The Latest Information on Thyroid Cancer

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

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller specializes in pain and palliative care. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or by phone at 1-888-234-4YCC. This evening, Ken Miller speaks with Dr. Robert Udelsman, Chairman of the Department of Surgery at Yale School of Medicine, and internationally known specialist in the treatment of thyroid cancer. The thyroid is a gland that sits in the front part of the neck and it produces hormones called the thyroid hormones, which are required for normal metabolism.

Udelsman  The thyroid is a gland that sits in the front part of the neck and it produces hormones called thyroid hormones which are required for normal metabolism.

Miller  What would happen if someone did not have a thyroid, or it was not working properly?

Udelsman  Let's say your thyroid gland is removed surgically, or simply does not work properly and thyroid hormone production is inadequate, over time there would be severe hormonal disturbances which would result in lethargy, weight gain and eventually, if it was severe, could result in death.

Miller  Cancer can develop anywhere in the body, can you tell us something that's different about thyroid cancer.

Udelsman  Thyroid cancer is not that common a cancer, although it seems to be increasing in incidence in the state of Connecticut. There are roughly 20,000 new cases of thyroid cancer diagnosed in the United States every year. For the most part, it is a fairly indolent, or slow growing tumor, and is not nearly as aggressive as many other cancers.

Miller  Is it possible for someone to have thyroid cancer where it never manifests itself and they live a lifetime where it is never a problem?

Udelsman  That is actually not unlikely and happens quite commonly. If you were to do an autopsy series in elderly patients, say above 80 years old, you will find a significant number of clinically insignificant thyroid cancers that have absolutely no clinical relevance.

Miller  In that way this reminds me of prostate cancer.

Udelsman  In fact, they are both endocrine in origin, which is kind of interesting.

Miller  Who develops thyroid cancer?

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Thyroid cancer is more common in women than in men. It is about a 3:1 incidence increase in women compared to men. It develops in all age spans. It does occur in children, but the risk does increase with age.

Are there any risk factors that we know of?

There are risk factors for thyroid cancer, particularly radiation therapy or radiation exposure as a child. For instance, back in the 40s and 50s when external beam radial therapy was used for things like acne and thymic enlargements that treatment resulted in an increased incidence in thyroid cancer 20-30 years later. In addition to that, because of accidents such as Chernobyl or other radiation exposure areas, those patients who were exposed, particularly as children, have a latency period where they develop thyroid cancer later in life.

If we talk about Chernobyl or any kind of exposure like that, what is the period between the exposure and the development of the cancer?

Generally it takes decades and there are a lot of other factors such as the extent of exposure and the age at the time. But interestingly enough, children are more likely to develop cancer whereas adults, if they are exposed to a very high dose of radial therapy, they do not develop thyroid cancer, they develop other forms of malignancies.

As you know one of my interests is cancer survivorship and people that have been through treatment for cancer. Many people have been treated for Hodgkin's lymphoma, for example, where they received radiation. Even though it was meant for the chest and for the neck, do they have to worry about thyroid problems that might develop?

They do. The mantle radiation used in Hodgkin’s patients does result in significant radiation exposure to the thyroid glands. Most new protocols protect the thyroid gland but there is scatter, and those patients are at risk. It is kind of a funny issue where we cure one malignancy only to see another develop down the road. They are at risk for the rest of their lives.

In terms of screening, who would you consider at high risk, who should have increased screening?

One of the things I failed to mention earlier is that there are also certain familial or genetic syndromes associated with thyroid cancer. Far and away, if someone comes from a family with a high incidence of thyroid cancer, all those children need to be screened, particularly if it is the familial forms. Interestingly, in the state of Connecticut, in addition to the more common medullary thyroid cancer which occurs in families, there is an incidence of papillary thyroid cancer which
is of great interest to us at the Yale Cancer Center. We are initiating a new screening program for some of those families. If a child is exposed they should be screened by their primary care doctor and perhaps by an endocrinologist. Fortunately, we have exquisite screening techniques that include a physical exam and a history, but ultimately an ultrasound examination can look in great detail at the thyroid gland and if necessary, we obtain a tissue diagnosis.

