

Yale CANCER
CENTER

answers

WNPR Connecticut Public Radio



Hosts

Lynn Wilson MD

Vice Chairman and Professor
of Therapeutic Radiology

Francine Foss MD

Professor of Medical Oncology

Understanding Treatment Options
for Melanoma

Guest Expert:
**Mark Faries, MD and Harriet
Kluger, MD**

Yale Cancer Center Answers

is a weekly broadcast on

WNPR Connecticut Public Radio

Sunday Evenings at 6:00 PM

Listen live online at

www.wnpr.org

OR

Listen to archived podcasts at

www.yalecancercenter.org

Welcome to Yale Cancer Center Answers with Dr. Francine Foss and Dr. Lynn Wilson. I am Bruce Barber. 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 1888-234-4YCC. This evening Francine and Lynn are pleased to welcome Dr. Harriet Kluger and Dr. Mark Faries. Dr. Kluger is an Associate Professor of Medical Oncology and a member of the Yale Cancer Center Melanoma Program, and Dr. Faries is an Associate Professor of Surgical Oncology specializing in the treatment of melanoma. Here is Francine Foss.

Foss Let us start off with a little education about melanoma. Could you tell us what it is?

Faries Melanoma is a cancer that starts in the skin, in the pigment cells of the skin, and it is associated with excessive sun or ultraviolet radiation exposure. It is typically treated by surgery in an early stage and with medical therapy if it is a more advanced stage. It is a concerning cancer because it is one of the fastest growing cancers in terms of incidence of any of the cancers.

Foss Mark, you are new to Yale, could you tell us a little bit about when you came to Yale, where you came from, and what your interests are?

Faries I just arrived at Yale, and I am coming from Santa Monica, California, so I did not come for the weather, but there are some really great things about the Melanoma Program at Yale. One is that it has a tremendous tradition in the treatment of melanoma patients. The Yale Melanoma unit goes back thirty five years and has been led by Steve Ariyan over the years, but there are a lot of exciting things that are happening in the program now with Harriet in the medical oncology group, and the new Smilow Cancer Hospital, so it is a great time to be here.

Wilson Harriet, tell us a little bit about your background. We have known each other a long time and you have been at Yale a pretty long time, but tell us your background and how you got interested in melanoma.

Kluger I came from a sunny place, I was born in South Africa where we had a lot of sun exposure with the high altitude in Johannesburg, so I became interested in it primarily from a personal perspective because myself and a number of relatives had this problem. When I moved to Yale in 1999 as an oncologist I decided to join the Yale Melanoma Unit for similar reasons to those that Mark gave. There was a lot going on at the time, there were a lot of opportunities for delivering novel therapies to melanoma patients as opposed to some diseases such as breast cancer where they had made much more progress. We viewed this as an opportunity to make progress and to really contribute to a disease for which there was very little to offer.

Foss Harriet, could you outline for us the Melanoma Program at Yale. I understand it is a multidisciplinary program. Could you, for our listeners, go through the different types of folks who are participating in the program?

3:22 into mp3 file <http://yalecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

