CANCER SURVIVORS
SYMPOSIA SERIES
Issues & Solutions for Life After Cancer

Living With "Survival":
Long-Term Effects of Cancer and Its Treatment

March 19, 2007

Late Effects of Radiation Therapy

Mitchell S. Anscher, M.D.

Dr. Anscher is Chairman of the Department of Radiation Oncology at VCU Medical Center.

Thank you very much. It's a great pleasure to be here tonight to talk about something that – radiation oncologists always get blamed for the late effects. Occasionally we see x-ray reports that say "changes consistent with radiation" in patients that have never actually had radiation. But, nonetheless, we do have to take some blame for this. I just want to talk to you a little bit tonight about some of the things that you can expect from radiation and there's a whole new future out there. These things used to be thought to be irreversible, but now as we learn more about what causes them, we're starting to work to develop ways to not only prevent late effects from radiation but also perhaps to treat them.

First, let me make an unpaid plug for the April 2007 issue of *Seminars in Radiation Oncology*, which I'm sure you all read. It's going to be devoted to late normal tissue injury as related to radiation therapy. It's going to be pretty dense reading for the most part, but there probably will be some stuff in there that is of general interest and I'll talk a little bit about volumes of tissue radiated and doses that can be tolerated, and also some of the new treatments that are coming down the road for these complications.

For those of you who have not had radiation, let me start by saying how radiation is given. There are two primary ways that we do it. Most commonly from the outside with a linear accelerator in which a patient is lying on a treatment table and positioned under the beam and the radiation beam comes out here and then is delivered precisely to the patient or, alternatively, in certain situations where the radiation source is actually placed inside an organ and inside a tumor, and radiation dose can be delivered directly in that manner. Typically, if it's external it's usually daily over several weeks and if it's internal it's usually either single-fraction of delivered over a much shorter period of time.

How do we determine radiation doses. A lot of it is empirical. It's based on past experience and reviews of what people have done over many years. But it's pretty clear from these experiences that humans are very sensitive to radiation, and that also this can vary from one person to another. We've all heard a lot about radiating food to sterilize it from bacteria. It takes about 100,000 rad, which is a unit of measuring radiation dose, to kill one bacteria. It takes about 1,000 rad or less as a lethal dose for a person. We have to obviously be aware of that and take that into consideration when we're trying to deliver radiation therapy. Normal organs are the things that limit the dose of radiation that can be safely given. Some organs are more sensitive than others – testicles, ovaries, kidney, lung and salivary glands are particularly sensitive – and others like muscles, bones and nerves are more resistant. As I'll show you, the normal organs can't be completely avoided, no matter what approach we use. No matter what type of high tech piece of equipment, there is always going to be some normal tissue that gets radiation.

This is an example of what a radiation dose distribution would look like. This is a chest. If you took me, facing you, and peeled the front of me off, this is what I would look like, this would be a lung, this would be my spine right here and, hopefully not, but a tumor sitting in the other lung. But in the area right here in red, what we would try to do when we're treating this particular individual would be to deliver this high dose right in here to the tumor. But in order to do that we may have another area of tumor, here, which also needs to have a high dose. By virtue of doing that, there is some dose that we end up delivering to these other areas, shown in blue, which is a relatively lower dose. You can see that in this other section here, where you see tumor, here's your heart, here's the lung, and you can see that the highest dose is concentrated around the tumor. But some of these other areas will, of necessity, be treated in order to be able to concentrate this high dose of radiation around the tumor.

How do we try to protect these normal tissues? We design a customized treatment approach for each patient. The technology to be able to do this is really evolving rapidly and this is really a major focus of research effort in our department at VCU. But, in essence, what we'll do is try to block out areas that don't need treatment and to limit the radiation dose as much as possible in those blue areas to try to avoid the normal tissues as best we can. There are some drugs that are available on the market that will actually help to protect normal tissues and at the same time not protect the tumors from radiation, which obviously is an important issue.

