



REVIEW ARTICLE

Advances in the treatment of non-melanoma skin cancer: a review of the current literature

Avances en el tratamiento del cáncer de piel no melanoma: revisión de la literatura actual

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ABSTRACT

Introduction: non-melanoma skin cancer (NMSC) is the most common malignant neoplasm worldwide. It includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Its incidence and mortality have increased, partly due to factors such as immunosuppression and sun exposure.

Objective: to structure the theoretical references on the most current procedures that allow for better treatment of non-melanoma skin cancer.

Methods: a systematic literature review was conducted following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Databases such as PubMed, Scopus, and Google Scholar were consulted. Studies addressing the main management and treatment approaches for NMSC were selected, and relevant findings were synthesized.

Development: non-melanoma skin cancer, which includes basal cell carcinoma and squamous cell carcinoma, is the most common type of cancer. Its management involves early diagnosis. Surgical treatment is the first-line option, although there are other therapeutic options such as HeberFERON® and the cryosurgery.

Conclusions: there are different treatment options for BCC and SCC. The decision regarding treatment is made based on the characteristics of the tumor and the overall health status of the patient.

Keywords: Non-melanoma skin cancer; Basal cell carcinoma; Squamous cell carcinoma; Treatment.

RESUMEN

Introducción: el cáncer de piel no melanoma (CPNM) es la neoplasia maligna más común a nivel mundial. Incluye el carcinoma basocelular (CBC) y el carcinoma epidermoide (CEC). Su incidencia y mortalidad han aumentado, en parte debido a factores como la inmunosupresión y la exposición solar.

Objetivo: estructurar los referentes teóricos sobre los procedimientos más actuales que permiten un mejor tratamiento del cáncer de piel no melanoma.

Métodos: se realizó una revisión sistemática de la literatura siguiendo los lineamientos PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Se consultaron bases de datos como PubMed, Scopus y Google Scholar. Se seleccionaron estudios que abordaron las principales formas de manejo y tratamiento del CPNM y se sintetizaron los hallazgos relevantes.

Desarrollo: el cáncer de piel no melanoma, que incluye carcinoma basocelular y carcinoma epidermoide, es el tipo más común de cáncer. Su manejo implica diagnóstico temprano. El tratamiento quirúrgico es el de

primera línea, aunque también existen otras opciones terapéuticas como el HeberFERON® y la criocirugía.

Conclusiones: existen diferentes formas de tratamientos para el CBC y el CCE. La decisión sobre el tratamiento se toma en función de las características del tumor y del estado general del paciente.

Palabras clave: Cáncer de piel no melanoma; Carcinoma basocelular; Carcinoma epidermoide; Tratamiento

INTRODUCTION

Non-melanoma skin cancer (NMSC) is characterized by the uncontrolled growth of abnormal cells caused by DNA damage. This damage triggers mutations or genetic defects that cause cells to multiply rapidly. Most authors agree that this condition is the most common malignant neoplasm worldwide. ^(1,2) It is divided into two major groups: melanoma (MC) and non-melanoma, the latter encompassing basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). ⁽³⁾

In recent years, both the incidence and mortality of skin cancer have increased, which has been associated with a higher number of immunosuppressed individuals (another risk factor for skin cancer) and an overall increase in population survival. However, Alonso-Belmonte C ⁽¹⁾ and Meléndez YR ⁽²⁾ affirm that the main environmental factor for developing skin cancer is sun exposure. ^(1,2,3)

According to the World Health Organization, this cancer is one of the most significant public health problems. Approximately ten million new cases of BCC and up to three million cases of SCC are diagnosed each year. Australia and New Zealand have the highest incidence worldwide, followed by the United States. In Latin America, Brazil has the largest number of affected individuals. ^(4,5,6,10)

Cuba is considered among the Latin American countries with the highest incidence of NMSC and ranks first in the Caribbean, with a rate of 55.46 per 100,000 inhabitants. Additionally, the Cuban Statistical Yearbook reported over thirteen thousand new patients in 2022. ^(2,10)

Therefore, considering these data and the fact that a quarter of the Cuban population is projected to be over 60 years old in 2025 ⁽⁴⁾ a factor associated with higher NMSC incidence it is necessary to direct all efforts toward its control and treatment. This led the authors to pose the following scientific

question: Which techniques are most effective in enabling better management of non-melanoma skin cancer?

Accordingly, the objective of this review is to structure the theoretical framework regarding the most current procedures that allow for improved treatment of non-melanoma skin cancer.

