CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Explain the impact of HPV infection on the incidence of head and neck cancer
- Explain the staging system used for head and neck cancer
- Describe the multimodal approach to managing head and neck cancer

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Understanding current and emerging therapies for HNC

Donald R. Fleming, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

Cancers that develop in and around the oral mucosa are collectively referred to as head and neck cancers (HNCs). Although the major risk factors (tobacco use and excessive alcohol use) and most prevalent population (persons older than 60 years) are well-known, a new patient demographic is emerging. A recently identified association between HNCs, particularly oropharyngeal cancer, and human papillomavirus (HPV) infection is reflected in increased incidence of oropharyngeal cancer in younger patients with no other risk factors. In addition, HPV status has an impact on response to treatment. This activity can help oncology nurses refresh their knowledge of the risks and treatments for HNCs, and keep pace with emerging trends in patient populations and new treatment approaches.

CE INFORMATION

Title: Understanding current and emerging therapies for HNC
Release date: December 31, 2013
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Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

Media: Journal article and Web site (myCME.com; OncologyNurseAdvisor.com; nphealthcarefoundation.org)

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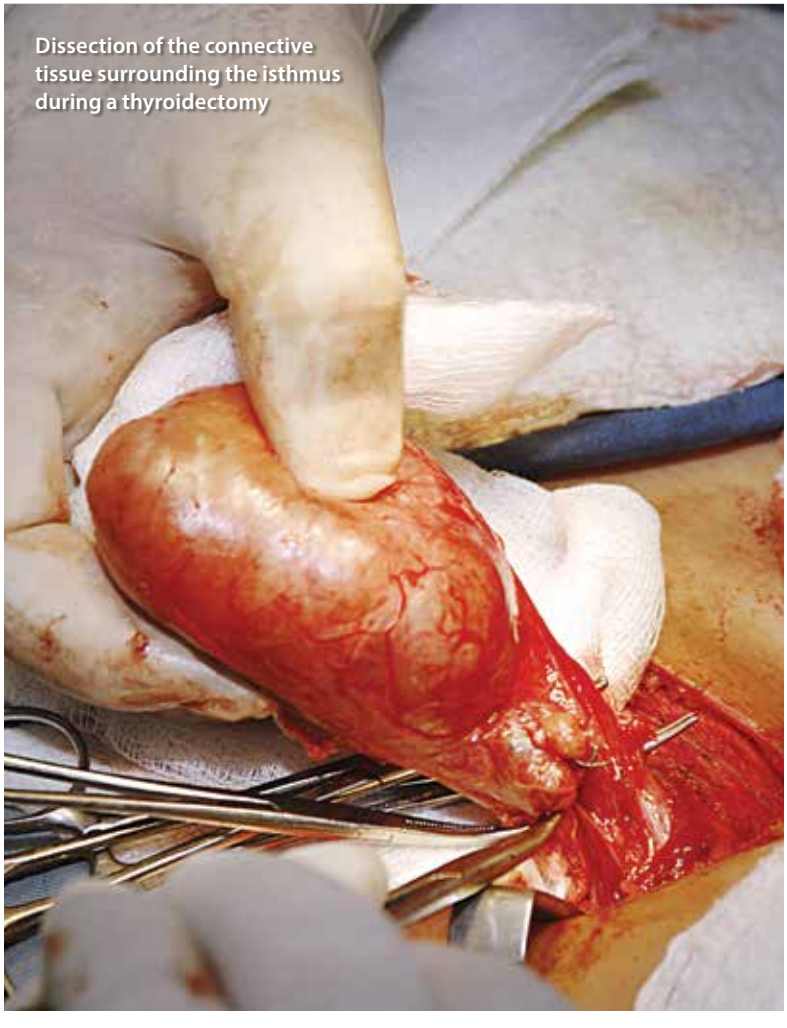
Understanding current and emerging therapies for HNC

Head and neck cancer treatments have high morbidity rates. Newer options reduce morbidities and offer patients better quality of life after treatment.