What are the types of side effects that you can anticipate from radiation therapy? The early side effects, or the acute side effects, these are the ones that develop during treatment and are more common and generally resolve within three months or so after treatment has been stopped. The late effects, which are the ones that everybody worries about, these typically will develop more than three months after the treatment has ended. The problem with these is that they may or may not go away. Then there is a third category, which is consequential

effects. These are basically late effects that develop as a consequence of early effects and, again, because they're late, they may or may not resolve.

What are late effects? They occur in organs that were exposed to radiation. Radiation is different from chemotherapy. Chemotherapy are drugs that go all over the body. Radiation is a targeted local therapy that really goes just where we aim it. If I have to radiate a tumor in your leg, it will affect your leg but it's not going to affect your brain. Usually what you'll see with late effects is a loss of the normal function in the exposed area, and that's usually due to two things. One is a build-up of scar tissue. The other is death of the stem cells that are important in the function of that particular organ. These stem cells are different from what Dr. McCarthy had to referred to as bone marrow stem cells, but every organ has its own stem cells that are important in its normal function. It usually does not affect unexposed areas. Every once in awhile people can have unusual reactions where you can, for example, treat one lung and develop an inflammatory response in the other lung, but that's pretty rare. It's generally confined to the area that you radiate. As I mentioned before, these were once felt to be permanent and irreversible, but now we're really questioning that assumption and a lot of work is being done to try and develop agents that can actually reverse the effects of radiation.

How common are these problems? Fortunately, most severe late effects are rare. Probably the major exception to that is the dry mouth that patients with head and neck cancers will develop if they have to have their salivary glands irradiated, but for the most part others are fairly uncommon. For milder late effects, it depends on how hard you look for them. I'm not really making a joke, for years and years people really didn't want to look very hard for late effects, and also in the earlier years of cancer treatment we weren't very successful and most patients didn't live long enough to develop them. But as we're getting better at delivering these treatments, as more folks are living longer and being cured of their diseases, we're starting to get a better handle for exactly how frequently these problems develop.

Let me give you an example. If we take the whole world of patients who get radiation to the lungs for whatever reason, for lung cancer, esophageal cancer, breast cancer. About 5-20% would develop some symptoms, most commonly cough, as a result of the scar tissue that develops. But if you get a chest x-ray or CAT scan you'll see scar tissue in almost all of them if you look hard enough for it. Are late effects without symptoms important? Is that an important problem since it doesn't really cause symptoms or problems for the patients? We'll talk about that in a little bit.

What predisposes people to developing late effects? Mainly things that affect wound healing. I think it's convenient to think of late effects as wound healing run amuck. Normally, if you cut yourself shaving or whatever, you'll heal. You may have minimal or no scarring, but often with cancer treatments the healing process isn't properly regulated, so things that predispose you to abnormal

wound healing may also predispose you to developing late effects. Radiation, in particular, diabetes, high blood pressure, smoking. This is a complex issue. Actually, in people who get treatment to the lungs who smoke actually have a reduced incidence of toxicity to the lungs. In most other organs that's not true. (I guess I can say that in Richmond – but not anywhere else.) Obesity, trauma to irradiated tissues – this can be a real problem. If you've had radiation and you're going to have surgery, if you've had radiation to the mouth and you need to have teeth extracted, be sure that you let your doctor know that you've had this so that they can properly prepare for that situation. There are certain connective tissue diseases like scleroderma or lupus that can predispose people to injury. And some uncommon genetic disease – Fanconi anemia, ataxia telangiectasis, diseases where people don't normally repair DNA damage, can be predisposed to radiation effects. There are other things that we don't fully understand. There are biological processes that we're really just beginning to understand about wound healing and how that's perturbed by radiation that may impact how people respond to it.

Let me give you an example with a disease I see fairly often, prostate cancer. Last year there were over 230,000 men diagnosed with prostate cancer. That makes it the most common cancer in the United States except for skin cancer. Radiation is one of the more commonly utilized treatments. The prostate sits in the low part of the pelvis, so when you're using radiation to that area you have patients that are at risk for injury to the bladder, to the rectum and for erectile dysfunction. How common are these problems? Can they be prevented? Are they treatable?

