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Bronchoscopy, EBUS-TBNA, and CT-Guided Biopsy

Announcer Intro:
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Dr. Edell:
Good evening. On behalf of the American College of Chest Physicians and my co-chair, Dr. Septimiu Murgu from the University of Chicago, I'm Eric Edell, and I'd like to welcome you to the second webinar in a series of five webinars on Lung Cancer Management in the Time of Crisis and Beyond. We're very honored and privileged to have two international and national speakers with us today to discuss the topic of this webinar, which is bronchoscopy, EBUS-TBNA, and CT-guided biopsy in the management of lung cancer.

Our first speaker – both of our speakers probably don't need a lot of introduction to the audience, but our first speaker will be Fabien Maldonado. Dr. Maldonado is Professor of Medicine and Thoracic Surgery at Vanderbilt University and also Professor of Mechanical Engineering. He'll be followed by Professor Nichole Tanner from the Medical University of South Carolina.

Dr. Murgu will be monitoring the chat box. We encourage you to send questions through. If a question comes through pertinent to one of the presentations during that presentation, we'd be happy to take it and have the speaker answer the question. We will have questions and answers at the end. And we'll summarize for the next webinars coming to you over the course of this next few months.

So sit back enjoy. I think there's an awful lot of information and knowledge that we'll be able to take from our illustrious speakers.

Dr. Maldonado, would you please take the slide deck?

Dr. Maldonado:
And well, thanks. First of all, thank you so much for the kind invitation. I want to thank the CHEST staff and my esteemed colleagues, Dr. Murgu and Edell. And my co-panel, Dr. Nichole Tanner. It's a pleasure to be here. We'll try to go through this in a timely fashion so that we have time for Q&As. This particular session is going to focus on the diagnostic approach to indeterminate pulmonary nodules. There's a chat box if you have questions. And we will keep - try to keep track of that and answer your questions either during the talk or after, during the Q&A session.

Here are my disclosures.

And we will go ahead and start with this question that I will read to you and not give you the answer. I guess that is the way it's supposed to work. So this is a 54-year-old male smoker with a 2.5-centimeter PET-positive right upper lobe spiculated nodule in the upper third of the lung with moderate emphysema who is referred for biopsy. The mediastinum is radiologically normal by both PET and CT. Which of

the following is correct? A: A bronchoscopy should be preferred as the risk of mediastinal lymph node involvement exceed 25%; B: Trying to move that box here. It's too small for me to read. There is no evidence that bronchoscopy is associated with a higher risk of COVID-19 transmission to healthcare workers than CT-guided biopsy. C: Rapid on-site evaluation during bronchoscopy is associated with improved diagnostic yield, or D: Forceps biopsies and larger needles are associated with a higher likelihood of successful molecular analysis. And we'll give you a few seconds to respond.

Okay, great, that's wonderful. So like I promised, I'm not going to give you the answer. And we'll keep going.

And we'll start with this particular case scenario. So this is a patient referred to us after being diagnosed with a 3.2-centimeter right upper lobe adenocarcinoma and a positive 10R node. And it turns out to have this small, somewhat suspicious lesion in the left lower lobe. And the question is what to do with this. The surgeon would like resolution - diagnostic resolution of this before proceeding with surgery, which is understandable. And this raises the question of what is the best modality for staging?

And I will start by pointing out the obvious fact that when we do biopsies of lung nodules, we try to do a number of things in the same setting, establish the diagnosis, but also establish staging if we can. And that it typically involves staging the mediastinum, for us, bronchoscopies, but also providing enough material for ancillary testing. And by that, I mean molecular testing. So here are some of the options we have available to us. Historically, I think CT-guided biopsy has been the traditional route for biopsies, we get great data, at least from a quantitative standpoint, perhaps not qualitative standpoint. But here's a nice meta-analysis that was published in the CHEST guidelines for lung cancer with 46 studies. Thousands of patients with a polled sensitivity of about 90%.

Now, the devil being in the details, if you look at lesions that are a little smaller, less than 1.5 centimeter, that sensitivity goes down to 70 and 80%. There are downsides. And the typical downsides that are referenced for CT-guided biopsy is the rate of pneumothorax, which is about 15% in a large population study, 6% really requiring chest tube, and 1% hemorrhage. But in fact, I think the main downsides of this procedure compared to bronchoscopy is that you can only biopsy one target lesion, but more importantly, staging of the mediastinum is not possible.

Now, bronchoscopy, on the other hand, may allow you to do this thing. Conventional bronchoscopy, however, and here I'm talking about the conventional bronchoscope with a C-arm is not particularly accurate. Here's another meta-analysis from the same CHEST guidelines, 34 studies over 5,000 patients, and the diagnostic yield is 34% for lesions less than 2 centimeters going up to 63% for the lesions that are over 2 centimeter. And we'll talk about how these data actually may be somewhat misleading. Now the rate of pneumothorax is arguably a lot less than with CT-guided biopsy, which as I pointed out, is usually the benefit of a bronchoscopy that is mentioned.

Here's a nice meta-analysis for guided bronchoscopy, that would include electromagnetic navigation, but also radio EBUS assisted bronchoscopy. And this is now a somewhat dated meta-analysis looking at mostly retrospective studies with an overall diagnostic yield of 70%. So better than conventional bronchoscopy, but again with a number of caveats that are inherent in the study design of these included studies.

Here's a prospective study which is the largest prospective single-arm non-comparative study on navigation bronchoscopy. The NAVIGATE study reporting a diagnostic yield of 73%, excluding unsuccessful navigation up to 78%, with lesion sizes that are very respectable, about half of them being less than 2 centimeters. And the bronchus sign, meaning having an airway going straight into the lesion also being present in less than half of the cases.

Now, what do we have in terms of comparative study regarding diagnostic bronchoscopy and CT-guided biopsy? Unfortunately, not a lot. This is a retrospective study looking at two cohorts. So cohorts of patient with CT-guided biopsy and a cohort of patients with electromagnetic navigation. This is out of the Cleveland Clinic about 150 procedures in each arm, and the diagnostic yield after adjustment for just about every possible confounder you could think of was favoring CT-guided biopsy dramatically. And I think that's intuitively what everybody would think about when we think about these two diagnostic modalities. The diagnostic yield forced you to get a biopsy was 86% versus 66%, which is again, the same number that keeps coming back for bronchoscopy about 70%.

