

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 is a medical oncologist specializing in pain and palliative care and he also serves as the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening we welcome Dr. Tom Rutherford. Dr. Rutherford is the Chief of Gynecologic Oncology and Associate Professor of Obstetrics, Gynecology, and Reproductive Sciences, at Yale School of Medicine. He joins Ken Miller to talk about ovarian cancer.

Miller Firstly, what is ovarian cancer and are there different types?

Rutherford There are many different types of ovarian cancer. Basically, it is a disease of the ovary. It can be seen in the young, such as teenagers. The earliest recorded age is 8, and it can be seen in women up until the age of about 30-35 where you then start seeing what is called a germ-line ovarian cancer. These are tumors that grow very fast and they grow in the ovary. Young ladies often look pregnant within a couple of weeks. If you developed one of these tumors prior to 1970, they were fatal. Today it is very rare to have a lady die of this disease. It does require surgery, where the ovary is removed and the affected tissue as well, but it is a conservative surgery so the patient should be able to go on and have children. It also requires chemotherapy.

Miller Is germ-line the most common type?

Rutherford For children it is.

Miller In my personal life, I have a neighbor whose daughter was 14 when she developed an ovarian cancer, but is that different?

Rutherford That would be a germ-line tumor.

Miller It sounds like you are saying it is a very curable disease.

Rutherford It is curable and is very rare.

Miller Thank God. I also wanted to ask you, before we start talking about the most common type, there is something called a tumor of low malignant potential, what does that mean?

Rutherford It is a cancer and there are different types of it. Basically it is a surgical exercise. That is a tumor that does not show a lot of invasion into the basement membranes of the cells, however, it also does not respond to chemotherapy. So, it is the surgical exercise to take the tumor out. The tumor can recur and it can have what is

2:34 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

called micro-metastatic ability where the patient could get into trouble, but most of the time they are localized within the ovaries and you can surgically remove them.

Miller When you go to operate on a patient do you know what kind of cancer or tumor you are dealing with?

Rutherford The only differential you are going to have is where the age breaks; if you have somebody 35-40, or 35 or less, that is probably going to be a germ-cell tumor. If they are 40 or over, then you start thinking that is the epithelial tumor, and that is the most common tumor that we encounter.

Miller Because a lot of these women that you are mentioning are around 35 or 40, childbearing age, are there situations where you can preserve fertility for women with various types of cancer?

Rutherford Yes, there are. We have younger women, aged 30-35 every now and then, with this epithelial tumor. If it is localized within an ovary, we will take that ovary out, maintain the uterus and the other ovary, and many times treat them with chemotherapy and observe from that point.

Miller What is the most common type of ovarian cancer, and what is a typical way that a woman presents to the doctor?

Rutherford The most common is the epithelial tumor where we think, Gilda Radner. These tumors often are present for up to 2 years before we diagnose them, and the problem with ovarian cancer is that it is a disease that whispers. You might go out to dinner and have some spaghetti sauce and your stomach is upset, but it goes away in a day or 2, and a couple of weeks later you have a little symptom while you are working out at the gym, and that goes on for 6 months to a year. Then when they finally examine you they do not see anything. About 5 to 6 weeks before the patient comes to us they have a lot of abdominal bloating, decreased appetite, change in their bowel or their bladder function, and at that point it is obvious that something is going on, but unfortunately, this tumor is very indolent and very quiet. It is there, it is giving you signs, but it is a backward-looking at it when you figure it out.

Miller With those symptoms I wonder about when a woman eventually finds out she has ovarian cancer, besides obviously being worried and scared, are they upset, angry at themselves or doctors, what is the feeling?

Rutherford Many times these patients have seen 3 or 4 physicians before they come to us. They are very disappointed in the medical system for not identifying these tumors upfront. They are disappointed that they did not act more proactively, but the real problem is that a lot of times you see the patient and the ovaries are normal, they

5:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

are small and are not becoming enlarged, yet they have this disease. We have operated on people laparoscopically with symptoms and you look and see nothing. You take the ovary out, or a piece of what is called the omentum, and you find disease in the omentum. A lot of this is microscopic that in the early stages you are not going to see.

Miller Even with the best technology, experts like you are self-examining women and everything looks okay.

Rutherford We've been fooled.

