

Review Article

Head and Neck Cancer Pathology: Old World versus New World Disease

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ABSTRACT

This review summarizes the development of head and neck pathology. Over the last decades, head and neck pathology cancer science began to examine the behavior of these cancers and to uncover the causative factors that lead to head and neck cancer. The avoidance of certain discovered carcinogens, lifestyle changes and certain vaccinations can reduce the risk of these cancers. Efforts in pathology are ongoing to aid the prevention and to delay the development of head and neck cancer.

KEYWORDS: Cancer, head, neck, pathology

INTRODUCTION

Globally, cancer is the second leading cause of death with 8.8 million deaths worldwide in 2015 according to the World Health Organization (WHO). Head and neck cancer represents the sixth most common cancer type with an incidence of more than 500,000 persons annually, most of which are squamous cell carcinoma.^[1,2] Head and neck cancer also represents the most common cancer in the developing countries.^[3] Oral cancer form of head and neck cancer is more predominant in India, Pakistan and other southeast Asian countries, where as the tongue and oropharyngeal cancers are more predominant in the Western countries.^[4]

Head and neck cancer can occur in the anatomical area between the skull base and the clavicles. Important biological functions such as breathing, swallowing, and speech can be compromised if the cancer affects the important corresponding areas of the human body.^[5]

HISTORY OF HEAD AND NECK PATHOLOGY

Head and neck cancer was seldom included in medical reports before the introduction of tobacco in the 16th century.^[6] The first report detailing oral cancer treatment was written in 1650 by Hayes Martin.^[7] In the late 1700s, theories about the pathogenesis of cancer emerged in Europe.^[8] Then, in France, Jean Godinot founded the first cancer

hospital in 1740.^[8] In approximately 1790, Onuigbo wrote about the recognition of lymph node metastasis.^[9] Subsequently, in the late 1800s, surgical pathology was born. Morell Mackenzi in 1871 published a book with detailed drawings of microscopic images of 100 consecutive biopsies.^[10] Diagnosis through biopsy procedures newly emerged in the late 1800s.^[10] In 1887, a biopsy from the larynx of Germany's Crown Prince Frederick was performed by Morell Mackenzi in which three biopsies were performed, following which the tissues were examined by Rudolph Virchow.^[11]

Numerous entities in head and neck pathology were described during the first half of the twentieth century, and information was published in clinical journals for radiotherapists, surgeons and otolaryngologists. In 1920, the surgical pathologist Albert C. Borders published a description of two fundamental innovative concepts; he established a grading system for squamous cancer of the lip and then applied it to oral cavity, tongue, nasopharyngeal, pharyngeal and laryngeal cancer cases. Subsequently, in 1932, he supported the concept of carcinoma *in situ*, which Stout later briefly addressed in 1952.^[10,12]

In 1947, Eggston and Wolff wrote "Histopathology of the Ear, Nose and Throat", which was the first book for

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ear, nose and throat pathology. Two atlases of head and neck pathologies were later available. The first, by Foote and Frazell in 1954, was the first Armed Forces Institute of Pathology (AFIP) fascicle on salivary gland tumors. Categories of mucoepidermoid tumors were discussed thoroughly by the authors. The second Atlas was by Ash and Raum in 1956 titled “An Atlas of Otolaryngic Pathology”, which covered multiple regions of the human body, including the larynx, sinonasal region, salivary glands, esophagus, tracheobronchial tree and lungs.^[10]

In 1953, Slaughter *et al.* proposed the term “field cancerization”, by which they associated the dysplastic cells around the cancer with local recurrence and multiple primary tumors after the treatment of head and neck cancer. This field now specifies the surgical margins after tumor resection, which is usually the surrounding mucosal epithelium that contains genetic alterations.^[13,14] In 1974, the second edition of the AFIP fascicle on the major salivary glands was published.^[10] Subsequently, in 1985, the first encyclopedia (“Surgical Pathology of the Head and Neck”) was published in the United States by Leon Barnes.^[10]

Many benign and malignant tumors were described between 1900 and 1960 along with their histological characterization, such as rhabdomyosarcomas, myoblastomas and subtypes of salivary gland tumors in addition to the characterization of noncancerous lesions such as Wegener’s granulomatosis.^[10]

Then, in the 1960s, the number of clinicopathological studies increased due to the development of laryngeal conservation therapy, and radiation therapy become more sophisticated. In 1974, John Batsakis published “Tumors of the Head and Neck”.^[10] Later, in the 1970s, the role of human papilloma virus (HPV) in the development of head and neck cancer was discovered.^[15,16]

