

Yale CANCER CENTER *answers*

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Head and Neck Cancer Program

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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 Yale Cancer Center, Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about 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 head and neck cancers with Dr. Barbara Burtness. Dr. Burtness is a Professor of Medical Oncology and Clinical Research Program Leader for the Head and Neck Cancer Program. Here is Dr. Steven Gore.

Gore This is a return to Yale for you, is that right?

Burtness That is correct, I trained at Yale in internal medicine. I returned after my fellowship and was here on the faculty for about 13 years before I left for Fox Chase in Philadelphia in 2005 and now I am back.

Gore And lucky for us. What was it that made you want to come back? What is the new mission here for you?

Burtness I think the first thing to say is that there has been such an explosive growth of research and clinical research, anatomic research and recruitment of fabulous people to the cancer center and it seemed like it would be one of the most exiting places in the country to work and the mission is to make huge strides in our treatment of head and neck cancer.

Gore And how long have you been here now, again for the second time?

Burtness Two months.

Gore Two months, so you are new. I am feeling like the old man of the mountain having arrived November 1st, so pretty soon we will be having you host the radio show.

Burtness Excellent.

Gore Tell us about head and neck cancer, it seems like there are a lot of parts of the head and neck, what are we talking about here?

Burtness There are lots of parts of the head and neck and they are all exactly the same. When we speak about head and neck cancer what we are referring to are cancers that arise anywhere sort of from the sinuses in the nose down to the top of the esophagus, so common cancers in those body parts are nasopharynx cancer, which is a virally associated cancer that is very common in East Asia, for

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example. Smoking related cancers like voice box cancer and tongue cancer, and now we are seeing a dramatic rise in the numbers of tonsil and base of tongue cancers and those arise because of exposure to human papillomavirus.

Gore I certainly want to talk about that in a little bit, are all these cancers treated the same?

Burtness No, they are not, that is one of the things that make it a really interesting field to work in. There is a lot of nuance, for some areas surgery can be done without horrible functional consequences and is highly curative and in other areas the surgery might be equally curative, but the functional consequences of removing a person's entire tongue, for example, are such that we look for nonsurgical ways to cure some of these cancers.

Gore I think that many of us have known people or seen people who have had surgeries for these kinds of cancer that are frankly somewhat disfiguring and the good news is, I have got a friend in Baltimore who has lived this way for many years and he functions fine, but it would seem to me that you really want to be able to do as much preservation of the anatomy as you can, how does one approach that?

Burtness Let me first say that surgery has made huge strides, we now have minimally invasive transoral surgeries that can remove smaller tumors in the tonsil or the base of the tongue and there has also been huge progress in reconstruction with the use of new materials like AlloDerm, the use of free tissue transfer, and we have a marvelous reconstructive surgeon here at Yale, so if you do need to do one of the big surgeries that in the past would have been terribly deforming, the results now are actually much better than they were in the past. However, many head and neck cancers are very responsive to radiation and so what we call the organ preservation strategy has long been to look at using radiation in combination either with chemotherapy or with a biologic treatment like cetuximab and doing that to curatively treat the area where the tumor is without having to do the large operation.

Gore So is the goal no longer to take out all the cancer surgically, that seems to be what I remember from when I was a medical student?

Burtness You start with a very careful assessment of, can you do that, are you likely to get clear margins, is it likely that the operation that you are planning would get everything out? And then if it got everything out, what would that mean for the patient in terms of functional impairment, the nature of the reconstructive surgery, how much rehab is involved to get back to speaking and swallowing normally, and if the consensus is either that the operation might not actually get all the way around the cancer or that the functional outcome even with reconstruction might not be that good, in that case then we think about using chemotherapy and radiation in place of surgery.

Gore Wow.

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Burtness Once the patient is done with the chemo/radiation we do reassess them to see, did it work? Has the tumor gone in the wake of the radiation? It can take between four to twelve weeks to know that answer for sure but if there is evidence that the cancer persists, the operation is then planned at that point. So you attempt to avert it, and I would say 90% of the time you do, but every once in a while you do end up doing the surgery.