Now, Dr. Murgu yesterday sent me this paper that I missed completely when it came out, and I spent a good 2 hours reading it because that was tried very, very hard to find something wrong with it. But this is an amazing paper, methodologically very robust meta-analysis at - with patient level data looking at 6 retrospective cohort studies, over 2,000 patients. And what they were trying to figure out was whether going through the pleura with a needle and biopsying the lung cancer may actually result in more involvement of the pleural space with malignant pleural effusion. And you can see here that the hazard ratio for isolated pleural recurrence was 2.5, and concurrent pleural recurrence with other metastasis about 2 as well. Again, I tried to do my best to figure out what was wrong methodologically with these, aside from the fact that meta-analysis, usually, we talked about garbage in, garbage out, which is probably the case here as well. But nonetheless, with patient level data that really strengthened this analysis. So this raises concern actually, that

I didn't have until yesterday about the potential for track seating [09:21] of cancer with CT-guided biopsy. Now the effect is probably very, very small. And actually the effect on patient important endpoints like overall survival, and lung cancer specific survival were not statistically significant except for the younger patients.

Here's a very simple algorithm of the way I would approach bronchoscopy versus CT-guided biopsy. And in fact, to be quite honest with you, for those that would benefit from either or we have an multicenter, randomized controlled trial going on right now where we're randomizing patients for navigational bronchoscopy versus CT-guided biopsy. But here's a pretty obvious self-explanatory algorithm. If you have abnormal lymph nodes, obviously you're going to favor bronchoscopy. The diagnosis will probably be reached with EBUS. And if you have several lung nodules that you think are amenable to bronchoscopy, then you probably should go for that as well. Otherwise, I think transthoracic needle aspiration remains the gold standard to this day.

Should you go to bronchoscopy because you believe that the mediastinum might be involved? And obviously I mentioned that if you have a radiologically abnormal mediastinum, this is probably what you should do, bronchoscopy, whether by PET or CT. But what if the rad - the mediastinum is radiologically – excuse me - normal by PET and CT? You have to estimate the likelihood of having N1, N2, or N3 disease, which, if high enough would probably lead you to consider bronchoscopy as a first diagnostic modality.

Now we get a fantastic study out of MD Anderson. So-called HOMER prediction model, which was derived from a cohort of over 600 patients and internally validated and externally validated in three different independent cohorts with fantastic AUCs. And so based on the patient's age, the cell type, if you know it; if you don't know it, you would put adenocarcinoma here, which leads you to the highest estimate of lymph node involvement. And according to the PET and CT stage, you – and the location of the nodule you get with a probability of N1, N2, or N3 involvement, which, if high enough, I think should lead you to consider bronchoscopy as a first step over transthoracic needle aspiration.

Now, I talked a lot about the diagnostic yield of conventional bronchoscopy and guided bronchoscopy. I should point out that if you look at the data, the data are all over the place. And here's real-life data from a registry including 15 centers in the U.S., over 500 patients. And you can see that the overall diagnostic yield is about 60%. But if you narrow it down to electromagnetic navigation, you go down below 40%, which is very interesting and raises, obviously all sorts of concern about the type of data that we have.

So why do we have such discrepancies in different studies? Well, they may be looking at different populations, lesions that are big or small or not aligned with an airway, maybe the operators are experienced differently. I think a major concern with navigation bronchoscopy to this day is the problem of so-called CT body divergence or navigation platforms operate on the basis of a preop CT, which is very different than the lung volume we're tackling during the bronchoscopy.

So we have new tools available to try to deal with this CT body divergence. And here's all the published data as of March 11, I believe, on robotic bronchoscopy ever 13:05 ___ audio cut off. bronchoscopy we've ourselves acquired a robot, I think to keep up with the Joneses more so than for the quality of evidence supporting its use. But here are all the papers that reported some diagnostic yield. And you can see that the amount - the total amount of patients enrolled in this study is actually quite low. This is not a great evidence to change practice, but for better or for worse, I think robotic bronchoscopy is unlikely to go away and get randomized data anytime soon.

Another possible way to deal with this limitations of current navigational bronchoscopy system is to use the cone beam CT. This is our group doing cone beam CT at Vanderbilt. And I'm just showing you these images to show you the amount of staff and effort that you have to put in to do these things. I mean, this is a big ordeal to patients intubated, mechanically ventilated, paralyzed, you get a number of people, including interventional radiology techs, along with us. These are beautiful images. But quite frankly, it doesn't really tell you what to do with the images once you've navigated and how to correct your trajectory. So I think this is still a work in progress. The data that we have is very limited. Here's one paper from an expert bronchoscopist that uses cone beam CT on a regular basis, you know, presenting diagnostic yield over 80%, which I think is unlikely to be reproduced with more conventional bronchoscopists like the rest of us.

There are ways to deal with this divergence using cheaper methods than cone beam CT, and more accessible techniques. There are two platforms on the market right now looking at augmenting conventional fluoroscopy by obtaining digital tomosynthesis images. Here's one system. The idea here is simple. You're going to rotate the C-arm around the patient, and hopefully make visible what were before fluoroscopically invisible nodule. So here's the example of a lesion that is not visible on fluoroscopy. Here's a coronal CT view. So it's pretty obvious where it's at. But this is a CT. And I will show you now, the digital tomosynthesis image, which is very similar to your coronal CT image. So this allows us to redirect and recalibrate the system to go after the target lesion more effectively. Here's our data on our original or initial 360-some nodules, and using a fairly conservative definition of diagnostic accuracy. Our diagnostic accuracy was about 77%. Now you're going to say this is not that great for us. Before digital tomosynthesis with the expertise that we have in navigational bronchoscopy, doing over 400 cases a year, our yield was about 55%. So this is a significant increment in diagnostic yield.