Dissection of the connective tissue surrounding the isthmus during a thyroidectomy

DONALD R. FLEMING, MD

The typical signs and symptoms that can arouse suspicion of cancers in the head, neck, and throat can lead to a delayed diagnosis, as they are manifestations of less morbid conditions. In addition, new associations have been discovered between potential causative factors and head and neck cancers (HNCs). Advances in radiation modalities, the advent of biologics, and evolving patient demographics challenge oncology clinicians to keep pace with a rapidly changing clinical environment.

The most definitive and significant risk factors for HNCs are tobacco use, excessive alcohol use, and poor oral hygiene. Further, recent research revealed that human papillomavirus (HPV) infection is also associated with these cancers, especially in younger patients.[1-5] Approximately 25,000 new cases of throat cancer are diagnosed in the United States each year.[2] The typical signs and symptoms that arouse suspicion of cancer in these areas are persistent cough, unexplained voice changes, persistent earaches, and an often-painless

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enlargement in the neck region.[6-8] This article provides a review of the anatomy, pathophysiology, and treatment options for head and neck cancers, with a focus on throat cancer. In addition, it will review recent findings on the association between head and neck cancers and exposure to HPV.

ANATOMY AND PHYSIOLOGY

Cancers within the head, neck, and throat, collectively referred to as HNCs, are pathologically similar. In medical parlance, throat cancer is a subset of HNCs that manifests along the 5-inch, muscular, tubelike structure (*pharynx*) that sits behind the nose and extends down to the anatomic voice box (*larynx*). Histologically, HNCs are squamous cell types. Consequently, cancers in the head, neck, and throat are treated similarly regardless of the precise tumor location.[6-8]

Cancers of the throat are referred to in subtypes: nasopharyngeal cancer (behind the nose), pharyngeal cancer (the back of the mouth), and hypopharyngeal cancer (the lower throat above the esophagus and trachea).[6,7] The remaining throat cancers manifest in the *glottis*, the opening inside the larynx between the true vocal cords. Glottic cancers are further classified as supraglottis and subglottis. The *supraglottis* is the upper portion of the larynx that extends upward from the glottis to the *epiglottis*, a flap that protects the trachea when swallowing. The *subglottis* is the area below the vocal cords and extends to the trachea.[2,9,10]

THE HPV CONTROVERSY

More than 100 types of human papillomavirus have been identified, but only a little more than a dozen types are associated with cancer, as opposed to being the cause of benign lesions, often referred to as *genital warts*. Types 16 and 18 are the most common cancer-causing HPV types. Whereas HPV16 and HPV18 cause cervical, anal, and penile cancers, only HPV16 has a confirmed association with oropharyngeal cancer.[11,12]

The choice of diagnostics for HPV has been debated. Various molecular testing techniques exist but a consensus on the optimal method is not established, as there are no reliable antibodies to the virus. Designation of p16 positivity by molecular testing is generally used in clinical settings and is believed to regulate the adverse prognosis *RB* gene, which is often unregulated in malignancies, to effect resistance. Reports show that up regulation of p16 expression via HPV downregulates/inactivates *RB* expression/activity.[11,12]

HPV-associated head and neck cancers usually involve the oropharyngeal region, including the tongue and the back of the throat.[13-16] Oropharyngeal cancer is historically prevalent in people age 60 years and older with a history of alcohol and tobacco product exposure. Currently, prevalence of oropharyngeal cancer trends toward an association with HPV infection in younger persons.[14] Although only 40% to 50% of nonsmokers with oropharyngeal cancer are HPV16-positive, more than 90% of those cancers are HPV16-associated.[16] Despite manifesting as larger tumors, the response to both radiation and chemotherapy is much better in patients with HPV-associated cancers than those with non-HPV-associated cancers.[13-16]

IDIOSYNCRACIES IN STAGING HNC

The American Joint Committee on Cancer (AJCC) delineates solid tumors in stages based on location of the primary tumor, nodal status, and metastasis. However, staging head and neck cancers is unique.[2,17]

Chemotherapy, often administered in conjunction with radiotherapy, was initially pioneered to avoid the need for morbid laryngectomy surgery.

