

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



Hosts

Anees Chagpar MD

Associate Professor of
Surgical Oncology

Francine Foss MD

Professor of Medical
Oncology

Studying Cancer from the Inside Out

Guest Expert:

Manju Prasad, MD, MBBCh, MBBS

Associate Professor of Pathology and
of Surgery (Otolaryngology); Director,
Endocrine, Head & Neck Pathology;
Director, Immunohistochemistry
Laboratory, Yale School of Medicine

Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at the Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Gore is director of hematological malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the most recent advances in the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about the pathology of cancer with Dr. Manju Prasad. Dr. Prasad is Associate Professor of Pathology and of Surgery in Otolaryngology at the Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Manju, maybe you could start off by telling us what exactly you do as a surgical pathologist.

Prasad Surgical pathology is the study of human tissues taken out during surgery. So the surgeon takes the tissue out but the pathologist gets to see it, feel it, and cut it into very thin slices in the laboratory. The slices are as thin as balloons and then we examine those cut surfaces and select areas of interest, areas of disease for microscopic examination. For the microscopic part, we stain these tissue sections with pink and blue, that is the staining, and those two are my favorite colors and the cancer cells tend to be very blue, blue is bad, whereas the benign cells they turn out to be quite pink like nasal polyps or very pink, and in between there are hundreds of shades of lilac, purple, pale grey, dark blue, and I really enjoy this colorful splendor of the cells that I am looking at.

Gore Well it sounds like a great study experience for you, but why is this important for the patient?

Prasad It is very important for the patient. The most important question for the patient is, do I have cancer, and that is the first question that the surgical pathologist is going to answer and I will highlight it with a story, the story of a young man who one day noticed a small ulcer in his palate, a biopsy was taken at a community hospital and he received the diagnosis of cancer. He transferred his treatment to Smilow and as you know our hospital policy is reconfirmation of all biopsies by in-house pathologists and when we looked at his biopsy we started seeing a peculiar pattern, a pattern of a very exuberant healing reaction to an ulcer which mimics cancer. We showed it around among other surgical pathologists and everyone was hesitant, it was just shy of cancer. We alerted the surgeon and the patient and both of them were incredulous, but they decided to wait and watch and in three years his ulcer was beginning to heal and a second biopsy proved that it was indeed benign in nature. So the diagnosis of cancer is life altering, had it been cancer he would have needed surgery or removal of his palate, his upper jaw, he would have required radiation and chemotherapy but when the diagnosis of cancer is overturned that too is a life altering experience and that is the job a surgical pathologist performs day in and day out.

Chagpar That is kind of a scary story because the diagnosis, the initial diagnosis that he got at a community hospital of cancer was also read by a pathologist, so it makes our audience and certainly me a little

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bit concerned about how frequently our pathologists are wrong because what would have happened if he did not get that second opinion from you and your team.

Prasad So, it helps in cancer confirming and reconfirming and reconfirming helps and most major cancer centers in this country will not treat a patient without having his original initial biopsy confirmed and reconfirmed. The entire team of oncologists and surgeons would meet up in tumor boards discussing the radiology, the patient's findings, clinical findings and pathology together and this team like approach in a cancer center is very important.

Gore Are second opinions for pathology available to patients who are in community hospitals who perhaps for whatever reason do not want to come to a referral center, is the pathology ever sent out to experts like you?

Prasad Yeah, absolutely. Second opinions are very easy to get, mailing a slide is a very low cost thing and most pathologists are very cautious about it. They could pick and choose which expert they seek second opinion from and then take it forward and if there is a difference of opinion watchful waiting is a very good approach.

Chagpar I think it is difficult for patients because on the one hand many patients want their diagnosis instantaneously. They had the biopsy, how come I can't get my diagnosis in 2 minutes?

Prasad Right.

Chagpar On the other hand, you talk about this process whereby you look at the specimen and you feel it and you slice it, then you make blocks and then you look at it with pink and blue stains and then you might need another opinion and all of that takes times. So, what is the balance there that patients should be looking at?