I've been talking about diagnostic yield a lot. These are terms that are thrown around without clear definitions. And I want to point out that the way that we've historically defined the term of diagnostic yield is very misleading. The way we've been defining diagnostic yield is whenever you get a hit on bronchoscopy, and you get malignant cells, you count this as a positive diagnostic bronchoscopy. And if you get something else, but the patient doesn't develop cancer in the year following the bronchoscopy, then you count this as a good diagnosis as well. As a successful diagnostic bronchoscopy. Now, this is misleading for the reason that this is primarily going to depend on the prevalence of cancer in your population. If you have 90% of nodules that are benign in your populations, and only 10% of cancers, you can miss every single nodule and still have a positive diagnostic yield of 90%. So let's imagine you're the absolute worst bronchoscopist in the world, you biopsy the heart every single time you tried to biopsy a nodule, and you don't find cancer, when there is cancer, but you do find non-cancer, it's just heart muscle in the other 90% of patients, you're going to count your diagnostic yield at 90%, because none of these patients will have cancer a year down the road. So that's - this is the big problem with diagnostic yield. And this is unfortunately the way that most studies have reported diagnostic yield up until recently. There's been a lot of discussions about this.

And both Dr. Murgu and I were involved with this very interesting simulation study looking at the impact of different definitions of diagnostic yield on the reported estimate of that yield. And you can see that with fairly conservative definitions, your yield will go from 66% to about 90% with more liberal definitions depict.

So depending on how you define this diagnostic yield, you will get very, very different answers. And unfortunately, we don't have great comparative data.

I'll just finish it here in the next couple of minutes talking about a topic that was very hot initially during the early days of the pandemic, which led to a number of guidelines published by the AABIP and CHEST. And we reviewed at the time, all the available literature on aerosol generating procedures and bronchoscopy in particular to make some recommendations with regards to best practices for bronchoscopy during a pandemic. And all of these recommendations that were made after reviewing hundreds of papers are essentially ungraded consensus-based statements. The actual only graded statement is the one that's the most useless and I'll show you that in a second. But what this slide boils down to is that if you have a transmission of COVID-19, or any airborne-spread disease in your community, you should obviously use PPE and N95, and discard your N95 after the procedure. And this goes without saying. I think these are become a standard of care from most or all of us.

One question that arose early during the pandemic is what to do with these semi-elective procedures that are workup for lung cancer. And we tried to come up with right period of time that should not be exceeded when we work up a patient for lung cancer that would be positive for COVID-19. And we could not come up with a specific time window, which means that we recommended that the bronchoscopy be performed in a “timely and safe manner,” which doesn't help anybody, but this is the best we could come up with.

Okay, and I'll finish here for the next couple of minutes on the question of acquisition of material for molecular testing and bronchoscopy which will be covered in more details in a further seminar from the pathology standpoint. And this is again an important part of the consideration when we go after a target in the lungs. We need to, A: Establish the diagnosis; B: Try to establish the stage of the disease but also acquire enough tissue for molecular analysis.

Several scientific societies have recommended, obviously, that molecular testing be performed at the diagnosis of patients, particularly in patients with advanced lung adenocarcinoma. And this should be done systematically regardless of clinical characteristics. And you see the recommendations from the scientific societies here.

In general, the NCCN will also recommend that you at least test for EGFR and ALK for nonsquamous non-small cell lung cancer and non-small cell lung cancer not otherwise specified, as well as metastatic squamous in non-smokers. And you should add to that, BRAF and ROS1 in lung adenocarcinoma. But of course, as you know, we're progressively moving towards next gen sequencing for many of these patients, which is a more sensitive and more comprehensive way to test for these mutations.

It goes without saying that in patients with progression of disease, you should rebiopsy and not necessarily rely on the initial molecular testing because things change, tumors evolve, they branch out, and mutations may not necessarily be the same during the time of progression as they were initially.

In terms of advanced molecular testing with EBUS, we have a great systematic review and metaanalysis of over 2,600 patients that was published in 2018. This was specifically looking at EBUS-TBNA samples, adequacy for EGFR and ALK, and found that this was the case in over 94% of the time. The recommendation was for three additional passes without rows of four without. In terms of next gen sequencing, a recent systematic review and meta-analysis was published just a few months ago, suggesting that EBUS-TBNA specimens actually adequate for next gen sequencing in the vast majority of cases, about 86% for providing a very reasonable amount of DNA. And what was interesting in that systematic review is they looked at the incremental value of additional passes with regards to

acquisition of adequate material for molecular testing, which went from 77% to 95%, with three to six passes, respectively.

The CHEST guideline recommend additional passes needed beyond the initial three which are reserved for the diagnostic part of the EBUS. So you should get a number of additional passes. That number is not quite specified in our practice, which is completely not evidence based. We've had great cyto-techs that look at the cell block and tell us, 'Yeah, I think you're okay,' and that's usually when we stop. But it can go for anywhere from additional three passes to an additional eight if need be.

ROSE with regards to - and that's rapid on-site evaluation, does that make any differences in terms of specimen acquisition for molecular testing? Not necessarily. There's one of these few areas in bronchoscopy medicine where we have randomized controlled trial, and this this is one of them. Adequacy was a little bit better with ROSE in terms again, of molecular testing than without ROSE; however, this difference was not significant. Just like has been had been shown for the value of ROSE for EBUS in general, it does seem to result in less stations needing sampling, and certainly, potentially a shorter procedure. In terms of needle size, is the 19-gauge better than the 21 to 23 or the 25, or whatever you want? There's just no great data to comment on this unfortunately, at this point.

And I'll finish here talking about PDL1. There's a lot of questions about PDL1 that - I should point out that this whole field is a very dynamic one and that changes are the norm. And so assays change and therapies change and the molecular testing needed changes. And so it's very difficult to provide you with information that will be somewhat useful today and two weeks from now.

But in terms of PDL1 testing, there's been a lot of discussion as to whether EBUS-TBNAs are sufficient. There's a very well-quoted paper from France actually not far from where I'm from, from Nice in the south of France, looking at resected specimen that were matched with prior biopsies and found that there was quite a bit of discrepancy between the needle biopsy and the resected specimen. One caveat of this study is that the test that they used, not because it's French; French tests are fine in general, but this one in particular was not felt to be a very consistent one. And so this was a major criticism of the study. One of Dr. Edell's colleagues at Mayo Clinic in Scottsdale, Ken Sakata, actually published a paper on the best TBNA and surgical resection concordance of PDL1 testing, and actually found that this was actually quite good; 87% for PDL1 over 1%, and 82% for PDL1 over 50%. And this again has been approved for formalin-fixed paraffin-embedded samples. There's really no great data on Cytolyt-fixed specimens of, although I believe that Dr. Murgu might be able to shed some light on this, as I believe they run a lot of this testing on Cytloyt-fixed specimens at the University of Chicago if I'm not mistaken.

