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Review Article

Treatment of skin cancer: From conventional to nanotechnological approaches☆

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ABSTRACT

Skin cancer represents a global health challenge with rising incidence rates, requiring the development of comprehensive therapeutic strategies. Although conventional therapies, both local (surgery, radiotherapy) and systemic (chemotherapy, immunotherapy, molecular therapy), remain the cornerstone of managing various types of skin cancer, nanotechnology approaches now represent the cutting edge of skin cancer treatment, offering targeted drug delivery and reduced systemic toxicity. However, some limits on clinical transfer are still present. This review examines current treatment modalities ranging from conventional approaches to emerging nanotechnological innovations, such as lipid-based nanosystems (vesicles, solid lipid nanoparticles), as well as polymeric nanocarriers (nanospheres, nanocapsules, dendrimers, polymeric micelles) and new programmable nanocarriers (framework nucleic acids and microneedles) in the treatment of the most aggressive skin cancers, such as basal cell, squamous cell carcinomas and melanoma. These delivery nanosystems demonstrate superior biocompatibility, controlled drug release, enhanced therapeutic efficacy compared to conventional formulations and treatments, enabling size-dependent skin penetration and effectively reaching dermal layers, avoiding off-target effects. Therefore, the integration of traditional therapeutic approaches with nano-technological systems represent a promising strategy to enhance patient outcomes by providing personalized, targeted treatment strategies in the management of skin cancer.

1. Introduction

The skin is the largest organ of the human body, and it is composed of several layers. From the outside in, the skin apparatus consists of the epidermis, dermis, and hypodermis. The first two strata are characterized by the presence of neurovascular, glandular, mesenchymal, and epithelial elements. The epidermis is composed of keratinocytes, which, during their differentiation, become corneocytes and allow the formation of a barrier capable of protecting the body from various physical, chemical, and immunological environmental agents. Consequently, the epidermis is the most vulnerable target for exposure to external stressors, including ozone, air pollutants, and ultraviolet radiation [1]. Melanocytes in the basal epidermal layer produce melanin, affording UV protection, while Langerhans cells and resident T-cells contribute to cutaneous immune surveillance. The dermis provides structural support, elasticity, and houses blood vessels, nerves, and various immune cells, whereas the hypodermis anchors the skin and insulates the body. The disruption of the skin barrier function may be responsible for the onset of skin diseases, including erythema, edema, dermatitis, psoriasis, photoaging, and cancer [2,3].

Among skin diseases, skin cancer is the most common and growing type, with a high incidence especially among Caucasians. Exposure to the ultraviolet (UV) radiation from the sun or artificial sources appears to be one of the main causes of skin cancer [4].

UVA, UVB, and UVC, being characterized by different wavelengths, are responsible for different biological effects. The intensity of UV radiation and ionizing radiation can vary greatly and increase their harmfulness to the skin, therefore skin cancer can be considered an environmental cancer that increases with human aging. [5,6]

Particularly, skin cancer is related to the uncontrolled proliferation of abnormal skin cells responsible for the formation of tumors and can be categorized depending on the cell type precursor, the histopathological pattern, and the clinical significance into (i) non-melanoma skin cancers, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC); and (ii) melanoma of the skin, known as cutaneous melanoma (CM) (Fig. 1) [5,7]. While non-melanoma skin cancer (NMSC)

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demonstrates higher incidence rates, melanoma is responsible for the majority of skin cancer-related deaths. Recent genomic and molecular advances have substantially enhanced our understanding of the complex pathogenesis underlying these malignancies, revealing distinct mutational signatures, signaling pathways, and immune microenvironments that characterize each subtype [8–10].

Although conventional therapies, including surgical excision, Mohs micrographic surgery (MMS), cryotherapy, and radiotherapy, still result very effective, especially for early-stage and NMSC, newer therapies such as immunotherapy, photodynamic therapy (PDT), targeted therapies with the use of delivery nanocarriers, have revolutionized outcomes, offering non-invasive alternatives for superficial lesions, aiming for more precise and durable responses in challenging skin cancers [11,12].

Moreover, considering that cancer can act to reprogram the body's neuroendocrine axes, supporting its own survival and expansion by releasing hormones, neurotransmitters, and immune mediators, that alter metabolism, stress responses, and immune function across the entire body, understanding how tumors hijack the body's neuroendocrine system opens several promising therapeutic approaches aimed at restoring host homeostasis and improving treatment outcomes, particularly in advanced cancers [4].

1.1. UV radiation and skin damage in cancer progression

UV-induced DNA damage is recognized as the principal etiologic factor in the development of skin carcinoma, promoting oxidative stress, DNA damage, carcinogenesis, and photoaging in NMSC (SCC, BCC) and melanoma. UV radiation (UVR) is categorized into UVA (320–400 nm: UVA2 320–340 nm, UVA1 340–400 nm), UVB (290–320 nm), and UVC (180–290 nm). The atmospheric ozone (O_3) layer absorbs UVC and partially filters UVB, so 90–95% of UV reaching the Earth's surface is UVA and 5–10% is UVB, with UVA1 constituting 80% and able to penetrate the deep dermal layer (Fig. 1). Recent decades have witnessed ozone depletion due to chlorofluorocarbon (CFC) emissions, which undergo UV-catalyzed photolytic dissociation, depleting ozone and correlating with increased dermatological pathologies and skin cancer [13].

Due to their different wavelengths and energies, UVA and UVB radiations are able to penetrate the skin at different levels and differ in their mechanism of action. UVB is absorbed mainly by the epidermis, forming pyrimidine dimers in DNA and inducing direct DNA mutations, while UVA penetrates deeper, reaching the dermis and leading to reactive oxygen species (ROS) generation that damages DNA indirectly. UVA also attacks other biomolecules and, although lower in energy, studies now show its significant role in photoaging, carcinogenesis, hyperpigmentation, and immune suppression [14]. DNA absorbs predominantly UVB (290–300 nm), producing cyclobutane pyrimidine dimers (CPDs) - the most carcinogenic photoproducts, inducing cell cycle arrest - and some other photoproducts that trigger apoptosis. UVA can also induce CPDs via triplet-triplet energy transfer and oxidative damage like 8-oxo-7,8-dihydroguanine (8-oxoGua), a biomarker for UVA-induced DNA damage [15]. While UVA is less efficient than UVB at forming CPDs and other photoproducts, UVA-induced CPDs concentrate in the basal epidermis, a carcinogenic site, versus UVB-induced CPDs which are found in the upper layer. Persistent UVA-induced CPDs in melanocytes are strongly linked to carcinomas, and “CPD hyper

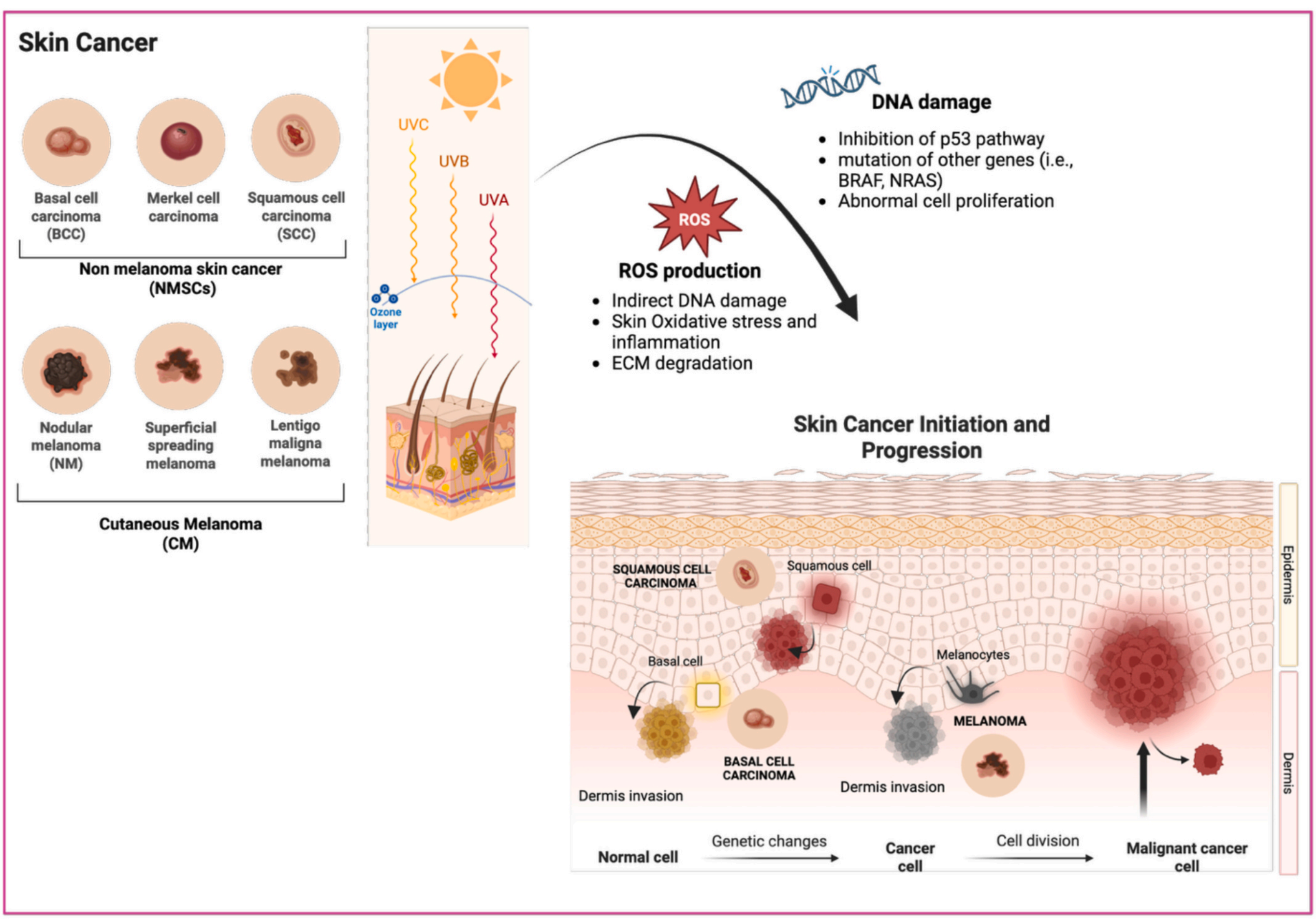

Fig. 1. Types of Skin cancers and pathway of skin cancer development due to exposure to UV rays. Original figure created with www.BioRender.com (accessed on 27 November 2025).

hotspots” in melanocytes and fibroblasts - hundreds of times more susceptible to CPD formation - may predict skin cancer risk from small biopsies [16–20].

UVR-induced DNA damage leads to mutations in genes regulating cell cycle arrest and apoptosis, such as the tumor protein 53 (TP53) [21]. Normally, TP53 mediates apoptosis to eliminate mutated cells, but mutation imbalance is a key factor in human cancer. As a matter of fact, >90% of SCC and 50% of BCC exhibit UVR-induced TP53 mutations, shown by changes in Caspase-3 and Bcl-2 in carcinomas including eyelid cancer [22]. UVR further promotes SCC progression by modulating microRNA expression, as shown by increased miR-7-5p, miR-29a-3p, and miR-183-5p in primary SCC post UV irradiation and maintained in metastasis [23].

Vitamin D occupies a paradoxical position in skin cancer biology acting as both a marker of UV exposure and a multifaceted anticancer agent. While UVB promotes melanoma and NMSC, it also enables skin synthesis of vitamin D_3, converted to calcitriol, a potent VDR ligand. Vitamin D blocks Hedgehog signaling in BCC (SMO/Gli1 suppression), inhibits proliferation, promotes DNA repair, inhibits Matrix Metalloproteinases (MMPs), and suppresses inflammation via COX-2 in melanoma [24,25]. However, higher serum 25(OH)D levels have been associated with increased skin cancer risk, likely reflecting cumulative UV exposure, not vitamin D action [26] and higher VDR expression has been observed in early melanoma [27,28]. Mendelian randomization confirms that elevated 25(OH)D mirrors UV exposure, with only local vitamin D metabolites showing cancer protection [26,29]. Despite the antioxidant role of vitamin D, NMSC patients have raised oxidative stress markers, whereas individuals with sufficient vitamin D levels show increased antioxidant capacity. [30].

This “sunshine paradox” underscores the need for balanced sun exposure: optimize vitamin D through moderate sun exposure during off-peak hours (5–15 min), combined with sun protection at high UV times, and supplement as needed in high-risk groups [31,32]. Controlled, educated sunlight exposure, integrated with photoprotection, may deliver systemic benefits even as excessive UVB remains a confirmed skin cancer risk.

1.2. *Non-melanoma skin cancer and melanoma: classification, etiology, and pathogenesis*

In the following sub-paragraphs and in Table 1, the different types of skin cancers and the related molecular pathways involved in their development are summarized.

1.2.1. *Non-melanoma skin Cancer (NMSC)*

NMSC encompasses several distinct histological subtypes, with BCC and SCC representing the two most common forms, accounting for approximately 80% and 20% of NMSC cases, respectively. Additional, less frequent NMSC types include Merkel cell carcinoma (MCC), a highly aggressive neuroendocrine tumor associated with Merkel cell polyomavirus (MCPyV) infection and ultraviolet radiation exposure [10,79,80].

NMSC represents the most common malignancy globally and the global burden is projected to increase substantially, with estimates suggesting a 20-fold increase for men and 15-fold increase for women over the next 25 years. In 2020, global NMSC incidence exceeded 1.2 million cases, with the highest rates in Northern America (607,867 cases, 49.2%), Europe (330,062 cases, 26.7%), and Oceania (72,145 cases, 5.8%) [80,81].

1.2.2. *Basal cell carcinoma subtypes*

BCC originates in the basal layer of the epidermis, from follicular germinative cells, and can appear anywhere on the body, most commonly developing in sun-exposed areas such as the head, face, neck, shoulders, and back, demonstrating variable biological behavior depending on histological subtype. More than 26 different BCC subtypes

Table 1
Summary of the different types of skin cancers and the related molecular pathways involved in their development.

