Support for Yale Cancer Answers is provided by AstraZeneca, working side by side by with leading scientists to better understand how complex data can be converted into innovative treatments. More information at astrazeneca-us.com

Welcome to Yale Cancer Answers with doctors Howard Hochster, Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week in honor of Ovarian Cancer Awareness Month, it is conversation about advances in the treatment of ovarian cancer with Dr. Peter Schwartz. Dr. Schwartz is the John Slade Ely Professor of Obstetrics, Gynecology and Reproductive Sciences and Vice Chair of Gynecology at the Yale School of Medicine. Dr. Hochster is a Professor of Medicine and Medical Oncology and Associate Director for Clinical Sciences at Yale Cancer Center.

Hochster Can you tell us a little bit about how long you have been in this field and how you got interested in it?

Schwartz Certainly. Actually, I have been in the field quite a while. I did first an obstetrics and gynecology training program here at Yale back in the late 1960s and after serving a couple years in the military I went to MD Anderson in 1973 and did a fellowship in gynecologic oncology. Prior to my leaving, I had an interest in rare ovarian tumors because my mentor, John McLean Morris was interested in it, and when I got down into MD Anderson, I had been told by Dr. Morris not to learn anything about radiation therapy, we did it better at Yale, he was right about that. I was going down there to learn about surgery, which he really was not comfortable in the idea of training, maybe for that, but he told me under no circumstance that I learn anything about chemotherapy because it never cured anybody. I got down to MD Anderson. It was the mecca for gynecologic chemotherapy. We treated huge number of patients with both common epithelial cancers as well as the rare germ cell tumors and sex cord-stromal tumors. So, I got very, very interested in ovarian cancer because this is what my mentors down there were interested in and it just became a natural part of my career.

Hochster So, specialized training programs in gynecologic oncology, surgery, and gynecologic oncology in general were pretty rare at that time?

Schwartz Yes. Actually, the first formal training program was approved in 1973 and I was in the first formally approved training program or the year of the first training program approved by the American Board of OB/GYN. There were 25 programs, there are now only about 40 in the United States, but these programs had to train the fellow in radical cancer surgery, which includes bowel, urinary tract surgery, as well as radical gynecologic cancer surgery. Chemotherapy, radiation therapy and all of the board-trained programs have either a 1- or 2-year commitment to laboratory research in addition to clinical care.

00:03:20 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Hochster So, how long of a program is that?

Schwartz Well, at Yale, it is 3 years. There are several programs where it is 4 years because the research years are 2 years. We believe 1 year is sufficient to accomplish the goals.

Hochster And that is after completing medical school and residency in obstetrics and gynecology?

Schwartz That is correct.

Hochster So, you are talking about 10 years of post-medical school training more or less.

Schwartz Well, it gets quite long. Of course, nowadays, we do not have military commitments as we did when I was going through the program, and we did not have a separate internship from our residency training program, which I had to go through when I was in my training era.

Hochster General surgical internship.

Schwartz Yes.

Hochster That is when you like worked every other night?

Schwartz On the short weeks. The long weeks, we worked 4 nights out of 7.

Hochster Well, that was easier, right. Things have changed. So, tell us a little bit about ovarian cancer. How common is it, what are we doing today to screen for ovarian cancer?

Schwartz Okay. Ovarian cancer remains fairly stable in terms of its incidence. It actually is the tenth most common cancer that women get in the United States. We see about 22,000 new cases a year. The problem with ovarian cancer is it has an extremely high mortality rate. Unlike the other more common gynecologic cancers, like uterine cancer, which has an obvious early warning signal of postmenopausal bleeding or cervical cancer which can be detected in a precancerous phase and treated before the cancer ever develops, there is no screening test for ovarian cancer, there is no obvious early warning symptoms. Indeed, at least 70% of ovarian cancers in the United States are not detected until they're advanced, the disease has not only spread outside of the ovary but involves the upper abdomen or beyond the abdominal cavity.

Hochster So, like the most common thing that women present with are bloating, distention, abdominal pain, pretty nonspecific symptoms.

