HEAD AND NECK CANCER

Treatment, Rehabilitation, and Outcomes

Third Edition

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PREFACE

We are proud to bring to you this third edition—almost 20 years after the first edition was released! The vision of the very first edition was to provide a clinical resource for speech pathologists working in the field of head and neck cancer care. While this third edition remains true to this original vision, the content has been expanded to embrace the broader allied health team, with new and expanded chapters covering dietetic management, neuromuscular management, lymphedema management, psychological support, and survivorship care. The flow of the content has also been reconsidered, with multidisciplinary management—the cornerstone of quality head and neck cancer care—now the second chapter of the book. This is to reflect the importance of having a team approach in cancer care and the need to adopt a patient-centered approach in all aspects and stages of management.

Since the release of the second edition, the field of head and neck cancer care has continued to progress, and this third edition reflects on many of these advancements. From the medical management perspective, improved radiotherapy techniques, more widespread adoption of transoral robotic surgery, and the addition of immunotherapy have changed the treatment landscape. Assessment techniques are continuing to be refined and new ones introduced (such as ICG lymphography, illustrated on the cover), giving clinicians new insights into treatment impacts and informing management. The evidence base for effective behavioral rehabilitation for treatment side effects has expanded, giving clinicians greater guidance for, and confidence in, care delivery. The past decade has also seen ongoing investment in research and development by the many companies providing equipment that supports laryngectomy care, offering more options for patients. Models of care have also continued to evolve. Delivering supportive patient care from the time of diagnosis and throughout survivorship is now a central goal for patient management. Furthermore, modes of service delivery, such as telehealth, are now well established and help to address issues of treatment burden and service equity. While we celebrate these advancements, continued and ongoing efforts are needed to address areas where challenges remain.

This book brings together almost 60 authors from seven countries, who represent just a small subset of the thousands of clinicians and researchers working daily to improve patient care and outcomes following head and neck cancer. It is also rich with clinical examples and resources to support patient care. These have been shared by many patients who are keen to ensure care continues to improve for the next person, such as Brien Hands, pictured here on the book cover with his wife, Lyn, receiving an Australia Day Award recognizing years of service as a laryngectomy support visitor. People like Brien and many, many others have given their consent for us to share their images and experiences so that we can continue to grow and learn. We hope your teams benefit from the personal, clinical, and research insights amassed in this textbook and we look forward to the next decade of enhanced patient care.

CANCER OF THE HEAD AND NECK

Sapna Balgobind, Dasantha Jayamanne, Ruta Gupta, and Alexander D. Guminski

CHAPTER OUTLINE

Introduction

Malignancy causes approximately one-quarter of all deaths in Western countries. Although improvements in the treatment of many cancers have occurred, resulting in lower death rates or improved survival, the increasing proportion of older people in Western countries, along with adverse lifestyle changes such as increasing obesity, is likely to result in greater absolute numbers of cancer patients. The most common form of such cancer is associated with smoking, alcohol consumption, and/or human papilloma virus (HPV) infection. In developing countries, head and neck cancers are more common than in the West. As developing countries become wealthier, mortality is reduced from other causes, especially infection, increasing the relative contribution from cancer. Head and neck cancer (defined as larynx, lip, oral cavity, oropharynx, hypopharynx, and nasopharynx primaries) contributes significantly to the global cancer burden, currently ranked the seventh most common type overall at approximately 878,000 cases per year or 4.6% of all cancers and eighth most common cause of cancer deaths at 444,000 and 4.47% (Sung et al., 2021).

Cancers of the head and neck are mostly squamous cell carcinomas (HNSCC) arising from the mucosa, or lining, of the upper aerodigestive tract. Such tumors frequently spread to local lymph nodes but may be cured even at this stage by aggressive localized therapy such as surgery, radiotherapy, or surgery followed by radiotherapy. Some variants with specific features are recognized, such as nasopharyngeal carcinoma. A variety of less common and rare tumors with diverse histology and origin (such as glandular, neurological, and structural elements) are seen, such as adenocarcinomas from salivary glands, carcinoids, sarcomas, and paragangliomas from the autonomic plexus of the carotid body and cutaneous origin such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Merkel cell carcinoma, and melanoma. The sites of origin and main histological subtypes of head and neck tumors are shown in Table 1–1.

Squamous cell carcinomas may arise from many different sites. The pattern and likelihood of spread, optimal treatment, and prognosis can differ according to the specific site from which the SCC has arisen. Management of head and neck cancers needs to accommodate the anatomical proximity and physiological requirements of structures vital to speech; swallowing; prevention of aspiration; sensory organs of smell, hearing, and vision; vascular supply to the brain; and critical neurological structures of the brain stem and facial nerves. The social and psychological impact of potential disfigurement for surgical patients, as well as impaired communication and swallowing, can be an invidious consequence of treatment. In this chapter, we discuss the biology underlying SCCs, the epidemiology of head and neck cancer (HNC) in both developed and developing countries, and the approach to clinical management of the common forms of HNC.

