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Head and Neck Cancer: An Evolving Treatment Paradigm

David M. Cognetti, MD[1], **Randal S. Weber, MD**[2], and **Stephen Y. Lai, MD, PhD**[1,2,3]

[1] Department of Otolaryngology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

[2] Department of Head and Neck Surgery, The University of Texas M. D. Anderson Cancer Center, University of Texas, Houston, Texas

[3] Department of Pharmacology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Abstract

Since the inception of this journal in 1948, the understanding of etiologic factors that contribute to and the treatment of head and neck cancer has evolved dramatically. Advances in surgery, radiation therapy, and chemotherapy have improved locoregional control, survival, and quality of life. The outcomes of these treatment modalities have shifted the focus of curative efforts from radical ablation to preservation and restoration of function. This evolution has been documented in the pages of *Cancer* for the past 6 decades. This review focuses on the evolution of treatment approaches for head and neck cancer and future directions while recognizing the historic contributions recorded within this journal.

Keywords

head and neck cancer; head and neck squamous cell carcinoma (HNSCC); head and neck surgery; neck dissection; radiation therapy; combined modality therapy; concurrent chemotherapy

Head and neck cancer includes epithelial malignancies of the upper aerodigestive tract (UADT), including the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx; and, as the sixth most common cancer worldwide, head and neck cancer represents about 6% of solid tumors. Approximately 650,000 new head and neck cancers are diagnosed annually, and there are 350,000 deaths yearly worldwide.1 In the United States, head and neck cancer accounted for approximately 45,660 new cancer cases in 2007, corresponding to 3% of all new cancer diagnoses in this country.2 Almost 66% of patients present with advanced-stage disease. Despite advances in treatment options, approximately 11,210 head and neck cancer-related deaths occurred during 2007 in the United States.2 The median age of diagnosis is in the sixth decade of life, and there is a large male-to-female predominance.1 Although there has been a slight decrease in overall incidence of head and neck cancer over the past 2 decades,3 an increase in base of tongue and tonsillar cancer recently has been observed.4

Address for reprints: Stephen Y. Lai, MD, PhD, Department of Head and Neck Surgery, Unit 1445, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030; Fax: (713) 794-4662; stephenylai@gmail.com.
David M. Cognetti's current address: Department of Otolaryngology, Head and Neck Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania.

Etiology

In the inaugural year of *Cancer*, Morton Levin documented sex disparity in cancers of the UADT as well as a rapidly increasing incidence of lung cancer during the 1930s.5 Despite providing detailed reviews of factors like age, socioeconomic position, and carcinogenic chemicals and radiation, the contribution of tobacco to these cancers never was mentioned. In 1953, Slaughter and colleagues introduced the concept of 'field cancerization' in squamous cell carcinoma of the oral cavity (Fig. 1).6 That landmark article provided a rationale for the high rate of second primary cancers in patients with head and neck squamous cell carcinoma (HNSCC). In their report, Slaughter et al suggested that the oral epithelium is preconditioned by an 'as-yet-unknown carcinogenic agent.' Again, the role of tobacco was not recognized.

Today, it seems difficult to imagine a time when tobacco and cancer were not causally linked. The Surgeon General's report of 1964 called public attention to the increasing amount of definitive evidence linking tobacco use and cancer.7 In 1954, Watson and Conte published a report on 301 patients with lung cancer and reviewed the available evidence.8 They concluded that cigarette smoking likely represents an additional carcinogenic factor in squamous cell carcinoma of the lung. It is noteworthy that 90% of the patients in their control group were smokers, highlighting the prevalence of tobacco use at that time. In fact, many tobacco promotional advertisements of that era featured physicians.9 Ernest Wynder of the Sloan-Kettering Institute of Cancer Research was the lead author of an 11-part experimental series demonstrating tobacco carcinogenesis in mice that was published in *Cancer* between 1957 and 1971.10–20 Wynder and colleagues also published reviews that demonstrated the causative roles of tobacco and alcohol in oral cavity, laryngeal, and esophageal cancers.21–24 In 1962, Vogler and colleagues similarly linked tobacco to cancer of the mouth, pharynx, and larynx.25 Today, tobacco use is accepted universally as a causative factor for HNSCC. In addition, it has been demonstrated that alcohol also increases the chance of head and neck cancer, and the combined risk of tobacco and alcohol use has synergism beyond their simple additive risk.26–28

More recently, human papillomavirus (HPV) has been recognized as an important independent risk factor in HNSCC. One of the earliest reports to recognize a molecular association between HPV and HNSCC was published in *Cancer*.29 Approximately 25% of HNSCC specimens contain HPV genomic DNA, primarily HPV type 16 and, less frequently, type 18.30 Expression of the E6 and E7 viral oncoproteins inactivate the tumor-suppressor proteins p53 and Rb, respectively.31 Subsite analysis within the head and neck demonstrated that HPV is associated most commonly with oropharyngeal tumors, especially of the tonsil, with HPV DNA identified in up to 60% of specimens.32–34 Certain high-risk sexual behaviors have been associated with HPV transmission and oropharyngeal carcinoma35,36 The association of HPV and HNSCC has important implications regarding prevention, treatment, and prognosis. The presence of HPV may be a favorable prognostic factor in HNSCC, especially in patients with no history of tobacco and/or alcohol use, possibly because of increased radiosensitivity.37,38 HPV-positive, locally advanced HNSCC tumors may respond well to standard therapy and may not require treatment

intensification. In addition, the role of vaccination against HPV in HNSCC remains to be explored.

Evolution of Treatment for Head and Neck Squamous Cell Carcinoma

At the turn of the last century, radiation had just been discovered, and surgical outcomes were hampered by the lack of antibiotics and the limitations of anesthesia. For these reasons, there was a tendency to use radiation therapy (RT) as primary treatment for the first half of the 20th century. In the middle 20th century, advancements in perioperative care, combined with the recognized side effects and treatment failures of early RT techniques, led to the emergence of primary surgical treatment with or without adjuvant RT for most head and neck cancers. Subsequent advancements in RT improved cure rates and decreased toxicities. Today, RT remains an important single-modality option in early-stage cancers and plays an important role in the adjuvant setting. In the second half of the 20th century, a focus on functional outcomes and an increasing role of chemotherapy led to both surgical and nonsurgical organ-preservation approaches. Recently, combinations of chemotherapy and RT have been used increasingly for advanced-stage cancers, both for primary and adjuvant treatment. Finally, the development of targeted molecular therapies offers new options in the management of HNSCC, which may further improve survival and functional results.

Surgical Treatment

The surgical management of head and neck cancer evolved rapidly during the history of this journal because of improvements in anesthesia, development of antibiotics and blood banking, and introduction of new techniques for reconstruction. Radical resection has given way to the goal of cure with preservation of function. Changing strategies in the surgical management of the neck and larynx in patients with HNSCC highlight this point.

