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

DORIANA CRISTEA-ENE IANCU[1,2], ANA FULGA[1,2], DOINA VESA[1,2], CONSTANTIN STAN[1,2], ANDREI ZENOVIA[3], FLORIN BUJOREANU[4,5], ALIN IONUT PIRAIANU[2,6], MIHAELA IONELA SARBU[2] and ALIN LAURENTIU TATU[2-5]

[1]Department of Otorhinolaryngology, 'Sfantul Andrei' Emergency Clinical Hospital of Galati, 800578 Galati; [2]Clinical Surgical Department, Faculty of Medicine and Pharmacy, 'Dunarea de Jos' University of Galati, 800010 Galati; [3]Department of Otorhinolaryngology, 'Cai Ferate' General Hospital, 800223 Galati; [4]Department of Dermatology, 'Sfanta Cuvioasa Parascheva' Clinical Hospital of Infectious Diseases; [5]Multidisciplinary Integrative Center for Dermatologic Interface Research (MIC-DIR), 800179 Galati; [6]Department of Forensic Medicine, 'Sfantul Andrei' Emergency Clinical Hospital of Galati, 800578 Galati, Romania

Received August 28, 2022; Accepted January 5, 2023

DOI: 10.3892/mco.2023.2624

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.

Correspondence to: Dr Ana Fulga or Dr Constantin Stan, Clinical Surgical Department, Faculty of Medicine and Pharmacy, 'Dunarea de Jos' University of Galati, 35 Alexandru Ioan Cuza Street, 800010 Galati, Romania
E-mail: ana.fulgaa@gmail.com
E-mail: const.stan@ugal.ro

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

Contents

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).

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).

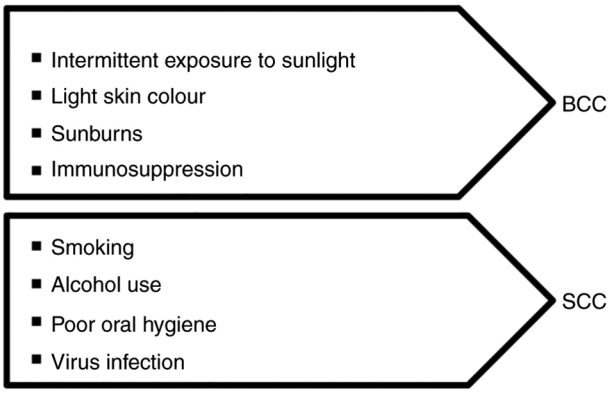

Figure 1. Risk factors for the development of BCC and SCC. In order of association, the most significant risk factors linked with head and neck SCC and BCC are provided. SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

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 G_2 and M phases of the cell cycle (63). Its oncogenic potential lies in its capacity to overcome the G_2-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.

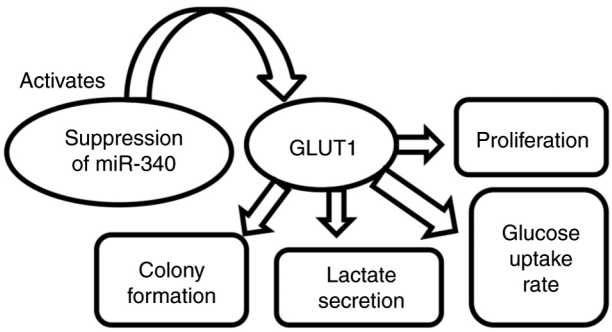

Figure 2. Metabolism of miR-340 in head and neck squamous cell carcinoma. The downregulation of miR-340 acts as a metabolic switch by regulating GLUT1 activity and promoting cancer cell growth. miR, microRNA; GLUT, glucose transporter.

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 Bc-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).

Acknowledgements

Not applicable.

Funding

The present study was supported by the 'Dunarea de Jos' University of Galati.

Availability of data and materials

Not applicable.

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.

References

1. Zhu G, Lin JC, Kim SB, Bernier J, Agarwal JP, Vermorken JB, Thinh DHQ, Cheng HC, Yun HJ, Chitapanarux I, *et al*: Asian expert recommendation on management of skin and mucosal effects of radiation, with or without the addition of cetuximab or chemotherapy, in treatment of head and neck squamous cell carcinoma. BMC Cancer 16: 42, 2016.

2. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE and Grandis JR: Head and neck squamous cell carcinoma. Nat Rev Dis Primers 6: 92, 2020.
3. Jicman Stan D, Niculet E, Lungu M, Onisor C, Rebegea L, Vesa D, Bezman L, Bujoreanu FC, Sarbu MI, Mihailov R, *et al*: Nasopharyngeal carcinoma: A new synthesis of literature data (review). Exp Ther Med 23: 136, 2022.
4. Kang H, Kiess A and Chung CH: Emerging biomarkers in head and neck cancer in the era of genomics. Nat Rev Clin Oncol 12: 11-26, 2015.
5. Marur S and Forastiere AA: Head and neck squamous cell carcinoma: Update on epidemiology, diagnosis, and treatment. Mayo Clin Proc 91: 386-396, 2016.
6. Boussios S, Seraj E, Zarkavelis G, Petrakis D, Kollas A, Kafantari A, Assi A, Tatsi K, Pavlidis N and Pentheroudakis G: Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: Where do we stand? A literature reviews. Crit Rev Oncol Hematol 108: 164-174, 2016.
7. Peng PJ, Lv BJ, Wang ZH, Liao H, Liu YM, Lin Z, Con YY and Huang PY: Multi-institutional prospective study of nedaplatin plus S-1 chemotherapy in recurrent and metastatic nasopharyngeal carcinoma patients after failure of platinum-containing regimens. Ther Adv Med Oncol 9: 68-74, 2017.
8. Tsai MH, Chuang HC, Lin YT, Yang KL, Lu H, Huang TL, Tsai WL, Su YY and Fang FM: The prognostic value of preoperative albumin to alkalin phosphatase ratio on survival outcome for patients with locally advanced oral squamous cell carcinoma. Technol Cancer Res Treat 21: 15330338221141254, 2022.
9. Lubov J, Labbe M, Sioufi K, Morand GB, Hier MP, Khanna M, Sultanem K and Mlynarek AM: Prognostic factors of head and neck cutaneous squamous cell carcinoma: A systematic review. J Otolaryngol Head Neck Surg 50: 54, 2021.
10. Nwabudike LC and Tatu AL: Reply to Gambichler T *et al*: Altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery. J Eur Acad Dermatol Venereol 33: e3-e4, 2019.
11. Liu GFF, Ranck MC, Solanki AA, Cao H, Kolokythas A, Wenig BL, Chen L, Ard S, Weichselbaum RR, Halpern H and Spiotto MT: Racial parities in outcomes after radiotherapy for head and neck cancer. Cancer 120: 244-252, 2014.
12. Wiser I, Scope A, Azriel D, Zloczower E, Carmel NN and Shalom A: Head and Neck cutaneous squamous cell carcinoma clinicopathological risk factors according to age and gender: A Population-based Study. Isr Med Assoc J 18: 275-278, 2016.
13. Wang G, Zhang M, Cheng M, Wang X, Li K, Chen J, Chen Z, Chen S, Chen J, Xiong G, *et al*: Tumor microenvironment in head and neck squamous cell carcinoma: Functions and regulatory mechanisms. Cancer Lett 507: 55-69, 2021.
14. Alsahafi E, Begg K, Amelio I, Raulf N, Lucarelli P, Sauter T and Tavassoli M: Clinical update on head and neck cancer: Molecular biology and ongoing challenges. Cell Death Dis 10: 540, 2019.
15. Mesia R, Iglesias L, Lambea J, Martinez-Trufero J, Soria A, Taberna M, Trigo J, Chaves M, Garcia-Castano A and Cruz J: SEOM clinical guidelines for the treatment of head and neck cancer (2020). Clin Transl Oncol 23: 913-921, 2021.
16. Burr A, Harari P, Wieland A, Kimple R, Hartig G and Witek M: Patterns of failure for hypopharynx cancer patients treated with limited high dose radiotherapy treatment volumes. Radiat Oncol J 40: 225-231, 2022.
17. Kao HF, Huang HC, Liao BC and Hong RL: Shourt-course pembrolizumab and continuous afatinib therapy for recurrent or metastatic head and neck squamous cell carcinoma: A real-world data analysis. BMC Cancer 22: 1228, 2022.
18. Jung K, Narwal M, Min SY, Keam B and Kang H: Squamous cell carcinoma of head and neck: What internists should know. Korean J Intern Med 35: 1031-1044, 2020.
19. Koh J, Walsh P, D'Costa I and Bhatti O: Head and neck squamous cell carcinoma survivorship care. Aust J Gen Pract 48: 846-848, 2019.
20. Kitamura N, Sento S, Yoshizawa Y, Sasabe E, Kudo Y and Yamamoto T: Current trends and future prospects of molecular targeted therapy in head and neck squamous cell carcinoma. Int J Mol Sci 22: 240, 2020.
21. Vasconcelos L, Melo JC, Miot HA, Marques ME and Abbade LP: Invasive head and neck cutaneous squamous cell carcinoma: Clinical and histopathological characteristics, frequency of local recurrence and metastasis. An Bras Dermatol 89: 562-568, 2014.