Introduction to Cancer Biology

Cancers occur when normal cells within the body accumulate a series of genetic and/or epigenetic changes that disrupt key cell and tissue functions. The term "genetic" in this context refers to damage caused directly to the DNA sequence within chromosomes via mutations, translocations, deletions, or amplification, which ultimately leads to a corruption of the gene-based programming of cellular function. The term "epigenetic" refers to alterations to cells that may not directly affect the DNA sequence but may alter the regulation of gene expression via DNA methylation, posttranslational modifications of histones, or infection of the cell by transforming viruses such as the human papilloma viruses. Due to the nature of the genetic and epigenetic changes that occur in cancer cells, the progeny of the cancer cell inherits the defects in cell regulation. For this reason, it is thought that the process of changing a normal cell into a cancer cell can only occur in dividing cells. In addition, it is apparent that the process of transforming a normal cell into a cancer cell requires more than one defect, usually requiring a series of damaging events that accumulate within the replicating cell and ultimately lead to sufficient alterations in cellular regulation to manifest as cancer.

The Biological Basis of Cancer Formation

Cancers are derived from normal cells that have received a number of sequential alterations to critical

Table 1–1. Sites, Common Histologies, and Notable Features of Head and Neck Cancers

Site	Tumor Histology	Notable Features
Lip	SCC (squamous cell carcinoma)	Arises from sun-exposed skin and is one of the most common forms of head and neck cancer.
Oral Cavity Tongue Alveolar ridge Floor of mouth Buccal mucosa Hard palate	SCC	One of the most common forms of head and neck cancer. May be related to oral irritants such as betel nut chewing.
Oropharynx Posterior/base of tongue Vallecula Tonsil Soft palate	SCC	One of the most common forms of head and neck cancer. Generally associated with human papilloma virus infection.
Hypopharynx Piriform fossa Postcricoid Posterior pharyngeal wall	SCC	One of the most common forms of head and neck cancer.
Larynx Supraglottic Glottic Subglottic Transglottic	SCC	One of the most common forms of head and neck cancer. Associated with poor outcomes.
Parotid gland	Benign: pleomorphic adenoma, Warthin tumor Malignant: mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma	Most common site for salivary gland tumors.
Intraparotid lymph nodes	Metastatic SCC	Often from previously excised head and neck skin primary lesions.
Skin	SCC, basal cell carcinoma, melanoma, and Merkel cell carcinoma	Most common site of malignancy worldwide, accounting for a higher incidence than all other malignancies combined.
Nasopharynx	Keratinizing or nonkeratinizing SCC	Strongly associated with Epstein-Barr virus infection. Early spread to lymph nodes, often bilaterally. Very radiation sensitive.
Thyroid	Papillary, follicular, medullary, and anaplastic subtypes	Papillary carcinomas have a good prognosis and mostly occur in young adults. Anaplastic carcinomas have a very poor prognosis. Medullary carcinomas may be part of a familial multiple endocrine neoplasia (MEN) syndrome.

continues

Table 1–1. *continued*

Site	Tumor Histology	Notable Features
Nasal sinus	Sinonasal adenocarcinoma (SNAC) Sinonasal undifferentiated carcinoma (SNUC)	Rare. Associated with multiple genetic rearrangements. SNUC may be associated with wood dust exposure.
Olfactory neurons	Esthesioneuroblastoma/ Olfactory neuroblastoma	Rare. Risk of CNS involvement.
Carotid body	Paraganglioma	Histologically resemble adrenal medulla pheochromocytomas but only rarely secrete catecholamines. May be familial.
Minor salivary glands	Benign: pleomorphic adenoma, Warthin tumor Malignant: mucoepidermoid carcinoma, adenoid cystic carcinoma	Rare in the minor salivary gland.
Nerve sheaths	Neurofibroma, schwannoma, malignant peripheral nerve sheath tumor	May be associated with familial neurofibromatosis.
Any mesenchymal tissue	Sarcomas	Many different subtypes. May be treated with surgery or radiotherapy. Some subtypes benefit from chemotherapy.
Any site	Neuroendocrine tumors (rare in the head and neck)	Treated with surgery and chemotherapy.
Any lymphatic tissue	Lymphoma	Usually treated with chemotherapy.
Supraclavicular lymph node (especially left side)	Metastatic carcinoma	Particularly from breast, lung, or stomach primaries.
Bone	Benign tumors Malignant tumors	Similar to bone tumors arising at other body sites.
Dental tissue	Ameloblastoma	Most frequently arise in the molar region of the mandible. Locally aggressive and destructive lesion.