Neck dissection

In 1951, Hayes Martin and colleagues' landmark report on neck dissection was published in *Cancer*.39 That report comprehensively reviewed the treatment of HNSCC cervical metastases. Although George Crile first described an en bloc dissection of the cervical lymphatics in 1906,40 the report by Martin et al is considered the greatest impetus to the popular adoption of the radical neck dissection (RND) (Fig. 2).41 Martin et al reported their experience with 1450 neck dissections performed at Memorial Hospital between 1928 and 1950. Whereas Crile reported preservation of the spinal accessory nerve (SAN) when the nerve was not involved with tumor, Martin insisted that "any technique designed to preserve the spinal accessory nerve should be condemned unequivocally."39 With Martin's report, RND with sacrifice of the internal jugular vein (IJV,) sternocleidomastoid muscle (SCM), and SAN became the surgical procedure of choice for clinically positive necks (Fig. 3). Martin did not advocate prophylactic dissection of the clinically negative neck, instead maintaining close follow-up observation and performing RND if lymph node disease became apparent clinically, acknowledging that RND was too 'radical' for elective use. 39,42,43

In 1963, Oswaldo Suarez described a technique for cervical lymphadenectomy in the Spanish-language literature that has become the modified RND (MRND).41,44 This technique permitted effective fascial compartment dissection of the cervical lymph nodes with preservation of the nonlymphatic structures (IJV, SAN, and SCM), improving function and cosmesis. Bocca and coworkers introduced this technique in the English-language literature, leading to its popularization.45,46 Advantages noted were the minimal surgical side effects in the elective management of clinically negative necks and the ability to perform simultaneous bilateral neck dissections without the risk of facial and cerebral edema seen with bilateral sacrifice of the IJVs.47

Given the effectiveness and decreased morbidity of MRND, interest in elective neck dissection (END) was renewed. In 1962, a study published in *Cancer* demonstrated that the regional failure rate was >50% for patients with early tongue cancers who had no clinically evident metastases and whose necks were managed by follow-up observation.48 Only 25% of these patients were salvaged for cure. In 1980, the first randomized clinical trial to compare the elective and the ‘wait-and-see’ therapeutic approaches of RND in oral cavity cancer was published.49 That study was limited by a small sample size (n = 75) and failed to demonstrate a difference in survival between the 2 approaches. However, the authors noted that the rate of occult metastases in the END group was 49%, and the rate of eventual lymph node involvement in the observation group was 47%. They concluded that END was advisable in patients who could not be followed regularly and suggested that an MRND was sufficient in this setting. Bocca and colleagues demonstrated that elective MRND had a much lower rate of recurrence compared with elective RND because of the ability to perform bilateral dissection in the MRND group.47 Surgeons soon began to perform elective MRND for patients with HNSCC with an occult metastasis rate ≥20%.43

Since the introduction of MRND, the trend toward conservative surgery has continued. A landmark study that established the clinical rationale for selective neck dissection (SND) was published in *Cancer* in 1972.50 Lindberg and colleagues reviewed the records of 2044 HNSCC patients at the University of Texas at Houston M. D. Anderson Hospital and Tumor Institute to identify distribution patterns for cervical metastases clinically apparent at presentation. He demonstrated that metastases from subsites within the head and neck follow predictable patterns to specific lymph node levels within the neck. In 1990, Jatin Shah and colleagues at Memorial-Sloan Kettering Cancer Center evaluated the histologic patterns of lymph node metastasis in patients undergoing elective and therapeutic RND for head and neck cancer.51,52 On the basis of these patterns of metastasis, elective dissection of select lymph node levels most at risk was offered as an alternative to elective MRND. In addition, extracapsular spread (ECS) was identified as the most important negative prognostic factor. 53–56 It was demonstrated that ECS was present even in small, positive lymph nodes and was identified in 20% of clinically negative necks in patients with supraglottic cancer who underwent END.56 Pathologic findings on END, including ECS and multiple positive lymph nodes, became indications for postoperative RT and, eventually, chemotherapy.57,58 Although the initial movement toward END and MRND was to avoid the functional and cosmetic issues associated with RND, the additional utility of END as a staging procedure soon was recognized.43,59 In the 1990s, several studies demonstrated that SND was as

effective as MRND and RND when used to electively treat and stage the clinically negative neck.60 Recent studies have suggested that SND can be used safely in patients with limited, clinically positive lymph node disease.61–63

The overarching principle in the evolution of the surgical management of the regional lymphatics in HNSCC has been disease detection and eradication with cosmetic and functional preservation. Sentinel lymph node biopsy (SLNB) has been proposed as an even more selective approach to the pathologic staging of the N0 neck in HNSCC compared with END. Gould and colleagues introduced the concept of SLNB in *Cancer* in 1960.64 Those authors described using an intraoperative frozen section of a facial lymph node during parotid surgery to determine whether a neck dissection should be performed for malignant tumors. Currently, SLNB with the use of a radiotracer to identify the sentinel lymph node is accepted as the standard of care in the treatment of breast cancer and melanoma. In 2001, a report in *Cancer* suggested that SLNB in HNSCC is accurate for staging the N0 neck.65 Multicenter trials investigating SLNB in the N0 neck for early-stage oral cavity cancer currently are in progress.66 Finally, an endoscopic approach to a lateral neck dissection has been described in a porcine model and in humans with papillary thyroid cancer.67,68 In addition, it has been demonstrated that the combination of an endoscopic approach with SLNB is feasible in pigs.69,70 These minimally invasive, highly selective techniques may play a role in the future staging of patients with HNSCC, especially because the ability to identify occult tumors is likely to improve with new methods to detect molecular markers.

Surgery for laryngeal cancer

At the beginning of the 20th century, lack of early diagnosis, anesthetic limitations, and a high surgical mortality rate made laryngeal carcinoma a hopeless situation in which most patients refused to submit to major surgery because of the small hope for perioperative survival and less likelihood for cure.71 In this setting, RT was a welcome addition to the treatment armamentarium and became the primary treatment for laryngeal cancer. By the inaugural issue of *Cancer*, the limitations of early RT techniques were recognized, and improvements in surgical techniques and perioperative care led to a ‘reversion’ to extensive surgery as the treatment of choice for laryngeal cancer with regard to laryngectomy and neck dissection.72 Hayes Martin noted a rapid increase in the number of laryngectomies performed in the United States during the first 5 years of this journal.73

At the same time, the knowledge of laryngeal anatomy was increasing through important experimental and observational work identifying the anatomic basis for the dissemination of cancer within the larynx as well as to cervical lymph nodes. Pressman et al recognized the highly compartmentalized organization of the larynx and identified the importance of this feature with regard to ‘subtotal laryngectomies.’74 In addition to existing open cordectomy and vertical partial laryngectomy, new approaches to partial laryngectomy emerged. The supraglottic laryngectomy was introduced in 1947 and was followed by the supracricoid laryngectomy in 1959.75,76 The goals of these procedures are to obtain cure through a less radical means while maintaining the functions of speech and swallow without a permanent stoma.77 In 1966, MacComb noted that the functional results were commanding as much attention as the curative results but that the cure had to remain the primary goal.78 In 1972,

the carbon dioxide (CO_2) laser was introduced for transoral resection of early laryngeal tumors, and it has produced cure rates equivalent to those achieved with open surgical approaches and RT.79,80 Endoscopic laser resection has been extended since then to include select, larger tumors. Recently, the feasibility of a robot-assisted supraglottic laryngectomy with and without the CO_2 laser has been demonstrated, which may expand further the indications for transoral laryngeal cancer resection.81,82

Reconstruction

In 1948, reconstruction and rehabilitation options were limited, and early descriptions in *Cancer* included skin grafting and local tissue flaps, which required multiple procedures.83,84 Patients typically were left with significant functional and cosmetic defects. Reconstruction of the oral cavity often consisted of intentional temporary oral-cutaneous fistulae, and fear of making a patient a ‘facial cripple’ was considered a deterrent to adequate surgical treatment of intraoral cancer.85 Implanted metallic prostheses for mandible defects were introduced to avoid the ‘Andy Gump’ deformity with its associated difficulty in swallowing and speaking.86 These plates were a temporary means to prevent contracture of the muscles of mastication before planned secondary reconstruction with a free bone graft, although most patients died of recurrence before successful reconstruction.85,86 Reconstruction of the pharynx and cervical esophagus was a particularly difficult problem and was complicated by high rates of wound breakdown, fistula, and stricture. Attempts at reconstruction with external diversion and secondary reconstruction with skin-lined local flaps or split-thickness skin graft-covered stents were considered palliative because of the poor prognosis of these patients.87 Alternatively, a closed pharyngeal pouch was offered after laryngectomy when the surgical defect could not be closed.88

A major advance in head and neck reconstruction occurred in 1965, when Bakamjian introduced the deltopectoral flap.89 This regional, pedicled, cutaneous flap allowed for reliable reconstruction of the pharynx and cervical esophagus. It was versatile and expanded the capabilities of head and neck reconstruction. However, limitations included the need for a skin graft at the donor site, requirement of a second stage for separation of the pedicle, lack of bulk for larger defects, and insufficient length to reach defects of the upper face and orbit. In 1977, McCraw et al recognized axial patterns for the blood supply of regional flaps and demonstrated the vascular territories for 13 myocutaneous flaps.90 In 1979, Ariyan introduced the pectoralis major myocutaneous flap, which overcame the limitations of Bakamjian’s deltopectoral flap.91 The pectoralis major flap is available to reconstruct defects as high as the orbit and cranial base; and, given its reliability and versatility, the flap quickly became a ‘workhorse’ in head and neck reconstruction.