And I will stop here. I hope I didn't go over too much. I'll - we'll finish with this question here. I'll just read it quickly. A 50-year-old female, never-smoker referred for management of a 3.5-centimeter PET-positive left hilar mass, biopsy confirmed as adenocarcinoma. The mediastinum is radiologically normal by CT. The patient is asymptomatic. Which of the following is correct? A: EBUS mediastinal staging should be considered as the risk of mediastinal lymph node involvement exceeds 10%; B: CT-guided biopsy is associated with a lesser risk of contamination with COVID-19 than bronchoscopy; C: Rapid on-site evaluation during EBUS staging may increase the risk of unnecessary biopsies: or D: Larger needles, such as a 19-gauge needle, should be used if next gen sequencing is considered?

Dr. Edell:
Thank you very much, Dr. Maldonado. Excellent. Nice review. Excellent presentation. I think, Dr. Murgu, we have some questions in the chat box. If you could prioritize those, and we'll ask dr. Maldonado to respond.

Dr. Murgu:
Yeah, there are several questions that were actually pre-submitted. In the chat box, there was one comment in regards to robotic bronchoscopy, if you see that as the future. And the question comes from a colleague from Europe, pointing out that it is not - robotic bronchoscopy is not yet available in Europe. So can you comment on that, Dr. Maldonado, before we move on to some of the pre-submitted questions?

Dr. Maldonado:
Yeah, I would say that I do not think that it is the future of bronchoscopy for the simple reason that it's, you know, unavailable for the vast majority of folks outside - in the United States and outside of the United States. I mean, I trained in France, where having a C-arm was pretty good. And so you know, we got all the luxury of using cone beam CT and all the advanced techniques, but that's really for a - a luxury for small minority of us.

There are issues with robotic bronchoscopy that still need to be resolved. And the main issue that I see is that we still don't have near real-time imaging during the procedure to see the nodule and be able to access it. And combining robotic with cone beam becomes, you know, again, a luxury very few can afford at this point.

Dr. Murgu:
There is another question in the chat box that is also pertinent to one of our incoming webinars. By the way, the webinar we have on May 10, will be a discussion between two cytopathologists and an oncologist with these moderators here, that's more pertinent to

specimen handling and processing in the pathology lab and molecular lab.

But the question that's here posted on the chat - in the chat room, is regarding specimen assignment once it comes out of the needle, I suspect, and what you actually send for molecular testing. And since you're thinking about that, Dr. Maldonado, there are many pre-submitted questions in regards to technical tips on what do you do to optimize that quantity and quality of the material for - not only for diagnosis, but also for molecular testing?

Dr. Maldonado:
Okay, yeah, so that's a broad question that I'll just briefly touch on. So like I said, I think one misconception is that all lymph nodes are equal and that you should have a uniform approach to lymph node biopsy with EBUS for every single patient. And I think that's not the case. There are very bloody lymph node where just advancing your small gauge needle and obtaining cell capillarity is going to be all you need to do, and some very hard notes where you're going to need to do a number of passes with suction to get enough material. It's very difficult to know if you get the luxury of having a good cyto-tech or cytopathologist in the room that can do a rapid on-site evaluation slide for you and tell you what your cellularity looks like. I think that's the best guide. And that's really all I can say about this. I think it really differs from patient to patient.

Dr. Murgu:
And I know there are several other questions. And I do want to take a couple more minutes to cover some of them because they're very pertinent to practice. One of them in the chat room is in regards to the needle change between each station. And since your at that, one of the pre-submitted question was in regards to your strategy of staging the mediastinum. So where do you start? And also, do you - if you have to biopsy the parenchymal lung lesion, do you start at a parenchymal lung lesion versus lymph node, especially in those patients that have a CT/PET normal mediastinum?

Dr. Maldonado:
Yeah, these are great questions. So with respect to the sequence of lymph node biopsy, you should always start with the highest stage because you don't want to - and this is obvious, I think, for the vast majority of people listening, but I'll repeat it, it bears repeating, you want to start with the highest stage and finish with the lower stage. You don't want to contaminate your lower stage lymph node N1 nodes, obviously. And so if you do it that way, it's okay. If you do it the other way, you should absolutely 100% change needles. You know, just rinsing the needle is not enough. We've had several cases of contamination of lymph nodes doing it that way. And so absolutely 100% change the needle.

The question of whether you should start with mediastinal, you know, again, I think the question is, what is your likelihood of lymph node involvement? We have great validated predictive tools to determine this. I think if it's more than 10%, you probably should go ahead and start with EBUS. I mean, the likelihood of avoiding an unnecessary navigational bronchoscopy with this inherent risk of pneumothorax, and so on, might be reasonable. And if that risk is lower, then it's difficult. You know, we, you know, we just published a simulation paper in CHEST. The question really, fundamentally, I should mention this is, if you start with EBUS and you can spare the navigational bronchoscopy, why don't you always start with the EBUS? Well, there's a potential for a lower diagnostic yield with navigational bronchoscopy if you reserve it for the end of the procedure. It's a theoretical risk because you've already spent 15-20 minutes staging the mediastinum, there's time for atelectasis to set in, and some bleeding and secretions that may make your navigation more difficult. We typically start with navigational bronchoscopy with a radiologically normal mediastinum, for this reason. I'm not sure there's a good answer or paper that we just recently published would suggest that with reasonable assumption, that's a reasonable thing to do. But again, that's not set in stone by any stretch of the imagination.

Dr. Murgu:
Thank you, Dr. Maldonado.

Now it is time to move on to the next speaker, Dr. Tanner. Welcome, and please share your screen. There are other questions in the chatroom that Dr. Edell and I will continue to monitor and answer some of them live. Dr. Tanner.

Dr. Tanner:
Great. Thank you guys for having me. It's a hard act to follow, Dr. Maldonado. He spent a lot of great time talking about the procedures done when you're suspicious of nodule, but I think we need to start at the beginning. Ad we'll talk about pulmonary nodule assessment. If I can get my screen to advance. There we go.

