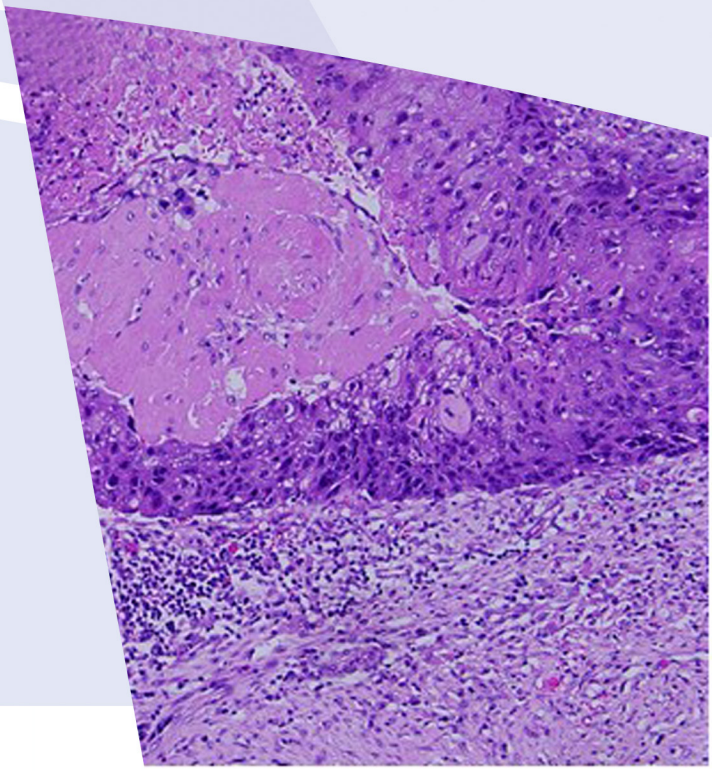
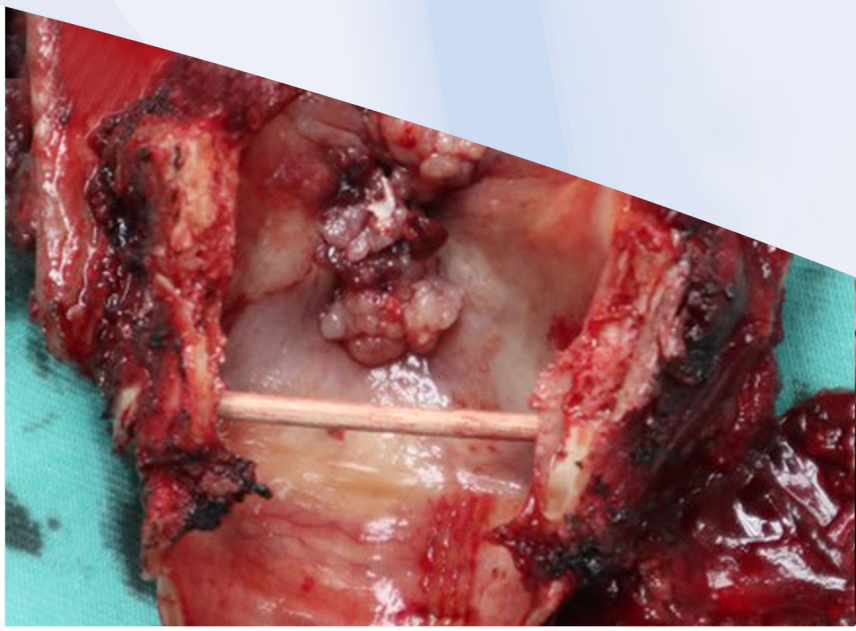
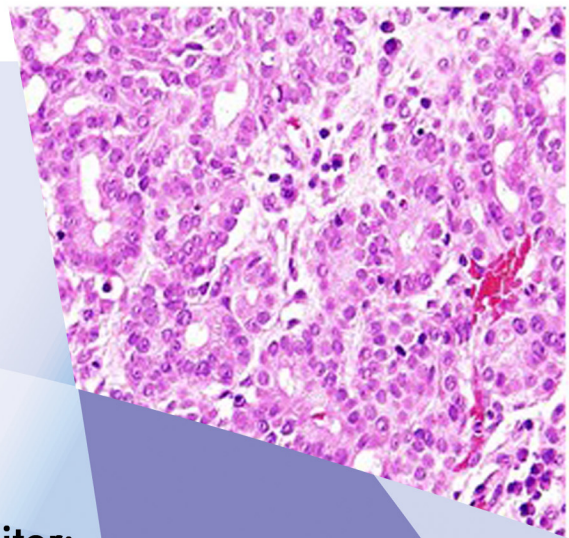
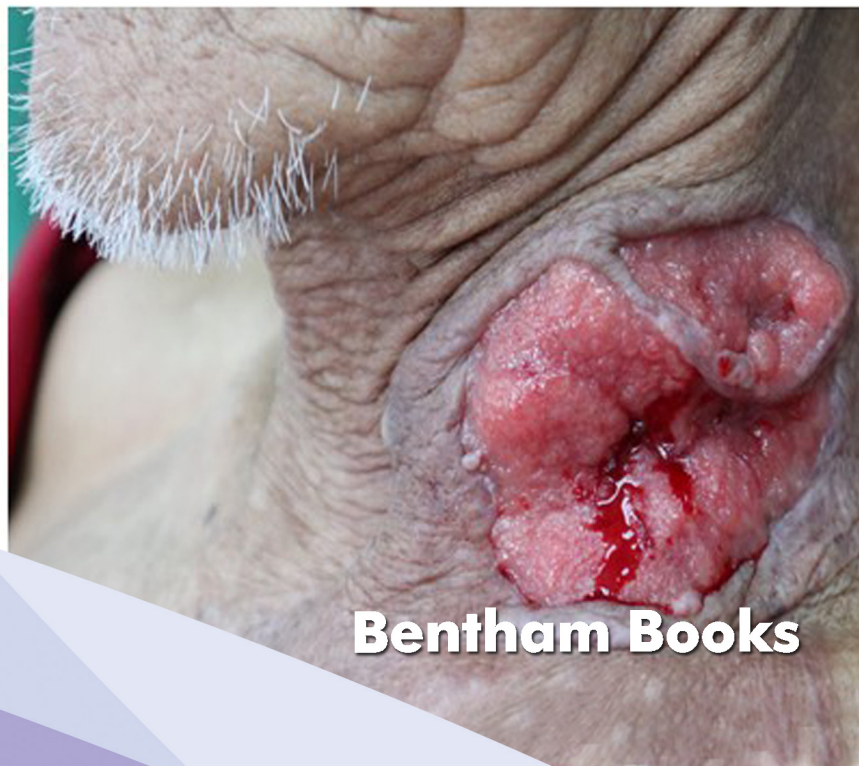
Head and Neck Cancer:
Hallmarks of the Inflammation Ecosystem









Editor:
Norhafiza Mat Lazim

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Frontiers in Inflammation

(Volume 2)

Head and Neck Cancer: Hallmarks of the Inflammation Ecosystem

Edited by

Norhafiza Mat Lazim

Department of Otorhinolaryngology-Head & Neck Surgery,
School of Medical Sciences,
Universiti Sains Malaysia,
Health Campus, Kubang Kerian,
Kelantan,
Malaysia

Frontiers in Inflammation

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FOREWORD I

It is a privilege to foreword this research book which is unique in ways more than one. I congratulate Assoc. Prof. Norhafiza Mat Lazim for her great initiative in conceptualizing this book. This book is in the arena of uncharted territory which will, in years to come, demand more attention and work. Assoc. Prof. Norhafiza Mat Lazim has shown that path into future thinking for all of us in this book.

The book offers several chapters in a systemic way written by competent authorities in their area of work.

We are increasingly aware that there are biomarkers which almost define the biological behavior of the tumor. This biomarker is used in diagnostic workup as detailed in the book which will guide the treatment planning. The book also deals with the detection of other virological markers which will help to prevent and plan surgical/radiation therapy.

The relation between the inflammatory process and malignancy is beautifully mentioned in the chapters. Prof. Norhafiza Mat Lazim has clarified the cascade of chemical reactions in inflammation and malignancy. She has driven similarities and conclusions. In her words, she has an opened a window of opportunity to control/treat head and neck cancer by intervening biochemically at these cascades. This philosophy of drawing parallels in inflammation and malignancy reflects through this book. Author compels us to revisit and strategize our treatment policies by studying the micro-environment, a complex ecosystem.

I wish Prof. Norhafiza Mat Lazim great success not only with this book but also for her in future in this new philosophy of micro-environment and complex eco system of the cancer cells. I also acknowledge the great contribution of all other contributory authors. I am sure this book will make very interesting reading and open a window of sort.

Madan Kapre
Neeti Clinics Pvt. Ltd.
Neeti Gaurav Complex; 21
Nagpur – 440010
Maharashtra
India

FOREWORD II

I am honored to write a foreword to the publication of this wonderful book. First of all, I would like to congratulate Assoc. Prof. Norhafiza Mat Lazim for making this book. I met Assoc. Prof. Lazim at the same session at the 2017 ASHNO conference in Bali, Indonesia. She presented the results of her basic research at this session. At this time, I found out that she was not only an excellent head and neck surgeon, but also an outstanding scientist in basic research on head and neck cancer. Two years later, I heard about a plan to publish a book on inflammation ecosystem in head and neck cancer, and now we have a wonderful and unique book like this.

Physiological inflammation is one of the body's initial immune defenses against infection and tissue damage. Researchers have previously identified that inflammation is frequently associated with tumor progression, but the underlying mechanisms to contribute to proinflammatory tumorigenesis are not fully understood. Much evidence has emerged regarding the infiltration of inflammatory cells into tissues and their contribution to the deleterious alterations of DNA, RNA, proteins, lipids, and metabolites in the local tissue microenvironment of chemical mediators.

In this book, based on the knowledge about the inflammatory ecosystem that has been obtained in the area of head and neck cancer, risk factors in development, diagnostic tools, biomarkers, the role of inflammation in the microenvironment associated with treatment, and tumor-related factors as therapeutic targets are also mentioned. This book brings new research into inflammatory ecosystems to significant progress in developing, diagnosing, and treating head and neck cancer.

Finally, I wish Professor Lazim a success in future, who has made a generous contribution to this book's production, and I would like to thank all other contributory authors who wrote this book.

