UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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VIRTUAL PUBLIC WORKSHOP – STUDY DESIGN CONSIDERATIONS FOR TRANSBRONCHOSCOPIC THERMAL ABLATION DEVICES FOR THE TREATMENT OF OLIGOMETASTASES TO THE LUNG

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April 6, 2022
11:00 a.m.

Via Webcast

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M E E T I N G

(11:00 a.m.)

DR. LEE: Good morning and I would like to welcome you to Day 2 of our workshop on the study design considerations for TTA devices for potential treatment of oligometastatic lung disease.

My name is James Lee and I am the Director of the Division of Sleep Disorder, Breathing, Respiratory, and Anesthesia Devices here at the FDA. I would like to give a special thanks to our panelists, speakers, and patients who participated in yesterday's session. FDA received great feedback on the panel questions yesterday and we are grateful for the fruitful discussion and candor in the conversation.

For our first panel today, I would like to welcome Dr. John Handy of the Providence Portland Medical Center, and Dr. Quynh-Nhu Nguyen of the University of Texas MD Anderson Cancer Center. This session focuses on the suitability of local treatments of OML and its dependence on histology and other parameters. Following the talk, we will roll into our panel that will be moderated by Dr. Jonathan Yang of the Memorial Sloan Kettering Cancer Center. I now turn over our time to Dr. Handy. Thank you very much.

DR. HANDY: I'm Dr. John Handy, a thoracic surgeon, originally in Oregon. Presently, I've been in Everett, Washington and I have no financial or conflicts of interest disclosures for this presentation.

I'll tell you why I'm asked to present here today. I was serving as a member on the Society of Thoracic Surgeons workforce on evidence-based surgery when I was approached by the Oregon Health Plan. The Oregon Health Plan goes back into the 1990s when it developed methodology about what Oregon Medicaid will or will not pay for, "will not" being based on lack of evidence to support the outcome. So for example, they had decided not to fund liver transplants on infants less than 2 kg because their outcomes were so poor.

As a past president of the Oregon chapter of the American College of Surgeons, I was selected to represent cardiothoracic and vascular surgery when the plan went through its periodic review of different procedural codes with specialists to try to figure out what should be reimbursed and what should not be reimbursed.

As I was going through this with the Oregon Health Plan representative who is a primary care physician, she arrived at pulmonary metastasectomy and stated well, of course, pulmonary metastasectomy shouldn't be funded because the literature on it is just terrible, and I admitted that the literature supporting pulmonary metastasectomy is terrible, which I'm going to go into in more detail, but there's also no literature contradicting the role of pulmonary metastasectomy and so I wasn't sure that it should not be paid for under all circumstances.

At that time, the primary care physician then asked me would I do a systematic review and I said well, even better than that, let me bring this to the STS workforce on evidence-based surgery, which I did, and therefore ended up as the chair of this particular taskforce.

So the taskforce resulted in a 7-year effort, ultimately published in 2019 with an expert consensus document, and I'll tell you why we did an expert consensus, because when you look at the literature on pulmonary metastasectomy, there's no randomized controlled trial, there's actually thousands of publications but there's pervasive selection bias because they're all a surgical series. There's no comparative survival analysis, there's an inconsistent description of local or systemic therapies that are accompanying metastasectomy with variable lengths of follow-up and no distinguishing between prognostic or predictive characteristics, prognostic characteristics being an aggressive malignancy versus an indolent malignancy, and predictive characteristics being lack of examples of lack of control of the primary, the number of metastasis, and the sites of

metastasis, and the disease variable, all of which can end up being surgical contraindications. And so the literature doesn't clarify the role of metastasectomy and the prolongation of survival or the possibility of cure.

So as the chair of this workforce or this task force, I invited 14 members, colleagues across the nation, which included 10 thoracic surgeons, three medical oncologists, one radiation oncologist, and the STS supplied support to join this task force, and we did a literature search looking at only the most recent literature using appropriate pertinent MeSH terms and authors were assigned sections in which they were interested. The authors were free to select additional relevant articles, there was no systematic review of the literature because there's no control in the groups.

Once the sections were completed, I then developed consensus statements summarizing each of the sections and then we subjected the consensus data to a modified Delphi method to arrive at or not arrive at consensus. We required an 80% response rate and to adopt the consensus statements required 75% of the participants to either agree or strongly agree.

If adoption criteria weren't achieved, then the consensus statement was minorly revised and subjected to a second round of voting with the same requirements. If it didn't achieve 75% consensus and it wasn't adopted, we actually had no consensus statements which were not adopted, but with each of the consensus statements we published in the document the amount of consensus that each statement received.

One of the things I was proud about with regard to the document is that it's a heavily nuanced document, that is to say we had a deep discussion concerning the overall conceptual framework of treatment in the role of pulmonary metastasectomy and what is a systemic disease, is not a local problem anymore, you have metastasis. And there is an overly simplified concept of metastasis as a systematic, routinely copied anatomic

distribution metastasis through, for example, the lymphatic system arborizing mechanically more proximally predictively, and the evidence doesn't support that for multiple characteristics of malignancy, including that each malignancy has a different site of preference for metastasis, but circulating tumor cells are present even in early stage disease, yet these patients don't develop metastasis. You have epithelial-to-mesenchymal transition and back and forth, so there's multiple phenotypes present within each individual patient, what we're learning about tumor genetics and epigenetics, and then the host tumor interaction requiring a permissive microenvironment angiogenesis and as we've learned, tumor blocking of host immune responses through checkpoint inhibition. All these complicate the use of local therapies for what, by definition, is a systemic disease.

In the overall conceptual treatment, the overall conceptual framework of treatment in the role of pulmonary metastasectomy, what is the goal? Is it cure? Is that manifest in disease-free survival, is it manifest in overall survival? What about prolonged survival without cure? The literature has lots of case reports of such cases.

One of the things I was most proud about of the document is our continual stressing and re-stressing of the requirement of the construct of a multidisciplinary team and the management of patients being considered for metastasectomy; in other words, it's not just the surgeon's opinion, it's concurrent between the surgeon, the medical oncologist, the radiation oncologist, and often the pulmonologist, at least in my --

(Audio malfunction.)

DR. HANDY: So if you're a candidate for pulmonary metastasectomy, you have to have control of the primary cancer, the metastasis has to be surgically removable or ablatable, and you have to be medically fit enough to undergo the proposed procedure. The metastasectomy goals are a complete resection or R0, pulmonary parenchymal sparing, since this is a systemic disease, not a local disease. Taking more lung doesn't make good

outcomes necessarily guaranteed. Importantly, to define the extent of disease, this is usually through lymph node sampling or dissection, and occasionally, relief of symptoms. Symptoms can include bleeding or obstruction, but these are really rare, most patients are asymptomatic, found on routine imaging, which makes this a problematic patient population to manage because goals of any medical intervention, much less surgical or ablative, should be either life prolongation or symptomatic improvement, and it's hard to make an asymptomatic patient better, so you better be prolonging their life if you're going to propose --

(Audio malfunction.)

DR. HANDY: When you're evaluating a patient to be considered for pulmonary metastasectomy, we use the same thought processes, often it is applied to early stage lung cancer with chest CT imaging to define the anatomy, plus or minus PET. Usually PET is gotten although there are some primaries that are not PET-avid, most notably renal cell carcinoma, but most patients end up getting a PET to look for other unsuspected disease.

And who should this be applied in? Well, when you look at the overall literature, we had a hundred and sixty-four references within the consensus document. There are some themes that come out, it's not strictly defined anywhere what oligometastasis is, but a recurring theme in the literature is generally it's considered less than or equal to three. I've operated on people that had many more than that, for example, a young Olympic athlete who had chondrosarcoma -- I'm sorry, osteosarcoma metastasis to his lungs.

Disease-free interval, what is the accepted disease-free interval to be considered for metastasectomy? In general, most of the concurrence of the broader body of literature, when you read it in whole, is about -- is less than or equal to 2 years. These things all have exceptions. And the patients subjected to risk assessment which, much like pulmonary resection candidacy for early stage lung cancer can involve dyspnea, performance data,

exercise capacity, and pulmonary function testing, and if you're not clear, then you do a more in-depth analysis of their physiology, as illustrated in stair climb, 6-minute walk test, or cardiopulmonary exercise test. All this ultimately should go back to the multidisciplinary team for discussion and is this oncologically, anatomically, or physiologically appropriate. One thing that is a clear indication is if you don't have pathologic confirmation that the patient actually has metastatic disease, this is the first episode, then a pulmonary resection for pathologic confirmation is often desirable.

The technical aspects of pulmonary metastasectomy include the ability to have a complete resection or R0 resection to spare lung and to sample the lymph nodes. There are patients in whom ablation is preferable, if you're high surgical risk, if you have ipsilateral recurrence after a prior surgical pulmonary metastasectomy or if you refuse surgery. Our document addresses pulmonary ablation with the literature being most voluminous on radiofrequency ablation.

When it comes to surgical approaches, MIS, minimally invasive surgery, is preferred because of the shortened recovery time and the overall decrease in the functional impact on the patient over open, but however, open is appropriate, too, if MIS is not applicable in this particular patient context with possibility of using thoracotomy, sternotomy, or clamshell.

The procedure should be less-than-lobectomy, is preferred over a lobectomy, and pneumonectomy is questionable in this circumstance because of the magnitude of surgery, the impact on the patient, who has systemic disease and now doesn't have very much pulmonary parenchymal left behind, with lymph node evaluation being recommended in those cases.

So the consensus statements summarized in the paper were 18 and I'm going to go through most of them. First and foremost, in the care of metastatic cancer patients,

pulmonary metastasectomy should be considered within a multidisciplinary team construct. MIS is preferred due to the shortened recovery and less impact on quality of life; open approaches are acceptable, however. Pneumonectomy is discouraged and generally prefer less than or equal to three lung metastases. Lymph node sampling or dissection is encouraged. Ablation is a reasonable alternative to surgery. Isolated lung perfusion, however, is not warranted, it's investigational and the literature so far is not in support of it and we delve into that deeply in the document, which was authored by -- that section was authored by Harvey Pass, who is an expert in this area. And then 10 through 18 are addressing multiple cell types that are often subjected to the possibility of pulmonary metastasectomy, those being colorectal cancer, renal cell carcinoma, melanoma, sarcoma, head and neck cancers, nonseminomatous germ cell tumor, and breast.

Importantly, since our document was published, a prospective randomized study did appear, the Pulmonary Metastasectomy and Colorectal Cancer, which had been accruing for many years, able to ultimately accrue approximately 95 patients, published in 2020, and you can see here the metastasectomy survival versus the control survival is in their paper. They're completely super-imposable, this is an important nuance because throughout the literature, the most common assumption is that people with pulmonary metastasis from malignancy have a low or 0% survival; therefore, any intervention is considered beneficial because of the survival prolongation. It turns out no intervention has a reasonable survival, too, with control patients having a 3.8-year median survival and metastasectomy patients having a 3.5 year median survival, so this throws the whole field of pulmonary metastatic management into question.

My own take on all this is that medical therapy has to continue to progress in maximizing tissue preservation and overall functional preservation while demonstrating therapeutic efficacy. So is pulmonary metastasectomy or ablation an incremental step to

technology development for the treatment of early stage lung cancer? I would say let's hope so, is that anything that a physician does that can prolong life or relieve symptoms that involves less invasion, that is no surgical incision, with the same outcome is better than a surgical incision with the same outcome, and increased function improvement, in other words, no decrease in the patient's function, so minimally invasive or noninvasive and no functional decrease, and that's where we should be driving the field of medicine and the only way to do this is through trials.

Thank you very much for allowing me to participate.

DR. NGUYEN: Good morning. I'd like to thank you for the opportunity to speak about metastasis to the lung workshop today. It's a pleasure and honor for me to talk about radiation therapy as a local therapy treatment modality for a patient with oligometastasis to the lung and discuss some of our parameters that we use as guidance for standards of practice and in our recommendations for our patients at MD Anderson.

I have no financial disclosures.

So Hellman and Weichselbaum first proposed the idea of oligometastatic state over 25 years ago. They suggested that oligometastatic state was a little bit unique in that it was a state with a limited disease burden and they suggested that for many cancers, a few metastases exist at first before malignant cells acquire widespread metastatic potential and thus, certain specific tumors have distinct tumor biology with distinct histopathology to portend a different outcome. If we, in theory, perceive a radical intervention during this oligometastatic state, we could perhaps change the disease progression for some patients who otherwise develop widespread metastases and be treated palliatively.

All right, and I'll be discussing some of our landmark trials that have been published, as well as retrospective trials that we use at MD Anderson to help guide us in the multidisciplinary setting and how we treat patients with oligometastatic, patients who

develop oligomets to the lung, and found there may be some opportunities for us to collaborate and develop ongoing trials with different disciplines to really demonstrate a benefit in outcome and optimal local therapy for our patients with oligometastatic disease.

And many of us are familiar with these three landmark Phase II trials that really separated patients with oligometastases and demonstrate there was a benefit in early local therapy, in proving outcomes, specifically, progression-free survival and overall survival.

The Gomez and Iyengar trial specifically enrolled patients with lung cancer, non-small cell lung cancer, with one to three and one to five limited metastases at the MD Anderson-Gomez trial, and their patients were treated with both radiation and surgery.

The other two trials treated -- the local therapy is radiation, but all of them demonstrated improvement, progression-free survival in the Gomez and the Palma, the SABR-COMET trial demonstrating an overall survival benefit with longer follow-up.

And the third trial, the Palma, the SABR-COMET, allowed patients with different histology, lung, breast, prostate, and colorectal disease with limited metastases up to five mets at each site and it was very exciting to see these three Phase II trials demonstrate that for specific patients with oligometastases, a limited burden of disease, aggressive local therapy did improve outcome, PFS as well as OS.

So I'll be talking about a few of our trials at MD Anderson that really help us guide our treatment paradigm. This is a retrospective study from our MD Anderson experience and it also included the patients on Dr. Gomez's prospective Phase II trial, but Dr. Mitchell, Antonoff et al. looked at 198 patients with synchronous oligometastatic lung cancer and they reported on these patients' outcome. Patients had one, two, or three metastatic sites and as you can see, the location of metastases include brain, bone, adrenal, or liver. The treatment, the local treatment modality included radiation, surgery, or none and the local therapy, the metastases is summarized on the table on the right which showed that 59% of

these patients received radiation and about approximately 23% of these patients received surgery, usually to the primary, and then these patients did subsequently receive systemic therapy, whether it be chemo or molecular-targeted agents.

When the authors reported their outcome, they noted that there was a survival benefit when these patients received comprehensive local therapy to all sites, including the primary. And when they broke it down to comprehensive local therapy versus non-comprehensive local therapy, there was an overall survival that was significant at 1, 3, and 5 years. At 5 years these patients who received comprehensive local therapy or local consolidation, whether it be surgery or radiation, their survival at 5 years was 32% compared to 19% if they didn't receive comprehensive local consolidated therapy.

Upon further analysis, the authors concluded that the survival benefit was dependent on histology. Patients with squamous histologies tend to do better, the thoracic disease burden and whether they had bone metastasis. The study really demonstrated that local therapy comprehensively with radiation and/or surgery did improve overall survival for patients with oligometastasis to the lung.

So the next few trials I'll review are ongoing prospective randomized trials that we have at MD Anderson. The first one is the LONESTAR, which included patients with Stage IV metastatic non-small cell lung cancer and these patients began with ipi-nivo as the stomach therapy with that and if they had no evidence of progressive disease, they're randomized to standard maintenance ipi-nivo or local therapy, local consolidated therapy plus ipi-nivo.

What's unique about this is that we wanted -- a secondary question was to really assess whether patients with oligometastatic disease express an even greater benefit with local therapy early on versus polymetastatic. So the patients with oligometastatic disease after immunotherapy, those patients received consolidative local therapy to all sites and for those with polymetastatic disease, then we offer local therapy to as many sites as feasible.

Ideally, these patients receive surgery to the primary if feasible and if not, radiation therapy as a local modality.

NORTHSTAR is a similar design but specific to patients with the EGFR mutation, so EGFR-positive patients with metastatic disease. They began their treatment with standard osimertinib and if there's no evidence of progressive disease, then get randomized to further-maintenance osimertinib or early local therapy with surgery or radiation plus osimertinib. Also noted the question of -- for patients with oligometastatic disease, our goal is to offer local therapy to all sites, and for those with polymetastatic disease, we would try to provide local therapy to as many sites as feasible.

Our last prospective trial was patients with ALK-positive Stage IV metastatic lung cancer and this is a single-arm prospective trial for patients with ALK-positive mutation, they are started on brigatinib and after restaging studies without evidence of progression, they would proceed with local therapy, local therapy to all sites for patients with oligometastatic disease, and for polymetastatic disease, as many sites as possible plus brigatinib.

These are the three trials that many of our patients with metastatic lung cancer or pulmonary mets are eligible for.

So shifting gears a little bit and talking about other patients with pulmonary metastasis that are not lung primary but other solid histology which is very common, those patients also can benefit from aggressive early local therapy whether it be surgery or radiation at MD Anderson. This is a report that really -- that early on showed that for patients who received stereotactic ablative radiation therapy, SABR, or interchangeably SBRT, as we call it, primary histology dose in the biology, the solid primary, does make a difference in outcome.

So the authors reported on 180 pulmonary metastases in 120 patients. All patients

received stereotactic ablative body radiation therapy; therefore, high dose, high precise techniques with curative intent, and they reported on patients with single mets, oligomets, and oligoprogressive disease. Oligoprogression is coined for those who have limited tumors that were progressing while on systemic therapy.

They demonstrated, on the curve on the right, that the 2-year local failure was significantly higher for patients with colorectal primaries compared to all other solid primaries, which is consistent with what's been reported in the literature and our own MD Anderson data. So perhaps there's room in terms of identifying an optimal therapy for these patients, perhaps it can be surgery, to remove limited pulmonary mets or even offer higher ablative stereotactic doses.

And we published this, Dr. Pasalic published our MD Anderson experience, including 406 pulmonary metastases in a single retrospective study. We took a deep dive in our database and all the patients that we treated with SBRT with pulmonary metastasis, so you can see on the summary table on the right, there are many different solid primary tumors, all of which had a limited pulmonary metastasis to the lung. We delivered ablative doses with SBRT, the most common fraction in each scheme was 54, and for those with central tumors, we offered 70 Gy in 10, but all biological doses of greater than a hundred gray.

When we looked at our responsiveness and outcome, we did note a difference in what we historically viewed as radioresistant tumors, such as adrenal, colorectal, pancreas, even sarcoma, that there was a difference in local failures between tumors that we thought were less responsive to radiation and those that we thought, we felt, was responsive. And when you look at the two curves, the more radioresistant histology did have a slightly higher local failure rate of 11% compared to 3% in terms of failure rate at 2 years, and at 5 years it was a little bit higher, 12.8% versus 5.1%. Between radioresistant tumors compared to radio-responsive tumors, the failure rate was low, it was 5% at 5 years.

We took a look at if there was a difference between oligometastatic versus polymetastatic, we did note a significant -- between a patient with oligometastatic disease versus polymetastatic disease. The overall survival was significantly different for patients with less than three pulmonary lesions. At 4 years, the overall survival was 47% compared to 35% and as well as the risks of intrathoracic distant failure were higher in patients with polymetastatic disease, meaning they were more likely to have a failure outside of the treated lobe, whether it be a contralateral lobe or another lobe.

When we reported toxicity after SBRT for pulmonary metastasis, we noted that it was very tolerable, there were very few Grade 3 radiation pneumonitis incidents and the Grade 1 and 2 in terms of radiation pneumonitis were also very low and not clinically significant. The rib fracture rate was 2% after SBRT.

We subsequently published our outcome for patients with head and neck primaries and noted that in 107 pulmonary metastases that were irradiated with SBRT, there were a little bit of differences in outcome in patients who had limited oligometastatic as well as polymetastatic disease. In our patient characteristics, you can see that a majority of the patients with head and neck primaries had oligometastatic disease, 60% of them had oligometastatic disease to the lung and 31% had polymetastatic disease. And since most of these patients had oligometastatic disease, they did not receive adjuvant systemic therapy after SBRT, most of them continued with observation.

In reporting our outcome between oligometastasis and polymetastasis state for head and neck primaries, you can note the difference in the curve, the overall survival curve, in that one, two, and three overall survival outcome was significantly higher in patients with oligometastatic disease versus polymetastasis and this was significant at 2 years. The rate of 2-year overall survival for patients with oligometastatic disease was 71.6% versus 43.8%. And we also noted that for patients with non-squamous cell histologies for head and neck,

those patients had a higher improved 2-year overall survival compared to those with squamous histologies for head and neck primaries. It's a unique biology.

In summary, for our treatment paradigm, in general, at MD Anderson for oligometastatic patients is based on the Phase II published randomized trials as well as ongoing studies, noting that there are a significant and distinct biology and outcome for patients with oligometastasis, that they would start with frontline systemic therapy. But for those without evidence of progression of metastasis, our intent would be to offer aggressive and radical local therapy, whether it be radiation or surgery or both to the primary as well the metastatic site and to offer comprehensive local therapy, consolidated local therapy to all sites. And generally, surgery was an option, and our surgical candidates, these patients would have surgery to their primary and then for the metastatic disease it can be surgery or radiation and/or both. And then depending on the histology, these patients will have continued maintenance systemic therapy or they would have observation.

And all of our patients are discussed in the site-specific multidisciplinary tumor board at MD Anderson for consideration of treatment recommendations and for those that are candidates for surgery, all these patients are discussed in the multidisciplinary setting and for those with up to five or less metastatic sites, we always request for a biopsy, tissue confirmation for metastasis. And for those patients who are surgical candidates, we recommend surgery, and the surgeons will weigh in whether it may be for thoracotomy or a VATS or lobectomy or wedge, and those patients who are surgical candidates will have no medical comorbidities which would put them at a higher risk of surgery. With good PFTs, good performance status, and no malignant pleural effusion, they would be candidates for surgery, and with the caveat that they don't have any evidence of progression on systemic therapy.

And for patients who are considered for radiation as a local therapy, again, we would be discussing it with the multidisciplinary tumor board and as long as they have less than five metastatic sites, biopsy, confirmed metastasis, all sites would be treated with ablative doses, SABR or stereotactic body ablative radiation therapy or SBRT, as long as they don't have any contraindications for radiation, being active lupus or scleroderma or no prior radiation to the same site. Other location, we do offer re-radiation if that's the only option. But many of our patients do have a combination of aggressive local therapy with radiation and sometimes surgery and we would have that discussion with our thoracic surgeons.

This is a patient that was treated with Stage IV non-small cell lung cancer. Initially, she presented with a Stage I early stage lung -- right lower lung primary and underwent lobectomy in 2015 and did well until 2017 when she was noticed to have a recurrence, and upon biopsy was found to have an EGFR mutation and sort of an allotment (ph.).

However, a couple months later she was found to have two new left lower lobe pulmonary metastases and was sent for ablative therapy and we treated her with 50 Gy/4 fractions with SBRT to both of those pulmonary lesions in the radiation treatment plans on the upper right. In 6-months post-treatment, she had a great response, the tumor shrunk and the penalty (ph.) had decreased significantly and it took 9 months for that area to scar down and she had a complete response and did very well and continued active -- close observation.

And in closing, some thoughts on future ideas in trials. These are the ongoing trials for a local, looking at local therapy for a patient with oligometastasis to the lung, the OMEGA trial, the SARON trial, the UK-CORE, the NRG-LU002. Three of the four offer stereotactic ablative body radiation therapy (SABR, SBRT) as local therapy, and the OMEGA trial offers patients surgery, radiation, as well as RFA. And the other, in terms of primaries, most of them include patients with lung cancer; however, the UK-CORE includes patients

with different primaries including lung, breast, prostate. And these are appropriate endpoints to look at, optimal modalities in treating patients aggressively with oligometastasis to the lung, specifically looking at progression-free survival and overall survival.

I'd like to thank everyone who contributed to these landmark trials and our ongoing trials, and it's really a collaborative effort amongst all of our disciplines at MD Anderson where we meet weekly with our thoracic surgeons, medical oncologists, and radiation oncologists to discuss all of our patients and our treatment recommendations.

DR. LEE: Thank you, Dr. Handy and Dr. Nguyen, for the session.

Now we will start our panel discussion that will be moderated by Dr. Jonathan Yang from the Memorial Sloan Kettering Cancer Center. Please welcome Dr. Yang and our panelists.

DR. YANG: Thank you. So I'm Jonathan Yang, I'm a radiation oncologist and director of our metastatic disease service in the Department of Radiation Oncology here at Memorial Sloan Kettering. I want to first thank everyone for joining us for this panel and participating in this important discussion. We'll have 60 minutes today to discuss five topics on defining an appropriate patient population and goals of local treatment for TTA. Next slide.

So in this panel, we'll have eight panelists: medical oncologists, Dr. Grilley-Olson and Dr. Feliciano; thoracic surgeons, Dr. Handy and Dr. Detterbeck; radiation oncologists, Dr. Chmura and Dr. Nguyen; and FDA panelists Dr. Lee and Dr. Stapleford. Next slide.

There was no conflict of interest declared. And next slide.

We'll move on to the panel questions. Next slide, please.

The first question: What are the current local treatment options for OML used in your facility?

Dr. Grilley-Olson, would you be able to open up this question?

DR. GRILLEY-OLSON: Yeah, so I think the -- you know, the potential options are somewhat of what was already outlined by the prior speaker, the VATS wedge section, yeah, certainly a more invasive surgery is potentially an option; SBRT done by radiation oncology and also ablation by interventional radiology are really the primary modalities.

DR. YANG: Dr. Feliciano.

