Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening, Francine is joined by Dr. Cary Gross. Dr. Gross is Associate Professor of General Medicine and the Associate Director of theRobert Wood Johnson Clinical Scholars Program at Yale School of Medicine. Here is Francine Foss. Foss Let's start off, Cary, by talking a little bit about where you came from, what got you interested in this field, and how you got to Yale? Gross I have been here at Yale for about ten years and my interest in treating older patients with cancer really started when I was a young physician in training. I was Chief Resident at Sloan-Kettering in the late 1990s, and at that time it became apparent to me that the majority our patients that were being admitted to the service were older patients who not only had cancer, but a variety of non- cancer conditions and problems that they were facing. I am a general internist and I have always wanted to be a primary care doctor and during that time, taking care of these cancer patients, I became very concerned about how the primary care physicians interact with medical oncologists and how we can all potentially do a better job learning about taking care of cancer patients. Foss Can you tell us what 'old' means now-a-days? Gross That is a great question, old is not and should not be defined as any chronologic age, and I would actually suggest that we consider using the terms frail and not frail, or just healthy or not healthy, because as we all know there are some people over the age of 80 that are running marathons, and some people who are 65 that are quite debilitated. Foss You talked about seeing these patients in the general medicine setting, is it true that many of these frail patients are actually being handled by primary care doctors and internal medicine doctors and not by medical oncologist? Gross Absolutely, certainly when we consider treating the older patient with cancer, the oncologist would be involved at some point. However, sometimes patients do not make it into the door of the oncologist's office, say if the diagnosing physician is assessing the patient and thinks that they may not be fit or suitable, or able to tolerate the therapy. And that leads to the other factor, which led to my interest in older patients with cancer, and that is furthering our understanding of how older patients, maybe I should use my own terms, how frail patients are able to tolerate cancer treatment, cancer screening, and cancer therapies. When I initially finished my clinical training I did a two-year research fellowship and during that time I became very interested in the process of research and studying what are we trying to do when we are conducting research at the national level. Are we just trying to generate new information, or are we really trying to improve the health and health care of our population? The first study I did, looking at this topic of research, was to 3:50 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-

__Dr__Gross.mp3look at patients enrolled in trials funded by the National Cancer Institute, or the NCI, and what we found was that only about 3% of adults under the age of 65 who had cancer, were being enrolled in cancer research studies. As a point of information for comparison, if you look at children with cancer, over 70% are enrolled in research studies. And this widespread participation in research is partly responsible for the tremendous gains that we have made in reducing the mortality rate of childhood cancers. So, like I said, we found that about 3% of adults were enrolled in research, but then for older adults it decreased even further, for ages 65 to 75, only about 1% were being included in research studies, and over the age of 75, less than half a percent. If you translate these numbers into a plain take home message, what we are finding is that there is really a paucity of data that is applicable to the older cancer patient to help guide decision making, and I did one other study where we were looking at what happens after a study was published and here we looked at a new surgical procedure and what we found was that the study that was published was a randomized trial where they took people up to the age of 80 and they randomized half of these people to get this surgical procedure on their neck, called a carotid endarterectomy to prevent strokes, and half the people were randomized to not undergo the surgery, and the take home point from this publication was under the age of 80, there is a modest benefit to undergoing this procedure and also the take home point from the author was that this trial was only done at hospitals that were very experienced and by surgeons who were very experienced in conducting the procedure. What we found, when we looked at Medicare data to look at patients who had actually been operated on and who are eligible for the surgery, was that after this research study was published, patients over the age of 80 would not even been eligible for this study or even more likely to undergo the surgery than patients who are younger than 80, and similarly patients who are low volume hospitals, patients at hospitals that had a higher mortality, were actually more likely to undergo the procedure. The take home point from that study, which was very disturbing and concerning for me, was that not only are older patients not being enrolled in studies, but when these studies are published the results are affecting the care of the older patients, sometimes leading to interventions that can potentially do more harm than good. Foss In terms of why older patients were not on the clinical trials, I think it was only recently that the NCI did not have an age cut off. I remember we use to have an age cut off of 65 for a lot of these clinical trials and now we do not have that. Have you seen more patients going into trials now that there is not an age cut off, or do you think that there are other problems that are keeping these older patients off the trial? Gross There has been an increased interest, and I do think there are more older patients going on to research studies, but there are still important barriers because some studies do not have explicit age cut offs but they still may have certain health problems, which could preclude you from joining the study. If a new study says we do not want anybody who has emphysema, heart failure, or kidney disease, but you can be any age, older patients are more likely to have these conditions, and therefore, they

