Yale CANCER CENTER answers

WNPR Connecticut Public Radio

Head and Neck Cancer Pathology

Guest Expert:
Manju Prasad, MD

Professor of Pathology; Director, Endocrine, Head & Neck Pathology, Yale School of Medicine

Hosts

Anees Chagpar MD

Associate Professor of Surgical Oncology

Susan Higgins MD

Professor of Therapeutic Radiology, Obstetrics, Gynecology, and Reproductive Sciences

Steven Gore MD

Director of Hematologic Malignancies

Yale Cancer Center Answers is a weekly broadcast on **WNPR** Connecticut Public Radio Sunday Evenings at 6:00PM

Listen live online at cpbn.org

Listen to archived programs at valecancercenter.org

Welcome to Yale Cancer Center Answers with your hosts Drs. Anees Chagpar, Susan Higgins, and Steven Gore. Dr. Chagpar is an Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on myelodysplastic syndromes. Yale Cancer Center answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join in, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about head and neck pathology with Dr. Manju Prasad. Dr. Prasad is Professor of Pathology at Yale School of Medicine and here is Dr. Steven Gore.

Gore When I think of pathology I tend to think of the old TV show *Quincy* which I guess would be considered forensic pathology. He used to solve a lot of crimes, for those in our audience who probably are too young to remember, but pathology is a lot more than who done it of course, is that right?

Prasad Sure, in the good old days that you mentioned, there was a colloquial term, doctor of death, used for pathology.

Gore Yes.

Prasad But that is really an outdated impression of a description of a pathologist. We still have forensic pathology that investigates the criminal nature of death, but pathology has evolved into diagnostic pathology and diagnostic surgical pathology, for example, there is absolutely no cancer that can be treated unless there is a solid diagnosis and that comes from pathology.

Gore I think that many of our listeners may be surprised to learn that among pathologists there are so many regional specialties or organ specialties, I think people are used to there being surgeons and gynecologists and internal medicine doctors and subspecialists within all those fields, but I guess it is true in pathology as well, is that right?

Prasad More and more now, especially in academic pathology, we are realizing that knowledge has exploded so much that rather than be a jack of all trades, we would like to be masters of one and so pathology has now developed several different sub-specialties like pulmonary pathology and breast pathology and gynecologic pathology. My area is head and neck and endocrine pathology, so it is simply to accommodate the explosion of knowledge and to bring the benefits of those discoveries and research to our patients in those areas.

Gore And was that true earlier in your career during your training? Were pathologists already focusing on certain areas? I can think back to when I was training which is probably longer ago than you, certainly in my field of blood malignancies, there were always hematopathologists in the places that I trained.

3:48 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Prasad Yeah, there were always hematopathologists because blood is not a solid organ, it is fluid. At the same time, there were also neuropathologists because the brain was so complex and at some point dermatopathology developed too because the skin is a huge organ from head to toe.

Gore Especially for those of us who are chubbier in our BMIs.

Prasad Right, they have more skin than others and then everything else used to be called general pathology. I remember doing gynecology, looking at uteruses as well as kidneys as well as lungs, and then head and neck, but then our challenges were easy. We had to determine is it benign or malignant and once we called it cancer, was it invasive or noninvasive and then the oncologist who had very limited choices in those days and the radiation oncologist, who just radiated everything that was malignant, so patients had fewer choices and pathologists also had fewer diagnostic areas but now the explosion of science both in treatment of cancers and in the nature of cancers and our own knowledge has exploded so much that we really need to know one field and know it really well.

Gore Fascinating, so when I think back to anatomy and full disclosure I was a Yale Medical Student where back in the day pathology was not highly emphasized in terms of having to really memorize a lot of things that should be known, but I do remember the head and neck to be among the most complex set of anatomical structures when I think of blood vessels and nerves and muscles and the larynx and the thyroid gland and parathyroid gland and tongue and mouth and adenoids and so many things, is that all in your purview?

Prasad It is all in my purview and thank you for elaborating that long list.

Gore I'm sure it wasn't exhaustive.

Prasad Within the head and neck area and bone and soft tissue and bone and soft tissue is everywhere else as well and head and neck also includes skin and almost 60% of the dermatologic cancers and lesions occur in the head and neck area which is very much exposed to the sun compared to the rest of the body, so in a way you could say it is a very large area to deal with but at the same time, it is above the neck, so at least I deal with a limited number of surgeons and oncologists and the radiation oncologists also make up part of the cancer management team.

