Early Detection and Treatment of Head & Neck Cancers

Practical Applications and Techniques for Detection, Diagnosis, and Treatment

Rami El Assal
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ISBN 978-3-030-69858-4 ISBN 978-3-030-69859-1 (eBook)
https://doi.org/10.1007/978-3-030-69859-1

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to the late Professor Sam Gambhir of Stanford.

Sam was the pioneer in the foundation of cancer early detection. He dedicated his life to developing methods of early disease detection, ushering in a new era of molecular imaging and nanotechnologies to flag signals of disease in its nascent stages. Dr. Gambhir was the Virginia and D.K. Ludwig professor of cancer research and chair of radiology at Stanford University School of Medicine. He was the founding director of the Canary Center at Stanford for Cancer Early Detection, Precision Health and Integrated Diagnostics Center at Stanford, and the director of the molecular imaging program at Stanford.

The editor-in-chief, Dr. Rami El Assal, would like to express his gratitude for the selfless devotion of Dr. Gambhir, a kind and honest man. Dr. El Assal commented, "In our last meeting while I was transitioning out of Stanford, Dr. Gambhir demonstrated the care and support to me at multi-level including stating that 'if you wanted to come back to Stanford, just let me know.'"

*Dr. El Assal added, "I still remember that in the 2015 Department of Radiology Retreat, Sam stated, '*I want to make an impact on human health even if it is not recognized in my lifetime.'" *"And I believe he did," Dr. El Assal said.*

Foreword

It is with great pleasure that I write this foreword for the first edition of *Early Detection and Treatment of Head and Neck Cancer* (HNC). The fields of early detection and early treatment in cancer biology are advancing rapidly as both the concept and practical applications have entered clinical practice.

The recent release of the most comprehensive genomic HNC data to date (Nature, 2015) from The Cancer Genome Atlas, a project funded by the National Institute of Health to characterize cancer genomes, is enabling scientists to refine their list of candidate biomarkers and to identify new ones for early detection of HNCs. Such an expanding body of knowledge is essential given that roughly two-thirds of HNCs present at advanced stages, and the prognosis remains poor. Therefore, new approaches are urgently needed for early HNC detection to improve treatment outcomes. For example, circulating DNA has shown great promise as a non-invasively obtained biomarker in a number of HNC cohorts. Using the known mutational signatures of HNC to identify tumor DNA in body fluids has demonstrated the potential for detecting tumors at early stages and for monitoring tumor relapse and response to treatment.

In the era of precision health and medicine, there are opportunities to select treatment plans that are most likely to succeed based on an individual's personal data. HNC can be monitored and treated more efficiently by taking multiple forms of medical data into consideration and by implementing more effective methodologies that are currently being validated, including liquid biopsy, salivary biomarkers, imaging, and treatments, including gene therapy, immunotherapy, surgery, radiotherapy, and many others.

Early detection is an evidence-based field in which we have come a long way, but it is still in its infancy. We have discovered many of the fundamental principles but still need to develop, translate, and improve detection and diagnostics as well as treatment standards to, hopefully, prevent cancer, including HNC.

Here, I would like to invite readers to enjoy the carefully and expertly prepared material by the authors of this book series (Volumes I and II), which are based on solid scientific evidence and diverse clinical experience achieved through many years of professional practice.

R. Bruce Donoff, DMD, MD
Dean of Harvard School of Dental Medicine (1991–2019)
Boston, MA, USA

Dean Emeritus R. Bruce Donoff in Few Words

Dr. R. Bruce Donoff served as dean of Harvard School of Dental Medicine (HSDM) from 1991 to 2019. He was born in New York City and attended Brooklyn College as an undergraduate. He received his DMD from HSDM in 1967 and his MD from Harvard Medical School in 1973. Dr. Donoff's professional career has centered on Harvard's Faculty of Medicine and the Massachusetts General Hospital's Department of Oral and Maxillofacial Surgery. He began as an intern in 1967, served as chairman and chief of service from 1982 through 1993, and continues to see patients today.

In addition to leading HSDM as its dean, Dr. Donoff has made major contributions in research to the specialty of oral and maxillofacial surgery with interest in oral and head and neck cancers. He has published over one hundred papers, authored textbooks, and lectured worldwide. He recently helped launch the HSDM Initiative – Integrating Oral Health and Medicine, a project of great importance to him.

