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Assessing and Interpreting pCR in Perioperative NSCLC

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
This is *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and joining me to discuss how pathologic complete response is assessed and interpreted following neoadjuvant therapy in perioperative non-small cell lung cancer is Dr. Alexander Spira. He's the Director of the Thoracic Phase I Program at Virginia Cancer Specialists Research Institute and a Clinical Assistant Professor at Johns Hopkins. Dr. Spira, welcome to the program.

Dr. Spira:
Thank you for having me.

Dr. Jackson:
To begin, Dr. Spira, can you walk us through how pathologic complete response is defined in perioperative non-small cell lung cancer and how it differs from related measures like major pathologic response?

Dr. Spira:
It's really one of the determining factors in clinical studies because pathologic complete response is the most important thing correlated with overall survival. It allows us in these neoadjuvant clinical trial protocols to determine if there's a pathologic complete response that is correlated with overall survival, so it makes our endpoint shorter and allows us to get these studies completed sooner as well. And it's one of these newly defined things taken from the breast cancer world.

So a pathologic complete response is defined as no viable tumor anywhere. So you give them preoperative therapy, and you can't find any viable tumor. To remind everybody, there could be something there microscopically, right? I mean, if you're looking at a four to five-inch tumor, you can't actually look at every last section there; it's infinite number of sections. But it's to the best level. There's specific things that they look at and specific ways of doing pathology, and if in that they find no viable tumor at all, it's a pathologic complete response.

There's also what's called a major pathologic response, which is less than 10 percent of residual viable tumor. Those are the two most important endpoints. Obviously, that still leaves out other patients as well, but those are used as early indicators of treatment efficacy in clinical trials especially. We can obviously extrapolate that to the real world when they're not in a clinical study to look at how the patients are doing, and again, that's an indicator that correlates with overall survival. Because remember: in these early-stage studies, the most important thing is overall survival. The challenge is that endpoint can take many years, which makes clinical studies hard to do and delays getting effective drugs to patients. In other words, this is a surrogate for that.

Dr. Jackson:
And once a patient undergoes resection after neoadjuvant therapy, how is pathologic complete response assessed in practice?

Dr. Spira:
Yeah, this is very important. And pathologists according to IASLC recommendations—and this is really a pathology thing—have specific ways of how they cut the tumor up and how many sections they have to look at. It's not just looking at one or two sections. They have to look at very specific intervals to make sure because you could miss something, right? I mean, again, a tumor has almost an infinite

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number of sections there. So it requires a comprehensive histopathologic evaluation. They have to quantify, is there viable tumor? Is there necrosis? Is there fibrosis? Is there immune infiltration? These are important things as we think about other surrogates.

But you also have to evaluate all sampled lymph nodes. And there's also certain criteria that have to be done for the number of lymph nodes that are evaluated as well. For the most part, we've gotten beyond that. When I started a quarter of a century ago almost, some surgeons were only doing a couple of lymph nodes, but now, there's a mandatory number of lymph nodes that are required for an appropriate evaluation in anybody undergoing surgical resection for their lung cancer.

Dr. Jackson:
Okay, so let's expand on that a little bit and look at the context of reviewing pathology reports. Which aspects of assessment or reporting variability matter most when you're evaluating pathologic complete response rates across trials or in practice?

Dr. Spira:
Yeah, and this is super important. How you sample has to be standardized across pathologists, and you have to be incredibly thorough, right? And over time, pathologists have gotten incredibly thorough by looking at these IASLC recommendations for how we evaluate lung cancer. So it's important that we follow these thorough procedures.

It's also very important that a pathologist be somewhat of an expert in this as well. It's looking not just for somebody that's doing breast cancer, colon cancer, or lung cancer; they really have to understand lung cancer because it is an experience thing, and you have to understand what these recommendations are.

That's why it's also very important to look at cross-trial comparisons because if you're looking at different pathologists and looking at different things around the world, have these been done by a standard? Modern protocols do involve a standard in how you have to look at it. But again, there's variability, and that variability is important. Most clinical studies right now actually have standard approaches that have to be done. Of course, that has to mean that it's done that way because you can ask your pathologist to do everything, but at the end of the day, pathologists may be part of the clinical study. We try and get everybody to follow, but of course, there can be variability there as well.

