Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about melanoma with Dr. Dale Han and Amanda Ralabate. Dr. Han is Assistant Professor of Surgery at Yale School of Medicine and Ms. Ralabate is a research nurse for the Melanoma Program at Smilow Cancer Hospital. Here is Dr. Chagpar.

Chagpar Dale, why don't we start off, and then Amanda you can join in as well, and tell us a little bit about yourself, and what you do?

Han I am a surgeon here at Yale and my specialty is in surgical oncology. My life is fairly nomadic. I moved about 16 times before college and I have lived in the Midwest, Northeast, Atlantic Coast, and then I finally decided to lay roots at SUNY Stony Brook, where I did a medical program both undergraduate and medical school there. I then went on to complete my surgical residency at the University of Pennsylvania, followed by a surgical oncology fellowship at the Moffitt Cancer Center in Tampa, Florida and then I was very fortunate to be able to join the faculty up here as part of the Section of Surgical Oncology.

Chagpar And your focus is primarily on melanoma?

Han Yes it is.

Chagpar And Amanda tell us about what you do?

Ralabate I am a clinical research nurse on the melanoma team. I started off my nursing career as an oncology inpatient nurse in Smilow and saw the opportunity to become a research nurse about a year and a half ago with the melanoma team and I did that.

Chagpar So we are here to talk about melanoma both from a clinical standpoint as well as a research standpoint and maybe a bit of education as

well in terms of what exactly this disease is and how we can prevent it. How we can treat it and what some of the advances are in melanoma. Dale, why don't you start off by telling us a bit about what exactly is melanoma?

Han Melanoma is one of the forms of skin cancer, although it actually is not the most common, more common are basal cell carcinomas and squamous cell carcinomas, but although melanoma represents less than 5% of all skin cancers, it actually represents 80% of skin cancer related deaths. So it is really the skin cancer that you have to treat appropriately and have to follow appropriately. Melanoma rises from specialized cells called melanocytes within all of our skin. These cells produce a pigment called melanin and the melanin is what gives us our skin tone and also is what

3:17 into mp3 file http://yalecancercenter.org/podcasts/2014%200907%20YCC%20Answers%20-%20Han%20and%20Ralabate.mp3

we see as tanning as we get darker, there is more melanin that gets produced. The melanin helps to absorb the radiation that we are exposed to on a daily basis from the sun or the environment, but when these melanocytes start accumulating damage to their DNA, they can start looking abnormal under the microscope and start proliferating out of control. When that process starts to break through the skin barrier, that is when it is called melanoma. So, essentially a lot of times, people will discover melanoma by looking on their skin, seeing an abnormal lesion or freckle or mole or something, a skin lesion that has changed in some way. It may have bled. It may have become itchy and that brings it to their attention, they have it evaluated and a biopsy often is performed and that is usually how melanoma gets diagnosed.

Chagpar Amanda, when Dale was talking about these melanocytes and how they respond to sunlight and they cause pigment, what can we do to prevent melanoma? Is this the cancer that all of us hear about on the news that we are supposed to wear sunscreen for and we are supposed to avoid tanning salons, how does that work?

Ralabate Yes, so we recommend that patients and their family members stay out of the sun and stay away from excessive sun exposure and stay out of tanning beds, and wear sunscreen while outside and cover up, hats, and long sleeves.

Chagpar Dale, does that really work? I mean does sunscreen really work and there are a lot of people, especially in the summertime and as we are heading

into fall, who like the 'healthy glow' that they get after they have been to a tanning salon, so what is wrong with that?

