Chapter 25
Head and Neck Cancer

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Introduction

Head and neck cancer (HNC) is a devastating disease that affects some of the most basic daily functions such as breathing, speaking, and swallowing. Because of its visible nature, HNC is also associated with significant disfigurement. The combined effect of disability and disfigurement and the added toxicity of treatment greatly increase symptom burden and reduce physical, emotional, and social functioning. Since its inception, the Head and Neck Oncology Program at MD Anderson Cancer Center has pioneered multidisciplinary care with the main goal of improving survival and reducing suffering in patients with HNC. Over the past 60 years, significant advances have been made in the treatment and rehabilitation of patients with HNC, resulting in improved disease control, survival, and organ preservation. The purpose of this chapter is to highlight some of the advances in treatment and improvements in outcome of patients with HNC treated in the Head and Neck Multidisciplinary Care Center at MD Anderson.

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Epidemiology

Cancer of the head and neck is a broad term that comprises malignant tumors, mostly squamous cell carcinoma, originating from the upper aerodigestive tract, namely the lip and oral cavity, nasopharynx, oropharynx, hypopharynx, larynx and nasal cavity, and paranasal sinuses. HNC is the sixth most common cancer worldwide, with approximately 650,000 new cases diagnosed annually and 350,000 deaths each year. In the USA, HNC accounted for approximately 52,140 new cancer cases and 11,460 deaths in 2011 [1]. It is estimated that approximately $3.2 billion is spent in the USA each year on treatment of HNC [2].

Changes in Etiology and Patient Demographics

The Emerging Role of the Human Papilloma Virus

For many decades, the majority of patients presenting with HNC were in their fifth or sixth decade of life, had a long history of tobacco and alcohol use, were of lower socioeconomic class, and experienced substantial comorbidity. In the past decade, however, a "new" demographic profile emerged for patients with HNC: presentation at a younger age and with no prior history of tobacco use. The role of human papilloma virus (HPV) as an etiologic factor in HNC, particularly cancer of the oropharynx, is becoming more evident. The presence of high-risk HPV 16 or 18, or p16 overexpression, or both can usually be detected in tumors of patients with cancer of the oropharynx who have no prior smoking history. There is growing evidence that HPV infection of the oropharynx is sexually transmitted, that HPV-related cancers respond better to therapy, and that HPV-related cancers are associated with improved survival compared with tobacco-related cancers of the head and neck [3]. Another area of ongoing research in MD Anderson's Head and Neck Program is determining the feasibility of both therapy "de-intensification" in patients with HPV cancer to reduce toxicity and the escalation of treatment in patients with tobacco-related cancers to improve efficacy. In addition, the role of vaccination against HPV in HNC remains to be explored [4].

Survival Trends of Patients with HNC Treated at MD Anderson Cancer Center

Figures 25.1, 25.2, 25.3, and 25.4 demonstrate the gradual, although significant, improvements in survival outcome for patients with HNC in the major sites who were treated at MD Anderson over the past six decades. The study population

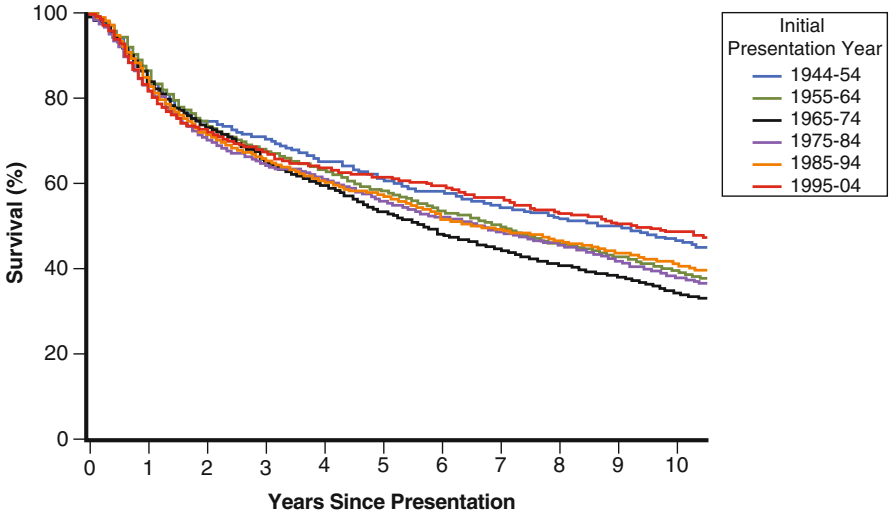

Fig. 25.1 Overall survival rates for patients with cancer of the head and neck with oral cavity primary sites (1944–2004) ($P = 0.014$, log-rank test for trend). See the appendix at the end of this chapter for graphs of local, regional, and distant stages at these primary sites (Figs. 25.8, 25.9, and 25.10).

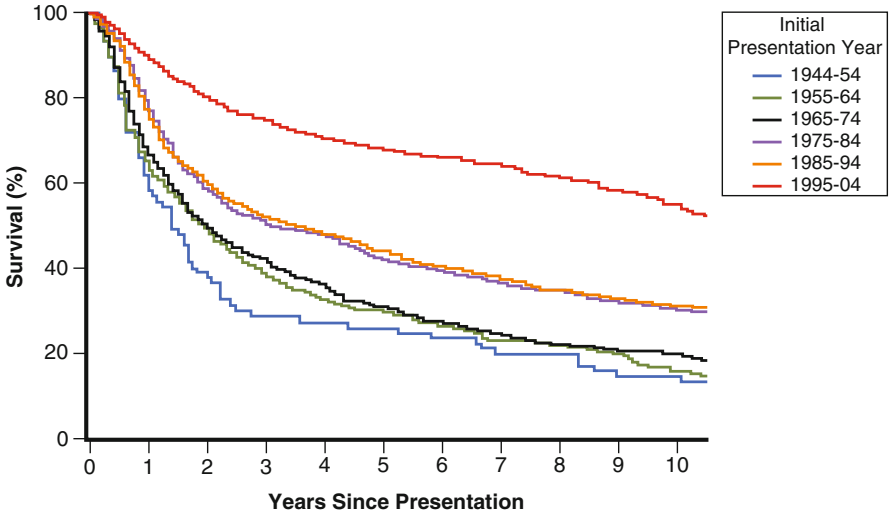

Fig. 25.2 Overall survival rates for patients with cancer of the head and neck with oropharyngeal primary sites (1944–2004) ($P < 0.0001$, log-rank test for trend). See the appendix at the end of this chapter for graphs of local, regional, and distant stages at these primary sites (Figs. 25.11, 25.12, and 25.13).

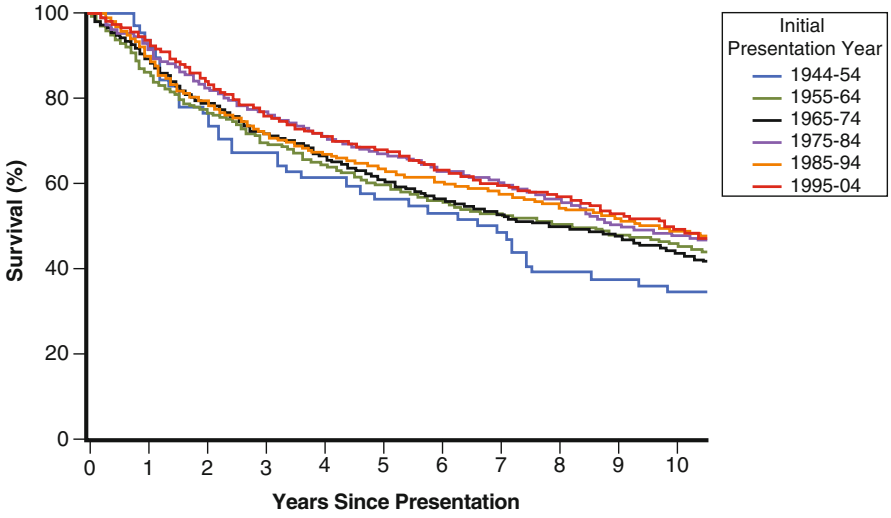

Fig. 25.3 Overall survival rates for patients with cancer of the head and neck with laryngeal primary sites (1944–2004) ($P=0.004$, log-rank test for trend). See the appendix at the end of this chapter for graphs of local, regional, and distant stages at these primary sites (Figs. 25.14, 25.15, and 25.16).