The biggest advance in head and neck reconstruction has been the introduction and acceptance of microvascular free flaps in the 1980s and 1990s. The radial forearm fasciocutaneous free flap that was introduced in China by Yang and popularized by Soutar et al for head and neck reconstruction revolutionized intraoral reconstruction.92,93 The fibula free flap permitted reliable primary bony reconstruction of the mandible.94 A wide array of microvascular free flaps now exist and have greatly improved the options and outcomes in head and neck reconstruction.95,96

Other surgical advances

Novel approaches beyond the lateral neck and larynx continue to develop with the goal of limiting cosmetic and functional consequences. Endoscopic sinus surgery provided the basis for expanded endonasal approaches to the anterior cranial base.97,98 Benign and malignant tumors that traditionally required open craniofacial resections are being removed at some institutions without external incisions. The use of endoscopes also has allowed for the development of minimally invasive approaches to thyroid and parathyroid surgery.99–101 Minimally invasive techniques that aim to cure patient disease while limiting the side effects of surgery may shorten hospitalizations and recovery periods and enhance quality of life.

Nonsurgical Treatment

Nonsurgical therapy, in the forms of RT and chemotherapy, can be used independently and in conjunction with surgery in HNSCC management. Many combinations have been investigated over the past 60 years. In the past 2 decades, randomized controlled trials with a focus on multimodality approaches have resulted in an evolution of both surgical and nonsurgical treatment of HNSCC. Recently, targeted therapies against specific cellular receptors and signaling molecules have emerged and likely will play a large role in the future management of HNSCC.

Radiation therapy

Before 1948, the administration RT was limited to orthovoltage generators and radium implants. Orthovoltage radiation was characterized by poor depth distribution with limited efficacy against deeper tumors and a high degree of skin damage. At that time, poor cure rates and complications led to a gradual trend toward surgery for the treatment of most head and neck cancers.102 In the 1950s, however, the era of modern RT began with the advent of the linear accelerator and telecobalt units, which generated supervoltage radiation.103 Supervoltage radiation, with its vastly improved depth distribution, allowed for the treatment of deeper tumors while sparing the skin. This advancement allowed radiation to maintain a prominent role in the treatment of HNSCC.

Definitive radiation therapy—RT has been used as primary treatment in all subsites of head and neck cancer, and its role compared with surgery has been evaluated continually.102,104,105 Earlier diagnosis and advances in RT accounted for a dramatic improvement in the cure rates of patients who were treated with irradiation during the second half of the 20th century. By 1984, a report in *Cancer* indicated that patients with early glottic cancer had a 5-year recurrence-free rate of 89% and an overall survival rate of 97%, and the vast majority of those patients had received RT.106 This was improved compared with a 1968 publication, which reported a 5-year cumulative survival rate of 81% with RT.105 RT as single-modality treatment remains an important option for early HNSCC and has produced high cure rates that are comparable to those produced with surgical treatment.107 Thus, as arguments for END evolved, so did the rationale for elective irradiation of the clinically negative neck in patients at risk for occult metastases.108,109 Usually, elective treatment of the neck corresponds to the chosen treatment of the primary tumor. Finally, RT is used

frequently in early-stage oropharyngeal and hypopharyngeal carcinomas, because it has a cure rate comparable to that achieved by surgery but with lower morbidity.110,111

Preoperative radiation therapy—Initially, the combination of RT and surgery for more advanced HNSCC was investigated in an effort to decrease recurrence rates in more advanced-stage cancers. The strengths of surgery for eliminating bulky disease and RT for eradicating subclinical foci of cancer were a logical combination.112 In 1966, the first randomized clinical trial to address this issue was published in *Cancer*. Strong and colleagues demonstrated that patients who received low-dosage preoperative RT to the neck had a reduction in the incidence of cervical recurrence.113 After direct comparison in clinical trials, preoperative RT was replaced by postoperative (adjuvant) RT.114,115

Adjuvant radiation therapy—The first randomized study to address preoperative versus postoperative RT in HNSCC was published in *Cancer* in 1977. Vandenbrouk and colleagues investigated the use of RT in combination with surgery for patients with hypopharyngeal cancers.116 They demonstrated that patients who underwent surgery and received adjuvant RT had a 56% 5-year survival rate compared with a 20% 5-year survival rate in the preoperative RT group. A phase 3 study performed by the Radiation Therapy Oncology Group (RTOG) demonstrated that locoregional control was significantly better with adjuvant RT compared with preoperative RT for HNSCC.114,115 In addition, high-risk pathologic prognostic factors, including multiple positive lymph nodes and ECS, were recognized in neck specimens.55 Adjuvant RT became indicated for multiple positive lymph nodes and ECS based on these findings and on the increasing success with the technique.112 Increased total dose to at least 63 Gy improves locoregional control when ECS is present.110 A *Cancer* review of 8795 patients in the Surveillance, Epidemiology, and End Results (SEER) database published this year demonstrated a 10% absolute increase in 5-year cancer-specific survival and overall survival for patients with lymph node-positive HNSCC who were treated with RT.117 More recently, chemotherapy has been added to RT in the adjuvant setting with increased locoregional control and disease-free survival in randomized controlled trials compared with RT alone.118,119 This is discussed below (see Adjuvant chemoradiation).

Salvage and palliative radiation therapy—Recurrent HNSCC is a difficult problem with a poor prognosis. Traditionally, surgery has been used for salvage after any definitive modality has failed if resection is possible. Radiation with or without chemotherapy can be used in patients who have not received RT in the past. Patients who have been irradiated previously and have unresectable recurrent disease pose a more difficult challenge; for these patients, palliative chemotherapy is the standard treatment option.120 However, a recent *Cancer* study suggests that postoperative reirradiation is feasible for patients who undergo surgery for recurrent or second primary HNSCC.121 A recent prospective phase 2 trial suggests that reirradiation with chemotherapy may be offered in this setting with acceptable toxicities as well.122 Survival rates remain very poor. In patients with distant metastatic disease, cure rates are extremely low. Palliation in this setting is achieved with chemotherapy and supportive care.120

Brachytherapy and intraoperative radiation therapy—Interstitial RT, or brachytherapy, has been described for many oral cavity and oropharyngeal cancers as well as for lymph node disease.123 Brachytherapy allows for an increase in the concentration of radiation at the implant site while minimizing effects on normal surrounding tissue and has been shown to provide benefit in patients with previously irradiated, unresectable, recurrent disease at the primary site or in the neck.124,125 A recent *Cancer* study suggests a role for brachytherapy together with surgery for recurrent HNSCC in the neck.126 Twenty-two patients underwent the placement of brachytherapy catheters at the time of salvage neck dissection, which resulted in regional control and survival rates that were improved from published historic controls. Direct intraoperative administration of radiation to the open operative site after surgical resection is another method that has been shown to be feasible in advanced and recurrent HNSCC.127 Both approaches for administering higher doses of radiation to the tumor bed are under further investigation.