Category	Skin Cancer Type	Molecular Pathways Involved	Skin Area Most Affected	References
NMSC	Basal Cell Carcinoma (BCC)	Hedgehog (Hh) signaling: PTCH1 loss, SMO activation, GLI1/2/3 activation, Cyclin D1/2, N-MYC; UVB-induced mutations; ROS/OGG1 DNA repair dysfunction	Sun-exposed areas: head, face, neck, shoulders, back; can occur anywhere	[33–43]
NMSC	Cutaneous Squamous Cell Carcinoma (cSCC)	TP53 mutations (UV-induced), NOTCH1 loss-of-function, CDKN2A, RAS (HRAS/KRAS/NRAS), TGFBR1/2, inflammatory pathways (TLR-4, NF-κB, AP-1), ROS generation	Sun-exposed skin; upper epidermis, rapid growth, common on face, hands, arms	[11,12,44–51]
NMSC	Merkel Cell Carcinoma (MCC)	MCPyV polyomavirus integration, UV-induced DNA damage, neuroendocrine markers	Mainly sun-exposed areas, especially elderly or immunosuppressed individuals	[44,52,53]
NMSC (Precancerous)	Actinic Keratosis	Early TP53 mutations, NOTCH1 loss, CpG methylation, TGF-β, EGFR, MAPK, reduced p38 phosphorylation, β-catenin alteration	Sun-exposed skin; manifests as scaly patches, especially face, hands, scalp	[11,46,54–60]
Melanoma	Melanoma	NRAS and BRAF mutations (MAPK, PI3K/AKT pathways), CDKN2A loss, NF1 mutation, RAC1, PREX2, ERBB4, KIT, melanin/ROS effects, TERT, MITF, BAP1	Common on trunk (young), legs (women), face, palms, soles, nail beds; varies by subtype; sun-exposed or intermittently exposed areas	[9,47,61–78]

have been described in the literature, although the most clinically significant variants are seven [52]. *Nodular BCC* is the predominant form (60% of cases), appearing as characteristic pearly nodules with visible blood vessels on sun-exposed skin. *Superficial BCC* grows as red, scaly patches in the upper skin layers, while *micronodular BCC* consists of small tumor clusters that can spread beyond clinically visible borders. The infiltrative BBC subtypes carrying a higher recurrence risk are *morpheaform (sclerosing) BCC* (5–10% of cases), which form cord-like tumor strands in dense, scar-like tissue with poorly defined margins, the *infiltrative BCC* which demonstrates irregular, spiky projections into deeper skin layers and *Pigmented BCC* that contains melanin pigment and occurs more frequently in individuals with darker skin tones. *Basosquamous (metatypical) BCC* represents the most aggressive variant, exhibiting mixed features of both basal and squamous cell carcinoma with the highest metastatic potential among all BCC subtypes [44].

Recognition of BCC subtype is essential for treatment planning, as infiltrative variants (morpheaform, infiltrative, and basosquamous) require wider surgical margins or more aggressive management due to their invasive growth patterns and higher recurrence rates.

The Hedgehog (Hh) signaling pathway plays a central role in BCC pathogenesis, with somatic mutations in the PTCH1 tumor suppressor gene occurring in more than 85% of sporadic BCCs.

UVR, particularly UVB, is the primary cause of mutations in the Hh signaling pathway, with PTCH1 (Patched 1) loss-of-function mutations occurring in 85–90% of BCCs and smoothened (SMO) gain-of-function mutations in 10–15% [33,53]. Under normal conditions, PTCH1, a 12-transmembrane tumor suppressor on chromosome 9q22.3, inhibits SMO, a 7-transmembrane G-protein-coupled receptor. However, loss-of-function PTCH1 mutations or gain-of-function SMO mutations result in constitutive SMO activation, releasing inhibition of the glioma-associated oncogene homologs GLI1, GLI2, and GLI3 transcription factors. These factors translocate to the nucleus and activate Hh target genes including GLI1, PTCH1 (feedback regulation), CCND1 (Cyclin D1), CCND2 (Cyclin-D2), N-MYC, and genes regulating cell proliferation, differentiation, and angiogenesis [34,35].

PTCH2 (Patched 2) also contributes to tumor suppression, and loss of both PTCH1 and PTCH2 confers a higher tumor risk than PTCH1 loss alone, evidence of their synergistic function [36].

Germline PTCH1 mutations cause nevoid basal cell carcinoma syndrome (Gorlin syndrome), an autosomal dominant condition characterized by multiple early-onset BCCs, further confirming the central role of Hh pathway dysregulation in BCC pathogenesis [37].

The identification of Hh pathway dysregulation has led to the development of targeted therapeutics, including the SMO inhibitors vismodegib and sonidegib, which have been approved by FDA for advanced and recurrent BCC following surgery or radiation therapy [38]. UVB exposure additionally induces production of proopiomelanocortin (POMC) peptides (β-endorphin, α-MSH, ACTH) and glucocorticoids at local and systemic levels, exerting immunosuppressive effects that facilitate BCC development, while UVA-mediated ROS cause secondary DNA damage through formation of 8-oxoGua and inhibition of the base excision repair system controlled by OGG1 (8-Oxoguanine DNA Glycosylase), contributing to increased gene mutations and cancer risk [33].

1.2.3. Cutaneous squamous cell carcinoma (SCC)

SCC originates in the upper epidermis, commonly arising on sun-exposed skin and growing rapidly over weeks. It is characterized by the malignant proliferation of keratinocytes with squamous differentiation, as evidenced by intercellular bridges and keratin pearls. SCC subtypes show variable behavior: well-differentiated forms have organized keratinization, whereas poorly differentiated types show minimal keratin, prominent nuclear atypia, and increased vascularity. Rare aggressive variants include acantholytic (loss of cellular adhesion, poor prognosis), spindle cell (25% lymph node metastasis), and basaloid (most aggressive, 40% two-year survival). In contrast, favorable subtypes such as verrucous (warty, exophytic) and papillary SCC (finger-like fibrovascular projections) have low metastatic potential and excellent prognosis when detected early [39].

Histological subtype classification is critical for SCC risk stratification and treatment planning. Aggressive variants (basaloid, spindle cell, acantholytic) warrant more intensive surveillance and adjuvant therapy, while favorable subtypes (verrucous, papillary) may be managed with local excision alone when detected early.

TP53 mutations represent a hallmark of UV-induced SCC pathogenesis, occurring early in the progression from normal keratinocytes to invasive carcinoma. The characteristic UV signature comprises C → T transitions at dipyrimidine sites, with hotspot mutations at specific codons (particularly codons 267 and 272 in murine models). In human SCC, TP53 mutations are detected in actinic keratosis, indicating their role as early driver events [40–42].

Wild-type keratinocytes demonstrate remarkable resistance to UV-induced mutagenesis despite decades of sun exposure, maintaining relatively low mutation burdens through intact p53-mediated apoptotic responses following DNA damage. However, acquisition of TP53 mutations eliminates this protective mechanism, allowing accumulation of additional mutations and clonal expansion of damaged keratinocytes [40–42].

NOTCH1 (Neurogenic locus notch homolog protein 1) mutations have emerged as critical early events in cutaneous squamous cell carcinogenesis, identified in approximately 75–82% of sporadic SCC cases and 70% of normal-appearing skin samples from sun-exposed sites. These predominantly loss-of-function mutations disrupt NOTCH receptor signaling, which normally functions as a tumor suppressor in keratinocytes by promoting differentiation and limiting proliferation [43].

The high frequency of NOTCH1 mutations in morphologically normal skin suggests that NOTCH1 acts as a “gatekeeper” gene, with its inactivation representing an early permissive event that primes keratinocytes for subsequent malignant transformation.

Additional frequently mutated genes include cyclin-dependent kinase inhibitor 2a (CDKN2A), RAS family members (HRAS, KRAS, NRAS; 17.6% combined), the Transforming Growth Factor Beta Receptors 1 (TGFBR1) (6%) and 2 (TGFBR2) (8%), and chromatin remodeling genes including the Collagen Type XI Alpha 1 Chain (COL11A1), with UV-induced ROS generation through the Nicotinamide Adenine Dinucleotide Phosphate oxidases (NADPH) and mitochondrial dysfunction activating inflammatory pathways (TLR-4, NF-κB, AP-1) that disrupt DNA repair mechanisms, promote immunosuppression, and create a tumor-permissive microenvironment [41,45,46].

1.2.4. Precancerous lesions: actinic keratosis

Actinic keratosis (AK) and Bowen's disease represent crucial precancerous conditions in the spectrum of SCC development. AK is characterized by intraepidermal proliferation of atypical keratinocytes, with annual progression rates to invasive SCC ranging from 0% to 0.075% per lesion-year, increasing to 0.53% in patients with prior history of keratinocyte cancer. Bowen's disease, representing SCC in situ, demonstrates progression to invasive SCC in 5–10% of immunocompetent patients and up to 30% in immunosuppressed individuals [11,12,47].

The progression from AK to SCC involves accumulation of mutations in multiple pathways, including p38 MAPK signaling (with reduced p38 phosphorylation correlating with progression), loss of E-cadherin expression, and alterations in β-catenin signaling [40,41].

Patient-level risk of developing SCC from AK lesions is substantially high, with 60% of invasive SCCs arising from pre-existing AKs and patients harboring 7–8 lesions face 10% risk of SCC within 10 years [48]. Histopathologically classified as keratinocyte intraepithelial neoplasia (KIN) grades I-III based on the extent of dysplasia, AK progresses via classical (full-thickness dysplasia before invasion) or differentiated pathways (direct invasion from KIN I), with severely dysplastic lesions (KIN III) and SCC in situ progressing most rapidly [48]. Molecular characterization reveals early TP53 mutations (>90% of SCCs), NOTCH1 loss-of-function mutations (75–82%), CpG island hypermethylation, and activation of TGF-β/EGFR/MAPK pathways, with genome-wide analyses identifying "CPD hyper hotspots" enabling potential risk prediction from small biopsies [49,50]. Management encompasses lesion-directed therapies (cryotherapy, curettage, excision) for isolated AKs and field-directed approaches (5-FU, imiquimod, PDT) for multiple lesions, with preventive strategies including SPF 50+ photoprotection, nicotinamide supplementation (500 mg twice daily), and emerging alpha-HPV vaccination [51].

1.2.5. Melanoma

Cutaneous melanoma (CM) is an aggressive cancer originating from melanocytes in the basal epidermis. It is the most challenging form of skin cancer due to its rapid dermal spread, high metastatic potential, and frequent resistance to treatment [44,54]. Incidence varies globally, peaking in Australia, New Zealand, Northern Europe, and North America. Melanoma mortality has decreased up to 50% in Australia and significantly in the US and UK since 2010 due to risk awareness, earlier diagnosis, and improved therapy, though survival gains may partly mask rising incidence [55–57].

Melanoma often arises from dysplastic nevi or isolated melanocytes, mainly in sun-exposed skin. Primary growth is initially supported by passive diffusion, but angiogenesis starts once tumors exceed 2 mm^3, supporting expansion. Progression involves two phases: an early radial (horizontal) growth phase with good prognosis, followed by a vertical growth phase with deeper invasion, increased proliferation, and high metastatic risk, a key factor for prognosis [58,59].

The WHO classifies melanoma into several major subtypes based on their growth pattern, anatomical site, and histological features. The most common is *superficial spreading melanoma or malignant melanoma (MM),* usually associated with BRAF (B-Rapidly Accelerated Fibrosarcoma protein) or NRAS (Neuroblastoma RAS viral oncogene homolog) mutations and gradual growth, making up about 70% of cases. *Nodular melanoma* follows with around 15%, known for aggressive vertical growth and worse prognosis. *Lentigo maligna melanoma*, often seen in elderly patients on sun-damaged skin, shows a distinctive proliferation of atypical melanocytes. *Acral lentiginous melanoma* is the most frequent subtype among people of Asian and African descent and affects palms, soles, and nail beds, often carrying KIT mutations. *Desmoplastic melanoma*, a rare fibrosing type, is challenging to diagnose and subtyped by the extent of desmoplastic tissue, with pure and mixed forms differing in their metastatic risk [60].

UV radiation is the leading environmental risk factor for melanoma. Intermittent, intense UV exposure and sunburns greatly increase melanoma risk, especially during childhood or adolescence, via multiple mechanisms including direct DNA damage, oxidative stress, immunosuppression and Melanogenesis dysregulation, with the lifetime risk rising in proportion to the number of blistering sunburns experienced [61,62].

Unlike in NMSCs, p53 mutations are rarely primary drivers in MM. Instead, melanoma is most often linked to mutations in the NRAS and BRAF oncogenes, which activate the MAPK (RAS-RAF-MEK-ERK) and PI3K/AKT pathways and in the tumor suppressor neurofibromin 1 (NF1). Together, these pathways are altered in about 91% of cases. BRAF mutations (30–50% of cutaneous melanomas, mostly V600E) are associated with acute sun exposure and arise more often in young, trunk-located, superficial spreading melanomas, with V600K variants especially tied to UV-induced, high-mutation tumors. NRAS mutations (13–28%; mainly codon 61) correlate with older age, nodular subtype, chronic sun exposure, increased tumor thickness, and more immunosuppressed tumors with higher risk of death, mostly involving NRAS mutations activating MAPK and PI3K/AKT pathways [63,64]. NF1-mutated melanoma is a distinct subtype found in about 10–15% of cases, usually in older patients and often on sun-exposed skin. NF1 is a tumor suppressor gene that normally regulates the RAS pathway; mutations lead to increased RAS/MAPK pathway activity and a high mutational burden, especially with UV signatures [65,66]. While BRAF, NRAS, and NF1 mutations converge on MAPK pathway activation, they have different subtype-specific patterns of downstream signaling [66].

