

Yale CANCER
CENTER
answers

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Hosts

Edward Chu MD

Chief of Medical Oncology

Francine Foss MD

Professor of Medical Oncology

Understanding Cancer Metastases

Guest Expert:

Gary Friedlaender, MD

*Wayne O. Southwick Professor of
Orthopaedics*

Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Dr. Ed Chu, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and is an internationally recognized expert on colorectal cancer. If you would like to join the discussion, you can contact Dr. Chu directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed is joined by Dr. Gary Friedlaender. Dr. Friedlaender is the Chair and Wayne O. Southwick Professor of Orthopedics at Yale School of Medicine.

Chu Our topic for this evening's discussion is metastatic cancer, specifically the spread of cancer to the bone. Gary, can you tell us a little bit about metastatic bone cancer? Why is it that cancer seems to like to head to bone?

Friedlaender I would be delighted. First of all the difference between a benign tumor and a malignant tumor is its ability to spread to other parts of the body. Sometimes it is close, sometimes it is far, sometimes it is to bone, and sometimes it targets organs. I am an orthopedic surgeon and I spent a little extra time learning about musculoskeletal oncology from a surgical point of view, and the most common malignant tumor to bone is metastatic, that is it came from somewhere else, and did not start in the skeleton.

Chu What are the types of cancers that typically spread to bone?

Friedlaender Virtually any cancer can spread to bone or to the musculoskeletal system, but some are far more common; prostate, breast, and lung are among the most common. There are two others that are worthy of mention, and those are thyroid and kidney cancers.

Chu That is interesting. I know in my own disease, colorectal cancer, that for a long time we did not see it spread to the bone, but as we are now getting better with treatments, interestingly enough, we are seeing more and more patients present with bone metastasis as opposed to metastasis to liver and the lung.

Friedlaender I think you are absolutely right. We have the good fortune of helping people live longer and in many cases be cured of their disease, but some of those that live longer will develop metastatic disease to the skeleton.

Chu Why is it that these various cancers like to home in on the bone?

Friedlaender I wish I had a succinct answer to that, and if you give me a little time maybe you, I, and some of our colleagues will have a better answer the next time around. But there clearly are tissues in the body that are more likely to host cancer, host metastatic disease, and bone is amongst them. There seems to be two general reasons, one is mechanical and one is

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biologic. With mechanical, I am referring to the filter system. There is a very interesting process called the metastatic cascade, how a tumor cell in one place gets to a place elsewhere in the body. But for a moment just think about that tumor cell being in the circulation, in the blood supply, and moving around the body, mechanically it may get filtered out, filtered out by one of two major organs; the lungs and the liver. Those two sites are very common for metastatic disease, and it may be purely a mechanical issue. The other is biologic, and there appears to be some tissues or organs that are receptive to spreading and some that are particularly unreceptive to spreading aside from their rich blood supply. Bone has a very rich blood supply, and I think it is a combination of being another filter and having so much blood flow, but there are organs like the spleen that have enormous blood flow, or the heart which has enormous blood flow. They are not immune from metastatic disease, but they are much less common sites of metastatic disease. So there is the mechanical filter system and there is the fertile soil concept.

Chu Are there any underlying risk factors on the patient's part that could predispose them, place them at higher risk for developing bone metastasis?

Friedlaender The simple answer is that it is not their fault. I commonly reassure people that it is not anything they think they did, or did not do, that caused their cancer in the first place, or caused it to spread. The main risk factor for metastatic disease is having a primary tumor. It is important to think of cancer, if you will, as having two components, one is where the tumor starts which we call the primary, the place it originates, and the second phase of cancer is everywhere else in the body. That is why you and I are team, we need to treat where cancer starts and we need to predict and treat where cancer may go.

Chu And I guess that is why we like to think of cancer as a systemic disease, even though it might be localized to an area initially. But the problem is, as you said, those cancer cells are pretty nifty and they find a way to spread throughout the body.

Friedlaender Absolutely.

Chu Are there are any bones in the body, Gary, which may be at higher risk for those tumor cells to spread?

Friedlaender It really boils down to the size of the bone. The long bones of the body are particularly prone to disease, but ribs are a very common site of metastatic disease. The spine, where the individual bones are a little smaller perhaps, are also a very common site because they have a very rich blood supply.

