

Insight on common forms of cutaneous head and neck carcinoma (Review)

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Abstract. To improve the outcome and quality of life for patients with head and neck carcinoma, an increasing amount of research has been performed on the particularities of this type of cancer and its treatment methods. Starting from clinical aspects, including histology and imaging features, up-to-date studies from different parts of the world have determined new data leading to a better understanding of the mechanisms behind the disease and proposed new treatment protocols. The head and neck areas are predisposed to almost all skin neoplasms, most commonly those related to ultraviolet exposure. Squamous cell carcinoma and basal cell carcinoma account for almost 90% of non-melanoma skin cancers in this region; therefore, reviewing the literature on cutaneous carcinomas of the head and neck area and sharing particular aspects of their physiopathology are beneficial for a great number of patients.

Contents

1. Introduction
2. Squamous cell carcinoma
3. Basal cell carcinoma
4. Treatment challenges
5. Conclusions

1. Introduction

The medical community is constantly concerned about the rising number of cancer cases. With today's knowledge and technology, there is high interest in studying the mechanisms behind cancer activity and finding new treatment options (1). Out of all human cancers, 5% are head and neck carcinomas, combining cancers of the epithelial lining of the nasopharynx, oropharynx, oral cavity, hypopharynx and larynx. The most common types of carcinomas evolving in the head and neck area are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) (2). There are certain risk factors associated with head and neck carcinoma, such as smoking, consumption of alcohol, nutrition deficiency, inadequate oral hygiene, Epstein-Barr virus, human papillomavirus (HPV) or *Candida Albicans* infections (3) (Fig. 1). With 60% of the cases already in advanced stages III or IV (4) by the time of the first medical examination, recent studies have focused their research not only on the activity of the cells but also on the behavior and evolution of the lesion, establishing new connections between action and reaction (5).

From a treatment perspective, decisions are frequently the result of multidisciplinary approaches, combining chemotherapeutic, radiotherapeutic, immunotherapeutic and surgical procedures (6). For improved outcomes with higher survival rates, new research has raised interest in the interaction between the immune system and cancer cells (7).

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Abbreviations: SCC, squamous cell carcinoma; BCC, basal cell carcinoma; HPV, human papillomavirus; UV, ultraviolet; TCR, T-cell receptor; MHC, major histocompatibility complex; HLA, human leukocyte antigen; GLUT, glucose transporter

Key words: squamous cell carcinoma, basal cell carcinoma, head and neck skin cancer

2. SCC

SCC of the head and neck is a type of epithelial neoplasm with 65,000 diagnosed cases in the US in 2019 (8). SCC frequently appears in the older age category (onset at >50 years of age), more common in men than in women, usually individuals with a light skin color (9). When located on the head, it has been discovered that ear and lip areas have higher chances of developing SCC than BCC and the most important etiologic factor is chronic exposure to ultraviolet (UV) irradiation, which leads to free radicals that form thymidine dimers in the DNA, affecting DNA repair and cellular immunity (10). Other factors, such as ionizing radiation, smoking, chronic inflammation and arsenic, have a huge impact as well. HPV has an important part in the epidemiology of oropharyngeal and head and neck cancers and it is frequently detected in younger patients. HPV is thought to be a unique entity with a better prognosis (11). Immunosuppression has a key role in the onset and evolution of SCC, and patients who have undergone this type of therapy or simply have a weak immune status are more likely to develop SCC and have an aggressive form of the disease (12). SCC appears clinically as a slow-growing nodule or plaque that may at times be ulcerated (13), with firm consistency and pink color or with no alteration of skin color (14). In numerous cases, SCC is associated with an inflammatory skin condition such as vitiligo, acne conglobata, lupus vulgaris, burn, scars or actinic keratosis (15). Actinic keratosis is described as multiple, small lesions that are erythematous and hyperkeratotic, usually seen on sun-exposed skin. The lifetime risk of progression from actinic keratosis to SCC is estimated to be ~8% (16).

Histological features of invasive SCC have anepidermal origin. Well-differentiated SCC is distinct with a keratinizing aspect, an eosinophilic cluster with squamous cells, intercellular links and minimal nuclear atypia (17).

Moderately-differentiated SCC types have more atypia and mitoses, while poorly-differentiated SCC types usually have limited keratinization, making them difficult to be recognized. In these cases, immunohistochemistry is helpful by using antibodies against keratins to demonstrate the squamous origin (18).

