**Pulmonary Complications from Lung Cancer Treatment, Part 2: Targeted Therapy- and Radiation-Induced Pneumonitis**
by Dr. Gerard Silvestri, Medical University of South Carolina

**Dr. Silvestri:**
So, you would think that as we develop new drugs we get better at making sure that they don’t damage the lungs, and that’s probably the case. But the newer so-called targeted agents, the EGFR tyrosine kinase inhibitors, that epidermal growth factor receptor inhibitors; the one that we use in the United States are Erlotinib (Tarceva), there is an incidence of Tarceva-induced pneumonias. So, Tarceva-induced pneumonitis, and that occurs in about 1% of patients treated in the United States.

Another drug, gefitinib (Iressa), which is not used in the United States but used in Europe and Japan, you can see up to 2% of patients who have this lung interstitial lung disease and hemorrhage. It’s usually seen within the first three months of treatment, and I have seen a fair bit of this.

Bevacizumab, another new drug, monoclonal antibody that binds the receptor in the lung, it’s used for non-small cell, nonsquamous lung cancer. It can cause hemoptysis or coughing up blood for the squamous histology. That’s why we don’t use it with squamous cell carcinoma, though that recommendation might be changing soon.

I mentioned in many of the previous slides that steroids are commonly used to treat chemotherapy-induced pneumonitis. What I’m going to tell you now is that even though we use them there are really no controlled trials; meaning when we see this happen, when we think it’s inflammatorily, we treat with the steroids. But there’s no trial that says that if we didn’t give steroids to half our patients randomly, and we did give it to half our patients, what would be the better outcome.

One of the things that’s important though is steroids dampen the immune system, and that’s what we want when we’re having some of these inflammatory reactions, but you got to make sure that the patients don’t have infections. When you have an infection you want your immune system to work really well. So oftentimes that’s why doctors will maybe want to do a bronchoscopy, that’s where we take a look in the lung and do a wash in the area of the x-ray changes and send that for culture.

So we don’t want to commit someone to steroids to treat an inflammatory drug-induced pneumonia if they in fact have a bacterial pneumonia. So sometimes your doctor will ask you to do that bronchoscopy to make sure there’s no infection before we give you steroids. If we’re going to treat patients we generally give them a Prednisone, 60 mgs a day for two to four weeks and then slowly take it away once the patient gets better.

Now I want to switch gears from drug-induced pneumonitis to radiation therapy induced pneumonia or pneumonitis. This occurs usually between one and three months after radiation, but can occur up to six months after radiation. So it’s not as if you have to have it immediately. But you can have this reaction weeks to months after your last radiation dose.
Radiation fibrosis, or a really bad scarring process, usually occurs within 6 to 24 months. So that's a bit more long term damage, and usually it stabilizes after 24 months. You don't have to see radiation fibrosis or scarring, you don't have to have had radiation pneumonitis to see the radiation fibrosis or scarring. That can occur independently of having a pneumonia first.

So about 7% of patients, which seems like a high number, I will tell you many of those are not severe cases – and many just are x-ray changes without too much symptoms at all – can occur after receiving chest radiotherapy. The lung injury increases with the volume of tissue irradiated and the dose. So the higher the dose the higher the volume, meaning if you have a larger tumor and they have to get a fairly sizable portion of the lung within the radiation port, the more likely you are to have radiation-induced lung disease.

There are different fractions, and I think anyone who has been through radiation know that you get 10 treatments in 10 days, some people go for 30 treatments in 30 days depending on your cancer, and the need for radiation are associated with a lower risk. So if you can get smaller fractions at different times during the day they're associated with lower risk of pneumonitis than single large fractions.

The hallmarks of having this radiation pneumonitis are a fever, generally a low-grade fever, and a dry cough – again, they don't produce much phlegm – and shortness of breath. When you see this, it's pretty classic, they'll tell you -- they finished the radiation three or four weeks ago, six weeks ago, eight weeks ago, “Gee Doc, I'm having a cough, I'm not putting any phlegm up. I feel I might have a low-grade fever. Boy, am I short of breath. Two weeks ago I was able to walk a football field, and now I barely can make it on half a football field.”

We also looked at their chest imaging which sometimes can be absolutely classic, and I'm going to show you a few pictures of that for radiation changes. Then again we want to make sure that other processes aren't going on. We want to make sure the patient doesn’t have infection or heart failure or drug-induced problem in that population. So we want to make sure it's not something else before we ascribe it to radiation pneumonitis.

In the early stages what happens is that you actually get some injury to the small blood vessels and you get some fluid leaking out into the lungs, that causes these membranes – I’m not going to go into very great detail – but it causes inflammation and scarring of the membranes, of the lining of the lung cells.

Then you can get problems with buildup of a more scarring – this slide is basically a way of saying a scarring process becomes apparent.

If the radiation damage is really mild, it can actually recede on its own. But it gets severe – again, six to nine months after the radiation – a chronic phase or a scarring phase develops.

If you give a fairly sizable dose of radiation therapy, you will see changes in up to 40% of people on x-ray. Now remember, the tumor is also in there as well and hopefully what that’s done is wipe out the tumor but leave a little bit of a scar behind. What you see down here, the dose – I don’t expect you to remember the name – the dose of 30 Gray. That’s just a fancy way of telling people how much total dose of radiation you’ve received. You seldom see any problems.

