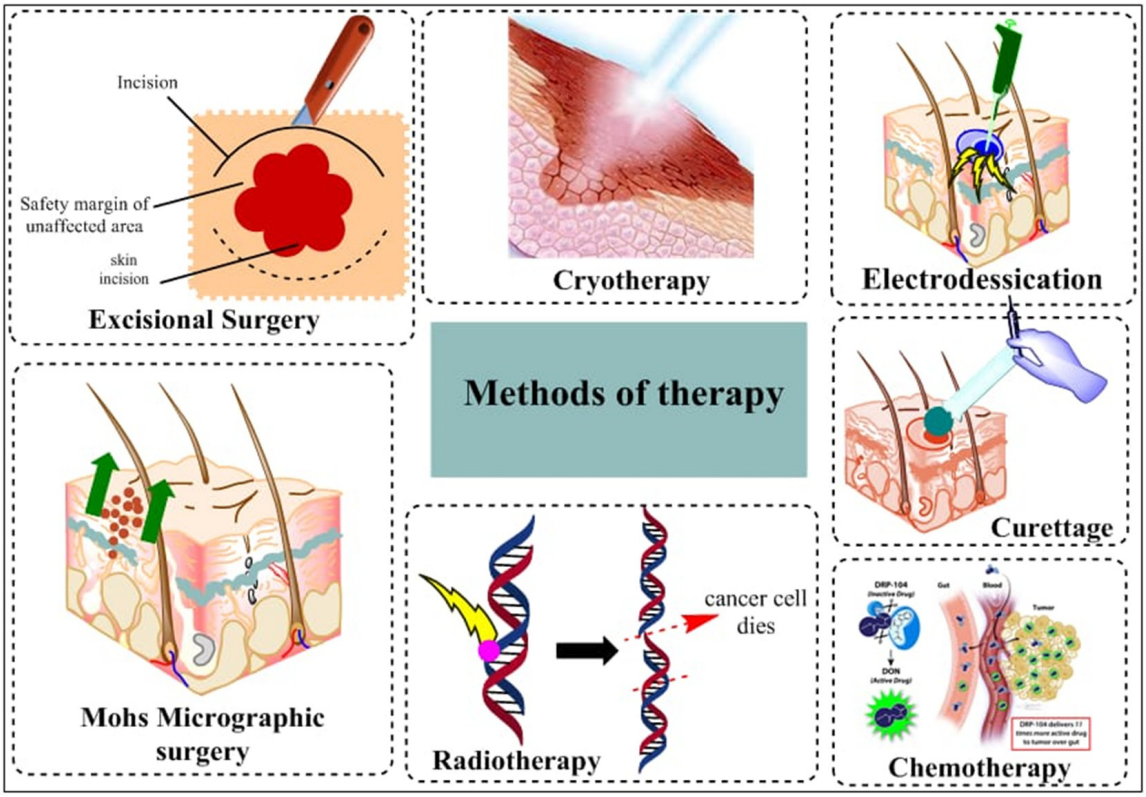

Figure 3. Conventional therapy for cancer treatment.

severity of sunburns, the precise pattern of UVR exposure, and the amount of time spent in the sun [43].

Methods of therapy currently used and their limitations

The sort, size, location, and stage of growth of the tumor dictate the most successful treatment option for skin cancer [44]. Excision, Mohs, radiation, immunotherapy, and targeted treatment are common procedures used to treat large-stage skin cancer in its early stages. Cryotherapy, photodynamic therapy, immunotherapy, laser therapy, curettage and electrodessication, and other minimally invasive treatments are available for skin cancers of varying sizes. Following surgical removal or physical eradication of a cancer, immunotherapy and targeted treatment aim to prevent its return. It is strongly recommended to provide chemotherapeutic medications orally, intravenously, or topically in advanced cases of skin cancer when the tumour has metastasized to other organs such the brain, lungs, liver, or bone [45, 46]. As shown in **Figure 3**, the following text offers a brief summary of the therapeutic techniques presently used for the treatment of skin cancer.

Excisional surgery

The standard method for treating skin cancer is excisional surgery. To prepare the tumour for histological examination, this method entails slicing it at 1.5 to 2 mm intervals. This method's main advantages are its short recovery time, small scar, and histologic confirmation of tumour margin. The danger of infection, seroma, hematoma, and significant wound growth are among the limitations linked [47, 48].

Mohs micrographic surgery

Skin tumours may be successfully removed using the state-of-the-art Mohs micrographic surgical procedure. This method involves observing the patient under local anesthetic and removing the biggest possible tumor using a microscope. Also, it helps keep healthy tissues safe from injury. This method of acquiring horizontal slices gives a complete view of the

object's inside and outside. Mohs surgery successfully reduces the risk of basal cell carcinoma (BCC) and squamous cell carcinoma recurrence while being more cost-effective than conventional surgical methods [47, 49, 50].

Curettage and electrodessication

Using a combination of cauterization and curette scraping, a specialist technique called curettage and electrodesiccation may kill malignant tumours and the healthy tissues around them. Small skin cancers are the only ones that can be treated with this method; large, high-risk tumours should not be treated with it. In addition, without the specimen, it is not feasible to evaluate the margin. Consequently, it is the strategy that has the lowest level of support [51, 52].

Cryotherapy

One treatment option for tiny tumors like basal cell carcinoma or squamous cell carcinoma is cryotherapy, which involves freezing the tumors in liquid nitrogen until they reach a temperature that destroys their cells. Along with a high success rate in tumor eradication, this surgery has the added advantage of not causing any visible scars or bleeding after treatment. This method is underutilized in skin cancer therapy due to the difficulty in determining tumor margins and the need to rely on skilled specialists [53, 54].

Radiation therapy/radiotherapy

Radiation therapy, generally known as radiation, is the best option for treating advanced and recurrent skin cancer in older patients who either cannot have surgery or whose tumors are too far away to remove surgically. External radiation therapy, superficial X-ray therapy, and brachytherapy are the three main types of this treatment. One non-invasive way to treat radiation is using volumetric arc therapy, which minimizes radiation exposure to healthy tissues by precisely controlling the dosage distribution. Yet, there are a number of downsides to this treatment, including the fact that it is costly, requires several therapy sessions, and may cause certain recurring tumors to develop dangerous traits [55].

Chemotherapy, targeted treatment, and immunotherapy

Treatments for basal cell carcinoma, squamous cell carcinoma, and melanoma that include immunotherapy, targeted therapy, and chemotherapy have shown promising results when used as adjuvants [56]. Immunotherapy, targeted therapy, chemotherapy, or radiation therapy are alternate treatments that are highly recommended for late stage skin cancer in order to cure it and avoid recurrence, regardless of the kind of treatment. In addition, research has shown that this method improves the prognosis for skin cancer patients. However, there is cause for worry over the drawbacks associated with targeted treatment and immunotherapy, including high costs and poor patient compliance. The focus of the patients is thereby redirected to their therapy. Although chemotherapy may reduce treatment costs for low- and middle-income families, it comes with serious drawbacks, such as chemoresistance in aggressive cancers and side effects caused by chemotherapeutic medications [57, 58]. As a result, an improved treatment plan is urgently required to assure patient adherence by successfully addressing the current issues with skin cancer treatment approaches. When it comes to effectively treating skin cancer, nanotechnology shows great promise.

Photodynamic therapy

A novel and non-invasive approach to skin cancer treatment, photodynamic therapy employs lasers and photosensitizers to eradicate cancer cells [59]. Patients are first administered photosensitizers, which are then instructed to congregate in the tumor area. The photosensitizers are then exposed to a laser beam, which triggers the production of reactive oxygen species and singlet oxygen. In the end, these chemicals kill cancer cells [60]. 5-aminolaevulinic acid [18, 61], hematophyrin derivatives [62], boron-dipyrromethene, and others are photosensitizers that are often employed [63]. According to research, combining photodynamic treatment with topical anticancer drugs is an effective strategy for removing skin tumors. The method has the drawback of not being able to remove expensive, deeply embedded tumors [66] effectively. To enhance the tolerability, efficacy [64-68], and convenience of PDT, several different approaches have been investigated. **Figure 4** shows the mechanism of PDT using Jablonski Scheme.

Improving patient experience and raising the possibility of future treatment adherence requires lowering downtime caused by local skin

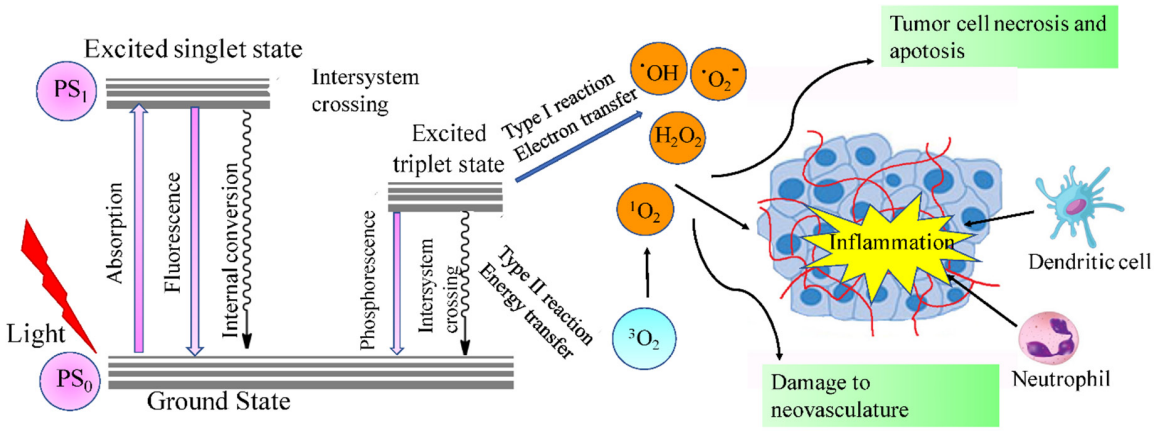

Figure 4. A revised Jablonski diagram showing the workings of photodynamic treatment [140].

reactions and boosting tolerability. To alleviate pain, researcher assessed a number of methods, noninvasive and invasive methods, such as administering numbing medication through a vein or artery, using ice or air to dull pain, or inhaling a vapor [69]. Research has also looked at the efficacy of topical analgesics such lidocaine and prilocaine, morphine gel, and tetracaine gel in alleviating pain. Nevertheless, no significant reduction in pain was seen in these investigations [70, 71]. Research on the efficacy of nerve blocks in reducing PDT-induced pain has been extensive. Among these studies, study contrasted the efficacy of [69]. According to research by the most effective method for relieving pain using a visual analogue scale was a nerve block. The administration of intravenous and cold air analgesics followed [72]. Compared to a control group, inhalation analgesia - specifically, a 1:1 combination of oxygen and nitrous oxide - greatly reduced pain, according to a research [73]. However, the results are not consistently the same since there isn't a single, agreed-upon methodology for PDT, and because different research have employed different approaches. For this reason, further studies examining other methods of pain treatment are required. Medical practitioners have explored many methods to improve the tolerance of ALA-PDT protocols, such as shortening the incubation time and using DL-PDT, since pain relief therapies may be seen as insufficient or too invasive. Not much is known about the correlation between the amount of time an ALA-PDT takes to incubate on the skin and the amount of pain that it causes. What incubation length will allow the photosensitizer to penetrate the material the most effectively is unknown [74]. After applying 20% 5-ALA to many AKs and surrounding tissue on the scalp and face, a kinetics of observation investigation discovered that the accumulation of PpIX changed compared to the control group. Half of the lesions had PpIX levels considerably higher than normal after 20 minutes, and all of the lesions had PpIX levels higher than normal after 2 hours of administration, according to the research [74].

The 5-ALA incubation period used in practice has been steadily reduced over the last 20 years, although this change has had no impact on the effectiveness of treatment. Two hundred thirty-four patients with actinic keratoses on the face or scalp were evaluated in a randomized controlled study to find out how effective blue light photodynamic therapy was after a large-area application of 20% 5-ALA with different incubation durations from one to three hours. At week 12 (29.8% vs. 27.7%) and week 24 (23.4% vs. 25.5%), the rates of 100% lesion removal were comparable for the 1-hour and 3-hour incubation treatments, respectively. Both treatments outperformed vehicle-PDT by a substantial margin. Interestingly, compared to patients who underwent the 3-hour incubation, those who underwent the 1-hour incubation reported lower rates of erythema (38.3% vs. 61.7% and 2.1% vs. 6.4%, respectively), moderate-severe stinging/burning immediately after the treatment (63.8% vs. 78.7% and 21.3% vs. 57.4%, respectively), and at the 2-week follow-up (63.8% vs. 78.7% and 21.3% vs. 57.4%, respectively). Patients with numerous actinic

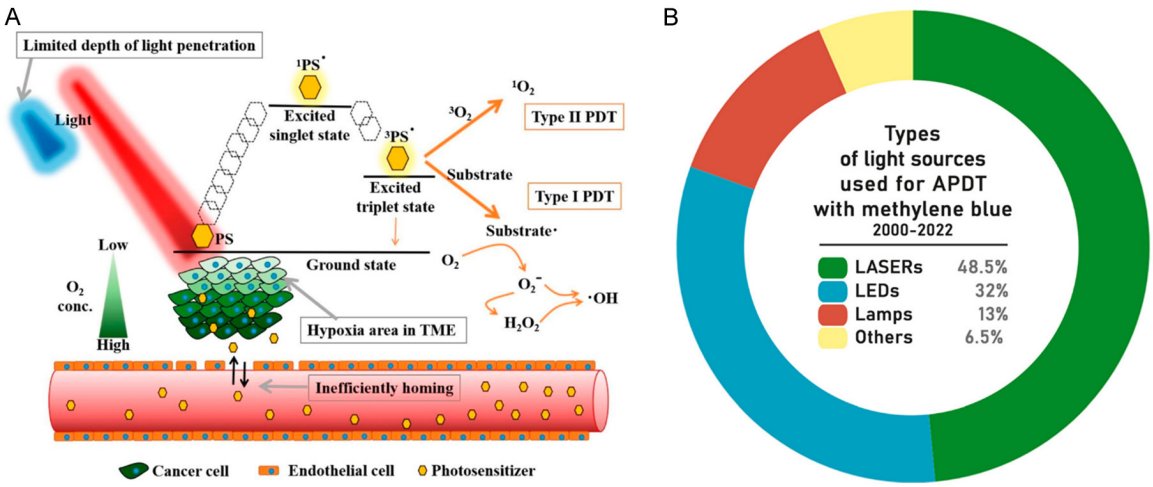

Figure 5. A. Concept of photodynamic reaction and its inherent limitations when used for treating tumors located deep within the body. PS: photosensitizer, TME: tumor microenvironment [97]. B. Different type of light source used [141].

keratoses on the scalp and face were randomized to receive blue light exposure either immediately after applying 20% 5-ALA or after waiting 1 hour. At the 3-month follow-up, the clinical efficacy was practically comparable for both treated sides. On the other hand, the side that got light first reported far less discomfort. A case study with a patient who had 5-ALA treatment followed by blue light photodynamic therapy revealed similar results. During the 4-month follow-up, the patient's scalp and face showed almost full eradication of actinic keratoses, and the treatment was painless [75]. Few details on the mechanism by which efficacy is preserved and discomfort is reduced are known. Photons may be continually degrading intralesional PpIX, which stops it from building up and spreading to nearby neurons, which is one possible explanation. In order to reduce field cancerization in high-risk individuals, one research examined the effectiveness of broad-area photodynamic therapy with 20% 5-ALA and blue light illumination. A vehicle-controlled randomized trial was conducted. The incubation period was so short that the experiment yielded positive results [76].

Alternative light sources

The efficacy of photodynamic therapy treatment is dependent on the light source and the absorption spectra of the photosensitizer (**Figure 5A**, **5B**). In order to lessen the discomfort of photodynamic therapy and increase tissue penetration, researchers have used coherent (photons that are in phase and focused) and noncoherent (photons that are out of phase and often dispersed) light sources throughout the last decade (**Table 1**).

One possible alternative to photodynamic therapy for non-melanoma skin cancers, such as actinic keratosis, superficial basal cell carcinoma, and in situ squamous cell carcinoma, is strong pulsed light devices [77]. Intense pulse light uses non-laser light with a high intensity to cover more skin with pulses of light with a wide range of wavelengths. A clearance rate of 68-90% after 3 months after 1-2 sessions is realized when 20% 5-ALA or MAL is used in conjunction with IPL-based PDT activation [78, 79].