Altered fractionation radiation therapy—Over the past 2 decades, efforts to improve patient outcomes have been sought through the intensification of RT delivery. In 1985, a biologic basis for alteration of conventional fractionation schemes based on tissue responses to radiation was reported in *Cancer*.128 Hyperfractionation and accelerated fractionation were potential means to increase the therapeutic gains of RT. Hyperfractionation was defined as dividing the treatment into smaller than conventional doses per fraction without changing overall treatment duration to increase the therapeutic differential between late-responding normal tissues and tumor. Accelerated fractionation was defined as shortening the overall treatment duration of a regimen using conventional dose fractions with a goal to minimize tumor growth during treatment. Two studies using twice-a-day fractionation schemes in HNSCC demonstrated acceptable patient tolerance129,130 and improved local control for advanced tumors.130 A meta-analysis of patients receiving RT for HNSCC suggested that tumors underwent rapid repopulation beginning 4 weeks after the initiation of treatment, confirming that an increase in dose could compensate for this effect.131,132

In 2006, the Meta-analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) Collaborative Group published a meta-analysis of 15 randomized trials addressing altered fractionation compared with conventional fractionation in definitive RT for HNSCC.133 Altered fractionation demonstrated a statistically significant absolute survival benefit of 3.4% at 5 years with the highest benefit for hyperfractionated therapy (8% at 5 years). There was also a benefit of 6.4% at 5 years on locoregional control in favor of altered fractionation therapy. A recent phase 3 randomized controlled study comparing accelerated fractionated RT versus conventional RT in HNSCC demonstrated that, in the postoperative setting, there was no difference in 2-year locoregional control and overall survival.134 The only scenario in which adjuvant accelerated fractionation trended toward improved control was in patients who had a delay in starting RT.

Highly conformal radiation therapy—Intensity-modulated RT (IMRT) is relatively new technology that was designed to increase the conformity of the radiation dose in an effort to minimize toxicity to normal tissues. Traditional 3-dimensional conformal RT uses computed tomography (CT) images to design volumetric portals and the resulting radiation

dose distribution.135 Typically, 3 RT portals are used in this technique to create a very basic shape for the resulting dose distribution. Inverse planning is used in IMRT to define specific target doses for the tumor and maximum acceptable doses to surrounding normal tissue.135,136 On the basis of these values, a computer optimization algorithm determines beam parameters that will lead to the desired, volumetrically conformed dose distribution and allow for tumor dose escalation. In contrast to 3D conformal RT, IMRT uses a large number of radiation portals to achieve the tailored distribution. IMRT also allows for the delivery of a simultaneous, integrated boost without treatment field modifications. In addition, the use of 2-deoxy-2(^{18}F)fluoro-D-glucose-positron emission tomography/CT fusion for IMRT planning may further enhance the ability to maximize radiation dose to tumor while protecting normal structures.137 In theory, the benefits of IMRT are attractive, and recent surveys published in *Cancer* indicate rapid and wide acceptance in clinical practice.138,139 Most of the current data are focused on nasopharyngeal cancer (NPC) and oropharyngeal cancer at single institutions, but these studies have demonstrated excellent locoregional control.135,136

Stereotactic radiosurgery (SRS) is a form of highly conformal RT that allows the delivery of large doses of radiation to the tumor in a small number of fractions. The first description of SRS use in HNSCC was reported in *Cancer* for the palliation of skull base recurrences.140 Recently, renewed interest in the treatment of recurrent HNSCC has been described.141,142 Early experience suggests it is an efficient, effective, and well tolerated means of providing treatment and palliation in this high-risk population.141,142

Chemotherapy

During the first half of this journal's existence, chemotherapy had little significance in the treatment of HNSCC. Chemotherapy often was reserved for the palliative setting, in which advanced disease and prior therapy were associated with a poor outcome.143 Early experimentation in mice included topical chemotherapy144 after studies published in *Cancer* were the first to report a high rate of malignant cells in washings from operative wounds in the head and neck.145,146 In 1959, Sullivan et al introduced an innovative approach of continuous intra-arterial infusion of the antimetabolite methotrexate while delivering the metabolite citrovorum systemically to prevent systemic toxicities.147 An early study demonstrated potential usefulness of intra-arterial chemotherapy in the palliative setting.148,149 Although the short-term response with intra-arterial chemotherapy usually was excellent, it seldom was sustained. Given the lack of a durable response and a high complication rate, the technique eventually was abandoned as a definitive treatment.150 With the introduction of cisplatin as an antineoplastic agent, further investigation of chemotherapy in the treatment of head and neck cancer flourished in the 1970s; since that time, chemotherapy had been investigated in both the induction and adjuvant settings as well as concomitantly with RT.151 During that time, chemotherapy evolved from a role in palliation to an essential component in curative multimodality programs for locally advanced HNSCC.152

Induction chemotherapy—Induction, or neoadjuvant, therapy, refers to a modality used before definitive therapy with the goal of maximizing the success of the definitive therapy.

Response to induction therapy also may be used in determining prognosis and selecting the definitive course of treatment. One of the earliest trials that investigated survival in an induction chemotherapy regimen was reported in *Cancer*.153 That study compared patients who received 5-fluorouracil (5-FU) intra-arterially before RT with patients who received RT alone. Chemotherapy resulted in good tumor regression but did not result in an increase in survival. In the 1980s, multiple pilot studies featured cisplatin in combination with other chemotherapeutic agents in the neoadjuvant setting.154–160 These nonrandomized studies reported high response rates with tolerable toxicities, but they could not address survival. The first randomized trial to investigate the effect of induction chemotherapy in HNSCC was published in *Cancer* in 1987.161 That study demonstrated minimal toxicity but lower response to induction compared with preliminary studies. There was no effect on survival. One year later, a randomized trial by the Southwest Oncology Group (SWOG) was reported. 162 That study produced response rates consistent with the preliminary trials but still did not demonstrate a survival benefit.

Despite the lack of survival benefit in the randomized trials, a significant finding in the preliminary studies identified a potentially valuable role for induction chemotherapy. Several studies demonstrated that response to initial chemotherapy predicted response to further treatment and that responders had significantly greater survival than nonresponders. 154,158,159 This concept was cited in the design of the Veterans Affairs Laryngeal Cancer Study Group trial.163 In that landmark study, which investigated nonsurgical laryngeal preservation, induction chemotherapy followed by RT was compared with surgery (laryngectomy) followed by RT in patients with advanced laryngeal cancer. In the induction arm, patients initially received 2 cycles of chemotherapy before they were assessed for response. Responders completed the organ-preservation protocol, and nonresponders underwent laryngectomy. A similarly designed study by the European Organization for Research and Treatment of Cancer (EORTC) in patients with hypopharyngeal cancer soon followed.164 In both of those randomized trials, induction chemotherapy followed by RT in responders offered survival rates comparable to what was achieved with laryngectomy followed by RT.163,164 RTOG 91–11 was a follow-up randomized trial that evaluated optimal nonsurgical treatment of patients with locally advanced laryngeal cancer using laryngectomy-free survival as the primary endpoint.165 No overall survival difference was evident between the 3 arms (induction cisplatin plus 5-FU followed by RT, RT with concurrent cisplatin, or RT alone), which may have be attributed to the effect of salvage laryngectomy.166 Laryngectomy-free survival and locoregional control were highest in the patients who received concomitant chemotherapy and RT.165