Dr. Donoff served 12 years on the board of the Oral and Maxillofacial Surgery Foundation and is former president of the Friends of the National Institute of Dental and Craniofacial Research. He is editor of the *MGH Manual of Oral and Maxillofacial Surgery* and a member of the editorial board of the *Journal of Oral and Maxillofacial Surgery* and the *Massachusetts Dental Society Journal*.

Dr. Donoff has received numerous honors during his academic career, including the American Association of Oral and Maxillofacial Surgeons Research Recognition Award, the William J. Gies Foundation Award for Oral and Maxillofacial Surgery, Fellow of the American Association for the Advancement of Science, the Alpha Omega Achievement Award, and the Distinguished Alumni and Faculty Awards from HSDM. In 2014, he was a Shils-Meskin awardee for leadership in the dental profession.

Acknowledgments

A Historic Perspective

> I shall be telling this with a sigh somewhere ages and ages hence;
> Two roads diverged in a wood, and I took the road less traveled by,
> And that has made all the difference.
>
> *– The Road Not Taken by Robert Frost, 1916*

I would like to acknowledge first and foremost my family:

To my mother who endured this long process with me, always offering support and for whom grace is all in her steps, heaven in her eye, in every gesture dignity and love. Everything I am or ever hope to be, I owe to my angel mother.

To my wife, Somayeh, and my son, Adam, you all are my world and reason for being. My gratitude for your understanding that my career being of service to others often entails long hours. Thank you for your patience and compassion.

To my sister, Lina, who always supported and guided me all the way, and my devoted brother-in-law, Ghiath, and my elegant nieces, Sana, Maria, Naya, and Zeina.

To my brother, Shadi, who was always there for me.

I can never forget my father, who was a blend of strength (may he rest in peace).

To my cousin, Hussein, whose friendship and support I treasure.

To my wife's family: my father- and mother-in-law; brother-in-law, Wahid; and my sisters-in-law, Susan, Samira, Sudaba, and Saeeda.

To my close friends whom I consider part of my family. They helped shape my education and supported me throughout my academic and professional journey.

Additionally, I would like to thank my friends and co-editors, Dyani and Thaddeus; without their help, this book would not have come to fruition. I am so proud of you and wish to let you know that your friendship touches me deeply. I know we will continue to work closely in the future and support one another's ideas and projects.

I would like to express my sincere gratitude to all authors who contributed to these two volumes; this project would not be possible without their contribution.

I feel a deep sense of gratitude to Emeritus Dean R. Bruce Donoff, who kindly wrote the foreword to this book series.

To all of my past teachers, mentors, and fellow students, I hope this book is worthy of the many contributions you have given me.

I am very grateful to all my colleagues and friends around the world.

Lastly, to head and neck cancer (HNC) patients, my respectful and gentle gratitude goes to you all. As a part of our commitment to service HNC patients, I recently co-founded with Thaddeus an "Early Disease Detection & Treatment Fund" to translate innovations from research labs, bringing them close to patients. We are proud to have partnered and invested with visionary entrepreneurs who are tackling head and neck cancers.

Palo Alto, CA, USA Rami El Assal

Preface

Head and neck cancer (HNC) is a heterogeneous group of cancers that, if combined, represent one of the most common cancer types. Patients with HNC suffer significant morbidity and mortality due to the importance of the structures involved. Over two-thirds of these patients are diagnosed at a late stage, leading to a poor prognosis. Therefore, advancements in early detection and treatment of HNC are crucial.

With the emerging fields of precision health and precision medicine, treatment of HNC is undergoing a paradigm shift to become more proactive instead of predominantly reactive. There is extensive literature to support early detection and early treatment, which has made a significant impact, not only in the field of HNC, but in the management of cancer overall.

Volume I begins with a general overview, including the industry landscape, of HNC detection, diagnosis, and treatment. Next, it covers the applications of innovative technologies such as microfluidics, nanotechnology, and deep learning to early detect as well as study HNC. For example, studying the cellular features at a single-cell level became possible with the advancement of technologies such as mass cytometry or specifically, Cytometry by Time Of Flight Mass Spectrometry (CyTOF), which has revolutionized the way we can study complex human diseases such as HNC. Finally, the last few chapters are dedicated to describing the standard of care of HNC.