00:05:32 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz Yes and that is the problem because about 10% of Americans have irritable bowel syndrome, and for many people, the symptoms of irritable bowel syndrome are virtually the same as those for ovarian cancer. One distinguishing feature is that when one has a pelvic mass, there frequently is pressure on

the bladder. So, urinary frequency is very common in women with ovarian tumors, both benign and malignant. You do not see that with the irritable bowel syndrome. But bloating is very, very common with both abdominal discomfort, change in bowel habits can occur, and so the symptoms are often put off initially to some dietary indiscretion one may have had and it delays the diagnosis.

Hochster And so, in terms of screening, is there any group that is recommended for screening and what would be done there?

Schwartz Well, screening programs have developed all over the United States. We had one of the very first that we started at Yale back in 1990 and that was based on family history. We now know that there is a particular group of women who have inherited mutation in either the BRCA-1 or BRCA-2 genes and these women are at a much higher incidence of ovarian cancer than women who do not have inherited the mutation. So, the National Cancer Institute recommends really screening only in patients who have high risk based on the mutation in the BRCA genes. For the patients with family histories of breast and ovarian cancer, these are the patients that should be screened genetically to be sure they do not have that mutation. But the women who have the mutation in the United States, the best recommendations are to complete fertility and then undergo either a removal of the fallopian tubes and ovaries or as a temporarizing measure, removing the fallopian tubes at a younger age and then coming back and removing the ovaries as one approaches menopause. But for just the population as a whole, the available tests that have been employed to try to screen for ovarian cancer have had a very high false positive rate leading to a lot of unnecessary surgery but not reducing the incidence of stage III or IV ovarian cancers.

Hochster So, the best test is just still seeing your gynecologist and getting a pelvic exam?

Schwartz At this moment, that is as good as any and we do recommend for reproductive age women seeing gynecologist on a routine basis.

Hochster And ultrasound, either vaginal or abdominal?

00:08:20 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz Yes. The ultrasounds and a blood test called CA-125 have been the 2 tests that have been most extensively studied. The ultrasounds always made the most sense to me because they looked directly at the ovaries. But unfortunately, ovarian cysts, very benign ovarian cysts are very, very common. Even in a post-menopausal women, one can find small ovarian cysts that are innocuous. And so, with ultrasound, there is a higher incidence of false positives because these cystic changes in the ovaries are found leading to surgery. CA-125 obviously circulates around the blood stream. It is a blood test, but it can be elevated in reproductive age women for a number of benign gynecologic indications, including benign ovarian cysts, pregnancy, inflammation of the fallopian tubes, it is a little more

accurate in postmenopausal women who do not experience these reproductive age problems, but any inflammation in the abdominal cavity, any reason for collecting fluid in the chest or the abdominal cavity can cause an elevated CA-125. So in our large tests that have been done in the United States and in Europe, it really does not seem like the CA-125 in a woman who has an inherent mutation for cancer, these can be valuable and the ultrasound has not been valuable in terms of early detection of ovarian cancer.

Hochster And on the other side of the genetic testing and screening, my understanding is now that ECOG has recommended that any women who has ovarian cancer gets tested for a BRCA mutation because it is much more common than indicated by the family history so to speak.

Schwartz That is exactly right, especially now with smaller families we do not always see all these cancers being expressed that we had when BRCA gene which was originally identified. It is very important for the patient because we now have new therapies that are active in patients with BRCA gene mutations for any important because of what the implications are for your offspring. So, we do recommend looking at the genomics of the ovarian cancer and studying patients who see whether they may have an inherited susceptibility to ovarian cancer regardless of their age.

Hochster So, that is something pretty new in ovarian cancer. What else has changed over the last decade in your experience?

00:11:15 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz I think very little had changed up until the very recent past. The introduction of platinum agents back in 1979 as first-line therapy, initial treatment for ovarian cancer, was really a milestone. It proved the median survival of ovarian cancer patients from about 12 months when I first started out in this field to 24 months. The introduction of the taxanes with the platinum agents back in the 1990s improved the survival to about 36-38 months, and then we have seen nothing of great excitement until the PARP inhibitors. Two years ago, a drug, Olaparib had become approved in patients who have an abnormality in their cancer either because they have an inherited mutation or somatic mutation and we now have agents -3 approved by the FDA- that can be used in women who have something called homologous recombination deficiencies, which include the BRCA gene mutation of patients and a number of other patients. About 70% of all ovarian cancers are serous cancers, high grade, and these are the cancers where about half of them, the patients will either have an inherited susceptibility to the cancer or have developed changes within the cancer itself that make them susceptible to these PARP inhibitors and that has been an exciting development.