Although HNSCC is highly responsive to cisplatin-based induction chemotherapy (80%–90%), multiple phase 3 trials comparing induction chemotherapy followed by locoregional treatment with locoregional treatment alone have had mixed results with regard to decreasing distant metastasis and improving patient survival.167–169 A meta-analysis of induction chemotherapy resulted in a nonsignificant survival improvement of 2% at 5 years (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.88–1.01; $P = .10$).169 However, there was a significant benefit from cisplatin plus 5-FU compared with the other induction regimens (HR, 0.88; 95% CI, 0.79–0.97). Interest in induction chemotherapy has continued

with the introduction of more active regimens that contain taxane. Three phase 3 clinical trials have demonstrated the potential for improved survival when a taxane is added to cisplatin plus 5-FU induction chemotherapy followed by RT or concurrent chemotherapy and RT (chemoradiotherapy [CRT]).170–172 Those studies did not include direct comparisons of induction strategies with concurrent CRT alone. Two additional phase 3 trials, Docetaxel Based Chemotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer (DeCIDE) and Paradigm, currently are underway and may help determine whether docetaxel-containing induction chemotherapy will confer benefit beyond concurrent CRT without induction.173,174

Adjuvant chemotherapy—On the basis of their findings of the poor prognostic value of ECS in the 1980s, Johnson and colleagues at the University of Pittsburgh began to offer adjuvant chemotherapy to patients with that pathologic finding.58 High-risk patients received postoperative RT and a subsequent chemotherapy regimen for 6 months. The results of that nonrandomized study indicated a survival benefit from adjuvant chemotherapy but also noted poor patient compliance with the regimen. A randomized controlled trial of postoperative chemotherapy followed by RT compared with postoperative RT alone, however, demonstrated no survival benefit from the addition of chemotherapy. 175 With the success of concurrent CRT, the role for sequential application of adjuvant chemotherapy was diminished.

Salvage and palliative chemotherapy—Approximately half of patients with locally advanced HNSCC develop locoregional or distant recurrences. Chemotherapy is the standard-of-care treatment option for patients with recurrent or metastatic HNSCC with a focus on palliation and prolonging survival. Bleomycin, taxanes, carboplatin, methotrexate, and 5-FU are active in recurrent HNSCC and produce response rates from 10% to 40%.176 Cisplatin and 5-FU typically serve as a standard chemotherapy regimen in patients with recurrent or metastatic HNSCC. Two-drug combinations may improve response rates, but not overall survival. Salvage surgery potentially is curative for a few patients with resectable locoregional recurrence.166,177 Reirradiation combined with chemotherapy after salvage surgery improved progression-free survival, but not overall survival.178 Overall, the prognosis is poor for patients with recurrent or metastatic HNSCC.

Concurrent chemotherapy and radiation therapy

The combination of surgery, RT, and chemotherapy has been critical for the curative management of locally advanced HNSCC. Concurrent administration of chemotherapy and RT has a significant preclinical and clinical rationale and represents a significant therapeutic advance.179 The concept of combining chemotherapy and radiation was discussed in *Cancer* as early as 1960.180 Chemotherapy improves efficacy through its radiosensitizing ability in locoregional disease and by providing systemic therapy against distant metastatic disease.181 Today, concurrent regimens are standard treatment in the definitive setting of locally advanced disease and in the postoperative setting for high-risk pathology. This advance reflects not only an improvement in the biologic treatment of HNSCC but also demonstrates the successful development of a truly multidisciplinary approach to head and neck cancer care.

Definitive concurrent chemoradiation—With no clear advantage of induction or sequential adjuvant chemotherapy in randomized trials, the role of concurrently delivered CRT was studied intensively in the 1990s.182 Some of the earliest feasibility studies that addressed concurrent cisplatin-based CRT for locally advanced disease were published in *Cancer* in 1987.183,184 The trials concluded that the approach was effective and safe and justified a randomized controlled trial comparing CRT with RT alone.183–185 A randomized controlled trial published in 1997 demonstrated that concurrent CRT in patients with advanced locoregional, but resectable, HNSCC resulted in improved recurrence-free survival, decreased distant metastases, and increased primary site preservation compared to RT alone.186 Treatment toxicity was increased but was deemed tolerable.

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) was designed to evaluate the effectiveness of different chemotherapy timing methods in the management of HNSCC.169 That meta-analysis of 63 trials, which included nearly 11,000 patients with cancer of the oral cavity, oropharynx, larynx and hypopharynx, demonstrated that the addition of chemotherapy to locoregional treatment conferred an absolute survival benefit of 4% at 5 years (HR, 0.90; 95% CI, 0.85–0.94; $P < .0001$); the benefit that was confined to CRT (HR, 0.81; 95% CI, 0.76–0.88; $P < .0001$) resulted in an absolute survival benefit of 8% at 5 years.166 An updated meta-analysis that included 24 additional studies confirmed these findings.169,187 The Meta-Analysis of Chemotherapy in Nasopharyngeal Carcinoma (MAC-NPC) also demonstrated a survival advantage from chemotherapy that was most apparent in the concurrent treatment group.188

In 1998, the phase 2 randomized Intergroup 0099 Study demonstrated a significant survival advantage (67% vs 37%) with the use of concomitant cisplatin and RT followed by adjuvant cisplatin and 5-FU for advanced-stage NPC compared with RT alone.189 A randomized trial that addressed stage III and IV oropharyngeal cancer demonstrated that concurrent CRT significantly improved the 3-year survival rate (51% vs 31%) compared with RT alone.190 In 2003, RTOG 91–11 was published as a follow-up to the Veterans Affairs Laryngeal Cancer Study Group trial.165 All 3 treatment arms, as described above (see Induction chemotherapy), were similar in terms of survival. However, concurrent CRT was significantly superior to induction chemotherapy followed by RT and RT alone with regard to laryngectomy-free survival and locoregional control. The findings of these reports have resulted in a markedly increased role of concurrent CRT in the definitive treatment of HNSCC.

Adjuvant concurrent chemoradiation—Because sequential adjuvant chemotherapy had a disappointing impact on overall survival and definitive concurrent CRT regimens were demonstrating promise and tolerability, concurrent CRT was applied in the postoperative setting for high-risk patients.151 These efforts culminated in 2 phase 3 trials that compared postoperative RT with or without concurrent cisplatin-based chemotherapy in patients with high-risk, resected HNSCC.118,119 The first study was conducted by the RTOG and was supported by the Eastern Cooperative Oncology Group (ECOG) and the SWOG.119 The second study was performed by the EORTC.118 Both studies used the same cisplatin schedule (100 mg/m^2 on Days 1, 22, and 43 during RT). Inclusion criteria and high-risk factors were similar. High-risk pathologic features included multiple lymph node

involvement, ECS, and positive surgical margins. Both studies demonstrated that the addition of cisplatin-based chemotherapy improved locoregional control and disease-free survival. The EORTC study showed a significant improvement in overall survival for the concurrent CRT group, whereas the RTOG showed a trend in that direction. There was no effect on distant metastasis control in either trial, whereas the incidence of acute adverse effects was greater with chemotherapy in both studies.

In an attempt to identify the patients who would most benefit from such intense treatment, the authors of both studies collaborated to perform a comparative analysis of the 2 trials.191 The goal was to define the most significant high-risk indicators that would improve direction of the escalated treatment regimen. ECS and microscopically involved surgical margins were identified as the most significant prognostic factors for a poor outcome. Accordingly, the authors recommended the addition of concomitant chemotherapy to postoperative RT in patients with either or both of these findings who were fit medically to tolerate the added modality. Other risk factors, such as stage III/IV disease, perineural invasion, vascular tumor embolism, and clinically enlarged level IV/V lymph nodes secondary to oral cavity or oropharyngeal primaries, which traditionally were considered high-risk features, showed nonsignificant trends in favor of postoperative concurrent CRT. It is noteworthy that patients who had 2 or more histopathologically involved lymph nodes without ECS as their only risk factor did not seem to benefit from the addition of chemotherapy in the analysis.

Targeted therapeutics and novel agents

Within the last 2 decades, our understanding of the molecular mechanisms underlying HNSCC disease progression and advances in molecular biology have led to the development of targeted therapeutic agents. The best example of targeted therapy development is imatinib for the treatment of chronic myeloid leukemia (CML).192 CML is caused by a chromosomal translocation, resulting in the formation of the constitutively activated fusion tyrosine kinase BCR-ABL. Imatinib was identified as a small-molecule antagonist of BCR-ABL and was approved by the US Food and Drug Administration in 2002 as first-line treatment for CML. Imatinib has dramatically altered the treatment of CML patients and has become a vastly superior treatment compared with any available alternatives.