22. Oliva M, Spreafico A, Taberna M, Alemany L, Coburn B, Mesia R and Siu LL: Immune biomarkers of response to immune-checkpoint inhibitors in head and neck squamous cell carcinoma. Ann Oncol 30: 57-67, 2019.
23. Kraft S and Granter SR: Molecular pathology of skin neoplasms of the head and neck. Arch Pathol Lab Med 138: 759-787, 2014.
24. Wang J, Chen X, Tian Y, Zhu G, Qin Y, Chen X, Pi L, Wei M, Liu G, Li Z, *et al*: Six gene signature for predicting survival in patients with head and neck squamous cell carcinoma. Aging (Albany NY) 12: 767-783, 2020.
25. Rahman S, Kraljević Pavelić S and Markova-Car E: Circadian (de)regulation in head and neck squamous cell carcinoma. Int J Mol Sci 20: 2662, 2019.
26. Zeng S, Fu L, Zhou P and Ling H: Identifying risk factors for the prognosis of head and neck cutaneous squamous cell carcinoma: A systematic review and meta-analysis. PLoS One 15: e0239586, 2020.
27. Ali SR, Strafford H, Dobbs TD, Fonferko-Shadrach B, Lacey AS, Pickrell WO, Hutchings HA and Whitaker IS: Development and validation of an automated basal cell carcinoma histopathology information extraction system using natural language processing. Front Surg 9: 870494, 2022.
28. Dika E, Scarfì F, Ferracin M, Broseghini E, Marcelli E, Bortolani B, Campione E, Riefolo M, Ricci C and Lambertini M: Basal cell carcinoma: A comprehensive review. Int J Mol Sci 21: 5572, 2020.
29. Szewczyk M, Pazdrowski J, Pabiszczak M, Wieckowska B, Danczak-Pazdrowska A and Golusinski W: Local recurrence risk in head and neck basal cell carcinoma. Otolaryngol Pol 76: 1-5, 2022.
30. Shavlokhova V, Vollmer M, Gholam P, Saravi B, Vollmer A, Hoffmann J, Engel M and Freudlsperger C: Deep learning on basal cell carcinoma in vivo reflectance confocal microscopy data. J Pers Med 12: 1471, 2022.
31. Yang X, Ren H, Guo X, Hu C and Fu J: Radiation-induced skin injury: Pathogenesis, treatment, and management. Aging (Albany NY) 12: 23379-23393, 2020.
32. Bertino G, Muir T, Odili J, Groselj A, Marconato R, Curatolo P, Kis E, Lonkvist CK, Clover J, Quaglino P, *et al*: Treatment of basal cell carcinoma with electrochemotherapy: Insights from the InspECT Registry (2008-2019). Curr Oncol 29: 5324-5337, 2022.
33. Farah CS: Molecular landscape of head and neck cancer and implications for therapy. Ann Transl Med 9: 915, 2021.
34. Yulek O, Batur S, Özcan K, Yol C and Aydın Ülgen Ö: Relationship between PD-L1 expression and prognostic factors in high-risk cutaneous squamous and basal cell carcinoma. Bosn J Basic Med Sci 22: 894-900, 2022.
35. Hasan A, Rabie A, Elhussiny M, Nasr M, Kamel MI, Hegab A, El-Kady AS, Nagaty ME, Seleem A, Abbas M, *et al*: Recurrent cutaneous basal cell carcinoma after surgical excision: A retrospective clinicopathological study. Ann Med Surg (Lond) 78: 103877, 2022.
36. Kara I, Vural A, Unlu M, San F, Benan Göçer G and Yildiz MG: Management of basal cell carcinomas: Clinical experience. Turk Arch Otorhinolaryngol 60: 9-15, 2022.
37. Kasumagic-Halilovic E, Hasic M and Ovcina-Kurtovic N: A clinical study of basal cell carcinoma. Med Arh 73: 394-398, 2019.
38. Castanheira A, Boaventura P, Pais Clemente M, Soares P, Mota A and Lopes JM: Head and neck cutaneous basal cell carcinoma: What should the otorhinolaryngology head and neck surgeon care about? Acta Otorhinolaryngol Ital 40: 5-18, 2020.
39. Chinem VP and Miot HA: Prevalence of actinic skin lesions in patients with basal cell carcinoma of the head: A case-control study. Rev Assoc Med Bras (1992) 58: 188-196, 2012 (In English, Portuguese).
40. Otsuka ACVG, Bertolli E, de Macedo AP, Pinto CAL and Duprat Neto JP: Intraoperative assessment of surgical margins using 'en face' frozen sections in the management of cutaneous carcinomas. An Bras Dermatol 97: 583-591, 2022.
41. Magnes T, Wagner S, Kiem D, Wiess L, Rinnerthaler G, Greil R and Melchardt T: Prognostic and predictive factors in advanced head and neck squamous cell carcinoma. Int J Sci Mol 22: 4981, 2021.
42. Hutchinson MKND, Mierzwa M and D'Silva NJ: Radiation resistance in head and neck squamous cell carcinoma: Dire need for an appropriate sensitizer. Oncogene 39: 3638-3649, 2020.
43. Zenda S, Ota Y, Tachibana H, Ogawa H, Ishii S, Hashiguchi C, Akimoto T, Ohe Y and Uchitomi Y: A prospective picture collection study for a grading atlas of radiation dermatitis for clinical trials in head-and-neck cancer patients. J Radiat Res 57: 301-306, 2016.