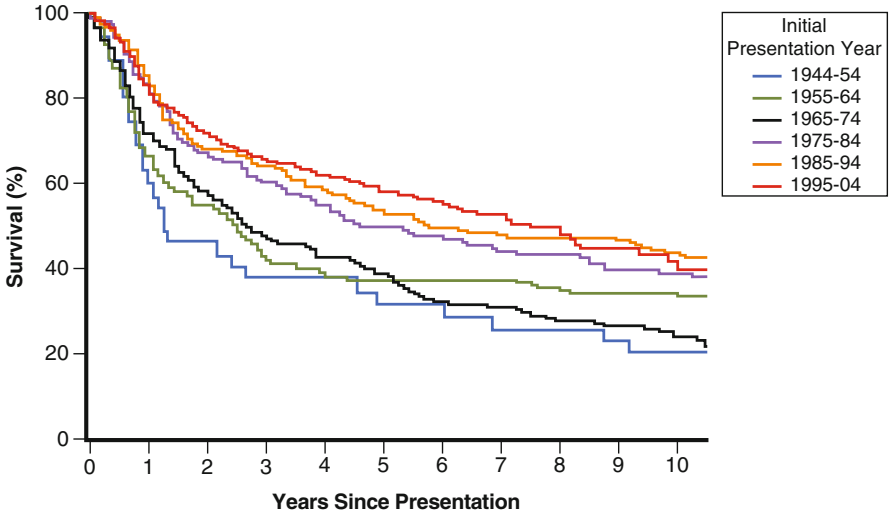

Fig. 25.4 Overall survival rates for patients with cancer of the head and neck with paranasal sinus and nasal cavity primary sites (1944–2004) ($P<0.0001$, log-rank test for trend). See the appendix at the end of this chapter for graphs of local, regional, and distant stages at these primary sites (Figs. 25.17, 25.18, and 25.19).

includes patients with previously untreated cancers of the oral cavity, oropharynx, larynx, and paranasal sinuses who received definitive treatment at MD Anderson from 1944 through 2004. Survival curves are shown for each of these sites by decade of initial presentation to MD Anderson.

Advances in Treatment and Rehabilitation of Patients with HNC at MD Anderson Cancer Center

During the past 60 years, significant improvements have been made in the treatment of HNC, and MD Anderson has led the way in designing and implementing key clinical and translational research that has contributed significantly to improvements in patient outcome. These advances shaped what is now being adopted as the standard of care in head and neck oncology. Key advances in surgery, radiotherapy, chemotherapy, targeted molecular therapy, rehabilitation, and outcome measurement are highlighted. Continued advances in the field of HNC treatment will focus on personalized cancer therapy that will be guided by the molecular profile of the patient's tumor.

Advances in Surgery

The goal of surgery is complete extirpation of cancer. In the 1940s, this meant radical and often mutilating surgery for patients with HNC. Radical neck dissections were routinely practiced and resulted in significant disability of the neck and shoulder. In 1972, Lindberg [5] published a landmark study that established the clinical rationale for selective neck dissection as an effective oncologic procedure that spared patients the morbidity of radical neck dissection. In this study, the records of 2,044 patients with HNC were reviewed at The University of Texas at Houston MD Anderson Hospital and Tumor Institute, the former name of our institution, to identify distribution patterns for cervical metastases clinically apparent at presentation. This study revealed that lymphatic spread of cancers from subsites within the head and neck follow predictable patterns to specific lymph node levels within the neck.

Building on this observation, head and neck surgeons at MD Anderson Cancer Center adopted the practice of less radical neck surgery, and in 1985, Dr. Byers reported the outcomes of 967 patients treated with modified and selective neck dissections. His landmark study demonstrated that for a primary tumor in the oral cavity or oropharynx, a supraomohyoid neck dissection was adequate treatment for the neck that was both clinically staged as N_0 or N_1 and pathologically staged as N_1 without evidence of extracapsular extension. For primary tumors in the larynx and hypopharynx, bilateral selective neck dissection (levels II–IV) is considered proper treatment if the nodes are not multiple or if connective tissue disease is not present. Dr. Byers also demonstrated that the selective use of postoperative radiotherapy can

more effectively decrease the incidence of neck recurrence compared with surgery alone in patients with a node more than 3 cm in size, multiple positive nodes, or nodes with extracapsular invasion. Many of the principles of these studies form the basis of modern HNC surgery practiced worldwide.

Another major breakthrough in the surgical management of HNC has been in the area of surgical reconstruction. Before the 1980s, reconstructive head and neck surgery was limited and consisted of local or regional flaps that accomplished little more than wound closure and did not in most cases restore form and function. The introduction of microvascular free flaps at MD Anderson in the 1980s revolutionized head and neck oncologic surgery and permitted for the first time aggressive resections of the laryngopharynx, mandible, and skull base that could effectively and reliably be reconstructed in a single stage. This type of surgical reconstruction also improved patients' posttreatment function, including speech and swallowing, and improved cosmesis. Major bone defects in the mandible and maxilla can now be effectively reconstructed using the fibula, scapula, or iliac crest free flap [6]. These vascularized bone flaps can receive primary or secondary osteo-integrated implants for dental restoration. Soft tissue defects in the oral cavity and pharynx can be meticulously reconstructed with a variety of soft tissue flaps including the radial forearm, rectus abdominus, or latissimus dorsi flaps. The anterior lateral thigh flap is becoming the most popular choice for reconstruction of oral and oropharyngeal defects, as well as circumferential defects of the pharynx, larynx, and trachea [7].

Until the early 1960s, tumors of the paranasal sinuses that invaded the base of the skull were considered inoperable because this area was considered surgically inaccessible. The development of the anterior craniofacial resection, a two-team surgical procedure involving an intracranial approach by neurosurgery and extracranial approach by head and neck surgery, allowed adequate access for safe and effective resection of skull base tumors. The adoption and refinement of these techniques is probably behind the dramatic improvement in survival of these patients, as shown in the survival curves for paranasal sinus and nasal cavity tumors (Fig. 25.4).

More recently, the skull base team at MD Anderson has been leading the development of minimally invasive techniques for resection of malignant tumors of the base of the skull. These techniques avoid the morbidity associated with the traditional open surgical approaches and allow patients a shorter hospital stay and faster recovery. In 2009, Dr. Ehab Hanna and colleagues [8] reported the largest U.S. series to date of patients with malignant tumors of the sinonasal tract treated with endoscopic resection. Their results suggested that, in well-selected patients and with appropriate use of adjuvant therapy, endoscopic resection of sinonasal and skull base cancer results in excellent oncologic outcome.

Advances in minimally invasive surgery have also been made in transoral resection of early laryngeal and pharyngeal tumors with preservation of speech and swallowing [9]. For more advanced tumors of the larynx and pharynx, organ-sparing laryngeal and pharyngeal surgery may be a viable treatment option for carefully selected patients [10, 11].

In the past 5 years, robotic surgery has emerged as a field with significant promise for increasing the accuracy and reducing the morbidity of many surgical procedures.

HNC surgeons at MD Anderson are exploiting the advantages of robotic surgery in the management of tumors of the oropharynx, larynx, and thyroid [12]. In a preclinical study, Dr. Hanna and colleagues [8, 13] described the first robot-assisted endoscopic approach to the anterior skull base and the pituitary gland. In their report of this novel approach, they describe the feasibility of repairing dural defects without the need for a craniotomy, which has the potential for reducing morbidity and improving outcome in minimally invasive cranial base surgery.

