

Dr. Robert Mayer, Systemic Therapies for Colorectal Cancer May 9, 2010 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of 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 1888-234-4YCC. This evening Francine welcomes Dr. Robert Mayer. Dr. Mayer is the Stephen B. Kay Family Professor of Medicine at Dana-Farber Cancer Institute at the Harvard School of Medicine. Here is Francine Foss. Foss Let's start off by talking a little bit about your interest in colon cancer, can you tell us how long you have been interested in colon cancer? Mayer When I was a medical student years ago, I was undecided whether to become a gastroenterologist or to become a cancer doctor. I always thought that the diseases of the bowel and nutrition and how food is absorbed, or not absorbed, was fascinating, and then when I learned about the cancers that were associated with it and the progress that could be made and also the needs of our patients, putting the two together seemed like a great idea and I have been doing this in large part since 1974. Foss Bob, colon cancer is one of the most common cancers in the United States, can you talk a little about the incidence of colon cancer. Mayer There will be close to 150,000 new cases of colon cancer this year and that will lead to about 49,000 deaths. The 49,000 deaths reflect the second most common cause of cancer death in the United States among all the cancers we deal with; that's the bad news. The good news is that the number of 49,000 is down from a level of about 60,000 20 years ago. So it's somewhere in the range of a 13% decrease in colon cancer deaths that have occurred right in front of our eyes. Foss Can you talk a little bit about why that might be? We have all heard the word screening and we use screening in many types of cancers, but this may be one instance where screening has really made a difference. Mayer It certainly has. Screening is very important in cervical cancer, it's very important in breast cancer, but there is no disease in which it is as effective as in colon cancer. The reason for that is that the cancers don't just develop out of the clear blue, rather, in the lining of the bowel, benign growths called polyps appear. Polyps occur in about half of Americans by the time they are at the age of social security, 65 or 70, and as a generality about 90% of colon cancers emerge from polyps. Many people think that going from a normal bowel, to a polyp, to a cancer occurs in a few weeks or a few months, maybe a year. It actually takes 3:17 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3> somewhere in the range of five to six years and it has become clear that removing these polyps prevents cancers from occurring, and as a result, the removal of polyps, so called polypectomies, that are performed at the time of a colonoscopy represents the single most effective means of primary prevention of colon cancer. Foss In terms of our recommendations now for screening for colon cancer, could you go over those with us? Mayer Years ago, the most common test that was used was checking the stool for the occult presence of blood. This turned out to be an effective but not sufficiently

effective approach because many times cancers don't bleed and looking for blood in the stool is a surrogate means, if you will, for finding a cancer or even a bleeding polyp, and also, the vast majority of times that blood was found in the stool it was falsely positive. As a result, people have looked for other tests. One intriguing test is actually an experimental approach of taking stool and extracting the genetic material from it, so called DNA, and looking for mutations that might be present which are often present in a colon cancer or a polyp, that probably isn't ready for primetime. Sigmoidoscopy, which means inserting a tube into the lower part of the bowel, has about a 75% accuracy rate meaning that the majority of cancers do occur on the left side of the colon, which a sigmoidoscope can reach, but it isn't 100%. So the two tests right now that are the most intriguing are a colonoscopy where a small tube is inserted through the entire large bowel from the anus to the appendix area in the right side of the colon looking not just for cancers, but for polyps and removing them. An x-ray test called a virtual colonography, sort of a CT test of the bowel, is not quite as accurate as a colonoscopy, it doesn't find every polyp, but it certainly avoids the need for being impaled, if you will, by a tube that goes through one's back side. However, both of those tests, the colonoscopy and virtual colonography, require cathartics because the bowel has to be sufficiently cleaned out, and at the present time, the colonoscopy is the preferred test because it is not just diagnostic, meaning you find an abnormality, but at the very time you find the abnormality you can biopsy it, or remove it, so it's both diagnostic and therapeutic. Nowadays, it's been recommended that for people who have no history of polyps and no family history of colon cancer, which is most of us in this country, we start to perform a colonoscopy at about age 50. The reason age 50 is chosen is the colon cancer usually occurs in people in their mid 60s, so doing it any earlier is probably doing too much testing, doing it any later might be missing some early lesions that could be identified and removed or cured. The notion has been put forth that if you have a completely negative colonoscopy and you don't have a family history, you probably need the test to be repeated only once every ten years, and maybe in your whole lifetime you will have it done two or three times and if it remains negative, you simply aren't going to make polyps and that's all the testing you need. Whereas, if you do find polyps, meaning you are one of the 50% of Americans who are polyp producers and 7:55 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3> have these pre-malignant growths in the bowel and they are removed, the colonoscopic examination should be repeated every three to four years. So having it done at about age 50 and then maybe at age 60 is a dividing path between a high risk and standard risk individual and determines how often screening should be performed. Foss Would you say that having a colonoscopy over age 50 is probably the most important thing that the average adult can do to prevent cancer? Mayer It certainly is the most important diagnostic or screening study. There are ways that all of us can prevent the polyps from occurring. The colonoscopy is there to identify the polyps once they appear. Folks who have a diet very high in red meat, folks

