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Q1 What sparked your interest in aerodigestive cancers?

This started, as it often does with oncologists, with family, or with a personal experience. My grandfather was diagnosed with small cell lung cancer in the early 1980s, when the treatments were rather limited, and somewhat toxic. I was fortunately, or unfortunately, able to see what he went through, which stuck in my mind. When I went off to college at North Carolina State University in Raleigh, USA, I knew I wanted to do something in healthcare, but I didn't know exactly what. So, I majored in biochemistry and microbiology, not having any idea what that really meant. Those majors provided me with the opportunity to work in a lab at the National Institute of Environmental Health Sciences (NIEHS) in Durham, North Carolina, with principal investigator Kenneth Korach, who was a tremendous mentor for me.

When I had to decide whether I would go to graduate school to study cancer biology, or go to medical school, I chose the latter, because I wanted to apply the science to patient care for those with cancer. I trained in internal medicine and medical oncology at the Johns Hopkins Hospital in Baltimore, Maryland, USA, and found my way into aerodigestive medicine because of my mentor there, Arlene Forastiere. I would say she's a rockstar of aerodigestive cancers. I didn't choose this specialty per se, but I chose her as my mentor because I also enjoyed treating head and neck and esophageal cancers.

Q2 As the director of the Esophageal Cancer Program at the Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA, what is your current mission and focus? What can other institutions learn from the approach taken at Vanderbilt?

As mentioned, I learned from Forastiere when I was a junior faculty member at Johns Hopkins. It was a great experience, and I made some close friends and colleagues out of that initial mentoring experience. As I gained more experience over time, and across different institutions, I decided my passion lay in treating esophageal gastric cancer. I was given an opportunity by our Division Director, Jordan Berlin, and our Gastrointestinal Cancer Group Leader, Cathy Eng, to do what I really enjoy. I do think what you need to figure out is what you enjoy. It doesn't mean the job is easy, but it certainly makes it easier to come to work every day, especially if I can surround myself with a team.

The fun part of this work is being a team builder, or a project builder. I enjoy bringing together colleagues in different oncology subspecialties. For this disease, it would include thoracic surgeons, radiation oncologists, and medical oncologists, amongst others. To

get a patient through treatments for cancer requires a much broader team, which will include collaborative practice nurses, physician extenders or advanced practice providers, nutritionists, pain management care, palliative care, psychosocial, and social work. I enjoy being part of a team that has a singular focus, to help our patients with esophageal cancer, and that's the clinical part that drives me. There's also the translational or scientific portion, which can drive discoveries in the underlying treatment for these cancers. We have a connection to a number of laboratory colleagues who help us to do that.

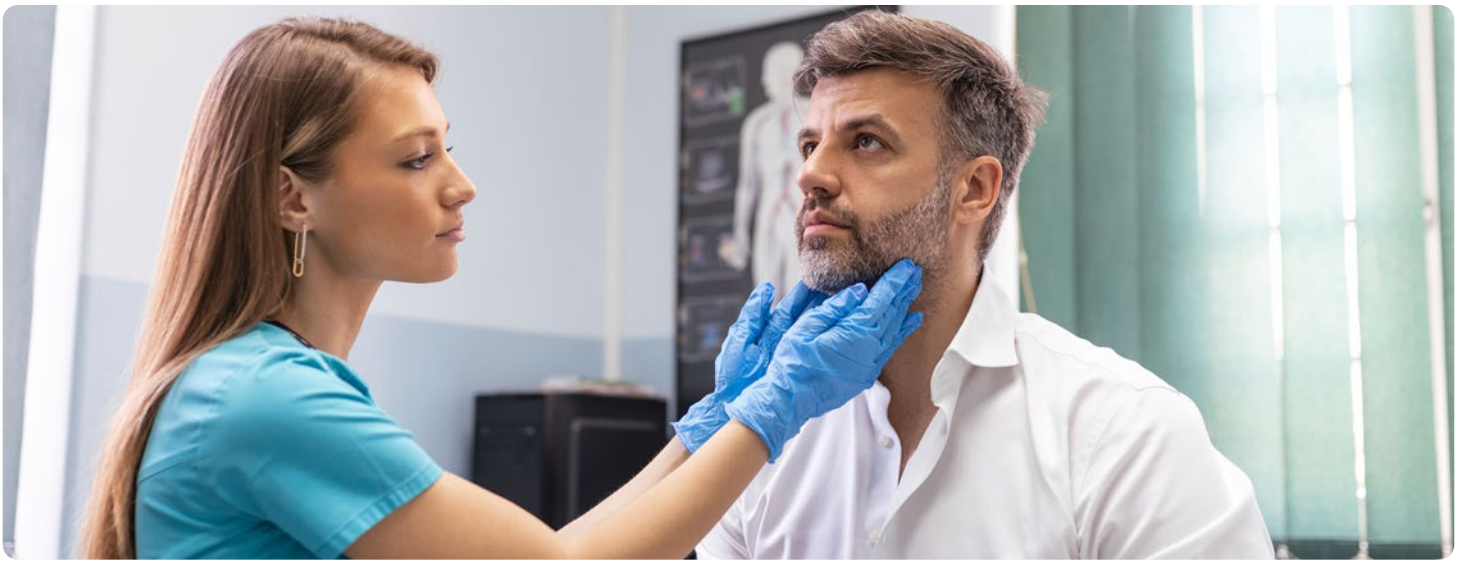
And finally, what advice do we have for other programs? I think, if you build the infrastructure at your own institution, then additional opportunities will come up. In our case, we are able to collaborate with biotech and pharma companies to bring new therapies to our patients through clinical trials. I might add that the default for clinical trials is that it won't work. I'm not saying that medical oncologists are universally negative, of course. Even if the trial does not work, I like to collaborate with colleagues to figure out why, because that may enable us to do the next study in a better way. Clinical trials really enable you to network and collaborate with people at other institutions.

