Yale CANCER CENTER answers

WNPR Connecticut Public Radio

An Update on Ovarian Cancer

Guest Expert:
Thomas Rutherford, MD
Associate Professor of Gynecologic Oncology

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

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I am Bruce Barber and this is Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Caner Center and an internationally known expert on colorectal cancer. Dr. Miller is a Medical Oncologist and the Director of the Connecticut Challenge Survivorship Clinic. He also specializes in pain and palliative care. If you like to submit a question about cancer, please e-mail us at canceranswers@yale.edu or call 1-888-234-4YCC. If you would like to hear past editions of Yale Cancer Center Answers, each segment is posted on the Yale Cancer Center website at yalecancercenter.org. This evening, Dr. Chu and Dr. Miller will be talking about ovarian cancer with Dr. Thomas Rutherford who is Associate Professor of Obstetrics and Gynecology at the Yale School of Medicine and Head of the Section of Gynecologic Oncology.

Miller — Thomas, let's start out the program by talking about what ovarian cancer is.

Rutherford — Ovarian cancer is a tumor of the ovary. The layer of the ovary that it comes from depends upon what point the patient is in their life. Early in life, the patient would have what is called a germ cell tumor. Germ cell tumors are usually seen up to the age of 35. These tumors grow very fast and are very responsive to chemotherapy. Back in the 1970s, women who had germ cell tumors would die three to four months after diagnosis. Currently, once detected, with the new chemotherapy the patient would undergo surgery and chemotherapy with cure rates approaching 95%.

Miller — Would this be a young girl, a teenager or someone in their early 20s?

Rutherford — The earliest documented patient is 12. In general when we think about an ovarian cancer we think about the Gilda Radner tumor. These are epithelial tumors and are generally seen after the age of 45 with a peak incidence around 65. These tumors, unfortunately, are diagnosed late and that is what makes it so deadly a tumor. They are very difficult to diagnose early, but if they are diagnosed early our cure rate approaches 95%. There is another tumor that is an epithelial tumor, called a borderline ovarian tumor. It is still a cancer; however it is a surgically treated tumor. It does not respond to chemotherapy as other epithelial tumors. It's considered borderline because once you take it out that should take care of it. Unfortunately, these can recur 10 to 15 years later in life.

Miller — In your experience, because you treat women of all different ages, which of those three are the most common and which are the least common?

Rutherford — The least common are the germ cell tumors in the younger women. The most common, unfortunately, are the epithelial tumors.

Chu — Tom, where does ovarian cancer rank relative to other women's tumors like breast cancer, uterine cancer, or cervical cancer?

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Rutherford The good thing with cervical cancer is that with Pap smears is it is becoming less and less a disease that we treat, especially now with the new Gardasil vaccine. Hopefully it will become a disease that we see even less. In this country cervical cancer is not really an issue. In third world countries this is the leading cancer that we deal with. One in eight patients is diagnosed with breast cancer. Ovarian cancer is 1 in 70; it is seen much less. With uterine cancers the problem we have currently is that as the weight of the American population increases, the incidence of uterine cancers is also increasing. This is due to the fact that the fatty tissue converts to estrogen at a higher rate and estrogen causes a proliferation in the uterine cavity.

Chu What are some of the risk factors, especially for, as you said, the Gilda Radner type of ovarian cancer?

Rutherford The bottom line is that we do not know. Family history definitely plays a significant role. Instead of risk factors, we know that if you have multiple children, if you are on birth control pills specifically for more than 5 years, if you have a prophylactic oophorectomy or if you have a tubal ligation prior to the age of 35, you can decrease the incidence of ovarian cancer.

Miller Why might a tubal ligation make a difference? That is interesting.

Rutherford When someone ovulates they have proliferation of cells, and those cells are ruptured and spread through the abdominal cavity during normal ovulation, birth control pills would decrease that incidence of rupture so you have less spread and less damage to repair. Tubal ligation has no effect at all on that. No one really knows how it works but we do know that if someone has a higher propensity due to family history, if we put her on the birth control pill and tubal ligation, it will decrease her incidence, but we do not understand the mechanism.

Miller We have an e-mail from a woman in Stamford. She said, "I have had numerous ovarian cysts over the years. Sometimes I have discomfort because of them and this makes me nervous. Am I at a higher risk of developing ovarian cancer because of these cysts?"

Rutherford The answer is no.

Miller Okay.

Rutherford Ovarian cysts are a normal physiologic response to normal menstruation. Ovulation is part of that cycle, so a cyst in and of itself is not a problem.

Chu There is an interesting relationship between breast cancer and ovarian cancer. Can you elaborate for our listeners out there?