Prasad Well time is certainly important if this is going to be a life altering experience for the patient, the last thing he or she wants to do is rush the pathologist. If it is a slam dunk benign or malignant, the biopsy results come back pretty quickly within two to four days, however, if there is any controversy you do not want to rush your pathologist, let them get their second opinions, let them take it to their conferences and then the final diagnosis must be what the oncologist and the surgeon are going to act upon.

Gore Is there anything you can do besides looking at the pink and blue patterns to increase your confidence that this is cancer or a benign lesion, I mean it is pretty scary to think that it is just you looking at this slide.

Prasad Cancers have personalities, they have what we call characteristics and the pathology training is extremely long. It is four years of usual training and then another two to three years of fellowship

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training and a fellowship in oncologic surgical pathology rounds out this experience, so we are talking about anywhere from a minimum of 5 to 7 years of training and this is hours and hours of looking at tissue slides under the microscope. I was talking about characteristics or personalities of these cancers. Some cancers are very aggressive, every cell appears to be in mitosis, normal cells, when they undergo mitosis they produce two daughter cells, cancers cells can produce multiple daughter cells. These characteristics to an experienced pathologist are as different as separating two human beings one from the other by just looking at them and in this case we are looking at them under the microscope.

Gore Do you ever have to do other kinds of tests on the tissue or is it mostly just how it looks?

Prasad Yeah, sure, there are additional techniques to predict a tumors behavior or response to therapy and one of the techniques, one of the labs that I run is the clinical immunohistochemistry lab.

Gore That is a lot of words.

Prasad Yeah, and what it does is, the cancer cells have altered protein because they have genetic mutations and it is one gene, one protein is a simplification of it, so if the gene is abnormal, so is the protein, and against these proteins, proteins are allergenic, so against these proteins there are antibodies that we use in our lab. These antibodies are tagged to a coloring agent, a chemical, and that gives it a brown color. Now the antibodies are pretty specific. They are monoclonal and they can pick out specific proteins. One example would be a protein called the mutated BRAF protein, which results from the mutated BRAF gene. On using this antibody, we can tell which cancers have the BRAF mutation and my area is thyroid cancer, and in the thyroid nodules any nodule or any tumor that shows this mutated BRAF protein is malignant, because benign nodules like goiters or adenomas do not show this mutation. So, the proteins can also be diagnostically very very useful. Other usage of immunohistochemistry is predicting response to certain drugs and one of the proteins is this HER2/neu protein or the human epidermal growth factor receptor protein. There is a monoclonal antibody against it, which is a drug that can be used for tumors that over express this very abnormal protein, and Anees, you are a breast surgeon, well 30% of breast cancers can over express this protein. In the head and neck, we have a protein that is called P16 protein where 100% of the cells are P16 positive and very sensitive to radiation, so a tumor that is P16 negative, would require a higher dosage of radiation, whereas a head and neck cancer P16 positive, we can reduce the dosage of radiation, which is less harmful to the patient. In contrast, head and neck cancers that are P53 positive, they behave really badly. Their outcome is bad and these patients would need surgery, radiation, and chemotherapy, the entire workup.

Gore It sounds like you are talking about using some of your tests and skills to help individualize the treatment for the patient. Is that what they call personalized medicine?

Prasad Yeah absolutely, and that is why I mentioned earlier that cancers have personality, so no two

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patients have exactly the same cancer. There is a garden-variety or a generic variety that we can go with, whereas other cancers like most thyroid cancers, I would say they are like sleepers, whereas some rare variants, uncommon variants, are killers. What I mean is the garden-variety thyroid cancer, the papillary cancer, is a sleeper. It is incidental. It does not kill the patient. The patients live with it for 20 years or longer. It is more like a chronic disease or a nuisance. Even when it comes back, it is more like a nuisance whereas the example of a killer is going to be something like the anaplastic thyroid cancer. It grows so rapidly, within months it wraps itself around the windpipe of the patient and it can kill by strangulating the windpipe. So each patient's cancer is unique to that patient and that is why the pathology report in great detail profiles this and this is what we do, we profile these cancers, we determine its lethality, how advanced is the cancer, how extensively has it spread, is it confined to the thyroid or has it gone outside the thyroid? So all these characteristics are put together and then discussed in the multidisciplinary tumor board to find a unique management scheme or strategy for the specific patient.