- Kluger We have physicians and scientists and then we have hybrids who do both science and clinical work. On the clinical side, we have dedicated radiologists who come to weekly meetings where we discuss patients. We have dedicated skin pathologists as well as surgical pathologists. We now have an epidemiologist who comes to our meetings and is involved in genetic screening of patients, we also have surgeons both on the plastic surgery side and the surgical oncology side. We have radiation therapists who focus on brain metastases for melanoma, a separate radiation therapist who does radiation on the other parts of the body and then we have the medical oncologists who deliver what we call systemic therapies, so therapies that are either injected or ingested. On the science side, we have Dr. Ruth Halaban who is the lead basic scientist, and we have computational scientists as well, so people who analyze data from the high throughput experiments that we do, we have statisticians as part of the group and we have a number of other scientists who do a lot of melanoma related research and drug development primarily.
- Wilson Mark, how is the diagnosis usually made? You mentioned that there can be some different treatments depending on early versus later disease. Tell us about that, and since you are a surgeon I take it you are probably involved in making this diagnosis fairly often.
- Faries Most often the diagnosis is made by a dermatologist or by the patient's primary care physician, and typically it will be a skin lesion that either the patient or the physician has noted is unusual, that has some suspicious features to it. The features that we look for are the A, B, C, D characteristics, where A is for asymmetry, something that is not nice and round or oval. B is for irregular or ragged border. C is for the color, which can have multiple colors in it, brown and red or blue and black or a color that is different from the color of the patient's other moles, and D is diameter which is a bit of a weak indicator but the larger it is, the higher the risk. Really the thing to look for is a skin lesion that is different, that is unusual, that does not match up with other things that a particular patient has on the skin and that would raise someone's suspicion that it might be a problem and should lead hopefully to an early biopsy.
- Foss How are most melanomas diagnosed? Are they diagnosed because a patient notices something or a primary care physician notices something? What is the most common way that these are picked up?
- Faries It can be in both ways, and it depends a lot on the awareness of both the physician and the patient and many times skin lesions can be ignored both by the patient and by a physician and melanoma is allowed to progress to a more advanced stage. It is important that does not happen. It is important that these are picked up early. The earlier the melanoma is picked up, the simpler the treatment the more likely that the patient will be cured and so at an early stage we would simply excise that area with or without lymph node evaluation and most of those patients will be fine.
- Wilson Are these usually brand new, or is it a mole that might have been present for thirty years and started to change, or are both scenarios possible?

6:54 into mp3 file <http://yalecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

- Faries Both are possible and it's fairly equally distributed between the two, so if you have a mole that has been there forever, but has recently changed, that's something you should be concerned about and if there is a new mole or a new dark spot that appeared where there had not been anything before, that is the other typical way that it appears.
- Wilson Do these have symptoms? Do they hurt, are they itchy, or do they bleed?
- Faries Often symptoms come though at a later stage and so optimally no melanoma would be picked up before there are any symptoms. Itching can sometimes be a symptom and then bleeding if a melanoma has got to a point where it is ulcerated.
- Foss Harriet, you mentioned epidemiology. I wonder if you could comment on whether there are any other associated risk factors for melanoma such as family history or other genetic risk factors that we should be aware of.
- Kluger Genetic risk factors have been identified, for example, there is a gene called the P16 gene, which is mutated in actually a very small percentage of patients with melanoma. There probably are lots of additional genes that we have not identified yet. We do know for sure that the strongest risk factor for developing melanoma is sun exposure. The second one would be family history, genetics, and so on. The other risk factor of course is lifestyle, location, where you live, how close to the equator and so on.
- Foss Can we just interject here, the average age for patients with a melanoma, how young and how old?
- Faries The peak incidence is in the 50s and 60s, but melanoma is one of the cancers that spreads across almost the entire age spectrum. Because it can affect so many people at a young age it robs us of more productive years of life than just about any other cancer other than leukemias and lymphomas. So it is unusual in very young children, but beyond that everyone needs to be aware of melanoma as a possibility.
- Foss I was just going to ask about the increasing incidence in teenagers and young adults, perhaps related to tanning bed use.
- Faries We are concerned about any unnecessary excessive ultraviolet radiation exposure and one of the groups that we have seen a great increase in melanoma has been relatively young woman who tend also to be the ones who are most likely to use tanning beds. With improved quality of some of the sunless tanning products that are available now, hopefully there will be less of an interest for some of these people.
- Wilson So a patient sees their primary care physician and a biopsy is done and the diagnosis of melanoma is made, and the biopsy was done in the primary care physician's office. What is the course of events that that patient would traverse at that point?

10:05 into mp3 file <http://yalecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