Research has shown that pulsed-dye lasers may effectively cure AKs. Before treatment with curettage and methyl aminolevulinate, participants in a prospective study with multiple actinic keratoses on the scalp or forehead were given a 3-hour incubation period. They were then treated with either conventional light-emitting diode treatment or pulsed dye laser illumination on the other side. When compared to traditional PDT at the 12-month follow-up, PDL-PDT had the same number of AKs. The standard deviation of the change relative to the beginning was -0.46 (95% CI -1.28 to 0.35; $P = 0.258$). According to the study, there was a significant decrease in pain scores when PDL-PDT was used instead of LED-PDT (mean difference in visual analog score, -4.55; $P < 0.01$) [80].

Table 1. Comparison of various studies studying effect of light exposure in PDT treatment

Study Type	Patient char	Anatomical location	Light exposure	Patient pop	Lesions	Intervention	PDT treatment	Result	Ref
Bilaterally controlled trial	Age distribution: mean 69.7 years, range 58-88 years For both 50 and 75 years	Scalp and face	First cohort: 30 minutes blue light Step 2: 45 Minutes Blue Light Stage 3: 60 Minutes Blue Light	23 individuals; 2 F, 21M	AKs	Compare PDT with standard lighting vs. simultaneous	without incubation, 20% 5-ALA	AK lesions responded similarly to cPDT (57.7% on the face and 59.1% on the scalp) with a modified PDT regimen that was nearly painless	[74]
Proof of concept	35-65 years	Forearms	N/A	A group of five actives, healthy individuals	Not applicable	Examined how TMFI affects skin 5-ALA absorption	(1) ALA gel (20%) (2) Gel that contains 10% 5-ALA (3) A 16.8 percent MAL cream A 20% solution of 5-ALA	tMFI pretreatment substantially enhanced 5-ALA and MAL percutaneous permeability	[67]
Observational	Age range: 54-93 years; mean: 71.3 years	Face	Epidermal cooling, interpulse delay of 100 ms, triple pulse mode of 3.3, 3.9, and 4.6 ms, fluence of 18 J/cm^2, and intense pulse light activation using the Photosilk plus device from DEKA M.E.L.A. S.r.l.	25 individuals (16 men and 10 women)	BD, sBCC, and AK	Patients receiving MAL treated with IPL in NMSC	MAL for three hours	AKs: 90% CR PR: ten percent sent by BCC: 80% CR Public Relations: 20% BD: Criteria: 100% Level of PR: 0%	[77]
Prospective	Among the 126 patients treated for photodamage, 88 had AK	Face	All light sources-PDL, IPL, and PDL + blue light-had fluences between 6 and 12 J/cm^2, pulse widths between 5 and 20 ms, and contact cooling	220 individuals; genders not specified	AKs	To activate PDT, is it better to use IPL or PDL with or without blue light	Twenty percent 5-ALA for two hours	IPL + blue light worked better than IPL or PDL alone	[64]
Prospective split-face trial	Average 67.7 years; range 49-86.	Forehead	Eight minutes of blue light exposure with a total fluence of 4.8 J/cm^2	48 individuals (40 M, 8 F) met pain objectives	AKs	Treatment with microneedles (690-micron length) as opposed to a control group	Incubated for 20, 40, or 60 minutes (microneedle side) or 60 minutes (sham side) with a 20% 5-ALA solution	Full AK response after 1 month (microneedle vs. sham): 20 min: 71.4%, 68.3% 40 min: 81.1%/79.9% 60 min: 72.1%, 74.2%	[82]
Retrospective	Age averaged 68.7 ± 9.4 years	Apparently face; also forehead, dorsal hands and scalp	Do IDL for thirty-five minutes	46 individiduals; 4 F, 42 M	> 5 AKs	Treatment of AFL with IDL DL-PDT	40 to 60 minutes with BF-200 ALA	Achievement rate of 71.7% in clear	[142]
Split-face RCT	Age mean ± SD: After 20 minutes: 62.8 ± 2.1 years 10 minutes: 65.4 ± 2.5 years	Face	Total fluence of 10 J/cm^2 and 1000 s of blue light illumination	22 M, 10 F; 32 patients	≥ 3 AKs of Grade II	Scaffolding vs. pretreatment with microneedles (200 μm length, roller device)	Incubated for 10 or 20 minutes is a 20% 5-ALA solution	A month after AK clearance, microneedle vs. sham: 20-minute group: 76% vs. 58% (P < 0.01) Ten-minute arm: 43% vs. 38% (P = 0.66)	[83]

Proof of concept	N/A	Hand, leg, lip, scalp, forehead, and temple	Light exposure to blue light for 16 minutes and 40 seconds	19 individiduals; sex nor specified	CSC, BCC, and various AKs	CO_2 laser AFR	20% of ALA for one hour	AKs and thin NMSCs cleared better with AFR retreatment than 5-ALA-PDT alone at 6 months	[66]
Prospective, single-arm	Age average: 74 ± 8.9 years	Face, or Scalp	Artificial 20 J/cm^2 DL-PDT for 1 h	28 people-6 women and 22 men were examined	AK	CO_2 laser AFR	1-hour 5-ALA nano-emulsion	The lesions count dropped by 91.3% after three months ($P < 0.0001$)	[68]
RCT	Average age 72.5 (52-85)	Scalp, chest, and face	Two-hour DL-PDT	18 patients; 2:1 M:F ratio	Areas affected by photodamage and AK	Comparing fractional 2940-nm Er: YAG lasers to MD	Debulking with fractional 2940 nm Er: YAG laser and 16% MAL or MD	Rate of AK clearance 81% from AFL-DL-PDT The results for MD-DL-PDT were 60% ($P < 0.001$)	[143]

Table 2. PS for skin cancer treatment

Design	Efficiency	Wavelength of excitation	Characteristic of PSs	Adverse Effect	Time window between PSs application and irradiation	Ref
Cats-SCC, in vivo	A mean progression-free interval of 35 months was observed, and the total response rate was 84%	Light-emitting diode laser 652 nm	0.15 mg/kg of body weight of LP phosphorylated m-THPC	Localized redness and swelling in 42% of cats soon after photodynamic therapy	10 J/cm^2 applied for 100 s six hours after injection, 20 J/cm^2 applied in 200 s	[144]
1) squamous cell carcinoma 15.1, and in vitro 2) an in vivo model of human tongue cancer using xenograft tumours in mice	1) increased absorption of PC 4 and substantial cell death 2) improved PC 4 uptake and tumour regression	1) exposed 400s to light 2) a two-beam split-diode laser operating at 672 nm	GE11-peptide-coated polymeric micelles containing silicon phthalocyanine-4 (Pc 4)	-	1) incubation durations ranging from 2 hours to 24 hours 2) two days after a bolus injection of 0.01 mL/g into the tail vein	[145]
Primary cSCC cells grown in vitro and in vivo from SKH-1 SCC mice that were triggered by ultraviolet light	When compared to free ZnPc, the ZCPP greatly improved the efficacy of PDT	670 nm laser diode	Chitosan/mPEG PLA NPs loaded with ZnPc	No toxicity to the dark areas, no toxicity to the system	After pretreatment with microneedles, applying topically	[123]
Approachable BCCs	Lesion clearance: 93.8% for MAL, 90.9% for BF-200 ALA, and 87.9% for HAL	-	Compare hexyl aminolevulinate at 2% with monomethyl allylamide at 16% and BF200 ALA at 7.8%	Discomfort, redness, edoema, swelling, and haemorrhage in the region that has been treated	Apply topital after 3 hours, lighted for 7 minutes and 24 seconds	[125]
Experimental melanoma models (MUG-Mel2, SCC-25, HaCaT cells)	The viability of SCC-25 (34%), MUG Mel2 (27%), and HaCaT (11%), all reduced at a concentration of 10 mM	A 2.5 J/cm^2 blue light beam	Hybridized soy phosphatidylcholine LPs with curcumin	-	Incubation for four hours	[119]
Non-aggressive BCCs in a phase III randomised, international, non-inferiority study in the UK and Germany	Among those who took the survey: 91% in the MAL group and 93.4 in the ALA group	A 635 nm red beam	BF-200 ALA gel compared to MAL cream	-	Atopically, followed by two PDT sessions spaced one week apart	[124]

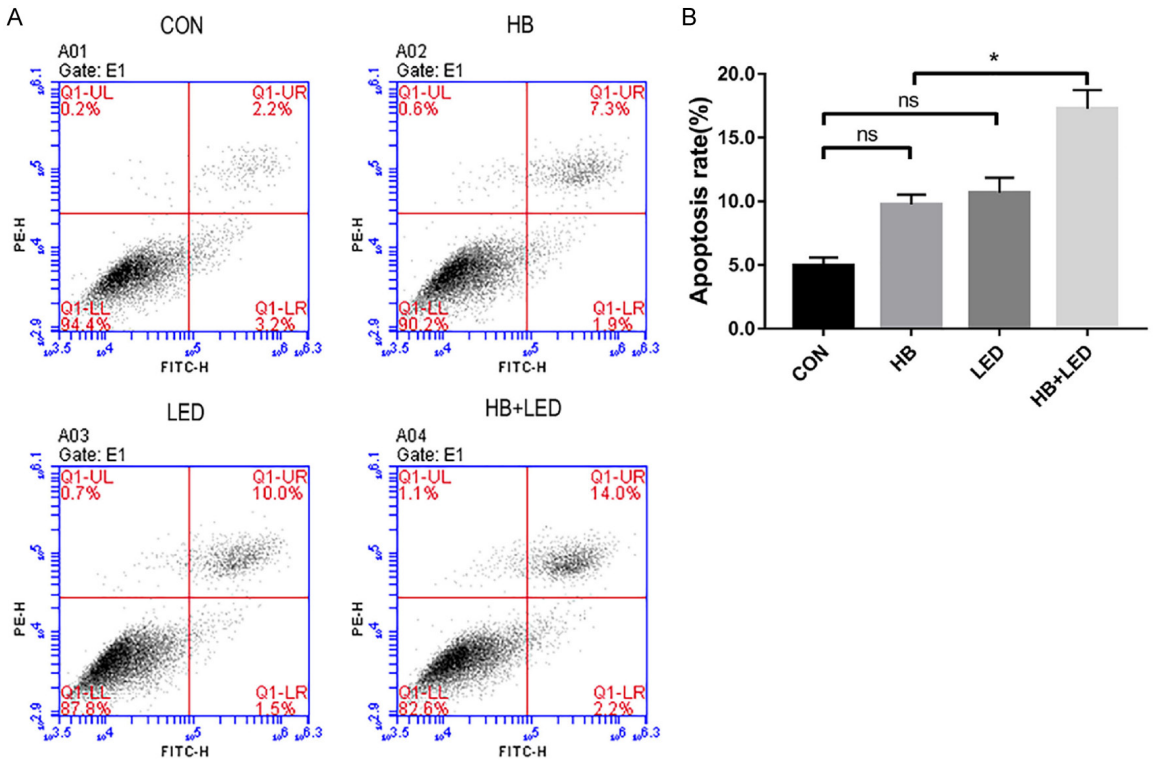

Figure 6. Increase in apoptosis in A431 cells caused by HB-LED PDT. (A) Flow cytometry was utilized to identify variations in apoptosis rates within the four groups, and (B) the statistical analysis of the apoptosis rate of A431 cells in each group was conducted [81].

Yuanyuan Liu et al. studied the pro-apoptotic effects and molecular processes of HB-LED PDT in A431 cells, which are a kind of cutaneous squamous cell carcinoma. This knowledge may provide a crucial theoretical basis for the practical use of HB-LED PDT in the treatment of cSCC. The proliferative activity of A431 cells was suppressed, and nuclear fragmentation was increased by HB-LED PDT. HB-LED photodynamic therapy (PDT) suppressed the functioning of mitochondria, enhanced the generation of reactive oxygen species, and induced programmed cell death (apoptosis) in A431 cells. Furthermore, the HB-LED PDT led to an increase in many crucial components of the apoptotic signaling pathway at both the transcriptional and translational levels in A431 cells. This suggests that the HB-LED PDT activated the apoptotic signaling pathway. The rate of programmed cell death (apoptosis) in A431 cells was significantly higher in the HB+LED PDT Group compared to the HB group. This suggested that the photodynamic therapy using HB enhanced the apoptotic impact of HB on A431 cells (**Figure 6A**, **6B**) [81].

In this prospective four-arm trial, 210 patients were split into four groups according to their therapy. There were 126 individuals with photodamaged skin and 88 patients with multiple actinic keratoses. After a 2-hour incubation time, 20% 5-aminolevulinic acid was activated by lighting it with blue LEDs. The next step was to provide some kind of powerful pulsed light, pulsed dye laser, or a combination of the two to the patients. In comparison to other light combinations (PDL, 70.5% reduction; PDL with blue LED, 69.3% reduction; IPL, 70.8% reduction) and IPL with blue LED, AK lesions were significantly decreased (84.4% decrease) after one month from the start [64].

Pretreatment

Priming the skin to increase photosensitizer absorption has been the subject of many experiments (**Table 2**). One of the easiest techniques for applying the photosensitizer to the skin is microneedle-assisted incubation, which involves puncturing the skin with a microneedling instrument. Outcomes have been inconsistent

across many clinical trials that used split-face designs, in which microneedling was performed on one side before photosensitizer and photodynamic treatment were administered on the other. Microneedling (90.5% success rate) and mild curettage (86% success rate) before MAL-PDT with red light illumination did not significantly affect AK clearance 90 days after treatment in a preliminary study that included 10 patients [64]. The AK full response rate was unaffected by microneedle pretreatment, as previously shown, during the four-week follow-up after PDT with a 20% ALA solution. An ALA solution was pre-incubated for 60, 40, or 62 minutes on the side that was microneedled, while the side that was treated with a sham was pre-incubated for 60 minutes. When comparing the control and microneedle-treated sides, the response rates were 71.4%, 68.3%, and 72.1%, respectively. Ten to fifteen people were involved in the research [82]. Using microneedles before administering a 20% ALA solution and blue light PDT significantly reduced AKs compared to the side without pretreatment in two more investigations where curettage was not conducted on the control side (with 16-19 subjects per treatment group). After one to four months, the decrease was between seventy-six and eighty-nine percent, whereas the untreated group only saw a loss of fifty-eight to sixty-nine percent [83, 84]. The absence of definitive outcomes from pretreatment with ALA-PDT prior to microneedle usage indicates the need for more research into this matter.

Carbon dioxide and erbium-doped yttrium aluminum garnet lasers are used in the suggested technique of ablative fractional resurfacing to produce tiny vertical channels. Photosensitizing compounds, such as 5-ALA, are able to penetrate and be absorbed more deeply via these routes [66]. Encircling the ablated vertical channels is a coagulation zone that might store the photosensitizer and release it gradually. A number of medical professionals have investigated AFR's potential as a pretreatment for ALA-PDT. After 29 participants were given CO_2 laser AFR pretreatment before ALA-PDT of actinic keratosis with a 20% 5-ALA solution or MAL cream, 70.6% of lesions showed a complete response after three treatment sessions. This was despite the fact that the MAL cream was only applied 70-90 minutes before illumination. The parameters employed in the investigation were a spot density of 100 spots/cm^2, a power of 30 W, a beam size of 120 μm, and a single pass with a 50 mJ pulse. The lack of a control group is a result of the study's single-arm design [85]. A similar research with 28 patients found that after only one treatment with CO_2 laser AFR, the number of lesions decreased significantly by 91.3%. Beam sizes varied from 4 to 18 mm in relation to diameter, while treatment settings were an 8 mJ pulse, 50 spots/cm^2, and 30 W of power. After that, an artificial daylight lamp was used to illuminate the ALA-PDT using ALA nanoemulsion [86]. Two 2.3 mJ pulses were released by the laser. The pulse duration was 50 μs, and the power output was set at 1.15 W. The treatment's density was 2.4%. The incidence of new AKs was also reduced by using AFR. A randomized split-side experiment was recently performed to measure the efficacy and long-term response of ALA-PDT for the treatment of AK and NMSC, with and without pretreatment with CO_2 laser AFR [66]. The study included nineteen individuals who had evidence of non-melanoma skin cancer, such as basal cell carcinoma or cutaneous squamous cell carcinoma, and who also had similar levels of photodamage, defined as at least one actinic keratosis per square centimeter, on their face, scalp, or limbs. Prior to undertaking AFR therapy, patients were given a topical or regional anesthetic. The therapy was administered to a randomly chosen side of the body.