DR. FELICIANO: Yeah, thank you for having me today. I would agree with Dr. Olson that those are the primary modalities that we use. Specifically, I'm a thoracic oncologist and so we tend to use more either surgical resection or stereotactic radiation. I'd say at our institution, some of the things like RFA or cryo are used more for the GI tumors, but in general, we use SRS and surgery, as well, and usually our patients will be presented at a multidisciplinary tumor board with radiology input, radiation oncology, thoracic surgery, to also help guide us in those decisions.

DR. YANG: Dr. Handy.

DR. HANDY: We use surgery or SBRT and we have really never done much ablation for pulmonary metastasis.

DR. YANG: Dr. Detterbeck.

(No response.)

DR. YANG: We can come back to Dr. Detterbeck.

Dr. Chmura.

DR. CHMURA: Yeah, I would agree with the other panelists, it's primarily SBRT or SABR and then surgical approaches such as wedge. Really, the IR stuff is, again, mainly for the GI tumors or peripheral tumors but not really for the thoracic ones.

DR. YANG: And Dr. Nguyen.

DR. NGUYEN: I agree with all the panelists. So here, it's usually presented in a

multidisciplinary setting and we tailor it to each patient, but really surgery or SBRT and then the RFA ablation, not necessarily for oligomets, but sometimes in multiple mets in a second line or even some GI tumors, but really if they fail SBRT, they're not surgical candidates.

DR. YANG: And Dr. Detterbeck, would you like to add to this?

DR. DETTERBECK: Yeah, so let's try again, I think I was muted before, but -- so we use primarily surgery and SBRT, as well. We do some ablation but we -- you know, we tend to prefer surgery or SBRT. Ablation is usually brought out if we think there are some contraindications, the surgery or SBRT.

I would also perhaps add that over time, I think things have shifted a bit from where surgery used to be the primary modality and SBRT was really a second thought, where I think it's kind of the other way around now a bit more commonly. Obviously, things that are -- if you need a tissue diagnosis, surgery has an advantage. If it peripheral surgery, it's easy but if it's more deeper within the lung, then SBRT definitely has some advantages.

DR. YANG: And in your practice, and this is for everybody, in what clinical scenario do you typically consider using IR approaches such as RFA, cryo?

DR. GRILLEY-OLSON: Well, I'm a sarcoma medical oncologist, so I think some of it is very histology driven. With sarcomas, the biology is sometimes quite different and some patients can proceed with all the sort of repeated oligometastatic disease that might be fairly peripheral if it's amenable or the patient is interested in a wedge resection, that's often sort of an easy preferred option. But after they've had extensive sort of sequential procedures, then something less invasive such as an IR ablation might be preferred in a patient at that later point where you don't need the histology, you don't need to prove recurrent -- you know, first recurrence you don't necessarily expect that it has a clear benefit other than it's a very short-duration treatment.

DR. DETTERBECK: So I would say, if you want to me to chime in here, I would say

that a big consideration is kind of eradication of all suspected disease, so doing SBRT to multiple sites gets to be a bit difficult; of course, doing surgery in multiple sites gets to be difficult, as well, but I think that's a big part of the consideration. I think, as I said before, where things are in the lung makes a difference.

I do think that things have eroded a little bit, we're a bit more willing to ignore some lesions that are small and don't really seem to be changing, you know, we might have some suspicion that they actually are mets but we're kind of willing to ignore them at times. I'm a little bit uncomfortable with that, it used to be that we really focused much more on eradicating everything that we thought was suspicious.

DR. YANG: And Dr. Chmura and Dr. Nguyen, I think you had mentioned that sometimes you will consider IR ablation after failing SBRT, is that a common practice at your institutions?

DR. NGUYEN: We do. Like it's been discussed before, really we discuss our patients in a multidisciplinary setting and if surgery is not an option and they've received SBRT and sometimes we do re-radiate, if it's feasible, and if not, if it's like a certain kind, like a colorectal or a renal, I'll consult IR colleagues to see if ablation in combination is an option or if it's like an ultra-central where I can't give ablative doses, we would consider that and we will discuss that with all of our colleagues.

DR. CHMURA: Yeah, I would actually concur completely there, it's sort of the algorithm of yes, the few patients who do progress with SBRT, can we offer actual surgery, you actually kind of wonder why they progress anyway, so it's kind of nice to have the tissue. Usually, it's a few years like down the road, which is nice, so it's kind of nice to do NGS again on it and then I think -- and I kind of agree, I think that before we weren't really doing a lot of re-SBRT but now that the plans are so conformal, the lung is already shot there anyways, and the real increase in like pneumonitis, if it's small, isn't really as bad as

we used to think. So I kind of view the IR call as the fourth down in 25 call, right, it's not really something I kind of want to do.

DR. YANG: If anybody else wants to provide any other input on this question, specifically?

DR. GRILLEY-OLSON: I guess just the one thing I'd say, sort of thinking ahead, is I think it's about a question of how comparable it is, I don't think we actually know. Maybe it's like SBRT was, like Dr. Detterbeck was mentioning previously, was sort of the option for poor performance status patients that couldn't undergo surgery. It may or may not be, but I don't think we actually know that, it's sort of convention, it's sort of the alternative.

DR. DETTERBECK: I have looked pretty carefully at what literature we have for lung primaries, you know, people that for whatever reason you're not going to resect but you're going to give them either SBRT or microwave or some radiofrequency, some other form of ablation. And I think that the literature is -- it's obviously not a randomized trial, you have to read between the lines, but I think that the efficacy is a step down for ablation techniques than SBRT and the complication rate is definitely higher than for SBRT. So I do think there is soft literature that kind of backs that up, but ablation is not as ideal, not as optimal as SBRT.

DR. FELICIANO: And just to --

DR. YANG: I think that's fair.

DR. FELICIANO: Sorry. Just to kind of add to that is, especially for the lung cancer patients, at least from what I had kind of seen, is that maybe the risks of complications like pneumothorax are higher but maybe whether or not, that's not something that we would want a lung cancer patient to undergo, they often don't have enough reserve to have that kind of complication, so that really plays a role, as well.

DR. HANDY: John Handy here. And so I just wanted to mention, within our practice

and our team, we don't do a lot of pulmonary metastasectomy and sort of preparing my head for addressing that project which I presented, we do about 40 or 50 pulmonary resections a year and I looked over 10 years and about 2% of them were for metastasectomy, so we don't do very much and we've done less lately.

And I think, I was kind of distressed yesterday that there was virtually no mention made of the PulMiCC yesterday and the PulMiCC, I think, really should cause us all to have some pause because when you see that the patients with no therapy in a comparable well-matched situation, it wasn't -- it was closed early because it couldn't accrue to come to definitive conclusions, but a certain, a clear conclusion is, is that the survival is not zero for people that have metastatic disease that meet the surgical criteria for intervention and it makes me really wonder about local therapies for what is a systemic problem.

DR. YANG: Great. Let's move on to the next question. Next slide, please.

So in your specialty, what factors are used to determine which local treatment option is appropriate for OML? And for which histology and disease state is treatment of OML considered conventional versus experimental? It's a two-part question.

Dr. Chmura, would you mind opening up this question for us?

DR. CHMURA: Of course, yeah. So I think kind of like the driving force is one of histology and the need to obtain histology, right? I think if there's any question of the histology, if there's a history of head and neck primary and a lung primary, and you really want to know, I think any question at all pushes us towards some type of surgical approach. We are far more likely to push surgery in the case of, say, like sarcomas. I think that the SBRT data on that isn't bad, but it's not great, either. But for the most part, I think it's the sort of driving reason we need to obtain histology for sarcoma itself is the only reason to choose that over SBRT.

DR. YANG: Dr. Nguyen, would you like to add to that, specifically, from a rad

perspective?

DR. NGUYEN: Yes, I agree with Dr. Chmura. You know, we do really discuss if patients are operable or not, but from our huge database we've demonstrated that you can SBRT these patients and really began with patients who weren't operable, but now that SBRT is really becoming a little bit more standard, there are multiple histologies that we will, if they're not suitable candidates, and then for those that we have been reporting in the literature, like colorectal and like Dr. Chmura said, sarcoma, for oligomets, we would discuss with our surgeons and recommend surgery and if not, SBRT is an option. But basically, most histologies are amenable to SBRT.

DR. YANG: And just to add on to that, is there any specific histology that you would consider is more conventional versus experimental for treatment of OML?

DR. NGUYEN: Yeah, if you really go by the Phase II trials by Gomez, Iyengar, and Palma, you would say lung, colorectal, breast, prostate. However, those are limited in eligibility and now I think we have a trial, ongoing oligomet trial, that Chad Tang is doing, it's not simply just lung, but it's really a basket of all histologies, really looking at the oligomet state and consolidating with SBRT.

DR. YANG: Dr. Handy, from the thoracic surgery perspective, how would you address these questions?

DR. HANDY: Well, as I had mentioned, we obviously first look at surgical candidacy and the ability to do pulmonary parenchymal sparing, so if pulmonary parenchymal sparing or surgical candidacy are better with a nonsurgical approach, then that's what they get referred to. And one of the things that we stressed in our document is that pneumonectomy -- I have a recent case, actually, notwithstanding. So like I said, all these things have exceptions, but we really -- I think pneumonectomy is poorly conceived in this particular context.

One of the things that no one has mentioned, it's not really sort of the subject of this, but sometimes you see people who have good control of their metastatic disease except for one, which is the proverbial rogue metastasis and those you often want to get into the pathologist's hands so you can do more thorough genetic analysis and understand what is going on with this particular one and should we be altering our systemic therapy.

DR. YANG: Dr. Detterbeck.

DR. DETTERBECK: Well, in terms of histologies, I think that melanoma is something I'm a bit more hesitant to consider, you know, eradication of pulmonary metastases, I wouldn't say never, but I think the outcomes are worse than with others. I think in sarcoma it's generally better. Residual masses from nonseminomatous germ cell tumors, that's definitely an area where you would consider resection. I guess that's all I have to add about that. Or treatment, I shouldn't limit it to resection, but treatment.

DR. YANG: Dr. Grilley-Olson.

DR. GRILLEY-OLSON: I think, again, the histology piece is really critical in my world. In sarcoma, it's -- yeah, surgery is really like -- the thoracic surgeon is like who I turn to first and foremost, I think. One of the other sort of advantages that's again a somewhat disease-specific consideration but it allows assessment of the pleural space which is sometimes a very significant decider of whether, say a wedge resection is appropriate or not in a sarcoma patient if they have extensive pleural-based disease. I think the flip side of it, though, is also that I've seen patients who have resections done by potentially inexperienced surgeons dealing with sarcoma and they have rapid seeding of the pleura after they have an oligometastatic lesion resected also, and so I think understanding that disease biology is important, too, say if it's done, is sort of a low volume community setting.

DR. YANG: And Dr. Feliciano.

DR. FELICIANO: Yeah, I agree with what the others have said. I'd say other factors,

though, that I use to consider local therapy is how well the primary is controlled. If it's a patient who is otherwise well controlled on immunotherapy, for example, and then they have either residual site or oligoprogression, something like that, then we might be more apt to do it or someone who's on tyrosine kinase inhibitor. So I'd say how well it's controlled, what type of therapy they're on, like if they're not responding well to chemo and then they have an area of progression, I'd be less likely to offer a local therapy there. And actually also, probably -- yeah, kind of what molecular testing results we've had, as well. So we always try to get more tissue, but if it's not possible, that can be tricky, too.

DR. YANG: And this is a question for the entire panel, you know, we hear that histology and obviously, operability, surgical candidacy, they're very important factors in terms of how you decide on which type of local treatment is appropriate and are there other factors that suggest number of OML or location of the OML that comes into your decision-making locker room?

DR. FELICIANO: I would say for us, especially if it's more like a oligoprogressive situation, possibly the pace at which the time in between the progression, like if I have an isolated met and then 2 weeks later I have another isolated met. It's going to be a different situation if it's been 6 to 12 months before another one pops up, so that kind of plays into my decision making. And in terms of histologies for lung, I'd say the ones that I'm most reluctant about are high-grade neuroendocrine tumors, small cells, don't tend to use it as much for that situation.

DR. DETTERBECK: So I would throw in there that certainly number, you know, I think you want to treat all of the disease that you think is progressing or active. So if it's a de novo situation, I think you want to treat all sites. If it's a progressive situation and if some are stable, I think that's fine, but you want to treat the ones that are progressive. I think that disease-free intervals, so number, you have to be able to treat all sites. In terms of

disease-free interval, I think that's very important. If you have a tumor that seems to be just rapidly progressing, I think we would be much more likely to treat them with systemic therapy and very disinclined to consider any local therapy. Another aspect is that in terms of progression, we tend to look at a site that is progressing in size, that is growing as different than progression with new sites appearing.

You know, when we see a lot of, or some new sites appearing, we are much more worried that there are other sites that we're just not aware of and that applying some form of local therapy to certain sites probably doesn't make much sense and we need to change the systemic therapy that they have, whereas if they have demonstrated no new sites of disease for some time and there is one site or two sites that are progressing while others are stable, we're much more inclined to say well, let's apply some local therapy to those sites.

DR. YANG: Great. Would anybody else like to add to this question?

DR. FELICIANO: I was just going to add also sometimes what we have to take into account is if we are going to pursue a local therapy, can we afford to have -- does a patient need to refrain from systemic therapy at the same time, especially for the patients who are on targeted therapies. Sometimes if the local therapy might be a little bit more prolonged, for example, and you might not want to combine it with radiation, we have to take into account that okay, well, it was controlling all the disease in the brain and now are we going to able to hold off for a while.

DR. YANG: Great. Let's move on to the next question. What oligometastatic cancer histologies would you not consider treating locally?

Dr. Feliciano, since we have you here.

DR. FELICIANO: Yeah, I think at least for lung, I'm reluctant to do that with any kind of small cell or small cell-type neuroendocrine cancers since they tend to be primarily

systemic from the get-go. Again, I do think we're sort of entering a new era where we've gotten control with chemo immunotherapy and we've had -- this has happened only once, but I had a patient with 2-years control, chemo-IO and had one area of progression and that was a small cell. So I think things may be changing, too, as we get better long-term control with our immunotherapy patients, but that tends to be one where I stay away from.

DR. YANG: Okay. Dr. Detterbeck.

DR. DETTERBECK: Well, I mentioned earlier melanoma is something we're -- you know, we're much more hesitant and more selective. I would throw out there other tumors like pancreatic cancer or small cell, you know, certainly aggressive tumors we'd be much more hesitant considering a local therapy.

DR. YANG: And the reason for melanoma and pancreatic cancer, as you mentioned, you felt that they're more aggressive in nature and therefore would benefit more from a systemic approach?

DR. DETTERBECK: Yes. And when I look at the literature for survival of patients that have undergone resection of mets, of melanoma mets --

DR. YANG: Um-hum.

DR. DETTERBECK: -- it's clearly worse than most other histologies.

DR. YANG: Dr. Nguyen.

DR. NGUYEN: Yes. So in general, I don't consolidate for oligomets if patients had a complete response. And the histologist also, and pancreas has been identified up and yeah, it is still controversial. For small cell, though, I'm going to let Dr. Chmura chime in because he's got the trial that he's starting and remember, too limited, if it's a small lesion, surgery is an option, also. And so is SBRT, but that's not in the oligomet setting. But in tumors like pancreas where we think do poorly, we have SBRT patients with oligomets along with pancreas primary. They're considered radioresistant, but they still do okay, the 4 or 5-year

local control is like 15 -- fill rates are 15%. So it's still a viable option if surgery is not an option. And we do like to get histology in those scenarios, but I'll let Dr. Chmura talk about his trial for small cell.

DR. CHMURA: Yeah, yeah. I would actually agree with all of that. I think in terms of like small cell, right, in terms of the actual limited stage, I think the surgery and the SBRT data actually looks really good, right, like in terms of obtaining control. I think now with the three IO trials and sort of looking at the patterns of failure, I think the patients who sort of almost like a redo of the RTOG study, right, trying to like obtain control of the three or four areas of disease with combination therapy may prove to be a benefit. So again, these are all clinical trials, but I wouldn't just exclude small cell because it's often thought to be everywhere and like always, especially in the area of chemo-IO where a small set of patients actually obtains a durable response.

DR. FELICIANO: Yeah, and I would just add, I think for me for small cell, it's really more of the extensive stage and I think oligoprogression and then metastatic stage, again, even that's changing. But certainly, we use local therapies for limited stage small cell.

DR. YANG: And Dr. Grilley-Olson.

DR. GRILLEY-OLSON: Yeah, I think the only other thing, it was kind of mentioned earlier in a slightly different context beyond the histology consideration is really the kinetics, I think, that probably really should be emphasized of the kinetics over disease.

DR. CHMURA: I would actually agree. I mean, in the CNS space we are already using brain met velocity on the NCI-sponsored trials, right, to actually try and really ask this question, who are the slower progressors and who are the longer ones. If you go all the way back to the original ideas about oligomets, it was actually defined as a slower growing state. So I agree, I mean, it would be nice and unfortunately, the Phase III trials are not all incorporating this except to have some calculation of the velocity of disease. The Phase III

trials like NRG-BR002 and other ones are really just sort of classifying it as like synchronous versus asynchronous, but having some idea of the velocity is a good idea and I wish we had those in the trials that are ongoing.

DR. YANG: And I'll come back to this in a little bit. And before we dive into that a little bit further, Dr. Handy, are there any specific histologies that you would not consider treating locally?

DR. HANDY: You know, I'm not sure I agree with what many of other speakers have said. I think it's hard to know what's going on, to tell you the truth, within your institution, is that if you get referred to surgery, I know about you if you're presented at our multidisciplinary conference, I know about you -- and our conference is very high volume, we have about 900 presentations a year, but I don't know what's going on in the radiation oncologist's office or the medical oncologist's office. So I don't know who doesn't get considered or who doesn't get referred, so I think a lot of these questions are hard because I doubt if anybody on this call has a protean (ph.) knowledge of what's happening in their institution.

DR. YANG: And yeah, Dr. Chmura, just to dive into the kinetics a little bit, is there an interval of time that you felt more comfortable applying local therapy for what we consider oligometastasis, that they don't have disease progression?

DR. CHMURA: Yeah, I mean, I have papers and things showing that they're like under 0.5 new mets per year are the ones who do well, but is it also because you are sort of doomed to do well if you are growing so slowly or not? I think trying to find some way to avoid the every 3-months scan you have a new met, right, I think that's key, right? So like for the NRG-BR002 trial, you basically had to show at least 6 months on systemic therapy of no progression. I think LU002 is the same, but I think some interval from the start of the systemic therapy to at least show stability is really needed.

DR. YANG: Dr. Grilley-Olson and Dr. Feliciano.

DR. GRILLEY-OLSON: I guess the only other thing I'd add, getting to the histology again, I think it concerns me, but I don't know the literature well enough. When I hear trials with carcinomas all being kind of -- you know, a wide variety of carcinomas being lumped into an oligometastatic trial, I mean, I think about like obviously sarcomas, sure, it's its own beast, but from the pediatric surgeon's perspective, osteosarcoma, oligometastatic disease is if they can count less than a dozen lesions and they expect to find another half dozen while they're in there, that can be curative. So I think putting breast cancer together with colorectal cancer, is it positive, is it triple negative, you know, it still seems like it's a very muddled answer, as a result. But again, I don't know the carcinoma literature as well.

DR. DETTERBECK: Jonathan, can I ask a question? My understanding of this workshop here is to think about how would we design a trial to look at the endobronchial type of -- or whatever, transbronchial types of ablation and we're talking a lot about what we do in practice and there are a lot of things that you do in practice where you say I don't really have good data, but I have a hunch that this might work or that might work, but that's very different from how you would design a trial to really test the therapy. So are we kind of getting off the track of what we need to focus on?

DR. YANG: Yeah, so that's a really good point. I think we want to capture both what you typically would do in your own practice to help in terms of defining a better patient population for the clinical trial, which leads to actually the next question, if you don't mind pulling that up.

So in defining a patient population, what would you recommend for inclusion/exclusion criteria for a study of using TTA and OML?

Dr. Detterbeck, since we have you speaking.

DR. DETTERBECK: Since I opened my big mouth?

(Laughter.)

DR. DETTERBECK: Well, so to me, I think the biggest question is what are the endpoints? So obviously there's a safety/toxicity endpoint, that's one thing. That would be a different choice of inclusion versus an efficacy endpoint and efficacy, I think I would be aiming for some sort of local control, you know, how well does this work in terms of local control, and I think you would want to select patients where the numbers of sites are relatively limited, where you're not going to be confused with "I treated one site but there was a new site that developed a centimeter away and I can't distinguish it."

So you'd want to have some limited number and I think you would also want to have something that has kind of an intermediate velocity, as we talked about earlier, where if the disease-free interval has been 10 years, well, sure, you can treat it but you really -- it's going to take a long time to find out whether your treatment was really effective or not, whereas if it's too short and it's too aggressive, then you probably also can't really tell that well.

So I think that it depends a lot on what the endpoints are and kind of the overall design of the trial and if you're saying I'm going to design a trial that's going to compare some sort of bronchial approach versus SBRT versus I'm just doing a single-armed trial of a transbronchial approach and I'm trying to get a signal on how what sort of efficacy we might expect in order to be able to design a trial that compares one modality to another, so it's hard for me to answer that question without knowing a little bit more about the rest of the question that is on the table.

DR. YANG: So what if we envision a trial assessing the efficacy of TTA and OML, and then you mentioned that the disease-free interval, the kinetic, which multiple panelists have mentioned would be an important inclusion or exclusion factor, are there any other factors that you feel that it's important to include in a study of this type?

DR. DETTERBECK: Well, I would focus on the traditional one, which is limited

number and I'll throw three out there, but of course, in a trial design, I'm sure that's going to be debated, and I would throw out disease-free interval as a more classic way of just kind of looking at the progression, what is the rate of progression, maybe we can come up with better criteria eventually, but I don't think we have them. And I would say if you have a disease-free interval of less than 6 months, probably not a good idea; greater than 3 years, probably not a good idea. Again, these things could be or would be debated if somebody is actually designing a trial.

So those would be my primary criteria and then I would think that depending on the trial that you may want to limit it to sort of more common types of cancers as opposed to opening it up to just any type, so maybe you would say I'm going to do colorectal and osteosarcoma is probably the most common ones. But that's how I would be thinking about designing a trial or discussing a trial.

DR. YANG: Dr. Handy, would you like to add to that?

DR. HANDY: I like those suggestions. I think I would choose fairly noncontroversial ones, as I put in my presentation, so I would look for three or less metastases. Disease-free interval, I think that 2 years is very defensible and sort of midway between what Frank is talking about, and I think an important one, since we're talking about an ablative therapy, is that the size of the tumor makes a huge difference with regard to possible success of ablation and that really hasn't been discussed yesterday or today.

And so when you review the literature on ablation with radiofrequency being the most common, anything less than two, I mean greater than 2 cm has a less good outcome and I think we're going to look at where this is most applicable, a size cutoff should be in there and I would suggest 2 cm.

DR. YANG: Dr. Grilley-Olson.

DR. GRILLEY-OLSON: I guess, just to back up a little bit, is -- would the goal of the

TTA be still more -- further defining endobronchial or is it looking at some of the new experimental parenchymal techniques? And I guess the other concern I have is, I think the -- what is the benchmark going to be, is it going to be in comparison to sort of a modestly better defined SBRT and surgery versus the interventional ablative approaches? So I think that all factors into the design, also.

DR. YANG: The experimental nature versus what is its comparators, comparison modality would be important.

DR. GRILLEY-OLSON: Yeah, even it's just trying to figure out what the historic control is.

DR. YANG: Yeah.

DR. GRILLEY-OLSON: Is it versus -- is TTA trying to improve upon say, SBRT as another sort of --

DR. YANG: Um-hum.

DR. GRILLEY-OLSON: -- you know, at least sort of a moderately less invasive approach than surgery, but I think those are all sort of other factors, you know, are they central big airways versus trying to get a little bit more peripheral?

DR. DETTERBECK: Raphael Bueno just threw that out there in the chat, as well, about size and location in the lung. But I'm assuming that this is more of a transbronchial approach in the lung parenchyma as opposed to an obstructive endobronchial tumor.

DR. HANDY: My understanding, also.

DR. GRILLEY-OLSON: Which, you know, I think those -- sort of my peripheral understanding of that is that the early trials of that, wasn't there recently a death in a parenchymal ablation from TTA?

DR. YANG: So location certainly will be part of the inclusion versus six for an *n* (ph.) factor and accessibility of the lesion.

And Dr. Chmura and Dr. Nguyen, anything else you would like to add to this question, specifically?

DR. CHMURA: Yeah, I mean, to me it just seems like we have a lot of ongoing Phase III trials which are histology specific, right? We have the NCI NRG-BR002, which will be presented at ASCO 2022 in just a few months. We have LU002. I mean, others are going to read out, right?

So it seems like if we're going to argue which local therapy is better and when, we should first figure out which histology this is going to work in, who the exact population is because it would be a lot easier then. If you knew it worked in Population X, Histology Y, use those criteria and you could set up a non-inferiority trial of local control like toxicity, have a co-primary endpoint and really answer then who these types of new technologies will be good in. It just seems like trying to do a study before we know if it even works or not when frankly, I don't think it's going to work, is sort of a little cart before the horse.

DR. NGUYEN: I think Dr. Chmura was very eloquent in saying that.

(Laughter.)

DR. NGUYEN: It's hard because you have two local modalities that have multiple trials demonstrate that you actually have great local control in a population that's potentially curative. To introduce a different modality where we don't know which histology, which location, and there has to be a stopping role in this design to say if it's worse than what's out there, I think we would have to stop, as well as toxicity, toxicity as well as outcome, there should be a stopping rule built in so that we know early and don't proceed and continue this trial, if it isn't efficacious and potentially could have more toxicity than SBRT.