are less likely to join. But there are a number of encouraging signs towards generating more evidence that is applicable to the older patient. 7:55 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3Foss I think one of the things that is inherent, and goes back to your example with the surgery, is that because we do not have experience treating these patients with severe medical issues, kidney failure, liver issues on clinical trials, we do not have experience with the drugs in that setting and then once these things get approved, they are used in the community, perhaps in patients that maybe do not need those strict criteria and so we do not have a lot of experience using the drugs in that setting. Gross Absolutely, and this speaks to the way research is designed, our system of research in our country is really broken. If you think about it, there are two halves of the research process. One half, in my perfect world, would be developing new treatment strategies and bringing them to the market, bringing them to the bedside, and then the second half, which would start after FDA approval or after the initial research study is completed, would be to see what happens in the real world when these drug agents are being used, particularly for the frail, elderly patient. We need to do a better job of generating evidence after the new treatments come to market. Foss Cary, we have talked a little about this but if you come right down to it, how much data is out there to guide us in the screening and treatment of older patients with cancer? We have the NCCN guidelines, which address diseases as a whole, but I do not believe that they really break it down by age. Are there any guidelines at this point, or are there any sources of information out there? Gross They are very few guidelines that are specific to the older patient because, as you rightfully said, there is a paucity of evidence. Guidelines are very helpful in guiding treatment decisions and even when there is no evidence, sometimes guidelines are written, actually, frequently guidelines are written when there is no firm evidence that can help to provide some expert consensus of opinion about what is felt to be the best approach to take. However, because there is so little evidence for treating the older patient, most guidelines, even with the expert consensus, even when there is no evidence at all, do not feel obliged, or maybe appropriate including these age-specific recommendations. Foss Another issue that we run into in clinical practice, particularly with our lymphoma patients who we expect to cure with chemotherapy, is that often times, if a patient is older they will not get full-dose treatment. There is also the bias on the part of some physicians that you should modify the doses of treatment for older people. Is that a problem from your point of view and do you see anyway that perhaps we could address that? Gross It is a problem, if there is no evidence to support it. Certainly we expect our physicians to make decisions based upon the information that they have at hand regarding what would be the best for their patient. Certainly one should not be criticized for dose reduction, for giving a lower dose of chemo, if you think it will do harm. But what I am trying to promote is the attitude that we need to generate this evidence and wouldn't it be great if we had a health system where

older patients are being evaluated for treatment of their lymphoma. If they could say, “Dr. Foss, what about patients like me, what about somebody who can’t walk up a flight of stairs and has kidney disease? Can 11:52 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3you look back at the past five years of data nationally and tell me what happens when I get chemo?” The frustrating thing for me as a clinician is that these data are out there. There are patients all across the country being treated that have very similar and very common problems but we are not capturing the data yet. We can then collect it and feed it back to the research and feed it back to the clinicians so that patients can make informed decisions. Foss We have what we call the ECOG performance status, which is a way we assess older, or anybody actually, for clinical trials. We assess them based on whether or not they are ambulatory and can dress themselves, basic levels of functioning, and that is a rough score from 0 to 4. Do you think that a score like that, if we perhaps were a little bit more specific and included more elements, could help us? Gross Absolutely, especially including more elements. At Yale Cancer Center we have imparted a multi-institutional study where we are enrolling, or have enrolled, over five hundred geriatric cancer patients. And again, speaking to the definition of age, we defined it as you had to be over the age of 65 and about to receive chemotherapy for cancer. And we collected quite a few variables including the ECOG performance status, but also we asked these patients, can you dress yourself? Do you need help shopping? How far can you walk, a lot of geriatric specific issues. What we found was that when we included some of these geriatric questions, our ability to identify patients who are going to run into trouble as far as developing toxicity from their chemotherapy, was much improved. What we found was that we were able to identify one group of patients that had very few of these problems, where only 20% would develop toxicity reaction, and the patients who are older and more frail and had more of these baseline disabilities, over 80% were developing disability. This is just starting out, this research process, but there are definitely ways that we can help guide decision making. Foss We would like to talk a little bit more about that after we break for a medical minute. Stay tuned to learn more about cancer in the elderly from Dr. Cary Gross. MedicalMinute This year over 200,000 Americans will be diagnosed with lung cancer and in Connecticut alone there will be over 2000 new cases. More than 85% of lung cancer diagnoses are related to smoking, and quitting, even after decades of use can significantly reduce your risk of developing lung cancer. Each day patients with lung cancer are surviving, thanks to increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving lung cancer survivors more hope than they have ever had before. Clinical trials are currently underway of federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for lung cancer. An option for lung cancer patients in need of surgery at Yale Cancer Center is a video-assisted thoracoscopic surgery, also known as a VATS procedure, which is a minimally invasive technique. This has been a medical minute more 15:22 into mp3

