

Dr. Robert Udelsman, A Focus on Thyroid Cancer May 17, 2009 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed and Francine welcome Dr. Robert Udelsman. Dr. Udelsman is the Chairman of the Department of Surgery at Yale School of Medicine and he is an expert on thyroid cancer. Chu Let's start off with a very basic question, what is thyroid cancer? Udelsman Thyroid cancer is a malignancy that originates in the thyroid gland and there are several subtypes of thyroid cancer. Chu Can you get into a little bit about the different subtypes of thyroid cancer? Udelsman There are four fundamental subtypes of thyroid cancer; papillary, follicular, medullary and anaplastic. They are derived from cells that originate in the thyroid gland. I should also mention that a primary thyroid lymphoma can also start in the thyroid gland, and in fact, thyroid lymphoma is more common than the rarest type of thyroid cancer, which is anaplastic thyroid cancer. Foss Tell us a little bit about how common thyroid cancer is. Udelsman Thyroid cancer is actually fairly common, but we should step back and think about the fact that thyroid nodules, where thyroid cancer develops, are very common in the population in America. There are about 35,000 new cases of thyroid cancer per year in the United States. Foss Are there any specific risk factors for thyroid cancer? Udelsman Yes, there sure are. One risk factor is radiation exposure as a child, particularly to the head and neck, although that process is no longer done, for instance, for acne or for thalamic enlargement. However, we still have a new population of patient's who have, for instance, mantle radiation therapy for Hodgkin's disease and they are at risk for thyroid cancer throughout their lives. In addition, individuals, especially children, who are exposed to radiation accidents, for instance, the Chernobyl population, are all at risk for thyroid cancer for the rest of their lives. 2:12 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-17-09.mp3 Chu How about the radiation that kids and/or adults might be exposed to with dental procedures? Udelsman It is thought that the typical x-rays that individuals get for dental procedures, or even spine surgery, is not a significant risk factor for thyroid cancers. Those parents should not be overly concerned about that population of patients. Foss Can we talk a little bit about thyroid nodules, which are very common? How often does a thyroid nodule lead to a thyroid cancer? Udelsman This is a very important and basic concept that a thyroid cancer in almost all cases starts out as a small thyroid cancer that grows, whereas if you have a thyroid nodule that is benign from the start, it will probably remain benign for the entire lifespan of that nodule. That thyroid nodule can be seen in up to 15% of the normal female population in the United States, but certainly 15% of women in United States do not have thyroid cancers. Chu Do thyroid nodules occur more frequently in women

than men, because your answer kind of suggested that? Udelsman Yeah, you are absolutely right. They sure do. There is about a 3:1 ratio of female to male predominance of thyroid nodules in the female population. It's a strange thing we see and there are other endocrine tumors that also have a female predominance. Chu Do we know why, for thyroid nodules, it occurs more frequently in females? Udelsman You would think there would be a simple estrogen explanation or a lack of testosterone or some other growth factor, but the truth is we don't really have a clear explanation why they are more common in women than men. Foss Do all women who have these nodules need to have them biopsied? Udelsman That's where we get into a little bit of complexity. What do you do if you have a thyroid nodule? The answer sort of depends on how it's found and the size. Unfortunately, or perhaps fortunately, because we do so much screening with ultrasound examinations, we are finding more and more thyroid nodules that are smaller and smaller and we have a real dilemma in the field. What is the smallest size that indicates that you should biopsy nodules as opposed to just watching it and monitoring it? 4:14 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-17-09.mp3 Foss Are most of these nodules picked up by physical exam? How does one know that one has a thyroid nodule? Udelsman It's not uncommon for someone to say, "I was looking at myself in the mirror and I saw a nodule," or "My doctor or my gynecologist felt a nodule," and that's how a patient gets referred. It also happens that a patient goes for an incidental ultrasound for carotid study to make sure they have adequate blood flow for their carotid arteries, and they find an incidental thyroid nodule, we also see that population of patients. We see both types of populations. Chu Rob, do these nodules ever cause any alterations in the normal function of the thyroid? Udelsman As you know, thyroid hormone is critical for life, it gives you the energy for living, and almost all thyroid cancers are nonfunctional, they do not make thyroid hormone, but remember, a thyroid nodule is just as thyroid nodule. For instance, we also see a wide variety of patients with thyroid hormone abnormalities, patients with Graves' disease or hot toxic nodules, these patients do have thyroid hormone abnormalities, but those are not cancers. Foss Are there symptoms that a patient would experience if they had a thyroid nodule? Udelsman The first symptom would be a mass. They would feel something in their neck or they might experience a coughing sensation or difficulty swallowing. Pain is an advanced symptom, or loss of function of a vocal cord such that they develop a hoarse voice, those are advanced findings usually of advanced tumors. Chu If any of these symptoms should be present in an individual, what should they then do? Udelsman As all things, if you have a hoarse voice for two days associated with the cold and it goes away, it's probably not a big deal, but if something persists or if there is a mass there, you should consult with your primary care doctor. Chu And that should be the general internist or primary care physician? Udelsman It feeds into many different ways in our society, it could be a pediatrician, it could be an internist, and these days the gynecologist is often the only primary doctor that many 6:11 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-17-09.mp3 women

