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Advances in Colorectal Cancer

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. 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 week Francine Foss is joined by Dr. Howard Hochster for a conversation about colorectal cancer. Dr. Hochster is Professor of Medicine and Medical Oncology, Associate Cancer Center Director for Clinical Research, and Director of the GI Oncology Program at Yale Cancer Center. Here is Francine Foss.

Foss Howard, you are new to Yale Cancer Center and I think we have spoken to you once before, but could you just tell our audience a little bit about your background and how you came to the Cancer Center?

Hochster I did my previous tour of New Haven while in Medical School, but then spent the next 30 years in New York at New York University Medical Center doing my training and then being on the faculty, but I have always had an interest in patient care and the latest clinical research and eventually concentrated on gastrointestinal tumors in GI oncology. So, as things started to become more emphasized at Yale Cancer Center in the area of clinical research, Dr. Lynch and some of the leadership asked me to come back to New Haven, and it has been a lot of fun.

Foss And we have been really happy that we have been able to steal you away from New York. Howard, you played a major role on a national level in clinical trials in the cooperative groups. Could you just tell our audience a little bit about what that is?

Hochster The NCI sponsored cooperative groups are your tax dollars at work to basically fund oncologists and cancer centers around the country to be able to conduct clinical trials that ask important questions for treatment of all kinds of cancers, but these are questions that we want to know as independent academic investigators, which are usually not the same questions that the pharmaceuticals companies want to know. Pharmaceuticals companies want to know what they can do to show a drug works and get it approved by the FDA. Sometimes we want to know how to put it together with other drugs to use it in a different situation and different disease, or to compare drugs between two different companies, which frankly they do not really have much interest in going head to head. So that is what these groups do and we become independent investigators and independent arbiters of the best standards of care in the treatment of cancer. This is a very important thing for people who have cancer and unfortunately this system is quite underfunded with all the budget pressures in Washington today, the NCI budget has been reduced about 6% to 8% and this system was already underfunded. So frequently we see that people in practices especially, volunteer their time to help put people on these trials and send in the data and it is one of the reasons that we do not have as great a participation as many of us would like to see.

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Foss Howard, Yale Cancer Center and Smilow Cancer Hospital, have placed a major effort in the future of clinical trials and you are heading up that whole area of investigation. Could you tell us a little bit about what is going to be moving forward?

Hochster The first thing I would like to say is that I personally believe that cancer clinical trials are the best treatment option when they are available for most patients because we are really offering the latest and best treatment with very specified treatment parameters so that it gets done correctly and we have a lot of people looking over your case like our research nurses and data people. So in general I would like to encourage people to participate in clinical trials, it is pretty straight forward if you do not have any other options and the clinical trial is some new drug and otherwise you would not have treatment and everybody wants to get into that kind of trial, but sometimes there are ones that are not quite as straight forward, but we do not do trials unless we think it is really in the patient's best interest. So, what we want to do with clinical trials is to create a broad variety of cutting edge and state-of-the-art trials that will be happening across all the disease teams within Yale Cancer Center. That the latest and best treatments are available here and that people would want to come to Yale Cancer Center for these kinds of cutting edge and state-of-the-art treatments can. And we are located between New York and Boston and there is a large population based between these big cities where people are traveling and looking for great oncology care and we can help fill that need.

Foss Howard, you are also head of the GI malignancy group here at Smilow Cancer Hospital and your area of expertise is colorectal cancer. Can you talk a little bit about colorectal cancer starting off perhaps with telling us how frequent it is and what some of the clinical symptoms are that patients present with?

Hochster Colorectal cancer is a kind of cancer people do not like to talk about or think about very much, even in this day and age when people are more willing to talk about cancer than they used to, but we have football players in the NFL wearing pink shoes to support breast cancer, but they are not doing that much to support colon cancer even though more of them have had colon cancer. So that kind of brings us to one of the main problems with colon cancer, but colon cancer is the third most common cancer in both men and women in the United States today and there are about 160,000 cases a year of colon cancer. The thing that I think is the most important message for people out there to take away from this program tonight is that colon cancer is largely preventable and having the right kind of screening test done and removing the polyps in the colon before they become cancers is huge. We could probably eliminate 90% of colon cancers today if people went and had the appropriate screening and colonoscopies regularly.

