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answers

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**New Methods for Treating
Colorectal Cancer**

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. 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, you will hear about new methods for treating colorectal cancer with Dr. Scott Kopetz. Dr. Kopetz is Associate Professor in the Department of Gastrointestinal Medical Oncology at MD Anderson Cancer Center. Here is Francine Foss.

Foss Let's start off by having you tell us a little bit about yourself and how you got interested in gastrointestinal cancers and what your role is at MD Anderson?

Kopetz Thank you. I have the privilege at MD Anderson to be a medical oncologist that treats patients with colorectal cancer. My research focus is trying to better understand therapies especially for advanced colorectal cancer through work in the lab and also trying to understand the mechanisms of these different cancers and the vulnerabilities that these cancers have that we can leverage with novel therapies.

Foss Can you tell the audience a little bit about colon cancer in general? What is the incidence in the United States and how common is it in men and women? Is it something that is becoming more of a health problem as we get older?

Kopetz Colorectal cancer is one of the most common malignancies independent of genders. It is the second most common type of cancer, yet it is present and diagnosed in about 150,000 patients a year in the United States. The incidence for colorectal cancer, fortunately, is declining and part of this is due to improved screening, the use of colonoscopies, especially to identify premalignant lesions and intervene on those before they turn into cancer, but nevertheless, there is still a large population that are diagnosed with colorectal cancer and novel therapies are needed in these settings.

Foss If we are doing all the screening, can you tell us why we still have patients out there who develop this cancer? Are they are not getting screened?

Kopetz It is an excellent question and it is a complex answer. A part of it certainly is the fact that screening with colonoscopies or other methodologies is not widely applied in all populations. So while in some populations with access to health care, the screening rates are now increasing up to 70% of the population, which is certainly encouraging, the majority of the population still is not receiving the screening either because of lack of access to health care or because they are not choosing to follow some of the recommendations of their doctors and this is due to a lot of the misconceptions perhaps about how difficult some of the screening is and what a colonoscopy entails, what is involved in that and I think there is a lot of work being done out there to really make the screening test more widely applicable and also more comfortable for the patients.

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- Foss Scott, can you go through that for us tell us how difficult a colonoscopy is and how often we need to get those done and at what age we need to start?
- Kopetz Colonoscopies are tests that involve putting an endoscopy or specialized camera through the rectum and looking at the internal surface of the colon and this is really the best way to screen for colon cancer. Not only can we identify lesions that may turn into cancer in the future, but the colonoscopy can also remove these lesions and prevent the cancer from forming and so it is really our best tool that we have to prevent colorectal cancer. Now the test itself requires a specialized bowel preparation for the gastroenterologist who performs these procedures to get the best view of the colon and this requires cleaning out any fecal material in the colon and many patients describe it as one of the difficult parts of it, but there are improvements on how one can prepare the bowel. The test itself now is very commonly done under very light anesthesia so that patients are sedated and comfortable and the procedure itself is described by many patients as not nearly as bad as they thought it would be and so I think part of our goal is to really educate the population to say that colonoscopies can be lifesaving and that they are not as invasive perhaps or uncomfortable as they once were.
- Foss And at what age should a person start getting colonoscopies?
- Kopetz There are several guidelines, but in general the recommendations are screening colonoscopies at the age of 50. There are certain guidelines that suggest for patient groups at a slightly higher risk that those screening should be done a little earlier. One such population is African-Americans where the incidence of colorectal cancer at an earlier age is higher and there are some guidelines that recommend screening starting at age 45 instead of 50. We also recommend family members of patients with colorectal cancer undergo screening and this is typically done at an earlier age especially for first degree family members, brothers, sisters or children of colorectal cancer patients. We recommend screening ten years before the age of onset of their family members.
- Foss Is there then a genetic syndrome or genetic link with colorectal cancer?
- Kopetz There is, and it is a minority of colorectal cancers and so I think one important message is that even if there is not a family history of colorectal cancer, the screening still is recommended, but in those that do have a predisposition in the family for a minority of these familial syndrome we can actually identify the genes that are involved and there is testing that can be done to identify affected family members and in those settings there is a much more intensive surveillance that can be done in order to prevent the cancer.
- Foss If a person is in that type of a family, do you recommend having that genetic testing or do you just recommend having the colonoscopies, or both?
- Kopetz We do if we have a patient where we suspect of a familial syndrome. There is testing that can be done and importantly this testing then can be done on other family members and those family

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members can, with appropriate counseling, understand the risks for developing the cancer. In those patients that are predisposed to this then there is much more intense surveillance, sometimes colonoscopy yearly that is required in order to prevent the cancer from forming.