The therapy made use of the SmartXide DOT laser, which had the following parameters: 25 W of power, 1200 ms of time, 500 μm of spacing, and 200 μm of spot size. A surface area ablation of 12% was the end outcome. A second pass was carried out after saline debridement if hyperkeratotic regions were detected. After that, a 20% ALA solution was applied to both sides and left to incubate for an hour. Then, for the next sixteen minutes and forty seconds, they were subjected to blue light. At the 6-month follow-up, it was observed that the pretreatment sides had a more significant reduction in AK (actinic keratosis), and the majority of individuals did not have any recurrence of AK. On the other hand, 13 instances were identified where AK continued on the side that had previously had conventional photodynamic treatment. Persistent non-melanoma skin cancer was seen in both treatment groups, leading to contradictory conclusions regarding

NMSC outcomes. The lack of cutaneous squamous cell carcinoma on the sides treated with conventional photodynamic treatment at the beginning of the trial may have impacted this discrepancy. Within an average of seven days following therapy, the facial and head lesions were entirely healed. The healing process for the forearm and hand lesions was around 14 days, whereas the lower extremities lesions required up to 21 days to fully disappear with no more bleeding or scabbing. The research found that patients still felt moderate to severe pain throughout the procedure, even after receiving topical or regional anesthetic [66].

To further improve absorption, researchers have also looked at thermo-mechanical fractional injury as a physical pretreatment prior to photosensitizer application. TMFI uses heat to evaporate water from tissues, creating micropores and causing fractional damage. A dermal and epidermal dry zone is formed during this process, which takes place in 5-18 ms. In theory, this improves photosensitizers' ability to penetrate the skin [67]. Two investigations showed that 5-ALA treatment greatly improved the absorption and penetration of PpIX fluorescence into TMFI-pretreated tissue compared to control locations ($P < 0.001$) in healthy persons with Fitzpatrick skin types I-III. There were few side effects associated with the TMFI treatment, including mild to moderate skin reactions and low levels of discomfort. No studies have investigated the therapeutic treatment of AKs or NMSCs using TMFI pretreatment in combination with ALA-PDT [65].

Because it cannot get deep into the skin, photodynamic therapy is not a very successful treatment for actinic keratosis. Cryotherapy isn't the way to go for field cancerization, although microneedling and fractional CO_2 laser may improve photosensitizer penetration. The goal is to determine how well PDT works with microneedling, fractional CO_2 laser, and cryotherapy to treat AK. Group A patients with actinic keratosis received microneedling in conjunction with photodynamic therapy; group B patients received fractional CO_2 laser in conjunction with photodynamic therapy; group C patients received cryotherapy in conjunction with photodynamic therapy; and group D patients received photodynamic therapy in isolation (**Figure 7**). After 12 weeks, the outcomes were assessed using clinical, dermoscopy, and reflectance confocal microscopy techniques. In all, 129 patients participated in this study, distributed as follows: 31, 30, 35, and 31 in each of the three groups. In each group, the percentage of clinical response was 90.3%, 93.3%, 97.1%, and 74.2%, respectively. A statistical study revealed a notable difference between the groups, as shown by a *p*-value of 0.026. In the case of RCM, the response rates were as follows: 71.0%, 80.0%, 85.7%, and 54.8%. These rates were found to be statistically significant, with a *p*-value of just 0.030. A total of 77.4%, 83.3%, 88.6%, and 60.0% of the subjects responded to the dermoscopy in that order. Results from clinical, dermoscopy, and RCM analyses showed that Group C was the most successful, with a *p*-value of just 0.039, indicating statistical significance [87].

For tumor penetration and photothermal cancer therapy, Zhengjie Zhou et al. created LST-loaded photothermal nanoparticles (**Figure 8A**). The photothermal agent used was a polydopamine nanoparticle because of its biocompatibility, photothermal conversion efficiency, and drug loading. Treatments were tested in vivo for anticancer activity. Different groups of 4T1 tumor-bearing mice received intravenous injections of PBS, PLST, LST, and PP. Two groups of PP and PLST-injected mice received NIR irradiation (**Figure 8B**). Tumor temperatures were collected 48 and 72 hours after the initial injection. When irradiated for 48 h after injection, the PLST + NIR group elevated tumor temperatures quicker than the PP + NIR group (**Figure 8C**). As shown in **Figure 5B**, the plateau temperature for the PLST + NIR group was 44.1°C, whereas for the PP group, it was 42.0°C. **Figure 8D** shows that after NIR irradiation, the tumor temperature was higher in the PLST + NIR group compared to the PP + NIR group. The PLST + NIR group achieved a plateau temperature of 43.9°C after 72 hours after injection, but the PP + NIR group only managed 41.1°C. According to these results, LST accelerated the formation of tumor nanoparticles. During treatment, the diameters of the tumors were monitored. The PLST and LST groups exhibited tumor growth rates comparable to those of the PBS group, indicating that LST had no effect. The PP + NIR group had slower tumor growth than PBS. Full tumor regression was seen in the PLST + NIR group (**Figure 8E**). The size and

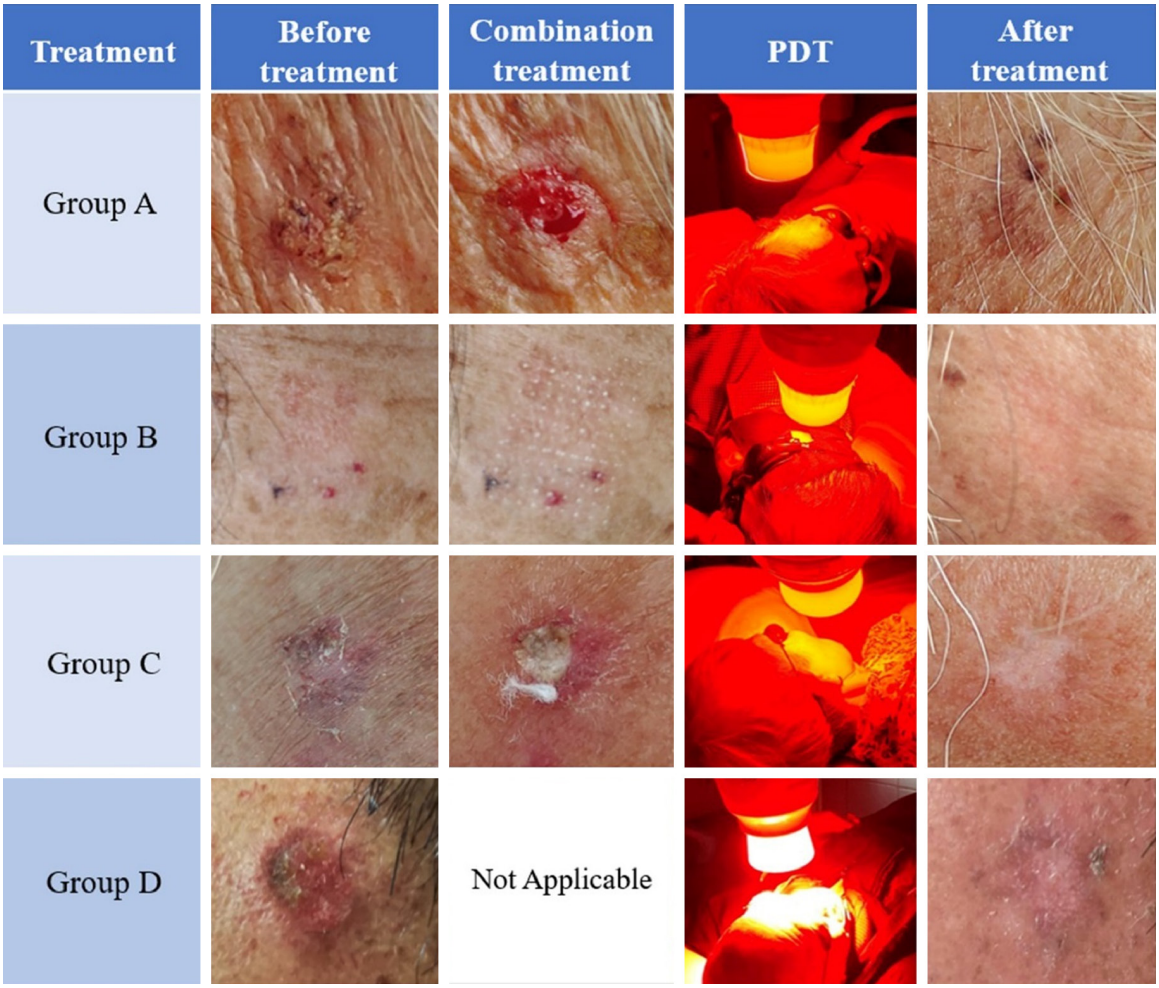

Figure 7. Analyzing the effects of four different treatments on four different groups of patients with facial actinic keratosis [87].

weight of PLST + NIR isolated tumors were the lowest (**Figure 8F-H**). Tumors were examined for apoptosis. The pictures demonstrate that the PLST + NIR group had many apoptotic cells, whereas other groups had few (**Figure 8I**). The immunohistochemical investigation of tumor tissues shows that LST and PLST dramatically reduced collagen and HA synthesis and blood vessel compression. All these findings show that LST on PLST increased tumor nanoparticle distribution and photothermal therapy efficiency. These therapeutic medicines demonstrated little in vivo toxicity since mice did not lose weight in any groups [88].

Thermal PDT

By 2040, it is projected that there will be 100,000 new cases of melanoma, a very aggressive kind of skin cancer that is strongly influenced by both genetic and environmental factors. This highlights the urgent requirement for treatment alternatives that are both efficient and safe. Researcher aimed to evaluate the effectiveness of a photosensitizer named Chlorophyll A (Chl-A) when combined with hydrogels (HGs) composed of chitosan (CS) and poloxamer 407 (P407) for the purpose of Photodynamic Therapy against the B16-F10 murine melanoma cell line. The HG was assessed using a range of tests, such as rheological examinations, low-power transmission electron microscopy, using analysis of time-varying infrared spectra and a cell viability assays. The hydrogels based on CS and P407 demonstrated efficient release of Chl-A and exhibited the essential characteristics required for topical application. The in vitro photodynamic activity

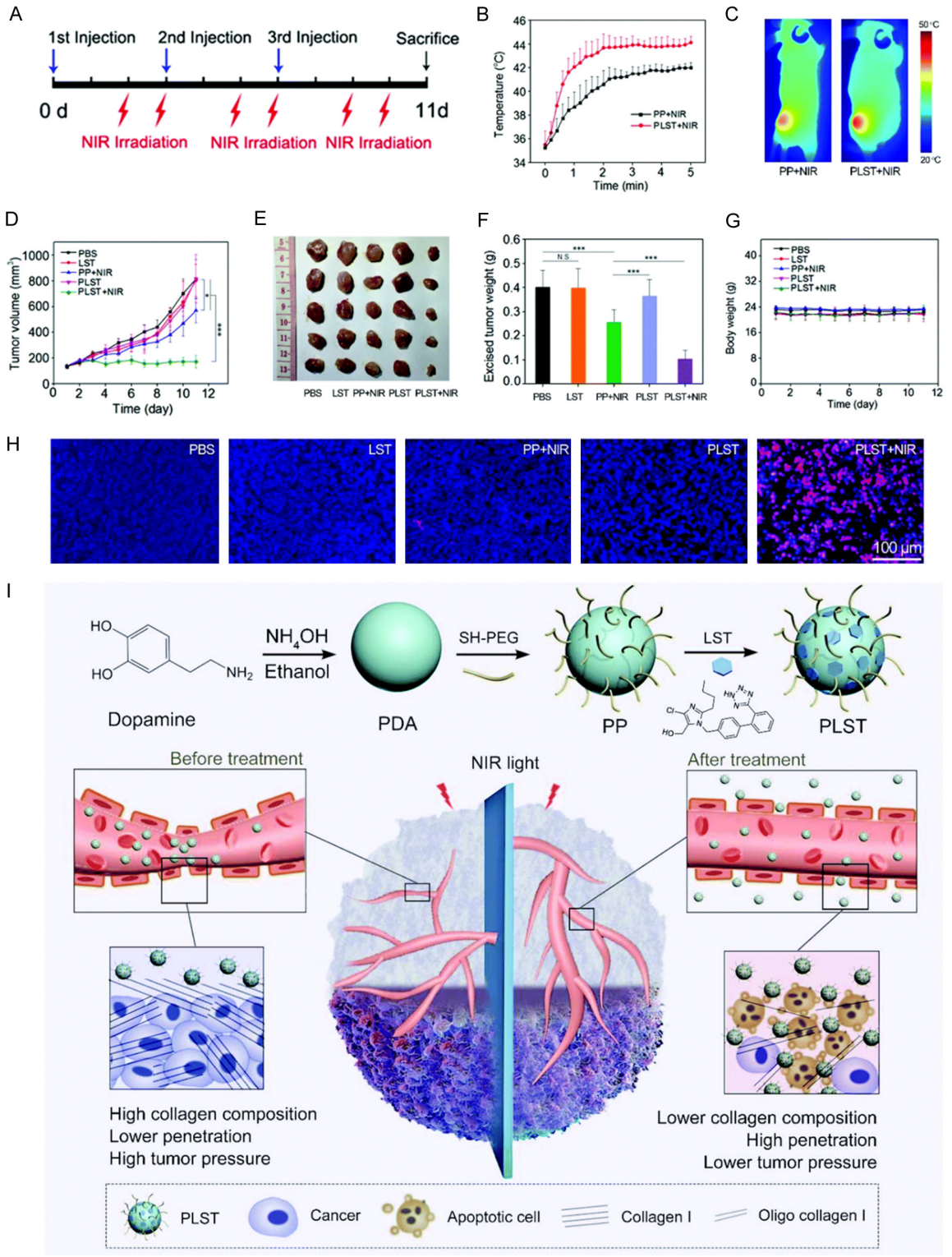

Figure 8. (A) The illustration shows that PLST (plasma-activated solution technology) decompresses the blood arteries in the tumor and breaks down the extracellular matrix. This process helps nanoparticles to penetrate and accumulate in the tumor, leading to enhanced photothermal death of tumor cells. (B) The experimental design. (C) The fluctuations in temperature of the tumors were seen when the mice were exposed to radiation 48 hours after injection. (D) The thermographs of mice after the first near-infrared (NIR) irradiation. (F) The tumor volume fluctuates over the course of the therapies. (G and H) Images of the surgically removed tumors (E) and their mean masses. (I) The progression of mice's body weight during the treatments. The TUNEL test quantifies the levels of apoptotic cells in malignancies after different therapies [88].

of the HG containing Chl-A was assessed, revealing significant therapeutic potential. The IC50 value of 25.99 μM obtained is particularly noteworthy, especially when compared to previous studies where cisplatin, a positive control medication, exhibited an IC50 value of 173.8 μM. The formulated combination of CS and P407, used as a thermosensitive system for topical applications, effectively regulated the release of Chl-A. Cellular studies conducted in a laboratory setting, known as in vitro studies, have shown promising results in the use of photodynamic therapy (PDT) against melanoma cells [89].

After applying photosensitizer topically, it may be helpful to get the skin temperature up to a comfortable level, particularly in areas of the body where the temperature is typically lower. This will increase the medication's absorption. The efficacy of blue light photodynamic treatment was examined in a pilot trial with 20 subjects. Researchers tested PDT's efficacy after subjects' distal extremities were incubated with 20% ALA for an hour at either 38.8 or 29.4 degrees Celsius. At both the 2-month and 6-month follow-ups, the data demonstrated that the heat-treated side had a much greater median clearance of AKs (actinic keratoses) than the control side. From the beginning, the median percentage difference was 88.0%, which was lower than 70.5% at 2 months and 67.5% at 6 months. Statistical analysis revealed that these variations were noteworthy ($P < 0.0001$) during the two study periods. Nonetheless, there were many more undesirable side effects, such as redness, burning, and stinging or oozing or crusting, on the heated side than on the control side [90]. Applying 20% 5-ALA to face actinic keratoses was the subject of a modest proof-of-concept research. Before being subjected to blue light, the lesions were incubated for 20 minutes at a temperature ranging from 38 to 42°C, with an average of 41°C. Five out of ten patients reached full clearance after two months of follow-up, and the research indicated that 91.5% of the lesions were eliminated on average. The intensity of porphyrin improved significantly after heat treatment ($P < 0.001$). Eight out of ten patients reported no pain at all throughout the incubation period, while two had moderate discomfort (graded at 3 out of 10) at most. Pain ratings during light therapy ranged from 3 to 9, with an average score of 5. Day 1 and week 1 discomfort were not mentioned by any of the patients [91].