Naoki Otsuki
Faculty of Medicine
Department of Otolaryngology
Kindai University Osaka-sayama
Japan

PREFACE

The idea for this research book 'Head and Neck Cancer and Hallmark of Inflammation ecosystem' was cultivated during an assembly with the international experts at one of Academy of Science Malaysia scientific events. This research book aims to highlight the significant roles of inflammation in head and neck malignancy. This entails the screening, diagnosis, treatment as well as follow-up schemes of head and neck cancer patients. Now, we know that the inflammation is the 7th hallmark of malignancy, and it has intimate relationship with the development and promotion of carcinogenesis, dictates the behaviour of cancer and may responsible for recurrent and metastatic disease.

Inflammation is significant, and the scope of this book is wide and encompasses all critical issues faced by clinicians, researchers, students, and other health-related personnel in managing head and neck malignancies. The book provides details on inflammation and its interaction in an ecosystem. Myriads of newly emerging inflammatory markers are interacting within a cohesive system in promoting carcinogenesis, tumour recurrent and metastases. Understanding these exquisite roles of inflammation may also serve for the development of potent therapeutic agents at the near future.

The chapters are nicely arranged with a start on a description of head and neck malignancy and its' types, followed by the risk factors where roles of inflammation in discovered and discussed in great depth. The inflammatory markers that are commonly studied which involved in the pathogenesis of head and neck malignancy are elaborated. Roles of specific inflammatory markers, especially in patient's stratification, prognosis, and survival, are pivotal, hence deserve critical attention from the scientific community.

I would like to express my deepest gratitude to Ms. Fariya Zulfiqar for her continuous commitment and dedicated work as well as to all managing team at *Bentham Science* for their relentless support. This book will be a great addition to current scientific literature on head and neck malignancy, especially in relation to the significant roles of inflammation.

Norhafiza Mat Lazim
Department of Otorhinolaryngology-Head & Neck Surgery
School of Medical Sciences, Universiti Sains Malaysia
Health Campus, 16150, Kubang Kerian
Kelantan, Malaysia

List of Contributors

Anani Aila Mat Zin	Department of Pathology, School of Medical Science, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia
Baharudin Abdullah	Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia
Belayat H Siddiquee	Department of Otolaryngology-Head and Neck Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka-1000, Bangladesh
Carlo Cavaliere	Scientific Institute for Research, Hospitalization and Healthcare - IRCCS, SDN, Naples, Italy
Gabriela Ramírez Arroyo	Otolaryngology–Head and Neck Surgery Department, Instituto Nacional de Rehabilitación, Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
Giacomo Spinato	Depatment of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso, Italy Department of Surgery, Oncology and Gastroenterology, Section of Oncology and Immunology, University of Padova, Treviso, Italy
Giuseppe Azzarello	Oncology and hematology department, ULSS 3 Serenissima, Mirano Hospital, Venice, Italy
Jose Gutiérrez Jodas	Department of Otorhinolaryngology-Head and Neck Surgery, Hospital Universitario Reina Sofia, Cordoba, Spain, Avenida Menendez Pidal, Cordoba, Spain
Juan Carlos Hernaiz-Leonardo	Otolaryngology–Head and Neck Surgery Department, Instituto Nacional de Rehabilitación, Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
Liberatore Tramontano	Scientific Institute for Research, Hospitalization and Healthcare - IRCCS, SDN, Naples, Italy
Marco Salvatore	Scientific Institute for Research, Hospitalization and Healthcare - IRCCS, SDN, Naples, Italy
Mario Sergio Dávalos-Fuentes	Otolaryngology–Head and Neck Surgery Department, Instituto Nacional de Rehabilitación, Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
Maria Cristina Da Mosto	Depatment of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso, Italy
Michelle Marvin Huergo	Otolaryngology–Head and Neck Surgery Department, Instituto Nacional de Rehabilitación, Luis Guillermo Ibarra Ibarra, Mexico City, Mexico
Norhafiza Mat Lazim	Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian 16150, Kelantan, Malaysia
Paolo Boscolo Rizzo	Depatment of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso, Italy
Rohaizam Japar Jaafar	Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia

Roman Carlos Zamora	Department of Otorhinolaryngology-Head and Neck Surgery, Hospital Universitario Reina Sofia, Cordoba, Spain, Avenida Menendez Pidal, Cordoba, Spain
Samuele Frasconi	Depatment of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso, Italy
Sharifah Emilia Tuan Sharif	Department of Pathology, School of Medical Science, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia
Simonetta Ausoni	Department of Biomedical Sciences, University of Padua, Padua, Italy
Zakinah Yahaya	Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
Zulkifli Yusof	Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia

CHAPTER 1

Introduction to Inflammation Ecosystem in Head and Neck Cancer

Norhafiza Mat Lazim*

Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia

Abstract: Head and neck cancer is on the rise around the globe. At present, the disease affects both the elderly and younger patient populations. This type of cancer is significant as it involves crucial anatomic regions of the head and neck, which are vital for breathing, mastication, swallowing, speech, and olfaction. The treatment options for head and neck malignancies are mainly surgery and chemoradiation, depending on the stage of the tumors. Inflammation plays an important role, and it has a strong relationship with the risk factors, assessment, and treatment of head and neck cancer. Multiple risk factors for head and neck squamous cell carcinoma like smoking, alcohol, viruses, chemicals, and foods have some elements of inflammation that play a dominant role in promoting and sustaining carcinogenesis. The inflammation cascades are complex, and multiple factors cohesively interact within the microenvironment that eventually leads to carcinogenesis, tumor recurrence, and metastasis. Recent evidence suggests that numerous anti-inflammatory biomarkers have effective therapeutic roles in the management of head and neck cancer. This chapter highlights the prominent relationship and interaction that exists between head and neck cancer and inflammation, not only in its etiopathogenesis but also in the assessment and overall management approaches. The significant focus is on the role of inflammatory agents that contribute to the process of carcinogenesis, as well as discussion on several significant inflammatory markers and molecules which may serve as a potential effective target for personalized treatment in head and neck cancer management armamentarium in the near future.

Keywords: Anti-inflammation, Carcinogenesis, Chemoradiation, Epstein Barr viruses, Head and neck cancer, Immunomodulation, Loco-regional recurrence, Malignancy, Metastases, Nasopharyngeal carcinoma, Oncogenic viruses, Oncologic surgery.

* **Corresponding author Norhafiza Mat Lazim:** Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia;
Tel: +60199442664, +6097676418, Fax: +6097676424; E-mail: norhafiza@usm.my

INTRODUCTION

At this juncture, the incidence of head and neck malignancy has shown an increasing trend, approaching similar incidence with lung and colon cancers globally. In our practice, we observed that not only the middle-aged and elderly populations are affected by the disease, but also the trend is on the rise in pediatric patients. The types of head and neck malignancy include an oral cavity carcinoma, oropharyngeal carcinoma, salivary glands carcinoma, thyroid carcinoma, sinonasal carcinoma, nasopharyngeal carcinoma, temporal bone tumors, soft tissues sarcomas, and laryngeal carcinoma. The most common histopathology of head and neck cancers is squamous cell carcinoma. Certain types of head and neck squamous cell carcinoma (HNSCC) are prevalent in specific geographic locations. For instance, nasopharyngeal carcinoma is common in China, Taiwan, Hong Kong, and South East Asia region, whereas oral and oropharyngeal carcinoma is prevalent in Europe, India, Middle East, and several other Western countries.

There are multiple identified risk factors for HNSCC, which include smoking, alcohol consumption, viral infections, dietary habits, chemicals, and other environmental pollutants. These so-called inflammation-associated molecules commonly acting in concert with the presence of other environmental and lifestyle-related co-factors promote carcinogenesis. These factors include sedentary lifestyles, stress, home environment, obesity, self-hygiene, and genetics, which together are thought to drive as much as 90% of all cancers [1]. In addition, selected endogenous and exogenous stimuli might lead to various genetic mutations and modulations, which can serve as a possible trigger for the tumor of the head and neck [2]. Certain head and neck cancer only take a short duration, *i.e.*, 5 to 10 years, to develop, whereas others appear in a case with long-standing head and neck masses of more than 20 years.

Clinical presentation of patients with head and neck cancer varies, and it depends on the patient's age, duration of symptoms, size of the mass, the location involved, presence or absence of distant metastases, and patient's comorbidities. Generally, a patient will present with a progressive mass or swelling at the head and neck region that causes constant pain or bleeding associated with reduced appetite and significant weight loss. Other associated symptoms will depend on the location of the mass. For instance, suspicious cancerous mass in the nasal cavity may cause epistaxis, mass in the nasopharynx may cause hearing complaints, mass in the oropharynx area may cause dysphagia and odynophagia, and so forth. The other symptoms such as cranial nerve involvement, pulmonary symptoms, or bony tenderness may present in aggressive and late-stage diseases.

Imperatively, the majority of patient presents at late-stage diseases, where the treatment is more challenging, and multimodality therapy is required.

The malignancy around the head and neck region deserves greater attention as it involves important anatomic regions that are crucial for breathing, speech, mastication, swallowing, hearing, olfaction, and vision. Preserving all the structures is paramount to maintain the function of all organs within the head and neck region, to ensure the patient's daily functioning and quality of life are maintained. To illustrate, for instance, facial nerve paralysis that is caused by malignant infiltrative parotid malignancy can cause significant social embarrassment and affect a patient's social interaction and integration within the community due to facial disfigurement. Thus, it is equally crucial to understand the true biology of head and neck malignancy and its sequelae in order to provide finesse care for these subsets of patients.

More than a century ago, Rudolf Virchow proposed the connection between inflammation and cancer, who found the infiltration of leukocytes in malignant tissues [3]. He noted leukocytes in the neoplastic tissue and indicated that the lymphocytic infiltrate might represent cancer origin at chronic inflammatory sites. From this evidence and documentation, there was a surge in the literature that reveals the association of inflammation in cancer formation as well as its roles in cancer therapeutics. Numerous studies have been performed to assess in-depth the relation of inflammatory cascades in the etiopathogenesis, risk factors, therapeutic and sequelae of procedures, and overall treatment in head and neck malignancy.

At this juncture, numerous studies include experimental, clinical, and epidemiological studies have revealed that chronic inflammation significantly contributes to carcinogenesis and cancer progression and predisposes to the occurrence of different types of human cancers [3]. Cancer-related inflammation is considered to be the seventh hallmark of cancer, according to Bonomi *et al.,* and numerous scientific researches have shown that the tumors develop and evolve in and from inflammatory diseases [4]. Imperatively, the steps of carcinogenesis always involve an inflammatory process as the initial step. The primary insult results in inflammation at the very beginning before other reactionary cascades coming in and subsequently promote the carcinogenesis and its sequelae.