- Faries That is the point in which they are frequently referred to the Melanoma Unit, typically to see one of the surgeons there, such as myself. One of the most important things that can happen is to have that biopsy looked at carefully because we get a huge amount of information about how serious the melanoma is from the characteristics of that original biopsy, so it is important that they biopsy is done well and that it is examined well by an experienced pathologist. From that point I would consult with the patient and go over what the options are. What types of treatments are available, and the best course for them to really complete the picture of where they stand and then to get that original primary melanoma treated.
- Wilson Why don't you both take us through some of the treatment options for a patient.
- Kluger Typically the patient starts with surgery, so I'll let Mark go first.
- Faries For melanomas that are clinically localized to their primary site, there is no sign of any melanoma anywhere else, what we do is remove the area where that biopsy was performed, where the original lesion was, with a rim of normal-appearing tissue around the outside of it to be sure that every last cell that is in the area that we can get out, we get out. It ends up being a fairly sizeable excision that we do to be as thorough as possible, and that is why reconstruction with plastic surgical techniques is important to be sure that the patient heals up as quickly and as normally as they can. In some instances, when there are characteristics of the melanoma that suggest it may have spread, the most likely place for it to spread is to the lymph nodes in the area of that primary melanoma. What we do in the modern era is something called a sentinel lymph node biopsy and that is the way that we can tell which one or two lymph nodes generally are the ones that receive direct drainage of fluid from the tissues around the primary tumor site. Those are the lymph nodes that will hold any melanoma if it is spread, so we can evaluate those in a minimally invasive way and complete the picture of where the patient stands in terms of their treatment, and if there is more advanced disease or more significant involvement of the lymph nodes, then it may require additional surgery to remove more lymph nodes and then the patient also begins to consider the possibility of medical or systemic treatment to decrease the chance of a melanoma showing up anywhere else.
- Kluger For systemic therapy, if the melanoma has only spread to the lymph nodes and it has been completely resected, the standard therapy at that point is a drug called interferon. We have a number of other experimental therapies that we are currently trying in clinical trials to see if we can improve the outcome and get better benefit than what we get from the interferon, which is a tough drug to take. Primarily, the focus is on immune therapies, so we are trying to boost the immune system to take care of any rogue melanoma cells that might have escaped beyond the lymph node that was just resected. If the melanoma has spread beyond the lymph nodes and is no longer resectable, then the patient has what we call stage IV disease and there too we have a number of standard therapies and a number of experimental therapies which we can discuss a little bit later on.

13:41 into mp3 file <http://valecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

Wilson Thanks guys, we are going to take a short break for a medical minute. Please stay tuned to learn more information about melanoma with Dr. Kluger and Dr. Faries.

*Medical
Minute*

Breast cancer is the most common cancer in women. In Connecticut alone approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide. But there is new hope for these women. Earlier detection, non-invasive treatments, and novel therapies provide more options for patients to fight breast cancer. In 2010 more women are learning to live with this disease than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risk factors associated with the disease. With screening, early detection, and a healthy lifestyle breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center to make innovative new treatments available to patients. A potential breakthrough in treating chemotherapy resistant breast cancer is now being studied at Yale combining BSI-101 a PARP inhibitor, and the chemotherapy drug irinotecan. 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 Public Broadcasting Network.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson, and I am joined by my co-host Dr. Francine Foss. Today we are joined by Dr. Harriet Kluger and Dr. Mark Faries and we are discussing melanoma. Harriet, before the break we were talking about more advanced disease and you were about to give us some more details about various treatment options. Why don't you discuss that with us and then talk to us a little bit about some of the clinical trials that are available for patients.

Kluger Once the melanoma has spread beyond the lymph nodes and is no longer resectable surgically, we have to try to treat the melanoma with either drugs that are ingested by mouth or something that is injected intravenously or subcutaneously. The standard of care in our minds is a drug called high-dose interleukin-2, and this drug has been available for well over a decade. The nice thing about this drug is that it is given in-house for a very brief period. They come in for one week, they go home for week and come back for another week, and then if it is working, we do that again. It is tough to take while the patient is in-house but once they are discharged a few days later they recover and they can go back to their normal lives. The patients that respond to that drug tend to have a really durable response, in fact, there were patients that were treated in the 1980s who have never had a recurrence. For that reason, we tend to try to start with it for the robust patient who can tolerate it. There are a few chemotherapy drugs that have been given over the years. They do work in a percentage of patients, but the duration of the response of those drugs tends to be a little bit more limited. We now have two new very promising drugs that probably will be approved by the FDA soon. One is an immune therapy that we hope will be approved sometime in 2011, it is a drug called Ipilimumab. I can test you afterwards to see if you remember the name, but we just call it Ipi for short. It is also an immune-based therapy, and essentially what it does is it takes the

17:07 into mp3 file <http://yalecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

breaks of the immune system so we get some nonspecific immune activation and patients tend to respond for prolonged periods of time and patients also tend to live longer when they receive Ipilimumab. The other drug that is looking very promising, is a targeted therapy developed by a company called Plexxikon. There were a number of articles about this drug in the New York Times recently and the patients who have a certain mutation in their melanomas, it is approximately 50% of the melanoma patients, have dramatic responses to this drug as well and the duration of response is probably in the order of nine months.

