



Pulmonary Nodules: Evaluation and Management

by Dr. David Yankelevitz

with Dr. H. Jack West

Dr. West:

Hello, and welcome to everybody. My name is Dr. Jack West, and I'm a medical oncologist and the founder and CEO of GRACE, the Global Resource for Advancing Cancer Education. I am based in Seattle, Washington and I am very happy to be joined today by

Dr. David Yankelevitz, who is a Professor of Radiology at Mount Sinai Medical Center in New York City, and he is also one of the world leaders in the topic of lung cancer screening, as well as detection and work-up of lung nodules. Today's program on Work-up and Management of Lung Nodules is supported by the LUNGeVity Foundation along with GRACE, and we thank them for their support.

I had the privilege and opportunity of seeing Dr. Yankelevitz talk about this subject just recently and thought it was a wonderful presentation. He covered a lot of issues that come up very, very frequently for our patients and on the website. And these issues cause a lot of anxiety, a lot of frustration, and a lot of questions, so there's really no one better to talk about these issues than Dr. Yankelevitz.

Dr. Yankelevitz:

Okay. Well thank you very much for that introduction, and I will be talking about pulmonary nodule evaluation and management because this is becoming a larger and larger topic, and I think it's one of the few areas where it's being driven very heavily by the technology. And in particular, I'm talking about CT scan technology.

From a historical perspective, we see that CT scans only started in 1972, was when the first CT scans were developed, and to take a picture of the chest at that time, or of the head actually, it would take several hours to generate a single image. By 1974 it took two-and-a-half minutes per slice, and by 1976, which is around the time I started reading them, each slice took about 5 seconds. And if you think about going through the chest, you had to back then, you would get about 20 or 30 slices to go through the whole chest.

As we move forward in time, the scanners improved, and instead of there being one row of detectors, they became multiple rows of detectors, and we started getting 4-row detectors, and 16-row detectors, which meant that we could get thinner sections through the chest, and also obtain the images at a much quicker pace so that literally now, this has been growing exponentially and now in 2011, we have 128-row scanners, and actually 256-row scanners so that you are actually in less than a second taking 256 slices of the chest as sub-millimeter thickness, which provides for an extraordinary amount of information.

So where are we with CT scans? There's been improvements in image quality, there's been improvements in spatial resolution meaning you can see thinner and smaller objects. Temporal resolution, meaning you can obtain the images much quicker. All of the artifacts that used to appear because of the way scanners were built are now gone. Some of these other things, dual energy, are newer techniques that allow you to see different materials more quickly, and there's

also been tremendous improvements in radiation dose, which I'll just show you briefly, because this has always been a concern with CT scans, and you hear a lot about that in the news about dose of radiation.

Well at least in the chest, the dose is being able to be dropped dramatically to the point now where this, this is an ultra low-dose scan that's sort of experimental. But this is basically the equivalent dose, this is one image of an entire CT scan of the entire chest, several hundred of these images make up the chest. And the total dose here is probably about two chest x-rays, so it's well under half the dose of a mammogram. And these dose reduction techniques are continuing and will continue to get better.

And you can see here on the box, I'm just showing you that you can still clearly see this small nodule, which measures about 2 or 3 millimeters.

Now why do we want thin sections? Well here's an example. If you look at this CT scan, and this is a CT scan, left lung, right lung, spine. You can see the ribs. You really can't see anything much wrong with the lung. Now this is an older generation scanner, and the section thickness is thick. This represents 10 millimeter thickness that we're looking through.

Now here's a newer generation, and I've sort of honed in a bit more. This is 1 millimeter thickness, and suddenly you can see something very abnormal here, and this is an early cancer that we can see with the thinner sections.

So what's happening? Mainly because of the technology, we're getting increased use of CT scanning and it's very hard now to go to a hospital and go to the emergency room and not get a CT scan done if you have any kind of chest abnormality. It's almost as fast to get a CT scan as it is to get a chest x-ray, and the amount of information is far greater. And now, especially with the recent results of the National Lung Screening Trial, we're going to see more and more lung cancer screening occurring where people are going to be looking to find small nodules.

