Multimodal Treatment for Head and Neck Cancer

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HEAD AND NECK CANCER

Head and neck cancer is a relatively uncommon malignancy, comprising 2% to 3% of all cancers diagnosed in the United States. In 2008, an estimated 47,560 patients were diagnosed with head and neck cancer, and an estimated 11,260 died of the disease. Fortunately, the incidence of smoking-related cancers appears to be declining in North America and Western Europe, possibly related to a decrease in smoking in these areas.

EPIDEMIOLOGY

Smoking increases the risk of head and neck squamous cell carcinoma tenfold, in a dose-dependent fashion. The association with smoking is strongest for laryngeal cancer, whereas the synergism between smoking and ethanol abuse is strongly linked to the development of hypopharyngeal cancer. Historically, smoking has been associated in the development of 80% to 90% of head and neck squamous cell carcinomas. The age-adjusted incidence of head and neck cancer has declined since the mid-1980s. Reductions in incidence are not uniform across all tumor sites however. In contrast to the decline in age-adjusted incidences of oral cavity, laryngeal, and hypopharyngeal cancers, a 2% increased incidence of base of tongue cancer and a 4% increase in tonsil cancer has been found.1 In addition, these cancers now are diagnosed more often in patients younger than 45 and in patients without the usual risk factors. Although the cause is unknown, there is mounting evidence that the human papilloma virus (HPV) is the etiologic agent responsible. The incidence of HPV-related oropharyngeal cancer has increased dramatically over the last 30. The observed improvement in clinical outcome for patients with oropharyngeal cancer over this period has been attributed to favorable tumor biology of HPV-related oropharyngeal malignancy1,2

TUMOR SITES

Head and neck cancers arise in the oral cavity (tongue and floor of mouth), oropharynx (base of tongue and tonsil), larynx (supraglottic and glottic larynx), and hypopharynx...
(pyriform sinuses and postcricoid region). Cancers of the larynx, hypopharynx, and floor of mouth are most strongly linked with a history of smoking (with or without alcohol abuse), while oral cavity and oropharyngeal cancers in patients without such risk factors are not uncommon.

MANAGEMENT OF HEAD AND NECK CANCER

In general, early stage disease may be managed with single modality treatment, while advanced stage disease is managed with multimodality treatment. Unfortunately, with the exception of glottic larynx and oral tongue cancers, most head and neck cancers remain asymptomatic until late in the disease course. As a result, most patients present with advanced-stage disease, with locally advanced disease or regional spread of cancer.

The management of head and neck cancer has changed over the last 20 to 30 years. Historically, most advanced-stage head and neck cancers were treated with surgery followed by radiation. Traditional surgical techniques, however, rarely resulted in functional organ preservation. Surgery for laryngeal and hypopharyngeal cancers most commonly involved total laryngectomy or laryngopharyngectomy with loss of natural speech, while oropharyngeal tumor extirpation frequently involved mandibulectomy or mandibulotomy approaches, and pharyngeal resections were associated with significant cosmetic and functional deficits. Until recently, cancer control using primary radiation was believed to be inferior to that of surgery, and radiation was itself associated with significant side effects. Nevertheless, incremental improvements in the nonsurgical management of laryngeal and hypopharyngeal cancer have led to primary radiation-based approaches being the preferred treatment for advanced-stage laryngeal, hypopharyngeal, and oropharyngeal cancers. In contrast, many significant morbidity associated with primary radiation to the oral cavity has led surgery to be the primary treatment modality for oral cavity carcinomas at most institutions.

ORAL CAVITY CANCER

Early cancers of the oral cavity (stages 1 and 2) may be treated with primary surgery or radiation with equivalent effectiveness, although primary surgery is favored at most institutions, and allows for a graded therapeutic approach permitting the use of adjuvant treatment in patients who have adverse pathologic features. For stage 1 and 2 oral tongue cancers less than 2 mm thick, partial glossectomy will be curative most of the time. The risk of occult regional spread of cancer increases when the primary cancer has a thickness greater than 2 mm, and observation of the neck in such patients, has been associated with treatment failure in almost 50% of patients, suggesting elective neck dissection is warranted. Patients who have adverse pathologic features on pathologic review of the surgical specimen require additional treatment.