MATERIALS AND METHODS

A systematic literature review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to guarantee the thoroughness and reproducibility of the process. The focus was specifically on basal cell carcinoma and squamous cell carcinoma as the main variants of non-melanoma skin cancer.

The following characteristics were prioritized in the selected sources: Thematic relevance: sources that directly addressed basal cell and squamous cell carcinoma, as well as their diagnosis, treatment, and clinical management, were chosen. Scientific quality: peer-reviewed articles and publications in high-impact journals were selected, which guarantees the validity and reliability of the findings. Recency: a review period was established in order to include the most recent advances in research and treatment. Diversity of perspectives: studies that offered different approaches, including clinical trials, systematic reviews, and meta-analyses, were considered to provide a comprehensive view of the topic.

To carry out an exhaustive search of scientific literature, search engines such as PubMed, recognized for its extensive biomedical database and offering access to peer-reviewed articles in the medical field; Scopus, to access a variety of scientific literature including original articles, reviews, as well as conferences and patents; and Google Scholar, which allows a broad search across various academic disciplines, facilitating access to documents that may not be indexed in more specific databases, were used. Search strategies were developed by combining key terms related to non-melanoma skin cancer. The terms used included: "Basal cell carcinoma," "Squamous cell carcinoma," "Diagnosis," "Treatment," and "Clinical management."

Boolean operators (AND, OR) were applied to combine these terms effectively. For example, combinations such as "basal cell carcinoma AND treatment" were used to restrict the results to those addressing both aspects. Additionally, specific filters were applied to limit the results to peer-reviewed studies and publications within the established period.

The final selection of articles was carried out following strict criteria that ensure the quality and relevance of the content. The inclusion criteria were: articles published between 2020 and 2025 to ensure the information is up to date; studies that specifically addressed the diagnosis, treatment, and management of basal cell and squamous cell carcinoma; systematic reviews, meta-analyses, and controlled clinical trials providing relevant clinical data; and publications available in English, Spanish, and Portuguese. On the other hand, the exclusion criteria were: articles that were not peer-reviewed or presented significant methodological deficiencies; studies focusing on types of skin cancer other than basal cell and squamous cell carcinoma; documents that did not provide relevant clinical data or focused solely on epidemiological aspects without practical implications.

The period considered for this review ranged from January 2020 to March 2025. This timeframe was selected in order to include the most recent advances in non-melanoma skin cancer research, thus ensuring that the review reflects the current state of knowledge in this area.

Since the present study is a bibliographic review, no experiments were conducted, nor were human or animal subjects involved; therefore, approval from an ethics committee was not required. Copyrights of the consulted sources were respected, with each reference correctly cited according to Vancouver guidelines.

DEVELOPMENT

Skin cancer can originate from different cells; it is divided into melanoma, which arises from melanocytes, and non-melanoma, which originates from cells derived from the epidermis. The latter, in turn, includes basal cell carcinoma and squamous cell carcinoma. ⁽⁷⁾

The risk factors for developing this neoplasm are varied, including immunogenicity, genetics, and age. However, knowing that excessive sun exposure is the main modifiable cause of this condition in individuals with fair skin, the American dermatologist Thomas B. Fitzpatrick developed a classification into phototypes, which depends on each individual's response according to their ability to burn, tan, or not, in order to determine the risk of developing this disease. ^(11,23)

-Phototype I: has very fair skin, with high susceptibility to sunburn and no ability to tan.

- Phototype II: high susceptibility to sunburn and low tanning ability.
- Phototype III: skin with moderate susceptibility to sunburn and good tanning ability.
- Phototype IV: low susceptibility to sunburn and very good tanning ability.
- Phototype V: very low susceptibility to sunburn and excellent tanning ability.
- Phototype VI: It is darker skin, does not burn, and has excellent tanning ability.

Basal cell carcinoma

Basal cell carcinoma, also known as basal cell epithelioma or basalioma, is a malignant epithelial tumor of cutaneous location, which arises from the stem cells of the basal layer of the epidermis and the outer root sheath of the hair located at the level of the lower isthmus and the bulge. Its name is due to the fact that it is formed by cells very similar to those of the basal layer of the epidermis and skin appendages. ⁽⁸⁾

Studies by several authors confirm that it is the most common skin cancer and that in approximately 80 % of patients, it develops in areas of skin damaged by the sun, often in the absence of precancerous lesions. Additionally, it rarely appears on the palms, soles, or mucous membranes. It is characterized by slow growth and very rarely produces metastasis; however, it can cause local destruction of the skin, subcutaneous tissue, cartilage, and bone, resulting in high morbidity. It is also noted that the area of the body where this condition most frequently appears is the face, mainly the nose. ^(7,9,12)