Miller 

It sounds like two parts of the screening are physical. How sensitive is a good physical exam?

Udelsman 

A good physical, by an experienced physician, particularly an endocrinologist who has experience examining thyroids, will pick up nodules greater than a centimeter in size. An ultrasound examination is far more sensitive, perhaps even too sensitive. This will see nodules in the millimeter size and that creates a dilemma for us, if you screen patients should you biopsy all nodules even less than a centimeter in size? For the most part we agree that anything greater than a centimeter should be biopsied, but smaller than that, I am not sure it is necessarily appropriate, in all patients, to obtain a tissue diagnosis.

Miller 

Over the years in practicing medicine a number of patients have said, "I have a thyroid nodule." Can you tell us what thyroid nodules are and how common they are?

Udelsman 

There is a good example where thyroid nodules are quite common. In fact, 15% of women in the United States have thyroid nodules and yet very few of them have thyroid cancer. We have a dichotomy there where we have a common incidence of the nodule disease, most of which are benign. We have a standard algorithm on how we work up these patients. Anyone with a thyroid nodule should be seen by an endocrinologist. A tissue diagnosis should be obtained and that is usually done with a fine needle aspiration. It is a very simple test. A needle is placed into the gland and we look at the tissue under a microscope. A majority of those will be benign diagnoses and will only require followup and no surgery. A subset will clearly be cancer and they should have surgery, and an intermediate group will have indeterminant nodules, which create difficulty for us because we do not want to be overly aggressive and yet we do not want to miss cancers.

Miller 

Of all the nodules that are found, what percentage ends up being cancer?

Udelsman 

1%.

Miller 

That’s very little.

Udelsman 

A very small percentage of nodules are cancers. In fact, if they have a large
multinodular goiter with multiple nodules, it is unlikely to be a cancer, but there are some risk factors. For instance, if they have a single dominant nodule, particularly in a male patient, that concerns us. If they have dominant nodule with history of radial therapy for Hodgkin disease, say if they are now age 40 and they were treated for Hodgkin’s at age 15 that would be worrisome to us. We can predict, to some extent, which nodules are high risk.

Miller Now in terms of biopsies, how are they done?

Udelsman It is very simple in the vast majority of patients. Thank goodness for the Scandinavian countries, because in the 1950s they developed the technique of fine needle aspiration cytology. We are able to put a needle into these nodules and obtain cellular specimens that we can look at under the microscope. Now, cytology is an art form and this is an area I am glad you asked me about because the quality of both the aspiratory, the person getting this sample, and the cytopathologist who look at the sample, is absolutely critical. The average pathologist does not have the training to look at these nodules. You need an expert cytopathologist to look at the specimen.

Miller Essentially the radiologist or the surgeon will take a thin, very skinny needle and basically take out cells.

Udelsman That is absolutely right. And in fact, most patients tell me it is easier than having their blood drawn.

Miller Which is not a particularly painful procedure.

Udelsman In the range of painful procedures, this is very low and extraordinarily well tolerated. It is often done under ultrasound guidance because with an ultrasound machine you can put that needle exactly in the nodule and be certain you are getting a good specimen.

Miller What are the different types of thyroid cancer?

Udelsman Again, the majority of biopsies will be benign showing a multinodular goiter or hyperplastic nodule. That is not what our conversation is about. There are 4 primary thyroid cancers; papillary, follicular, medullary and anaplastic. I will also say that the third most common malignancy of the thyroid gland is not anaplastic, it is actually primary thyroid lymphoma which is an interesting subgroup. Of those thyroid cancers papillary and follicular are by far the most common and comprise about 85% of all thyroid cancers. Almost all of those patients can be cured of their disease with the appropriate treatment. We consider those well-differentiated thyroid tumors. There are subsets within both papillary and follicular that act more aggressively and there are more subsets of those that need more aggressive treatment. The medullary thyroid cancers comprise 10%-15%, about half of which are familial, that is genetic abnormal
cancers or sporadic, they just occur sporadically in the community. They are an interesting and unusual subtype that we have a particular interest in. Anaplastic cancers are extremely aggressive and many patients will actually succumb to their disease in spite of exquisite treatment. Thyroid lymphoma, for the most part, is a nonsurgical disease. The surgeons' role is to help make the diagnosis, but those patients do extremely well with nonsurgical treatment.