Advanced stage oral cavity squamous carcinomas require multimodal treatment. At most institutions, radiation or chemoradiation therapy follows surgical ablation. Tumor extirpation most often is performed directly through the mouth. Mandibular resection may be required if cancer is fixed to the mandible or if bony erosion is identified. Following surgical ablation, various reconstructive options are available. For large resections, microvascular free-tissue transfer effectively restores soft tissue loss, and generates good cosmetic and functional results. Oral cavity resections may result in variable alterations in speech, but swallowing usually is well preserved, even when large resections are performed.

Most patients who have advanced staged oral cavity cancers will require adjuvant treatment. Pathologic findings following surgical resection determine the need for and
intensity of adjuvant treatment. In the presence of multiple positive nodes, perineural invasion, or angiolymphatic invasion, adjuvant radiation is recommended. In the presence of positive surgical margins or extracapsular spread in metastatic lymph nodes, more aggressive management may be recommended. Adjuvant concurrent chemoradiation has been found to diminish locoregional recurrence and improve survival relative to radiation alone in such high-risk patients.5–7

OROPHARYNGEAL CANCER

Oropharyngeal cancer treatment may involve primary surgical or radiotherapeutic approaches. For locally advanced disease (T3-4) or metastatic disease (N2-3), combined modality treatment generally is needed. No randomized studies for oropharyngeal cancer comparing primary surgery versus radiation have been done. Traditionally, these tumors were removed through the mouth if such an approach yielded sufficient exposure, but more often, external approaches were required. Mandibulotomy (splitting of the jaw) provided excellent exposure, but was associated with significant morbidity. Lateral pharyngotomy and transhyoid approaches were possible in select cases but resulted in dysphagia and the need for a temporary tracheotomy. To obtain adequate surgical margins, relatively large resections of apparently normal muscle and soft tissue were required. Functional outcomes were especially poor with total glossectomy, which frequently necessitated total laryngectomy to prevent life-threatening aspiration. In the absence of significantly improved local control with surgery, it became increasingly difficult to justify the perceived functional and cosmetic alterations following traditional radical surgery. As a result, nonsurgical approaches, perceived as being less morbid, have been increasingly employed for the management of oropharyngeal cancer.

Primary Radiotherapeutic Approaches for Oropharyngeal Cancer

To enhance locoregional control with radiation for locally advanced head and neck cancer, treatment intensification was pursued vigorously and tested in clinical trials over the last 30 years. Studies of accelerated and hyperfractionated radiotherapy demonstrated an improvement in locoregional control and survival.8–10 Locoregional control was improved further by the addition of chemotherapy.11 In 1987, the Radiation Therapy Oncology Group, and the Eastern Cooperative Oncology group in 1992 reported favorable results from combining standard radiation with concurrent high-dose cisplatin (100 mg/m²) given every 3 weeks during radiation for unresectable head and neck cancers. The use of high-dose concurrent cisplatin with radiotherapy was associated with an improvement in locoregional control and survival in patients with unresectable cancers. This approach subsequently was tested in resectable cancers, where it improved locoregional control but not survival.12,13 Other chemoradiation schemes also have shown promise. Local control in patients who have locally advanced disease remains suboptimal, however. In one study of oropharyngeal cancer treated with induction chemotherapy with carboplatin and paclitaxel followed by concurrent chemoradiation with paclitaxel, although an overall 3-year locoregional control rate of 82% was reported, greater than half of patients classified as T4 relapsed locally. In general, local recurrence remains a common site of failure. It is unclear that the aggressive use of multiagent systemic therapy, prior to or during radiation, will have an effect on this endpoint.15
Surgery After Radiotherapy

After the completion of radiation, a determination of the response to radiation both at the primary site and neck is necessary, but hampered by treatment-related changes. Imaging of the neck using a CT scan 4 weeks after the completion of radiation has been found helpful in identifying patients with residual cancer in the neck who would benefit from neck dissection. Findings on imaging studies of the primary site have been less reliable. Early operative restaging of the primary site performed 4 to 8 weeks after radiation has been associated with improved outcomes for patients requiring surgical salvage. Although the morbidity of surgery after failure of radiation is considerable and oncologic outcomes variable, effective salvage with acceptable operative complications has been reported.