It can present in different clinical forms, which may be pigmented or non-pigmented. These include: nodular or noduloglobular, superficial, morpheaform or sclerodermiform, scar-like flat, ulcerated, perforating or infiltrative, and Pinkus fibroepithelial. The most common form is nodular. ^(11,12)

According to the consulted sources, dermoscopy is a non-invasive technique that demonstrates high efficacy in the early detection of basal cell carcinoma, based on changes in pigmentation. In addition, it allows for the identification of cellular damage caused by intense sun exposure, recurrences, or variants of this carcinoma. Currently, this method is the most recommended for the follow-up of patients with risk factors, as—when combined with anamnesis—it helps prevent greater damage. Nevertheless, biopsy remains the gold

standard for diagnostic confirmation of BCC, providing a conclusive histopathological result on the affected cells. ^(13,14)

In immunocompromised patients, early biopsy is important to allow treatment of premalignant and malignant lesions as soon as possible. ⁽¹⁴⁾

If the disease is extensive, it is recommended to perform 3D imaging studies. Among these, magnetic resonance imaging (MRI) with contrast is preferred to determine the presence of perineural invasion or periorbital spread, while contrast-enhanced computed tomography (CT) is the most recommended option to evaluate bone involvement. Additionally, genetic testing is important for patients presenting with BCC before the age of 20 to rule out possible genetic syndromes. ⁽¹⁴⁾

In general, the authors agree that this neoplasm carries a low risk due to its locally invasive nature and low metastasis rate. It is recognized that—although it is the most common skin cancer—its prognosis is favorable if detected early. Most cases can be effectively managed with various treatments and prevented through sun protection.

Squamous cell carcinoma

Squamous cell carcinoma is a malignant neoplasm originating in the keratinocytes of the spinous layer, which develops predominantly in photo-damaged skin. It most frequently affects areas chronically exposed to ultraviolet radiation, such as the face, neck, scalp, décolleté, and extremities. Clinically, it presents a diverse spectrum of skin lesions, including papules, plaques, or nodules with a smooth, ulcerated, or hyperkeratotic surface. ^(18,21)

Squamous cell carcinoma accounts for approximately 20 % of all skin cancers, ranking as the second most frequent after basal cell carcinoma. Its incidence has experienced a significant increase, mainly associated with population aging and cumulative sun exposure, especially during early stages of life. ^(19,20)

According to recent estimates, the global incidence rate of SCC reaches 38.16 cases per 100,000 people per year, reflecting its growing impact on public health. ^(19,20)

As in BCC, the most important risk factor for the development of SCC is chronic exposure to ultraviolet radiation. However, smoking, human papillomavirus (HPV) infection, immunosuppression, and recently transplanted patients are also described as predisposing factors for this type of carcinoma. ⁽²¹⁾

SCC, according to its degree of infiltration, presents different clinical forms: in situ forms are considered precursor lesions, including actinic keratosis with transepidermal atypia, Bowen's disease, Erythroplasia of Queyrat, and Bowenoid papulosis. Infiltrative forms include exophytic (vegetative or keratotic), endophytic (ulcerated), and exoendophytic (ulcerovegetative). Additionally, there are special forms such as verrucous carcinoma or keratoacanthoma. ⁽¹¹⁾

For diagnosis, a set of clinical, dermatological, and histopathological criteria is used. Factors such as age, sex, phototype, and exposure to biological, chemical, or physical agents are considered. Additionally, using dermatoscopic evaluation, criteria related to keratin, the presence of vascular structures, and those related to pigment are differentiated. However, both the international community and Cuban authors agree that, for a definitive histopathological confirmation, a biopsy of the lesion must be performed. ^(11,21)

In contrast to BCC, authors consider squamous cell carcinoma a tumor with a higher potential for aggressiveness and metastasis. Although it is also treatable—especially in early stages—the need for early detection and proper management is emphasized due to its ability to spread to adjacent tissues. Continuous monitoring of patients with risk factors, as well as education on sun protection and other predisposing factors, is strongly highlighted.