Chagpar It sounds like you are really a part of tailoring treatment for patients with cancer and highlighting the role of a pathologist as part of that multidisciplinary team. We are going to find out more about how exactly you do that after we take a short break for a medical minute. So please stay tuned to learn more information about cancer with our guest Manju Prasad.

*Medical
Minute*

It is estimated that over 200,000 men in the United States will be diagnosed with prostate cancer this year, with almost 3000 of these diagnoses here in Connecticut. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the numbers of men who die from the disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and Smilow Cancer Hospital at Yale New Haven to test innovative new treatments for prostate cancer. The Artemis machine is a new technology being used at Smilow that enables targeted biopsies to be performed as oppose to removing multiple cores from the prostate for examination, which may not be necessary. 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 the WNPR Connecticut's public media source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Steven Gore. Today, we have Dr. Manju Prasad with us, who is a pathologist, who studies cancer and one thing, Manju, that I was struck by in our conversation before the break was that it must be so difficult to really be able to look at this pattern of pinks and blues, and be able to tell what is cancer and not cancer and use this immunohistochemistry to make these

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diagnoses, and it struck me that you are a very specialized pathologist. In other words, you do not do every kind of cancer. You do not do every body part. You are very specialized in terms of head and neck pathology. Can you talk a little bit about why you are so specialized and the team work that you have with head and neck surgeons, because I know as a surgeon we tend to be very specialized. Talk about how that is important?

Prasad In head and neck cancer, and also endocrine cancers, these areas or these organs are very different from, for example, prostate cancer or breast cancer. In the head and neck area, the surgeon has very little room to take out wide margins. For example, if there is a melanoma of skin that a surgeon is taking out, an adequate margin would be 5 cm. We have plenty of skin, we can spare that margin or even larger if possible, but inside a patient's throat there is not a whole lot of room there. Otherwise, the patient would have to live with the complications of surgery like being unable to swallow, unable to taste food, unable to speak clearly, maybe speak with a slur. If too much of his tongue is taken out for a tongue cancer. So in head and neck surgeries, margin evaluation at the time of surgery in real time is very very critical. The surgeon has to keep on going until he gets clear margins and these clear margins are from very precious tissue that cannot be spared really for other functions for the normal functions of the patient. So, our role is from diagnosis to the patient's intraoperative care and after the surgery is over to staging the cancer and to characterizing it further, sometimes the head and neck surgeries can go on for eight hours if margins are not cleared. Sometimes the surgery can be stopped half way. If the cancer turns out to be a variant that best responds to chemotherapy, such as if the cancer turns out to be a lymphoma. Then the course of surgery is entirely changed and the patient would be referred to the chemotherapist.

Gore So are you doing the pathology as they are operating on the patient?

Prasad Yeah, we call that intraoperative consultation or frozen sections, in this case we do not have the luxury of three or four days to give a diagnosis, we do it within 10 to 15 minutes per tissue piece, we look at it very rapidly, we freeze it to harden the tissue, so that we can cut it, a couple of microns thin and we continuously look at it and call into the OR and help out the surgeon.

Chagpar Manju, people are listing to you and saying, how come in the operating room you can give a diagnosis in 15 minutes, but in the office the surgeon tells me you are going to have to wait a week to get the pathology report back. What is the difference?

Prasad There is a big difference, in the OR, we are simply guiding the surgeon's hand, we are simply giving him some directions as to how much or how far he needs to go to take the cancer out. The frozen section diagnosis is not final, it is a preliminary diagnosis to help the surgery along. The final diagnosis is to guide not just the surgeon, the radiation oncologist, the medical oncologist to tailor the right combination of chemotherapeutic agents as well as the dosage of radiation needed

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to treat the patient. The final diagnosis also uses a lot of biomarkers to predict the behavior of the tumor, which one is going to come back, which one can be let go and which patient requires radioactive iodine, which will convert her into a radioactive woman for a couple of days, which patient can be let go and does not have to be treated any further? All of that has to come from the final pathology diagnosis, and it is worth waiting for.

Chagpar It seems to me that you have a breadth of knowledge in head and neck that expands beyond simply looking at the patterns. It really is an astronomical amount of information that ties together how your pathologic diagnosis influences all of the treatments. Is that why we have dedicated pathologists in each disease team, because you really dictate the treatment in a lot of cases?

