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Key Insights on Screening for HPV-Positive Oropharynx Cancer

Dr. Sands:

Human papilloma virus, most commonly known as HPV, is a common cause of oropharynx cancer. To learn more about HPV-positive oropharynx cancer, we'll get the latest insights on screening and diagnosis from a leading surgeon in the field.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And joining me today to talk about human papilloma virus oropharynx cancer, or HPV-positive oropharynx cancer, is Dr. Eleni Rettig, an Assistant Professor of Otolaryngology-Head and Neck Surgery at Harvard Medical School and an ENT surgeon at Brigham and Women's Hospital and Dana-Farber Cancer Institute.

Dr. Rettig, thanks for joining me today.

Dr. Rettig:

Thank you so much for having me.

Dr. Sands:

So, Dr. Rettig, let's start out with just discussing the prevalence and burden of HPV-positive oropharyngeal cancer. Can you just give us a little bit of background on this first?

Dr. Rettig:

Sure. So, to begin with, just some very, basic information about oropharynx cancer. So the oropharynx refers essentially just to the back of throat, and that includes the smooth mucosa of the soft palate and the pharyngeal wall as well as the palatine tonsils that you can see through the mouth and the lingual tonsils that are at the back of the tongue that you would, you need to be in an ENT's office to see.

So HPV-positive oropharynx cancer mostly arises from that lymphoid tissue of the tonsils, both the palatine tonsils and the lingual tonsils.

So HPV now causes around 70 to 90 percent of the oropharynx cancers in the US and in other developed countries, although there is a significant regional variation, with HPV-positive cancers, again coming mostly from the tonsil tissue. The other oropharynx cancers that we see are primarily caused by smoking, just like most of the other head and neck cancers that we see. Now, the incidence of oropharynx cancer overall has been rising in the US since about the year 2000. There has been a 3 percent rise in incidents per year since 2001, and it continues to increase today. Now, this is primarily among men and among white individuals, although we are now seeing a rise among women in some regions as well. Oropharynx cancer has now surpassed cervical cancer as the most common HPV-related cancer in the US, but it's also important to remember that it's still much less common than some other cancer types. So there's around 20,000 cases of oropharynx cancer diagnosed annually in the US compared with more like 230,000 cases of lung cancer or 190,000 cases of prostate cancer, so it is rising in incidence, but it is still not a very common cancer.

Dr. Sands:

Now, you mentioned that there's the smoking-related oropharynx cancer and then HPV-positive related oropharynx cancer. Are there differences in the presentation of those? And what are the risk factors in getting an HPV-positive oropharynx cancer?

Dr. Rettig:

So, historically, most of the head and neck cancers we've seen, including oropharynx cancers, have been caused by primarily tobacco use and also alcohol use. However, since around the year 2000, again, we started to see HPV emerge as really the most common cause of oropharynx cancer. Now, smoking continues to remain a risk factor for oropharynx cancer, and there's some interaction with HPV there because smoking does also increase the risk of oral HPV infection and persistence. However, HPV really is the primary risk factor for oropharynx cancer that we're seeing now. It

is a sexually transmitted infection, so, of course, sexual behaviors are strongly linked to the risk of HPV-positive oropharynx cancer and that's primarily oral sexual behaviors, as has been shown in some very elegantly designed case control studies early on.

The presentation of an oropharynx cancer that is caused by HPV is most commonly, actually a painless neck mass and most commonly among men in middle age, and again, we tend to see this mostly among white men. Most commonly, a patient will come in having noticed a neck mass while shaving and then we'll do a biopsy, and, potentially find a small tumor in the tonsil or on the back of the tongue. Some patients also can come in with a tonsil mass or with chronic or worsening throat pain or even trouble swallowing. And the difference in presentation between HPV-positive and HPV-negative oropharynx cancer mostly has to do with the demographics. So the HPV-positive cancer patients actually tend to be a little bit younger. They have less of a smoking history, and interestingly, there's also some socioeconomic status differences. They tend to be more educated and higher socioeconomic status, although, of course, that's variable by the patient.

Dr. Sands:

Now, you've described a mass in the neck or noticing while shaving. I'm assuming that that's adenopathy. What's the best way of catching this earlier? Is there a better way of screening that one should really insist on?

Dr. Rettig:

Right. So there's currently no screening available for HPV-positive oropharynx cancer. It's not the same as cervical cancer where screening has been shown to, of course, be highly effective. There's not an equivalent of a Pap test. We don't know of any sort of early premalignant lesion necessarily. Oral HPV infection presumes to be the precursor for this disease, but oral HPV infection is also, actually, fairly common, and there's nothing really to do about it. Most of those infections clear on their own. So there's really no kind of biomarker screening akin to screening for cervical cancer.

That said, I think that awareness and education of what the presenting symptoms are of this cancer is very important. So we do see patients who come in with a neck mass that may have been there for years because it can be also an indolent cancer and sometimes a needle biopsy may not give a diagnosis because the lymph adenopathy often is cystic, and so sometimes, you need a few needle biopsies or even an excisional biopsy to get a diagnosis, and so just awareness that this disease exists and that an adult with a neck mass should always be kind of worked up to and including an excisional lymph node biopsy. I think those are kind of the important take-home points for this, but there's no screening available right now.

