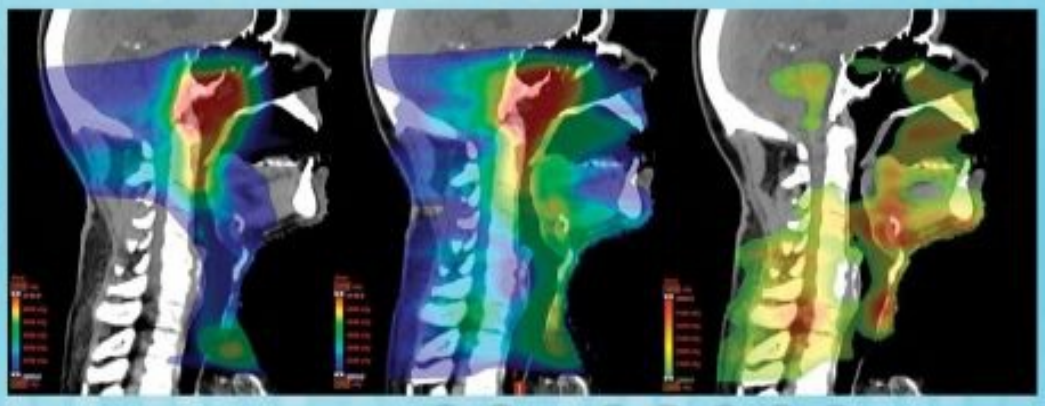
FIFTH EDITION

Radiotherapy for Head and Neck Cancers

INDICATIONS AND TECHNIQUES



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Wolters Kluwer

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Dedication

The current edition is dedicated to the memory of K. Kian Ang. Kian was a cherished mentor, colleague, and friend.

Over his career, he led multiple seminal phase III trials in head and neck cancer, with a focus on radiation. He helped define the role of altered radiation fractionation, as well as the role of cetuximab, the first biologic agent approved as a radiation enhancer for the treatment of head and neck cancer. He spearheaded international efforts in clinical research of radiation and head and neck cancer through his role as leader of the RTOG head and neck section in the 1990s and 2000s. He further enhanced the role of radiation as a former president of the American Society for Radiation Oncology (ASTRO).

Kian was the principal author of this text. He cowrote the original edition over 25 years ago and was the principal author of subsequent editions, such that the text was often referred to as “The Ang Manual.” It was a great honor and privilege to cowrite the previous three editions with him. He was always insistent that each edition combine common and still-used techniques with the latest advances in the field, through clinical applications of both biology and physics. Prior to his passing, we had several conversations regarding this work and its direction. I hope he would be proud of this current edition that continues the legacy of a teaching manual of head and neck radiotherapy aimed at a wide audience of both those new to the specialty and those experienced and interested in the latest advances.

Preface

It is difficult to believe that the first edition of this textbook was conceived over 25 years ago. My two mentors, Lester Peters and Kian Ang along with our fellow at the time, Johannes Kaanders, wrote this original work based on a desire to create a handbook useful for a day-to-day reference. Based on encouragement from our residents and many visitors, the three authors took a compilation of teaching materials, and in particular case studies, and created the first edition.

Lester and Johannes moved on to continue successful careers as leaders in the head and neck radiotherapy field in Australia and Europe, and Kian asked me to join him to write the second edition. There was an 8-year gap between the first and second edition; during that time in the late 1990s and early 2000s, many advances had been made, including the more routine integration of systemic therapy with radiation for treating head and neck cancer and technologic advances in radiation planning and delivery with the development of intensity modulated radiotherapy (IMRT). However, concurrent chemoradiation and IMRT were just starting to be brought into the clinic, and this 2nd edition included just a few examples, ultimately serving as a “sneak preview” of things to come. Additionally, the results of radiation fractionation trials had been completed, and the 2nd edition incorporated these schedules when applicable into our dose/fractionation regimens.

The 3rd edition saw two changes. The most significant change, just 10 years ago, was the incorporation of color images into the text. The second change was due to the recognition that IMRT was practice changing and likely to become the standard of care for the mode of radiation for head and neck cancers. As such we expanded the case examples, showing more case studies of IMRT for most of the site-specific chapters and began to formalize our presentation. IMRT not only was a newer way to plan and deliver radiation, but also represented a change in how to think about head and neck cancer with regard to treating with radiation. This principal change was a shift from field design based on anatomic landmarks (principally on two-dimensional images), to designing treatment based on identifying and delineating target volumes. The most common sites

investigated for a role of IMRT at that time were the oropharynx, nasopharynx, and paranasal sinuses; the text introduced target definitions (GTV, CTV, and PTV) for tumors originating from those sites.