Now what's so important about small nodules? Well here's a picture. This is a CT scan. This is the right lung. This is the major airway here. And it's very hard to see anything, but here is a little tiny nodule. I have a little "X" on it.

And this is what happened. Nobody did anything, nobody noticed this little small nodule at that time. It looks very much like these other small dots, which are actually just normal blood vessels, and nobody noticed this. But look what happened in a year's time. It got much bigger. This is clearly now a cancer that would have had a better chance had we seen it at this smaller size. Now it's at a slightly larger size. The patient still did very well, but it's always nice to be able to find things when they're at their smallest size.

So the challenge for all these small nodules is to develop useful criteria to efficiently diagnose them, and currently we're at the point where many small nodules are being dismissed as not being clinically important. However, what really needs to develop, and it's a rapidly-developing area because of the technology and what we're seeing, is to develop better and better scientific criteria to know which ones we can dismiss, and which ones we really need to follow and do additional work-up on before we make decisions.

Well, it turns out that there are certain things that we can look at that can tell us for sure. If we see that a nodule is calcified, and there are certain patterns of calcification that we can be 100 percent sure that a nodule is benign, and there's another pattern: if we see a nodule and we know that we have old pictures of this patient, and the nodule hasn't changed in size for several years, then we

can also be certain that it's benign. And these two criteria, it turns out, have been around since as early as the 1950s from chest x-rays. So these are two that have really stood the test of time, and these are patterns that if you thought of this as a nodule, this is what a benign – and the white would be the calcium. If it's centrally calcified, or if it has these kind of ring-shape calcifications, these are the typical benign patterns. These two are two other patterns that are also benign.

Now we can look at other things. Sometimes that can give us a clue to some small nodules being benign, and these are more subtle findings that we're really just learning about because of the high resolution CT. Well it turns out the lungs are separated, each lung is separated into different lobes, and the lobes are lined or separated by what we call fissures. And in this picture here, you could see one fissure over here, and then very subtly there's another fissure over here. And it turns out we can get these little nodules that appear right on the fissures, and these are called fissural plaques, and these are almost always benign, and we can dismiss those.

And similarly, there are other little findings that we sometimes see. This is another – this is the right lung, and here we see a very small nodule, and this nodule has a little tail coming off that goes to the surface of the lung. Turns out that these are little ducts that come out of the nodule, and when we see this pattern, we can be almost certain that this represents a benign small lymph node inside the lung, which occur and sometimes they're a little larger, like this size. But when we see these kind of patterns, this smooth border and a little duct going to the surface, we can almost be certain that it's benign. Now in this case, if you notice, some of you may have noticed that this is a needle coming, so at that time we hadn't seen that many so we weren't so certain. So we were actually doing a needle biopsy on this case to make sure, but this was the pattern before we put the needle through the skin and muscle into the lung.

Now there are lots of tests out there for looking at nodules. We can do many types of CT scans, we can inject intravenous contrast. I'm sure you've all heard about PET scanning. Then we can look at things like how quickly a nodule is growing, and we could also look at the shape of the nodules, and that sometimes tells us some information just like some of the examples I've shown you.

There are other tests that become more invasive. There's bronchoscopy, where they put the tube down the throat and try to go out into the lung to locate the nodule and take a sample of the nodule with a needle through the bronchoscope. Or there's a technique called transthoracic needle biopsy, which is something that I have a lot of experience in, and we put a needle through the skin and into the lung.

And then there are the more invasive techniques. There's a technique called video-assisted thoracoscopy (VATS), which is kind of like laparoscopy, where they make three small incisions and they put scopes inside the chest, and they can remove small amounts of lung. This does require general anesthesia. And then there's the larger surgeries. Hopefully for the diagnosis of nodules, nobody's going through these last tests, thoracotomy, where they really have to make a major incision.

So as you can see, there's a wide range of tests that are available, and there's no absolute one way to evaluate these nodules. There's many ways that we can look at them, different orders and different sequences of the test, and it depends to an extent on what equipment the hospital has. Some of the techniques require certain individual skills to perform them. And in that way, different places will have different management protocols.