INFLAMMATION AND CANCER

The strong relationship and interaction that exist between cancer and inflammation are evident not only in the etiopathogenesis of head and neck cancer but also in investigative procedures, assessment tools, and treatment strategies that take place during head and neck cancer management. The process of

CHAPTER 2

Types of Head and Neck Malignancy

Gabriela Ramírez-Arroyo[1,*], Juan Carlos Hernaiz-Leonardo[1], Michelle Marvin-Huergo[1] and **Mario Sergio Dávalos-Fuentes[1]**

[1] *Department of Otolaryngology–Head and Neck Surgery, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra", Mexico City, Mexico*

Abstract: Head and neck cancer (HNC) is a heterogeneous group of malignant neoplasms, and its classification is a challenge. Based on the primary site, most literature comprehends five types of HNCs: laryngeal, pharyngeal, oral cavity, nasal cavity, and salivary gland cancer. More than 90% of HCNs are of epithelial origin, making squamous cell carcinoma the most common histological type. The prototypic HNC is a moderately differentiated squamous cell carcinoma associated with tobacco and alcohol consumption that affects older men more frequently. They are usually treated in a similar fashion. Currently, the human papillomavirus epidemic and a shift in tobacco consumption patterns are changing this trend. HNCs have a high rate of genetic heterogeneity, and molecular profiling has gained importance in the classification and future treatment of HNCs.

Keywords: HPV-positive, Laryngeal cancer, Molecular profile, Nasal cavity cancer, Oral cavity cancer, Pharyngeal cancer, Salivary gland cancer, Squamous cell carcinoma, Unknown primary.

INTRODUCTION

To talk about HNC is a complex task, as the term itself is ambiguous. In oncologic terms, the type of cancer in any region of the body is determined by its primary site and histology. Following this train of thought, the term HNC could comprise all tumors arising between the thoracic inlet and the skull base. Some textbooks on HNC follow this approach and include most cancers occurring in these primary sites in their discussion, but most publications concerning HNCs do not consider skin, thyroid, parathyroid, cervical esophagus, and other primaries of this anatomical region a part of HNCs.

[*] **Corresponding author Gabriela Ramírez-Arroyo:** Department of Otolaryngology–Head and Neck Surgery, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra", Mexico City, Mexico; Tel: +525534882547; E-mail: gabyra18@hotmail.com

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Based on a definition proposed by the American Joint Committee on Cancer [1], most cancer societies reserve the term HNC for malignant neoplasms that arise in salivary glands or in the squamous cells that line mucosal surfaces within the head and neck [2]. These tumors are aggressive, mostly develop from squamous cells [3], are classically associated with tobacco and alcohol consumption [4], and their diagnosis and treatment are similar [5]. HNCs deeply affect the quality of life, interfering with the patients' daily life activities such as speech, swallowing, breathing, and even social interaction [6]. Hence, tumors held under the umbrella term HNC are classified into 5 main groups, each named according to the anatomic region of the head and neck where they develop:

1. Laryngeal cancer
2. Pharyngeal cancer
3. Oral cavity cancer
4. Nasal cavity and paranasal sinus cancer
5. Salivary glands cancer

Laryngeal, pharyngeal, oral cavity and salivary gland neoplasms are further classified according to the anatomic subsite or the affected salivary gland.

The metastatic carcinoma of unknown primary (MCUP) of the head and neck is another type of HNC. MCUP refers to the state in which cervical adenopathy is identified, but the primary tumor cannot be diagnosed even after an aggressive evaluation [7]. As the diagnostic workup has become more thorough, it must include a surgical search, taking biopsies of suspected primary sites and detection of Human Papillomavirus and Epstein-Bar Virus, the true incidence of MCUP is close to 1-2%. Up to 90% of the MCUPs are primaries of the oropharynx [8].

Besides the site of origin, histology is the other criteria used to classify malignant neoplasms (Table **1**). More than 90% of HCNs are of epithelial origin, making squamous cell carcinoma the most common histological type. Salivary gland tumors represent the biggest exception to this rule, as the most common histologic type is mucoepidermoid carcinoma [9]. Certain clinical guidelines on HNC management refer only to squamous cell carcinomas, coining the term head and neck squamous cell carcinoma (HNSCC). HNSCC represents the prototype of HNC that arises from the mucosal lining of upper aerodigestive tracts, is associated with tobacco and alcohol consumption, affects older males, and thus, is treated similarly. This prototypic HNSCC is a moderately differentiated squamous cell carcinoma. Other histologic subtypes or variants of HNSCC are described: spindle cell variant, papillary variant, basaloid squamous variant, and verrucous carcinoma, all of which exhibit different biologic behaviors [10].

Table 1. Main subtypes of HNC according to the primary site and histological type.

HNC Type	Subtypes	Histological Types
Laryngeal cancer	• Supraglottic carcinoma Includes the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids • Glottic carcinoma Includes the true vocal cords and the anterior and posterior commissures • Subglottic carcinoma 1 cm below the true vocal cords and extends to the lower border of the cricoid cartilage	Squamous cell carcinoma* Variants of SCC Includes verrucous, spindle cell and basaloid SCC Adenocarcinoma Lymphoma Includes Hodgkin's lymphoma and non-Hodgkin's lymphoma ** Sarcomas Includes chondrosarcoma, and leiomyosarcoma Miscellaneous Includes minor salivary gland tumors, malignant melanoma, neuroendocrine carcinoma, among others
Pharyngeal cancer	• Nasopharynx	Nasopharyngeal carcinoma Keratinizing squamous Non-keratinizing squamous Basaloid squamous Extranodal natural killer/T cell lymphoma***
	• Oropharynx Includes soft palate, tonsil, tonsillar pillars, base of tongue, vallecula and posterior oropharyngeal wall	Squamous cell carcinoma, HPV-positive Includes basaloid and papillary SCC, adenosquamous, undifferentiated, spindle cell, and ciliated adenosquamous carcinoma. Squamous cell carcinoma, HPV-negative Squamous cell carcinoma, HPV not tested, morphology highly suggestive of HPV association Small cell carcinoma Lymphoma Sarcomas Minor salivary gland tumors
	• Hypopharynx Includes pyriform sinus, postcricoid region, posterior pharyngeal wall	Squamous cell carcinoma* Variants of SCC Includes verrucous, spindle cell and basaloid SCC Adenocarcinoma Lymphoma Includes Hodgkin's lymphoma and non-Hodgkin's lymphoma ** Sarcomas Includes chondrosarcoma, leiomyosarcoma, and others Miscellaneous Includes minor salivary gland tumors, neuroendocrine carcinoma, among others

CHAPTER 3

Histological Classification of Head and Neck Tumors

Sharifah Emilia Tuan Sharif[1] and **Anani Aila Mat Zin**[1,*]

[1] *Department of Pathology, School of Medical Science, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia*

Abstract: Head and neck constituency tumor display many types of cell depending on the lineages, which can develop in a variety of tumor types. Nodaway, all these types and variants of tumor have been recognized based on histomorphological features and their molecular behavior. The most updated and receptive classification is provided by the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC). In the chapter, the discussion will include the common neoplasm, which can occur in oropharynx, nasopharynx, sinonasal region, salivary gland, thyroid gland and other adjacent structures. A brief overview, clinical presentation, histomorphology, genetic profile and outcome/prognosis will be highlighted.

Keywords: Genetic profiling, Head and neck tumor, Miscellaneous tumor, Molecular, Morphology, Predictive factor, Prognostic, Salivary gland tumor, Tumor with and without squamous differentiation, WHO and AJCC classification.

INTRODUCTION

The head and neck areas have numerous specialized tissues giving rise to many types of malignancies. There are a few types and subtypes of lesions that will be described according to their histomorphology and molecular profiles, especially salivary gland, sinonasal tract, and oropharynx. Nasopharyngeal carcinoma had undergone a few classification changes. But, the most accepted classifications are from the World Health Organization (WHO). The same goes for the former in which the evolved classifications had been recognized by the WHO and American Joint Committee on Cancer (AJCC).

In this chapter, we focus on the most recent developments in the head and neck cancer classification. We will discuss the clinical features, pathological features, ancillary studies, prognostic and therapeutic considerations for each entity. These

* **Corresponding author Anani Aila Mat Zin:** Department of Pathology, School of Medical Science, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia; Tel: +60199624272; E-mail: ailakb@usm.my

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cancers are further categorized by their histomorphological differentiation and the location of the head or neck in which they arise. These categories are described below, including the miscellaneous one.

HISTOPATHOLOGICAL CLASSIFICATION OF TUMOUR

Here, we discussed the histopathological classification based on histological features or differentiation (Fig. **1**).

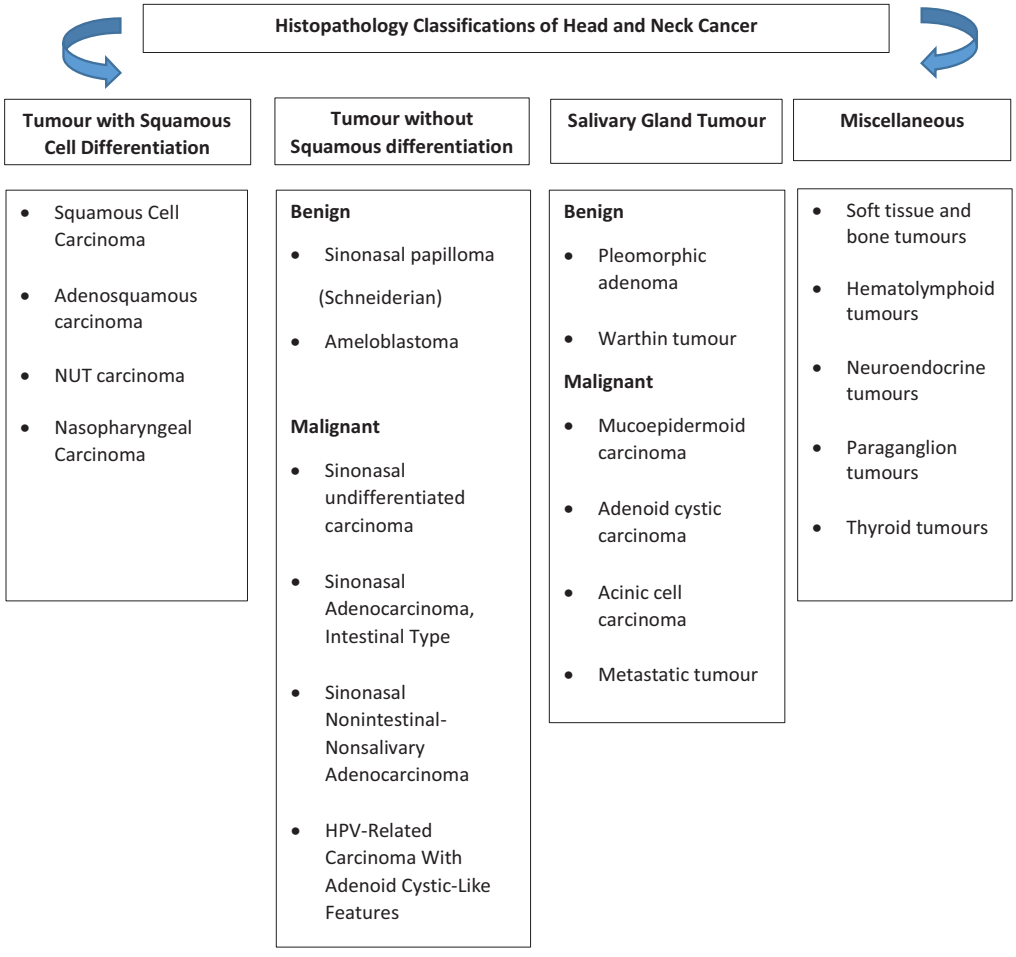

Fig. (1). Classification of head and neck tumor.

