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Diagnosing and Staging Non-Small Cell Lung Cancer: Key Updates and Evolving Strategies

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:
This is *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 discuss updates in diagnosing and staging non-small cell lung cancer are Drs. Anne Gonzalez and Jeffrey Velotta.

Dr. Gonzalez is a pulmonary and critical care physician, a researcher in the Translational Research and Respiratory Diseases Program, and an Associate Professor in the Department of Medicine at McGill University in Montreal.

Dr. Gonzalez, welcome to the program.

Dr. Gonzalez:
Thank you. It's a pleasure to be here.

Dr. Silvestri:
Also joining us is Dr. Velotta, who is a leading thoracic surgeon specializing in complex cancers, a Clinical Professor in the Department of Clinical Science at the Kaiser Permanente Bernard J. Tyson School of Medicine, and a Clinical Assistant Professor in the Department of Surgery at UCSF School of Medicine in California.

Dr. Velotta, it's great to have you with us as well.

Dr. Velotta:
Thank you. Happy to be here.

Dr. Silvestri:
Okay, let's jump right in. For the first half of the program, I'd like to focus on EBUS as a diagnostic and staging tool and hear insights from Dr. Anne Gonzalez.

So, Dr. Gonzalez, when mediastinal staging is indicated, what do you consider to be an acceptable minimum for a thorough EBUS staging?

Dr. Gonzalez:
Yeah, thank you. That's an important question and, in fact, one that both Dr. Velotta and myself are very interested in. We're currently working with a group of experts on an ATS clinical statement on this very topic, and so really, that tells you that there isn't currently one broadly accepted standard. But really, generally, when it comes to EBUS staging of the mediastinum, I think what's essential is to carefully review the available CT and PET imaging but then proceed with systematic sampling of the mediastinum as opposed to selective sampling where only the CT and/or PET positive nodes would be targeted.

And generally, in the presence of a normal mediastinum on PET and CT, the recommended minimum standard would be to have sampling of all nodes that are at least 5 millimeters in diameter. And generally, some guidelines, including from ESTS, have recommended to have sampling of at least the lower paratracheal nodes—right and left—and the subcarinal nodes. Although, again, if

there are no nodes at those stations that are greater than 5 millimeters, then it may not be possible to sample the stations. But that's a minimum that has been recommended.

Dr. Silvestri:
And would you say that if you had a peripheral 2-centimeter nodule and you were doing a procedure to go after that and then did mediastinal staging prior to surgery, is that a different kind of EBUS compared to, let's say, somebody with bulky stage 3A-looking, right paratracheal, right hilar, right subcarinal lymph node in terms of the depth that you have to go into it, and the length of time it takes to do that type, versus someone with little to no mediastinal adenopathy on CT or PET?

Dr. Gonzalez:
Yeah, absolutely. I think that chasing CT or PET-positive nodes—so, CT meaning nodes that are at least 10 millimeters in short axis on a pre-procedure CT is generally a much more straightforward and quicker procedure and one that can be shortened by the availability of ROSE, right? If there are suspicious nodes and we start from the contralateral hilar mediastinal nodes, depending on the setting and the imaging, and have positive ROSE, then that may preclude sub sampling of N2 or N1 nodes. If we have a positive N3, and then we just can focus on ensuring sufficient tissue is acquired for molecular testing as opposed to really doing systematic sampling of the normal mediastinum in cases where, in fact, such staging of the mediastinum is indicated—so, generally, whether it's centrally located lesions, lesions greater than 3 centimeters, or in the presence of hilar nodes. But to go after those smaller and normal sized but over 5 millimeter mediastinal nodes is a procedure that takes longer to have sufficient samples—a minimum of three samples per nodal station that is targeted and to have a thorough procedure.

And I think a challenge is doing those types of systematic staging procedures in the absence of general anesthesia. So, I know across the US, a lot of advanced bronchoscopy is now performed with anesthesia. In my healthcare setting in Montreal, Canada, we still have challenges accessing anesthesia, so we do the vast majority of our EBUS under conscious sedation. And of course, that is more challenging when you're trying to sample multiple normal-sized nodal stations.