see. It's an acceptable way to feed into it as well, as well as an internist or family doctor. Foss Does it make any difference in women whether these nodules are palpated at certain times of the month? Do they vary with the menstrual cycle or with hormonal replacement therapy or any other factors? Udelsman I know of no data to answer that question specifically, although you mention hormonal therapy, you are obviously thinking of estrogen and progesterone, but if you do give thyroid hormone, sometimes you can shrink these nodules. But I know of no clear relationship between estrogen and progesterone in shrinking these nodules. Chu If a nodule or mass is identified by the primary care physician, what would be the next step? Udelsman Often, but not always, these patients are then sent to an endocrinologist. An endocrinologist is an internal medicine doctor with specialty training in endocrinology. At that point they do some basic work, generally a history and physical examination and measure some selective hormone levels, particularly a TSH, or thyroid stimulating hormones, and that can suggest the function of the thyroid gland. But in most cases, most patients will progress on to a biopsy and that's performed with a technique that we refer to as FNA, which stands for fine needle aspiration. Foss Do patients need to have any form of x-ray before they go into the biopsy? You mentioned that they have an ultrasound for the diagnosis, but do they need to have other x-rays like CAT scans? Udelsman There has actually been a dramatic shift in how we manage these. Back, I would say 15 years ago, most patients would go into a nuclear medicine study, an I-131 study. We almost never do that in the primary management. As far as CT scans, PET, or MRI scans, those are expensive studies that are unnecessary, they lack the sensitivity that we need and we find a simple ultrasound to be the ideal study in the initial work-up of a thyroid nodule. Chu Once a biopsy is done, then obviously the pathologist is going to play a critical role in terms of evaluating that tumor tissue or that tissue. Udelsman I am so glad that you asked me to be on the this show, because it gives me a chance to talk about the pathology inside of pathology, and the art form that it is. Reading the slides from a thyroid biopsy is an art form and there are a few people who really have exquisite skills. 8:22 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-17-09.mp3 in doing that, and the subtle abnormalities that they can see under the microscope, not all people who read slides have those well-developed skills. The quality of the person who biopsies a nodule, and the person who reads it, are critical to making good decisions for a patient. Foss One thing that's really different about thyroid cancer compared to some of the other tumors that we treat is that we require a piece of tissue. We are not satisfied with the fine needle aspirate, and you have touched on this a little bit about the critical nature of the cytopathology. Do you often have to go on to get a bigger piece of tissue? Udelsman The answer is yes. But when have to go on, it usually involves more than just a piece of tissue, it usually involves an operation. The fine needle aspirate cytology, when we get a good quality specimen, can be diagnostic of cancer, and if it unequivocally shows a cancer, we go straight to definitive surgery; we do not do any in between steps because we have essentially 99.9% confidence in that. However, about 20% of the aspirates

