HPV a game changer in head, neck tumors

Karen Titus

December 2013—Not that any cancer is ever "easy," but until relatively recently, the culprit in head and neck squamous cell carcinomas was clear. The vast majority were caused by "smoking, smoking, and smoking," says William Westra, MD, professor of pathology, oncology, and otolaryngology/head and neck surgery, and associate director, surgical pathology, The Johns Hopkins Medical Institutions. Call this HNSCC's antediluvian era.
In the last decade or so, however, physicians have seen a surge in the HPV-related form of head and neck cancers. The impact on patients, pathologists, and clinicians has been compelling, to say the least. And the new era is only in its genesis.

Dr. William Faquin, left, and Dr. James Rocco will begin work with others on an evidence-based guideline for high-risk HPV testing in head and neck squamous cell carcinomas. Says Dr. Rocco, "We're rapidly approaching a time where HPV status is going to dictate what happens."

As with so many other cancers—breast, lung, colon—molecular insights now mean HNSCCs no longer fall into one conveniently labeled bin. Instead, they're distinguished by whether they're mediated by the human papillomavirus, which, among other things, has sparked no shortage of interesting conversations among physicians. One pathologist recalled the clinician who expressed surprise at learning of a patient's papilloma in the oral cavity, since the patient was "a good Christian woman." Another said that at many conferences, physicians shift into the role of patient, asking thinly veiled questions about their own lives: "You don't have to pay attention very long to figure out that the risk factor for this is something everyone in the room has done."

Tempting though it is to focus on sex, there are plenty of other, equally intriguing issues to draw pathologists' attention. What do laboratories need to know about HPV-related head and neck squamous cell carcinomas?

One of the first things to understand is that these tumors are clinically distinct from smoking-related cancers, says

Dr. Westra, who is also director of The Head and Neck Pathology Consultation Service at Johns Hopkins. They're associated with much-improved clinical outcomes, which has helped transform the pathologist's role. "It's my job not just to diagnose the presence of the cancer, but also to make this distinction. That's now a big part of what I do as a diagnostic head and neck surgical pathologist," he says.

For years, head and neck tumors primarily affected older individuals with a history of smoking and drinking. The tumors were aggressive, and they didn't respond well to traditional chemoradiation therapy. The good news is they've also been decreasing, due in part, perhaps, to a decrease in smoking incidence.

HPV-related head and neck squamous cell carcinomas, on the other hand, have been increasing fairly dramatically over the last few decades, says William Faquin, MD, PhD, director, head and neck pathology, Department of Pathology, Massachusetts General Hospital. Epidemiologically, they're different. They're more common in men, primarily middle-aged or older, who neither drink nor smoke. "And they usually have a history of sexual activity that would expose them to oral infection by HPV."

"Head and neck" might be a slight misnomer. The majority occur in the oropharynx, or tonsils and base of the tongue. It's a fact worth noting, since physicians don't always appreciate the difference.

When clinicians ask Margaret Brandwein-Gensler, MD, to perform HPV testing for head and neck cancers, her response is a pointed, "Why do you want to know?" Too often, the request is made for specimens from the oral cavity in general, rather than the oropharynx specifically, says Dr. Brandwein-Gensler, section head, surgical pathology, Division of Anatomic Pathology, Department of Pathology, The University of Alabama at Birmingham. "Oral cavity and oropharynx—they sound alike, right?" she says with a laugh. "But there's a big difference in how we treat those two sites."

Dr. Westra, too, sees increased interest in HPV testing among his clinical colleagues. That's not entirely good. As more physicians tune into the importance of HPV status in head and neck cancers, Dr. Westra says, many are ordering HPV testing on all such cancers, regardless of anatomic subsite. Because HPV-related HNSCCs are restricted in distribution to the oropharynx, there's no role for HPV testing outside that site, he says, such as the oral tongue or lip.

Interestingly, says Dr. Faquin, the tonsils are a specialized structure related to the immune system and antigen presentation. They're covered by squamous epithelium, which has specialized crypts where the squamous epithelium dips down underneath the surface epithelium. Deep within these crypts the squamous epithelium transitions into more of a lymphoepithelial-lined mucosa. "There's an intimate association between the crypt-lining epithelium and the surrounding lymphocytes," says Dr. Faquin. It's here that HPV causes infection and the development of HPV-related squamous cell carcinomas.