Dr. Silvestri:
While we use PET scan to help direct where we do our first biopsy, particularly in bulky disease, can we trust PET if just to say, well, that's a positive lymph node, I'm going to send them on to chemotherapy, radiation, or immunotherapy without doing a biopsy of those nodes?

Dr. Gonzalez:
No, I think it’s very important to remember that even with integrated PET CT scans, the sensitivity and specificity is far from perfect. And so you can have false negative PET scans where if the nodes are small or they're just microscopic deposits of malignant cells—those may be missed by PET. But importantly, we can also have false positive PET results, whether that's due to inflammation, sarcoid, anthracotic nodes, or infection, histoplasma being an example in my area and other areas. And so, of course, a false positive PET scan result has important implications, right? It means potentially you are going to exclude someone from curative treatments. So it's very important to have a tissue confirmation of those PET findings.

Dr. Silvestri:
And very quickly, our surgical colleagues have done a really good job of holding their own society to task as it comes to metrics for what is an adequate mediastinoscopy and how many nodes are adequately resected during proper resection for a lung cancer. Do we have any metrics or guidance there from the ACCP or ISLC as the benchmarks? Or is that something you're developing with your new statement?

Dr. Gonzalez:
Yeah, I think that's something we want to look at. There's been some recommendations, particularly from the European Society of Thoracic Surgeons, where as part of their guideline recommendations, they stated that a good minimum would be to have stations for R4 L7 and focus on nodes that are at least 5 millimeters. But it's not been something that's broadly established. It has been used in the UK as a quality metrics following both using quality indicators inspired by the last addition of the CHEST guidelines and also those ESTS recommendations.

But I think that is part of what this latest ATS clinical statement that we're working on aims to achieve—to try to have some sort of consensus on what is an acceptable minimum for a thorough mediastinal staging with EBUS.

Dr. Silvestri:
As a follow-up, are you mostly using cytologic specimens and are they as good as people have talked about core and needle biopsies versus cytology? Are your cytologic specimens for EBUS good enough for NGS testing, PD-L1 testing, and other assays?

Dr. Gonzalez:
Yeah. How cytological specimens are processed varies and there isn't one perfect way to do it. So at my institution, we put needle samples in saline and add CytoLyt at the end once the sample is complete, and then those get eventually spun down and our formalin fixed and paraffin embedded and used successfully for NGS testing and PD-L1 testing. We do have good data looking at feasibility of EGFR testing and ALK testing as well as PD-L1 testing in EBUS samples. And some data we reviewed as part of a systematic review that was published last year in CHEST comparing cytological versus histological samples for PD-L1 assessment, examining from all the studies we were able to find where there were paired specimens of both cytology and histology where PD-L1 testing had been done, and showing that cytological samples, including EBUS samples, are adequate in the vast majority of cases to assess PD-L1 expression at the 1 percent and 50 percent cut-off. So the vast majority of our EBUS samples are 21- or 22-gauge and processed as cytological samples where we've gotten into sending samples, and formalin has really been, as part of clinical trials, a requirement. The reality is that a lot of the clinical trials still require formalin samples, or what they call core needle biopsies. So we may, in that setting, send 19-gauge needle samples in formalin to meet those requirements.

Dr. Silvestri:
Well, thank you for that. 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. Anne Gonzalez and Jeffrey Velotta about the diagnosis and staging of non-small cell lung cancer.

So, in the first half of our discussion, we heard from Dr. Gonzalez, but now let's turn to you, Dr. Velotta, for the surgical perspective. The American Joint Committee on Cancer recently updated the TNM staging system for lung cancer. Can you walk us through what's new and what these changes mean for surgical planning?

Dr. Velotta:
Yes, absolutely, Gerard. So, I think the main thing to remember is that the T stage hasn't changed, which I think is a great thing. So size cut-offs are still the same. So memorizing that is not really an issue and that hasn't changed. But what really has changed is the N and the M. So, for the N, N2A and N2B, that's been broken down and that's made it a little bit more complex. However, with that being said, N2A means one single station mediastinal node, and N2B means multi-station, 2-plus, essentially. And I think the way that's changed things is that for surgeons, that's allowed us to be slightly more "aggressive" than what classically was stage 3A. So, prior to this 7th and 8th edition, it was always N2 disease is stage 3A plus or minus B disease, but it was considered not always surgical disease.