Statistically, the recurrence risk is 3.7-10.9, and the metastatic risk is up to 3.3% (19). Risk factors for recurrence and metastasis are immunosuppression, lymph node status, poor differentiation, location or perineural invasion (20). Special attention is required for lesions from burns or radiated areas, chronic ulcers or scars. Regarding the location, lip SCC is the most aggressive one, with recurrence and metastasis rates of >10% (21). In the pathophysiology of SCC, the importance of the TP53 gene has been frequently described. The main role of the gene is tumor suppression by regulating cell cycle progression, apoptotic cell death and DNA repair. In cutaneous SCC, the TP53 gene frequently displays a characteristic UV pattern with 'C' to 'T' or 'CC' to 'TT' mutations at dipyrimidine sites (22). Experimental p53-deficient mice develop UV-induced SCC after very short exposure, proving not just the protective role of the gene but also the harmful action of UV (23). Even if today this neoplasm is totally curable through surgery (24), the patients' outcome is affected by the size of the tumor at diagnosis (>2 cm), the depth of invasion (>4 mm),

poor or undifferentiated histological grade and the presence of metastasis (25). However, it has been discovered that cutaneous SCC in the head and neck region has a different evolution compared with its evolution from other origins, such as the oral cavity, mucosa or lungs, where the chances of metastatic invasion are higher (26).

3. BCC

BCC, formerly known as basal cell epithelioma, was first described by Jacob in 1824 and is the most common type of cutaneous carcinoma on the head and neck area, frequently as a result of acute, intermittent UV exposure (27). Other important risk factors are immunosuppression due to certain treatments or infections (human immunodeficiency virus infection, transplants) and ionizing radiation. The next affected areas are on the trunk, arms and legs but have been reported cases of BCC on breasts, axillae, genitalia, perianal area, palms and soles (28). It has a low mortality rate and rarely exhibits metastatic behavior, but it has a high recurrence rate, particularly when the invasion is perineural (29). It usually affects males more than females, presumably because of the typical male professions, which imply more exposure to UV. Males are also known to be susceptible to a greater number of tumors (30). The typical patient is a Caucasian, light-skinned man, over 40 years of age, with blue eyes and light or red hair.

Due to the aging of the population all around the globe and the thinning of the ozone layer, which provides higher UV exposure, BCC is affecting an increasing number of individuals (31). The number of cases increases with age and the peak is known to be between 60 and 70 years of age. This is due to a reduced capacity of DNA repair ability and a weaker immune system (32). In addition, an important factor in BCC ethology is individual susceptibility. It refers to each individual's amount of melanin deposited in the skin and the capacity to tan when exposed to UV. Usually, darker skin is more protected by melanin storage. With a locally aggressive characteristic, it may easily invade cartilage and bone, resulting in deforming lesions with high morbidity rates (33). The primary location of the tumor is in the epidermis, and it has a slow-growing evolution (34). Facial BCC, particularly in the nose and ear areas, may have a recurrent evolution in time, but in general, metastasis is rare and exhibits no precursor lesions (35). Clinically, it appears as a distinct, translucent papule with telangiectasias which may at times be ulcerated (36). The subtypes of BCC are nodular, micronodular, superficial, infiltrative and fibroepithelioma of Pinkus. In the head and neck area, the nodular one is the most common subtype. This subtype is distinguished by nodular lobules of tumor cells with mucin-rich stroma that strip in the epidermal layer with little invasion into the dermis (37). In most cases, it takes 15 to 20 years to get from primary UV damage to the diagnosed lesion. The direct impact is major at the DNA and RNA level, forming covalent bonding between adjacent pyrimidines and resulting in mutagenic products (38). Another mechanism involves reactive oxygen species that directly attack the DNA and slow down the cutaneous immune system by affecting the local antitumor monitoring activity of dendritic cells (39).

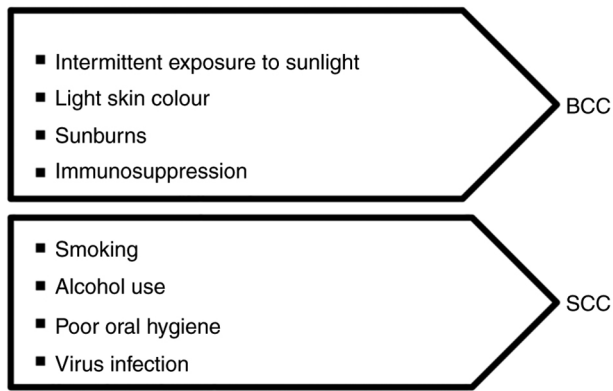


Figure 1. Risk factors for the development of BCC and SCC. In order of association, the most significant risk factors linked with head and neck SCC and BCC are provided. SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

4. Treatment challenges

The outcome of head and neck cutaneous carcinoma treatment strategies has improved over the past decade. Multidisciplinary teams frequently obtain better results by prioritizing toxicity reduction and the patients' quality of life (40). Early detection and surgical procedures have higher chances of cancer-free outcomes and the standard nonsurgical option in most cases is still chemoradiotherapy with epidermal growth factor receptor cetuximab treatment (41).