Gore How does this work, let us say a patient is having some kind of surgery in the neck, and something is removed, do you know about that ahead of time or does it get triaged at a center of pathology, how does that work?

7:19 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Prasad Let's start from the very beginning, let us say a patient has a painless ulcer on his tongue. It does not hurt him. He is not too bothered but he has noticed it and he goes to a dentist first for his routine visit and the dentist notices that there is this small painless ulcer that the patient is not even complaining about and suggests a biopsy, so it starts from that point. That biopsy would come to a surgical pathologist like me and the question would be to rule out cancer and then if it does turn out to be cancer, the patient would be referred to a head and neck surgeon or cancer surgeon at that point. Now, this surgeon would do an extensive radiological work up, a CAT scan and MRI, try to figure out has the cancer already spread to his neck lymph nodes and all of this could still be painless. The patient has still no complaints, has not yet started to lose weight and at the same time, the cancer could have spread and may not be a very early cancer at that point. Based upon all this radiological imaging, the surgeon would have to then decide how much of the tongue needs to come out and can he get the entire cancer out with the minimum amount of surgery so that the patient can still speak clearly and still swallow and those critical functions are not affected and make sure that the cancer does not come back and if possible avoid both radiation and chemotherapy because they have for their own side effects. When the patient goes for surgery and is under anesthesia, the intraoperative pathology consultation becomes very critical, so the question the surgeon asks the pathologist is, are the margins clear, did I get all the cancer out and if they are clear, how close is the closest margin, is it 1 mm or 5 mm? Now in the oral cavity, the patient does not have the luxury of a lot of spare tissue like in the skin. You can give a 5 cm margin. In the oral cavity, it is a couple of millimeters, but if those margins are negative and the pathologist has to decide very quickly using what we call frozen section within 10-20 minutes or 30 minutes how far every margin is.

Gore So the patient is still under anesthesia?

Prasad Very much so.

Gore And you get this piece of frozen tissue and you have got 10 or 20 minutes while that person is still anesthetized to come up with this really critical answer?

Prasad Absolutely.

Gore That seems very stressful.

Prasad It is and actually in our frozen section laboratory, the biggest users are the head and neck surgeons because these margins are so critical for them, they would like to get it all out during the first surgery and not be told a week later that 3 of the margins were positive and have to take the patient back to the OR to get more margins, so that is a very critical involvement of the pathologist and then when the final specimen comes, we would reexamine it after fixing it in formalin embedding the slices and the slices are 3 mm each, as thin as you can imagine and those would be then embedded in liquid paraffin and

11:26 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

then cut at 5 microns and then examined under the microscope and then an entire synoptic summary is generated of the patient's cancer, how large it is, how deep is it invading, is it beyond the surface of the tongue, into the muscle of the tongue, is it infiltrating the blood vessels, is it wrapping itself around the nerves and spreading further, all of this cannot be visualized during gross examination when in the patient's mouth or when we are looking at the tissue grossly, so this has to come from the microscope and some biomarkers predict the cancer's response to radiation, so then we would apply those biomarkers and prepare a final report. This is guiding not only the surgeon's hand during surgery but also the radiation and the medical oncologists and guiding the therapy for the patient as well as predicting how well will the patient respond to those therapies.

Gore How often does it happen that you have given clearance during the surgery that it seems like there are clean margins but then when you reviewed the final pathology, it turns out that they need further surgery, does that happen very frequently?

Prasad It does happen because the frozen section is a preliminary diagnosis and there are National Guidelines revising those diagnoses and those preliminary diagnoses because the technique used is rapidly freezing the tissue in liquid nitrogen and then cutting it very rapidly and these sections are not 5 micron, they are twice the thickness, so there is room for error in the interest of speed and helping the surgeon intraoperatively, so the error rate is nationally dictated and is less than 5% and in our setting, it is less than that, we would like to keep it less than 2%.

Gore Less than 2%?

Prasad Yeah.

Gore That is pretty good.

Prasad It is and it is still devastating when the permanent sections disagree with the frozen requiring the surgeon to go back or requiring the radiation oncologists to give targeted radiation to a specific area.

Gore This is really a fascinating area and I personally am learning a lot about the actual mechanics of pathology, so let us pick this up after our break, but right now, we are going to take a short break for medical minute. Please stay tuned to learn more information about head and neck pathology with Dr. Manju Prasad.