Additional oncogenes, such as RAC1, PREX2, and ERBB4, also contribute to drive melanoma proliferation, primarily through the PI3K/AKT pathway and its interaction with MAPK signaling [67]. Another important gene commonly mutated in melanoma is CDKN2A, accounting for roughly 39% of familial cases and 2% of all melanomas. It encodes the tumor suppressors p16INK4A (controlling the cell cycle via CDK4/6) and p14ARF (regulating p53-dependent apoptosis) [68–70]. Other high-penetrance genes such as the BRCA1-associated protein 1 (BAP1), the Protection of telomeres 1 (POT1), the Microphthalmia-associated transcription factor (MITF), the Ataxia-telangiectasia mutated (ATM), and the Telomerase reverse transcriptase (TERT), account for only about half of hereditary melanoma cases, highlighting significant genetic heterogeneity [69].

Phenotypic factors, including numerous common or atypical nevi, fair skin, red or blonde hair, and susceptibility to sunburn, significantly increase melanoma risk. Individuals with more than 100 common melanocytic nevi have a relative risk of 7.6, while those with at least 5 atypical (dysplastic) nevi show a relative risk of 6.1 compared to those with none. Although approximately 30% of melanomas arise from pre-existing nevi, UV-induced melanin production can paradoxically contribute to melanoma-genesis through mutagenic quinone and semiquinone intermediates that damage DNA, RNA, and regulatory proteins [9,62,71]. Regarding melanogenesis, UV has been shown to induce melanin production, which, while photoprotective, may paradoxically contribute to melanoma-genesis through the generation of quinone and semiquinone intermediates that can modify DNA, RNA, and regulatory proteins [37].

It is worth mentioning that melanin and melanogenesis exhibit paradoxical "Yin and Yang" effects in melanoma. While eumelanin provides photoprotection, pheomelanin generates ROS and melanogenesis intermediates that are cytotoxic, genotoxic, and immunosuppressive, promoting tumor progression. Consequently, pigmented melanomas demonstrate greater resistance to radiotherapy and chemotherapy, with higher melanin content correlating with shorter overall survival, increased metastatic potential, and worse clinical outcomes. Since melanogenesis activates the Hypoxia-Inducible Factor-1 Alpha (HIF-1α), stimulates glycolysis, and induces FasL expression—-creating an immunosuppressive microenvironment—melanogenesis inhibition (using agents like *N*-phenylthiourea or D-penicillamine) represents a promising adjuvant strategy to enhance immuno-, radio-, and chemotherapy responses in advanced melanotic melanoma [72].

2. Conventional therapies against skin cancer

The clinical management of cutaneous malignancies necessitates a multifaceted therapeutic approach, integrating both localized and systemic interventions (Fig. 2). These modalities are critically crucial for addressing the diverse pathological presentations and disease progression observed in NMSC, encompassing BCC and SCC, as well as melanoma, which represents the most aggressive cutaneous neoplasm [47]. Local therapies demonstrably achieve adequate disease control in early-stage and circumscribed cutaneous neoplasms. Conversely, the advent of systemic therapies has fundamentally advanced outcomes in patients with advanced-stage disease, thereby establishing a personalized and dynamic treatment paradigm that prioritizes maximal tumor regression and optimized patient quality of life [73]. The contemporary treatment landscape for skin cancer is characterized by a synergistic application of local and systemic therapeutic strategies, meticulously individualized to the specific tumor type and disease stage. Ongoing advancements in surgical techniques, targeted local treatments, and novel systemic agents underscore the evolving nature of skin cancer management [74].

The collective integration of these advanced approaches consistently contributes to reductions in mortality rates and improvements in the

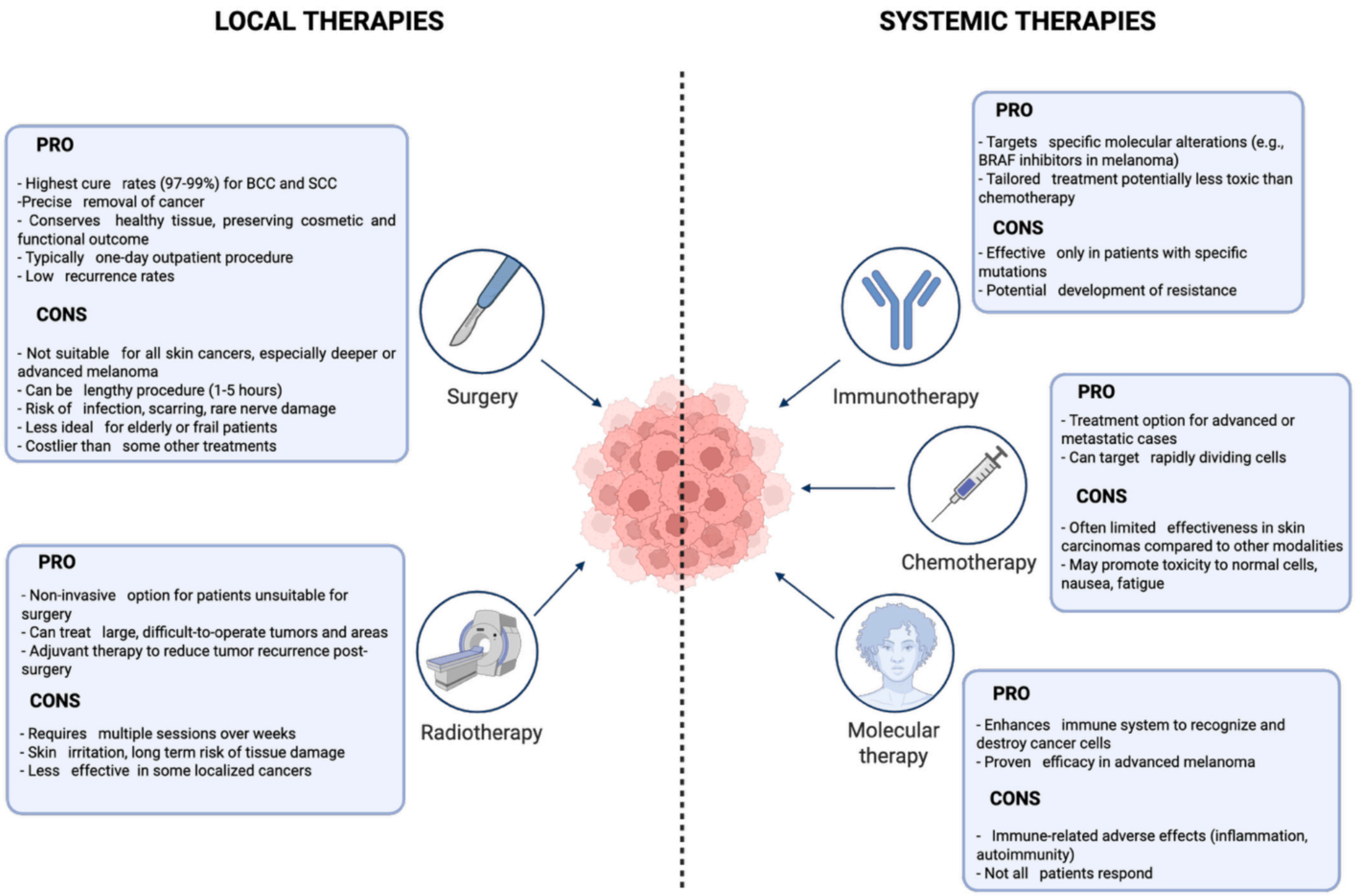

Fig. 2. Schematic representation of the available conventional therapeutic strategies against skin cancer. Original figure created with www.BioRender.com (accessed on 27 November 2025).

overall quality of life for individuals afflicted with this prevalent malignancy, as described in the following paragraphs and summarized in Fig. 2 and Table 2.

2.1. Local therapies

2.1.1. Surgery

Local therapies primarily focus on the destruction or excision of tumors within the targeted area. Surgical intervention remains the fundamental treatment for localized skin cancer. MMS, noted for its high cure rates, allows for meticulous removal of cancerous tissues while sparing surrounding healthy skin, effectively minimizing recurrence rates [75,76]. Some retrospective studies suggest that MMS may improve survival for patients with high-risk skin cancers like head and neck melanoma, *lentigo maligna* melanoma, and invasive SCC. Additionally, this study highlighted the substantial tissue preservation that MMS offers, accompanied by minimal morbidity and high patient satisfaction related to cosmetic outcomes [77]. In the management of high-risk SCC, a randomized controlled trial involving 350 patients demonstrated that MMS significantly decreased recurrence rates at two years compared with standard excision (1.5% vs. 8.7%). The MMS group also experienced better functional outcomes and fewer complications, supporting its preferential use for high-risk lesions that require meticulous margin control [78,82]. Furthermore, MMS presents economic benefits compared to other cancer treatments. For instance, a cost-effectiveness analysis of MMS for facial nonmelanoma skin cancers found that although MMS has higher initial procedural costs, it leads to overall cost savings by reducing recurrence-related retreatments and improving quality-adjusted life years (QALYs) [83]. These findings validate MMS as a cost-effective approach, particularly for tumors in cosmetically sensitive facial areas, where tissue conservation is crucial. Expanding its applicability, a multi-institutional retrospective study analyzed outcomes in 150 patients with invasive melanoma treated with MMS. The study reported a local recurrence rate under 5% over a five-year follow-up and noted the advantage of tissue conservation in anatomically complex regions, such as head and neck, concluding that MMS represents a valid surgical option for select invasive melanoma cases, further broadening its clinical utility [84]. Collectively, these studies provide high-quality evidence supporting the superior efficacy, safety, patient satisfaction, and cost-effectiveness of Mohs micrographic surgery compared to alternative treatments for nonmelanoma and selected melanoma skin cancers. MMS's precision in margin control not only minimizes recurrences but also preserves healthy tissue, yielding better functional and cosmetic outcomes that improve overall patient care in dermatologic oncology.

2.1.2. Radiotherapy

Radiotherapy remains a vital modality in managing various skin cancers, especially for patients who are not candidates for surgery, or have locally advanced or unresectable tumors, or as an adjunctive treatment following excision to ensure complete tumor clearance [85]. Nowadays, innovative radiotherapeutic techniques are also emerging to provide better outcomes in terms of tumor removal.

Image-Guided Superficial Radiation Therapy (IGSRT) is increasingly recognized as a first-line non-surgical option for NMSC, achieving low recurrence rates with excellent cosmetic outcomes. Updated data from over 3000 lesions treated with IGSRT reaffirmed its efficacy and patient tolerability, highlighting its role particularly for patients who cannot undergo surgery due to comorbidities or lesion location [86].

Diffusing Alpha-Emitter Radiation Therapy (DaRT), a novel

Table 2
Summary of local and systemic conventional therapeutic strategies against skin cancer.

LOCAL THERAPY Subgroup	Therapy Used	Skin cancer type	Outcomes/impact	Citation
Surgery	Mohs micrographic surgery (MMS)	Non-melanoma, selected Melanoma	High cure rates, tissue preservation	[75,76]
		Non-melanoma, Melanoma	Minimized recurrence rates, patient satisfaction	[76]
		Head and Neck Melanoma, LM Melanoma, cSCC	Improved survival, tissue conservation, minimal morbidity	[77]
		cSCC (high risk)	Lower recurrence (1.5% vs 8.7%), better functional outcomes	[78]
		cSCC (high risk)	Fewer complications, improved recurrence rates	[82]
		Facial NMSC	Higher initial cost, overall cost savings via reduced retreatment, QALYs	[83]
		Invasive Melanoma	<5% five-year recurrence, strong tissue conservation in complex regions	[84]
Radiotherapy	Radiotherapy (general)	Skin cancers (NMSC, unresectable)	Improved clearance, advanced techniques enhance removal, function/QOL	[85]
	IGSRT	NMSC	Low recurrence, excellent cosmetics, suitability with comorbidities	[86]
	DaRT (diffusing alpha-emitter therapy)	Recurrent/unresectable skin cancers	100% complete response at 12 weeks, mild side effects (erythema, edema)	[87]
	Rhenium-186 SCT	NMSC (BCC, SCC)	97.2% complete response @ 6 mo, improved QOL, minimal adverse events	[88]
	Radiotherapy + Immunotherapy	cSCC	Enhanced antigen presentation, lymphocyte infiltration (biological evidence)	[89]
	Cemiplimab + hypofractionated RT	Locally advanced cSCC	Well-tolerated, minimal toxicity, improved multimodal outcomes	[90]
	Immuno-RT with cemiplimab (clinical trial)	Stage III/IV cSCC	Investigating survival, morbidity (trial ongoing)	[91]
Topical/Cryo/PDT	Imiquimod, 5-FU	Superficial BCC, AK	Comparable efficacy/safety, good wound healing/ cosmetics	[92]
	Imiquimod vs 5-FU (split-face trial)	Superficial BCC, AK	Comparable efficacy, equal patient preference	[93,94]
	Imiquimod (monotherapy, periocular)	Periocular BCC	High clearance rates, favorable cosmetics	[94]
	Imiquimod 5%	Superficial NMSC	Superior sustained clearance, better cosmetics	[95]
	Cryotherapy + ICI	BCC	Synergistic anti-tumor effect (pre/clinical data)	[96,97]
	Curettage + Cryo (2023)	BCC	Faster, less resource-intensive, effective in BCC	[97]
	Cryo + Topical Imiquimod	BCC	High clinical response rates (combined schedule)	[98]
	Cryotherapy + ICI (Phase II trial)	Metastatic Melanoma resistant to ICI	23.5% ORR (non-abl lesions), safe, modulates immune microenvironment	NCT03949153
	Photodynamic therapy (PDT)	NMSC, BCC, SCC	Effective, non-invasive, tissue sparing	[99]
	Photodynamic therapy (PDT)	NMSC (BCC, SCC)	High remission rates for BCC (~91%)	[100]
	PDT immunomodulation	NMSC	Stimulates immune response (adjunct potential)	[101]
	PDT vs Surgery (RCT)	Superficial BCC	Superior cosmetics, equivalent safety, nodular BCC responds less	[101]

