Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/treating-patients-with-nscls-decision-making-and-surgical-considerations/16362/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Treating Patients with NSCLC: Decision-Making and Surgical Considerations

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss surgical considerations and decision-making when treating patients with non-small cell lung cancer, or NSCLC for short, is Dr. Ravi Rajaram. He's an Assistant Professor and the Clinical Medical Director in the Thoracic Center in the Department of Thoracic and Cardiovascular Surgery, Division of Surgery, at the University of Texas MD Anderson Cancer Center in Houston.

Dr. Rajaram, thanks for being here today.

Dr. Rajaram:
Thank you, Charles. Pleasure to be here.

Dr. Turck:
Well, to get us started, what can you tell us about the role of neoadjuvant chemoimmunotherapy before NSCLC tumor resection?

Dr. Rajaram:
Well, that's certainly where the field has moved, and it's taken a lot of years to get here. I think there's been a recognition for well over 20 years now that surgery alone is not sufficient to treat many stages of non-small cell lung cancer. Early trials well over 20 years ago showed that chemotherapy had a benefit, and that was typically done in the adjuvant setting, so we did surgery first, and then gave chemotherapy after, particularly for stage II and III patients. But as the years have gone on there's been more and more recognition that additional therapeutic agents are needed, and systemic agents that better control disease are going to benefit patients who go to surgery, so to that end, a number of trials have shown that immunotherapy combined with chemotherapy truly benefits patients with locally advanced lung cancers.

Dr. Turck:
I'd like to dive into an article you coauthored, titled "*Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial, The Phase 2 Platform NEOSTAR Trial*," which was published this year in *Nature Medicine*. Would you give us a little bit of background about how you and your team developed your study's objective?

Dr. Rajaram:
Sure. So NEOSTAR is a multiplatform trial. What I mean by that is it's a phase 2 trial with multiple arms looking at different combination therapies in the setting of resectable lung cancer. And so this particular article really pertains to publishing the outcomes from a combination of nivolumab and chemotherapy followed by surgery, as well as looking at outcomes related to nivolumab plus chemotherapy plus another immune checkpoint inhibitor, called ipilimumab. And so we studied these various combinations in these two arms and reported the results in this study.

Dr. Turck:
So what can you tell us about the specifics of the clinical trial design? And what details can you give us about the study's patient population?

Dr. Rajaram:
Right. So part of the reason and the interest here is that immunotherapy, or immune checkpoint inhibitors in general, many of them work via inhibition of PD-L1 or PD-1, and so combination—so drugs that you'd commonly hear about, like nivolumab or pembrolizumab, etc. Ipilimumab works a little bit differently. It is a CTLA-4 inhibitor, so again, immune checkpoint inhibitor, but with a different

mechanism of action, so it was really that combination of therapies in conjunction with chemotherapy that was particularly interesting. With respect to this study design, this is a phase 2 study looking at patients with stage 1B to 3A non-small cell lung cancer who are deemed surgical candidates, and the primary outcome was major pathologic response, which we define as 10 percent or fewer residual viable tumor cells.

Dr. Turck:
So speaking of outcomes, what can you tell us about the survival and response rates you saw in this study?

Dr. Rajaram:
Right. So the major pathological response rate was quite good. In the nivolumab plus chemotherapy arm, it was a little over 30 percent of patients had a major pathologic response, and that's much higher than we typically see with just, for example, chemotherapy prior to surgery. And then when you look at the group that had nivolumab plus chemotherapy plus ipilimumab, it was over 50 percent in terms of major pathologic response rate. And we've known for some time now that patients who have certain targetable mutations, like EGFR and ALK, those patients don't typically respond as well to immunotherapy, so if we actually exclude those patients from the study, those numbers, of course, drift even higher. So overall, I think this showed while it's difficult to compare our results with other studies due to differences in patient population, it showed that that combination of two immune checkpoint inhibitors working in different ways plus chemotherapy had a particularly strong outcome when it came to major pathologic response.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Ravi Rajaram about the phase 2 NEOSTAR trial for patients with NSCLC.

Jumping back a moment, what more can you tell us generally about the surgical approach to stage 3 NSCLC, Dr. Rajaram?