Medical Minute *The American Cancer Society estimates that over 1500 people will be diagnosed with colorectal cancer in Connecticut alone this year. When detected early, colorectal cancer is easily treated and highly*

14:26 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

curable and as a result, it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the one at Yale and at Smilow Cancer Hospital to test innovative new treatments for colorectal cancer. Tumor gene analysis has helped improve the management of the disease by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in a more patient-specific treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I have been talking tonight with our guest, Dr. Manju Prasad about pathology and cancer in her special area of the head and neck. Manju, before the break you were telling me about how critically important your role is in the intraoperative evaluation of the pathology specimens and I am wondering, are you in some ways made aware ahead of time of what kind of surgery the surgeon is anticipating, in terms of what kind of questions she is going to have to have about the lymph nodes or is this just, you get the tissue and you figure out what to do?

Prasad It works both ways depending upon what the nature of the surgery, typically we will have a tumor board where the surgeon in a multidisciplinary conference will present the patient and then the radiologist will present all the imaging.

Gore Before they have had surgery?

Prasad Before they have had surgery, so we know what the extent is, the pathologist is sitting there and trying to understand how far spread the tumor is, the surgeon then discusses what he is planning to do. There are also oncologists, radiation and medical oncologists, and when the patient comes to the OR, the head and neck pathologist who has been at these tumor boards knows how bad or how extensive this tumor is. The surgeons also momentarily would scrub out and come to walk over to pathology and this whole suite is right adjacent to the OR and there would be direct face-to-face contact and discussion with the surgeon.

Gore Really?

Prasad While we are evaluating all these margins.

Gore How interesting, I did not realize it was right there.

17:25 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Prasad It is right there, our head and neck permanent sign-out desk is right outside the OR in this area.

Gore Is that typical in many hospitals?

Prasad Yes, in many hospitals it is typical. We would like to be very close to the OR so that no time is lost and that face-to-face communication is critical because so much can be lost just in translation, but then on the other hand, there could be something where the surgeon does not know what he is biopsying, it is just a growth, it could be benign or malignant and he is trying to determine that, it could be a lymphoma, in which case, he would send a frozen section to triage to the pathologist to ask these questions, what should be the future plan if it is a lymphoma, do you have enough material to work it up and Steven that is your area of expertise. If it is a lymphoma, then we would tell the surgeon, stop right there, this is not your case, just give enough tissue for a lymphoma work up and the medical oncologist will take over so with those they needn't have discussed it at the tumor board.

Gore Now you mentioned these patients coming, for example, the asymptomatic painless ulcer, I am sure like me, many of our patients get canker sores, common name for what we would call aphthous ulcers which in my case are often painful but should we be worried about those kinds of ulcers that come and go so frequently?

Prasad Not really, I get aphthous ulcers all the time, especially when I was kid too. The magic word is they go, they go on their own whether you treat them or not. These painless ulcers are somewhat different.

Gore Different how?

Prasad They keep on growing even though they are painless and they are not going away.

Gore So anything that sort of resolves and goes away, we do not have to worry about too much.

Prasad Yeah, the body has this fantastic ability to heal itself, and if it does not, that is when you start worrying, also there are patients, some high-risk patients who should worry more when they have a non-healing ulcer.

Gore Who are those patients?

Prasad The head and neck cancers are very closely linked to both smoking and alcohol and also the chewing of tobacco and in certain cultures, they would chew tobacco and keep that quid.

20:09 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Gore Yes, that is that Maryland culture from where I come.

Prasad Yes, that is right.

Gore Pretty common in the eastern shore of Maryland, the rural parts of Maryland.

Prasad And I come from India and beetle nut chewing, pan chewing, my grandmother always had a quid in her mouth.

Gore Wow!

Prasad She would go to sleep with the quid in her mouth. She was very lucky, she lived till 82 and all she had was leukoplakia, white patches and never got cancer, so those are definitely predisposing factors to head and neck cancer and actually more lately in the last 10 years, the knowledge has exploded in terms of virus-related head and neck cancers, so nearly 20% of all of the worlds' cancers are associated with viruses.

Gore Really?

Prasad In the head and neck, in Asia, we always knew that Epstein-Barr virus was a common cause of cancers in the young.

Gore That is the virus that causes mononucleosis right?

Prasad True, that too and also in immunosuppressed individuals, it can cause some hematological malignancies, but lately in the last 1 to 2 decades, human papillomavirus has come up as a major cause of tonsillar cancers in middle aged Caucasian male population in the developed world, not the developing world but in the developed countries.

Gore So is it not the papillomavirus like a warts virus?