This is no mere biology lesson, he hastens to add. "For all clinicians, it's important to understand that the HPV-related squamous cell carcinomas are developing in these deep crypts. If there's a clinical exam done by an ENT doctor, for example, they will often not see any abnormality, because these cancers can be very small." Like Achilles lounging in his tent, they're hidden from view.

Some physicians play the curiosity card when they ask for HPV testing, Dr. Brandwein-Gensler says. "They have this idea of, 'W-e-l-l, I just want that information. Maybe I can do something with it. Maybe I can use it in a study.'" In such cases, HPV status is less of a testing issue than one of clinician education. "People are well-meaning," she says diplomatically. "They're hearing HPV is a big deal, and they're interested." But they need to understand that HPV testing in clinical settings needs to be driven by laser-like focus, rather than good-hearted expansiveness.

Adds Dr. Westra: "Even among my clinical colleagues here at Hopkins, still a very fundamental question is, 'When should I perform HPV testing?' And how?"

As Dr. Brandwein-Gensler suggests, "Why?" is another question worth posing.

One reason is that HPV status—high-risk HPV specifically—is perhaps the most powerful prognostic indicator for patients with head and neck cancer. Of three major retrospective analyses, in which researchers looked at HPV-positive versus -negative tumors in patients who received the same treatment, patients who were positive did about three times better in terms of overall survival: 80 to 85 percent versus approximately 35 to 38 percent. “To the outside world, these tumors would look the same,” says James Rocco, MD, PhD, the Daniel Miller Chair of Otology and Laryngology, Harvard Medical School, and director, head and neck research, MGH.

While there are many types of high-risk HPVs, some 95 percent or more are type 16. Any lab that tests for HPV-related HNSCC will need an assay that can pick up that type, “but you also want to be open to detecting other high-risk types,” says Dr. Faquin. Low-risk types, most commonly 6 and 11, can cause laryngeal papillomatosis. While this can be a morbid disease and is frequently seen in pediatric ENT pathology, low-risk HPVs do not lead to cancer.

HPV testing can also help localize the primary site of tumor origin for patients who present with metastatic disease. One unusual aspect of these tumors, says Dr. Westra, is that they often arise in the tonsils and are sometimes so small that they elude clinical and radiographic detection. “It’s not uncommon for the patient to present with an enlarged cervical lymph node,” Dr. Faquin says. When an FNA is performed on these lymph nodes, the diagnosis is a metastatic, nonkeratinizing SCC. “If you can tell the clinician that this metastatic squamous cell carcinoma in the patient’s cervical lymph node is HPV related—and specifically high-risk HPV-related—they know with a fair degree of certainty that the cancer is coming from the oropharynx.”
This, in turn, can affect treatment, Dr. Faquin says. If the site of origin is identified as the oropharynx, then radiotherapy can be directed more specifically to that spot, rather than irradiating a patient in a wider range of the head and neck structures.

“At the same time,” he continues, “because HPV status is so important now, both in terms of prognosis and, in the very near future, actually directing specific therapy, we have been advocating for routine testing of all cancers arising in the oropharynx.”

Indeed, says Dr. Rocco, “We’re rapidly approaching a time where HPV status is going to dictate what happens,” including possible deintensification of therapy.

Some suggest that HPV-positive and HPV-negative tumors also differ in their rates of distant relapses. Dr. Rocco calls it “an anecdotal feeling” among many who treat people with head and neck cancers that the metastases from HPV-related disease seem to behave slightly differently than those from HPV-negative tumors. For a traditional patient with head and neck cancer, the risk of distant metastases is under five percent, says Dr. Rocco. When they do occur, it’s usually after a bilateral, bulky neck adenopathy; they almost always go to the lung.

In HPV-related tumors, published data indicate the rate of distant metastases is similar—about three percent. “What’s different is you don’t necessarily need to have this big, bulky disease or advanced disease for it to happen,” Dr. Rocco says. It also seems to occur in different locations. In his own practice, Dr. Rocco sees maybe one to three cases of distant mets annually. “I don’t think I’ve ever seen distant mets go to the cervical spine in my old practice—pre-HPV—but I’ve seen that happen with HPV,” he says. “I’ve seen brain mets, and liver mets, and spine mets, which I’ve never seen before.”

“But remember: The numbers are small,” he says. And about 80 percent of the patients he cares for who have head and neck cancers have HPV-related tumors; at his institution overall, about 90 percent of patients with oropharyngeal cancers have HPV-related tumors. The numbers, in short, are skewed—clinicians aren’t seeing an equal number of non-HPV-related HNSCC. “So that could be fooling us as doctors into drawing conclusions that aren’t there.”