Combination therapy

Evaluating the Reliability and Precision Participants whose hands had several actinic keratoses of Grades I-III were studied. A split-face design that was randomized and controlled was used in the investigation. Before the skin was treated with DL-PDT for two hours, it was pretreated with 5-FU twice a day for a week. The results showed that compared to using only DL-PDT, the average lesion response at the 3-month follow-up was much better when this combined therapy was used. It is pointless to try to set up uniform quality standards for quantitative and qualitative methods. Researchers found that patients with multiple Grade I-III AKs on the scalp and face had a better chance of achieving complete clinical remission when they received calcipotriol before applying 16% MAL cream and underwent 2 hours of DL-PDT, as compared to when they received DL-PDT alone [92]. Unlike qualitative research, which is highly dependent on the unique circumstances of each study, quantitative research may be used to a broader variety of contexts and is thus more generalizable. Because qualitative research is inherently subjective and prone to ambiguity, standards are required to guarantee its validity and reliability [93].

ICG and ICGD have been widely employed for near-infrared imaging as well as for photothermal and photodynamic therapy [94, 95]. The coordinates are (40, 41). This work examined the combined effect of chemotherapy and phototherapy utilizing hICP NPs that contain ICGD, as shown in **Figure 9A**. In order to determine the photothermal conversion efficiency, Zhaoqing Cong et al. quantified the temperature increase that occurred when ICGD and hICP NPs were exposed to laser light in different solutions. All groups with the same quantity of ICGD show a rapid increase in temperature within 30 seconds (**Figure 9B**). Under the influence of continuous laser irradiation for a duration of 240 seconds, the temperatures in various hICP NP solutions gradually rose to a range of 62.2-80.6°C. The highest temperature observed was 49.4°C for free ICGD, however it

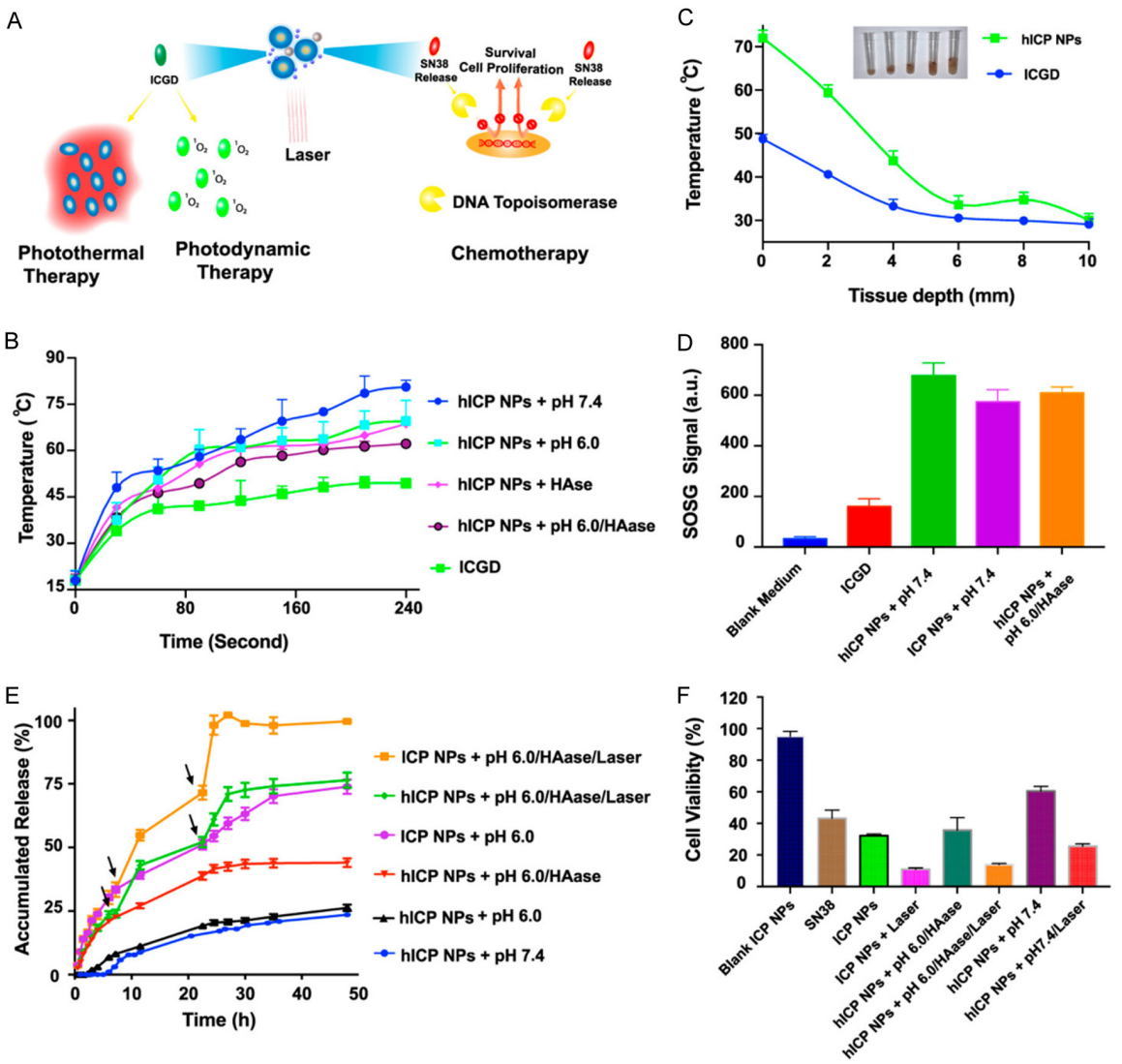

Figure 9. A. Diagram showing the three different ways in which hICP NPs might cause cell death. B. Temperature profiles of ICGD and hICP NPs solutions in water shown against laser irradiation time at an ICGD concentration of 25 μg mL^{-1}. C. The temperature fluctuations of ICGD and hICP NPs were measured during a 240-second laser exposure at an ICGD concentration of 25 μg mL^{-1}. D. Singlet oxygen generation (as detected by the SOSG signal) profiles of ICGD, ICP NPs, and hICP NPs cultured with B16 cells for 4 hours under laser irradiation for 120 seconds at an ICGD concentration of 25 micrograms per milliliter. E. The release of SN38 from aqueous solutions of ICP NPs and hICP NPs during in vitro experiments, with or without laser irradiation for 120 seconds, if used. F. The cell viability of B16 cells was assessed after treatment with 50 ng mL^{-1} of SN38 and exposure to laser irradiation for 120 s, if applied. The laser power density used was 1 watt per square meter [96].

was much lower for hICP NPs in a pH 7.4 environment. We investigated the temperature of hICP NPs at different depths of tissue in order to evaluate them in vivo applicability. This was done by subjecting mice muscle samples enclosed in tubes of varying thicknesses to laser irradiation at a wavelength of 808 nm, simulating a surrogate tissue barrier. According to **Figure 9C**, when a 2 mm muscle slice was exposed to a 1 W cm-2 lasers for 240 seconds, the temperature of the free ICGD group reached 40.6°C, while the temperature of the ICP NP group reached 60.5°C. **Figure 9D** shows that a cellular examination provided additional confirmation of the improved photodynamic effectiveness of ICP or hICP NPs. The SOSG signal was more than doubled in the presence of ICP or hICP NPs compared to free ICGD. **Figure 9E**

shows that after laser irradiation, the drug release was much faster. Reduced thermodynamic stability as a result of the laser's increased temperature is likely responsible for the increased release seen during laser irradiation. In order to examine the photocytotoxicity of hICP NPs in a laboratory setting, a specific region of B16 cells that were grown in a single layer was treated with hICP NPs and then exposed to light. The cells were then analyzed to compare the effects of laser treatment on cells with and without hICP NP treatment. The application of laser treatment seemed to enhance the combined effect on the ability to destroy B16 cells (**Figure 9F**) [96].

Photosensitizers in PDT

Applying light stimulates the photosystem. The activation of the PS by light energy leads to its engagement with neighboring oxygen molecules. The Type II and Type I processes, respectively, are responsible for producing free radicals and singlet oxygen as a result of this interaction. Because it is the most common result of PDT, this article primarily focuses on the Type II process, which produces singlet oxygen. Our primary focus is on the photochemical and photophysical mechanisms that lead to the generation of singlet oxygen in photodynamic therapy [97], although other processes may also be at work. There is a process similar to fluorescence that triggers the creation of 1PS• by a photosensitizer.

The excited state in conventional fluorescence is subjected to a little amount of non-radiative de-excitation in its surrounding surroundings before it releases a lower-energy photon with a reddened spectrum. However, there is another method for de-exciting photosensitizers, and it involves the excited molecule going through an intersystem crossover and entering a triplet state. It is possible for the PS to transmit energy to neighboring oxygen molecules during this phase of photosynthesis. The transfer is crucial to the efficacy of photodynamic therapy because it generates singlet oxygen. It also resets the PS to its ground state, which is its most fundamental configuration. Highly reactive singlet oxygen interacts with neighboring cells to generate cytotoxic effects; it is an integral part of PDT's cell-killing capabilities. Since one PS molecule may produce several singlet oxygen molecules, the detrimental consequences are magnified. In addition to the 0.974 eV direct energy transfer, there is an extra amount of energy required for the irreversible synthesis of singlet oxygen by the 3PS•. The majority of PSs readily meet the minimal energy requirement of 1.13 eV for the operation [98, 99].

While singlet oxygen generation and PDT principles have received much of the attention, it's crucial that the PDT mechanism might be impacted by other processes including energy shifts [100]. A better understanding of the intricate mechanisms underlying the field of PDT may be gained from the thorough study offered in these sources. For Photodynamic Therapy to work its magic, the photosensitizer must release just the right amount of ROS to destroy cancer cells while sparing healthy ones.

Level of oxygen in the air since the photosensitizer may only work if molecular oxygen is present, this oxygen may be in short supply in cancer tissues. Photodynamic treatment works best with photosensitizers that can generate reactive oxygen species even in oxygen-poor conditions.

Because it has a direct impact on the concentration of molecular oxygen in the targeted tissue, the photodynamic cell killing process is highly dependent on the fluence rate of light illumination (W/cm_2). Photodynamic therapy may reduce or stop working altogether if oxygen depletion happens at high fluence rates, which is used to eliminate tumors [101].

Mechanism of biological events: Not only does PS activation result in ROS production, but it also sets in motion a cascade of other biological processes that make PDT more effective. One such occurrence is the secretion of chemokines and cytokines, which signal immune cells to the location of the treated lesion. Perhaps the immune reaction will aid in removing any residual cancer cells from the lesion and preventing their recurrence [102]. Furthermore, PDT may cause cancer cells to undergo apoptosis, a kind of programmed cell death. As part of this process, signaling pathways are initiated, which in turn induce DNA to divide and cellular components to break down, ultimately leading to the death of the cancer cell. The following

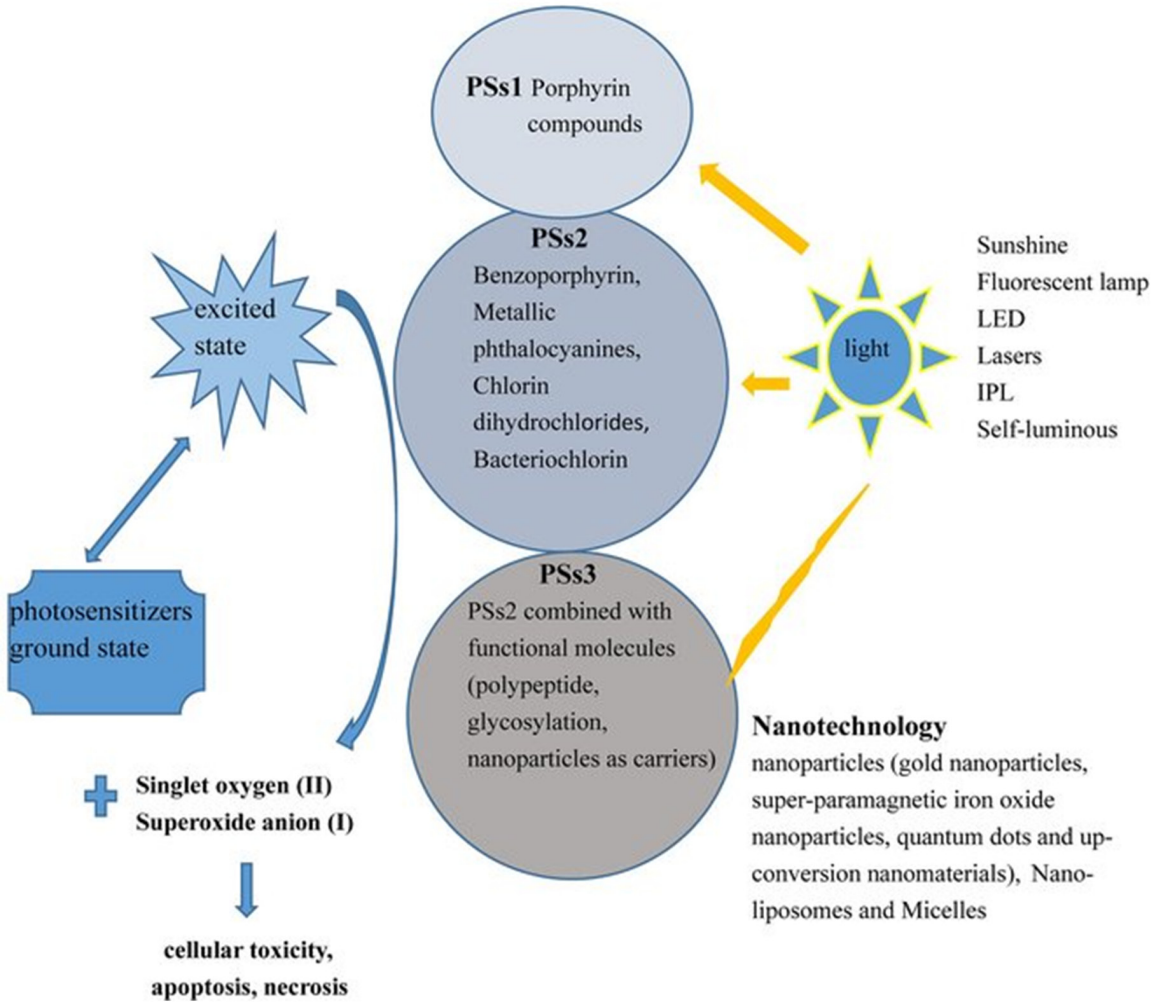

Figure 10. The PDT action mechanism. In order to destroy cells, first-, second-, and third-generation PSs absorb light from various sources, convert energy between their excited and ground states, and then produce superoxide anion or hydrogen peroxide [118].

resources will provide you with further information on cell death pathways [103-105]. Another important component of PDT's action mechanism is the "bystander effect" [106]. Regarding PDT's ability to damage both directly exposed cells and nearby cells that have not been treated to the photosensitizer, this is relevant. Reactive oxygen species migrate out of treated cells and into the surrounding tissue, where they cause damage to cells nearby. As a result of the bystander effect, PDT may be more effective overall by targeting a larger region of the tumor and reducing the likelihood of disease recurrence. The efficacy of photodynamic treatment is affected by several variables. Among these factors are the photosensitizer type, the dosage of light and PS, the interval between the two, and the wavelength and intensity of the light [107]. Choosing the right photosensitizer is critical for photodynamic therapy to work. There are a number of factors that need to be considered, such as the toxicity profile, pharmacokinetics, and absorption spectrum. Thoroughly adjusting the light and PS dose is essential for achieving the desired level of therapeutic efficacy while minimizing any possible side effects. Various generation of PS for cancer treatment are shown in **Figure 10**.

Approved PSs for skin cancer diseases: A small number of photosensitizers have been authorized for the treatment of skin cancer and other medical issues, despite the fact that there are several potential PSs for photodynamic thera-

py. This is mostly due to the lengthy and arduous procedure that new medications and therapies must undergo before they can be made available to the general population. There are a lot of moving parts in the process of making photosensitizers that are effective for photodynamic therapy. These characteristics include being triggered by light falling within a certain wavelength range, being able to efficiently create reactive oxygen species, and having the capacity to target cancer cells in particular. These aren't the only qualities that any possible PS will have; in fact, some may have additional restrictions that make them useless in real-world applications.