Now, with the advent of neoadjuvant chemo/immuno or perioperative chemo/immuno and N2A—for example, a T1B N2A lesion—is now a stage 2B tumor. So that therefore implies that that could be more of a surgical disease with a perioperative neoadjuvant approach. But that's changed the lay of the landscape versus an N2B, when you have multi-station lymphadenopathy, that seems to suggest, and we see that from the survival curves from the World Lung—that in N2B, the survival is much worse than, say, N2A. So that may shy surgeons alone and/or oncologists from recommending perioperative neoadjuvant chemotherapy and then surgery, and then those patients may be better qualified for, let's say, a PACIFIC trial with chemoradiation followed by durvalumab.

So I think that's what's changed the landscape a little bit more. It's made it more complex, but it's made N2 disease now potentially more operable because we have better systemic chemoimmunotherapy than we had four or five years ago.

Dr. Silvestri:
Yeah, not to push back, but the trials—816 for example, CHECKMATE-816—didn't distinguish between those two patients. And actually, patients with 3A in the old 3A did really well with neoadjuvant. Can you answer why then I should shy away, if I'm a surgeon, from N2 multi-station disease?

Dr. Velotta:
Absolutely. And you hit the nail on the head, Gerard. That's the issue right now, is that all these trials, like for example CHECKMATE-816, it was the wild west. Even though you had these top centers, you can't compare. It's like comparing apples to oranges. Some may have been bulky, some have been one big for our lymph nodes, so it was totally subjective.

And that's kind of what I'm getting at. The controversy now is that depending on what surgeon you talked to or what tumor board you're at, you'll see five different answers; whether it's resectable or not, or whether they would take that patient to the operating room with 2R, 4R and 7. You may get a different answer from me than you may get from another surgeon. So that could be potentially operable, so it's not to say that the N2A and N2B makes it that you're not going to operate on N2B per se. It just helps delineate and stratify your risk and prognosis, meaning I may be more aggressive about a patient that's maybe older or not super fit, but it's just an N2A lymph node, about potentially offering surgery, versus, if they're already N2B and they're pretty less healthy, that may push you towards nonoperative. Now, if they're healthy and you have N2A or N2B, yes, I think that's when some of us surgeons would say, "Well, we would still operate on that now." Especially when in the past, a lot of surgeons shied away from multi-station lymphadenopathy for N2B disease because of

the fact that we didn't have great data or we didn't have great perioperative immunotherapy-type approaches. But now you're seeing that we do because some of these patients in these trials did have multi-station lymphadenopathy—we just don't know exactly which ones.

But the bottom line is that opens the door for us as surgeons to actually absolutely operate on N2A plus N2B with better systemic therapy. So, for example, for me, I think the way it opens it up is that it can risk stratify, and it can go and tell me that it is okay to potentially offer a surgery with an N2B component.

Dr. Silvestri:
That's great. I want to go on talk a little bit about mediastinal staging in your practice. When do you decide upfront to do mediastinoscopy as opposed to how that's evolved with the newer technologies and data around minimally invasive with EBUS? Can you tell us when you say, "I think mediastinoscopy is needed here?"

Dr. Velotta:
Yeah, absolutely. So our practice out here in Northern California follows NCCN and CHEST guidelines. However, we're not as dogmatic. We're a little bit more subjective. So, for example, like Dr. Gonzalez pointed out correctly, as the CHEST guidelines and the NCCN guidelines basically show, if you have a negative CT for nodes and negative PET for nodes, but you have a central tumor, usually less than the inner one-third to two-thirds of lung, no matter what the size, or a peripheral tumor greater than 3 centimeters—or, say, on the CT scan, you see a 1.1 centimeter hilar lymph node that didn't light up on a PET scan—those patients all, based on the guidelines right now, are recommended for mediastinal staging.

I would say in my current practice, or what we've solidified here as our guideline here in Northern California in our system, is a little bit less rigid. So, for example, if I have a negative CT and a negative PET on a 3.5 centimeter peripheral lesion, I will not go and do mediastinal staging because the difference is—and I'm just giving that as an example—now, especially in the surgery literature and the surgery guidelines from the American College of Surgeons and this commission on cancer, we've finally come to grips with making surgeons do proper lymph node dissection sampling and staging in the operating room.