The 4th edition, published in 2012, mainly reflected the change in practice from conventional therapy to IMRT. For the clinician, target definition involves identification of the gross target (GTV) and clinical target volumes. Many patients come to radiation after other therapies (surgery or chemotherapy), and as such the original GTV is altered, so we also included the concept of a virtual GTV (vGTV). Further, we formalized CTV definitions to high-dose, intermediate-dose, and low-dose targets (CTV_{HD}, CTV_{ID}, CTV_{ED}). Each site-specific section was expanded to include guidelines for target definitions. This edition also evolved with the times and included online access. Additionally, we added a chapter on reirradiation, as conformal therapies are now allowing us to retreat patients with recurrent cancers or second primary cancers that develop in irradiated tissues. The hard copy version was expanded 50%, but our goal was still to keep it more as a manual rather than an encyclopedic tome.

The current edition attempts to continue to both be a day-to-day reference and also incorporate the advances in the field. To the best of our ability, we have attempted to update the suggested readings and background tables. Based on feedback, we have added a “bridge” chapter between general concepts and site-specific chapters. As target delineation is the main activity for clinicians to design their patients’ radiation treatments, we include guidelines for normal tissues as well. We expanded the case examples and also included cases of patients treated with proton therapy, as this half-decade has seen an introduction of proton therapy being used for head and neck cancer. Similar to IMRT a decade ago, we are starting to see in the literature retrospective clinical series reflecting the use of protons and anticipate prospective and multiinstitutional trials to be the next step in exploring and developing this technology.

We are excited to share new advances in the field, but we also recognize that many are still not able to use the latest technologic advances to treat patients. As such, while we have removed some examples of 2D therapy, we have kept those principles of field design in the current edition. We hope this 5th edition both reflects our current practices and provides general guidelines for clinicians to help treat their patients who will be irradiated for head and neck cancer.

Preface to the First Edition

Primary cancers of the head and neck region are relatively rare. The estimated yearly number of new cases, excluding skin cancers located in the head and neck area, is about 42,000, which represents 4% to 5% of the total number of cancers diagnosed per annum in the United States. Although the vast majority of head and neck cancers arise from epithelial elements, their natural history differs considerably according to the disease location. This is related to regional anatomical peculiarities that dictate patterns of contiguous and lymphatic spread. The extent of the lesion and the presence of numerous critical normal tissues in the head and neck area, injury to which could result in serious functional impairment, are obstacles to local-regional disease eradication. Therefore, failure to achieve local-regional control is the leading cause of cancer-related death in patients with head and neck neoplasms.

Radiotherapy plays a very important role in the management of patients with head and neck cancers. In early-stage lesions, radiotherapy is frequently preferred because it is as effective as surgery in controlling the disease and is generally better in preserving cosmetic and organ functions. In advanced tumors, radiation treatment is complementary to surgery in obtaining maximal local-regional control. Sound knowledge of the behavior of various head and neck cancers is essential for selecting proper indications for radiotherapy for different subsets of patients. Thorough command of the regional anatomy, technical bases of radiotherapy, and awareness of available data on radiation effects on critical normal tissues are necessary for optimizing the treatment outcome. The choice of radiation target volume and dose is based on the best trade-off between control probability and likelihood of severe treatment-induced complication.

The natural history of head and neck cancers, general treatment strategies, and therapy results obtained at different institutions are summarized in a number of textbooks and chapters. However, so far there is no handbook on the technical detail of radiotherapy for head and neck cancers. This manual serves as a practical reference to head and neck radiotherapy. We chose to present the basic concepts and specific

indications and techniques for various common types of head and neck cancers, i.e., carcinoma and melanoma, as practiced at The University of Texas M.D. Anderson Cancer Center rather than compiling all available techniques in an encyclopedic fashion. The treatment policies described in this manual evolved during the past one-half century through gradual refinements based on results of systematic analysis of causes of failure and complications in cohorts of patients treated in a disciplined and consistent way. This philosophy introduced by the late Dr. Gilbert H. Fletcher has continued to the present day.