Han As far as I am concerned, there is no healthy glow. And it is all about being cognizant of skin protection is what it all comes down to. It does not mean that you live your life in a bubble, and in a dark cave somewhere, it just means you have to be more cognizant of the fact that you have to try to minimize the exposure to your skin and that involves sun protective clothing, long sleeves, there are plenty of companies out there that produce very fashionable clothing, there are hats and long sleeved shirts, and so forth, they are light weight, breathable material, so these are things that we recommend to patients just as simple measures. Also, as Amanda was mentioning about using suntan lotion, absolutely. Suntan lotion does help lower the exposure that your skin gets and of course just to add to what Amanda said, reapply every couple of hours after you have gone in the water and come out, reapply then. It is about being able to minimize the amount of sun exposure and UV radiation exposure that your skin is actually exposed to.

Chagpar What about tanning beds? There has been a lot in the media about tanning, particularly in youth and laws coming out, warning against, particularly young people, going to tanning salons. What's new with that?

Han That has been a very controversial topic. There is a push, the Society of Surgical Oncology at their last meeting had started to try to create a consensus statement about tanning salons and tanning beds. When you look at the Australian data, they show that once they were able to make tanning



illegal or that it was not allowed for up to a certain age group, the rate of actual incidence of melanoma went down in that age group. There is data out there to suggest that there may be a causal link, but again, the data is still controversial in terms of how to interpret it, and certainly here in the United States, there seems to be more people willing to go to these tanning salons, beds and unfortunately they are marketed and they are on every street corner. So kids seem to have ready access to a lot of these, especially college students.

Chagpar Amanda, how do you get the word out to people about wear sunscreen, reapply more often, do not go to tanning salons, how do you get

the word out about melanoma and ways of preventing it, aside from coming on shows like this and getting the word out this way?

Ralabte I think we have to target the youth population, as you had mentioned. It seems that the youth population seems to want that summer glow. We also have a melanoma symposium coming up in September that will provide education and awareness regarding melanoma to patients, survivors, and those interested in learning more about the disease.

Chagpar And when you mention this symposium, as I understand, this is part of a nonprofit advocacy group called AIM at Melanoma and they are targeting people from getting melanoma, wanting to get the word out to people about this disease. Dale, take us through a little bit more about how you go about making that diagnosis. Let's say somebody misses the symposium or catches it a little too late and says "I stayed out in the sun, I did not reapply my sunscreen, I visited the tanning salon, I did not wear long sleeved clothes or hats or anything like that, and now I find a freckle that is itchy and bleeding, and scabby, and so on, and they go and they see their family doctor who says "Hmm that looks strange," is that when they come to see you?

Han Oftentimes the patients, once they find a suspicious lesion, they bring it to the attention of their primary care physician and are often referred to a dermatologist initially and the dermatologist then evaluates the lesion, takes a biopsy, and these biopsies can either be a shaved biopsy or punch biopsy, which gives you full thickness of the skin in that area and then a diagnosis is made based on the pathology of that biopsy. Sometimes patients are directly referred to a surgeon or surgical oncologist, and oftentimes, if it is suspicious lesion, it is best to just go ahead and biopsy it, because aside from the A, B, C, D and E that everyone has been told about, one of the big things is what is the patient feeling. Is this something that has changed? A patient is the best person in terms of gauging changes in their body. So, if it suspicious enough for the patient to bring it to attention, it warrants having a biopsy done. So, when we take the biopsy and the diagnosis comes back as melanoma that is when we go ahead and start initiating discussions about prognosis, treatment, and so forth.

Chagpar I want to take a step back for just a minute. You said, the A, B, C, D, Es that everyone learns about, but many people in our listening audience may know exactly what you were talking

11:10 into mp3 file http://yalecancercenter.org/podcasts/2014%200907%20YCC%20Answers%20-%20Han%20and%20Ralabate.mp3

about, but some may have thought, those are just the first five letters of the alphabet. So, lets take a step back and go through what exactly you meant by the A, B, C, D, Es?

Han So first you are going to look for asymmetry and then pigmented lesion changes in the borders, the color, the diameter of the lesion, and essentially, the last part, I am actually making it as an F, is the feeling, what the patient feels about the lesion itself. Has it changed and if it has, if the patient is really concerned about it, it warrants the biopsy in itself, but these are some of the things that we look at, especially the dermatologist when they go through and take a look.