Gore And are some patients actually cured with the chemotherapy and radiation without surgery?

Burtness Absolutely, the majority are now-a-days.

Gore That's really exiting. I want to talk more about that as well. Let us get back on track here though, how would I know I had a head and neck cancer? What would be my symptoms that would be brought to a physician's attention?

Burtness Just as there are many sub-sites, there are many ways that these cancers can present. A common thing for a person with tongue cancer might be a non-healing sore on the tongue that might be a little bit painful. There might just be thickening. Sometimes people do not really feel the mass, but they start to notice trouble swallowing or thickening of their speech, speech is not as clear as it was. People with voice box cancer might develop hoarseness or an inability to project if they were trying to speak loudly. People with the tonsil and base of tongue cancers, those tumors are small and they are in a sort of a forgiving part of the back of the throat and many of those patients present not with a feeling where the primary tumor is, but they feel a mass in the neck and that is a lymph node that started to expand because cancer cells have traveled to the lymph node. There are some symptoms that people develop that are so similar to things that we get normally have, that they can lead to a delay in diagnosis because people blow them off. For example, a bit of nose bleeding can be the first sign of nasopharynx cancer or what seems to be chronic sinusitis and might actually start in allergy season and is slow to resolve because there is a mass at the back of the nose, or earaches, so it turns out that it is not normal for an adult to develop an ear infection and there are a couple of other causes that are not related to cancer, but head and neck cancer is one of the most common causes of an earache in an adult.

Gore And is the diagnosis usually made by a primary care doctor? What has been your experience there?

Burtness I think that there is much more awareness of the need to work-up a neck mass, in particular, very carefully than there was even a few years ago. What one would hope is that if a person went to their primary care doctor with a swollen lymph node in the neck and the doctor thought maybe it was from an infection and put them on antibiotics that that would not turn into many months of switching around the different antibiotics and so forth, which can happen, but ideally if there is a mass in the neck it would be sampled with a fine needle aspirate, which is a way of obtaining some cells to look at under the microscope without making an incision in the neck, we do not want an incision in the neck because many of these patients will need a lymph node dissection where we

9:47 into mp3 file <http://yalecancercenter.org/podcasts/2014%200706%20YCC%20Answers%20-%20Dr%20Burtness.mp3>

want to remove all of the lymph nodes together as a package and anything that has been done surgically to change the lymph node drainage or change the anatomy in that area is not good. So, hopefully what happens is the person has a fine needle aspirate and some kind of imaging test, either a CAT scan or an MRI. The lymph nodes that turn up with these human papillomavirus associated tonsil cancers tend to be very cystic and I won't call it an epidemic but there are certainly a lot more of these cancers than there was 10 or 15 years ago. Early in the period of the increase of these HPV associated cancers, sometimes you would get a CT report calling the cystic masses as branchial cleft cyst and there has been a big effort to educate the community that new onset branchial cleft cysts are not seen in middle-aged people.

Gore Is a branchial cleft cyst a serious thing somebody would worry about otherwise?

Burtness No, it is a benign developmental abnormality.

Gore For something benign that is an awful name.

Burtness Yes.

Gore Just for our listening audience, that sounds really scary.

Burtness It is a benign abnormality but it is one that if you are going to have it you should know by the time you are a kid and so when a 50-year-old person comes in with a new mass in the neck that is not the diagnosis, and I think there has been good improvement in the ability to make this diagnosis in recent years.

Gore I think about 5 or 10 years ago, my dentist in Baltimore, and I happen to get my teeth cleaned four times a year because I am a plaque former, but every time he does this oral cancer screen, and I have always felt like how has something formed in three months or whatever, but in some ways it is a little reassuring that somebody is looking out for it.

Burtness I do think that dentists are the only people that really look carefully in our mouths on a regular basis and it is a good thing that they are trained to be responsive to things that aren't always teeth problems, but they might be the first person to see.

Gore Yeah, it is interesting, I am fascinated by what you are talking about, these virally mediated cancers and I think that our audience will probably be interested in that as well. You are talking about this HPV virus, is that the same virus that is involved with genital warts?