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- Chu What would be the common symptoms that one should look out for?
- Friedlaender The primary symptom is pain. As tumors grow they sometimes cause a bump, or a lump, something noticeable, but primarily it is pain. Occasionally, one of the early signs of metastatic disease to the skeleton is a fracture. The tumor itself weakens bone by removing normal strong bone making it weaker and it breaks.
- Chu As we age we all experience aches and pains and backaches, so when should someone who has some of these symptoms begin to think maybe it is something more serious and seek medical attention?
- Friedlaender A very important point, and I have the privilege of talking about metastatic disease to the skeleton to students on a regular basis, and I always come to a pause when we talk about lower back pain. I have got back pain, actually I have a little bit right now, and three out of four Americans have significant lower back pain. Almost all the time this is degenerative, or a strain, or sprain, totally devoid of the tumor issue, but every once in a while somebody has multiple myeloma, or somebody has some malignant process that is involving the skeleton causing lower back pain. Sorting out the everyday, frustrating, painful, incapacitating lower back pain that we see frequently, from something dangerous is very difficult sometimes. It is important that people who have back pain that feels different, or is longer lasting than usual, or does not respond to a little bit of rest or anti-inflammatory medication, seek medical attention. And then it is a matter of being questioned carefully, examined reasonably, and following those symptoms. When they do not behave the way regular back pain behaves, those individuals need to be evaluated much more thoroughly. You cannot, in our healthcare system, or anyone else's, have an MRI every time you have back pain. I wish it was that simple, but the judicious use of our intellect and our tools should help us find back pain caused by tumors relatively early and then get down to the business of treating them.
- Chu So, if the pain does not resolve immediately with rest, or a little Advil here and there, or Tylenol, who should they see first? Should they see their general internist, should they go to their oncologist, should they seek you out, an orthopedist? Who is the best person to see initially?
- Friedlaender I think all of the above are correct answers, but I certainly think that seeing one's primary care physician initially, the person that really should know you the best, is in an excellent position to help guide you through the rest of the system.
- Chu If in fact an individual sees their primary care physician, what would be some of the tests

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that would be done to try to figure out what is going on?

Friedlaender I am a surgeon, so I am perhaps a little bit more bottom line about it, and there are lots and lots of tests one can do to prove if a person is healthy or not, but in the end a plain x-ray of the part that hurts, after a careful history and physical examination, will answer most of the questions. We do have some superb tools to look more critically as the challenges and the mysteries deepen.

Chu If x-ray or a CAT scan shows something suspicious in one of the bones, is there ever any role for a biopsy to see what is going on?

Friedlaender Absolutely. One of the highlights of my day in the office is telling people they do not have anything wrong. As we use some of our tests for other purposes, our CAT scans, MRIs, PET scans, or bone scans, looking for other disorders and diseases, we stumble upon changes that are sometimes hard to clarify. At centers that are used to seeing unusual things, such as ours that has a team approach that allows us to make good judgments, we do windup seeing people who have questions on other tests and just by looking at these tests we can determine they are harmless, but when they are still in question, a biopsy is a very important tool. Biopsies can be done in two general ways. One is with a needle and Novocain, we have got lots of Novocain, and we have some superb pathologists that are used to looking at very, very small pieces of tissue. Over 90% of the time we can help an individual know if they have something serious or not. The other option is in the operating room, making a small incision and getting more samples to look at.

Chu People have heard about this term called the bone scan, which is commonly used to try to figure out for someone who has cancer if it has spread to the bone, can you tell us what a bone scan is and what it does?

Friedlaender A bone scan is a very important tool. It needs to be used for the right reasons in the right places, but simply put, and I apologize I am not used to simple answers, or at least short answers, but a bone scan involves the injection of a radiopharmaceutical, a compound that has two characteristics. One is it emits a little bit of radiation so you can see it on a scan, and the second is it homes in to bone. It finds bone that is particularly active. A bone scan is a thermometer, it goes up and down, but it does not tell you why, it tells you where. So a bone scan shows positive, if you will, or we sometimes use the word hot, a hot spot, if it's infected, if its broken, sometimes it has a benign tumor or a malignant tumor, anything that makes the bone irritated or more active makes the bone scan positive.