Dr. Rajaram:
Stage 3 disease is almost referred to as the most heterogeneous stage when it comes to non-small cell lung cancer. You have patients in there who have very large tumors but no lymph nodes positive. You have patients with larger tumors but N1 disease. You may have patients who have very small tumors in terms of the size but have N2 or mediastinal nodal disease, and so it's quite a grab bag or a bit of a larger bucket of patients who comprise stage 3.

For some time now there's been some controversy on how you manage stage 3. Part of that results from randomized controlled trials from well over 10 years ago that did not show a benefit when you look at combination therapy with surgery compared to, for example, chemoradiation, and there's been some equipoise between the two regarding what's the best approach. When it comes to stage 3 disease now, I think there's still some differences in practice variation across the board institution to institution, but a number of these trials looking at neoadjuvant chemotherapy and immunotherapy followed by surgery included stage 3 patients, and the results were quite strong. And as a result of that, I think a lot of surgeons think of stage 3 in appropriately selected patients as being a surgical disease ultimately coming down to everything from imaging characteristics patient's overall health and performance status.

Dr. Turck:
Now getting back to your study, Dr. Rajaram, I was wondering if you would elaborate on what you saw with respect to perioperative and surgical therapy outcomes.

Dr. Rajaram:
Yeah. So one of the things we look at as surgeons is what's the complete resection rate or R0 resection rate, meaning did we get a normal tissue completely around the tumor and the absence of any microscopic or macroscopic disease for that matter left behind, and in this study the R0 resection rate was 90 percent or higher in both arms. So overall, quite good. The complication rates were acceptable, and 30-to-90-day mortality rates for both arms were zero percent, and so ultimately, we consider surgery to be done fairly safely within this patient cohort of individuals getting chemo and immunotherapy.

Dr. Turck:
And is there anything we should know about what you found during the genetic sequencing and expression analysis of the tumors?

Dr. Rajaram:
I think when we're talking about mutational analyses within lung cancer in general, it's helpful to take a bit of a step back. As I kind of alluded to earlier, patients who have targetable mutations, like EGFR and ALK, they don't usually respond as well to immunotherapy, so as a result of that, a number of trials now exclude those types of patients from trials involving immunotherapy. But the important consideration here is that when it comes to lung cancer, not just advanced or stage IV lung cancer, which we've known for a while now that certain targeted agents benefit those individuals when it comes to patients with resectable disease, individuals who have certain mutations or alterations in their molecular profile of the tumor, well those are individuals who may benefit from a targeted therapy. So

the best example of that is going to be EGFR. EGFR mutations have been shown in a randomized controlled study using osimertinib to benefit individuals when compared to individuals who didn't get osimertinib. So that is one of many trials that are ongoing looking at the role of targeted therapies in resectable lung cancer.

So I think, ultimately, what we're probably going to see as these trials accrue and as more data becomes apparent is that patients who have certain targetable mutations are going to be probably treated with a combination of targeted therapies, like Osimertinib, in that example with EGFR, potentially with chemotherapy and surgery. And those without those targeted mutations for which we don't have an antibody-based therapy will probably get immunotherapy. There's more data, obviously, to come, but that's, I think, where the field is headed.

Dr. Turck:
Finally, Dr. Rajaram, would you like to leave our audience with any global takeaways about the role of neoadjuvant chemoimmunotherapy before NSCLC tumor resection?

Dr. Rajaram:
I think the big things here are that it's become standard of care for, as I mentioned, a lot of these patients. The results so far have shown that surgery can be done safely. They certainly can be more challenging, but overall, the safety profile for both surgery, as well as just the adverse event rate with that combination of drugs has shown to be fairly safe and comparable to just chemotherapy alone and that ultimately, this is going to be a very dynamic evolving process when it comes to the specific indications of chemoimmunotherapy depending on a patient's individual molecular profile. And we as surgeons certainly recognize that, and I think the field will be changing rapidly in the years to come.

Dr. Turck:
Well, those are some great insights as we close our discussion today, and I want to thank my guest, Dr. Ravi Rajaram, for joining me to share his insights about his recent study on NSCLC. Dr. Rajaram, it was great having you on the program.

Dr. Rajaram:
Thank you. Pleasure to be here.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.