1. Epithelial tumor with squamous differentiation.
2. Epithelial tumor without squamous differentiation.
3. Salivary gland tumors.

4. Miscellaneous – neuroendocrine carcinoma, hematolymphoid tumor, soft tissue and bone tumor, paraganglion tumors, thyroid neoplasm, *etc.*

EPITHELIAL TUMOUR WITH SQUAMOUS DIFFERENTIATION

Head and neck squamous cell carcinoma (HNSCC) and its variants are the most common types, usually developed in males of older age group. It develops from the lining of mucosa of the upper aerodigestive tract and is classified by its location; oral cavity/tongue, oropharynx, nasal cavity, and paranasal sinuses, nasopharynx, larynx or hypopharynx. Nasopharyngeal carcinoma (NPC) and other rarer tumor, such as NUT carcinoma, will also be discussed under this histopathological type.

Grossly, the tumor exhibits infiltrative exophytic or endophytic growth pattern with tan to white cut surface. The tumor can show variable degrees of ulceration, necrosis, and hemorrhage [1]. There are a few variants of HNSCC that depend on microscopic features and their associated etiologies will be discussed.

Keratinising Squamous Cell Carcinoma (KSCC)

It is the most common variant of HNSCC, which is most often described in head and neck malignancy.

Clinical Features

The presenting features vary depending on their location. Usually, they presented with non-specific symptoms, which include nasal obstruction and discharge, epistaxis, facial pain, a nasal mass, ulcer, or even eye-related symptoms [2].

Morphology

It is characterized by malignant squamous epithelial cell proliferation with evidence of keratinization and invasive growth pattern. Keratin pearl formation is common. Invasion into the stromal tissue is often accompanied by a desmoplastic changes, accompanied by chronic inflammatory cells (Fig. **2**). In general, it is graded into well-, moderately-, and poorly differentiated. Well-differentiated SCC exhibits mild nuclear atypia with keratin pearls, whereas poorly differentiated SCC display highly pleomorphic and hyperchromatic cells, with numerous typical and atypical mitoses, minimal keratinization, and sometimes necrosis. In this case, the presence of intercellular bridges is an important diagnostic clue for squamous differentiation or origin. Most SCCs are moderately-differentiated, which exhibit features in between well-differentiated and poorly differentiated carcinoma. HNSCCs express most epithelial markers such as cytokeratin. However, in well-differentiated SCC, diagnosis can be made by H&E without additional stains. In

CHAPTER 4

Inflammation, Risk Factors and Etiopathogenesis of Head and Neck Cancer

Norhafiza Mat Lazim*

Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian 16150, Kelantan, Malaysia

Abstract: Head and neck malignancy is a critical disease across the globe as its incidence is on the rise. This malignancy comprises the oral cavity, oropharynx, larynx, nasal cavity, paranasal sinus, nasopharynx, salivary glands, and thyroid malignancies. Multiple known risk factors have been strongly associated with the majority of these malignancies. Importantly, the majority of these known risk factors are intricately involved in the inflammation and its ecosystem. Of note, inflammation cascades and inflammatory markers play a dominant role in the pathogenesis of head and neck malignancy. Thus, it is crucial to understand the true process of each identified risk factor and its related inflammation process in the etiopathogenesis of head and neck malignancy. This can serve as an effective platform for the future development of potential agents for screening, prevention, and treatment of head and neck malignancy. This chapter will discuss the significant risk factors of head and neck malignancy and highlight the spectrum of inflammation process that governs the basis of carcinogenesis and its etiopathogenesis.

Keywords: Alcohol, Dietary factor, Epstein Barr virus (EBV), Head and neck malignancy, Human papilloma virus (HPV), Inflammatory markers, Nasopharyngeal carcinoma, Smoking.

INTRODUCTION

Head and neck malignancy is paramount as it involves a critical anatomic region that plays an important role in humans' basic functioning. Its incidence is on the rise with some geographical variations. It affects both the adult and pediatric patients population. In addition, there are some ethnic and racial differences among patients afflicted with this disease. However, the majority of head and neck malignancies share common etiopathogenesis and risk factors. For instance, the human papilloma virus (HPV) is closely related to oropharyngeal carcinoma,

* **Corresponding author Norhafiza Mat Lazim:** Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian 16150, Kelantan, Malaysia; Tel: +60199442664, +6097676418, Fax: +6097676424; E-mail: norhafiza@usm.my

tongue carcinoma, laryngeal carcinomas, and salivary glands carcinoma. Epstein Barr virus (EBV) is a significant risk factor for nasopharyngeal carcinoma, lymphoma and sinonasal carcinoma. The other risk factors include smoking tobacco products, drinking alcoholic beverages, dietary factors, factory and chemicals products, wood dust and other environmental carcinogens.

It is estimated that 75% of head and neck squamous cell carcinoma (HNSCC) in the US is due to cigarette smoking and alcohol consumption. This is also true for other parts of the world, where alcohol and cigarette smoking remain the dominant risk factors for human malignancy. This is attributed to many carcinogenic substances that are found in cigarettes and alcohol. The mucosal contact with this carcinogenic substance plays a critical role in the carcinogenesis of head and neck cancer. Laryngeal carcinoma is commonly associated with cigarette smoking, whereas oral cavity carcinoma is related to alcohol consumption. There are other factors include genetic alteration, individuals biometabolism and epigenetic changes that interact with the carcinogenic agents in promoting carcinogenesis and lead to HNSCC development and progression [1]. This can be true for other geographical locations also, such as the Indian subcontinent, where the majority of the population are heavy smokers and alcohol drinkers.

Dietary factors such as consumption of salty fish, smoked seafood and pickled vegetables are also significant risk factors for the development of head and neck malignancy especially nasopharyngeal carcinoma (NPC). NPC is prevalent at certain geographic locations like South China, South East Asia, Northern Africa, Artic and selected Mediterranean countries. These are attributed to different dietary and lifestyle habits. The risk factors can have synergistic effects where for instance, the dietary factor and familial inheritance can act in combination and increase the risk of the selected population to four times of having NPC instead of two-fold. At the other end of the spectrum, oral cavity carcinoma is associated with betel nut chewing and reversed smoking. Reversed smoking is commonly practiced in the Indian population and this has been linked to carcinoma of the hard palate. In this scenario, the carcinogens from the cigarette smoke have direct and close contact with the hard palate.

Other than the dietary factors, the oncogenic viruses such as EBV and HPV have emerged as crucial risk factors. It also dictates the treatment strategy and prognosis of selected HNSCC patients. Numerous research works have been performed on these two critical viruses and will continue in the future. This will enable better management and treatment outcomes of patients with HNSCC. NPC also is strongly associated with EBV where the virus serology has been utilized as a diagnostic tool at the majority of head and neck surgical oncology centers

worldwide. The other immunomarkers of EBV are also under intense investigation by many scientists in order to come up with novel diagnostic and therapeutic targets.

Clinical presentation of head and neck malignancy varies, and it depends on the anatomical site and structures involvement, the tumor size, the specific pathology of the tumor as well as the patient's factors such as an immune response. Some of the significant symptoms include odynophagia, dysphagia, throat pain, trismus, airway obstruction, epistaxis, hearing impairment, facial nerve paralysis, hoarseness, and so forth. Oral cavity and oropharyngeal carcinoma tend to cause odynophagia and dysphagia, whereas laryngeal and hypopharyngeal carcinoma can lead to fatal airway obstruction. Epistaxis and trismus are significant features of sinonasal carcinoma and facial nerve paralysis can be due to parotid glands malignancy. All these symptoms and signs can give clues for nearby structure's involvement and can be used as part of the clinical staging for each type of HNSCC.

EPIDEMIOLOGY AND SURVIVAL RATES OF HEAD AND NECK MALIGNANCY

As aforementioned, certain head and neck malignancy types are prevalent at certain geographic locations. This is attributed to factors namely dietary consumption, lifestyle habits, environmental pollutants as well as genetic inheritance. In the last decades, we can observe an improve the overall survival rate of patients with HNSCC, and this differs for various subtypes of head and neck cancer. However, this is partly true only for certain geographic locations due to factors such as better facilities and expertise, and the availability of a strong rehabilitation team and support system at a specific center. Importantly, if we see statistics in the European country, 5-year survival rates for oral and pharyngeal cancers have also improved over the years [2]. These can be partly due to limited local logistic factors for instance the facility, instrumentation, expertise, funds, and so forth. The patient's compliance due to lack of awareness and education, a low socioeconomic background also contributes to the overall survival of HNSCC patients.