In the 30 to 40 you can see it; Grays at 40 you almost always see some kind of scarring process. I'll tell you, the average lung cancer patient for an average tumor – and you know there’s a lot of
variation here – receives around 70 Gray, which is to say that again, most of my patients who get radiation will have some scarring process.

This is the chest x-ray on the left of a classic radiation finding. What I want to show you on the right is they made a pattern on this patient for where they wanted the radiation to go. They want to get the center of the chest where the lymph glands are, and the tumor which is right over here. So now you superimpose that pattern on to what it looked like after their radiation, you see what’s called a straight line sign, which means that in this patient – you almost never see this with anything else - everything else respects the lobes of the lung.

But when you get radiation you see this square or straight line sign which is actually the pattern of the block of radiation that was put through the patient’s chest. Now this patient may not have any symptoms at all, this might just be the scarring process that occurs after radiation treatments.

So serial x-rays in these people can helpful, sometimes your doctor will want to make sure that he looks to see how this radiation changes or progressing. Some of the chronic changes, the one I’d like to tell you about is once a scarring process starts you can get a loss of long volume. It can pull the lung, that lung will scar up so that it kind of squeezes together – I’ll show you an example of that – you actually lose some lung space. Now, again, hopefully underneath all that the cancer has been cured.

This is a case of that, here is a normal left lung and here’s the heart border along here, what you see is in the right lung there’s very little air in the right lung in the bottom. Up top what you see is a loss of lung volume from the scarring process that occurs. Again, you can be completely asymptomatic, not have any symptoms, be able to walk two flights of stairs and play golf if that’s what you like to do. But sometimes this can cause a loss of lung tissue, and in certain patients it can cause shortness of breath.

Sometimes the radiation scarring process, the radiation pneumonia process causes changes in the x-ray outside of where they were radiated, and I’ll show you that. But when that happens it’s generally allergic reaction. So you get radiation therapy to one area of the lung, but it causes a diffused inflammatory process in both lungs.

So, we’re using newer techniques to radiate smaller cancers. One of those radiation techniques, you may be hearing lots more about in the future, is called stereotactic body radio therapy or SBRT. Some people call it the CyberKnife, some people call it tomotherapy. It’s all a fancy way of saying that what we can do is instead of placing all of the radiation on block, from front of the patient’s chest to the back, we can actually bring the radiation in from different angles and have it converged o on the tumor.

So, single radiation in from a bunch of different angles, one single beam of radiation, from many angles that converge on a tumor, which is here in the arrow, what that does is it causes all the radiation to meet in one place but you don’t get the radiation in the normal portion of the lung. So each of the portions of the regular lung receive very little dose, the dose then ends up just at the tumor where you want it. You can see that after radiation there’s just this very focal area of radiation changes. This is perfectly agreeable. It’s a nice scar that you should see at radiation therapy.

So with some of the newer techniques that we have, stereotactic radiation therapy, a very, very high profile technique that’s being used in the better cancer centers throughout the United States and the world, I think what you’re going to be seeing is maybe less radiation pneumonitis in the
future. Not everybody’s tumor is eligible for that, but certainly when you have a tumor eligible for that it’s a really, really nice way to go.

So these are focal areas – that’s a fancy way of saying scarring, and it doesn’t correspond to the planned target volume and it differs from radiation pneumonitis after conventional radiation therapy because conventional will be a big block area. With this type of radiation pneumonitis it's a small tightly bound area.

But some of these scarring processes from the treatment of lung cancer mean that we do have to deal with these problems for a longer term, which is great by me. I’d rather have them alive with a few problems than not alive at all. But what you should be aware of is that the longer a patient lives with lung cancer and is treated for lung cancer, a lot more likely we are to see some of these chronic changes on x-ray.

So the treatment for radiation-induced pneumonitis, again experts recommend prednisone at 60 mgs a day for two weeks with a tapering dose over the next three to twelve weeks. There’s no controlled trials telling me that that’s the absolute dose that we should use, but we certainly do use that. I will tell you in my practice I try to get patients better with the prednisone and then as quickly as I can I get to the lowest dose possible so that I don’t have to deal with the side effects or the patient don’t have to deal with the side effects of prednisone. The guidelines for the taper aren’t clearly defined, but if symptoms recur sometimes you have to put patients back on steroids, certainly at the lowest possible dose.

There’s a drug called pentoxifylline which is actually, believe it or not, used for patients with hardening of the arteries. There is some evidence that using it reduces radiation pneumonitis. There’s not yet enough evidence and larger trials to warrant and choose, but I just put it out there as something you may hear about in the future.

Just to summarize, about 2% of lung cancer patients have complications not from the lung cancer but from the medicines and the radiation we use to treat lung cancer.

You really have to have a high index of suspicion both on the patient side to say, “Hey Doc, this doesn’t feel right. I got this drug four hours ago and this is what’s happening to me.” Also on the doctor’s side, we have to be very good detectives and try to pick up on what our patients are telling us, what the imaging shows us and just not write it off to cancer or an infection. Finally, radiation pneumonitis can be both localized to the area of radiation or diffuse in both lungs. Treatment is used with corticosteroids, but sometimes the damage can be permanent.