Tumor (T) The greatest variation in staging is relative to the T status.[17] Stages T1, T2, and T3 are based on the size of the tumor in some cases (lip and oral cavity, oropharynx, and hypopharynx), but most are staged according to the structure(s) into which the tumor extends (eg, T1 nasopharynx tumors are confined to the nasopharynx; T2 tumors extend to the oropharynx and nasal cavity).

Nodal status (N) Staging nodal status is generally the same among the various subtypes, with nasopharyngeal cancer a lone exception.[17] Most notably, N2 status of HNCs is defined differently for tumors of the nasopharynx than for tumors on the other head and neck sites (**Table 1**). In addition, N3 status is includes two subcategories based on whether nodal metastasis greater than 6 cm extends to the supraclavicular fossa.[17]

Metastasis (M) Head and neck cancer is also somewhat unique in that stage IV disease may not be metastatic per se, but rather is locally advanced, unresectable disease. In almost all other malignancies, stage IV indicates distant metastasis.

Positron emission tomography (PET) is useful for staging HNCs at the start of treatment. PET is also useful for monitoring whether the cancer has remained in remission. Regardless of disease stage or treatment, diligent follow-up for evidence of recurrence is necessary for all patients regardless of disease stage or treatments used. Recent data demonstrated that a 12-week posttreatment CT/PET scan is very predictive of sustained disease-free survival.[18-20]

Continued on next page

TABLE 1. Nodal (N) staging for head and neck cancers

N stage	All sites except nasopharynx	Nasopharynx
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	• Metastasis in a single ipsilateral lymph node • Tumor ≤3 cm	• Unilateral metastasis in lymph node(s) ≤6 cm • Above the supraclavicular fossa[a]
N2	• Metastasis in a single ipsilateral lymph node, 3-6 cm OR • Metastasis in multiple ipsilateral lymph nodes, none >6 cm OR • Metastasis in bilateral or contralateral lymph nodes, none >6 cm	• Bilateral metastasis in lymph node(s), ≤6 cm • Above the supraclavicular fossa
N2a	Metastasis in a single ipsilateral lymph node 3-6 cm	
N2b	Metastasis in multiple ipsilateral lymph nodes, 3-6 cm	
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm	
N3	Metastasis in a lymph node >6 cm in greatest dimension	• Metastasis in a lymph node(s), ≤6 cm • Extends to supraclavicular fossa
N3a		>6 cm
N3b		Extends to the supraclavicular fossa

[a]Nonthyroid/salivary gland cancers

TREATMENT REGIMENS

As with most solid tumors, surgical excision is the treatment of choice. In some cases, however, adequate surgical margins are difficult to achieve without significantly impairing the swallowing mechanism; radiation therapy is preferred in these cases. Advances in robotic surgery have improved morbidity associated with surgical resection, especially for oropharyngeal tumors. As a result, definitive surgery is an additional option for early-stage cancers in this anatomic location, whereas combined chemotherapy/radiation (*chemoradiation*) were used in the past.[21]

Early stage disease Stage I or II HNC typically is fairly localized to where it originated; either resection or radiation alone provides effective treatment. Intervention is based on existing comorbidities, and at times, patient preference. A multimodality approach may be necessary if the lymph nodes or surrounding organs are involved (stage III or IVa disease or possibly metastatic stage IVb). However, most patients with stage IV disease and some patients with stage III disease are treated for palliative purposes only because relapse is likely and prognosis is poor. The goal is to minimize the side effects of progressive cancer.[6,7,22]

Complete resection of the tumor often results in extreme disabilities (eg, permanent tracheotomy, loss of functional swallowing); therefore, organ preservation is a strong secondary goal.[23,24] Chemotherapy, often administered in conjunction with radiotherapy, was initially pioneered to avoid the need for morbid laryngectomy surgery, after which the patient's inability to talk normally is permanent. However, this regimen still produces many side effects including extreme irritation or burning of the tissue treated and difficulties with swallowing for a long time afterward, possibly indefinitely.[23,24]

Advanced disease Chemotherapy for HNC consists primarily of regimens of cisplatin and fluorouracil (5-FU). More recent regimens incorporate alternative platinum-based drugs, such as carboplatin, and the taxanes (eg, docetaxel [Docefrez, Taxotere, generics] and paclitaxel [Abraxane, Taxol]).[25-27] Locally advanced disease (stage III or greater) requires aggressive therapy (ie, chemoradiation).