DR. FELICIANO: I was just going to add I think it also -- to Dr. Nguyen's point, that maybe it's a situation where it's a trial for people who aren't eligible for current treatments,

if it's a more central tumor, for example. And also to Dr. Detterbeck's point, that no efficacy in terms of relative to another local therapy versus say, efficacy for palliation. Now, if it's more of a palliative procedure for symptom management or something, then I think you can be more open to the histologies and the broadness of who's allowed, or more of a safety endpoint. But I agree, it would be hard to put someone on a study when there's more and more data that these local therapies improve survival.

DR. YANG: Anybody else to this question, specifically?

DR. GRILLEY-OLSON: I guess the only other thing is defining the pulmonary reserve.

DR. YANG: Right.

DR. GRILLEY-OLSON: Sort of stating the obvious, but --

DR. YANG: Great. So let's move on to our last question. So in your specialty, which of the following goals are appropriate for each local treatment option for OML? And what factors do you consider when defining the goals of local treatment, are they palliation, prophylactic palliation, prolongation of life, quality of life, cure, or others?

Dr. Feliciano.

DR. FELICIANO: I think it's all of those and it just depends on what type of trial you're looking at to -- whether or not to assess all of those and I think for patients where we're thinking of curative intent, that's a very different study and study design than if we're talking about palliative management of an obstructed airway or something like that. So all of these are important but I think are more applicable to different trial designs. And so I consider all of these in our practice.

DR. YANG: Dr. Detterbeck.

DR. DETTERBECK: Well, I think palliation is really pretty rare. I mean, there certainly are occasionally patients that have some symptoms but -- you know, hemoptysis or whatever. But I think generally, the parenchymal metastases that we're talking about are

asymptomatic and so I think palliation or prophylactic palliation is so rare that I think it's hard to design any kind of a trial around that, so I would take those off the table. I think the goal is really prolongation of life or cure. You know, certainly the data on treatment of oligometastatic diseases made us at least believe that there is a benefit to prolongation of life even if it's not a cure, so I think those are really the main goals. I think quality of life, of course, is always in there and certainly if your treatment is going to hurt your quality of life to a certain extent then that has to be balanced against whatever benefit, so I think that's an important endpoint. But to me it's prolongation, primarily, and cure perhaps secondarily, I think it's a little harder to define.

DR. YANG: Dr. Nguyen.

DR. NGUYEN: Yes, I agree with Dr. Feliciano and Dr. Detterbeck. Really, for oligomets, though, when I see patients it's really oligomets versus polymets. So most oligomets aren't as symptomatic unless it's just one met invading the pleura, potentially causing pain, but even then those patients we treat aggressively or with intent to cure and in terms of the prolongation of life, it really depends on the velocity, they develop another met.

Then we still offer aggressive local therapy, with the goal of prolonging life, in combination with systemic therapy. And then in terms of symptoms, we do -- I mean, we still ablate that, we don't really palliate these oligomets. Polymets, potentially, but not really palliation, prophylactic palliation because they're just distinct. Those are really for polymets.

DR. YANG: Great. And Dr. Chmura, would you like to add to this?

DR. CHMURA: Yeah, I would concur with everyone else. I would just like to point out that we can study aggressive palliation, I mean, we have trials looking at SBRT for spinal mets and quality of life and I think these are really important, and --

DR. DETTERBECK: For sure.

(Cross-talk.)

DR. CHMURA: -- so that being aggressive with your palliation actually helps. So I think it depends on the trial design but you absolutely shouldn't think about the fact that with moderately systemic therapies people are living longer and just sort of doing the 4 Gy times 5 to a met and then it grows back in 12 months and people are still alive, this isn't great care, either. So I think there is absolutely room to look at the technologies in terms of the impact on both control and quality of life and even pain control.

DR. DETTERBECK: Yeah, but if we're talking about transthoracic, a bronchoscopic type of lung metastasis, that's a little bit different. That takes spine mets or those sorts of things out of the picture.

DR. CHMURA: Yeah. Right, except though, they can grow where they can cause obstruction, right? I mean, I see patients all the time who are 2 years out, had 3 Gy times, like, 10 to like an essential structure and now it's growing, and it's the only thing hurting them, right, and it's like well, you already treated her whole spine and I can't give any more there. And so I just think, as it were, systemic therapies improve, we should be counting people out of dying soon less maybe and consider that if we are going to intervene, if we can do it in a safe way, there's really no harm in obtaining good long-term control even on the off chance that somebody is alive in 3 or 4 years.

DR. YANG: Dr. Handy?

DR. HANDY: I've always presented to the patient that we don't exactly know what we're doing when we embark into this particular context, but we hope that we're prolonging your life or providing a cure and I think those would still be my goals. I agree with Frank, is that most people, these are imaging, discover things that are largely asymptomatic so we actually have room to hurt people versus making them better, so we

better be prolonging their life or providing the possibility of cure.

DR. YANG: Dr. --

(Cross-talk.)

DR. YANG: Go ahead.

DR. FELICIANO: No, I was just going to also say, especially if it's hard to do comparative studies say against the back drop of SRS for oligometastatic disease, I think it could be really important, too, to have registry opportunities for these types of procedures so that maybe you can look at larger populations over time.

DR. YANG: Dr. Grilley-Olson.

DR. GRILLEY-OLSON: Yes, the one other thing I'd throw out there as a medical oncologist, you're sort of often, I guess, quarterbacking the metastatic disease care. There's probably, you know, I think the thoracic surgeons and radiation oncologists are seeing the selection bias that the medocs (ph.) bring into it. So if somebody has some impending airway obstruction I'm going to refer them to a radiation oncology colleague rather than a thoracic surgeon and so that may be why there's some bias as far as what the goal is between cure or prolongation of life versus palliation.

DR. YANG: Does anybody else want to provide any input on this question?

(No response.)

DR. YANG: And we have a couple minutes left, does anybody else have any other input on any of the questions we discussed today?

DR. DETTERBECK: Well, I'd be interested to hear, I guess, what the output of this whole initiative is. Are we going to get any feedback on that?

DR. YANG: I wonder if Dr. Lee or Dr. Stapleford can answer that question more specifically?

DR. LEE: Sure. Thank you, Dr. Detterbeck. You know, one of the things why we're

here is so that the Agency can work collaboratively with the community to try to get better data and certainly, one of the goals of the workshop is to basically be transparent about our thinking and our process. And I thank you so much, all the panel, for the discussion and yes, where the rubber meets the road is looking at trying to collect better studies and better information so that FDA could make decisions regarding trials that are before us or what next steps have to be basically focused on. Thank you.

DR. YANG: I think this concludes our panel and thank you, everybody, for participating. And I'll hand this back over to Dr. Lee.

DR. LEE: Again, thank you, Dr. Yang. Thanks so much for the panelists and the speakers today, thank you. Special thanks to Dr. Yang for moderating. We will be breaking for lunch and we will be returning here at 1:00 p.m. Eastern Daylight Time. Thank you.

(Whereupon, at 12:35 p.m. a lunch recess was taken.)

AFTERNOON SESSION

(1:05 p.m.)

DR. BLAKELY: Hello, everyone. I am Brandon Blakely, the Assistant Director for the Respiratory Devices Team, and it is my pleasure to introduce our third session, an Overview of Prior and Ongoing Study Designs for Evaluating the Safety and Effectiveness of Local Therapies for OML.

Our session will begin with three amazing speakers: Dr. Daniel Gomez from Memorial Sloan Kettering Cancer Center, Dr. Ross Camidge from UCHealth Lung Cancer Clinic, and Dr. Tom Treasure from University College London, UK. We will then hold a panel discussion on clinical trial design for TTA devices for OML moderated by Dr. Raphael Bueno from Brigham and Women's Hospital. Thank you.

DR. GOMEZ: Thank you very much for joining me today in this very valuable workshop to discuss the overview of prior and ongoing study designs for evaluating the safety and effectiveness of local therapy in the setting of oligometastasis in the lung. My name is Daniel Gomez, I'm attending physician at Memorial Sloan Kettering Cancer Center, where I currently am part of our thoracic radiation oncology group.

These are my disclosures listed here: honoraria, research grants, and consultancies. And I wanted to add the additional disclosure that many conclusions that I'll draw in this presentation represent a personal interpretation of the data and the standards of research. So my goal here is really to present issues and to raise provocative points on critical questions in trial design, but certainly you are welcome to have different impressions and I'm sure that we'll have a good discussion by the panel in this vein, as well.

In this talk, I'm going to discuss four important questions to address this issue of optimal study design of oligometastatic disease. The first is the role of randomized versus

non-randomized data. I know that there's a lot of discussion and controversy about this, particularly in the setting where accrual has been difficult. The second is the appropriate balance of broad versus narrow inclusion criteria with respect to changes in practice. The third is the role of endpoints that really represent the control of disease locally, like progression-free survival and local control. And finally, I want to touch on some less standard or ubiquitous endpoints that can also have utility in this setting.

So this is a recent review of ongoing studies in the setting of oligometastatic disease and this covers not only lung cancer but other oligometastasis settings and you can see on the right, from a literature review, there were several studies that are ongoing but they spanned again from Phase I all the way from Phase III randomized studies. The majority of them are nonrandomized. So I think it's reasonable to conclude that a role exists for both randomized and non-randomized studies in oligometastatic disease of the lung. So what is that role?

So I think the first point to acknowledge is that a tradeoff exists between these two paradigms. Non-randomized studies are often easier to accrue to because there's only a therapeutic arm. Investigators are able to answer provocative questions using less patients and resources, therefore often making them more feasible.

And then the question is raised of whether we need a randomized study to answer every question in medicine and this is something that has been brought forth through a couple of studies that have come to be quite well known, including this one, which was a systematic review of using parachutes to prevent death and major trauma right at the gravitational challenge, so a randomized study of parachutes versus no parachutes and jumping out of a plane.

You can see the conclusions: "As with many interventions intended to prevent ill health, the effectiveness of parachutes hasn't been subjected to randomized controlled

trials" and the authors concluded in the last sentence, "We think that everyone might benefit if the most radical protagonists of evidence-based medicine organized and participated in a double-blind, randomized, placebo-controlled trial." So the point being that not every study necessarily needs, not every clinical question necessarily needs a randomized study.

However, in my view, the primary limitation of non-randomized studies in oligometastatic disease is that of immortal time bias. This is a slide that was a given to me some time ago by David Palma and I'll explain it a bit here.

So let's say that we take a group of patients, either retrospectively or prospectively, and we follow them and we want to treat them aggressively with either surgery or radiation or something for oligometastatic disease and we look how they've done and we compare them to historical controls, those patients that haven't been treated aggressively. Often what's done then is that these two groups of patients are compared from the date of diagnosis and survival is measured and oftentimes the conclusion will be that whatever survival endpoint is used, it's superior in those patients that are treated.

Now, the issue with this is that patients in the aggressive therapy arm, the "treated" patients, in order to be in that arm typically had to have received some initial systemic regimen that they tolerated well and that they survived, such that by definition, by being in that arm, they survived to the point where they received or underwent a metastasectomy.

Therefore, while the base value, the comparison from these two groups is at the date of diagnosis, in reality, these treated patients have a misclassified immortal time whereby all patients must have survived systemic therapy and are being compared erroneously from the date of diagnosis, in a misleading way, the date of diagnosis and the control patient. This is a very difficult factor to control for, particularly in retrospective studies, but even in prospective studies that are being compared to historical controls.

So in terms of the benefits of randomized trials, I think the most prominent controls for confounding factors such as this provides a higher level of evidence that can often be directly implemented and sometimes it yields unexpected results. There's a follow-up study, there have been a couple to that initial parachute meta-analysis, there was an actual randomized controlled trial that was published that demonstrated that parachute use did not reduce death or major traumatic injury when jumping from aircrafts in this randomized fashion.

However, it should be noted that the trial was only able to enroll patients on a small stationary aircraft on the ground. So not only does this demonstrate that -- attempt to demonstrate that randomized trials often can yield unexpected results, but that you'll see in the last clause here that caution should be used regarding the effectiveness of an intervention in the community, such that randomized trials may selectively enroll individuals with a lower perceived likelihood of benefit and thus diminish the applicability of the results in clinical practice.

So randomized trials, I think we can conclude, are preferred in the setting of oligometastatic disease, but they often close and I think the reasons are multifactorial. They often have a limited budget, they're difficult at categorizing patients that make them difficult for accrual, and there's a lack of physician or patient equipoise in actually randomizing patients.

And this is one my favorite studies or favorite publications that demonstrates how off-trial options often make accrual more difficult. So this is a study of systemic therapy regimens and you can see the X-axis is time and the Y-axis is cumulative proportion of complete accrual. And these two curves represent two things, the first, the blue line represents a scenario where no off-trial options are made available to the patient. So the physicians say you can have this regimen or you can get treated off trial. The yellow line

represents a scenario where the treatment is available off study and you can see intuitively, but also impactfully, that accrual is much slower when that regimen is being offered off study. And that is relevant in the setting of oligometastases because randomized trials can be difficult when there's not equipoise in the patients and the physicians and therefore aggressive local therapy is offered off study, which can then both delay accrual and really prevent the more impactful results from coming to fruition.

So how do we overcome barriers to clinical trials? I think there are several ways. The first is pragmatism, designing studies that are pragmatic in design in the context of multiple acceptable treatment approaches, treatment choices, using appropriate endpoints, those that are clinically important yet feasible with short-term follow-up. And finally, widening the net involved in multiple institutions, centers, and departments when possible.

So then a follow-up question from this is how do we balance pragmatism and appropriate inclusion criteria and endpoints? When do we use more broad inclusion criteria versus more narrow?

So a case can be made for using more broad inclusion criteria when accrual is difficult. It's probably not going to be feasible to start a clinical study where we enroll patients that have an EGFR mutation and up to one, only one, sole oligometastatic disease in the lung, who have an ECOG performance test of a hundred. A study like that probably would not accrue very well, so it allows us to increase our accrual while generating a signal and then creating a discussion on changing the paradigm. More narrow inclusion criteria is leveraged when a direct clinical question can be answered in the context of accrual feasibility.

So I think the general approach here that tends to be effective is to start too broad and to demonstrate a paradigm and when the signal is generated, then focus on specific patient subsets. And it's important to note that if the inclusion is too broad or the inclusion

criteria are too broad, then these clinical questions can't stand alone to change clinical practice. I'll give an example right now.

So these are two small randomized Phase II studies that demonstrated accrual feasibility and a general paradigm signal in the setting of oligometastatic non-small cell lung cancer, the first that was published by MD Anderson followed by those by Dr. Iyengar in 2017. But none of these were sufficient to change clinical practice. So what they did is they led into a Phase III clinical study that used more narrow, defined inclusion criteria after accrual was demonstrated and lessons were learned to more definitively establish practice.

Second question: How do we balance pragmatism and appropriate inclusion criteria endpoints? So what is the role of PFS and local control as endpoints? Do we need overall survival?

So I think there are strengths and limitations of using these ablative endpoints on their own: (1) they can be assessed with shorter follow-up, (2) they're relevant in other scenarios of cancer care such as systemic therapy, and (3) they do have a strong relevance and they do represent disease control.

However, there are limitations in foregoing an endpoint like overall survival and use these instead. One is that they aren't the gold standard for changing practice. While PFS has been used in systemic therapy to change practice, it's not the gold standard. And it can be difficult to assess for local control after radiation as opposed to surgery where the disease just goes away or is removed. In radiation, we're often looking for stability of disease and that can be difficult to interpret.

And finally, one can argue that this is an intuitive endpoint in the setting of oligometastatic disease when in one arm aggressive local therapy is being used to control malignancy and ablate known lesions, and one could argue it's intuitive, that as you're "spot welding" the PFS and local control rates will be increased.

However, it should be noted that this assumption depends on patterns of failure. If the predominant pattern of failure is within known sites of disease, this will drive these endpoints and overall survival. If patients are much more prone to fail outside of known sites, then PFS won't change regardless of whether those lesions are ablated.

So I think PFS is a stronger endpoint than local control and that it could potentially be used in conjunction with other data in this scenario to alter practice.

Finally, I'm going to touch upon alternative endpoints in oligometastatic non-small cell lung cancer and I think the goals for incorporating these endpoints is that they need to be clinically applicable to this specific scenario, it should be evaluated at shorter time frames in standard survival data and really be used as a surrogate endpoint that was important and finally, being meaningful to the patient and/or the treating physician. So I'll go over three right now.

The first is time to new site failure. So this is something that we used in our initial Phase II randomized study and the thought being, specific to this scenario, that if ablative therapy is effective, then the driver for overall control should be that ablating known lesions reduces the time to the development of new lesions. And this could be due to one of two reasons, either due to effects on tumor seeding, so reducing tumor seeding by ablating known lesions or by stimulating a host response that suppresses new metastases, such as the immune response. So we've found this to be significant in our initial publication and it really, I think, spoke to the potential benefit of this approach in suppressing metastases.

The second is the time to initiate or switch systemic therapy. And when we look at ablative therapy in this context, one goal, one stated goal could be to prolong the time that either patients have to initiate systemic treatment or that they can stay on their current regimen that's well tolerated. Presuming that outcomes are similar in each scenario, there

is utility in isolation of delivering ablative therapy that can prolong the time to which patients have to switch therapy in the setting of an effective regimen. And this has been recently demonstrated in a Phase II study in the setting of renal cell carcinoma by Chad Tang.

Finally, I think that patient-reported outcomes and quality of life have a particular niche in the setting of oligometastatic disease. Now, these are a lot more widely used in the other two endpoints that I discussed, but I think they're particularly relevant in this scenario to assess the risk-benefit ratio. What we typically would expect if ablative therapy was beneficial in this scenario would either be a same to slightly reduced quality of life in the short term while patients are getting treated, followed by a same to improved quality of life in the long term with prolonged time to progression and time off systemic therapy, etc.

And in the SABR-COMET study that's been published, quality of life essentially has been found to be the same, which I think speaks to the utility of ablative therapy if there's not a detriment in -- if there's also an improvement in survival outcomes.

So finally, many trials are ongoing in oligometastatic lung cancer that will define the treatment approach.

Non-randomized trials do have a place in the utility of presenting paradigms and generating signals, but randomized trials are really needed in the vast majority of scenarios to establish standard of care.

Broad inclusion criteria with short-term endpoints can be effective in establishing feasibility and addressing novel questions in limited time frames.

And extrapolation of these concepts is now occurring in more defined and large clinical trials.

And finally, this is a scenario where novel endpoints can be tailored and useful in providing supplementary data that can support the justification when data is incomplete or

insufficient in establishing a standard of care.

So thank you again for allowing me to speak today and I look forward to the following discussion. Thank you.

DR. TREASURE: Hello. I appreciate the invitation to talk to you today about studies of local therapies for oligometastases in the lung. I have no financial or clinical practice conflicts of interest.

Radiofrequency ablation is ready for prime time in the treatment of pulmonary metastases. That's a forthright declamatory title that appears in an editorial in 2020 and it is a comment on a paper by Hasegawa in *Radiology*, in the same journal. The patients included were 70. Four of the 70 had thoracic complications associated with death. There was same-site recurrence in six and other-site recurrence in 35. So that 35 out of 70, 50% of the patients went on to have disease elsewhere within the next 3 years and the 3-year survival was 85%. Along with all other studies of this kind, there was no control data.

In 2019, the American Society of Thoracic Surgeons published an expert consensus document on pulmonary metastasectomy. Let me read you three statements from the preamble.

"Since 1980, greater than 1,000 publications addressed pulmonary metastasectomy without a single randomized controlled trial."

"Historical controls are used or metastatic disease survival is assumed to be zero, a contention not supported by the literature."

"Thus, surgical case series manifest inherent selection bias and do not clarify the role of metastasectomy in prolongation of survival or cure."

Now, interestingly, the document goes on for about another 18 pages detailing recommendations for treatment. There are caveats that should be discussed in multidisciplinary teams, but the general drift is it should be business as usual with this

established practice.

The PulMiCC trial recruited 512 patients. Three hundred and ninety-one were treated electively, 93 were randomized, and there were 28 patients excluded mainly because they did not have colorectal cancer metastases; about half were the malignancies and about half were benign nodules. This is important because this is information which is really not available in the many observational studies.

Here are the 5-year results for the electively managed patients above the 263 who have a survival at 5 years of about 60%, which replicates the best real-world reported observational studies. Below are the 128 with a survival at 5 years of 22% which robustly refutes the zero, indeed, and the less than 5% survival assumptions.

But of course, these patients were expertly selected and because we had exactly equivalent data in both arms, we were able to explore this. So the proportion of patients with solitary metastases was much higher, 69 versus 35. Fewer had elevated CEA, 12% versus 20. Fewer had liver metastases and these were prior liver metastases already treated, 28% versus 36%. They had a 10 percentage point better FEV1. And two-thirds of them versus about a third had zero ECOG performance scores and they were about 5 years younger.

Those differences in risk factors based on known and published hazard ratios would be enough to account for all of that difference. Whether there is a true difference attributable to operation requires a controlled trial. We have good balance of all those risk factors in both arms, between the two arms, and that we had because the patients at the time of recruitment provided the same data, whether they're observational or subsequently randomized, and we knew that in the randomized trial there was excellent balance for age, sex, the primary cancer stage, the interval since the primary resection, liver involvement, number of metastases, tumor marker, lung function, and ECOG. All were well matched and

there was no difference in survival. Because of the size of the study with 93 patients, we cannot prove non-inferiority. But all other statements that I make are robust, but this excludes zero survival and excludes anything other than a relatively small survival difference attributable to lung metastasectomy.

We learned some important lessons along the way in doing the PulMiCC trial. One was that the patients were not the major obstacle to randomization, it was clinicians' prior beliefs. So in this analysis of 155 patients from the three most active recruiting centers, we identified 41 patients who opted out, they stayed in the study but wanted to choose their own treatment and chose metastasectomy or not, in approximately equal numbers. On the other hand, the clinical teams overrode the trial protocol to electively operate or not and they chose metastasectomy for 77 patients, that's 99% of 78.

Here I'm going to talk about three lessons learned along the way from careful analysis and observation of the data. Each of these lines represents a lifeline plot for an individual patient. There are 51 in blue who had no metastasectomy. In the middle, largely in the light brown color, 114 who had one metastasectomy only. The bottom 55 had multiple interventions, a second metastasectomy, and anything up to four or five further interventions including radiofrequency ablation and radiotherapy.

The first thing I want to draw your attention to is at the very top, the blue line is the line of the shortest survivor of patients who had no metastasectomy from the time of inclusion, so there were no deaths within 180 days of this less well-favored group of patients who did not get a metastasectomy.

The next group down, the blue line is their time until they had a metastasectomy and then is their survival afterwards, marked with black for the deaths and no black, non-black, for the censored. And again, they're stacked so that you can appreciate the shape of the curve. The curve at the top is concave, there's an early fall after the first death,

patients begin to die, and then that curves out with a concave profile, rather like a typical cancer survival curve.

The middle one has a bulge. Their lives are longer than you would expect from the natural history and this is because not only are they selected to be natural survivors at the beginning, longer survivors, but also the process of reconsideration, possibly intervening treatments with chemotherapy as happens with liver resection, and the gradual losing of the patients who are not doing well, and so you end up with a group of patients who have a guaranteed time of living long enough to be able to go through the treatment. And that's inherent in all prospective studies, it's seen also in randomized trials, but then it affects both arms so it's balanced out.

Now, in the bottom, these are patients with multiple treatments, they are very similar to those that only had one treatment contrary to the idea that a second treatment gets even more benefit than the first which is, of course, a bit implausible. But I want you to think the other way around. It is longer-surviving patients who provide more opportunities for treatment, so the association between more treatment and survival might be reverse causation.

Here are some conclusions I believe we can make from PulMiCC. So above, the electively managed patients with metastasectomy in the dark red and below, the randomized patients and again, the same color code and wider confidence intervals because of smaller numbers of patients. And I believe we can say confidentially that selection makes much more survival difference overall than surgery.

Within the randomized component we studied health utility and quality of life. There was no improvement in health utility shown. When the more sophisticated tests of quality of life were done, the quality of life was lost; in particular, respiratory function. The assumption of minimal survival, which is implicit in the consensus document, is very

misleading. Patients are not the obstacle to randomized controlled trials and there are very good examples, particularly in the prostate cancer in the ProtecT trial, when the process of introducing patients to the uncertainty of different treatments was handled neutrally, not by radiotherapists, surgeons or oncologists, each explaining the merits of their own treatment and of course, advising against if they thought it didn't have a good prospect, but with a heavily engaged professional bias, whereas these were neutral and able to get patients to accept going into a randomized trial and we saw it also in our own study. And guarantee time bias is a major driver of the illusion of benefit.

This and the next slide are about evidence which was coming out in the time we were running the PulMiCC trial. Now over quite a long period there have been 16 randomized controlled trials of surveillance programs after primary resection of colorectal cancer largely aimed at detecting metastases. Two meta-analyses have been conducted, both published in 2016. One was more selective and included 11 in the analysis and the other more liberal and used 15, but basically the same material but with the same conclusion. Consistently, the diagnosis was brought forward by nearly a year, but there was no survival benefit seen in the individual studies nor in the meta-analysis.

Here are five trials, randomized controlled trials, which reported during the time PulMiCC was running. The two at the bottom used progression-free survival as the outcome measure and in a treatment which ablates or removes the metastases, that really becomes a self-fulfilling endpoint and we wouldn't trust it. The surrogate above was freedom from androgen deprivation therapy, which again is a not very secure outcome. And then the upper two, CLOCC and COMET, much better known studies, both had imbalance in the numbers of metastases. So patients with fewer metastases were more numerous in the treatment arm, which was a serious imbalance, and in the case of COMET there was also an excess of prostate cancers, which have naturally longer survival. They are

of interest, but they provide examples to guide us away from these sorts of limitations.