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Chu You are listening to Yale Cancer Center Answers. We are here this evening discussing options and approaches for treating patients with metastatic bone cancer, and our guest is Dr. Gary Friedlandaer from Yale Cancer Center.

Medical Minute

Here in Connecticut the American Cancer Society estimates that almost a thousand people will be diagnosed with colorectal cancer every month. The good news is that when you are detected early colorectal cancer is easily treated and highly curable. That means that if you are over the age of 50 you should have regular colonoscopies to screen for this disease. In the case of patients that develop colorectal cancer, there are more options than ever before thanks to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. Patients enrolled in these trails are given access to 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.

Chu Welcome back to Yale Cancer Center Answers, this is Dr. Ed Chu and I am here in the studio this evening with Dr. Gary Friedlandaer, Chairman of the Department of Orthopedics at the Yale School of Medicine. Gary, before the break we were talking a lot about why bone is so predisposed for developing metastasis from primary cancers. When you were talking earlier you had mentioned this metastatic cascade, can you tell us a little bit more about what that means?

Friedlaender It is a fascinating sequence of events that begins with the fact that there is a massive tumor cell somewhere growing. Cells have to break away from the primary tumor and move through tissue, which is not easy, it involves enzymes that dissolve some of those tissues, find a blood vessel or a lymphatic, attach to the outside of that vessel, drill a hole in that vessel, squeeze a hole in to the blood vessel or lymphatic, swim upstream I guess it would be, and then create another hole in the vessel and then move out and grow. That is the metastatic cascade. It is not a very simple process; it is not an easy process. It requires special cells with special equipment, and those are some of the malignant cells of the primary tumor. If you could interrupt any one of those steps, you could prevent metastatic disease and you would turn cancer into a chronic disorder instead of a progressive disease.

Chu By understanding that metastatic cascade process, are there ways to try, as you said, to interrupt the ability of the tumor to spread specifically to bone?

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- Friedlaender Yes, and there is a lot of work going on at Yale, and many other institutions, but perhaps the endpoint has received the most attention. In order to grow in bone, you need to make room for yourself and you need to dissolve bone. If you do not dissolve away bone, you have no place to grow, so one of the effective adjuncts to treatment are antiresorptive agents, the same kinds of drugs were use to treat osteoporosis, to make it difficult for tumor cells to dissolve bone. These antiresorptive drugs are being used regularly and they do decrease the incidence and severity of metastatic disease to bone. They are called bisphosphonates.
- Chu And two of the ones that have been widely used are Zometa and Aredia. What is fascinating, it is amazing what research tells us, but there is now recent evidence to suggest that these bisphosphonates have direct effects on the tumors themselves, and can sort of kill those tumor cells in addition to having effects on the bone.
- Friedlaender That is correct. Breast cancer comes to mind in particular, and multiple myeloma is certainly another disease where these drugs have been used extensively. Not only the incidence of bone metastasis goes down, but the incidence of spread to other organs goes down as well.
- Chu Is there ever any role for surgery in patients who develop bone metastasis?
- Friedlaender Yes. By removing normal bone it makes the bone weaker and more susceptible to fracture. It is important sometimes to recognize that a bone has a high likelihood of breaking, fix it before it breaks, if you will, and put a pin in it to do something that will reduce the likelihood of it breaking. Radiation therapy is another excellent way for certain metastatic disease to the bone to be controlled in terms of pain and its progression and to stop the weakening before it gets to the danger point.
- Chu What you are saying is it really takes a team effort of surgeons, orthopedic surgeons like yourself, radiation oncologists, and medical oncologists, to work together to try to come up with a game plan for patients who have metastatic bone involvement.
- Friedlaender It is absolutely critical. I am an optimist, you and our colleagues have found ways to cure, literally cure, many people of their malignancies and there is more to come, but those that wind up with widespread metastatic disease are generally ill in important ways that require a team approach. They are anemic from their chemotherapy, or from the replacement of their marrow with tumor, they do not breathe as well because they have tumor in their lungs, they do not clot appropriately, they have more vein blood clot disease, their nutrition is poor, and their calcium metabolism is affected. These patients are sick and they require

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a team approach in order to make their journey through the operating room more efficient and effective. The reason we want to operate on them in those cases is to relieve their pain, and they are entitled to pain relief. We want to preserve their function or improve their function so that they can walk, or so that their spine disease does not cause loss of nerve functions. We want to restore some dignity to their lives so they can be more self-sufficient; that is a team approach to a very individual problem.