SYSTEMIC THERAPY Subgroup	Therapy Used	Skin cancer type	Key Outcomes/Results	Citation
Chemotherapy	Cytotoxic drugs, platinum agents	Melanoma, NMSC (SCC, MCC)	Limited durable efficacy, resistance in advanced stages	[102,103]
	Platinum agents	Skin cancers	DNA crosslinking, systemic toxicity, resistance issues	[103]
	Chemo + Immuno/nano delivery	Melanoma	Combination regimens: exploring improved outcomes, reduced toxicity	[104]
	Chemo + Immuno/nano delivery	Melanoma	Combination strategies under study	[105]
	Chemo + Immuno/nano delivery	Skin cancers	Improved outcomes with advanced agents	[106]
	Chemotherapy in MCC/NMSC	MCC, NMSC	Tumor shrinkage, short-lived responses, chemo as salvage	[107]
	Chemotherapy in MCC/NMSC	MCC, NMSC	Chemo less favored vs immunotherapy: short-lived response	[108]
	Nanocarriers in chemo	Skin cancers	Drug targeting, lower toxicity, Improved delivery, overcoming resistance	[109]
Immunotherapy	Anti-PD-1 /CTLA-4 ICIs	Melanoma, NMSC	Lasting responses, survival benefit	[110]
	Anti-PD1/ CTLA-4 ICIs	Melanoma, NMSC	Improved outcomes, expanded indications	[111]
	ICIs & targeted therapies	BCC, SCC, MCC	Improved advanced disease outcomes, manageable toxicity	[73]
	ICI + local immunotherapy	Skin cancers	Minimized systemic effects	[112]
	Pembrolizumab, Cemiplimab	NMSC, Melanoma	Durable responses, first-line for advanced NMSC	[113,114]
	Cemiplimab for BCC resistant to HPIs	BCC	Durable responses in resistant cases	[115]
	Hedgehog (Hh) pathway inhibitors (vismodegib, sonidegib)	BCC	Tumor shrinkage, immune infiltration improvements	[116]
	EGFR inhibitors	SCC	Under evaluation, secondary/combinatory role	[117]
	Anti-PD-1/PD-L1 in MCC	MCC	High response rates, lasting remission in MCC	[118]
	ICIs as last-line therapy (registry EOL study)	Advanced melanoma	63% last-line, timing/patient selection impact benefit	[119]
	Neoadjuvant pembrolizumab, systemic ICI	Advanced melanoma	First-line for unresectable/metastatic cases, improved long-term outcomes	[120]
	TIL therapy (FDA-approved)	Advanced melanoma	Newest approval, promising in refractory advanced cases	[121]

brachytherapy delivering highly conformal alpha radiation, was studied in a prospective multicenter pilot involving 10 patients with recurrent or unresectable skin cancers. DaRT demonstrated excellent feasibility and safety, with all patients achieving a complete tumor response at 12 weeks and experiencing only mild, manageable side effects, such as erythema and edema [87]. This targeted approach delivers a potent tumoricidal dose with minimal collateral damage, offering a promising option for heavily pretreated cases that are traditionally difficult to manage.

Another cutting-edge modality, Rhenium-186 skin cancer therapy (SCT), was evaluated in the EPIC-Skin study for NMSC including BCC and SCC, offering an alternative for lesions in locations unsuitable for surgery or conventional external beam radiotherapy. Interim results from 81 patients showed a 97.2% complete response rate at six months post-treatment, along with significant improvements in patient quality of life and minimal adverse events [88].

The integration of immunotherapy with radiotherapy has gained increasing interest, especially in SCC. The synergy between radiotherapy and immunotherapy has a strong biological rationale, supported by both preclinical evidence and clinical observations. Radiation can potentiate the immune response by enhancing the presentation of tumor antigens and promoting lymphocyte infiltration [89]. A 2025 study proposed a therapeutic algorithm incorporating upfront cemiplimab immunotherapy followed by hypofractionated radiotherapy for persistent disease in locally advanced SCC. The combined modality was well tolerated, demonstrating minimal toxicity and suggesting improved outcomes by leveraging the immunomodulatory effects of radiation alongside immune checkpoint inhibition [90]. Furthermore, the ongoing NRG-HN014 phase III trial is evaluating whether adding neoadjuvant immunotherapy with cemiplimab before surgery and adjuvant radiation improves survival outcomes compared to standard surgery and radiation alone in patients with resettable stage III/IV SCC. This trial addresses the challenge of achieving effective tumor control while minimizing morbidity in anatomically complex head and neck regions, reflecting a critical unmet need given the rising incidence of SCC and treatment-related functional impairments [91].

Taken together, these research efforts underscore the evolving role of radiotherapy in skin cancer management, transitioning from a primarily palliative or adjuvant tool to a central component of multimodal curative strategies. Advances in radiation delivery technology and integration with immunotherapy hold promise to improve survival while minimizing toxicity and preserving function and quality of life for diverse patient populations.

2.1.3. *Other local therapies*

Cryotherapy and topical treatments, such as 5-fluorouracil (5-FU) and imiquimod, serve as alternative local therapies. These modalities are particularly beneficial for superficial skin cancers, acting by either directly destroying cancer cells or stimulating an immune response against the tumor [92]. Recent studies show that imiquimod and 5-FU are effective topical treatments for superficial BCC and AK, offering similar efficacy, safety, wound healing, and cosmetic outcomes. A 2025 split-face trial comparing imiquimod 3.75% with 5-FU 4% found comparable results and equal patient preference [93]. Imiquimod 5% was found to be a promising tissue-sparing option for periocular BCC, achieving high clearance rates and favorable cosmetic outcomes, especially when combined with cryotherapy for durable remission up to 5 years [94]. Studies also show that imiquimod monotherapy provides superior sustained clearance and better cosmetic results compared to 5-FU and cryotherapy. Both agents are well tolerated with mild to moderate local side effects and remain widely used as non-invasive therapies for superficial NMSC [95]. Recent original research continues to support the use of cryotherapy and topical immunomodulatory agents as effective local treatments for various skin cancers, particularly BCC and SCC. Studies have shown that cryotherapy not only physically destroys tumors but also stimulates an immune response by releasing tumor antigens that activate both innate and adaptive immunity [122]. This immunostimulatory effect can be enhanced when cryotherapy is combined with immune checkpoint inhibitors (ICIs), creating a synergistic anti-tumor effect. Evidence from preclinical and clinical studies highlights improved tumor-specific T cell activation and systemic immune responses following cryoablation, supporting this combination strategy [96]. Clinical and preclinical data confirm an increase in CD3+ and CD4+ lymphocytes, natural killer cells, and cytotoxic mononuclear cells after cryotherapy, indicating an enhanced cellular immune response [123]. A 2023 study on curettage plus cryosurgery for BCC reported excellent treatment outcomes, emphasizing cryotherapy as a faster and less resource-intensive alternative to surgery, with well-defined protocols showing consistent efficacy. The combination also holds promise for improving systemic responses through enhanced tumor antigen release and immune activation [97].

Additionally, a randomized controlled trial combining cryotherapy with topical imiquimod examined different schedules and revealed that sequential or concurrent application yields high clinical response rates for BCC, supporting combined immunocryosurgery as a promising treatment modality in select superficial tumors [98].

Beyond local tumor ablation, cryotherapy also exerts immunological effects when paired with systemic checkpoint inhibitors [123]. A recent Phase II study investigated image-guided cryoablation combined with continued immune checkpoint inhibition in metastatic melanoma that progressed on ICI therapy. This combination was safe and feasible, resulting in an objective response rate of 23.5% in non-ablated lesions, which suggests that cryotherapy has the potential to modulate the tumor immune microenvironment synergistically with immunotherapy [97]. Complementary to this, a prospective clinical trial combining local cryotherapy with in situ immunotherapy (nivolumab and ipilimumab) in advanced melanoma lymph node metastases indicated feasibility and immune activation, opening avenues for integrated loco-regional and systemic treatments [124].

Additionally, PDT is another local treatment option used to treat skin cancer. This technique relies on the use of photosensitizing agents activated by light to induce cell death selectively within the tumor, characterized by its minimal invasiveness and favorable side effect profile compared to conventional therapies, particularly valuable when surgery is contraindicated or not preferred [99,100]. Recent studies affirm PDT as an effective, non-invasive treatment for NMSC. A 2025 bibliometric analysis highlights PDT's selective tumor destruction and growing clinical use, reporting high remission rates (~91% for BCC) and long-term disease control [125]. Clinical updates from 2023 emphasize PDT's immunomodulatory effects, where PDT-induced tumor damage stimulates local immune responses, making it a promising adjunct to immunotherapies [126]. Additionally, randomized controlled trials confirm PDT's safety and superior cosmetic outcomes compared to surgery for superficial BCC, though nodular subtypes respond less effectively [101]. Collectively, these findings support PDT as a potent, tissue-preserving option with potential immune benefits in skin cancer management.

2.2. *Systemic therapies*

Systemic therapy has become integral in the management of locally advanced, unresectable, or metastatic skin cancers, although indications and standards of care differ substantially among CM, SCC, MCC, and BCC. Current treatment recommendations are guided by disease subtype, stage, molecular profile, and patient-specific factors, as reflected in ESMO and NCCN guidelines.

For most NMSC, including BCC and SCC, surgery with or without radiotherapy remains the standard of care in early-stage disease, whereas systemic therapy is reserved for patients who are not candidates for curative local treatment. In advanced disease, immune checkpoint inhibitors (ICIs) and targeted therapies are preferred over conventional chemotherapy, based on superior efficacy and durability of response

[73,127].

2.2.1. Chemotherapy

The role of chemotherapy in skin cancer has markedly diminished and is now generally limited to selected patients in the palliative or later-line setting, particularly when more effective or guideline-preferred therapies are not available or have failed.

In CM, cytotoxic chemotherapy is not recommended as first-line therapy in current guidelines. It may be considered as a subsequent-line option in patients with unresectable or metastatic disease who have progressed on, or are ineligible for, ICIs and (if BRAF V600–mutant) BRAF/MEK-targeted therapy. Reported responses are typically modest and short-lived, with no clear survival advantage compared with modern systemic therapies [102–106].

In advanced SCC and MCC, chemotherapy was historically used in metastatic disease; however, it is no longer considered a preferred regimen due to limited durability of response. Current guidelines recommend chemotherapy only in selected cases, such as patients who are not eligible for immunotherapy or who have progressed after ICI treatment [107,108].

In advanced BCC, chemotherapy is not included among recommended systemic treatment options.

Overall, chemotherapy is associated with limited durability, cumulative toxicity, and inferior outcomes compared with ICIs, and its use has been largely supplanted by immunotherapy-based strategies.

2.2.2. Immunotherapy

Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 are now cornerstones of systemic therapy, although their use is disease-specific and indication-dependent.

In CM, anti-PD-1–based therapy (nivolumab or pembrolizumab), either alone or in combination with ipilimumab, is recommended as first-line systemic treatment for patients with unresectable stage III or stage IV disease, irrespective of BRAF mutation status. Combination therapy may be considered in appropriate patients based on risk–benefit assessment due to higher toxicity. Additionally, neoadjuvant or adjuvant anti-PD-1 therapy is recommended in selected high-risk resectable disease, according to recent guideline updates [110,111,120,128].

In advanced SCC, PD-1 inhibitors (cemiplimab or pembrolizumab) are recommended systemic therapies for patients with metastatic or locally advanced disease not amenable to curative surgery or radiotherapy, and are generally considered preferred first-line options in this setting.

In Merkel cell carcinoma, ICIs targeting PD-1/PD-L1 (avelumab, pembrolizumab, or nivolumab) are recommended as first-line treatment for advanced disease, based on durable response rates and improved long-term outcomes compared with historical chemotherapy.

In advanced BCC, hedgehog pathway inhibitors (HHIs) (vismodegib or sonidegib) are recommended as first-line systemic therapy for patients with locally advanced or metastatic disease not suitable for surgery or radiotherapy. Cemiplimab (anti–PD-1) is recommended as a subsequent-line option in patients who progress on or are intolerant to HHIs, rather than as initial therapy [114–116,129].

Despite the substantial clinical benefit of ICIs, primary and acquired resistance, immune-related adverse events, and optimal sequencing strategies remain ongoing challenges. Current guideline-based approaches emphasize appropriate patient selection and management of toxicity, while ongoing studies are evaluating combination regimens and biomarker-driven strategies to improve outcomes [130–132].

Emerging therapies, including tumor-infiltrating lymphocyte (TIL) therapy, have demonstrated activity in heavily pretreated advanced melanoma and have recently entered clinical practice in this setting, further expanding treatment options [121,133].

3. Classification of nanotechnological systems in the treatment of skin cancer

The use of nanotechnology as an advanced drug delivery system for skin application has been largely explored over the past decades. As previously described, the presence of physical and immunological barriers in the different skin layers, as well as the limitations of conventional approaches, require advanced technologies for the treatment of skin cancer [134]. Notably, the advantages of nanoparticles in improving drug stability, controlling drug release with targeted action, reducing systemic side effects and increasing cellular uptake, make these systems promising candidates to treat skin pathologies. Moreover, the possibility to engineer nanoparticles' surface or composition promotes the passage through cell membrane and targeting. Then, the ability to deliver different therapeutic agents, such as chemotherapeutics or antioxidants, favors the treatment of NMCS as well as melanoma [135].

Another parameter responsible for cellular uptake mechanisms is the size of the nanosystems. Depending on dimensions, small nanoparticles follow preferably phagocytosis, macropinocytosis, and clathrin- or caveolin-mediated endocytosis pathways, passing the stratum spinosus and reaching the dermis, while large nanoparticles accumulate around hair follicles and pass-through transmembrane penetration, resulting in a different distribution in the tumor site [134,136,137]. Generally, the primary penetration route selected by nanosystems depends on the type of skin cancer to be treated. Small nanoparticles following an intracellular route would benefit melanoma treatment, thus being able to reach the basal layer or systemic circulation. Conversely, larger nanosystems (up to 600 nm) preferentially follow the appendageal route and can be considered for BCC or SCC treatment, creating drug reservoirs in follicle bulge or exploiting the leaky barrier of inflamed skin.