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1

General Principles of Head and Neck Radiotherapy

Head and neck cancers have been the subject of intensive laboratory research and clinical investigations. Advances in molecular biology techniques have facilitated research addressing molecular epidemiology, genetic predisposition, genetic tumor progression models, and personalization of treatment. Because of the ease of clinical assessment and a relatively low incidence of systemic spread, head and neck cancers are good models for testing the efficacy of new therapy concepts that are aimed primarily at improving locoregional disease control. Most of the clinical radiobiology research on altered fractionation and combinations of radiation with chemotherapy or novel agents, for example, has been conducted on patients with locally advanced head and neck squamous cell carcinoma (HNSCC).

Long-term investment in cancer research has come to fruition for certain cancers. After increasing for decades, the mortality rate of most cancers in the United States has decreased since 1975.[1] More recent data, for example, showed that while the incidence of all cancer has been stable in men and has increased by 0.3% annually in women between 1993 and 2002, the overall death rate has declined by an annual rate of 1.1% during this period.[2] This improvement has been attributed, at least in part, to advances in cancer treatment and better dissemination of guideline-based

treatment into the community.

Many advances have been achieved in the understanding of the biology, natural history, and treatment of HNSCC. A detailed depiction of recent progress is beyond the scope of this handbook—this brief introductory summary highlights a few recent findings contributing to the better understanding of the biology of the disease and to expanding treatment options for head and neck cancers.

1

Overview of Recent Advances

BIOLOGY OF HEAD AND NECK SQUAMOUS CELL CARCINOMA

Key Points

- HNSCCs are classically associated with tobacco and alcohol exposure. However, the incidence of HPV-related oropharyngeal carcinomas has been increasing steadily in the industrialized world since the 1970s.
- Advances in molecular studies, accompanied by research into HPV-associated cancer, have led to a recognition that HNSCCs represent a group of biologically heterogeneous carcinomas. For the present time, the most prominent subdivision of these cancers is into two subgroups: those that are viral associated (HPV or Epstein-Barr virus [EBV]) and those that are not.
- Clonal genetic changes occur early in malignant cellular transformation and in the histopathologic continuum of tumor progression.
- Newer molecular assay techniques, such as comparative genomic hybridization and next-generation sequencing technology, have

greatly increased the ability to interrogate genetic changes and thereby improve the understanding of genetic predilection (host susceptibility) and cancer biology.

- Whole genome sequencing has confirmed *TP53* is the most commonly mutated gene in HPV-negative HNSCC; *NOTCH1* is the second most commonly mutated gene.
- The understanding of tumorigenesis of nasopharyngeal carcinoma (NPC) continues to grow. Adding to the recognition of an endemic group with genetic predilection (including deletions on 3p and 9p) harboring latent EBV infection are findings of numerous oncogenes and tumor suppressor genes that lead to initiation of tumorigenesis, and EBV then contributes to transformation.
- HPV has an active role in carcinogenesis, particularly of oropharyngeal cancers, mainly through the actions of E6 and E7 oncoproteins. HPV-positive tumors have fewer mutations than HPV-negative tumors.

Lifestyle-Related Risk Factors

Tobacco and alcohol exposure have long been recognized as the dominant risk factors for HNSCC. Other risk factors include low fruit and vegetable consumption and betel quid chewing. In an overview, Petti[3] estimated that, worldwide, 25% of HNSCCs are attributable to tobacco use, 7% to 19% to alcohol consumption, 10% to 15% to dietary deficiency, and, in regions of prevalence, >50% to betel quid chewing. Carcinogenicity is dose dependent and magnified by exposures to multiple carcinogens.

Although tobacco and alcohol consumption is estimated to account for a significant proportion of oral and pharyngeal carcinomas in the United States,[4] neoplasms develop in only a small fraction of exposed individuals. This intriguing information raised the notion of the contribution of genetic susceptibility or predisposition and other cofactors (for examples of cofactors, see “Viral Etiology” section) to carcinogenesis. The potential pathways are thought to include genetic polymorphisms influencing environmental carcinogen absorption and detoxification and individual sensitivity to carcinogen-induced genotypic alterations, among others. These ideas can now be tested more comprehensively because of recent progress in molecular biology concepts and assay methodology. For example, the ability to identify smokers at high risk for developing cancer

will have important practical clinical implications in selecting individuals for more aggressive screening programs or for enrollment into intensive chemoprevention trials.