Chagpar Amanda, you were a nurse prior to being a research nurse. When people come in and they have had this biopsy done and they are told that this is melanoma, do lot of patients know what that means, and what sense of fear and anxiety do they have with that diagnosis?

Ralabate Well Dr. Han can probably speak better to newly diagnosed melanoma patients, I primarily deal with those who are newly diagnosed metastatic melanoma patients.

Chagpar What does that mean? Give us a sense of what a metastatic patient is?

Ralabate A metastatic melanoma patient is when somebody's melanoma has metastasized to another organ, so for example the lungs or the liver.

Chagpar And does that happen very often?

Ralabate Yes.

Chagpar And so that must be pretty devastating when people have melanoma that has now spread.

Ralabate Yes.

Chagpar Dale, do they get that sense of dread when they are newly diagnosed or are they, well it is a freckle, it is diagnosed with melanoma, but it's a freckle.

Han You see a wide spectrum of patients and certainly the vast majority come in very, very concerned, rightly so. When you hear a diagnosis of cancer, it is the unknown. All you hear about are the worst case stories and scenarios, but some patients come in and are not really concerned about it, but oftentimes those patients do not really understand their diagnosis. So, you see a wide spectrum, but certainly when most patients hear that diagnosis of skin cancer, melanoma, most patients are usually very very concerned and obviously want to know about prognosis and treatment and so forth.

13:53 into mp3 file http://yalecancercenter.org/podcasts/2014%200907%20YCC%20Answers%20-%20Han%20and%20Ralabate.mp3

Chagpar And we are going to talk more about prognosis and treatment for melanoma right after we take a break for medical minute. Please stay tuned to learn more information about melanoma with my guests, Dr. Dale Han and Amanda Ralabate.

Medical

Minute There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut. Completing treatment for cancer is an exciting milestone, but cancer and its treatment can be a life changing experience. Following treatment, cancer survivors can face several 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 to keep cancer survivors well and focused on healthy living. The Survivorship Clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life and longevity. This has been a medical minute brought you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR, Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guests, Dr. Dale Han and Amanda Ralabate. We are talking about melanoma and right before the break, Dale you were talking about how there is really a spectrum of people's emotional reactions to getting a diagnosis of melanoma, but I think that for many people,

very much like as you said at the beginning of the show, this is not the classic basal cell cancer which is really pretty indolent. Most people know that melanoma is one of those really aggressive cancers and as Amanda was saying, it is the kind to spread to other organs and certainly can carry a prognosis that is not so favorable. Dale, take us through what happens after the diagnosis of melanoma. The dermatologist has done a biopsy and it comes back as melanoma, they come to see you. Is this like okay that is it, write your will or are there good options available for these patients?

Han Absolutely, there are very good treatment options for patients and the biggest thing is most patients that come in with the diagnosis of melanoma, the vast majority of them have what we call local disease. So they do not come in with disease that has spread to their lymph nodes or anywhere else in their body. 70% of patients actually present with thin melanomas which are less than equal to 1 mm in thickness and what we do look for in the pathology of the biopsies is how deep has that melanoma gone? We define thin lesions as less and equal to 1 mm which is what the vast majority of patients present with. So for these patients and for patients with local disease, treatment options are excellent and many of these patients can actually be cured of the cancer, but the standard recommendation for local disease is to do a wide local excision which consists of excising the tumor or biopsy cavity or the lesion site with a margin of what appears to be normal skin and that is done in order to make sure that we get out all that melanoma and are able to decrease recurrence rates at that local site about 1% to 2%. The real question then is about further staging procedures and one of the biggest ones is something called sentinel lymph node biopsy where we try to detect



if there is any microscopic spread of melanoma to the draining lymph node basins. Now, as I mentioned, most patients do not present with clinically palpable lymph nodes that you can feel are enlarged, really it is about trying to detect these microscopic spreads and we use radiotracers and blue dye to find the sentinel node and excise that node and then the pathologists can take a look for any microscopic disease in that node, so really as a staging procedure that will determine quite a bit. But for the patients who present with just localized disease and we have done the wide local excision, particularly for thin melanoma, the patient's survival of 10 years can be over 90%.

