

Current Standards of Care in Locally Advanced Non-Small Cell Lung Cancer (NSCLC)

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Intro GRACE, the Global Resource for Advancing Cancer Education, is pleased to provide the following presentation on Current Standards of Care in Locally Advanced Non-Small Cell Lung Cancer, by Dr. Shirish Gadgeel, Associate Professor of Medicine, Karmanos Cancer Center at Wayne State University in Detroit. Dr. Gadgeel spoke at the GRACE Non-Small Cell Lung Cancer Patient Forum in Seattle in September of 2009, a program supported by OSI Pharmaceuticals and Swedish Cancer Institute.

Dr. Gadgeel: Thank you very much, Jack. I think what he's initiated *um* is quite unique and the services providing pretty much on his own time is quite incredible.

What I'm going to talk about basically is how do we decide about stage III lung, how do we decide to include surgery as part of the treatment in what call as Stage III lung cancer. It's truly something that is individual patient-based, but I hope to provide some considerations that we take into account before making a decision.

I just wanted to point out that this is not an uncommon situation that we lung cancer doctors face. What this is in a pie-chart form are what is the stage of lung cancer at diagnosis; if you took all the lung cancer patients diagnosed in the United States, what we find is that there is about a third of patients that are what we call as regional disease and what I mean by regional disease is where the lung cancer is not restricted just to the lung, but has spread to the nearby lymph nodes. That is what we are talking about how to manage.

Here we're talking about a lung cancer that is large enough that is either sort of invading into the central structures that we have in the middle of the chest and so cutting it out is not going to be very easy. All of this lung cancer that has already gone to lymph nodes in the middle of the chest and in those situations we know starting off with surgery is not a good thing to do.

So the main feature for stage III are what we call regional lung cancer is the involvement of the lymph nodes. And what I've meant shown here are the different lymph nodes that are present in the middle of the chest. And of course depending upon the location of the cancer, whether it's on the right side or whether the left side, but ends upper part of the lung or low part of the lung, there are certain lymph nodes that are more likely to be involved.

Now, why is this different from having lung cancer that is limited to the lung or lung cancer that has spread to lymph nodes that are closer to the lung? And the reason is different is that once you have involvement of these lymph nodes, it's a marker of the fact that the cancer has spread to other areas of the body even though we don't see it on the scans.

So what is not going to be sufficient even if the surgeon can go around and take out any of the lymph nodes that are involved, or the cancer itself, it is not going to be sufficient. So you're going to need something more than just going to be able to remove the cancer.

Before we go ahead, I thought it would be worthwhile to remind and probably most of you are aware that when it comes to the lung there are three different compartments in the right lung and two separate compartments in the left lung. And whenever we talk about surgery we talk about doing either a lobectomy which is removing a compartment of the lung; or we talk about a pneumonectomy where you're talking about removing the entire lung. And clearly, the implications are different. Obviously, one has to be in much more robust condition to tolerate surgery that involves removing the entire lung as opposed to removing one compartment of the lung.

Now, the problem about cancer that has spread to the lymph nodes is that there is a whole lot of variability in how these patients do. Even if all the patients got the same treatment, and we'll come to what treatment, there is a great deal of variability on how well the patients can do.

One factor that influences the variability is the number of lymph nodes that are involved. Now if you go back to what I showed of the lymph nodes, you can have just one of these lymph nodes involved or you can have lymph nodes involved but only in one area of the middle of the chest, or multiple lymph nodes involved in multiple areas of the middle of the chest. And depending upon the extent of the lymph nodes that are involved, even though all that is stage III according to us, the outcome of these patients is quite variable.

What are the sites where the cancer comes back? The cancer for the most part comes back in what we call as distant sites: that is, sites outside the lung or outside the area of where the lung cancer started, maybe in the opposite lung. But it is outside of where the lung started. And so what is clearly important in treating these patients is not something that is just focused on their chest, but something that sort covers the entire body because the cancer could be almost anywhere. And so you want something that involves the entire body.

It is for this reason, what you're trying to control is not only the disease that you see, what we call local regional disease the disease that you can see on the scans, but you're also wanting to control the disease that we know has spread to other areas of the body, but not detectable. And one major area is the brain.

And so because of the great deal of variability that exists in the outcomes of these patients, because the extent of the cancer can be very variable in these patients who have this Stage III disease, I think what is very important is that before we initiate treatment that are involved in lung cancer care --surgeons, medical oncologists, radiation doctors, including radiologists, because they can really tell us looking at the scans where they feel there are suspicious areas, really get together as a team before we make a decision as to exactly what, decide as a team what to do.

If you look at stage III lung cancer patients, most of these patients are treated with chemotherapy and radiation. Why chemotherapy and radiation? Because I told you that there are two aspects of the disease that we are trying to address: the disease that you can see in the chest, lung cancer; and the metastases to the lymph nodes; but we're also trying to take care of the disease that we don't see.

Now as far as the disease that we don't see is concerned, we deal it with chemotherapy, because chemotherapy generally is given intravenously. It not only goes to the lung, it goes to all other parts of the body. And generally chemotherapy does have the capacity of eradicating cancer that is not big enough to be seen on the scans.

So disease that is outside the chest that is not big enough to be seen on the scans, chemotherapy can in at least some patients eradicate that disease. It cannot by itself eradicate the disease that is big enough to be seen on the scans. And so to that area, we add radiation, and the hope is that when we do chemotherapy and radiation together, we can address all aspects of the disease.

Initially this was done when this was first introduced where chemotherapy was done first and then radiation, and this was compared to radiation alone and what was found was when you added chemotherapy to radiation; those patients did better than patients who just got radiation.

