

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week, Dr. Chagpar welcomes Dr. Robert Udelsman. Dr. Udelsman is William H. Carmalt Professor of Surgery, Surgeon in Chief for Yale-New Haven Hospital and Clinical program leader for the endocrine cancers program at Smilow Cancer Hospital. Here is Francine Foss.

Foss Let us start off by having you introduce our audience to the whole area of endocrine cancer, what are endocrine cancers and what is your exact role at the Cancer Center?

Udelsman Endocrine cancers can be broadly defined as any cancer of the endocrine system, which would include the thyroid, parathyroid, adrenal as well as GI cancers of the gastrointestinal tract as well as ovarian cancer, breast cancer, and cancers of the male gonad, but many of those areas of endocrine cancers are taken care of by specialists such as urologists or gynecologists, or breast surgeons. So, my area of expertise is the endocrine cancers that include the thyroid gland, the parathyroid, and the adrenal.

Foss You lead the endocrine cancer program at the Cancer Center. Can you tell us how long we have had an endocrine cancer program here?

Udelsman I am actually not sure of that. I can tell you that I have been here for roughly twelve years and the endocrine cancer program coincided with the development of Smilow Cancer Hospital and the Cancer Center. We have been around awhile, although Smilow is relatively new.

Chagpar Let's talk a little bit about the endocrine cancers that you deal with primarily. So thyroid, parathyroid, and adrenal, how common are each of those?

Udelsman By far the most common is thyroid cancer. There are roughly 45,000 new cases of thyroid cancer in the United States per year. Whereas parathyroid cancers are so rare that in my entire career I have probably taken care of a maximum of 20, and there are roughly 300 new cases of adrenal cancers in the entire United States per year, although we have a particular interest in

them. So when you are talking about endocrine cancers, for the most part you are talking about thyroid cancer.

Foss Before the program started, you told me that the incidence of thyroid cancer is rising, and it is an epidemic. Can you talk a little bit about that?

2:42 into mp3 file <http://yalecancercenter.org/podcasts/2013%200428%20YCC%20Answers%20-%20Dr%20Udelsman.mp3>

Udelsman It is actually scary on the one hand, and interesting on another, and that is that the most commonly, or most rapidly increasing cancer in the United States and certainly in Connecticut is thyroid cancer, and one has to ask the question, is this increase real? Is it a new cancer developing? Or is it really a detection bias based upon our ability to detect very small thyroid cancers?

Chagpar Tell us a little bit more about thyroid cancer. What are the risk factors for thyroid cancer? How does one get it? How does one pick it up and how is it detected?

Udelsman First, what are the risk factors? Well there are certain clear risk factors such as genetics that there are certain families in which thyroid cancers occur based upon a genetic predisposition. This is particularly true in medullary cancer of the thyroid, which is in fact a relatively rare cancer. There are certain families that we follow that clearly have risk factors based upon genetic traits. In the state of Connecticut there is actually an interesting incidence of papillary thyroid cancer, which is not as common as far as genetic traits are concerned, but papillary thyroid cancer is actually the most common of all of the thyroid cancers, although the vast majority have nothing to do with genes, at least as best as we can determine. And finally there are other rare cancers that may have genetic predispositions, but they are so unusual. By far and away, the really big topic, is that 95% are thyroid nodules, and thyroid nodes are actually very common in the US population, in fact 15% of women in the United States have thyroid nodules and another interesting thing about thyroid nodules and thyroid cancers is that they are three times more common in women than they are in men.

Foss Can you talk about the age of onset of thyroid cancer and whether that is in fact changing.

Udelsman First of all there is a clear incidence that the older you are, the more likely you are to have a thyroid cancer and that is picking up, but the fact of matter is that children have thyroid cancers as well. We are actually particularly interested in children with thyroid cancers because of the dramatic effect upon the management of these tumors by the experience of the individuals taking care of them. I myself, my career is actually evolving that I am getting more involved in children in many ways and it is technically interesting and challenging to manage these kids with thyroid cancers.

Foss How young?

Udelsman You can see them in utero in fact. In fact, the patient's with genetic abnormalities such as MEN2B actually probably developed their cancers in utero and so we basically try to diagnose them shortly after birth.

Chagpar I want to go back to this epidemic, because one of the things that you said was we do not really know why this is. It may just be that we are picking more of these up. It may be a detection issue.