The effectiveness of preemptive or *induction* chemotherapy followed by chemoradiation, surgery, or both for locally advanced disease is controversial. The primary indications for induction chemotherapy are breathing or swallowing is compromised, comorbidities necessitate delaying other modes of therapy, and presence of T4 laryngeal lesions. In these patients, immediate improvement is desired to avoid clinical decline. HNC is immensely chemosensitive; therefore, induction chemotherapy is effective. In randomized trials, the TPF regimen (docetaxel, cisplatin, 5-FU) demonstrated optimal outcomes in this setting.[28] However, despite early evidence that radiation treatment ports may be reduced to a less morbid size, improved outcomes have not been demonstrated.

Radiation, with or without chemotherapy, is often needed after initial surgery to prevent disease recurrence. Although extracapsular invasion and positive margins mandate the additional therapy, no consensus of opinion is established on whether multiple sites of lymph node involvement and lymph vascular/perineural invasion are reasons for additional postoperative therapy.[25,26]

The initial effects of radiation are an acute inflammatory, painful response followed by permanent scarring of normal tissue, rendering the tissues dysfunctional. At the very least, xerostomia can result; in more severe cases, lifelong problems with dysphasia and odynophagia can result. Some patients may need to use a percutaneous endoscopic gastrostomy (PEG) tube for nutritional support permanently.

Advances in intensity modulated radiation therapy (IMRT) have changed how radiotherapy is used to treat locally advanced HNC. The computer-directed precision of IMRT reduces the radiation exposure to normal tissue surrounding the tumor. IMRT-based radiation therapy is more appropriate for early-stage and nasopharyngeal primary tumors, rather than large invasive primary tumors or bilateral lymph node involvement.[29,30]

Nasopharyngeal cancer Nasopharyngeal cancer deviates from the staging parameters used for other head and neck cancers.[31,32] Likewise, nasopharyngeal carcinoma is also an unusual exception in treatment approach. Induction chemotherapy with a platinum-based doublet regimen is a common initial therapy, followed by chemoradiation. Surgery plays little if any role in treating nasopharyngeal carcinoma outside of diagnostics. Weekly, low-dose, platinum-based therapies, as opposed to bolus dosing, are used only in high-level studies conducted in this setting.[32]

HPV-associated HNC Higher doses of chemotherapy may not be necessary for HPV-associated head and neck cancers, as these tumors tend to have a high sensitivity to older treatment modalities. Thereby, side effects can be avoided yet cure is still achieved. Researchers postulate that HPV infection downregulates the *RB* gene expression, as well as the p53 mutation effect on cancer cells; in return, the cancer cells are more susceptible to apoptosis when insulted with radiation and chemotherapy. HPV status may become an intricate part of treatment decisions based on this theory as nearly all clinical trials involving oropharyngeal cancers are being stratified based on HPV status to allow attenuation of therapy.[11,12]

A very recent discovery has led to the potential development of a medication that can block the ability of HPV to convert normal squamous cells to squamous carcinoma cells.[33] The results are very preliminary, but appear to indicate the protein E6 can interact with the p53 gene to prevent its conversion from a tumor suppressor gene to a powerful tumor promoter. If these results translate to clinical applications, even previously infected people may be able to minimize their risk of developing cancer.[33]

Another area of molecular testing that impacts patients with HNC involves gene mutations. Mutant-allele tumor heterogeneity (MATH) is a measure of the degree of genetic mutations and directly correlates with the prognosis for patients with HNC.[34] As the MATH score increases, the prognosis worsens. As one may expect, HPV-negative patients have a significantly higher MATH score than HPV-positive patients. This is a dynamic property of the tumor, as the more chemotherapy a patient receives the higher the MATH score can become.[34]