Our program has done two things. One is working with the National Cancer Institute (NCI)'s clinical trials effort, and the Eastern Cooperative Oncology Group (ECOG). We have a couple of trials that are run through that, and are open across the country at community level, as well as at academic sites. This enables us to accrue patients a little faster, but also to offer our research to those in the community. We also have an international collaboration with Juntendo University in Tokyo, Japan. That's important because the principal investigator over there, Hajime Orita, an esophageal gastric surgeon, is a good friend of mine. We met when we were both in Baltimore, and have continued our work together. This allows us, as an American institution, to see patients with squamous cell cancer (SCC) of the esophagus, which is very rare here in the USA. As the webs and connections are built and woven together, you manage to make progress in your own institution, as well as in other ones.

Q3 Esophageal cancer is an area of your expertise. What are the unique features and challenges associated with its two main histologic types, adenocarcinoma and SCC?

I'm one of the discussants at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers symposium, for two studies looking at immunotherapy for SCC of the esophagus. For SCC, that's 90% of all esophageal cancers in the world. The great majority of cancers, in particular outside of Western Europe and the USA, are SCC. So, I feel that any progress in SCC, even if small, is multiplied quite a lot, since there are around 600,000–700,000 cases of SCC of the esophagus worldwide each year. Other things that separate SCC from adenocarcinoma include that SCC is typically in the upper to mid-esophagus, and these squamous cells are the same as those that cause the majority of head and neck cancers, which is what makes the esophagus a part of the aerodigestive triad.

There are some differences in the way you manage it, and what you do for curative intent. For example,



you can cure SCC of the esophagus that is localized with definitive chemoradiotherapy, without doing surgery. On the other hand, what I think makes my field even more interesting is that the esophagus lives in two 'worlds'. The upper world is SCC, and the lower is adenocarcinoma. Adenocarcinoma is what you see in the other tubes of the gastrointestinal tract, such as the stomach, pancreas, small bowel, and large bowel. It means that the lower part of the esophagus is not, per se, an aerodigestive cancer; it is more of a gastrointestinal cancer, and so the causes and the treatments are a little bit different. Whereas SCC is usually the result of smoking, alcohol use, and diet, adenocarcinoma is often related to reflux of acid and bile salts, which lead to a precursor lesion called Barrett's esophagus. That provides an opportunity for screening, which may not exist for SCC of the esophagus, since you have a premalignant condition. If you find it before it becomes cancer, you can potentially intervene, and therefore prevent its progression; however, that is easier said than done. Many smart people have tried to figure out how to screen, prevent, and treat Barrett's progression to esophageal adenocarcinoma. We haven't found the grand unified theory for that yet, but I do like the fact that I can live in two so-called 'worlds', aerodigestive, as well as gastrointestinal. It keeps me challenged.

Q4 You recently co-authored a paper entitled, 'A phase 2 study of neoadjuvant chemotherapy plus durvalumab in resectable locally advanced head and neck squamous cell carcinoma'. Could you tell us more about the emerging role of immune checkpoint blockade for the treatment of head and neck SCC, and how your findings have contributed to the field?

We know immunotherapy is the wave of the current, and the future. We know that immunotherapy works in a disease agnostic way, meaning on pretty much all solid tumors. Immune checkpoint inhibitors are beneficial, but the question, of course, is, how do you use it? Where do you apply it? How can it be safe? How can it improve outcomes? We collaborated on the durvalumab paper with my colleague, Jared Weiss, at the University of North Carolina at Chapel Hill, USA, so we were a contributing institution, but not the primary institution. Nevertheless, what we tried to do is evaluate one of two ways to treat locally advanced head and neck SCC, with immunotherapy. Generally speaking, there are several ways to treat locally advanced head and neck cancer. You can do something called definitive chemoradiotherapy, where you cure it without cutting it out. This is also known as an organ-preserving approach, and laryngeal cancer with voice preservation is the big paradigm there. The other approach would be to incorporate surgery in some shape or form into that collection.