Miller  Thankfully, most of the types of thyroid cancer including lymphoma are curable.

Udelsman  Absolutely.

Miller  Let us focus for a couple of minutes on medullary since, as you say, there is a higher incidence perhaps in Connecticut than elsewhere. Can you give us an example, a family you have taken care of, where you made that diagnosis of it being familial?

Udelsman  In the familial form it comes in three basic varieties; MEN2A, MEN2B and isolated familial cancer of the thyroid.

Miller  What is MEN?

Udelsman  MEN stands for multiple endocrine neoplasia. It is quite interesting that these patients have multiple endocrine abnormalities. Not only do they have medullary cancer of the thyroid, they develop rare tumors of their adrenal glands called pheochromocytomas. They also develop tumors of their parathyroid glands which are glands in their neck. That is an MEN2A. In MEN2B, they develop lesions of their tongue or their mucosa throughout their gastrointestinal tract. They do not develop hyperparathyroidism, but they do develop pheochromocytomas and they have very aggressive medullary cancers of the thyroid. These medullary cancers are quite unusual. They are very different than the garden variety papillary or follicular, because they are derived from a different kind of cell called the C cell which produces a hormone called calcitonin. The beauty of it is that we can use calcitonin as a tumor marker. We can know with very high degrees of confidence whether the patients are cured or if they will develop a recurrence by measuring these tumor markers.

Miller  In a family, would all the daughters and sons be screened?

Udelsman  This is a classic autosomal dominance inheritance pattern, which means 50% of the children will develop it and there is no predilection for boys or girls. Many people do not understand this. Each new birth is a flip of the coin. You could have three children who have it and the next one may or may not have it, but there are independent risk factors. The fact that three have it does not mean that
the next one is spared, or you could have three children who do not get it. It is an independent flip of the coin every time a child is born.

Miller If someone has a family history of medullary thyroid cancer, is there a test that they can have done to know if they are at risk?

Udelsman Yes. This is a great example of where medicine has really pushed itself forward. There is now a genetic test for these families called the RET proto-oncogene. We can measure these proto-oncogenes with great confidence. If you are positive and we know the genetic abnormality, we can predict with near 100% certainly whether the child has it or not. It is incredibly important because if we know the child has it, even if the child is asymptomatic and has no nodules, we are going to recommend surgery in early phase, and we can cure those patients with a high degree of confidence. This is an example where a genetic marker can result in a treatment paradigm that can result in a preemptive curative procedure and the child will be protected for the rest of their lives.

Miller So you are using a preventative procedure before a cancer even develops?

Udelsman Absolutely. If we know the child has the genetic abnormality, we are going to recommend surgery even though the ultrasound of the thyroid gland looks normal. Because we know that the incidence of disease approaches 100% in these patients, if we intervene at a young enough age, usually in MEN2A around 5-6 years of age, we can cure virtually all of these patients.

Miller What a wonderful thing to be able to prevent a cancer from developing.

Udelsman It is a beautiful example of medical science, and I want to mention Sam Wells who really is the guy who early on developed the calcitonin stimulation test which has pushed us to develop these curative things for these children.

Miller We would like to remind our listeners to e-mail their questions to us at canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about thyroid cancer with Dr. Robert Udelsman from the Yale Cancer Center

Medical Minute

*It is estimated that over 2 million men in the US are currently living with prostate cancer. 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 number of men who die from this 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*

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cancer centers like the one at Yale that has innovative new treatments for prostate cancer. Patients enrolled in these trials are given access to experimental medicines not yet approved by the Food and Drug Administration. This had been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR health forum from Connecticut Public Radio.