who are obese, and people who smoke a great deal, those are all people that have a greater likelihood of developing polyps and secondarily, developing cancer. There are things that we can do in our own lifestyle. There are some rather strong hints that utilizing Aspirin, one Aspirin tablet each day, is not only helpful in protecting the coronary arteries from having a heart attack, but also may prevent polyps from occurring. There are data just emerging that perhaps having a little bit more vitamin D in ones diet could be useful as well. So, there are added lifestyle efforts that one can incorporate into our day-to-day existence that will diminish the polyp risk and the cancer risk as well.

Foss When you talk about risk factors for colon cancer, we have talked about a couple of things, but could you go into a little more detail about other risk factors, for instance, are there familial cases of colon cancer? Are there specific genes associated with colon cancer that we should know about?

Mayer Yes, somewhere in the range of 15% to 25% of colon cancers occur in individuals who's families or members of their family also have or have had a colon cancer in the past. We really only understand the molecular genetics, the reasoning behind them developing this condition in maybe 5% to 6% of that 15% to 25% group, so maybe about a third or a quarter of that group. There are two syndromes that one quotes quite often, 1% of colon cancer occurs in families in which by about age 20, thousands of polyps cover the entire large bowel, and that's something called familial polyposis. It is conveyed through families by what is known as an autosomal dominant, which means it is very commonly spread from one member of the family to the next generation and essentially everybody who develops this condition, the polyps throughout the large bowel, will develop a colon cancer generally by about age 35 to 40; now that's the bad news. The good news for this is that there is a blood test that can identify the carriers of this gene, even when they are teenagers before polyps have developed by something called the familial adenomatous polyp, or adenomatous.

12:03 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3>

polyposis gene, located on one of our chromosomes, chromosome 5, and in people who have this carrier condition, in early adulthood, around age 20, a prophylactic operation can be performed to remove a good part of the large bowel. In the past, that required the construction of a bag, a permanent colostomy where fecal material would come through the abdominal wall, but there are now ways to do that through ones back-side and avoid that and greatly reduce the cancer risk. Sometimes people with this uncommon syndrome also have other associated findings, which range from bone cysts to malignancies in the small bowel to pigmentation in the retina, but certainly in folks who have this condition prompt referral to a genetic counselor would certainly be mandated. The other major genetic syndrome has a lot of words associated with it, it's called hereditary nonpolyposis colon cancer and it was described by a gastroenterologist and geneticist by the name of Henry Lynch in Nebraska, and it is sometimes known as Lynch syndrome. This is a condition in which people develop colon cancer in their late 30's. The cancers generally are found on the right side of the colon, meaning closer to the appendix rather than at the part nearer to the anus. People who have

