A major shift in the epidemiology of oropharyngeal cancer is leaving researchers and clinicians with a pile of questions and few answers.

Over the past decades, evidence has mounted that these cancers of the middle part of the throat are increasing, that many are associated with human papillomavirus (HPV) infection, and that HPV-positive oropharyngeal tumors have a better prognosis than HPV-negative ones. A major study in the New England Journal of Medicine (NEJM) in July confirmed that HPV-positive patients have better survival rates and strengthened the view of many researchers that this form of oropharyngeal cancer is a distinct disease entity.

In the study’s wake, some experts are calling for a different approach to treating the disease.

The NEJM study was a retrospective analysis of the association between tumor HPV status and survival among patients with stage III or IV oropharyngeal squamous-cell carcinoma who were enrolled in a randomized treatment trial (RTOG 0129). Some 64% of the patients (206 of 323) had HPV-positive tumors. Those patients had better 3-year rates of overall survival (82.4%) than those with HPV-negative tumors (57.1%). HPV-positive patients also had better progression-free survival (73.7% vs. 43.4%) at 3 years.

The authors, led by Kian Ang, M.D., Ph.D., a professor of radiation oncology at the M. D. Anderson Cancer Center in Houston, concluded that those results were “consistent with the hypothesis that HPV-positive and HPV-negative oropharyngeal squamous-cell carcinomas are distinct and have different causes, risk-factor profiles, and survival outcomes.”

The differences are striking. The main risk factor for HPV-positive throat cancer is multiple sexual partners. A potential cofactor is marijuana use. By contrast, HPV-negative cancer is associated with cigarette smoking, heavy alcohol use, and poor oral hygiene but not with sexual practices or marijuana.

Also, HPV-positive cancer tends to occur in younger, white, male patients. They present with smaller tumors, have a better performance status, are more responsive to chemotherapy and radiation, and have a lower risk of second primary cancers.

The two tumor types also have clear molecular differences: Nearly all HPV-positive cases express the viral E6 and E7 oncoproteins, which “may render the HPV-positive tumors more immunogenic,” wrote Douglas Lowy, M.D., of the National Cancer Institute, in an editorial accompanying the study.

New Trials

For clinical trials, head and neck cancers have traditionally been lumped together as a single disease entity. But experts now generally agree that future trials will have to be designed separately for HPV-positive and HPV-negative cancers.

Maura Gillison, M.D., Ph.D., a head and neck cancer specialist and researcher at Ohio State University in Columbus, and one of the authors of the NEJM study, said aggressive therapies—including aggressive chemoradiation and the addition of biologics—should focus on HPV-negative patients, whose prognosis is generally poor.

But for HPV-positive patients, researchers should look at less intense options that might spare them some of the long-term morbidities of concurrent chemoradiation.
Both the Eastern Cooperative Oncology Group (ECOG) and the Radiation Therapy Oncology Group (RTOG) are moving in that direction. ECOG recently launched the first trial specifically designed for HPV-positive patients, ECOG 1308, to test a less intensive regimen. “Perhaps we can take advantage of the increased chemoresponsiveness of HPV-positive disease by treating these patients with three cycles of induction chemo,” Gillison said. “Those with a complete response will then go on to receive a reduced overall dose of radiation.”

RTOG is planning two separate trials, one for HPV-positive and the other for HPV-negative patients, according to Ang. The group has approved a randomized phase III protocol for HPV-positive patients that will test the standard chemoradiation with cisplatin against radiation and cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor. “Our impression is that the latter is less toxic overall,” said Ang. “The question is, can we deintensify treatment so the patient will have fewer long-term side effects without compromising survival?” The trial is expected to take 4 years to complete accrual once it’s open.

For HPV-negative patients, on the other hand, “the emphasis is still on intensifying treatment,” Ang said. “The protocol is not finalized yet, but we’ll test whether adding a new agent to radiation, cisplatin, and cetuximab will improve the outcome.” That will be a phase I trial.

Gillison said the ECOG trial has already screened six patients for eligibility and is expected to complete accrual in 18 months,
“so I think we’re probably 3 years away from getting some preliminary data there.”

Several centers have their own smaller studies. The University of Chicago is conducting a randomized phase II trial, looking at decreasing the irradiated area in HPV-positive patients. “That may have benefits for swallowing and speech down the road,” said Ezra Cohen, M.D., who specializes in head and neck cancer there. “Our hope is that we’ll be able to maintain the cure rate while improving long-term toxicity.

“It’s a testable hypothesis—but it is a hypothesis,” Cohen stressed. “We don’t know the answer yet.”

Changing Practice
Some oncologists may already be deintensifying treatment for their HPV-positive patients, according to experts interviewed for this article. Gillison argues strongly against this practice, and David Adelstein, M.D., professor of medicine at the Cleveland Clinic, agrees. “There are no data to support changing current standards of care,” he said. “We’re just recognizing the importance of HPV-associated head and neck cancer and just starting to ask the questions. Answers are still years off.”