Here are some key points in evaluating local therapies for metastases:

- The oligometastatic state has no pathological or statistical basis.
- The claims for survival benefit from interventions are inflated.
- The patients are predominantly asymptomatic. It is all about survival gain.
- Without untreated controls we will never know the size of the effect, if any.
- Overall survival is the only primary outcome of worth. Progression-free survival has no validity in this context.

Thank you.

DR. CAMIDGE: Hello, I'm Ross Camidge from the University of Colorado and I'm going to contribute to your thoughts along the topic of using a local ablative therapy when considering pulmonary deposits in the setting of oligometastatic disease. The title of my talk is "Whose oligo is it anyway: OMD, ORD, OPD?" I'll explain what those are in a second and whether any of it matters. So I am a thoracic oncologist and so I'm going to focus on lung cancer, but I'm going to be on one of the panels that we can talk about other things, as needed.

These are my disclosures. I've highlighted two, given the companies we're talking about. I have advised Medtronic on their ablative therapy. I haven't specifically advised Johnson & Johnson on their ablative therapy, but I have advised a related company, Janssen, on drug development.

It is my understanding that transbronchoscopic thermal ablation (TTA) is being considered distinctly from the existing percutaneous ablative techniques. Those percutaneous techniques have tool-type claims for ablating soft tissue and that's all they can really be marketed for. In contrast, Johnson & Johnson and Medtronic are considering a specific claim to TTA based on the idea of maybe using it to ablate pulmonary

oligometastatic disease. This would be a potential Class III device and would require premarket approval based on valid scientific evidence of reasonable safety and effectiveness to justify its indication for use.

I thought a figure might be helpful. So this is a schematic really showing the organs in someone's body, so the brain at the top, the lungs in the middle and the liver in the triangle at the bottom. On the left-hand side, this is the easiest scenario. I never get to see this in lung cancer, but if I was a colorectal cancer doctor, maybe I would. So metastases just in the lungs, maybe a relatively small number, and then we could debate whether that sort of oligometastatic disease might be suitable for local ablation. And the debate there is how many sites of disease is acceptable and how do we define safe and effective?

I wanted to illustrate two additional complexities. So the one in the middle relates to the fact that sure, you've got a certain number of lesions within the lung, your organ of interest when you have a bronchoscopic technique, but the concept of oligometastatic disease may have to count the total number of active sites in the body. Here we can see we've added an additional lesion in the liver and certainly, I think we do have to view the total number within the whole body and not just within in our favorite organ of origin.

The other thing is, if it's outside of the lungs, you may need a multimodality approach if you're actually going to pursue this as an oligometastatic disease that you can treat with local ablative therapies. And there, how do you pull apart the efficacy of each individual component, and can you?

Finally, on the right-hand side, where your primary is a lung cancer, you've also got to remember that OMD at diagnosis is going to have the primary and possibly regional lymph nodes involved, too. That's certainly going to increase your complexity in terms of how you count the number of sites of disease. I can tell you now that most radiation oncologists will view the whole of the mediastinum as one site, rather than individual lymph

nodes or lymph node stations; similarly for the primary, if they can encompass that within the same field. The second thing is obviously, when you're talking about mediastinum on primary, especially if it's close to the trachea, you are going to be using multimodality approaches whether you like it or not and how you're going to have to assess those within your concept of safety and effectiveness.

So let's start with the classical definition of oligometastatic disease, or OMD, at diagnosis, a limited number of sites in the setting of Stage IV disease, that you might consider adding in local ablative therapy in addition to just systemic therapy. The real question is how oligo do you have to be in order to consider this an appropriate approach? And as we've already mentioned, generally speaking, you should really be doing that across the whole body and not just within the organ that you're personally interested in.

To give you a clue, well, the NCCN does have some wording in terms of how you should manage lung cancer with regard to limited sites of metastatic disease. The original wording that suggested that you might add in local therapy was written for very specific body sites, brain and adrenal. But an initiative actually driven by a patient advocacy group and then helped out by Cory Langer and myself, pushed to have that broadened to just simply say limited sites of metastatic disease.

If we look at the current NCCN guidance, or actually these are 2020 but the wording has changed that much, you can see that we're already very comfortable with the brain, such that it flows very nicely at limited sites of metastatic disease just involving the brain. Everyone seems very comfortable with treating that with radiotherapy and then treating the rest of the diseases if it was just earlier stage, surgery or radiation.

But you can see where it says other site, that's where our inclusion criteria have broadened. So it now says "Including select patients with Stage M1c disease," that means outside of the thorax, the limited number and volume of disease suitable for local ablative

therapy, you could do that and then manage the thoracic disease separately. And when I say the thoracic disease, I mean the primary and the nodes. They state specifically, "Limited number is undefined but clinical trials have included up to three to five metastases." The one thing I would caution you is to clarify whether three to five metastases, is that on top of the primary and lymph nodes or is that including the primary and lymph nodes? And at least in my experience, it should probably include the primary and lymph nodes in this setting.

So with regard to OMD, the number of acceptable metastases to act on separately from polymetastatic disease is in the eye of the beholder. I think everybody is very happy if it's a single site of disease or a single lesion suitable for local ablative therapy. Probably if it's three, everybody's happy. By the time you get up to five, everybody's starting to grumble a little bit. People tend to have more of an appetite when it's obviously the central nervous system, maybe less of an appetite about other organs; we're talking about the lung here. Again, do you count the primary and the nodes within your counting? I think you probably should, although you should remember that we're thinking in terms of radiation in a multimodality setting and so it's really the fields that we might be talking about as opposed to individual lesions.

So this is really the money slide and this will be repeated to some extent when we start talking about oligo-residual and oligoprogressive disease. Let's imagine you had oligometastatic disease at diagnosis and you were thinking about a local ablative technique such as TTA. Well, you could do a trial of benefit from some kind of multimodality approach together with the systemic therapy. And really, what you'd be talking about is everyone gets systemic therapy that has Stage IV disease plus or minus your local ablative approach and you should probably start using any or all available techniques, be that surgery or radiation or an ablative technique such as TTA. In that setting you totally could have

progression-free survival or overall survival or time to sites of new metastases as the endpoints. However, it will be hard, if not completely impossible, to dissect out the benefits of the individual techniques to those primary endpoints like PFS and overall survival. All you could be able to pull out is the safety and local control from the individual modality.

So safety of the technique, that's pretty easy. For me, I would expect less than 5% rate of serious or severe adverse events. You know, these are people who are expected to do pretty well.

In terms of efficacy for that local control rate, it would be based on non-progression at that site. Progression elsewhere is not a failure of that technique. If those other sites are going to drag down that progression-free survival, then your median might also get messed up; it will end up being censored. So probably you have to do some kind of landmark analysis for local control and probably I would use the metric derived from some of the SBRT literature and I'll show you that later, but it's probably at about 6 months that I've been looking to measure that landmark non-progression in that lesion endpoint.

I think you really have to standardize the disease and the drug variables here. You can't just have oligometastatic disease of a gazillion different counters and on a gazillion different systemic therapies, it's ridiculous.

I think if you were doing this, even in an exploratory setting, if you had a very short time to progression elsewhere, sort of less than 3 months, I'd start to question the usefulness of the whole approach in this group and I'd be wanting to make sure that people were adequately staged, did we really know they were oligometastatic, did they have a PET and an MRI at baseline? You know, how many number of sites of metastases? How many different organs were involved? Is it three lesions in the lung and the same with one in your lung, your liver, and your bone? The number of nodal stations that may be involved, again

predicting that systemic disease. And finally, histology probably does make a difference and I have some data to support that in the thoracic world.

So if you look in the NCCN guidelines again for a non-small cell lung cancer, for early-stage cancer, so at T3, so that's more than 5 cm across and no negative, they will still suggest resecting it. But the same thing for small cell, they will not. Why? Because the assumption is that small cell is much more aggressive and by the time you're that size, your risk of metastatic disease, even if you can't see it, is so much higher that we feel very uncomfortable just relying on surgery.

Let's use the second example of oligometastatic disease, what you're going to call an oligo-residual disease, that's when you give the systemic therapy and you take it to the point of maximum response and then you have a small number of sites of disease left or active and then you go in with your local ablative therapy. That's probably somewhat cleaner than the OMD at diagnosis scenario, because you've somewhat eliminated the really bad actors, so you have not progressed during your initial systemic therapy and sort of responded, taking it to the maximum response. So it's probably a slightly easier trial to do.

The concept of it goes back to 2009. So Kyle Rusthoven was a radiation oncology fellow here and he came up with a thought experiment, so together we looked at several hundred non-small cell lung cancer patients with Stage IV disease who'd gone through systemic therapy and then he looked at them at the point of maximum response and he sort of said look, if you'd ask me and if you'd show me the scan, could I do local ablative therapy with radiation at that time, answer yes or no. And of the ones that he felt that he could have said yes to, we then followed them up and none of them got it, this is a thought experiment to say well, where did they actually progress. Well, of those people that he felt he might have been able to give local consolidation to, something like 17% of them only

progressed in those same sites of disease. The cancer wasn't suddenly spreading and that raised the idea that maybe consolidation would make sense and it certainly supported the idea of a prospective study, which we later did, together with MD Anderson and London, Ontario by Gan and Gomez.

It was a very pragmatic design, patients could have been on a platinum doublet or if they were EGFR or ALK-positive on the appropriate TTI, they were treated to the point of maximum response, which was after at least four cycles of chemo or at least 3 months of the TTI, and then they had three or fewer sites of disease remaining and then the radiation oncologist, so he's talking about sites, so fields of radiation, not lesions. So the mediastinum was one site, the CNS was one site. Although many of the patients got PET scans, it wasn't mandated in the study, so our ability to truly say this was oligo-residual was occasionally compromised.

It was a multimodality approach considered from the get-go. Some of the authors, you can see Steve Swisher is the second-to-last author, he's a surgeon, so both surgery and local ablative radiation were used. It could be standard fractionation, it could be stereotactic, but there was a clear progression-free survival advantage, a hazard ratio of 0.35.

In 2016, when this data was shown, we refused to just Photoshopping the patients, "oh, you've taken those out, that's why the PFS is better, it doesn't mean anything." And then in 2019, with longer follow-up, we were able to show a significant survival advantage, 41 months versus 17 months, and very provocative endpoint, time to the appearance of new lesions: 14 months for those who got local ablation, 6 months for those who didn't, again with a suggestion of maybe you are actually altering the natural history in these patients. You can certainly do that same kind of trial design that we talked about, about oligometastatic disease with all of the same issues, but at the maximum response time to

do it in the oligo-residual disease setting. You would also have some additional scientific interest from something like TTA because maybe you'd get a biopsy and be able to analyze the residual disease, which may be useful in the future.

Finally, let's talk about oligoprogressive disease. So this is where you're on a systemic therapy and you're benefiting. It doesn't matter if you have 500 sites of disease when you begin, but when you progress, only a small number of sites are progressing and that's where you stay on the systemic therapy and you add in the local ablative therapy to put off changing drug or going on to something nasty like chemotherapy. And that's potentially an even cleaner setting than oligometastatic disease or oligo-residual disease, because you're less likely to have the primary and the nodes being active in lung cancer; it's often just a single site of disease and if that happened to be in the lung, that could certainly be a potential candidate for something like TTA.

This goes back to 2012, so Andrew Weickhardt was my fellow at the time. We essentially made up the term oligoprogression between myself and Brian Kavanagh, who's the radiation oncologist, and we focused very much on targeted therapy in lung cancer. Patients who were EGFR and ALK-positive, they were doing well on therapy and then they progressed. We didn't know how many to make it, so we just made a number up, so we chose four, so four sites or fewer progressing, and you got local ablative therapy. It wasn't a randomized study, it was just observational. The time to the second progression and then after that, it's what we call PFS2 in this setting, it was 6.2 months. If you had only progressed in the brain, it was 7.1 months before the next progression event. If you had only progressed in the body, it was 4 months.

Again, we go and accuse that this was meaningless, that somehow these times before the next progression event was what would've happened anyway or the fact that they were manifesting oligoprogression was telling you something about its biology and this

was just the natural history of the disease. And yet this concept of local ablation for progression, for oligoprogression, has really, I think, captured the imagination in lung cancer. Greg Gan was a radiation oncology fellow who dove a little bit more into detail into the radiation, focusing just on the ALK patients. In this follow-up paper in 2014, you can see here, when we looked at the single fraction effective dose, doses of more than 25 Gy had about 100% local control rate; those with 25, so that's about a 60% control rate, but if you look at the figure here, you can see that if you're going to progress, it's really happening within about the first 6 months. So I think that 60% at 6 months is the kind of minimal hurdle I would expect something like TTA to achieve in terms of being a landmark analysis of what effectiveness might be.

The other thing that Greg showed that wasn't statistically significant, not surprisingly, the number of sites of disease progressing influence your time to the next progression event. If you had one or two, it took 7 months before it progressed again. If you had three or four, it took 2 months. That's not a big surprise, although the question is does it matter? If your next progression event is still oligoprogression, you can just repeat the problem, you can just repeat the technique. So I think capturing the details of the progression, oligo versus poly, which organ they're occurring would be important. And of course, in this setting there's also even more scientific advantage to being able to re-biopsy with a technique that's bronchoscopic, as we try and understand the mechanisms of acquired resistance.

So to tie this all together, TTA offers a potential biopsy and ablation technique. It's likely to be used as part of a multimodality approach. I think you can assess the full techniques, you know, all of the possible techniques together and its value in a randomized trial, added in or not, to systemic therapy. You could do it the classic -- at diagnosis, oligometastatic disease or oligo-residual disease or oligoprogressive disease setting. It's not

going to be possible to show benefit in those bigger endpoints, PFS or overall survival or time to new met. For an individual technique, even the Gomez et al. study was multimodality. But for a given technique you can certainly assess safety and you can certainly assess local control, for example, at that landmark analysis, e.g. 60% at 6 months. And you could assess that in a single or a randomized study. And the oligometastatic disease, that definition of oligo is in the eye of the beholder. In a registrational study, though, I do think it makes sense to try and restrict some of this. I would argue three to five total sites of disease, including those in primary, and the whole body should be considered and it absolutely should be the same disease and the same systemic therapy.

(Pause.)

DR. BUENO: You're muted.

DR. BLAKELY: Apologies for that. Thank you to all of our wonderful speakers. We will now begin our panel discussion regarding clinical trial designs for TTA devices for OML. I have a quick scheduling announcement to make. Unfortunately, Dr. Tony Mok from Chinese University of Hong Kong was unable to attend due to an urgent conflict. I will now hand it over to Dr. Raphael Bueno, from Brigham and Women's Hospital, to moderate the discussion.

Dr. Bueno.

DR. BUENO: Thank you and welcome, everybody. We just heard from Dr. Treasure, Gomez, and Cambridge (sic). And we, in addition, have Dr. Blackmon, Dr. Olson, and Dr. Uboha on the panel.

Do you want to show the slides, the question slides, or shall I share it or how would you want me to --

DR. BLAKELY: I believe they're being displayed now, Dr. Bueno.

DR. BUENO: Okay. Okay, so really, what we have to answer is a number of

questions and the first question -- and we've heard two slightly, three very different conversations. So the first question we have to answer is which would be the most appropriate primary and secondary endpoints? And the list shows three and we can come up with others. So who wants to take first crack at it? Maybe someone who hasn't talked yet.

Shanda.

DR. BLACKMON: Thank you. As you can see, there's a lot of controversy in the literature. I've been following Dr. Treasure's publications since I was a resident and one of my favorite ones is the inherent bias in many of these publications and the lack of randomization.

Obviously I think, in cancer clinical trials, improvement in overall survival is the most convincing measure of efficacy as well as consistent measure of patient benefit. But in an ideal situation, that would be the endpoint that I would recommend; however, it would be the most difficult one to follow.

A randomized controlled trial of SBRT versus wedge versus ablation with overall survival as the primary endpoint would obviously be a gold standard for us, but obviously very difficult to organize and historically has been difficult to enroll to. SBRT trials with the same goals have failed to accrue and been shut down routinely, at least three times that I'm aware of.

So the other issue with overall survival is that it doesn't reflect how prognosis changes in time in surviving patients. When we consider all of these other endpoints, smaller surrogate endpoints, we recognize that they do require a shorter amount of time and they are easier to measure but, in circumstances, for example, where all the disease is removed and the patient is rendered NED, I think in that case I would still recommend that we follow overall survival but look at recurrence-free survival and time to recurrence.

In summary, I think we need to define, through a trial, a consort diagram so that all of the patients that are included in the trial and excluded in the trial are recognized. We need to simplify the histology that we look at. I agree with Dr. Gomez's presentation, that we need to look for patterns and carefully select the patient cohorts that we test this in.

Salvage treatments will really confound which outcome you look at. Many of these patients that fail get salvage treatment and might have a prolonged viable but not because of the original treatment they received. I think that we need to look at these patients very carefully, understand the complexity of the question that we're asking, and focus our question. Are we really just looking at the safety and the efficacy of this treatment and if that's it, then it's a much simpler question to answer.

DR. BUENO: Thanks, Shanda.

Nataliya, do you want to add anything to that?

DR. UBOHA: Sure. Hi, everybody. And thank you so much for inviting me to participate. I am a medical oncologist, I specialize in treating GI cancers with a particular focus on upper GI cancers.

I think this area of discussion is of great interest to me because I'm a national chair for the ECOG-ACRIN Phase III study for ablations with oligometastatic upper GI cancers, and as we were designing the study, which initially started as a Phase II trial and subsequently progressed to a Phase III trial, which is actually enrolling patients, we were discussing all of these questions. What is the most relevant endpoint for this trial? And the question in this trial is really if you take patients with oligometastatic disease, does incorporating radiation therapy to all of the sites of the disease after a period of systemic therapy change outcomes? And ultimately, we have decided that if we are going to run a study that has potentially practice-changing implications, overall survival is the right endpoint for this type of study. I do think there are other clinically relevant endpoints, but the gold standard for

approving treatments or for making treatments a part of standard of care, especially treatments that carry toxicity -- you'll have toxicity implications aside from costs -- need to make people live longer.

DR. BUENO: Thank you. So would you be more in favor -- so I suspect if you were to select a disease, you'd go for colorectal cancer.

DR. UBOHA: The trial that I run is upper GI. I think colorectal cancer is a bit tricky already. If you're talking about lung specifically, it's hard. But I think -- I'm sorry?

DR. BUENO: That's what we're talking about, we're talking about --

DR. UBOHA: Yeah, lung metastases we're talking.

DR. BUENO: Yeah, lung metastases in the lung.

DR. UBOHA: Right.

DR. BUENO: The intervention is a bronchoscopy.

DR. UBOHA: Right.

DR. BUENO: So the real fundamental question is what cancer is a suggestion and what endpoints?

DR. UBOHA: I think it's really -- you know, the SABR-COMET trials were great, right, they were just presenting Phase II data, hypothesis-generating data. I don't think, personally, you can take just the site of metastases separately from the type of disease, from the biology of the disease, you have to take -- you have the trial -- for the trial to be meaningful, it has to be lung disease and you can study it within the context of breast cancer or colon cancer or oligometastatic upper GI cancers, but it can't just be a lung metastases. A lung metastasis from pancreas cancer is very different from a lung metastasis from prostate cancer.

DR. BUENO: I understand, but it's like a grant, this is not our fate, we're not tasked with that. The company, as I understand, wants to show technology that's delivered

bronchoscopically to -- I'm not trying to pick on you, I'm letting everybody else know the goal, but to pick up a trial -- and the FDA can correct me if I'm wrong -- that will work for a bronchoscopic therapy device. So while I understand everything else, that's what we're tasked with and if the FDA tells me that I'm wrong, please do it now. So that's the issue. Why don't we give Rob Olson a chance.

DR. OLSON: Great. So I agree with most of the comments and my summary is overall survival. If we didn't already have methods with good local controls such as SABR or surgery, I think local control would be a reasonable thing. But given we're already proposing that overall survival is the potential benefit -- and again, potential benefit from SABR -- I think that we have to say that that's the outcome we're looking at. It's really the only outcome that's going to also capture potential toxicity that exists and we don't actually know if the toxicity and even fatal toxicity is higher with this group. So I think capturing local control, you would miss that. I do think you would still capture progression-free survival and local control as secondary outcomes because they're important, but I think overall survival is the main one.

The other thing that I really want to highlight is that we haven't yet shown an overall survival advantage to SABR, so -- or surgery, right? So like that's really important. So I think one of -- like, I actually have been listening the last couple days and people keep interpreting our SABR-COMET study like it's a positive study. Like, it was positive in that we should go to Phase III trials, so I think that's really important. And one of the companies even said we should do local control as the primary outcome. If it's equivalent, we can therefore infer the survival advantage, but that's -- like, that argument is fatally flawed. So I think anybody listening that has anything to do with that, should throw that argument away. So I think overall survival is still needed, that's my summary.

DR. BUENO: Well, that's great because you're getting us now -- we're on the fourth

step, okay, for the first question. So we have something we can pose to the team and then people can say yea or nay, but we have lots of questions. So you propose that overall survival is the primary endpoint and local control is the secondary endpoint. Am I stating it correctly?

DR. OLSON: Yeah, I think local control and progression-free survival are important secondary outcomes, yeah.

DR. BUENO: So do we have any disagreement on that? Does anybody --

DR. GOMEZ: I guess the question is, given that there are already ongoing Phase III studies looking at overall survival that will close in the next few years, presuming that they show a benefit, can we take that as proof of principle that any analogous ablative regimen that provides similar control rates and acceptable safety can also be incorporated into that paradigm? Or do we need a separate study evaluating this specific modality?

DR. BUENO: If I may, we're presuming the results of an ongoing trial.

DR. GOMEZ: Yeah. I mean, I'm saying there are two ways you could do it, you could either -- are we saying that we need to -- can we extrapolate the results from the current ongoing study, which are years in the making and will likely take another few years to close or is the overall consensus that we didn't need a separate distinct randomized study looking at this modality? And --

DR. BUENO: Please, I might interrupt. And the FDA can tell me differently. I think there is a question that is specific to this technology and it's specific to today. So for the sake of proceeding forward, let's assume that unless something is published and validated, it ain't. Or it isn't. So if that's the case, as we're sitting here today with what we know, not what we think, our overall survival is primary and local control or PFS is secondary, are reasonable approaches. I mean, I heard from the three speakers and the other three commentators that they're okay with that and Daniel, we can't presume to answer to the

trial. We're not a funding agency. None of us is here and this is not a cooperative trial, this is the company who wants to move forward.

DR. BLACKMON: So Dr. Bueno, I don't want to rock the boat too much, but -- well, maybe I do and I just don't want to admit it, but I think the primary and secondary endpoints, as you discussed, are relevant. But if you really want to get to the bottom of this and answer about this specific technology, oligometastatic disease is complex and variable and difficult to measure in the best of circumstances with one modality.

If you really want to answer this question, Stage Ia, early lung cancer, primary lung cancer, non-oligometastatic primary lung cancer is the best way to answer that question.

DR. BUENO: I'm not sure that that's true. It may or may not be true, we don't know, but that's not what's on the table. I mean, I hate to be pushy, we're in a lane, we got to stay in the lane.

DR. BLACKMON: Well, you asked for histology, so I just thought I would open that up because you did ask about it.

DR. BUENO: But they're calling it metastatic. So Stage Ia lung cancer is not oligometastatic. So I'm trying to stay in the lane and again, overall survival, local control, PFS. Any other suggestions as to endpoints? I'm asking about endpoints because that's what the FDA gave us.

DR. GOMEZ: I think to establish standard of care, overall survival is a primary endpoint and PFS as a secondary endpoint is quite reasonable.

DR. BUENO: How about local control, because -- and the reason, as a surgeon, I think about local control and then we can define local, is that we're in the lung and let's pretend that we're taking colorectal cancer, which in a subset of patients have reasonable survival and local control surgery is the comparator right now.

DR. UBOHA: But you have issues with other studies that use local control as one of

the endpoints, studies with Y-90 have looked at liver-specific progression-free survival that resulted in no improvement in overall PFS and OS and you can question how clinically relevant those endpoints are. I mean, I agree with some of the comments that Dr. Blackmon made about local control in the lungs. However, if they are looking for the indication for oligometastatic disease, then we need to talk about metastatic disease, which is without improvements in overall survival or at least PFS, I'm not sure how meaningful your local control will be.

DR. BUENO: Well, the only reason I mention local control is it speaks -- you're taking care of the disease with overall survival and PFS versus local control. Local control speaks to the technical feasibility.

Okay, any other comments on this question? We have like --

DR. TREASURE: Yeah. Yeah, yeah. Sure. Am I on? Yes. I thought you were making good headway there, concentrating on that this is about oligometastasis in the lung. That's at the top of the paper. And I don't want to be deflected from overall survival mattering, because the whole objective of lung metastasectomy over 40 years is to do with survival and as you said, with surgery local recurrence is pretty uncommon but new mets in the lung are common, but usually the primary cause is retroperitoneal in the liver. And so the lung metastases are asymptomatic and can be dealt with but may be irrelevant to the survival of the patient and that's what is all important and you were getting there, I just didn't want to see any backsliding.

DR. BUENO: No, no, I'm not. I think --

DR. TREASURE: No, not you.

DR. BUENO: I think the primary objective is overall survival. The only question is the secondary --

DR. TREASURE: Yeah, sure.

DR. BUENO: What's a secondary, PFS or local control?

DR. TREASURE: You're asking the wrong person, don't know the answer to that.