5:26 into mp3 file <http://yalecancercenter.org/podcasts/2013%200428%20YCC%20Answers%20-%20Dr%20Udelsman.mp3>We talked a little bit about thyroid nodules. Is that how people find these, they go for their usual yearly physical exam and the doctor feels their neck and says "My gosh, you have a thyroid nodule" and away we go?

Udelsman You are exactly right. The fact is that we are doing so many diagnostic screening tests such as ultrasounds of the neck for reference during carotid artery screening and we find these incidental thyroid cancers. The fact is many of these incidental thyroid cancers or thyroid nodules are less than a centimeter in size and people are putting needles into these tiny little nodules and many of those tiny little nodules prove to be thyroid cancers. So the surgeon is posed with the problem of what to do with an incidentaloma of the thyroid gland, a tiny tiny thyroid nodule that someone biopsied and in fact may actually be a thyroid cancer. It is very hard for most people not to intervene.

Foss In the past, most of the thyroid cancers were picked up because they were actually palpated as a mass.

Udelsman That is true and now we are picking them up because of these imaging studies. It is actually quite interesting that the management of thyroid cancer varies dramatically depending where you live both in United States, but particularly internationally. One of our colleagues in Japan who will be visiting us soon has been following a population of biopsy-proven subcentimeter thyroid cancers, nonoperatively. That is, they know they have thyroid cancer under the microscope, it is unequivocal that these are thyroid cancers and yet they are following these patients nonoperatively for up to ten years time and most of these patients, that is roughly two-thirds, do not appear to require surgical intervention.

Foss And we do not know in patients who present with the lumps, we do not know how long those cancers may have been sitting there?

Udelsman That is true too. Our guess is that the average patient that we see with a biopsy-proven thyroid cancer probably has had that nodule for at least five years. That is based upon doubling times of tumors in the epidemiology, but the truth of the matter is that I think we need to really settle down the public a little bit. If you have a thyroid nodule, it needs to be evaluated, but you probably do not have a thyroid cancer and even if you do have a thyroid cancer, the odds of that thyroid cancer shortening your life span are actually quite small. The vast majority of patients with thyroid cancer will live a normal lifespan. The issue is not so much cancer demise, but disease recurrence and the effect that this disease recurrence will have upon them.

Chagpar As you were talking, I was thinking about a conversation that we had here on Yale Cancer Center Answers with Peter Schulam about prostate cancer and it is sounds very much the same, that you may have a cancer, but if it is small or low grade, perhaps it does not need anything further to be treated.

8:13 into mp3 file <http://yalecancercenter.org/podcasts/2013%200428%20YCC%20Answers%20-%20Dr%20Udelsman.mp3> Udelsman Like prostate cancer, thyroid cancer is complicated. Unlike prostate cancer, where there are clear Gleason scales and the ability to predict which of those tumors are likely to cause trouble, in the thyroid we're not quite as good. So the garden variety papillary thyroid cancer, which is the most common type, we really cannot discriminate between one that is going to be aggressive and cause serious trouble and one that is probably indolent and could be left alone. We just do not have that ability. Although

recently there have been a series of molecular markers particularly something called BRAF, which is a molecular marker of aggressiveness and for the most part there is a correlation between the presence of this BRAF mutation and the aggressiveness of the tumor, although even more studies need to be done to really understand that.

Foss Just to clarify for the audience, are we absolutely certain that we can make a clear cut diagnosis of thyroid cancer when somebody presents with one of these small nodules? How certain can we be that it is benign or malignant on either side of the spectrum?

Udelsman This is where we are really dependent upon our colleagues in cytology. The standard workup of a thyroid nodule is to carefully perform a history and physical exam in all patients, but once you document the thyroid nodule, the next step is usually an ultrasound examination, and ultrasounds are completely safe. There is no radiation involved and they are very accurate. We have a wonderful diagnostic study, perhaps too accurate. The next step would be a fine needle aspiration cytology examination that is under ultrasound guidance where one usually puts a tiny needle into these nodules and then looks at the cytologic features. Cytologists are exquisitely accurate in a subset, if they are well-trained cytologists. Unfortunately, many cytologists are not. In many hospitals and many locations they are pathologists who kind of do cytology as an avocation, that is on the side. You need a really well-trained cytologist, because cytology is more of an art form than it is a science. That is it is the eye of the observer, or the quality of the cytopathologist looking under the microscope with these lesions. However, when a well-trained cytologist makes the diagnosis of cancer, the accuracy of that is about 99.9%. So you can pretty much take it to the bank that when they call it a cancer, it is. However, in some subsets of patients, and no fault of the cytologist, the cytologic details are just not there and the best they can do is say yes it is an indeterminate nodule or a worrisome lesion that will need further diagnostic studies, and it is not that they are not good, it is just that the information is not there under the microscope.