Miller Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller and I am speaking today with Dr. Robert Udelsman from the Yale Cancer Center about treatment and treatment options for patients with thyroid cancer. Why don’t we start by talking about what happens after someone has been diagnosed. What is the primary formal treatment for thyroid cancer?

Udelsman There are 3 fundamental treatments for thyroid cancer; surgery, radiotherapy and long-term TSH suppression, or thyroid stimulating hormone suppression by administering thyroid hormones. Let me start with surgery, which is the primary and initial treatment. A thyroid cancer develops in the thyroid gland and the primary treatment is to remove the thyroid gland. If it were that easy, everybody would be doing it. It is actually not difficult to remove the thyroid gland, what is difficult is removing the thyroid gland without injuring associated structures like the recurrent nerves, nerves to the vocal cords and the sensitive parathyroid glands. That is why patients do better when they are referred to an expert thyroid surgeon.

Miller You are saying that even though it is easy to take out, it is hard to take out well.

Udelsman Yes. That is exactly right. It is a technical exercise done by people with expertise who do it day after day. There is good data out there to suggest that if your thyroid surgeon is not performing at least 100 thyroidectomies a year, they may not be the right one to send your patients to.

Miller How is the operation removing the thyroid with cancer different than just removing the thyroid as prevention?

Udelsman It is a different operation. Our goal in thyroid cancer surgery is to remove not only the abnormal portion of the thyroid gland, but the normal thyroid tissue as well. In well-differentiated thyroid cancer, most patients will receive radioactive iodine treatment, and if you leave a lot of tissue behind, it makes the treatment more difficult.

Miller Let's talk about radioactive iodine. Can you explain for us how that works?

Udelsman It is a miracle Ken. Thyroid hormone is made by taking iodine from the diet and incorporating it in the thyroid cell and producing thyroid hormones, that is

16:57 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Nov-25-07.mp3
why we have T4 and T3. T4 is how many iodine molecules remain there. T3 has 3 and T4 has 4. Since we have this very unique situation where iodine is used, we take advantage of that and make iodine radioactive, which we call I-131 radioactive iodine. We can give the patient radioactive iodine, which is in fact a magic bullet because it goes to thyroid cells with such a high degree of specificity that it spares normal tissues with issues of about a 1000 to 1 therapeutic ratio compared to normal tissues. This is in contradistinction to external beam radiotherapy, which basically will injure any rapidly dividing cell. We can take advantage of that specificity and give very high doses with great safety which is what radiotherapists do.

Miller We have talked a lot on this show about targeted therapy and yet it sounds like radioactive iodine might have been one of the first.

Udelsman It certainly is, and it is one of the most targeted therapies. It is by pure chance alone that we can take advantage of the fact that we have a very specific molecule, the iodine that is specific to the thyroid gland, if only we had such molecules for pancreatic cancer and esophageal cancer or lung cancer! Unfortunately, although we tried, we don’t.

Miller After you have operated on someone and have gotten the pathology report back, how do you decide who needs the radioactive iodine and who does not?

Udelsman I am so glad you asked that question. I want to emphasize it is not a unilateral decision. It is a group decision between the surgeon, the endocrinologist and the radiotherapist. We talk together and discuss if it is a very high-risk patient or a low risk patient. For instance, if we remove a thyroid gland for Graves disease, a benign condition, and we find a 0.1 cm thyroid cancer, we do not treat that patient. We put them on thyroid hormones and recommend routine follow-ups with an expert endocrinologist. They do not need additional treatment. On the other hand, if the patient has a thyroid cancer that is greater than a centimeter in size, close to a margin, multicentric in multiple locations, particularly if they have positive lymph node involvement, then we will treat that patient with radioactive iodine therapy. The pathology helps us make those decisions.

Miller How is it administered, and what are the side effects?