Chagpar Wow, that is really terrific. Do the patients then need chemotherapy or radiation or are they done, cured, live long and prosper?

Han That is a very complicated question. For patients with just local disease and no evidence of spread to their lymph nodes, surgical excision is all they will need. For the patients who have been found to have spread to the lymph nodes, the standard recommendation is then to go back and one, surgically remove the rest of those lymph nodes in that basin and that procedure we call a completion lymph node dissection because when you take all comers about 15% to 20% of patients will have an additional node with metastatic melanoma, so we want to clear that entire lymph node basin of any disease. After that point, the patient gets referred to a medical oncologist. We have excellent medical oncologists here in the melanoma unit who have inordinate experience in treating patients with metastatic melanoma and what they do is essentially have a discussion with patients who have evidence of spread to the lymph nodes in terms of either being treated with interferon or being placed on a clinical trial, or just being under surveillance at that point. This situation is obviously a little bit different as Amanda was saying for patients who develop distant metastatic disease. These patients are primarily treated with systemic therapies and since 2011 there has been a real turning point because there are so many new powerful therapies that either have been developed or are in the pipeline at this point either as immunotherapies or targeted therapies and they have really opened the gateway in terms of developing further agents for the treatment of metastatic melanoma.

Chagpar So Amanda, this is where you come in, right? When Dale talks about these powerful novel therapies that are in development or in the pipeline we are really talking about clinical trials and I think that a lot of tremendous work has been done in melanoma. As a research nurse, you talk to patients about clinical trials for melanoma, how do people respond when you talk to them about clinical trials, are they like, sign me up, I would love to be part of a clinical trial and help to move therapies forward and potentially get tomorrow's treatment today, or is there some trepidation on the part of the patients?

Ralabate I would say there is a little bit of both. Immunotherapies have been the hot topic in melanoma for the last several years and so patients are usually pretty excited to have these opportunities and this



option to receive an immunotherapy through a clinical trial but again, there is always some hesitation on their part because these clinical trials can be time consuming, there can be side effects, so I would say both.

Chagpar Dale can you talk a little bit about some of these novel targeted therapies and immunotherapies, what exactly are they? I know that certainly immunotherapies have been taking the world by storm and there have been some very big publications in the New England Journal of Medicine and others particularly geared around immunotherapy in melanoma and actually one that came out of Yale.

Han Absolutely, 2011 marked a turning point in the treatment for metastatic melanoma and prior to that therapies for the patients with metastatic disease was fairly limited. You had chemotherapy but response rates are only in the order of about 10% to 15%. You had biochemotherapy which is a combination of the immunotherapies we had back then, high dose interferon along with chemotherapy and then vaccine therapies and adoptive cell therapy but in 2011 two lines of therapies came out and one was called vemurafenib and that is a targeted therapy against BRAF-mutant melanoma. BRAF is a gene they found was a driver mutation that essentially drove the progression of melanoma so that if you inhibited it you could actually cause lesions to regress. The other line of therapy, an immunotherapy, was ipilimumab and again, as we were mentioning, a lot of work has been done in immunotherapies, and in this particular therapy, they showed that about 10% to 15% of the patients, or approximately 10% of the patients will develop a complete response which was unheard of for a while and there was significant improvements in survival. So in one year you suddenly went from very limited options to two very good options potentially for the treatment of metastatic melanoma. But more importantly, what ipilimumab did was it opened the gateway for developing further therapies for treating melanoma through immunotherapy, and one of the biggest ones is anti-PD-1 therapy and that is being extensively studied here at Yale and a lot of research is going into that and now the big clinical questions on top of developing these therapies is trying to find combinations of these therapies and then incorporating multimodality therapies such as surgery into the treatment algorithm for patients with metastatic melanoma, it is a really exciting time now and lot of clinical questions to answer.