Hochster So, about a third of women with ovarian cancer may have these drugs be useful and their tumors that have something wrong with the DNA repair

mechanism, be it from the inheriting BRCA or the tumor itself having developed some kind of defect in DNA repair.

Schwartz Correct.

Hochster And so, that is really pretty amazing. So, those people get chemotherapy and then they go onto these PARP inhibitor drugs?

Schwartz They do as a maintenance or if they have already had 2 or 3 different treatment regimens, they can receive the PARP drugs as treatment for their cancer.

Hochster And those are pills?

Schwartz Yes.

Hochster So, you just take a pill once a day, do they have a lot of side effects, these PARP inhibitors?

Schwartz They vary a little bit from one to the next, but like so many of the new drugs, some nausea, some diarrhea can be associated with them. In some of them, we see a little bit more bone marrow suppression, particularly low platelet counts, but it varies a bit from one to the next.

Hochster But not like chemo? It is a lot easier than chemo?

00:14:05 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz It is a lot easier than chemo. You take one or two pills once or twice a day and that is the extent of your treatment. So, it has been a great breakthrough we believe for those patients who are susceptible to the cancer.

Hochster And how long do people stay on these PARP drugs?

Schwartz At this moment, we would consider maintenance for at least 1 year after you complete the first-line chemotherapy. But in patients who are taking it for recurrent disease, we simply will continue until the disease manifests itself again.

Hochster Okay, so really interesting approach to maintenance therapy of ovarian cancer. Well, we are going to take a short break for a medical minute. Please stay tuned to learn more information about ovarian cancer with Dr. Peter Schwartz.

Medical Minute Support for Yale Cancer Answers is provided by AstraZeneca, a biopharmaceutical business that is pushing the boundaries of science to deliver new cancer medicines. More information at astrazeneca-us.com. It is estimated that over 200,000 men in the US will be diagnosed with prostate cancer this year, with almost 3000 new cases in Connecticut alone. One in six American men will develop prostate cancer in the course of his life time. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who will die from this disease. Screening for prostate cancer

can be performed quickly and easily in a physician's office using 2 simple tests. A physical exam and a blood test. Clinical trials are currently underway to test innovative new treatments for prostate cancer. The Artemis machine is a new technology being used at Smilow Cancer Hospital that enables targeted biopsies to be performed as opposed to unnecessarily removing multiple cores from the prostate. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Hochster Welcome back to Yale Cancer Answers. This is Dr. Howard Hochster and I am joined tonight by my guest, Dr. Peter Schwartz, and we are discussing ovarian cancer. So, we were just talking about maintenance therapy with PARP inhibitors that work for like a big subset of patients with ovarian cancer, about a third who have some kind of DNA repair deficiencies. When I was in medical school, which is the time that you first came to Yale, we used to think of DNA as kind of being static, but it turns out that the DNAs are always reproducing and opening and closing, so you need a lot machinery in the cell to keep the DNA intact, there are a lot spilling errors and breakage of DNA, so these drugs take advantage of that, and by putting people on this maintenance approach with the pills, how long are patients surviving now?

Schwartz In the prospect of randomized trials, the improvement has gone from 5 months with the placebo out to 19 months with one of the agents. So, that is dramatic. That is in patients who have had the inherited mutation.

00:17:26 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Hochster That is how long it takes for the tumor to progress, but not survival. Like, how long do you think that patients are surviving now if they get this kind of maintenance approach.

Schwartz With the maintenance, well we still do not have the final results back on that, we have the progression-free survivals but the overall survivals are longer, much longer by at least a year longer, but we do not really have long-term data.

Hochster So, routinely you are saying people who are out 4-5 years with ovarian cancer, even though it presents with kind of the spread in the beginning.

Schwartz Yeah. Ovarian cancer has become for many patients a chronic disease like diabetes or cardiac disease, the patients are on medications, the medications have to be changed at times or doses have to be altered, sometimes there is surgery involved, but basically our patients live many years longer now even with advanced stage disease at the initial presentation than they have had in the past. And we have many patients between 5 and 10 years out who are alive and well but most of them are on some form of treatment. Typically, it has been standard chemotherapy. Today, if we can get the mono PARP inhibitor, we get them on as soon as possible.