RISK FACTORS ASSOCIATED WITH HEAD AND NECK CANCER

The development of head and neck cancer is multifactorial and is related to several etiological factors such as geographic location, diet, habits, exposure to sunlight and genetic background.^[2] Tobacco use and alcohol use are the main principle factors for the development of head and neck cancer, and their risks are associated with the intensity and duration of use.^[17,18] A forty-fold increased risk of head and neck squamous cell carcinoma exists with the use of tobacco and with the use of alcohol compared to non-smokers and non-drinkers, respectively.^[19] Nitrosamines and polycyclic hydrocarbons are the main carcinogenic

components of tobacco that have genotoxic effects. Tumor suppressor protein 53 (TP53) mutations that occur with head and neck cancer are observed more frequently with tobacco smoking patients than with nonsmoking patients.^[20] Alcohol use can amplify the effect of smoking in a synergistic manner.^[21] Alcohol can function as a chemical solvent, increasing the mucosal exposure to tobacco-derived carcinogenic components. Acetaldehyde, the metabolite of alcohol, can interfere with DNA synthesis and repair.^[22] Tobacco consumption can lead to increased tumor aggressiveness in cancer cells by stimulating proliferation, angiogenesis, and migration and can decrease the response to radiotherapy and chemotherapy.^[23,24] Platek *et al.* reported an increased risk of mortality among current smoker oropharyngeal squamous cell carcinoma patients who underwent concurrent chemoradiotherapy by approximately four-and seven-fold for HPV-related and-unrelated cancer patients, respectively.^[25]

HPV is another principle risk factor in approximately 25% of head and neck cancers, independent of other factors, in cases where HPV was detected in the tumor tissue.^[26] HPV is a non-enveloped DNA virus with a genome of 8 kb and a diameter of 50 to 60 nm.^[27,28] HPV has a predilection for the mucosal or cutaneous squamous epithelium existing in the cervix, anogenital region and oropharynx; moreover, the virus can infect the keratinocyte progenitors in the basal layer of the stratified squamous epithelia.^[16,29] Therefore, HPV infection can be transmitted by direct viral access to the basal keratinocytes of squamous epithelia. Additionally, the virus can be transmitted by microabrasion of the epidermis that may occur due to sexual or other physical contact.^[30] In contrast, physical disturbance of the squamous epithelium covering the tonsillar crypts is not necessary due to the natural interruption of the lymphoreticular squamous epithelium covering the tonsillar crypts, which facilitates HPV viral transmission to the basal keratinocytes.^[31]

Nearly two hundred genotypes (types) of HPV have been discovered. HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58 are the genotypes known to have oncogenic effects. The role of HPV in malignancies was established during the 1970s with the discovery of the HPV-16 genotype.^[32]

HPV-16 can cause oropharyngeal and oral cavity cancer, as concluded by the WHO.^[33] Ndiaye *et al.* in 2014 published a global meta-analysis on the identification of the type of HPV in head in neck cancer from 44 countries between 1990 and 2012; they found that 82% were related to the HPV-16 genotype.^[34]

HPV has nine viral proteins, 7 early proteins and 2 late proteins. HPV carcinogenesis occurs due to the action of E6 and E7. The E6 oncoprotein can degrade TP53, which interrupts its function and reduces apoptotic capacity in response to DNA damage, producing uncontrolled proliferation and genomic instability. The viral oncoprotein E7 can degrade another tumor suppressor, retinoblastoma protein (pRb), causing a perturbation of cell cycle regulation in infected cells, which represent the initial transforming stages from normal epithelium to carcinoma.^[15,16]

HPV has a known role in oropharyngeal cancers, including those of the base of the tongue and of the tonsils, coinciding with the Waldeyer ring of lymphoid tissue to include the nasopharynx, while involvement of the rest of the oral cavity is considered to occur at HPV-unrelated sites.^[35]

Only 16% of oropharyngeal cancers in the United States during the 1980s were related to HPV, while in 2013, more than 75% of oropharyngeal cancers were related to HPV infection.^[36] Between 1988 and 2004, the incidence of head and neck squamous cell carcinoma in the United States increased by 225%. The annual incidence of oropharyngeal cancer related to HPV in the United States is 2.6 per 100,000 persons.^[37,38]

Data from the Surveillance, Epidemiology, and End Results (SEER) between 1973 and 1999 showed that the five-year survival rates for nasopharyngeal, oropharyngeal and hypopharyngeal carcinoma improved significantly; however, they declined for regional-stage oral cavity and early-stage laryngeal cancer.^[35] Head and neck cancer is related to younger age, such as under 45 years of age, particularly for oropharyngeal cancer; however, previously, head and neck cancer was related to old age. Recent trends of decreased tobacco and alcohol consumption were not accompanied by decreased rates of oropharyngeal cancer, which indicates the participation of nontraditional behavioral and environmental factors.^[39,40]