Dr. Westra

Given the importance of knowing HPV status, should all head and neck squamous cell carcinomas be tested for HPV? “So many pathologists come up to me when I’m lecturing at various meetings and want to know that,” Dr. Faquin says.

The answer is yes—if they’re from the oropharynx. At Johns Hopkins, high-risk HPV testing is done reflexively on all oropharyngeal cancers. But for nearby squamous cell carcinomas—the lip, the oral tongue, the nose, the buccal mucosa—the answer is no. At these other head and neck sites, the risk of having an HPV-associated squamous cell is low.

“That’s not to say it doesn’t happen,” Dr. Faquin concedes. But the rate of HPV-associated squamous cell carcinomas in the oropharynx dramatically dwarfs the risk in other sites in the head and neck—with one exception. There is, says Dr. Faquin, a highly unusual group of mostly high-grade tumors that occur in the sinonasal tract, about 25 percent of which are HPV-related. The HPV association doesn’t appear, for now, to impart the improved prognosis it does with oropharyngeal cancers. “It’s a different beast,” Dr. Faquin says. “The only place right now where HPV makes a difference, where it’s efficient to test, is the oropharynx.”

Then there’s the matter of how.

Laboratories have plenty of testing options, but no one clear choice. “If you were to ask me what is the standard, what is the consensus—well, there is none at this point,” says Dr. Westra.
In the not too distant future, this should change. Dr. Westra is part of a CAP panel (headed by Dr. Faquin) that will establish an evidence-based guideline for appropriate testing—both surgical pathology and cytology—for high-risk HPV in HNSCC. The panel includes clinical and epidemiologic experts as well as pathologists.

Until then, labs will need to weigh the strengths and limitations of current assays. The most sensitive and specific assay for HPV detection in clinical samples is an RT-PCR assay for the presence of viral messenger RNA transcripts of the E6 and E7 viral oncoproteins, says Dr. Westra. “In fact, that’s really the gold standard by which all these other assays are measured. The problem is, it’s a very sophisticated assay, which at this point is restricted to the research laboratory.”
By far the most common molecular tests are PCR-based amplification and DNA in situ hybridization. The two tests are widely available and widely used in most U.S. labs, thanks to their efficiency, relative ease of use, and cost-effectiveness.

PCR amplification of HPV DNA is very sensitive, Dr. Faquin notes, but it’s less specific than in situ hybridization. But ISH is less sensitive.

There’s also the ever-popular immunohistochemistry—speedy, inexpensive, routinely used—to evaluate p16 expression, which is used as a surrogate marker for high-risk HPV infection.

At Hopkins, any oropharyngeal primary tumor automatically initiates HPV testing. The p16 IHC and DNA ISH are performed concurrently, the latter using a type 16-specific probe. In addition to those two tests, Dr. Westra says, “I should add routine microscopic evaluation—HPV-related cancers have a very distinct microscopic appearance. I’m to the point I don’t need additional stains,” he says with a laugh. “I can now look at a tumor and pretty much have an idea of whether it’s HPV-related or not. But we need to integrate all this information.”

At MGH, the testing routine for oropharyngeal cancers is also fairly straightforward, says Dr. Rocco, who is also part of the CAP guideline panel. All cases undergo p16 immunohistochemistry testing, and many are also tested for in situ hybridization against high-risk HPVs.

If the gods are smiling, IHC and ISH results will be in concordance. Usually, the gods are indeed munificent. But not always. In these rare cases, the next step would be to retest the tumor using a much broader spectrum DNA ISH probe, one that covers a dozen or so of the most common types of high-risk HPV.

“Are these tumors really infected with high-risk HPV?” Dr. Faquin asks. “I’ve discussed this with other experts in the field. The thinking is that many of these cases are truly high-risk HPV infected. But maybe the DNA copy number is low,” making it more difficult to detect with the less-sensitive ISH test.

The other possibility, he says, is that the lab may be dealing with one of the rare types of HPV that may not be included in the assay’s “cocktail.” Incongruent results may also be due to a rare technical failure—a cut from the tissue block may not contain tumor cells, for example.

Such conflicts are rare, like in a ‘50s family sitcom. When they do occur, says Dr. Rocco, the tumor is almost always p16 positive and ISH negative. “It’s a sensitivity issue,” he says. “I think the p16 immunohistochemistry is more sensitive than HPV-16 in situ hybridization.”