Hochster So, if somebody is diagnosed with ovarian cancer, as you said, most of the time it is kind of a spread, but first approach still is surgery.

Schwartz The management of ovarian cancer is changing. Back in 1979, I treated our first patient with cisplatin.

Hochster And cyclophosphamide no doubt.

Schwartz No, I was more modern than that. It was cisplatin and Adriamycin. We had a patient who was referred to me who had been on a medical service in one of our community hospitals for about 3 weeks and finally a radiologist yelled at the gynecologist to transfer her to Yale. She came to us. She had not only massive disease in her abdomen and massive distention fluid, but she had bilateral pleural effusion. She had fluid on both sides of the chest. I put her on the OR schedule and on the morning of her surgery, about 4 a.m., she woke up in acute pulmonary distress, I came in and I drained the fluid off both of her chest walls. I waited 2 days, rescheduled her, she did the same thing at 4 a.m. I then came in and drained the fluid off. I waited over a weekend, put her on the schedule and at 4 a.m. I had to come in and this time I put chest tubes in both of her chest walls to drain the fluid and she was given cisplatin. She was the first patient to be treated at Yale New Haven. Cisplatin had become available 4 days before and data had been presented at Mount Sinai suggesting it was very active for recurrent disease. I gave her Adriamycin and cisplatin. I pulled her chest tubes, she continued to leak fluid from her left chest wall, so I put a urostomy bag on her chest wall. I sent her home and told her to come back 4 weeks later. I never expected to see her again. That patient came back 4 weeks later. Her abdomen had shrunk.

00:20:47 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz There was no fluid in her chest. We treated her for 5 cycles of chemotherapy before a mass developed. I operated on that lady, she had massive adhesions. The mass was a benign change in the pelvis, infarcted appendix epiploica and she lived 12 years with no further therapy. So from that time on, once or twice a year, patients who were medically unstable or had such massive disease, I knew I could not get out enough cancer to make it difference surgically, they were given upfront chemotherapy, and then followed by surgery and typically some additional treatment with chemotherapy.

Hochster That was not exactly the normal paradigm?

Schwartz That was a contradiction. The normal paradigm was what you suggested -- aggressive surgery as the initial step in the treatment of the patients followed by chemotherapy. We changed that paradigm at Yale for very sick patients with very advanced disease. We presented that in 1989 and published it a year later. It was not met with great success amongst the gynecologic oncology community. Three years later, we published another paper with more updated results and what we found which was very important was that patients

who had advanced stage disease, who we could not perform what we call optimum surgical cytoreduction, in other words removing the overall majority of the cancer so that only tiny little implants were left behind. We found that in those patients where we gave chemotherapy first and then operated, they had survival equivalent to doing upfront surgery, but still leaving little pieces of the cancer behind. We found their survival was no different doing it upfront with the chemo rather than doing the surgery, but in terms of the trauma to the patient, the need to resect bowel, spleen, parts of the liver, it was dramatically less if we gave the chemotherapy upfront, and we really thought that what we have was an alternative to the management of the patients with very advanced disease who could not be optimally surgically approached.

Hochster So, we are talking about 35 years ago the primary dogma was to operate and remove all the tumor as much as possible even if it meant taking out parts of the bowels and the other organs you mentioned. But you were describing for people who really had, would require very extensive surgery, you give them some chemo first and seem to have the same survival and the same benefit. So, it took a while for people to adopt that approach.

Schwartz Yeah, the dogma was definitely surgery first and actually it was why I was brought to Yale was to do just this kind of surgery, and indeed in the beginning, the first decade that we used this approach, we only used it on one or two patients a year, whereas we were seeing 50-70 new advanced ovarian cancers per year. So, it was not a common thing at that time. However, subsequent to that, we were challenged because of lack of really long-term followup. We provided that long-term followup and I got involved with the debate at our major national-international meetings with the leaders in our field.