Patients with HPV-related cancers are typically nonsmoking white males with higher socioeconomic status who are younger than patients with HPV-unrelated cancers.^[39] The mode of transmission of HPV-related cancers is not clear; however, the risk is increased for patients with a history of multiple sexual partners.^[39,41] Viral infection may be associated with some conditions and behaviors that alter antitumor immunity. HPV is found more frequently in the oral cavity of patients positive for human immunodeficiency virus (HIV) infection than in those who are HIV negative.^[42] HPV

is also associated with users of marijuana, which has immunomodulatory effects.^[40,43,44]

The survival rates of HPV-related cancers appear to be higher than those of HPV-unrelated cancers. Fakhry *et al.* evaluated the association of HPV-related head and neck cancer with the response to chemoradiotherapy in 96 patients and with their overall two-year survival rate. The HPV-related cancers had higher response rates to chemotherapy than the HPV-unrelated cancers (82% vs. 55%, respectively). Additionally, the HPV-related cancers had higher response rates to chemoradiotherapy than the HPV-unrelated cancers (84% vs. 57%, respectively). Furthermore, the HPV-related cancer patients had higher survival rates at the two-year interval than the HPV-unrelated cancer patients (95% vs. 62%, respectively).^[45] Ang *et al.* evaluated the overall three-year survival rates of patients with oropharyngeal squamous cell carcinoma; they also reported higher survival rates for patients with HPV-related cancer than for patients with HPV-unrelated cancers (82% vs. 57%, respectively).^[46]

In 2015, Hayes *et al.* observed a significant difference in the molecular landscape between HPV-related and-unrelated head and neck cancers that may affect therapeutic options in the future.^[47] HPV-related cancers are more responsive to chemotherapy and radiotherapy than HPV-unrelated cancers, and they are more susceptible to immune surveillance of tumor-specific antigens. HPV-related head and neck cancer is more responsive to radiotherapy than HPV-unrelated cancer. The reason for this radiosensitivity may be that HPV-unrelated cancer is associated with mutations of TP53 and a component of the pRb suppressor network, unlike HPV-related cancer in which impaired function of TP53 and pRb occurs without mutations, leading to more effective apoptosis.^[48] Kimple *et al.* found that the reason for the greater radiosensitivity of HPV-related cancer was increased TP53-induced apoptosis after radiotherapy.^[49] The response of HPV-related cancer to radiotherapy might also be due to other factors such as the tumor micro-environment, including tissue oxygenation.^[50] Newly developed microvessels in the tumor mass have several structural and functional abnormalities that may affect tissue oxygenation and subsequently may affect the concurrent response to radiotherapy.^[51,52] Superior tissue oxygenation was associated with HPV-related cancer, which may increase the radiosensitivity, whereas inferior tissue oxygenation was associated with HPV-unrelated cancer.^[53,54]

Additionally, Epstein-Barr viral DNA was found in nasopharyngeal cancer tissue. Epstein-Barr virus is common in some North African and Asian countries, which leads to Burkitt's lymphoma. The identification

of the virus in the metastasis often indicates the origin of the tumor, which is usually from the nasopharyngeal area.^[55]

SIGNS AND SYMPTOMS OF HEAD AND NECK CANCER

Patient signs and symptoms depend on the location of the primary tumor site and on the tumor stage. Vague symptoms and minimal physical findings are associated with the cancer in its early stages. Nasal obstruction, epistaxis and serous otitis media may be present in patients with nasopharyngeal cancer. Sinusitis and unilateral obstruction of the nostril may be considered early symptoms of nasal cavity and paranasal sinus cancer. Persistent hoarseness may be associated with laryngeal cancer. Non-healing oral ulcers, changes in denture fitting and pain may be related to early cancer of the oral cavity. Persistent unilateral sore throat and otalgia are the common symptoms for cancers of the oropharynx, hypopharynx and supraglottic region, which are usually diagnosed at late stages.^[55]

The poor prognosis associated with head and neck cancer is usually due to the late diagnosis in which the cancer is at an advanced stage. Therefore, an understanding of the cancerization and molecular genetics of the cancer is important to enhance the interventional and therapeutic approaches.