Considering the different site of action, the engineering of nanoparticles becomes crucial in exerting the therapeutic effect on skin surface, in diffusing to the dermis or being retained in tumoral tissue, becoming effective and beneficial for SC, BCC or CM treatment [134,138].

Several nanodelivery systems have been proposed for skin cancer treatment, enhancing the diagnosis and the therapy, in particular for melanoma. However, the difficult translation of the production to clinical use, the lack of regulatory guidelines and safety assurance, make the research in the field still challenging. Overall, these nanosystems can be broadly categorized into platforms that primarily optimize drug delivery, improving pharmacokinetics, skin penetration, and local tolerability of established agents (e.g., lipid-based nanosystems, polymeric nanocarriers), versus those designed to enable novel therapeutic functions such as immunomodulation or gene silencing (e.g., framework nucleic acids-FNA, advanced polymeric systems), thereby modulating the tumor microenvironment or silencing oncogenic pathways. The benefits and drawbacks of four major categories of nanosystems, namely lipid-based, polymeric, framework nucleic acids and microneedles, together with their mechanisms of action, are outlined and explored (Fig. 3).

3.1. Lipid-based nanocarriers

The composition of lipid-based nanosystems plays an important role in the treatment of skin pathologies. The similarity with the lipid matrix of skin layers, in particular *stratum corneum* that represents the first barrier for drug diffusion, makes these nanosystems biocompatible, sustainable and less toxic compared to other categories [139]. Moreover, the increased hydration derived from the occlusion effect of lipid components, or the fluidization of lipid matrix enhance drug absorption and therapeutic effect. These platforms predominantly function as delivery-optimizing systems, enhancing penetration, stability, and local tolerability of conventional agents.

The physical properties and biocompatible composition along with targeted delivery and reduced toxicity, allowed the advancement of

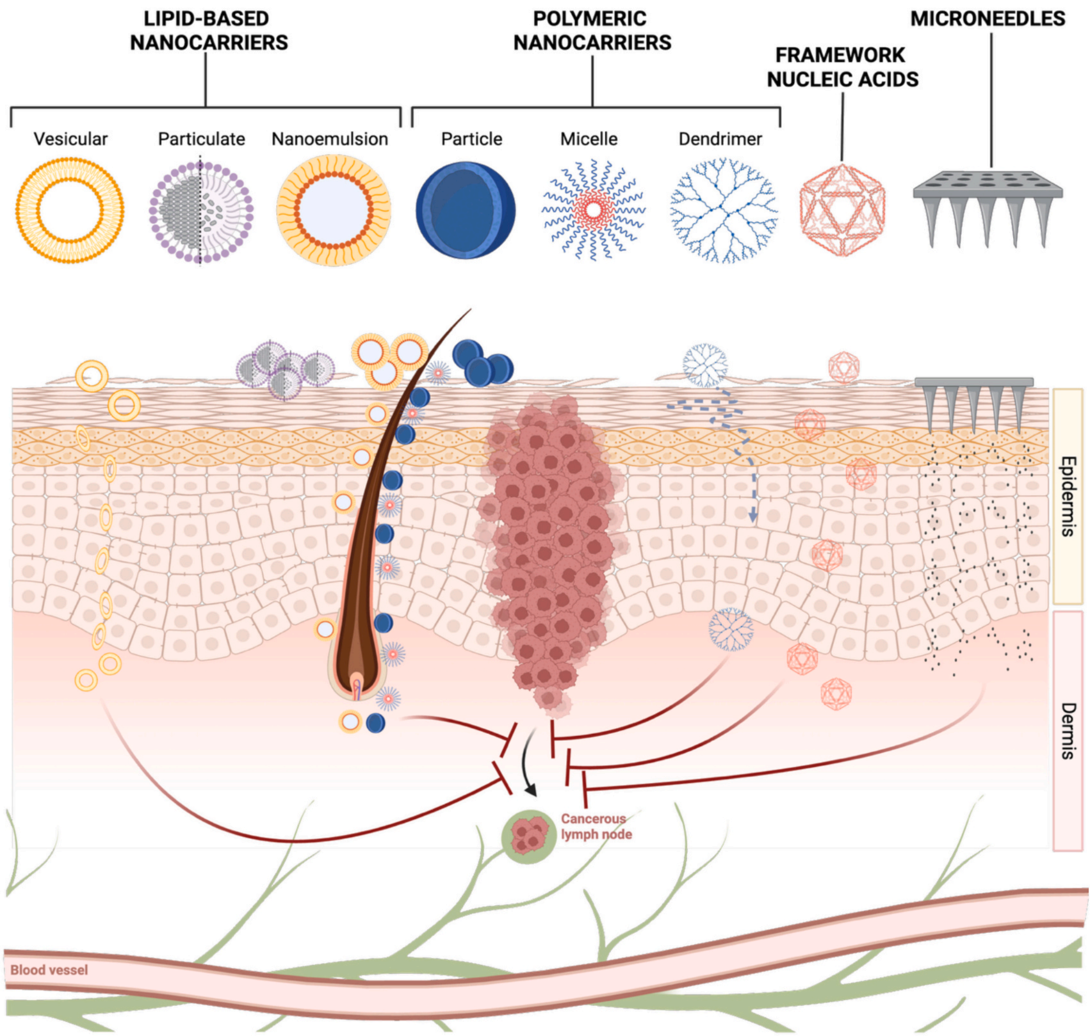

Fig. 3. Schematic representation of the mechanism of action of the different nanosystems described in this review concerning skin cancer. Original figure created with www.BioRender.com (accessed on 27 November 2025).

clinical trials and the evaluation by regulatory agencies, such as European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA), positioning lipid-based nanosystems as promising treatment of melanoma and non-melanoma skin cancer [140].

Nanoemulsions, liposomes and solid lipid nanocarriers (SLN) represent the main types of lipid-based nanosystems, from which different vesicular or particulate systems were developed, namely ethosomes, transfersomes, niosomes and nanostructured lipid carriers (NLC) [140,141].

3.1.1. *Nanoemulsions*

Nanoemulsions are emulsions in nanoscale size ranging from 20 to 200 nm, composed of oil or water droplets suspended in immiscible liquid and stabilized by surfactants [12]. Mainly, two types of nanoemulsion can be produced considering the solubility properties of the entrapped active compound, e.g. hydrophilic or lipophilic. In the case of water-soluble drugs, water-in-oil nanoemulsions (W/O) are used to deliver the active ingredient that is dispersed in the water droplets. Conversely, in the case of oil-in-water nanoemulsions (O/W), the lipophilic drug is located in the oil droplets.

The small size of droplets and the ratio between oil, water, and surfactants are responsible for higher stability and bioavailability with respect to traditional emulsions, allowing enhanced drug penetration and release, greater surface area, and improved kinetic stability. In the context of skin cancer, nanoemulsions can be considered for superficial or deep activity. In fact, the small dimensions enable reaching the deepest layers with a targeted effect, particularly for CM, while the thickening of nanoemulsions with gelling components, generating a viscous formulation, can be considered for the treatment of superficial pathologies, as in the case of SCC [142]. Hence, depending on the size, nanoemulsions diffuse following the trans-follicular route in the case of small dimensions, or deposit on the skin surface and then partially diffuse via hair follicles.

Recent studies have demonstrated the effect of nanoemulsions against melanoma in vitro and in vivo. The increased solubility of norcantharidin in nanoemulsions demonstrated a significant antiproliferative effect against melanoma cells [143]. Similarly, another study reported the effect of nanoemulsion encapsulating *Mentha Pulegium* essential oil in inducing apoptosis in human melanoma cells [144]. Regarding in vivo evidence, loaded nanoemulsions demonstrated enhanced targeting, penetration, and cytotoxic effect of curcumin and piplartine on melanoma using a skin cancer animal model [145,146].

Concerning NMSC management, the administration of 5-FU and tretinoin-containing nanoemulsions in a sprayable formulation led to an effective localized treatment with enhanced skin permeation and patient compliance [147]. A similar result was reported by Musallam and colleagues using a nanoemulsion-foam, demonstrating that the formulation development can ameliorate the management of topical skin cancer [148].

Notwithstanding the considerable benefits of nanoemulsions, their formulation development is presently constrained by a trial-and-error methodology, inadequate regulatory frameworks, and frequently insufficient long-term stability, making the research in nanotechnology ongoing.

3.1.2. Liposomes and vesicles

Liposomes are the most explored formulations for the treatment of skin cancer. First introduced in 1961 by Bangham and came into market in early 1990's [149], they have been continuously investigated and modified leading to upgraded vesicular structures, such as ethosomes, transfersomes and niosomes. Liposomes are vesicular delivery systems formed by amphiphilic molecules that spontaneously organize into a spherical, closed bilayer structure in aqueous solution. The presence of a lipid compartment, made of phospholipids and cholesterol, and an aqueous core, allows the encapsulation of both hydrophilic and hydrophobic compounds. Nonetheless, their therapeutic potential is constrained by several limitations, including the propensity for phospholipid oxidation, the use of organic solvents during formulation, poor storage stability, drug leakage, rapid systemic clearance, and restricted malleability. Consequently, all these drawbacks led to the formulation of new generations of vesicular nanosystems.

Firstly, the addition of ethanol in the composition at high concentration ranging between 20 and 45%, results in the formation of ethosomes. They exhibit greater stability and higher malleability than conventional liposomes. However, their main feature is the ability to overcome skin barrier, in particular *stratum corneum*; ethanol, acting as penetration enhancer, disorganizes and fluidizes the lipid structure of the skin, allowing the efficient delivery of drugs into deeper layers and systemic circulation [150].

The second strategy to increase the transdermal effect of vesicles is the addition of non-ionic surfactants in phospholipid composition, giving the formation of transferosomes, highly elastic vesicles able to pass intact the *stratum corneum* by squeezing through the pores [151]. The non-ionic surfactants, generally polysorbates, act as "edge-activators" responsible for their deformability [152]. Rather, the complete replacement of phospholipids with non-ionic surfactants led to the development of niosomes. These non-ionic surfactant vesicles are more chemically stable, and less toxic compared to liposomes resulting as a promising alternative for controlled release of therapeutic drugs [153].

The role of liposomes in the management of SCC and BCC is mainly related to topical PDT, where they have been shown to be effective in the delivery of chemotherapeutic agents and photosensitizers [154]. For the treatment of NMSC, ethosomes and transferosomes demonstrated higher permeation, targeting effect, and cytotoxic activity against cancer cells, thanks to the ability to overcome the skin barrier [155–157]. Among vesicular nanosystems, niosomes also showed advantages in treating SCC and BCC. For example, their coupling with hyaluronic acid improved targeting to cancer cells, then leading to the accumulation of the loaded 5-fluorouracil in tumor tissue with controlled therapeutic release and reduced systemic toxicity [158].

The most investigated activity of vesicular nanosystems in the field of skin cancer is the treatment of melanoma, and several studies explored liposomes drug delivery. The use of naturally derived compounds encapsulated in liposomes demonstrated the potential of this strategy. Particularly, loaded aloe-emodin showed enhanced photosensitizing effect, apoptosis, and reduced migration of melanoma cells [159]. Similarly, glabridin delivered by a melanocyte-targeted liposomal formulation accumulated in melanocytes and enhanced the lightening effect, demonstrating the effect of the functionalization in selectively targeting the receptor expressed on melanocytes [160]. The encapsulation of natural molecules with anti-melanoma activity was also explored mainly with advanced vesicular nanosystems [161]. The remarkable activity of malleable vesicles, such as ethosomes and transferosomes, in delivering genistein, gossypin, curcumin and quercetin was demonstrated by the skin penetration effect resulting in increased anti-proliferative activity [162–165]. Also, niosomes effectively enhanced dermal deposition of ozonated olive oil, improving cellular uptake, antiproliferative, and pro-apoptotic effects [166].

A different approach demonstrated an innovative use of vesicular nanosystems in counteracting melanoma with a co-delivery of mRNA vaccine and gardiquimod, a TLR7 agonist. The synergistic immunotherapy strategy led to tumoral cells apoptosis with targeted effect and immune activation, stimulating CD8+ T lymphocytes to reorganize the tumor microenvironment [167].

3.1.3. Lipid nanoparticles

Solid lipid nanoparticles (SLN) represent the first generation of lipid-based particulate nanocarriers, differing from vesicular nanosystems for the rigid crystalline lipid structure and the absence of an aqueous core. They are composed of solid lipids that generate a solid core matrix also stabilized by surfactants and co-surfactants, able to encapsulate active compounds [168]. The development of SLN is related to the need of overcoming drawbacks of liposomes and derivatives, such as poor physical stability, use of organic solvents and poor hydrophobic drug loading, while maintaining the biocompatibility, biodegradability and sustained release profile of the formulation.

In view of preventing drug leakage from the solid lipid core, a new generation of lipid-based nanoparticles have been developed, namely nanostructured lipid carriers (NLC). Particularly, the presence of a blend of solid and liquid lipids generally recognized as safe (GRAS) in the composition as well as the presence of structural imperfections, assure an improved drug loading and stability, especially for those anticancer drugs commonly water poor soluble and sensitive to environmental factors.

Along with key advantages described for nanosystems, such as increased drug stability and protection, increased drug loading, sustained drug release and biocompatibility, lipid nanoparticles possess peculiar properties that contribute to the enhancement of targeted delivery. As with nanoemulsions, SLN and NLC application on skin generates increased hydration and permeation, resulting in reduced transepidermal water loss (TEWL) [139,169]. In fact, the occlusive effect derived from the adhesion of nanoparticles onto the skin, reduces water loss and favors diffusion of active compounds through the skin. Additionally, the possibility to deliver chemotherapeutic drugs and phytochemicals in a targeted and sustained release makes lipid nanoparticles a promising drug delivery system for skin cancer treatment [170]. Lastly, the ability of NLC to increase the activity of UV blockers, as with the use of sunscreens, represents an important factor in preventing skin cancer [171].