- Foss Harriet, can you tell us how surgery is being integrated with medical oncology in terms of clinical trials and developing new strategies for treating these melanomas?
- Kluger Sometimes we have a patient who has a single site of metastasis or a couple of sites of metastasis and we can then give medical therapy before we go for surgery and that gives an opportunity to learn a lot about the disease. We call that neoadjuvant treatment and sometimes we do that for patients whose disease has spread beyond the draining lymph node, sometimes we only do it for regional disease as well and perhaps Mark can elaborate on that a little bit because he has been involved in some of those trials at John Wayne Cancer Center in the past.
- Faries From a surgical perspective the developments that Harriet has described, these new medical treatments, are really exciting and something that has not happened in melanoma before to have these new treatments that are effective when so few things have been shown to be effective in the past, and what that allows us to do is that in some patients who have a response to some of these new treatments but not a complete response, there is perhaps one or two lesions that are left in place that have not gone completely away, is go ahead and remove those lesions surgically and what we have seen with some of the systemic treatments where patients have partially responded, is that if we go ahead and remove those other spots those patients tend to do just as well as the patients who had everything disappear on the medical therapy and so there has been a great increased interaction between the medical and surgical parts of therapy. The other very important thing that allows us to do is to learn more about how the treatments work and specifically why they do not work, and so if there is a specific metastases that has not gone away we can remove that both for the benefit of the patient but also then to study that to try to find out what characteristics are there that prevented that particular tumor from responding to the treatment and by doing that we can find out why those tumors are resistant and perhaps develop new therapies to overcome those resistance mechanisms.
- Foss Mark, would you ever give some of these biological therapies before you operated on a patient?
- Faries In the past, I would have definitely said if the tumor is resectable we should resect it right away. We do not want to give it a chance to get to the point where we cannot take it out. And in the past, the success for most of the chemotherapies and other more standard older medical treatments for melanoma, was so low that that would be a reasonable thing, but with the improved efficacy of

20:40 into mp3 file <http://valecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

a number of these treatments, the chance of getting a response and making it easier for us to do the surgery after the treatment is pretty good and we learn more about the treatment by sequencing the treatments in those orders. I think that will be something that we do more and more as time goes on.

Foss Harriet, we talk a lot about personalized medicine now and identifying specific mutations in a patient's tumor and then directing therapy towards specific genes that are mutated, and you mentioned this new agent that is available targeting a specific mutation in melanoma. Could you talk a little bit about that?

Kluger Yes, I think it the first incidence in cancer treatment where there is a specific mutation that actually drives the cancer cell and is not found in other cells in the body, so that enables us to give a drug that targets that particular mutation and only that mutation, and does not affect normal cells to the degree that other cancer therapies do. This enabled the developers of this drug to push the doses up in patients with very little side effects and that is probably why this drug is so effective. For example, in breast cancer you give targeted therapies as well, tamoxifen or antihormonal therapy, and that is a targeted therapy against estrogen receptor. But because estrogen receptor is located in other parts of the body too, you are limited in how much of the drug you can give in order to kill cancer cells. That is probably why this drug has been so effective in melanoma and we are hoping that going forward we are going to find additional mutations that drive other subsets of melanomas, for example we know that another 15% of the melanomas are driven by a mutation called N-ras mutation, so if we had a drug that specifically targeted those N-ras mutations we may be able to use that as well and we are hoping that in the future we will have a menu of drugs that we can give and from the menu we pick the best thing for the patient. The flip side of that is trying to identify which of the patients are going to respond to the immune therapies that we mentioned because there the predictor would supposedly be found in the immune system and not in the tumor, although we do not really know that yet.

Foss Where are we in terms of personalized medicine in melanoma? Are these particular mutations screened for in all melanoma patients at this point of time?