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Rutherford There are a series of tumors that run together as a family. Those are ovarian, breast, uterine, colon, prostate and pancreatic. There is definitely a higher incidence of breast cancer, fallopian tube cancer and ovarian cancer. The most common tumor that we see in patients with ovarian cancer is breast cancer and one of the more common tumors we see in a breast cancer patient is ovarian cancer. The other thing you see with ovarian cancers or breast cancers is that we can have metastatic disease to the ovaries. The ovaries are like a sponge, so if a patient has breast cancer or colon cancer, many times we find a mass in the ovary that is metastatic from the primary site.

Chu Is there a genetic mutation that is common to both breast and ovarian cancer?

Rutherford The mutation that we know of today is the BRCA 1 and 2 gene. BRCA 2 seems to have a higher incidence of ovarian cancers than tubal carcinomas.

Chu When do you test women for BRCA 1, BRCA 2?

Rutherford With our patients that have breast cancer we look at their family history. If the history is significant, we would get genetic counseling. However, if you see that family of tumors together, then definitely there is benefit to testing the entire family.

Miller If we look at a woman who, for example, has a family history that includes a mother that had breast cancer, or there were other types of these cancers in the family, what kind of screening would be done for ovarian cancer as the woman approaches middle age and beyond?

Rutherford Unfortunately, there is no standard of care for screening for ovarian cancer at the current time. What we have done at Yale is come up with a serum blood test that looks at six different markers for early detection for ovarian cancer. This is currently going to a national trial to see the validity of the testing. What we have recognized ourselves is that it does have some validity, not only in detecting early stage tumors, but also in screening people for recurrent disease. The other thing that people will do is use an ultrasound. Patients who currently have family risk for ovarian cancer will follow-up with the CA-125 as well as ultrasounds. The problem with this CA-125 test is 40% to 60% of patients with early stage ovarian cancer have a normal CA-125. When the CA-125 is elevated, that tells us we have advanced disease. The other problem with the CA-125 is that you can have an elevation in that number due to fibroids, menstrual cycle, pregnancy or endometriosis. Because of this it is a very poor screen for a cancer.

Miller In prostate cancer the PSA is a very good screening. There are some issues with it, but you are saying that with ovarian cancer we are not there yet?

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Rutherford That's correct.

Miller That is unfortunate. Where do you predict things will go in terms of screening? Do you see any major breakthroughs, for example, with your blood test?

Rutherford Yes, I think so. We are fortunate to be finding tumors early. Some of the patients have been operated on and underwent prophylactic bilateral salpingo-oophorectomies which found a very early tumor based upon screening and family history.

Chu One thing to emphasize for our listeners out there is that the screen you have talked about comes from laboratory efforts.

Rutherford Correct. It was developed predominantly through the efforts of Dr. Gilmore, and currently the test can be obtained through LabCorp. We have an outreach program so that blood can be drawn at a local office and sent to Yale for evaluation.

Chu This is also part of your Discovery to Cure efforts, right? Can you elaborate a little bit more and tell our listeners what that is all about and how they can support this effort?

Rutherford The Discovery to Cure is looking for early detection methods. Out of that program we developed this screening technology. The technology also looks at people who have cancer and how we can treat them. There are a lot of research efforts looking at once you have cancer. We obtain a piece of tumor at the time of a surgery, we send it out for testing for specific chemotherapy, or more importantly to find out what not to treat you with.

Miller In terms of treatment, if a woman is found to have, lets say, early stage ovarian cancer, she goes to a doctor, they feel something on the ovary, how is treatment then approached with those women?

Rutherford If you have a woman with a complex ovarian or adnexal mass, by complex we mean it has either solid or cystic components together, normally the first thing we do is obtain a pelvic ultrasound. We use an entity on the ultrasound called Doppler flow. It measures blood flow to that ovary. If it looks like it has tendencies towards being malignant, we would recommend that they undergo a surgical exploration to look at that ovary. We would do either a conservative management or a complete surgical staging based upon what we find. It also depends upon her age. Somebody who is thinking about having children and has an ovarian mass, this does not necessarily mean you lose your ability to have fertility, so the patient needs to be evaluated. If an ovarian cancer is found early, generally what needs to be done is to take out that ovary and/or the uterus and

cervix, look at the lymph nodes along the major vessels in the abdomen and pelvis. There is a fat pad that looks like an apron that hangs off the stomach called the omentum which we would need to remove as well. Based upon those findings, we will decide whether or not the patient will need chemotherapy.

Miller There are some women who undergo this surgery and really do not need anything else.

Rutherford That is correct.

Miller What are some of the criteria that you look for in women that you operate on that would make you follow-up with chemotherapy or some other treatment?