Treatment-Related Toxicity

The intensification of nonoperative management has been associated with a dramatic increase in acute treatment-related toxicity and mortality. Gastrostomy tube placement is needed in most patients undergoing intensive treatment with chemoradiation as a result of inadequate oral intake caused by severe (grades 3 and 4) mucositis. Many centers advocate prophylactic feeding tube placement in head and neck cancer patients to prevent the rapid weight loss associated with aggressive treatment with chemoradiation. Reported treatment-related mortality rates of 2% to 5% are not uncommon. Such reports are all the more striking, because subjects in clinical trials tend to be relatively young and healthy. Trotti and colleagues identified systematic under-reporting of acute and late adverse events in head and neck cancer clinical trials, favoring high intensification treatment schemes. Aggressive chemoradiation regimens may not be tolerated well by average head and neck cancer patients, who as a group are not as motivated as those enrolling in clinical trials. Results of clinical trial results thus may not be generalizable, and clinical judgment is required when treating individual patients with head and neck cancer.

Novel strategies to ameliorate some of the chronic effects of radiation such as xerostomia and chronic dysphagia have been explored. Persistent xerostomia, virtually universal in patients treated with radiation, is ameliorated by using intensity-modulated radiotherapy (IMRT) to spare salivary glands from radiation toxicity, with patients reporting improvement in quality of life. The need to spare the contralateral parotid gland in patients requiring bilateral neck radiation is now an accepted indication for IMRT. Chronic dysphagia is common in oropharyngeal cancer patients treated with chemoradiation, with most patients being unable to resume unmodified regular diets. Silent aspiration is highly prevalent in this patient population. The use of chemoradiation also has been associated with an increased incidence of prolonged feeding tube dependence, with 5% to 25% of patients requiring nutritional support long after the completion of radiation. Using IMRT to spare specific structures important for swallowing function such as the pharyngeal constrictors or esophagus appears promising and is an active area of investigation.

The toxicity profiles of biologic agents make them attractive alternatives to traditional chemotherapeutic agents. Of the large number of agents currently under investigation, the epidermal growth factor receptor antagonist cetuximab has been studied most. A recent clinical trial of radiation therapy for advanced-stage head and neck cancer revealed improved survival in the group treated with concurrent cetuximab. Interestingly, the survival benefit was confined to patients receiving altered radiation fractionation. In the absence of a standard chemoradiation arm, results of this study are difficult to interpret. Nevertheless, the use of biologic agents in
combination with or as substitute for traditional chemotherapy with radiation is likely to continue to increase.

**Oropharyngeal Cancer and Human Papilloma Virus**

The relative incidence of oropharyngeal cancer has increased, particularly in subjects less than 45 years old. This increase in incidence has been accompanied by a decline in mortality and an increased prevalence of HPV in oropharyngeal tumor specimens. Although mortality from oropharyngeal cancer has declined, mortality rates for patients with oral cavity and laryngeal cancers have remained stagnant or increased. There is mounting evidence that HPV may be causally related to these observations. Patients who have HPV-related oropharyngeal cancers are believed to have an improved prognosis. In a prospective trial of 96 oropharyngeal cancer patients treated with chemoradiation, the overall 2-year survival was 95% for patients who had HPV-positive tumors, compared with 62% for patients who had HPV-negative tumors (P = .005). Risk stratification by HPV status likely will serve as the basis for treatment modification in future clinical trials for patients who have oropharyngeal cancer.