00:24:13 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz I must say with one exception, I won every debate and I had proposed actually in 1993 that we do a prospective randomized trial for patients with advanced disease that based on CT scanning suggested that we could not remove virtually all the cancer. That was not looked upon favorably by any of our colleagues, but finally the Europeans picked up this approach and there are 2 prospective randomized trials from Europe which show that the patients who have advanced stage ovarian cancer, stage IIIC and IV, who undergo surgical cytoreduction, if the initial disease volume in a metastasis, the largest mass outside of the pelvic mass is less than 4.5 cm, those patients do well, much better with surgery than they do with giving the chemotherapy upfront - the neoadjuvant approach. But once the disease in the upper abdomen is more than 4.5 cm with stage IIIC disease or if the patient has stage IV disease, the patients in both prospective or randomized trials have done better with the neoadjuvant chemotherapy approach than they have with the conventional upfront surgery followed by chemotherapy.

Hochster So, basically, for ovarian cancers which spreads around the abdomen,

if you do a CAT scan and it looks like they got a fair amount of disease there, 4.5 cm and that big, so more than a little bit of disease that you can see there, then you normally would start with chemo today?

Schwartz I have to hedge a bit on that answer. Today, the latest approach seems to be when you are not certain as to whether or not you can take out the mass or masses that have spread from the ovary, laparoscopy is being employed. Certainly, if one has a 4.5 cm or even a 7 or 8 cm mass involving the omentum but no disease in the diaphragm or liver or spleen, this is a patient that you should be operating on in my opinion. But if you have disease coating the diaphragms, involving the splenic capsule, these patients usually have such extensive disease that you know you are going to leave something behind. The data suggests that optimum surgical cytoreduction is removing everything today, not leaving little parts behind as we did in the past. So, our goal is to remove all of the cancer with whatever the surgery is, whether it is the upfront primary surgical cytoreduction or following neoadjuvant chemotherapy.

Hochster So, you said, back in the old days and when you started doing this, it was a couple of cases a year. What percent today would you get neoadjuvant chemotherapy as opposed to surgery first?

Schwartz Well, this is interesting because there have been some surveys now of academic medical centers which are the centers that usually lead the field in terms of determining management, and many centers, up to 50% of the advanced stage ovarian cancers are now initially treated with neoadjuvant chemotherapy.

Hochster It must be pretty rewarding for you to feel like that approach has been really validated and being used appropriately for the people who have the most advanced disease.

00:27:46 into MP3: https://ysm-websites-live-prod.azureedge.net/cancer/2017-YCA-0924-Podcast-Schwartz_316430_5_v1.mp3

Schwartz It certainly is. But what we would like to see is really in improvement in the overall cure rate and that is the challenge for the future generations of oncologists.

Hochster And one other new drug that has come around besides these PARP inhibitors is an antibody that blocks blood vessel growth which is called bevacizumab or Avastin. How is that being used in ovarian cancer today?

Schwartz Well, that had been a very exciting drug initially. It certainly is effective in recurrent ovarian cancer. It is effective combination with chemotherapy for recurrent ovarian cancer. Unfortunately, after we really were convinced in medicine that this is the way to treat people, something happens that changes our minds. There was a recent prospective randomized trial that compared standard chemotherapy which is carboplatin and Taxol plus bevacizumab, the drug you are talking about, to giving the chemotherapy in a what we call the dose-dense fashion. This was a trial done by the GOG and the major group of patients had bevacizumab plus carbo and Taxol, the bottom-line is there was a

group that did not receive the bevacizumab and had the dose-dense carbo and Taxol, they had the same results as patients who received the antiandrogenic.

Hochster I see. So, giving the chemo a little more intensively may be equally a step forward. Well, we are getting close to the end, so what advice would you give for the next generation of GYN oncologists. You have a pretty long prospective on the field and what you tell your students today?

Schwartz Well, I think it is a great field because you take care of the patients from the time you first meet them until virtually the rest of their lives. But I think for those entering into gynecologic oncology, minimally invasive surgery is definitely taking over the field, they must become skilled in minimally invasive surgery, they must stay tuned to what is going on in the laboratory research because the changes that are coming through now are amazing and I think they always have to be prepared to challenge the dogma of how we approach management of patients because it is the young people that really will make the difference in the future.

Dr. Peter Schwartz is the John Slade Ely Professor of Obstetrics, Gynecology and Reproductive Sciences and Vice Chair of Gynecology at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.