Burtness Yes, and with cervix cancer, and it is a virus many people have been exposed to. There are over 200 types of human papillomavirus and there are several, particularly HPV 16 and 18, that are

12:36 into mp3 file <http://yalecancercenter.org/podcasts/2014%200706%20YCC%20Answers%20-%20Dr%20Burtness.mp3>

much more likely to lead to cancer than the others and people are exposed to these viruses sexually and if the tonsil becomes infected, in most people, the infection is cleared, but there are some people and we have not yet really defined what is different about them, if it is a genetic difference, or if it is related to the immune reaction they have to this virus when they were exposed, but in some people the infection is not cleared and it can lead to cancer.

Gore We are definitely going to want to talk more about this fascinating subject after the break, but right now we are going to take a short break for a medical minute. Please stay tuned to learn more information about head and neck cancer with Dr. Barbara Burtness.

*Medical
Minute*

Genetic testing can be useful for people with certain types of cancer that seem to run in their families. Genetic counseling is a process that includes collecting a detailed personal and family history, a risk assessment and a discussion of genetic testing options. Only about 5% to 10% of all cancers are inherited and genetic testing is not recommended for everyone. Resources for genetic counseling and testing are available at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven. The Yale Cancer Center cancer genetic counseling program is a new frontier in the fight against cancer. The program provides genetic counseling and testing to people at increased risk for hereditary cancer and helps them to make informed medical decisions based on their own personal risk assessment. 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.

Gore Welcome back to Yale Cancer Center Answers. This is Dr. Steven Gore and I am joined tonight by my guest Dr. Barbara Burtness. We are discussing head and neck cancer. Barbara, before the break you were telling us about human papillomaviruses and how they are involved with tonsillar cancer, which you said was increasing in frequency?

Burtness Yes, it is increasing in frequency by several percent per year. It is one of the cancers that is on the most dramatic rise.

Gore Is that because the viruses are more common or changes in sexual practices or does anybody know?

Burtness People have tracked the rise in these cancers beginning in the late 1960s, so there is a soft hint that it may be related to lifestyle changes. There are data that show that a larger number of partners or a larger number of people that you have kissed is associated with a higher risk for this. Partners of women who had abnormal Pap smears might be more likely to have it and there are many things we do not know about why it is on the rise.

15:34 into mp3 file <http://yalecancercenter.org/podcasts/2014%200706%20YCC%20Answers%20-%20Dr%20Burtness.mp3>

Gore And is there a gender predisposition to this cancer?

Burtness Yes, the gender predisposition is for men and it is quite striking, about six men get this cancer for every one woman.

Gore Wow, I know for women, to prevent cervical cancer, it is now recommended that young adolescents or preadolescents receive vaccines against HPV. Is there anything like that to prevent the tonsillar cancers?

Burtness We believe that it is quite likely that the identical vaccines will protect people from tonsillar cancer and it is now been recommended that boys as well as girls who are between the ages of 11 and about 20 should receive the vaccine. It is clearly going to prevent genital warts, prevent cervix cancer and quite likely I think also prevent tonsil cancer.

Gore So this is a cancer that we could hope could go away if our vaccination policies are applied rigorously?

Burtness Yes, that is right.

Gore It is always good to have cancers we can get rid of by not letting them start in the first place. Does insurance pay for the vaccine, do you know?

Burtness I believe that it does.

Gore We had my son vaccinated but this was kind of early on and there was a question about whether they would cover it or not. I was willing to pay anyway because it seems so important, but I am sure things have gotten better since, at least I hope so. So what happens to patients who get these cancers? Is this another kind of surgically treated cancer like some of the other ones you are mentioning?