Now one of the things that we started to think about more and more is when we do these CT scans and they become such powerful tools and their resolution is so high, we have to start

thinking about what it means to say somebody has an abnormal scan. The reason being is that with these CT scans now, if we take high-resolution CT scans of virtually anybody, even healthy, young adults, we'll virtually find at least one tiny nodule in every single person, which is to say that if we can find something on everybody, does that mean it's still abnormal? The answer is sort of no.

Now we know for example that if we find a calcified nodule, we can say surely that's not an abnormal result. It's a benign result. It doesn't need any further work-up.

Well what about these small tiny nodules that I say exist on everybody? I wanted to give you some other examples, and many of you are familiar with this, have had other tests – Holter monitors to check your heart rates or your heart rhythms. When you wear a Holter monitor all day long, there's always at least a couple of beats that are skipped beats or abnormal beats, and that doesn't mean that you have an abnormal heart. It doesn't even mean you have an abnormal test. It's basically normal to occasionally have an extra beat. And similarly when they do the guaiac tests to check for blood in the stool, there's always at least a tiny amount, a couple of red blood cells. That doesn't mean it's an abnormal test.

So what we're starting to understand is that with small nodules, there's at least some sized nodule where we'll know that everybody has it, and we're not sure what that size is yet. It's probably going to be around 1 millimeter where we'll say, "Listen. It's just normal. Completely forget about it." For some size that's a little bigger than that, maybe 5 millimeters which is still very tiny, we're going to do something slightly different and we put this in sort of an intermediate category now. We don't – they're so common and they're so hard to really prove anything, whether they're abnormal or not, that we don't call them completely normal, but we call them semi-positive. And in those cases, we wind up repeating the scan in one year's time because even if it was malignant, it's still so small that it would hardly have grown, and the chances of it being malignant are exceedingly small. So overall, at some size, and that's around 5 millimeters – some people say 4 millimeters – we just watch it for a year. So this allows us to not do work-ups with invasive procedures and many tests on every single nodule we see, otherwise there's be – every person would have work-ups on every scan.

This is just some of the definitions. There were three large screening studies that have been done. There's the International Early Lung Cancer Action Program, which I have been part of; there was the recently published National Lung Screening Trial; and then there's the Dutch-Belgian study called the NELSON Study. These are large screening studies, and you can see how each of them defined a result that would be positive. So for the I-ELCAP, any nodule greater than 5 millimeters required work-up. For the NLST, it was 4 millimeters. And for the NELSON, they used a slightly different criteria. They didn't use a diameter, they used the actual volumetric 3-dimensional volume measure to decide when a nodule was large enough that it required extra evaluation. And this is just a summary of what I've been saying, that at some point when it's bigger than 5 millimeters, it's positive and it needs additional work-up. When it's somewhere between, say, 1 and 5 millimeters, we can just wait a year, and when it's less than some size, possibly 1 millimeter, we can just forget about it completely.

When we look at all these different protocols, some things become apparent and this is the basic way that all of these nodules are ultimately evaluated. The first thing we try to look at now, especially with small nodules, is what's the size because that really determines what's going to happen next. If it's below a certain size, we do nothing. If it's above a certain size, the next step is typically to try and figure out whether it's growing, and we order a second scan at some time interval – sometimes one month, sometimes three months, sometimes six months depending on

its size so that we can see whether it's growing, and if the growth rate suggests that it's growing at a malignant rate. And all of these protocols that I've shown you use some variations of these other tests to help in the diagnosis. Some use PET scans and biopsies, some use antibiotics more frequently to see if things go away. They vary the time between the scans, but there's all a basic similarity.

Now why is it so important to have a good protocol? Well this is one of the studies that was done. This was a screening study done in Pittsburgh, and it was called the P LuSS Study. And the P LuSS Study was done where they had a protocol, but what happened was they didn't follow the protocol very well. And so what they noticed was that the CT detected many small nodules, but once they had the nodules, people were going out into the community, and different doctors were working them up completely differently without following any protocol, and they wound up having a lot of surgeries that probably weren't necessary. And so they recognized that this really underscores the importance of adhering to a good protocol, particularly in a place that has a multi-disciplinary team where they have an established protocol and they know how to manage these things, otherwise too many extra tests are done, including sometimes invasive tests where they actually do surgery.