VIRAL ETIOLOGY

Epstein-Barr Virus

Although the association between EBV and NPC has been recognized for almost four decades, elucidating the association between EBV and oncogenesis has been challenging. The advances in molecular technology have allowed for greater insight into the relationship between EBV and NPC. The EBV genome was characterized (reviewed by Liebowitz)[5] to consist of a linear, 172-kb, double-stranded DNA having five unique sequences separated by four internal repeats and two terminal repeats. The DNA circularizes by homologous recombination at random locations within terminal repeats in the nucleus of infected cells. The length of the terminal repeat is specific for each infected cell, and this is the basis for clonality assays, which may be useful in determining the putative primary tumor in patients presenting with nodal metastasis from an unknown source. The genome encodes several families of proteins, such as early antigens, Epstein-Barr nuclear antigens (EBNAs), and latency membrane proteins (LMPs). Many of these proteins control viral behavior and affect cell proliferation regulatory mechanisms; these are thought to play a role in transformation and carcinogenesis and to influence tumor response to therapy. EBNA-1 regulates viral genome replication during cell division and was found to induce growth and dedifferentiation of an NPC cell line not infected by EBV.[6] LMP1 and LMP2A drive clonal expansion and transformation.

More work has been done on the molecular genetics of NPC. Similar to other tumors, NPCs appear to follow a multistep tumorigenesis model. Among the questions regarding NPC and EBV are whether the presence of EBV is ubiquitous and why is EBV associated with NPC in Southern China and with Burkitt lymphoma in equatorial Africa but not clearly related to other neoplasms elsewhere in the world. One observation is that many NPCs have been found to have deletions of the short arm, or some regions of the short arm, of chromosomes 3 and 9, suggesting the possibility of the existence of tumor suppressor genes (TSGs) in these

regions.[7,8] Next-generation sequencing technologies have shown that a frequent deletion region is one covering the *CDKN2A* gene of 9p21.[9]

While these chromosomal changes are consistent in NPC, irrespective of the patient's origin, studies of normal nasopharyngeal epithelium show a preponderance of these findings among the people of Southern China, lending evidence to an underlying genetic susceptibility for NPC. This has led to a hypothesis that these genetic changes lead to premalignant changes due to p16 inactivation or cyclin D1 overexpression that promotes maintenance of latent EBV infection.[10]

Once a stable EBV infection has been established, latent gene proteins will drive rapid clonal expansion and transformation. During this phase, multiple events will occur, including alteration of host immune response, microenvironmental changes, as well as altered genetics and epigenetics. These and additional events will occur through progression and metastasis.

Additional new findings using whole-exome and targeted deep sequencing in over 100 NPC cases include observing a relatively low mutational rate, though one with wide diversity. In particular, high rates of derangements in chromatin modification, ERBB–PI3K signaling, and autophagy machinery were observed. ERBB–PI3K mutations were linked to more advanced-staged cases with poorer survival.[9]

Human Papillomavirus

The causal relation between HPVs and some human neoplasms has long been appreciated. First described for carcinoma of the uterine cervix, it has also been associated more recently with anal, penile, and oropharyngeal cancers. HPV DNA is categorized into low- and high-risk groups. Low-risk HPV includes HPV-6 and HPV-11, which are associated with benign lesions. The most common of the high-risk types associated with malignancies are HPV-16 and HPV-18.[11] Cell culture studies clearly demonstrated that the high-risk HPVs can transform and immortalize epithelial cells from the cervix, foreskin, and oral cavity.[12–14] Expression of the *E6* and *E7* open reading frames of HPV-16 or HPV-18 genome is sufficient for immortalization.[15,16]

The evidence implicating HPVs in carcinogenesis of tonsillar carcinomas is quite strong because these tumors not only contain HPV DNA in most of the cells but also express readily detectable levels of HPV

RNA.[17] In a series of 253 patients, Gillison et al.[18] detected HPV in 25% of tumors, with HPV-16 present in 90% of the positive neoplasms. The presence of HPV was most common in oropharyngeal carcinoma occurring in individuals with no history of smoking or alcohol consumption whose tumors were of a basaloid subtype without TP53 mutation. Laboratory data showing the persistence of transcriptionally active, integrated HPV-16 DNA in an oral carcinoma cell line with features indistinguishable from those of the primary tumor[19] provide strong evidence that HPV has an active role in carcinogenesis.