Treatment of basal cell and squamous cell carcinoma

The therapeutic approach for cutaneous squamous cell carcinoma and basal cell carcinoma is fundamentally based on surgery, considered the first-choice treatment when the patient's clinical conditions allow. Conventional surgical excision and Mohs micrographic surgery stand out as the most commonly used surgical techniques, with the latter being particularly useful in critical anatomical locations or tumors with poorly defined borders. ^(14,15,22)

For cases in which surgical intervention is not feasible, there are various equally effective non-invasive or minimally invasive therapeutic alternatives. Topical options include Imiquimod and 5-fluorouracil, while photodynamic therapy and cryosurgery represent valid alternatives for superficial lesions. HeberFERON® and intralesional/perilesional interferon offer biological treatment options, particularly in selected cases. ^(14,15)

Radiotherapy constitutes another important therapeutic alternative, especially indicated for elderly patients or when there are contraindications to surgical procedures. The selection of the optimal treatment should be based on a

comprehensive evaluation that considers the tumor characteristics, patient conditions, and available resources, always ensuring the best oncological and functional outcome. ^(11,22)

Mohs surgery constitutes the first-line treatment for non-metastatic squamous cell carcinomas, allowing precise control of tumor margins through intraoperative histological evaluation. This technique offers the highest cure rates by ensuring complete resection of the neoplasm while preserving healthy tissue as much as possible, thereby minimizing the risk of recurrence. ⁽²²⁾

For basal cell carcinomas, conventional surgical excision represents the standard therapeutic option in primary low-risk cases (slow-growing, non-aggressive pattern), particularly when located on the trunk or extremities. In BCCs with aggressive behavior or infiltrative pattern in these locations, this surgical approach may also be considered. The main advantage of this method lies in the possibility of complete histopathological analysis of the excised specimen, although it should be noted that approximately 10–15 % of cases may require reintervention due to involved margins. ^(11,15)

For low-risk BCC, a lateral surgical margin of 4 mm down to the subcutaneous tissue (SCT) is recommended, which provides an adequate rate of tumor-free margins. In high-risk cases (aggressive, recurrent tumors or in the H-zone), margins should be extended to 6–10 mm. When positive margins persist after resection, adjuvant radiotherapy may be considered. ^(11,15)

For primary SCCs without high-risk factors, a 5 mm margin offers a 95 % probability of obtaining histologically clear margins. For high-risk SCCs (size >2 cm, poor histologic grade, H-zone location, perineural invasion), margins of 6–10 mm are recommended. It is essential to evaluate each case individually considering: 1) the subclinical extent of the tumor, 2) proximity to critical anatomical structures, and 3) potential aesthetic-functional impact. ^(11,22)

On the other hand, HeberFERON® is a drug produced in Cuba for the treatment of individuals with skin cancer that reduces non-melanoma skin tumors and prevents surgical sequelae in facial areas. This medication avoids complex surgeries in regions with a high frequency of recurrence, such as the ears, nose, eyelids, and periorbital area, as well as their sequelae. It has a distant curative effect, as it is injected into a lesion and surrounding lesions decrease in size or are eliminated. It helps improve the aesthetics of patients with this type of condition, thereby overall enhancing the quality of life of affected individuals. The treatment involves diluting 10.5 million units of the lyophilized powder in 1 cc of injection-grade water and applying it perilesionally in the superficial dermis. A total of three weekly sessions are

performed over three weeks. An appropriate doctor-patient relationship is maintained to monitor any reported adverse effects, all of which are tolerable and managed with medical treatment. The response is evaluated by dermoscopy sixteen weeks after starting the treatment to determine whether complete disappearance of the lesion has occurred. (8,10,16,22)

Cryosurgery is considered a physical treatment in which subzero temperatures with a continuous flow of nitrogen cause the temperature to drop extremely, thereby inducing the local destruction of damaged cells and tissues effectively and in a controlled manner. Cryosurgery is one of the most accessible treatments due to its low cost and also allows preservation of the anatomy in areas with large lesions. Although it is a treatment that takes more time than standard surgery to remove the lesion, it achieves excellent results in healing and, above all, in preserving aesthetics. (15,17,24)

CONCLUSIONS

Non-melanoma skin cancer has surgery as the first-line treatment, which is effective and presents a low recurrence rate. Alternatives such as HeberFERON® and cryosurgery are options for patients who are not surgical candidates or wish to preserve aesthetics. The choice of treatment is based on tumor characteristics and the patient's overall well-being.

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STATEMENT OF AUTHORSHIP

EPC: Conceptualization. Data curation. Formal analysis. Funding acquisition. Investigation. Methodology. Writing – original draft and Writing – review & editing.

MVG: Conceptualization. Data curation. Formal analysis. Funding acquisition. Investigation. Methodology. Writing – original draft and Writing – review & editing.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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