Neoplasma 2024; 71(2): 153–163

doi:10.4149/neo_2024_240315N118

Nanocomposite hydrogels in skin cancer medicine

Review

Lucia BALINTOVA*, Michaela BLAZICKOVA, Monika SRAMKOVA

Department of Nanobiology, Cancer Research Institute, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia

**Correspondence: lucia.balintova@savba.sk*

Received March 15, 2024 / Accepted April 20, 2024

Skin cancer is one of the most common malignancies in white populations. The therapy strategy is important in skin cancer treatment, depending on several criteria such as stage, size, and localization. Removal of cancerous tissue following anticancer therapeutic administration is considered as gold standard in skin cancer treatment. However, annually rising drug resistance, local inflammation, and ineffective treatment result in a reduction in the effectiveness of the patient's treatment. Nanotechnology has emerged as a prospective in the field of skin cancer medicine, offering innovative, promising solutions for therapeutic procedures and targeted drug delivery. Different nanomaterials are investigated for their potential in skin cancer treatment. Nanohydrogels as a hybrid material, have gained considerable attention due to their unique biomedical and pharmaceutical properties, such as biocompatibility, high water content, and tunable physicochemical characteristics. The principal problem with common skin melanoma chemotherapy is the strong side effects because therapeutics used for treatment do not distinguish cancer cells from healthy cells. Nanohydrogels, as a new-generation, versatile system with the possession of dual characteristics of hydrogels and nanoparticles have shown great potential in targeted delivery in cancer therapy thanks to the possibility of their various modifications, and by that overcome problems with side effects of treatment. This scientific review provides an analysis of the current state of research on nanohydrogels in skin cancer medicine, highlighting their design principles, synthesis methods, and applications in drug delivery, imaging, and combination therapies.

Key words: nanotechnology; nanocomposites; cancer; skin melanoma

Cancer continues to pose a significant global health challenge, requiring the advancement in therapeutic approaches. Specifically, skin cancer stands out as a frequently diagnosed cancer type in both developed and developing nations. Skin melanoma is the 17th most common cancer worldwide. It is estimated, that 97,610 new melanoma cases were diagnosed in 2023 [1]. Skin cancer is categorized into three main types: melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). BCC and SCC are commonly grouped under the term non-melanoma skin cancer (NMSC). NMSCs, predominantly BCC and SCC, are typically less aggressive and can often be effectively treated with surgery, thus they are not usually included in most cancer registries globally. On the other hand, melanoma represents the most lethal form of skin cancer, requiring prompt and comprehensive medical attention [2, 3]. Various risk factors contribute to its rising incidence and prevalence, such as high UV light exposure in occupational and recreational activities, aging populations, exposure to specific chemicals and smoking [4].

Cutaneous malignant melanoma is experiencing a rapid rise, particularly in white populations. The incidence of this cancer is closely linked to the skin color and varies depending on geographical location. Australia has reported the highest rates, with nearly 20,000 new cases in 2022 [5]. Melanoma mortality rates have stabilized in the USA and European countries. Epidemiological studies present the notion that a significant part of melanoma cases is attributed to excessive sunlight exposure. In contrast with non-melanoma skin cancer, melanoma risk appears to be linked to discontinuous

rather than cumulative sunlight exposure. While standard cancer treatment methods include surgery, chemotherapy, and radiotherapy, challenges like drug resistance in chemotherapy, systemic side effects, and elevated toxicity, represent huge obstacles to effective cancer management. Consequently, early detection and prevention are necessary for successful treatment [6].

Nanotechnology has demonstrated exceptional potential to enhance the efficacy and safety of cancer treatment. Diverse applications of hybrid nanohydrogel find their use in drug delivery, tissue engineering, implantable devices, and biosensors [7]. Particularly in cancer therapy, where nowadays conventional chemotherapy lacks specificity and often leads to negative adverse effects due to the inability to distinguish between normal and cancerous tissues, nanohydrogels play an important role [8]. Nanohydrogels are three-dimensional colloidal systems composed of hydrophilic polymer networks in combination with nanoparticles (NPs) with the ability to encapsulate a variety of drugs, capable of absorbing high amounts of water while retaining structural integrity. They are also able to respond to various stimuli, such as ionic strength, temperature, magnetic field, electric field, biological molecules, etc. which is important in drug release. Nanohydrogels represent a versatile platform for the delivery of therapeutic agents to targeted cancer cells [9]. Nanohydrogels, due to their structural similarity to the extracellular matrix, offer also advantages in encapsulating cells for various therapeutic purposes [10]. These gels have been extensively studied for delivering drugs such as doxorubicin (DOX), cisplatin, and paclitaxel to cancerous tissues, particularly as stimuli-responsive hydrogels [11–14]. Despite the expansion of studies on nanohydrogel drug delivery systems, comprehensive articles summarizing these findings are rare.

A large number of nanomaterials are tested for their unique properties depending on the type of disease. Specifically for skin cancer treatment, magnetic hydrogels have attracted attention related to their biomedical and pharmaceutical applications [15, 16]. The use of magnetic NPs (e.g., iron oxide NPs) dispersed in a hydrogel structure, forms adaptive conditions under a magnetic field. This type of nanohydrogels can combine magnetic susceptibility, high elasticity, softness, and are useful platforms for diagnostics, drug delivery, and treatment using hyperthermia. These properties identify them as a suitable candidate for skin cancer treatment [17].

This review explores the employing of magnetic nanohydrogels in skin cancer medicine and outlines the key challenges addressed by this technology.

Design and synthesis of nanohydrogels

The success of nanohydrogels in cancer medicine relies on the precise control of their size, shape, surface charge, and drug-loading capacity. This section discusses various synthetic approaches, including chemical and physical methods, for tailoring nanohydrogel properties. Additionally, it explores the incorporation of targeting ligands, stimuli-responsive elements, and imaging agents to enhance the specificity and functionality of nanohydrogels.

Hydrogel synthesis. Broadly, hydrogels can be categorized into three main types based on their source and origin: natural and synthetic polymeric network-based hydrogels or a combination of both. The synthesis of hydrogels, whether natural or synthetic, is achievable through diverse methods including chemical cross-linking, ionic cross-linking, self-assembly, electrostatic interactions, reverse mini emulsions, hydrophobic interactions, and micelle cross-linking. It is noteworthy that synthetic polymer-based hydrogels may employ comparable mechanisms to produce distinct and more effective nanohydrogels compared to natural polymer-based hydrogels [18].

Those derived from natural polymers fall into the category of natural polymer hydrogels, including materials such as proteins and peptides (e.g., collagen, elastin), polysaccharides (e.g., chitin, cellulose, glycosaminoglycans), nucleic acids (DNA, RNA). These natural polymers, obtainable from diverse sources, are further categorized as neutral, cationic, or anionic. Notably, they are easily accessible, abundant, cost-effective, non-toxic, and biodegradable, with various attractive biological properties. The intricate relationship between structure and function, particularly in biologically active compounds, has instigated considerable interest. The advancements in structural and functional substances over recent decades have led to a growing array of materials for biomedical technology. Natural polymer hydrogels, characterized by well-defined, larger structures formed through covalently bonded monomeric units, find applications in various biomedical fields such as controlled and targeted drug release, tissue engineering, and wound healing [19–21].

Synthetic polymers are attractive for synthesis as they have highly controllable physical and chemical properties compared to natural polymers. Synthetic polymers can be produced with long-chain structures and high molecular weight. On the other hand, synthetic hydrogels have lower biological activity than natural hydrogels. Synthesis of these synthetic polymer hydrogels is mediated via numerous ways, employing chemical crosslinking of polymers or polymerizable vinyl monomers. For example, synthetic polymers used in the synthesis of hydrogels are poly (ethylene glycol) (PEG), poly (acrylamide) (PAAm), poly (ethylene oxide) (PEO), poly (acrylic acid) (PAA), poly (lactic-co-glycolic acid) (PLGA), etc [22].