The design and features of popular PSs allow us to classify them into three separate generations. Using a combination of porphyrins generated from a raw hematoporphyrin preparation known as Hematoporphyrin Derivative, the first PSs for photodynamic treatment were created in the 1970s. Many different types of cancer were treated with HpD and its derivatives with encouraging outcomes in clinical practice for many decades. However, later PSs like Photofrin had limitations that prevented them from being widely used [108]. These phototoxic chemicals are known to bring about skin damage and photosensitivity reactions due to their capacity to create long-term photosensitization. The broad light absorption spectrum of first-generation photosensitizers is not the primary mechanism by which they produce reactive oxygen species in healthy tissues. In contrast, PSs of the second generation may work either alone or in tandem with other agents. In the optimal therapeutic range, they show improved absorption. Among the PSs that were listed are phthalocyanines, chlorins, and bacteriochlorins. Their improved photophysical properties include lower dark toxicity and higher quantum yields. Photodynamic treatment often makes use of these photodynamic sensitizers, which have been through extensive testing [60].

More selective targeting of sick tissue is achieved in third-generation PSs with the use of specialist methods such encapsulation or bioconjugation during construction [109]. All the various compartments of the tumour, Myeloid-derived suppressor cells, cancer stem cells, tumor vascular endothelial cells, and cancer cells should ideally express the target protein [110]. Nanotechnology also offers the possibility of creating smaller drug delivery vehicles for example, nanocapsules or nanospheres that are less than 100 nm in diameter. These drug carriers have a lot of cool features, such being able to control the release of pharmaceuticals, having a high distribution capacity, and carrying hydrophobic drugs in the circulation [111]. By adhering preferentially to certain tumour cells, third-generation PSs enable targeted therapy while minimising damage to off-target effects and normal cells [112]. To better understand PSs and their role in PDT, it is useful to first sort them into three generations. Specifically, for the purpose of making PDT more targeted and successful in the treatment of cancer, further study is needed. The most significant problem with PS is the time and effort required to get approval from the relevant medical regulatory bodies.

Since of its intricate process, photodynamic therapy is an excellent choice for treating skin cancer since it is both selective and effective. This treatment has a lot of potential for treating many skin cancers since it can precisely target skin regions, kill cancer cells nearby, stimulate the immune system, and be repeated as needed without accumulating toxicity or damage to good tissue. Numerous factors influence the efficacy of photodynamic therapy, such as the photosensitizer used, the amount of light and PS applied, the interval between the two, and the light's wavelength and intensity. Modulating the light beam appropriately to limit oxygen depletion is required to avoid the reduced tumor-killing efficacy induced by extended exposure to high-intensity light [113]. In order to account for potential drops in oxygen levels during the lower intensity phase, when the amplitude-modulated beam is at its strongest, the beam's modulation needs to be fine-tuned.

Consistent results in PDT are hard to come by due to the fact that several factors need to be carefully controlled. One reason PDT hasn't been used more often in therapeutic contexts is because of its heterogeneity. Nevertheless, PDT shows potential as a powerful weapon in the fight against skin cancer, particularly with the continuous developments in research and technology.

In addition to the problems highlighted in this research, the photobleaching phenomena must also be considered. The efficacy of treatment might be significantly affected by photobleaching, which is the irreversible decrease in photosensitizer activity when exposed to light. The photosensitizer molecule's breakdown or impairment causes the phenomena by lowering its concentration, which in turn limits the production of reactive oxygen species, a key component for cell death. Researchers have explored many methods to mitigate the effects of photobleaching. One approach is fractionated light administration, which entails exposing the photosensitizer to light in many sessions separated by intervals to allow it to recuperate. Improving the photosensitizer's dosage and formulation, in addition to using photostabilizers, has shown the ability to reduce photobleaching. It is possible to learn a lot about how to improve photodynamic therapy by monitoring the rate of photobleaching throughout sessions. Research in the future should aim to find ways to make photodynamic treatment more effective overall and less photobleaching so that patients may have the greatest possible therapeutic results.

When it comes to skin cancer, photodynamic therapy with ALA and MAL is considered to be the gold standard. Cancer cells produce more of the photosensitizing chemical protoporphyrin IX via metabolic processes. This molecule activates itself when exposed to light. Ameluz®, Photofrin®, Levulan®, and Metvix® are the most significant brands [114].

5-Aminolevulinic acid is the active ingredient in both Ameluz® and Levulan®, however they are marketed under different names due to their respective compositions. The most important difference is whether the 5-ALA is administered in a gel or a vehicle. The use of the 5-ALA gel Ameluz for the treatment of actinic keratosis has been licenced. It is often used in conjunction with a blue light source to initiate its effects. Levulan is a 5-ALA solution or cream that may help with a variety of skin issues, including as acne and actinic keratosis. Levulan may be triggered by various light sources, including powerful pulsed light and blue light, depending on the intended use. Both formulations have been clinically approved after extensive testing in several countries. Both formulations include the risk of photosensitivity of the skin and localised discomfort during therapy. The cellular localization and elimination of both medications are similar. In contrast to Ameluz, which usually requires a longer waiting period before treatment and is activated by red light, Levulan has a shorter waiting time and is triggered by blue light. While DUSA Pharmaceuticals, Inc. manufactures Levulan, Biofrontera AG makes Ameluz [115].

Various cancer types and precancerous lesions on skin may be treated with Metvix®, a photosensitizing medication used in photodynamic treatment. Metaryl aminolevulinate is the main ingredient in Metvix®. It is a prodrug that, when exposed to light, converts to protoporphyrin IX. Then, when exposed to a certain frequency of light, PpIX accumulates in the targeted cells and tissues, killing them. At the last step of heme synthesis, ferrochelatase incorporates Fe^{2+} into PPIX, which is the principal factor determining selectivity. Reduced ferrochelatase activity often leads to decreased iron levels in cancer cells. The observed selectivity is caused by a decrease in activity and iron levels. Metvix® has a wavelength (λ) of about 635 nm, which is in the red light spectrum [115]. Depending on the patient's features and the specific medical issue being treated, the post-dose therapeutic delay could be anywhere from one to three hours long.

The bulk of Metvix® is eliminated from the body within 24 hours due to its fast metabolism and clearance. Metavix® is now clinically approved for the treatment of superficial basal cell carcinoma and actinic keratosis. The therapy of several cancers, including bladder and lung cancers, has also made use of it off-label. Metvix® is most often associated with the following side effects: skin irritation, swelling, and redness at the injection site; moderate to severe nociception; and nausea, vomiting, and other gastrointestinal side effects during and after photodynamic treatment. Rarely, more serious side effects such blistering, scarring, and skin infections may occur. Skin carcinogenic or precancerous lesions are examples of the kinds of cells and tissues that Metvix® is most concentrated in. Light activates the photosensitizing chemical, which then releases reactive oxygen

species that destroy cells and harm tissues in the targeted areas. Light exposure is the primary mechanism of action for Metvix®, which kills cells and eliminates the targeted tissues by producing reactive oxygen species. Metvix® is manufactured by Galderma, a global pharmaceutical company that focuses on skin care and dermatology.

A variety of dermatological problems, including acne, some types of skin cancer, and actinic keratosis have been treated with these photodynamic therapies. Actinic keratosis is often treated with Metvix® and Ameluz®, whereas basal cell carcinoma and squamous cell carcinoma have been treated with Photofrin® and Levulan® [116].

Nanotechnology in PDT for NMSC treatment

Nanodrug delivery techniques such NPs, LPs, micelles, and microvehicles were developed in response to 5-ALA/MAL's limited skin penetration and weak luminous efficacy. When compared to free 5-ALA, liposomes improve skin penetration and reduce medicine absorption in the circulation, according to the research. This results in less cellular damage and less light sensitivity after treatment [117]. Researchers looked into feline cSCC to see if a liposomal form of PS had any negative effects. Treatment, which included injecting 0.15 mg m-THPC/kg into the cephalic or femoral vein, was well-received by all cats. After one year, 75% of patients were able to successfully manage their disease. Liposomal PS was shown to be safe and effective, according to the findings [118]. After injecting cats with liposomal phosphorylated mTHPC and subjecting them to a 652-nm diode laser, researchers studied the long-term effects and variables that predict feline cSCC. A total of 84% of patients responded, with 61% experiencing full remission and 22% experiencing partial remission. On average, patients went 35 months without any signs of illness progressing. An investigation of the photosensitizing effects of LPs loaded with curcumin was carried out in vitro [119]. Researchers found that curcumin-mediated photodynamic therapy was more effective in photosensitizing skin malignancies when administered in a liposomal formulation, while causing less harm to healthy keratinocytes [119]. Finally, they looked at the effects of PDT response on subcutaneous SCC-15 xenografts in mice, which the Pc4 nanoformulation had. The researchers found that the higher the tumor's uptake of Pc4, the better the PDT performed in both laboratory testing and live individuals, which was in line with the findings of the cell study.

Photodynamic therapy (PDT) is mostly used to treat skin problems. Conventional PDT is not as successful for melanoma, a kind of skin cancer that contains melanin pigment, since melanin absorbs a wide range of ultraviolet and visible light. This diminishes the efficacy of conventional photosensitizers (PSs) in photodynamic therapy (PDT). Researchers have presented pyrene-based two-photon (TP) photosensitizers that can be easily synthesized. Researcher verified that asymmetric pyrene (Py3) is capable of producing reactive oxygen species in conjunction with π-extended pyrene derivatives. Researcher put forward a mechanism that elucidates the greater efficiency of Py3 in generating reactive oxygen species (ROS) compared to its symmetric derivatives. Py1 and Py2 had emission peaks at 450 and 600 nm and absorption peaks at 400 and 474 nm, respectively (**Figure 11A**, **11B**). Between Py1 and Py2, Py3 had absorption and emission peaks at 450 and 590 nm. Specifically, spectral maxima moved to longer wavelengths in the sequence Py1 < Py3 < Py2. Pyridinium has a greater electron-withdrawing ability than benzothiazole, and Py2 has superior intramolecular charge transfer (ICT) capabilities than Py1, while Py3 has an intermediate tendency. Py3 had the lowest fluorescence efficiency and the highest TPA and OP spectrum characteristics of Py1 and Py2. After irradiating the aqueous solution with white light and ABDA, ROS were detected. Compared to Chlorin e6, Py1 had no influence on ABDA's absorption spectra (**Figure 11C-F**). The ABDA spectrum altered significantly for Py2 and more quickly for Py3. In trials with DHR 123, Py1 and Py2 showed opposing inclinations. Py1 increased DHR 123's fluorescence spectrum by more than five-fold over Chlorin e6, whereas Py2 performed similarly. Py3 caused a 60-fold spectral increase in DHR 123 compared to Chlorin e6 [120].

Both the sample size and the tumour depth determine how effective PDT is. For example, photodynamic treatment has the potential to successfully treat cutaneous squamous cell

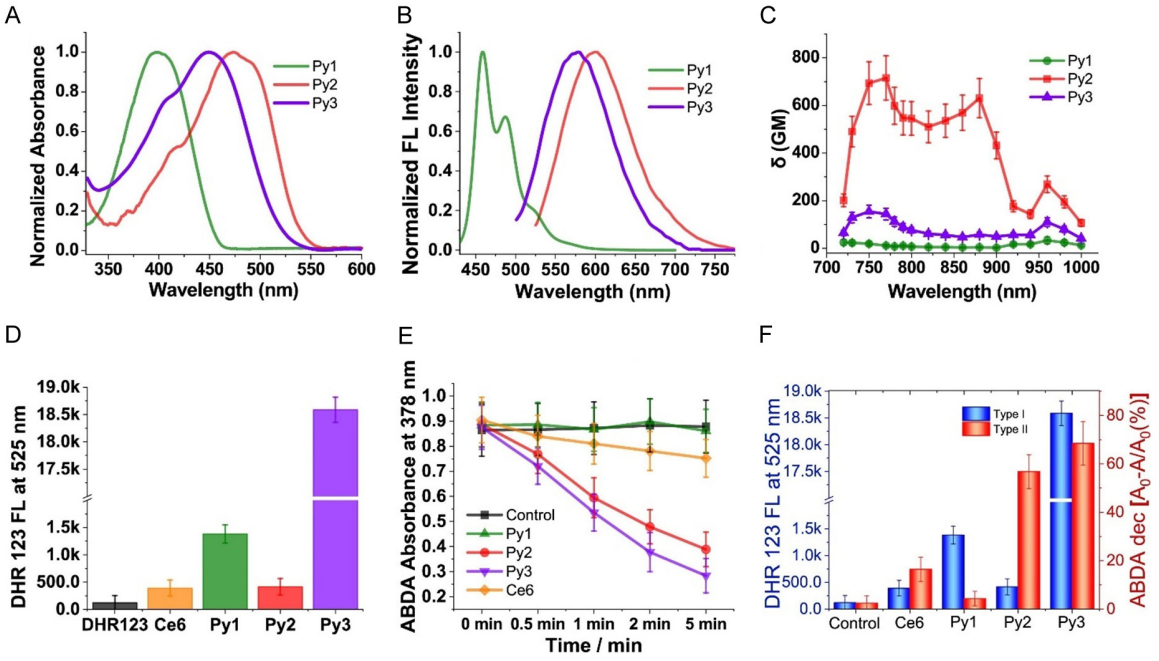

Figure 11. A. Py1, Py2, and Py3 UV-Vis absorption spectra were obtained in DMF at a concentration of 1 μM. B. Py1, Py2, and Py3 fluorescence emission spectra were acquired with an excitation wavelength that matched each of their λmax values. C. Py1, Py2, and Py3's TPA spectra were found in DMF. D. Evaluation of ROS production by the probes Ce6, Py1, Py2, and Py3 by monitoring the fluorescence intensity at 525 nm after 30 s (5.5 mW incident power) of white light irradiation for 5 μM of each probe and 5 μM of dihydrorhodamine 123 (DHR 123). E. A comparison study to assess the production of $^1O_2$ by Ce6, Py1, Py2, and Py3 (at 5 μM concentrations) in PBS buffer upon exposure to white light (5.5 mW incident power). As a comparison, 9,10-anthracenediyl-bis(methylene)dimalonic acid (ABDA) was compared to this. F. DHR 123 (for 0.5 min) and ABDA (for 5 min) spectrum alterations after white light irradiation in the presence and absence of Ce6, Py1, Py2, and Py3 [120].

carcinoma that is limited to the papillary dermis [121]. A formulation of a cream containing 5-ALA-loaded polylactic-co-glycolic acid nanoparticles [122]. Together, helium-neon laser irradiation and the application of these nanoparticles to tumour surfaces produced the desired effect. Compared to free 5-ALA at the same dosage, the 5-ALA-PLGA nanoparticles mediated photodynamic treatment for cSCC more effectively, according to the research. Using in vivo and in vitro investigations, the dark toxicity and efficacy of topical photodynamic treatment in squamous cell carcinoma were investigated using NP, which is composed of ZnPcs loaded on chitosan/methoxy polyethylene glycol-polylactic acid. Using Z-CPP for PDT was much more effective than using free ZnPcs and the compounds did not exhibit any dark toxicity, according to the results [123].

One well-established therapeutic option for low-risk basal cell carcinoma is photodynamic therapy, which mainly targets superficial and primary nodular BCC. For the purpose of determining whether BF-200 5-ALA, a nanoemulsion gel containing 5-ALA, or MAL, a cream containing MAL, is non-inferior in the treatment of superficial basal cell carcinoma or nodular basal cell carcinoma using photodynamic therapy, a phase III trial was carried out. While 91.8% of those in the MAL group responded, 93.4% of people in the BF-200 ALA group did. The results demonstrated that BF-200 ALA-PDT was as effective as MAL-PDT, with a non-inferiority margin of 1983. For non-aggressive basal cell carcinoma, researchers confirmed in a prospective, double-blind study that BF-200 5-ALA and low-concentration hexyl aminolevulinate were as efficacious and well-tolerated as MAL in photodynamic treatment [124, 125].

Nanotechnology-based PDT for melanoma

Melanoma may be classified into two categories: pigmented and unpigmented. Both varieties are very aggressive and dangerous forms of

skin cancer. The European Interdisciplinary Guideline on Melanoma included recommendations for the identification and management of cutaneous melanoma. Although adjuvant therapy with PDT was not indicated, surgical excision was underlined as the major treatment for melanoma [126]. However, several published sources have shown that superficial and localized cutaneous MM, PDT is a successful therapy option.