file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3 information is available at YaleCancerCenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network. Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my guest today Dr. Cary Gross and we are discussing cancer care in the older, or frailer, patient. Before the break, we talked a little bit about this clinical trial that you did actually looking at elderly patients enrolled in cancer treatment at Yale, and you told us that you identified some factors that predicted whether or not those patient would have a good outcome. Do you want to just go through what some of those were? Gross Sure, we looked at, as I mentioned, a variety of factors, and not surprisingly we did find that increasing age was associated with a higher risk of toxicity, but it was not the single strongest predictor. We also found that the people taking multiple medications, people who have kidney problems, people who needed help with some of their activities of daily living such as bathing, shopping, taking care of themselves, and finally one thing that was interesting what that people who had social isolation, people with less social support, were also more likely to develop toxicity reaction and the interesting thing is when we compared these factors with the physician assessment of the patient's performance status, the physician assessment was no longer helpful, so it is basically these few simple questions that might help us to do a better job than just having the physician eyeball the patient and predict who is going to develop toxicity. Foss These were questions where the patient answered a questionnaire? Gross Yes, and our goal now is to then take this initial study and validate it, meaning confirming our findings in another population of patients with cancer. Foss I was just going to bring up that point, and that is, was this study done primarily at Yale, or was it done also in community settings, because perhaps there is a difference in terms of the patient population? Gross It is a great question. It was done actually at about 10 different medical centers, but they were all academic medical centers that were participating in this project and yes there are definitely differences in the approach to treatment, and frankly, the mean age of the patient's at academic medical centers tend to be younger healthier patients than at community settings. So, in the future, I think it will be important to include both the academic and community providers. Foss Can you talk a little bit about the extrapolation of this kind of research on a national level? Are there national studies looking at the same kinds of issues? Gross The goal of this geriatric oncology research team is to integrate this geriatric assessment as we are calling it into other ongoing studies such as the one led by Dr. Arti Hurria at City of Hope. And this initial assessment is being integrated into some large NCI sponsored clinical trials so that they 18:42 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3can assess the impact of these geriatric factors on patient outcomes. My hope is that eventually this will become something that becomes integrated into clinical care, so that it is part of your initial forms that you fill out when you are seen by the doctor, not only your insurance informa-

tion but also rigorous assessment of your health status. Foss Cary, can you talk a little bit about what other steps have been made in recent years to enroll older patients in research studies? Has this been changing over the last couple of years? Gross There have been a few exciting developments. One is that there are some changes to the way studies are being designed. A few moments ago we talked about removing these age cut offs and no longer excluding patients over the age of 65, but actually if you take that a step further there are some other studies which have a new concept toward an age minimum. There are some studies that only include the patient over the age of 75 because there are some questions that are really pertinent for the elderly that can only be answered by looking at the older population. For instance, one study of radiation after breast conserving surgery for women with breast cancer was published about four years ago. In this study they looked at patients over the age of 70 with small favorable risk tumors, meaning that they had a low likelihood of metastasis, and by focusing on this group they answered the question, do these women really need to get radiation or will they be okay without it? And what they found was that 4% of these women who did not receive radiation had a recurrence of their breast cancer, and only 1% of women who did receive radiation. So, it was 4% versus a 1% difference. In some editorials and guidelines after this study was published, they highlighted that there was only 3% absolute difference in the risk of a breast cancer recurrence and suggested that older women should be provided with this information and told that, listen if you do not get radiation there is a 96% chance you are not going to have a recurrence and if you do get radiation, then it's a 99% chance. You have to make up your mind, to raise your chances from 96% to 99% do you want to get the radiation, and that is a question that each person needs to decide for themselves but the key issue is that now we have the data, so we can present it to older patients. Foss Do you think that in terms of the eligibility criteria for some of these large national trials that there should be some loosening of the criteria to take into consideration the fact that some of the more frail people do not have the best kidney function and they do not have the best liver function, for instance? Gross Absolutely, I would love to see a new requirement for research proposals that describe the target population in terms of their health status. For instance, say that 20% of women with breast cancer have kidney problems, and 30% have diabetes. I do not know those numbers for sure, but for argument sake, wouldn't it be great if in your research study proposal you had to explain if you are going to exclude people with diabetes or kidney problems and therefore exclude that 30% or 40% of women from the potential to benefit from your research, need to explain why? I think we need to relax the enrolment criteria for research studies. However, there are different types of studies. I 22:41 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3 think it is fine for initial testing of a new potentially toxic therapy if you want to restrict it to patients who we feel are most likely to benefit, but then there is a next step beyond that. What we need to is to then say okay it worked in the young healthy patients, now let's try