DR. BUENO: I mean, as a surgeon, I think local control is what was used in SBRT. I guess they can define local control and PFS would be to some degree included in overall survival. So I'll leave it as that and --

DR. TREASURE: I'm good with that.

DR. BUENO: And then the second question we've arrived at is what alternative endpoints could support patient benefits in a TTA trial? And one is technical success and two is local control.

Shanda. But now brief.

DR. BLACKMON: One of the issues that I have with technical success is so many of these trials don't prove that there is cancer there in the beginning. So I think you need to start with a biopsy to prove that there is cancer there, as we did with the MARK trial. And then when you look at technical success, most of these will be equivalent and that's where other things become important, such as quality of life and PRO data. But I think for technical success we could use something very similar to the ECLIPSE trial. Was that brief enough?

DR. BUENO: That's great. Can you tell everybody about the ECLIPSE trial, just the measures of the use, so everybody can opine?

DR. BLACKMON: For technical success, I think the ECLIPSE trial mainly looked at the amount of the ablation zone that was covered and then they defined that completely separate from overall local control. So they defined it into different categories, so they looked at -- like we did in the ABLATE and RESECT trial for EMPRESS and we used NADH staining for technical success. But for the ECLIPSE trial, they basically looked at complete coverage of the lesion and then subsequent follow-up.

DR. BUENO: Thank you, that's a good point. Let's go in no particular order to include everyone. I just want to make sure I see everyone and let's -- Daniel, do you want to give it a shot?

DR. GOMEZ: I think what Dr. Blackmon said is very reasonable. I think that I agree with that.

DR. BUENO: And if you had a choice between defining technical success as the ablative size you'll find and local control would be -- how would you define local control?

DR. GOMEZ: Yeah. I think in this scenario, probably it would be -- because you don't -- the standard RECIST approaches are difficult to integrate, so I would say probably just a lack of -- that's a good question.

DR. BUENO: In some area?

DR. GOMEZ: What's that?

DR. BUENO: Lack of regional recurrence?

DR. GOMEZ: Yeah, I guess you could do that. I mean, it would have to relate to the specific target and yeah, I wouldn't define regional control, I wouldn't incorporate that and like regional recurrence in the local control.

DR. BLACKMON: I'll just add that, in the ECLIPSE trial, when they looked at local control they had a very clear definition and the problem with microwave ablation, specifically which we're addressing in this, is that unlike cryotherapy or radiofrequency ablation, you can see the ablation zone and you can measure how much that overlaps beyond the tumor. In microwave ablative therapy, whether it's delivered bronchoscopically or percutaneous, you cannot see that ablation zone, it looks like nothing's happening. When you're watching on CT, you're thinking that it's not turning on and it's not doing anything because the lung looks the exact same even on single-lung, very well-controlled ventilation, as we did discover in the EMPRESS trial. And so what these other trials did with

ablation is they created a new baseline at 3 months and then they looked at the percent shrinkage or response based on that 3-month new baseline. And that has a lot of error with it because each therapy will have a different response, so you can't compare one therapy to another, but you would basically set the same type of follow-up, as they did for cryotherapy, that you would do it for microwave ablation, which is very well described in these trials.

DR. BUENO: Perfect, that was very helpful. Thank you, Shanda.

Nataliya, any comments?

DR. UBOHA: No, I don't think I can add much more to what's already been said. I appreciate the issues with monitoring local progression, since we use this stuff and we should have ways to treat it.

DR. BUENO: Well, thank you. Anyone else on the panel has a comment about this question?

(No response.)

DR. BUENO: Okay.

DR. BLACKMON: I want to add one more thing. The big problem that we've had comparing SBRT to surgery is that they're completely two different definitions that two different specialties use and until we all agree on the same definitions of local recurrence and response to treatment, we really can't create a database and compare these therapies to one another. It makes meta-analysis impossible.

DR. BUENO: So you'd be pleased to know -- and I'll show you the slides when I'm done -- that the answers to these questions are going to be get a biopsy to confirm disease and maybe assess the lymph nodes with something. Local control, no recurrence of the target area (define). Technical success in ablative zone, if you can see (define). Would that address those issues?

(No audible response.)

DR. BUENO: Okay. If there's no comments on this slide, because if we can get through the slides, then we have time to review them.

DR. TREASURE: Raphael, we can't see, it would be very useful to see that paper. Perhaps the organizers should do it. You've got it up there right at the top, it's about that big.

DR. BUENO: Yes.

DR. TREASURE: Can that be --

DR. BUENO: Yeah.

(Cross-talk.)

DR. TREASURE: -- critical, critical to be able to see what we're talking about.

DR. BUENO: And can I get the FDA to do that because -- okay, perfect. Does that address the issue? That's perfect.

DR. TREASURE: Well, it's not with me, I still can only see --

DR. BLACKMON: If you double click on it, Dr. Treasure, it will become big.

DR. TREASURE: Oh, I went up and tried to do something but didn't double click. Okay.

DR. BUENO: Okay.

DR. TREASURE: Thanks, Shanda. Thank you very much indeed.

DR. BLACKMON: You're welcome.

DR. BUENO: And the next question is what -- that I have here is what trial design would best be suited for the assessment of safety and effectiveness of transbronchial ablation here? You know, would it be RCT, single arms, local controls, others? I mean, what I heard already from essentially every speaker was that we need to have a randomized trial. I think everybody would agree with it. Should that be the first trial or the second trial?

DR. TREASURE: I think, as professionals and many of us of a scientific bent, we should push for a proper control group and the control group, ideally, would be a no treatment control group. And I've shown you the results of the PulMiCC trial. Nobody else has a control group, nobody else has even got untreated observational patients and you've seen both of them in a study of over 500 patients, if you take the whole study.

And I would, right to the end, even if I have to be the lone voice, say you must have a control group and you must aim for a no treatment control and you choose your patients accordingly, for patients where there are other factors which make them rather unattractive, perhaps unlikely kind of it's for a big success, but we could have this novel therapy tested against patients who don't get this novel therapy to see if it influences survival because it's actually rather improbable that radiofrequency ablation of a few pulmonary metastases is going to influence survival.

DR. BUENO: Well, I mean, I'm all for RCT and I think if you select the cases correctly, there are some oligomets to the lung that are currently not treated with systemic therapy as the standard of care. So I'm okay with that. How's everybody else, is anybody not okay with that?

DR. BLACKMON: No, but I would add if that's not feasible, that as an alternative you could include the Society of Thoracic Surgeons database, as Dr. Mitchell mentioned, that has robust data of a large cohort of patients that could be looked at for outcomes for safety and effectiveness. Unfortunately, that does not continue to have data long term for recurrence, but you could include it in a data registry such as what STS did with the TAVR.

DR. TREASURE: Well, I think the safety, you can use other observational data, you've got to be --

DR. BLACKMON: Yeah.

DR. TREASURE: -- smart and compare like with like. But if you consistently get lung

abscesses, bleeding, pneumothorax and so on, at a rate and it doesn't even have to be common, it just has to be a rate which is troublesome and higher than the background, so I agree with that, but if you want to know about whether this saves lives, prolongs lives, I think you've got to test it, probably. I know it will be difficult, but you've got to start by designing a trial with a trial center which will put staff in place, properly trained to present the patients with equipoise. And I showed you what happened in our trial, the patients understood equipoise. It was the doctors overrode them 99% of the time.

DR. GOMEZ: Dr. Treasure -- oh, sorry.

DR. BUENO: I just want to say, in fact, since we selected our primary objective as overall survival --

DR. TREASURE: Yeah.

DR. BUENO: -- not safety.

DR. TREASURE: Right, okay, that's fine. I was just --

DR. BUENO: Daniel, you were going to say something.

DR. GOMEZ: Well, I was just thinking about a trial that probably would be a very common one to enroll in terms of the scenario and it's where a patient has a limited number of sites of active disease, has been on systemic therapy and has either -- just classifying them in different ways, either a residual metastasis or a single site of progression. In that scenario, I think the potential control no treatment arm would be just to continue the standard therapy, which is what they're already on, no ablative arm, but the control arm being systemic therapy as is. I think that's close to no therapy because it's not working on that site and it would be clean and probably rather than taking them off treatment --

(Cross-talk.)

DR. TREASURE: No. I think, Daniel, I think you're right and after all, that is written

into all our therapeutic trials. If you've got to -- you can't deny the patient reasonable treatment and that point was sane and I agree with you. So it's an add-in on top of standard --

DR. GOMEZ: Right.

DR. TREASURE: -- to get you somewhere there.

DR. UBOHA: And that's exactly the way our trial was designed for oligometastatic upper GI, it's continuation of systemic therapy versus radiation followed by continuous systemic therapy, so that people get at least what's standard.

DR. TREASURE: Yeah.

DR. BUENO: So if I may, the response I have here is RCT with no treatment control would be ideal (or continue systemic therapy).

DR. TREASURE: Yeah.

DR. BUENO: Then the second line is alternative with single arm with STS control for safety.

DR. GOMEZ: Another question that comes up, that I would be curious to hear the panelists, is if the outcome is overall survival, do you allow crossover upon progression or do you continue or is crossover not allowed?

DR. TREASURE: I don't think you cannot allow. It is a real difficulty, but you try and avoid it, but -- and it gets a bit messy, but the intention to treat was to treat weakness in modality.

DR. GOMEZ: Right.

DR. TREASURE: And if you don't see it through with that, that's if you like a failure, but overall survival is still what you need. And if eventually the treatment isn't working and you've just got to get on with something else palliative, you still started with an intention to treat with a new treatment.

DR. BUENO: Okay, any other --

DR. OLSON: I have one other comment. I'm somewhat wondering if -- like, I totally think we need a randomized controlled trial of overall survival, but I'm wondering if we're one step too early. Like, we wouldn't do a drug randomized controlled trial of a standard treatment versus another without first seeing what the toxicity rates are and I don't know what the rates of bleeding and pneumonitis and lung collapse, etc., are. But do they first need to do like population based, if possible, and then only allow it on trial, toxicity studies, while they're waiting for the SABR trials to evolve? And many design the Phase II trial after.

DR. BUENO: The assumption is that that's what they're doing in anticipation. Without a trial, without a safety trial, I don't think the FDA would let them go to a Phase III trial.

DR. OLSON: Okay.

DR. BLACKMON: So I would argue that they are not allowed to do a safety trial in humans in the United States right now. There was a trial that began and was closed. Outside the United States, safety trials have continued. But if we are to embark on just a safety trial that's not overall survival, an effectiveness trial, that safety trial should mandate that patients stay overnight on a thoracic surgery ward because the biggest risk of this technology, as unfortunately some of us have seen, is massive hemoptysis or CO_2 embolus or pneumonia or bronchopleural fistula. Having seen all of those in different patients, I think we have to be very careful about how we follow these patients and I truly believe that what Dr. Olson just announced is the primary objective here, which is to determine safety before you launch an RCT.

DR. BUENO: So I'm adding here, in the trial design, the following line: A safety trial should be required first, with a supervising thoracic surgeon.

DR. BLACKMON: And we have a session on that following this, but as we saw in the

EMPRESS trial, the effectiveness is not easily measureable in microwave ablative therapy right now. The EMPRESS trial just got published and it demonstrates that we were only effective 55% of the time. You can't really do a randomized trial in a treatment that only kills the tumor 55% of the time. So you could argue that we did the ABLATE-RESECT too early and we didn't give the tumor time to die, but nobody else has done a trial demonstrating that it's any better.

DR. BUENO: So this is a great segue for the next question, which is what should the success criteria for a TTA trial should be? Should it be success criteria for changes in subgroups, etc.? So I would say that what -- quoting you, I would say demonstration of safety and the second thing is demonstration of ability to kill tumors.

DR. BLACKMON: And I would argue, software planning that allows you to be more accurate in treatment, which we don't currently have.

DR. TREASURE: Shanda's descriptions really are rather alarming, I had no idea it was as bad as that. But can you put a denominator to it, can you give a rate, and is this going to be published? I mean, if it's that --

DR. BLACKMON: Yeah.

DR. TREASURE: -- hair raising.

DR. BLACKMON: They just got published --

DR. TREASURE: Uh-huh.

DR. BLACKMON: -- and they're tiny studies, which is why no one's really excited about publishing them, they're very hard to accrue to. The EMPRESS trial was run by Medtronic and it was a multi-institutional trial and that was the trial where histologic ablation based on ablation under the same general anesthetic and then resection under the same general anesthetic with a wedge resection and then an ADH histologic assessment of tumor kill, that was 55%. So the --

DR. TREASURE: But you were telling us about all these complications.

DR. BLACKMON: Right, so --

DR. TREASURE: That was the bit that made my hair stand on end.

DR. BUENO: Yeah.

DR. BLACKMON: Right, so most of these are -- most of these complications are happening outside of the realm of clinical trial and there's no data registry, which is why I argued for a prospective --

DR. TREASURE: Yeah.

DR. BLACKMON: -- systemic-wide data registry like we do for STS. It captures most lung cancer surgery done in the United States. There's already a mechanism to capture data on metastasectomy. If you're just doing a randomized controlled trial, it's a highly selective group of patients with experts doing the procedures and what you really need to look at is what's happening out in the real world, if you want to know what the other adverse events are, because they're rare.

DR. BUENO: But that's more of a Phase IV study.

DR. BLACKMON: Yeah.

DR. BUENO: But in any event, we have -- let me -- let's answer this question, go to the next and then we'll roll them together. So I put here, as an answer to what should the success criteria be, is first: demonstration of safety. (2) demonstration of ability to kill tumor, which you can call it like does the device work? Does the device work? And then (3) accurate software planning. And all after that, the RCT should follow if the device passes.

DR. OLSON: Does that need to be an overall survival advantage to no treatment, as I think Tom was saying? Or should it be non-inferior to SABR or regular, other surgery?

DR. BUENO: I think that is a good question and the easiest way to do it is to define a type of a tumor and that the oncologist would now send a patient to surgery. And I keep

getting stuck on colorectal metastases because these are rather common and I would say that that is the comparison. Is that reasonable?

DR. TREASURE: Yeah, I think if you don't want a rag bag and set that upon all sorts of pathologies and if you want to have a consistent primary pathology so you have something stable, colorectal seems to me to be the best bet because it is the commonest reason for treated lung metastases, I think.

DR. BUENO: Okay. Okay, so --

DR. GOMEZ: It's also relatively rigor-resistant and so yeah, I think it's a good clinical study.

DR. BUENO: Yeah, it's not going to compete with a lot of other things. There is a trial from MD Anderson we're trying to -- for Dana, with chemotherapy with colorectal cancer and we can't get the oncologists to be interested. Dana Farber. So I guess that would be -- that's why I was thinking about it.

Okay, so is the study of OML -- oh, this is the Shanda question. Is the study of OML the best way to initiate TTA study in the lung? Is there another disease state more amendable to the study? This is why I held you off before, Shanda. So you're recommending less than 2 cm lung cancer, maybe?

DR. BLACKMON: Yes.

DR. BUENO: Or 1 cm?

DR. OLSON: If you're looking at toxicity first, you could do it in anything, like you could do it in polymetastatic disease, you could do in oligoprogression. But the overall survival question --

DR. BLACKMON: For efficacy.

DR. OLSON: -- would have to be -- that would have to be well-defined oligomets and if we're saying there's two phases they still need.

DR. BUENO: Okay, so --

DR. UBOHA: I agree. I think of those as two separate questions. One, is this a good tool to control any local disease? Yes or no. And then it doesn't matter what stage. And then we have all these other trials ongoing to say does it make sense to control all of the mets. And if the answer is yes, then we can use any tool that's available to us to control the oligometastatic disease. I don't know, do other panelists think about it this way? I just have a hard time getting a particular tool approved for oligometastatic lung cancer, there just seems like there's two separate questions here.

DR. BLACKMON: I agree with what Nataliya is saying, these are two totally separate questions and they're addressed with two totally different trials. I would just add that if we're doing this in oligometastatic disease, we want to pick three or less tumors because the more tumors, the more ambiguous the measurement of response. Some patients have 2 mm non-detected lesions that are in the area and do you call that a recurrence or do you call that a distant metastasis? I mean, you have to figure out how you're going to measure response and the more numbers of metastases, the more complicated your results and your findings will be.

DR. BUENO: Okay. Okay, so let me just, if I may -- dear FDA, can I share the slides that I created to make sure that everybody agrees with them?

DR. BLAKELY: Sure thing. Studio, can you confirm that Dr. Bueno can do that?

(Pause.)

DR. BLAKELY: Yeah, they're saying go ahead, you should be able to share your screen.

DR. BUENO: Okay, so I can share the screen even though you are here. Okay, let me just make sure that I have the correct slide open. Cancel that. Okay, share. Okay, so can I -- may I assume that everybody can see this?

DR. TREASURE: Yeah.

DR. OLSON: Yeah.

DR. BUENO: I was asked --

DR. BLACKMON: Yes.

DR. BUENO: -- to insert and show. So these are the questions and now we can agree or disagree on how I placed the answers. So comments on this, because this is what we'll present at 4:30.

DR. BLACKMON: So I would just say primary objective, overall survival for efficacy.

DR. BUENO: Primary objective. And this would be secondary objective. And do you guys have a strong preference for local control versus PFS?

DR. TREASURE: I would vote for local control, but I don't mind being -- I just put it up to make a start.

DR. BUENO: Okay. Anyone violently disagrees?

DR. OLSON: I'm okay with local control.

DR. BUENO: Okay. Okay, so is everybody else -- has any concerns about this slide, the answers? I just want to make sure it reflects everybody.

(No response.)

DR. BUENO: Okay, hearing none, let's go to Number 2. I added to assess lymph nodes because it would affect things, but you can tell me that that's wrong. And the lymph node, I'm not suggesting a biopsy, I'm suggesting perhaps a CAT scan or something else. Or a PET scan. And then as we discussed, the local control issues and the technical success.

DR. OLSON: I have a slight concern with this, is that the wording says what supports the patient benefit. I think this is more -- this confirms there's no harm, these ones. Like, the benefit is overall survival, nothing else is going to really show that.

DR. BUENO: Okay.

DR. OLSON: So either the question is wrong or these answers don't -- or else there isn't another -- there isn't a good surrogate endpoint for overall survival.

DR. BUENO: Well, what alternative endpoints could support benefit?

DR. OLSON: I don't know that --

DR. BLACKMON: So quite frankly, you could do pulmonary function testing, you could do quality of life, you could do survival. I mean, you could do more objective things, like a PFT assessment is objective, but you would want to have survival and control superior to that. If it's equal to another measure, then those things matter.

DR. OLSON: Yeah, that's kind of the other thing I was trying to get at, is that it's support of benefit in comparison to the gold standards, which we don't know what they totally are, but people say surgery or SABR. So neither do we now have a survival advantage, either.

DR. GOMEZ: Oh, I read that as support of patient benefit compared to not doing it.

DR. OLSON: But there's a cost of doing this intervention, it's like you're stealing the other options.

DR. BLACKMON: If the options are equivalent, these factors might lean you in one direction over the other. If one was terribly painful and the other one was painless, you would choose the painless one.

DR. OLSON: Yeah, yeah. But somewhere we need to put that clarifier in, because I don't want people to think that we think technical success alone is good enough. If technical success is okay, if it's not inferior to an overall survival.

DR. GOMEZ: Yeah. Yeah, that's a good point. I mean, I presumed that this was in the context of the primary benefit of overall survival would also support it.

DR. OLSON: Okay.

DR. GOMEZ: But yeah, I mean, it's a good point.

DR. BUENO: Well, that's why I said they're supportive to overall survival, which is the primary benefit, right?

DR. OLSON: Okay, that clarifier makes it easier for me to swallow.

DR. BUENO: Is that okay? Except my spelling. Are we okay with this?

DR. TREASURE: Yeah.

DR. BUENO: Okay.

DR. BLACKMON: Pain.

DR. BUENO: Pain, okay.

DR. BLACKMON: Sorry.

DR. BUENO: No, no.

DR. BLACKMON: I'm thinking of the patient.

DR. BUENO: No, no, it's good. We're trying to do it as a group think. Okay, so this is the third question and one option was RCT with no treatment control or continued systemic control. And it kind of depends on the cancer and on the histology. And then we made our point, alternatively, single arm, STS and control for safety. A safety trial shouldn't be required first with supervision, with supervision of a thoracic surgeon. Does that answer the question satisfactorily for everyone?

(No response.)

DR. BUENO: I hear nothing, so I assume yes.

DR. TREASURE: Yeah, it's all right.

DR. BUENO: Okay. And 4: What should be successful criteria for a TTA trial? Should success criteria change for certain subgroups? So we discussed demonstration of safety, ability to kill tumor, accurate software planning, the RCT should follow if the device passes the above.

DR. TREASURE: It's all right with me.

DR. OLSON: Yeah, I'll second.

DR. BUENO: Is everybody okay with that?

DR. BLACKMON: Yeah.

DR. UBOHA: Is demonstration of ability to kill a tumor, is this the same as local control?

DR. BUENO: I'd say --

DR. BLACKMON: Yeah.

DR. BUENO: -- not quite.

DR. UBOHA: But do we need it, I guess?

DR. BUENO: Local control, in my view, is in 3 months if it recurs locally versus elsewhere, and demonstration to kill tumor is -- you know, Shanda has quoted the situation where the ablation didn't kill the tumor, so the device is not working the way it's supposed to.

DR. UBOHA: But if the tumor doesn't grow for 3 months, do we care?

DR. BUENO: I don't know. We do can it either way. What does the team think?

DR. UBOHA: Because I guess having -- to demonstrate the tumor is killed, is it growing in there with another, how do you even -- I mean, I don't know.

DR. TREASURE: Well, we probably can only float our ideas because eventually, people will sit down and do this for hours, won't they?

DR. BLACKMON: Right.

DR. BUENO: So I added that.

DR. TREASURE: Yeah.

DR. BLACKMON: Yeah, I think the first phase is that first part of that second bullet and the second phase is the latter half of that second bullet.

DR. BUENO: Okay, so I'll address all. So is everybody okay with this slide?

DR. BLACKMON: Yes.

DR. BUENO: Okay.

DR. TREASURE: Yeah, yeah.

DR. BUENO: So I may be able to say it better, but I was trying to encapsulate what you guys all said. Any way to better articulate it?

DR. TREASURE: Well, you'll polish it up, I'm sure, Raphael. But that's got it, doesn't it? That's the point.

DR. BUENO: Yeah.

DR. BLAKELY: Well, this is Brandon from FDA, I just want to thank you all for the really amazing discussion. I know we're running short of time, so I'm going to just wrap it up and again, thank you all. Thank you, Dr. Bueno, for moderating. And we're going to take a quick break and come back and Dr. Eric Mann will introduce Session 4. Thanks, again.

(Off the record at 2:48 p.m.)

(On the record at 3:00 p.m.)

DR. MANN: Good afternoon, everyone, and welcome to the fourth and final session of the workshop and this is centered around how safety should be assessed for transbronchoscopic thermal ablation systems in a clinical trial. I am Eric Mann, a medical officer and senior advisor in the Office of Health Technology 1 in CDRH. We will begin this session with two presentations from Dr. Alda Tam, an interventional radiologist at MD Anderson Cancer Center, followed by Lonny Yarmus, who is an interventional pulmonologist at Johns Hopkins. These presentations will then be followed by the panel discussion. So let's begin with Dr. Tam's presentation, please.

DR. TAM: My name is Alda Tam and I'm a Professor of Interventional Radiology at the University of MD Anderson. I'll be discussing what we know about the safety profile of transbronchial thermal ablation.

Here are my financial disclosures.

The objective of the presentation is to provide the audience and panel a baseline understanding of the standard of evidence required to support safety for local treatments, particularly transbronchial thermal ablation for the treatment of patients with oligometastatic disease. We will review existing safety endpoints that have been established and also take a look at the data surrounding adverse events in percutaneous ablation, as well as discuss what may possibly be different and what we should potentially be expecting in terms of adverse events for transbronchial thermal ablation.

There are five published retrospective studies, all originating from China or Hong Kong, that have used transbronchial thermal ablation for a variety of patients. What you'll notice is that none of these actually are patients with oligometastatic disease and rather, they are patients with either early-stage non-small cell lung cancer or patients with the potential for multifocal adenocarcinoma.

The other interesting aspect here is that this is a very heterogeneous population and although the patients underwent biopsy prior to their microwave ablation, for those reporting their malignancy results, they were at least 50% of the nodules were negative for malignancy and in one study 96% of the lesions were negative for malignancy, which makes it difficult to make conclusions regarding efficacy from these small series.

The second point here in this slide is, I think, that you can appreciate that there is a lack of standardization in terms of a treatment algorithm. Many of the papers describe that the ablation modality and timing was operator dependent and based on judgment from a review of the images. However, we are looking at a variety of energy applied and also a variety of time for the energy applied when you look at the different papers. In addition, some papers had the capability of real-time cross-sectional imaging with cone-beam CT during the procedure, while others did not, effectively constituting a blind ablation.

Complications were equally hard to decipher in these papers because a lot of the designs were patients undergoing surgery at the same time as microwave ablation for multiple lesions, and so it's difficult to determine exactly which complication belongs to either the surgical modality or the microwave modality. However, on the papers that are evident, there were at least two cases of pneumothorax and two cases of hemoptysis that were noted to be related to the thermal ablation itself.

When we look at the published research in the American sphere, we don't actually see anything in the literature, but when we look at on clinicaltrials.gov we see that there were three trials that were studying transbronchial microwave ablation. The first is actually registered in China and the status of its accrual and results is unknown. The second was withdrawn and the third was the study that was terminated earlier due to two deaths in the first 10 patients who enrolled.