Foss Would you say that colon cancer is kind of like lung cancer where if you do not smoke the chances of you getting it are very low, so maybe we can prevent it, and if we are able to do colonoscopies on everybody, do you think that we would be able to prevent colon cancer? Or are there still going to be some cases that are going to happen anyway?

Kopetz It is an excellent question and I can say that colonoscopy is the single best tool that we have to reduce colorectal cancer. Like many screening tests it is not perfect and there are cases where the type of precancerous lesions that develops in the colon is not readily detected by colonoscopy and there are new techniques being identified to improve the colonoscopy, whether it is using dyes to try to enhance these abnormal regions of the colon that may improve our screening techniques, but despite colonoscopy there are still a minority of patients that can develop the cancer.

Foss Can you tell us then how most patients present with colon cancer?

Kopetz Fortunately many patients are caught with early stage disease and this is caught with screening and certainly the outcomes for patients whose cancer is detected early is much better and it is one of the best predictors of how well patients will do. For other patients the symptoms can be some blood in the stool, it can be changes in bowel movements and these symptoms should really be something that is discussed with your primary care doctor to see whether screening colonoscopy is appropriate.

Foss Blood in the stool is something that can happen to a lot of people, when does somebody really need to worry about that or do we always need to worry?

Kopetz While blood in the stool certainly can come from other etiologies besides cancer, it is something that should it happen on more than one occasion, for example, or be associated with any other symptoms, it certainly should prompt evaluation. For many patients that have decided not to undergo screening colonoscopy, blood in the stool is the first warning sign that there is something going on in the colon.

Foss Can you take us through the steps once the patient has a colonoscopy and it shows that there is a malignant condition of cancer, what happens next to that patient? Is it surgery? Is it seeing you first before surgery, how does is that all worked up?

Kopetz The initial steps in treatment really depend on where the cancer is found. We use the term colorectal cancer to describe cancers that derive anywhere in the large intestine. The rectum is the last portion of the large intestine and has slightly different treatments. For the patients with rectal cancer the initial treatments are to do some chemotherapy combined with radiation prior to

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undergoing surgery. This is because the rectum is a very narrow space where there is a higher risk of local recurrence of the cancer even with very good surgery and so doing this chemotherapy and radiation prior to treatment can really reduce the risk of local recurrence. Conversely in the colon, the cancer does not have this higher risk of local recurrence and the recommendations are to go to surgery first to remove this.

Foss So are most patients seen in the multimodality clinic?

Kopetz They are, and that involves both the surgical oncologist as well as a medical oncologist. For rectal cancer, we also involve the radiation oncologist and a lot of the best outcomes have been shown to occur when this planning is done with many different specialties in the room together to come up with the best plan for a patient.

Foss So prior to getting any treatment what kind of staging tests does a patient need and is there a role for PET scanning say in this setting?

Kopetz So the recommendations for newly diagnosed colorectal cancer is to undergo CT scans to see if the cancer has spread anywhere outside of the colorectum. For rectal cancer, sometimes we need a more specialized test such as an ultrasound or MRI to better define the anatomy of the cancer in the pelvis. We do not recommend PET CT scan as a screening method. So while it is a useful technology, the resolution of the PET CT scan is worse than what we can get with traditional CT scans, and so we use PET scans to follow up on any abnormalities that we see on some of these other imaging tests, but it is not a very good screening method.

Foss This has been a great discussion and we unfortunately have to take a quick break for a medical minute after which we will talk a little bit more about some research. Stay tuned to learn more information about new methods for treating gastrointestinal cancers with Dr. Scott Kopetz.

Medical Minute

There are over 12 millions cancer survivors in the US right now and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors may face other long term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers like the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut's Public Broadcasting Network.

Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined tonight by my guest Dr. Scott Kopetz from MD Anderson Cancer Center and we are discussing colorectal

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cancers. We talked a little bit in the beginning of the show Scott about some of the logistics of diagnosing a patient and getting a patient into treatment. We didn't mention one of the markers that we have talked about for a long time as a marker for colon cancer, which is CEA, a blood test, and that has been used in the past as a way of predicting who might have a colorectal cancer or perhaps how you are doing when you have your cancer. Can you comment on the use of that marker and any other blood markers that might be helpful to our patients?