The National Comprehensive Cancer Network guidelines for oropharyngeal cancer state that HPV status may be valuable for prognostic information but “should not change management decisions, except in the context of a clinical trial.”

Adelstein also pointed out that HPV-positive oropharyngeal cancer patients are not a uniform population. For example, “smokers who are HPV positive have a less favorable prognosis,” he said. Indeed, many experts suggest stratifying oropharyngeal cancer patients into three groups on the basis of data from the recent NEJM study: high risk are all those with HPV-negative tumors; medium risk are HPV-positive patients with a history of smoking; and low risk are nonsmoking, HPV-positive patients.

While the cooperative trialists work on incremental improvements in existing treatments, laboratory research teams are working on a targeted drug. Lowy hopes that a treatment will be developed that targets a specific characteristic of the HPV-positive tumor cells, such as the E6 and E7 oncogenes. Nearly all HPV-positive oropharyngeal cancers express those genes, but normal tissue does not, so a molecularly targeted therapy that takes aim at them (or the proteins they encode) would have few, if any, side effects.

Prevention Issues
Myriad issues remain, not only for treating existing oropharyngeal cancer patients but also for screening, early detection, and prevention of this newly recognized entity, whose natural history is not well understood.

“There are a lot of unanswered questions,” said Adelstein. “What are the implications for behavior? How long do people carry the virus? How long are they infectious? Is there a way to screen for people carrying the virus?”

Right now no good ways exist of detecting oral HPV early or screening people to see who might be at high risk of developing an HPV-related oral cancer, although some researchers are working on oral rinses or brushing the back of the throat to collect exfoliated epithelial cells. “There’s no equivalent to the Pap test in the oropharynx,” said Adelstein.

One problem is that, unlike cervical, penile, and anal cancers, oropharyngeal cancer produces no identifiable precancerous lesion. Oropharyngeal cancers often begin deep in a tonsil or the base of the tongue and may be very small. Moreover, the existence of the virus by itself does not reliably predict progression to malignancy, because healthy oral mucosa often contains HPV.

Given the obstacles to screening and early detection, many experts say the focus should be on prevention—including expanding the use of existing HPV vaccines to presexual males as well as females—and on public education measures. Gillison and others had plans for a clinical trial of HPV prophylactic vaccines to prevent oral HPV infection, but they were derailed earlier this year. “We were 6 weeks from enrolling the first patient when I got an e-mail saying it was no longer in the interest of Merck to conduct the trial,” said Gillison.

Pam Eisele, a spokeswoman for Merck, manufacturer of the quadrivalent vaccine Gardasil, said, “The link between HPV infection and head and neck cancers continues to be an area of scientific interest for Merck; however, we currently do not have any plans to study the potential of Gardasil to prevent HPV-related oropharyngeal cancers. In 2008, we did conduct a small pilot study to assess our ability to obtain adequate and valid oropharyngeal samples. While the results of the pilot study were promising, due to competing research and business priorities we ultimately decided not to move ahead with an efficacy study at this time.”

Jeff McLaughlin, a spokesman for GlaxoSmithKline, which makes the bivalent vaccine Cervarix, said only, “[GlaxoSmithKline] does not have any planned studies for Cervarix in throat cancer.”

Gillison believes that Merck may be willing to supply the vaccine for a trial if alternative funding can be arranged. Meanwhile, researchers will be monitoring the epidemiology of oropharynx cancers as coverage of the two U.S. Food and Drug Administration–approved HPV vaccines increases over the coming decades.

“We’re pretty confident that the current vaccines for cervical cancer should work effectively against HPV-positive oropharyngeal cancer,” said Cohen. “It hasn’t been demonstrated yet, but everything we know about this disease indicates it should be prevented by these vaccines.”

John Deeken, M.D., director of the head and neck medical oncology clinic at Georgetown University’s Lombardi Comprehensive Cancer Center in Washington, D.C., agrees. “It’s going to be a while before we know if it works,” he said, “but it beats the alternative. We need to do a better job of public education, to get parents to give the vaccine to their children. Potentially,
that will not only prevent cervical cancer but also stop the rising tide of head and neck cancer.”

Ang isn’t so sure. Like everyone else, he’s waiting to see the longer-term results of the Merck and GlaxoSmithKline trials. “When we vaccinate against two or four strains of the virus,” he asked, “will it really prevent cancer, or will it cause other strains to take over—strains that are now less virulent and that may take longer to cause cancer? Until that question is answered, I’m not convinced we need to rush out and vaccinate boys.”

© Oxford University Press 2010. DOI: 10.1093/jnci/djq403