Dr. Sands:

Now, you mentioned that after having a neck mass, which is presumably a node in many cases that on exam you see something on base of tongue or tonsils. Is there any way for individuals to have more direct visualization or screening of these areas, or is this kind of more of a be aware of any lumps in your neck that you see and get those worked up?

Dr. Rettig:

Yeah, it's a little bit of both. So it's hard, you can't see the lingual tonsils, of course, and so, that would need to be visualized in an ENT's office, and so I think awareness of, you know, maybe throat pain that doesn't go away after a few weeks or months should really be investigated by a primary care maybe with a referral to ENT. And of course a neck mass should always be thoroughly investigated. We do see a lot of patients who come in after having seen their dentist, which is, of course, what most adults in the US, one of their primary contacts with the healthcare system is, of course, the dentist. And so dentists do tend to do good oral cavity exams, and they can see the palatine tonsils, and often they'll, feel your neck as well.

Dr. Sands:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Eleni Rettig about HPV-positive oropharynx cancer.

So, Dr. Rettig, what kind of role does double testing have in reaching an accurate prognosis for patients with HPV-positive oropharynx cancer?

Dr. Rettig:

So there are essentially two markers that we look for in oropharynx cancers to determine HPV tumor status, and that's what the term double testing refers to. So there's looking at HPV DNA or RNA directly, either using in situ hybridization or PCR-based methods, and this tends to be more expensive and less readily available than the other method, which is looking for P16 using immunohistochemistry. P16 is a protein that's overexpressed by HPV-positive tumors.

Now, because P16 I see is widely available and it's less expensive, it has been used and is also mentioned in guidelines including for staging guidelines and College of American Pathologists guidelines as a surrogate for HPV positivity in oropharynx tumors. It's also expressed in other types of cancers and so it's really only useful as a surrogate for HPV positivity in the oropharynx. Importantly, there are a certain percentage of tumors that are discordant, so they are P16-positive but HPV-negative or P16-negative but HPV-positive, and that's going to be about 10 percent of tumors that are P16-positive but HPV-negative, and we'll call these the discordant tumors.

There's some emerging evidence that there is a significant difference in outcomes in survival among these different groups of patients. So, just to go back to kind of the prognostic implications of HPV positivity in the oropharynx patients who have HPV-positive oropharynx cancers have a much better survival than those with HPV-negative oropharynx cancers, but there's this middle group that we've seen that has these discordant tumors that are P16-positive or HPV-negative or vice versa, and they tend to have a middle survival. There's a number of clinical trials for HPV-positive cancers looking at whether we can deintensify treatment but still maintain excellent survival outcomes, and the implications of this are essentially that we really should be looking at both P16 and HPV when determining who, you know, will actually have a better prognosis and who may qualify for these deintensification clinical trials.

Dr. Sands:

I want to ask you about a specific biomarker: circulating tumor tissue-modified viral HPV. How is this biomarker clinically relevant to HPV-positive oropharynx cancer?

Dr. Rettig:

So, circulating tumor tissue-modified viral HPV DNA is a blood test that we're using in HPV-positive oropharynx cancers. It's under the umbrella of CT DNA, or circulating tumor DNA, also called liquid biopsy. It's a very exciting new tool that we're learning a lot about in this cancer. It essentially detects fragments of tumor-derived DNA in the blood, and it actually looks at the HPV genome there. And so it's detectable in about 90 percent of oropharynx cancers at the time of diagnosis, and it is very dynamic, so it varies with the burden of disease, although we don't entirely understand everything about that, you know, why the levels vary so much yet. It is commercially available now as a test that's called NavDx, which has led to its fairly rapid widespread use in the US, although there's a number of other tests that are still under study.

So it's under study for a number of different applications. So it's been looked at for early diagnosis and screening, determining HPV tumor status at the time of diagnosis and also helping guide treatment by looking at mid-treatment changes, and in surveillance, so after treatment to hopefully lead to earlier detection of recurrence. And the early studies indicate that it may become a very powerful tool, but there's definitely some significant limitations and nuances that are very important to understand when using it clinically. So this is why carefully controlled research in this field is so critical to really maximizing its benefit for patients while avoiding inadvertent harms, but I think we're going to see some very exciting advances in clinical applications in the next few years.

Dr. Sands:

Well, we've covered various aspects of the diagnostics and screening of HPV-positive oropharynx cancer. Dr. Rettig, do you have any final words or other aspects of the discussion that you'd like to highlight?

Dr. Rettig:

Sure. So one thing we haven't really touched on is HPV vaccination, so I just did want to take the opportunity to remind everyone that HPV vaccination is now FDA approved up to age 45 years old with an indication for preventing HPV-positive head and neck cancers. So, while we don't expect HPV vaccination to really impact the incidence of HPV-positive oropharynx cancer for at least several decades there is emerging evidence that it can prevent oral HPV infection, which is the precursor to this disease. So, if your patients or friends or family ask about HPV vaccination, this is yet another reason to encourage it.

Dr. Sands:

Well, with those final thoughts in mind, I want to thank my guest, Dr. Eleni Rettig, for joining me today to look at screening for HPV-positive oropharynx cancer. Dr. Rettig, it was wonderful having you on the program.

Dr. Rettig:

Thank you so much.

Dr. Sands:

I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can be Part of the Knowledge. Thanks for listening.