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Clinical Updates in Non-Small Cell Lung Cancer: From Surveillance to Treatment

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This program is produced in partnership with the American College of Chest Physicians and is sponsored by AstraZeneca. And now, here's your host, Dr. Gerard Silvestri.

Dr. Silvestri:
Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, a pulmonologist and the Hillenbrand Professor of Thoracic Oncology at the Medical University of South Carolina. Joining me today to break down new findings in lung cancer management that were presented at 2025 conferences are Drs. Adam Fox and Anurag Singh.

Dr. Fox is a pulmonologist and Assistant Professor of Medicine at the Medical University of South Carolina in Charleston. Dr. Fox, thanks for being here.

Dr. Fox:
Thanks for having me on.

Dr. Silvestri:
And also joining us today is Dr. Anurag Singh, who's a Professor of Radiation Oncology and the Director of Radiation Research at the Roswell Park Cancer Center in Buffalo, New York. Dr. Singh, it's great to have you with us as well.

Dr. Singh:
Happy to be here, Gerard.

Dr. Silvestri:
We'll hear from Dr. Singh later on, but Dr. Fox, let's begin by discussing some updates in lung nodule management presented at the American Thoracic Society conference. If we start with the Watch the Spot trial, which explored surveillance strategies for monitoring patients with indeterminate pulmonary nodules, what stood out to you about that study and its findings?

Dr. Fox:
Well, it's the first prospective trial looking at surveillance strategies for small lung nodules. They had to measure 1.5 centimeters or less, and most of them ranged in the five to seven millimeter range. It was a large cluster randomized trial of 24 sites and included almost 35,000 patients. So this data is going to bring higher quality evidence for the management of the thousands of lung nodules that are identified each year.

They used a comparative effectiveness design between existing guidelines in past and present that were either more or less aggressive. So, "Does a less aggressive approach lead to more upstaging at the time of diagnosis?" is one of the key questions they're asking. Remember, the cancers in the trial were small. They're all stage one, and they should all be a tumor stage 1B small cancer if these nodules represent cancer. What about, "Does this conservative or aggressive approach impact survival or time to treatment when these are cancer?" These are the primary outcomes that were described in ATS this year in abstract form.

Not included in those results were three other categories of outcomes. They also looked at patient-reported or patient-centric outcomes around things like anxiety and satisfaction. They looked at resource utilization, so the number of visits or biopsies or scans that were in each of these groups. And they also looked at adherence to the recommended surveillance strategy.

When they have all this data reported, it will really shed light on important questions surrounding the management of small nodules.

Dr. Silvestri:
So Adam, is it fair to say that, just for example, tight follow-up—meaning getting a scan in three months, another one in six months, and nine months, and 12 months—is it fair to say that it compared a strategy of three-month follow-up as a general rule to a six-month follow-up strategy? Is that what the comparators were in this trial?

Dr. Fox:
Yeah, within those different risk and size categories, they compared those two strategies. And the conclusion was the more conservative approach was non-inferior to the more aggressive approach. They didn't see a difference in those lung cancer outcomes between the two groups in terms of the stage at diagnosis, the proportion of people who were diagnosed with a greater than stage T1b tumor, or survival.

Dr. Silvestri:
Okay, and what do you think about those other patient-centered outcomes? This grant was funded by PCORI, the Patient-Centered Outcome Research Institute, which really focuses on patient-centered outcomes. Can you tell me what you think about why they were or were not important things to look at?

Dr. Fox:
Well, seeing lung nodules and potential lung cancers is a large part of my practice. I see a lot of differing levels of anxiety about different things surrounding nodules, lung cancer, and waiting for these results. So I think taking a patient-centered approach is very important.

When I'm determining the timeframe and recommending the next scan, I'm also gauging the patient's anxiety level to try to see if there's more reassurance that I need, or if the patient really does prefer a more aggressive approach that may suit their needs better. So I do try to match my recommendations with the risk that is before me. But I see a lot of patient anxiety around lung nodules, even ones that almost certainly are not going to be end up being cancer. There is still a lot of anxiety that some patients experience with this condition.

Dr. Silvestri:
I think that's true. And I would say the other part of this is the resource utilization and biopsies, and the fact that patients sometimes have to go through biopsies of very small nodules and not get a diagnostic result, which can be equally as anxiety provoking. What are your thoughts on that?

