



Is It Time to Abandon the Nomenclature of Non-Melanoma Skin Cancer?

Isabel Longo M*

Department of Dermatology, University of Florida Health, USA

Editorial

Classically, Non-Melanoma Skin Cancer (NMSC) encompasses Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) which affect more than 3 million people yearly in the United States [1]; but, depending on the source consulted, it can also include sarcomas and lymphoproliferative neoplasms, among others. Therefore, we do not have a unifying concept for defining non-melanoma skin cancer.

What was the original purpose for this classification of melanoma and NMSC? The first reference to the term “non-melanoma skin cancer” in the English literature appeared in 1974; two years after the first cases of what is known today as Merkel cell carcinoma were reported. The article mainly addressed the demographic characteristics of BCC and SCC, excluding “Bowen’s disease, carcinoma in situ and a few cancers of unknown and varied types” [2]. Was the purpose to classify the most common types of skin cancer based on the cell of origin: Melanocyte vs. keratinocyte? If that was the original goal, soon it became clear that the distinction was mostly related to prognosis. With time, and mostly for didactic purposes, the category of NMSC ended up including all types of malignant neoplasms that are not melanoma, some of which are more aggressive than it.

Forty-seven years ago, the panorama of skin cancer was strikingly different from what it is today. The increased life expectancy, especially of patients with chronic immunosuppression due to drugs, infections (HIV) and malignancies, has brought a rising incidence of skin cancer types that were a rarity at that time, and has changed the biologic behavior of, otherwise, mostly indolent neoplasms. A similar or an even greater number of patients die from cutaneous SCC compared to melanoma given the increased incidence of aggressive tumors in high risk patients [3], but the lack of registries hinders this assessment. Merkel cell carcinoma, whose overrepresentation in immunosuppressed patients pointed towards a possible infectious cause that was described in 2008 [4], has a higher mortality rate than melanoma. It is also thought to have a dual origin from the keratinocytes and fibroblasts based on the positivity for polyomavirus [5,6]. Adnexal carcinomas such as sebaceous carcinoma [7] and microcystic adnexal carcinoma have a high rate of recurrence that is not comparable to the generally more indolent behavior of most basal cell and squamous cell carcinomas [8]. All these skin cancers, and many more, are included under the “non-melanoma” group making “melanoma” the paradigm of a highly aggressive skin tumor, leading to the misconception that “non-melanoma skin cancer” has a more favorable course.

Our knowledge about the pathogenesis of BCC and SCC has evolved from being regarded as merely sun-related skin neoplasms to the identification of specific mutations which, together with a better understanding of the role of immune surveillance in tumor biology, has led to the development of targeted therapies. The identification of the PTCH mutation in sporadic and hereditary basal cell carcinoma in 1996 allowed the development of inhibitors of the Hedgehog pathway for the treatment of locally advanced and metastatic disease [9,10]. Immune checkpoint inhibitors, initially developed for metastatic melanoma, are current therapies for locally advanced or metastatic cutaneous SCC and metastatic Merkel cell carcinoma. The identification of genetic alterations of specific factors related to squamous cell differentiation such as NOTCH, TP63 and SOX genes in cutaneous squamous cell carcinoma highlights their common biology with squamous cell carcinomas of other anatomic sites, and marks the significant differences in pathogenesis with other keratinocytic tumors such as BCC [11]. Indeed, it has been shown that one particular feature of SCC of any site is their high degree of cellular heterogeneity, with cell populations at different stages of differentiation, which can be reversed to an increased proliferative stage or enter into a dormant state. This may explain the higher reduction of SCC incidence compared to BCC in solid organ transplant recipients receiving acitretin as chemoprophylaxis [12].

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*Correspondence:

Isabel Longo M, Department of Dermatology, University of Florida Health, 4037 NW, 86th Terrace Gainesville, FL 32606, USA, Tel: 352-594-1922; Fax: 352-627-4336; E-mail: mlongo@dermatology.med.ufl.edu

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As of 2020, the National Comprehensive Cancer Network (NCCN) guidelines include BCC, SCC, dermatofibrosarcoma protuberans [13] and Merkel cell carcinoma under “non-melanoma skin cancer”. Therefore, this classification is not accurate for distinguishing melanoma from non-melanoma skin cancer based on prognosis or cell type.

Maybe it is time to reconsider the nomenclature of “non-melanoma skin cancer” as its definition is becoming more confusing in light of epidemiological changes and new insights regarding tumor pathogenesis. Some authors have suggested replacing the term “non-melanoma skin cancer” for basal and squamous cell carcinoma by “keratinocyte carcinoma” but this nomenclature is still inaccurate given the genetic heterogeneity and the fact that other highly aggressive skin cancer such as Merkel cell carcinoma [14] can have a keratinocytic origin too.

The complexity of skin cancer biology makes it challenging to develop a practical classification. The skin is the organ system with the highest diversity of malignant neoplasms, and some lack a defined differentiation. There are over 50 recognized malignant skin tumors (excluding hematological malignancies) with three types (BCC, SCC and melanoma) comprising more than 95% of all skin cancers [15].

Maybe it is time to start naming the most common skin cancers individually by their full name with type and histological subtype for “first” and “last” names, respectively. Basal cell carcinoma, cutaneous squamous cell carcinoma and melanoma have each ten distinct histological subtypes, besides additional types that are not included in the World Health Organization (WHO) classification. Distinct subtypes can have widely different prognosis in terms of risk of recurrence and metastases. It is imperative that the histological subtype is specified in the pathology report as this determines recommendations for management. The course of the disease strongly depends on the tumor characteristics and patient’s condition, mostly related to the immune status.

Given that skin cancer is a major public health issue, heavily referenced in the media to increase awareness among the general population for early diagnosis, possibly, a simple classification based on frequency and prognosis can better serve the interests of patients and health care professionals. Explaining to patients what skin cancer is and what they should expect can be more straightforward by avoiding the nomenclature of “Non-Melanoma Skin Cancer”. This provides reassurance and accurate information in the face of misleading concepts regarding the overall fatality associated with melanoma, and the underestimated aggressiveness of other “Non-Melanoma” types of skin cancer. An individual nomenclature for basal cell carcinoma and squamous cell carcinoma may favor the development of registries, especially for high-risk lesions, which will build robust epidemiological data that can be used to facilitate coverage of specific drugs for their treatment and prophylaxis.

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