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Choosing Between Neoadjuvant and Perioperative Strategies in NSCLC

Announcer:

This is *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Steve Jackson.

Dr. Jackson:

Welcome to *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and today, we're taking a closer look at how perioperative treatment strategies in resectable non-small cell lung cancer are evolving and how clinicians are deciding between neoadjuvant-only therapy and full perioperative approaches in real-world practice. Joining me in this conversation is Dr. Raghava Induru, a medical oncologist specializing in thoracic oncology at the Atrium Health Levine Cancer Institute in North Carolina. Dr. Induru, thanks for being here today.

Dr. Induru:

It's my pleasure, Steve. Thank you very much for having me here.

Dr. Jackson:

Our pleasure. To start us off, Dr. Induru, how has the integration of immunotherapy into perioperative care changed the way you think about treatment sequencing in resectable non-small cell lung cancer?

Dr. Induru:

That's a great question, Steve. I think one has to look at this from a historical standpoint as well to understand, how did we come here? I think the key aspects to know is lung cancer remains the deadliest cancer. In 2024, we had about a quarter of a million new cases of lung cancer diagnosed every single year. It still is the leading cause of cancer mortality. About 30 percent of the patients with non-small cell lung cancer are still diagnosed at an early stage. That means, at this stage, curative surgery is the treatment of choice. So what we know historically is the five-year survival data for non-small cell lung cancer with surgery alone in early stage is about 60 percent, especially when there is no nodal metastasis. But that survival rate drops to 37 percent when there is regional node metastasis. So these statistics really demonstrated the impact of systemic therapies that need to be part of the treatment for surgically resectable non-small cell lung cancer.

So that led to the adjuvant chemotherapy trials. I won't quote all the trials, but the latest meta-analysis showed a 5.4 percent absolute survival benefit with adjuvant chemotherapy. But we all know how difficult it is to tolerate adjuvant chemotherapy. In fact, only about 61 percent of patients complete the planned adjuvant chemotherapy. That led to the thought process of neoadjuvant chemotherapy to achieve better outcomes by helping the patients to complete the planned systemic therapy. And while that has demonstrated better completion, overall there has been no significant statistical overall survival benefit, whether you give neoadjuvant or adjuvant, indicating that there is a role for systemic therapy.

But lately, immunotherapy has really incorporated itself in the treatment of metastatic lung cancer, paving the way for using immune checkpoint inhibitors in the treatment of earlier-stage non-small cell lung cancer as well. So the addition of immunotherapy to the neoadjuvant, whether it's a pure neoadjuvant or perioperative systemic therapy, certainly has become the big change in the treatment of lung cancer now.

Dr. Jackson:

Alright, now let's take your last couple statements a step farther. When you're mapping out a treatment plan, what factors help you decide between a neoadjuvant-only approach and a full perioperative strategy?

Dr. Induru:

A very practical question in my view because most of our patients that we see in the community really do not fit into the clinical trial population where all these patients are studied. So when we come across an early-stage lung cancer or a new diagnosis of early-stage lung cancer or non-small cell lung cancer, the first and foremost step we take is a multidisciplinary discussion, usually at the level of the tumor board involving a cardiothoracic surgeon, radiologist, radiation oncologist, medical oncologist, pathologist, as well as a pulmonologist, and of course, the subsequent treatment team is involved, including a navigator. This is an extremely important step in order to approach this the right way.

The first decision we have to make is, is this resectable or not resectable? Because at this point of time, we still don't have any trial data to show that we can actually downstage the cancer. That means we do not approach early-stage lung cancer thinking, 'oh, we can downstage it and then decide if we can resect it or not.' So we have to determine the resectability of this early-stage non-small cell lung cancer. So that is the key factor.

The second step we look at is now that we have the resectability established, what is the best way to approach this—neoadjuvant versus perioperative? We really don't have the head-to-head data, but a typical patient for a neoadjuvant-only approach based on the CheckMate 816 data is someone who has a lower tumor burden, someone who is not keen on long-term systemic therapy, someone who is opposed to longer duration of chemotherapy, someone who may not be in the best state of their medical health—that means they're not too frail, but their performance status is not at the best—and someone who has social situations that limit them to get a more perioperative approach. So this is somewhat of a typical patient that we approach in a neoadjuvant setting.

Whereas, a perioperative patient is someone who has a larger tumor burden or more robust performance status, someone who is motivated to continue the treatment long term, someone who has a more of a multistation mediastinal disease, someone who has a large tumor size, or someone whom we anticipate is going to likely have residual disease. So these are some of the clinical factors we do consider when we're deciding between the neoadjuvant approach versus the perioperative approach.

Dr. Jackson:

And building off that, how do tumor-specific features like nodal involvement or histology shape your decisions?

Dr. Induru:

Yeah, great question. Nodal involvement is one of the key aspects of the tumor-related factors we consider when we're thinking of neoadjuvant versus a perioperative approach. For example, if someone is presenting with the multistation N2 lymph nodes, then our approach tends to be leaning towards a perioperative approach because of the risk of micrometastatic disease and the risk of distant disease that they would present with.