Chagpar When you have a really good cytologist and the cytologist says this is cancer, I am thinking back to your friend from Japan who is following the subcentimeter papillary thyroid cancers, if you do not have a good score like a Gleason score and BRAF may or may not be the Holy Grail, there are people who are listening to us and they are thinking, but how can they follow a cancer when they do not know if it is a cancer that is not going to kill them, or it is a cancer that is.

Udelsman Those are wonderful questions and a complex paradigm and it is where you really need to work with people who have a lot of insight. It is very easy to intervene on every patient. Surgeons love to operate. They operate, they cure the patient and everybody is happy. However, the treatment should not be worse than the disease. So, if we talk about epidemiologic studies and if we look at 11:57 into mp3 file <http://yalecancercenter.org/podcasts/2013%200428%20YCC%20Answers%20-%20Dr%20Udelsman.mp3> certain countries where you do a routine autopsy and you do micro sectioning that is very careful of the thyroid glands of a patient who died from non-thyroid related causes, the fact of the matter is that in up to 35% of patients, or even higher, they will find subclinical incidental thyroid cancers and lord knows that the majority of these patients would not have benefited from surgical intervention. That is where this balance thing comes in. When do you intervene and when do you follow.

Foss But in the United States, it sounds like we tend to intervene more and to operate on these things rather than to observe them.

Udelsman That is absolutely right. The average American has a real hard time knowing, they have a biopsy proven thyroid cancer or any cancer, and being followed nonoperatively, but in reality that is not a reasonable paradigm for the subset of patients, what you need to do is find yourself in the hands of an expert in managing these problems.

Chagpar Tell us what the follow-up would be like, because certainly it is fine to say, you have got a small papillary thyroid cancer, this is likely not going to kill you, but we do not really have a good differentiator, you are a world renowned thyroid expert, but you are going to follow that patient. Tell us about what that follow-up is like so that the patient has some reassurance, that when this thyroid cancer if it is going to be an aggressive thyroid cancer that will do something bad is going to do that. That it is going to be picked up.

Udelsman Well, first I think it is fair to say that in the United States and for the most part in the world, the standard treatment of biopsy-proven thyroid cancer is surgical intervention, that is where we are right now. I do know that the NIH is starting to organize consensus groups and in fact treatment groups and I am actually a part of that, to say maybe there is a subset of patients who should not and would benefit from non-operative intervention. However, those trials have not been initiated in the United States and as the gold standard, all trials are randomized prospective trials. It is difficult to do that in a single institution because the numbers would have to be created on something that

we call a power analysis, that is the ability to predict what is the population of patients required to answer the question in a safe manner. I actually believe those trials will get started eventually. I have actually been involved in such trials, in designing such trials, and I am actually the guy who said we should do the trial in thyroid cancer. However, in thyroid cancer there are many other questions such as whether or not one should routinely remove the lymph nodes for instance, in what we call the central neck, and in our group, the first author of that study is Tobias Carling and I am the senior author, which demonstrated that because the power analysis predicted that the size of the population would literally be in the thousands, that this trial should never be done because it is just not possible. Unfortunately, many people do trials that are underpowered, that is they do not have enough patients in the population to answer these important questions and they go down the garden pathway of saying yeah the trial shows no significant difference, but there are not enough patients in the studies.

15:07 into mp3 file <http://yalecancercenter.org/podcasts/2013%200428%20YCC%20Answers%20-%20Dr%20Udelsman.mp3> Chapar We are going to talk more about trials in thyroid cancer right after we take a short break for a medical minute.

Medical

Minute It is estimated that nearly 200,000 men in the U.S. will be diagnosed with prostate cancer this year and 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. With screening, early detection and a healthy lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patients at Yale that uses three dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and more information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Francine Foss. Our guest today is Dr. Robert Udelsman and we are discussing thyroid cancer, in particular, endocrine cancers as a global topic, and right before the break we were talking about the treatment of thyroid cancer and I thought we could go back to that. Often on this show we talk about the treatment of various malignancies and it is really a team approach. Is this true in thyroid cancer?