Different categorization hydrogels depend on the cross-linking of the hydrogel, they can be divided also into physical and chemical hydrogels [23]. Physical hydrogels are usually cross-linked by hydrogen bonds, from amphiphilic graft and block polymers, polymers of PLGA and PEG, polymers of PEO and PEG, hydrophobized polysaccharides, cross-linked by crystallization, protein interaction, antigen-antibody interactions. On the other hand, chemically cross-linked hydrogels

by complementary groups of chemical reaction, photo cross-linking, and enzymes that gives hydrogel higher strength [20, 21]. Very interesting is a group of hybrid hydrogels that combine hydrogel with different compounds (NPs, drugs, imaging agents, etc.). In the field of medicine, employing a combination of hydrogel with NPs as multifunctional hybrid nanohydrogels attracts more and more attention [24].

Nanohydrogels. Utilizing nanotechnology for drug delivery represents various of benefits, encompassing high loading capacity, the potential for combination therapy, controlled release mechanisms, extended circulation times, and targeted delivery capabilities. Consequently, a diverse array of NP-based drug delivery systems has emerged, aiming to optimize the therapeutic potential of drugs by modulating their pharmacokinetic and biodistribution profiles. The ongoing advancements in biotechnology and biomedicine are propelling the continuous evolution of innovative therapeutic NPs, poised to further elevate therapeutic efficacy in medical treatments. Within nanotechnology development, therapeutic NPs have been combined with other biomaterials such as hydrogels, to form hybrid systems for advantageous applications.

NPs can be integrated into a gel matrix in the process by allowing the gel network to swell and then absorb NPs, particularly useful when NPs disrupt the gelation process [25]. Additionally, inorganic NPs are frequently synthesized within the gel matrix through a process involving the loading of NP precursors into the gel, followed by reactions to induce NP formation [26]. Hydrogels, with certain compositions, maintain the structural integrity and functionalities of the encapsulated NPs and by that enhance overall therapeutic efficacy. Apart from NP entrapment within hydrogels, an alternative approach uses NPs directly as cross-linkers to construct a three-dimensional hydrogel network, resulting in NP colloidal hydrogels [27–29]. In this method, NPs can be linked together via strong hydrophobic interactions or by combining NPs with opposite surface charges. Alternatively, NPs can be covalently linked, serving as nodes to form the hydrogel network.

Iron oxide NPs (IONPs) are magnetic inorganic NPs, classified as core-and-shell type [30, 31]. Due to the hydrophobic nature of the iron core, IONPs are typically synthesized with various hydrophilic coatings (e.g., chitosan, PEG, dextran, heparin, pluronic, polyethylene imine, etc.) to ensure suspension stability [32–36]. The choice of coating material influences IONPs' properties, mostly cytotoxicity and pharmacokinetics.

IONPs offer advantageous properties for medical applications, particularly in cancer diagnostics and therapy. They exhibit low toxicity and biocompatibility, leading to clinical applications as an MRI agent (feridex®) and a therapeutic for iron-deficient anemia treatment [37]. IONP-enhanced MRI aids in distinguishing between malignant and benign liver lesions, despite the increasing preference for gadolinium due to higher MRI resolution and shorter retention time [38].

Moreover, IONPs possess superparamagnetic properties, allowing them to be magnetized and guided to specific organs or locations, such as tumors, with the application of an external magnet [39]. IONPs can also be used as drug carriers, loaded with chemotherapeutics to enhance targeted drug delivery. Importantly, IONPs can generate heat through alternating magnetic fields (AMF) or near-infrared (NIR) laser applications [40]. Magnetic hyperthermia has been extensively studied and translated into clinical trials for cancer treatment, leveraging deep tissue penetration and selective tumor cell killing [41]. However, the practical application of this modality is hindered by the low thermal conversion efficiency of IONPs, necessitating high doses [40]. In comparison, photothermal therapy (PTT) relies on laser irradiation of the PTT agent for selective tumoricidal effects, depending on laser and agent accessibility to the tumor site. Due to its high photothermal activity, IONP is a widely studied candidate for PTT in tumor treatment [42–44].

The incorporation of IONPs into hydrogel structure to prepare multifunctional nanohydrogel represents an innovative approach to treating skin cancer.

Drug delivery

Nanohydrogels offer a versatile platform for incorporating different types of drugs, controlling drug release, minimizing systemic toxicity, and improving therapeutic outcomes. There are many mechanisms of drug loading and release kinetics. These mechanisms impact nanohydrogel characteristics and drug delivery efficiency. Furthermore, recent advancements in nanotechnology can mediate overcoming biological barriers and achieving targeted drug delivery to cancer tissue [45].

The effective preparation and modification of nanohydrogels for controlled drug delivery and release requires a precise procedure to achieve a biologically active compound. A drug release regulation strategy of molecules initially trapped within a hydrogel involves controlling the degradation of the network. As the hydrogel network degrades, the mesh size expands, enabling the diffusion of drugs out of the hydrogel. Degradation can take place within the polymer backbone or at the cross-links and is commonly mediated by processes such as hydrolysis or enzymatic activity. Degradation can be induced through externally provided stimuli. For instance, acidic environments often expedite hydrolysis. High-energy ultraviolet light can also prompt the degradation of microgels containing o-nitrobenzyl ether moieties (NBE) by causing cleavage of the NBE bonds. External stimuli-response also includes temperature, magnetic field, ultrasound, or light [46, 47].

Internal stimuli responses involving mechanisms like pH, redox, glucose, and lysosomal enzyme functionalization mimic the activity of biomolecular components, in the extracellular matrix and biomolecules within cells. This approach is used for the release of entrapped drugs and involves the

controlled swelling of hydrogels. Hydrogel swells along with the mesh size expands. The degree of swelling in a hydrogel is determined by a balance between forces that restrict network deformation and osmotic pressure that drives water absorption [48]. These stimuli have been widely utilized in drug delivery applications. Achieving optimal therapeutic efficacy in drug, nucleic acid or polypeptide delivery requires spatial control and the right timing of release.

Transdermal delivery of skin melanoma drugs offers the advantage of achieving therapeutic drug concentrations locally while maintaining low systemic levels, thus minimizing off-target toxicity, but delivering therapeutic molecules through the skin represents many challenges, primarily in impermeability of the topmost skin layer stratum corneum to compounds larger than 500 Da [49].

Various techniques have been developed to increase drug penetration through the skin, including sonophoresis, electroporation, microneedles, magnetophoresis, iontophoresis, and electron beam irradiation [49–51]. However, these techniques often result in undesirable side effects such as pain, skin irritation, and potential skin infection. Several chemotherapeutic drugs, including 5-fluorouracil (5-FU), platinum compounds, dacarbazine, temozolomide, and paclitaxel, are currently used for skin melanoma treatment. Unfortunately, the overall response rate remains below 20%. Each of these agents comes with undesirable systemic side effects.

NPs can enhance the penetration of large molecules through the stratum corneum (SC), without compromising the skin barrier against pathogenic microbes, and also improve bioavailability [52]. They function as drug carriers, enhancing the hydrophobicity, and stability characteristics compared to the drug alone, or as co-administered adjuvants. However, the size of NPs can be an obstacle for transdermal applications. In general, larger NPs (20–30 nm) can only penetrate through hair follicles, limiting their usefulness. In contrast, NPs smaller than 10 nm can permeate both the SC and hair follicles. Nevertheless, *in vivo* aggregation of small NPs may restrict tissue penetration and increase toxicity [53–55]. The surface charge (cationic or anionic) of NPs also plays an important role in determining their ability to penetrate the skin. The cationic surface charge of embedded NPs into hydrogel favors access to deeper skin. A positive surface-charged composite facilitates the adhesion to the negatively charged cell membranes. Keratinocytes took up the positively charged nanocapsules rapidly [56]. Carbon nanotubes loaded with DOX demonstrated the induction toxicity against melanoma cell death *in vitro* and the inhibition of tumor growth in xenograft mouse models [57].

Superparamagnetic iron oxide NPs (SPIONs) are promising in drug delivery for skin melanoma treatment, due to their magnetic properties, biocompatibility, low toxicity, easy separation methodology, and flexibility of surface modification [58, 59]. SPIONs have been shown to be non-toxic *in vitro* and *in vivo* and can be prepared with different coating compositions and functional groups at the end of stabilizers which helps to deliver them to the desired area [60, 61]. Co-administration of these NPs with cytotoxic drugs has been demonstrated to enhance drug penetration in an *in vitro* spheroid model [62]. Topical co-administration of these SPIONs was found to improve transdermal delivery and enhance the anti-tumor responses of mouse melanomas to chemotherapeutic drugs.

