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Clinical Trials for Thyroid Cancers

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Yale Cancer Center Answers

is a weekly broadcast on

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Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. I am Bruce Barber. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. 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 evening, Francine welcomes Dr. Julie Ann Sosa. Dr. Sosa is Associate Professor of Surgery and Medical Oncology and she is the Director of the Yale Endocrine Surgery Clinical and Health Services Research Group. Here is Francine Foss.

- Foss Can you start off by just briefly telling our audience what thyroid cancer is? I guess a more basic question would be, where is the thyroid gland located and what does it do?
- Sosa The thyroid gland is a butterfly-shaped gland that sits in the front of the neck right over top the windpipe, and those of us who treat the thyroid gland think of it as the most important organ in the body. I am sure you hear that from a lot of different physicians, but the thyroid secretes substances called hormones, which actually control most if not all of the other organs in the body, most importantly, your body's metabolism.
- Foss What are the different types of cancers that arise in the thyroid?
- Sosa Thyroid cancer is very common and it is actually becoming more common with time. It is right now one of the fastest growing cancers in American women, up about 240% in the last three decades. Based on the most recent data in 2010, there were nearly 45,000 new cases of thyroid cancer, and fortunately, survival overall is excellent in excess of 95% to 96%. I think of thyroid cancer a little bit like ice cream, in that it comes in a million different flavors and varieties. The most common, sort of like the vanilla of thyroid cancers, is a kind called papillary thyroid cancer, and it represents over 90% of all thyroid cancers now and it is the kind of thyroid cancer that is rapidly increasing in incidence, not only in the United States but really throughout the world, and it is poorly understood why this is the case. There are other less common kinds of thyroid cancers. Follicular thyroid cancer is probably second behind papillary thyroid cancer and its sister, Hurthle cell cancer. Another kind of thyroid cancer, which is relatively rare but which can be inherited, is a kind called medullary thyroid cancer, and that represents just 3% or 4% of all thyroid cancers. And then the very, very rare kinds of cancers, which we actually see not infrequently at Yale, but overall are very rare, are kinds such as the poorly differentiated thyroid cancers, primary thyroid lymphoma, and anaplastic thyroid cancer.
- Foss If you look at the incidence of all cancers in the United States, I was actually surprised when I went back and looked at this the other day, I am not sure exactly which number thyroid is, but it is right up there in the first 7 or 8 most common cancers.
- Sosa That is exactly right. And, as I said, it is rapidly increasing largely because of this epidemic of papillary thyroid cancer, and the interesting thing is that this epidemic is being observed not only in the developed countries, such as the United States, but also in Africa, Asia, and Australia,

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suggesting that there might be some environmental component contributing to the incidence of the disease.

Foss Julie, that was my next question for you, which is, what are the things that can lead to thyroid cancer? What are the major risk factors?

Sosa The one that has probably gotten the most attention, unfortunately recently in the news, is exposure to radiation. Back in say the 1930s and 1950s there was radiation in the form of x-ray treatment that was delivered to children for things like tonsils and acne. A lot of those children went on to develop thyroid cancer and we now know that we should use radiation and medicine sparingly, and when it is used today, the benefits almost always outweigh the risks. But today, the radiation we are concerned about is things like radiation fallout from nuclear disasters such as Chernobyl and the like. Other risk factors that we need to think about are things like a family history of thyroid cancer. This is frequently seen associated with medullary thyroid cancer, but also now we know that papillary thyroid cancer can be inherited. A family history of goiters or a history of growths in your bowel or colon, which is called familial polyposis, is associated with an increased risk of thyroid cancer. Being a woman is a risk factor for the development of the disease. Women have a three times greater risk of developing thyroid cancer than men. The interesting thing there though is that while men do not have as many thyroid nodules as women, when a man has a thyroid nodule, it is much more commonly a cancer than in a woman. Lastly, I think the other risk factors we think about are things like advanced age, do not kill the messenger, but being over 45 is a risk factor. Iodine probably would be the final risk. When you do not have enough iodine, you are more likely to develop follicular thyroid cancer, and there is some weak data to suggest that an increase in iodine exposure is a risk factor for papillary thyroid cancer.

Foss Do these thyroid cancers occur in children, or is it primarily a disease of adults?

Sosa Thyroid nodules occur rarely in children, but it is important to note that the incidence of malignancy in thyroid nodules in children is greater than in adults. When children get thyroid cancer, they more often have lymph nodes that are involved by their cancer at the time of diagnosis. We think as many as 80% of children have lymph nodes involved by their cancer compared to fewer than 50% of adults, and they also more often at presentation have evidence of spread of their cancer outside of the neck. Nevertheless, it is important to understand that children with thyroid cancer overall do very well as long as they receive appropriate treatment for their disease, and most people think of long-term survival in children with thyroid cancer to be in excess of 90%.