Advances in Nonsurgical Therapy and Organ Preservation

Generally, early primary tumors of the head and neck (stages I–II) can be effectively treated with either surgery or radiotherapy. For example, patients with early glottic (T1 or T2) cancer can be successfully treated with either transoral microsurgical or laser resection or definitive radiotherapy with good oncologic and functional outcomes. In contrast, locoregionally advanced HNC (stages III–IV) usually requires multimodality therapy. For several decades, radical resection followed by radiotherapy was the cornerstone of treatment of locoregionally advanced HNC. Patients with advanced cancer of the larynx or hypopharynx were usually treated with total laryngectomy or total laryngopharyngectomy, respectively. This resulted in loss of the normal laryngeal voice, and patients had to either rely on an electrolarynx or esophageal voice for speech. The permanent anterior neck stoma added a significant deformity and impaired quality of life.

In 1979, Dr. Ki Hong and colleagues [14] explored the role of neoadjuvant (induction) chemotherapy and reported a high (76%) response rate in advanced, previously untreated HNC. They found that a major response to chemotherapy may predict the response to subsequent radiotherapy; they also demonstrated the feasibility of avoiding surgical resection in selected patients who experience complete tumor regression after receiving induction chemotherapy followed by definitive radiotherapy [15]. Their findings formed the basis for the Department of Veterans Affairs Laryngeal Cancer Study Group, a landmark phase III clinical trial of induction chemotherapy to select patients with advanced laryngeal cancer for either radiotherapy or total laryngectomy [16]. The findings from this trial defined a new role for chemotherapy in patients with advanced laryngeal cancer and indicated that a treatment strategy involving induction chemotherapy and definitive radiotherapy can be effective in preserving the larynx in approximately two-thirds (65%) of patients without compromising overall survival. This started a new era of "organ preservation" in patients treated for advanced HNC, but the value of adding chemotherapy to radiotherapy and the optimal timing of chemotherapy were unknown. For this reason, the Radiation Therapy Oncology Group (RTOG), led by Dr. Helmuth Goepfert and others, launched a three-arm randomized clinical trial comparing induction cisplatin plus fluorouracil followed by radiotherapy, radiotherapy with concurrent administration of cisplatin, or radiotherapy alone [17]. This landmark study demonstrated that radiotherapy with concurrent administration

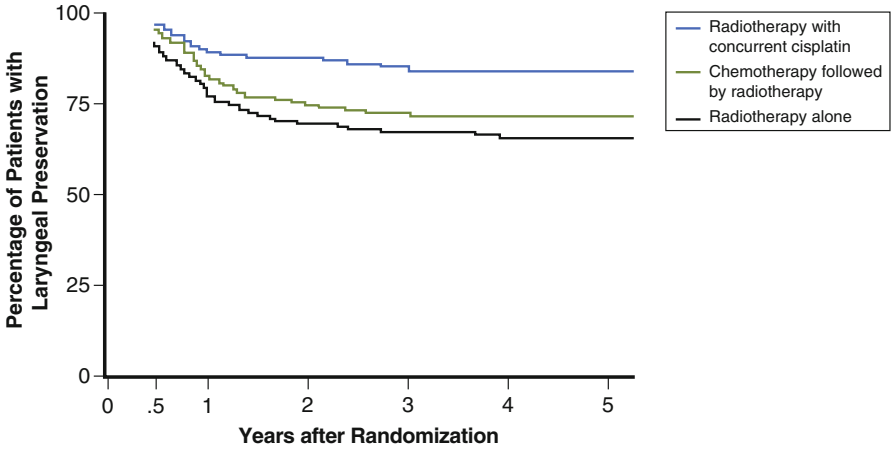

Fig. 25.5 Rates of laryngeal preservation according to treatment group in RTOG trial [16].

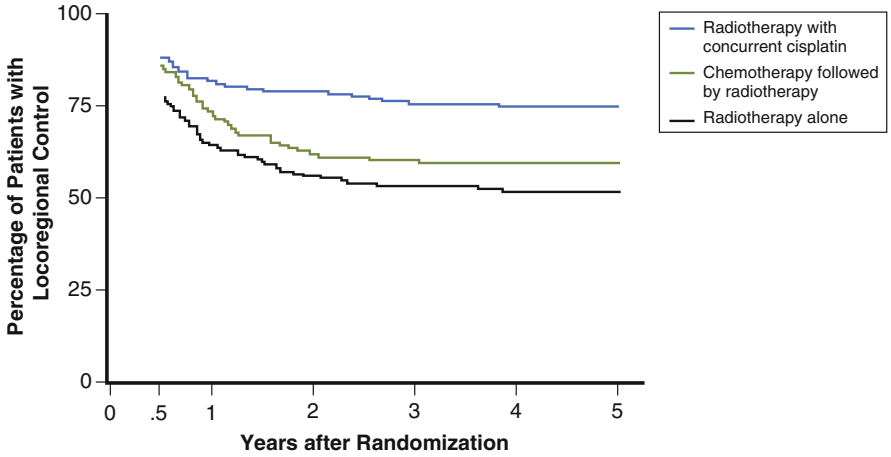

Fig. 25.6 Rates of locoregional control according to treatment group in RTOG trial [16].

of cisplatin is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control (Figs. 25.5 and 25.6). The findings from this and other studies established concurrent chemoradiotherapy as a new "standard of care" for organ preservation in patients treated for advanced HNC.

The improved rates of locoregional control and organ preservation associated with concurrent chemoradiotherapy came with a heavy price of increased toxicity, however, and alternative treatment strategies, particularly targeted therapy, were sought. To this end, Dr. Kian Ang and his colleagues focused their research efforts on studying the synergistic effects of cetuximab, a monoclonal antibody against the

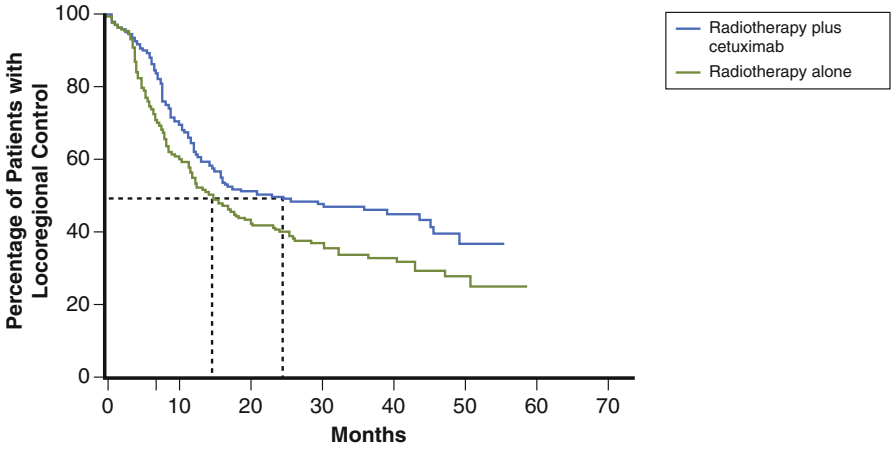

Fig. 25.7 Kaplan–Meier estimates of locoregional control among all patients randomly assigned to radiotherapy plus cetuximab or radiotherapy alone in phase III trial [19].

epidermal growth factor receptor (EGFR), and radiotherapy. Their findings from preclinical [18] and biomarker studies [19], for example, were the bases of a landmark phase III clinical trial that compared radiotherapy alone with radiotherapy plus cetuximab in the treatment of locoregionally advanced HNC [20]. This study demonstrated that treatment of locoregionally advanced HNC with concomitant high-dose radiotherapy plus cetuximab improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiotherapy to the head and neck (Fig. 25.7).

Dr. Merrill Kies and colleagues [21] have also reported the results of a phase II clinical trial demonstrating the promising role of adding cetuximab to induction chemotherapy in the treatment of advanced HNC.

Ongoing clinical trials at MD Anderson are investigating the evolving role of targeted therapy in the multimodality treatment of advanced HNC. For example, Dr. Bonnie Glisson and colleagues are currently investigating the role of the insulin-like growth factor receptor (IGFR) targeting and co-targeting IGFR and EGFR in HNC. Other examples of promising targeting agents include the EGFR tyrosine kinase inhibitor erlotinib, which demonstrated modest single-agent activity in recurrent or metastatic head and neck squamous cell carcinoma and is currently being evaluated in combination with standard chemotherapy regimens and prior to surgery for advanced HNC. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is also currently being evaluated in combination with cetuximab in the treatment of recurrent disease. Dr. Vasiliki Papadimitrakopoulou has recently completed a phase I–II trial of vandetanib, a tyrosine kinase inhibitor of both EGFR and VEGF receptor 2 (VEGFR2), with radiotherapy and chemoradiotherapy. There is reason to believe that co-targeting of key drivers of the malignant phenotype, such as EGFR, VEGF/VEGFR, and IGFR, in biologic platforms with established radiotherapy and chemotherapy regimens may lead to more effective

and less toxic therapy. Furthermore, through correlative assessment of biomarkers in tumor and blood, these studies should lead to increased personalization of treatment for patients with HNC.