So these are my disclosures. I do a lot of research related to biomarker development and validation with a number of industry folks. The objectives are listed here. And we'll get started with a quick case and a question.

So you have a 70-year-old woman who presents for a 9-millimeter left lower lobe solid pulmonary nodule. One week ago, she was in a motor vehicle accident, so she has no imaging for comparison. Minimal injuries. So she was previously walking 2 miles 3 times a week.

She does have a medical history of hypothyroidism, and she is someone who previously smoked and quit 20 years ago. What is the next step in the management of this pulmonary nodule? Is it A: There's no need for further workup; B: A referral to CT surgery for resection; C: Determine the pretest probability for malignancy; or D: Minimally invasive biopsy with bronchoscopy or CT-guided biopsy?

Great, and I will not tell you the answer. Let's see here, I'm trying to get it to advance. Okay.

So how do we manage nodules? There are a series of guidelines that have been put together by some very bright folks including the CHEST guidelines, most recently published in 2013, now under current redo. There is the British Thoracic Society guidelines, which was published in 2015. And then most recently, the Fleischner Society guidelines that were published in 2017. So there are guidelines for these. And I'd encourage everybody to take a look.

So all of the guidelines really have some key components that are similar across. And so really, in general, the workup of these nodules are based on the likelihood of malignancy. What we know is that there's really lack of high-quality evidence for any of the guidelines. And there are trade-offs for patients, and this really depends on patient level concern as well as the shared decision making. So it's important to talk about patient preferences, especially around these risk thresholds that are arguably arbitrarily assigned.

So there are recommendation categories overall, and then the smaller nodules that are solid and less than 8 millimeters, solid nodules that are greater than 8 millimeters, and the subsolid nodules. Now, I'll tell you, each of these categories warrants its own discussion, but for the purpose of this, we'll be general.

So what you can do as it relates to assessing pretesting probability of malignancy, which is what you should do every time a nodule comes across your monitor is ask yourself: What's the likelihood of cancer? Now you can do that with a gut check or clinical intuition, or there are a number of really great validated risk models. However, when you use these risk models, it's really dependent on the prevalence of malignancy. And so when you look at the VA Model, also known as the gold 36:25 model, this was developed in a population with a 40% cancer rate. The Mayo Clinic model, which was developed from a large cohort of chest x-rays, was found - was developed in a group that had a 24% cancer rate. Now, when you look at the Brock model, which was developed in a screen detected population, the prevalence of malignancy was 3 to 5%.

So well, before you apply the model, you have to ask yourself, what is this patient like? Is this a screen detected nodule? If so, maybe you should be using the Brock model. Is it a general community patient, maybe the Mayo model. If you're fortunate enough to work with the VA, perhaps the VA model.

And I bring this up because this is our patient. And as we plug in these calculators which are available online, you can see that the risk - the pretest probability for malignancy changes based on the model. So here it is in the Mayo Clinic model, which again, was a 24% prevalence of malignancy, you can see that in our patients, the probability of malignancy was - is about 20%. If you plug this into the VA model, it's higher at 26%. And then lastly, if you put this in at the Brock model, and I'm sorry that covers it, but it's much lower around 9%. So really, again, it depends on the prevalence of malignancy in the population.

So for any nodule, you assess the likelihood of cancer, you use clinical judgment or a risk calculator. If the patient is low risk, then serial imaging might be a reasonable thing to do. And depending on which set of guidelines you look at, the CHEST guidelines that mark that is less than or equal to 5%, the British Thoracic Society guidelines are a bit more generous at 10% risk thresholds. If the person is at intermediate risk, which is probably the largest bucket and what we see the most of anywhere between 5 and 65%, for the CHEST guidelines, 10 to 70% for the British Thoracic Society guidelines. Really, it's everything, right? You can do a PET scan, you can do a biopsy, but it's really important to talk to the patient, right? And then in anything greater than 65%, if the patient is considered a good surgical candidate and the lesion is in a location that is amenable to a wedge biopsy, this would be someone you could consider taking straight to surgery versus doing a biopsy. But there's obviously some nuances there, if the lesion is very central, and would require a lobectomy, it might be that your friendly thoracic surgeon would like to know that it is in fact cancer before taking them for a lobectomy. So there are a lot of things that come into play.

So I think you know, the Fleischner Society guidelines are probably good to review in that they're at the bottom of a lot of radiology reports that we see. They changed their guidelines most recently in 2017 to try to reduce the number of follow-up examinations and provide greater discretion for the radiologists, clinicians, and even the patients.

So these guidelines are for incidentally detected nodules, not screen detected nodules, alright? And certainly not meant for anybody under the age of 35, anyone who has a known history of cancer, or is immunocompromised. Again, not for lung cancer screening population, and anyone who's obviously symptomatic for – with symptoms of lung cancer, hemoptysis, etc., these guidelines are not meant for those.

The changes that are notable are solid and subsolid nodules are now included in the same guidelines, and the new minimal threshold

for reaching follow-up was actually raised to 6 millimeters from a lower side criteria before. And follow-up recommendations for nodules greater than 1% risk of cancer. And there are longer monitoring from those dreaded ground-glass nodules, they went from at least 3 years, to at least 5 years. And important detail, if you look at this, it's really because we see lots of patients with multiple nodules, these guidelines are meant for dominant nodules. The size should be measured on the long and the short axis and then an average taken. A subsequent exam should implement low-dose protocols to minimize cumulative radiation exposure. And I think that's something that a lot of us probably don't do when we're ordering a diagnostic CT for nodule follow-up. I often encourage folks to put in the comments, please utilize a low-dose protocol, especially as it relates to younger women.

So the biggest view here is that for solid, you're going to stratify low risk versus high risk, single versus multiple, and then subsolid nodules has their own group. And I would encourage any - all of you to pull these up, I think it's really helpful.

You're going to assess your risk factors. And as we know, there are patient level risk factors and nodule level risk factors that fall into all of these calculators that we talked about. And increase risk, obviously, the larger the size, upper lobe, and when you hear the dreaded spiculated or lobulated. And interestingly, the more nodules we have, the less likely it is to be a cancer. Obviously, not in the metastatic setting.

