

I am Bruce Barber and this is WNPR Health Forum, your information source for health news you can use. The health forum is a part of connecting our communities. Connecticut Public Broadcasting's initiative is designed to create and broadcast a rich stream of community based programs in dealing with civic engagement, lifelong learning, health education, diversity, the economy and the environment. Production funding is provided in part by Yale Cancer Center. This week on Yale Cancer Center Answers Drs. Ed Chu and Ken Miller interview Dr. Gary Friedlaender, Chairmen of the Orthopedic Department at Yale, about bone metastasis.

Miller Gary let me start out with a very basic question. We think of bone as being sort of static and not doing much, what is the real truth about that?

Friedlaender Bone is very much alive. It is constantly turning over. Some of it is being removed and then it is being replaced again. That is true as you are sitting there, and if you listen real closely to Ed you might hear his bone turning over. This is organized by a group of cells; some make bone and some take it away. They talk to each other with molecules and cytokines and this same system is in place when bone breaks and fractures and needs to heal, or when we use bone grafts and need to incorporate them. Bone is very much a dynamic tissue, which is a very important factor when you consider metastatic disease to bone and how it happens and how to treat it.

What makes cancer as special and dangerous as it is, is its ability to spread, which is metastatic disease. Cancer has two parts to it. One is where it begins and the other is its potential to be anywhere else in the body and that is why it takes a team approach. That is why we get together on a daily basis with our colleagues in radiation oncology, pathology, diagnostic imaging as well as medical oncology to take care of both parts of this disorder. Even when you cannot see it, we know that there is a potential for a cancer to spread. Getting back to the definition of metastatic disease to bone, you can either have a tumor that starts in the bone, which we call primary tumors of bone, osteosarcoma being the classic prototype, or this large group of cancers that has the ability to spread to bone, which is metastatic disease to bone. They start in other locations such as the prostate, breast, lung, thyroid or kidney and come to bone. Many people are in the habit of referring to those metastases as bone cancer.

Miller They really are different.

Friedlaender They are very much different.

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- Chu What has always been fascinating to me is that there seem to be certain types of cancer, as you mentioned breast cancer, prostate cancer, multiple myeloma for instance, which is a hematologic malignancy, that seem to hone in on the bone as their sites of metastatic disease. Do we have any sense of how that happens?
- Friedlaender There are two general theories about metastatic disease. One is that it is random or mechanically filtered out; the tumor cells get into the blood stream, and they are then filtered out by the huge systems in the body that serve that purpose, the lung and the liver being high on the list. The other theory is that there are eight characteristics of certain organ systems that either encourage metastasis or discourage metastasis. If you take, in a laboratory situation, a mouse, and you put the tumor that spreads widely in this mouse, you will find it in the lungs, in the bone, in the brain. If you take the tumor that spread to the brain and reinject it into another volunteer mouse, it will preferentially often go to the brain. There are some characteristics about tumors that hone in on different systems and the receptivity of certain systems. The spleen is an interesting organ. It is highly vascular, yet there are very, very few metastases. The answer is just not as simple as a filter, and it probably is not as simple as the biology of the honing system, and that is why people like you spend a good deal of time in the laboratory sorting this out.
- Miller Gary, in your practice of oncology, are primary bone tumors more common than metastatic cancers of the bone, and if metastatic ones are, what are the most common types of tumor that you see?
- Friedlaender By far the most common malignant tumor in a bone is metastatic cancer. I tell my students they have to read the question on the exam very carefully. If it is asked of you what the most common primary tumor of bone is, if it is written by an orthopedist, it is osteosarcoma, if it is written by one of you, you probably consider multiple myeloma, which is much more common than osteosarcoma, but we consider the disorder disease of the marrow cells, not specifically the bone. But if the question is what is the most common malignant tumor in bone, metastatic tumors are far and away the more common, 100 times more common. It can come from breast, prostate, kidney or thyroid. Thyroid and renal are notorious for being what are called silent primaries, that is, you find the metastatic disease because it is causing

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pain before you actually realize there is something growing in your kidney or your thyroid.