The Head and Neck Cancer Early Detection and Treatment book series is highly pertinent to the next generation of interdisciplinary clinicians, scientists, residents, and students who are particularly interested in HNC and in the translation of early detection methods, technologies, and research to clinical practice.

This series is the joint work of many healthcare enthusiasts who share a common vision towards advancing the field of cancer early detection and early treatment. We thank all those individuals who contributed to this book, without whom this effort to fight HNC would not have been possible.

Finally, the editors and contributing authors of this book humbly thank our readers for taking this journey to gain essential knowledge, to refine skills, to inform future research directions, and, above all, to treat our patients suffering from HNC.

Palo Alto, CA, USA — Rami El Assal
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Chapter 1
Overview of Early Detection, Diagnosis, and Treatment of Head and Neck Cancers

Ryan Spitler

Introduction

Cancer is the second most common cause of death in the United States [11]. Often, symptoms are not specific or present, until tumors have already metastasized. Head and neck cancers (HNCs) include all malignancies from nasal and oral cavities, pharynx, larynx, and the paranasal sinuses with smoking and alcoholism being known predisposing factors. HNCs make up 3% of all cancer cases in the United States each year with over 90% of HNCs arising from squamous cell carcinomas and head and neck squamous cell carcinoma (HNSCC), which is the sixth common cause of cancer mortality globally [38]. When compared to other cancers such as breast or colorectal cancer, the five-year survival rate of HNSCC after diagnosis is significantly lower and with little to no improvement in mortality rates even with ongoing research efforts [40]. Failure in early diagnosis and insufficient effectiveness of therapeutic modalities lead to poor clinical outcomes [36]. Thus, the ability to diagnose cancer at an early stage is critically important, since the predominant cause of mortality is regional and/or distal metastatic spreading of tumor cells from the primary site. There is a significant need for rapid, highly accurate, and noninvasive tools for cancer screening, early detection, diagnostics, and prognostics. Screening methodologies should have high sensitivity and specificity, be noninvasive, and be inexpensive to allow widespread applicability. Even though molecular alteration precedes clinical symptoms and detection by imaging or histopathology-based diagnosis, many disorders remain undiagnosed until an advanced stage, which is often irreversible, and treatment is inefficient/ineffective. However, there have been many recent developments that are beginning to demonstrate promise.

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R. El Assal et al. (eds.), *Early Detection and Treatment of Head & Neck Cancers*, https://doi.org/10.1007/978-3-030-69859-1_1

In the era of precision health and medicine, there are opportunities to diagnose cancers early and to select treatment plans that are most likely to succeed based on an individual's personal data. Importantly, cancers originating from different parts of the body have different characteristics and require different diagnoses and treatment approaches [51]. In order to address this need, HNCs can be monitored and treated more efficiently taking into consideration multiple forms of medical data and implementing more effective methodologies that are currently being validated including liquid biopsy, salivary biomarkers, imaging, and treatments including gene therapy, immunotherapy, surgery, radiotherapy, and many others [1, 7, 10, 12, 15, 37]. In this review, recent developments in diagnostics and treatment management for HNCs are described.

Big Data in HNC

A large part of being able to detect and treat cancers "precisely" is having sufficient data available to make informed and actionable clinical decisions. HNCs represent an opportunity to explore "big data" applications in oncology. In the era of growing big data and artificial intelligence capabilities, there exists tremendous potential to implement computational strategies to better understand molecular mechanisms and complex biological systems, identify prognostics and predictive biomarkers, and for the discovery and monitoring of treatment. Big data may assist with broad applications including driving and sustaining guideline recommendations, expediting the period between research and clinical practice, monitoring guideline applications and quality assurance, and helping work toward a personalized healthcare decision support system [42]. Aggregating and sharing research data can be particularly useful in the case of rare cancers. However, even with great promise, there are still many challenges that exist to implement big data strategies.