EMERGING OPTIONS

In recent years, targeted and biologic therapies have entered into the mix of therapeutic options. These agents target epidermal growth factor receptors (EGFRs), which are expressed by 90% of head and neck squamous cell carcinomas (HNSCCs). When activated, EGFRs promote cancer growth and metastasis.[35,36] Cetuximab (Erbitux) is currently the only EGFR inhibitor FDA approved for HNC. It is approved for initial therapy of locally advanced head and neck cancer, in conjunction with radiation.[37-39] The agent effectively inhibits the growth of head and neck cancer cells as monotherapy; however, its effect is more profound when combined with radiation. The agent also seems to enhance the activity of chemotherapy drugs such as cisplatin and, therefore, is also approved for use in conjunction with cisplatin for advanced/metastatic head and neck cancer.[37-39]

Panitumumab (Vectibix), an EGFR monoclonal antibody FDA approved for the treatment of colorectal cancer, is fully humanized and has no murine proteins; because of this, it seems to be less likely to cause the hypersensitivity reactions seen in some patients taking cetuximab. Early evidence in a recent study indicates panitumumab, which is not currently FDA-approved for HNC, was effective in patients with head and neck cancrs.[40] The randomized Spectrum trial showed that adding panitumumab to conventional chemotherapy for advanced HNC improved outcomes; however, HPV-positive patients did not seem to benefit from EGFR inhibition.[40] No trial to date supports combining an EGFR inhibitor with chemotherapy and radiation for locally advanced disease. The standard of care remains chemotherapy or radiation with an EGFR inhibitor but not both, as toxicity is increased but not efficacy.[41,42]

As in the emerging options for other solid tumors, biologics are likely to play an increasingly significant role in the treatment of HNCs.

Integrating alternative forms of anti-EGFR therapies such as oral tyrosine kinase inhibitors (TKIs) has had limited success when erlotinib (Tarceva) was used. Afatinib (Gilotrif), a combination EGFR-inhibitor and HER-receptor inhibitor, may prove more efficacious, but the data are not complete.[13,14] Nevertheless, as in the emerging options for other solid tumors, biologics are likely to play an increasingly significant role in the treatment of HNCs.

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Dental issues should be evaluated and corrected prior to therapy, especially if the prescribed regimen is chemoradiation.

SUPPORTIVE CARE

In addition to the psychological, social, and spiritual care needs of all patients with cancer, patients with HNCs may be challenged by side effects unique to the location of their tumor. Supportive care that minimizes or relieves the side effects of the cancer and its treatment is essential for a desired outcome. For example, impaired eating and swallowing are frequent side effects of HNC treatment. A percutaneous endoscopic gastrostomy tube is often placed prior to initiating therapy in anticipation of the risk for moderate-to-severe oral mucositis associated with radiation therapy. Patients undergoing concurrent chemotherapy and radiation are at higher risk for oral mucositis, and PEG tube placement ensures adequate nutrition can be maintained without interrupting treatment. Although preemptive PEG tube insertion is supported, nonprospective data indicate the practice delays recovery of functional swallowing. A central infusion access device is more universally utilized in patients undergoing chemotherapy.[43]

Dental hygiene is another form of essential supportive care. Patients with head and neck cancer should undergo a pretreatment dental consultation, preferably by a dentist or orthodontic surgeon subspecializing in head and neck cancers. Any dental issues should be evaluated and corrected prior to therapy, especially if the prescribed regimen is chemoradiation.[44]

CONCLUSION

Head and neck cancers represent a significant form of cancer. Treatment is often associated with extreme morbidity, and mortality rates in patients with HNCs are high. New interventions, however, including biologic therapy to treat and immunologic therapy that prevent these cancers, may significantly improve patient outcomes in the near future. As with all cancers, prevention by avoiding risk factors is the best defense against head and neck cancers. ■

Donald Fleming is an oncologist/hematologist at the Cancer Care Center, Davis Memorial Hospital, Elkins, West Virginia, and a member of the *Oncology Nurse Advisor* editorial board..

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