cellular functions. For mucosal cancers, Vogelstein et al. (1988) described a model of carcinoma development through precancerous phases such as epithelial dysplasia, carcinoma *in situ* (CIS), and invasive carcinoma (Figure 1–1). The precancerous phases may involve variable parts of the mucosa showing phenotypic changes of cancer, through to CIS, in which the entire thickness of the mucosa demonstrates phenotypic changes of cancer but there is no invasion through the basement membrane. Invasion through the basement membrane is required for the cancerous cells to have access to blood vessels and nerves. Hence, the phenotypically altered cells in the precancerous phase cannot spread to other parts of the body. Once the basement membrane is breached and the cancer cells can invade nerves and blood vessels, the cancer can spread to other parts of the body (e.g., lymph nodes) and organs (e.g., lung, liver, brain) in the body.

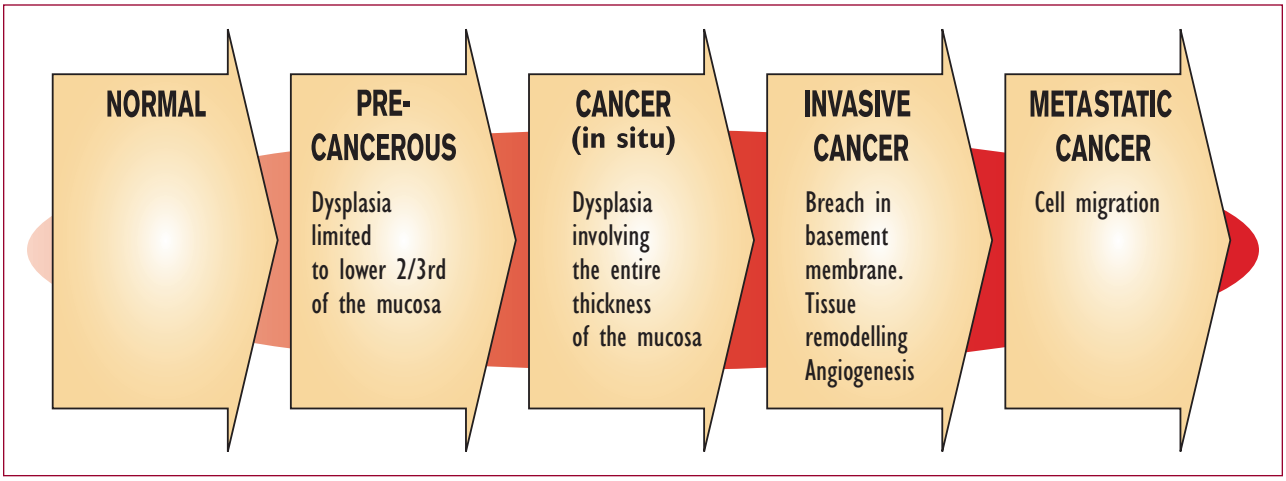

Figure 1–1. Simplified scheme of the progression from normal to metastatic disease.

It is now generally accepted that, for a normal cell to become cancerous and exhibit metastatic behavior, a number of critical cellular functions must be disrupted, namely: (a) DNA repair, (b) growth regulation, (c) apoptosis (programmed cell death), (d) replicative senescence, (e) differentiation, (g) angiogenesis, (h) tissue remodeling and migration, and (j) immune evasion (Hanahan & Weinberg, 2000, 2011; Serewko et al., 2002).

DNA Repair

DNA repair is an important process by which a cell is able to monitor the integrity of its DNA or the fidelity of DNA replication. This process is essential if cells are to avoid passing incorrect genetic information to their progeny. To achieve this, cells have acquired complex regulatory mechanisms that allow them to monitor the DNA for damage and to repair any identified damage. Sensors of DNA damage include the tumor suppressor gene, p53. There are a large number of enzymes and factors involved in DNA repair. In general, these enzymes/factors play a role in correcting errors introduced during replication. In addition, another series of enzymes/factors may be involved in the repair of DNA damage that occurs outside of replication.

Mutation of the p53 gene is the gatekeeper alteration that occurs in cancer cells (Hanahan & Weinberg, 2000, 2011). It is estimated that approximately 50% of all human tissues have acquired defects in the activity of p53. The gene p53 is a transcriptional regulator that responds to DNA damage. In response to DNA damage (e.g., γ-irradiation or UV-irradiation), p53 can increase the expression of a factor called p21, which in turn prevents cells from dividing. This halt in cell division lasts until the DNA can be repaired; cell division is then resumed. Alternatively, if the damage to the DNA is perceived as too great, then p53 can initiate apoptosis of the cell. In this way, p53 ensures the integrity of the DNA is maintained throughout cell division. For this reason, p53 is sometimes referred to as the "guardian of the genome." Given the central importance of p53 in normal cellular function, it is not surprising that, for tumors to arise, defects in p53 control are frequently observed. Defects in p53 function are most frequently seen as a loss of function mutations. Such mutations are observed in head and neck cancers.