Considering the beneficial behavior for topical therapy, SLN and NLC were considered for non-melanoma and melanoma treatment. As demonstrated in vitro and in vivo, the controlled and sustained delivery of standard anticancer drugs, such as docetaxel and 5-fluorouracil, governed by lipid nanoparticles allowed to enhance the therapeutic effect and reach deeper tumor cells, minimizing dosage and side effects [172,173]. Similar results were obtained ex-vivo with gelled NLC containing ribociclib, where the increased permeation and retention of the drug allowed to optimize the efficacy of the drug in the treatment of non-melanoma skin cancer [174].

Also, in the case of SLN and NLC, the delivery of natural molecules with anticancer activity were found effective in skin cancer management. Apigenin-loaded SLN coated with hydrogel demonstrated higher in vitro permeation than the non-encapsulated drug, resulting in increased cytotoxicity against melanoma cells [175].

3.2. Polymeric nanocarriers

Polymers can also be used for nanocarrier development, and depending on material, internal structure or form and morphology, different polymeric nanostructures can be classified accordingly. Similarly to lipid-based nanocarriers, these platforms can enhance penetration, stability and tolerability of conventional agents.

Considering the nature of the materials used in the formulation, polymeric nanoparticles can be classified into natural, synthetic, biodegradable or non-biodegradable. In lipid-based nanosystems, the similarity of the components with skin tissue plays a fundamental role in guaranteeing the biocompatibility of the formulation when topically applied. In the case of polymeric nanosystems, it is essential to underline that the polymers replacing the biomimetic material must maintain biocompatibility to reduce the potential toxicity. Natural polymers derived from biological sources and often used are chitosan, alginate, cellulose, or gelatin. Artificially synthesized polymers, such as poly (lactic-*co*-glycolic acid) (PLGA), polycaprolactone (PCL), polylactic acid (PLA), and polyethylene glycol (PEG), are commonly biodegradable. Conversely, the use of non-biodegradable polymers, such as polystyrene or polymethacrylates, is generally limited to diagnostic purposes or long-lasting effects [176].

The internal structure of polymeric nanoparticles is related to the lodgment of the encapsulated drug into the nanoparticle. When the polymer forms a continuous and solid network, the drug is uniformly dispersed into the matrix or adsorbed onto the surface, and the nanoparticle is recognized as nanospheres. On the other hand, when the nanoparticle presents an inner core surrounded by a shell, the system, known as a nanocapsule, acts as a reservoir and the drug, dispersed in the core, even aqueous, is released gradually [177].

Along with the distinction between nanospheres and nanocapsules, other polymeric structures are particularly interesting for drug delivery and skin application. Among them, polymeric micelles, dendrimers and polymeric nanogels possess peculiar advantages. In view of clinical application, the scalability and the higher circulation time of polymeric nanocarriers make them promising candidates for the treatment of skin cancer.

3.2.1. Nanospheres and nanocapsules

In order to obtain a therapeutic effect and reach the desired site of action, polymeric nanoparticles need to cross skin barriers, firstly *stratum corneum*. The primary recognized mechanism of diffusion is the appendageal pathway, principally depending on particle size: smaller particles can accumulate in follicles and then penetrate in deep layers, while larger particles act as reservoir or depot systems. Besides, they can reduce TEWL, promoting drug diffusion, as previously described [178]. Polymeric nanoparticles in the form of nanospheres and nanocapsules are emerging therapeutic systems for the treatment of melanoma, recognized as the most aggressive form of skin cancer. The possibility of encapsulating chemotherapeutic agents as well as phytocompounds was considered to improve drug solubility and effectiveness, overcoming systemic toxicity. For instance, paclitaxel, extensively used as multispectral chemotherapeutic drug, demonstrated higher efficacy in vitro and in vivo when delivered by functionalized PLGA nanospheres [179]. Another strategy involved the encapsulation of propranolol in nanocapsules with off-label treatment: the localized therapy of melanoma, favored by the bioadhesive properties of the polymer selected in the formulation, enhanced drug release and reduced cell migration and viability [180]. Also, phytochemicals showed enhanced antitumoral and antimetastatic effect, as in the case of nanocapsules containing pomegranate oil [181].

The use of polymeric nanoparticles also showed promising results in the management of NMSC, particularly SCC, suggesting their potential as an alternative to surgical intervention. Results obtained in vitro and in vivo demonstrated the tumor targeting and inhibition, acting on PTD or on skin disorders [182,183].

3.2.2. Polymeric micelles

Polymeric micelles are self-aggregate structures with an average diameter comprised between 10 and 200 nm, composed of amphiphilic block copolymers that assemble in water above a critical micelle concentration (CMC) that is generally lower than surfactant micelles [184]. Commonly, the hydrophilic moiety, e.g. polyethylene glycol (PEG) chains, surrounds the hydrophobic core of the structure, where the drug is located, when they are used as encapsulating agents.

Concerning the local treatment, as for nanoparticles, also polymeric micelles follow the appendageal pathway, thanks to the small dimensions that facilitate their accumulation. Another interesting feature of polymeric micelles is their suitability for intravenous administration. The passive accumulation of polymeric micelles in the tumor site, especially when the sizes of the micelles are very small, is particularly indicated for the treatment of melanoma. Then, for SCC and BCC treatment, the topical application is preferable for the ability of polymeric micelles to overcome the skin barrier, minimizing systemic toxic effects while enhancing drug penetration [185]. Finally, the multifunctional use in theragnostic, by combining a therapeutic with an imaging agent, and in immunotherapy, by a co-delivery with siRNA for gene silencing, expands the field of application of polymeric micelles in managing skin cancer.

3.2.3. Dendrimers

Among polymeric nanocarriers, dendrimers are engineered systems composed of a core, an inner shell or branches and an outer shell, characterized by specific functional groups responsible for physicochemical properties [186]. The peculiar architecture of dendrimers, also defined as a branched structure, is spherical or globular, with nanoscale dimensions similar to those of biological macromolecules and monodispersed formulations [187]. The size and charge are the main responsible characteristics for the different pathways of diffusion. Small and neutral dendrimers diffuse through the extracellular route by disturbing lipid components of the *stratum corneum*, while charged dendrimers, interacting with keratin, proceed with transcellular diffusion, acting as penetration enhancers.

In the field of nanomedicine, the ability to modify their size or surface by varying external functional groups, and to encapsulate drugs in the core, provides several benefits compared to conventional therapies for skin cancer treatment [188]. As previously reported for other nanocarriers, also dendrimers are suitable nanosystems to encapsulate chemotherapeutics and phytochemicals in the inner core. The synergistic effect of paclitaxel and curcumin loaded in Polyamidoamine (PAMAM) dendrimers for the treatment of melanoma demonstrated an increased solubility, bioavailability, and activity of the hydrophobic drugs against melanoma cells [189]. PAMAM dendrimers were also effective in the local treatment of BCC.

Ybarra and colleagues observed that the administration of vismodegib via anionic dendrimers enhanced skin penetration, as evaluated by studies on human skin explants, even reaching the dermis [190]. Furthermore, skin penetration was validated thanks to the intrinsic fluorescence of dendrimers, establishing them as promising delivery systems for theragnostics, which integrate the therapeutic activity of the encapsulated drug with the imaging capabilities of the system.

The peculiar tool of chemically modifying external functional groups of dendrimers through PEGylation has emerged as an effective strategy to improve targeting and accumulation in tumors, thereby advancing precision cancer therapy [191].

3.3. Framework nucleic acids

Unlike conventional nanocarriers, Framework Nucleic Acids (FNA) offer a novel approach to melanoma treatment by acting as programmable carrier platforms for delivering drugs and immune adjuvants trans-dermally to tumor tissues. There are many potential uses of FNA to treat melanoma, including transdermal drug delivery, immune adjuvant delivery, and targeted gene therapy.

In the first two cases, FNA can carry chemotherapy drugs, such as doxorubicin, and deliver them directly to the tumor through the skin barrier, bypassing systemic side effects. In addition, FNA can also carry immune stimulants, such as CpG oligodeoxynucleotides, which are incorporated into the framework. These adjuvants trigger dendritic cell maturation and stimulate systemic tumor-specific immune responses. Indeed, their unique size-dependent skin penetration and excellent biocompatibility allow for effective delivery of doxorubicin and CpG oligodeoxynucleotides, which can induce immunogenic cell death and systemic anti-tumor immune responses [192]. Notably, the group of Wiraja proposed the use of tetrahedral FNA designed for CM local therapy loaded with doxorubicin. They found that these constructs enhanced the antitumoral effect of the drug and their topical treatment was able to inhibit the growth of volume and weight of the tumor better than other topical nanosystems containing doxorubicin [193]. Histological analysis of tissue from melanoma-affected mice showed deep skin penetration of FNA into the subcutaneous tumor region with an almost 6-fold increase in doxorubicin accumulation. The high skin penetration and permeation capacity of FNA make them interesting and innovative nanosystems for the topical therapy of CM.

As a third case, by incorporating specific aptamers and small interfering RNAs (siRNAs), FNA can deliver genetic material to block the mutated genes, offering a versatile and potentially less toxic alternative to conventional melanoma treatments. In the study of Xiao and colleagues, FNA were loaded with vemurafenib and connected to a DNA aptamer AS1411 [194]. It was found that the FNA formulation was safe and able to transfer the drug across the skin barrier, penetrating tumor tissue. Moreover, in vivo transdermal delivery of the drug, on the other hand, FNA formulation was able to inhibit the growth of human A375 melanoma, with a stronger inhibitory effect than conventional intravenous administration of vemurafenib, demonstrating the potential therapeutic effect on CM of combined applications of FNA with chemotherapy [194]. Another study reported the complexation of FNA with anti-BRAF siRNA in order to downregulate the BRAF gene, which was found to be involved in many CM. The obtained results demonstrated a more potent activity of the FNA complex in cleaving BRAF mRNA compared to free siBRAF, providing a possible proposal for a combination therapy to achieve gene silencing [195].

Taking into consideration the above-reported results, it emerges that FNA-based therapies express some advantages, such as enhanced skin penetration, improved efficacy, reduced toxicity, and systemic immune response. Indeed, FNA has demonstrated superior skin penetration compared to other nanocarriers, such as liposomes and polymeric nanoparticles, allowing for deeper delivery into tumor tissues [193]. Transdermal delivery via FNAs can minimize systemic side effects by delivering the drug directly to the tumor site, leading to less toxicity in normal tissues and organs [196]. Moreover, FNA-drug formulations have shown enhanced anti-tumor activity in mouse models, with some studies reporting higher drug delivery efficiency and more effective tumor inhibition [194]. Finally, the combined delivery of chemotherapeutics and immune stimulants via FNA can induce immunogenic cell death in tumor cells, exposing tumor antigens and triggering a systemic immune response that can also target distant tumors [197]. This technology holds potential not only for melanoma treatment but also for other skin conditions, including abnormal scarring and atopic dermatitis, and even for other sites like mucosal tissues.

3.4. Microneedles

The use of microneedles (MN) is emerging as a transdermal drug delivery method. Indeed, MN can penetrate the human outermost skin, forming hundreds of reversible microchannels to enhance the drug's penetration and delivery to the diseased sites, thus representing a hybrid platform, capable of both enhancing delivery of conventional agents and enabling the administration of biologics such as vaccines, siRNA, or immune modulators.

In general, MN are composed of micronized needle arrays between 10 and 2000 μm in length and 10 and 50 μm in width, solving the "size-dependent penetration" problem by creating temporary microchannels. Due to their dimensions and shapes, MN can reach the dermis after passing through the cutaneous stratum corneum and epidermis [198]. It must be underlined that MN can be prepared with different materials, methods, and arrangements, giving rise to insoluble, dissolving, coated, hollow, and solid MNs with unique drug release mechanisms. However, each type of MN displays advantages and disadvantages.

Regarding solid MN, the materials used are generally refractory, including silicon, stainless steel, titanium, alumina, and certain polymers. These materials confer ultra-high mechanical strength and physical stability on the system, but also compromise biocompatibility and degradability, and are prone to skin damage. The delivery mechanism of solid MN, known as "poke and patch", is associated with challenges in dose administration control. Therefore, solid MN are preferred for skin pretreatment administration [199].

To overcome these advantages, solid MN were covered at the surface with the drugs in the liquid, allowing the so-called "coat and poke" delivery [200]. However, despite the poor biocompatibility, low drug loading, and easy-to-detach coating solution, this type of MN is currently used to deliver vaccines [201].

On the other hand, the miniature version of the traditional subcutaneous injection, namely hollow MNs, acts with a delivery mechanism called "poke and flow" [202]. Hollow MN are prepared with some inorganic materials, such as metals, silica, or ceramics, and show a higher drug delivery capacity as compared to the previously described MN, allowing continuous drug release and accurate dosing. Thus, hollow MN are used to deliver unstable drugs, including proteins, nucleotides, and vaccines, even if they present some drawbacks, such as complex structures and ease to block [203].

For these reasons, recently dissolved MN have attracted great interest. The materials used for dissolved MNs are biocompatible and biodegradable, such as polysaccharides or water-soluble matrices. Precisely, these MN dissolve into the skin, allowing the release of the encapsulated drug with a delivery mechanism called "poke and release" [204]. Although they are easy to use, they are expensive. Furthermore, their mechanical strength and physical stability are low, and they are prone to residue formation [205,206].

Hydrogel MNs represent the last type of MN; they possess excellent swelling properties and a three-dimensional network structure able to absorb large amounts of liquid, enabling a "poke and swell" release mechanism [207]. Similarly, to dissolved MN, hydrogel MN are highly biocompatible and easy to use, but they do not leave residue after applications. However, their mechanical strength and physical stability are low [205].