Researchers tend to use many different platforms to store and analyze data, which present significant challenges for handling large volumes of data. Moreover, researchers often do not have access to raw or primary data sources and lack the necessary infrastructure. One potential solution has been to use "data clouds" to better integrate and improve overall access to data. However, even if these resources become accessible, there is still the question of how best to protect patient privacy and share data while keeping it de-identified. As efforts continue to increase in this area and with some patience and the right know-how, these mountains of data can significantly contribute to our understanding of cancer's inner workings.

Diagnostics and Early Detection

It is known that the chance of survival and quality of life in HNC is directly related to the size of the primary tumor at detection. One challenge is that most patients, even those at risk (smokers), will likely not participate in screening programs until

they present with symptoms. In order to have a significant impact on early detection, primary (measures that prevent the onset of disease) and secondary prevention (measures for early diagnosis and treatment of disease) will need to be improved. Screening for cancer can be population-based, opportunistic, or targeted, but ultimately, patients have to elect to participate. Some community-based screening has shown value in reducing oral cancers in high-risk groups. The most powerful tools in early detection for HNC are medical history, risk factors, and clinical examination [19]. Recent advances in early cancer detection methods have improved clinician's ability for early diagnoses, such as using saliva specimens to identify asymptomatic patients at cancer risk. For oral cancers, visual examination remains the primary initial screen method. Additionally, there is a need to further examine cost-effectiveness for cancer screening and early detection methods. HNCs are diagnosed most often among people over the age of 50. Common symptoms of HNCs include a lump or sore that does not heal, sore throat that does not go away, difficulty swallowing, and hoarseness. Other symptoms may include discoloration of the lining of the mouth, swelling of the jaw, trouble breathing, trouble hearing, blocked sinuses, and paralysis of the muscles in the face [18]. Yet once symptoms present, the likelihood for successful treatment outcomes greatly diminishes.

Liquid Biopsy and Circulating Tumor Cells

HNC remains one of the leading causes of death, which is why early detection is critically important [53]. Liquid biopsy has emerged as a promising tool for detecting and monitoring disease status at all stages. Analyses of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomal miRNAs have paved the way for precision health and medicine approaches. Circulating biomarkers have demonstrated efficacy for detection, treatment, and monitoring response as well as prognosis assessment [41]. While these new biomarkers may have broad clinical application, no validated circulating biomarkers have been integrated into clinical practice in the context of HNC. However, there is great potential for the clinical utility of these biomarkers from multiple body fluids. In general, ctDNA in the plasma could be useful for the early detection of HNC [2]. CTCs released from metastatic lesions can be analyzed for surface expression of drug targets including EGFR and PD-L1 for planning therapeutic interventions [54, 55]. Additional information can be gained from biomarkers such as exosomal miRNAs, and the ability to target multiple types of biomarkers may improve the specificity and sensitivity of cancer diagnosis [43]. Analyzing biomarkers from multiple body fluids in conjunction with other measures could enable better delivery of personalized medicine approaches (Fig. 1.1).

Of particular interest for screening purposes is saliva, which is a mixture of secretions from major and minor salivary glands. These secretions contain proteins, microorganisms, and cellular debris. The use of whole saliva is an attractive diagnostic method since it is relatively easy to work with, is noninvasive, and can