So because of that, it's pushed a lot of surgeons that didn't always do full lymph node dissections and sampling for small peripheral tumors. They're now really forced to. You have to be 80 percent compliant at least, and pretty soon, you're going to have to be 90 to 95 percent compliant. So that forces you if for, say, you may have missed that small micrometastatic node that was maybe positive or plus or minus, although the EBUS may not have gotten it because it's less than 5 millimeters, we'll get that during our surgery. So what I'm saying is, now that the surgeons we're forcing the rest of the country to get 3N, 2N and 1, you can be a little bit more liberal and not as dogmatic, I think in some of these, getting preoperative, invasive staging already, where that's another procedure and plus, you may not even be able to biopsy anyways, because it's a less than 5 millimeter lymph node—now I'd bypass that.

An essential tumor, a 1-centimeter central tumor with a negative CT and negative PET, I don't do EBUS or mediastinoscopy beforehand. So, following the guidance, modification of it because I know that I'm going to do really good lymph node staging during my operation.

Dr. Silvestri:
That's a great answer, and I would just add a couple quick points before we close up. One is that, as a pulmonologist, you try not to have an ego in these things, so sometimes, I would think, "You know what, I'm sure this lymph node is positive, but I just didn't get it on EBUS. And so, I asked my surgeon to go in and do the med." And I think those discussions are important.

I'd also say that, look, between 5 and 8 percent of CT and PET negative have micrometastatic disease upon resection, and I think it's okay to resect those patients because then you have the data, as you said, and then you can give them adjuvant therapy coming out. So I appreciate your answers on both of those.

As we approach the end of the program, I'd like to bring both guests back together and ask each of them to share a key takeaway from our discussion. Dr. Gonzalez, can you care to start us off, please?

Dr. Gonzalez:
Yeah, sure. As a pulmonologist, I think it's important to remember that we have a really central role to play on the intake in terms of the evaluation of these patients with lung cancer and their staging, and EBUS has had a major impact, obviously. But if you're going to do it, then it's important to do it well and do systematic sampling and thoroughly sample at minimum the lower paratracheals, subcarinal stations, and any nodes that are at least 5 millimeters, and to remember that those are adequate samples for PD-L1 testing and molecular testing. And so I think that's also a really important point.

And as much as possible, certainly at our institution, the integration of reflex testing has been extremely helpful in improving timeliness

and an access to therapy and clinical trials.

Dr. Silvestri:
I would add that I'd like people to take at least five to six samples for molecular testing as opposed to three, which makes the diagnosis adequately but doesn't give you enough to adequately do molecular analysis.

And Dr. Velotta, I'll give you the final word.

Dr. Velotta:
I think the 9th edition TNM staging where it revolves the complexity of N2A and N2B and now M1C with the extrathoracic sites and whatnot—I think staging has now come center stage even more so. We've all known about staging and that's important, but now with the complexity, especially with the great neoadjuvant strategies and whatnot, and even the stage 4 therapies, that we have to do better at staging. And so, this is a great avenue to say we need to be staging patients better. Dr. Gonzalez talked about appropriate and adequate minimum lymph node routine mediastinal staging, so for sure that.

But from a multidisciplinary view, I would say the take-home point is that, as a thoracic surgeon, medical oncologist, radiation oncologist, and pulmonologist/interventional pulmonologist, we work a lot more together in tandem than I think we ever have. Five years ago, it was like you talked to pulmonologists, but not as much intersection, not as much interaction. But now, with all this new advance of whether you get surgery first, or you don't get surgery, or you can do ablation, or do all these different things, I think I find myself now, with the new staging, really being involved with our pulmonologists and interventional pulmonologists a lot more so because staging is so important. And we as thoracic surgeons are so reliant on our pulmonologists, now even more so.

So I think having that good relationship is really nice to weigh in on things on when they should be staged and when they should not be.

Dr. Silvestri:
As those key insights bring us to the end of today's discussion, I want to thank my guests, Dr. Anne Gonzalez and Dr. Jeff Velotta, for joining me to share their perspectives on the diagnosis and staging in non-small cell lung cancer, early stage. Anne and Jeff, thank you so much for being here.

Dr. Gonzalez:
Thank you.

Dr. Velotta:
Thank you.

Announcer:
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