Microneedle arrays (MNAs) offer promising advancements for skin cancer by enabling targeted, minimally invasive diagnosis and treatment. They deliver anticancer drugs, vaccines, and therapeutic agents directly to superficial and deeper tumor sites, improving efficacy and reducing side effects from systemic drug exposure. Additionally, MNAs can extract biomarkers for early detection and are being combined with other therapies like immunotherapy, photothermal therapy, and gene therapy for synergistic treatment approaches.

It has been discovered that CM growth can induce a change in the dielectric constant and electrical conductivity in the dermis [208], therefore Caratelli et al. evaluated the possibility of using a piezoelectric MN sensor and, after applying an appropriate low-frequency control voltage to the electrodes, it was possible to apply the MN probe on the skin surface and highlight the signal variation due to the change in dielectric constant and conductivity of the dermis affected by melanoma, compared to normal human skin used as a control. In this way, it is possible to obtain an early diagnosis of melanoma [209].

Concerning the therapeutic use of MN against skin cancer, the main advantage as compared to conventional treatment (such as surgical excision) is the low invasiveness and the reduction of adverse reactions after use [210]. Indeed, MN can penetrate the dermis layer of the skin, achieving a local targeted therapy.

To this aim, it was interesting that the evaluation of hyperycin release from hollow MN combined with PTD aimed to reduce the invasiveness of NMSC [211]. On the other hand, the in vitro comparison of imiquimod efficacy delivered by MN and a commercial product has been evaluated by Sabri and colleagues, finding a comparable intradermal penetration [212].

Another study demonstrated that a core-shell MN drug delivery system can achieve targeted co-delivery of inhibitors to melanoma, preventing systemic exposure, and at the same time demonstrating high transdermal delivery and improved antitumor efficacy compared to intratumoral injection [213]. On the other hand, Chen and colleagues showed that the intralesional co-delivery of a photosensitizer and indoleamine 2,3-dioxygenase blockade allowed the in vivo eradication of 80% of the melanoma tumor and subsequent long period of relapse-free survival, suggesting the inhibition of metastasis [214].

The possibility of using coated MN to deliver macromolecular siRNA as a topical anti–melanoma treatment on mice was investigated by Ruan et al., finding that the coated MNs significantly inhibited the tumor growth and induced the tumor cells apoptosis. In addition, a significant in vivo silencing and downregulation of the BRAF gene and protein in the tumor occurred [215]. Moreover, the use of hollow MN to deliver drugs combined to the administration of immune stimulants to treat melanoma showed interesting anti-tumor activity. Indeed, this combination and the employment of cold atmospheric plasma-mediated immune checkpoint blockade therapy allowed a facilitated transport within the skin, accelerating the melanoma cells death [216]. The use of MN for the release of antitumoral compounds proposed by the groups of Boone and Lopez-Ramirez allowed a significant increase in the immunological response in melanoma mouse models, prolonging the survival of tumor-bearing mice [217,218].

Also, cryomicroneedles (cMNs) can be mentioned as suitable systems for the release of active molecules, especially of biological origin, since they guarantee the maintenance of low temperature during administration. Regarding the treatment of CM, Chang et al. proposed the loading of cMNs with an immune cell, allowing the easy cutaneous penetration, the drug release at the tumor site, and demonstrating a higher inhibitory effect on CM as compared to conventional injections [219].

Currently, several types of MN have been studied and proposed for drug delivery, and their obtaining techniques are continuously improving. For instance, 3D printing technology is being increasingly applied to the preparation of MN, enabling their customization. The use of MN for drug delivery has demonstrated interesting potential in the treatment of malignant melanoma, both in monotherapy and combination therapy regimens.

Nanotechnology-based drug delivery systems represent a promising innovation in therapy for skin cancer. The different categories, each with distinct characteristics outlined in Table 3, enhance drug solubility, tumor targeting, and bioavailability while minimizing systemic toxicity, holding potential to revitalize the role of chemotherapy within multimodal treatment strategies [109].

Table 3
Classification and main therapeutic characteristics of nanosystems proposed for skin cancer treatment.

Type of Nanocarrier	Skin Cancer Type	Mechanism of Diffusion through the Skin	Mechanism of Targeting	Type of Loaded Agent	Primary Function	Citations
Lipid-based Nanocarriers Nano emulsions	CM, SCC	*trans*-Follicular route (small particles); Deposition and partial diffusion through follicles (large particles)	Passive targeting (size-dependent)	Chemotherapeutics (e.g., Norcantharidin, Curcumin, 5-FU, Tretinoin); Phytochemicals (essential oils)	**Delivery optimization** (enhanced solubility, penetration, tolerability)	[142–148]
Liposomes and Vesicles	CM, SCC, BCC	Penetration enhancer (ethosomes) Squeeze through the pores (transferosomes) Lipid fluidization (liposomes and niosomes)	Passive + ligand-mediated (e.g., HA targeting)	Chemotherapeutics; Phytochemicals (e.g., Aloe-emodin, Glabridin); Photosensitizers	**Delivery optimization** (penetration, controlled release, reduced toxicity)	[150–160]
SLN and NLC	CM, SCC	Occlusive effect, ↑ hydration, ↓ TEWL	Passive targeting	Chemotherapeutics (Docetaxel, 5-FU) Phytochemicals (Apigenin) Photosensitizers (Sunscreen agents)	**Delivery optimization** (controlled release, stability, reduced irritation)	[170–175]
Polymeric Nanocarriers Nanospheres/ Nanocapsules	CM, SCC	*trans*-Follicular route (small particles) Deposition and partial diffusion through follicles (large particles) Reduced TEWL	Passive targeting	Chemotherapeutics (Paclitaxel, Propranolol) Phytochemicals (Pomegranate oil)	**Delivery optimization** (local retention, reduced systemic toxicity)	[179–181]
Polymeric Micelles	CM, SCC, BCC	Trans-follicular route; EPR effect (intravenous administration)	Passive + functionalization	Chemotherapeutics siRNA Therapeutic agents and Imaging agents (Theranostics)	**Mixed** (delivery optimization + emerging gene delivery)	[185,220,221]
Dendrimers	CM, BCC	Extracellular diffusion (small and neutral) Transcellular (charged)	Surface-functionalized targeting	Chemotherapeutics (Paclitaxel, Vismodegib) Phytochemicals (Curcumin)	**Mixed** (delivery optimization + targeted/functional delivery)	[190,191]
Framework Nucleic Acids (FNA)	CM	Size-dependent transdermal delivery Gene silencing	Aptamer-mediated targeting, gene-level interaction	Chemotherapeutics (Doxorubicin, Vemurafenib) siRNA Immune stimulants (CpG oligodeoxynucleotides)	**Mechanism-enabling** (immunomodulation, gene silencing)	[192–195,197]
Microneedles (MN)	CM, SCC, BCC	Mechanical penetration through epidermis and stratum corneum, reaching dermis	Local delivery to dermis/ tumor	Chemotherapeutics Photosensitizers siRNA Immune stimulants	**Hybrid** (delivery optimization + mechanism-enabling)	[198–216,219]

3.5. *Critical synthesis and evidence tiering of dermatological delivery platforms*

In order to evaluate the current translational status of major nanotechnological and physical delivery platforms in dermatology, the considered technologies have been categorized into a four-tier evidence structure, allowing the separation of experimental "proof-of-concept" data from "clinically actionable" findings. Specifically, four levels can be individuated, namely Guideline-supported / FDA-approved (Tier 1) which considers routine clinical use with proven safety and efficacy; Randomized controlled clinical trials (RCTs) (Tier 2), which consider high-level human data supporting specific indications; Early human feasibility (Tier 3), which therefore includes pilot studies or Phase I/II studies demonstrating basic safety and efficacy in humans and Preclinical / Proof of concept (Tier 4) with data limited to in vitro (cell culture) or in vivo (animal) models.

In Table 4 the comparative evidence tiering is reported from which it emerges that the transition from Tier 4 (Preclinical) to Tier 2/1 (Actionable) is most successful when the technology addresses a specific physical barrier (Microneedles) or a formulation stability issue (Nanoemulsions). Modalities like FNAs and Dendrimers remain highly sophisticated in "proof-of-concept" stages but lack the longitudinal human safety data required for clinical adoption.

4. Nanosystems functionalization for skin cancer targeting

The above-mentioned advantages in the use of nanotechnological systems for skin cancer treatment with respect to conventional therapy, shed light on one of the major challenging aspects, that is the targeting effect characterized by simpler cell membrane passage, receptor-mediated interaction and higher cellular uptake. Besides the possibility of loading and carrying different therapeutic agents in the nanosystem's matrix, their engineering and surface decoration can promote the specific targeting.

The peculiar physical characteristic of the described nanosystems, i. e. the small nanometric size, contributes to reach and accumulate to the target site. In fact, the primary mechanism is the passive targeting governed by the appropriate dimensions of nanosystems. This aspect is defined Enhanced Permeability and Retention (EPR) effect, and it is responsible for the accumulation of nanostructures in cancer tissue, also favored by the tumor microenvironment, that is commonly characterized by hypoxia, acidosis, irregular vasculature and defective lymphatic drainage [222]. Small particles, generally ranging between 10 and 200 nm, can escape the permeable vessels, penetrate and be retained in the tumor site, release the active drug and increase the local drug concentration and the therapeutic effect with lower toxicity. Hence, the optimization of physical properties of nanosystems, such as size and surface charge, results in higher delivery effectiveness [223].

Another approach to increase tumor targeting is the combination of EPR effect with the decoration of nanocarriers surface with specific ligands able to promote the so-called active targeting or receptor-mediated targeting. The presence of antibodies, peptides or polymers with high affinity to specific receptors overexpressed in tumoral cells increases the interaction promoting the binding and retention in the desired site of action. This approach ensures the selective binding of the nanocarrier with tumoral cells, allowing the release of the loaded agent in high dose via receptor-mediated endocytosis. Additionally, the direct activity to the tumoral environment consequently reduces the systemic toxicity or undesired effects on healthy tissues. Lastly, the active targeting can favor the transdermal delivery of the delivery system after topical application, ultimately reaching the deepest skin layers.

Specific receptors can be considered for targeting melanoma and non-melanoma skin cancer. The main overexpressed or dysregulated receptors for ligand targeting in melanoma are melanocortin-1 receptor (MC1R), integrins (αvβ3), programmed death-ligand 1 (PD-L1) and epidermal growth factor receptor (EGFR). They are involved in multiple pathways that contribute to tumor progression. Particularly, MC1R is responsible for melanin production, and is involved in pigmentation and melanoma progression [224], thus it represents an investigated target for therapeutics. Barkey and colleagues [221] synthesized different α-melanocyte-stimulating hormone (α-MSH) analogues to increase the binding affinity with the MC1R receptor. The promising peptides were used to functionalize triblock polymeric micelles demonstrating higher specificity to melanoma cells and stability in vitro [221]. Concerning lipid-based nanosystems, liposomes containing camptothecin were also functionalized with α-MSH to target melanoma cells [225]. As a result, the loaded chemotherapeutic agent exerted a higher cytotoxic effect, and cellular internalization was achieved thanks to receptor-mediating binding.

Afterwards, upregulation of integrins in melanoma promotes invasion and metastasis, becoming another promising target for anti-metastatic drugs [226]. In vitro and in vivo findings demonstrated that the use of functionalized cationic liposomes with cyclic RGD peptide (Arg-Gly-Asp) on the surface efficiently delivered anti-STAT3

Table 4
Comparative evidence tiering table.

Type of Nanocarrier	Evidence Tier	Status	Primary Proof-of-Concept (Preclinical)	Clinical Actionability (Current)
Lipid-based Nanocarriers Nanoemulsions	Tier 2	Randomized Data	enhanced solubility of hydrophobic drugs in animal models	improved bioavailability for topical steroids and retinoids; widely used in OTC cosmeceuticals
Lipid-based Nanocarriers Liposomes	Tier 1/2	Guideline/RCT	targeted delivery to the hair follicle in porcine skin	standardized for stabilization of Vitamin C/E; localized anesthetic (Lidocaine) delivery
Lipid-based Nanocarriers Vesicles (ethosomes / transfersomes)	Tier 3	Early Human	delivery of insulin or large proteins through intact mouse skin	pilot studies for transdermal NSAIDs and deep-tissue anti-inflammatories
Lipid-based Nanocarriers SLN and NLC	Tier 3	Early Human	in vitro extended drug release profiles (up to 72 h)	occlusive moisturizing effects; UV filter stabilization in sunscreens
Polymeric Particles (micelles, dendrimers, particles)	Tier 3/4	Preclinical/ Pilot	stimuli-responsive "smart" release (e.g. pH-triggered release in acne)	targeted acne treatments (e.g. benzoyl peroxide/retinoids) to reduce irritation
FNA (DNA Nanostructures)	Tier 4	Preclinical Only	siRNA delivery to silence pro-inflammatory cytokines in psoriasis models	None currently actionable; high potential for future precision gene therapy
Microneedles	Tier 1/2	Guideline/RCT	painless delivery of high-molecular-weight vaccines	cosmetic skin resurfacing (solid MN); vaccine delivery and lidocaine patches (dissolving/coated)

siRNA, resulting as a promising strategy for melanoma treatment with gene therapy [227]. Receptor-mediated endocytosis led to higher cellular uptake, and consequently effective gene silencing and high cytotoxicity and apoptosis. The same evidence was confirmed in B16F10 melanoma xenograft tumor-bearing mice, where imaging techniques demonstrated accumulation in tumor site and growth inhibition.

Furthermore, PD-L1 is involved in cancer immunotherapy, being expressed on T cells' surface, and its overexpression causes tumor growth and immune evasion [228]. Seung-Hwan and colleagues considered this receptor to enhance cancer immunotherapy for melanoma via dissolvable self-locking microneedle patches co-loaded with two immunomodulators, namely anti-PD-L1 antibody (aPD-L1 Ab) and a TGF-β inhibitor [229]. The microneedle patches demonstrated a synergistic anti-cancer activity and activation of cytotoxic T cells in melanoma mouse models, shedding light to this innovative localized nanotechnological treatment with respect to conventional intratumoral injections [229].