CANCER STAGING

Cancer staging determines the severity of the cancer based on the size of the original tumor and its spread in the human body. The tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most widely used staging system for head and neck cancer, where (T) indicates the primary site of the cancer. T1 to T3 represent the increase in the size of the primary tumor, and T4 represents the involvement of adjacent structures. (N) indicates the involvement of lymph nodes; N1 to N3 signify involvement of regional lymph nodes (metastasis size, number of lymph nodes, extent of spread and location). (M) indicates the presence of distant metastasis of the cancer. Additionally, pathological cancer staging can be done after surgery, which combines clinical cancer staging with the surgical pathological results.^[55-57]

COMMON HEAD AND NECK CANCER

Erythroplakia and leukoplakia are common premalignant lesions with histological features of dysplasia or hyperplasia that can progress and transform to invasive cancer, with a higher risk for erythroplakia.^[55] However,

lichen planus, actinic keratosis and oral submucous fibrosis are designated as premalignant lesions.^[58] Eighty-five percent of premalignant lesions are associated with leukoplakia. The transformation to invasive cancer depends on multiple factors such as tobacco and alcohol consumption, the clinical appearance, the lesion location and the size and grade of dysplasia on tissue biopsy.^[59] Specific genetic changes in tumor suppressor genes or proto-oncogenes lead to the transformation of a premalignant lesion to malignant cancer. Disturbances of the TP53 and retinoblastoma (RB) pathways, which control cell growth, are important in head and neck carcinogenesis.^[60] Early carcinogenesis starts with a loss of heterozygosity at chromosomes 3p, 9p, and 17p, which occurs in dysplasia, while changes in chromosomes 11q, 4q, and 8 correspond with late carcinogenesis.^[61]

Squamous cell carcinomas arising from mucosal surfaces represent more than 90% of head and neck cancers.^[2] Specifically, these tumors arise from the epithelium lining the oral cavity, pharynx, sinonasal region, nasal cavity and larynx.^[62] These diseases are heterogeneous with different patterns of behavior and presentation.^[63]

Squamous cell carcinoma begins as squamous dysplasia, which constitutes changes of the surface epithelium that precede the invasion of the subepithelial connective tissue. The dysplasia can be graded into three categories depending on the degree of epithelial atypia. Mild dysplasia is associated with the lower one-third of the epithelium. When two-thirds of the epithelium is affected, this finding is considered moderate dysplasia. Carcinoma *in situ* or severe dysplasia occurs when the atypia involves the full thickness of the epithelium. Subsequently, carcinoma *in situ* may progress to invasion of the subepithelial connective tissue and extend to the skeletal muscles, bone and skin.^[62]

HISTOLOGIC SUBTYPES OF SQUAMOUS CELL CARCINOMA

Conventional (keratinized) squamous cell carcinoma accounts for 80% of squamous cell carcinoma in head and neck cancer regardless of the oropharyngeal and nasopharyngeal region. The staging depends on the extent of keratinization, cytological maturation and growth pattern (well, moderately, poorly differentiated). Usually, this type is associated with tobacco and alcohol use.^[2] However, when it is associated with HPV, the squamous cell carcinoma will present with limited keratinization compared with conventional squamous cell carcinoma, poorly differentiated basaloid types of histology and will be considered a biologically more aggressive form of cancer.^[64]

Verrucous carcinoma comprises less than 5 percent of squamous cell carcinoma and is considered a locally aggressive carcinoma. Generally, these tumors lack any significant atypia and do not metastasize unless they coexist with conventional squamous cell carcinoma.^[2] Clinically, they appear as an exophytic mass with a papillary or warty appearance. Parakeratotic squamous cells appear on histological examination, which thicken the squamous epithelium.^[62]

Wain *et al.* in 1986 first described basaloid squamous cell carcinoma as a distinct histological variant of squamous cell carcinoma with an aggressive clinical behavior. It is characterized by a lack of keratinization or by focal keratinization with lobular to solid infiltration by basaloid cancer cells. Therefore, it is an aggressive and rapid expanding cancer related to poor patient outcomes. When it arises from the oropharyngeal region, it is usually HPV-related.^[62,65]

Papillary squamous carcinoma is a poorly recognized type with a favorable prognosis. Clinically, it presents as an exophytic mass with a prominent papillary growth pattern.^[2]

Sarcomatoid squamous carcinoma (spindle cell carcinoma) is considered a rare, poorly differentiated form of squamous cell carcinoma commonly reported to occur in the larynx. It is recognized to be a monoclonal dedifferentiated type of conventional squamous carcinomas.^[66,67]