Advances in Rehabilitation

With improvements in cure and survival rates, more emphasis is now being directed to rehabilitation and quality of life in patients with HNC. In addition to surgeons, medical and radiation oncologists, pathologists, and diagnostic radiologists, the MD Anderson head and neck multidisciplinary team includes outstanding rehabilitative and supportive services.

Dental oncologists provide comprehensive preventive and therapeutic oral and dental care for patients undergoing and recovering from intensive multimodality treatment of HNC. For example, Dr. Mark Chambers and his colleagues are investigating novel approaches to the management of treatment-associated xerostomia, mucositis, trismus, and osteoradionecrosis. Maxillofacial prosthodontists provide innovative techniques for dental, palatal, orbital, and facial restoration such as osteointegrated implants.

The Section of Speech and Language Pathology provides comprehensive and innovative services for assessment and rehabilitation of critical functions such as swallowing, voice, speech, hearing, and balance. With increasing trends of organ preservation, the function of the "preserved organ" has been the subject of much attention. For example, after intensive chemoradiotherapy for laryngeal and oropharyngeal preservation, a substantial number of patients experience significant dysphagia and may become dependent on tube feeding to meet their nutritional needs. Dr. Jan Lewin and her colleagues defined comprehensive measures of evaluation and rehabilitation of the swallowing function before, during, and after treatment. They also developed a world-class program in voice and speech rehabilitation after laryngectomy or other major head and neck resection. Novel treatments of postoperative and post-radiotherapy lymphedema of the head and neck are also currently being investigated. Chemotherapy and radiotherapy may have toxic effects on the auditory and vestibular systems affecting hearing and balance, respectively. Dr. Paul Gidley and his staff in the Section of Audiology developed a program that offers MD Anderson patients comprehensive assessment of and rehabilitation for hearing and balance disorders.

HNC and/or its treatment may have a profound effect on nutrition due to difficulty eating, chewing, and swallowing and altered taste perception. Nutritionists in the Head and Neck Center developed algorithms for nutritional support of patients with HNC throughout their treatment and recovery. Patients with HNC also have significant psychosocial burdens, and social services are provided throughout the cycle of care. Physical and occupational therapists are integrated into the multidisciplinary team

to help patients recover as they return to their daily activity and employment. Dr. Michelle Fingeret and her colleagues are currently conducting intensive research in "body image" perceptions of patients with HNC and are evaluating methods of intervention to reduce the psychological burden that cancer or its treatment has left on these patients.

Advances in Outcome Measurement and Reporting

In 2006, Michael Porter, Professor of Economics in the Harvard Business School, published a book titled *Redefining Health Care: Creating Value-Based Competition on Results*. Porter defines *value in health care* as "the health outcome divided by the cost expended." To test this definition in cancer care, Porter and his team analyzed the care provided at MD Anderson's Head and Neck Center as a case study of a value-based system. The study focused on the multidisciplinary care center concept of our clinic system where patients are treated within a highly specialized integrated care model. Under the leadership of Drs. Randal Weber, Tom Burke, Ron Walters, and Tom Feeley, the case study offered our organization an opportunity to partner with Porter and the Harvard Business School to critically examine the value proposition as it relates to cancer care delivery.

The study evaluated the outcomes of care for 2,467 patients with previously untreated cancers of the oral cavity, larynx, and oropharynx. In addition to traditional oncologic outcomes such as survival, the study sought to evaluate some basic functional outcomes, which included the absence of a tracheostomy or feeding tube after treatment. We also evaluated selected care process metrics such as the timing from referral to completion of multidisciplinary evaluation, presentation at the treatment planning conference, and treatment completion time.

The results of this study demonstrated that more than 80% of patients were alive at 2 years after treatment for laryngeal and oropharyngeal cancer and that nearly 75% of patients with cancer of the oral cavity survived at least 2 years. In the entire cohort, 98% of patients were eating without a feeding tube at 1 year, and 91% were tracheostomy-free at 1 year. Of the process metrics, the average time from referral to evaluation by the multidisciplinary planning committee was 17 days, and 100% of patients were evaluated by the multidisciplinary planning committee and completed treatment within 100 days.

Cost measurement in health care is complex and is beyond the scope of this chapter. Under the leadership of Dr. Tom Feeley, the Institute for Cancer Care Excellence, whose mission and goal is to deliver improved value to cancer patients and individuals at risk of cancer, is using the Head and Neck Case Study to explore novel cost accounting systems that capture the entire cost of treating a medical condition throughout the whole cycle of care.

This study also demonstrated a critical need for an informatics infrastructure that can be queried for detailed clinical care events, interventions, and outcomes. Our current experience in this study of manual abstraction of key outcome information from medical records was both time- and labor-intensive and will not meet the needs of public reporting of outcomes, which is foundational to the "value" proposition and to improving the quality of care. The Head and Neck Center is currently piloting the use of a structured clinical documentation enhancement of the electronic medical record. It is our goal to continue to improve our outcome measurement and reporting to fulfill our unwavering commitment to improve the care we deliver to our patients.

Appendix

See Figs. 25.8 through 25.27.

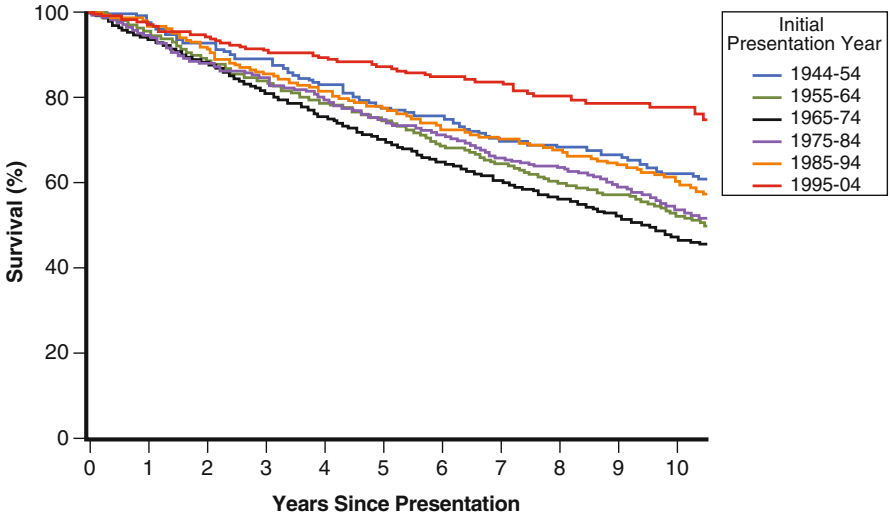

Fig. 25.8 Survival rates for patients with local (SEER stage) cancer of the head and neck with oral cavity primary sites (1944–2004) ($P < 0.0001$, log-rank test for trend).