Nazir et al. demonstrated the optimized swelling, biodegradation, and wetting properties of encapsulated Capecitabine in Pluronic F-127 hydrogel as a copolymer solvent system for sustained release of therapeutic agents for melanoma skin cancer treatment and also against bacterial infection. These nanocomposite hydrogels have proven to be pH-sensitive under certain conditions for controlled and sustained release of 5-FU. Moreover, this type of nanocomposite presents significantly high antibacterial and anticancer activities against *S. aureus* and *P. aeruginosa*, and U-87 cell lines compared to the individual components [63].

Gazzi et al. prepared the nanoencapsulated imiquimod (superficial basal cell carcinoma drug) to provide a higher cytotoxic effect against SK-MEL-28 compared to the free drug. The incorporation of the drug-loaded nanocapsules in the pectin-based hydrogel enabled control of drug release. The control of drug release is important to decrease the adverse effects caused by imiquimod. Adhesiveness and deeper penetration of the drug into the skin were achieved by using pectin-based hydrogel (PEC-NCimiq). PEC-NCimiq composite was able to penetrate all skin layers, mainly the dermis, and also to permeate the tissue, important features viewing the melanoma treatment [64].

Gonsalves et al. developed the nanocomposite hydrogel system as a pH-responsive drug-releasing nanocomposite by preparing PEG 200, maleic acid, and citric acid polymer with PLGA and carboxymethyl cellulose (CMC) NPs incorporated. It is a biocompatible platform that can effectively cause cancer cell death while minimizing infections at the site due to its demonstrated antibacterial properties [65].

Amatya et al. prepared dextran-coated magnetic NPs (DEX-IONP) inside of Carbopol 940 gel that retained a high viscosity that is favorable to maintain at the applied site. The DEX-IONP gel could induce effective heating by laser irradiation. The *in vitro* and *in vivo* studies evidenced the applicability of DEX-IONP in topical PTT. The preliminary efficacy study results in the mice model demonstrated that tumor volumes could be significantly reduced by the topical PTT with DEX-IONP gel. By a single PTT treatment with DEX-IONP gel and applying 0.5 W laser power, tumor growth could be significantly inhibited by 85% [66].

Imaging and diagnostic applications

Early diagnosis of skin cancer is crucial for effective treatment and optimizing clinical outcomes for patients. Currently used optical imaging techniques, including positron emission tomography (PET), reflectance confocal

microscopy (RCM), magnetic resonance imaging (MRI), near-infrared (NIR) bioimaging, optical coherence tomography (OCT), offer non-invasive imaging that can aid in the early identification of cutaneous tumors and assist in surgical planning. These techniques are well-suited for observing dynamic processes such as immune cell activation, blood flow, and tumor energy metabolism, providing valuable insights relevant to the progression of the disease [67–70].

However, potential drawbacks such as overdiagnosis and overtreatment, false diagnoses, and risks associated with radiation exposure caused by the diagnostic approaches are still present. Overdiagnosis may occur when imaging identifies an asymptomatic condition that would not have manifested clinically during an individual's lifetime [71, 72]. This highlights the challenge for imaging techniques in distinguishing between lesions with a carefree course and those with an aggressive direction [73]. False positives refer to suspicious findings suggesting cancer presence that are not confirmed as tumors through histopathology, imaging, and clinical follow-up tests [74, 75]. False negatives indicate results incorrectly suggesting the absence of a particular disease when the person has the condition. Both false diagnoses can lead to significant harm, psychological distress, unnecessary invasive procedures, and treatments, as well as a financial impact on both the individual and society.

In addition to drug delivery, nanohydrogels have shown promise as imaging and diagnostic agents for cancer and monitoring treatment response. Magnetic NPs (MNPs) have been effectively employed in magnetic resonance imaging (MRI). In the MELAMAG clinical trial, sentinel lymph node biopsy (SLNB) detection utilizing MNPs was compared to the standard diagnostic technique. In this investigation, MNPs containing small iron NPs were injected intradermally. During surgery, a hand-held magnetometer was utilized to identify the accumulation of MNPs. The results demonstrated the feasibility of the magnetic technique for SLNB detection. The highest identification rates were observed for inguinal and axillary lymph nodes, while the lowest detection rates were noted in the cervical region. Among the 129 recruited patients, the study reported a sentinel node identification rate of 95.3% using this MNPs-based technique [76].

Another NPs explored for contrast-enhanced MRI lymphography are gadolinium-loaded NPs. The utilization of these NPs has been shown to enhance the specificity and sensitivity of MRI lymphography in melanoma mice [77]. Zhou et al. introduced an efficient and noninvasive strategy for detecting melanoma metastasis in lymph nodes using Gd-embedded iron oxide NPs (GdIOP) functionalized with Zwitterionic Dopamine Sulfonate molecules. Through T1-T2 dual-modal MRI, GdIOP@ZDS NPs exhibited high uptake by dendritic cells and macrophages in lymph nodes, contrasting with lower uptake by melanoma B16 tumor cells. This discrepancy generated pseudo-contrast images, potentially useful for the detection of melanoma metastasis in lymph nodes [78].

Combination therapies and synergistic approaches

The increasing prevalence of skin malignancies underlines the necessity for different available treatment approaches. The selection of an appropriate treatment strategy depends on disease conditions such as tumor location and size, stage of melanoma, and margins [79]. Despite novel advanced approaches, surgical methods continue to be fundamental for skin cancer treatment [80–82]. There are three primary goals of the treatment strategy: removal of cancer, restoration of normal skin function, and maintenance of appearance.

Excision biopsy stands as the gold standard for treating skin malignancies. Alternative treatments for non-melanoma skin cancers (NMSC) include curettage and diathermy, liquid nitrogen therapy, imiquimod, or 5-FU, radiotherapy, and excision followed by margin repair [83]. Electrodesiccation and curettage are often beneficial for treating superficial basal cell carcinomas (BCCs) and *in situ* squamous cell carcinoma (SCC) of the epidermis. Liquid nitrogen is also very effective for superficial lesions located on the body. Topical chemotherapeutics such as 5-FU are suitable for managing SCC, while imiquimod is preferred for treating superficial BCCs when surgery or other treatments are not feasible. Unfortunately, these topical agents in many cases induce a local inflammatory response when dosage adjustment is necessary. On the other hand, radiotherapy is typically reserved for elderly patients, it boasts an exceptional cure rate and provides a particularly valuable approach for margin control or treating large or difficult-to-reach lesions. When feasible, lesions should ideally be excised or treated with Mohs micrographic surgery, where subsequent layers of skin are removed in several rounds. This technique is used for challenging tumors that are poorly defined, anatomically complex, and recurrent. Photodynamic therapy (PDT) is employed for superficial BCCs, involving the application of a photosensitizing cream (e.g., methyl aminolevulinate) followed by exposure to intense light, optically activating a photosensitive agent and converting local oxygen into harmful radicals [79, 81, 84, 85].

Recent advancements in drug development have significantly enhanced the outlook for patients diagnosed with metastatic melanoma. With the increasing utilization of targeted therapies and immunotherapies, the reliance on chemotherapy has notably decreased. Metastatic melanoma treatment has improved in recent years with the introduction of treatments such as BRAF, CTLA4, and PD1 inhibitors. While surgery remains the standard treatment for non-melanoma skin cancers (NMSC), newer nonsurgical agents targeting cellular receptors or immunological responses, such as imiquimod, interferon (IFN), and 5-FU, have significantly reduced morbidity and mortality while enhancing patients' quality of life. Moreover, PDT has proven effective either alone or in combination with topical immunomodulators for treating NMSC and premalignant lesions [86–88].

In patients with stage II and III melanoma, IFN-α treatment can serve as an adjuvant therapy, despite its significant associated toxicity. Systemic treatment becomes necessary when surgical options are not feasible. For certain metastatic patients, systemic chemotherapy (such as dacarbazine, temozolomide, or carboplatin/paclitaxel) remains crucial. Additionally, BRAF inhibitors like vemurafenib are beneficial for BRAF-mutated patients, while ipilimumab antibody offers promising therapeutic beyond traditional chemotherapy. However, determining the appropriate therapeutic approach for stage IV patients is contentious and should primarily involve an interdisciplinary oncology team.