Prasad That is how it started. Pathology is so vast that it was very hard to keep up with the most recent scientific developments if we remain generalized. So, Yale Pathology started subspecializing about 15 years ago with GI pathology and then gynecologic pathology, breast pathology. Head and neck and endocrine pathology became a subspeciality in 2009 and we are realizing that the amount of new information, scientific knowledge, that has been created in the last couple decades is so overwhelming that our fields are getting narrower and narrower.

Gore Does your expertise in endocrine pathology include endocrine organs besides the thyroid, are you examining adrenal glands for example?

Prasad Actually, we do, we have four dedicated surgeons who take out thyroids, parathyroids and adrenal glands and so it does spread to adrenal tumors as well.

Chagpar When you think about head and neck cancers and you think about risk factors for head and neck cancer, smoking, alcohol even viruses now, does any of that impact you as a pathologist? Does it matter to you how the cancer came about or are you just looking at the patterns under the microscope?

Prasad I do. It is very-very important and that comes down to guiding the management or individualizing the treatment of the patient. To me, the cause is just as important as the treatment, what caused the cancer. If we knew the cause of the cancer we could then eliminate the causes, probably address causes, be it environmental or lifestyle related issues. In the last two decades in head and neck cancer, the human papillomavirus or HPV has been written about to play a very important role and actually patients who get HPV associated head and neck cancers they fit a certain profile, they are young, Caucasian, middle aged male patients. The good news about HPV related cancers is that their outcome is much better than the tobacco or alcohol related cancers. So the cause really matters here. Other good news is if we know the cause we can address it through vaccines against the viruses through other lifestyle or environmental changes, so it is very important to know and actually my lab also does the in situ hybridization test for the HPV virus in addition to p16 HPV

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viruses that are associated with a very abnormal p16 protein. So, these two tests help us determine or split apart the HPV associated head and neck cancers with better outcome from the tobacco or alcohol related cancers with poorer outcomes.

Gore Is that the same HPV virus that the teenagers are getting vaccinated for to prevent cervical cancer?

Prasad Yeah, absolutely and in fact there is a recommendation that it should also apply to young boys.

Gore But boys do not get cervical cancer.

Prasad No, but as I mentioned, for the HPV associated head and neck cancers, the profile is a young, white male, so yes boys do not get cervical cancers but head and neck cancer is not fun either.

Chagpar HPV is what Michal Douglas had, right, in the head and neck?

Prasad That is what I heard from the news, yes, and it is actually fairly common place in my practice. I see about 5 to 10 HPV associated head and neck cancers a month.

Gore And this is sexually transmitted, is that correct? The HPV virus?

Prasad Absolutely, there are studies from South Korea and also from Africa where in the general population HPV related cervical cancer is very common in women, but HPV related head and neck cancer is exceedingly uncommon in men, so certainly there are lifestyle differences there. In fact among men in Asia and in Africa, it is the tobacco and alcohol related cancer that affects the head and neck area and in India head and neck cancers are number one among men and it is related to tobacco chewing.

Chagpar So, if you have an HPV associated head and neck cancer, is treatment different because could you still get the vaccine even after you have the cancer?

Prasad That particular question is what clinical scientists are looking at and currently we do not have the data on how useful the vaccine would be after a patient gets the cancer. There is one study from Costa Rica where after the vaccine, Gardasil, they found that the incidence of oral HPV infection was reduced significantly, but to actually see whether the incidence of HPV related head and neck cancers is significantly reduced, one would have to follow these young patients who received vaccine for decades to show that, so we would have to wait a few decades to get that kind of information. The vaccine has certainly been shown to be exceedingly successful in reducing the incidence of cervical cancers in the western world.

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Dr. Manju Prasad is an Associate Professor of Pathology and of Surgery in Otolaryngology at Yale School of Medicine. We invite you to share your questions and comments with Dr. Foss, Dr. Chagpar, and Dr. Gore. You can send them to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC. As an additional resource, archive programs from 2006 through the present are available in both audio and written versions at yalecancercenter.org I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNP, Connecticut's Public Media Source for news and ideas.