Udelsman Radioactive iodine is actually quite safe. It is given orally, usually in the form of a liquid. The radiopharmacist can design a cocktail that is very specific to the patient and can dose it with exquisite accuracy. We know exactly how much is given and we can predict the effects. For instance, if the patient has localized disease that is not beyond the thyroid gland, we give a relatively low dose, perhaps 29 millicuries. If, on the other hand, they have metastatic disease

to their lungs, we would give a higher dose with a goal of curing that patient. Believe it or not, in thyroid cancer unlike other diseases, lymph node involvement and even metastatic disease to the lung and bones does not mean that they do not have a curative option. In fact, our goal is not cure; our goal is that the patients outlive their disease. If they were to die from the disease, but live up to age 90 or 95, then we have probably done a pretty good job.

Miller   Yes you have.

Udelsman   Another basic principle is that the treatment should not be worse than the natural history of the disease itself.

Miller   Which is a good principle in general for oncology. We do not use the word cure a lot in oncology, and I think we should more than we do. Let us go back to the patient where the cancer has spread. They come in, they have thyroid cancer and in a small number of people it has gone elsewhere. Are those patients able to be cured of that disease or outlive the disease?

Udelsman  The answer is yes. We see children with metastatic disease to their lungs and essentially they will enjoy normal life spans. But are they cured? That is a debatable issue. Are they in remission for decades? Absolutely. So yes, some are cured and some are in remission. It is not whether they outlive the disease that important to us, but that they do so with a high quality of life. On the other hand, we also see aggressive disease that will decrease life spans. It is that balance between giving the treatment that is appropriate for the individual.

Miller   It sounds like for some patients with a papillary or follicular cancer they would have surgery and perhaps radioactive iodine. Let's go back to medullary cancer, which I know you have tremendous expertise with. What is new at the Yale Cancer Center in terms of treatment for those patients?

Udelsman  The first thing I want to emphasize is that the primary treatment for medullary cancer is surgery, and the more aggressive the initial surgery the better, because these have early predilection for lymph node metastases. In medullary we recommend not just a total thyroidectomy, which we do, but we also recommend a variety of lymph node dissections, either the central neck or what we call modified radical neck dissection. They are tricky because they can have microscopic disease in these lymph nodes. They look totally normal in imaging, but we know the incidence of metastatic disease of the lymph node is actually quite high in these patients. However, once they have had surgery and have done relatively well, if they have elevated calcitonin and/or CEA levels, which is another tumor marker postoperatively, we know with virtually 100% confidence that they have residual disease. Then the question is what to do for them. Should we re-operate? Perhaps you can do a lymph node dissection.

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At the Yale Cancer Center, we have a new trial that is being run. The principal investigator is Julie Ann Sosa. It is a trial in cooperation with a drug company called AstraZeneca, and is a very incredible and interesting concept in that it is a tyrosine kinase inhibitor, a drug that inhibits the tyrosine kinase inhibitor, and the early data is extraordinarily promising. The toxicity of the drug is also really quite minor compared to other drug trials where there can be significant toxicities. We are involved in both a familial form of trial for this drug as well as the more recent sporadic trial. The patients are doing quite well and we are very excited about this trial.

Miller This would be in pill form. When it is absorbed in the blood stream, it sounds like it turns off an enzyme in cancer cells. Do the patients feel better or are the tumors shrinking? What kind of results are you getting?

Udelsman Both. The first thing we see is a decrease in the calcitonin and CEA levels. Again we have this exquisite tumor marker we can follow and these levels fall, but in addition to that, we image these patients. In some patients we are seeing dramatic shrinkage of their tumors in tumors where there really is no other treatment available. A couple of my patients are being treated by Dr. Sosa in collaboration with her oncology colleagues in the Yale Cancer Center, particularly Hari Deshpande, and it is remarkable. It is remarkable that two of my patients, in particular, with widespread disease are doing remarkably well with this drug treatment.

Miller We have been fortunate in other parts of oncology. Chronic leukemia is now treated with a tyrosine kinase inhibitor, a different one called Gleevac, hopefully we will have more treatments like that for other types of cancers as well.