Miller With men we are able to have a PSA drawn and have our prostate examined and that is how prostate cancer is being found early. What progress has been made in terms of finding ovarian cancer?

Rutherford In the past, the CA-125 was the big test. The CA-125 and the ultrasound is basically what we had for screening and neither one of them really improved detection, but every now and then you got lucky. However, in the laboratory we have been playing with a test that looks at 6 different protein markers, and this is currently being marketed by LabCorp. It is a serum test and it is being looked at for women who have a family history or suspicion for ovarian cancer, and hopefully this will help in detection. There is some controversy about it and it needs to be put through a big pilot study because we need a large number of people to see how well it is really going to do, but so far the test has been holding up relatively well. We are able to identify some people with very early ovarian cancer. It is not 100%, none of them are, but we are going to have to wait a little while for the numbers.

Miller It sounds like, eventually, there may be a way to do a blood test and test it early, but we are not quite there. Who would you want to screen really carefully and how would you screen them right now?

Rutherford We always talk about the BRCA1 and BRCA2 population, the Ashkenazi Jewish population, and that helps. If you are from that lineage, and you have a family history of a BRCA1 or BRCA2 positive disease, that is fine. In my family history, I have two uncles with pancreatic cancer, I have an aunt with breast cancer, and two aunts with ovarian cancer; all BRCA1 and BRCA2 negative, all on my mother's side. It does not have to be your mother's side. It could be from your father's side as well. Basically the tumors that ride together and increase your risk are; ovarian, breast, uterine, colon, prostate, and pancreatic. If you have a BRCA1 and BRCA2 defect, that helps, because now we can go and screen the rest of the family and if they also have the defect then they are at a higher risk of developing one of those tumors. If they do not have a defect or deletion, then you have the problem. We are playing in the laboratory with an entity called microRNA. MicroRNAs are little

8:30 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

RNAs. It is a little different because it is not used in transcription or in translation into protein. It helps regulate the cell and we have found that some of the RNAs, these microRNAs are missing in patients with ovarian cancer.

- Miller We are talking about microRNA. For the listening audience, and for me too, tell us again what microRNA is. What does it look like, what does it do?
- Rutherford They are short fragments of RNA and they help regulate the cellular function of how the genes work. There are only about 480 or so of these little microRNAs in the body that we have detected so far. They seem to be able to be identified in tumors as a deletion, or a single nucleotide polymorphism, or SNP, and we have been able to identify some of these abnormalities in ovarian cancer and they are very specific which is interesting.
- Miller Assuming that we looked at these patient's cells, the other cells in the body, does that tell us something about them, or something about the tumor?
- Rutherford We can use what is called a buccal smear on the inside of the mouth, and from the swab we are able to identify if you have that deletion. This is relatively new and is probably one of the hottest topics in science at the current time. Most of what is being published just came out over the last 18 to 24 months or so.
- Miller If you know someone at high risk based on family history, genetics, or eventually let us say, based on microRNA, what would constitute topnotch screening for them?
- Rutherford One, we would use the Ova-Sure blood test from LabCorp. We would use the ultrasound and we would use the CA-125. Once we get the population figured out on the microRNA, we have a specific deletion that we know, and probably we would start looking into that as a screening program as well. There is no one test that is going to do it, and even with the best of technologies, we are still probably going to miss something. The question comes down to, how do we manage that risk?
- Miller Who would you recommend for surgery and to have the ovaries removed?
- Rutherford What you want to do is look at where the family history is. The prophylactic surgery, we prefer to do around age 35. With the removal of the ovaries you decrease the risk of an ovarian cancer and the risk of a breast cancer, but you do not decrease the risk of ovarian cancer to zero. There is an entity called a primary peritoneal cancer which can occur even if you remove the ovaries, and it is just like an ovarian cancer because it is the same lining inside abdomen as it is out of the ovary. The problem is that when an ovary releases an egg during normal ovulation, a portion of the surface of the ovary ruptures and it spreads through the abdomen. That in and of itself can cause little implants later if a tumor develops. There are

two ways to reduce the risk. One is birth control pills, and that seems to be very effective and we would want to put somebody on birth control very, very early. You do that to prevent ovulation, because we believe that the tumor is being caused by inflammation, so during an ovulation cycle if you rupture the surface of the ovary it undergoes a repair mechanism and inflammation occurs that we believe has some impact on malignancy. Where the theory falls apart a little bit is the other way to reduce the risk of ovarian cancer is by tubal ligation. That also decreases your risk of breast cancer. Tubal ligation has nothing to do with ovulation. It interrupts the tube and the blood supplies going to the tubes, so the question comes down to, how does tubal ligation decrease the risk?