Chu Is there any role for using radioisotopes in terms of treating patients who have say, widespread disease?

Friedlaender Again the simple answer is yes, and decades ago one of the very common ways of trying to treat bone cancer was with an isotope called strontium. This is a radioactive material that preferentially goes to bone, and the radiation part of the molecule destroys the cells around it. It did not work out well then, but the concept has come back because it is a very useful approach. You find a molecule that finds its way to your target, be it the bone or the tumor or both, and you attach to it something that either has radiation effects or pharmaceutical effects, drug effects, which can be delivered locally; it is like the milkman going to your house. It is finding the right address and delivering the right pharmaceutical to help fight the cancer, and there are many new approaches that are very promising in that regard, both for treatment and for diagnosis. The PET scan, for example, involves these kinds of molecules that find particularly active groups of cells and help us understand where the problem is, so we can better deliver our treatments to those areas.

Chu It is interesting, over the last 5 to 8 years we have been developing these new novel targeted therapies for colon cancer, lung cancer, and breast cancer, and it sounds like a similar type of targeted approach has also been developed for metastatic disease, metastatic bone disease.

Friedlaender Correct.

Chu Gary, you and your group at Yale School of Medicine have been very actively involved in research. Can you tell us a little bit about what is going on at Yale?

Friedlaender Yale, like many of our colleague academic medical centers, is very interested in cancer. As you know, we have a new hospital opening that is going to focus a lot of attention; the Smilow Cancer Hospital. This is going to help bring together the different members of the team and increase efficiency and make it more effective, and that is about to happen shortly. We have scientist who are interested in how bone is made and how bone repairs itself because when you understand what happens normally, you have a better chance of

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understanding the consequences of what went wrong when it has cancer in it, and how to help it repair itself. At Yale our primary focus is understanding bone in general, and the cells that make bone. For example, if you are going to remove bone to make room for yourself as a cancer, there are special groups of cells that do that called osteoclasts, and we are looking at how osteoclasts are formed normally, how they are turned on, and how they are turned off. If we can selectively turn them off, we can improve bone mass, we can change the course of osteoporosis, and we can change the course of metastatic disease to bone. There are other opportunities as well, in our parlance, to up-regulate or down-regulate these special cell populations that remove bone or make bone.

Chu It is interesting because a number of tumor types, breast cancer and multiple myeloma in particular, seem to have the ability to up-regulate the number of these osteoclasts that work to breakdown bones. Obviously, if you could figure out how to turn that process off, that might be a very effective way to develop new therapies.

Friedlaender That is right. Some of our tools look like hammers and screwdrivers and others of our tools are molecules. We are learning how to combine all of these opportunities to the best advantage of our patients. We are much more able to remove parts of the skeleton and replace them with functional parts. Sometimes those are donated bones from other generous individuals; sometimes those are metals and plastics.

Chu One of the things that just dawned on me, Gary, that we did not touch upon, is general recommendations for medicines that can help relieve pain that results from metastatic bone involvement. Could you just quickly tell us a little bit about what is going on in that field?

Friedlaender I would be glad to. Pain relief is a right. When we can safely accomplish it, patients deserve to address their pain in any way we can. As I said, sometimes it is radiation, sometimes it is surgery, but very often it is medicine. A lot of pain comes from inflammation and some of the simple anti-inflammatory agents are remarkably helpful in dealing with this type of pain and should not be overlooked; then there are other narcotic medications. When used correctly, this group of drugs is appropriate and important.

Chu Any last minute words of advice to our listeners out there about metastatic bone disease?

Friedlaender It is a fact of malignant life that many people who have malignancies will suffer some of these consequences. There are increasing opportunities to interrupt the metastatic cascade and I do think there is a light at the end of that tunnel. Until we get there, there are teams of people at places like Yale that are prepared to help individuals successfully deal with their diseases and disorders in a compassionate and effective manner.

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Chu On that note, I would like to thank you Gary for joining me this evening on the show. You have been listening to Yale Cancer Center Answers. Until next time, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.