this condition, particularly women, are more likely to have ovarian and uterine cancer in association with it and men may have more prostate cancer. So those are the two genetic syndromes that we know a great deal about, but taking a family history, and if other members of ones family have developed colon cancer, particularly before age 50, screening at an earlier age should be undertaken.Foss This has been a really great discussion about screening and prevention of colon cancer. We are going to take a break now for a medical minute. Please stay tuned to learn more about the therapies for colon cancer when we come back with our guest Dr. Robert Mayer.15:45 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3>Public Broadcasting Network.Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and we are here today with my guest Dr. Robert Mayer who joins us to discuss colon cancer. We talked a lot about the epidemiology of colon cancer in the beginning of the show, but at this point, if you are a patient say who has been diagnosed with colon cancer, who has had a colonoscopy that's positive for colon cancer, what are the next steps?Mayer Francine, the first step is to be certain that this is only a single cancer, so one wants to be sure that a full colonoscopy has been performed. After that, a CT scan of the chest, abdomen, and pelvis is generally carried out because one wants to be certain that there hasn't been any disease spread. If there has, God forbid, been spread to the liver or the lungs, unless somebody is quite symptomatic from the cancer one might want to think twice about subjecting them to an operation. If the cancer is located in the very far end of the colon in what's called the rectum, one might want to consider giving patients chemotherapy and radiation therapy before an operation. One really wants to have their ducks in a row and know what's happening, draw blood studies, but let's assume that nothing further is found. Then I think it's very appropriate for that patient to be seen by a surgeon who has experience in operating on cancers in general, and gastrointestinal cancers in particular, and unless there is a reason against it, an operation should be performed.Foss Bob, is this a disease that is approached from a multimodality point of view at the very beginning?Mayer It may be and it really depends where the cancer is and it also depends on what the extent of the disease is, the so called stage. Furthermore, since many people with colon cancer tend to be elderly and a big operation with an incision, the types of operations that we think about where people have scars on the abdominal cavity and a long time for recovery, that may be something that is hard for a grandparent to successfully endure. Now, with what we call noninvasive surgical approaches where there is really no scar, but just probes placed into the abdomen, and this is all done with very fine technique with just as much tissue removed, and the results are just as good as the big traditional operation, it's very important that a patient be seen by a surgeon who is up-to-date and knowledgeable on contemporary techniques, both to enhance the cure, potential for cure, and to diminish the likelihood of side effects.Foss Now that we are doing colonoscopies on everybody over the age of 50, are we finding more disease at early stage?18:58 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers->

mayer.mp3Mayer Well we think that's probably why the number of cancer deaths are dropping, but I think we are also finding polyps and removing the polyps. Both of those factors come into play. Clearly, if we find a cancer that has not invaded deeply into the wall of the bowel or has not spread to the adjacent regional lymph nodes, then the likelihood of cure with surgery alone is well over 80%, and probably over 90%. If, on the other hand, the disease has spread to the lymph nodes, and the only way one knows that for certain is after the operation is performed, but if that turns out to be the case, without further treatment, the likelihood of cure is only 50% to 60%. That's the very setting where a medical oncologist might recommend prophylactic, postoperative, or the jargon that's used, adjuvant chemotherapy, for several months and that approach has increased the likelihood for cure for these people from the 50% to 60% range to about 70% to 72%, which is a major step forward.Foss Could you clarify for our listeners, in patients who have had surgically resected colon cancer, which of those patients requires adjuvant therapy, and which of those patients will do well without the additional chemotherapy?Mayer The first issue is, was the tumor from the rectum or was the tumor from inside the abdominal sac, the peritoneum, that tissue that wraps around the abdominal cavity, and when it gets infected, we call it peritonitis. If it's in the rectum, which is deep in the pelvis, we often offer radiation therapy and chemotherapy, even if lymph nodes have not been involved. For the rest of the abdomen, for most patients who have no evident spread of the tumor to lymph nodes, we generally, but not always, think that surgery, if it's a good operation with an adequate sampling of lymph nodes, is all that a patient might need. Now that's not for everybody, but for the majority of patients. Every patient with spread to a lymph node or more, should be strongly considered as being a candidate for receiving six months of prophylactic or adjuvant chemotherapy.Foss Could you go through just briefly for us what the adjuvant therapy entails?Mayer The adjuvant therapy now-a-days entails the administration of 3 drugs. One is a very traditional and older drug called 5-FU, or the chemical name which is 5-fluorouracil. That's a drug that we have had available for 50 years. The efficacy of that drug has been enhanced when a vitamin or vitamin-like molecule similar to folic acid, something called folinic acid or leucovorin, is added. For many years 5-FU and leucovorin were the standard adjuvant treatment given once a week, but more recently adding a third drug called oxaliplatin seems to enhance the likelihood of cure, and makes the treatment more effective. This combination of drugs is usually given every two weeks for a total of 12 treatments over six months. We are not certain that the six months is chiseled in marble and there is soon to be an effort throughout the United States to determine whether 12 weeks/3 months is as good as 2422:54 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3>weeks/6 months and my own suspicion is that less will be as good as more and that we will find the same very encouraging results with three months of therapy.Foss What are the side effects of this therapy? What will a patient experience during the course of this treatment?Mayer The major side effect will be neuropathy. Neuropathy is a fancy word that means