Foss Are the risk factors for children the same as those for adults?

Sosa Yeah, they are similar and, in fact, they are more poignant in children than in adults. Radiation exposure clearly is associated with a greater risk of developing a thyroid cancer than when radiation exposure occurs in the adult. And in children, we always need to think very carefully

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about inherited forms of thyroid cancer that are passed along in genes, we are thinking about medullary thyroid cancer, and there are three kinds of medullary thyroid cancer that can be passed from generation to generation. Those are called familial medullary thyroid cancer, and two syndromes called MEN 2A and MEN 2B. The important thing is if we recognize this before the child is born and do the right testing of their chromosomes, we actually will operate early with the idea being to prevent the development of the cancer in children, and therefore a sure cure.

Foss Can you talk a little bit more about the genetics, since we now have these genetic tests available to us? Should everybody with thyroid cancer have one of these genetic tests?

Sosa No, I think that would lead to hysteria, unnecessary testing and unnecessary cost. Whether you should have genetic testing is really driven by the kind of thyroid cancer that you have, and there we are thinking about medullary thyroid cancer. I would say that before a family and their physicians embark upon genetic testing, it is often very useful to enroll onto the medical team, a geneticist or a genetics counselor so that the most cost-effective genetic testing is performed to avoid unnecessary hysteria, which can really disrupt families.

Foss What about the issue of low-level radiation, such as dental x-rays? I know there has been some controversy about that as well and should parents allow their children to have dental x-rays every year and does that significantly increase the chance that they will develop thyroid cancer later on?

Sosa I think routine x-rays in the United States are associated with very low levels of radiation, and the benefits almost always outweigh the risks. What I think is always appropriate is for parents or patients to talk to their dentist or the physicians to find out the precise need for x-rays that are being ordered, and also to ensure that a thyroid shield is employed in order to protect the thyroid from being exposed to what I am sure is otherwise necessary radiation.

Foss The other thing you touched on is iodine. When we grew up, we always had iodized salt, and the question I guess is should parents be looking out for that, should children be getting iodine?

Sosa In the United States, it is really a non-issue. Historically, iodine deficiency has been associated with the development of goiters, particularly in landlocked countries and in the developing world, but even in those areas, there has been the spread of access to iodine, but certainly in the United States, one does not need to worry.

Foss Going back to the whole issue of diagnosing a thyroid cancer, can you go through what the signs and symptoms would be? How would a person know that they have something to worry about?

Sosa Thyroid cancer can demonstrate itself in a number of ways. Probably, the most common presentation is with a lump or lumps in the front or side of your neck, and this can be identified either by patients themselves, while men are shaving or while women are applying makeup or washing, or on routine physical examinations, and I would say it is important to assure that your

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primary care physician or your internist, or your pediatrician, or your obstetrician, gynecologist, examines your neck for nodules. Other symptoms or signs that are associated with this kind of cancer include a swelling of the neck, hoarseness, or a change in your voice, a chronic cough or difficulty swallowing, and I would just say that none of these symptoms necessarily mean that you have thyroid cancer. They should certainly just raise a flag and lead you to make an appointment with a physician who can then interrogate them appropriately.

Foss We have to pause in a minute for a medical minute, but when we come back I would like to touch on that issue a little bit more and talk about the benign thyroid masses as well, which I am sure confuse a lot of people. Right now, we are breaking for a medical minute, please stay tuned to learn more about thyroid cancer with Dr. Julie Ann Sosa.

Minute Breast cancer is the most common cancer in women. In Connecticut alone, approximately 3,000 women will be diagnosed with breast cancer this year, and nearly 200,000 nationwide, but there is new hope for these women. Earlier detection, noninvasive treatments, and novel therapies provide more options for patients to fight breast cancer. In 2010, more women are learning to live with this disease than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center, to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy-resistant breast cancer is now being studied at Yale combining BSI-101, a PARP inhibitor with a chemotherapy drug, irinotecan. This has been a medical minute, brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my guest today, Dr. Julie Ann Sosa, and we are here discussing thyroid cancer. Before the break we talked about the fact that thyroid cancer usually presents as a mass or a lump in the neck. There are a lot of people out there who may have these benign lumps and other people who are on thyroid medication because their thyroid is overactive or underactive. To what degree do any of these conditions contribute to thyroid cancer and how often are those lumps actually cancer?