Sometimes the problem stems from testing tumors that are outside the oropharyngeal site. As Dr. Rocco notes, other tumors can contain subcutaneous squamous cells and be p16 positive by IHC. “But it’s not the classic look [of an HNSCC], and it’s not at the site. Usually, if it’s in the oropharyngeal site, there’s strong correlation. Very, very, very, very strong correlation,” says Dr. Rocco.

In maybe three to five percent of the cases, p16-positive, ISH-negative cases can’t be explained by technical failure. “We usually report them both,” says Dr. Rocco. “And what we do next depends on what we think is going on.”

If the case is a “pure” oropharyngeal cancer, as Dr. Rocco puts it—tonsil, base of tongue, white male, nonsmoker—“there’s an overall assessment that that’s probably an HPV-related head and neck cancer. On the other hand, if you found that scenario in the oral cavity, hard palate, or buccal space—something outside the oropharynx—there would be more skepticism,” he says.

Given the usually close concordance between p16 IHC and HPV ISH, is it reasonable to rely solely on p16 testing?

It is a robust biomarker and robust predictor, says Dr. Brandwein-Gensler. She and her colleagues conducted a study (Schlecht NF, et al. Mod Pathol. 2011;24:1295–1305) looking at 110 prospectively collected fresh cancer specimens from all three major head and neck cancer sites—oral cavity, oropharynx, and larynx—comparing the sensitivity and specificity of three tests (two direct, one indirect) for HPV detection. One conclusion, says Dr. Brandwein-Gensler, is that there was a moderate to strong degree of p16 overexpression in both the nuclear and cytoplasmic component of the tumors. “That was an excellent predictive ability as compared to RT-PCR,” she says.

But that’s not to say p16 alone can direct clinical decisions. “Not at this point,” Dr. Brandwein-Gensler says. The research is promising, but it’s still research.

Dr. Rocco says p16 alone might be a reasonable approach, but he packs that notion with plenty of caveats. The patient must be a nonsmoker, with a robust and characteristic classic oropharyngeal cancer. And he throws in another caution: Current NCI guidelines say that therapy should not be changed based on HPV status.

Even if p16 does prove worthy as a sole test for high-risk HPV, says Dr. Faquin, “the problem is that some folks are using it outside the oropharynx.” At that point, clinical usefulness begins crumbling, because the test is no longer specific for high-risk HPV. As an example, p16 is often positive in benign neck lesions such as branchial cleft cysts, which is one of the more common clinical scenarios Dr. Faquin encounters. “I field a fair number of consults where these metastatic squamous cell carcinomas of the head and neck are misinterpreted as a branchial cleft cyst.” These cystic squamous lesions tend to occur more in younger individuals, he says. “When you see [one] in a

middle-aged or older patient, metastatic squamous cell carcinoma should be included in the differential." Additional testing is needed in these cases; ISH or PCR analysis would be appropriate, as would Ki-67 immunohistochemistry, since the ancillary marker is usually elevated in these cases.

And, Dr. Faquin continues, there are other types of carcinoma besides squamous cell carcinoma that are positive for p16, including some small cell carcinomas of the lung. In short, using p16 alone to look at potentially metastatic disease might fool physicians. Is it HPV-related? Or is it a tumor whose mutations result in p16 overexpression? Moreover, he says, p16 is not specific enough for metastatic lesions.

As a final caution, Dr. Faquin says that he sees cases where p16 results are misinterpreted, even though it's a basic immunohistochemical test. Both cytoplasmic and nuclear staining of the tumor cell are required for a result to be considered positive, and 50 to 70 percent of tumor cells should be stained positively. But a cell block may contain only a small percentage of the tumor. "For all practical purposes, you can't make an estimate of what percentage of the tumor is staining positively with p16 if you use it on a cell block. For that reason, it may not be appropriate to use p16 as a surrogate marker of HPV in cell block material." The p16 stain itself will often stain the cytoplasm, he explains, which can lead to the false impression that the nucleus is also being stained. "You have to be very, very careful to look specifically for nuclear staining."

Nevertheless, Dr. Faquin sounds optimistic about p16's future role. "Going forward we may find, when we look at the evidence, that p16 is sufficient. That would be great, because a simple, very inexpensive immunohistochemical test would be fantastic."

Cytology testing of FNA specimens will likely play an important role in the future as well, says Dr. Faquin. Because so many HPV-related HNSCCs present as metastasis in a cervical lymph node, they're oftentimes detected through fine needle aspiration.