HPV infection is extremely common, and in the vast majority of cases, the infection is cleared and malignancy does not occur. Epidemiologic studies have identified social risk factors associated with HPV-associated oropharyngeal cancer,[20] but further understanding of risk factors associated with and causing viral persistence leading to oncogenesis remains under study. The question of how high-risk HPV induces cell transformation has been studied mostly in cervical cancer, and the findings have been summarized in several review articles.[21–23] Briefly, two viral oncoproteins, E6 and E7, are crucial in the transformation process. E6 binds to and inactivates the tumor suppressor protein p53, affecting many cellular functions including impairment of DNA repair after damage by other agents and suppression of the ability of cells to die by apoptosis. E7 degrades pRb, thereby releasing transcription factors such as E2F, which in turn induces the expression of other cellular proteins including p16. The increase in p16 expression has led to p16 immunohistochemical staining to be used as a surrogate test for HPV association. E6 and E7 can also directly bind to several other host proteins, such as Bak and $p21^{Cip1}$, thereby contributing to amplification of genetic instability. The expression of E6 and E7 alone does not seem to be sufficient for transforming cells, but the additional genetic alterations necessary for neoplastic conversion remain uncertain. Recent profiling of head and neck cancers performed by the Cancer Genome Atlas network[24] has demonstrated that the genomics of HPV-positive cancers are very different from HPV-negative cancers. HPV-positive cancers have fewer mutations and in particular rarely have mutations of TP53. HPV-associated cancers are dominated by mutations in *PIK3CA*, amplification of the cell cycle gene E2F1, and loss of TRAF3, a gene associated with antiviral activity.

Numerous studies conducted over the last decade support a global trend in an increase in oropharyngeal cancer. Chaturvedi et al.[25] used data

from the *Cancer Incidence in Five Continents* (CI5) Volumes VI to IX (1983 to 2002) and observed that the incidence of oropharyngeal cancer increased significantly, particularly in economically developed countries. The magnitude of increase among men was significantly higher in younger men. The Surveillance, Epidemiology, and End Results (SEER) program has a separate Residual Tissue Repository (RTR). Using oropharyngeal cancer samples from the RTR, Chaturvedi et al. divided the samples obtained over two decades into four calendar groups and analyzed the samples for the presence of HPV. The authors showed that HPV prevalence increased over the four calendar periods, with a fourfold increase from 1984 to 1989 to 2000 to 2004. Based on this data, the group predicted that by 2030, HPV-associated head and neck cancer will continue to increase and account for nearly half of all head and neck cancers.

An increasingly large body of data shows that the prognosis for patients with HPV-related oropharyngeal carcinomas (OPSCCs) is consistently better than for those with HPV-unrelated OPSCCs after treatment with surgery,[26] radiotherapy,[27,28] induction chemotherapy followed by chemoradiation,[29] and concurrent radiation plus cisplatin.[30] The principle hypothesis for this improvement in response to chemotherapy and radiation and overall improved prognosis is based on genomic studies describing fewer mutations in and less cellular dysregulation of HPV-associated cancers. The high survival rates seen in patients with HPV-associated oropharyngeal cancer have led to investigations of treatment deintensification. The RTOG recently completed a study (RTOG 1016) testing if cetuximab is less toxic as a concurrent radiation agent than cisplatin for HPV-associated oropharyngeal cancer. The NRG is now conducting a trial testing lower doses and elimination of systemic therapy for the most favorable patients (those with smaller tumor burden and minimal tobacco exposure). However, until such trials yield conclusive results, head and neck oncologists should not change the current treatment policies for patients with HPV-positive OPSCCs.

Genetic Alterations in Non–Viral-Associated Head and Neck Cancers

For head and neck carcinomas, Califano et al.[31] described a preliminary tumor progression model using allelic loss or imbalance as a molecular

marker for oncogene amplification or TSG inactivation. They identified *p16* (9p21), *p53* (17p), and *Rb* (13q) as candidate TSGs and cyclin D1 (11q13) as a candidate protooncogene. About one third of histopathologically benign squamous hyperplasias already consist of a clonal population of cells with shared genetic anomalies characterizing head and neck cancer. Identification of such early events facilitates discovery of genetic alterations associated with further transformation and aggressive clinical behavior.