Rutherford If the tumor is a well-differentiated tumor and totally encapsulated within the ovary and is located on just one ovary, that woman would not need chemotherapy. When you look at what the tumor looks like, if it is a poor histology, meaning it looks like it has more chance for distant spread, those patients would need chemotherapy. If you have an ovary that is stuck to other pelvic organs, stage II disease, those patients will need chemotherapy.

Chu Is there ever any role for radiation therapy after surgery has been performed?

Rutherford Years ago radiation therapy was sort of the standard of care, mainly before chemotherapy came along, but the answer is still yes. We do use some chemotherapy. It depends upon if the disease is within the pelvis. If the entire disease is in the pelvis, radiation will give us a relatively good cure rate; however, the effects of radiation are permanent and can cause some damage or changes to the bowel and bladder that never totally heal. With chemotherapy we do not have those effects. It is really a judgment call based on where that tumor is located.

Miller We would like to remind you to e-mail your questions to us, and Dr. Thomas Rutherford, to canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more about ovarian cancer with Dr. Rutherford from the Yale Cancer Center.

Medical Minute

This year over 170,000 Americans will be diagnosed with lung cancer. More than 85% of lung cancer diagnoses are related to smoking, and quitting, even after decades of use, can significantly reduce your risk of developing lung cancer. Each day, patients with lung cancer are surviving. Thanks to increased access to advanced therapies, specialized care and new treatment options, lung cancer survivors have new hope. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale, to test innovative

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new treatments for lung cancer and 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. For more information, go to yalecancercenter.org.

Miller — Welcome back to Yale Cancer Center Answers. This is Dr. Ken Miller, and I am here with my co-host, Dr. Ed Chu, and our guest Dr. Tom Rutherford, discussing the latest treatment options for women with ovarian cancer. Tom, one of the concepts that has come up in treating other cancers is using chemotherapy early before surgery, is that being done with ovarian cancer, and what are some of your observations about that approach?

Rutherford — Actually what we call it is neoadjuvant chemotherapy. This was initiated here at Yale under Dr. Peter Schwartz. When I first came here in 1993, I met a patient with advanced ovarian cancer and Dr. Schwartz asked how I was going to treat the patient. At that time it was standard care to take her to the OR but he said that was wrong because it should be treated with chemotherapy. I looked at him and said "Wow, okay." We treated her with chemotherapy and then took her to the OR. This patient had marked reduction in tumor disease. She had a much easier postoperative course and did not go to the intensive care unit. She stayed in the hospital for maybe 3 days. She had a marked decrease in blood transfusions, 0 units versus 5-6 units. More importantly, what happens with neoadjuvant chemotherapy, especially in ovarian cancer since they present with bloating and fluid in the abdomen, is that all that resolves as the nutritional status is improved and you are healed much quicker and better.

Miller — Potentially, surgery is actually safer when you do operate. Are the outcomes better?

Rutherford — Currently there is a trial in Europe which is starting to show that there is benefit to treating a patient with neoadjuvant chemotherapy. In the past we were taking the worst of the worst patients and putting them on neoadjuvant chemotherapy. Those patients did not do worse as compared to the other group; however, the group where you started was much worse as a starting point. As time goes on and the group gets larger in population so that more and more patients with stage 3 and 4 tumors are being treated upfront with chemotherapy, you will see patients with survival improvement. We see that trend here at Yale.

Chu — If a woman undergoes this neoadjuvant chemotherapy, then goes to surgery and has a successful operation, will she then receive additional chemotherapy afterwards?

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Rutherford If they have residual tumor they would get chemotherapy. That is an easy one to answer. The question comes down to if you take a patient to the OR after neoadjuvant chemotherapy and find no disease, what do you do with that patient? Do you put them back on chemotherapy or not? Currently, that patient would receive 4 other cycles of chemotherapy.

Chu It is very similar to the disease that I know very well, colorectal cancer. In patients who have an advanced liver disease, we give them chemotherapy, take them to the OR, then if there is no evidence of disease usually there is nothing to do, but we give them additional chemotherapy. This sounds very similar.

Rutherford Very similar, correct.

Chu If a woman has either early stage or a bit more advanced cancer, getting chemotherapy after surgery is the usual recommendation for follow-up. How often should they come back and be evaluated by you and your team?

Rutherford We follow-up with patients every three months with a physical exam and with the CA-125 if it is a marker for them, and in 80% of the patients that blood test is a marker. What we hope to do is obviously not find anything that has recurred; however, many times we start seeing the CA-125 slightly increased and somewhere between 3 to 6 months that number continues to rise. Most of the time, the CA-125 will rise somewhere between 3 and 6 months before you see any CT scan evidence of any lesions.

Miller We had an e-mail from Sarah who lives in Norwich. She says, "I am 56 years old and I have been treated for ovarian cancer which recurred. What is new in terms of new therapies for ovarian cancer, and are there any other vaccines or more targeted therapies?"