Miller What is the answer?

Rutherford We do not know.

Miller Alright, let us take a break. When we come back we are going to talk more about ovarian cancer. You are listening to Yale Cancer Answers with Dr. Tom Rutherford, Director of the Gynecologic Oncology at Yale Cancer Center.

Medical Minute

Here in Connecticut, the American Cancer Society estimates that almost 1000 people will be diagnosed with colorectal cancer every month. The good news is that when you detect it early, colorectal cancer is easily treated and highly curable. That means that if you are over the age of 50, you should have regular colonoscopies to screen for this disease. In the case of patients that develop colorectal cancer, there are more options than ever before. Thanks to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. The patients enrolled in these trials are given access to medicines not yet approved by the Food and Drug Administration. This has been a medical minute. You will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut public radio.

Miller This is Dr. Ken Miller and I am here with Dr. Tom Rutherford who is Director of Gynecologic Oncology at Yale Cancer Center. We would like to remind you that you can e-mail questions to Yale Cancer Answers by sending them to canceranswer@yale.edu. Tom, I did not know about your family history, what led you into gynecologic oncology? Was it related to that?

Rutherford Actually it was not.

Miller Okay.

14:21 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

- Rutherford I did a PhD in molecular genetics and I was looking at an enzyme called glycosol transferase. We were looking at leukemia and I worked with a gentleman out in Toledo, Ohio who was a gynecologic oncologist. He was working on a young lady who had ovarian cancer and at that time subtraction hybridization was the big technique. I thought it would be as easy as, this is a normal ovary, this is an abnormal ovary, I should be able to figure this out. I was a little naïve. And that's what got me interested.
- Miller That is interesting, and I have to say, it is like that with all of us. Sometimes it is one patient or one mentor that we have. How is ovarian cancer treated?
- Rutherford It really depends upon the stage. In early stage, we treat it predominantly with surgery, plus or minus chemotherapy. Anything beyond the early stage usually requires surgery and chemotherapy. The question is, which do you do first? With any tumor, there are basically four stages. Stage I is confined to the organ. Stage IV means it is metastatic, somewhere distant. Stage II is metastatic to whatever organs are closest and stage III is a little farther wide. That is pretty much true for any tumor. So, stage I ovarian cancer is located within an ovary and is what is called a well-differentiated tumor; the surface is not involved. We would take the ovary out, do a hysterectomy, and remove the lymph nodes along the major vessels in the abdomen and pelvis. There is also a fat pad that hangs off the stomach called the omentum, we would remove that as well. If just the ovary is involved, we would stop. We would just treat the patient with surgery and she would not need chemotherapy. However, if it is a high-grade tumor, meaning a poorly differentiated tumor, we would then go on and treat the patient with chemotherapy.
- Miller Of all the patients you see, or in gynecologic oncology in general, what percentage have these very early tumors that are well differentiated?
- Rutherford Unfortunately, very few; probably 10 to 15%.
- Miller In those women it sounds like many of them are cured surgically.
- Rutherford That is correct.
- Miller And for women who do not fit that criteria, maybe stage I or stage II but the tumor looks a little wilder underneath the microscope, what would be the sequence of events for them?
- Rutherford The lady would still undergo the surgery. You do the hysterectomy, do the lymph nodes, the omentum, remove any tumor you see, and then the patient would receive chemotherapy. The chemotherapy we are using today is a platinum taxane base, plus or minus a drug called Avastin which affects the vasculature to the tumor. It looks like Avastin is going to be moved up into the front line. It has a major

advantage for the patients and there are several clinical trials being run currently in the nation. One is being run by a Gynecologic Oncology group looking at Avastin in advanced stage disease. A second one is run by Genentech on recurrent disease that they are bringing in as a second line therapy. Both of these trials are showing that there seems to be some advantage to moving these drugs up and I think in the future, you are going to see platinum, taxane and Avastin or an Avastin like compound.