These can be partly due to limited local logistic factors, for instance, the facility, instrumentation, expertise, funds, and so forth. The patient's compliance due to lack of awareness and education, and the low socioeconomic background also contributes to the overall survival of HNSCC patients. In addition, HNSCC patients are known to have high rates of recurrent disease and distant metastasis. The incidence of second primary malignancy in the head and neck region is also a common phenomenon and is associated with poor prognosis and a high risk of

CHAPTER 5

The Diagnostic Tools for Head and Neck Cancer

Giacomo Spinato[1,2,*], Paolo Boscolo Rizzo[1], Marco Salvatore[3], Simonetta Ausoni[4], Samuele Frasconi[1], Giuseppe Azzarello[5], Carlo Cavaliere[3], Liberatore Tramontano[3] and **Maria Cristina Da Mosto[1]**

[1] *Depatment of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso, Italy*

[2] *Department of Surgery, Oncology and Gastroenterology, Section of Oncology and Immunology, University of Padova, Treviso, Italy*

[3] *Scientific Institute for Research, Hospitalization and Healthcare - IRCCS - SDN, Naples, Italy*

[4] *Department of Biomedical Sciences, University of Padua, Padua, Italy*

[5] *Oncology and Hematology Department, ULSS 3 Serenissima, Mirano Hospital, Venice, Italy*

Abstract: Diagnosis plays a key role in overall patient assessment and accurate staging of the malignancy. Diagnosis is the starting point to choose treatment strategies for the disease, as well as the basis upon which therapy success, prognosis and the patient's quality of life will vary. Considering a high level of clinical suspicion of any mucosal alteration or laterocervical swelling is important until medical examinations provide evidence of the contrary. Diagnosis investigation continues with the search, among data collected on the patient's history, of objective signs on which clinical suspicions will focus through further medical and instrumental examinations. Imaging techniques that can be used are ultrasound scan, computerised tomography, magnetic resonance and, in the most complex cases, positron emission computerised tomography. Ultrasonography is the most commonly used imaging technique for head and neck mass, especially for the assessment of lymph nodes, thyroid glands and salivary glands. Magnetic resonance is also considered an important examination in the diagnosis of head and neck tumours, especially for lesions involving the oral cavity, oropharynx, nasopharynx and larynx. Computerised tomography (CT) scan is especially useful when assessing the skull base involvement and the morphology of laryngeal malignancies, for example when the tumour extends over the perichondrium of cartilage structures, as well as when assessing function, *i.e.* evaluating the degree of chordal motility. In head and neck cancers (HNC), predictive factors namely biological characteristics that can be used to predict tumor response to a specific treatment, are currently remarkably lacking. Conversely, some bio-molecular parameters are recognized as prognostic factors of the disease, since they indicate tumor characteristics that inform about cancer outcome,

* **Corresponding author Giacomo Spinato:** Department of Neurosciences, Section of Otolaryngology and Regional Centre for Head and Neck Cancer, University of Padova, Treviso, Italy;
Tel: +39 0422322324; and Department of Surgery, Oncology and Gastro-enterology, Section of Oncology and Immunology, University of Padova, Treviso, Italy;
E-mail: spin.giacomo@gmail.com

Norhafiza Mat Lazim (Ed.)

independently of treatment the patients will undergo. The most prominent prognostic factor for head and neck cancers is viral etiology, specifically HPV-mediated disease for oropharyngeal carcinomas and EBV-mediated disease for nasopharyngeal carcinoma.

Keywords: Biomarkers, Diagnostic tool, Head and neck cancer, Investigation, Imaging, TNM classification.

INTRODUCTION TO DIAGNOSTIC INVESTIGATIONS IN HEAD AND NECK CANCER

Head and neck cancers may, due to the onset and evolution of the disease and variability of its histology, present in either full-blown or subtler forms. Diagnosis plays a key role in overall patient assessment and accurate staging of the malignancy. Diagnosis is the starting point to choose treatment strategies for the disease, as well as the basis upon which therapy success, prognosis and the patient's quality of life will vary. Approximately half of all head and neck cancers are diagnosed when the disease is at an advanced stage, most likely because the patient tends to see a specialist only when the disease is full-blown because earlier symptoms are often vague or neglectable [1, 2]. Diagnostic errors occur when, in light of one or more patient-reported symptoms, the physician diagnoses the wrong disease or when examinations and tests that are necessary for a correct diagnosis are not performed on the patient.

THE ANAMNESIS ROLE IN THE DIAGNOSIS

The first step to avoid errors in diagnosis is to proceed with an adequate investigation of the patient's history, especially with the aim of building, from the very beginning, a trust relationship between the patient and physician that will last throughout the diagnosis and treatment pathway [3 - 5]. When investigating the patient's history, in addition to examining the patient's familiarity in relation to head and neck cancers, another important aspect is to investigate their lifestyle and habits to identify risk factors associated with this type of malignancies, especially tobacco and alcohol abuse and, more recently, promiscuous sexual habits [6 - 9].

In addition to lifestyle factors, investigating the patient's profession is also fundamental at this stage, given the known correlation between prolonged exposure to toxic/irritating agents such as heavy metals or wood dust and the onset of upper aerodigestive tract tumours [10]. Agents that are irritating for the mucosa of the upper aerodigestive tracts produce a chronic mucosal phlogosis and can lead to metaplastic or dysplastic phenomena. Factors favouring the onset of chronic mucosal phlogosis in the upper aerodigestive tracts may include

gastroesophageal reflux disease, a diet low in antioxidants - especially group A and E vitamins - and viral aetiologic agents, which should be investigated by testing malignant cells for EBV or HPV DNA in patients with nasopharyngeal or oropharyngeal carcinoma respectively [11, 12].

In the case of tumours of the thyroid and salivary glands, investigating any previous exposure to radiation therapy, especially during paediatric age, or high accidental exposure to radiation, as occurred in the past in the Chernobyl disaster, is essential.

Finally, the patient's history investigation should focus on any patient comorbidities, organ failures, home-delivered therapies and allergies that may impact treatment decisions once the precise clinical staging is complete [13 - 15].

CLINICAL ASSESSMENT IN HEAD AND NECK CANCER

The analysis and accurate interpretation of reported symptoms and clinical signs is of extreme importance in the setting of head and neck cancers, because the signs and symptoms that may present based on the site of disease onset may vary and differ [16, 17].

Often, during the initial stage of the disease, symptoms might be silent or vague; often, head and neck cancer patients are socially marginalised or live in poor social conditions and thus do not see a specialist until symptoms are full-blown and the disease is already at an advanced stage [18]. Symptoms at onset may be local and most frequently include, based on their site, sore throat, the feeling of a lump, hoarseness, unilateral nasal bleeding and reported symptoms at onset such as ear pain and headache. The most typical symptoms of a malignant evolution in the upper aerodigestive tracts are odynophagia, increasingly severe dysphagia [19], "hot potato" voice, salivary pooling, dyspnea (initially upon exertion), cacosmia, bleeding in the mouth, weight loss. Symptom evolution and the relatively rapid increase in severity are an index for mass growth speed evaluation and, indirectly, tumour malignancy [20, 21].

A typical feature of tumours of the nasopharynx [22] is that the patient reports a generally unilateral feeling of ear fullness associated with the onset of otitis media with effusion after a generally short period of time - a typical onset manifestation in this tumour type. Regarding salivary glands, a setting in which tumours are more frequently benign, the generally slow growth of a lump, alternated with periods of regression (as typically occurs with *cystadenoma lymphomatosum*), is observed in the tail of the parotid gland near the angle of the mandible relative to the superficial parotid gland, or in the mouth and pharynx in some cases of deep parotid lobe cancer, where malignancies may resemble a peritonsillar abscess

CHAPTER 6

The Emergence of New Inflammatory Markers of Head and Neck Cancer and their Potentials

Norhafiza Mat Lazim[1,*] and **Baharudin Abdullah**[1]

[1] *Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia*

Abstract: Inflammation plays a critical role in the process of carcinogenesis as well as in modulating treatment effects of many therapeutic agents for head and neck malignancy. Current research indicates that a myriad of new diagnostic tools and treatment modality works in harmony in producing a desired effective cancer treatment regime. Imperatively, multiple inflammatory markers have surged in the genomic and molecular ecospheres as highly potential agents that can be used in screening, diagnosis, treatment as well as follow up of head and neck cancer patients. These markers include arrays of cytokines, peptides, macrophages, acute phase proteins, growth factors, and many more. The tumor microenvironment is a complex ecosystem and has an intricate relationship with its surrounding biosphere. The multiple interactions within the molecules in the cancer microenvironment play significant roles in mediating and promoting carcinogenesis as well as mitigating the treatment response. These complex ecosystems are also responsible for the occurrence of metastatic diseases, recurrences, and residual diseases. This chapter highlights some of the critical inflammatory markers that can be potentially used as a potent theranostic approach for head and neck tumors in the near future.

Keywords: Carcinogenesis, Chemokines, Head and neck malignancy, Immunomodulation, Inflammatory cascades, Inflammation ecosystem, Tumor microenvironment.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is known to be aggressive, with a high incidence of local recurrence and distant metastases despite multimodality treatment. This may be attributed to the heterogeneity of the populated tumor cells as wells as tumor and patient's biology. Patients who are exposed to inflammatory agents such as alcohol, smoke, viruses, environmental

[*] **Corresponding author Norhafiza Mat Lazim:** Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia; Tel: +60199442664; E-mail: norhafiza@usm.my

chemical agents, and selected dietary factors are at greater risk of developing HNSCC. Selective groups of HNSCC are resistant to treatment and prone to develop metastatic disease. They are known to have aggressive natures and a tendency to recur. Clinical presentation of each type of HNSCC varies and depends on the primary anatomic locations and organ involvement. The majority of the patients are in the middle and older age group, with a smaller percentage of the pediatric patient population, who are at increased risk of developing HNSCC. Assessment of HNSCC requires a multi-step process and numerous procedures, and the involvement of a dedicated team is a pre-requisite for optimal treatment planning and execution.

Importantly, the risk factors of HNSCC are strongly related to inflammation. For instance, viruses, dietary factors, and environmental carcinogens always cause acute inflammation as an initial insult, which then progresses to chronic inflammation. This later will be followed by the development and promotion of carcinogenesis. Multiple factors and molecules are involved in the process of carcinogenesis originating from the initial inflammation insult. The interaction between these factors in the tumor microenvironment is responsible for the progression of carcinoma. Several excellent reviews have discussed the probable role of cell and molecular inflammation in cancer growth. Most studies reported consistent associations between chronic inflammatory conditions and inflammatory-inducing risk factors, such as alcohol and tobacco consumption, the oncogenic viruses (EBV and HPV), wood dust exposure, in carcinogenesis of head and neck malignancy [1 - 3].

The process of carcinogenesis is complex and involves multifactorial tissue elements. It is an intricate process, which commonly involves a primary insult, mitigated by factors that can further promote carcinoma development. Peyton Rous was the first to identify that cancers arise from “neoplastic substrate states” induced by viral or chemical carcinogens that trigger somatic changes. These somatic changes are critical insult points in cancer progression. They can be induced by carcinogenic stimuli like chemical carcinogens, nitrosamines in the preserved vegetables and salted fish, acetaldehyde from alcohol, and many chemical components in tobacco, aflatoxins, aromatic amines, and other genotoxic compounds [4]. The steps of initiation and promotion are crucial in carcinogenesis and are both modulated by multiple factors. Significant DNA changes occur during the initial stage, and they are mostly permanent. Chronic exposure to inflammation-induced factors serves as the second stage *i.e.* the promotion. This multistep process of carcinogenesis is very complex and requires intricate genomic changes and chronic exposure of the mucosa of head and neck cancer subsites [5]. It is crucial to understand the true process of carcinogenesis involving the inciting agents that illicit inflammatory cascades.