So in this flexible microwave system, 10 patients were enrolled in the study and the all-cause mortality was 20%. The serious adverse events was 30%, listed as infection, ataxia, respiratory and thoracic disorders, likely an exacerbation of the COPD, as well as hemorrhage. Interestingly, 9 out of 10 patients experienced some sort of symptoms after the ablation, leading to a reporting threshold of 90% for other adverse events that were not deemed to be serious.

So with only five published trials reporting on adverse events from transbronchial thermal ablation, I don't think we actually have any sufficient data to establish a baseline of safety for this modality as of yet. I think it's also important to remember that, of the published patient population that participated in the studies, most of these patients had lung cancer and they were not patients with oligometastatic disease. Of the series that were published, it represented a total of 139 patients with 186 lesions that were treated. What was also apparent to me was that there was a lack of standardization of technique for

the ablation and the follow-up time periods in the studies themselves were short. The trial design of what has come before or what was published in the literature also make it very difficult to isolate safety events related solely to transbronchial microwave ablation.

One of the things we have learned in percutaneous ablation of the lung is that the ablation volume can differ depending on the location of the lesion within the lung, and this is likely due to the differences related to ventilation and perfusion when you are in the center of the lung versus when you're in the periphery and similarly, when you're working with lesions in the upper lobe versus the lower lobe. Therefore, it is difficult at this time to have predictability around ablation size and we also suspect that this will be a likely similar challenge for the transbronchial ablation modality.

This is a schematic representing a transbronchial microwave ablation in a porcine lung, and the expectation is that the catheter will be directed down to the bronchus to localize the lesion, denoted in green, and that the ablation probe will exit the bronchus into the nodule and then deliver the ablation energy. So similar to what we know is happening with percutaneous ablation, the proximity to the bronchi and the vessels, as well as the location of the lesion in the lung will likely affect what type of ablation technique should be used in order to maximize tumor kill while minimizing potential for complication.

So this is a percutaneous ablation case of a patient of mine who had a solitary left lower lobe lung nodule that was biopsied and proven to be metastatic colorectal cancer. This case is meant to illustrate the point in terms of controlling the energy and being aware of exactly what is being deposited in the lung and the effects of it on associated structures. During the ablation period, I wasn't very happy with the ground glass zone after the first ablation at 65 W in 5 minutes and so I repositioned the needle to the more lateral margin to try and get coverage of that aspect of the nodule. After the overlapping ablation, the immediate post-ablation imaging looked pretty good, with the ground glass surrounding the

nodule and extending all the way back to the pleura.

However, one of the challenges of ablation is to understand exactly how much energy is being deposited and clearly, from her postoperative course, this was probably too much energy. Not only did she develop a postoperative effusion, she had a very large cavitation in the left lower lobe, putting her at risk for infection. In the end, after 3 to 6 months, she eventually did scar down and the nodule was controlled, but not knowing how much energy is being deposited in the nodule and the surrounding tissue is something that can cause complications for patients when in any form of ablation.

And so the lack of standardization of the techniques and the timing and the wattage being used in the transbronchial studies that were published is something that I think may put patients at risk of having complications in which too much energy has been delivered.

Similarly, this is another patient of mine who had supraglottic squamous cell cancer and his status post-chemoradiation 5 years ago. He had a biopsy proven of recurrence, which is a failure in the field of prior SBRT. He was not a surgical candidate due to underlying chronic obstructive pulmonary disease and so he came to us for ablation. Due to the close proximity of the lesion to the pleura and its size, I actually opted for cryoablation and you can see the ice ball surrounding the nodule after its treatment.

Interestingly enough, 2 months post-ablation he had a large cavitary lesion in the nodule that was ablated and returned with an abscess and it's likely that there was a bronchus leading to the lesion itself, as denoted by the red arrow, and it is one of the signs that, I think, has been described in the transbronchial literature, is that you can find a pathway directly into the lesion. But the question remains of whether or not, when you're using this pathway, this would actually lead to the creation of a cavity that would then be subsequently infected due to the introduction of bronchial flora from the access pathway itself.

Hopefully, the prior two case examples have given you an idea that the ability to control and predict and know what the energy deposition is doing to the nodule is an important key aspect for determining complications, and also when using a transbronchial route, the introduction of flora into the ablated nodule is something that I'm not sure has been thoroughly studied in the literature that has been presented to date.

So here I've listed the clinically significant and possible adverse events for transbronchial thermal ablation, which are relatively similar to what we consider when reporting adverse events for percutaneous ablation. I think probably these four may be the most important: procedure mortality; bleeding related to either hemoptysis or hemothorax or pseudoaneurysm formation from too much heat deposition directed at a vessel, which can either be immediate or delayed; respiratory issues related to effusion, COPD exacerbation, and the possibility of pulmonary function loss as well as infarction, because the ablation needle and device will be so close to the bronchi and the adjacent vessels.

It is anticipated that significant or possible adverse events may be immediate and/or delayed for up to 6 months and intra-procedural cross-sectional imaging would be key to determining something that is happening immediately, and it would probably be wise to have contrast-enhanced CT scans for up to 6 months post-procedure to follow for those delayed complications such as the development of pseudoaneurysm from either erosion from the cavity or direct vessel injury.

Although this paper was published in 2011, it remains one of the largest series that has catalogued complications after lung ablation. This is a paper that took a retrospective evaluation of 420 patients who underwent lung radiofrequency ablation in a thousand sessions. The most common major complication was aseptic pleuritis and the overall major complication rate was 9.8% and that was categorized as CTCAE Grade 3 or above complications.

The second most common complication was pneumothorax requiring pleural sclerosis, so that's just not an uncomplicated pneumothorax that either didn't require a chest tube or required a short duration chest tube that came out the next day. These were air leaks that had to be treated with long-term chest tube and additional measures such as sclerosis.

The mortality rate for this group of patients was 0.4%. Three people died of interstitial pneumonia and one person died of hemothorax.

This is a more recent paper out of the international radiology group at the Mayo Clinic and they looked at National Cancer Database and evaluated the complications cost and mortality of percutaneous lung ablation. The study group consisted of 3,344 patients including 1,277 patients who were treated for pulmonary metastatic disease.

This is a table listing the complications with an in-hospital mortality of 1.3% or 43 patients and median length of stay of 1 day. In addition, there was a 38.4% pneumothorax rate, but whether that was a complicated or uncomplicated pneumothorax requiring prolonged chest tube drainage, that was not further delineated.

The interesting fact about the in-hospital mortality is that the majority of patients, or 38 out of the 43 who died, were actually patients with non-small cell lung cancer and when you calculate the percentage mortality based on the treatment group, this represents a 1.8% in-hospital mortality for patients treated for primary lung cancer, and a 0.4% in-hospital mortality rate for patients being treated for metastatic disease.

If we go back to the original question as to whether or not we can establish thresholds for safety endpoints for transbronchial thermal ablation, it's my belief that based on currently what is published, we cannot, beyond that of mortality.

In summary, the five papers plus the clinicaltrials.gov results indicate that 139 patients have been treated with transbronchial thermal ablation and a total of 186 lesions

have been treated. The overall complication rate reported is 10.8%. With specific reference to mortality, the transbronchial thermal ablation rate is 1.4%. The literature in percutaneous ablation reports a range of 0.4 to 1.3%.

However, a deeper dive into the National Cancer Database, specifically related to patients treated for pulmonary metastatic disease, indicates that their expected mortality rate is on the order of 0.4%. This is in line with what is expected after mortality from VATS, where two recent surgical meta-analyses indicated zero deaths and therefore, I put down the expected mortality rate post-VATS as being less than 0.5%.

Beyond mortality, I don't think we have enough data on the possibilities of adverse events that could occur with transbronchial thermal ablation, and coming up and curating a list of the possibilities and what ought to be reported will be important in designing future trials.

In conclusion, when thinking about the safety profile for future clinical designs regarding transbronchial thermal ablation, we have to keep in mind that the oligometastatic patient population differs significantly from that of the non-small cell population, in that they have probably a better inherent prognosis, and therefore one of the things that we must resolve before we think about anything else is that the mortality rate of transbronchial thermal ablation should be held to the same standard as that for VATS or percutaneous ablation in the metastatic population, which is around 0.5%.

Determining safety endpoints should also be dependent on biopsy-proven disease, may differ based on histology, and there is likely a need for the development and validation of standardized burn protocols so we know the type of energy and expected damage that it will do the pulmonary parenchyma, as well as an agreement on the standardization of treatment technique with respect to intra-procedural monitoring.

Lastly, I suspect that the adverse events will be slightly different than that of what

we've seen with percutaneous ablation and that there is a real risk of immediate and/or delayed vascular injury related to energy deposition and the possibility of more infectious complications because we're using the bronchus as a route to the tumor itself. Thank you.

DR. YARMUS: Hi, everyone. My name is Lonny Yarmus, I'm an Associate Professor of Medicine and Oncology and Director of Interventional Pulmonology at Johns Hopkins University. I'll be talking today regarding adverse events associated with transbronchoscopic thermal ablation for the treatment of oligometastatic disease, specifically looking into what we, as investigators, should anticipate to protect our patients.

My disclosures related to this talk. For consulting is predominantly clinical trial design consulting work with Intuitive Surgical, J&J, Olympus, and Erbe. I have NIH-funded research listed below. I serve on the FDA Anesthesia and Respiratory Devices Panel and have a Cryoprobe patent with no financial or ownership conflict.

So the objectives of this talk are focused on one of the most clinically significant and likely adverse events associated with transbronchoscopic thermal ablation, what are the acceptable adverse events, and what are safety endpoints needed to support TTA as a treatment modality for oligometastatic disease.

Some quick background in terms of where the field is currently for bronchoscopic technologies. There are multiple modalities that you've heard about: radiofrequency ablation, microwave ablation, photodynamic therapy, cryotherapy, vapor ablation, and brachytherapy. However, overall there's very limited data on the use of these technologies and we'll get a little bit further into this, specifically microwave ablation is less than a hundred patients that have been studied in the literature to date. But as you can see in the image presented here, the concept of bronchoscopic ablation does have merit. There is clearly cases shown here where the target can be accessed bronchoscopically and there's proposed benefits over other modalities such as percutaneous ablation that I'll get into as

to why this may present potential benefits to our patients.

So why consider bronchoscopy over percutaneous modalities, radiotherapy or surgical approaches? This is a nice image here presented on a recent article that was just published in *AJR* looking at updates on percutaneous image-guided thermal ablation for thoracic neoplasms, and you could look at the indications for society guidelines of multifocal primary lung cancer, pulmonary mets, salvage of post-radiation recurrence, and palliation of tumors involving the chest wall.

And it's easy to understand there's a lot of overlap on the bronchoscopic realm, but specifically looking at oligometastatic disease, the advantages really have nice overlap with lung preservation with no permanent lung function reduction and if surgery down the road or radiotherapy are options, it does not preclude subsequent resection, radiation, or repeat ablative procedures, with just simple imaging follow-up.

In addition to the advantages of a percutaneous approach, what bronchoscopic approaches offer is a very attractive combination of staging, diagnosis, and treatment potentially into a single procedure. I know there's a long ways to go before we can get to that point, but this is one of the things the field is really interested in working towards, where patients can come in and get an endobronchial ultrasound for staging with on-site pathology followed by confirmation of a peripheral tumor followed by subsequent treatment in a single procedure. One of the advantages of this over percutaneous radiotherapy or surgical approaches is certainly potential reductions in cost, potential reductions in radiation exposure, hospital stay reductions and length of stay and comfort. And these are all, I think, viable reasons for consideration.

But in order to get there, we need to do more work looking at studies and study design and certainly safety is paramount. So I'll spend the bulk of the rest of the talk just talking about potential adverse events, definitions, and where, from my perspective, study

design should move.

So given the context of the other modalities available, radiotherapy, surgery, and percutaneous approaches, we have a long history of evidence and a long history of outcomes and I think we need to keep our investigational track aligned with those. So certainly serious adverse events and any adverse events are going to be a critical piece of this.

But I'll just take a moment to really define standard definitions of a serious adverse event, which is any adverse event resulting in death, one that is life threatening or places the participant at immediate risk of death from the event as it occurs, one that requires prolonged hospitalization, one that may cause persistent or significant disability or incapacity, or is another condition which investigators consider representative of significant hazards which can be defined in protocols.

So how does this all relate to bronchoscopic ablation? Well, as I stated earlier, there's very limited data with specifically microwave ablation and my review of less than a hundred cases performed in vivo, but there is some data in existence, and I pulled one recent paper here, published in 2021, which studied 30 patients who all underwent bronchoscopic microwave ablation and just listed the complication table here and you can see it's nicely laid out. Out of the 30 patients, four patients or 13% had pain; two patients had pneumothorax, and I'll get further into that; two patients had a post-ablative reaction or fever; one patient had hemoptysis and one patient had an empyema.

Now, if we compare this to some of the current literature for percutaneous approaches, mainly pneumothorax, the overall pneumothorax rate for percutaneous ablation in the current literature is upwards in the range of about 60% with a 30% rate of chest drain insertions. So you can see right off the bat, there are certainly some physiologic advantages to a bronchoscopic approach over a percutaneous approach by not traversing

the pleura and ideally reducing pneumothorax risk. That being said, again, 30-patient study and certainly needs a lot more data before consideration in widespread clinical use, but I think small pilot studies like this can really help frame how we proceed with further investigation.

I'll make a couple of comments here. Given the smaller size, you can see I highlighted some things such as the fact that in this small cohort the procedure-related mortality was zero, which is certainly promising, but I think we're all familiar with the prior attempts in the U.S. a few years back, trying to initiate a trial for microwave ablation where there was a very early death from massive hemoptysis. So the risk of death is certainly real, and protecting patients with standardized and regimented protocols is going to be critical here.

Another piece that's going to be hard to measure, but I think is going to be one that needs to be closely monitored, is actually radiation exposure. As we progress with peripheral bronchoscopy with new technologies and the utilization of cone-beam CT, which I do think is a critical and necessary piece for these types of interventions to ensure that we have an accurate targeting of the lesions, we need to be mindful of radiation exposure.

You can see that it's not insignificant, even in the small study of only 30 patients. Out of all cases, the overall range for number of CTs done during the case was between 4 and 12 or up to 12, and radiation dosages here in millisieverts per meter squared, up to 45,000. So, you know, that's also not an insignificant radiation dose. When we compare it to some of our colleagues with radiotherapy, it certainly is within an acceptable range, but at least in my literature review is significantly a higher dose than would be expected with a percutaneous approach. So difficult again to measure, but something that should be tracked for something that could end up being clinically significant and lead to adverse events.

So when we measure adverse events, another important piece is ones that are expected versus unexpected and I'll just briefly define the intuitive aspects of this, but an unexpected adverse event is one in which the nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure or investigator brochure. One that is expected is known to be associated with the intervention or condition under study.

An example here, looking at the percutaneous literature for ablation with a recent guideline published just earlier this year for pneumothorax, where the group is advocating that for percutaneous ablation, although pneumothorax has been identified in studies listed as a complication, it is typically an expected event as a result of the ablation procedure. And this group was suggesting that a future trial should consider reporting pneumothorax as an expected outcome.

Now, that is going to be a little bit different than how we would approach this bronchoscopically because bronchoscopic approach is thought to be -- one of the reasons thought to be beneficial is to reduce that risk of pneumothorax, so we're going to actually want to track these carefully and consider the fact that it would be an unexpected adverse event given the nature of the ablative approach versus a percutaneous approach.

However, for things that might be expected under the bronchoscopic events that would be consistent with standard bronchoscopic procedures and the side effects of that, like pain, fever, cough, sputum, mild hemoptysis, and even mild exacerbations and probably obstructive pulmonary disease, which would be considered an expected complication after a standard bronchoscopic procedure, and these could fall under the same light but would need to be tracked carefully and closely, as well.

And then finally, safety endpoints in terms of what we should be following with these patients as we progress. I think this is a critical piece because there is so little data

out there to help us really understand how these patients are going to respond, both from a disease entity, but also from a safety entity.

And as these trials are designed, I think we need to be quite mindful about patient selection and inclusion to reduce complications and improve patient safety, and those types of approaches should include type inclusion criteria or exclusion criteria where patients, for example, should be declined for, or declined standard-of-care surgery if they were candidates, in order to be considered for these types of therapies.

I think critical in this is a multidisciplinary inclusion panel to screen these patients on multiple levels with close collaboration with radiation oncology, thoracic surgery, and pulmonary for consideration of these patients, and obviously image guidance is a critical must with cone-beam or fixed CT scanning to ensure that targeting is appropriate and accurate.

With that, I think critical safety endpoints to be measured are certainly bleeding in multiple contexts here, so obviously intraoperatively followed by hemoptysis, both intraoperative and postoperative, with standard grading scores of mild, moderate, severe, and life threatening. Hemothorax is a potential known complication and should be tracked closely. Infection, post-infectious ablation with abscess formation in the ablative zone. Pneumonia post-bronchoscopy and potentially empyema, as we saw in one case in the initial small case series. And then pneumothorax, as I alluded to earlier, really in this context should be considered an important adverse event, given the potential advantage of a bronchoscopic approach, so looking not only at overall pneumothorax rate and chest tube rates, but also closely following for evidence of prolonged air leak and the ramifications of that. Exacerbations I addressed earlier, specifically the severity of those exacerbations and hospitalization as a result of that. Consideration of pneumonitis as a potential concern in the context of local ablation. Pain with standardized VAS scales for pain management and

pain assessment. And then also given the unknown context of the bronchoscopic approach, even in the context of oligometastatic disease, radiographic evidence of disease progression locally and the potential effect of local spread from the procedure itself and further metastases should also be evaluated and considered as a potential safety endpoint.

So in summary, hopefully I've conveyed that bronchoscopic ablation is certainly a promising approach, but there is very limited data that exists towards the bronchoscopic treatment of cancer.

Well-designed studies are desperately needed before any approval should be considered, and these studies should be held to the same high standards that our surgical and now radiation oncology colleagues have produced.

Thank you very much for listening and if anyone has any questions after the session, I can be reached with the e-mail below. Thank you very much.

DR. MANN: Thank you very much, Dr. Tam and Dr. Yarmus, for those really outstanding presentations, that really set the stage well for our current panel discussion on the safety evaluation of TTA devices in clinical trials. I would like to now introduce our moderator for this session, Dr. Robert Suh, who is an interventional radiologist at UCLA.

Dr. Suh.

DR. SUH: Thank you, Eric, it's a pleasure to be here. My name is Robert Suh, I'm a thoracic interventional radiologist at David Geffen School of Medicine at UCLA and at UCLA Health, and I've been practicing image-guided thermal ablation in the lung for almost 25 years. I'd first like to thank the organizers of the workshop for inviting me to moderate this panel on the safety evaluations of TTA in the treatment of oligometastatic disease to the lung. And I'll briefly introduce our panelist speakers, so if we can go to the -- yeah, perfect.

First we have two interventional radiologists, Alda Tam from The University of Texas MD Anderson Cancer Center, and Brad Wood at the NIH Clinical Center. We have two

interventional pulmonologists, Lonny Yarmus from Johns Hopkins Medicine, and Momen Wahidi from Duke Health. And to keep us all honest, we have Robert Olson, a radiation oncologist from the University of Northern British Columbia, and Shanda Blackmon, a thoracic surgeon from Mayo Clinic. We're also joined by Eric Mann if there are regulatory concerns.

And lastly, this is a 60-minute session and we're faced with the task of addressing two important questions in today's session, so if we can move -- advance the slide to the disclosures. And the first question, advance one more, please. One more. Perfect.

Okay, so the first question is: What safety endpoints should be measured by TTA? And this sort of a two-parter: What are acceptable rates of specific adverse events to support safety performance goals for those endpoints? And I guess this sort of a third part: Are there any subgroups where higher risk is acceptable for a given benefit?

So let's just focus first of all on the first part of this, so what are the safety endpoints and what are acceptable specific adverse event rates? So maybe we can start off with Shanda Blackmon because in that last session you saw a lot of what happened with percutaneous ablation, so maybe you can translate your experience of at least dealing with some of these and see also how these may translate to this transbronchoscopic approach.

DR. BLACKMON: Thank you. I would like to first acknowledge the multidisciplinary ablation tumor board that I've been honored to be a part of here at Mayo Clinic with Matt Callstrom, Pat Eiken, our interventional radiologists, radiation oncologists, and radiologists. It's a really tight-knit group that's really focused on putting the patient first in safety and one of the things that we started doing when I first arrived at Mayo Clinic was we agreed that every patient, after ablation, would be hospitalized on my service for observation for 24 hours to make sure that no massive hemoptysis went without a chance for salvage.

We've published two trials, one is the MARK trial, which is ablation followed by just

observation, and the EMPRESS trial, which was treatment efficacy and safety evaluation, sponsored by Medtronic. The EMPRESS trial had 21 adverse events from 11 different subjects and there were about five serious adverse events in that series. When we look at the different adverse events, they ranged from respiratory failure, required CT insertion for a pneumothorax, prolonged air leak. We had one patient that developed Guillain-Barré, and we had another patient that required prolonged intubation for respiratory arrest. Almost all of our -- I think all of our patients were ablated with double-lung endotracheal tube intubation, single lung ventilation, and arresting ventilation with the lung in the inflated position just for reference.

On the MARK trial, which has just come out in publication, is a series of six different patients, some of whom had more than one ablation, but we did have one Grade 3 upper respiratory infection.

Adjunctively, outside of these trials, we've ablated a lot of other patients off of protocol and off of trial, none of which I have been directly involved with for bronchoscopic ablation, but some were treated at our institution for that and there was one death that I know of from massive hemoptysis.

To answer this question, I would just save us time by saying I agree with all the lists that were put up by Dr. Yarmus, as well as our interventional radiologist from MD Anderson. A couple that I did not see and that I have seen in these patients is potentially a CO_2 embolus that was not manifesting as a stroke. We had a cardiopulmonary arrest from CO_2 embolus that was delayed on the floor. Rib fracture, cavitation, needle track, tumor spread, which I have not seen but that would be something that we would additionally follow, that I didn't see listed. Injury to the heart, fistula formation, diaphragm injury or nerve injury, noticing that the phrenic and the recurrent laryngeal and other nerves are potentially damaged. Long-term complications of pain and disability I hadn't seen

mentioned and so I think they're worth adding. And then subgroups where I think it would be tolerable to have a higher risk, I don't really think that would be reasonable because we have plenty of alternatives. Thank you.

DR. SUH: Great. Maybe we can move on to Dr. Olson. Any thoughts?

DR. OLSON: Yeah, happy to. So I think the acceptable rate of toxicity depends on the efficacy. So if somehow it's demonstrated that it's more efficacious than SABR or surgery, then I think you actually could accept higher rates of toxicity, but I think it's probably safe to assume that the overall survival is going to be similar from one ablative intervention versus another for specifically a SABR comparison. So I think that a toxicity rate should be about the same or lower.

And so given I'm a rad onc, it's easy for me to talk about rad onc toxicity rates and I think that there's lots of people who have published on single-arm studies which are fraught with potential bias. And so one that we did in D.C. that was presented at ASTRO last year, was called SABR-5, which you wouldn't know in your groups and it's under review right now for publication, but it was 400 patients in D.C. where they only could get SABR on trial, so it was during an era before we allowed it off protocol and so it's population-based toxicity rates and of the 400 patients, 188 had their lung treated, so that's really the population we're looking at, and the rates of Grade 2 and above toxicity was 9% and then the rates of Grade 3 plus were less than 5%, no deaths and no Grade 4 events, either, from the lung treatment. The only death that we had was from abdominal, which is not applicable to today's discussion.

The SABR COMET study, which is pretty well quoted, it had some pulmonary toxicity, so it had a radiation pneumonitis death, a Grade 5 toxicity, and a pulmonary abscess, which is very uncommon but potentially related, is how we coded it on our study. So like I think it's possible. So I guess I would quantify it as like I have specific criteria based on the SABR-

5 studies and the SABR COMET, I would say Grade 2 and above, less than 10%; Grade 3 and above, less than 5%; Grade 4 and above, less than 2%; and then Grade 5, ideally, would be less than half a percent, although to get confidence of that you'd have to have a very large population.

Again, I agree with -- I don't think there's really any subsets that I would accept a higher toxicity with the exception being if you're comparing to SABR, we accept higher rates of pain at the chest wall, so I think it's reasonable that there could be pleuritic pain. I don't know how easy it is to access near the chest wall, but if that is -- if TTA can do that, I think you'd probably accept higher rates of pain there.

DR. SUH: Okay, very good. Let's maybe open the discussion to our interventional pulmonologists. Dr. Wahidi, any thoughts about what safety endpoints should be measured for TTA and what are some of the acceptable specific adverse events rates?

DR. WAHIDI: Thank you. Yeah, I agree with the other speakers that obviously the safety events that they mentioned, mortality and all that list, the comprehensive list that Dr. Yarmus and Dr. Tam presented. I think that when you talk about rate, again, I agree with Dr. Olson, it's about efficacy and how efficacious this treatment is to make us tolerate a rate of adverse event.

But in my mind, I think what matters the most is severe adverse events, so obviously massive hemoptysis, pneumothorax with persistent air leak, and obviously, death. I think those have to be really low, otherwise this procedure is not worth it. You know, we can tolerate pneumothorax that you can treat with a chest tube and they resolve, we can tolerate mild hemoptysis, we can treat pneumonia, but really, the serious adverse events, in my mind, have to be really low for us to tolerate this treatment and introduce it as a possible new tool.

DR. SUH: And do you see any subgroups that were maybe a higher risk? I mean, I

know, in terms of patients with interstitial lung disease, again, some of the radiation literature points that there is a higher rate of toxicity, also in connective tissue disease, whereas ablation may be an alternative in this group, although there's not a huge amount of supportive data otherwise, but given that this -- you know, these patients may have no alternatives in some cases, would you foresee any patient groups at all?