So we'll just go here. And then duration of monitoring. You know, this is a question that often times we say 2 years of follow-up is necessary. But again, that was based on chest x-ray literature. And I think we're seeing more and more studies that would suggest that 1 year of monitoring with CT scans is probably adequate, in someone especially those that are at lower risk of having cancer.

And these are the subsolid nodule guidelines that the Fleischner Society guidelines really kind of meld very well with the CHEST guidelines. And I point this out here for those buckets of pretest probability with very low with less than 5%, low to moderate 5 to 65, and high greater than 65%. So those are guidelines, but what do we as physicians do? We've done a number of studies that show that doctors don't necessarily follow the guidelines. And so in one observational review of 33 outpatient pulmonary clinic with patients being referred with incidentally detected pulmonary nodules, interesting the prevalence of malignancy matched that of the Mayo cohort at 25%. And we found that 44% of low-risk patients, that's with a pretest probability of less than 5%, had an invasive procedure for benign disease. And so these are kind of shocking and alarming really. And they resulted in no difference in the rate of surgical resection for nodules based on pretest probability of cancer.

And another assessment of physician assessed pretest probability for malignancy relating to the adherence for guidelines for evaluation, and a prospective trial of over 337 patients with a higher prevalence of malignancy at 47%. It actually showed that physician assessed pretest probability did better than nodule prediction calculators. So clinician gestalts did better. But physicians didn't follow, despite being better, the indicated guidelines and selecting the next test in 61% of cases, low-risk patients were managed more aggressively 52% of the time, and high-risk patients are managed more conservatively 75% of the time, which is good, in that 92% of those with benign disease avoid surgery. So, you know, again, guidelines are just meant to be just that, guidelines, and there's a lot that comes into play.

So as we evaluate pulmonary nodules, what do we have beyond pretest probability? And this just kind of illustrates all of the many areas of development including radiomics, proteomics, bronchoscopy procedures, exhaled breath analysis for volatile organic compounds. There are just so many things, I should throw a soak in there for AI that combines all of these. And so, it’s a very exciting time.

We'll talk very quickly about bronchoscopic diagnostics. These studies were already highlighted by Dr. Maldonado. The way - the meta-analysis that came out of our group actually showed a way to diagnostic yield of 70%. We're in the process of updating that. Spoiler alert, it will be at the CHEST meeting. And then the paper that came out of the AQuIRE registry, which I think is really interesting, when you look at the diagnostic yield for - sorry, I should go backwards - for guided bronchoscopy, you know, it makes you ask yourself, you know, are we just doing more because we have these types of tools at our hands? And so - and the last one I'll point out, and there's a slew of papers that go along with, you know, guided bronchoscopy, and I think the jury's still out. But when we looked at thinner bronchoscopy with fluoro, which is what the bread-and-butter pulmonologists has versus a thin bronchoscope with radial EBUS, there really was no great diagnostic yield improvement there. It was kind of the flip of a coin.

So other technologies are available that Dr. Maldonado talked about. And those are all being evaluated now and obviously not readily available. But what more can be done during the time of bronchoscopy?

And so I will bring it to this paper which was published in 2015 in the *New England Journal*. And what we know is that bronchoscopy is often nondiagnostic. And so this was the first time that a bronchial airway gene classifier was used to look at the performance in those that had a nondiagnostic bronchoscopy. So we all have our new fancy tools, navigational bronchoscopy, robotic bronchoscopy. So what do we do next if the results are actually nondiagnostic? And that happens quite frequently.

And so, this evaluation showed that 43% of bronchoscopies were non diagnostic, which just kind of goes along with everything else.

And then subsequently, 35% of individuals who had nondiagnostic bronchoscopies, then went on to further invasive procedures. And so in this intermediate-risk group of pretest probability in that large bucket that I talked about, 83% of bronchoscopies were nondiagnostic. And so remember, that's the group where you can get a PET scan and/or a biopsy and/or bronchoscopy. And this is despite the prevalence of malignancy of 41%.

And so what can be done and patients with an intermediate pretest probability for cancer that then have a nondiagnostic bronchoscopy? So it turns out, if this classifier comes back with a score that is negative, it actually improves the negative predictive value for your bronchoscopy. So you can see where you might be attempting to get a cancer diagnosis in a patient, but you fail. That's going to happen frequently, according to the literature. If at the time of bronchoscopy, you do this classifier and you get a nondiagnostic result and the classifier comes back negative, you can feel more comfortable maybe not doing another invasive procedure for your patient.

And so, the clinical utility, which is really just this classifier change practice, has been evaluated with a registry study at 35 U.S. centers and was published in CHEST most recently. And it found that those are the negative Percepta results down-classified the risk of malignancy in 34%. So it was actionable. And the majority of the time, there was a change in the management plan from an invasive procedure to surveillance. So it's doing what you would like to see it do.

So what about proteomics are all things biomarker related? I just throw this up because there are biomarkers available for everything. And so you can use a biomarker to assess a patient's individual risk for developing cancer. And then when you have a nodule, you can do a biomarker to assess whether a nodule is benign or malignant. And then, further, when someone has a cancer diagnosis, you can use biomarkers to comment on prognostic value, diagnostic, and then of course, personalized treatment, as we talked about all of the biomarkers that are being drawn in those that - with advanced cancer, and even an early stage cancer nowadays.

And so this is a really great paper that I would encourage anybody who's curious about biomarkers to look at. This was published in the *Blue Journal* in 2017. It kind of stratifies what types of categories of biomarkers there are, which I just highlighted, and it talks about the phases of biomarker evaluation. I think this is really important, because there are a lot of company reps going around talking about their biomarkers. And I think before we use these things in clinical practice, it's really important to know the data and where they are on this spectrum. Is it clinically valid? Is it clinically useful? And is it cost effective? And so again, this is all taken from that paper by Mazzone and colleagues.

But really, we want a biomarker to improve the accuracy of clinician judgment, the risk calculators, PET imaging, alone or in combination. So we want something that's going to improve on what is already out there. The accuracy of the biomarker should be high enough to suggest that it could move the pretest probability of malignancy beyond a decision threshold. And again, the consequences of applying the biomarker if the result is interpreted as positive or negative is to lead to improved clinical outcomes for our patients, right?