Nanohydrogels enable the simultaneous diagnostics and delivery of multiple therapeutic agents, facilitating combination therapies to enhance anticancer efficacy. The conventional administration of chemotherapeutic drugs lacks specificity in targeting, resulting in inefficient tumor uptake and unnecessary drug distribution through the body, leading to side effects. Therapeutic agents with characteristics such as limited permeability, poor half-life, low solubility, and instability under physiological conditions often fail to achieve the desired outcomes [89, 90]. In NMSC compared to other organs such as bones, lungs, and liver, direct delivery of therapeutic agents to the skin tumor site has the potential to minimize systemic toxicity and reduce overall treatment costs [91]. Ineffective permeation of therapeutic agents into the cutaneous region of skin tumors caused by the skin's outermost barrier can be overcome by nanotechnology, which emerges as a promising strategy to address these challenges and combat skin cancer effectively, including passive tumor targeting via the enhanced permeability and retention (EPR) effect [92, 93], evasion of the reticuloendothelial system (RES) [94], and enhanced skin permeability.

The findings of Raviraj et al. research validate that the simultaneous administration of SPIONs not only amplifies the permeation and effectiveness of DOX and 5-FU through the subcutaneous and epidermal layers but also extends into the dermal layer of a living animal's skin. Notably, this enhancement occurs without the necessity of DOX being covalently bound to the NPs. While the full spectrum of molecules experiencing improved transdermal penetration with these SPIONs, absent covalent attachment, is yet to be determined, it is plausible that it could encompass other drugs with anticancer and immunomodulatory properties. This study demonstrated that the topical application of SPIONs on skin melanoma boosts the cytotoxic effects of 5-FU, leading to elevated necrosis and a deceleration in tumor growth. The increased necrosis is attributed to a combination of improved 5-FU penetration, heightened leukocyte infiltration, and diminished tumor vascularity. The impacts of SPIONs on tumor vascularization and immune cell infiltration remain significant even in the absence of 5-FU. A recent investigation involving magnetically localized polyethyleneimine-coated SPIONs similarly observed an augmentation in macrophage infiltration and a reduction in tumor vascularization, independently of cytotoxic drugs [88].

Wadajkar et al. described the preparation of magnetic-based core–shell particles (MBCSPs) designed to target B16F10 melanoma skin cancer cells. These MBCSPs are composed of a thermoresponsive core made of PLGA and a shell composed of poly(N-isopropylacrylamide-acrylamide-allylamine) embedded with magnetite NPs. The targeting of melanoma cancer cells was achieved by conjugating MBCSPs with Gly-Arg-Gly-Asp-Ser (GRGDS) peptides, which specifically bind to the α5β3 receptors present on melanoma cells. Encapsulating magnetite within a biodegradable polymeric core mitigates aggregation and toxicity concerns, ensuring sustained, long-term drug release. Moreover, these particles demonstrate efficient uptake by targeted melanoma cells while maintaining good cytocompatibility with healthy cells [87].

Despite the promising advancements, several challenges persist in the development and clinical translation of nanohydrogels for cancer medicine. Issues related to biocompatibility, pharmacokinetics, and scalability. Furthermore, it outlines potential future directions, including the integration of artificial intelligence in personalized nanomedicine and the exploration of novel materials and fabrication techniques. The combination of diagnostics and treatment by nanohydrogels creates a potentially useful theranostic platform for skin melanoma treatment.

In conclusion, magnetic nanohydrogels present a promising approach to the treatment of skin cancer. This mini-review highlights their potential as innovative drug delivery systems, offering targeted and controlled release of therapeutic agents to melanoma lesions. By presenting the unique properties of magnetic nanoparticles within a hydrogel matrix, these nanohydrogels enable precise targeting of treatment and enhanced permeation into the skin. Additionally, their stimuli-responsive properties allow the preparation of drugs with release response to external triggers, further enhancing therapeutic efficacy while minimizing systemic side effects. Despite the early stage of research in this field, the potential of magnetic nanohydrogels for advantageous skin cancer treatment is evident. Continued exploration and advancement of this technology hold promise for improving patient outcomes and advancing the fight against skin cancer. Collaborative efforts among researchers, clinicians, and industry stakeholders will be essential in translating these findings into clinical applications, ultimately benefiting patients worldwide.

Acknowledgments: This article was supported by projects: ENM III/2019/861/TENTACLES, COST Action CA21108, and VEGA 2/0121/21.

References

[1] CAZZATO G. Histopathological Diagnosis of Malignant Melanoma at the Dawn of 2023: Knowledge Gained and New Challenges. Dermatopathology (Basel) 2023; 10: 91–92. https://doi.org/10.3390/dermatopathology10010013

[2] ELGAMAL M. Automatic skin cancer images classification. Int J Adv Comp Sci Appl 2013; 4: 287–294. https://doi.org/10.14569/IJACSA.2013.040342

[3] KATALINIC A, KUNZE U, SCHAFER T. Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumour stages and localization (epidemiology of skin cancer). Br J Dermatol 2003; 149: 1200–1206. https://doi.org/10.1111/j.1365-2133.2003.05554.x

[4] FAGUNDO E, RODRÍGUEZ-GARCÍA C, RODRÍGUEZ C, GONZÁLEZ S, SÁNCHEZ R et al. Analysis of Phenotypic Characteristics and Exposure to UV Radiation in a Group of Patients With Cutaneous Melanoma. Actas Dermosifiliogr 2011; 102: 599–604. https://doi.org/10.1016/j.adengl.2011.03.011

[5] RASHEED N. Melanoma awareness programs and their impact on the life of Australian Queenslanders: A concise analysis. Int J Health (Qassim) 2024; 18: 1–3.

[6] KALIA S, KWONG YKK. Relationship between sun safety behaviours and modifiable lifestyle cancer risk factors and vitamin D levels. Photodermatol Photoimmunol Photomed 2019; 35: 429–435. https://doi.org/10.1111/phpp.12494

[7] MATTAM BL, BIJOY A, THADATHIL AD, GEORGE L, VARGHESE A. Conducting Polymers: A Versatile Material for Biomedical Applications. ChemistrySelect 2022; 7: e202201765. https://doi.org/10.1002/slct.202201765

[8] REYES-HABITO CM, ROH EK. Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer: Part I. Conventional chemotherapeutic drugs. JAAD 2014; 71: 203e1–203e12. https://doi.org/10.1016/j.jaad.2014.04.014

[9] MURPHY EA, MAJETI BK, MUKTHAVARAM R, ACEVEDO LM, BARNES LA et al. Targeted Nanogels: A Versatile Platform for Drug Delivery to Tumors. Mol Cancer Ther 2011; 10: 972–982. https://doi.org/10.1158/1535-7163.MCT-10-0729

[10] FOROUTAN Z, AFSHARI AR, SABOURI Z, MOSTAFAPOUR A, FAR BF et al. Plant-based synthesis of cerium oxide nanoparticles as a drug delivery system in improving the anticancer effects of free temozolomide in glioblastoma (U87) cells. Ceram Int 2022; 48: 30441–30450. https://doi.org/10.1016/j.ceramint.2022.06.322

[11] QU J, ZHAO X, MA PX, GUO B. pH-responsive self-healing injectable hydrogel based on N-carboxyethyl chitosan for hepatocellular carcinoma therapy. Acta Biomater 2017; 58: 168–180. https://doi.org/10.1016/j.actbio.2017.06.001

[12] SALIMI F, DILMAGHANI KA, ALIZADEH E, AKBARZADEH A, DAVARAN S. Enhancing cisplatin delivery to hepatocellular carcinoma HepG2 cells using dual sensitive smart nanocomposite. Artif Cells Nanomed Biotechnol 2018; 46: 949–958. https://doi.org/10.1080/21691401.2017.1349777

[13] RAZA F, ZHU Y, CHEN L, YOU X, ZHANG J et al. Paclitaxel-loaded pH responsive hydrogel based on self-assembled peptides for tumor targeting. Biomater Sci 2019; 7: 2023–2036. https://doi.org/10.1039/C9BM00139E