Other tissue factors are also equally crucial in the development of carcinoma and mitigating carcinogenesis. This can involve vascularization, genetic aberrations, and other deranged physiological processes in a specific microenvironment. Indeed, inflammation is a mechanism that facilitates many forms of cancer. It is suspected to influence the development and progression of cancer through many etiological pathways. These include increased levels of DNA adduction, mutations of oncogenes and tumor suppressor genes, increased vascularization, aberrant anti-apoptotic signaling, and immune evasion [1, 6, 7]. DNA methylation especially hypermethylation, has been known to cause certain HNSCC such as oral cavity carcinoma and salivary glands carcinomas. The process of angiogenesis is paramount as most of the tumoral mass displays various patterns of vascularization. This angiogenic pattern is responsible for tumor characteristics and the true biology of the HNSCC. Several of these processes may interact with each other in producing harmful effects that lead to carcinogenesis and malignant mass formation.

INFLAMMATION AS A PRIMARY CAUSE OF CANCER PROGRESSION

Although cancer is multifactorial in origin, various epidemiological and experimental studies suggest that chronic inflammation has an important role in all stages of cancer, from initiation to progression and even survival of the patient. Inflammatory products like cytokines, chemokines, leucocytes, prostaglandins, cyclooxygenase, reactive oxygen, and nitrogen species are all involved in the development of carcinomas. The other equally important elements are the aberrant genetic factors and processes such as metalloproteinase that able to induce genetic and epigenetic changes in normal cells and damaging their DNA. They can also inhibit their repair, modify transcription factors, suppress apoptosis, and induce angiogenesis, resulting in carcinogenesis. All these markers play a vital role not only in promoting cancers but also in diagnosis, assessment, treatment, and post-treatment surveillance. Thus, these inflammatory mediators have a potential role to become cancer biomarkers for all stages of cancer as many of them can be measured in a cost-effective manner [8]. These biomarkers may emerge as potential therapeutic agents in combatting head and neck malignancy from the very beginning.

The role of inflammation in cancer is indisputable. To illustrate this strong relationship further, the recent literature has highlighted many chronic inflammation reactions as the primary causes of the majority of solid and epithelial malignancies in humankind globally. Numerous writers have reported that many studies highlight the strong association of inflammation with chronic diseases. Accumulating data indicates that chronic inflammation is a precursor to

CHAPTER 7

Inflammation and Current HPV Status in Head and Neck Malignancy

Roman Carlos Zamora[1,*], Jose Gutiérrez Jodas[2] and **Norhafiza Mat Lazim[3]**

[1] *Department of Otorhinolaryngology-Head and Neck Surgery Hospital Universitario Reina Sofia, Cordoba Spain. Direction: Avenida Menendez Pidal, s/n, Postal code 14004, Cordoba, Spain*

[2] *Department of Otorhinolaryngology-Head and Neck Surgery, Hospital Universitario Reina Sofia, Cordoba, Spain, Avenida Menendez Pidal, s/n, Postal code, Spain*

[3] *Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia*

Abstract: Head and neck malignancy is on the rise, where the majority of the tumors are squamous cell carcinoma (HNSCC). Previously, alcohol and tobacco are reported to be the well-established risk factors for HNSCC development. Currently, the HPV driven HNSCC has shown an increase in incidence globally, with oropharyngeal and oral cavity carcinoma predominating at certain geographic locations. HPV associated oropharyngeal squamous cell carcinoma commonly occurs in Europe and certain Western countries. They have different biological profiles compared to HPV-negative HNSCC. HPV-positive HNSCC patients have different characteristics and prognosis, which remarkably affect the management of this subset of patients. HPV is a significant inflammatory agent that can promote carcinogenesis *via* multiple critical mechanisms that are discussed in the chapters. Targeting HPV for future research is a great promising avenue for the discovery of novel screening, diagnostic, and therapeutic targets.

Keywords: Alcohol and tobacco, Chronic inflammation, Head and neck cancer survival, Head and neck carcinoma, Human Papillomavirus (HPV), Prognosis, Treatment outcomes.

INTRODUCTION

This chapter focuses on chronic inflammation, HPV, and its relation to head and neck malignancy, as well as its various treatment and preventive options. It is well documented that chronic inflammation in the complex world of the immune system plays an important role in malignancy. Currently, the tendency of

[*] **Corresponding author Roman Carlos Zamora:** Department of Otorhinolaryngology-Head and Neck Surgery Hospital Universitario Reina Sofia, Cordoba Spain. Direction: Avenida Menendez Pidal, s/n, Postal code 14004, Cordoba, Spain; Tel: +34634219251; E-mail: romanchos@hotmail.com

treatment options for HNSCC patients is becoming less invasive, more conservative, and aims to have a more molecular approach. This can be ideally achieved by incorporating inflammation markers as promising therapeutic agents in the near future. Prevention plays an important role in combatting HNSCC.

As early as the 1800s, the perception of inflammation associated with cancer has been thought of but not demonstrated. In recent years, molecular studies have been able to show that inflammation contributes to the survival and proliferation of malignant cells [1]. Many of the well-established risk factors for head and neck malignancy are associated with inflammation. For instance, the environmental carcinogens such as sharp tooth and periodontitis for oral cavity carcinoma, Epstein Barr virus (EBV) for nasopharyngeal carcinoma (NPC), wood dust exposure for sinonasal malignancy and human papillomavirus (HPV) for oropharyngeal carcinoma. HPV-related HNSCC is significant as this tumor group has a different biological profile and treatment outcomes compared to HPV-negative tumors.

CHRONIC INFLAMMATION AND HEAD AND NECK ORAL CARCINOMA

Squamous cell carcinoma is the most common malignant lesion in the oral cavity. There is a significant increase in oral cancer incidence in young people, with 350,000-400,000 new cases worldwide per year. Bacteria, viruses, and fungi have been implicated and highly related to certain cancers [2]. For these reasons alone, it is important to gather more research and investigations about the risk factors of head and neck squamous cell carcinoma (HNSCC) in patients under 45 years old [3]. The oral cavity contains many bacterial species, with some of them being able to produce oral pathology. In recent years, the relationship between oral flora and head and neck cancer has been a subject of interest. Emerging evidence suggests that chronic inflammation could play an important role in the development of cancer. Importantly, studies have shown that periodontitis can promote carcinogenesis and lead to oral cavity cancers.

There is a strong association between head and neck carcinoma risk and oral leukoplakia, oral fibrosis, and repetitive dental ulcer injury [4]. There is a complex inflammatory process involved in the progression of premalignant lesions to squamous cell carcinoma. The role of T-cells (Tregs) and tumor-associated macrophages in immunohistochemical staining of cytokines showed that there was an increase in disease progression in premalignant oral lesions. In the early stages of premalignant lesions, IL-10 was seen to be increasing [5]. All of these inflammatory markers play a crucial role in the pathogenesis of head and

neck malignancy, and some have been discussed in the other chapters in this book.

Generally, during the progression of oral dysplasia, IL-4$^+$ macrophages were seen from premalignant lesions. However, TGF-β1$^+$ macrophages were seen in oral squamous cell carcinoma (OSCC) in less quantity than premalignant lesions as well as the expression of IFN-γ. These findings suggest that chronic inflammation promotes tumorigenesis in OSCC, rather than initializing it [5]. Overpopulation of pathogenic oral bacteria may be secondary to poor oral hygiene. This, in turn, can switch the chronic inflammation process and progression into OSCC. Three species of oral bacteria associated with an increased risk of oral squamous carcinoma were *Fusobacterium nucleatum*, *Prevotella tannerae*, and *Prevotella intermedia*. Additionally, it was also seen that alcohol, cigarettes, and poor oral hygiene were associated with an increase in oral pathogenic bacteria. Salivary IL1β was associated with a rise in periodontal-pathogenic bacteria and OSCC risk, which in turn can be influenced by genetic factors and lifestyle. Critically, all these results suggested that good oral hygiene may reduce OSCC risk and should be part of a prevention campaign [6].

The risk of cancer can potentially be predicted through alterations seen in the oral microbiota. Further understanding can be achieved by molecular advances in monitoring the role of oral microbiota and oral carcinogenesis [7]. For example, the formation of *8-oxo-7,8-dihydro-2'-deoxyguanosine* and *8-nitroguanine* are mutagenic DNA lesions associated with inflammation-related cancers. The formation of these mutagenic DNA has been seen in precancerous lesions due to infection and pro-inflammatory factors. Several studies have suggested that cancer development is triggered by inflammation associated-DNA damage in cancer stem-like cells. An increase in oxidative stress due to dysfunction of anti-oxidative proteins, DNA methylation, and microRNA dysregulation can lead to carcinogenesis. One example is Epstein-Barr virus-related nasopharyngeal carcinoma, in which quantitative RT-PCR analysis confirmed the downregulation of miR-497 in cancer tissues and plasma. These findings can be useful biomarkers in liquid biopsy for prevention and early detection [8] of HNSCC.

C-reactive protein (CRP) is an acute-phase protein that serves as a marker for inflammation and the progression of various cancers. A study by Metgud *et al.* compared CRP in saliva and serum in 20 normal individuals, 20 patients with OSCC, and 20 patients with oral premalignant lesions to assess as a prognostic indicator for OSCC. Mean CRP levels were more elevated in patients with premalignant lesions and OSCC compared to controls [9]. Oral cancer has become an important problem in many parts of the world, with more cases seen in developing countries. This is the reason why molecularly targeted prevention of

CHAPTER 8

Treatment of Head and Neck Cancer and Relation to Inflammation

Rohaizam Japar Jaafar[1,*], **Zulkifli Yusof**[1] and **Zakinah Yahaya**[2]

[1] *Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia*

[2] *Hospital Kuala Lumpur, Kuala Lumpur, Malaysia*

Abstract: Over the past decades, the survival rate of head and neck cancers has not significantly changed. Recently, the importance of the inflammatory responses in head and neck cancer has been a hot topic and of increasing interest. There has been suspicion about the relationship between inflammation and carcinogenesis, and thus, many works had proven these relations. Manipulation of the inflammatory mediators has been experimented with, to reduce the tumor burden, treat as well as prevent the cancer occurrence or second primary. This chapter summarizes the relationship between inflammation and cancer, emphasizing epidemiological and clinical evidence and proposing the current potential targets of anti-inflammatory agents for the therapeutic approach of head and neck cancer (HNC). We hope this knowledge will help us combat carcinogenesis and reduce the morbidity of the current conventional treatment for a better quality of life.