Although there has not been a success story as dramatic as imatinib for HNSCC treatment, several targeted therapeutic agents are being pursued. The epidermal growth factor receptor (EGFR) is a member of the ErbB growth factor receptor tyrosine kinase family.193 EGFR commonly is overexpressed in HNSCC. Increased expression of EGFR and the ligand, transforming growth factor-alpha (TGF-α), have been associated with disease recurrence and worse patient survival.194,195 EGFR-dependent signaling pathways are activated in HNSCC, leading to disease progression through tumor cell proliferation and antiapoptosis. Within several similar tumors, including colorectal cancer, nonsmall cell lung cancer, and HNSCC, Mendelsohn and colleagues have proposed that EGFR blockade inhibits tumor growth.196,197

Several strategies have been developed to target EGFR, including antibodies that target the extracellular ligand-binding region of EGFR and small-molecule inhibitors of the intracellular tyrosine kinase domain of EGFR (tyrosine kinase inhibitors). Cetuximab, an

immunoglobulin-G1 chimeric monoclonal antibody directed against EGFR, was the first molecularly targeted agent to result in improved survival in patients with HNSCC. In combination with RT, cetuximab demonstrated improved locoregional control (HR, 0.68; 95% CI, 0.52–0.89; $P = .005$; 3 years, 47% vs 34%), progression-free survival (3-years, 42% vs 31%; $P = .04$), and overall survival (3-years, 55% vs 45%; $P = .05$) compared with RT alone.198 RT plus cetuximab is an alternative to CRT that should be considered strongly in patients who cannot tolerate chemotherapy, because this regimen is not associated with increased myelosuppression or mucositis. However, no randomized trials have been completed comparing RT-cetuximab versus platinum-based concurrent CRT. In addition, ongoing studies are focused on the incorporation of EGFR inhibitors into various CRT regimens. A recent phase 2 study evaluated the combination of cetuximab with cisplatin and accelerated boost RT with promising preliminary efficacy, although there were concerns regarding enhanced toxicity.199

Other novel agents currently are under active investigation. These include other EGFR antibodies, such as the fully human panitumumab, which has demonstrated significant single-agent activity in colorectal cancer with increased progression-free survival.200 In addition, the EGFR tyrosine kinase inhibitor erlotinib has demonstrated modest single-agent activity in recurrent or metastatic HNSCC and currently is being evaluated in combination with standard CRT regimens.201,202 Activation of the Src kinase family is important in HNSCC progression.203 Dasatinib is an oral agent with activity against Src kinase family members, and clinical trials in HNSCC currently are under development. Finally, angiogenesis is the formation of new blood vessels, which are required to supply oxygen and nutrients as a tumor rapidly grows. Of the many factors that influence angiogenesis, vascular endothelial growth factor (VEGF) and its receptors are the most important.204 Bevacizumab, a monoclonal antibody against VEGF, currently is being evaluated in combination with concurrent CRT or erlotinib in HNSCC patients. In addition, vanitinib has become an interesting candidate agent given its ability to competitively inhibit EGFR and VEGF receptor 2 (VEGFR2). The combination of these agents with conventional CRT may be a promising strategy for novel and potentially more efficacious treatments for patients with HNSCC patients as more targeted therapeutic agents are developed.

Summary of Current Treatments and Future Directions

Caring for patients with head and neck cancer is complex and requires the expertise of many specialists, including the head and neck surgeon, radiation oncologist, medical oncologist, plastic/reconstructive surgeon, radiologist, pathologist, dental prosthedontist, nurse, nutritionist, and speech/swallow therapist. Within each of these fields, subspecialty dedication to head and neck cancer has allowed for marked improvement in patient care. More importantly, cooperation across these fields has created an integrated multidisciplinary approach that maximizes patient outcomes and facilitates the development of better treatment regimens.

In patients with early-stage HNSCC, single-modality treatment with surgery or RT remains the therapy of choice. Factors like the patient’s performance status, the expected degree of functional impairment with surgery, and patient and physician preferences guide the

decision between RT and surgery.205 For T1/T2 laryngeal cancer, RT long has been considered equivalent to surgery in terms of survival outcomes.206,207 Guidelines for the use of larynx-preservation strategies in the treatment of laryngeal cancer were published in 2006.207 Management options for early tumors include endoscopic resection and RT. The decision to use RT versus endoscopic resection is influenced by tumor location and expertise available at a specific treatment center.208,209 Similarly, RT is an option in early-stage oral cavity cancer as either external beam or brachytherapy; however, in this setting, RT is limited by xerostomia, mucositis, and osteoradionecrosis.210,211 Surgery has the advantage of shorter treatment time and minimal morbidity for small tumors with RT available as a treatment option in the event that a second primary tumor arises. NPC and some oropharyngeal carcinomas are treated primarily with RT for early-stage tumors because of their radiosensitivity and the relative increased morbidity of surgical resection in these anatomic regions.

HNSCC that presents with a cervical metastasis from an unknown primary site represents a unique situation given its inherently high stage despite an occult primary tumor. Although the standard treatment for cervical metastases with unknown primary is neck dissection followed by RT, a study in *Cancer* suggested these patients would benefit from treatment with CRT, which is being used increasingly.212,213 The favorable treatment response to CRT is understandable, because it is believed that most cervical metastases originate in the oropharynx. A meta-analysis reported in *Cancer* demonstrated that positron emission tomography/CT imaging enhances the ability to identify the primary site beyond the traditional panendoscopy with directed biopsies, thus allowing more directed treatment.214

In patients with resectable, locally advanced HNSCC, surgery followed by postoperative CRT or CRT alone may be the primary therapy chosen. Oral cavity primary lesions usually are treated with surgery, because the cosmetic and functional results are considered satisfactory, and experience with primary CRT has been less extensive. Locally advanced oropharyngeal primaries usually are treated with CRT, which produces good efficacy and functional results.215 Patients with locally advanced hypopharyngeal and laryngeal primaries should be considered for organ-preservation approaches.207 Although organ preservation is an important goal, such treatments must preserve both anatomy and function. The current standard of care of NPC (stage IIB or higher) is concurrent cisplatin and RT followed by adjuvant cisplatin and 5-FU according to the protocol of the Intergroup 0099 study.189,213 In patients with unresectable, locally advanced HNSCC, CRT is standard unless the addition of chemotherapy is not indicated because of poor performance status or comorbid illnesses.216

Clinical trial data have provided a range of potential combinations for CRT regimens. Although an in-depth discussion of different chemotherapeutic agents and combinations is beyond the scope of this review, meta-analyses shed some light on this decision process. Browman and colleagues performed a pooled analysis of 18 randomized controlled trials of concurrent CRT.217 They demonstrated that platinum-based CRT, especially platinum with 5-FU, was associated with a significant survival benefit compared with conventional RT alone. Current standard chemotherapy-containing regimens for HNSCC include cisplatin or carboplatin with or without 5-FU based on the treatment defined in randomized controlled

trials.118,119,163–165,189,190,218 However, the addition of a taxane to cisplatin and 5-FU induction chemotherapy led to improved results, which support the addition of taxane in induction regimens.170–172 The DeCIDE trial and the Paradigm study will help to define the role of taxane-based induction chemotherapy and concurrent CRT regimens.173,174