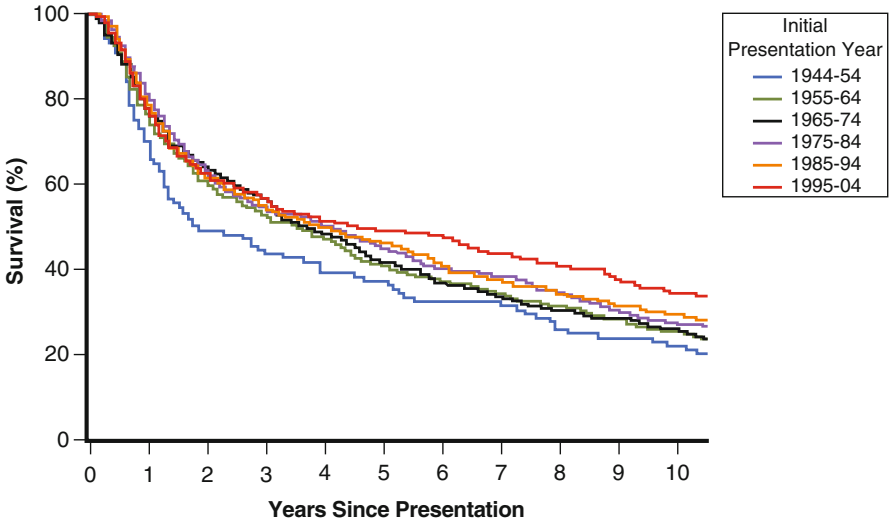

Fig. 25.9 Survival rates for patients with regional (SEER stage) cancer of the head and neck with oral cavity primary sites (1944–2004) ($P = 0.001$, log-rank test for trend).

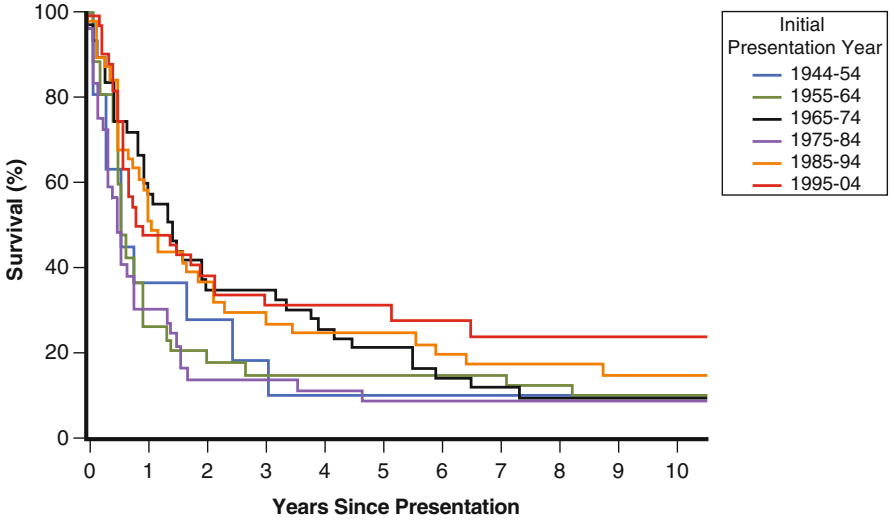

Fig. 25.10 Survival rates for patients with distant (SEER stage) cancer of the head and neck with oral cavity primary sites (1944–2004) ($P = 0.062$, log-rank test for trend).

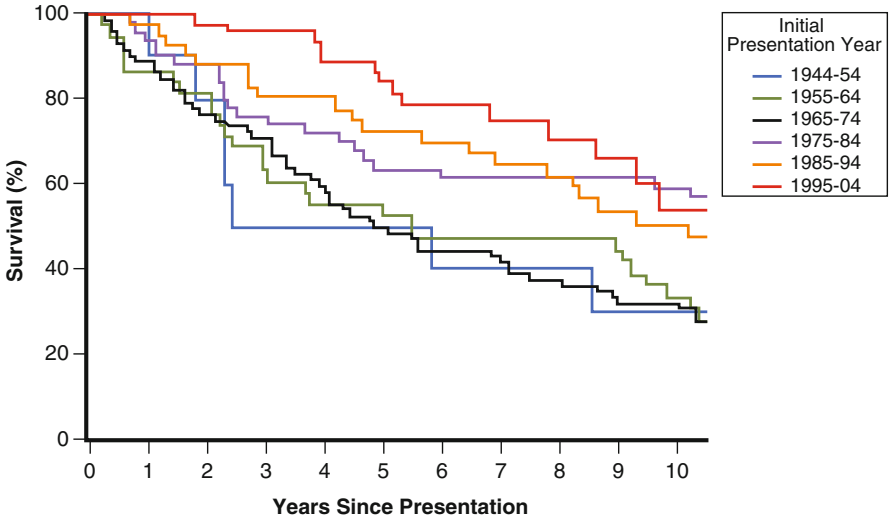

Fig. 25.11 Survival rates for patients with local (SEER stage) cancer of the head and neck with oropharyngeal primary sites (1944–2004) ($P<0.0001$, log-rank test for trend).

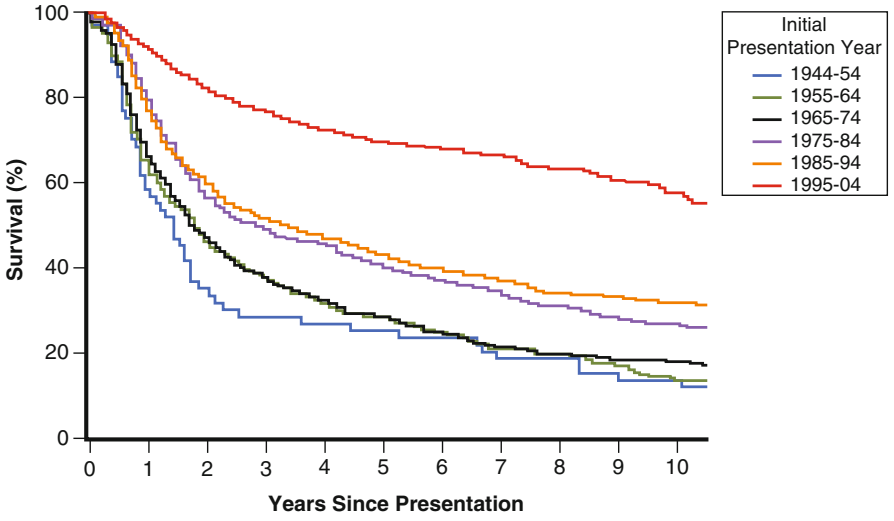

Fig. 25.12 Survival rates for patients with regional (SEER stage) cancer of the head and neck with oropharyngeal primary sites (1944–2004) ($P<0.0001$, log-rank test for trend).

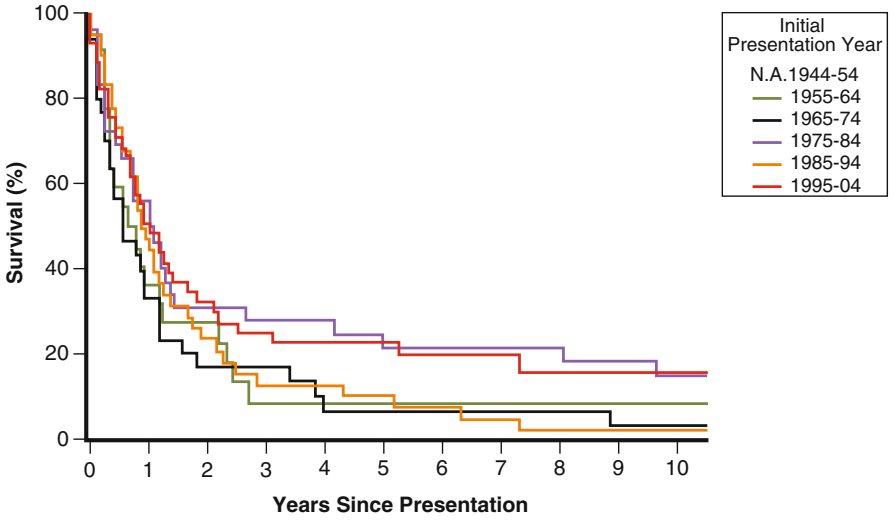

Fig. 25.13 Survival rates for patients with distant (SEER stage) cancer of the head and neck with oropharyngeal primary sites (1944–2004) ($P < 0.159$, log-rank test for trend). Because of the very small number of individuals with distant cancer of the head and neck with oropharyngeal primary sites seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