Skin toxicity and radiation dermatitis. Irradiation of the skin causes tissue damage and inflammatory cell recruitment by damaging epidermal basal cells, endothelial cells, vascular components and reducing the number of Langerhans cells (42). Radiation dermatitis is a particularly common side reaction to radiotherapy for head and neck carcinoma. Most patients experience mild to moderate degrees of skin lesions (such as grades I and II) but up to 25% develop severe reactions. In severe radiation dermatitis (grades III or IV), the epidermis is infiltrated with neutrophils and there are high rates of apoptosis in the deeper layers (43). The standard administration of radiation involves successive doses and it frequently prevents tissue healing due to cellular repopulation, even if the patient takes a few days to break during cures of daily fractionated therapy, thereby compromising the result (44). The general management of radiation dermatitis includes washing once or twice a day with pH-5 soap, moisturizing shaving to prevent folliculitis, debridement and checking for systemic inflammation (45). Is it highly recommended to use aloe vera and to avoid exposure to sunlight, scratching and local trauma. To prevent severe skin toxicities, patients and physicians must look for early signs of radiation dermatitis (46).

Vaccination options. The development of vaccines is currently the most widespread method to prevent infections with different germs or the development of cancer cells (47). Head and neck squamous cell carcinoma, including cutaneous locations, is caused by both external conditions and genetic mutations. Cancer vaccines may be of two types, prophylactic and therapeutic (48). Therapeutic vaccines use the host's immune system to recognize

and eliminate cancer cells (49). It acts in the opposite direction of tumor invasion mechanisms (50), targets antigens associated with tumors, and induces a widespread mediated immune response (51). Current research includes modified virus tumor vaccines, DNA, proteins, peptide-based vaccines and combined strategies, all demonstrating encouraging results (52).

Peptide-based vaccines. The purpose of peptide-based vaccines is to stimulate the body's immune system. After the administration of the vaccine, the antigens are taken up and processed by the antigen-presenting cells (53). The antigen is then delivered via the T-cell receptor (TCR)/major histocompatibility complex (MHC) complex to CD8+ T-cells (54). These may differentiate into cytotoxic T-cells that are capable of directly killing cancer cells. Compared to classic vaccines, the peptide-based ones have no mammal cytotoxicity, are less likely to induce allergies or autoimmune responses, are relatively simple to produce and are cost-effective, allowing the expansion of production depending on the need (14). The addition of lipids, carbohydrates and phosphates is allowed in order to improve stability and immunogenicity (55). Peptide purity may be evaluated by techniques such as mass spectrometry. In addition, peptide stability may be demonstrated by standard physicochemical characterization (56). They contain several epitopes and may be designed to target single or multiple pathogens in different phases of the cell life cycle (57). Genetic recombination has not been associated with any documented risks (58). The main issue with using peptide-based vaccines remains poor immunogenicity and the need for an administration system or adjuvants such as TCR ligands, cytokines or co-stimulatory molecules to obtain the intended effect (59). Another limitation of vaccines is the restriction of MHC molecules. They must match the patient's human leukocyte antigen (HLA) (60). In individuals with different MHC class, I molecules, a specific trigger may not induce cell-mediated immunity. In addition, due to HLA polymorphisms, it is difficult to create a universal, effective vaccine for the entire human population. The solution to this problem may be the development of a long peptide containing multiple antigenic epitopes (61). For instance, patients with positive HLA-A24 who suffer from oral cancer may safely use the Survivin-2B peptide vaccination in order to achieve tumor regression (62). Survivin-2B is a novel member of the inhibitor of apoptosis protein family and may be found in most malignancies but is rarely expressed in normal adult tissue. This apoptosis inhibitor is the only one that is expressed in the G₂ and M phases of the cell cycle (63). Its oncogenic potential lies in its capacity to overcome the G₂-M checkpoint for mitotic progression (64). Survivin-2B80-88-specific cytotoxic T-lymphocytes were induced from peripheral blood mononuclear cells after stimulating the peptide *in vitro*. The vaccine may be injected subcutaneously or intratumorally with important therapeutic potential and no adverse events (65).