[14] PENG M, XU S, ZHANG Y, ZHANG L, HUANG B et al. Thermosensitive injectable hydrogel enhances the antitumor effect of embelin in mouse hepatocellular carcinoma. J Pharm Sci 2014; 103: 965–973. https://doi.org/10.1002/jps.23885

[15] BRUSCHI ML, COLOMBELLI DE SOUZA NUNES G. Magnetic Gels in Skin Cancer Treatment: A Review of Potential Applications in Diagnostics, Drug Delivery and Hyperthermia. Pharmaceutics 2023; 15: 1244. https://doi.org/10.3390/pharmaceutics15041244

[16] SGHIER K, MUR M, VEIGA F, PAIVA-SANTOS AC, PIRES PC. Novel Therapeutic Hybrid Systems Using Hydrogels and Nanotechnology: A Focus on Nanoemulgels for the Treatment of Skin Diseases. Gels 2024; 10: 45. https://doi.org/10.3390/gels10010045

[17] DE TOLEDO LAS, ROSSETO HC, SANTOS RS, SPIZZO F, BIANCO LD et al. Thermal Magnetic Field Activated Propolis Release From Liquid Crystalline System Based on Magnetic Nanoparticles. AAPS Pharm Sci Tech 2018; 19: 3258–3271. https://doi.org/10.1208/s12249-018-1163-4

[18] KAVIMANDAN NJ, LOSI E, PEPPAS NA. Novel delivery system based on complexation hydrogels as delivery vehicles for insulin–transferrin conjugates. Biomaterials 2006; 27: 3846–3854. https://doi.org/10.1016/j.biomaterials.2006.02.026

[19] CARVALHO SM, MANSUR AAP, CAPANEMA NSV, CARVALHO IC, CHANGAS P et al. Synthesis and in vitro assessment of anticancer hydrogels composed by carboxymethylcellulose-doxorubicin as potential transdermal delivery systems for treatment of skin cancer. J Mol Liquids 2018; 266: 425–440. https://doi.org/10.1016/j.molliq.2018.06.085

[20] YANG X, ZHANG CH, DENG D, GU Y, WANG H et al. Multiple Stimuli-Responsive MXene-Based Hydrogel as Intelligent Drug Delivery Carriers for Deep Chronic Wound Healing. Small 2022; 18: 2104368. https://doi.org/10.1002/smll.202104368

[21] PARHI R. Cross-Linked Hydrogel for Pharmaceutical Applications: A Review. Adv Pharm Bull 2017; 7: 515–530. https://doi.org/10.15171/apb.2017.064

[22] BAZYLÍNSKA U, KULBACKA J, SCHMIDT J, TALMON Y, MURGIA S. Polymer-free cubosomes for simultaneous bioimaging and photodynamic action of photosensitizers in melanoma skin cancer cells. J Colloid Interface Sci 2018; 522: 163–173. https://doi.org/10.1016/j.jcis.2018.03.063

[23] SIKDAR P, UDDIN M, DIP TM, ISLAM S, HOQUE S et al. Recent advances in the synthesis of smart hydrogels. Mater Adv 2021; 2: 4532–4573. https://doi.org/10.1039/D1MA00193K

[24] APPEL EA, TIBBITT MW, WEBBER MJ, MATTIX BA, VEISEH O et al. Self-assembled hydrogels utilizing polymer–nanoparticle interactions. Nat Commun 2015; 6: 6295. https://doi.org/10.1038/ncomms7295

[25] SALLOUM M, MA RH, WEEKS D, ZHU L. Controlling nanoparticle delivery in magnetic nanoparticle hyperthermia for cancer treatment: Experimental study in agarose gel. Int J Hyperthermia 2008; 24: 337–345. https://doi.org/10.1080/02656730801907937

[26] GAO W, VECCHIO D, LI J, ZHU J, ZHANG Q et al. Hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery. ACS Nano 2014; 8: 2900–2907. https://doi.org/10.1021/nn500110a

[27] BERTSCH P, ANDRÉE L, BESHELI NH, LEEWENBURGH. Colloidal hydrogels made of gelatin nanoparticles exhibit fast stress relaxation at strains relevant for cell activity. Acta Biomater 2022; 138: 124–132. https://doi.org/10.1016/j.actbio.2021.10.053

[28] XU X, SABANAYAGAM CR, HARRINGTON DA, FARACH-CARSON MC, JIA X. A hydrogel-based tumor model for the evaluation of nanoparticle-based cancer therapeutics. Biomaterials 2014; 35: 3319–3330. https://doi.org/10.1016/j.biomaterials.2013.12.080

[29] QIAN Q, WANG D, SHI L, ZHANG Z, QIAN J et al. A pure molecular drug hydrogel for post-surgical cancer treatment. Biomaterials 2021; 265: 120403. https://doi.org/10.1016/j.biomaterials.2020.120403

[30] AMATYA R, KIM D, MIN KA, SHIN M. Iron oxide nanoparticles-loaded hydrogels for effective topical photothermal treatment of skin cancer. Journal of Pharmaceutical Investigation 2022; 52: 775–785. https://doi.org/10.1007/s40005-022-00593-9

[31] NICOLÁS P, SALETA M, TROIANI H, ZYSLER R, LASSALLE V et al. Preparation of iron oxide nanoparticles stabilized with biomolecules: Experimental and mechanistic issues. Acta Biomater 2013; 9: 4754–4762. https://doi.org/10.1016/j.actbio.2012.09.040

[32] AMATYA R, HWANG S, PARK T, MIN KA, SHIN MC. In vitro and in vivo evaluation of pegylated starch-coated iron oxide nanoparticles for enhanced photothermal cancer therapy. Pharmaceutics 2021; 13: 871. https://doi.org/10.3390/pharmaceutics13060871

[33] ABUSHIRA A, ELHUNI I, TARESCO V, MARCIANI L, STOLNIK S. A simple and efficient method for polymer coating of iron oxide nanoparticles. J Drug Deliv Sci Technol 2020; 55: 101460. https://doi.org/10.1016/j.jddst.2019.101460

[34] GUTIERREZ FV, DE FALCO A, YOKOYAMA E, LA FM, LUZ-LIMA C et al. Magnetic characterization by scanning microscopy of functionalized iron oxide nanoparticles. Nanomaterials 2021; 11: 2197. https://doi.org/10.3390/nano11092197

[35] HWANG YH, KIM YJ, LEE DY. Hepatic and renal cellular cytotoxic effects of heparin-coated superparamagnetic Iron oxide nanoparticles. Biomater Res 2021; 25: 36. https://doi.org/10.1186/s40824-021-00241-7

[36] YATHINDRANATH V, REBBOUH L, MOORE DF, MILLER DW, LIEROP J et al. A Versatile Method for the Reductive, One-Pot Synthesis of Bare, Hydrophilic and Hydrophobic Magnetite Nanoparticles. Adv Functional Mater 2011; 21: 1457–1464. https://doi.org/10.1002/adfm.201002111

[37] STABI KL, BENDZ LM. Ferumoxytol Use as an Intravenous Contrast Agent for Magnetic Resonance Angiography. Ann Pharmacother 2011; 45: 1571–1575. https://doi.org/10.1345/aph.1Q431

[38] JEON M, HALBERT MV, STEPHEN ZR, ZHANG M. Iron oxide nanoparticles as T1 contrast agents for magnetic resonance imaging: fundamentals, challenges, applications, and prospectives. Adv Mater 2021; 33: 1906539. https://doi.org/10.1002/adma.201906539

[39] VEMULKAR T, MANSELL R, PETIT DCMC, COWBURN RP, LESNIAK MS. Highly tunable perpendicularly magnetized synthetic antiferromagnets for biotechnology applications. App Physics Lett 2015; 107: 012403. https://doi.org/10.1063/1.4926336

[40] SHAW SK, SHARMA A, KAILASHIYA J, GUPTA SK, MEENA SS et al. Mesoporous Fe3O4 nanoparticle: A prospective nano heat generator for thermo-therapeutic cancer treatment modality. J Magn Magn Mater 2023; 578: 170817. https://doi.org/10.1016/j.jmmm.2023.170817