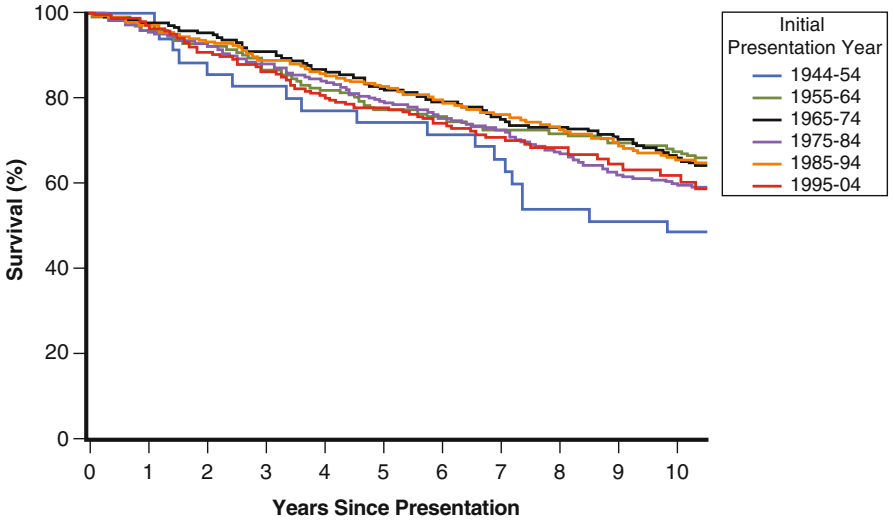

Fig. 25.14 Survival rates for patients with local (SEER stage) cancer of the head and neck with laryngeal primary sites (1944–2004) ($P = 0.645$, log-rank test for trend).

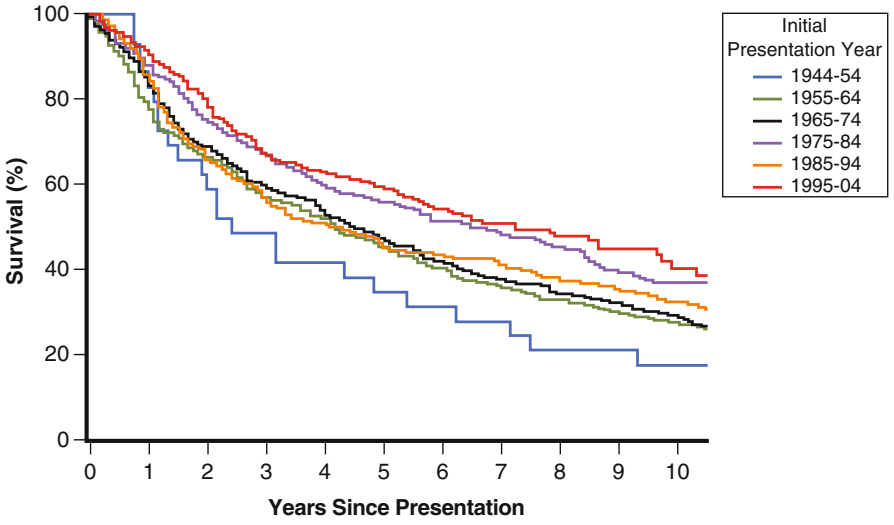

Fig. 25.15 Survival rates for patients with regional (SEER stage) cancer of the head and neck with laryngeal primary sites (1944–2004) ($P<0.0001$, log-rank test for trend).

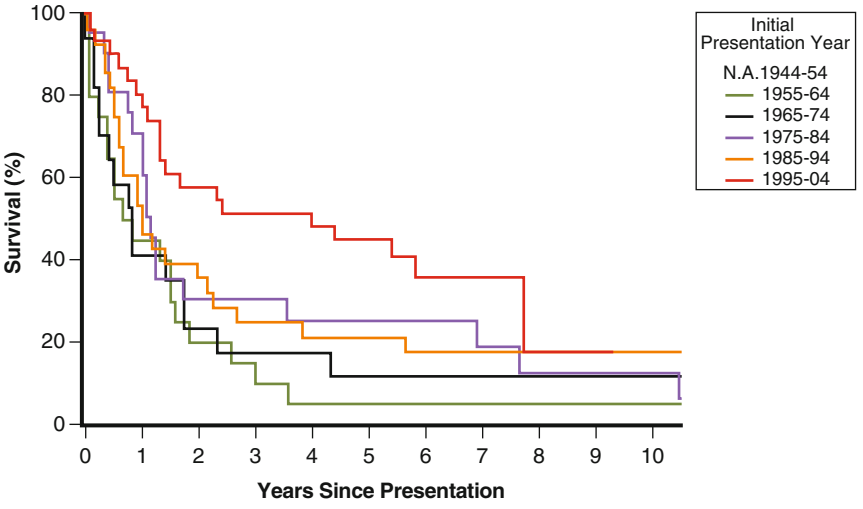

Fig. 25.16 Survival rates for patients with distant (SEER stage) cancer of the head and neck with laryngeal primary sites (1944–2004) ($P=0.027$, log-rank test for trend). Because of the very small number of individuals with distant cancer of the head and neck with laryngeal primary sites seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

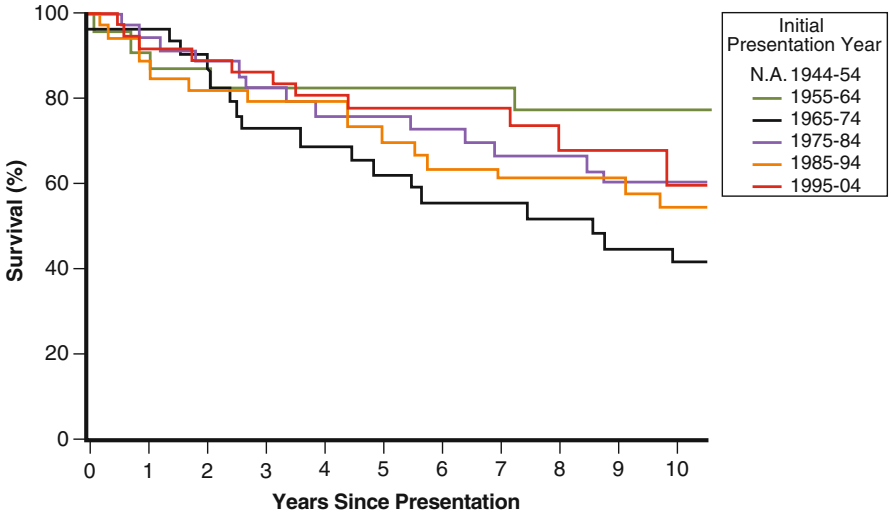

Fig. 25.17 Survival rates for patients with local (SEER stage) cancer of the head and neck with paranasal sinus and nasal cavity primary sites (1944–2004) ($P=0.166$, log-rank test for trend). Because of the very small number of individuals with local cancer of the head and neck with paranasal sinus and nasal cavity primary sites seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

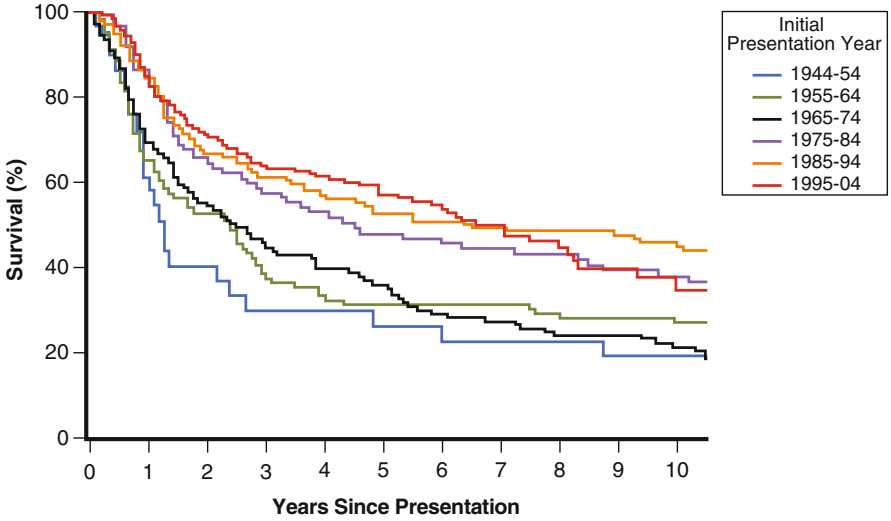

Fig. 25.18 Survival rates for patients with regional (SEER stage) cancer of the head and neck with paranasal sinus and nasal cavity primary sites (1944–2004) ($P<0.0001$, log-rank test for trend).