Keywords: Head and neck cancer, Inflammation, Treatment.

INTRODUCTION

The investigation toward inflammatory-associated carcinogenesis and approaches to reach the inflammatory targets is a relatively new area in cancer research [1]. When Rudolf Virchow introduced the term inflammation-related carcinogenesis in 1863, many epidemiological studies and research support the theory only years later [1, 2]. To date, inflammation is widely recognized as a hallmark for carcinogenesis. The idea for inflammation-related malignancies allows us to target the inflammatory response as therapeutic management of cancer at the molecular level.

The role of medical treatment in head and neck cancer has evolved over the years with a better understanding of tumor genetics and biology. Although it is a clear

[*] **Corresponding author Rohaizam Japar Jaafar:** Hospital Sultanah Bahiyah, Alor Setar, Kedah, Malaysia; Tel: +60126306022; E-mail: rohaizamjaafar@me.com

Norhafiza Mat Lazim (Ed.)

connection that an inflammation leading to cancer; for example, hepatitis due to hepatitis B virus or C or toxic compounds as the initiation in the development of hepatocellular carcinoma, association between chronic esophagitis and Barrett's metaplasia with esophageal cancer, chronic pancreatitis and pancreatic cancer, inflammatory breast cancer as a result of unresolved breast inflammation and Helicobacter pylori infection with gastric adenocarcinoma [2], but the inflammation-related head and neck cancer is still new. Understanding inflammatory pathway blockage, overexpression of inflammatory mediators and targeting the cancer microenvironment can be the promising approach for head and neck cancer treatment.

In 2008, about 16.1% of newly diagnosed cancers were related to infections [3], while epidemiologic studies indicate that at least 20% of all cancers begin as a direct consequence of chronic inflammatory processes [2]. Undoubtedly, inflammation-related oncogenesis is complex; it involves numerous cells and mediators through multiple mechanisms. There is a crosstalk between two pathways, the extrinsic pathway, driven by non-cancerous cells and the environment, and the intrinsic pathway, which is driven by oncogenes expression. The extrinsic insult such as infection, obesity, smoking, alcohol, microparticles, for example, silica and asbestos, and chronic inflammatory diseases is an established risk factor related to chronic inflammation [2, 3]. For example, cigarette smoking is proven to modulate an immune response. The effects are complex; both pro-inflammatory and suppressive effects may be initiated. Nevertheless, it contains toxins and bacterial lipopolysaccharide responsible for mucosal damage, and molecular derangements leading to oncogenesis by increasing cytogenic abnormalities, inactivation of tumor suppressor genes, and changes in the intracellular signaling pathway. As a direct consequence, smoking impairs immunity in the oral cavity, promotes gingival and periodontal disease and oral cancer. Smoking is also a risk factor in developing premalignant lesions, including leukoplakia and erythroplakia, which can progress to invasive carcinomas [4].

On the other hand, the intrinsic factor can be triggered by mutations, recruitment, and activation of inflammatory cells [4, 5]. It directly affects the initiation, angiogenesis, cell migration, progression, and aggressiveness of the tumor. At a molecular level, this process activates the apoptotic pathway either by down-regulate pro-apoptotic or up-regulate anti-apoptotic molecules. Inflammatory cytokines are major inducers that play a vital role in oncogenesis, and even there is emerging evidence that tumor cells and tumor-associated leucocytes can produce inflammatory cytokines and chemokines by themselves [5]. The inflammatory cytokines are tumor necrosis factor-α (TNF-α), interleukin- 1β (IL-1β) and interleukin-6 (IL-6), and chemokines are prostaglandins, oncogenes,

cyclooxygenase-2, inducible nitric oxide synthase, 5-lipoxygenase, matrix metalloproteinases, vascular endothelial growth factor, hypoxia-inducible factor-1α, nuclear factor-κβ (NF-κβ), nuclear factor of activated T-cells, signal transducers and activators of transcription 3-STAT3, activator protein-1 (AP-1), cAMP, and enhancer-binding protein. Additionally, activation of various kinases, including Iκβ kinase (IKK), protein kinase-C, mitogen-activated protein kinase, and phosphoinositide-3 kinase/protein kinase B (PI3K)/AKT, participates in inflammation-related oncogenesis [6 - 10]. Anti-inflammatory agents are believed to alter the tumor microenvironment, reduce cell migration, increase apoptosis, and increasing sensitivity to other therapy [3, 6].

There are several genetic alterations associated with chronic inflammation in head and neck cancer (HNC). An example of the interplay between inflammation and genetic alteration is HPV-related oropharyngeal squamous cell carcinoma. They present at a younger age, who is non-smoker and do not consume alcohol. HPV-16 DNA has been found in up to 72%, and inactivation of p16 is a frequent event witnessed in >80% of oropharyngeal tumour specimens [11 - 13]. The HPV integrates into host DNA expresses oncoproteins E6 to target the tumor suppressor genes p53 and E7, which act on the pRb for ubiquitin-mediated intracellular degradation, inactivate the normal cell cycle resulting in oncogenic transformation [11]. HPV-16 and HPV-18 are the most common oncogenic variant [14, 15]. Notably, it has been found that 50% of all oropharyngeal tumor specimens contain p53 mutations [16].

Another example is the Epstein-Barr virus. It is known to have a causal relationship in lymphoma, nasopharyngeal carcinoma, and gastric carcinoma, in which it mainly infects human lymphocytes and oropharyngeal epithelial cells. Multiple and diverse pathways are involved in EBV-related oncogenesis. The interaction of virus and host genes during its latency period leads to G1/S phase transition and inhibition of cell apoptosis. The latent proteins and miRNAs encoded by EBV activates the oncogenes such as Bcl-2 and MYC, activate signaling pathways such as NF-κB, JAK/STAT, and PI3K/Akt, and inhibit tumor suppressor genes such as p53, PTEN, and $p16^{INK4A}$. EBV is known to facilitate the oncogenic courses with specific oncogene activation [17].

In this chapter, we would like to list several strategies, possibly to reduce the tumor burden, treat and prevent cancer. There is an increasing number of FDA-approved anti-inflammatory agents concerning cancer. Since monotherapy or conventional modality insufficiently to eradicate cancer, a combination supposedly to be introduced [6]. The majority of agents target rapidly proliferating cells, resulting in cell death. Others can alter the tumour or the therapeutic agents' pharmacokinetics and pharmacodynamics on the molecular

CHAPTER 9

Behind the Screen: The Emergence of New Evidence

Belayat H. Siddiquee[1,*] and **Norhafiza Mat Lazim**[2]

[1] *Department of Otolaryngology-Head and Neck Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka-1000, Bangladesh*

[2] *Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia*

Abstract: Head & Neck Squamous Cell Carcinoma (HNSCC) is a heterogeneous group of malignancies that collectively constitute a significant group of cancer worldwide. It affects not only the elderly patients but more so the middle age and the pediatric patient population. Around 90% of these tumors develop from the mucosal lining of the head and neck region *i.e.* Head & Neck Squamous Cell Carcinoma (HNSCC). These mainly include oral cavity carcinoma, oropharyngeal carcinoma, hypopharyngeal carcinoma, laryngeal carcinoma, sinonasal carcinoma, nasopharyngeal carcinoma, and salivary glands carcinomas. Different types of these carcinomas are prevalent at some geographic locations due to various environmental, dietary, social, and genetic factors. Head and neck cancers are critical as these affect many vital functions of the human being, such as breathing, eating, smell, hearing, and vision. Clinical and epidemiologic studies show aetio-pathological relation between chronic inflammation and cancer in several organs, including the Head and Neck region. A huge number of inflammatory mediators and markers have been identified and investigated in the current genomic era. Significant inflammatory biomarkers have a potential role not only in screening and prevention but also in treatment and assessing the prognosis of HNSCC. This chapter will highlight the recent facts, the discovery of evidence of the inflammation, and biomarkers for HNSCC.

Keywords: Alcohol and smoking, Biomarkers, Head and neck malignancy, HNSCC, Human papilloma virus, Immunoscore, Inflammation and cancer, Nasopharyngeal carcinoma, Oncogenic virus.

INTRODUCTION

Head and neck malignancies are increasing throughout the planet. It affects not only the elderly patients but more so the middle age and the pediatric population.

* **Corresponding author Belayat H. Siddiquee:** Department of Otolaryngology-Head and Neck Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka-1000, Bangladesh; Tel: 01917374020; E-mail: drbelayat@gmail.com

In the UK, HNSCC incidence has been rising by almost a quarter in the last decade, with an estimated annual burden of 11,400 new cases. Since the early 1990s, Oropharyngeal cancers (OPCs) have seen the biggest rise among head and neck squamous cell carcinoma (HNSCC), with incidence rates is doubling yearly. In contrast, there is a 20% decrease in the incidence of laryngeal cancer in the same period, though the rate has become steady more recently [1]. Lifestyle factors play an important role in the etiology of these cancers. Around 75% of HNSCC have been attributed to the individual or combined effects of tobacco and alcohol consumption. Tobacco use is an established primary risk factor for HNSCC, which causes adverse outcomes, including increased overall and cancer-specific mortality and risk for developing a second primary cancer. Continued smoking is also strongly associated with treatment toxicity [2]. Human papillomavirus (HPV), predominantly HPV-16 infection, is also recognized as a primary risk factor for oropharyngeal cancers (OPCs), especially in younger age groups. Despite an overall decline in mortality rates of HNSCC, survival remains poor. The overall 5- year survival rate is around 50% but ranges from 33% for hypopharyngeal cancers to 60% for laryngeal cancers. People with HPV positive oropharyngeal tumors have consistently demonstrated improved survival compared to their HPV negative counterparts, although they are frequently diagnosed at a later stage [1].

There is a marked difference in HNSCC incidence by gender, race, and geographical distribution. The development of HNSCC is the result of interaction among environmental factors and genetic inheritance and is, therefore, multifactorial. HNSCCs are molecularly and genetically heterogeneous diseases, encompassing a wide array of carcinogenicity involving tissue and organs of the head and neck. Over the last few decades better understanding of the etiological factors, that cause HNSCC contributes to the management of these serious diseases dramatically. Besides smoking and alcohol, other factors like viruses, chronic inflammation in the territory, nutritional elements deficiency, chronic irritations even the genetic pre-disposition drawing the attention of the researchers. Despite this lot of things are yet to be explored. Because this is often observed that having a risk factor or even several risk factors does not mean that one will get cancer, many people having an HNSCC may not have had any known risk factor exposure.