Dr. Faquin lists the five currently available tests to detect HPV in cytology:

• *Cervista HPV.* This uses Invader chemistry to amplify and detect specific nucleic acid sequences. The assay is essentially two tests: Cervista HPV 16/18 identifies HPV types 16 and 18, the most common high-risk types; Cervista HPV HR assay targets 14 high-risk HPV types, including 16 and 18.

• *Hybrid Capture 2.* This is an in vitro nucleic acid hybridization test that uses microplate chemiluminescence for detecting 13 different high-risk types of the virus, though it doesn't distinguish which type. "Right now there is no particular advantage for the patient to know which type they have. That may change in the future," Dr. Faquin says.

• *Roche Cobas HPV.* This PCR-based assay also identifies types 16 and 18 specifically; otherwise, results are categorized as high risk or not.

• *Aptima HPV.* This targets the E6 and E7 mRNA.

Any of these tests could be validated by a laboratory to detect high-risk HPV in cytology samples of HNSCCs, Dr. Faquin says. All are widely available and fairly cost-effective. There are slight differences in sensitivity and specificity. "But overall they all tend to perform fairly well for detecting high-risk HPV." Published studies are now starting to compare the Cervista and Roche Cobas to standard surgical pathology methods of in situ hybridization and PCR, but validation studies have yet to emerge for the other cytology assays. "We need them. Because in the future, more and more cytology [will] be used" for FNAs of the cervical lymph node, Dr. Faquin predicts.

Large academic centers are routinely testing FNAs of metastatic squamous cell carcinoma in the head and neck, of unknown primary, for high-risk HPV, Dr. Faquin says. While no recommendation for this exists, the CAP group will address it. "I would predict we would recommend it," he says.

Even though the majority of people with HPV-related HNSCC do well, what about the 10 to 15 percent who don't? What is so unique about these HPV-related cancers that they don't respond the way the others do? "That's an area of very active investigation, looking at additional genetic alterations that may help explain that very different clinical behavior," Dr. Westra says.

The Bcl-2 protein might provide clues. When Dr. Rocco and colleagues looked at Bcl-2 immunohistochemistry, they found it was an independent variable alongside HPV status. Used together, Bcl-2 and HPV status could better identify whether a patient's therapy might fail than HPV status alone.

The problem, says Dr. Rocco, is that Bcl-2 is an anti-apoptotic protein. To explain how Bcl-2 functions, he uses the following model: Think of Bcl-2 as a cup, he says. If Bcl-2 levels are low, that is, if the cup is small, then a cell being treated with chemotherapy will overflow with the toxic liquid caused by chemo and kill the cell. If the Bcl-2 cup is big, however, the liquid won't overflow, and the tumor cell will remain alive. "When we do immunohistochemistry against Bcl-2, we're saying to ourselves, 'Is the cup big or small?'" Dr. Rocco says. But IHC can't measure another variable: Is the cup already full or empty? Dr. Rocco and colleagues are starting to address that question using an experimental, live-cell assay developed by Anthony Letai, MD, PhD, at Dana-Farber Cancer Institute.

Dr. Rocco and colleagues are also looking at how next-generation sequencing might fit into the picture. It might, he says, address one of the more vexing issues of HNSCCs—tumor heterogeneity, which isn't easily identified under the microscope. "They're poorly differentiated," he says. Next-gen sequencing has allowed them to take a so-called read depth, allowing researchers to tell from multiple reads what percentage of tumors have mutations, and to develop a qualitative measure of genetic heterogeneity called MATH, for mutant-allele tumor heterogeneity (Mroz EA, et al. Cancer. 2013;119:3034–3042).

"What we found was interesting," Dr. Rocco says. HPV-positive tumors tend to be very homogeneous, which might explain why HPV-positive tumors tend to respond so well to therapy. Tumors that are heterogeneous, on the other hand, are likely that way because of a lifetime of smoking and drinking (by the patient, not the tumor), leading to genetic change and proliferation.

But won't HPV status alone reveal that? "The interesting thing is that this measure of intra-tumor heterogeneity can divide between high- and low-risk groups," Dr. Rocco answers. The tumors with low MATH (that is, more homogeneous) and HPV positivity were 100 percent cured; those with high MATH "were where we found our failures."

MATH also offered insight into HPV-negative tumors. Even though these tumors tend to be very heterogeneous, "When you find an HPV-negative tumor that's homogeneous, it actually does very well," Dr. Rocco says.