Our study was looking at giving immunochemotherapy before surgery for resectable oral cavity SCC. The idea would be that the preoperative treatment would decrease the pathologic stage of the tumor, and therefore potentially increase survival for those who get chemoimmunotherapy followed by surgery. This is a Phase II study, or a signal-finding study. We don't have a comparative or control arm

for this, so we can't really say if it's better or not, but the control arm would be if there was a Phase III trial of chemotherapy followed by surgery. The intervention of this Phase III single arm study is chemoimmunotherapy followed by surgery. What we found out is that there was an impressive reduction in the staging of these cancers at surgery. In fact, in just a couple of patients, when they were operated on, there was no leftover living cancer in the specimen. The other component of this trial was looking at whether we could modulate the postoperative or adjuvant approach, because all patients with oral cavity cancer that is lymph node positive or at a higher T stage, will get at least adjuvant radiation, or adjuvant radiation plus chemotherapy. We designed this so that if the patients had a certain pathologic response, we could give either less radiation, or radiation plus chemotherapy postoperatively. I think we achieved that.

The other way you could look at immunotherapy for the treatment of head and neck cancer is in the definitive chemoradiation setting. This study was in patients who had surgery as part of their curative intent; but again, there are organ-preserving approaches where you give definitive upfront chemoradiotherapy and you don't operate, but you still cure them. What if we add immunotherapy to the chemoradiation? It appears that in that setting, where you give chemoradiation plus immunotherapy, it doesn't really work. There are some thoughts that maybe radiation suppresses the local immune environment, and blunts the ability of the immunotherapy to kill the cancer.

Q5 A number of biomarkers currently guide treatment decisions for patients with esophageal and gastric cancers. Have there been any recent advances in biomarker identification with the potential to shift the treatment landscape? Are there any research areas that merit greater attention?

The main advantage in the treatment of adenocarcinoma of the esophagus is that we have at least four predictive biomarker targets: HER2, CLDN18.2, FGF receptor β, and PD-L1. What we're trying to figure out is not only whether they work, but also how they work. The challenge is, how do you sequence them and combine them if you have a tumor that has several markers at the same time? I think for now, this is one of the main challenges, especially if you have more than one biomarker expressed in adenocarcinoma of the esophagus.

Q6 There has been interest from all areas of life sciences and healthcare towards artificial intelligence (AI). Do you think there is room for AI in your field, and do you believe AI will accelerate research and development?

I'm a huge novice when it comes to AI, but I do have a couple of things I can say. I have played around with ChatGPT (OpenAI, San Francisco, California, USA). One of our faculty here, Douglas Johnson, put a paper together where he pulled different specific experts, and asked us to provide three different types of questions. One was a yes/no question, one was a multiple choice question, and the other was an open question, like what clinical trials are available for esophageal cancer. I was very impressed with how correct ChatGPT was in answering these questions.

What I don't know about AI is how it can help me sort through data, like a needle in a haystack. When doing genomic studies, you get so much data, it's hard to get a correlation from one particular part of it. I'd like it to help me with that. I also think we could put in a couple of patient variables for a particular patient we're seeing, and draw up which clinical trial options exist. I wonder if AI could tell me what the next research questions are, and how I should go about answering them; although, if that's the case, I think a lot of us would be looking for other positions. I do think it's going to be a useful thing. To that end, Vanderbilt did put together our own AI that has appropriate firewalls and connections, since we may put some unassociated patient data in there, although nothing identifying, based on the Health Insurance Portability and Accountability Act (HIPAA).

Q7 Where can we see your research and clinical focus lie in the coming years?

I would like to be able to do three things. The first is that, by doing smaller clinical trials in several institutions, we might be able to answer questions more quickly than a big pharma study, because it's very hard for academic centers to do a large Phase III study. If we have specific questions that might not be answerable, for example, microbiome or circulating tumor DNA, that we can do on a smaller scale to collect the data we need, we might be able to answer why it works or doesn't, and then move

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that forward to a larger venue. So, signal-finding studies at academic institutions will be important. Secondly, I think the identification of new biomarkers is critical. There are many types of biomarkers, some of which are clearly impacting patient care, such as HER2 or PD-L1, but there are also biomarkers that can tell you whether a patient has completely responded for curative intent, whether they've recurred and when, and when to start subsequent therapies down the road. Finally, I think doing trials across borders may become more and more important, because underserved areas deserve research and therapies that are available everywhere else, and if we could somehow unify studies, so that we have unified treatment approaches across the world, perhaps that would lead to some more efficiency in further studies and treatment options.