DR. WAHIDI: Yeah, to me, I think patient selection and safety are tightly connected and I don't know if we'll have a more detailed discussion about patient selection, but yeah, we need to be very mindful of the patients that we're going to put through general anesthesia and bronchoscopy. We need to have lower limits of FEV1 and DLCO, that below a certain threshold which we know from clinical practice they're not going to do well. We need to know how much oxygen they're on and make sure that it's compatible with anesthesia and safety.

So there are many mitigation strategies with patient selection, they have to have stable COPD, can't be on a high dose of prednisone, all these, I think that's why the multidisciplinary matters here where a pulmonologist is part of the multidisciplinary team and tight control over entry criteria in the study.

DR. SUH: Okay, great. Dr. Yarmus, any thoughts to these? I know you gave an excellent presentation and so you're speaking from obviously a lot of experience in this area, what are some of your thoughts?

DR. WAHIDI: You're on mute.

DR. YARMUS: Yeah, I'm one of those people. Sorry. So I obviously agree with all of the colleagues on the panel. I think one piece that was just brought up is focusing on the acceptable risk for a different subset of patients, like you mentioned, Dr. Suh. You know, I think ILD and certain patient populations that were essentially -- you know, that would be too high risk for the other modalities presented, that's worthwhile of consideration because

I do think the bronchoscopic approach has some potential safety merits with the approach. Now, obviously, the 20% mortality data is concerning and we need to be mindful of that. But, again, I think that's where there is a potential option.

You know, as interventional pulmonologists we're late to the game, right? I mean, we have amazing data with radiotherapy, we have amazing surgical outcomes and obviously, immunotherapy is marching forward faster than I think anybody really anticipated, so I think we also have to be mindful of that; we don't need to find a treatment just because we can treat, right? I mean, I think we need to be very mature and regimented in regards to figuring out if there is a space for this, and I'm not sure there is.

DR. SUH: Okay, great. For our two interventional radiologists, I want you to like, as we talk about these safety endpoints, I know there are a lot of complications that we've certainly seen with the percutaneous approach with microwave as well as cryoablation, RF ablation. But really think about maybe enlightening the audience on how the transbronchoscopic delivery of this energy is inherently different than a percutaneous approach, albeit they do still impart energy to the lung, but the delivery mechanism to the airway can maybe have some complications intimately associated with that.

So Dr. Wood, would you care to comment?

DR. WOOD: Sure. I think location is like real estate, it's all about location, location, location, and I think from the outset many percutaneous procedures might not be done at all with central location so you have to assume some complete patient selection bias in any study and have to be really rigid with stratification. So if we're talking about toxicities, figuring out what they are and what you're actually talking about takes a long time to paint that picture, so what we're seeing now in the early numbers is a very incomplete swath of an Impressionist painting that takes years and years to develop. So granted, it's new technology, but that's the point. A new technology is going to need a standardized

approach in order to assume that what you're seeing is, in fact, representation and can be generalized about what the technology means and what it can do and what's going to happen. So inclusion criteria is really key. Stratification, whether it's molecular or histology specific, or location is critical because you're comparing apples and oranges otherwise and you're getting a picture.

And Alda Tam did a wonderful job of sort of over-viewing where everything was with competing technologies and what complications look like and toxicities, but essentially we're dealing with this non-standardized approach that takes time to standardize, so don't expect to squeeze juice out of a rock, it's going to take time, the early stuff is not going to be representative.

It's key to take the toxicities a little step further and think about what's the causes. So you have central location, you're going to have certain fistulas nearby, airways are going to be a problem, hitting vessels is going to be a problem maybe, but speaking to the real critical nature of imaging during procedures, you know, what is the feedback going to tell us, how does that influence toxicities, how does the presence of training on cone-beam CT influence toxicities, if so. What sort of guidance systems for treatment planning for identification of tumor undertreated for realization of complications immediately on the flyway can address them with other interventional or surgical or pulmonary tool.

So I think the question is not a simple one, the answers to most of these things are multidisciplinary opinions and teams, we're seeing that move towards that, and tumor boards across the world and that should happen and I'm glad to see it, people represented here. Not all the panels today have had complete representation from specialties and that's unfortunate, so people are allowed to take low-level evidence, things, and if they're on this panel, they must be true. Well, you've got to be real careful of what any of us say, including myself, you know, we're all biased by our experiences, and I think multidisciplinary is key

and imaging is key to stratification of the toxicities according to levels of evidence, as well. We do levels of evidence for follow-up all the time for overall survival, PFS, time to progression, disease-free interval, whatever it is, but we don't really think about levels of evidence for some of the safety issues. Some of the early signals don't mean anything. Now, granted we want to run safe studies, but they don't mean anything when you have such low levels of evidence early on.

DR. SUH: Okay, great. Dr. Tam, you gave a really nice summary of the complications certainly associated with percutaneous ablation and then you mentioned a few that may be more pertinent to the bronchoscopic approach including procedure mortality, bleeding, given the closeness of the arterial bed next to the bronchus, as well as maybe issues with airway breakdown and cavitation and infection, and now I think, based on some of the discussion, I think radiation exposure or over-radiation exposure now becomes a consideration. Do you have any other potential safety endpoints that we should measure with the TTA approach? And maybe give us an idea of maybe what those performance goals may be.

DR. TAM: Yeah, thanks, Rob. I agree with what everyone has said but I stick with what I sort of concluded, that I don't think we have yet established a baseline. So probably for any trial going forward, we just want to open up the collection of anything that could possibly be related to a safety event and get more numbers so that we know. I want to echo Brad's thoughts about the FDA really putting together an inclusive panel for this discussion and I appreciated the patient panel, as well, the day before and one of my patients was on there. I guess one thing I would say is that inclusion does not necessarily mean equity and hopefully, I speak for my interventional pulmonology colleagues when I think having some of us represented on the clinical design and clinical discussion panels would've been beneficial because to Dr. Blackmon's point, we are sitting in multidisciplinary

conferences and we are participating and ultimately, we hopefully will be the ones that are doing the procedures and running the trials for this.

I do have one comment in terms of the potential for higher risk acceptable in given populations or subpopulations. I think the discussion that I've learned over the past couple days needs to be much more nuanced when we come to putting out the final report. There's definitely the non-small cell lung cancer population and inherently, those patients are sicker, they have more comorbidities and, per the National Cancer Database, they have higher rates of associated complications with percutaneous ablation.

So if you're going to consider oligometastatic non-small cell lung disease, it's a different sort of underlying patient that you're dealing with similar to a patient with interstitial lung disease. Totally different if you want to design a trial for metastatic colorectal cancer patients or even sarcoma patients. And if we're going for overall survival, I would say that sarcoma patients may be something to look at because although it's a rare disease it does metastasize often to the lungs, it's relatively radioresistant, and there are very few systemic options. I have many patients who have come for repeat percutaneous ablations every 1 or 3 years and they have been at it for 6, 7 years, you know, with that type of population.

So I would say that if you're going to cut it in different populations, we have to have a little bit more of a detailed discussion because maybe the acceptable risk for transbronchial should be less than what we have now as standard of care options for colorectal and sarcoma, but may be acceptable to equal what we have now for percutaneous ablation for non-small cell lung cancer. And one caveat is that any of the literature we published on percutaneous ablation has always been based on patients that have either been not surgical candidates, unsuitable to SBRT, or had recurrence after SBRT and can't be re-radiated, so you're already dealing with a baseline sicker population given

what has happened in the past in the patients that we've seen.

DR. SUH: Great, okay. Before we move on to the next question, are there any other thoughts about -- again, I think we should focus specifically on what the anticipated safety measures for TTA should be, as well as potentially the treatment patient population given that again, we're not talking, as Dr. Tam mentioned, about non-small cell lung cancer or this sort of medically inoperable group, we're talking about oligometastatic disease, and before we move on to the next question, do any of the panelists have any other thoughts about any of these questions that we're sort of faced to answer?

DR. BLACKMON: I would just advocate for a multidisciplinary, standardized, defined set of events that goes across different disciplines. The STS national database has well-defined events and I think that what we definitely need in this area is an extension across specialties where the interventional pulmonary colleagues, the thoracic surgeons, the radiation colleagues, and the interventional radiologists all band together and start to collect common databases and registries going across the discipline treating the same disease. Disease-centered databases, not specialty-centered databases with common standardized definitions. It's impossible to compare the outcomes because we all use different definitions. I would just advocate for that.

And then I echo what Dr. Tam said, I think it's really important that we look at the sequence of treatments. A patient who has failed radiation and had prior surgery and goes for an ablative procedure is not a normal patient. If they have massive hemoptysis but they've also been massively radiated, that's not a normal patient, and that hemoptysis is maybe perhaps more expected than it would be in a regular normal patient. Thank you.

DR. WOOD: To take a step further, the multidisciplinarity of the whole approach of the research team, of the multicenter team, of the actual procedure, if you have an interventional pulmonologist and IR doc together doing a cone-beam CT procedure, less

risk, absolutely. Now, is that --

DR. BLACKMON: Yes.

DR. WOOD: -- ethical down the road? No. But that's the way to do these upfront studies, I can't emphasize that enough. And maybe requiring a multidisciplinary DSMB, as well, where every discipline is represented.

DR. BLACKMON: In our particular institution, our interventional pulmonologist is married to the interventional radiologist, I highly recommend that, it works best.

DR. SUH: Right, that was my next sort of point is that do you advocate a team of maybe -- a team that would maybe partake in the evaluation and also, to some degree, monitoring the safety of this procedure, TTA, as it unfolds at centers, coupled with obviously the interventional pulmonologist, thoracic surgeon, and an interventional radiologist who has some knowledge on thermal ablation, if that's in the lung.

DR. BLACKMON: Yeah, I mean, just like we started kyphoplasty, those patients were cared for by spine surgeons and interventional radiologists, and then if you look at other models, I think it has to be a multi-d approach to work.

DR. TAM: I think it should be a multi-d approach because at this point we're talking about the robotic guided. But Dr. Solomon, who we all know, an interventional radiologist at Memorial Sloan Kettering, we recently collaborated on a study in which we were able to do an endobronchoscopic approach without the robot, right, so it's really like the path. It's not a referendum of does ablation exist, should it exist, whatever, it's like does the new path differ from what we can already deliver.

DR. WAHIDI: And I just want to add on, I echo Dr. Blackmon's note about definitions. If you read bronchoscopic studies, there are a million definitions out there for what's mild versus moderate versus severe hemoptysis, for instance, and I think we need to really define it and stick to it for all the adverse events in a trial like this and make sure that we

are consistent with our definition and criteria.

DR. SUH: Great. I think it's time, if there are no other questions or comments from the panel, I'd like to move on to the next question, so if you can advance the slide. So the second question is what unique safety issues are anticipated with TTA compared to local therapies in your specialty? And we've kind of touched a little bit on this. And secondly, how should these be captured and at what time points, which we haven't talked about too much.

DR. WOOD: I think Alda touched on this a little bit with the realization that there's a bimodal peak in toxicities around procedure and then you can have delayed cases of toxicities, as well, so a 6-month time point for local control makes sense for defining things and likewise, a 6-month time point for toxicity.

DR. SUH: Sorry, that was 6 months?

DR. WOOD: I think that was what Alda was reviewing in the literature and I think that makes sense, I mean, I'm throwing it out there, I'm not --

DR. SUH: No, no, I was --

DR. TAM: I think --

DR. SUH: It was hard to hear, sorry.

DR. WOOD: Oh, sorry.

DR. TAM: Yeah. No, I think I said we need inter-procedural imaging, you know, cross-sectional imaging to catch the immediate complications but that obviously, we're going to time the imaging follow-up to assess for efficacy, so I just arbitrarily used a 6-month cutoff of cross-sectional imaging to say that would be delayed complications, right? So if you see nothing, if you don't see a pseudoaneurysm from time zero to 6 months then we don't have a pseudoaneurysm or infection, etc. So that's arbitrary, but I think that monitoring of delayed complications needs to be tied to the timing of scanning for efficacy

and we normally do a 1-month post-ablation on CT scan to reestablish baseline and then 3, 6, and 12 months to look at resolution of ablation changes. So something like that, when you build it into the trial, could double for assessment of toxicity or adverse events.

DR. SUH: I think if we are dealing with oligometastatic disease, I think most of these patients have semi-active disease and their oncologists are generally doing kind of anywhere between 3 and 4-month interval follow-ups and so I think if we are to do a trial on this, they could fit in very nicely. I guess any thoughts from our interventional pulmonologists?

DR. YARMUS: Yeah, I was just going to advocate for actually maybe a little bit earlier tighter, so especially post-procedure. So I think, given this is so poorly studied, I think the post-procedure 24 to 72-hour period is pretty critical, as well as up to 6 weeks for simple things like delayed pneumothoraces but also the infectious concerns that I think were appropriately raised to see where we had it. So I think at least post-24 hours CT after ablation and then I think 6 weeks and then pumping up to that, you know, the 3-month and more standardized imaging regimens would be appropriate.

DR. SUH: And Lonny, you were saying that this should be a contrast-enhanced CT within the first 24 to 48 hours or would that be more just a chest X-ray or --

DR. YARMUS: I don't know if contrast is -- I mean, I kind of defer a little bit to the panel, as well, but I think certainly CT, you know, so I think at a minimum non-contrast CT. I don't think simple chest radiography and/or ultrasound would offer enough of safety endpoints that we would need to follow serially what's happening after the ablation.

DR. WAHIDI: Yeah, I agree with Lonny and Dr. Tam, and I think intra-procedural -- I'm assuming we're going to advocate for observation/hospitalization at least for 24 hours for these patients, so that's what I think Lonny's referring to, and then a probably 4 to 6-week follow-up, then 3 and 6 months. I think those are very appropriate safety endpoints.

I would just want to -- and I don't know if we're going to go there, you know, what worries me a little bit about this procedure is standardization of the procedure and I think Dr. Tam alluded to this, I worry about energy dosing, do we know, are we going to protocolize that and know how to dose the energy? What are we going to do if the probe is not in the middle of the lesion, do we allow peripheral ablation and how do we deal with these situations? Not to discuss these details, but I think part of the protocol is these mitigation standardization strategies to make sure that we don't end up with safety endpoints. So I think that's an important topic, in my mind, is how are we going to determine these strategies to mitigate all these safety issues?

DR. SUH: I'm glad that you brought that up because that was a question that I wanted to pose to the panel, is that given that this technique is relatively new and there's maybe not the best understanding of how to deposit or how to prescribe that burn energy into your ablation zone, what studies, if any, would you like to see be performed before this sort of gets out there into the public's hands?

DR. BLACKMON: We did in the ABLATE-RESECT trial, but it doesn't really measure efficacy, it does measure the energy that was delivered. We were estimating that we were under-treating about 50% of those tumors and that the software planning wasn't treating as we expected. When you look at the trials that have been published, there's tremendous variety in the wattage and the time and imaging. I think standardization would be really important. And a software program that could help you to more accurately plan how long, at what watt, how much energy you're delivering and be more consistent in the delivery of that energy is strongly needed before you launch this.

DR. WOOD: Although to be devil's advocate, some of this is going to be hard to be -- I think tightly, tight standards so you can reproduce things is key and I think it's a great point, I totally agree with what Shanda said, but I think, like surgery in many cases, it's hard

to mandate exact clinical judgment during a procedure and I would advocate for it. Early on that might be a great longer goal and certainly if it could be done now, we would. But one way to sort of assure that early on is to have someone who's done a hundred, 500, a thousand, whatever the number is, lung ablations with that technology, whether it's microwave or whatever, and if you have that sort of a background, you know some of those parameters.

Granted, it's going to be different, essentially, that's where this multidisciplinarity comes to play, but Alda showed a case where she did a 5-minute 65 watts and then a 3-minute 30 watts, I think it was, so those -- you know, that's not in the cookbook and she saw that one part of the tumor was a little outside the edge and she adjusted it. If we get to mandate the multidisciplinarity early on, you will accomplish what you'd like to accomplish and are able to do it early because it's going to be really -- I mean, here we are 25 years out from kidney and liver and bone and we don't have those parameters right now for those structures, really. So I think that's a great goal, but I think early on just multidisciplinarity gets you there as much as you can.

DR. YARMUS: And can I just add, I totally agree, and I think this is a unique opportunity for trial design where we could look at really an experienced, tight, multidisciplinary inclusion review committee for all patients, right, that are not involved with the study sites. These are elective procedures, so these can be very tightly reviewed in a timely fashion. We found it with some other studies and it works incredibly well and I think it's the safest way to do this, and then I'll also add I think we need the same thing with data safety monitoring.

DR. WOOD: I think that's a great idea. One more brief comment is that the robotics in this space and the amount of money invested in standardization of this therapy doesn't guarantee anything when you're talking about what Lonny just said, which is patient

inclusion criteria and that incredible bias and input.

DR. YARMUS: Yeah. And Dr. Blackmon just put on the chat as I was about to ask about a multidisciplinary DSMB that meets very regularly and has a lot more power than I think most would traditionally have to stop the studies and I think we learned from that initial study in the U.S. where we had a patient death, that trial, to my knowledge, went on for several more patients before anybody really intervened and I think we need to avoid that.

DR. SUH: Yeah, I guess it's been brought up, but how does the panel feel about robot navigation software enhancements to be mandatory or do you really think that this would ensure or could ensure or better ensure safety with this procedure?

DR. BLACKMON: I don't favor that.

DR. YARMUS: Yeah, I don't either. I do favor CT imaging. How you get there may or may not be relevant and I think that's probably a separate discussion, but knowing that we're there accurately at the time of ablation, I think, is critical and that's where either fixed or cone-beam CT imaging is critical.

DR. WOOD: And Lonny's idea of multi-d with that DSMB would be able to address that. You look back at a case, see how long you treated, see how it was monitored, see whether cone-beam CT was used appropriately, I mean those are really powerful.

DR. WAHIDI: Yeah, I would agree. I think we don't dictate the modality to be used to get to the nodule, I think naturally the technology of navigation robotic bronchoscopy radial EBUS, it's going to make it easier to get to the nodule but, like Lonny said, ultimately we need a cone-beam CT to confirm the probe is within lesion. I want to bring one point, Lonny reviewed it, saying that there was a range of CTs being done in the procedure, up to 12, and that always bothered me. You know, with bronchoscopy sometimes you don't get right in the lesion, you do it again, you navigate again, do another CT and keep going, and in

that enthusiasm of the operator we lose track of how many CTs have we done, because I --

DR. WOOD: Be careful. Be careful with assumptions, though, because --

DR. WAHIDI: Oh, no. No, I'm just saying --

DR. WOOD: Full cone-beam CTs might be less than one regular CT.

DR. WAHIDI: Right, so I'm asking actually our radiology colleagues here, because I don't know, is there -- should a study put a limit? How many CTs per sitting can you do safely, we think, or maybe there's no limit, Dr. Wood.

DR. WOOD: No limit. You can't mandate the tools, and people use it because of what it's used for and they need it and when you -- we did a study on -- off topic, but Nadine Abi-Jaoudeh did a great randomized control trial for taste and measured radiation with cone-beam CT and it's much less than you would otherwise think, the tools are getting really better, so a CT dose is not a CT dose, be careful.

DR. SUH: Okay, any other comments? I mean, I think we've -- I'm just kind of tabulating some of this. So the feeling that I'm getting is that it doesn't matter so much how we get to where we need to go per se, but what's important is to be able to monitor what we're doing with CT, whether it's incremental CT, I suppose, or CT fluoroscopy or in many cases, cone-beam CT, is that correct? And I think --

DR. OLSON: Yeah, I would -- oh, sorry.

DR. SUH: Oh, sorry. Please add.

DR. OLSON: I was just going to add one thing just because everyone sort of stopped at 6 months and I would advocate for much longer follow-up for two purposes. One of them is we don't know what we don't know yet and we might just be assuming that there's no late toxicity because we were totally surprised, like the average radiation luminitis after breast cancer is like 5 years, so that's probably not true, but I don't know. The other one is if you're comparing against SABR, SABR does have late toxicity, so if you want to compare

toxicity curves over time, you're doing yourself a disservice by stopping at 6 months because you might actually have an inverse relationship to us where you had more upfront toxicity but less long term.

DR. SUH: So Rob, would you favor a year, a year and a half, 2 years? Because, I mean, some of the post-radiation effects after SABR, I mean, they manifest themselves very -- you know, a year and a half sometimes.

DR. OLSON: Yeah.

DR. SUH: Two years.

DR. OLSON: No, I would say two at the minimum.

DR. WAHIDI: Okay. I think we were talking --

DR. BLACKMON: I would argue 5 years.

DR. WAHIDI: Yeah. We were saying 6 months for safety, but the assumption is there's going to be a 1-year CT scan and up to 5 years of CT scans, right, for efficacy.

DR. OLSON: But I would also get safety into the 5 years. I do agree, I was just being -- I was being conservative because everyone said 6 months, but yeah.

DR. WOOD: And I think interventional pulmonologists can speak to adding EBUS to the list of monitoring tools that we've mentioned. You know, they're good at it, they would assume, they would apply it much more appropriately than an interventionalist might and so you need -- again, going back to the theme, everybody, you know, one plus one is five.

DR. YARMUS: I'm going to just make one -- I'm thinking back to the modality of approach to the tumor and I don't know the answer, but one thing that should be considered is stability, which is probably the biggest advantage of a robotic-assisted approach right now and how that is impacted or the lack of traditional stability with conventional bronchoscopy may impact the ablation. So I don't think it limits what we just talked about but it should be tracked, right, so differences in approach and the accuracy of

the ablation tied to the approach should be looked at.

DR. SUH: Any other thoughts or just -- I guess anything come up in your mind that we may have missed or not covered amongst these two -- or these two questions or major topics?

DR. WAHIDI: I just want to go back to, again, some procedural details because when I think of safety, I think do we know enough about if a nodule is next to a big vessel, next to the fissure, next to the heart, we really need to have these parameters in the protocol and summarize the prior experience and make sure that we know so we don't cause these safety events, and it looks like Dr. Blackmon has done some and probably can chime in, but it's really important to make that standardized for everybody who's going to do this procedure first in a clinical trial and then maybe after that in clinical practice.

DR. SUH: I think that's --

DR. BLACKMON: And I would just say until we really get--

DR. SUH: Oh, sorry.

DR. BLACKMON: Sorry, until we really get it figured out, 2 cm or less. A lot of the trials say 3 cm or less, but when you look at what they actually ablate, it's 2 cm or less and a centimeter away from the pleural surface would be a great place to start and no central lesions. That's just a really clean group.

DR. WAHIDI: And I think that you would get five different answers about what's central versus peripheral, especially that middle part of the lung. So definition of what we mean there, again, it goes well with the standardization we're talking about.

DR. WOOD: You can say if an ablation zone or a planned treatment volume, let's call it, superimposed over a vessel above X millimeter size, then you'd get a Day 1 contrast-enhanced CT. Some arbitrary rule like that, that helps. And maybe it's an optional rule but it goes beyond the minimum of monitoring.

DR. SUH: That, I guess, brings up another point. Do any of the panelists have a thought about what pre-procedure evaluation might be useful to plan out the actual ablation? I mean, I know there are some loose rules of 2 cm or less than that or less than 1 cm from vital structures, for example, but what other things? Should we get a full, a very good contrast-enhanced CT to really understand the relationship of the airway and the blood vessel to these lesions? Are there any other things that the panelists feel that might be helpful to sort of maybe stave off a complication or potentially a difficult procedure?

DR. YARMUS: I think I like the contrast. You know, contrast CT is not something we typically would do for bronchoscopic approach for diagnostics, but given the reasons here, I think it makes a lot of sense to mandate that pre-procedure.

DR. TAM: I think that's a good idea. For my patients, I usually have a contrast-enhanced CT within a month of the procedure date just so you can track what else is going on in the body and make sure that it's the size that you think, but in this case it will allow you to do 3D reformats and figure out the pathway and the relation to the vessels.

DR. WOOD: And that will take off points to avoid vessels.

DR. BLACKMON: Another safety issue, as I would -- in the beginning until we really understand this better, always take the safest approach as possible. Some of the trials that have published outcomes haven't done this, but I would advocate for a double-lumen endotracheal tube, single lung ventilation, general anesthesia in the beginning because some of the other trials that were looking at cryoablation, there was some variety in outcome whether it was conscious sedation or intubation.

DR. WAHIDI: Yeah, I mean, I would support standardizing, again, anesthesia protocol, use a muscle relaxant. I'm not sure if double-lumen intubation is necessary, maybe it's suggested, but --

DR. BLACKMON: That's for the hemoptysis.

DR. WAHIDI: Well, hopefully, hopefully it's not happening right then, right? Hopefully, we're seeing what we're ablating and it's delayed, but I get your point.

DR. YARMUS: I actually -- sorry. I would, for the hemoptysis management, it's actually --

DR. BLACKMON: Rigid.

DR. YARMUS: -- safer for us to manage with a large single-lumen ET tube bronchoscopically because we can't get the larger tools down the double-lumen tube. So I think, I'm not sure I would restrict where -- I think a blocker, right, certainly could -- you know, mandating blocker entry pre-procedure --

DR. TAM: Yeah, that's --

DR. YARMUS: -- or something like that.

DR. TAM: That's typically what we do if we have a high-risk lead lesion is a blocker, just in preparation with a large ET tube.

DR. WAHIDI: Deflated blocker in the bronchus proximal to the target --

(Cross-talk.)

DR. YARMUS: The other limitation with a double lumen would be the other -- like robotics, right?

DR. BLACKMON: You can't get through, yeah.

DR. YARMUS: Currently not designed, that I'm aware of, for double lumen.