Such findings suggest that the MATH score, and not HPV status, might be what determines response to therapy, he says. "This measure of intra-tumor heterogeneity is probably a very important biomarker." Dr. Rocco and colleagues will look at this next, this time in a prospective trial. "We always say a lot of great things that are figured out retrospectively then crash on the shores of a prospective trial," he jokes.

Other groups are looking at alternative testing methods. While mass spectrometry appears to be too sensitive for clinical use, RNA sequencing looks like a promising means of identifying p53 mutations in the oropharyngeal subsite; p53 is the most commonly mutated gene in head and neck cancers.

Another hot research topic is the role of a person's immune response to these tumors, says Dr. Westra. It's thought that one reason people with HPV-related HNSCCs do well is because their own immune-host reaction is able to mount an immune response. If researchers could unravel the immunology behind the tumors, he says, it might be possible to "rev up" immune response by way of tumor clearance, potentially via therapeutic HPV vaccines.

All those possibilities lie on a distant horizon. That's not the case with deintensification (also known as de-escalation) of therapy. Current treatments for head and neck cancers are highly toxic, with short- and long-term

complications. “So the big question now facing this epidemic of HPV-related head and neck cancers is, Can we back off some of that very toxic therapy and still maintain those very favorable clinical outcomes?” Dr. Westra asks.

In the past, the traditional patient with HNSCC who was lucky enough to be among the 30 to 40 percent who survive was likely to die of another disease related to a lifetime of smoking, such as stroke, heart attack, or lung cancer. Few one- to two-pack-a-day smokers live to be 70, Dr. Rocco points out.

Put another way, the morbidity of HNSCC treatments took a back seat to survival. “Not to say that we wouldn’t want to lower the morbidity of treatment in all patients,” Dr. Rocco says. “The feeling was you weren’t going to cure a high percentage of them, and they weren’t likely to live another 20 years to suffer through all the long-term side effects.”

Now the situation is different. Dr. Rocco describes the classic “new” HNSCC patient: a biotech CEO, aged 45 or 50, who runs the Boston Marathon and who’s never smoked a cigarette in his life. Such a patient, when given radiation and chemotherapy, has a 90 percent cure rate; with no other health problems, life expectancy is 90. Long-term consequences will weigh heavily on such patients.

The one physicians worry about the most, Dr. Rocco says, is disruption of saliva production. Teeth get about half their nutrients from saliva, it’s now known, and when the quality of saliva declines, dental problems ensue. “It’s very unusual to look at somebody five to eight years after having head and neck radiation and see a full set of normal teeth.” Related inflammation has also been associated with heart disease; in extreme cases, osteoradionecrosis occurs, dissolving the jaw. Lack of saliva can also lead to severe swallowing dysfunction, requiring, in some cases, enteral nutritional support.

Patients sometimes develop skin fibrosis of the neck, causing stiff neck, hard, rough skin, and an unattractive appearance. “It’s uncomfortable for the patient,” Dr. Rocco says. Traditional therapy can also expose the carotid artery to radiation, potentially accelerating arteriosclerosis and increasing the risk of stroke. “It could be a ticking time bomb,” Dr. Rocco says.

All these problems are dose-related: The higher the dose, the worse the side effects. “If HPV-related head and neck cancers are so curable, then maybe we can give a lower dose,” Dr. Rocco says. “We’re guessing. We’re hoping. We don’t know.”

Deintensification should not be done without evidence to support it, Dr. Rocco cautions, though he says “there’s a feeling that there’s kind of a grass-roots movement where people are doing this.”

But clinical trials may not easily yield answers, either. It’s a matter of statistics. A typical starting point for a clinical trial would be to look for a five percent improvement in five-year survival with 80 percent certainty, says Dr. Rocco. Each arm—one with traditional radiation and chemotherapy and one with just chemotherapy—would need about 385 patients. If the survival rate is 90 percent, as is the case with HPV-related HNSCC, each arm would need 700 to 800 patients. “The likelihood of that happening in head and neck cancer is unlikely,” Dr. Rocco says. “Our cure rates are already very high.” By comparison, a trial to compare new treatment in pancreatic cancer, to try to boost the typical cure rate from 15 to 20 percent, could probably be done with 40 to 50 patients. “But when you have really high cure rates—which, by the way, everyone agrees is a great thing—then it makes it much harder,” Dr. Rocco says.

In the meantime, pathologists and clinicians have plenty of issues to address in making sure that patients with HNSCCs receive appropriate testing—perhaps the only circumstance in which an HPV-positive test might be welcome news.
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