Overexpression of EGFR promotes tumor growth and development [230], and it is also recognized in the case of non-melanoma skin cancer, mainly in SCC, representing a promising target for nanotherapy.

In a recent study, affibodies, a class of small high-affinity proteins with nonimmunogenic properties, were selected to produce polymeric nanoparticles with a conjugated cytotoxic agent, in order to target EGFR overexpressed in epidermal SCC [231]. In vitro and in vivo experiments demonstrated high cytotoxicity and tumor growth inhibition. Moreover, the combined small dimensions and affinity for the receptor guaranteed a precision nanotechnological therapy.

The characteristics of the tumor microenvironment suggest an interesting interaction platform with nanosystems to increase targeting and therapeutic action. This strategy, known as stimuli-responsive targeting, involves the release of the encapsulated active ingredient and acts on the variation of pH, temperature or oxidative balance when the nanocarrier reaches the target site. For example, pH-sensitive or temperature-sensitive liposomes containing cytotoxic agents demonstrated stability at physiological conditions, while increasing intracellular drug release within acidic endosomal compartments or when externally stimulated, i.e., by localized heating [232]. Also in this case, merging the presence of specific ligands on stimuli-responsive nanocarriers could represent a promising strategy to maximize the active targeting on cancer site.

5. Clinical trials and key barriers to clinical application of nanosystems for skin cancer treatment

As clearly evidenced in this review, nanocarrier technologies have gained increasing attention in dermatologic oncology for their ability to improve drug solubility, enhance intratumoral penetration, and reduce systemic toxicity. Clinically validated examples include both systemic nanomedicines, such as albumin-bound paclitaxel nanoparticles (nab-paclitaxel) and PEGylated liposomal anthracyclines, as well as topical nanosystems designed to overcome the formidable barrier properties of the stratum corneum.

Among systemic formulations, nab-paclitaxel represents one of the earliest nanocarrier platforms tested in metastatic melanoma. By binding paclitaxel to albumin nanoparticles, tumor deposition was enhanced. Phase II studies demonstrated objective response rates of 22% in chemotherapy-naïve patients and 3% in previously treated cohorts, with median progression-free survival of 3.5–4.5 months, though efficacy remains modest compared to modern immunotherapies [233,234]. Similarly, PEGylated liposomal doxorubicin (PLD) has been evaluated in cutaneous T-cell lymphoma and is well established in AIDS-related Kaposi sarcoma [235]. In advanced T-cell lymphoma, PLD has achieved overall response rates exceeding 80% in phase II trials with reduced cardiotoxicity relative to free doxorubicin [236]. For Kaposi sarcoma, multiple randomized trials comparing PLD to a system doxorubicin–bleomycin–vincristine or bleomycin–vincristine have demonstrated superior response rates, improved symptomatic control, and a more favorable safety profile, cementing PLD as a standard regimen in this setting [235,237].

Summarizing, nab-paclitaxel has demonstrated modest activity in melanoma, primarily improving drug solubility and tolerability rather than producing major survival gains, while PLD has achieved high response rates in T-cell lymphomas and remains a standard therapy for Kaposi sarcoma due to superior efficacy and reduced cardiotoxicity compared with older anthracycline regimens.

Parallel to systemic approaches, topical nanocarrier systems have emerged as promising non-invasive therapies for early-stage keratinocyte cancers and their precursors. Nanostructured 5-FU systems, including nano-emulsions, liposomes, and ethosomes, have reached pilot clinical evaluation for actinic keratosis and superficial basal cell carcinoma [238,239].

Clinical investigation has also advanced nanotechnology-enhanced PDT. Liposomal and nano-dispersed 5-aminolevulinic acid (ALA) have been evaluated in phase I/II trials for AK and superficial BCC, yielding increased intralesional protoporphyrin IX accumulation, shorter incubation times, and in some studies improved complete response rates relative to standard ALA or methyl-ALA creams [240,241]. Additionally, SLN and NLC have been tested for chemoprevention in photo-damaged skin, showing enhanced delivery of retinoids and antioxidants with reduced irritation, though tumor-specific outcomes remain preliminary [242,243]. Emerging approaches, including nanoparticle-assisted imiquimod delivery and nanoparticle-facilitated laser or microneedle penetration, have demonstrated feasibility in early human studies for superficial BCC and even melanoma in situ, but remain in early development [244,245].

Clinical experience so far suggests that most cancer nanocarriers are “safe enough” when used correctly, but each platform comes with its own pattern of toxicity, biodegradability, and immunogenicity. Precisely, from the clinical data we have, nanocarriers in skin oncology mostly improve the safety of old drugs rather than introduce new, severe toxicities, with some notable caveats around PEG immunogenicity and dose-dependent local reactions. The “safest” platforms so far are biodegradable protein and lipid carriers used either systemically (i.e. PLD, nab-paclitaxel) or topically (i.e. BF-200 ALA nanoemulsion), while non-degradable components such as PEG require active immunogenicity monitoring as they move into broader use and higher cumulative exposures. Therefore, despite the encouraging clinical signals, translation of both systemic and topical nanocarriers into widespread dermatologic oncology practice continues to be limited by significant challenges, as summarized in Table 5**.**

Challenges include large-scale manufacturing, batch-to-batch reproducibility, and the high costs associated with GMP production of multicomponent nanosystems and low process yields-further restrict commercial viability, especially in skin cancers where low-cost treatments already exist. Moreover, long-term safety concerns persist, as the biodistribution, degradation products, and potential immunogenicity of nanoscale materials remain incompletely characterized. These scientific and logistical barriers are compounded by regulatory uncertainty, with

Table 5
Principal barriers to clinical application of nanocarriers for skin cancer.

Barrier	Reasons of importance	Practical impact
Large-scale manufacturing	Complex, multicomponent systems difficult to scale	Slow commercialization Cost increase
Reproducibility	Slight variations → big biological effects	Regulatory rejection Inconsistent efficacy
Cost	Specialized materials and GMP processes expensive	Limited adoption Reduction of investment
Long-term safety	Unknown chronic toxicity or accumulation	Requirement of extended trials Regulatory caution
Regulatory hurdles	No clear pathways, complex characterization	Delayed approval Uncertainty

agencies requiring extensive physicochemical characterization and long-term toxicology data but lacking standardized frameworks for evaluating nanomedicine equivalence and quality. Together, the clinical evidence suggests that nanocarriers, systemic and topical, can enhance drug delivery, improve tolerability, and offer non-invasive alternatives for selected skin cancers. However, only a small number of nanocarrier formulations have progressed from promising preclinical results to successful clinical adoption in skin cancer care, highlighting the need for improved manufacturing processes, safety, and regulatory hurdles, as well as the completion of larger, well-controlled trials to fully realize the potential of nanomedicine in dermatologic oncology.

To translate these concepts into practical recommendations, a structured "Regulatory and Chemistry, Manufacturing, and Controls (CMC) Checklist" has been developed. This analysis translates the theoretical advantages of nanosystems into the practical data packages required by agencies, such as the FDA and EMA. This list can be summarized in three fundamental points, namely 1) Minimum Characterization Package, 2) Long-Term Safety of topical and systemic platforms and 3) Strategies to Reduce Regulatory Friction.

Regarding point 1 (Minimum Characterization Package), prior to clinical use, a "gold standard" characterization suite must be established to ensure batch-to-batch reproducibility. These include: Size and morphology, which can be assessed using dynamic light scattering (DLS) and cryo-TEM or SEM; Surface charge (zeta potential), which is essential for predicting colloidal stability and potential interaction with biological membranes or serum proteins; Polydispersity index (PdI) to ensure a uniform pharmacokinetic profile; Drug loading and encapsulation efficiency; In vitro release testing using USP equipment or accepted methods such as dialysis to determine the release mechanism at physiological pH or in acidic tumor microenvironments; and Purity, contaminants, residual solvents, and sterility levels, which must comply with internationally accepted guidelines.

Concerning point 2 (Long-term safety), safety challenges vary significantly depending on how the drug reaches the tumor. For example, in the case of nanotechnology formulations for topical application (e.g., nano-ALA, 5-FU ethosomes), systemic bioavailability must be considered, i.e., assessing whether the carrier facilitates inadvertent systemic "leakage" of the drug through the stratum corneum into the bloodstream. Another important parameter is skin sensitization, which requires long-term studies with repeated doses to assess type IV hypersensitivity or chronic follicular accumulation. The fate of the carrier is also an important parameter to consider. Indeed, when using non-biodegradable lipids or polymers, it is necessary to assess whether the carrier remains in the epidermis or is eliminated by the lymphatic system.

However, when considering systemic nanosystems (e.g., NAB-paclitaxel, PLD), the so-called "ABC" (Accelerated Blood Clearance) phenomenon must first be assessed. For example, accelerated blood clearance caused by anti-PEG antibodies can reduce the half-life of subsequent doses. Another phenomenon to consider is off-target accumulation, which is the quantification of uptake by the "mononuclear phagocytic system" (MPS), specifically, how much of the dose ends up in the liver and spleen versus the skin tumor. Finally, infusion reactions must be assessed by monitoring for Complement Activation-Related Pseudo-allergy (CARPA), a common problem with lipid-based nanoparticles.

Finally, for point 3 (Strategies to reduce regulatory frictions), it should be kept in mind that regulatory bodies favor simplicity over complexity, so designing with the result in mind can save clinical delays. For example, using fats, oils, or polymers already listed in the FDA database of inactive ingredients avoids the need for new and in-depth toxicological qualifications. Furthermore, using enzymatically degradable esters or bonds (e.g., PLGA or albumin) ensures that the body can eliminate the "structure" after the active ingredient is released. Favoring "one-pot" synthesis or microfluidic mixing over complex multi-step chemical conjugations also facilitates technology transfer to GMP facilities. Furthermore, considering previous systems can facilitate this process; indeed, liposomes and nanoparticle albumin-bound (NAB) platforms have established regulatory "roadmaps" compared to novel carbon nanotubes or metallic clusters.

6. Conclusion

Skin cancer is a growing concern due to its rising incidence rates, thus requiring the need for rapid and accurate diagnostic and therapeutic techniques. In this view, the management of skin cancer with a multifaceted approach integrating established local and systemic therapies with next-generation nanotechnologies could be interesting to overcome the limitations of conventional treatments. Notwithstanding, surgical excision and radiotherapy remain indispensable for early-stage non-melanoma and chemotherapy and immunotherapy have revolutionized outcomes in advanced disease, the systemic toxicity, drug resistance, and insufficient tumor targeting are still critical challenges. The integration of nanotechnology and oncology allows the improvement and accuracy of the diagnostic approach but also the advancement of therapeutic strategies. In summary, the use of nanodelivery systems, including lipid-based carriers (either vesicles or particles), polymeric nanoparticles framework nucleic acids, and microneedle arrays, offers tailored solutions by enhancing drug solubility, stabilizing labile agents, controlling release kinetics, and enabling targeted skin and tumor penetration.

Overall, these nanotechnologies have demonstrated superior biocompatibility to conventional therapies, improved pharmacokinetics, improved dermal permeability, and increased therapeutic efficacy in preclinical and early clinical studies.

However, despite the generally favorable safety outcomes, translational challenges remain substantial due to many barriers, such as batch-to-batch reproducibility, large-scale GMP manufacturing, high production cost and complex regulatory evaluation. Therefore, topical nanocarriers still remain at an investigational level. Continued progress and future efforts should focus on the convergence of nanocarrier engineering with precision medicine, through theragnostic platforms, stimuli-sensing intelligent systems, and combination regimens integrating immunotherapy and photodynamic therapy, promises to transform skin cancer treatment paradigms, offering personalized, site-specific interventions that maximize tumor control while minimizing side effects.

Acronyms list

8-oxoGua	8-oxo-7,8-dihydroguanine
AK	Actinic Keratosis
BCC	Basal Cell Carcinoma
CM	Cutaneous Melanoma
CPDs	Cyclobutane Pyrimidine Dimers
DaRT	Diffusing alpha-emitters radiation therapy
EGFR	Epidermal Growth Factor Receptor
EPR	Enhanced Permeability and Retention
FNA	Framework Nucleic Acids
GLI1/2/3	Glioma-Associated Oncogene Homologs 1/2/3
Hh	Hedgehog
HPIs	Hedgehog pathway inhibitors
HRAS	Harvey Rat Sarcoma Viral Oncogene Homolog
ICIs	Immune checkpoint inhibitors
IGSRT	Image-guided superficial radiation therapy
KIT	KIT Proto-Oncogene, Receptor Tyrosine Kinase
MC1R	Melanocortin-1 Receptor
MCC	Merkel Cell Carcinoma
MAPK	Mitogen-Activated Protein Kinase
MITF	Microphthalmia-Associated Transcription Factor
MM	Maligna Melanoma (Superficial Spreading Melanoma)
MMPs	Matrix Metalloproteinases
MNs	Microneedles
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NF1	Neurofibromin 1

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N-MYC	N-Myc Proto-Oncogene Protein
NLC	Nanostructured Lipid Carriers
NMSC	Non-Melanoma Skin Cancer
NRAS	Neuroblastoma Rat Sarcoma Viral Oncogene Homolog
NOTCH1	Neurogenic locus notch homolog protein 1
PD-1	Programmed cell death protein 1
PD-L1	Programmed Death-Ligand 1
PDT	Photodynamic Therapy
POMC	Proopiomelanocortin
PTCH1	Patched 1 (Hedgehog receptor gene)
PTCH2	Patched 2 (Hedgehog receptor gene)
RAC1	Ras-Related C3 Botulinum Toxin Substrate 1
ROS	Reactive Oxygen Species
SCC	Squamous Cell Carcinoma
SEC	Size-Exclusion Chromatography
SLN	Solid Lipid Nanoparticles
SMO	Smoothened
TEWL	Transepidermal Water Loss
TIL	Tumor-infiltrating lymphocyte (therapy)
TLR-4	Toll-Like Receptor 4
TP53	Tumor Protein p53
UVR	Ultraviolet radiation
VDR	Vitamin D Receptor

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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