Another important concept in DNA repair is mismatch that can occur between the original and replicated strand due to introduction of errors in the replicated strand. These errors are corrected by mismatch repair proteins encoded by mismatch repair genes MLH1, MSH2, MSH6, and PMS2. Patients with mismatch repair deficiencies often respond well to immunotherapy.

Growth Regulation

Growth regulation refers to the control of cell division. One of the hallmarks of cancer is that cancer cells are

characterized by deregulated proliferation. This occurs in numerous ways. For instance, in normal cells, certain secreted proteins activate cell surface receptors and stimulate cell division by activating signal transduction within the cells, leading to the initiation of a round of cell division or passage through the cell cycle. In contrast, many cancer cells exhibit semiautonomous growth insofar as they are being stimulated to replicate in the absence of normal stimuli. This constitutive activation of growth stimulatory pathways in cancer cells may come about through disruptions to the normal regulation of molecules involved in the regulation of proliferation. A prototypic example of this would be the mutation or amplification of the epidermal growth factor (EGF) receptor in several human cancers. EGF is a secreted cytokine that binds to receptors on the plasma membrane of cells and can activate a signal transduction pathway that results in the initiation of cell division. In many human cancers, such as head and neck cancers, the EGF receptor is either mutated or overexpressed (Ishitoya et al., 1989). Mutations in the EGF receptor frequently result in changes that maintain the receptor in a constitutively active state. Alternatively, overexpression of the EGF receptor can lead to overactivity of this growth-promoting pathway, resulting in deregulated proliferative signaling in these cells.

Another mechanism by which growth can be deregulated in cancers is through the loss of growth inhibitory signaling pathways. A classic example of this would be the loss of transforming growth factor β1 (TGFβ1) signaling in cancer cells (Dahler et al., 2001; Smith et al., 2004). TGFβ1 is a secreted cytokine that can bind to receptors on the plasma membranes of most epithelial cells and activate a signal transduction pathway that can inhibit proliferation in cells. Many cancers, including head and neck cancers, have sustained defects in this pathway either through aberrant receptor expression or loss of the signaling proteins (SMADs) that control TGFβ1-mediated growth inhibition.

Apoptosis

Apoptosis refers to a process of programmed cell death and is a normal process by which cells may be removed from the body. This removal is required to make way for younger maturing cells, as occurs on the surface of the tongue. This process also occurs following DNA damage to the cells. For example, if a cell is exposed to high concentrations of carcinogenic stimuli such as radiation or toxins, it can initiate apoptosis. This response is essential, as it protects the tissue from replicating damaged DNA. As with growth regulation, apoptosis is a complex process with many regulators, some of which are proapoptotic (e.g., caspases) and some of which are antiapoptotic (e.g., Bcl-2). Hence, the rate of apoptosis is dictated by the ratio of proapoptotic to antiapoptotic signals. In normal circumstances, cancer cells that have a heavy burden of mutated and damaged DNA would be expected to be removed via apoptosis. However, evidence shows that a prerequisite for many cancers is that they have disruptions in the regulators of apoptosis, such that the ability of cells to undergo apoptosis has been deregulated (Hanahan & Weinberg, 2000). Thus, it is not uncommon to find that cancer cells overexpress antiapoptotic genes such as Bcl-2 and/or are deficient in proapoptotic genes such as caspases.

Differentiation

Differentiation refers to the process by which a cell changes to take on specific functions related to its stage of maturity. For instance, the stratified epithelial lining of the upper aerodigestive tract is composed of cells that sit on a basement membrane. These cells have a basal cell phenotype and are capable of proliferation. Their primary function is to replace the older keratinocytes (epidermal cells that make keratin and form the bulk of skin) as they are shed from the external surface of the epithelium (Figure 1–2A). When the basal cells have replicated, they then pass into the next layer of the epithelium toward the external surface. As they do so, they stop proliferating. This is an irreversible process. The cells then start to express genes that are important for the maintenance of the barrier function. This process is referred to as terminal differentiation as, once started, the process is irreversible and ultimately leads to apoptosis.

This process of terminal differentiation is complex since it involves both the loss of proliferative capacity and the gain of barrier functions. If a normal cell were to become transformed through exposure to carcinogens, yet retained the ability to terminally differentiate, then the transformed cell would eventually be