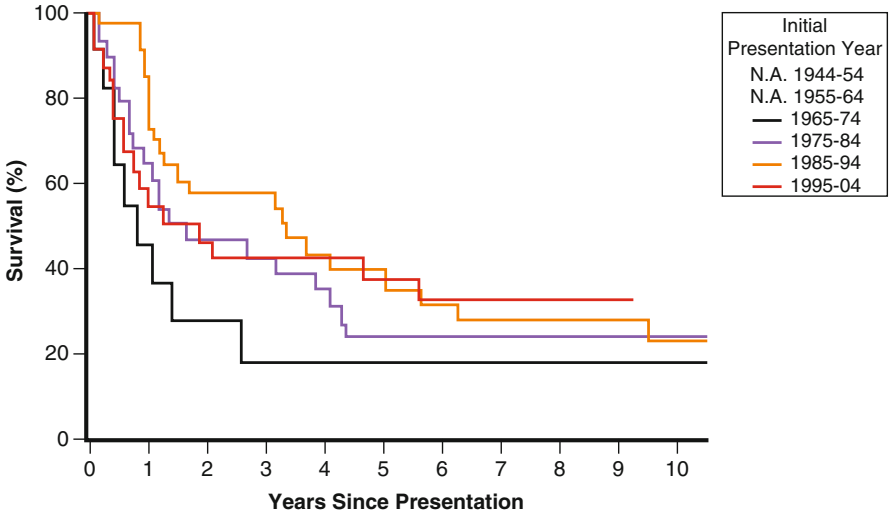

Fig. 25.19 Survival rates for patients with distant (SEER stage) cancer of the head and neck with paranasal sinus and nasal cavity primary sites (1944–2004) ($P=0.001$, log-rank test for trend). Because of the very small number of individuals with distant cancer of the head and neck with paranasal sinus and nasal cavity primary sites seen from 1944 to 1954 and from 1955 to 1964, data from these periods were excluded. *N.A.* not applicable.

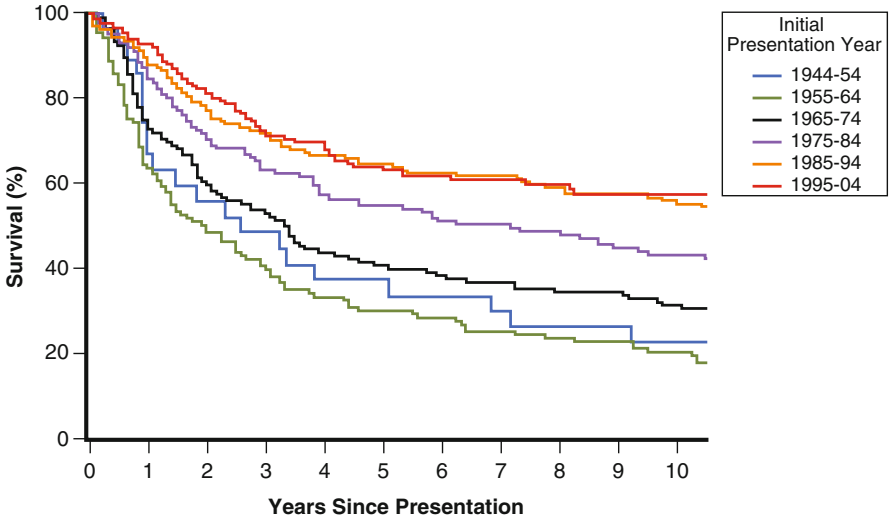

Fig. 25.20 Overall rates for patients with cancer of the head and neck with nasopharyngeal primary sites (1944–2004) ($P<0.0001$, log-rank test for trend).

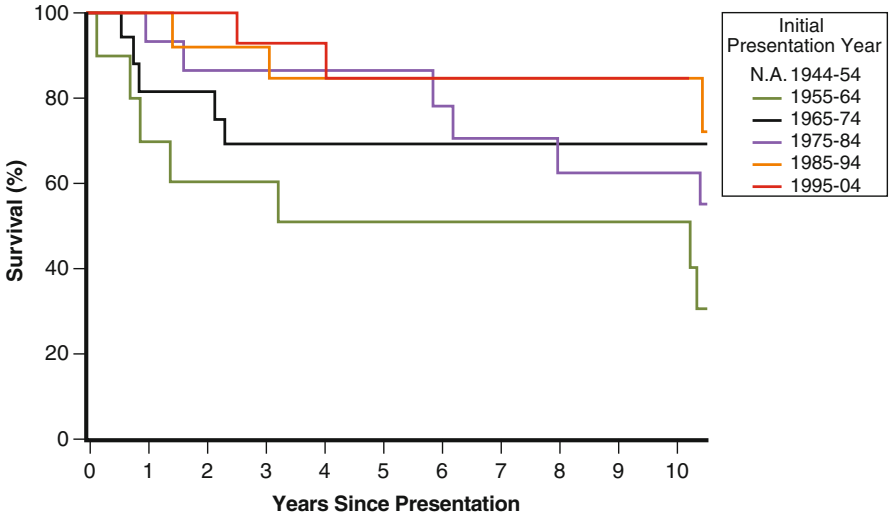

Fig. 25.21 Survival rates for patients with local (SEER stage) cancer of the head and neck with nasopharyngeal primary sites (1944–2004) ($P = 0.153$, log-rank test for trend). Because of the very small number of individuals with local cancer of the head and neck with nasopharyngeal primary sites seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

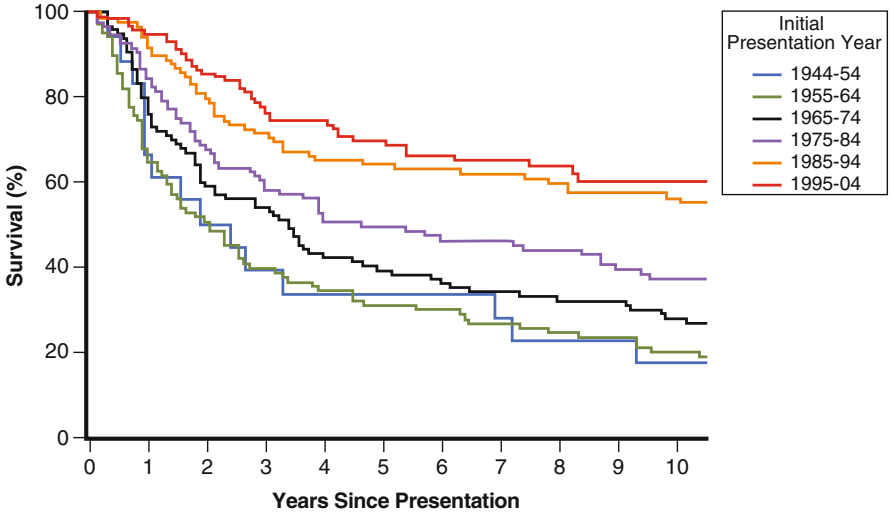

Fig. 25.22 Survival rates for patients with regional (SEER stage) cancer of the head and neck with nasopharyngeal primary sites (1944–2004) ($P < 0.0001$, log-rank test for trend).