Burtness So the primary cancer is usually pretty small. The bulkier area is the lymph node metastases in the neck and there are data that stretch back about 15 years now demonstrating that for these patients who are treated with chemo/radiation, the cure rate is much higher than for the traditional tobacco and alcohol kind of associated cancers. So actually the chance of dying of one of these cancers if you are treated with chemo/radiation is only about a 5th of the chance of dying, if you have tobacco or alcohol associated cancer. However, with the advances in surgery, there is now also the option for some patients, if the primary tumor is small enough, to have a transoral removal of the tumor, have a neck dissection and then go on to receive hopefully radiation without chemotherapy and so an important part of the conversation when a patient comes in to see the multidisciplinary clinic and meets the medical oncologist and radiation oncologist and the surgeon is to define

18:21 into mp3 file <http://yalecancercenter.org/podcasts/2014%200706%20YCC%20Answers%20-%20Dr%20Burtness.mp3>

whether the primary tumor is small enough and the nodes seem contained enough that minimally invasive surgery is the right way to go, or if there is a hint that the surgery would not get all the way around the tumor or that the cancer has started to break through the capsule of the lymph nodes, then we prefer to go with the chemotherapy and radiation. Given that the cure rates with our traditional treatments are so high for the HPV associated cancers, and also given that we figured out how to give these treatment in patients with the other kinds of head and neck cancer, the question that has risen in our research in the past several years is, are we actually over treating some of the people who have HPV associated cancers and could we be giving them a lower dose of radiation and still cure them, but leave them with less side effects in the long run? So we recently completed a study where people with human papillomavirus associated cancer received a few cycles of chemotherapy before they started their radiation and we looked at their response to chemotherapy and if they were somebody who got a clinical complete response to the chemotherapy, we assign them to get a lower dose of radiation and also to get a biologic instead of chemotherapy.

Gore What is a biologic?

Burtness Biologic is a medicine like cetuximab, which is an antibody rather than a straight forward DNA poisoning chemical, it targets something called the epidermal growth factor receptor, which is common in head and neck cancers and it leads to less long term toxicity when it is given with radiation.

Gore Okay.

Burtness In this study what we found was that if you were a nonsmoker and you had an HPV associated cancer and you had had a complete response to your chemotherapy, the cure rates appeared to be 96% even with getting a two-week shorter course of radiation.

Gore Wow! That is spectacular.

Burtness We thought it was very good and so our goal is to refine what is the least toxic chemo regimen we can use to pick out these patients and then for nonsmokers who have HPV associated cancers to try to do a larger study that can definitively prove that people do not really need seven weeks of radiation anymore for their cancer.

Gore Did you have a hard time getting patients to agree to being treated less, I mean that seems so scary if you know something works, it seems like going off the cliff.

Burtness Yeah, although if you think about their experience, having them lie down on the radiation table every day, 5 days a week, the patients actually loved this concept and when this study was done

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enrolling there were still many people who were calling up to ask, did we have enough data yet to do this off study. Where we had trouble actually was in the approval process, I think the medical community was extremely conservative when we first proposed this.

Gore I think I lost a step here, say I am at my dentist getting my oral exam and he sees something in my tonsil, I am assuming he will send me to a surgeon, how do I get into one of these multidisciplinary things because I do not want to go to a surgeon who wants to rip everything out and not talk to these other people like you and the radiation oncologist who might be able to do some more conservative surgery. How do we get into one of the multidisciplinary specialty clinics?

Burtness You call up. Many people may not have cancer at the front of their minds when they first feel something on their tongue or have an earache or feel a mass in the neck and it is quite likely that many of these people might be going to a local ear, nose and throat doctor. However, I think once the diagnosis of cancer is made, it is very rational to seek an opinion at a comprehensive cancer center where essentially all patients with this sort of diagnosis are seen by a multidisciplinary team where if the person is going to be treated here they also meet our speech and swallowing experts, we set them up for evaluation before the treatment. We make sure that they get exercises that continue during the radiation to minimize any impairment to their swallowing. We make sure that there is good rehabilitation when they are done. We meet as a team on a regular basis to discuss all the cases, to review the pathology, to look at the x-rays. So, I do think that if a person does have this diagnosis established then it is an uncommon enough cancer that being treated by a team that sees a high volume of it makes a big difference.

Gore Is it your experience that many private or local community head and neck surgeons will routinely make a referral to this kind of comprehensive clinic or is this something patients should be very proactive about if they are interested in getting that kind of care?