Udelsman Yes, there couldn't be a better example of a team approach than in thyroid cancer because we as surgeons are just one small piece of a much bigger equation. We rely upon our colleagues in endocrinology, cytopathology, pathology, nuclear medicine, ultrasonography, and advanced axial imaging including CT and MRI. There is just so much involved and it is why patients benefit from coming to a place that has this whole team approach to the treatment of cancers and it is not just Yale or M.D. Anderson or Sloan-Kettering, all of these institutions have put together these team approaches to the treatment of cancer and not just cancers, but the diagnosis of cancers and every part of that equation is critical.

Foss If you have a nodule and you come into the clinic like the one at Smilow Cancer Hospital, who do you see first and how many patients actually end up seeing the surgeon?

Udelsman The majority of patients with thyroid nodules will never see a thyroid surgeon and shouldn't. The way the screening process works in the United States is that the majority are managed by endocrinologist, exquisitely well trained endocrinologists and if they have a thyroid nodule they

18:04 into mp3 file <http://yalecancercenter.org/podcasts/2013%200428%20YCC%20Answers%20-%20Dr%20Udelsman.mp3>

will likely be referred to an ultrasonographer and the ultrasonographer will obtain a biopsy and the specimen would be sent to a cytopathologist to review the biopsy results.

Udelsman That alone will screen out the majority of patients who do not need intervention because a majority of thyroid nodules have no indication of malignancy.

Foss So by the time the patient sees you they have been through all of that and it has been determined that they need surgery. How do you approach a patient like that?

Udelsman Yes, they may need surgery. A legitimate cause of referral to the surgeon is for a conversation about whether or not surgical intervention is appropriate, and if so, what the appropriate intervention is. I would like to

emphasize again, that every patient who gets referred to either an endocrinologist or a surgeon needs a well performed history and physical examination to think about not just the primary tumor, but other risk factors. For instance, if they have underlying cardiovascular disease how would that affect their disease management?

Chagpar Let us say that they have been through the screening process, they have had a biopsy that shows thyroid cancer, you see them, tell us a little bit more about what the surgical options are? What are the side effects of that surgery and how other team players may affect that therapy as well?

Udelsman Biopsy-proven thyroid cancer once used to be a controversial topic about whether they want to do a lobectomy or a total thyroidectomy. For the most part our societal groups, including the American Thyroid Association, have recommended for the most part a total thyroidectomy for most well differentiated thyroid cancers. There is still a subset of patients who might benefit from a lobectomy or partial removal of the thyroid gland but most people would agree that a total thyroidectomy is the treatment of choice for thyroid cancer. It gets controversial when we start to get into the lymph nodes and whether we want to do a lymph node dissection, at least in the central neck, for the majority of patients. Nonetheless, we do believe that ultrasound screening of both the central, and particularly what we call the lateral neck or the area of the neck outside or lateral to the carotid arteries, should be performed in all patients. We and the American Thyroid Association believe that that is appropriate in virtually all patients.

Foss Can you talk about how important it is from the patient's point of view to know that their surgeon has done a lot of these cases? Is this technically a difficult operation to do and is this an area where expertise is really an important thing that patients should be looking for?

Udelsman It is like all things, it is like a plumber or an electrician. In the majority of cases, your average trained electrician or plumber can do a perfectly fine job. However, one can't predict when in the operating room one is going to run into a problem and when you run into a problem having a well trained expert is so beneficial to the patient and there is well performed data to suggest that those with experience have better results as far as decreased complication rates and in fact decreased

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tion. So this is the area where experience really does count.

Chagpar Let's get back to what potential complications there are with thyroid surgery.

Udelsman It is like real estate, it is all about location, location and location. The truth of the matter is removing the thyroid gland in itself is not a technically difficult tour de force. What is difficult is to remove the thyroid gland adequately and at the same time not to remove or harm proximal structures such as the nerve to the vocal cords that control your voice, or the parathyroid glands so called because they live next to the thyroid gland and in this case the parathyroid glands control calcium homeostasis and removing or injuring the parathyroid glands can result in long term problems such as low calcium levels, low parathyroid hormone levels and bone disease.

Foss If the patient successfully goes through the surgery, can you tell us how long it takes to recover and what the patient will experience during that recovery?