In reaction to the oxidative stress brought on by photodynamic therapy, tumour cells may initiate the formation of an antioxidant defence system and partly activate their own defensive mechanisms. Among the several advantages of nano-sized photosensitizers (Nano-PSs) are their high reactive oxygen species generation, ease of customisation, and outstanding stability. On top of that, they could be able to overcome photodynamic treatment resistance. Nanoparticles may directly kill cancer cells in MM by inducing DNA damage, cell membrane damage, and oxidative stress, as Tang et al. found. Additionally, they proved that NPs may attach to chemotherapeutic medicines via electrostatic force or hydrophobic/hydrophilic interactions, making them suitable carriers for these substances. This improves nanodrug targeting and biocompatibility [127]. When used as a tumour treatment, small interfering RNA may successfully decrease gene expression. Having said that, siRNAs degrade quickly in the circulation due to their intrinsic instability. Nanoparticles based on PEGylated chitosan were created for the transport of siRNAs [128]. In luciferase-expressing B16 melanoma cells, they showed that these NPs efficiently inhibited gene expression, were relatively non-toxic, and retained their stability.

Clinical trials conducted in living organisms cannot be predicted by monolayer cell culture models developed in a laboratory. Melanoma cells work in a three-dimensional setting, really forming interactions with nearby cells. By simulating physiological gradients like a hypoxic environment, 3D culture models - specifically melanoma spheroids - are able to capture tumour heterogeneity. While photodynamic treatment has the potential to mimic tumour architecture, very little is known about its application on melanoma spheroids. Because melanin's principal function inhibiting the effective penetration of light to the desired targets, photodynamic therapy is less successful in treating pigmented melanoma than non-melanoma skin cancer. According to study, photodynamic treatment for MM has made use of many photosensitizers [129]. Researchers found that 5-ALA PDT successfully reduced MM-A375 and A431 cell survival. Both the concentration and the length of administration were shown to have a role in this inhibition. Reducing Bcl-2 levels while increasing Bax and cleaved-PARP levels was the mechanism that the researchers found to be responsible for this outcome [130].

The passive or active delivery of photosensitizers to certain cancer cells was improved by conjugating nanoparticles with antibodies or targeting molecules. The degree to which nanocarriers are absorbed determines whether they are considered passive or active. Some of the passive drug delivery methods used materials such as silica, metal oxide, dendrimers, micelles, and liposomes [131].

Melanoma pigmentation reduces the efficacy of photodynamic treatment, thus researchers utilised phenylthiourea, a chemical that suppresses melanin formation, to compensate. Melanoma cells devoid of pigmentation were obtained in this way. The cells were then treated with liposomes that contained sodium ferrous chlorophyllin. The chemicals mostly accumulated in mitochondria and nuclei, as seen by transmission electron microscopy, which increased cellular internalisation and improved the efficacy of Fe-CHL-mediated photodynamic treatment. Topical photodynamic therapy was shown to be more successful in B16-F10 melanoma cells when LPs coated with chitosan enhanced drug stability and penetration, drug absorption into cells, and overall efficacy [132]. Polish researchers used mPEG-b-PLGA micelles to create a co-delivery system that mixes IR-768 with daunorubicin. The A375 cell line's singlet oxygen generation during photodynamic treatment was enhanced by this dual drug-loaded delivery method. By adding palladium porphyrin to layered metal oxide nanoparticles, researchers improved the biocompatibility and durability of the nanocomposites while increasing the solubility of hydrophobic PS-PdTCPP [133, 134]. The ability of LDH to modify surfaces with different functional groups was made possible by its enhanced loading capabilities.

Using PdTCPP-LDH with photodynamic treatment in B16F10 cells significantly reduced cancer development.

To combat cancer, nanoparticles may be engineered with targeting molecules that bind to receptors found on cancer cells in excess. This enhances the effectiveness of photosensitizers or medications by increasing their absorption. Photodynamic treatment has made use of active targeting using monoclonal antibodies, aptamers, DNA/RNA, and other molecules that target certain cells or tissues. This method makes use of nanocarriers, such as quantum dots, self-illuminating nanocrystals, and materials based on metal oxides or capable of upconverting their energy [135].

Melanin pigment is most absorbent at around 335 nm and almost completely absorbs light at wavelengths over 700 nm. In photodynamic treatment, photosensitizers and gold nanoparticles subjected to near-infrared light may produce synergistic effects due to their photothermal capabilities and tunable optical properties. In a controlled laboratory environment, the researchers tested the efficacy of PDT and PTT in conjunction with zinc phthalocyanine complexes linked to gold nanorods. They subjected B16F10 melanotic cells and B16G4F amelanotic cells to 635 nm light for the studies. Research showed that photothermal impact and photodynamic activity might kill more than 90% of melanoma cells [136]. A therapeutic nanosystem that reacts to near-infrared light [137]. The device uses indocyanine green-loaded gold nanoparticles to combine photothermal treatment with photodynamic therapy. In comparison to findings obtained for AuBPs alone, the $^{1}O_{2}$ generation was doubled and the PTT effect was much improved when the nanosystem was simulated using NIR. In their 1999 study, Urszula and coworkers created a mixture of xanthene-based RB molecules and upconverting NaYF4 nanoparticles doped with lanthanide ions (2% Er^{3+} and 20% Yb^{3+}). After that, PLGA and two non-ionic surfactants, Cremophor A25 and Span 80, were added to these nanoparticles. With remarkable selectivity, biocompatibility, and photodynamic therapy effects, the findings showed that the hybrid fluorophores were successfully delivered to human melanoma cells (Me-45 and MeWo) by the dual-core nanoplatform.

As a new nanocarrier with exceptional solubility, stability, and high quantum yield, N-doped carbon quantum dot (CQD) nanoparticles were synthesised to overcome the Indocyanine Green (ICG) impediment in photodynamic treatment (PDT) while maintaining simultaneous cell imaging properties. Research on cell culture and in vivo evaluations using C57BL/6 mice harbouring melanoma cancer cells were conducted. According to the results, the size of the CQD increased marginally from 24.55 nm to 42.67 nm after ICG injection. The reactive oxygen species (ROS) detection test showed that CQD enhanced the capability to generate ROS and the photo-stability of ICG under laser irradiation. According to a cell culture research, ICG@CQD might reduce the survival rate of B16F10 cell line melanoma cancer cells from 48% for pure ICG medication to 28% for ICG@CQD. Confocal microscopy pictures confirmed the nanocarrier's enhanced capacity for qualified cell imaging and increased cellular uptake of ICG@CQD. In vivo tests using C57BL/6 mice harbouring melanoma cancer cells demonstrated the clear suppression of tumour development for ICG@CQD relative to free ICG. Fluorescence pictures captured in vivo verified that in the tumour area, ICG@CQD significantly accumulates more than free ICG. To sum up, ICG@CQD is suggested as a novel nanocarrier with enormous promise for PDT and diagnostics [43].

Future directions

Photodynamic therapy (PDT) holds significant potential for the future of skin cancer treatment, and several novel pathways can be explored to enhance its efficacy and application. One critical area is the enhancement of photosensitizer design and delivery systems, particularly through nanotechnology. Developing multifunctional nanoparticles can improve the stability, bioavailability, and targeting of photosensitizers to tumor cells, minimizing damage to healthy tissues. Additionally, combining PDT with other therapies, such as immunotherapy and traditional treatments, can provide a comprehensive approach to managing skin cancer. Advanced light delivery techniques, including interstitial PDT and dynamic light exposure, offer opportunities to treat deeper lesions and optimize reactive oxygen species (ROS) production. The development of novel photosensitiz-

ers with higher specificity and improved tissue penetration, alongside photosensitizer bioconjugation, can further enhance PDT's therapeutic outcomes. Mechanistic studies and the identification of biomarkers for PDT response are crucial for personalizing treatment plans and guiding patient selection. Furthermore, large-scale clinical trials and translational research are essential to validate new PDT protocols and ensure their applicability in diverse patient populations. Finally, a patient-centered approach focusing on minimizing side effects and enhancing patient education can improve treatment adherence and quality of life for those undergoing PDT.

1. Future developments in PDT for skin cancer may include the use of nanoparticles as carriers for photosensitizers, enhancing their delivery and effectiveness. This approach could improve the selectivity and penetration of photosensitizers into cancerous tissues, reducing side effects and improving outcomes [18]. 2. Research into coherent and non-coherent light sources, such as pulsed dye lasers and intense pulsed light, could make PDT more effective and less painful. These light sources can be tailored to specific wavelengths that optimize photosensitizer activation and tissue penetration. 3. Combining PDT with other treatments like immunotherapy, chemotherapy, or cryotherapy could enhance the therapeutic outcomes for skin cancer patients. Such combination therapies can target multiple pathways involved in cancer progression, potentially leading to better eradication of tumors and reduced recurrence rates. 4. Advances in genetic and molecular profiling of tumors can enable more personalized approaches to PDT. By tailoring treatment plans based on individual patient's genetic makeup and tumor characteristics, the effectiveness of PDT can be maximized. 5. Development of photosensitizers that can specifically target cancer cells while sparing healthy tissues will enhance the specificity and reduce the side effects of PDT. 6. Research into new analgesic methods, both invasive and non-invasive, can help reduce the pain associated with PDT. Methods like nerve blocks, topical analgesics, and improved procedural protocols can make PDT more tolerable for patients. 7. Continuous improvement in the optimization of PDT parameters, such as light dose, photosensitizer concentration, and incubation time, will contribute to better patient outcomes and fewer side effects. 8. Prophylactic use of PDT could be explored for high-risk populations, potentially preventing the development of skin cancers in patients with a history of significant UV exposure or genetic predispositions.

Conclusion

This review highlights the significant advancements and current treatment approaches for skin cancer, focusing particularly on the potential of photodynamic therapy (PDT). Conventional treatments such as surgery, radiation, and chemotherapy, while effective, often come with limitations including non-specificity and adverse side effects. PDT emerges as a promising alternative, leveraging photosensitizers and light exposure to generate localized reactive oxygen species (ROS) that selectively target cancer cells.

The review underscores the efficacy of PDT in treating non-melanoma skin cancers like basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), while acknowledging its limitations in treating melanoma due to the latter's resistance and aggressive nature. Innovations in nanotechnology are poised to enhance PDT by improving the delivery and penetration of photosensitizers, thereby increasing treatment specificity and reducing collateral damage to healthy tissues. Furthermore, the integration of PDT with other therapies, such as immunotherapy and chemotherapy, holds promise for more comprehensive treatment regimens. Improved pain management techniques and the optimization of PDT parameters are essential to enhance patient comfort and treatment adherence. Looking ahead, the personalization of PDT based on genetic and molecular profiling of tumors could significantly improve treatment outcomes. The expansion of PDT applications to other dermatological conditions and its potential use in preventative treatments for high-risk populations are exciting future prospects. In conclusion, PDT represents a versatile and effective modality in the treatment of skin cancer, offering targeted, less invasive options with fewer side effects compared to conventional therapies. Continuous research and technological advancements are vital to fully realize the potential of PDT and integrate it as a mainstream treatment for various dermatological conditions.

Disclosure of conflict of interest

None.

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References

[1] Ciążyńska M, Kamińska-Winciorek G, Lange D, Lewandowski B, Reich A, Sławińska M, Pabianek M, Szczepaniak K, Hankiewicz A, Ułańska M, Morawiec J, Błasińska-Morawiec M, Morawiec Z, Piekarski J, Nejc D, Brodowski R, Zaryczańska A, Sobjanek M, Nowicki RJ, Owczarek W, Słowińska M, Wróbel K, Bieniek A, Woźniacka A, Skibińska M, Narbutt J, Niemczyk W, Ciążyński K and Lesiak A. The incidence and clinical analysis of non-melanoma skin cancer. Sci Rep 2021; 11: 4337.

[2] Artosi F, Costanza G, Di Prete M, Garofalo V, Lozzi F, Dika E, Cosio T, Diluvio L, Shumak RG, Lambiase S, Di Raimondo C, Campa S, Piscitelli P, Miani A, Bianchi L and Campione E. Epidemiological and clinical analysis of exposure-related factors in non-melanoma skin cancer: a retrospective cohort study. Environ Res 2024; 247: 118117.

[3] Kaur H, Bhardwaj A, Sehgal A, Mohi GK and Kumar R. Skin cancer: an overview. Handbook of Oncobiology: From Basic to Clinical Sciences 2024; 403-416.

[4] Algorri JF, López-Higuera JM, Rodríguez-Cobo L and Cobo A. Advanced light source technologies for photodynamic therapy of skin cancer lesions. Pharmaceutics 2023; 15: 2075.

[5] Alcalá Ramírez Del Puerto A, Hernández-Rodriguez JC, Sendín-Martín M, Ortiz-Alvarez J, Conejo-Mir Sánchez J and Pereyra-Rodriguez JJ. Skin cancer mortality in Spain: adjusted mortality rates by province and related risk factors. Int J Dermatol 2023; 62: 776-782.

[6] Algarin YA, Jambusaria-Pahlajani A, Ruiz E and Patel VA. Advances in topical treatments of cutaneous malignancies. Am J Clin Dermatol 2023; 24: 69-80.

[7] Jia HX and He YL. Efficacy and safety of imiquimod 5% cream for basal cell carcinoma: a meta-analysis of randomized controlled trial. J Dermatolog Treat 2020; 31: 831-838.

[8] Ou-Yang Y, Zheng Y and Mills KE. Photodynamic therapy for skin carcinomas: a systematic review and meta-analysis. Front Med (Lausanne) 2023; 10: 1089361.

[9] Qu Z, Wang Z, Qiu S, Cui G and Li C. Efficacy of photodynamic therapy with 5-aminolevulinic acid for the treatment of cervical high-grade squamous intraepithelial lesions with high-risk HPV infection: a retrospective study. Photodiagnosis Photodyn Ther 2022; 40: 103068.

[10] Shanazarov NA, Zare A, Mussin NM, Albayev RK, Kaliyev AA, Iztleuov YM, Smailova SB and Tamadon A. Photodynamic therapy of cervical cancer: a scoping review on the efficacy of various molecules. Ther Adv Chronic Dis 2024; 15: 20406223241233206.

[11] Tang D, Yu Y, Zhang J, Dong X, Liu C and Xiao H. Self-sacrificially degradable pseudo-semiconducting polymer nanoparticles that integrate NIR-II fluorescence bioimaging, photodynamic immunotherapy, and photo-activated chemotherapy. Adv Mater 2022; 34: 2203820.

[12] Zhang S, Sun X, Wang Z, Sun J, He Z, Sun B and Luo C. Molecularly self-engineered nanoamplifier for boosting photodynamic therapy via cascade oxygen elevation and Lipid ROS accumulation. ACS Appl Mater Interfaces 2022; 14: 38497-38505.

[13] Zhang X, Wan J, Mo F, Tang D, Xiao H, Li Z, Jia J and Liu T. Targeting bone tumor and subcellular endoplasmic reticulum via near infrared II fluorescent polymer for photodynamic-immunotherapy to break the step-reduction delivery dilemma. Adv Sci (Weinh) 2022; 9: e2201819.

[14] Morton CA, Szeimies RM, Basset-Séguin N, Calzavara-Pinton PG, Gilaberte Y, Haedersdal M, Hofbauer GFL, Hunger RE, Karrer S, Piaserico S, Ulrich C, Wennberg AM and Braathen LR. European Dermatology Forum guidelines on topical photodynamic therapy 2019 Part 2: emerging indications-field cancerization, photorejuvenation and inflammatory/infective dermatoses. J Eur Acad Dermatol Venereol 2020; 34: 17-29.

[15] Zhu C, Zhu X, Li H, Wang S, Shi N, Li W and Liu N. Recent advances in photodynamic therapy for vascular abnormalities. Photobiomodul Photomed Laser Surg 2024; 42: 501-508.

[16] Khosravaninezhad Y, Zavareh SA, Saadabad FP, Babapour N, Ghasemi Z, Esfahani A, Fouladi S, Choolabi RH, Mirfakhraei N and Noorali S. Mohammad Faranoush.

[17] Maleki H, Doostan M, Shojaei S, Doostan M, Stamatis H, Gkantzou E and Bonkdar A. Nanofiber-based systems against skin cancers: therapeutic and protective approaches. J Drug Deliv Sci Technol 2023; 104367.

[18] Zeng L, Gowda BHJ, Ahmed MG, Abourehab MAS, Chen ZS, Zhang C, Li J and Kesharwani P. Advancements in nanoparticle-based treatment approaches for skin cancer therapy. Mol Cancer 2023; 22: 10.