So an earlier diagnosis of malignant nodule without a substantial increase in procedures performed in patients with benign nodules or fewer procedures for patients with benign nodules without delaying a diagnosis of cancer in patients with malignant nodules. So these are kind of the trade-offs that we have to think about. And so really, I would just have you read this, but in bold, we should insist on additional evidence of clinical utility before changing practice.

And so this is a real quick snapshot of all of the different biomarkers that are out and where they are and what categories they are suggested for. And these slides will be available to you as part of the webinar, and I'm sure there are updates that I'm probably missing on here. But you can see there are ongoing clinical utility trials in many of these.

Okay, and so I'll just highlight very quickly a one of the biomarkers that has been clinically validated and is now on to clinical utility trials. This is a prospective multicenter trial of 685 patients who had a new nodule that measured between 8 and 30 millimeters. This is a combined biomarker that takes two plasma proteins and clinical risk factors, including nodule size, etc., to identify nodules that are likely benign. So this is a rule-out biomarker. The clinician assessed the pretest probability of malignancy at the time of enrollment. And what you can see here is that 178 patients had a pretest probability of less than 80%, and the prevalence of cancer was 16%. With the use of the integrated classifier, it had pretty good performance as it relates to sensitivity and negative predictive value. And what was estimated was that had been used to direct clinical care, 40% fewer procedures would have been done on benign nodules.

And I'm just realizing now that there's a typo, it's meant for patients with a pretest probability of less than 50%, not less than 80%. So if you have a patient that you're seeing with an indeterminant pulmonary nodule, you do your pretest probability calculation, and it winds up being less than or equal to 50%, you can send this blood test. And you know, if it comes back with the results, it could downshift the patient into a lower risk category.

And I will just point out that the outcomes were the same at 2-year follow-up.

And so it's currently there's a registry trial for clinical utility that's been done. And it's going to present – be presented in abstract - or

was presented in abstract form in CHEST 2021. And there's an ongoing prospective multicenter clinical utility trial.

Alright, so the last question. Biomarkers for pulmonary nodule evaluation are ready for clinical use when, A: Discovery cohorts demonstrate good sensitivity and specificity in the intended use population; B: Discover and validation studies demonstrate good sensitivity and specificity in the intended use population; C, The FDA approved the test for clinical use; D: Clinical utility studies demonstrates that the test results change patient management in a way that reduces time to cancer diagnosis or reduces invasive procedures?

Okay, and with that, I think that is the last slide I have. And I thank you all for your attention on this Tuesday evening.

Dr. Edell:
Excellent job, Dr. Tanner. Very, very nice job. Tim, are there any questions in the chat box? You're muted, Tim.

Dr. Murgu:
Yeah, I apologize is the first time I use Zoom. There are a couple of questions in the chat box, and quite a few that are pre-submitted. So Dr. Tanner, thank you for a very objective review of the guidelines and the key landmark articles on biomarkers.

One of the questions in the chat box is regarding the Fleischner Society guidelines for follow-up of pulmonary nodules. I suspect the question is relevant to when the clock starts. All those recommendations about follow-up CT in 3 to 6 months, 18, 24 months? What is time zero?

And since you're going to be thinking about this, you know, one of the pre-submitted questions in regards to follow-up of pulmonary nodules, can you clarify like who are those patients that need a follow-up per Fleischner versus all pulmonary nodules that we see in our practice? Because I can only think about nodules that are referred to us by our oncology colleagues that have their follow-up scans because they are following a certain type of malignancy that was treated with a curative intent. Is that patient population included in those guidelines or not? So let's address the question in the chat. and then my question.

Dr. Tanner:
Okay, so two-part question. So the first thing is the first question as I understand it, and when is time zero? So you know, the best scan is the last scan. So if you have a scan for comparison sake, then that would be the baseline. But it starts on the day of the scan as I see it. That's time zero, right? And so then, you know, you have to ask yourself was this an incidentally detected nodule, meaning they came in for chest pain or, you know, they're having a scan for something else? And how high risk is this person? And so is it a low-risk nodule like less than 8 millimeters in a young person who has not smoked cigarettes? And you might even make the argument if Fleischner doesn't, you don't need to follow up that nodule, you can just let it be, especially, you know, if this individual lives where Dr. Maldonado lives, in an area of endemic mycoses, right? And so you kind of have to ask yourself those questions. But in someone who maybe is someone who smokes cigarettes without a history of malignancy and a nodule that is 8 millimeters or larger, you have to ask yourself, you know, like, when do you get the next scan? And so it depends, right? And so Fleischner, kind of the reason they changed in 2017 was to give you more of a leeway. You know, you could arguably get a scan 6 months later, and then march it out, you know, to the 12 months. I like to do the math easy, right? So I like to get somebody on a year. And if it's stable at a year, I bring them back for the year two. And some folks would even argue that you don't need to bring them back on year two. I think it's highly dependent on the patient, how worried they are, and what their prior histories are, including risk factors, family history, own private history of malignancies.

That brings me to your question, Tim, about, you know, patients that are referred to a pulmonologist or even to a pulmonary nodule clinic from - with a history of a malignancy. So by virtue of that alone, they are already at high risk. And so, you know, oftentimes these folks are getting continued scans because of their treatment, and you can't dictate when they get their next scan, you know, I've had patients that are getting PET scans every 3 months, or you know, and so you just kind of follow along and try to calm folks down from being aggressive. But I think when you're in control of the follow-up again, it depends on what stage their primary cancer was at the time of diagnosis, and what type of recurrence they've had. Are there multiple nodules, suggestive of, you know, metastatic disease and something that's like slow growing, like adenoid cystic cancers, there can be lots of them and they just grow incredibly slow. But Fleischner is not meant for these people. It's not. And I think that's the short answer to your question.

Dr. Edell:
No, I leave it to Dr. Murgu to give you a couple of questions that lead to a full lecture.

Dr. Tanner:
Sorry about that, I'm a little –

Dr. Edell:
No, no. You did a very nice job. Those questions are very difficult. The use of the Fleischner as a society for these, they're all certain -

all individual populations, as you as you pointed out.