Rutherford Targeted therapies are becoming the thing that everybody is trying to do. So the answer to that is, yes, things are becoming much more targeted and we are starting to understand the biology of the tumor. On recurrent patients, we have the ability to take a piece of tumor, send it off and do chemo sensitivity testing. Some of the testing that we are looking at is actually using the Fas/Fas ligand system, look in to cap says three activity and tumor sensitivity.

Miller What is that?

Rutherford All cells are programmed to die and Fas/Fas ligand is a marker for cell death. What we can do is treat the tumor with chemotherapy and see if that will become activated. Within that system we have drugs that are trying to manipulate that pathway such that if a tumor is resistant to cell death, called apoptosis, then we can use that drug. Currently we are looking at a drug called phenoxodiol that will

actually reverse this resistance to platinum. We are looking at two other proteins; one is called MyD88, which is myelodysplastic #88. We know that if a tumor has MyD88 positivity and you treat that patient with Taxol that tumor will grow. If it is MyD88-negative those patients do much better and we can almost treat them with anything and they are going to respond.

Miller So does the chemotherapy cause it to grow, or does it just not prevent it?

Rutherford Chemotherapy causes it to grow. It is a growth factor for the tumor.

Miller Which is a scary concept.

Rutherford Very scary. Instead of doing what is good for the patient as we want too, we are actually causing them problems because the gold standard for ovarian cancer is carboplatin with Taxol. By treating a patient who is MyD88-positive, we may be doing harm. We currently have a trial looking at that. The next question is what to do with those patients who are MyD88. The story gets a little harder because it has to do with immunotherapies and how to manipulate it. We are looking at a CD-44 cell, which is part of the immunotherapies. We have some ideas about how to go about reversing this; specifically, reversing what is called an NF-kappaB inhibitor is one of the ways. We have another gentleman, Dr. Alexander Santane, who will be joining us later this fall. He is bringing with him Dendritic therapy. This is becoming a very specific immunotherapy towards these tumor cells.

Chu One point to emphasize is that all of this work really comes from the laboratories here at Yale within the GYN Oncology Group and is part of this whole Discovery to Cure Program.

Rutherford Correct.

Miller It is quite a unique program throughout the country.

Rutherford Very unique. On our accreditation they were surprised at how many trials from the laboratory to the patient bed care we have been able to do.

Chu As a cancer center, this is a high priority to be able to take innovative ideas from the laboratory and bring them to the clinic, as you are doing, and then bring ideas and observations from the clinic back to the laboratory. It really is a very cyclical process.

Rutherford Correct. We have been lucky that we have been helped quite a bit by many people.

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Miller Let me ask you about phenoxodiol. I understand that Yale has helped develop the drug in what we call phase 1 and phase 2 trials, and there is about to be a phase 3 trial. Can you tell us about that?

Rutherford Phenoxodiol was actually started six or seven years ago. Early on we were looking at estrogen receptors and ovarian cancer and what we found is that as the tumor becomes metastatic, it loses one of the estrogen receptors called the beta. We have compounds that are estrogen like, and phenoxodiol is an estrogen like compound. We treated some cell cultures with this compound and the cultures died. So, initially we thought that we had contaminated the cultures. However, we repeated it many times and found that we could definitely take cells and kill, or at least stabilize them, with the phenoxodiol. In that phase 1 trial, we accumulated forty patients and within six months we found that 40% to 50% of the patients had at least stable disease and one had regression of the tumor with that drug alone. It acts as a biologic modifier. At the same time, in the laboratory, we were using phenoxodiol with chemotherapy and found that we needed one one thousandth the chemotherapy to affect the same response of cell death with the phenoxodiol. Based on that data we did the phase 2 trial looking at phenoxodiol with chemotherapy and the response rate was 56%, which is pretty good when you look at recurrent disease, especially when somebody is down fifth and sixth line, your normal responses is somewhere between 7% to 12%.

Chu If anyone wants to learn more, or gain access to your clinical trials, how can they do so?

Rutherford On our website www.yalecancercenter.org

Miller They can also call the Yale Cancer Center. Tom, I want to thank you for joining us and sharing some very interesting information about ovarian cancer. It was new to me and hopefully to our listening audience. Thanks for joining us.

Rutherford Thank you for inviting me.

Chu Thanks for joining us. We look forward to hearing more about Discovery to Cure from you and your colleagues in the future.

Until next week, this is Dr. Ed Chu and Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our Podcast, go to www.yalecancercenter.org where you will also find past broadcasts in written form. Next week, we will discuss some of the legal issues surrounding genetic testing with Connecticut's Attorney General Richard Blumenthal.