Udelsman It is quite remarkable because there is a new concept of chemotherapy; it is not the traditional kind of chemotherapy that had a fair amount of toxicity. These patients do have a lot of complications of the disease. I have one poor patient down in Pennsylvania who is not doing as well and has developed local airway problems; it is really devastating when you cannot control the local disease.

Miller How about for the other type of cancer, anaplastic cancer, what is new in that field?

Udelsman Anaplastic is a devastating tumor. The majority of patients ultimately will die of their disease, no matter how aggressively it is treated. We are interested in starting a new trial in anaplastic thyroid cancer for a variety of reasons. One is that these patients need to go to a tertiary medical center for a whole variety of reasons. It is a collaborative effort between surgeons, oncologists and radiotherapists. We are actually interested in starting a new trial. We are in the early phases of organizing this trial, and once again Dr. Sosa is the primary
investigator. She is a co-investigator again with Harry in the Medical Oncology Center. This is a good example where surgeons and medical oncologists are working side by side. It is important to have surgeons because we are the ones that see the patients, but we recognize we are not going to cure the majority of these patients. Medical oncologists have expertise that we do not in managing these patients.

Miller I want to talk a little bit about people that have had surgery for thyroid cancer and go on hormone replacement therapy. How do you regulate that and is that well tolerated? What are the side effects?

Udelsman Everybody has both conceptions and misconceptions about thyroid hormone. Fortunately, we know exactly what thyroid hormone is. We know its chemical structure and we can give it with exceeding confidence with what the right doses are. The reason for this is that there is an internal thermostat. The internal thermostat is the pituitary gland. When we administer thyroid hormone, the pituitary gland will respond by changing the levels of TSH, and therefore, we can regulate every individual patient. It is the ultimate of individualized patient care because we can get the exact right dose based on their TSH levels. This is again managed by our endocrinology colleagues and there is virtually no patient where we cannot figure out the right dose for.

Miller I have heard a few patients that they are on the thyroid medicine, but still don’t feel like they did before. Are there other things that thyroid hormone does?

Udelsman It does and in fact there is more than one thyroid hormone. The fact is that the thyroid gland makes a combination of thyroxine T4 as well as T3 and it is the combination of the two in normal glands that is controlled. The fact of the matter is T4 thyroxine is converted to T3 in the periphery, so generally speaking, for the majority of patients, we administer T4 alone. However, particularly in the psychiatric literature, there is at least some thought that you want to recapitulate normal physiology as much as possible. Some patients are given a combination of T4 and T3, which we call Cytomel, the drug that we administer. For the vast majority of patients I am not sure that there is great efficacy for giving the combination of drugs because again, T4 is converted to T3; it is T3 that is the active drug that actually has the action, but some patients are given a combination of the 2 drugs. It is less convenient. The beauty of T4 is that it has a long half life, which means that if you miss a dose, it is okay. If you are going away for the weekend and forget your bottle and you are already across that bridge, just keep on driving. It will be okay to miss a couple of doses and for patients this is a wonderful thing. As you know, compliance is directly related to the ease of the medication. Fortunately, patients like to take their thyroid hormone because when they do not take their thyroid hormone, they feel bad. For this reason they tend to take their medicines. Unlike other
medicines like antihypertensive medicines, that can actually make them feel worse even though the drugs are good for them, these make you feel better.

Miller This has been a wonderful discussion about thyroid cancer and actually pretty uplifting in terms of all the progress that has been made. I want to thank you Dr. Robert Udelsman for joining us on Yale Cancer Center Answers.

Udelsman It has really been great fun for me to be here. I would like to emphasize that thyroid cancer, like many diseases, involves multiple doctors across disciplines. It is a sure thing that a cancer center can do the best because it has different levels of expertise that help the patients.

Miller From all of us, Dr. Udelsman, myself and Dr. Ed Chu who was off this week, we would like to wish you a safe and healthy week.

*If you have questions, comments or would like to subscribe to our podcast, go to yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, Ed and Ken speak with Barbara Oliver about Y-ME Connecticut.*