**LARYNGEAL AND HYPOPHARYNGEAL CANCER**

The indications for total laryngectomy have decreased over the last 20 years, as larynx preserving therapies have become standard of care. Laryngeal-preserving surgeries including open partial laryngectomy, and transoral approaches have yielded excellent control of disease in patients who have localized disease (T1-2N0). At this time, most patients with locally advanced disease or bulky nodal disease are treated with concurrent chemoradiation. The use of larynx-preserving surgery for advanced disease is currently an active area of investigation.

**Primary Radiation for Laryngeal Cancer**

In the United States, most patients who have advanced-stage laryngeal or hypopharyngeal cancer are treated with chemoradiation. Until the early 1990s, the standard treatment for locally advanced (T3-4) laryngeal cancer and hypopharyngeal cancer was total laryngectomy and laryngopharyngectomy, respectively. A landmark study conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group demonstrated the feasibility of a chemoradiation approach for laryngeal preservation. In this study, patients with stage 3 and 4 laryngeal cancers were randomized to induction chemotherapy using cisplatin and 5-fluorouracil followed by radiation for responders or an immediate laryngectomy. Using such an approach, the larynx was preserved in 64% of those treated with induction chemotherapy, without a difference in survival between groups. The European Organization for Research and Treatment (EORTC) conducted a phase 3 trial for hypopharyngeal carcinoma with a similar design. Induction chemotherapy selected a subset of patients who had advanced-stage pyriform sinus cancer for organ preservation without any apparent decrease in survival. A subsequent trial, the Radiation Therapy Oncology Group (RTOG) 91-11 trial, randomized patients who had laryngeal cancer to one of three groups: induction chemotherapy followed by radiation, concurrent chemoradiation using cisplatin, or radiation alone. In this study, concurrent chemoradiation improved locoregional control and larynx preservation compared with the other two arms. The morbidity of nonsurgical treatments of laryngeal cancer however was significant in this trial, and associated with a 3% risk of treatment-related death. The addition of chemotherapy to radiation was associated with a greater than threefold increase in acute toxicity.
burden without an improvement in survival.\textsuperscript{22} Thus, organ preservation comes at a cost.

**Indications for Total Laryngectomy**

Primary laryngectomy remains the best treatment option for some patients who have advanced laryngeal cancer. Patients who have laryngeal cancer must be capable of compliance and have an adequate performance status to undergo chemoradiation. Patients who have locally advanced larynx cancer, with cartilaginous destruction and organ dysfunction are also poor candidates for chemoradiation. Anatomic organ preservation in a patient who will remain tracheotomy tube- and gastrostomy tube-dependent is senseless. Care of the laryngectomy stoma is simpler, associated with less pain, and has little or no aspiration or problems with foul tracheal secretions.

Total laryngectomy also is indicated as salvage after failure of nonsurgical treatments. At this time, failure of previous therapy may be the most common indication for total laryngectomy. Salvage laryngectomy has been associated with an increased risk of wound complications, relative to those performed before radiation. Major wound complications have been reported in 27\% of patients, with a range between 5\% and 48\% in a recent review of the literature.\textsuperscript{21} Similarly, pharyngocutaneous fistulas have been reported in 15\% to 80\% of patients undergoing salvage laryngectomy, although the wound complication rates, fistula rates, and oncologic outcomes appear to be influenced by surgeon and hospital experience. Fistula may result in rupture of the carotid artery, a catastrophic and usually fatal complication of surgery in this setting, rarely seen in the absence of antecedent radiation. Referral of such complex patients to high-volume centers is recommended.