In fact, when we look at some of the perioperative data, if you take an example of a stage three disease that is N2 versus non-N2 disease, the event-free survival in both of those patients are relatively similar. But if I take the similar population—stage three—but N2 single-station versus N2 multistation, certainly adding the perioperative chemotherapy tends to be superior to chemotherapy in the multistation lymph node disease. But that superiority when we compare against a single-station is certainly higher than the N2 single-station disease. For someone with a larger tumor size, but especially multistation N2 disease, really we are leaning towards the perioperative approach.

In addition to that, from a histology standpoint, squamous tends to be a difficult histology to treat in the world of lung cancer because of the high tumor mutation burden and underlying medical comorbidities, as well as a high risk of presenting with distant disease and also overall long-term outcomes. So hence, when I see a squamous histology, we tend to lean towards a perioperative approach as opposed to the neoadjuvant-only approach.

Dr. Jackson:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Raghava Induru about therapeutic decision-making in resectable non-small cell lung cancer.

So, Dr. Induru, how do you incorporate pathologic response into your decision to either continue or stop therapy after surgery?

Dr. Induru:

The way I would approach that is if you take the neoadjuvant only or the CheckMate 816 data, these patients received three cycles of chemotherapy plus immunotherapy. And in patients with residual disease, it is at the physician's discretion to receive any subsequent adjuvant chemotherapy after surgery. But when we take the perioperative approach, irrespective of whether they achieve pathologic complete response or not, they continue to receive the adjuvant immune checkpoint inhibitors to complete the total of 12 months of treatment.

So at this point of time, when it comes to changing the approach based on pathologic complete response alone, we don't have clear

data on that. There are subsequent trials. Hopefully we'll have those answers soon. Meaning if I have a clinical situation where I start with a neoadjuvant approach with the three to four cycles of chemotherapy plus an immune checkpoint inhibitor and if I do achieve a pathologic complete response in these patients, should I forgo the need for adjuvant chemotherapy or should I continue the adjuvant chemotherapy based on the perioperative trials? We still don't have a clear answer on that.

But what I can tell you is in patients who have achieved pathologic complete response, the exploratory analysis from the CheckMate 816 trial shows that their survival is really high. That means a five-year 88 percent survival rate in patients who achieve pathologic complete response. Whereas in patients who do not achieve pathologic complete responses, that five-year survival drops down to 35 percent, indicating that while pathologic complete response is really a good benchmark to decide about the role of adjuvant therapy, at this point of time, based on that factor alone, we are not switching from a neoadjuvant approach to a perioperative approach based on that alone.

But in a practical world, if I have a patient who does achieve pathologic complete response, I do discuss with my patients the data, but not having clear prospective data plays into the shared decision-making. But if the patient feels like, 'you know what? I really don't want to continue any more systemic therapy,' I may err on the side of not proceeding with adjuvant immunotherapy. So the bottom line is: we still need clarity on the data. But the neoadjuvant data that we have so far looks very promising in patients achieving pathologic complete response.

Dr. Jackson:

And when you see residual disease after neoadjuvant therapy, how does that influence your next steps?

Dr. Induru:

These patients certainly have a very high risk of presenting with distant metastasis. In fact, when we see patients with residual disease, their five-year overall survival based on the CheckMate 816 study is about 35 percent. That means the majority of these patients present with distant metastasis, and these are the patients where we are strongly inclined towards completing the adjuvant perioperative regimen, meaning receiving the rest of the immunotherapy or immune checkpoint inhibitors. But I do not necessarily incorporate any further chemotherapy even in patients with residual disease, but I do prepare patients for a higher risk of presenting with distant metastasis.

Dr. Jackson:

And finally, Dr. Induru, how do patient-specific factors like performance status, surgical recovery, and personal preferences shape your choice between these strategies?

Dr. Induru:

Absolutely. That is in many ways the key aspect of decision-making, especially in a community setting—patient preference or their goals of care—and the shared decision-making is a key part when we are deciding between the neoadjuvant or perioperative approach while understanding the tumor-related factors—the histology, the grade, as well as the multistation N2 disease, the stage of the disease, etc. But the patient factors really play a bigger role.

Considerably though, patients ultimately weigh those factors, but still, it's in relation to the tumor-related factors. Meaning, for example, if I'm seeing a patient who is in their 40s diagnosed with a four-centimeter tumor with a single-station N2 disease and if the patient is not keen on taking four cycles of chemotherapy or continuing immunotherapy beyond surgery, I'm okay to proceed with CheckMate 816. But if I have a similar kind of a patient who strongly decides to continue on the perioperative regimen, irrespective of the pathologic component, but understanding that there is no prospective data to decipher that, I'm okay to continue as well. So ultimately, the patient factors play a big role in making that final decision.

Dr. Jackson:

Those are great insights for us to keep in mind as we come to the end of today's program. And I want to thank my guest, Dr. Raghava Induru, for joining me to share his perspective on tailoring perioperative therapy in patients with resectable non-small cell lung cancer. Dr. Induru, it was great having you on the program.

Dr. Induru:

Thank you.

Announcer:

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