Prasad Right, papillomavirus is a huge family of like more than 165 genotypes. Out of that, only the genotype HPV16 is the one linked to tonsillar cancers and there is a small number of other high-risk genotypes. I think about 13 to 15 of those, more than 165 genotypes, are cancer associated. The others are relatively benign. Many of them lead to skin warts, warts on mucosae which are benign, which just need to be taken out or even if you leave them and do nothing, they would not develop into cancers.

22:27 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Gore But these tonsillar cancers, this HPV virus, that is a sexually transmitted virus, or am I mistaken about that?

Prasad HPV16 is a sexually transmitted virus.

Gore Through oral and genital contact.

Prasad Right.

Gore Gotcha.

Prasad And already because we are able to determine what causes this cancer in healthy middle-aged Caucasian males who are not smoking and not chewing tobacco, because we know what causes it, we can prevent it, so the recent introduction of HPV vaccine in school-age children is going to make this cancer go away over the next generation.

Gore This is the Gardasil vaccine.

Prasad Yes.

Gore But I understand that the uptake of this vaccine, especially in boys has not been so great as it has been apparently in girls where is prevents cervical cancer, if I am not mistaken.

Prasad Exactly, initially some governments proactively made laws to vaccinate all girls at a certain age, but it is very important to educate the public and the boys too and tonsillar cancer is just as horrendous and if it is just as preventable as cervical cancer, then boys too must be vaccinated with this.

Gore I read in the New York Times this week some recent study about the papilloma vaccine, the HPV vaccine, already bringing down the rate of cervical cancers, if I am not mistaken, I do not know if you saw that story.

Prasad I read that article too.

Gore Very exciting, I thought.

24:15 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Prasad Very exciting and cervical cancers are already becoming very uncommon in the developed world, but in the developing world, it is still the #1 killer in women. In the developed world of western society, the tonsillar cancer which is HPV related, that is preventable, so it makes complete sense to prevent it early on and make this an extinct disease.

Gore I think in our society which still has its puritanical roots unfortunately, I think that parents of preadolescent boys have a difficult time thinking about vaccinating for something that is clearly sexually related and then there is also this feeling, I think in the sexist society that boys are going to be sexual in a way that they do not really worry so much about in the same way that we worry about girl's sexuality, so I wonder if some of these factors play a role in people's resistance to vaccinating their young boys?

Prasad I think they do and it is really unfortunate.

Gore You were telling us about biomarkers, at least you mentioned it, and I am wondering if you could tell us a little bit more about how biomarkers play in your area of head and neck and endocrine cancers.

Prasad So continuing on the theme of these tonsillar cancers in middle-aged young men who are nonsmokers, who also never chewed tobacco, it was a huge mystery as to why someone who has good habits still has this cancer, so it turns out that a certain marker of protein called P16, in these cancers, this protein is seen in almost 100% of the cancer cells, greater than 90%, so these cancers even without doing the HPV testing, P16 itself is a very reasonably priced very economical test and a pathologist like me can look at the slide under the microscope and say it is greater than 90%. It is a huge game changer in these tonsillar cancers. What that means is these patients, their prognosis is much better than those related to smoking, also these patients, their radiation therapy can be deescalated, so they would require lesser dosage of radiation and Steven you know that radiation burns tissues.

Gore Yes.

Prasad It burns the mouth, it burns the gullet, it burns the esophagus and the respiratory mucosa; it is very painful. In some patients, it can lead to so much scarring and necrosis of normal tissues and also necrosis of the bone, so sometimes the jaw is in the way to the tonsil and the jaw which is completely healthy can undergo necrosis and that is a known complication, although rare. So reducing the dosage of radiation and spending fewer number of weeks giving the patient radiation is a huge deal and a huge cost cutting measure for the patient, so I think that is one biomarker which has come up in the last 10 years or so that is altering therapy. Also these patients do not need chemotherapy.

Gore Really?

28:20 into mp3 file https://az777946.vo.msecnd.net/cancer/2016%200320%20YCC%20Answers%20-%20Dr%20Prasad_248886_5.mp3

Prasad With this kind of profile and this kind of basic stain of over expression, they would do well without chemotherapy. In contrast, tonsillar cancer related to smoking, those are P16 negative but they are P5 positive. These cancers are going to behave poorly, very badly. They need more radiation and they need additional chemotherapy. So it is important to spend the dollars on the right patient and not escalate therapy in a patient who is going to do well with lesser therapy and hopefully fewer complications.

Dr. Manju Prasad is a Professor of Pathology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.