DR. BLACKMON: Yeah, I should've said single lung ventilation and taken away double lumen in the tracheal tube. Single lung ventilation, then.

DR. YARMUS: Yeah.

DR. BLACKMON: Not conscious sedation, that was the discriminator I was trying to push.

DR. SUH: Okay. Okay, let's see, there was one other thing that I was wanting to ask

the panel. Moving forward, I guess, what would you -- I mean, I know we sort of touched on it with like obviously, a data monitoring or safety monitoring board and so forth. But let's say eventually this gets out, gets approved, and eventually becomes more accepted practice, do you envision or can you think of any things that might sort of get maybe the interventional pulmonologists or for that matter, anybody who uses this technology endobronchially to be better adept at doing this so you ensure -- because there's going to be a learning curve, so what do you envision might be that sort of proctoring, if you will, or some sort of tiered learning moving forward in the future?

DR. YARMUS: So just a quick comment, which is, I think most of the panel is aware -- but this is a proof, right -- these devices have FDA approval for soft tissue lesions to the lung, I believe is the most recent approval, and there are people using those bronchoscopically. I don't advocate for that, I would not do it and I have not done it and I think we need this type of data before any of that is actually out there, but I think that's an important piece to understand that this is out there, so I think the way this is designed is pretty critical. Even if we're concentrating on oligometastatic disease, you know, the interpretation of this data is going to leak out into other disease entities and I think we have to be mindful of that in terms of trial design and safety endpoints that we're talking about.

DR. SUH: So if people are already using this, right? But how do we ensure public safety, that this is done correctly when anybody could buy this and a patient goes on the table? I mean, this could be manufactured directly and I don't --

DR. BLACKMON: You could mandate it like the TAVR trials were done. When cardiologists were deploying percutaneous valves in the aortic position and then later in the mitral valve position, there was a mandated partnership between surgeons and interventionalists so that safety was always mandated, and by doing that you're avoiding the chance that this might get done in a cath lab with no heart surgeon around for miles. If

you mandate good partnership and backups and multidisciplinary teams, then it almost inevitably makes the situation safer.

DR. MANN: Hi, this is Eric Mann. I just want to clarify that although these devices have been cleared for a general soft tissue claim, they have not been cleared for lung parenchyma ablation.

DR. YARMUS: But to my understanding, the interpretation of that by industry and some providers is that that is inclusive of lung, which resulted -- has resulted in people using it. Off label, I suppose. I'm not even sure if it would be considered off label.

DR. MANN: I think we would consider it off label, yeah.

DR. YARMUS: Right. You know, I think that's something that FDA also, as a partnership, should consider if there are ways to provide a tighter restriction than what was originally approved because I don't think the understanding of the initial approval was that it was going to have the implications that it's had.

(Pause.)

DR. YARMUS: I'm sorry. You know, in terms of how do you limit inappropriate use, I think it starts with approval, right? So it probably should be readdressed.

DR. SUH: Given that there seems to be, from the discussion, that there is -- I mean, even though ablation has been around for many years now and performed percutaneously and now obviously going to a bronchoscopic approach, but what, if any, studies, whether it be animal or other kinds of studies would ensure, make you feel more confident that you knew how to control these devices and how to impart that energy, especially if you -- again, I think you could say well, let's just only treat peripheral lesions, but you know people eventually will start treating central lesions, for example. So what studies, animals studies, in particular, would need to be performed to give everybody a little bit more confidence in what they were doing was safe, especially around maybe, again, in the off -- the sort of

peripheral centimeter lesion, for example?

DR. WOOD: Good question. I think some 20 years ago during the early lung percutaneous history, there were a few strokes, CVAs, TIAs, associated with very -- just a few case reports and there was -- ended up, I think -- I think Cameron (ph.) and Rogers (ph.) did a nice study at MD Anderson, at Dr. Tam's place, on animals looking at MR diffusion-weighted imaging in the brain after ablating and I think the long and short of it is it's safe unless you sit up because it turns out some of the olester (ph.) bubbles returning was going straight up after crossing the heart. So, anyway.

DR. BLACKMON: We did report MR diffusion-weighted imaging after microwave ablation in the MARK that's just come out this week.

DR. YARMUS: Briefly, I think Dr. Blackmon, the treat and resects I think would be more -- you know, as long as it's out there and people are able to study it, would be much more valuable than animal studies at this point, with sequential kind of push-outs of resection date, right, to get a better sense of --

DR. BLACKMON: Yeah.

DR. YARMUS: -- where we're treating, what the zones are, how much of a response we have over time, and it would allow us to get a much better understanding than animal models at this point.

DR. BLACKMON: And that trial is relatively easy to do.

DR. YARMUS: Yeah.

DR. SUH: I mean, again, I think by doing critical -- or a critical structure or a lethal injury model would be important to understand how much energy near a critical structure could be given?

DR. BLACKMON: Lateral thermal spread and first pressure of adjacent vessels, just like we do for any energy device in surgery, should have the same rules apply. You should

be able to get that with the labeling of the device.

DR. YARMUS: Yeah, a lot of that has been done, the two companies that have current approval of devices have done much of that, that I've seen.

DR. SUH: Okay, I think that brings us to the close of the hour, right? Any other final comments before we wrap up?

DR. WOOD: Thank you for hosting, Rob.

DR. SUH: Yes. Thank you, everybody.

DR. BLACKMON: I would just add PRO data, that FDA wrote a nice summary of how important PRO data is and putting our patients first and advocating for the quality of life in our patients is really important, and the FDA has taken the lead and published a really nice summary of that for approval of devices, and so I'll just throw a pitch in there that we don't want to forget about their quality of life, does it really make a difference.

DR. MANN: Well, thank you very much, Dr. Suh. And thank you to all of the panelists for this really thoughtful and useful discussion, there was a lot of actionable recommendations that we will definitely carefully consider moving forward in helping industry design future clinical trials.

So now at this point, I think we will transition to the final segment of the workshop and during this segment, we have asked the moderators for each of the four panels to briefly summarize the key points of their respective panel discussions before concluding the workshop today. So I think we will begin with the summary from Dr. Offin, who moderated Panel 1 regarding the definition of OML for clinical trials for TTA devices.

DR. OFFIN: Good afternoon, everybody, my name is Michael Offin and it was my pleasure yesterday to serve as the moderator for the Panel 1 discussion on parameters defining oligometastasis to the lung. Today I would like to take the opportunity to review some of our key findings.

The first question we discussed was: What is the maximum number of lung nodules appropriate for classification as oligometastasis to the lung, and how are other metastatic sites factored into this calculation?

Our consensus opinion was the likely best definition here was to be conservative and limit the number of metastatic nodules in the lung to one to three. The location of these nodules are likely to matter insofar as if the nodules are all contained within the same lobe of the lung versus ipsilateral lobes of the lung versus bilateral lung involvement may well portend different biology and clinical outcomes, and annotation of such location would be important in prospective trials.

It is also important to account for mediastinal involvement and nodal stations as this may well portend different ability for local modality therapy from a safety and feasibility perspective.

The total number of metastatic sites matter with the general literature stating three to five sites being consistent with the diagnosis of oligometastasis with most on the panel agreeing that limiting to approximately three sites from a trial perspective would be reasonable.

There is a need to be able to treat the primary disease as well as the metastatic sites, so in a prospective trial setting it is important to make sure that the primary lesions are also amenable to a local modality therapy.

As we'll discuss in future questions during this panel, there's a need to account for other things, not just the number of nodules or metastatic sites but also histology, actionable alterations, and systemic therapy.

The second question we reviewed was: Are all tissue histologies potentially encompassed within the definition of oligometastasis to the lung, and is this definition modified by specific histology?

The consensus of our panel was that histology and site of origin clearly matters, as treatment options and the natural history of the disease are distinctly different. For instance, a Stage I non-small cell lung cancer versus a Stage I small cell lung cancer have very different clinical outcomes and treatment options, as would a Stage I renal cell carcinoma with oligometastasis to the lung versus an earlier stage lung cancer, for instance.

There's also a clear need to integrate modern predictive and prognostic biomarkers as this dictates care, and there are potential differential response rates to systemic therapy, as well as potential different side effect and toxicity concerns when combined with local modality therapies.

There's a need to balance the need for robust accrual on clinical trials while at the same time evaluating subtleties based on tumor biology, and one way to possibly balance this is to integrate smaller pilot studies trying to evaluate specific biology and select populations treated with certain systemic therapies and/or certain genomic alterations.

The third question we reviewed was: How does timing and clinical setting of occurrence impact one's definition of oligometastasis to the lung?

The biology and natural history is likely different for oligo-residual versus oligoprogressive versus oligorecurrent disease and as such, the response to systemic therapy and the time at which the disease advances is important to annotate in a clinical trial setting.

There is likely differential biology based off the disease-free interval from the time of initiation of therapy to the time of recurrence, be it oligometastatic or polymetastatic, and this needs to be further evaluated and studied.

It is also important to delineate in a trial setting synchronous versus metachronous tumors, leveraging or understanding of genomics as these represent distinct clinical entities.

One idea discussed during the panel was consideration of the role of a more consolidative approach for local modality therapy after prolonged stability on systemic therapy. So for instance, a patient who has been on systemic treatment for 1 to 2 years with prolonged stability may be eligible for radiation or other local therapies to consolidate the residual disease.

We also discussed the importance of considering treatment sequence and risk of potential toxicity with concurrent versus sequential local modality therapy, specifically when combining interventions such as radiation or ablation with systemic therapy such as immunotherapy with specific concerns for the potential risk of pneumonitis when it comes to oligometastasis to the lungs.

Furthermore, we discussed from a trial endpoint perspective, if one is looking at safety and feasibility, we can likely be more liberal about the clinical setting, but if the endpoint is something such as overall survival, we would likely need a more homogenous population for an adequate analysis.

The fourth and final question we reviewed during this panel discussion was: What other parameters in your specialty are used to define oligometastasis to the lung?

We felt that rigorous staging and annotation of disease sites is obviously warranted in any prospective trial evaluating oligometastasis which would also include the annotation of nodal disease and mediastinal involvement. Such anatomic considerations have direct implications on the ability to deliver a given local modality therapy. An example of this would be the ability to adequately give a local therapy to a patient who has advanced mediastinal involvement involving the great vessels or esophagus.

The evaluation of safety and tolerability of combining a given systemic therapy with a specific local intervention is obviously of key importance, especially when considering oligometastasis to the lung with particular attention needed for pneumonitis.

Integration of quality of life metrics into any prospective trial is of key interest here and there is a need for continued multidisciplinary approaches and collaborations as we continue to roll out the next line of prospective trials in this field.

I want to thank you all for your time and attention today. Thank you.

DR. MANN: Thank you, Dr. Offin.

We will now move on to Session 2, which was moderated by Dr. Yang. The session dealt with identifying a population of OML patients suitable for treatment with TTA.

Dr. Yang.

DR. YANG: So I will share my screen, I believe. Let's see. So for Panel 2, which we focused on defining the appropriate patient population and dose of local treatment for TTA, these are our panel members, there was no disclosure.

So the first question: What are the current local treatment options for OML use in your facility?

And we discussed multiple factors are considered with administering a local treatment for OML including histology, performance status, number of lesions and location of the lesion, and the ability to eradicate all sites of disease, especially in the oligometastasis setting, as well as surgical candidacy, and that these usually require some multidisciplinary discussion.

In terms of the actual treatments, the options include surgical approach, radiation approach, as well as ablation. The panelists felt that surgery and SBRT or the radiation approach have been the primary approaches and there also appears to be a shift from surgery to SBRT over time in some of the practices.

Ablation, it's not generally used in an upfront setting and that was discussed among our panelists, and it was felt that its primary use is for GI histologies, peripheral tumors, and at times failed prior local therapies. In that setting, repeat radiation as well as surgery may

also be an option. Again, the panel felt that and again, emphasized the need for multidisciplinary decisions for these types of scenarios.

A concern that was brought out was that how would it be comparable to the other local therapy approaches in terms of outcome and what would be the appropriate patient selection for TTA?

The panelists expressed that based on literature review, that they felt that ablation may have lesser efficacy and higher complication when directly compared to SBRT radiation, and that multiple panelists felt that the patient risk for TTA is of a concern.

The second question that was discussed was: What factors are used to determine which local treatment option is appropriate for oligometastasis to the lung, and which histology and disease state is treatment of oligometastasis to the lung considered conventional and experimental?

And then here we see quite varied opinions between specialties. There are some consistencies in terms of histology. For example, radiation oncologists felt that -- the radiation oncologists on the panel felt that sarcoma for surgery, using a surgical approach for sarcoma metastasis to the lung is the standard and that in addition to histology surgical candidacy, another factor to consider is deciding on which type of local therapy.

And in terms of histology, that was felt to be more conventional for radiation approach for oligometastasis including non-small cell lung cancer, breast cancer, colorectal cancer, prostate cancer; however, there are basket trials including all histology that's ongoing that will help us better understand this question.

From the thoracic surgeons' perspective, surgical candidacy and as well as histology, being melanoma and pancreatic cancer, they would be more hesitant for surgery, while sarcoma and germ cell tumors favor resection or other forms of local therapy.

Medical oncologists also agreed that histology, such as sarcoma for surgery, as well

as location are some of the factors that need to be taken into consideration. They also brought up how well the primary disease is controlled, systemic therapy options, as well as molecular testing results are also other considerations that they would integrate in terms of deciding which local treatment option. They also mentioned the high-grade neuroendocrine tumors as well as small cell carcinoma, they tend not to favor local therapy for these histologies.

There are other considerations, as well, such as pace of progression and disease-free interval, pace of progression of disease or the disease-free interval. If there is a short disease interval, short disease-free interval, the favored approach is systemic therapy, while longer disease-free interval, local therapy would be considered.

And new sites versus persistent site of disease or progressing is also a treatment decision to treat that our panelists felt had a use in terms of deciding on local therapy or none.

Number of metastasis with all sites being able to be addressed is also a factor to be considered, as well as systemic therapy washout period as needed for local therapy.

Number 3: What oligometastatic cancer histology would you not consider treating locally?

Some of the histologies that were brought up included small cell lung cancer, there are very rare instances where local therapy is offered in terms of oligometastasis. Radiation oncologists on the panel felt that this may still be a viable option for a patient with small cell lung cancer in a clinical trial setting and there's currently a trial that's ongoing evaluating this question. Overall, it was felt that extensive stage small cell lung cancers are not favorable for local therapy while limited stage small cell lung cancer warrants some consideration. Again, melanoma and pancreatic cancer were brought up as not favorable histologies for local therapy, and it was also brought up that the basket trial design may not

be the best approach to figure out which histology would most benefit from local treatment for oligometastasis.

Again, outside of histology, the kinetic of disease, which I mentioned on the previous slide, as well as response to systemic therapy, were also factors that people would take into consideration in terms of offering local therapy.

And Number 4: In defining a patient population, what would you recommend for inclusion/exclusion criteria for a study of TTA and OML?

I think this was -- the main take-away from this is that the panelists felt that we need to know the nature of the study in better detail, are we looking for safety, are we looking for efficacy? If it's efficacy, what is it comparing to, to have a benchmark in terms of comparison?

It was felt that for inclusion criteria disease kinetic was a topic of discussion, that patients should have disease progression-free interval of 6 months to 3 years; number of metastasis, one to three; and histology-wise, colorectal and osteosarcoma were felt to be -- should be included in terms of inclusion criteria. This was the size of the tumor, 2 cm or less; the location of the tumor, as well as well pulmonary reserve.

Some concerns were brought up that there are multiple ongoing studies evaluating oligometastasis specific histologies, such as NRG-BR002 and NRG-LU002, and to figure out which histology would really benefit from local therapy. So there were panelists who felt that this should be addressed first prior to investigating another modality for oligometastasis.

And another consideration was that a TTA trial maybe should focus on a population that may not benefit from surgery or SBRT and that the trial should have a stopping rule for toxicity as well as outcome.

Lastly, in your specialty, which of the following goals are appropriate for each local

treatment option for OML, and what factors do you consider when defining the goals for local treatment?

The consensus of the panel was that the priority for oligometastasis is prolongation of life, long-term local control, the quality of life, and potential cure in this setting. Palliative management alone -- I'm sorry for the typo -- is rare and not necessarily a goal for oligometastasis management, but it is more consistent with the polymetastatic setting. And I think that is it, those are my slides.

DR. MANN: Thank you very much, Dr. Yang.

We will now have the summary session for Session 3 regarding study design considerations that was moderated by Dr. Bueno. We have a hard stop time at 4:53, so if the remaining moderators can please keep their comments as succinct as possible, thank you.

(Pause.)

DR. MANN: Dr. Bueno?

DR. BUENO: I'm afraid I'll be much briefer. So can you see my slides? Okay. So I'm grateful to the two previous speakers who covered 99% of everything.

The first question was what kind of a study that we would propose, and we felt strongly that it's going to have to be a carefully selected cohort and you guys dealt with that. We thought that the primary objective ought to be overall survival, and we thought that the secondary objective ought to be local control, but local control needs to be very precisely defined as our technical success.

So what alternative endpoints? We thought that quality of life, pulmonary functions, pain, but we want to emphasize that these would be supportive to overall survival, which is the primary benefit we would recommend as a group.

Now, whereas for the final analysis, we believe that a randomized clinical trial now

depending on the type of cancer either with no treatment control or with continued systemic therapy control, again depending on the histology, would be the ideal ultimate trial.

A less good alternative was a single-arm trial and we can use the STS database as a control for safety, etc., but we truly believe, given the safety profile discussed in a couple of meetings, that a safety trial needs to be done and Shanda made the point that a supervising thoracic surgeon has to be part of the multidisciplinary team and the patients have to be admitted overnight, given the prior complications.

So what is the successful criteria for the trial? You know, one is demonstration of safety, that's important; demonstrating an ability to kill the tumor either early and eventually, so that will be local control; it's important to have accurate software planning and if the device passes all of the above, an RCT to follow, and since you're doing the therapy, depending upon the case, comparative arm to surgery.

And finally, is this the best study to do it? So we had a debate about the possibility of doing a safety trial in oligomet versus OML and then down the road, maybe lung cancer, early lung cancer is a possibility and I think that was already discussed.

And just an overall idea for this type of device, perhaps a registry for all of these cases done nationally, off line, off label, etc., or through a trial would be helpful, it will help multidisciplinary physicians to agree on the definition of specific terms because we have radiation oncologists, surgeons, interventional pulmonary oncologists, it's best that we use the same words, that every trial should include the appropriate cancer diagram, and FDA guideline PRO data capture, and help -- and the FDA will need to figure out how to define endpoints for the trials because if you look at the literature, they're different. So I think I'm keeping with the time, thank you.

DR. MANN: Great. Thank you so much, Dr. Bueno.

And lastly, we have a summary from our last panel on safety from Dr. Suh.

DR. SUH: Okay, let me just -- okay, so this is Panel 4: Safety Evaluations for TTA. I'd like to thank our panel.

And so for the first question, "What safety endpoints should be measured for TTA? What are the acceptable rates of specific adverse events to support safety performance goals, are there any subgroups where a high risk is acceptable?"

So I'll show you on the next slide, because we had a catalog of complications that came over from the percutaneous literature summarized by Dr. Tam, but the panel felt overall the safety of transbronchoscopic thermal ablation is not yet established and so there still needs to be a lot of work in that regard.

Obviously, Grade 3 or higher toxicities must be low. Some panel members felt that these Grade 3 or higher toxicities needed to be equivalent or better than that of image-guided thermal ablation. We all felt that these toxicities needed to be well defined, standardized, so that they can be easily compared.

Overall, the group did not feel that there were any subgroups where maybe a higher risk is acceptable, although they were open to some extreme cases of potentially cases of interstitial lung disease, connective tissue disease, or perhaps other patients where there are no other local therapies that may be feasible following a multidisciplinary decision.

Everybody advocated a multidisciplinary tumor board discussion of these patients, advocated a disease-based database creation. Often, an M.D. group or multidisciplinary group, but those who are involved in the treatment paired with the interventional pulmonologist in the form of a thoracic surgeon and an interventional radiologist who is familiar with thermal energies within the lung and certainly, for a trial there needs to be tight oversight with a data safety monitoring board.

Here's the list of complications that we have seen with percutaneous ablation, but

those that are highlighted or bolded in red are those that may be specifically or pertain to the transbronchoscopic approach, so procedure mortality, certain complications of bleeding, given that the airway or, as you know, every airway is accompanied by an accompanying artery and so certainly, bleeding complications or vessel complications are first and foremost.

In addition, because one of the benefits of doing TTA over a percutaneous route is the lesser occurrence of air leak and so certainly that needs -- will be looked at or need to be tracked and unique to this approach. Respiratory might be also an issue given that the airway is being occluded or being ablated through. Infection, as we've seen, and a very nice point about radiation because now with the increased use of cone-beam CT, potentially, or other CT real-time imaging, this may drive up the radiation dose that the patient receives.

And for the second question, "What unique safety issues are anticipated with TTA compared to local therapies in your specialty?" We kind of covered that in the last question more or less, but how should these be captured and what time points?

And so the group really focused more on, for TTA, what should we be doing, and I think everybody felt very strongly that during the procedure there needed to be CT imaging, whether that's incremental CT, CT fluoroscopy, or cone-beam CT, to see exactly what is being treated and how it's being treated and what the effects of that treatment, especially in the immediate period, would be.

There was, again, with regards to robotic assistance, navigation software confirmation and planning, these were all niceties but they were not necessarily considered critical to doing this procedure; however, these should be tracked then to see if they add or enhance performance.

Again, in the lung we really only have CT to look at for the most part and so the panel felt that chest CT with contrast would be favorable, if possible, and the patient can

receive contrast. Immediately after the procedure, or I should say within a 24 to 48-hour period, chest CT would be nice, this coupled with at least a minimum of 24-hour overnight hospital admission observation, as well.

Other time points, the ablation literature talks about 1 month to 6 weeks after the ablation as kind of a new baseline and so this should continue, as well as chest CT follow-up between 3 and 6 months and certainly in some cases, longer. I don't think this will be too difficult given that it is being used for oligometastatic disease. Most oncologists will follow their patients at 3 to 4-month intervals during the process, but again, there were panel members who expressed that we should follow these patients 2 years or even up to 5 years given that we don't know what the necessary outcomes may be and certainly, if we're looking at efficacy of treatment, then we would follow these patients for a longer period.

There were some other sort of topics that came up during this to perhaps enhance or aid in the safety of this modality going forward. Much focused on burn prescription standardization, meaning what energy should we work at, what is this going to give us, and how does that sort of look during the imaging and afterwards.

There has to be software evaluation of the ablation zone or validation of that, given that there was one study that was presented earlier where the software overestimated the true coagulation necrosis or the ablation zone. Further, ablate and resect protocols may be useful to get a better understanding of the ablation zone as well as neighboring or potential collateral injury to maybe the major structures that may be affected by the ablation zone.

There should be well-defined parameters for who gets treated or what types of lesions get treated with TTA, maybe at first, and that can be generalized over time, but some felt that the lesion should be 2 cm or less, 1 cm or less from the periphery or the pleura, and no central lesion should be tackled.

Chest CT with contrast may be useful for planning before the ablating, ablation,

especially with coronal and saggital reformats to really get an idea of how to plan your approach and what potential structures may be within the ablation zone. This was particularly brought out in the case of neighboring larger blood vessels and so these blood vessels would be segmental or larger and may be next to the tumor you're ablating given that you're coming through the airway and immediately adjacent to that airway is that blood vessel.

The group felt that close monitoring of the patients during the procedure was critical in the form of general anesthesia and intubation with single lung ventilation, deflated blocker in place in case there is massive hemoptysis or hemoptysis that needs to be controlled, and certainly, patient-reported outcome data given that this is going to be potentially a less traumatic or minimally invasive type of procedure.

Moving forward, as this technique becomes greater adopted by the masses, I suppose, some of the panel mentioned that there should be mandated partnerships and these certainly can be driven by industry, like in the form of a proctorship, and so you have to do so many under some sort of supervision before you can kind of go on, on your own, and in some cases you may always need a partnership given that these procedures can be risky.

And I think that does it and I appreciate the opportunity to present the findings from our panel. Thank you.

DR. MANN: Great. Thank you so much, Dr. Suh, and many thanks to all of the moderators for doing such a great job leading the discussion of the various questions that were posed.

I'd like to now introduce our office director, Dr. Malvina Eydelman, who will provide some closing remarks for the workshop.

DR. EYDELMAN: Thank you, Dr. Mann. Thank you, everyone. Good afternoon.

Wow, it has been an exceptionally productive 2-day meeting and I would like to sincerely thank everyone who participated.

During the meeting we heard from professional societies, industry, and experts from diverse clinical specialties. And very importantly, we heard directly from patients themselves about the challenges they experience in dealing with OML. They voiced what is important to them in terms of therapies to treat their condition.

I want to assure you that all of us at FDA have been listening carefully throughout these discussions. We will thoroughly consider all of the input we received as we move forward with our regulatory approach to transbronchoscopic thermal ablation devices intended for the treatment of OML.

Our Center's mission is to assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices. Your input during this 2-day meeting will help us fulfill that mission.

In closing, I would also like to thank the FDA team that worked so hard to make this event a success. Kudos to everyone. And with that, I now officially close this workshop.

(Whereupon, at 5:04 p.m., the meeting was adjourned.)

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C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

VIRTUAL PUBLIC WORKSHOP – STUDY DESIGN CONSIDERATIONS FOR TRANSBRONCHOSCOPIC THERMAL ABLATION DEVICES FOR THE TREATMENT OF OLIGOMETASTASES TO THE LUNG

April 6, 2022

Via Webcast

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

TOM BOWMAN

Official Reporter