I want to compliment the two speakers again. One of the themes that I think they both brought forward is the pretest probability prediction and assessing basically what patient's risk is for lung cancer. And then utilizing the tools needed for managing those patients. I think sometimes we forget every nodule doesn't need to be biopsy, every mediastinum doesn't need to be sampled. And the guidelines are pretty strict. When you have a high risk patient over 65 to 80%, the likelihood of cancer using the models, it's a stage 1 cancer, and the mediastinum was clean on PET, the guidelines say if you can, as Dr. Tanner said, resect it. You don't need - if it can go out with a wedge, you can do an excisional biopsy. And I think we forget that sometimes. The rest of the ones that you've guys have reviewed in the intermediate probability, that's going to keep us busy for the rest of our careers. I'm going to take and screen them. Tim, you can keep going.

Dr. Murgu:
I would say there is another question in the chat. But you know, Dr. Tanner, you published extensively on the biomarkers. I mean, we were familiar with your papers from CHEST and JAMA other reputable journals. I'm personally still confused in their applicability in the clinic. So walk me through your decision-making process for those nodules in the indeterminate probability. You see the patient in clinic, you do your risk calculator, which seems like is the natural knee-jerk reaction we should all have when we see a pulmonary nodule. And then what, in regards to commitment to a biopsy? And then is there going to be bronchoscopic or IR? Which were several questions raised today, including the pre-submitted questions, you know, people still struggle with the decision making. And then do you do a blood test for a biomarker in clinic at the time? And then after the biopsy is done, when do you take the decision to do the genomic classifier? Right there during the actual bronchoscopy or subsequently? So what walk us through your clinical approach.

Dr. Tanner:
Sure. So I think it's important again, just to highlight as it relates to biomarkers, I'm still waiting on clinical utility in our site as part of the trial that is looking to determine the clinical utility. So I know that the biomarker is valid, based on the studies that we've published. And you know, there's a registry study that suggests that it's useful, but I'm kind of a purist as it relates to that, in that, you know, all I see are nodules. That's my job in clinic on the – at the university and at the VA. And so I tend to reserve – well, I am reserving biomarker testing as part of the trial to show clinical usefulness. As it relates to the way I go, again, you always want to talk to your patient, right? So if you're in that indeterminate bucket of 5 to 65%, you could kind of cut it down the middle, right? So you've got your low-risk intermediate group, and then your higher-risk intermediate group. And I think that shared decision-making conversation where you outline, you know, these are the things that we can do, I think the location of the nodule really is important.

In the beginning of my career, I think I was doing a lot more PET scans than I am now. Now, I think that really just kind of depends on the patient in a way, that's like a radiographic biomarker, right? We're going to see if this thing is active.

So I think depending on the size, you know, if it's less than a centimeter, I always preface telling my patients look, it's really small, it's probably going to be difficult to biopsy at this time, the PET scan might not be helpful because it's below the threshold of PET, there really isn't much harm in waiting 3 months. I am of the mentality that it's going to take - 3 months buys you time and you can see if it changes. And I present it that way. But there are people that are very risk averse and want to know immediately, you know, 'I'm very scared. I can't sleep.' And so those folks, I might offer a PET/CT scan to further say, you know, if it's cold, then we feel much more comfortable about following this. But you need to know that if it's hot, it might push us to do a biopsy for something that turns out not to be a cancer, right? So I try to have a balanced discussion. And you know, what I often say is like, this is a freckle, I don't know how long it's been there. It could have been there for years and we're just now finding it. I think it depends on the circumstance. Now if that patient had cancer before, my conversation is a little bit different. So I take it that way.

And so then the next question is, what if I'm going to go and do a navigational bronchoscopy? Should I think about how poor we all are as bronchoscopists at reaching this and do the Percepta test ahead of time? You know, initially, we were part of the registry trial, so you know, I was using it that way. And I kind of fell out of doing it, as we recently got a robot. I was very excited that you know what was going to have a better diagnostic yield. But now as I think about it, if I'm left with a nondiagnostic bronchoscopy, it makes sense to then run that Percepta test and say, okay, well, if this comes back as a negative classifier, then maybe I don't need to send Mr. Smith for a risky CT-guided biopsy, and we can just watch and wait and see what happens.

And so, you know, that's kind of the process I take. It really, again, depends on the patient's history and how nervous they are. And each individual is unique. So I don't know if that's helpful to you, if that answers your question.

Dr. Murgu:
And, Dr. Tanner, yeah, thank you. They're – the questions keep coming. Of course, you know, again, this is triggering the probably topics for future talks. But I do think we should answer a few of the live questions here. So one that came in the Q&A box is in regards to the duration of follow-up after curative intent surgery. And so for how long do you continue that follow-up after segmentectomy or

lobectomy?

Dr. Tanner:
So we – our practice is 5 years and then depending on how well that patient is, meaning could they tolerate another surgery, we might then consider doing lung cancer screening if they still meet the CMS criteria for screening, meaning like maybe they just quit smoking 10 years ago, and they're still eligible for screening for the next 5 years. But as it relates to curative intent surgery for stage 1 disease, it's 5 years. That's what we do.

Dr. Murgu:
So that actually answers another question in the chat room that had to do with screening. There are a couple of questions in the chat room in regards to specimen handling and processing with number of passes and Cytolyt, and how can you assure the quality of a Cytolyt? We warmly suggest you join us in our next webinar on May 10, when we have a cytopathologist from Mayo Clinic, a cytopathologist from the University of Chicago, and an oncologist from Dana Farber Institute in Boston, with Dr. Edell and I as moderators. And that will be the topic of that webinar: How do we optimize the quality and the quantity of the bronchoscopic or CT-guided specimens for diagnosis and downstream analyses? Dr. Edell -

Dr. Edell:
You - nice segue into again, thanking our sponsors, the American College of Chest Physicians. You can see the support that we've received from outside industry as well. I'd like to again, thank our expert panelists for an excellent presentation. And I'd also like is Dr. Murgu said, to remind you that this is the second in a series of five webinars. And you see here the next three webinars we'd encourage everyone to sign up if they can. Those of you who have attended this webinar, you will be receiving questions in about 30 days through Qstream to see how well we've done in transmitting information and to test your knowledge, and then another set of questions at 60 days. You – we'll be also sending you an email on how you can secure your CME credit for attending this webinar.

Thanks again, and especially thanks for those people in Europe who are staying up late to attend this webinar. We appreciate your support. And we wish everyone a very good evening. Thank you all.

Dr. Murgu:
Good night, everyone. Stay safe. Thank you.

Announcer Close:
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