- Chu Are there any specific bony areas within the body, the arms, the legs, the spine, that seem to be at increased risk for metastatic spread?
- Friedlaender The spine is a very common site for metastatic disease, but in fact, the entire skeleton is at risk.
- Miller What symptoms would a patient have?
- Friedlaender Pain, primarily because metastatic disease removes normal bone and makes the bone weaker so sometimes you are in pain because the weakened bone is about to break. Sometimes you are in even more pain because the bone does indeed fracture, but pain is the primary presenting symptom.
- Chu What would you suggest for our listeners out there who may have a diagnosis of cancer and then present with a discomfort or pain, say in the long bones of the arms for instance. What should they then do?
- Friedlaender Well pain or discomfort is a part of daily living and the mere fact that you have discomfort does not mean that you have metastatic disease. On the other hand, I always encourage my patients, as I am sure you do, that when they have a concern or worry to check with their care providers because there are relatively easy ways to clarify what is going on and eliminate this fear or concern. If in fact there is a problem, it is better to know about it early.
- Miller There are many studies now that people can have done. There are x-rays, CAT scans, PET scans, MRIs, how do you approach this situation in terms of making the diagnosis?
- Friedlaender There are some studies that are superb as surveys and bone scanning has been around for a long time and it is outstandingly capable of detecting many bone changes. Bone scans are thermometers. They go up and down, they light up or they don't for a wide variety of reasons. It tells us where but not why. It will light up with a fracture, and with arthritis. It will light up with some benign tumors, as well as with malignant tumors and infection, but it is very helpful as a baseline to sort out the health of the skeleton in

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terms of malignancy. PET scanning is becoming much more helpful and many times it is an appropriate test. Let me also add that the pain that comes from skeletal metastasis, skeletal tumors, is sometimes subtly different from other pains in that it may or may not be activity related; it is common, especially at night when you are not active. It tends to be an aching pain. The bottom line is that when somebody has cancer, part of their care is this notion of making sure we understand where that cancer is at any point in time and helping this patient sort that out.

Chu How about if a patient does not have a preexisting history of cancer. Does one go through the same kind of check list in terms of what the possibilities are?

Friedlaender It is different, and in fairness, we have to be responsive to people's anxieties and concerns. We have to use the healthcare system wisely. We spend a lot of money on healthcare and I am not ashamed of that. I think, perhaps, we could do it a little better but as part of our assistance to the public and our patients, when somebody has pain and they come to a physician, we are obligated to listen to them and examine them, and when necessary image them and provide them with the feedback they are seeking.

Miller As you were talking, I was thinking to myself that we were all taught at medical school that the history is the primary thing along with a physical exam and then imaging studies are next.

Friedlaender That is correct, and then a biopsy becomes number four on our list, but there is nothing like talking to a patient, which is where it all begins. I often tell my house staff not to trust anyone, and then tell them that I am always right. I do not mean it in a pejorative way, but from time to time patients do not understand what has happened to them in the past, that their fibroid was really a fibrosarcoma, or a more aggressive tumor, and somehow they did not hear it, or were not told in terms that they understood. So we have to be a little bit skeptical and be advocates for our patients as well.

Miller We would like to remind you to email you questions to us at canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about bone metastasis with Dr. Gary Friedlaender from the Yale Cancer Center.

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Medical Minute

It is estimated that over the two million men in the US are currently living with prostate cancer. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of this disease have dramatically decreased the number of men who die from prostate cancer. Screening can be performed quickly and easily in a physician's office using two simple tests, a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for prostate cancer. The patients enrolled in these trials are given access to experimental medicines not yet approved by the Food and Drug Administration. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut public radio.

Miller

We are with Dr. Gary Friedlaender who is the Director of Orthopedic Surgery and the Chairman at Yale. We have been talking about cancers that spread to the bone. When a patient is diagnosed with a metastatic cancer, let's say it went from the breast to the bone, how do you treat that problem?