have what we call indeterminate cytology and getting more tissue or a bigger core piece of tissue would not help us. We are actually forced to remove the lobe containing the thyroid gland to actually remove a piece of the organ to answer the question whether it's malignant or benign. Chu Are there any specific types of thyroid cancers that might have an increased risk for spreading beyond the local confines of the thyroid? Udelsman By definition any thyroid cancer could spread to many areas of the body, but different subtypes that I mentioned earlier have different rates of spread to different systems. For instance, papillary carcinoma of thyroid spreads to lymph nodes very early in its course, whereas, others such as follicular, has more of a blood stream spread to other areas such as the lungs, or perhaps the bones. Medullary cancer of the thyroid tends to stay localized to the local area and the lymph nodes, and anaplastic can basically go anywhere and is very aggressive locally. Each has their own flavor to them. Foss A lot of times in advanced cancer we see patients who develop what we call an unknown primary; they present with a cancer of indeterminate origin and in some cases that turns out to be a thyroid cancer. How often do you see thyroid cancer presenting as an unknown primary? Udelsman That's a wonderful question. Occasionally, we will see a patient who presents with a lesion somewhere else in the body, maybe their leg or bone somewhere, and finally we get enough tissue and it is the pathologist or the cytopathologist that says, "You know, this10:51 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-17-09.mp3 looks like a thyroid primary." There are special tests they can do by measuring certain markers like thyroglobulin that can answer that question. If in fact they have wide spread metastatic disease outside the thyroid gland, believe it or not in that situation we are actually relieved to some extent, because that is a treatable cancer. Perhaps not curable, but treatable, and we can then go and remove the thyroid gland and treat those patients with radioactive iodine. The radioactive iodine can have great efficiency in treating tumors even outside the neck and even in areas of bone. In some ways it's a convoluted way to get there, but sometimes it works. In addition, every once in a while we see a patient with a thyroid nodule who actually has metastatic disease from something else, particularly something like renal cell carcinoma that goes to the thyroid gland, and occasionally that can cause a real diagnostic dilemma for us figuring out what's going on. Chu I guess that's why the I-131 scans were so in vogue, because people used it as a way to see if the thyroid tumor had spread outside the thyroid. Udelsman They do, but of course, we use a lot of I-131 probes and scans once we have removed the thyroid gland. Can I digress to I-131 for just a moment? Chu Sure. Foss Sure. Udelsman In the treatment of thyroid cancer there are really three functional treatments. The first is surgery, we remove the tumor. The second is we use I-131, which I will discuss it in a little bit more detail, and the third is we administer thyroid hormone long term to suppress the pituitary secretion of TSH. But what's so exciting about I-131, Ed, is that it's a magic bullet. Because of the way thyroid hormone is made, it's made from three molecules of iodine or four molecules of iodine resulting in T3 and T4, it's so concentrated in thyroid producing cells we can then administer

radioactive iodine like a magic bullet and have tumor kill ratios that are so advantageous with little toxicity to normal tissues. It's a wonderful thing that we have for the thyroid gland and part of the reason our patients do so well. If only we had such a thing for other tumors that was so specific for the cancer that we treat.

Foss Is the I-131 therapy equally effective for all the different types of thyroid cancer?

Udelsman No it's not, and as you might predict, the more its like normal, the more likely I-131 is to work, and it's exactly as such. So, papillary cancers are very effectively treated. Follicular is fairly well, but a little less. Hurdle cells a little bit, but much less likely, and finally anaplastic is probably a waste of time; it doesn't work in almost any of those patients.

Chu I know we already began to talk about the different treatment strategies, but one thing that might be good to refresh our memory on is, is there any kind of genetic component to the development of thyroid cancer?