Foss There has been a lot of talk about screening and the government paying for screening. Could you go over for us what is the appropriate screening for colon cancer, when do you get started, and how frequently do you get screened?

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- Hochster Well the recommendation today by the American Cancer Society and the Society of Gastroenterologists is to begin screening at age 50 for the people who are at normal risk. If you are at higher risk, with a strong family history, and perhaps also for African-Americans, they should start a little earlier, at age 40. If your parents had colon cancer then you should start getting screened 10 years before the age at which they developed colon cancer, so that could even bring people into their 30s if they have the appropriate family history and today screening is most commonly a colonoscopy, though there are still tests around to look for blood in the stool and there is virtual colonoscopy where they do a CAT scan and take pictures that look a lot like a colonoscopy and there is even potentially still barium enemas, though I do not know anybody is actually doing barium enemas anymore.
- Foss So most patients will come in say for their first colonoscopy at age 50, and how often do they need to come back?
- Hochster That is a little bit in flux. Today I think most people would say between 3 and 5 years and that depends a little bit on if they find any polyps or not. A lot of times things are called polyps, but on the pathology they are some kind of hyperplastic polyp, and that does not count, what we mean by polyps here is something called an adenoma, which is again a kind of polyp that is premalignant.
- Foss Is there is an upper age limit at which point patients do not need colonoscopies, because I know that some of our older patients are being told say after age 80 that they do not need to undergo this procedure anymore?
- Hochster Right, and that has been discussed and the reason is that the expectation for people at age 80 is they are not going to live that much longer, but I think in people who are very healthy and have a longer life expectancy, they do not have a lot of other medical illness, it is still reasonable to do, but I think the major organizations have not put an upper age limit on it today.
- Foss In terms of risk factors you have mentioned family history, are there genetic risk factors as well?
- Hochster Yes, there are a couple of syndromes that are known to run in families and predispose people to colon cancer. One that is quite rare is called FAP or familial adenomatous polyposis and that is in very few families, but even at a young age people get hundreds of polyps and they almost all develop colon cancer eventually. So that requires preventative surgery to remove the colon, but more important is what we call Lynch syndrome, or hereditary nonpolyposis colon cancer, HNPCC, that is a really bad name, so I apologize to people for that, but especially in medicine we love to name things by what they are not, that is why we call this nonpolyposis because it is not FAP, but in any case, HNPCC, or Lynch syndrome, does run in families and it happens when you inherit a gene that is defective for the production of some enzymes that are kind of like the DNA, spell checker enzymes, we call them mismatch repair enzymes, so we used to think of DNA when I first learned about it as kind of being this double helix of all these bases that does not change,

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but actually the DNA is always undergoing changes, it is opening, it is getting copied, and closes again and mistakes happens, so the body develops ways to fix these spelling errors in the DNA and if you lose one or more of these spell checker enzymes in the normal colon tissue, then that can lead to a polyp and eventually colon cancer. That is what happens in these families that have HNPCC, they inherit a gene that is defective for one of these enzymes and they can develop other cancers as well. The second most common cancer in the Lynch family is endometrial cancer. There is a slightly higher risk of pancreatic cancer as well.

Foss How would a patient know whether he or she has one of these syndromes?

Hochster The hallmarks of Lynch syndrome, or HNPCC, are having a parent, brother or sister who is diagnosed with colon cancer under the age of 50. They usually involve younger people or people who are younger than the normal age of onset and it runs very strongly in families. The testing for it is pretty easy. There is a DNA test where they just take some blood or a cheek swab and they can test to make sure these enzymes are intact, or defective.

Foss We have to take a break now for a medical minute. Please stay tuned to learn more about colorectal cancer treatment with Dr. Howard Hochster.

*Medical
Minute*

It is estimated that nearly 200,000 men in the US will be diagnosed with prostate cancer this year, and one in six American men will develop prostate cancer in the course of his lifetime. Fortunately, major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from this disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using two simple tests, a physical exam, and a blood test. With screening, early detection, and a healthy lifestyle, prostate cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers, like the one at Yale, to test innovative new treatments for prostate cancer. The da Vinci Robotic Surgical System is an option available for patients at Yale that uses three-dimensional imaging to enable the surgeon to perform a prostatectomy without the need for a large incision. This has been a medical minute and 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 today by my guest, Dr. Howard Hochster and we are here tonight talking about colorectal cancer. Howard, in the first part of show we talked a little bit about the incidence and the risk factors for colon cancer and the fact that this is predominantly a preventable disease if the patient undergoes

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colonoscopy, but for patients now that are diagnosed with colon cancer, where do we go from here? Take us through the steps if you have a colonoscopy that shows that you have a malignancy, what happens next?