Incontinence – this is probably the bladder-related problem that most men are concerned about. After radiation true incontinence is rare, less than 5%. Most of the time it's what we call stress incontinence where if you cough or sneeze or lift you might leak a little bit. Interestingly, that's not very much affected by radiation technique and it may respond to medicines that are readily available – some over-the-counter cold medicines actually can help with that.

Rectal injury, which is most commonly bleeding, we see in about 5 to 30% of men. It's very technique dependent. Some of the newer techniques which people call IMRT or IGRT are very good at reducing this closer to the 5% level. And the treatment can depend on the severity.

Erectile dysfunction is the most common problem that we see in men getting radiation. About 30 to 60% will develop it. Most of the time it will respond to some of the drugs that you see on television, like Viagra. That's generally what we would try first if a man develops this problem.

This is an example of radiation-related injury. You can see why bleeding is most common. You see these areas here, which are these abnormal blood vessels that are developing. You get thinning of the lining of the rectum here. These abnormal blood vessels can develop and they can be either mild or much more

severe. In situations where someone may develop constipation, they may stretch out the rectum and actually break these blood vessels and that can manifest as bleeding. Fortunately, it's rarely a severe problem, and rarely requires transfusion. But when people see bleeding coming from where it's not supposed to be coming from that raises a concern, and it should. It should get checked out.

Getting back to the question that I posed earlier – are late effects without symptoms a problem? They teach us a lot. They teach us about the biology, the underlying cause, what's going on in the body that predisposes people to developing these injuries. That allows us to develop more treatments that may prevent or actually improve the effects that people have. But since late effects are rare these are really orphan diseases. There has not been a lot of money spent on research trying to develop new treatments for these diseases. That's starting to change recently, mainly as an after effect of 9/11, if you can believe that. The government is worried about the possibility of dirty bombs and nuclear terrorism. As a result of that there is now some money being spent on the development of treatments that may prevent effects from that type of warfare. But the focus of research really remains on prevention especially with the perceived threat of nuclear terrorism. Few studies have really been done to treat established late injury.

What is out there that works now? One of the things that is actually quite effective is hyperbaric oxygen, or oxygen delivered under high pressure. That is very good at promoting wound healing and improving the circulation to these areas that are not able to heal well. That can often be tried in areas of particularly the skin, in the head and neck area, if side effects develop. Pentoxifylline is an old drug that's been used for years and years for people who develop poor circulation, often related to smoking. That has helped to actually reduced the viscosity or thickness of the blood among other things and allows the blood to deliver oxygen better to the tissues and that, in combination with Vitamin E, has been shown to be effective in scar tissue that develops in the treatment of breast cancer or other soft tissue areas. Steroids have been tried for some of the rectal bleeding issues that have developed. Sometimes they work, sometimes they don't. But they're generally tried because they're easy to use and have relatively low toxicity because they're not given systemically but given topically. Ace inhibitors, or angiotensin-converting enzyme inhibitors, are blood pressure medicines. These are in clinical trials now for reducing kidney toxicity that can develop sometimes in the setting of bone marrow transplantation. Again, sort of a recurring theme that we've been hearing from our other speakers as well, risk reduction, healthy lifestyle, avoid developing conditions that really interfere with wound healing.

There are always new things that are being researched. There is some evidence that the statins, the cholesterol lowering drugs that quite a number of people are taking, may actually work to allow healing to occur after radiation injury. These

drugs are going to be going into clinical trials for this purpose and in Europe they actually already are.

What's the future? Continued improvement in radiation delivery technology. This is a major focus of what we do. Drug therapies for prevention which can be targeted to specific processes or specific molecules that are implicated in these processes, and more general therapies. As I mentioned, one of the statins, lovastatin, is about to go into a clinical trial to prevent rectal injury in the treatment of prostate cancer. And also just as important, targeted therapies for reversing injury, again both targeting the specific molecules that we think are involved in the process and also, something coming down the road may be stem cell replacement therapy or stem cell protective radiation therapy, in which we're actually able to identify areas where the stem cells reside in a particular organ and reduce the dose of radiation to these sites.

So, I think the future is bright, and I thank you very much for your time and your attention.