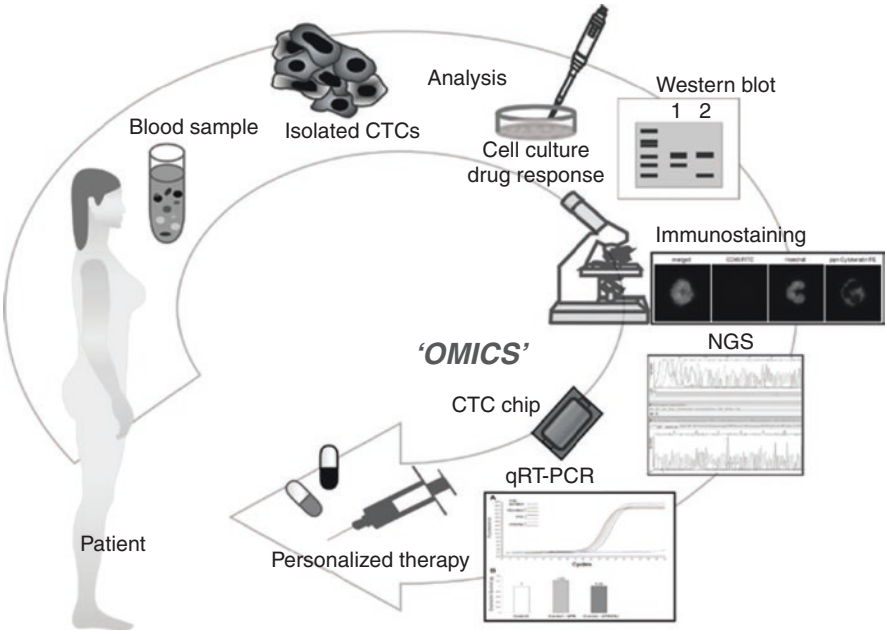

Fig. 1.1 Overview of analysis of patient-derived CTCs. CTCs are isolated from a patient's blood sample and analyzed using methods such as immunostaining, Western blotting, NGS, CTC-chip analysis, and qRT-PCR. The results can then be used to develop better precision health and medicine approaches. (Figure reproduced with permission from [23])

provide informative diagnostic information regarding disease state. Moreover, a unique subset of exosomes from tumors appear to be present in saliva and are highly variable even in patients with the same tumor types and stages [54, 55]. More work is needed toward the creation of simple and affordable technologies to screen for circulating biomarkers; however, further characterization will be required in order for implementation to be possible.

There is a significant demand for simple less invasive blood tests to determine disease state. Standard clinical diagnostics, such as imaging, often lack the sensitivity to enable the detection of CTCs. Techniques are also required for molecular characterization to better enable understanding of the underlying biology, which could then lead to improved tumor targeting capabilities. The ability to identify high-risk patients prior to disease presentation or metastasis could significantly improve rates of survival. Current methods are limited by specificity and sensitivity. However, nanotechnology-based methods could improve efficiency, sensitivity, specificity, and accuracy [23].

Salivary Biomarkers

Saliva has emerged as a potential source of cancer biomarkers including proteins, DNA, mRNA, and metabolites [54, 55]. It is composed of secretions from the major and minor salivary glands and is extensively in the lining of the mouth and throat. Saliva is simple to collect and process, is cost-effective, and does not cause patient discomfort. Unlike other bodily fluids, saliva tends to have a lower background of inhibitory substances and materials when compared with blood [48]. Saliva for the screening of oral cancer has great potential, due to the shed of cancer cells in the oral cavity. Several salivary biomarkers for clinical use have been discovered using ELISA, quantitative PCR, microarrays, immunoblot, and LC/MS. Some of these biomarkers could be used to monitoring for cancer diagnosis and cancer risk prediction using differences in the expression of proteins, genes, RNA, and/or inflammatory cytokines [22]. While most of these biomarkers have limitations in clinical diagnosis, one notable example is interleukin (IL)-8 and melanoma-associated genes, which have demonstrated good sensitivity and specificity [25]. Similarly, IL-8 and IL-1ß have been found to be elevated in HNSCC patients as well as having a significantly different microbial environment compared to healthy controls [52]. Further, advanced stages of oral cavity squamous cell carcinoma (OSCC) have shown higher levels of proteins complement factor H (CFH), fibrinogen alpha chain (FGA), and alpha-1-antitrypsin (SERPINA1) [8]. Overall, these predictive and prognostic markers can hopefully one day be used as therapeutic targets to treat HNCs including HNSCC.

Imaging

Many optical tools are being used to enhance diagnostics and treatment beyond the clinician's trained eye. Approaches such as chromoendoscopy and autofluorescence can help identify altered mucosal areas. While hyperspectral imaging can be used to discover suspicious lesions, optical coherence tomography and confocal endomicroscopy can be used to better identify structural abnormalities or when subcellular resolution is needed [9]. For the head and neck area with complex lymph drainage, it is important to be as exact as possible with functional imaging techniques (e.g., positron emission tomography/computed tomography (PET/CT) scanning) [35]. This is especially important during the early stages of tumor development, so that the resection margin is minimized to preserve the organ. This type of imaging is also important after a treatment and during the recovery phase.