This is one of the common protocols. I'm not going to go through it, but there's a society called the Fleischner Society. It's a very robust society made up of a multidisciplinary team, and a few years ago they published their recommendations for how nodules should be worked up, and they divided them into two categories: low-risk patients – meaning in essence, younger non-smokers – and high-risk – basically being smokers and of an older age – and different protocols. But basically the protocols depended on the size of the nodule, less than 4, 4 to 6, 6 to 8, and greater than 8, and that gave you information as to when you should get your second scan to see if something was growing.

And this just tells you that it was made for incidental nodules that were picked up by accident, basically. That persons have other diseases like tumors somewhere else that are known, then the whole management of nodules is totally different because it has a totally different meaning. It could be spread from a prior tumor, so it was meant – the Fleischner Society guidelines – for people that had no prior history of malignancy.

Now there's another organization called the American College of Chest Physicians, and they published their own set of guidelines for how nodules should be followed, and they actually had 29 recommendations for the management of solitary nodules. Now I'm not going to, obviously, go through them, but it's actually interesting that it was, in essence, it agreed with the Fleischner Society. There was really no difference in the overall work-up. And this is a flow chart of what their work-up is, and you can see it's all based on patient's risk, high-risk, or low-risk, and then based on various sizes of the nodules, what the work-up would be.

Now this topic of growth of nodules is really an interesting topic, and it starts to get a little bit technical, but I'll try and go through some of it, and you can see what some of the challenges really are I said with these small nodules. We like to try and measure tumor volumes. That's becoming the way to do things now, not just a simple diameter, but we actually try to measure the volume of a tumor. And the way we do that is with 3-dimensional techniques, and the reason we do it is because when volumes change, there's a higher – you see for any given change in diameter, the volume changes to a much greater extent. So if the diameter increases by just 26 percent, meaning the diameter goes from 1 centimeter to 1.26 centimeters, the volume has increased a hundred percent. So it's very powerful to use these volumetric techniques. You can see more subtle changes when you measure that way.

And we can apply computer-aided techniques to measure volumes of these nodules, and these techniques continue to get better and better over time as we collect more and more cases. The way computer-aided diagnoses work is that they really train on very large data sets. It needs lots and lots of proven cases so that it can learn and can recognize what things are, and can learn how to find the boundaries better. And that's ultimately what's happening. That plus the fact that the CAT scan images are getting so good, and with such high resolution it allows the computer-aided techniques to work even better.

Now this is just an example of why this technique is so powerful. Here's a small nodule, and you can see it's kind of round. This is in the right lung. This is a blood vessel. You see this nodule, and this is a three-dimensional image of this nodule. This is an 8 millimeter nodule and we took another 3-dimensional picture of this six months later, and you can see just by looking at them, if you compare there's very little change. They really look almost identical, and they've changed by less than half a percent in volume, and this is typical of a benign abnormality.

Now here's another example. This nodule here we see, and we'll show you the 3-dimensional picture at time one. Here it is. And now you can see it time two. Now this box that it's in is the same size. You can see on the right-hand side just how much bigger this nodule actually appears, it's actually filled in much greater. And this is growing; this grew 22 percent in volume in just one month's time, so in a year's time this would have more than doubled. It would have gone four or five times the volume in one year's time. So that's a malignant rate of growth. So that's why these volumetric techniques are so powerful.

Now unfortunately, it's not always so simple. It turns out there have been some experiments where we found that when we tried to measure volumes, there are some inherent inaccuracies in our measurements, which tells us that we have to do still a lot more work in getting these techniques down so that they become a hundred percent. So this is a study that said that there's errors in the measurements, and what we did was we took nodules. These three different studies, they took nodules, they scanned them, and then they re-scanned the patient 5 minutes later so that there was no chance for the nodule to change, and they measured the volumes of the nodules. And it turned out that even though we were positive the nodules didn't change, they actually still had some change in volume, sometimes up to 20 percent, which tells you that the techniques are not that accurate, especially for small nodules.