Burtness I think there are many ENT surgeons who understand the importance of high volume surgery, high volume radiation and a multidisciplinary team. It is not everyone though and so what I would say directly to the patient is, you are your own best advocate. If you have been told that you have a cancer, seek out the best possible care.

Gore That is a great advice. You said that these cancers tend to be more curable than the routine tobacco and alcohol related head and neck cancer, do we have any ideas why the tumors are fundamentally different genetically, what is known about that?

Burtness They are much different. There is a gene called P53, which is responsible in our cells for repairing damage that comes into our genetic code and once you stop being able to repair damage to your genetic code, every time your cells divide they become more and more bizarre and they behave more aggressively and the cancers are more treatment resistant. So a P53 mutation, an

24:34 into mp3 file <http://yalecancercenter.org/podcasts/2014%200706%20YCC%20Answers%20-%20Dr%20Burtness.mp3>

abnormality in that tumor suppresses the gene, the most common abnormality in tobacco associated head and neck cancer, and it is not present at all in the human papillomavirus associated cancers.

Gore How interesting. Why don't we just get drugs that treat the mutant P53 then?

Burtness Yes and that would also be a great way to get the Nobel Prize. People have been working on that for about 30 years and there are new indications that there are new strategies for getting at that with P1 inhibitors that might be more successful. It has been the Holy Grail for a long time.

Gore Every good idea I have, somebody else had it first, that is story of my professional career. Since we cannot target the P53 right now, what can we offer that is interesting and new to patients with these harder to cure head and neck cancers?

Burtness Two things, one is that their biologic treatment that I mentioned, cetuximab, does have some activity in the tobacco-associated cancers also and a big focus of our research has been trying to find out if there are any hallmarks in the cancer cell that predict they are resistant to those EGFR inhibitors, but that we could still target and so making combinations of the EGFR inhibitor with another targeted therapy that would shut the whole pathway down and we had some early trials that look fairly encouraging with drugs that target an enzyme that is called urokinase. So that is one thing people are pursuing. Another thing that has been the big story in oncology in the past two years are new drugs that manipulate the immune system and there has been such an explosion of knowledge of how the immune system is regulated and these immune cells that are described as exhausted, so they are all lined up in the cancer but they are not fighting, and they are looking at new medications that have the ability to reactivate those immune cells. There was a report at the cancer meeting in Chicago, ASCO, using one of these drugs in head and neck cancer and the response rate was about 19% and some of the responses were very durable. These were easy drugs to use. They do not have a ton of side effects and so it is certainly going to be an area where clinical trials are going to be available for people with head and neck cancer and I think it is very promising.

Gore That is really exciting for that 19%, but that is leaving 80% that are still underserved, how we are going to get there?

Burtness There may be ways to prime the cancers so that we could turn, and we just started studying this drug this year, but turn something that is a 19% drug into a more active drug, there are also ways of checking the expression of some of the immune markers in the cancer that can select outpatients who are more likely to respond and that has been shown in melanoma, when you combine two or three drugs that have targets in the immune system but it is not the same target you can

27:45 into mp3 file <http://yalecancercenter.org/podcasts/2014%200706%20YCC%20Answers%20-%20Dr%20Burtness.mp3>

dramatically increase the response rate. So I would look for clinical trials using radiation therapy to prime using combinations of immunotherapies and using biomarkers to select out the most sensitive patients.

Gore How do people find clinical trials if they are not being treated here at Smilow? Where do people go or how do they even start to negotiate that?

Burtness I think asking your medical oncologist what clinical trials are open at their office or if they know what is available at cancer centers that are nearby. There is a website called ClinicalTrials.gov, where you can just put in the name of your cancer and many trials will come up, many probably that are not that appropriate and many that are in different parts of the country, but there are a lot of resources if the patients want to find clinical trials and I think for people with head and neck cancer there are so many new ideas now that it is worth seeking these out.

Dr. Barbara Burtness is a Professor of Medical Oncology and Clinical Research Program Leader for the Head and Neck Cancer Program at Yale Cancer Center. We invite you to share your questions and comments. You can send them to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber and we are hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.