Surgery still remains the first-line choice for treating HNC patients. However, surgeons must often balance between extensive cancer resection and a better quality of life, given the complicated anatomy in the head and neck region. To improve

clinical outcomes, early diagnosis and treatment of premalignancies are necessary. Moreover, many real-time imaging approaches can be used for *in vivo* detection of surgical margins to better identify cancers and minimize the resection of normal tissues. Such approaches include autofluorescence imaging, targeted fluorescence imaging, high-resolution microendoscopy, narrow-band imaging, and Raman spectroscopy [56]. Another approach is to combine new approaches with existing ones, such as using imaging guidance and a surgical robot [33]. However, even with decades of research in this area, still many challenges exist. For instance, Raman spectrometers are generally not as commercially available or portable and as such are generally not used for routine clinical procedures. Additionally, more clinical trials are needed to demonstrate benefits beyond diagnostic accuracy.

For early-stage cancers, typically a single modality, usually contrast-enhanced CT, is sufficient for adequately staging. However, it is often desirable for the management of advanced cancers (stage III/IV) to use a combined modality approach (PET/CT with or without contrast-enhanced CT or MRI). This combines the advantages of both modalities providing improved cross-sectional anatomical details and superior soft-tissue contrast, both especially important in the context of head and neck squamous cell carcinoma (HNSCC). Multidisciplinary treatment is often required and includes surgery, radiotherapy, and chemotherapy [49]. One such probe that has proven especially useful for these patients is fludeoxyglucose F 18 PET/CT [16].

Extracellular Vesicles

Extracellular vesicles (EVs) are heterogeneous membrane-enclosed vesicles, which play a key role in intercellular communication for processes such as proliferation, metastasis, angiogenesis, and immune regulation [58]. Studies have shown that tumor-derived EVs, mainly exosome and microvesicles, transfer oncogenic cargo such as proteins, lipids, messenger RNAs, microRNA, noncoding RNAs, and DNAs that may influence the tumor microenvironment (TME) and impact tumor progression [57]. While the molecular mechanisms and clinical applications of EVs in HNC still require further investigation, the ability to better understand this complex signaling network in mediating tumor progression, angiogenesis, and cancer drug resistance, as well as immune regulation, could be very valuable. EVs can be sampled and assessed from saliva and circulating blood diagnostics and have the potential for early screening, monitoring, and risk assessment of HNCs. EVs may also be useful for creating more precise anti-tumor treatments for individual therapy due to their inherent biocompatibility, being modifiable, and low immunogenicity [21]. An example is EVs derived from nasopharyngeal carcinoma, which have been reported to facilitate proliferation, metastasis, and immune escape [6]. These EVs could serve as biomarkers as well as therapeutic targets, given their unique nucleic acid and protein content profiles.

Multiplexed Biomarker Profiling

We have discussed a number of potential diagnostic tools that are actively being implemented for early cancer detection and intervention. While these tools can be implemented on an individual basis, there is often also the possibility of enhanced diagnostic power through the combination of biomarkers. For instance, in the context of immune-based biomarkers, panels have been used that consist of multiple cytokines, chemokines, growth factors, and other relevant tumor biomarkers [27]. Additionally, immune profiling of HNSCC patients using a multiplex immunofluorescence panel has produced evidence to suggest that p16 tumors could be immunosuppressed through increased expression of PD-L1, while CD8+ cells cannot infiltrate the tumor [20]. Another study used an electrochemiluminescence multiplex assay and was able to classify OSCC versus normal subgroups using IL2, IL_1R_a, and macrophage inhibitory factor (MIF) with a sensitivity of 0.96 and specificity of 0.92 [28]. It is likely that combinations of biomarkers will become used more frequently, which are expected to improve clinical outcomes.

Treatment and Cancer Management

Great care must be given to the treatment of HNCs especially due to the potential toxicity of treatment proximity to critical structures [30]. This is also why it is important to initially exhaust noninvasive and/or lower-morbidity approaches prior to performing more invasive procedures. Optimal treatment should also include (i) early detection of recurrence or residual disease and (ii) minimalization of toxicity and morbidity and (iii) should be cost-effective for the healthcare system and the patient. Posttreatment surveillance is critically important, such as the use of imaging modalities including PET-CT. However, in the context of imaging, there is no consensus guidelines on the frequency and modality (i.e., CT, ultrasound, MRI, and PET-CT) used for posttreatment imaging [59]. More work is needed to improve the current guidelines as well as to come up with individualized surveillance plans that better address patient's needs.