DNA and RNA vaccines. Nucleic acid-derived vaccines may be synthesized faster than peptide-based ones, which is one of their advantages. DNA vaccines are used with molecules such as IL-2 and macrophages or granulocytes, which are relatively stable and able to activate CD4+ and CD8+ T-cells (66). Furthermore, plasmid DNA may also activate the inborn immune system by recognizing the double-stranded DNA structure. To be effective, DNA vaccines require to

Table I. Trials evaluating treatment strategies for head and neck carcinoma.

Trial registry details/number	Condition	Intervention	Phase	Endpoints	Years
Trial of intratumoral administration of HF 10, a replication-competent herpes simplex virus type 1, in patients with refractory head and neck cancer or solid tumors with cutaneous and/or superficial lesions; NCT01017185	Refractory head and neck cancer, SCC	Drug: HF 10	I	Assessment of the local tumor response of HF10	2015-2019
Addition of pembrolizumab to postoperative radiotherapy in cutaneous SCC of head and neck; NCT03057613	SCC of head and neck	Drug: Pembrolizumab; Radiation: IMRT 60-66 Gy	II	Number of subjects with dose-limiting toxicities	2017-2022
Study of Lenvatinimib and Cetuximab in patients with recurrent/metastatic head and neck SCC and cutaneous SCC; NCT03524326	Head and neck SCC, cutaneous SCC	Drug: Lenvatinimib pill, Cetuximab	I	Maximum tolerated dose of Lenvatinimibwith Cetuximab	2018-2022
Study of radiation therapy and Vismodegib for advanced head/neck BCC; NCT01835626	Locally advanced BCC	Drug: Vismodegib; Radiation: Radiation therapy	II	Local-regional control rate at 12 months from protocol therapy completion	2013-2021
Clinical trial of survivin-derived peptide vaccine therapy for patients with advanced or recurrent oral cancer; UMIN000000976	Advanced or recurrent oral cancer; HLA-A24 positive	Drug: Survivin-2B eptide	I	Level of tumor regression	2003-2010

SCC, squamous cell carcinoma; BCC, basal cell carcinoma; HLA, human leukocyte antigen.

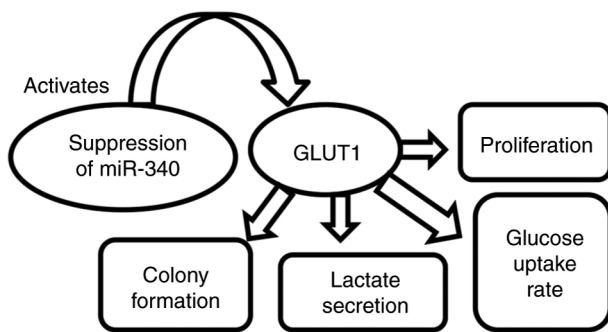


Figure 2. Metabolism of miR-340 in head and neck squamous cell carcinoma. The downregulation of miR-340 acts as a metabolic switch by regulating GLUT1 activity and promoting cancer cell growth. miR, microRNA; GLUT, glucose transporter.

penetrate the cell membrane and the nuclear membrane (67). RNA vaccines do not need to penetrate the nuclear membrane but are less stable compared to DNA vaccines. In a previous study, RNA epitopes were given as liposomal complexes. The complex was successfully taken up by dendritic cells, producing an immediate antigen-specific T-cell response (68). Currently, these vaccines are in the experimental phase and are personalized, but they may become the standard for head and neck SCC immunotherapy (69).

MicroRNA (miRNA) biology. MiRNAs are single-stranded RNA molecules with a length of 21-23 nucleotides that control the expression of >50% of human genes. Each miRNA molecule is able to recognize numerous mRNA transcripts and regulate a great number of genes downstream (70). The activity of miRNA involves modifications of the cell cycle, cellular differentiation, proliferation, survival, motility, apoptosis and morphogenesis, which are all involved in the carcinogenesis of head and neck carcinoma (71). Metabolic reprogramming is an important indication of cancer, and as a highly dynamic process, it facilitates the transformation of a normal cell into a malignant cell (72). Aerobic glycolysis is an altered metabolic pathway frequently observed in cancer cells. The mechanism changes the role of cell energy, making it less efficient but supporting invasion, migration and drug resistance. For this substantial amount of energy, cancer cells require a higher glucose intake (73). The glucose transporter (GLUT) protein family has 14 members, but only GLUT1 and GLUT3 are aberrantly expressed in carcinomas of the head and neck (74). MiR-218 is a tumor-suppressor mRNA that downregulates the proliferation, invasion and metastatic potential of numerous types of cancer cell. Inhibition of miR-218 by activating GLUT1 expression increases proliferation and glucose uptake (75). Related to miR-218, miR-340 regulates GLUT1 expression by increasing glucose absorption and lactate secretion. Inhibition of miR-340 activates GLUT1 and