[19] Cives M, Mannavola F, Lospalluti L, Sergi MC, Cazzato G, Filoni E, Cavallo F, Giudice G, Stucci LS, Porta C and Tucci M. Non-melanoma skin

cancers: biological and clinical features. Int J Mol Sci 2020; 21: 5394.
[20] Cameron MC, Lee E, Hibler BP, Barker CA, Mori S, Cordova M, Nehal KS and Rossi AM. Basal cell carcinoma: epidemiology; pathophysiology; clinical and histological subtypes; and disease associations. J Am Acad Dermatol 2019; 80: 303-317.
[21] Derebaşınlıoğlu H. Distribution of skin cancers of the head and neck according to anatomical subunit. Eur Arch Otorhinolaryngol 2022; 279: 1461-1466.
[22] Seidl-Philipp M, Frischhut N, Höllweger N, Schmuth M and Nguyen VA. Known and new facts on basal cell carcinoma. J Dtsch Dermatol Ges 2021; 19: 1021-1041.
[23] Wortsman X. Top advances in dermatologic ultrasound. J Ultrasound Med 2023; 42: 521-545.
[24] Waldman A and Schmults C. Cutaneous squamous cell carcinoma. Hematol Oncol Clin North Am 2019; 33: 1-12.
[25] Bou-Dargham MJ, Khamis ZI, Cognetta AB and Sang QA. The role of interleukin-1 in inflammatory and malignant human skin diseases and the rationale for targeting interleukin-1 alpha. Med Res Rev 2017; 37: 180-216.
[26] Que SKT, Zwald FO and Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol 2018; 78: 237-247.
[27] Rischin D, Migden MR, Lim AM, Schmults CD, Khushalani NI, Hughes BGM, Schadendorf D, Dunn LA, Hernandez-Aya L, Chang ALS, Modi B, Hauschild A, Ulrich C, Eigentler T, Stein B, Pavlick AC, Geiger JL, Gutzmer R, Alam M, Okoye E, Mathias M, Jankovic V, Stankevich E, Booth J, Li S, Lowy I, Fury MG and Guminski A. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. J Immunother Cancer 2020; 8: e000775.
[28] Yeh I and Bastian BC. Melanoma pathology: new approaches and classification. Br J Dermatol 2021; 185: 282-293.
[29] Scolyer RA, Rawson RV, Gershenwald JE, Ferguson PM and Prieto VG. Melanoma pathology reporting and staging. Mod Pathol 2020; 33 Suppl 1: 15-24.
[30] Tinca AC, Moraru R, Cocuz IG, Șincu MC, Niculescu R, Sabău AH, Chiorean DM, Szoke AR, Morariu SH and Cotoi OS. Actualities in the morphology and immunohistochemistry of cutaneous and ocular melanoma: what lies ahead? A single-centre study. Biomedicines 2022; 10: 2500.
[31] Carr S, Smith C and Wernberg J. Epidemiology and risk factors of melanoma. Surg Clin North Am 2020; 100: 1-12.
[32] Matthews NH, Li WQ, Qureshi AA, Weinstock MA and Cho E. Epidemiology of melanoma. Exon Publ 2017; 3-22.
[33] Larønningen S, Skog A, Engholm G, Ferlay J, Johannesen TB, Kristiansen MF, Knoors D, Kønig SM, Olafsdottir EJ, Pejicic S, Pettersson D, Skovlund CW, Storm HH, Tian H, Aagnes B and Miettinen J. Nordcan.R: a new tool for federated analysis and quality assurance of cancer registry data. Front Oncol 2023; 13: 1098342.
[34] Matthews NH, Li WQ, Qureshi AA, Weinstock MA, Cho E, Ward W and Farma J. Cutaneous melanoma: etiology and therapy. Codon Publ 2017.
[35] Nasser N, Silva JLD and Corrêa G. Epidemiology of cutaneous melanoma in Blumenau, Santa Catarina state, Brazil from 1980 to 2019. An Bras Dermatol 2023; 98: 611-619.
[36] Guitera P, Menzies SW, Coates E, Azzi A, Fernandez-Penas P, Lilleyman A, Badcock C, Schmid H, Watts CG, Collgros H, Liu R, van Kemenade C, Mann GJ and Cust AE. Efficiency of detecting new primary melanoma among individuals treated in a high-risk clinic for skin surveillance. JAMA Dermatol 2021; 157: 521-530.
[37] Apalla Z, Lallas A, Sotiriou E, Lazaridou E and Ioannides D. Epidemiological trends in skin cancer. Dermatol Pract Concept 2017; 7: 1-6.
[38] Zhou W, Qiao Z, Nazarzadeh Zare E, Huang J, Zheng X, Sun X, Shao M, Wang H, Wang X, Chen D, Zheng J, Fang S, Li YM, Zhang X, Yang L, Makvandi P and Wu A. 4D-printed dynamic materials in biomedical applications: chemistry, challenges, and their future perspectives in the clinical sector. J Med Chem 2020; 63: 8003-8024.
[39] Yang S, Wei J, Cui YH, Park G, Shah P, Deng Y, Aplin AE, Lu Z, Hwang S, He C and He YY. m6A mRNA demethylase FTO regulates melanoma tumorigenicity and response to anti-PD-1 blockade. Nat Commun 2019; 10: 2782.
[40] Seebode C, Lehmann J and Emmert S. Photocarcinogenesis and skin cancer prevention strategies. Anticancer Res 2016; 36: 1371-1378.
[41] Bohn T, Bonet ML, Borel P, Keijer J, Landrier JF, Milisav I, Ribot J, Riso P, Winklhofer-Roob B, Sharoni Y, Corte-Real J, van Helden Y, Loizzo MR, Poljšak B, Porrini M, Roob J, Trebše P, Tundis R, Wawrzyniak A, Rühl R and Dulińska-Litewka J. Mechanistic aspects of carotenoid health benefits - where are we now? Nutr Res Rev 2021; 34: 276-302.
[42] Hart PH and Norval M. Ultraviolet radiation-induced immunosuppression and its relevance for skin carcinogenesis. Photochem Photobiol Sci 2018; 17: 1872-1884.

[43] Blatchley III ER, Brenner DJ, Claus H, Cowan TE, Linden KG, Liu Y, Mao T, Park SJ, Piper PJ and Simons RM. Far UV-C radiation: an emerging tool for pandemic control. Crit Rev Environ Sci Technol 2023; 53: 733-753.
[44] Gandhi SA and Kampp J. Skin cancer epidemiology, detection, and management. Med Clin North Am 2015; 99: 1323-1335.
[45] Jain AK, Jain S, Abourehab MAS, Mehta P and Kesharwani P. An insight on topically applied formulations for management of various skin disorders. J Biomater Sci Polym Ed 2022; 33: 2406-2432.
[46] Nawaz M, Mehmood Z, Nazir T, Naqvi RA, Rehman A, Iqbal M and Saba T. Skin cancer detection from dermoscopic images using deep learning and fuzzy k-means clustering. Microsc Res Tech 2022; 85: 339-351.
[47] Garbe C, Peris K, Soura E, Forsea AM, Hauschild A, Arenbergerova M, Bylaite M, del Marmol V, Bataille V, Samimi M, Gandini S, Saiag P, Eigentler TK, Lallas A, Zalaudek I, Lebbe C, Grob JJ, Hoeller C, Robert C, Dréno B, Arenberger P, Kandolf-Sekulovic L, Kaufmann R, Malvehy J, Puig S, Leiter U, Ribero S, Papadavid E, Quaglino P, Bagot M, John SM, Richard MA, Trakatelli M, Salavastru C, Borradori L, Marinovic B, Enk A, Pincelli C, Ioannides D, Paul C and Stratigos AJ. The evolving field of Dermatooncology and the role of dermatologists: position paper of the EADO, EADV and task forces, EDF, IDS, EBDV-UEMS and EORTC cutaneous lymphoma task force. J Eur Acad Dermatol Venereol 2020; 34: 2183-2197.
[48] Dekker PK, Mishu MD, Youn R and Baker SB. Serial excision for treatment of non-melanoma skin cancer. Plast Reconstr Surg Glob Open 2021; 9: e3607.
[49] Bittner GC, Cerci FB, Kubo EM and Tolkachjov SN. Mohs micrographic surgery: a review of indications, technique, outcomes, and considerations. An Bras Dermatol 2021; 96: 263-277.
[50] Prickett K and Ramsey M. Mohs micrographic surgery. Stat Pearls; 2022.
[51] Chandra J, Hasan N, Nasir N, Wahab S, Thanikachalam PV, Sahebkar A, Ahmad FJ and Kesharwani P. Nanotechnology-empowered strategies in treatment of skin cancer. Environ Res 2023; 235: 116649.
[52] Work Group; Invited Reviewers; Kim JYS, Kozlow JH, Mittal B, Moyer J, Olencki T and Rodgers P. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol 2018; 78: 540-559.
[53] Ferry AM, Sarrami SM, Hollier PC, Gerich CF and Thornton JF. Treatment of non-melanoma skin cancers in the absence of Mohs micrographic surgery. Plast Reconstr Surg Glob Open 2020; 8: e3300.
[54] Kim DP, Kus KJ and Ruiz E. Basal cell carcinoma review. Hematol Oncol Clin North Am 2019; 33: 13-24.
[55] Rogers SJ, Puric E, Eberle B, Datta NR and Bodis SB. Radiotherapy for melanoma: more than DNA damage. Dermatol Res Pract 2019; 2019: 9435389.
[56] Nguyen LB, Vu LG, Le TT, Nguyen XT, Dao NG, Nguyen DC, Huyen Thi Dang T, Vu TMT, Boyer L, Fond G, Auquier P, Latkin CA, Zhang MWB, Ho RCM and Ho CSH. Impact of interventions on the quality of life of cancer patients: a systematic review and meta-analysis of longitudinal research. Health Qual Life Outcomes 2023; 21: 112.
[57] Musyuni P, Bai J, Sheikh A, Vasanthan KS, Jain GK, Abourehab MAS, Lather V, Aggarwal G, Kesharwani P and Pandita D. Precision medicine: ray of hope in overcoming cancer multidrug resistance. Drug Resist Updat 2022; 65: 100889.
[58] Aquino MFS, Chua CT and Agustin ER. Shelter-based food preparation intervention and subjective well-being of pediatric cancer patients in Manila, Philippines. Philipp J Sci 2022; 151.
[59] Champeau M, Vignoud S, Mortier L and Mordon S. Photodynamic therapy for skin cancer: how to enhance drug penetration? J Photochem Photobiol B 2019; 197: 111544.
[60] Algorri JF, Ochoa M, Roldan-Varona P, Rodriguez-Cobo L and Lopez-Higuera JM. Photodynamic therapy: a compendium of latest reviews. Cancers (Basel) 2021; 13: 4447.
[61] Shi L, Liu P, Liu J, Yang Y, Chen Q, Zhang Y, Zhang H and Wang X. Application of 5-aminolevulinic acid-photodynamic therapy in common skin diseases. Transl Biophotonics 2020; 2: e201900028.
[62] Hamblin MR. Photodynamic therapy for cancer: what's past is prologue. Photochem Photobiol 2020; 96: 506-516.
[63] Xing X, Yang K, Li B, Tan S, Yi J, Li X, Pang E, Wang B, Song X and Lan M. Boron dipyrromethene-based phototheranostics for near Infrared fluorescent and photoacoustic imaging-guided synchronous photodynamic and photothermal therapy of cancer. J Phys Chem Lett 2022; 13: 7939-7946.
[64] Abrouk M, Gianatasio C, Li Y and Waibel JS. Prospective study of intense pulsed light versus pulsed dye laser with or without blue light in the activation of PDT for the treatment of actinic keratosis and photodamage. Lasers Surg Med 2022; 54: 66-73.
[65] Foged C, Haedersdal M, Bik L, Dierickx C, Phillipsen PA and Togsverd-Bo K. Thermo-mechanical fractional injury enhances skin surface- and epidermis-protoporphyrin IX fluorescence: comparison of 5-aminolevulinic acid in cream

and gel vehicles. Lasers Surg Med 2021; 53: 622-629.
[66] Miller MB and Padilla A. CO2 laser ablative fractional resurfacing photodynamic therapy for actinic keratosis and nonmelanoma skin cancer: a randomized split-side study. Cutis 2020; 105: 251-254.
[67] Shavit R and Dierickx C. A new method for percutaneous drug delivery by thermo-mechanical fractional injury. Lasers Surg Med 2020; 52: 61-69.
[68] Falkenberg C, Schmitz L, Dicke K, Dervenis V, Szeimies RM and Dirschka T. Pretreatment with ablative fractional carbon dioxide laser improves treatment efficacy in a synergistic PDT protocol for actinic keratoses on the head. Photodiagnosis Photodyn Ther 2021; 34: 102249.
[69] Ang JM, Riaz IB, Kamal MU, Paragh G and Zeitouni NC. Photodynamic therapy and pain: a systematic review. Photodiagnosis Photodyn Ther 2017; 19: 308-344.
[70] Silic K, Kammer M, Sator PG, Tanew A and Radakovic S. Efficacy of two different methods of cold air analgesia for pain relief in PDT of actinic keratoses of the head region - a randomized controlled comparison study. Photodiagnosis Photodyn Ther 2022; 40: 103190.
[71] Borgia F, Giuffrida R, Caradonna E, Vaccaro M, Guarneri F and Cannavò SP. Early and late onset side effects of photodynamic therapy. Biomedicines 2018; 6: 12.
[72] Klein A, Karrer S, Horner C, Werner A, Heinlin J, Zeman F, Koller M, Landthaler M, Szeimies RM, Gruber M, Graf B, Hansen E and Kerscher C. Comparing cold-air analgesia, systemically administered analgesia and scalp nerve blocks for pain management during photodynamic therapy for actinic keratosis of the scalp presenting as field cancerization: a randomized controlled trial. Br J Dermatol 2015; 173: 192-200.
[73] Fink C, Uhlmann L, Enk A and Gholam P. Pain management in photodynamic therapy using a nitrous oxide/oxygen mixture: a prospective, within-patient, controlled clinical trial. J Eur Acad Dermatol Venereol 2017; 31: 70-74.
[74] Kaw U, Ilyas M, Bullock T, Rittwage L, Riha M, Vidimos A, Hu B, Warren CB and Maytin EV. A regimen to minimize pain during blue light photodynamic therapy of actinic keratoses: bilaterally controlled, randomized trial of simultaneous versus conventional illumination. J Am Acad Dermatol 2020; 82: 862-868.
[75] Gandy J, Labadie B, Bierman D and Zachary C. Photodynamic therapy effectively treats actinic keratoses without pre-illumination incubation time. J Drugs Dermatol 2017; 16: 275-278.
[76] Piacquadio D, Houlihan A, Ferdon MB, Berg JE and Marcus SL. A randomized trial of broad area ALA-PDT for field cancerization mitigation in high-risk patients. J Drugs Dermatol 2020; 19: 452-458.
[77] Piccolo D and Kostaki D. Photodynamic therapy activated by intense pulsed light in the treatment of nonmelanoma skin cancer. Biomedicines 2018; 6: 18.
[78] Monfrecola G, Megna M, Rovati C, Arisi M, Rossi M, Calzavara-Pinton I, Fabbrocini G and Calzavara-Pinton P. A critical reappraisal of off-label use of photodynamic therapy for the treatment of non-neoplastic skin conditions. Dermatology 2021; 237: 262-276.
[79] Farberg AS, Marson JW and Soleymani T. Advances in photodynamic therapy for the treatment of actinic keratosis and nonmelanoma skin cancer: a narrative review. Dermatol Ther (Heidelb) 2023; 13: 689-716.
[80] Zeitouni NC, Bhatia N, Ceilley RI, Cohen JL, Del Rosso JQ, Moore AY, Munavalli G, Pariser DM, Schlesinger T, Siegel DM, Willey A and Goldman MP. Photodynamic therapy with 5-aminolevulinic acid 10% gel and red light for the treatment of actinic keratosis, nonmelanoma skin cancers, and acne: current evidence and best practices. J Clin Aesthet Dermatol 2021; 14: E53-E65.
[81] Liu Y, Cao Z and Wei G. Effects of photodynamic therapy using Red LED-light combined with hypocrellin B on apoptotic signaling in cutaneous squamous cell carcinoma A431 cells. Photodiagnosis Photodyn Ther 2023; 43: 103683.
[82] Lev-Tov H, Larsen L, Zackria R, Chahal H, Eisen DB and Sivamani RK. Microneedle-assisted incubation during aminolaevulinic acid photodynamic therapy of actinic keratoses: a randomized controlled evaluator-blind trial. Br J Dermatol 2017; 176: 543-545.
[83] Petukhova TA, Hassoun LA, Foolad N, Barath M and Sivamani RK. Effect of expedited microneedle-assisted photodynamic therapy for field treatment of actinic keratoses: a randomized clinical trial. JAMA Dermatol 2017; 153: 637-643.
[84] Spencer JM and Freeman SA. Microneedling prior to levulan PDT for the treatment of actinic keratoses: a split-face, blinded trial. J Drugs Dermatol 2016; 15: 1072-1074.
[85] Jang YH, Lee DJ, Shin J, Kang HY, Lee ES and Kim YC. Photodynamic therapy with ablative carbon dioxide fractional laser in treatment of actinic keratosis. Ann Dermatol 2013; 25: 417-422.
[86] Wen X, Li Y and Hamblin MR. Photodynamic therapy in dermatology beyond non-melanoma cancer: an update. Photodiagnosis Photodyn Ther 2017; 19: 140-152.