Friedlaender

After identifying that somebody does have a cancer in the bone, we want to protect the bone from breaking and relieve their pain; we want to make them healthier in general. Some other things that go along with metastatic disease are anemias, rises in calcium and poor nutrition, but let me focus on the bone, and we have some choices. First of all chemotherapy affects not only the primary tumor but it affects the tumor when it spreads, or as its spreading to bone, which is really the mainstay of treatment for metastatic disease in many ways. We can eradicate tumors. Eradication is like surgery. We point it at a specific location and it is very effective in slowing down the growth of cancer and the pain associated with it, but there may come a point when the hole in the bone is weakening to the point that it might break. It is much better to fix the bone before it breaks than after it breaks because this involves metals, screws, plates and rods. Sometimes it is even better to remove that portion of the bone rather than just fix it and replace it with metals, plastics, and things of that sort. The ideal prophylactic intervention is to interfere with the tumor cell from getting from its primary location to the bone. That is a fascinating process and is wide open to different treatments.

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- Miller I am glad you brought it up, I am wondering what some of the latest advances are and how we might be able to prevent that from occurring.
- Friedlaender Let me describe what is called the metastatic cascade. You have a tumor cell in the breast or the prostate, in order to get somewhere else it has to break away from the tumor mass and move through other normal tissues, find a blood vessel or a lymphatic and attach to the outside of that vessel, make a whole in the vessel, wiggle inside, swim downstream to another point, get out of the blood vessel and work its way into this other normal tissue, in this case bone, and in bone it has to first dissolve away some of the calcium to make room for itself to grow. Every step of the way, this cell is actively working. It has to either produce enzymes, have the motility, or some other factors that allow it go from A to B to C to D, and in each of those situations there is an opportunity to frustrate it. Let's start where it ends, in the bone. We found that the drugs we use for osteoporosis to prevent the resorption of bone make it harder for bone metastasis to make room for itself. So we are treating patients with bisphosphonates, anti-resorptive drugs, with good results. It is not perfect and is not the whole answer, but that is one example. I mentioned that these bone cells communicate with each other through cytokines and we now use drugs and antibodies to these cytokines, or to the receptors on the cells, that turn them on and say do this or do that. There are a wide variety of antibodies, or analogs drugs, that compete with normal proteins and frustrate the metastatic cascade. If you can keep the tumor from spreading you reduce it to a chronic disease rather than a disease that is going to ravage the rest of the body.
- Chu In the world that Ken and I live, where we treat for instance, breast cancer, prostate cancer and multiple myeloma, there are in fact two drugs of the class that you just mentioned, bisphosphonate. One drug is called Zometa and the other is called Aredia. Both of those are approved to try to prevent the metastatic spread to bone for each of those different diseases.
- Friedlaender Absolutely, and again this is a reflexion of the teamwork that goes on in cancer care and I enjoy my opportunities to work with the team.
- Miller Have you found in the last few years that with the use of those drugs you are seeing fewer patients with pain problems for metastasis, or less fractures. Has it had an impact?

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Friedlaender Personally, I seem a bit busier.

Miller Okay.

Friedlaender I think that comes with age, but if you think nationally there is no question that the incidence of bone metastasis has been reduced by the use of those drugs and it has been shown several times.

Chu What is also interesting, as we are getting better in terms of treatment of various cancers, the treatment seems to eliminate the common metastatic spread, but we are seeing an increase in the incidence of bone metastasis. I know in my own area of colorectal cancer where we have developed some pretty effective treatments so that we're preventing metastatic spread to the liver and the lungs, which as you say may be the filters, I would say over the last two or three years I have seen a lot more patients who are presenting with metastatic disease from their colon to bone, it is quite fascinating.

Friedlaender As you are helping people live longer with their primary cancers, it is giving them further opportunities to metastasize. We are seeing tumors that traditionally had a very dismal survival rate now much improved, but with that improvement comes the opportunity for metastatic disease.

Miller I would like to talk about symptoms, in particular about pain, what are some options for treating patients who have bone pain?