Dr. Jackson:
Those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Alexander Spira about interpreting pathologic complete response in the perioperative non-small cell lung cancer setting.

Now, we often think of pathologic complete response as a favorable signal, but it doesn't tell the whole story. So, Dr. Spira, how do you interpret pathologic complete response in the context of other clinical and pathologic factors?

Dr. Spira:
There are clearly other things, right? And we know this is a risk. So we know that pathologic complete response is a very meaningful indicator, not only of treatment response, but of course overall survival. I've said that a couple of times.

But there are other things as well. Just because you don't have a pathologic CR doesn't mean your cancer is going to come back by no stretch. It's reflected by stage, right? I mean, early versus late stage—an early stage one that meets criteria to do neoadjuvant therapy for a centimeter tumor that may not have a pathologic CR may still do very well. So it's based upon tumor biology, size, molecular features, and adequate staging. We're staging our patients as best as we possibly can, but obviously, the tests are only as good as those are.

So it's very important, especially as we talk about patients, right? Patients can read; we are trained to think that pathologic CR is a very important thing, but there are many other things that go into this as well.

Dr. Jackson:
And after a patient undergoes surgery, what role do pathologic findings and molecular features play in guiding decisions about adjuvant therapy?

Dr. Spira:
Yeah, this is actually very challenging and unknown. There are a lot of different ways of approaching patients and a lot of different neoadjuvant protocols, as almost every IO drug has now been published.

The challenge that we have is who needs more therapy? Pathologic complete response is defined of neoadjuvant therapy for three to four cycles followed by surgical resection, and we're looking at that point. And there's two very important questions that we have: If you had a pathologic CR, does that mean more therapy is better or not? We actually don't know that. If you had a pathologic CR, maybe you had enough and you don't need any more. Or the contrary is if you haven't had a pathologic CR, is more better or not? Some could

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argue that more is better. I've heard some physicians say, "Oh, I feel like I have to give them more because they didn't have a pathologic CR." But the real question is: is that additional therapy going to change anything? If you've given them three to four cycles, is more better? We actually don't know that. It's important as we think about it, and these are really important scientific questions that need to be answered over time and need to be looked at. It's beginning to be undertaken by the cooperative groups.

Furthermore, we need molecular profiling. Are there other biomarkers, etc., especially as we get to new therapies, for example RAS, and vaccines. There's lots of different things that we need to do, and it's very important that we think about this. And I tell my patients that I try and have a plan for them at the beginning because while the pathologic findings are important, there's still much of an unknown afterwards in terms of how we do it. And now we're actually adding more therapies in. It's not just IO therapies. There are clinical studies looking at ADCs and vaccines as we should. And there's lots of different questions here. These studies are very hard to do because you're looking at the benefit of preoperative therapy and you're looking at the benefit of postoperative therapy, so there are a lot of different variables. So these are very important questions, but not easy clinical studies to do.

Dr. Jackson:
If we look at this from a practical standpoint before we close, Dr. Spira, how can we ensure pathologic complete response is accurately and consistently incorporated into clinical workflows?

Dr. Spira:
It's super important. We have to have multidisciplinary teams. You have to get your pathologists trained to really look at those standards, right? Many big academic institutions do. There is a falloff as you get to other institutions as well, and that's important. It may or may not change the actual patient in front of you, but we do need standardization. We do need good evaluation here because we can now look back and say, who does better? If you think about all the patients and you have AI, you can really look at all these charts and figure out who's going to do better and who's not going to do better with these huge datasets. But it's also very important that we gather this data and look in a very systematic way.

And it's important that our surgeons talk to pathologists and oncologists both preoperatively and postoperatively. You know, there are physician shortages. There cannot be enough thoracic pathologists in the world. That's not realistic. So we have to get all our pathologists to understand where possible, and in the ideal world, have people that at least do this consistently.

And of course, you need institutions to buy in, right? They're the ones ultimately hiring pathologists as well as some of the other multidisciplinary team members as well. So it's something we've gotten better at over time, but we need to continue to work at.

Dr. Jackson:
And with those calls to action in mind, I want to thank my guest, Dr. Alexander Spira, for helping us better understand pathologic complete response in the perioperative non-small cell lung cancer setting. Dr. Spira, it was wonderful having you on the program.

Dr. Spira:
Great. Thanks.

Announcer:
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