Udelsman There sure is. Most thyroid cancers are sporadic and there is no clear genetic component, there is a risk factor for radiation therapy, but there are clear families that have thyroid cancer. For instance, medullary thyroid cancer, the third type that I mentioned earlier, occurs in three settings in the familial setting. It occurs in isolated familial medullary thyroid cancer, and it occurs in a syndrome that we refer as MEN2A and MEN2B. MEN means multiple endocrine neoplasia. All three of those are autosomal dominant patterns, which means that half the children, boys or girls, will be effected by the disease by a random event during conception. 50% of the children will inherit this gene and once they inherit the gene the likelihood of developing thyroid cancer in their lifetime approaches 100%, and we have a genetic screening test for these children. Now when we have a family, and we usually know who these families are shortly after birth, we can screen the child's blood and tell the parents with virtually 100% confidence that yes, your child will develop thyroid cancer in their lifetime.

Foss Thank you for that information. I would like to talk in detail about that as well as other therapies for thyroid cancer when we return from the break. You are listening to Yale Cancer Center Answers, and I am here discussing thyroid cancer with Dr. Robert Udelsman.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Robert Udelsman, Chairman in the Department of Surgery at Yale School of Medicine, and we are here today talking about thyroid cancer. We talked a little bit about familial thyroid cancer and detecting it using a genetic test, detecting people in the family that are prone to develop this. Can you spend a minute telling us what kind of screening tests should be done on those family members?

Udelsman It's really fortunate for us that we now have a sensitive blood test. So for a child, or anybody in the family, potentially a parent of someone with this, we simply draw peripheral blood, and that blood is sent to a special laboratory to be screened and the genetic test, which in this case is called the RET proto-oncogene, has a very high sensitivity, but not 100%.

Foss Do those children then go on to

get frequent ultrasounds of their thyroid? Udelsman They could, but we also have other tumor markers in this case. In this case, medullary thyroid cancer makes a very specific marker called calcitonin. It also makes another marker, which is less sensitive and specific, called CEA, but if the calcitonin level is elevated, we know these children already have minimum C cell hyperplasia, and more likely disease in the form of cancer, but it doesn't really matter, because once they have the genetic abnormality, we recommend prophylactic surgery at certain ages once we know they have a genetic abnormality. This is an example of where, because of a genetic screening test, we can now do prophylactic or preemptive surgery and prevent cancers from developing in the first place. Chu That's pretty impressive. Let's go backwards to the therapeutic options. Again, the most common type of thyroid cancer is papillary thyroid cancer. Udelsman Yes. Chu And the typical approach in that setting would be? Udelsman The patient presents with the nodule and usually that patient will then go on to a fine needle aspiration biopsy. In papillary cancer, the fine needle aspiration techniques are very sensitive, so usually if we get a diagnosis and it's positive, the next question is, what's the next step? Well in our hands, we recommend at minimum for all patients with biopsy proven papillary thyroid cancer, a total thyroidectomy, removing the entire thyroid gland. But there is a big debate in the world right now about whether or not we should also be doing routine lymph node dissections in what we called the central neck, and just to mention for the second, we are in the process of designing a randomized prospective trial to address this very question, because experts in the field in their heart of hearts don't know whether it's the best thing in individuals who have no evidence of lymph node disease. Because, as you might imagine, nothing comes for free, and if you routinely remove lymph nodes, you are more likely to also cause injury to the parathyroid glands, the nerves, or to the vocal cords. To do the proper study, you have to randomize patients to yes and no treatments. Foss I was actually going to ask you that question. Could you talk a little bit about the complications from a total thyroidectomy? Udelsman First, I would like to mention to you that there is clear relationship between the experience of the surgeon and the frequency of complications; it's so fundamental to everything that we do. But the most common significant complications after thyroid surgery or injury to the nerve to the vocal cords would result in a hoarse voice. Whereas, the other complication is injury to the parathyroid glands and the parathyroid glands are glands that sit next to the thyroid gland and control calcium metabolism. Now we can replace those with vitamin D and calcium, but if you do that to a 5-year-old child and they don't have normal calcium metabolism, that child will never grow normally. The risk in children is actually greater than in the adults. Chu And in the old days, a lot of times along with the thyroid, the parathyroid would also be taken out, but now you really try to preserve the parathyroid. Udelsman We go to great trouble to preserve the parathyroid, and in fact, the best thyroid surgeons are also very good parathyroid surgeons. They live in the same neighborhood and