it in other patients where we are not sure if they are going tolerate the treatment? Foss Can you talk a little bit about some of the ethical issues that come up in terms of dealing with older patient in clinical trials? For instance, there might be some ethical issues in terms of whether or not a physician even presents a trial to a patient. Gross That is the first thing I was going to say actually. The first ethical issue I would say is that we need to include these patients in our studies if we are treating them and it is not ethical to continue to try to make decisions in a vacuum, and we are trying at least to fill that vacuum. Obviously we should not coerce patients and say they have to enroll in a study but all patients should be offered the opportunity to participate in a study. In addition to that, there are a few more ethical concerns. For all patients, but particularly for the older patient, there is this issue of family dynamics of understanding who is making the decisions. Who really wants to be in a research study? Who really wants the aggressive treatment and who does not, and I think it is really important to make sure that when appropriate, the patients themselves are the ones who are steering the car and that they are not being pushed into getting more aggressive therapy or pushed into enrolling in a study by a family member. These family dynamics and issues of control are important for all patients, but particularly for older patients. The third issue relates to the issue of when appropriate the patient should be in the driver's seat. What I meant by that is that it is important to recognize that there are cognitive impairments and there is increased risk of dementia with increasing age, and about 5% of patients in their 60s have dementia. Another 10% to 15% may have mild cognitive impairment, but when you get up into the 80s, more than 10% have dementia and another 20% will have mild cognitive impairment. It is important that we, as treating physicians, assess patients to make sure that they have a capacity to make decisions about their care. Foss In addition to that, there are ways that we can still offer those cognitively impaired patients treatment, we just have to go through decision makers? Gross Absolutely, and to make sure that the people who are charged with making decisions with and for that patient are included in the process. Foss Can you talk a little bit about the whole process of cancer screening for older people? Do you think that there are also biases in terms of whether or not older people are offered cancer screening to the same degree as younger people? Gross I think the bias may actually be towards over screening. There are very few studies that are providing evidence for us about whether screening works. Let me give you an example for mammography, for breast cancer screening. There was recently a very thorough review of the literature and they looked at it as a function of age. The authors complied all of the evidence from 26:22 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3all studies that have been done. They found that for women in their 40s, there were 8 large randomized trials, and they found there is very good evidence that mammography is helpful, but in their 40 it turns out it was only a little bit helpful. In that age group, you had to invite about 2000 women to get a mammogram to save one life and then in their 50s they found

6 studies that looked at the effectiveness of mammography, and in the 60 year old age group, there were only two studies that looked at mammography and it was found to be helpful there, 400 women needed to be offered mammography in order to save one life. But then in the 70s, the authors only found one study looking at the impact of mammography on health outcomes. And actually that study did not find any benefit from mammography because there was only one study to take from. And this review is not to say that we should not do any mammography, but that there is just not enough evidence to make a decision. Against this backdrop of lack of evidence, I think what we tend to do is to continue to offer screening and there are several reasons for this. If you think about our health system the deck is really stacked towards treatment. We have a fee for service systems, so physicians and hospitals are reimbursed when they do more and some people may be concerned about litigation, so there is concern about defensive medicine, so it makes us want to do more. Think about mammography in particular for cancer screening, we are putting out these postal stamps and billboards and all these public service announcements and no one is ever saying, you know, over the age of 75, we do not know if it is really helpful or not, because they may not be. So, there are these messages towards screening. Everything is gearing towards more and more screening and it becomes challenging when you are considering the older patient who might not benefit to try to reach a decision or have that conversation about why some might not benefit. Because the idea is the impact of screening takes years to begin to accrue. Again using mammography as an example, if you get a mammogram today and then again a year from now, the benefit of mammography really does not begin for five years and the reason for that is because mammography helps patients by diagnosing their early stage, very-very early stage cancers. Those are the tumors that will be removed and will result in a decrease in your risk of mortality. If you have a mammogram and find a metastatic cancer, the mammogram probably did not help you nearly as much. Given the fact that there is a 5 year lag time between starting cancer screening intervention and even beginning to get some benefit, as people age and their life expectancy becomes shorter it is important to consider that the benefits will decrease with time. Foss Are there clinical trials or other areas of research in this area that we should know about? Gross There are a couple really interesting developments. One is comparative effectiveness research and that is something that has been pretty politicized and is kind of a hot button issue, but the idea behind high comparative effectiveness research to compare existing treatments in the population in the real world, and this is especially pertinent to the older patient. In The American Recovery and Reinvestment Act that was passed a couple of years ago there were 1.1 billion dollars devoted for this comparative effectiveness research to help us understand which treatments are better. Now, if you compare that to the fact that we have 800 billion dollars being spent on healthcare, it is still a 30:32 into mp3 file http://medicine.yale.edu/cancer/podcasts/2011_0807_YCC_Answers_-_Dr_Gross.mp3 drop in the bucket, but it is a great step in the right direction toward helping us to decide what is the best way to treat our patients in the

community. Dr. Cary Gross is Associate Professor of General Medicine and Associate Director of the Robert Wood Johnson Clinical Scholars Program at Yale School of Medicine. If you have questions or would like to share your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.