Hochster Sure, I'm happy to do that. The first thing that we do after diagnosis, or at the time of the colonoscopy, is to remove the polyp and if there is something that is kind of stuck and too big for removal as part of the colonoscopy, they will do a biopsy, and then we will get the biopsy to see if it is in fact cancer or not. Usually it takes a couple days, but should be available in less than a week. The next thing is we want to get some idea of where this cancer might be and whether it has spread or not. The best test for that is a CAT scan, a computerized x-ray that can show how extensive the tumor is in the colon area and sometimes we can see if it spread to lymph nodes around the colon or to other parts of the body, most often the liver. Assuming that there is no evidence that it has spread on the CAT scan then we would do surgery. The primary treatment for localized colon cancer is surgical removal of the colon and that is an operation that can be done fairly routinely today, in fact, they mostly do it with small incisions through operating periscope devices called laparoscopy. So, people today have really teeny tiny incisions and they have portions of their colon removed and they are out of the hospital in a couple days. I mean the difference is quite dramatic and it does not require large scars as had been seen previously. The other thing people worry about a lot is if they need some kind of colostomy or some kind of bag, and that is very unusual today. That may happen if we are dealing with either a large tumor that caused a hole in the colon before we diagnosed it and thankfully that does not happen often today, or in tumors that are way down towards the bottom in the rectum, so sometimes for the rectal surgeries, one might need a temporary diverting colostomy. For a little while, you might need to have a bag, but it is pretty unusual today.

Foss Can you talk a little bit about the potential role of either chemotherapy or radiation therapy?

Hochster Radiation we use in the situation were it is in the rectum and again the rectum is the last five inches of the colon just before waste passes out of the body, that part of the colon is a little different and it is in a constricted area anatomically, so radiation can be directed there very effectively, which can help. Otherwise we do not really use radiation, but we do recommend some additional chemotherapy to help cure more people if the colon cancer was removed and we found out that there is some evidence of spread in the lymph nodes. The lymph nodes are the glands that are right around the colon and can be looked at under the microscope after the surgery is done and we ask our pathologist to tell us if there is any sign of spread to the lymph nodes. If there is a sign of spread to the lymph nodes, then the chance of being cured is still good, but it can be made better by giving preventative chemotherapy, which usually is a six-month course.

Foss Can you tell us how toxic that chemotherapy is and how most patients do with it?

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- Hochster Most people tolerate it very well and can continue to work and so forth. I mean it is not easy, but it is pretty manageable and I would say that most people who have this are able to carry on normal functions and perform most of their normal daily activities and continue working, but it is a little inconvenient and there are a number of side effects and people do not feel great all the time. So, it is doable for six months.
- Foss If you find that the cancer has spread outside of the lymph nodes, is there a different approach?
- Hochster Once the tumor has spread elsewhere, then our consensus tends to be to treat with chemotherapy more often than go to surgery. Sometimes we still do surgery first, if we think it is urgent to do surgery. But what we found is with now having better chemotherapy drugs in the last 10 to 15 years, most of the time the tumors are going to shrink, more than 50% maybe up to 2 out of 3 times we are going to have the tumor shrink with chemotherapy, and by starting with chemotherapy early it allows us to have a better chance of killing the larger, and also the microscopic, cancer cells. So, if it is not urgent to operate then we will probably do chemotherapy for a few months first and then do the surgery after three to four months.
- Foss There have been a tremendous number of advances recently in the treatment of colorectal cancer and you have been involved with a number of these. Recently, at the ASCO meeting, the American Society of Clinical Oncology meeting that just completed, we heard about some of these. Could you bring us up-to-date with some of the newer treatment approaches and some of the newer drugs?
- Hochster In the news folks tended to talk more about the breast cancer treatments, but there were two new drugs that presented very positive findings for colon cancer at the meeting this year and I expect that both of them will be approved by the FDA for use widely in the United States, so these are two new options for treatment of patients who have colon cancer that is more advanced and has spread. The first one is a drug that is a novel way of blocking blood vessel growth, an angiogenesis inhibitor, it is in a way similar to a drug that we already have called bevacizumab, or Avastin, which binds to a molecule that stimulates blood vessel growth, and we know that tumors require a lot of blood vessels to grow up and become big tumors. So, they secrete these little signals to say to the blood cells grow, grow, grow, grow, grow and if we block those then the chemotherapy works better and also the tumors either shrink or they stay the same for a while and we are seeing these kind of drugs being applied in many cancers today, but one of the first, or the first for that drug bevacizumab, was colon cancer. So now there is another drug that is kind of a manmade molecule that is a little better than bevacizumab in a theoretical sense. It has not been compared directly, so I cannot say it is actually better in the clinic, but it is basically like a made up antibody that has two receptors instead of just the one antibody binding site. So it binds more of these VEGF signaling molecules in the regular bevacizumab and that drug is called aflibercept or VEGF Trap and will be sold under the brand name Zaltrap. We saw that in colon cancer for people who had one chemotherapy program and the tumor is still growing, that if we gave this