The introduction of newer molecular assay techniques has greatly increased the ability to detect genetic changes and thereby improve the understanding of cancer biology in general. An overview by Ha et al.[32] summarizes recent findings on genetic alterations in HNSCC grouped by assay techniques, such as comparative genomic hybridization, *in situ* hybridization, single nucleotide polymorphism, and microarray technology, and provides excellent illustrations of the complexity of HNSCC and how that complexity will require much more research to reveal the full picture. This complexity has been further explored with whole-exome sequencing. Two separate studies[33,34] confirmed mutations in many known genes, including the most common mutation of TP53, but additionally found mutations in other genes known to regulate squamous differentiation including NOTCH1, which was the second most frequently mutated gene after TP53. The Cancer Genome Atlas Network[24] reported their preliminary analysis of 279 samples of HNSCC. The majority were HPV negative, obtained from the oral cavity or larynx, from a patient population predominantly consisting of heavy smoking males. The analysis again confirmed near universal loss-of-function TP53 mutations but also identified 10 other mutations occurring frequently enough to warrant further study. CDKN2A inactivation was common as was high genomic instability reflected by a mean of 141 copy number alterations. With further validation, this knowledge will contribute a great deal to the development of screening strategies focusing on the earlier steps of genetic alterations required to generate an invasive tumor phenotype and to the conception of early pharmacologic or genetic therapy approaches.

BIOMARKERS

Key Points

- Three strong prognostic biomarkers have emerged for HNSCC. The absence of circulating EBV DNA titer, the presence of HPV in cancer cells, and low tumor EGFR expression are associated with better outcome after current standard therapies for patients with nasopharyngeal cancer, oropharyngeal carcinoma, and HNSCC not associated with EBV or HPV, respectively.
- Patients with NPC and persistent circulating EBV DNA after completion of radiotherapy with concurrent cisplatin have a high distant relapse rate and are thus suitable candidates for intensification of systemic therapy.
- With current standard therapies, patients with HPV-associated OPSCCs have much better locoregional control and overall survival rates than those with HPV-unrelated OPSCCs.
- HPV-associated OPSCC is now considered a distinct cancer entity, and protocols focusing on reducing long-term morbidity are being designed for such patients.
- The search for biomarkers that can predict the likelihood that a certain cancer subset will respond to a given therapy (predictive marker) has not yielded promising leads.
- High-EGFR–expressing HNSCCs are more proficient in repairing radiation-induced DNA injury and hence recur more frequently after radiotherapy, but whether inhibitors of EGFR can preferentially enhance the radiation response of these tumors has not been resolved.
- Because the cost of cancer treatment has been increasing steeply with only modest improvements in efficacy, the identification, standardization, and validation of predictive biomarkers are crucial for rational selection of specific therapies for a given subset of patients to improve outcome, reduce overall toxicity, and contain cost.

Although mortality rates from cancer have gradually declined in the United States over the past 10 years,[35] the cost of cancer therapy has increased drastically during that time (American Cancer Society report on *Cancer Facts & Figures 2009*). This increase in cost results from progressive intensification of therapies, such as the addition of chemotherapy to radiation or to surgery plus radiation, the emergence of expensive novel agents, and the lack of validated markers to guide rational patient selection for available therapies. Consequently, expensive and

complex combined therapy regimens have often been prescribed to large groups of patients that benefit only a small subset of those patients and often at the cost of increased acute and long-term morbidity. Therefore, identification and validation of biomarkers to guide the rational selection of specific therapy for a given subset of patients have become critical for improving the outcome, reducing the toxicity burden, and containing the costs of cancer treatment.

Progress in searching for useful markers for early detection of tumor, estimation of tumor burden, prediction of response to therapy, and monitoring disease progression has been slow. A prototypical marker is prostate-specific antigen, which proved to be quite useful for prostatic cancer screening, prognostic grouping, and monitoring of response to therapy. Unfortunately, equivalent markers have yet to be identified for most other solid tumors. However, recent studies in head and neck carcinomas have generated some optimism, as discussed in the sections that follow.

Prognostic and Predictive Biomarkers

The distinction between prognostic and predictive biomarkers has not been widely appreciated. Therefore, until recently, these terms have been used rather loosely and interchangeably. Figure 1.1 illustrates the concept and definition for different classes of markers. The rates and extent of separation among the curves will vary with the disease type and stage and the efficacy of therapy, but the general principles and the relative ranking are applicable. In Figure 1.1A, marker X represents an aggressive tumor feature, the presence of which is associated with poorer survival rate after both treatment (Rx) regimens 1 and 2, though Rx 2 is more effective than Rx 1. Marker Y (Fig. 1.1B), on the other hand, exemplifies a predictive marker for response to Rx 2. Hence, its presence is associated with better survival after Rx 2 (solid brown curve). Figure 1.1C illustrates that some markers could have both prognostic and predictive values. The absence of marker Z is associated with better prognosis (solid and dotted black curves vs. dotted purple curve). However, since this marker also predicts response to Rx 2, its presence is associated with a better outcome after Rx 2 (solid purple curve) relative to Z+ after Rx 1 (dotted purple curve) and Z− after Rx 2 (solid black curve).