Dr. Fox:
I'm really looking forward to those results being published because the average nodule size they included any nodule less than 1.5 centimeters, and most nodules in the centimeter to centimeter and a half range are usually decent candidates for biopsy. But the median size was five millimeters with a standard deviation—I think around four to seven millimeters total if I'm remembering correctly. And with a lot of nodules in the five to seven-millimeter range, I think you're going to have diminishing yields from biopsies. So it'll be interesting to see how many procedures were attempted and at what size.

Dr. Silvestri:
And lastly on this study, the adherence to recommended surveillance—we know that adherence for things like coming back for a lung cancer screening is actually quite low. Does it matter if you're meant to follow closely or a little further out, conservatively or a little less aggressively? Does it really matter if they don't come back at all? How important is that adherence metric for this trial?

Dr. Fox:
I think that's critical. Much like we've seen in the benefits for lung cancer screening, a single scan of a nodule this size is unlikely to be of much benefit at all because it's difficult to biopsy and it's not very actionable. While the risk is low, I think in their trial, they had just about 1.5 percent of their nodules having cancer. So that was about 500 of those nodules. That's still relevant to those patients for sure, and so even though risk is low, confirming that with stability, the time-honored tradition of surveillance of these small lung nodules for 18 months to two years, I think is critical for people to have that follow up.

Dr. Silvestri:
Thank you. And we're going to now turn to the VERITAS study published in the *New England Journal of Medicine*, which randomized patients to either have a needle biopsy for their nodule or have a guided bronchoscopy for their nodule. Can you tell us a bit about the trial itself and what we learned from that trial?

Dr. Fox:
Absolutely. So historically, the transthoracic needle biopsy approach has always had this description of a higher diagnostic yield, commonly in the literature around 90 percent of a likelihood of getting the answer if cancer is to be found. And over the last couple of decades, we've seen a lot of advancements in technology for bronchoscopy. So over that time of advancement, the question becomes,

how much better is bronchoscopy potentially becoming? And how does it stack up to the transthoracic needle biopsy?

The design of this trial has many strengths. It has clearly defined outcome measures for diagnostic accuracy and yield, which has plagued the diagnostic biopsy literature for some time. It recruited from several sites, so it's a multi-center trial. Consecutive patients at these sites who are referred for biopsy were screened for eligibility. And importantly, they had to be eligible for both procedures. Both pulmonary and interventional radiology had to say for their type of biopsy that their case was reasonable. And patients were randomized in a 1:1 fashion.

And finally, they had a central blinded review of both that eligibility for both procedures, and for that final outcome of diagnostic accuracy, they had a blinded central review of what the pathology showed and whether it should count as diagnostic or not. So this really helps to guard against the largest concerns for validity for a trial like this, which is selection bias between the two groups. I think they've guarded against that pretty well.

In the end, navigational bronchoscopy was found to be non-inferior to transthoracic needle biopsy with less complications. The lower rate of complications has been described in the literature for some time, particularly for pneumothorax. But the surprising thing was the diagnostic yield and accuracy were both in the 70 to 80 percent range. And Gerard, you led one of the more recent systematic reviews for peripheral lung nodule biopsy with bronchoscopy and found a similar pooled diagnostic yield around 70 percent. The surprising thing was that transthoracic needle biopsy really underperformed those past reports of near 90 percent and performed similarly in that 70 to 80 percent range.

Dr. Silvestri:
Well, thank you so much. I'm going to leave it there for now.

And for those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, and I'm speaking with Drs. Adam Fox and Anu Singh about multidisciplinary updates in lung cancer care presented at major conferences in 2025.

Turning to you now, Dr. Singh, let's shift over to treatment advances across early and locally advanced stages, starting with the STARS trial and the five-year follow-up data comparing SBRT with surgery. It sparked a lot of discussion at ASTRO. What's your take on the findings and their implications for early-stage patients?

Dr. Singh:
Thanks, Gerard. The long-term data 10 years from the revised STARS trial compared two prospective matched cohorts of 80 patients each, taken from an SBRT group and a surgical group. So this was not a randomized trial, but two prospective matched cohorts. And what it showed is that SBRT, also known as SABR, had equivalent outcomes in terms of overall survival, event-free survival, and quality of life when compared to VATS lobectomy with mediastinal sampling.

There are several randomized trials comparing SABR and surgery, which are ongoing, and hopefully the VA trial called VALOR will report sometime soon, and we will have a prospective answer. Until then, SABR and surgery should remain as a multidisciplinary option for all patients to be considered depending on their needs and specific circumstances.