**LARYNGEAL PRESERVATION SURGERY AND MINIMALLY INVASIVE SURGERY FOR HEAD AND NECK CANCER**

Surgical extirpation may be accomplished with laryngeal preservation for many patients who have laryngeal cancer. For T1-2 and select T3 and T4 laryngeal cancers, avoidance of a permanent tracheal stoma is possible using laryngeal conservation surgery, which includes several procedures, including supraglottic partial laryngectomy, supracricoid partial laryngectomy, and others. In a supracricoid partial laryngectomy with cricohyoidepiglottopexy or cricohyoidopexy as described by Laccourreye,\textsuperscript{34,35} resection of the endolarynx is followed by impaction of the cricoid cartilage and hyoid bone. Acutely, the surgery is associated with swallowing impairment and aspiration. As a result, a temporary tracheotomy is required. Because the entire endolarynx is resected, wide surgical resection margins frequently are obtained, achieving high local control rates. Dufour reported laryngeal preservation rates of 90\% and local control rates of 91\% for 118 T3N0-3 laryngeal cancers.\textsuperscript{36} In general, larynx-preserving surgery is not offered to patients who are anticipated to require adjuvant radiation for tumor control, since radiation exacerbates airway edema and swallowing dysfunction, and increases the risk of chondronecrosis. Open partial laryngectomy, including supracricoid partial laryngectomy, are successfully used in the salvage setting with acceptable oncologic and functional outcomes in properly selected patients.\textsuperscript{37,38}

In contrast to laryngeal preservation surgery, performed through incisions in the neck, minimally invasive surgical approaches involve tumor ablation performed through the mouth. Typically, transoral approaches are associated with restricted surgical exposure. By means of technologic advances, many of these limitations have been overcome. The evolution of minimally invasive surgery for tumors of the upper aerodigestive tract began with the development of the CO\textsubscript{2} laser coupled to an
operative microscope initially described by Strong and Jako in 1972. The subsequent development of bivalved laryngoscopes and specialized endoscopic instrumentation enabled larger tumors from various aerodigestive tract sites to be removed transorally. Steiner and colleagues reported effective local control following endoscopic CO₂ laser resection for laryngeal, base of tongue, and hypopharyngeal cancers. Surgical resections were customized for the extent of the primary tumor. Transoral laser surgery was compared with Mohs micrographic surgery for cutaneous malignancies, in which tumor transection, followed by narrow margin extirpation with preservation of noninvolved tissue, was associated with high rates of local tumor control. Tracheotomies and feeding tubes rarely were required. Transoral robotic surgery using the daVinci Surgical System has been adapted for use in the head and neck, for extirpation of various upper aerodigestive tract cancers. The angled telescopes and wristed instruments used with robotic surgery significantly improve exposure and access. The use of the photonic gap band fiber, a flexible carbon dioxide laser fiber, has the potential to further enhance tumor extirpation. The CO₂ laser cuts through tissues with little bleeding or charring, and transmission through a flexible fiber enables laser delivery to previously inaccessible sites. Recovery from minimally invasive surgery is generally rapid. Bleeding in the postoperative period is while infrequent may be severe.

Functional outcomes following minimally invasive surgery are better than those following open approaches. For patients treated with minimally invasive surgery who do not require adjuvant treatment with radiation, rehabilitation from surgery is generally prompt and functional outcomes are expected to be excellent. The long-term functional outcomes of patients who require radiation and chemotherapy due to the presence of adverse pathologic features, or advanced stage disease, are not likely to be as favorable. Many patients requiring additional therapy could have been treated with primary radiation, albeit to a higher radiation dose. Does surgery contribute to local control? How much of a decrease in the intensity of adjuvant treatment yields a clinically significant difference in quality of life? Rigorous assessments of therapeutic trials incorporating surgery are lacking. Long-standing barriers to randomized clinical trials involving surgery, including patient preferences and institutional biases, will continue to pose challenges. A multicenter database registry with a well-defined cohort and standardized clinical protocol as described by Higgins and colleagues creating a well-defined study population would be a good start. In the absence of data, the role of minimally invasive surgery for advanced-stage head and neck cancer remains ill-defined.

SUMMARY

The multimodal treatment of head and neck cancer has been associated with improvements in locoregional control and organ preservation, but at the cost of significant acute and chronic toxicity. Various strategies to describe and quantify outcomes in a meaningful way, devise methods to diminish acute and late effects, and enhance quality of life are under investigation. Risk stratification may allow treatment modification based on tumor biology. The ultimate goal includes improved survival with preservation of function and quality of life.

REFERENCES