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drug together with a second chemotherapy program compared to placebo that this particular drug helped people live longer, and that is a pretty good demonstration that it is very effective and again as I said, we do not know how much better it is or if it is better at all than the drugs we have, but it is another option, especially for people who have already had bevacizumab and might want to switch to this at some point in their treatment course. The second drug is a pill and it will actually add a new treatment option after other chemotherapy drugs. That drug is called regorafenib and that drug was used in a study for people who had had all the chemotherapy and antibody drugs that are approved for colon cancer, and again that was compared with a placebo treatment, and the people in that study also live longer. So, this will be an option, after going through all the drugs we have today, and we expect to have this drug available at Yale Cancer Center within six weeks as part of a trial.

Foss Howard, when these new drugs come out, a lot of times patients read about them and they want to know why they are not getting them. Could you just clarify why we use drugs say in the first line and why do we use some of these newer drugs later on, or should we be using these newer drugs in the first line?

Hochster In a way that kind of brings us back to our first discussion about the cooperative groups. One of the hard parts about doing trials to get FDA approval is trying to figure out pieces of the puzzle, where you can put your drug that is kind of an open area. It is a little bit easier to take people when there is no treatment option, then to try to add in or combine or compare it to a more standard treatment in the first or second line, and those also are much bigger trials that require a longer time and they are more complex to do. It is little easier for everybody and much more clear cut if it gets approved in that kind of setting, where you say, take people who have already ran out of options and there are no other good options for them. Then we usually try to do trials and sometimes within the cooperative groups to move these drugs into a different setting, like an earlier line of treatment, but it's not like you couldn't use it. If you are a physician, once it's approved it can be prescribed, it is just that we do not really have enough information to tell us how effective it would be and how it would combine with the standard drugs and we just cannot make up these things as we go along, because there are a lot of side effects and sometimes the drugs can even interfere with each other, so we really need studies to tells us how to combine new drugs with the older drugs.

Foss That is the importance of having clinical trials. Can you talk a little bit about the clinical trial program at Smilow in GI malignancies, particularly in colorectal cancer?

Hochster In the GI malignancy group, we treat more than colon cancer. We treat stomach cancer, we treat pancreas cancer, and liver cancer as well, and we try to have trials available for all of them. So, for example, for first line colon cancer, today we are taking the standard treatment 5-fluorouracil with oxaliplatin, we call that FOLFOX, and this antibody we already talked about bevacizumab, or Avastin, and we are adding a new antibody to it that blocks another signaling molecule called

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MET. So, when people have a lot of this MET signaling, it makes tumors grow. We think that by using two antibodies together, maybe we will have a better outcome. That trial again is a blind trial, so we do not know who is getting what, but either the patients will get the regular antibody or they get two antibodies, and we have a similar trial in second line looking at a new antiangiogenesis drug, we are going to have this regorafenib study that is kind of a bridging study until it's approved, called an expanded access program. There is a lot I can talk about and can come back and do another whole program about our clinical trials.

Dr. Howard Hochster is Professor of Medicine and Medical Oncology, Associate Cancer Center Director for Clinical Research and Director of the GI Oncology Program at Yale School of Medicine. If you have questions or would like add your comments, visit YaleCancerCenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.