[41] SALIMI M, SARKAR S, HASHEMI M, SABER R. Treatment of Breast Cancer-Bearing BALB/c Mice with Magnetic Hyperthermia using Dendrimer Functionalized Iron-Oxide Nanoparticles. Nanomaterials 2020; 10: 2310. https://doi.org/10.3390/nano10112310

[42] WANG L, WU M, PAN Y, XIE D, HON D et al. Sequential targeting biomimetic nano platform for enhanced mild photothermal therapy and chemotherapy of tumor. CSBJ 2023; 21: 2780–2791. https://doi.org/10.1016/j.csbj.2023.04.024

[43] OGNJANOVIC M, RADOVIC M, MIRKOVIC M, PRIJOVIC Ž, DEL PUERTO MORALES M et al. 99mTc-, 90Y-, and 177Lu-Labeled Iron Oxide Nanoflowers Designed for Potential Use in Dual Magnetic Hyperthermia/Radionuclide Cancer Therapy and Diagnosis. ACS Appl Mater Interfaces 2019; 11: 41109–41117. https://doi.org/10.1021/acsami.9b16428

[44] ZHANG D, WU M, ZENG Y, WU L, WANG Q et al. Chlorin e6 Conjugated Poly(dopamine) Nanospheres as PDT/PTT Dual-Modal Therapeutic Agents for Enhanced Cancer Therapy. ACS Appl Mater Interfaces 2015; 7: 8176–8187. https://doi.org/10.1021/acsami.5b01027

[45] YOON TJ, YU KN, KIM E, KIM JS, KIM BG et al. Specific Targeting, Cell Sorting, and Bioimaging with Smart Magnetic Silica Core–Shell Nanomaterials. Small 2006; 2: 209–215. https://doi.org/10.1002/smll.200500360

[46] ELSAEED SM, FARAG RK, MAYSOUR NS. Synthesis and characterization of pH-sensitive crosslinked (NIPA-co-AAC) nanohydrogels copolymer. J. Appl. Polym Sci 2012; 124: 1947–1955. https://doi.org/10.1002/app.34912

[47] DONG L, XIA S, WU K, HUANG Z, CHEN J et al. A pH/Enzyme-responsive tumor-specific delivery system for doxorubicin. Biomaterials 2010; 31: 6309–6316. https://doi.org/10.1016/j.biomaterials.2010.04.049

[48] LOUF JF, LU NB, OCONNELL MG, CHO HJ, DATTA SS. Under pressure: Hydrogel swelling in a granular medium. Sci Adv 2021; 7: eabd2711. https://doi.org/10.1126/sciadv.abd2711

[49] LOMBRY C, DUJARDIN N, PRÉAT V. Transdermal delivery of macromolecules using skin electroporation. Pharm Res 2000; 17: 32–37. https://doi.org/10.1023/a:1007510323344

[50] PRAUSNITZ MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev 2004; 56: 581–587. https://doi.org/10.1016/j.addr.2003.10.023

[51] HERDON TO, GONZALEZ S, GOWRISHANKAR TR, ANDERSON R. Transdermal microconduits by microscisson for drug delivery and sample acquisition. BMC Medicine 2004; 2: 12. https://doi.org/10.1186/1741-7015-2-12

[52] ALVAREZ-ROMÁN R, NAIK A, KALIA YN, GUY RH, FESSI H. Skin penetration and distribution of polymeric nanoparticles. JCR 2004; 99: 53–62. https://doi.org/10.1016/j.jconrel.2004.06.015

[53] ZVYAGIN AV, ZHAO X, GIERDEN A, SANCHEZ W, ROSS J et al. Imaging of zinc oxide nanoparticle penetration in human skin in vitro and in vivo. J Biomed Opt 2008; 13: 064031. https://doi.org/10.1117/1.3041492

[54] HANSEN S, LEHR CM, SCHAEFER UF. Improved input parameters for diffusion models of skin absorption. Adv Deliv Rev 2013; 65: 251–64. https://doi.org/10.1016/j.addr.2012.04.011

[55] LIU X, CHEN Y, LI H, HUANG N, JIN Q et al. Enhanced Retention and Cellular Uptake of Nanoparticles in Tumors by Controlling Their Aggregation Behavior. ACS Nano 2013; 7: 6244–6257. https://doi.org/10.1021/nn402201w

[56] CONTRI RV, FIEL LA, ALNASIF N, POHLMANN AR, GUTERRES SS et al. Skin penetration and dermal tolerability of acrylic nanocapsules: Influence of the surface charge and a chitosan gel used as vehicle. Int J Pharmaceut 2016; 507: 12–20. https://doi.org/10.1016/j.ijpharm.2016.03.046

[57] CHAUDHURI P, HARFOUCHE R, SONI S, HENTSCHEL DM, SENGUPTA S. Shape Effect of Carbon Nanovectors on Angiogenesis. ACS Nano 2010; 4: 574–582. https://doi.org/10.1021/nn901465h

[58] ALI LMA, SHAKER SA, PINOL R, MILLAN A, HANAFY MY et al. Effect of superparamagnetic iron oxide nanoparticles on glucose homeostasis on type 2 diabetes experimental model. Life Sci 2020; 245: 117361. https://doi.org/10.1016/j.lfs.2020.117361

[59] PETRI-FINK A, HOFMANN H. Superparamagnetic Iron Oxide Nanoparticles (SPIONs): From Synthesis to In Vivo Studies-A Summary of the Synthesis, Characterization, In Vitro, and In Vivo Investigations of SPIONs With Particular Focus on Surface and Colloidal Properties. IEEE Trans Nanobioscience 2007; 6: 289–297. https://doi.org/10.1109/TNB.2007.908987

[60] EAMEGDOOL SS, WEIBLE MW, PHAM BTT, HAWKETT BS, GRIEVE SM et al. Ultrasmall superparamagnetic iron oxide nanoparticle prelabelling of human neural precursor cells. Biomaterials 2014; 35: 5549–5564. https://doi.org/10.1016/j.biomaterials.2014.03.061

[61] BRYCE NS, PHAM BTT, FOMG NWS, JAIN N, PAN EH et al. The composition and end-group functionality of sterically stabilized nanoparticles enhances the effectiveness of co-administered cytotoxins. Biomater Sci 2013; 1: 1260–1272. https://doi.org/10.1039/C3BM60120J

[62] GERAMI P, ALSOBROOK JP, PALMER TJ, ROBIN HS. Development of a novel noninvasive adhesive patch test for the evaluation of pigmented lesions of the skin. J Am Acad Dermatol 2014; 71: 237–244. https://doi.org/10.1016/j.jaad.2014.04.042

[63] NAZIR S, KHAN MUA, AL-ARJAN WS, RAZAK SIA, JAVED A et al. Nanocomposite hydrogels for melanoma skin cancer care and treatment: In-vitro drug delivery, drug release kinetics and anti-cancer activities. Arab J Chem 2021; 14: 103120. https://doi.org/10.1016/j.arabjc.2021.103120

[64] GAZZI RP, FRANK LA, ONZI G, POHLMANN AR, GUTERRES SS. New pectin-based hydrogel containing imiquimod-loaded polymeric nanocapsules for melanoma treatment. Drug Deliv Transl Res 2020; 10: 1829–1840. https://doi.org/10.1007/s13346-020-00805-5

[65] GONSALVES A, TAMBE P, DUONG L, THAROKE D, WADAJKAR AS et al. Synthesis and characterization of a novel pH-responsive drug-releasing nanocomposite hydrogel for skin cancer therapy and wound healing. J Mater Chem B 2021; 9: 9533. https://doi.org/10.1039/d1tb01934a

[66] AMATYA R, KIM D, MIN KA, SHIN MC. Iron oxide nanoparticles-loaded hydrogels for effective topical photothermal treatment of skin cancer. J Pharm Investig 2022; 52: 775–785. https://doi.org/10.1007/s40005-022-00593-9

[67] FERRIS LK, JANSEN B, HO J, BUSAM KJ, GROSS K et al. Utility of a noninvasive 2-gene molecular assay for cutaneous melanoma and effect on the decision to biopsy. JAMA Dermatol 2017; 153: 675–680. https://doi.org/10.1001/jamadermatol.2017.0473