OTHER COMMON TYPES OF HEAD AND NECK MALIGNANCIES

Lymphoma is the second most common primary malignancy in the head and neck area and constitutes approximately 3% to 5% of the total malignancies in the area.^[68] This type of cancer can be found in oral and para-oral regions, particularly in Waldeyer's ring, which is a ring of lymphoid tissue arising in the palatine tonsils, nasopharyngeal and oropharyngeal wall and base of the tongue. Lymphoma in the head and neck region accounted for merely 2.5% of total lymphomas affecting the lymphatic tissue of humans.^[69] Lymphoma originates from the main cells of the immune system, which are B and T lymphocytes and natural killer (NK) cells at variable stages of maturation. Several biologic features of these malignant cells reflect their normal counterparts.^[70]

Lymphoma can be classified as Hodgkin (HL) and non-Hodgkin lymphoma (NHL) as proposed by the WHO depending on the presence or absence of Reed-Sternberg cells.^[70] In total, 75% of head and neck lymphomas are considered non-Hodgkin types of lymphoma.^[68]

Usually, NHL is diagnosed at older ages between 70 and 90 years, whereas HL is usually diagnosed at younger ages between 20 and 30 years.^[71] Lymphoma usually affects immunocompromised patients, and it occurs in almost 15% of patients with acquired immunodeficiency syndrome (AIDS).^[72-74] Cervical lymphadenopathy is the common clinical presentation; the enlarged lymph nodes do not appear as indurated as metastatic lymph nodes related to squamous cell carcinoma and commonly do not adhere to the skin or deep planes.^[71,75] Lymphoma may manifest as a swollen or ulcerated lesion in the oral cavity and demonstrates radiographic destruction of the bone with swelling and loosening of the teeth when the maxilla or mandible is involved.^[75,76]

Malignant mucosal melanoma is a rare and aggressive disease arising from mucosal epithelium containing melanocytes; 85% of its incidence is related to head and neck sites.^[77,78] First described by Weber in 1859, malignant mucosal melanoma usually affects the nose and the paranasal sinus areas from which it originated from respiratory non-squamous mucosa.^[78] It is related to poor clinical outcomes with less than 20% of patients achieving 5-year disease-free survival.^[79]

The salivary glands can be affected by multiple types of malignancy, such as mucoepidermoid carcinoma, adenoid cystic carcinoma and adenocarcinomas. Mucoepidermoid carcinoma is the common form of salivary gland cancer and occurs frequently in the parotid and salivary gland of the palate and buccal mucosa.^[80] It is associated with a range of clinical outcomes and its prognosis depends on the tumor grade with low-grade tumors having a good prognosis and high-grade tumors having a poor prognosis.^[81]

HEAD AND NECK CANCER PREVENTION

Cessation of tobacco and alcohol use, avoidance of environmental carcinogens, maintenance of good oral and nutritional health, stress management and HPV vaccination may prevent or delay head and neck cancer.^[82,83] The United States Food and Drug Administration in 2006 approved the use of HPV vaccine (quadrivalent HPV) (Gardasil™, Merck and Co., Inc.) against HPV types 6, 11, 16 and 18, which cause cervical cancer and precancerous lesions.^[84] Therefore, HPV vaccination was first administered to girls and young women to prevent cervical cancer. However, with an increased number of HPV-induced head and neck carcinomas that is not gender specific, vaccination was recommended for girls and boys before the onset of sexual activity; its use in the United States for boys was approved in 2009, and its routine use in the United States for boys was approved in 2011.^[85,86]

Currently, in the United States, there are three different commercial HPV vaccines licensed for use: bivalent (2vHPV) Cervarix from GlaxoSmithKline, 9-valent (9vHPV) Gardasil 9 and quadrivalent (4vHPV) Gardasil from Merck. The advisory committee on immunization practices in the United States in 2015 recommended the routine use of HPV vaccines that can be started at the age of 11 years. Additionally, their use was recommended for females aged 13 through 26 years and for males aged 13 through 21 years. The recommended vaccination types for females are 2vHPV and 4vHPV, or 9vHPV in cases of unavailability of the two former formulas. The recommended vaccination type for males is 4vHPV, or 9vHPV in cases of unavailability of the former formula.^[85]

When a vaccinated person is exposed to the virus, the immune system can induce high titers of neutralizing antibody that will block viral cellular entry and prevent the development of the infection. Additionally, the vaccination can be used as an adjunct therapy to clear microscopic infection after HPV-related cancer treatment.^[87]

CONCLUSION

Over the past decades, the pathology of head and neck cancer has advanced. Cancer behavior was studied and new discoveries have emerged in the field of disease pathogenesis along with an understanding of the etiological factors of these cancers and methods of cancer prevention. The field continues to expand to prevent and delay the onset of head and neck cancer.

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