Biomarkers are biological molecules identified in the cancer tissue or blood. Research surrounding biomarkers help in opening a new horizon in the diagnosis and treatment of HNSCC. They used to correlate with the presence or absence of a disease, are prognostically related to the disease course, and sometimes predictive of a tumor’s response to a specific therapy. Biomarkers should be objective, independent, and require validation by clinical testing and patient

outcome. Ideally, biomarkers should be easy to analyze, quantitative, affordable, and must be subjected to quality control and assurance [3].

Risk Factor Analysis

Tobacco is associated with HNSCC [4]. More than 70 known carcinogens were found in cigarette smoke [5]. Among the toxic and carcinogenic substances absorbing in the body from tobacco, exposure are tobacco-specific nitrosamines (TSNA) and polycyclic aromatic hydrocarbons (PAH), which are mostly studied with regard to carcinogenicity. TSNA found in tobacco and tobacco smoke, essentially formed during the curing and processing of tobacco. They are found both incombustible and smokeless forms of tobacco. TSNA can be formed through various chemical reactions [6]. Seven TSNA have been identified in tobacco products and N′- nitrosonornicotine (NNN), 4(methylnitrosamino)-1- (3-pyridyl)-1-butanol (NNAL) are two of them [6]. Two prospective cohorts, the Shanghai Cohort Study and the Singapore Chinese Health Study help us to gain valuable epidemiologic data regarding the use of NNN and NNAL to give information about cancer risk [7]. Recently, a control study was performed to see tobacco-related carcinogens in HNSCC. Urinary levels of 1-HOP, NNN, and NNAL were measured in smokers with newly diagnosed cases of HNSCC and compared to smokers without cancer. Levels of 1-HOP and NNN were raised in the smokers with the HNSCC group compared to the control group who are matched on several other variables, including age, gender, number of cigarette sticks consumed per day [8].

Alcohol plays a role as a solvent to increase mucosal exposure to carcinogens and enhance cellular uptake of these. Acetaldehyde, a metabolite of alcohol can form DNA adducts that interfere with DNA synthesis and repair [9]. The synergistic effect of tobacco and alcohol is supported by an analysis of combined data from 17 European and American studies. The population attributable to risk was 72%, which included 4% for alcohol alone, 33% for tobacco alone and 35% attributable to both alcohol and tobacco. This effect was more than multiplicative. Similar steep rises in the risk of HNSCC among alcohol and tobacco users, especially those using high amounts of each product, have been demonstrated by Dal Maso *et al.* [10]. Consumption of tobacco along with alcohol increase the HNSCC risk. All smokers and alcohol users may not develop cancer, suggesting that individual variation in genetic susceptibility plays a critical role [11]. In general, there is a strong association between alcohol and tobacco use and the combined use of these further increases the risk [12].

Although tobacco smoking and alcohol drinking are responsible for most new HNSCC cases, the prognostic role of smoking status and alcohol intake during

CHAPTER 10

Targeting Inflammation: Window for Therapeutic Strategy in Head and Neck Malignancy

Norhafiza Mat Lazim*

Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia

Abstract: Inflammation is a hallmark of cancer. Inflammation is closely linked to head and neck malignancy and other solid tumors. Arrays of inflammation cascades and markers have been identified and proven to play significant roles in carcinogenesis. Many substances and molecules are secreted in response to the inflammation and its ecosystem and can be effectively measured and quantified at various stages of the carcinogenesis process. A spectrum of available inflammatory biomarkers can be a potentially effective therapeutic approach in the management armamentarium of head and neck malignancy. However, the cost, practicality, and availability are some of the major obstacles that need to be counteracted in order to progress in this challenging oncologic arena. Together with the continuous commitment from scientists, clinicians, laboratory personnel, and other related health staff, with the combination of technology updates, this new treatment approach and strategy are coming to reality. This chapter will discuss selected inflammatory biomarkers of significance critical for the armamentarium management of head and neck malignancy. Hopefully, this will escalate the treatment response of head and neck cancer patients. Hence, this ensures the patient's survival with the best quality of life.

Keywords: Carcinogenesis, Chemoradiation, Cytokines, Growth factors, Head and neck malignancy, Inflammation markers, Macrophages, Metastases, Neck nodes, Prognosis, Quality of life, Residual diseases, Survival.

INTRODUCTION

Nowadays, head and neck malignancy is showing great progress in its management due to the advancement and refinement of the technology, instrumentation, and operation theatre set up. Head and neck squamous cell carcinoma (HNSCC) continues to be a challenge as the incidence is on the rise and its involvement with vital facial and head anatomic complexes that respons-

* **Corresponding author Norhafiza Mat Lazim:** Department of Otorhinolaryngology-Head and Neck Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus 16150, Kubang Kerian, Kelantan, Malaysia; Tel:+60199442664; Fax: +6097676424; E-mail: norhafiza@usm.my

ible for breathing, speech, eating, hearing, and vision. Late presentation is a common feature of HNSCC patients, and this may be attributed to ignorance, poverty, poor access to health services, and patients consulting traditional healers and usage of traditional medicines [1]. Clinical presentation will depend on the regional anatomic involvement. Computed tomography is the mainstay for assessing and staging the head and neck malignancy whereas magnetic resonance imaging is the preferred tool for evaluating cartilage, bone, perineural, and perivascular invasion. Furthermore, in selected cases, a combination of fine-needle aspiration and neck ultrasonography increases the accuracy of cervical lymph node staging [2]. The prognosis of selected groups of HNSCC remains dismal despite extensive multimodality treatment incorporating surgery and chemoradiation.

With a median overall survival of less than 1 year, patients with chronic or metastatic HNSCC have a poor prognosis. This population includes patients whose disease has recurred locally or who, after initial treatment for localized disease, have developed distant metastases. A fair number of head and neck cancer patients present with loco-regional advanced disease or distant metastases at first presentation. The rate of second primary tumors after a diagnosis of HNC is about 3-7% per year [3]. A small number of patients with a limited recurrent disease can still be treated with curative intent, but the vast majority are treated with systemic therapy for palliative care [4]. Early-stage diseases are mainly treated with surgery and most patients experience a good quality of life with a regular follow-up scheme. A selected patient who presented with recurrent disease, locally or regionally, may be offered salvage surgery or chemoradiation.

For instance, conventionally, the normal treatment of NPC requires chemoradiation and surgery, in the majority of cases. Radiation therapy alone is known to be the main approach to NPC treatment, especially for early-stage disease. The concurrent chemoradiation has been a standard practice for stage III-IV diseases. Surgery mainly involves neck dissection in recurrent cases, in the patient who had exhausted chemoradiation and present with neck nodes that is not amenable to radiation. Surgery can also be performed in case of the patient had a small and limited recurrent tumor at the nasopharynx that can be addressed *via* transnasal nasopharyngectomy. Critically, deciding the best possible treatment method for a specific patient will depend on multiple factors such as tumor factors, patient's comorbidity, expertise and equipment availability, and committed rehabilitation team.

At the time, as more treatment choices become available, it is rational to postulate that the results for HNSCC patients could be optimized with an acceptable succession of treatment regimens. This translates to better prognosis and survival

for this subset of patients. One of the most effective instruments for providing full benefit to the patients is to increase the number of therapy lines and choices and refine the order in which these therapies should be delivered. Therefore, to produce a maximally efficient and tolerable multi-line continuum of care, it is important to incorporate as many potentially effective therapies as possible into the treatment model of head and neck malignancy [3]. In addition, only a minority of patients with HNSCC benefit from immunotherapy in clinical practice, and the need to discover novel biomarkers to improve treatment strategies is becoming increasingly important. Immunotherapy is based on host immune system functional restoration to counteract different strategies of tumor evasion. Immunotherapeutic approaches generally comprised of tumor-specific antibodies, cancer vaccines, cytokines, adoptive T-cell transfer, and immune-modulating agents [5]. Immune checkpoint inhibitor and EGFR inhibitor is a strong example of immune-targeted therapy [6, 7]. EGFR inhibitor overexpression is seen in most head and neck cancer and is associated with poor prognosis [8, 9].

Presently, many ongoing trials focusing on discovering new biomarkers that can be used in managing head and neck malignancy are in progress. For instance, a study assessing the outcomes of using a combination of antiepileptic plus cisplatin and cetuximab that might escalate treatment outcomes with minimal complications [10]. There are other scientific studies that look at other combinations of therapy in order to escalate the treatment outcomes of head and neck malignancy [11]. This effort needs full support from the government and non-governmental bodies in terms of financial assistance and mutual collaborative work and programs. This will have a great impact on the discovery of potent new therapeutic markers or agents for HNSCC. These new agents can be made available locally at a fair cost and accessible to all disadvantaged HNSCC patients.

With regards to the management of HNSCC, primary tumor management is essential in order to reduce the progression of the tumor and later appearance of distant metastases. However, the side effects of radiotherapy cannot be overlooked, as it can cause second primaries and many significant related toxicities that can impair the patient's quality of life. Multiple new techniques of radiation have been investigated in head and neck cancer patients in order to improve survival rates whilst minimizing the morbidities associated with radiation toxicity. Such regimes include hyperfractionated radiotherapy with the intention to reduce malignant cell repopulations by shortening the treatment interval time [10].

Critically, *via* modifying the tumor microenvironment, radiotherapy can also induce distant metastases. This may be partly attributed to the radioresistance that

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Norhafiza Mat Lazim

Associate Professor Dr. Norhafiza Mat Lazim is a consultant ORL-Head and Neck Surgery at School of Medical Sciences, Universiti Sains Malaysia. She obtained her MBBS from The University of Queensland, Australia. She had her Clinical Fellowship in Head and Neck Surgical Oncology from Netherland Cancer Institute (AVL-NKI), Amsterdam, in 2014 and at VUMC, Free University Hospital in 2015. She also had clinical training at Sydney Head & Neck Cancer Institute, Chris O'Brien Lifehouse, Australia. She has a strong interest in head and neck surgical oncology and acquired several research grants on head and neck tumors, inclusive of a multi-center clinical trial on tongue carcinoma based in the USA. She has multiple publications in peer-reviewed journals. She is a prominent reviewer for multiple international journals including Oral Oncology and IJPO. She is a member of AHNS, EHNS, ASHNO, ATA, BAHNO, IAOO, AIMS, IFHNOS, ESTM, and ATF.