Miller Might that be the case even for women with early tumors?

Rutherford I think it is going to be. If you can improve your advanced stage, you want to improve your early stage, but even in early stage there is a 20% recurrence rate.

Miller In other parts of oncology the same thing is happening. In terms of lung cancer treatment and colon cancer treatment, Avastin is a very exiting drug. There is another approach being used in other types of cancer where you treat someone upfront by using chemotherapy first. When might that be useful in your field?

Rutherford Neoadjuvant chemotherapy was started with Peter Schwartz and when I came here in 1993 I saw a lady with a very advanced cancer and he asked me what we should do and I said, we go to the OR, and he promptly told me I was wrong. We treated her with chemotherapy and then we went to the OR. When a lady comes in with advanced tumors or advanced stage disease, she has abdominal bloating, a lot of fluid in the abdomen, and a lot of times they can have fluid in their lungs and when you take them to the OR all the tissue is soggy. It is like putting her hands in a dishwasher for a week. Therefore, you have increased bleeding. The patient would often end up in intensive care for prolonged periods of time and depending on who you want to believe, somewhere between 60% to 80% of the time you can debulk the patient to no residual disease, and that is in the best of hands. You can get trials to show any number you want, but the patient ultimately has a pretty rocky course. They can re-accumulate the fluid in the abdomen postsurgically and you're always chasing them in the intensive care and they are pretty sick. The other thing that is true is that with the advanced stage disease the patient has not been eating all that well so approaching status is very poor. If I can get that patient to eat, we build her protein status, get rid of fluid, decrease the volume of the tumor that would decrease my operative time and that would make her recover faster postoperatively and reduce blood loss. So, we treat him with chemotherapy upfront and what we have been able to show over the last 15 years is that if you have a stage IV tumor in a patient, the proper way to treat that patient is to treat that patient with chemotherapy upfront because we have increased survival. If it is a stage III, meaning it is bad, but it is not the worst, if you can debulk that tumor, and we can use CAT scan criteria to determine that, that's fine and you treat them with chemotherapy. If you cannot debulk the tumor to no residual disease, which is what we are looking to do

20:24 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

anytime we go to the OR, remove all tumor, then that patient should probably be treated with chemotherapy upfront followed by surgery.

Miller When we talk to women about using chemotherapy upfront instead of operating, and we have these discussions in breast cancer as well, what do women typically say to you, what concerns do they have?

Rutherford For ovarian cancer, if you asked this 10 years ago, the standard of care was to treat the patient with surgery followed by chemotherapy. Gynecologic oncologists do not always do the chemotherapy; a lot of times we send the patient into medical oncology, like they do at Memorial Sloan-Kettering, they have a split division on who is doing what. If you go and see the gynecologic oncologist he is going to tell you that you need an operation, in fact, that is what they push. The question is, is this the right thing to do? When you look at recovery time, how the patient does long term is what really drives it. We have a frank discussion of how well our patients do and how long, or short, they are going to be in the hospital for and what the postoperative recovery time is.

Miller You were saying that it looks like survival may be better in those patients who get preoperative therapy. Is that because the postoperative course is easier, or do you think it really gets rid of more cancer cells?

Rutherford We have a theory. In the laboratory, under Gil Mor, we have been able to identify what we call the stem cell. That stem cell was chemo resistant. So, when you treat an ovarian cancer, the biggest problem you have is that over time that disease comes back. We can get to no residual disease, and it can stay dormant for a couple of years and then, unfortunately, many times it comes back. The cell that is coming back is what we believe to be the stem cell, a chemo resistant cell. If I treat a patient with chemotherapy, I kill all the soldier cells, leave the chemo-resistant cells behind and at the time of surgery, we can remove it. I think that might be what is happening.

Miller In your department, you and Gil Mor in particular, have been leaders with other members like Dr. Schwartz in terms of treating women with chemo resistant ovarian cancer. Can you tell us a little bit about some of the work that you are doing?