pins and needles in the fingers and toes, and why that is the most common side effect is because the other possible toxicities that were associated with this treatment such as nausea and vomiting, and low blood counts that could make somebody prone for infection, can be controlled very nicely with prophylactic medication. The ability to control cancer, chemotherapy related nausea and vomiting, has grown and increased and developed in a wonderful manner, so that patients now eat lunch while they are getting their chemotherapy and don't even know what the nausea and vomiting is about. The low blood counts can be prevented in people who are prone to it with a stimulant to the bone marrow, so the neuropathy which is pins and needles in the fingers and toes is the major concern, as this develops somewhere in the range of 40% to 50% of the patients. Within 6 to 9 months of the completion of treatment, it's resolved in three quarters of patients, but there is still a small percentage, a definite percentage of patients who have received this potentially curable form of treatment, who have as a long-term reminder of that treatment numbness in their feet when they walk and a loss of touch sensation in their fingers, which makes working on a Word Processor or perhaps playing the piano or some other tactile activity a bit more difficult than it was before. So it's a matter of balancing the potential risks and the potential benefits in the sense of somebody who has a large number of lymph nodes involved in colon cancer. There is no question that the benefits outweigh the risks for one involved lymph node, it's a marginal decision and that's something that I would very much encourage all our listeners, if they are in that position, discussing openly with their physician, their oncologist.

Foss You have been involved and are at the forefront of a lot of this research on the national level, and I think one of the major advances in colon cancer has been this recognition that there is a benefit to adjuvant therapy as you have said, even though there are some downsides for the patient.

Mayer Absolutely, I think there were two major steps forward. One is better treatment in the adjuvant treatment, but I want to get back to something we talked about earlier and that is the notion that has now been embraced by the medical community and the public in the United States, of the importance of screening. I especially want to acknowledge the courage of Katie Couric who underwent a colonoscopy on national television; some scientists, some26:19 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3> epidemiologists showed that the frequency by which the American population underwent colonoscopy screening rose immediately thereafter. We have learned a lot more about what causes the disease, and there are lifestyle changes we can do to prevent it. We know that there are certain families that are more prone, and we have better screening tests and better ways to treat the disease. On the one hand, it's not surprising that the number of deaths have dropped by 13% or 14%. On the other hand, the challenge that we all have is to make certain that decrease in the number of deaths continues because there is every reason to think that the present 49,000 deaths a year from colon cancer can be reduced by at least another 50% in the near future.

Foss What about those unfortunate individuals who have metastatic disease, or who have relapse disease and don't respond to their

adjuvant therapy?Mayer Or people who were given the adjuvant therapy and their disease recurred. There are alternative forms of treatment. There are different forms of chemotherapy. There are the uses of targeted, so called monoclonal antibodies, directed against the formation of new blood vessels that feed tumors, particularly metastatic tumors, tumors that have spread. There are monoclonal antibodies that block sites on the cell, almost like putting your auto- key into the ignition that when it's turned on get the engine going, get the cells dividing, make the cancer spread, there are ways of blocking that. The most common site where colon cancer spreads is to the liver and there have now been several reports where one can give chemotherapy to people with spread to the liver, the liver spread shrinks, that area can be surgically removed, and these people can be cured. On the other hand, most people who have metastatic disease will eventually succumb to their illness. In the past that mortality time might have occurred within 6 to 12 months, now it occurs much later, people live 24 or sometimes 36 months. Even in this situation the life span can be prolonged and our challenge is to identify newer and more affective treatments, fashioned directly for a given patient's tumor by the biological characteristics of the tumor, so as to enhance the cure to a greater extent than we already have.Foss So personalized medicine is going to be applied and even is being applied to colon cancer patients as we speak.Mayer Absolutely, there are blood and genetic tests that are called biomarkers and these biomarkers are teaching us in the most sophisticated manner in which patients the disease is going to act badly, in which patients the disease is going to respond better to treatment X versus treatment Y, which patients don't need any treatment at all, and which patients might require some29:38 into mp3 file <http://www.yalecancercenter.org/podcast/may0910-cancer-answers-mayer.mp3>experimental form of therapy because standard therapy is unlikely to benefit them. This is a brave new world that has begun as the laboratory work of the last 20 years has really come to the clinic, to the doctor's office, to the bedside, but I really hope and expect that this progress is going to continue full force in the years to come.Foss It's really been terrific having you on the show tonight talking about colon cancer therapies and it sounds like we could easily have another whole show talking about some of these new approaches. This is Dr. Francine Foss, until next week wishing you a safe and healthy week.If you have questions or would like to share your comments, visit yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.