have very different functions, but are intimately associated with each other because of their blood supplies. Foss If a patient doesn't respond, say to the radioactive iodine, and they have persistent or metastatic thyroid disease, a thyroid cancer, what do you do at that point? Udelsman That starts a staging work-up. Firstly, we can also measure something else called thyroglobulin to measure the amount of disease that they have. For instance, if we have lymph nodes in the neck and we know they have disease, we might consider going back and doing surgery because in two or three hours in the operating room we could remove more tumor than you can kill with I-131. I-131 is very good for microscopic or small disease, but for gross, or what we called macroscopic disease, surgery is better. In other areas such as a weight bearing extremity surgery in combination with radiotherapy, other treatments would be considered. The goal of course is to remove all the disease, but there are critical areas that we can't because it would cause so much destruction to normal tissues. Chu Rob, is there ever any role for external beam radiation therapy to the neck? Udelsman There is. External radiotherapy will kill any rapidly dividing cells including thyroid tissues, but of course external beam isn't intelligent like I-131. Not to demean it, but what it will do is also destroy other tissues like the tissues in the esophagus. The complication rate associated with it is higher than with I-131. In addition, the patient gets what we call a woody indurated neck, its very firm and fixed and makes subsequent surgery difficult, and at times impossible. Foss When we think about chemotherapy approaches for thyroid cancer, traditionally we thought that chemotherapy doesn't work very well. Are there any novel approaches that are being developed? Udelsman For the most part, as you stated, chemotherapy is not the main stream treatment, and that's why endocrinologists tend to manage these patients the most, but we have two great interests in clinical trials right now at Yale Cancer Center. One is in the treatment of advance medullary thyroid cancer, and the other one is that very rare form of anaplastic thyroid cancer. There are two open protocols right now. The medullary thyroid cancer involves a new type of a drug and early results look very promising in this trial. These are for patients who don't have a good surgical option. Foss Are these new drugs small molecules like we have talked a lot about angiogenesis molecules and signal transduction inhibitors? Are those types of therapies pertinent in thyroid cancer? Udelsman They sure are, and in fact, in the medullary cancer trial it's a tyrosine kinase receptor type molecule to block these receptors. The beauty of this particular trial is the toxicity profile is very low compared to more traditional forms of chemotherapy. So, the preliminary results are pretty exciting. Chu What's really fascinating about the small molecule is that it's targeted specifically at the pathway that's responsible for the development of medullary, the carcinoma of the thyroid. Udelsman Absolutely, and I would also like to say this is a good example where one of our surgeons, Julie Ann Sosa, worked with one of our oncologists, Hari Deshpande, as well as with other colleagues and it's a true multidisciplinary approach to the treatment

of thyroid cancer, and I think that's exactly what Yale Cancer Center does so well, bringing different groups of people in with various expertise to treat these tumors, because from the patients perspective, they just want to know they are getting the best care in the world.

Foss Can you talk about quality of life issues for patients who have thyroid cancer as they move through this process with surgery and radioactive iodine? What are some of the issues that patients face?

Udelsman There are a lot of issues they face. Of course, surgery is a relative negative, but it's a short duration event. You come in, you get an operation, and you go home, and most patients are very happy with that. Sometimes we do things like thyroid hormone withdrawal, where we take away their thyroid hormone, we make them hypothyroid before we give the radioactive iodine, and some patients don't like that and there is a new technique where we actually stimulate them with synthetic TSH and then give them the radioactive iodine treatment, and I believe that will become more and more common in the future. The radioactive iodine is not a difficult thing to do and it's almost always done now as an outpatient. The only issue there is protecting, for instance, children in the house, to make sure we don't expose them to the radioactivity. The other forms of treatment, for instance, chemotherapy, do have some consequences to it, but for the most part the great majority of patients with thyroid cancers will be cured of the disease, or if not cured, they will live with a low grade indolent disease and most of them will actually have a normal lifespan.