promotes proliferation and colony formation with high glucose uptake. Another mRNA with an oncogenic role in head and neck SCC is miR-10a, which acts like an upstream regulator of GLUT1 (76). The metabolic processes regulated by miR-340 in head and neck SCC are presented in Fig. 2.

The Cancer Genome Atlas data confirmed the upregulation of another mRNA in head and neck SCC, miR-31-5p. The overexpression of miR-31-5p increases free fatty acids aggregation and lipid droplet formation by targeting acyl-CoA oxidase 1, enhancing prostaglandin E2 (77). MiR-31-5p promotes migration and invasion of cancer cells (78).

As head and neck SCC is a group of different cancers, various anatomical areas may serve as a starting point with diverse characteristics and outcomes. Currently, studies are devoted to the identification of site-specific miRNA signatures for every subtype of SCC (79).

Downregulation of anti-apoptotic proteins. Tumor progression and drug resistance are strongly associated with defects in apoptosis signaling (80). Dysregulation of apoptosis chaotically prolongs cancer cell life, resulting in gene mutations (81). The Bcl-2 family of proteins is relevant in the apoptosis signaling process through their anti- and pro-apoptotic members, which may interfere with one another's functions while heterodimerizing and controlling the death signaling pathway. Members of the Bcl-2 family are frequently expressed in head and neck SCC, with various locations, including on the skin, where they have a key role in tumor initiation and evolution (63). Since overexpression of Bcl-2, Bcl-X_L or survivin is associated with Cisplatin and Etoposide chemoresistance in head and neck carcinomas, biological research indicates that antisense oligonucleotides may be used as a competitor in favor of tumor cell death (82). Antisense oligonucleotides have therapeutic potential by inhibiting Bcl-2 proteins and blocking tumor cell progression. In addition, decreasing Bcl-X_L expression induces apoptosis in gastric cancer cells (83). *In vitro* experiments demonstrate an increased apoptosis rate and high drug sensitivity when antisense oligonucleotides are used against survivin expression (84).

Several studies have been performed with different strategies regarding the treatment of head and neck carcinoma. Whether combining drugs with radiation or just using immunotherapy, recent trials indicated positive results regarding not only the regression of the tumors, control of metastatic rates and recurrent behavior, but also severe adverse events (85). The trials looked at the effects of specific drugs such as HF-10, pembrolizumab, Lenvatinimib, cetuximab, vismodegib or survivin-2B peptide alone or in combination with radiotherapy. The most common events were radiation-induced skin injuries, decreased lymphocyte count, dysgeusia (86), myalgia and fatigue (87). Table I provides a summary of the trials evaluating treatment strategies for head and neck carcinoma.

5. Conclusions

SCC, a keratinocyte malignancy (88), is the second most common skin cancer and accounts for almost 20% of epithelial neoplasms. Its invasive character may evolve into metastases in the lymph nodes or distant organs (89). BCC is the most common form of cutaneous cancer (90). BCC development is a combination of genotype, phenotype and exposure factors

since >80% of all cases are located in sun-exposed areas. For the head and neck area, the nodular and pigmented types are found in most patients (91). In terms of prevention and recommendations, first of all, acknowledging the risk factors is important, but so are early diagnosis and proper treatment strategies (92). A better understanding of the underlying mechanisms of SCC and BCC may improve the future treatment standards for head and neck cancer, with high chances of increasing survival rates and minimizing local reactions (50). Combining existent resources with newer, experimental therapies will not only improve the quality of life for these patients but also give them a higher life expectancy (93). Even though immunotherapy has a growing potential in cancer treatment as a single agent, strategies with more than one target are proven to be more successful (37).

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Availability of data and materials

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Authors' contributions

AF and CS revised the manuscript and are the corresponding authors. ALT summarized the literature findings and wrote the manuscript. DI, DV, AIP, FB and MIS analyzed the literature data. AIP, DV, FB and AZ searched and selected the articles that were included as references. DI, AF, CS, DV, AZ and MIS reviewed the literature findings, critically revised the manuscript and approved the review in its current form. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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