Udelsman Yes, this is actually a nice thing because in many cases the surgery may be harder on the surgeon than it is on the patient. Because this patient comes in the morning for the most part, has an operation, and almost always goes home the very next day and they actually feel pretty good. Because in almost all circumstances we do not cut any major muscles and anesthesia management these days is so good, it is so unusual to have an anesthetic complication. So the complications are almost all technical in nature and for the surgeon it is procedure related.

Chagpar For many cancers we talk about additional therapies that may be needed, chemotherapy, radiation therapy, what are the adjuvant therapies that are needed for patients with thyroid cancer?

Udelsman For the most part, thyroid cancer, at least well differentiated thyroid cancer, is treated with radioactive iodine in the majority of patients. This is such a wonderful thing though. Just imagine if we had a magic puller that could clearly hone in on to disease treatment in the majority of patients and we have such a treatment with a very high specific and therapeutic ratio in thyroid cancer because thyroid hormone is based upon iodine. Iodine is the backbone of thyroid hormone and we have the advantage of taking iodine and making it radioactive and then giving the patient a liquid to drink or to swallow that hones

in on the cancer and does very little harm to associated structures. In contraryt distinction, the other treatments such as external beam radiotherapy which will kill rapidly dividing cells but unfortunately have significant toxic effects upon all cells that are in the pathway of the radial beam and yet we can still give external beam radiotherapy for cancers because our talented physicians tailor those beams relatively selectively to minimize trauma to associated structures.

Foss So do all patients need the radioactive iodine therapy?

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Udelsman No, there are a subset of patients who have such well differentiated and small cancers that they probably would not even benefit from radioactive iodine therapy. However, because the toxicity of radioactive iodine is so low we tend to have a relatively low ratio or threshold for giving it to many patients.

Chagpar Rob, clearly one of the nice things about the thyroid is that you do have this magic bullet. It is one of the few organs that have that, but another thing that is nice about endocrine organs in general is that they make hormones, hence they are called endocrine. How do you utilize that fact in the treatment of thyroid cancer?

Udelsman You are absolutely right, so in addition to just having this wonderful therapeutic treatment with radioactive iodine, it turns out that most endocrine tumors are under hormone control and there is good scientific data to show that the pituitary gland secretes a hormone called TSH, thyrotropin or thyroid stimulating hormone and if we suppress that we can decrease the growth and spread of cancer, so for virtually all patients with thyroid cancer we administer thyroid hormone to suppress the secretion of TSH by the pituitary gland and this will result in decreased tumor growth or spread.

Foss Is this a life-long therapy for the patient?

Udelsman It is indeed for two reasons. First of all if we remove the thyroid gland we have to give thyroid hormones or the patient will have a very bad outcome, and in fact, die eventually of hypothyroidism. Furthermore, patient's do not like being hypothyroid so it is very easy to convince them to take their thyroid hormone because otherwise they would not feel well. Unlike other drugs, hypertensive drugs or other drugs that make you feel bad, thyroid hormone

makes you feel good. The danger being that there is the temptation to take too much and the patients have this concept sometimes that they can decrease their weight or have more energy by taking too much thyroid hormone which is in itself not a technique for weight loss.

Chagpar It sounds like we have some really great therapies for thyroid cancer. How do people with thyroid cancer do overall? What are their outcomes like?

Udelsman The overwhelming outcome, and I would say 90% to 95% of patients with well differentiated thyroid cancer, have long-term survival, that is the disease will not decrease their life span, however, all patients are at risk for recurrence and 15% of patients will have recurrence. Recurrence as manifest by recurrent disease in the central or lateral neck in the lymph nodes will result in intervention and intervention in itself can have complications or morbidity associated with it. So the goal is to minimize prevention or to treat prevention and to minimize complications.

Foss Do patients go back for surgery again if they have a recurrence?

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Udelsman Well, the next step would be to stage them. If they have a localized recurrence in the lymph nodes, the least toxic form of long term treatment is to re-do surgery. Now we are in the era where we are detecting recurrence in these tiny little nodules and yet we have to ask is surgical intervention the ideal treatment for these patients and we have this discussion on a routine basis.

Dr. Robert Udelsman is William H. Carmalt Professor of Surgery, Surgeon in Chief for Yale-New Haven Hospital and Clinical Program Leader for the Endocrine Cancers Program at Smilow Cancer Hospital. If you have questions or would like to add your comments, visit yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.