Kopetz This is an area of considerable interest. We certainly recognize that if we can develop a blood based marker for screening that will lower the barriers for screening for many patients who may be reluctant to undergo a colonoscopy or who do not have access to it. CEA is a marker that is associated with colorectal cancer. It is detectable in the blood. However it is not a very specific marker. There are other reasons that this can be elevated and there are also many cancers that can occur despite the fact that the marker is normal in the blood. So while there was enthusiasm years back about using this as a screening test, it is not recommended because it does not perform as we like. However, there is very exciting work being done to try to develop new blood based screening markers and some of these have looked at small fragments of DNA that are detectable in the blood and looking at the sequence of those for some findings that are associated with early colorectal cancer. Likewise, there are new techniques for screening the molecular markers in the stool and the hope is that some of these markers may be appropriately validated over the next several years and provide another option for patient.

Foss At this point are those tests being used in the community setting or in academic centers or is this still very experimental?

Kopetz These are still being researched. There are several studies that have been completed. We are looking forward to those results, but at this point, it is still research.

Foss So it may in fact be that by taking a sample of stool in the future will be able to detect colon cancer?

Kopetz Correct, looking at some of the molecular changes, but there have also been advances and really more basic tests looking for occult blood in the stool as well and so for some patients this can be a screening methodology used by primary care doctors in the clinic and so this can be useful as a prescreen, but we recommend that patients undergo colonoscopy as the best method to reduce recurrence or reduce the risk of cancer forming.

Foss Scott, we talked a lot about colonoscopy, but we did not talk about the newest concept in colonoscopy, which is this virtual colonoscopy. I do not know if our audience is really familiar with this, but could you tell us what it is and how valuable it might be for patients?

Kopetz The virtual colonoscopies are a CT scan that requires certain reformatting of the image that allows a virtual evaluation of the inside lumen of the colon. Now, the difficulties of this are one, it still

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requires a bowel preparation, this idea of removing the fecal material and for many patients that is the biggest barrier to undergoing screening and unfortunately, the virtual colonoscopy does not eliminate that. Two, there is also some radiation associated with the CT scans, which needs to be further evaluated, and unfortunately with the virtual colonoscopy, if a polyp is found, which is not uncommon since about one out of five patients who undergo colonoscopy we will find a polyp, we cannot intervene or remove that polyp and so that requires a follow-up colonoscopy.

Foss Do you think this is going to play a major role in screening?

Kopetz I think there has been some reluctance on the part of many insurance companies to pay for this. I think there are still further tests that need to be identified and for a very select group of patients where there are technical problems in being able to do the colonoscopy, it can be an option for them.

Foss Can you back up and talk a little bit about patients with colon cancer, so a patient gets a colonoscopy, is found to have colon cancer and comes to see you, you spoke about the role of the multimodality clinic, but if a patient is deemed to need chemotherapy, what kinds of chemotherapy are given? How long does it take to get that chemotherapy and what are the potential side effects?

Kopetz For patients with localized cancer that is in the rectum or colon and the surrounding lymph nodes, in addition to the surgery and radiation, there is what we call adjuvant chemotherapy or chemotherapy administered after the resection of the cancer. This can reduce occult microscopic disease that we may not see on the CT scan but could recur in the future and we can reduce the risk of the cancer coming back fairly substantially with this adjuvant chemotherapy. There is a lot of work trying to identify which patients are at highest risk for recurrence to better identify who should get treated so we are trying to avoid treating those patients who are cured with surgery alone and really use this chemotherapy for those patients that have a higher risk of recurrence. The chemotherapy itself is treatment for six months; it is a combination of chemotherapy either through vein or pills. It is a reasonably well tolerated regimen for some patients with highest risk of recurrence, a chemotherapy is administered that can cause some neuropathy or some pain in the nerves and cold sensitivity that can interfere with quality of life and there are efforts ongoing now to ask the question of do we need that full six months of chemotherapy given some of the toxicities that can accumulate over time? And there is a large international effort now to really ask the question of can we do just as well with less treatment.

Foss So there is still some controversy as far as with what the first-line therapy should be?

Kopetz There is some debate about the duration of therapy. I think we have arrived at a consensus as a community about what the appropriate therapies are. These combinations of 5-FU, 5-fluorouracil chemotherapy potentially with oxaliplatin, which is the one associated with the neuropathy.