44. Bhatt S, Mandal S, Mehrotra G, Arora V and Singh U: Multidetector computed tomography perfusion in head and neck squamous cell carcinomas: Evaluation of a dose reduction strategy. Indian J Radiol Imaging 32: 451-459, 2022.
45. Haubner F, Ohmann E, Pohl F, Strutz J and Gassner HG: Wound healing after radiation therapy: Review of the literature. Radiat Oncol 7: 162, 2012.
46. Ramirez M, Ravichandran S, Ronald L, Pabon-Ramos WM, Smith TP, Kim CY and Ronald J: Recognition and management of dermatologic complications from interventional radiology procedures. Diagn Interv Imaging 100: 659-670, 2019.
47. Lecocq M, Poncin A and Sautois B: Immunotherapy for head and neck squamous cell carcinoma. Rev Med Liege 76: 398-402, 2021 (In French).
48. Amit M, Takahashi H, Dragomir MP, Lindemann A, Gleber-Netto FO, Pickering CR, Anfossi S, Osman AA, Cai Y, Wang R, *et al*: Loss of p53 drives neuron reprogramming in head and neck cancer. Nature 578: 449-454, 2020.
49. Lim KP, Chun NA, Gan CP, Teo SH, Rahman ZA, Abraham MT, Zain RB, Ponniah S and Cheong SC: Identification of immunogenic MAGED4B peptides for vaccine development in oral cancer immunotherapy. Hum Vaccin Immunother 10: 3214-3223, 2014.
50. Jiang H, Zhou L, Shen N, Ning X, Wu D, Jiang K and Huang X: M1 macrophage-derived exosomes and their key molecule lncRNA HOTTIP suppress head and neck squamous cell carcinoma progression by upregulating the TLR5/NF-κB pathway. Cell Death Dis 13: 183, 2022.
51. Mora Román JJ, Del Campo M, Villar J, Paolini F, Curzio G, Venuti A, Jara L, Ferreira J, Murgas P, Lladser A, *et al*: Immunotherapeutic potential of Mollusk Hemocyanins in combination with human vaccine adjuvants in murine models of oral cancer. J Immunol Res 2019: 7076942, 2019.
52. Malonis RJ, Lai JR and Vergnolle O: Peptide-based vaccines: Current progress and future challenges. Chem Rev 120: 3210-3229, 2020.
53. Filderman JN and Storkus WJ: Finding the right help in the tumor microenvironment. J Clin Invest 132: e161052, 2022.
54. Ferris RL: Immunology and immunotherapy of head and neck cancer. J Clin Oncol 33: 3293-3304, 2015.
55. Albers AE, Qian X, Kaufmann AM, Mytilineos D, Ferris RL, Hoffmann TK and DeLeo AB: Phenotype of p53 wild-type epitope-specific T cells in the circulation of patients with head and neck cancer. Sci Rep 8: 10716, 2018.
56. Leroux-Roels G: Unmet needs in modern vaccinology: Adjuvants to improve the immune response. Vaccine 28 (Suppl 3): C25-C36, 2010.
57. Chen X, Yang J, Wang L and Liu B: Personalized neoantigen vaccination with synthetic long peptides: Recent advances and future perspectives. Theranostics 10: 6011-6023, 2020.
58. Sun Z, Sun X, Chen Z, Du J and Wu Y: Head and neck squamous cell carcinoma: Risk factors, molecular alterations, immunology and peptide vaccines. Int J Pept Res Ther 28: 19, 2022.
59. Calvo Tardón M, Allard M, Dutoit V, Dietrich PY and Walker PR: Peptides as cancer vaccines. Curr Opin Pharmacol 47: 20-26, 2019.
60. Bezu L, Kepp O, Cerrato G, Pol J, Fucikova J, Spisek R, Zitvogel L, Kroemer G and Galluzzi L: Trial watch: Peptide-based vaccines in anticancer therapy. OncoImmunology 7: e1511506, 2018.
61. Shibata H, Zhou L, Xu N, Egloff AM and Uppaluri R: Personalized cancer vaccination in head and neck cancer. Cancer Sci 112: 978-988, 2021.
62. Sakakura K, Takahashi H, Motegi SI, Yokobori-Kuwabara Y, Oyama T and Chikamatsu K: Immunological features of circulating monocyte subsets in patients with squamous cell carcinoma of the head and neck. Clin Immunol 225: 108677, 2021.
63. Miyazaki A, Kobayashi J, Torigoe T, Hirohashi Y, Yamamoto T, Yamaguchi A, Asanuma H, Takahashi A, Michifuri Y, Nakamori K, *et al*: Phase I clinical trial of survivin-derived peptide vaccine therapy for patients with advanced or recurrent oral cancer. Cancer Sci 102: 324-329, 2011.
64. Idenoue S, Hirohashi Y, Torigoe T, Sato Y, Tamura Y, Hariu H, Yamamoto M, Kurotaki T, Tsurama T, Asanuma H, *et al*: A potent immunogenic general cancer vaccine that target survivin, an inhibitor of apoptosis proteins. Clin Cancer Res 11: 1474-1482, 2005.
65. Farnevo L, Tiefenbock K, Ansell A, Thunell LK, Garvin S and Roberg K: Strong expression of survivin is associated with positive response to radiotherapy and improved overall survival in head and neck squamous cell carcinoma patients. Int J Cancer 133: 1994-2003, 2013.