Sosa Thyroid nodules are widespread in the United States. Estimates range from 5% to 50% of adult Americans having a thyroid nodule and the overwhelming proportion of thyroid nodules are benign, meaning non cancerous, probably about 95% are nothing. Having said that, when a thyroid nodule is identified, it should be interrogated, if it is either worrisome in appearance or bigger than about 1 cm to 1-1/2 cm in size what is generally done is an ultrasound of the neck is ordered, which can be accompanied by a biopsy or a sampling of the tissue within the nodule, which then gives the diagnosis cancer or no cancer.

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- Foss Does either hypothyroidism or hyperthyroidism lead to the development of thyroid cancer?
- Sosa Most patients with thyroid cancer are 'normal thyroid', and in medicine we call that euthyroid, but that means normal thyroid. There are some data now to suggest that patients who have low thyroid hormones over time may be at slightly greater risk for certain forms of thyroid cancer, but I would say, overall, patients with thyroid cancer can be low thyroid, normal thyroid, or even hyper or high thyroid.
- Foss Can you step us through the process now of a patient who say has a suspicious nodule? What is the process to get the diagnosis, and then what is done as part of the staging after the diagnosis?
- Sosa That person would usually be sent to an endocrinologist, who is a gland doctor. It would be best if this doctor has expertise in thyroid diseases specifically. The encounter should begin with a good history and physical examination, and then once the thyroid nodule has been documented, an ultrasound and biopsy should be attained. Often along with those tests, other tests are ordered, and here it really depends on the findings on the first part of the examination, but those other tests might include thyroid function tests. There are some tests that are markers for certain forms of thyroid cancer. A calcitonin level is useful for patients who may have medullary thyroid cancer. Thyroglobulin is useful for those with papillary, follicular and Hurthle cell cancers. Sometimes, a thyroid scan, an uptake scan, is ordered, but this is not essential and does not guarantee whether a nodule is cancer or not cancer, and finally an examination of the vocal cords may be obtained, and that is called laryngoscopy.
- Foss Once the patient then has a diagnosis of thyroid cancer, do all patients undergo surgery?
- Sosa The type of treatment for thyroid cancer really depends on the type of thyroid cancer that the patient has. Almost uniformly, thyroid surgery should be the first part of the treatment regimen, and for most forms of thyroid cancer, that surgery should be near-total or total thyroidectomy, that is the removal of the entire thyroid. In most patients, say those with papillary thyroid cancer or the other differentiated thyroid cancers, radioactive iodine, or I-131, which is a radioisotope, is then administered anywhere from 4 to 8 weeks after surgery. Sometimes, radiation in the form of external beam radiation can be directed to the neck if the cancer is more advanced. Chemotherapy has been shown to be poorly effective for most forms of thyroid cancer, and therefore is rarely employed, and finally, clinical trials or experimental treatments for locally advanced, that is big tumors in the neck or tumors that have spread outside of the neck, can be used.
- Foss How dangerous are these procedures? How risky is the subtotal thyroidectomy and how risky is receiving radioactive iodine?
- Sosa It is an extremely important question, and this question generally pertains to the surgery. The best predictor of how a patient is going to do is based on the relative experience of their surgeon, and if

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a patient can ask their surgeon only one question, the question should be, how many of these thyroid surgeries do you do a month, or a year? The more the better. Most of us who specialize in thyroid surgery and perform total thyroidectomy for thyroid cancer, quote an overall risk of complications as 1% or less.

Foss What about the radioactive iodine?

Sosa Radioactive iodine is very safe when it is used in medicine in controlled situations, which is not what we are reading about going on in Japan, obviously, right now. Radioactive iodine really should be used with caution in one group of patients, and that is young children. Here, we do worry about the effects long-term on young children, but certainly in older children and adults, benefits outweigh risks and it should be delivered as an addition to surgery for many forms of thyroid cancer.

Foss And how often does thyroid cancer metastasize outside of the neck area?

Sosa There it depends on the kind of thyroid cancer we are talking about. If we are going to talk about papillary thyroid cancer, since 9 in 10 thyroid cancer patients have papillary, up to 50% of patients have microscopic or tiny spread of their tumor to the lymph nodes in the neck. This is amenable to treatment either with surgery, and that is the removal of the lymph nodes in the area by the thyroid or elsewhere in the neck, or radioactive iodine.

Foss Can you tell us a little bit about what a patient does when a patient has a diagnosis of thyroid cancer? Is it important for that patient to come to a center, such as your center, and can you tell us a little about your multimodality approach?