Dr. Silvestri:
Dr. Singh, I'm going to push back on that a little bit and ask you—in the past, it's always been surgery is the gold standard, and SBRT for those who are not capable of undergoing surgery due to multi-comorbidity—can you tell me if you think that's changing over time? I'd particularly like you to address what you do with octogenarians who come to see both the surgeon and a medical radiation oncologist, irrespective of their comorbidity score. Is that something that you think might be changing over the past few years and into the future?

Dr. Singh:
I think in general, as patients themselves become more educated about radiation options, there is an increasing percentage of patients who ask for radiation first. And these are sometimes even younger patients in whom perhaps we tend to be more circumspect about that.

Now, obviously, as the patients get older and they have a clear discussion with both the radiation oncologist and the surgeon about what's involved in their respective treatment modalities, it is becoming increasingly clear that older patients in particular maybe want to avoid general anesthesia and other things so that even when they have the choice, they are tending more towards radiation than they would have in the past.

Is that the majority of patients? Absolutely not. But there is an increasing group of patients who've had surgery and then at some later point develop another nodule and have SBRT for that nodule. And what we're finding is that patients, when they've experienced both, have a lot of decision regret about choosing surgery first.

Now, when we look at decision regret issues and patients who've just had radiation, they also have decision regret. So it's not clean data by any means, but there is at least increasing data amongst a population of people who are very familiar with both modalities because they've had them that patients who have had both seem to prefer the radiation option, likely because there's no general anesthesia, there's no post-operative pain, and they can continue on with their lives with really little to no immediate side effects.

But what we do know is that long-term side effects of radiation and surgery do even out. And so while there is an acute difference, there's not a long-term difference. And so this type of nuanced discussion really requires both the surgeon and the radiation oncologist to see the patient and fully educate them before coming to a decision.

Dr. Silvestri:
Yes, and I couldn't agree with you more. That decision really should be patient centered. At the end of the day, it's the patient who's going through either of those procedures, and it sure would be nice to get the results of a randomized trial.

Moving along to another important update that came from an ASCO presentation on the trial SWOG/NRG S1914, which looked at dual checkpoint inhibition—so dual immunotherapy after chemoradiation—what stood out to you here? And before you answer that, it built on the PACIFIC trial, which pulmonologists may not be aware of. So could you just tell us briefly what the current standard of care is within the PACIFIC trial, and then add on what we learned from this trial?

Dr. Singh:
Sure. So in the PACIFIC trial, they were dealing with stage three patients who had gotten chemoradiation therapy and were randomized to placebo or immunotherapy thereafter durvalumab. And what they found was that patients who got durvalumab had significantly improved overall and relapse-free survival. And so based on that, adjuvant durvalumab became the standard of care for stage three lung cancer patients receiving chemoradiation therapy.

This intergroup study wanted to build on that by asking the question, in early-stage patients—stage one patients, those patients who still have a high likelihood of distant failure—and so the question was, they're getting SABR, but by adding chemotherapy before, during, and after, could you actually improve on that rate of distant failure, and therefore improve the overall survival? And the agent used was atezolizumab, and unfortunately, there was no improvement in overall survival or event-free survival. Making matters worse, the toxicity was significantly increased in the atezolizumab arm.

So what we've found here is that immunotherapy after chemoradiation in stage three is definitely better than not. But in a study called PACIFIC-2, we looked at the stage three population with adding chemoradiation plus immunotherapy together with adjuvant immunotherapy, and there was no benefit compared to chemoradiation alone.

So it appears that this may be an issue where the timing is actually very relevant. And so in the early-stage setting, we can say that neoadjuvant, concurrent, and adjuvant immunotherapy is not the answer, at least when given with atezolizumab. There is a trial called PACIFIC-4, which uses durvalumab adjuvant with SABR, and that trial has yet to report.

Dr. Silvestri:
Well, thank you for those comments, Dr. Singh. And I think for pulmonologists, not necessarily understanding the trials, but understanding that immunotherapy has a major role now in almost all aspects of treating non-small cell lung cancer and even small cell lung cancer, it's not perfect for every case, and we need to look out for the side effects, particularly immunotherapy-induced pneumonitis.

As those key insights bring us to the end of today's discussion, I want to thank my guests, Drs. Adam Fox and Anurag Singh, for sharing their perspectives on these new findings in lung cancer and their implications for patient care. Dr. Fox, Dr. Singh, thanks so much for being here.

Dr. Singh:
Thanks, Gerard, it was great.

Dr. Fox:
Thanks for having me on.

Announcer:
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