Kluger We do at Yale as part of a research program. We have a grant called the SPORE grant which stands for Special Programs of Research Excellence, and it is a grant that has been given to us by the National Cancer Institute and we are one of five melanoma sites. The SPORE has some funding and what we call a tissue core, so all of the specimens go to the core and that gives us the opportunity to actually screen for these mutations. If it is done in a routine pathology lab sometimes we have issues with payment for the mutational analysis because it has not yet been FDA approved and it is not recognized by all insurances.

Wilson Do we think that the incidence of melanoma is increasing in Connecticut because the disease is more common, or is it because we are better at screening and detection, or both?

23:53 into mp3 file <http://valecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

- Kluger We think it is the combination of both. Certainly nationally the incidence is increasing but also the death rate for melanoma is increasing, which leads one to believe that some degree of this might be true increasing incidence rather than just an increasing diagnosis, because people are more aware. Even though our latitude is fairly far north, we still have a fairly large fair population over here, we have the shoreline, and lakes and people are outdoors quite a bit despite the weather.
- Wilson Do we have screening programs at Yale that are offered from time to time?
- Kluger Yale Dermatology Associates does have a free screening day where people can walk in and get a full body skin screen and there are dermatologists within the dermatology department that focus on screening for melanoma, that is their area of interest and their area of research interest, so we have a bunch of really competent dermatologists who do this on a regular basis.
- Foss Mark, for a patient who say had one of these very early superficial melanomas removed, of which there are a growing number of patients out there now, what kind of follow-up should that patient expect?
- Faries There are really two things for the patient to watch out for as time goes on. The first is the possibility that the first melanoma might come back, might have spread somewhere else and might reappear, and the risk of that depends a lot on the characteristics of the original primary and then whether the nodes were involved or not. Typically, that risk is fairly low and the patient can be followed with physical examinations and just regular routine testing. The other risk though that patients need to worry about once they have had one melanoma is the risk of getting a second melanoma and that risk is substantially higher than the risk for someone who has never had melanoma, and over the course of the rest of their life it might be between 5% and 10%, so it is not a huge risk but it is substantial, particularly compared to the patient that has never had melanoma. The most important component of the follow-up for that is regular skin examinations and that can be with the surgical oncologist, it can be with the dermatologist, or their primary care physician and they can check themselves as well, but if they undergo that sort of regular surveillance program chances are if they do get a second melanoma, it will be caught at least as early or usually earlier than the first one and should not be a threat to the life and can be treated and cured as well.
- Wilson Getting back to the biopsy or excision procedure in the sentinel lymph procedure, is it something that the patient would have to stay overnight in the hospital for, or do they go home that day and what are some of the side effects that might be associated with say a sentinel lymph node procedure?
- Faries The sentinel node procedure is a minimally invasive procedure, it is outpatient surgery. It involves first a test which is a radiology test where the site of the primary melanoma is injected with a bit of radioactive trace, then can be followed to where this sentinel lymph node is and then during the surgery, we also inject a blue dye that allows us to see the sentinel node as well. We find through

27:17 into mp3 file <http://valecancercenter.org/podcast/oct2410-cancer-answers-faries-kluger.mp3>

a small incision that node that has taken up those tracers, take that node out, and close up the little incision. The patient can then go home the same day, return to work generally within a day or two and if that lymph node is okay, that means the rest of the lymph nodes are almost certainly okay as well and they can avoid any other more invasive, more substantial operations.

Foss Harriet, you talked about the SPORE grant at Yale, which is a research grant for melanoma. I wonder if you could talk to us a little bit about clinical trials, ongoing clinical trials and new developments in melanoma.

Kluger We have a number of experimental therapies that we can offer patients that are not available in routine oncology practices. When we look at clinical trials and drug development we go through a bunch of phases. Some of these drugs are in the early phase of development, some are at later stages of development, and we definitely have some really exciting immune based therapies in the pipeline right now that hopefully within a year or two will expand and we are seeing some very nice responses to some of them, but on a regular basis we typically have about six different experimental therapies available for patients with metastatic melanoma.

Dr. Harriet Kluger is an Associate Professor of Medical Oncology and a member of the Yale Cancer Center Melanoma Program. Dr. Mark Faries is an Associate Professor of Surgical Oncology specializing in the treatment of melanoma. If you have questions for the doctors or would like to share your comments, visit yalecancecenter.org where you can also subscribe to our pod cast 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.