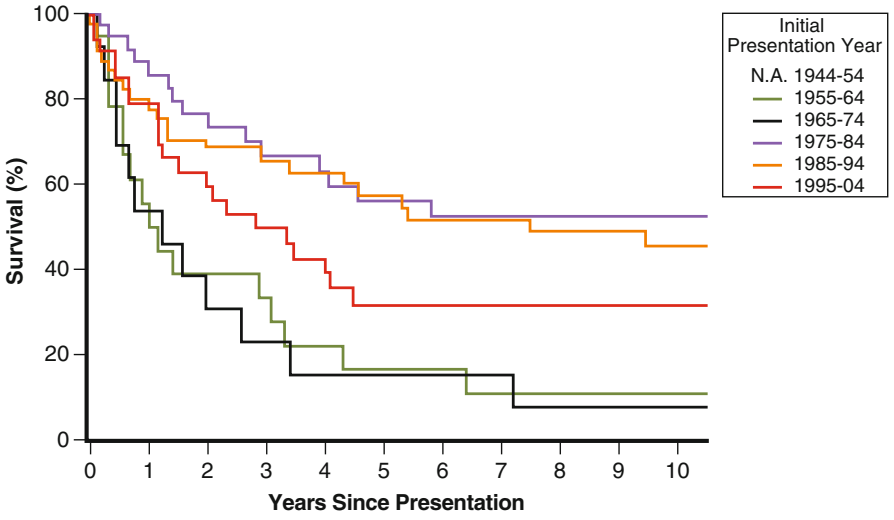

Fig. 25.23 Survival rates for patients with distant (SEER stage) cancer of the head and neck with nasopharyngeal primary sites (1944–2004) ($P<0.0001$, log-rank test for trend). Because of the very small number of individuals with distant cancer of the head and neck with nasopharyngeal primary sites seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

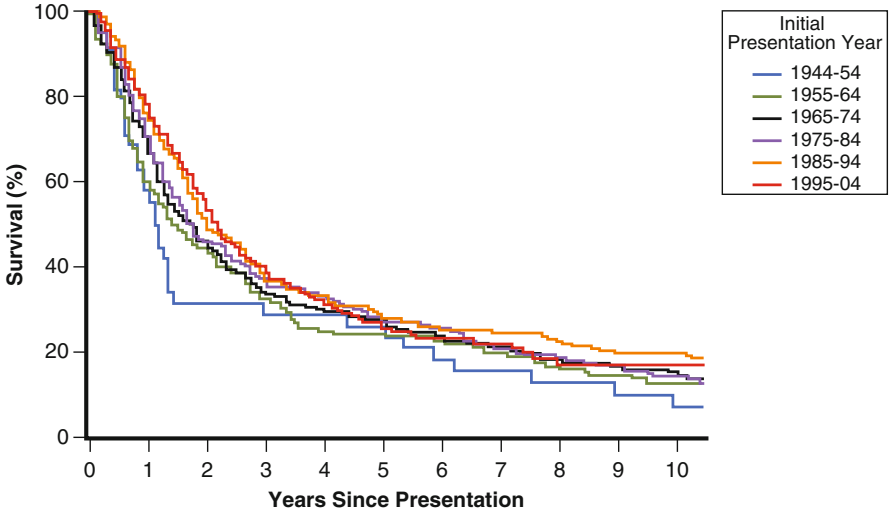

Fig. 25.24 Overall rates for patients with cancer of the head and neck with hypopharyngeal primary sites (1944–2004) ($P=0.020$, log-rank test for trend).

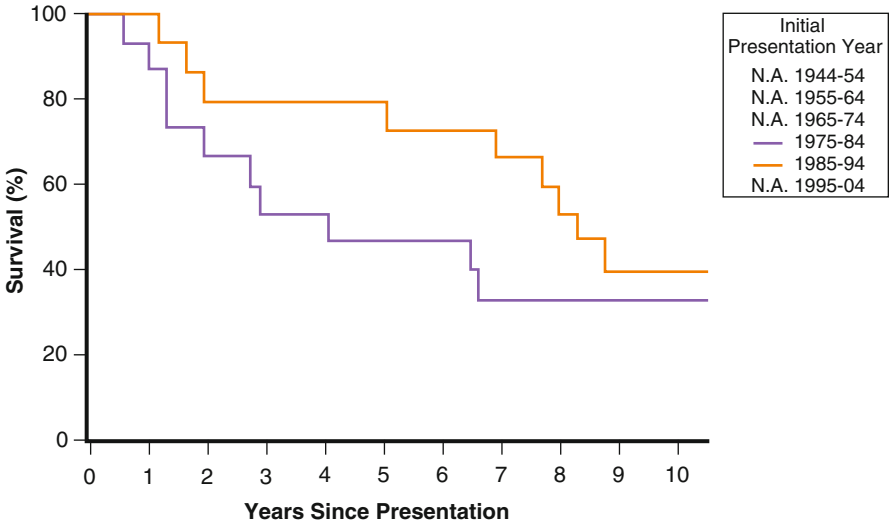

Fig. 25.25 Survival rates for patients with local (SEER stage) cancer of the head and neck with hypopharyngeal primary sites (1944–2004) ($P = 0.375$, log-rank test for trend). Because of the very small number of individuals with local cancer of the head and neck with hypopharyngeal primary sites seen from 1944 to 1954, from 1955 to 1964, from 1965 to 1974, and from 1995 to 2004, data from these periods were excluded. *N.A.* not applicable.

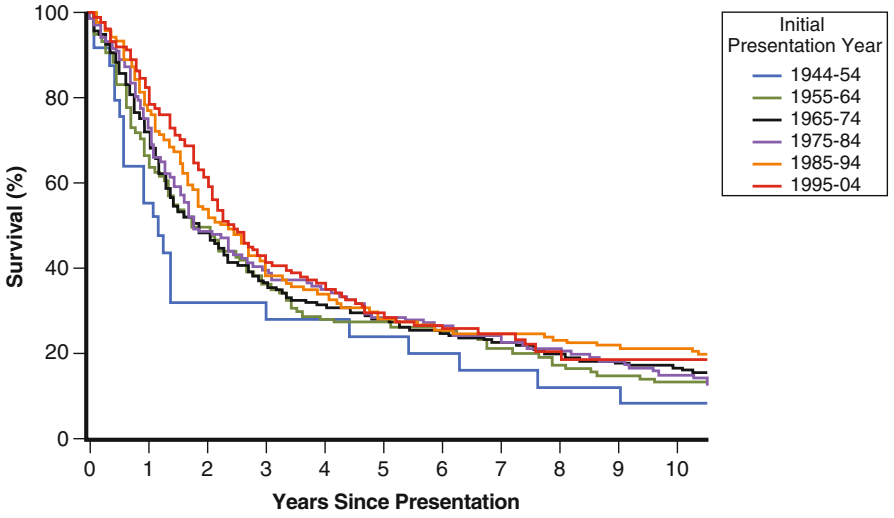

Fig. 25.26 Survival rates for patients with regional (SEER stage) cancer of the head and neck with hypopharyngeal primary sites (1944–2004) ($P = 0.246$, log-rank test for trend).

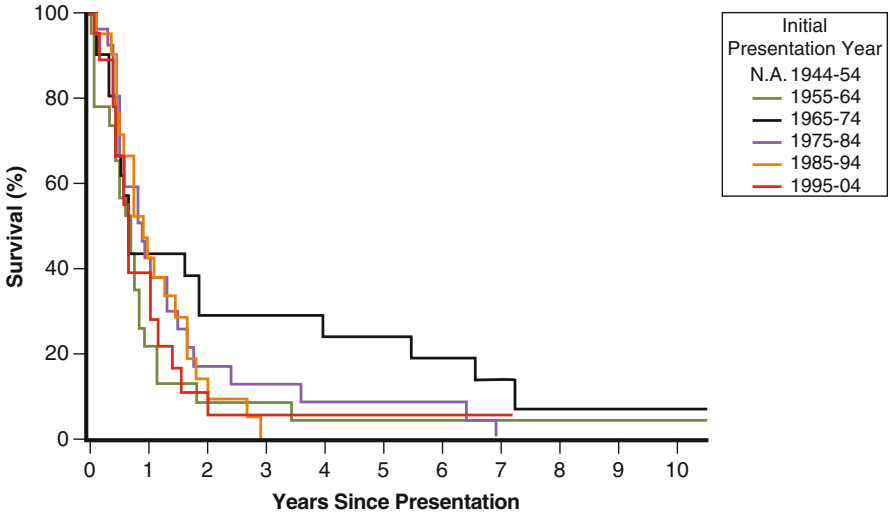

Fig. 25.27 Survival rates for patients with distant (SEER stage) cancer of the head and neck with hypopharyngeal primary sites (1944–2004) ($P = 0.358$, log-rank test for trend). Because of the very small number of individuals with distant cancer of the head and neck with hypopharyngeal primary sites seen from 1944 to 1954, data from this period were excluded. *N.A.* not applicable.

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