66. Wang C, Zainal NS, Chai SJ, Dickie J, Gan CP, Zulaziz N, Lye BKW, Sutavani RV, Ottensmeier CH, King EV, *et al*: DNA vaccines targeting novel cancer-associated antigens frequently expressed in head and neck cancer enhance the efficacy of checkpoint inhibitor. Front Immunol 12: 763086, 2021.
67. Tseng SH, Liu L, Peng S, Kim J, Ferrall L, Hung CF and Wu CF: Control of spontaneous HPV16 E6/E7 expressing oral cancer in HLA-A2 (AAD) transgenic mice with therapeutic HPV DNA vaccine. J Biomed Sci 28: 63, 2021.
68. Wu A, Zeng Q, Kang TH, Peng S, Roosinovich E, Pai SI and Hung CF: Innovative DNA vaccine for human papillomavirus (HPV)-associated head and neck cancer. Gene Ther 18: 304-312, 2011.
69. Abd-Aziz N and Poh CL: Development of peptide-based vaccines for cancer. J Oncol 2022: 9749363, 2022.
70. Shiah SG, Chou ST and Chang JY: MicroRNAs: Their role in metabolism, tumor microenvironment, and therapeutic implications in head and neck squamous cell carcinoma. Cancers (Basel) 13: 5604, 2021.
71. Wong TS, Wei G and Chan JY: Interactions between E-cadherin and microRNA deregulation in head and neck cancers: The potential interplay. Biomed Res Int 2014: 126038, 2014.
72. Chen D, Cabay RJ, Jin Y, Wang A, Lu Y, Shah-Khan M and Zhou X: MicroRNA deregulation in head and neck squamous cell carcinomas. J Oral Maxillofac Res 4: e2, 2013.
73. Derakhshan A, Chen Z and Van Waes C: Therapeutic small molecules target inhibitor of apoptosis proteins in cancer with deregulation of extrinsec and intrinsic cell death pathways. Clin Cancer Res 23: 1379-1387, 2017.
74. Schiliro C and Firestein BL: Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. Cells 10: 1056, 2021.
75. Faubert B, Solmonson A and DeBerardinis RJ: Metabolic reprogramming and cancer progression. Science 368: eaaw5473, 2020.
76. Greten FR and Grivennikov SI: Inflammation and cancer. Triggers, mechanisms and consequences. Immunity 51: 27-41, 2019.
77. Lai YH, Liu H, Chiang WF, Chen TW, Chu LJ, Wu JS, Chen SJ and Tan BC: MiR31-5p-ACOX1 axis enhances tumorigenic fitness in oral squamous cell carcinoma via the promigratory Prostaglandin E2. Theranostics 8: 486-504, 2018.
78. Oshima S, Asai S, Seki N, Minemura C, Kinoshita T, Goto Y, Kikkawa N, Moriya S, Kasamatsu A, Hanazawa T and Uzawa K: Identification of tumor suppressive genes regulated by miR-31-5p and miR-31-3p in head and neck squamous cell carcinoma. Int J Mol Sci 22: 6199, 2021.
79. Leemans CR, Braakhuis BJ and Brakenhoff RH: The molecular biology of head and neck cancer. Nat Rev Cancer 11: 9-22, 2011.
80. Moskovitz J, Moy J and Ferris RL: Immunotherapy for head and neck squamous cell carcinoma. Curr Oncol Rep 20: 22, 2018.
81. Li J, Xie Y, Wang X, Li F, Li S, Li M, Peng H, Yang L, Liu C, Pang L, *et al*: Prognostic impact of tumor-associated macrophage infiltration in esophageal cancer: A meta-analysis. Future Oncol 15: 2303-2317, 2019.
82. Bras L, Driessen DAJJ, de Vries J, Festen S, van der Laan BFAM, van Leeuwen BL, de Bock GH and Halmos GB: Patients with head and neck cancer: Are they frailer than patients with other solid malignancies? Eur J Cancer Care (Engl) 29: e13170, 2020.
83. Sharma H, Sen S, Lo Muzio L, Mariggio MA and Singh N: Antisense-mediated downregulation of anti-apoptotic proteins induces apoptosis and sensitizes head and neck squamous cell carcinoma cells to chemotherapy. Cancer Biol Ther 4: 720-727, 2005.
84. Farnebo L, Jedlinski A, Ansell A, Vainikka L, Thunell LK, Grenman R, Johansson AC and Roberg K: Proteins and single nucleotide polymorphisms involved in apoptosis, growth control and DNA repair predict cisplatin sensitivity in head and neck cancer cell lines. Int J Mol Med 24: 549-556, 2009.
85. Plavc G and Strojan P: Combining radiotherapy with immunotherapy in definitive treatment of head and neck squamous cell carcinoma: Review of current clinical trials. Radiol Oncol 54: 377-393, 2020.
86. Goel B, Tiwari AC, Pandey RK, Singh AP, Kumar S, Sinha A, Jain SK and Khattri A: Therapeutic approaches for the treatment of head and neck squamous cell carcinoma-on update on clinical trials. Transl Oncol 21: 101426, 2022.
87. Fortpied C and Vinches M: The statistical evaluation of treatment and outcomes in head and neck squamous cell carcinoma clinical trials. Front Oncol 9: 634, 2019.