And there's many reasons for this uncertainty, and I don't have to go through all of this, but just like everything you buy, there are different types of CT scanners, and the CT scanners have many different parameters that you can adjust how quickly you go through the scan, how thin the slices are, the resolution, the dose, and every time you change one of those parameters, you actually have an effect on any measurement. So it gives you some information as to why the measurements are not always consistent.

Now I'll just give you an example of why it's so difficult, especially with these small nodules. Here's the challenge: you look at a 5 millimeter nodule, which I'm showing right here in the middle screen. The volume of a 5 millimeter diameter nodule is 65 cubic millimeters. 65 cubic millimeters. If when you try to find the boundary you're off by just a half a millimeter all along the surface, say your computer program decides to try to find the boundary and it tries to draw it very tightly, if it draws it tightly by just half a millimeter along the surface, it turns out the volume would shrink to 33 millimeters, 33 cubic millimeters. And if it tried to find the boundary a little bit loosely by another half a millimeter, it would have a volume of 113. So literally this just tiny amount of wiggle room in terms of where you decide to put the boundaries can change your volume from 33 to 113, so it

tells us that we have to do these things very, very carefully. We have to use the techniques on the same scanners, use the same software, get the highest resolution images possible so that we can avoid any kinds of errors.

And this is just one final challenge that we have. This is a small cancer over here. This is a cancer, this is a spine. This is the aorta. Here's the lungs. And this is the pathology slide of the cancer right here. Well it turns out when you look at the borders of these cancers, it's not always solid. This is normal lung tissue out here. This is solid tumor in the middle, and right at the edges it's a combination of both. And when you get the average thickness of this combination area where it's not purely tumor, and it's not purely normal lung, turns out that if you average that out along the whole surface, it sometimes comes out to nearly a millimeter in diameter, which makes it very hard to know exactly how the computer can pick the area. So in essence it tells us that even when we do these very sophisticated computer techniques, the human body introduces a certain amount of inherent uncertainty.

Now I want to talk about one other technique that is very popular. We do quite a lot of it at my institution. It's called fine-needle biopsy. This is when you're starting to get really concerned that an abnormality may be a tumor and you want to obtain a small amount of tissue in a relatively non-invasive way.

Now I started doing needle biopsies, oh, some 25, 30 years ago and when I first started doing them, this was the typical size of the biopsy, of the nodule they would have to biopsy, and these are about 4 centimeters in diameter in the right lung. Here's the airway, this is the blood vessels coming from the heart, and here's this big tumor.

When I look nowadays at the kind of nodules I'm being asked to biopsy, they really are in this range, this size range here. Frequently I get asked to biopsy these kind of abnormalities and I don't know if you can see where the needle is coming in over here, but it shows that we're biopsying much smaller nodules than we used to.

Now I'll just talk a little bit about the biopsy because it requires a lot of practice, but you'll see just what goes into making a diagnosis. Here's a small nodule, and sometimes we can take the needle and we put it through. This patient's lying on his stomach here. This is his breastbone, here's his heart, here's his spine, so he's lying face-down. And here's the small nodule. And we have the needle and it went right to it. But that's not usually the case.

Sometimes when you try to put a needle inside a nodule, when you're trying to move the needle this is the back of the patient here diagrammatically. Here is the nodule that's 10 centimeters deep inside the chest. If you try to advance this needle in through the skin while the patient is breathing, sometimes the needle just doesn't go through a straight course. It moves a couple of millimeters. And if that needle in the course of advancing it is off by just two or three degrees, which is very likely because as I said, the patient is breathing, sometimes there's a little bit of a pinch when the needle goes into the lung. If you're off by just 2 or 3 degrees and advance it just by simple geometry, you can see that the needle will follow a path that will not allow it to hit the nodule. And if you miss the nodule, you may as well have missed it by a mile if you don't get it inside because you won't get any material.