Gene Therapy

Gene therapy can be a viable approach for HNC as there is a current lack of systemic options, there are many potential targets, and tumor tissue is accessible. There are multiple types of gene therapy used for HNCs including corrective, cytoreductive, and gene editing [10]. While gene therapy has been an emerging area, most patients will still require the inclusion of standard therapy methods such as surgery,

radiation, and chemo- or immunotherapy. In order to successfully deliver gene therapy, it is essential to first understand a patient's unique genetic profile. For example, in the case of HNSCC, patients' common mechanisms to target include oncogenes, EGFR receptor, p53 gene correction, prodrugs for suicide gene therapy, and immunomodulatory strategies [45]. Some of these approaches will be generalizable between cancer types, whereas others will be patient-/cancer-specific in order to improve successful outcomes. This is yet another example of how precision medicine is already beginning to shape cancer care.

Cancer Immunotherapy

Cancer immunotherapy is driven by the body's ability to recognize tumor cells as a foreign antigen, thereby triggering the activation of the immune system. One potential advantage of immunotherapy over cytotoxic chemotherapy is possible durable response of memory T cells, with induction of T cell immunity being a critical step to success [5]. This field is already seeing great progress with FDA-approved anti-PD-1 antibodies including nivolumab and pembrolizumab showing efficacy in clinical trials [47]. However, there are still challenges for clinicians to better understand when to use immunotherapy and in which clinical setting in order to provide improved clinical benefit. Additionally, cancers such as HNSCC are known for their immunosuppressive character, reducing the effectiveness of immune-based approaches. Moreover, many patients generate immune responses to the presented antigen, but they still do not respond to conventional treatment or immunotherapy [44]. Yet patients with preexisting endogenous immune response have better outcomes than those lacking an activated phenotype. To advance the field of immunotherapy, more robust markers of treatment efficacy must be developed as well as an increased understanding of patient immune responsiveness and how to best leverage combined therapies (Fig. 1.2).

Robotic Surgery

Many minimally invasive approaches for head and neck surgery now incorporate robotic surgery. Transoral robotic surgery has been used for resecting oropharyngeal, hypopharyngeal, and laryngeal tumors [17]. Other applications include transaxillary, transoral, and retroauricular robotic approaches for the neck and thyroid also exist. Important factors to consider are safety, cost, availability, and outcomes when considering the utility of robotic surgery. It is also necessary to have a skilled operator. Fortunately, many new surgeons have been receiving formal training in robotic surgery. It is anticipated that minimally invasive robotic head and neck surgery will continue to be pioneered and lead to more positive clinical outcomes.