[68] MALVEHY J, HAUSCHILD A, CURIEL-LEWANDROWSKI C, MOHR P, HOFMANN-WELLENHOF R et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international, multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014; 171: 1099–1107. https://doi.org/10.1111/bjd.13121

[69] DINNES J, BAMBER J, CHUCHU N, BAYLISS SE, TAKWOINGI Y et al. High-frequency ultrasound for diagnosing skin cancer in adults. Cochrane Database Syst Rev 2018; 12: CD013188. https://doi.org/10.1002/14651858.CD013188

[70] DEY R, ALEXANDROV S, OWENS P, KELLY J, PHELAN S et al. Skin cancer margin detection using nanosensitive optical coherence tomography and a comparative study with confocal microscopy. Biomed Opt Express 2022; 13: 5654–5666. https://doi.org/10.1364/BOE.474334

[71] KUTZNER H, JUTZI TB, KRAHL D, KRIEGHOFF-HENNING EI, HEPPT MV et al. Overdiagnosis of melanoma – causes, consequences and solutions. J Dtdch Dermatol Ges 2020; 18: 1236–1243. https://doi.org/10.1111/ddg.14233

[72] WU WYY, TORNBERG S, ELFSTROM KM, LIU X, NYSTROM L et al. Overdiagnosis in the population-based organized breast cancer screening program estimated by a non-homogeneous multi-state model: A cohort study using individual data with long-term follow-up. Breast Cancer Res 2018; 20: 153. https://doi.org/10.1186/s13058-018-1082-z

[73] YAFFE MJ, MAINPRIZE JG. Overdetection of Breast Cancer. Curr Oncol 2022; 29: 311. https://doi.org/10.3390/curroncol29060311

[74] NIJHUIS AAG, DIENG M, KHANNA N, LORD SJ, DALTON J et al. False-Positive Results and Incidental Findings with Annual CT or PET/CT Surveillance in Asymptomatic Patients with Resected Stage III Melanoma. Ann Surg Oncol 2019; 26: 1860–1868. https://doi.org/10.1245/s10434-019-07311-0

[75] SINGH H, DICKINSON JA, THÉRIAULT G, GRAD R, GROULX S et al. Overdiagnosis: Causes and consequences in primary health care. Can Fam Physician 2018; 64: 654–659.
[76] ANNIGA B, WHITE SH, MONCRIEFF M, DZIEWULSKI P, GEH JL et al. Magnetic technique for sentinel lymph node biopsy in melanoma: The MELAMAG trial. Ann Surg Oncol 2016; 23: 2070–2078. https://doi.org/10.1245/s10434-016-5113-7
[77] PARTRIDGE SC, KURLAND BF, LIU CI, HO RJ, RUDELL A. Tumour-induced lymph node alterations detected by MRI lymphography using gadolinium nanoparticles. Sci Rep 2015; 5: 15641. https://doi.org/10.1038/srep15641
[78] ZHOU Z, LIU H, CHI X, CHEN J, WANG L et al. A protein-corona-free T1–T2 dual-modal contrast agent for accurate imaging of lymphatic tumor metastasis. ACS App Mater Interf 2015; 7: 28286–28293. https://doi.org/10.1021/acsami.5b08422
[79] KEUNG EZ, NAYLOR MF. Chapter 15 Practical Management of Melanoma, pp 241–256. In: MacFarlane DF (Eds.). Skin Cancer Management. Springer Nature, Switzerland AG, 2021. ISBN 978-3-030-50593-6
[80] GALICZYNSKI EM, VIDIMOS AT. Nonsurgical treatment of nonmelanoma skin cancer. Dermatol Clin 2011; 29: 297–309. https://doi.org/10.1016/j.det.2011.01.011
[81] CLARKE P. Nonmelanoma skin cancers – treatment options. Aust Fam Physician 2012; 41: 476–480. https://doi.org/10.1016/j.jgyn.2012.04.018
[82] GRAHAM GF. Chapter 7 Cryosurgery, pp 99–107. In: MacFarlane DF (Eds.). Skin Cancer Management. Springer Nature, Switzerland AG, 2021. ISBN 978-3-030-50593-6
[83] WINKELMANN RR, DESAI TD, FARSI M, TORRES A. Chapter 2 Topical Therapies for Nonmelanoma Skin Cancers, pp 9–30. In: MacFarlane DF (Eds.). Skin Cancer Management. Springer Nature, Switzerland AG, 2021. ISBN 978-3-030-50593-6
[84] LONCASTER J, SWINDELL R, SLEVIN F, SHERIDAN L, ALLAN D et al. Efficacy of photodynamic therapy as a treatment for Gorlin syndrome-related basal cell carcinomas. Clin Oncol (R Coll Radiol) 2009; 21: 502–508. https://doi.org/10.1016/j.clon.2009.03.004
[85] BOIY A, ROELANDTS R, DE WITTE PAM. Photodynamic therapy using topically applied hypericin: Comparative effect with methyl-aminolevulinic acid on UV induced skin tumours. J Photochem Photobiol B Biol 2011; 102: 123–131. https://doi.org/10.1016/j.jphotobiol.2010.09.012
[86] TOGSVERD-BO K, PAASCH U, HAAK CS, HAEDERSDAL M. Lesion dimensions following ablative fractional laser treatment in non-melanoma skin cancer and premalignant lesions. Lasers Med Sci 2012; 27: 675–679. https://doi.org/10.1007/s10103-011-0997-8
[87] WADAJKAR AS, BHAVSAR Z, KO CY, KOPPOLU B, TANG L et al. Multifunctional particles for melanoma-targeted drug delivery. Acta Biomat 2012; 8: 2996–3004. https://doi.org/10.1016/j.actbio.2012.04.042
[88] RAVIRAJ V, PHAM BTT, KIM BJ, PHAM NTH, KOK LF et al. Non-invasive transdermal delivery of chemotherapeutic molecules in vivo using superparamagnetic iron oxide nanoparticles. Cancer Nanotechnol 2021; 12. https://doi.org/10.1186/s12645-021-00079-7
[89] REJINOLD S, CHENNAZHI KP, TAMURA H, NAIR SV, JAYAKUMAR R. Multifunctional Chitin Nanogels for Simultaneous Drug Delivery, Bioimaging, and Biosensing. ACS Appl Mater Interfaces 2011; 3: 3654–3665. https://doi.org/10.1021/am200844m
[90] KAR A, ROUT SR, SINGH V, GREISH K, SAHEBKAR A et al. Chapter 22 Triblock polymeric micelles as an emerging nanocarrier for drug delivery, pp. 561–590. In: Polymeric Micelles for Drug Delivery, Woodhead Publishing, 2022. ISBN 9780323898683
[91] HMED SA, NUR HASAN M, BAGCHI D, ALTASS HM, MORAD M et al. Nano-MOFs as targeted drug delivery agents to combat antibiotic-resistant bacterial infections. R Soc Open Sci 2020; 7: 200959. https://doi.org/10.1098/rsos.200959
[92] DING Y, XU Y, YANG W, NIU P, LI X. Investigating the EPR effect of nanomedicines in human renal tumors via ex vivo perfusion strategy. Nano Today 2020; 35: 100970. https://doi.org/10.1016/j.nantod.2020.100970
[93] WONG AD, YE M, ULMSCHNEIDER MB, SEARSON PC. Quantitative Analysis of the Enhanced Permeation and Retention (EPR) Effect. PLoS ONE 2015; 10: e0123461. https://doi.org/10.1371/journal.pone.0123461
[94] LI T, FAN J, WANG B, TRAUGH N, CHEN Q et al. TIMER: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. Cancer Res 2017; 77: e108–e110. https://doi.org/10.1158/0008-5472.CAN-17-0307
[95] AHEARNE M, YANG Y, LIU KK. Mechanical Characterisation of Hydrogels for Tissue Engineering Applications, pp 1–16. In: N Ashammakhi, R Reis, and F Chiellini (Eds.). Topics in Tissue Engineering, Vol. 4., 2008. ISBN 978-0-12-824459-3
[96] ONO K, ISHIHARA M, OZEKI Y, DEGUCHI H, SATO M et al. Experimental evaluation of photocrosslinkable chitosan as a biologic adhesive with surgical applications. Surgery 2001; 130: 844–850. https://doi.org/10.1067/msy.2001.117197
[97] DODERO A, PIANELLA L, VICINI S, ALLOISIO M, OTTONELLI M et al. Alginate-based hydrogels prepared via ionic gelation: An experimental design approach to predict the crosslinking degree. Europ Polymer J 2019; 118: 586–594. https://doi.org/10.1016/j.eurpolymj.2019.06.028
[98] BIGI A, COJAZZI G, PANZAVOLTA S, RUBINI K, ROVERI N. Mechanical and thermal properties of gelatin films at different degrees of glutaraldehyde crosslinking. Biomaterials 2001; 22: 763–768. https://doi.org/10.1016/s0142-9612(00)00236-2
[99] BURDICK JA, PRESTWICH GD. Hyaluronic acid hydrogels for biomedical applications. Adv Mater 2011; 23: 41–56. https://doi.org/10.1002/adma.201003963
[100] XING R, LIU K, JIAO T, ZHANG N, MA K et al. An Injectable Self-Assembling Collagen–Gold Hybrid Hydrogel for Combinatorial Antitumor Photothermal/Photodynamic Therapy. Adv Mater 2016; 28: 3669–3676. https://doi.org/10.1002/adma.201600284
[101] CAPANEMA NSV, MANSUR AAP, CARVALHO SM, CARVALHO IC, CHAGAS P et al. Bioengineered carboxymethyl cellulose-doxorubicin prodrug hydrogels for topical chemotherapy of melanoma skin cancer. Carbohydate Polymers 2018; 195: 401–412. https://doi.org/10.1016/j.carbpol.2018.04.105