Chu Are there any potential concerns with the use of radioactive iodine? You know, long term consequences pertaining to the development of secondary cancers?

Udelsman Ed, as usual, you are right on the money. The more radioactive iodine you get, the more complexity and the more complications you will have. So, yes, as you approach higher and higher doses, and ballpark that's about 1000 mc, you will see other cancers develop, particularly leukemia's, and you won't be surprised by that because the radioactive iodine can go to the blood stream. So, as we start upping our dose we start to get more and more concerned and start thinking about alternative therapies.

Foss If the patient has radioactive iodine and their disease goes into remission and then say a couple of years later it comes back again, can they get radioactive iodine a second time?

Udelsman A second, a third, and even a fourth time, and there are different ways of regulating how much to give, but yes, it can be repeated multiple times.

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Chu Do the thyroid tumor cells ever become resistant to radioactive iodine?

Udelsman Yeah they do, and that's a problem for us. As a ballpark figure, we talk about well differentiated thyroid cancer, which basically means papillary, follicular, and sometimes medullary, but roughly 85% of those take up the radioactive iodine, of course, that means that 15% don't, and as you go farther and farther into the treatment it's as if the radioactive iodine kills out the sensitive cells, and the resistant cells remains, and then they become the predominant cells. So, yes tumors will lose their ability to take up radioactive iodine and that does cause great problems for us.

Foss Can I go back and just ask another question about prevention? We talked a lot about the potential role

of radiation in patients with let's say with Hodgkin's disease, what about therapeutic tests such as CAT scans? Some of our patients get CAT scans every three months and traditionally we do not shield the thyroid, is that something the patient should be worried about? Udelsman I think the short answer is yes. CAT scans actually have a fairly high dose of radiation compared to a common chest x-ray, for instance, and in fact, James Brink, the Chief of Radiology at Yale-New Haven Hospital, and the director of the department, has a particular interest in this area. When I last discussed this with him, he actually thinks we ought to be a little bit more conservative about it. The danger is patients go to one hospital to get the CAT scan, and then get recurrent kidney stones perhaps, and some patients are getting four or five CAT scans a year and so, yes, overtime I do believe that radioactive exposure can accumulate in some of those patients. Chu Obviously you know thyroid is removed with surgery, what's the need for thyroid hormone replacement overtime? Udelsman Thyroid hormone is a requirement for life. If you don't have a thyroid hormone you will eventually not survive, although you can go a very long time becoming hypothyroid. The answer is, we replace all of our patients with thyroid hormones who have surgical removal of the thyroid gland, it's relatively easy to do, we give them a synthetic form of thyroid hormone because we can accurately calculate the dose and we can easily monitor TSH levels to prove that they are in perfect homeostasis or in perfect balance. Foss Let's just go back to that issue of the testing that could be done for the patients who may have inherited thyroid cancer. Are those blood tests pertinent also in terms of screening other populations of patients for thyroid cancer? 27:49 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-17-09.mp3 Udelsman Generally speaking, in the United States, we do not do wide screens of patients for these genetic screens. Although in Europe, what they do for patients with the dominant nodule, is they measure a serum calcitonin level, which is the screen for medullary. The reason its relevant is the operation that we do for medullary is somewhat more aggressive than for papillary, and the best time to do the best operation is the first operation, that is 20% of my practice is remedial surgery. I wish that 0% was for medial surgery, because the second operation, and third, or fourth operations, are much more difficult than the initial exposure, so there is some logic to doing it, but it's probably not cost effective in doing calcitonin screening because it's relatively expensive and it's a relatively rare disease. Chu Rob, it's amazing how quickly the time has gone and we would like to thank you for joining us this evening. We look forward to having you come back to hear more about the latest advances in your thyroid cancer program. Udelsman Thank you Ed and Francine. Chu You have been listening to Yale Cancer Center Answers. I would like to thank our guest expert Dr. Robert Udelsman for joining us. Until next time, I am Ed Chu from the Yale Cancer Center wishing you a safe and healthy week. If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.