Rutherford We have looked in the past into a drug called phenoxidiol. What happens with chemotherapy is that it works for a while and then it stops working. So, the question is, does the cell figure out how not to undergo self-death called apoptosis, or can we modulate that mechanism to make it reactivate? We came up with a drug in the laboratory called phenoxidiol and we found that if you use that in the laboratory, and even in the clinical trials, it seems to have an effect on chemo

resistant reversal. We went from a phase I, II clinical trial, and currently we are on a multinational trial, phase III, looking at phenoxidiol in combination with chemotherapy to see if we can reverse the resistance, and so far, we have had some encouraging results.

Miller Just looking back in the last 10 years, the combination you are talking about, Taxol or the taxane and the platinum drug, have been used for quite a while. Are there any other drugs proven to be useful that may take the place of these other two?

Rutherford What we are going to see is biologic modifiers being used, and I think that is where the push is going to come from. There are a lot of different trials currently that everyone is looking at. I do not think anybody has anything that they can say, this is going to be the next drug that we are going to use. There are other drugs we have looked at such as topotecana and gemcitabine. Doxil is a very nice drug in the sense that it has been repackaged from Adriamycin so that you do not have the cardiotoxicities. In fact, we have gone back and have started to use a drug called Alkeran which everybody is surprised on line 13 or 14 works.

Miller It sounds like there are also a large number of women who are living with cancer.

Rutherford Correct, we have many people that we treat off and on with chemotherapy. I have patients out anywhere from 8 to 15 years that receive chemotherapy off and on.

Miller And they are leading a relatively good life?

Rutherford A very good life. Quality of life is very important.

Miller What other clinical trials are you involved in, in your department?

Rutherford We are members of the Gynecologic Oncology Group which is a multinational group of GYN oncologists. There are multiple trials going on right now. We have a lot of phase III and some phase I and II to see which drug combination seems to have the best effect. We also do a lot of industrial trials. We work with Genentech and GlaxoSmithKline. We have a series of trials that are in design because we think we knock out that stem cell by playing with one of the receptors between cell membranes, and if that holds true, that is going to be a real breakthrough. It works in the animal model so if we get it to work in a person, I think we got this one.

Miller One of the things I am impressed with is that at the start of my career a lot of times surgeons would say, I got at all, and a lot of diseases like breast cancer are treated very much surgically, but it sounds like what you are talking about is a collaborative effort.

26:19 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

Rutherford Oh, absolutely. What happens is that when that ovary ovulates and that cell ruptures it's like rupturing a balloon; it just bursts through the abdomen. When we say, we got it all, that means we took out everything we could see. The problem is what we cannot see. We have all taken out an ovary or a piece of tissue that looks totally normally, put it under the microscope and it is completely malignant.

Miller So ultimately it is really a matter of, you remove as much as you can to your vision and touch and then the rest is using chemotherapy and some of these newer agents.

Rutherford Correct.

Miller Has the prognosis for women with ovarian cancer improved since the start of your career?

Rutherford The actual cure rate may not have improved all that much, but it has improved a little. What we are definitely seeing is that women are living much longer with the disease and have a functional life. It is closer to diabetes; we cannot cure diabetes.

Miller Correct.

Rutherford But people are living longer and more functional lives with it.

Miller Wrapping up, let me just ask you, how do women avail themselves of being involved in clinical trials, at Yale or elsewhere?

Rutherford I would encourage people to participate in these trials. The only way to get Avastin today for ovarian cancer is in a clinical trial. We know that the drug has activity, and some people will say, I do not want to be the guinea pig, but you want to be the guinea pig for this trial. I am not saying you do for all trials, but sit down and talk with you physician about this one. I think most physicians are going to be very honest with you and say that they would do this trial if they were you, or if it was a family member. A lot of the trails we are doing today are bringing you the drugs that I cannot get you any other way.

Miller There is very careful monitoring on clinical trials and the other gift the patients are giving is knowledge to science and to medicines, so that hopefully other women will benefit along with them.

Rutherford That is correct.

Miller Tom, I want to thank you for joining us. It has been a very, very interesting session as it always is when you come. Until next week, this is Dr. Ken Miller from Yale Cancer Center wishing you a safe and healthy week.

28:49 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-14-08.mp3

If you have questions, comments, or would like to subscribe to our podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, Dr. Francine Foss talks to Dr. Ken Miller about the latest developments in the treatment of lymphoma. I am Bruce Barber, and you are listening to the WNPR Health Forum from Connecticut Public Radio.