[87] Qiao S, Tang H, Xia J, Ding M, Qiao S, Niu Y and Jiang G. Efficacy and safety of microneedling, fractional CO2 laser, and cryotherapy combined with 5-aminolevulinic acid photodynamic therapy in the treatment of actinic keratosis: a multicenter prospective randomized controlled study. Photodiagnosis Photodyn Ther 2023; 43: 103700.
[88] Zhou Z, Yan Y, Zhang Q and Cheng Y. Melanin-like nanoparticles loaded with an angiotensin antagonist for an improved photothermal cancer therapy. Biomater Sci 2020; 8: 1658-1668.
[89] Araújo JL, da Silva PB, Fonseca-Santos B, Báo SN, Chorilli M, de Souza PEN, Muehlmann LA and Azevedo RB. Photodynamic therapy directed to melanoma skin cancer by thermosensitive hydrogel containing chlorophyll A. Pharmaceuticals (Basel) 2023; 16: 1659.
[90] Austin E, Geisler AN, Nguyen J, Kohli I, Hamzavi I, Lim HW and Jagdeo J. Visible light. Part I: Properties and cutaneous effects of visible light. J Am Acad Dermatol 2021; 84: 1219-1231.
[91] Willey A. Thermal photodynamic therapy for actinic keratoses on facial skin: a proof-of-concept study. Dermatol Surg 2019; 45: 404-410.
[92] Nissen CV, Heerfordt IM, Wiegell SR, Mikkelsen CS and Wulf HC. Pretreatment with 5-fluorouracil cream enhances the efficacy of daylight-mediated photodynamic therapy for actinic keratosis. Acta Derm Venereol 2017; 97: 617-621.
[93] Galimberti GN. Calcipotriol as pretreatment prior to daylight-mediated photodynamic therapy in patients with actinic keratosis: a case series. Photodiagnosis Photodyn Ther 2018; 21: 172-175.
[94] Liu K, Jiang Z, Lalancette RA, Tang X and Jäkle F. Near-infrared-absorbing B-N lewis pair-functionalized anthracenes: electronic structure tuning, conformational isomerism, and applications in photothermal cancer therapy. J Am Chem Soc 2022; 144: 18908-18917.
[95] Han X, Zhao C, Wang S, Pan Z, Jiang Z and Tang X. Multifunctional TiO2/C nanosheets derived from 3D metal-organic frameworks for mild-temperature-photothermal-sonodynamic-chemodynamic therapy under photoacoustic image guidance. J Colloid Interface Sci 2022; 621: 360-373.
[96] Cong Z, Zhang L, Ma SQ, Lam KS, Yang FF and Liao YH. Size-transformable hyaluronan stacked self-assembling peptide nanoparticles for improved transcellular tumor penetration and photo-chemo combination therapy. ACS Nano 2020; 14: 1958-1970.
[97] Li WP, Yen CJ, Wu BS and Wong TW. Recent advances in photodynamic therapy for deep-seated tumors with the aid of nanomedicine. Biomedicines 2021; 9: 69.
[98] Hamblin MR and Huang Y. Imaging in photodynamic therapy. CRC Press; 2017.
[99] Algar WR, Massey M, Rees K, Higgins R, Krause KD, Darwish GH, Peveler WJ, Xiao Z, Tsai HY, Gupta R, Lix K, Tran MV and Kim H. Photoluminescent nanoparticles for chemical and biological analysis and imaging. Chem Rev 2021; 121: 9243-9358.
[100] Sharma D, Misba L and Khan AU. Antibiotics versus biofilm: an emerging battleground in microbial communities. Antimicrob Resist Infect Control 2019; 8: 76.
[101] Niculescu AG and Grumezescu AM. Photodynamic therapy-an up-to-date review. Appl Sci 2021; 11: 3626.
[102] Wan Y, Fu LH, Li C, Lin J and Huang P. Conquering the hypoxia limitation for photodynamic therapy. Adv Mater 2021; 33: 2103978.
[103] Kwiatkowski S, Knap B, Przystupski D, Saczko J, Kędzierska E, Knap-Czop K, Kotlińska J, Michel O, Kotowski K and Kulbacka J. Photodynamic therapy - mechanisms, photosensitizers and combinations. Biomed Pharmacother 2018; 106: 1098-1107.
[104] Kushibiki T, Hirasawa T, Okawa S and Ishihara M. Responses of cancer cells induced by photodynamic therapy. J Healthc Eng 2013; 4: 87-108.
[105] Gunaydin G, Gedik ME and Ayan S. Photodynamic therapy for the treatment and diagnosis of cancer-a review of the current clinical status. Front Chem 2021; 9: 686303.
[106] Dahle J, Kaalhus O, Moan J and Steen HB. Cooperative effects of photodynamic treatment of cells in microcolonies. Proc Natl Acad Sci U S A 1997; 94: 1773-1778.
[107] Kim MM and Darafsheh A. Light sources and dosimetry techniques for photodynamic therapy. Photochem Photobiol 2020; 96: 280-294.
[108] Pham TC, Nguyen VN, Choi Y, Lee S and Yoon J. Recent strategies to develop innovative photosensitizers for enhanced photodynamic therapy. Chem Rev 2021; 121: 13454-13619.
[109] Mfouo-Tynga IS, Dias LD, Inada NM and Kurachi C. Features of third generation photosensitizers used in anticancer photodynamic therapy: review. Photodiagnosis Photodyn Ther 2021; 34: 102091.
[110] Gomez S, Tsung A and Hu Z. Current targets and bioconjugation strategies in photodynamic diagnosis and therapy of cancer. Molecules 2020; 25: 4964.
[111] Mesquita MQ, Dias CJ, Gamelas S, Fardilha M, Neves MGPMS and Faustino MAF. An insight on the role of photosensitizer nanocarriers for photodynamic therapy. An Acad Bras Cienc 2018; 90 Suppl 2: 1101-1130.

[112] Park W, Cho S, Han J, Shin H, Na K, Lee B and Kim DH. Advanced smart-photosensitizers for more effective cancer treatment. Biomater Sci 2017; 6: 79-90.
[113] Algorri JF, Ochoa M, Roldan-Varona P, Rodriguez-Cobo L and López-Higuera JM. Light technology for efficient and effective photodynamic therapy: a critical review. Cancers (Basel) 2021; 13: 3484.
[114] Gunaydin G, Gedik ME and Ayan S. Photodynamic therapy-current limitations and novel approaches. Front Chem 2021; 9: 691697.
[115] Alexiades M. Photodynamic therapy. Procedures in Cosmetic Dermatology: Lasers, Lights, and Energy Devices-E-Book. 2022. pp. 127.
[116] Assikar S, Labrunie A, Kerob D, Couraud A and Bédane C. Daylight photodynamic therapy with methyl aminolevulinate cream is as effective as conventional photodynamic therapy with blue light in the treatment of actinic keratosis: a controlled randomized intra-individual study. J Eur Acad Dermatol Venereol 2020; 34: 1730-1735.
[117] Wiehe A and Senge MO. The photosensitizer temoporfin (m THPC)-chemical, pre-clinical and clinical developments in the last decade. Photochem Photobiol 2023; 99: 356-419.
[118] Zhang P, Han T, Xia H, Dong L, Chen L and Lei L. Advances in photodynamic therapy based on nanotechnology and its application in skin cancer. Front Oncol 2022; 12: 836397.
[119] Woźniak M, Nowak M, Lazebna A, Więcek K, Jabłońska I, Szpadel K, Grzeszczak A, Gubernator J and Ziółkowski P. The comparison of in vitro photosensitizing efficacy of curcumin-loaded liposomes following photodynamic therapy on melanoma MUG-Mel2, squamous cell carcinoma SCC-25, and normal keratinocyte HaCaT cells. Pharmaceuticals (Basel) 2021; 14: 374.
[120] Juvekar V, Cao Y, Koh CW, Lee DJ, Kwak SY, Kim SM, Park TJ, Park S, Liu Z and Kim HM. Overcoming melanin interference in melanocyte photodynamic therapy with a pyrene-derived two-photon photosensitizer. Chem Eng J 2024; 493: 152796.
[121] Keyal U, Bhatta AK, Zhang G and Wang XL. Present and future perspectives of photodynamic therapy for cutaneous squamous cell carcinoma. J Am Acad Dermatol 2019; 80: 765-773.
[122] Wang X, Shi L, Tu Q, Wang H, Zhang H, Wang P, Zhang L, Huang Z, Zhao F, Luan H and Wang X. Treating cutaneous squamous cell carcinoma using 5-aminolevulinic acid polylactic-co-glycolic acid nanoparticle-mediated photodynamic therapy in a mouse model. Int J Nanomedicine 2015; 10: 347-355.
[123] Keyal U, Luo Q, Bhatta AK, Luan H, Zhang P, Wu Q, Zhang H, Liu P, Zhang L, Wang P, Yang D, Zhang G, Yao J, Wang X and Shi L. Zinc pthalocyanine-loaded chitosan/mPEG-PLA nanoparticles-mediated photodynamic therapy for the treatment of cutaneous squamous cell carcinoma. J Biophotonics 2018; 11: e201800114.
[124] Morton CA, Dominicus R, Radny P, Dirschka T, Hauschild A, Reinhold U, Aschoff R, Ulrich M, Keohane S, Ekanayake-Bohlig S, Ibbotson S, Ostendorf R, Berking C, Gröne D, Schulze HJ, Ockenfels HM, Jasnoch V, Kurzen H, Sebastian M, Stege H, Staubach P, Gupta G, Hübinger F, Ziabreva I, Schmitz B, Gertzmann A, Lübbert H and Szeimies RM. A randomized, multinational, noninferiority, phase III trial to evaluate the safety and efficacy of BF-200 aminolaevulinic acid gel vs. methyl aminolaevulinate cream in the treatment of nonaggressive basal cell carcinoma with photodynamic therapy. Br J Dermatol 2018; 179: 309-319.
[125] Salmivuori M, Grönroos M, Tani T, Pölönen I, Räsänen J, Annala L, Snellman E and Neittaanmäki N. Hexyl aminolevulinate, 5-aminolevulinic acid nanoemulsion and methyl aminolevulinate in photodynamic therapy of non-aggressive basal cell carcinomas: a non-sponsored, randomized, prospective and double-blinded trial. J Eur Acad Dermatol Venereol 2020; 34: 2781-2788.
[126] Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Bastholt L, Bataille V, Del Marmol V, Dréno B, Fargnoli MC, Grob JJ, Höller C, Kaufmann R, Lallas A, Lebbé C, Malvehy J, Middleton M, Moreno-Ramirez D, Pellacani G, Saiag P, Stratigos AJ, Vieira R, Zalaudek I and Eggermont AMM; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). European consensus-based interdisciplinary guideline for melanoma. Part 2: treatment-update 2019. Eur J Cancer 2020; 126: 159-177.
[127] Tang JQ, Hou XY, Yang CS, Li YX, Xin Y, Guo WW, Wei ZP, Liu YQ and Jiang G. Recent developments in nanomedicine for melanoma treatment. Int J Cancer 2017; 141: 646-653.
[128] Cunningham FJ, Goh NS, Demirer GS, Matos JL and Landry MP. Nanoparticle-mediated delivery towards advancing plant genetic engineering. Trends Biotechnol 2018; 36: 882-897.
[129] Naidoo C, Kruger CA and Abrahamse H. Photodynamic therapy for metastatic melanoma treatment: a review. Technol Cancer Res Treat 2018; 17: 1533033818791795.
[130] Cai J, Zheng Q, Huang H and Li B. 5-aminolevulinic acid mediated photodynamic therapy inhibits survival activity and promotes apoptosis

of A375 and A431 cells. Photodiagnosis Photodyn Ther 2018; 21: 257-262.
[131] Ashfaq UA, Riaz M, Yasmeen E and Yousaf MZ. Recent advances in nanoparticle-based targeted drug-delivery systems against cancer and role of tumor microenvironment. Crit Rev Ther Drug Carrier Syst 2017; 34: 317-353.
[132] Lee EH, Lim SJ and Lee MK. Chitosan-coated liposomes to stabilize and enhance transdermal delivery of indocyanine green for photodynamic therapy of melanoma. Carbohydr Polym 2019; 224: 115143.
[133] Tokarska K, Lamch Ł, Piechota B, Żukowski K, Chudy M, Wilk KA and Brzózka Z. Co-delivery of IR-768 and daunorubicin using mPEG-b-PLGA micelles for synergistic enhancement of combination therapy of melanoma. J Photochem Photobiol B 2020; 211: 111981.
[134] Chen ZA, Kuthati Y, Kankala RK, Chang YC, Liu CL, Weng CF, Mou CY and Lee CH. Encapsulation of palladium porphyrin photosensitizer in layered metal oxide nanoparticles for photodynamic therapy against skin melanoma. Sci Technol Adv Mater 2015; 16: 054205.
[135] Bi Y, Hao F, Yan G, Teng L, Lee RJ and Xie J. Actively targeted nanoparticles for drug delivery to tumor. Curr Drug Metab 2016; 17: 763-782.
[136] Freitas LF, Hamblin MR, Anzengruber F, Perussi JR, Ribeiro AO, Martins VCA and Plepis AMG. Zinc phthalocyanines attached to gold nanorods for simultaneous hyperthermic and photodynamic therapies against melanoma in vitro. J Photochem Photobiol B 2017; 173: 181-186.
[137] Campu A, Focsan M, Lerouge F, Borlan R, Tie L, Rugina D and Astilean S. ICG-loaded gold nano-bipyramids with NIR activatable dual PTT-PDT therapeutic potential in melanoma cells. Colloids Surf B Biointerfaces 2020; 194: 111213.
[138] Łasińska I, Zielińska A, Mackiewicz J and Souto EB. Basal cell carcinoma: pathology, current clinical treatment, and potential use of lipid nanoparticles. Cancers (Basel) 2022; 14: 2778.
[139] Lazar AD, Dinescu S and Costache M. Deciphering the molecular landscape of cutaneous squamous cell carcinoma for better diagnosis and treatment. J Clin Med 2020; 9: 2228.
[140] Wang X, Luo D and Basilion JP. Photodynamic therapy: targeting cancer biomarkers for the treatment of cancers. Cancers (Basel) 2021; 13: 2992.
[141] Piksa M, Lian C, Samuel IC, Pawlik KJ, Samuel IDW and Matczyszyn K. The role of the light source in antimicrobial photodynamic therapy. Chem Soc Rev 2023; 52: 1697-1722.
[142] Paasch U and Said T. Treating field cancerization by ablative fractional laser and indoor daylight: assessment of efficacy and tolerability. J Drugs Dermatol 2020; 19: 425-427.
[143] Wenande E, Phothong W, Bay C, Karmisholt KE, Hædersdal M and Togsverd-Bo K. Efficacy and safety of daylight photodynamic therapy after tailored pretreatment with ablative fractional laser or microdermabrasion: a randomized, side-by-side, single-blind trial in patients with actinic keratosis and large-area field cancerization. Br J Dermatol 2019; 180: 756-764.
[144] Flickinger I, Gasymova E, Dietiker-Moretti S, Tichy A and Rohrer Bley C. Evaluation of long-term outcome and prognostic factors of feline squamous cell carcinomas treated with photodynamic therapy using liposomal phosphorylated meta-tetra(hydroxylphenyl)chlorine. J Feline Med Surg 2018; 20: 1100-1104.
[145] Ferrisse TM, de Oliveira AB, Surur AK, Buzo HS, Brighenti FL and Fontana CR. Photodynamic therapy associated with nanomedicine strategies for treatment of human squamous cell carcinoma: a systematic review and meta-analysis. Nanomedicine 2022; 40: 102505.