[102] MOSAFER J, ABNOUS K, TAFAGHODI M, JAFARZADEH H, RAMEZANI M. Preparation and characterization of uniform-sized PLGA nanospheres encapsulated with oleic acid-coated magnetic-Fe3O4 nanoparticles for simultaneous diagnostic and therapeutic applications. Colloids Surf A: Physicochem Eng Asp 2017; 514: 146–154. https://doi.org/10.1016/j.colsurfa.2016.11.056

[103] FREUDENBERG U, LIANG Y, KIICK KL, WERNER C. Glycosaminoglycan-Based Biohybrid Hydrogels: A Sweet and Smart Choice for Multifunctional Biomaterials. Adv Mater 2016; 28: 8861–8891. https://doi.org/10.1002/adma.201601908

[104] ZHAI L, ZHU L, LIU F, LIU CH, WANG Q et al. pH triggered injectable amphiphilic hydrogel containing doxorubicin and paclitaxel. Int J Pharma 2011; 410: 83–91. https://doi.org/10.1016/j.ijpharm.2011.03.034

[105] KIM YA, JEONG JO, PARK JS. Preparation and Characterization of Ionic Conductive Poly(acrylic Acid)-Based Silicone Hydrogels for Smart Drug Delivery System. Polymers 2021; 13: 406. https://doi.org/10.3390/polym13030406

[106] NIRMALA JG, AKILA S, NADAR MSAM, NARENDHIRAKANNAN RT, CHATTERJEE S. Biosynthesized Vitis vinifera seed gold nanoparticles induce apoptotic cell death in A431 skin cancer cells. RSC Adv 2016; 6: 82205. https://doi.org/10.1039/c6ra16310f

[107] DASARI S, YEDJOU CG, BRODELL RT, CRUSE AR, TCHOUNWOU PB. Therapeutic strategies and potential implications of silver nanoparticles in the management of skin cancer. Nanotech Rev 2020; 9: 1500–1521. https://doi.org/10.1515/ntrev-2020-0117

[108] AMATYA R, KIM D, MIN KA, SHIN MC. Iron oxide nanoparticles-loaded hydrogels for effective topical photothermal treatment of skin cancer. J Pharm Investig 2022; 52: 775–785. https://doi.org/10.1007/s40005-022-00593-9

[109] TUPAL A, SABZICHI M, RAMEZANI F, KOUHSOLTANI M, HAMISHEHKAR H. Dermal delivery of doxorubicin-loaded solid lipid nanoparticles for the treatment of skin cancer. J Microencapsul 2016; 4: 372–380. https://doi.org/10.1080/02652048.2016.1200150

[110] DAPKUTE D, STEPONKIENE S, BULOTIENE D, SAULITE L, RIEKSTINA U et al. Skin-derived mesenchymal stem cells as quantum dot vehicles to tumors. Int J Nanomed 2017; 2017: 8129–8142. https://doi.org/10.2147/IJN.S143367

[111] MI Y, LI P, TANG J. Multi-Parametric Study of the Viability of in Vitro Skin Cancer Cells Exposed to Nanosecond Pulsed Electric Fields Combined with Multi-Walled Carbon Nanotubes. Technol Cancer Res Treat 2019; 18: 1533033819876918. https://doi.org/10.1177/1533033819876918

[112] SCODELLER P, CATALANO PN, SALGUERO N, DURAN H, WOLOSIUK A et al. Hyaluronan degrading silica nanoparticles for skin cancer therapy. Nanoscale 2013; 5: 9690–9698. https://doi.org/10.1039/C3NR02787B

[113] ALI D, ALARIFI S, ALKAHTANI S, ALKAHTANE AA, ALMALIK A. Cerium Oxide Nanoparticles Induce Oxidative Stress and Genotoxicity in Human Skin Melanoma Cells. Cell Biochem Biophys 2015; 71: 1643–1651. https://doi.org/10.1007/s12013-014-0386-6

[114] VAKAYIL R, MURUGANANTHAM S, KABEERDASS N, RAJENDRAN M, PALVE AM et al. Acorus calamus-zinc oxide nanoparticle coated cotton fabrics shows antimicrobial and cytotoxic activities against skin cancer cells. Process Biochem 2021; 111: 1–8. https://doi.org/10.1016/j.procbio.2021.08.024

[115] BEHNAM MA, EMAMI F, SOBHANI Z, DEHGHANIAN AR. The application of titanium dioxide (TiO2) nanoparticles in the photo-thermal therapy of melanoma cancer model. Iran J Basic Sci 2018; 21: 1133–1139. https://doi.org/10.22038/IJBMS.2018.30284.7304

[116] GUO H, LI F, QIU H, LIU J, QIN S et al. Preparation and Characterization of Chitosan Nanoparticles for Chemotherapy of Melanoma Through Enhancing Tumor Penetration. Front Pharmacol 2020; 11: 317. https://doi.org/10.3389/fphar.2020.00317

[117] MOVAHEDI F, GU W, SOARES CP, XU ZP. Encapsulating Anti-Parasite Benzimidazole Drugs into Lipid-Coated Calcium Phosphate Nanoparticles to Efficiently Induce Skin Cancer Cell Apoptosis. Front Nanotechnol 2021; 3: 693837. https://doi.org/10.3389/fnano.2021.693837

[118] YOSHIHISA Y, HONDA A, ZHAO QL, MAKINO T, ABE R et al. Protective effects of platinum nanoparticles against UV-light-induced epidermal inflammation. Exp Dermatol 2010; 19: 1000–1006. https://doi.org/10.1111/j.1600-0625.2010.01128.x

[119] KIRWALE S, POOLADANDA V, THATIKONDA S, MURUGAPPAN S, KHURANA A et al. Selenium nanoparticles induce autophagy mediated cell death in human keratinocytes. Nanomedicine (Lond) 2019; 14: 1991–2010. https://doi.org/10.2217/nnm-2018-0397

[120] CHAKRABORTY R, BASU T. Metallic copper nanoparticles induce apoptosis in a human skin melanoma A-375 cell line. Nanotechnology 2017; 28: 105101. https://doi.org/10.1088/1361-6528/aa57b0

[121] SINGH SP, ALVI SB, PEMMARAJU DB, SINGH AD, MANDA SV et al. NIR triggered liposome gold nanoparticles entrapping curcumin as in situ adjuvant for photothermal treatment of skin cancer. Int J Biol Macromol 2018; 110: 375–382. https://doi.org/10.1016/j.ijbiomac.2017.11.163