But, the next step that was done was that patients got chemotherapy and radiation together instead of one after the other, and this was compared to patients who got chemotherapy first and followed it by radiation. And what we have seen is that chemotherapy and radiation given together is better than doing chemotherapy first followed by radiation.

However, when we do chemotherapy and radiation together, it does have certain side effects. And what I would like to direct you is that there are two main side effects: esophagitis and pneumonitis. And what esophagitis means is that we have food pipe that connects the mouth to the stomach that lies right behind the lung, and even though radiation doctors have become very good at targeting the radiation only to the cancer, there's clearly some overlap of the radiation to the surrounding areas.

The reason we do chemotherapy and radiation together is because the chemotherapy makes the radiation stronger against the cancer than what it would be by itself. The problem is that when it comes to the overlap to the surrounding areas, there is also a greater effect of the radiation and so there can be an increase in the risk of what we call esophagitis: patients have a difficulty in swallowing, and this generally happens about two to three weeks into the treatment. In about 5% to 10% of the patients, it can be so severe that the patients may not be able to swallow solids or may even have to be admitted to the hospital for IV hydration.

The good part about this is that it is only generally in most patients it is short lived, so once you stop treatment, the esophagus sort of cools off, and the patient can swallow again. But the other more sort of dramatic side effect is that of what is called pneumonitis. Pneumonitis basically is that about two to six

months after completing chemotherapy and radiation, patients can develop something called as pneumonitis or basically swelling the lungs. So its usually in the area where the patients got radiation. And about two to six months after the radiation, the patients may present with a picture very typical of pneumonia, where patients have cough, have some fever, have increasing shortness of breath and these patients for the most part can be salvaged with some treatment; that is their pneumonitis can be made better with some medications called steroids. And most patients recover.

However what I wanted to indicate is that, yes chemotherapy and radiation together is better. However, it is not for every patient that we see. You have to be very selective because if we are not proper in selecting which patients to do this treatment, in attempting to benefit the patient, we may actually harm the patient if we gave treatment that the patient was not able to tolerate.

So you're talking about chemotherapy and radiation, and now you're trying to see if you should add surgery to this treatment paradigm.

But as you can imagine that after doing chemotherapy and radiation doing surgery can be challenging. Surgery by itself, lung surgery by itself can be challenging in any patient, but more so after chemotherapy and radiation. And it is for this reason that there was a study done, a randomized study done where patients with stage III disease were randomized to chemotherapy and radiation followed by surgery versus chemotherapy and radiation alone. And the chemotherapy and radiation alone was considered the standard treatment.

You can see that the amount of radiation that the patients who were randomized to get surgery was lower. The reason is that if you get a higher dose, than this 45 gray, then the chances of having side effects after surgery are greater. And so if you're considering surgery for the most part, we give a bit of a lower dose of radiation than what you would get if you were just getting chemotherapy and radiation. And what this study showed is that there was no difference, that the outcome of the patients as a whole, so if you looked at the outcome of the patients who got chemotherapy and radiation together versus the outcome of the patients who got chemotherapy and radiation followed by surgery, there was no difference.

Based on this study, what one would say is that the standard treatment for regional lung cancer is chemotherapy and radiation. But I told you right in the beginning, there's a great deal of variability when you look at regional disease. There are patients who have only a couple of lymph nodes in the middle of the chest involved. There are a couple of, there are patients that have multiple lymph nodes involved, and we know that those two patients are not the same. And it would be wrong to say that because of these results, all these patients should be considered the same.

And this was suggested when these investigators went back and looked at something, what they found was that when they looked at patients who had undergone just lobectomy as opposed to patients who required the full lung to be removed, there did appear to be a benefit in patients who underwent just

lobectomy following chemotherapy and radiation as opposed to patients who underwent just chemotherapy.

So this was suggested that patients who underwent lobectomy only, those patients did appear to have a benefit with surgery as opposed to patients who got just chemotherapy and radiation. Now this is what we call retrospective analysis, and in the scientific literature whenever you look at retrospective analysis that is always viewed with a level of caution.

What is important to recognize is that the patients who underwent pneumonectomy, that is where the whole lung was removed, actually they had an inferior outcome. Why? Because there was a higher rate of patient death following pneumonectomy primarily, because of respiratory failure.

So generally what has emerged based on this study and some of the other studies is that, yes, we do consider surgery in patients where you have limited amount of disease and where you think that you can get away by removing only a compartment of the lung and not the whole lung. However, it is extremely important that we take into consideration what is the patient's condition, how well the patient is, what are the general other medical problems that the patient has. And I also feel that it is very important that this is done in the context of a team approach with the right surgeon doing it.

So what are the guidelines? The guidelines are that in patients who are considered resectable. we consider chemotherapy and radiation upfront and follow it up with surgery.

And how do we decide what is resectable or not resectable? I've listed what is not resectable, because to be honest with you that is the more common scenario. If you have large lymph nodes, so you may have limited number of lymph nodes but they are pretty large or if you're multiple lymph nodes involved, then in those patients they're not going to consider surgery and in those patients they're going to do chemo/radiation straight through.

But in patients who have limited number of lymph nodes, small lymph nodes where you think you can remove the entire cancer with just a compartment of the lung, in those patients we would do chemotherapy and radiation, but give a smaller dose of radiation because there is a concern that you may have increased toxicity and then proceed with surgery.

What I'm going to finish off by saying that never miss an opportunity to talk about smoking cessation. This is definitely a disease that is highly preventable, not in all patients, there are definitely never smokers who do develop lung cancer, but in a large proportion of patients this could be avoided if they stop smoking or encouraged our friends and relatives to stop smoking.

Thank you very much.