Sosa I think it is, and it starts as early as the evaluation they undergo, but it becomes much more relevant when the treatment phase begins, and as I said, the surgeon performing the operation is critical, in that he or she must be experienced and do a high volume of those procedures. Here at Yale, we have a unique situation where we have four dedicated endocrine surgeons, that is four surgeons whose career is based on the management of patients with thyroid cancer and related diseases. The nice thing about going to a center like Yale, and there are other centers around the world, is that you can stay at that center to receive all phases of your treatment, whether that is surgery, the radioactive iodine, which is delivered typically by nuclear medicine doctors, then the followup as patients with thyroid cancer must be followed for at least the first 5 years, and many for the rest of their lives with a combination of radiology studies and blood tests, and finally if a patient is in the unfortunate minority of patients who have either big tumors in their neck or spread of their cancer out of the neck, Yale offers experimental therapies via clinical trials that really for the first time are offering a great deal of hope to patients.

Foss Can you talk a little bit about the clinical trial program here at Smilow Cancer Hospital?

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- Sosa This is a multidisciplinary effort through Yale Cancer Center, and it involves collaboration between endocrine surgery, medical oncology led by Dr. Hari Deshpande, endocrinology, as well as genetics counselors, radiologists, and pathologists. At any one time, Yale has between five and seven clinical trials open for the treatment of advanced thyroid cancer, and also other kinds of gland cancers including adrenal cortical cancer, and I am very proud to say that Yale has been critically involved in the development of two drugs, one of which hopefully may be going to market as early as later this year, and another for which there is very hopeful data on the horizon that may lead to eventual consideration by the Food and Drug Administration.
- Foss Can you share with us any details of either one of those trials?
- Sosa Sure, one drug that has received a great deal of attention is a drug called vandetanib, formally called Zactima, or ZD6474, this is a drug that went to the FDA, the Food and Drug Administration, in December, and the FDA recommended approval at that time for this drug for the treatment of medullary thyroid cancer, and what was seen in a group of 331 patients with medullary thyroid cancer around the world is that there was a 54% decrease in the rate of medullary thyroid progression during the trial. Now the FDA is currently setting up a construct to assure that side effects associated with this drug are outweighed by benefit, but this is probably the drug that is furthest along, and Yale was one of the highest enrolling centers in the world in that trial.
- Foss Would it be easy for a patient with medullary cancer to come and get enrolled in a trial like that at Yale?
- Sosa Absolutely! We have open clinical trials for patients with advanced papillary thyroid cancer, follicular thyroid cancer, Hurthle cell thyroid cancer, medullary thyroid cancer, the adrenal cortical cancer, and we are also focusing energies on developing treatment for the very rare but unfortunate patients who have anaplastic thyroid cancer as well.
- Foss Do you feel that there have been significant advances overall in the management of thyroid cancer and what do you see happening in the future?
- Sosa I think this is one of the most exciting areas in medicine today, and as a surgeon, while I spend most of my day doing surgery, I think the developments on the horizon are those that pertain to the development of new drugs or small molecule therapies that will help patients who no longer benefit from surgery, and as a surgeon, I understand my shortcomings and I would like to focus on this area going forward.
- Foss We have heard a lot of about personalized medicine in the context of other tumors where a tumor tissue is obtained and various genetic tests or other tests are done on that tissue to determine whether a specific therapy would be appropriate for a specific patient. Has this whole area entered the treatment of thyroid cancers yet?

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Sosa It has. The management of medullary thyroid cancer in babies and in children now is driven really at the mutational level, meaning the specific change that has occurred in genes on chromosomes in children, such that we can actually figure out at what point, whether it is in the first year of life, the first 5 years of life, for the first 10 years of life, to intervene in order to prevent medullary thyroid cancer, but the same is now becoming true for adults with thyroid cancer, and I would say at Yale, patients who have papillary thyroid cancer routinely have their tumors analyzed for a mutation called the BRAF mutation, and this mutation was just discovered a couple of years ago, but it is associated with a more aggressive kind of papillary thyroid cancer. This is a routine part of pathology now at Yale and based on whether patients have the mutation or do not is affecting the kind of surgery we do, the kind of adjuvant or additional treatment we do, say with radioactive iodine, and how aggressively we follow them, short and long term.

Dr. Julie Ann Sosa is Associate Professor of Surgery and Medical Oncology, and Director of the Yale Endocrine Surgery Clinical and Health Services Research Group. If you have questions or would like to share your comments, visit 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 on the Connecticut Public Broadcasting Network.