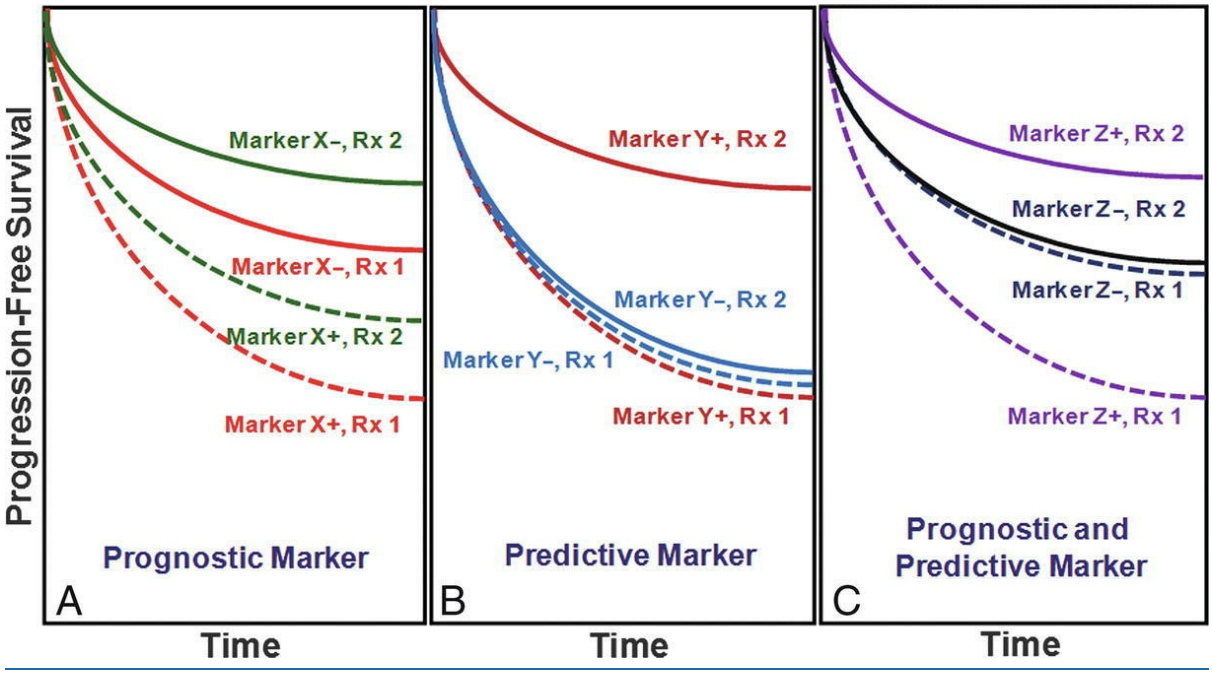

Figure 1.1 Schematic illustration of prognostic and predictive biomarkers. X and Y **(A,B)** represent pure prognostic and predictive markers, respectively, whereas Z **(C)** stands for a marker that predicts favorable response to treatment (Rx) 2 in addition to prognosis (see text for details).

Figure 1.1 shows that carefully designed clinical trials incorporating patient stratification according to biomarkers and randomizing patients to received distinct therapy modalities are needed to yield a conclusive answer as to whether a marker is prognostic, predictive, both, or neither.

Three potent prognostic biomarkers for HNSCC have emerged in recent years. Two of these biomarkers are related to virus-associated head and neck carcinomas: circulating EBV titer for NPC and the presence of the HPV genome or its surrogate marker, p16, for OPSCC. The third biomarker, epidermal growth factor receptor (EGFR), seems to be more applicable for other HNSCCs.

Circulating EBV DNA Titers in Nasopharyngeal Carcinoma

The association between EBV and NPC was summarized in a previous section. Lo et al.[36] have developed a real-time quantitative polymerase chain reaction assay for measuring circulating levels of tumor-derived EBV DNA in the serum or plasma of patients with NPC. They found in a longitudinal follow-up of 17 patients that elevations in serum EBV DNA