Chagpar Tell us a little bit more about anti-PD-1, I mean, when we first heard about it, it was kind of like helping your immune system to overcome the cloaking of the cancers.

Han Essentially PD-1 is a receptor and lymphocytes are essentially the marker for exhausted T-cells. So that if you can inhibit that you can basically up-regulate these T-cells to then become more active and then therefore with more active white cells she may be over to then start finding the melanoma cells

or the metastatic melanoma cells and the tumor cells that are around.

Chagpar That is incredible. So have people looked at combining these therapies, using some targeted chemotherapies along with immunotherapies, along with other types of therapies?

25:16 into mp3 file http://yalecancercenter.org/podcasts/2014%200907%20YCC%20Answers%20-%20Han%20and%20Ralabate.mp3

Han There is an ongoing trial that is looking at both ipilimumab with anti-PD-1 therapy, this is a little out of my scope and I know the medical oncologists here, Dr. Kluger and Dr. Sznol would certainly know more about it, but certainly the big thing is looking at combinational therapies, whether it is targeted therapy or immunotherapy or different combinations of immunotherapies together. One of the things that would be interesting to look at is to see if you can use these agents in a neoadjuvant setting, meaning treating the patients with advanced disease that are borderline resectable and seeing whether or not the patient will have good enough response to go on to surgery. Other ways to look at it are that patients with metastatic disease are treated with these agents. These agents are so powerful that they can stabilize disease for long periods of time or patients can have a significant response and then the patients may be surgical candidates to remove any residual metastatic lesions and certainly, more and more patients are being referred for evaluation for that and I think it is a very exciting time, but again, a lot of clinical questions to answer and it is still very early.

Chagpar Do you think that there will ever come a time when surgery will not be needed? That people could do a biopsy of a cancer and say, we know that this particular melanoma is fed by this gene and that gene, and if I turn on this switch or that switch of your immune system, we can eradicate this melanoma and you will never need surgery again.

Han Selfishly, I hope not because that means I am out of a job, but certainly that would be the way of the future, gene expression profiling and targeting those mutations that drive cancers and certainly that is the ultimate goal. I certainly hope that we someday reach that point.

Chagpar We have talked a little bit about surgery, we have talked a little bit about chemotherapy, targeted therapies, immunotherapies, but we have not talked a lot about radiation. Does radiation play a role in melanoma?

Han It does, melanoma cells are generally not very radiosensitive, meaning they are not effected by radiation as much as other cancer cell may be, but we do use radiation oftentimes in a palliative sense, for instance, patients may have lesions to their spine or to their brain and we will use radiation to try to control these lesions, especially patients that are having pain, for instance, in their spine or if they have multiple lesions in their brain and so forth. Other places where we may use radiation are in the regional draining nodal basins. The Australians have published studies giving criteria for use for adjuvant, meaning after surgery, use of radiation. I think a lot of us would favor not doing that because if the patient did recur, using radiation could complicate any subsequent surgeries but there is a potential role there.

Chagpar Amanda, what if there was one message that you could give patients? You see patients when their disease is already metastasized. What would that one message be if you were going to give everyone who is listening to us tonight one message in our last minute, what would you tell them?

28:56 into mp3 file http://yalecancercenter.org/podcasts/2014%200907%20YCC%20Answers%20-%20Han%20and%20Ralabate.mp3

Ralabate I would tell patients to stay out of the sun or use the correct protective sunscreen and if they notice changes in moles or freckles or changes on their skin, to see a dermatologist and seek help.

Amanda Ralabate is a Research Nurse for the Melanoma Program at Smilow Cancer Hospital and Dr. Dale Han is Assistant Professor of Surgery at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC. And as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber and hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for news and ideas.