Friedlaender Patients deserve relief from pain, and I think sometimes physicians do not fully accept their responsibilities, but with pain management specialists and anesthesiologist, physical medicine and rehabilitation, sub-specialties in addition to the medical oncologist, it is superb. If I had to pick a group that really has been excellent in pain management medical oncologists would be well at the top of the list. There are drugs that treat pain, but it is also helpful to try to change the reason that you are having pain, not just treat the symptom. That is where I have an opportunity, and the combinations of radiation to slow down growth, the opportunity to fix a bone that is bending and partially breaking, to keep pain from happening by fixing the bone is really a wonderful opportunity. It is the dignity and the ability for these patients to go on with their life.

Chu Before the show we were talking about this upcoming program that I

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received a flier for; it is called Pain Management through Music Therapy. It is a CME accredited program that is going to be held here on the Yale campus Saturday, October 20. I was just curious what your thoughts are with respect to using music therapy or art therapy as adjuncts for pain management.

Friedlaender Absolutely, as you know it's hard to predict how much pain a person has and it varies. One person will tell you on a 10 point scale their pain is an 11 and another will tell you 3 even though they appear to have exactly the same problem. I never tell a person they do not have pain. It is our obligation to listen and to be flexible and open about other modalities that might help. A portion of pain is biologic, pharmacologic, physiologic, and a portion of it is intellectual and there are things that clearly help. Reducing stress has been shown a number of times to increase the speed at which an incision heals, and probably other diseases and disorders. Relaxation through music, art or through other therapies such as acupuncture and herbal supplements can help. Bottom line, if it hurts and I can make a person feel better without injuring them I am in favor of those kinds of approaches.

Miller In terms of some new advances, let's talk about radiopharmaceuticals. What are those?

Friedlaender I believe you are referring to the targeted molecules. We know that certain compounds will hone in on certain structures. Bone is actually a crystal and there are elements like strontium that will go into the crystal structure of bone. There are also antibodies that will seek out certain cells and proteins on the surface and if you couple with these delivery molecules, something that will affect the tumor, you have a radiopharmaceutical. I do not know if you are talking about the radiation therapy sensitizers, that would be another group of compounds, but basically there is an opportunity to take a molecule that goes somewhere predictably and attach it to another compound, that will affect the cancer in a positive way.

Miller I have seen some of the amazing things that you and your department have done in terms of replacing joints and replacing parts of limbs, can you tell the listeners a little bit about some of the things that are possible now in terms of joint replacement and replacing some of the long bones.

Friedlaender Absolutely. For the last 10 to 20 years there has been a growing trend for

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what we call limb-preserving procedures. When I started taking care of patients with osteosarcoma, 35 something years ago, we used to argue about how high up on the body part to amputate. If the tumor is in the knee, should we go through the hip, should we go through the middle of the thigh, and the survival rate was dismal. Then my medical oncology colleagues came along with multidrug chemotherapy. We learned that we were treating the other part of cancer, metastatic disease, and that freed us to do more limited operations; to take out parts of the thigh bone, take out parts of the muscles and preserve the rest to the limb, which was very gratifying. Then the challenge was, how do you put things back together? Sometimes, as with the biologic use of bone grafts, tissues donated by thoughtful people when they pass away, bone is also something that can be donated, or we turn to the metals and plastics of our space age.

Miller A lot of us in medical oncology enjoy that kind of collaboration using preoperative therapy, trying to shrink tumors and then with the wonderful things that your group can do, I think life has gotten lot easier for people that are facing cancer.

Friedlaender It is very, very gratifying and again, I cannot stress enough the team approach that really makes this work.

Miller I want to thank Dr. Gary Friedlaender for joining us at the Yale Cancer Center Answers.

Friedlaender Thank you very much. I have enjoyed it as well.

Chu Gary, this has been great and we look forward to having you on our future show. Until next week, this is Dr. Ed Chu and Dr. Ken Miller from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments or you would like to subscribe to our Podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcast in written form. Next week, we will spend some time with the doctors that host Yale Cancer Center Answers, Ed Chu and Ken Miller.