88. Kawaguchi M, Kato H, Tomita H, Hara A, Suzui N, Miyazaki T, Matsuyama K, Seishima M and Matsuo M: Magnetic resonance imaging findings differentiating cutaneous basal cell carcinoma from squamous cell carcinoma in the head and neck region. Korean J Radiol 21: 325-331, 2020.
89. Weed DT, Zilio S, Reis IM, Sargi Z, Abouyared M, Gomez-Fernandez CR, Civantos FJ, Rodriguez CP and Serafini P: The reversal of immune exclusion mediated by Tadalafil and an anti-tumor vaccine also induces PDL1 upregulation in recurrent head and neck squamous cell carcinoma: Interim analysis of a phase I clinical trial. Front Immunol 10: 1206, 2019.
90. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A: Global cancer statistics, 2012. CA Cancer J Clin 65: 87-108, 2015.
91. Basset-Seguin N and Herms F: Update in the management of basal cell carcinoma. Acta DermVenereol 100: adv00140, 2020.
92. Marzuka AG and Book SE: Basal cell carcinoma: Pathogenesis, epidemiology, clinical features, diagnosis, histopathology and management. Yale J Bio Med 88: 167-179, 2015.
93. Firnhaber JM: Basal cell and cutaneous squamous cell carcinomas: Diagnosis and treatment. Am Fam Physician 102: 339-346, 2020.