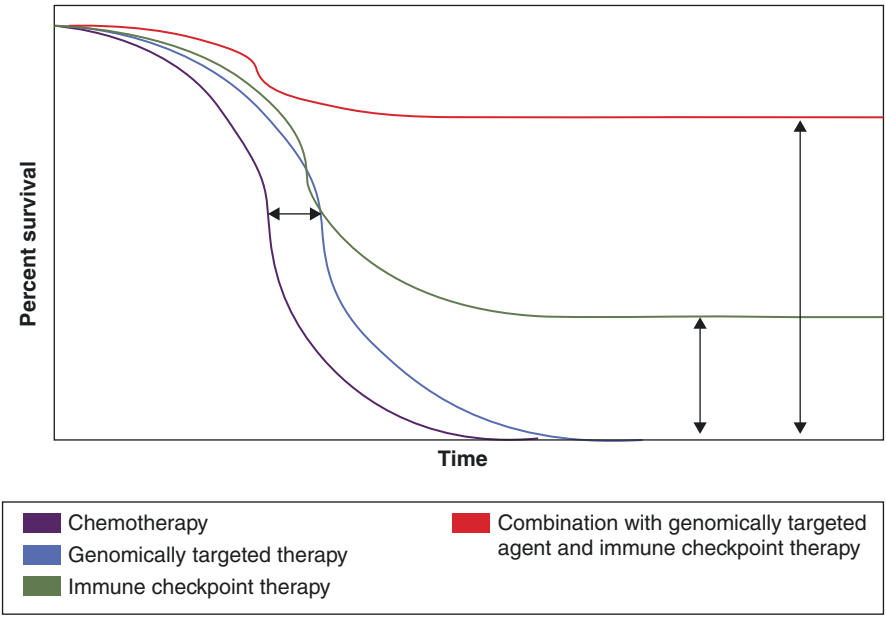

Fig. 1.2 The potential of immunotherapy. The Kaplan-Meier curve tail demonstrates how the combination of complementary approaches used in conjunction with other immunotherapies could lead to better outcomes. (With permission from [46])

Radiotherapy

In general, patients with early-stage HNCs limited to the site of origin are good candidates for radiation therapy or surgery. The treatment plan and behavior of the cancer is dependent on the primary site of origin. A "simulation" of the particular treatment plan can be generated using scans such as X-rays and CTs. Based on these data, the ideal medical physics can be determined. Much care must be taken based on the cancer location with the side effects of treatment dependent on the site and extent of cancer. Definitive radiotherapy or adjuvant management has been demonstrated to be a reasonable treatment for early- and late-stage cancers such as nonmelanoma skin cancers and Merkel cell carcinoma [32]. Altered fractionation radiotherapy has been shown to improve survival in patients with HNSCC. When comparing different types of altered radiotherapy, evidence suggests that hyperfractionation provides the greatest benefit [1].

Molecular Diagnostics for Personalized Treatment

In order to develop personalized treatment plans, it is necessary to have biomarkers that are effective for predicting therapeutic response and large-scale molecular profiling to identify subgroups for particular prognostics. While next-generation

sequencing is readily being used for genetic profiling, this technique is still limited by cost, interpretation of data, and validation of results. There are, however, a number of statistical techniques that have been developed to address the challenge of interpreting large data sets. Microarray analysis has also been used but has challenges such as the use of different platforms, experimental protocols, and other variables. Functional genomics is also adding to the possibilities of discovery and implementation. Some examples of how this can be implemented are described.

At present, only the site and stage of tumor are used for treatment planning of HNSCC [31]. Both molecular profiling and SLNB are promising tools to optimize lymph node staging and adequate management of HNC. Prognosis of HNSCC improved only moderately during the last decades. This improvement may relate to a steady increase in oropharyngeal cancers caused by human papillomavirus (HPV) that have a very favorable prognosis. Detection of residual cancer cells may provide early discovery of recurrent disease and tailoring of postoperative radiation or chemoradiation therapy but is hampered by sampling error. Detection of premalignant fields by molecular markers reliably predicts malignant transformation. Noninvasive diagnostics may further enhance clinical implementation. At present, two clinically relevant molecular subgroups are recognized: HPV-positive tumors and HPV-negative tumors. Personalized treatment of HPV-positive tumors is within reach, but accurate detection of HPV in formalin-fixed paraffin-embedded specimens is still challenging. A third molecular subgroup is emerging, which is characterized by few chromosomal aberrations, wild-type TP53, and a favorable prognosis. Other molecular subgroups of HNSCC have been established with gene expression profiling, but the clinical relevance still remains to be established.

Cancer Tumor Cells and Cancer Stem Cells

CTCs represent a subset of cells that escape the primary tumor and enter the bloodstream and can be an important point of early cancer detection given that even high-resolution PET/CT and MRI are currently unable to detect the early spread of tumor cells. Moreover, even with improvement in current treatment approaches, there is still up to 50–60% local-regional recurrence and/or distant metastasis [39]. CTCs can form metastatic deposits and can sometimes reestablish themselves at the primary cancer site. These cells tend to be more aggressive and accumulate genetic alterations, due to additional modifications acquired when in circulation [24]. Liquid biopsy is an emerging technology to create a reliable method for minimally invasive analysis (i.e., genotyping) of small-volume blood samples. The data can then be applied beyond early detection as well as developing treatments, treatment monitoring, and assessing mutational changes in cancer resistance and radiation sensitivity. While this is a promising new area, there is currently limited guidance in utilizing CTC data. The true prognostic value of CTCs is still to be determined and will require a deeper understanding of the complex interplay at the cellular level.