Now I'll just show you a few examples of some nodules, the type of nodules we can biopsy. Here's a small nodule here. And to do this one we turn this patient on the side because if we go back, you can see there's a lot of breast tissue here that I didn't want to travel through. So when I turn him over on his side, all the breast tissue moves over to the front, and I have a much

straighter path to go through, and there I can put a needle straight through into this very small nodule. Here's another nodule right here, very small. This is the patient's heart. This nodule was located very near the heart, and they did a PET scan. This is an actual PET scan and it's very hard. This very faint area was where the nodule is, and it's a little brighter than it should be, which suggests that it was malignant, but nobody was sure, so they wanted to try and get a small amount of material before they operated.

And here you can see I went the long way. I lied the patient face-down. Here's his heart, here's his spine, and I put the needle all the way through, right down here into the nodule to obtain the sample.

And just to show you, there's lots of newer techniques that we're looking at with computers to help locate these nodules, and to assist in getting the needle inside the nodule. It turns out that if you think about advancing a needle, and you're trying to go to a target and the needle is here, you're never quite certain as you advance it whether it's going to go straight, or whether it may curve a little bit one direction or the other, and so we started doing some research into this area, and we realized that one of the best models for predicting where something will go, and how much the uncertainty is where these models that were used to predict the course of hurricanes. So as you see here, here's where the hurricane starts and you can see that as it goes, they know it's going to be probably along this path with this measure of uncertainty. It could be here or here, most likely here. And as you get further and further from your starting point predicting out further, you could see that this cone of uncertainty really starts to widen and widen, and that's what happened the same with the needles.

And this was an example. As we're advancing the needle, depending on where it is, when the needle tip is over here, the yellow marks the uncertainty of the path. As I advance this needle further up to around this point here, the uncertainty becomes much tighter. And this was the nodule we were trying to go after. So that's the basic idea in some of these nodules.

Now what do we get from these needle biopsies? We get cytology, and here you can see an example. When I do these cases, I put the needle in. I have – it's done inside the CT scanner. I have a nurse there, I have a technician there, and I also have a cytologist present so that they can look at the specimen I obtained almost immediately, and we can tell whether or not we have an answer or not, and we can tell whether or not I need to obtain a second sample. And these are cells that are malignant that were obtained from this tumor, and we were able to tell this immediately.

So nowadays what's happening is that there's lots of new things that we can test for. It used to be we just wanted to know whether something was malignant. Now there's many different molecular markers that people want to look at because that can determine the treatment. So nowadays we try to obtain enough material so we can do these various molecular markers because that will define what type of treatment a patient will get, and so this is the new area and it's one of the reasons that we're doing more and more of these needle biopsies. And we're suggesting that every institution that's involved in this approach that does multidisciplinary research, and multidisciplinary care should have a protocol set-up so that they can handle these small amounts of tissue, and so that they can do these kind of analyses so that these patients can get the best treatments possible using the information that's available. And these type of protocols should be set up at each institution.

And these are just some of the different things that can be evaluated aside from just looking at the cells, there's immunohistochemistry, there's something called FISH, there's micro-arrays, and there's just a whole host of other things now that are available on these small amounts of material

that you can take through a needle that's actually thinner than the needle that you use to draw blood from a vein in your arm.

So I'm going to conclude now by saying that there's an increasing prevalence of small, less than 5 millimeter nodules. Conservative approaches are being recommended for the follow-up with careful attention to really developing these protocols by harnessing all the data that's been collected from some of these very large screening studies. And make protocols that are based on these kind of data is not just experience, but really data-driven kind of protocols, and this is being developed by some major organizations, and I think this will be very, very helpful in the future. And I want to also say that there have been major advances in image processing techniques, and the ability to process small tissue samples need to be incorporated in any program that's used to evaluate small nodules. And I'll conclude there. Thank you very much.

Dr. West:

Well thank you so much. This was a terrific program, and the kind of issue that comes up all the time. I also want to thank again LUNGeivity Foundation for their partnership with GRACE in making this educational program possible.