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- Foss Can you talk to us about a patient who say is found to have lymph node involvement or other involvement other than just within the colon itself. How bad is that and does that change the therapeutic approach?
- Kopetz When patients have involvement of the lymph nodes, that certainly still can be cured with surgery and adjuvant chemotherapy. However, when the cancer spreads outside of the region that is resected by surgery, when it has spread to other organs such as the liver or lungs or perhaps distant lymph nodes, that does indeed change the approach that we take. Historically in years past, it was felt that these patients could be managed with chemotherapies but cures were not possible. I think increasingly over the past several years we have recognized that perhaps as in as many as 1 in 5 patients, the cancer has spread to a distant organ such as the liver where there can be aggressive chemotherapy combined with surgery for these isolated metastases that can cure a proportion of the patients and this is a bit of a change in the approach that we have taken to colorectal cancer recognizing that the biology of colorectal cancer when it is spread in a proportion of the patients can allow cures despite diagnosis of metastatic or stage IV disease.
- Foss So this is good news for patients then.
- Kopetz It is absolutely, and this is an area where there is really a lot of need to educate the patients and physicians about these options. This has been work that has come out of many academic medical centers over the past decade to 15 years and evidence continues to accumulate about the benefit and the cures in this population. However, it does require accesses to a multidisciplinary team, a specialized hepatobiliary surgeon to remove these areas in the liver and these are not always available to many patients in the community and so this is certainly an area where we are continuing to educate.
- Foss Do they still use ablation trying to inject materials to clot up these tumor cells and also inject chemotherapy into those?
- Kopetz There is research on other modalities to try to address the cancers in the liver. The outcomes are best if they are able to be surgically resected but in those patients where surgery is not an option due to the location or perhaps the health of the patient, there are other approaches such as heating the tumor with radio-frequency waves to try to ablate them. There are techniques to try to inject chemotherapy or particles directly into the tumor itself in a process we call chemoembolization and increasingly the use of beads that have a certain amount of radioactivity implanted in the beads can be administered to the tumor through an artery and deliver radiation directly.
- Foss Scott, can you talk a little bit about other novel therapies, we are hearing about targeted therapies and lots of different cancers and anti-angiogenesis drugs that are being used. I wonder if any of these can be applied to colorectal cancer?

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- Kopetz Absolutely, I think fundamentally with our understanding of colorectal cancer we are seeing a change and are understanding the biology. We use the term colorectal cancer meaning arisen in the large intestine, but the reality is there are a variety of different subtypes of colorectal cancer and we are just starting to better understand these and be able to classify them. A lot of the exciting work in the field right now is trying to identify biomarkers that can segregate these colon cancers into molecularly homogenous groups of tumors that then we can apply appropriate therapies to try to utilize some of the vulnerabilities of the cancer, so a lot of the targeted therapies that are being developed, moving forward, are really being developed for particular molecular subtypes of colorectal cancer and this is an area where there is much enthusiastic about.
- Foss Are there any clinical trials using any of these novel agents right now that we should know about?
- Kopetz There are a variety of studies ongoing. There is one particular molecular subtype that is defined by a mutation in a gene called BRAF. We now recognize that this is a very distinct type of colorectal cancer that has a different precursor lesion, different location, epidemiology, different pattern of spread when it does spread and is a very aggressive subtype. This type of colorectal cancer does not respond to traditional chemotherapy so its outcomes with current standard of care chemotherapies are very poor and there has been some exciting work over the past year on really trying to understand how do we target this and it is a fascinating story about how both targeting the BRAF protein that is mutated and turned on itself and then actually hitting one of the compensatory feedback mechanisms that occurs really appears to be providing benefits. So it is a fascinating story not only targeting the main driver but then targeting how those cancer cells respond to that driver being inhibited.
- Foss So this is an example of personalized medicine?
- Kopetz It absolutely is and this particular subtype of colorectal cancer is somewhere between 5% and 10% of all cancers that have spread, what we call stage IV. So, it is a small subset of colorectal cancer patients but is one that we desperately need novel therapies for.
- Foss So would all tumors be screened for this at diagnosis or would you only screen them at a certain point when they did not respond to treatment for instance?
- Kopetz Increasingly these molecular tests are being incorporated into standard of care and they are in the guidelines, the BRAF gene and other related genes, are part of an appropriate work-up of advanced colorectal cancer. I think increasingly these research tests both at MD Anderson as well as Yale Cancer Center and others, the patients are undergoing larger and larger panels of screening for these particular genetic mutations that are found in the tumor itself. Now we still do not have as many tools and treatments to really target all the aberrations that we see and so there is still a lot more work to do but I think we are encouraged by the progress that we have seen over the last several years.

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Dr. Scott Kopetz is Associate Professor in the Department of Gastrointestinal Medical Oncology at MD Anderson Cancer Center. If you have questions or comments, we invite you to visit yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Connecticut's Public Media Source for news and ideas.