Budach and colleagues performed a meta-analysis to define the role of altered fractionation RT in concurrent CRT regimens.219 They discovered that concurrent CRT using 5-FU, cisplatin, carboplatin, and mitomycin C as single agents or combinations of 5-FU with any of the other drugs resulted in a large survival advantage regardless of the RT schedule. Only when RT was used alone did hyperfractionation lead to a significant improvement in overall survival, whereas accelerated fractionation alone did not increase overall survival. Several multi-institutional randomized trials investigating IMRT also are in progress, including 2 RTOG studies: 1 investigating IMRT versus conventional RT in early-stage oropharyngeal cancer and another examining IMRT with and without chemotherapy in NPC.135,136 The Groupe d'Oncologie Radiotherapie Tête et Cou (GORTEC) is evaluating IMRT with concomitant cisplatin versus conventional RT and cisplatin in patients with stage III and IV HNSCC.135 That study is designed to assess the efficacy as well as the potential for decreased toxicity with IMRT. RTOG 0522 is designed to define the effect of cetuximab added to concurrent CRT by comparing concurrent cisplatin and accelerated RT with and without cetuximab.220

It is important to reflect on the results of the past as we look to the future for continued improvements in HNSCC care. In 2000, Ries and colleagues published a report in *Cancer* on the status of cancer within the United States and indicated that oral cavity/pharyngeal cancer had one of the highest decreases in death rate of all cancer sites over the previous decade.221 Unfortunately, the opposite may be true for laryngeal cancer. The MACH-NC demonstrated that there was a nonsignificant increase in death for laryngeal preservation protocols compared with surgery followed by RT.169 In 2006, an analysis of the National Cancer Data Base (NCDB) confirmed that laryngeal cancer was the only cancer type that trended toward decreased survival when the 1990s were compared with the 1980s.222 More recently, an analysis of the NCDB that specifically examined advanced-stage laryngeal cancer from 1995 through 1998 showed increased survival for total laryngectomy compared with chemotherapy plus RT or RT alone, suggesting that clinical practice outcomes may differ from those of structured randomized trials.223 Although this dataset predated RTOG Study 91–11, vigilance must be maintained regarding the applicability of randomized controlled clinical trial regimens to wider clinical practice. Careful evaluation of the potential effects on survival as well as the likelihood of retained function must precede the use of organ-preservation regimens for advanced-stage laryngeal cancer. Just as resection of a structure that can be cured oncologically and preserved functionally with nonsurgical treatment does not seem reasonable, resistance to excision of resectable tumors that are likely to have poor residual function after organ-preservation CRT regimens is similarly problematic. This is especially true in the latter instance if the nonsurgical approach has the potential to result in decreased survival or increased morbidity. List and colleagues demonstrated that the top pre-treatment priority by far for patients with HNSCC was achieving a cure.224 Better pretreatment selection criteria, such as responsiveness to

induction chemotherapy or molecular markers, may facilitate the selection of optimal treatment modalities in the future. Inclusion of patients in clinical trials not only is encouraged but is necessary for continued advancement of the field.

Conclusions

In the inaugural year of *Cancer*, Karnofsky et al published the Karnofsky performance status scale as a means to quantify the activity levels of patients as affected by their disease.225 This scale still is used widely to describe the functional status of patients and to define eligibility for clinical trials (Fig. 4). Despite the continued application of the Karnofsky performance status scale, much has changed in the knowledge and treatment of cancer since 1948. In the earliest issues of *Cancer*, the 'Current Cancer Literature' section grouped oral cavity cancer with cancers of the stomach, liver, pancreas, and anus. Specialists dedicated exclusively to the treatment of head and neck cancer were nonexistent. Radiation often was delivered by dermatologists, and surgeons and oncologists had limited roles in the management of head and neck cancer. Today, each issue of *Cancer* dedicates an entire section to head and neck cancer, reflecting the consolidation and advancement of this field.

The development of novel chemotherapy regimens and targeted therapeutic agents potentially may improve locoregional control and overall patient survival. Large cooperative groups, like the RTOG, ECOG, SWOG, and EORTC, facilitate patient recruitment into multiinstitutional prospective randomized trials, which have provided us with the necessary data to define current and future standards of care. Efforts to identify biomarkers that predict disease behavior will continue as individualized therapy evolves. Validated quality-of-life measures further define treatment outcomes,226,227 and intensification of combined treatment likely will require significant attention regarding treatment-induced toxicities. The use of tobacco-related products remains significant globally, but additional etiologic factors such as HPV also affect HNSCC presentation, behavior, and treatment. Although progress has been made during the past 60 years, a great deal remains to be accomplished.

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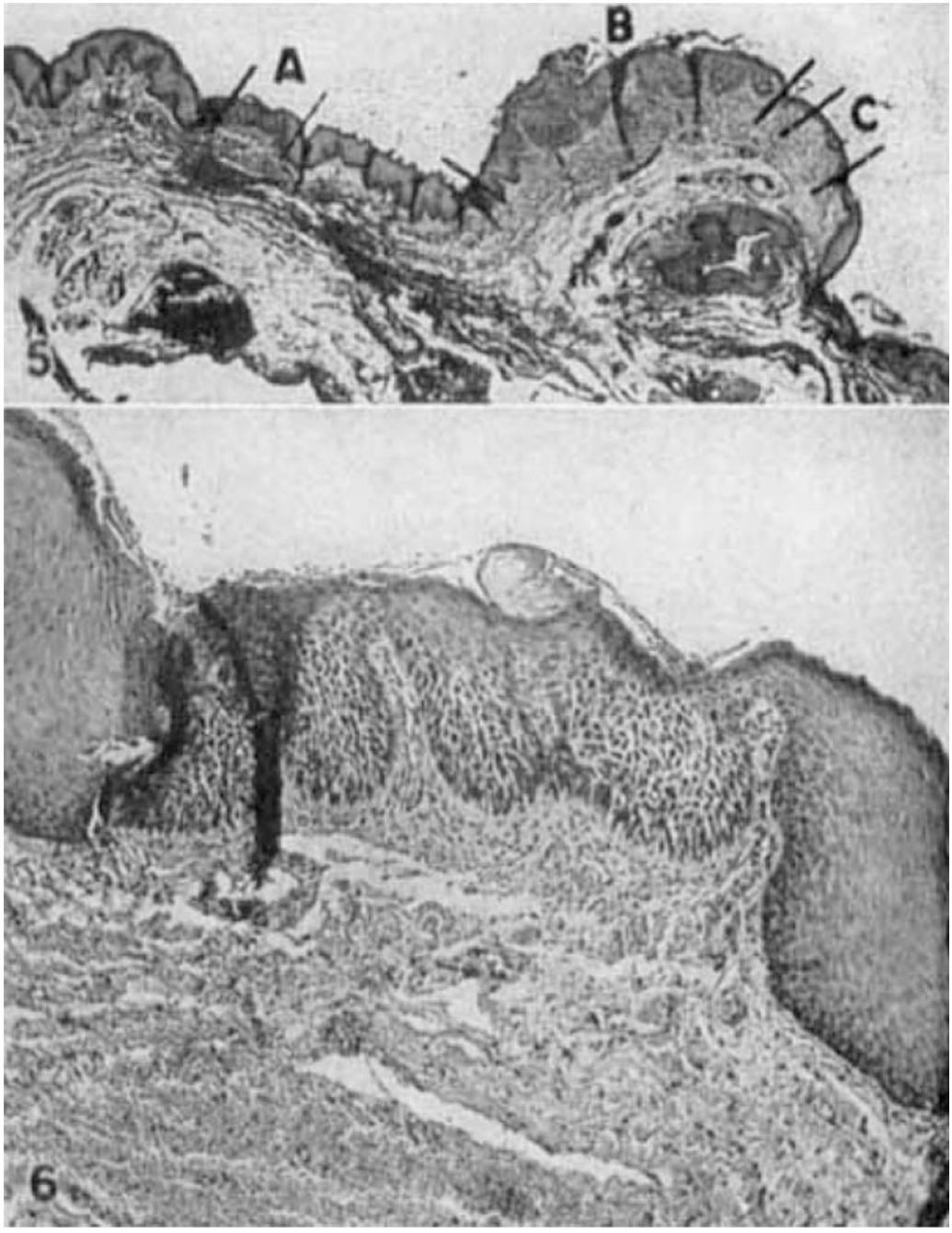

FIGURE 1.

Slaughter et al introduced the concept of ‘field cancerization’ in *Cancer* in 1953.6 This material is reproduced with permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc. *Cancer*. September 1953;6(5):963–968. Copyright 1953 American Cancer Society.

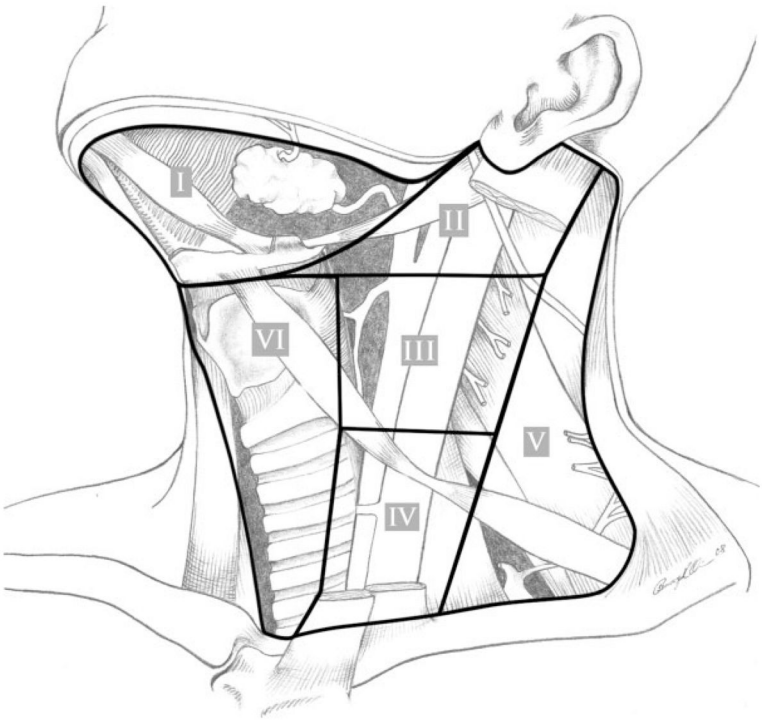

FIGURE 2.

Lymph node levels of the neck. A radical neck dissection (RND) includes all lymph node levels I through V as well as the internal jugular vein, the spinal accessory nerve, and the sternocleidomastoid muscle. A modified RND (MRND) includes the same lymph node levels as an RND but spares 1 or more of the nonlymphatic structures. The selective neck dissection preserves 1 or more of the lymph node groups normally included in an MRND. Therapeutic neck dissection refers to treatment for clinically positive disease. Elective neck dissection is for the prophylactic removal of lymph node levels based on the known risk of occult metastases.

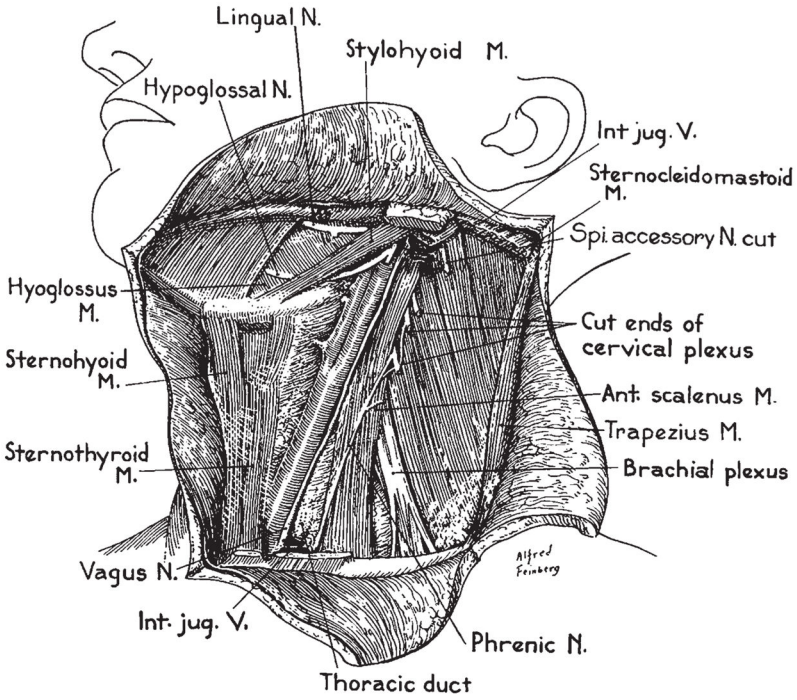

FIGURE 3.

The radical neck dissection as described by Hayes Martin in 1951.39 N indicates nerve; M, muscle; V, vein; Int. jug. V., internal jugular vein, Ant., anterior. This material is reproduced with permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc. *Cancer*. May 1951;4(3):441–499. Copyright 1951 American Cancer Society.

PERFORMANCE STATUS

Definition	%	*Criteria*
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

FIGURE 4.

The Karnofsky performance status score as introduced in 1948.225 This material is reproduced with permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc. *Cancer*. November 1948;1(4):634–656. Copyright 1948 American Cancer Society.

TABLE 1

Landmark Randomized Controlled Trials With Cisplatin With or Without 5-Fluorouracil

Year	Reference(s)	Cancer Type	Regimen
1991	VA Laryngeal Cancer Study, 1991163	Larynx	Induction cisplatin and 5-FU followed by radiation in responders vs surgery followed by radiation
1996	Lefebvre, 1996164 (EORTC 24891)	Hypopharynx	Induction cisplatin and 5-FU followed by radiation in responders vs surgery followed by radiation
1998	Al-Sarraf, 1998189 (Intergroup 00–99)	Nasopharynx	Concurrent cisplatin and radiotherapy followed by adjuvant cisplatin and 5-FU vs radiation alone
1999	Calais, 1999,190 Denis, 2004218 (GORTEC 94–01)	Oropharynx	Concurrent carboplatin, 5-FU, and radiation vs radiation alone
2003	Forastiere, 2003165 (RTOG 91–11)	Larynx	Induction cisplatin plus 5-FU followed by radiation in responders vs concurrent cisplatin and radiation vs radiation alone
2004	Cooper, 2004119 (RTOG 9501)	Oral cavity, oropharynx, hypopharynx, or larynx	Postoperative concurrent cisplatin and radiation vs postoperative radiation alone
2004	Bernier, 2004118 (EORTC 22931)	Oral cavity, oropharynx, hypopharynx, or larynx	Postoperative concurrent cisplatin and radiation vs postoperative radiation alone

VA indicates Veterans Administration; 5-FU, 5-fluorouracil; EORTC, European Organization for Research and Treatment of Cancer; GORTEC, French Head and Neck Radiation Oncology Radiotherapy Group; RTOG, Radiation Oncology Group.

TABLE 2

Important Head and Neck Cancer Publications in Cancer

Year	Reference(s)	Notes
1948	Karnofsky, 1948225	Introduction of performance status scale
1951	Martin, 195139	Description and application of radical neck dissection
1953	Slaughter, 19536	Concept of field cancerization
1956–1971	Hoffmann & Wynder, 197110; Wynder, 1957,11,15 195819, 1959,20 196817; Wynder & Hoffmann, 1959,12 1961,13 196914; Wynder & Mann, 195716; Wynder & Wright, 195718	Series confirming tobacco carcinogenesis
1960	Gould, 196064	Concept of sentinel lymph node biopsy
1972	Lindberg, 197250	Distribution patterns of cervical metastases
1987	Head and Neck Contracts Group, 1987161	Randomized trial of induction chemotherapy
1995	Shindoh, 199529	Identification of HPV in oral squamous cell carcinoma

HPV indicates human papillomavirus.