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Evolving Strategies in Limited-Stage Small Cell Lung Cancer Management

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

Dr. Silvestri:
This is *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, a pulmonologist and the Hillenbrand Professor of Thoracic Oncology at the Medical University of South Carolina. Here with me today to discuss the current landscape of limited stage small cell lung cancer are Drs. Adam Fox, Mariam Alexander, and Anurag Singh. Dr. Fox is a pulmonologist and Assistant Professor of Medicine at the Medical University of South Carolina in Charleston. Dr. Fox, welcome to the program.

Dr. Fox:
Hey there. Thanks so much for having me.

Dr. Silvestri:
Also joining us is Dr. Anu Singh, who is a Professor of Radiation Oncology and the Director of Radiation Research at the Roswell Park Cancer Center in Buffalo, New York. Dr. Singh, thanks for being here.

Dr. Singh:
It's wonderful to be with you.

Dr. Silvestri:
And last but certainly not least, we have Dr. Mariam Alexander, a medical oncologist and Assistant Professor of Medicine at the Medical University of South Carolina. Dr. Alexander, it's great to have you here with us as well.

Dr. Alexander:
Thank you so much for having me, Gerard.

Dr. Silvestri:
Well, great. Let's get started. Dr. Fox, could you explain how the epidemiology of small cell lung cancer has changed in recent years?

Dr. Fox:
Of course. Most studies suggest that the changes we've seen over the last couple of decades are linked to changes in smoking. So in the United States, we've seen over the last couple of decades less people smoking. And smoking is a really important association with small cell lung cancer in that almost all patients in the U.S. who are diagnosed with small cell lung cancer have a history of tobacco use.

And the overall incidence of small cell lung cancer, just like the incidence of smoking in the United States, has been decreasing, and we're seeing the downstream effects of that. Where it used to be about 15 percent of all lung cancers were small cell lung cancer, it's down to about 10 percent in total.

There were also some pretty big differences between men and women, in that men were diagnosed at a much higher rate two to three decades ago, and women much less. And with the changes in smoking in these groups and over time, we're listing those to be about equal now—about 50 percent men and about 50 percent women.

Dr. Silvestri:

Thanks. That's great. And I think the take-home message there is that, again, one in 10 lung cancers is going to be small cell. Adenocarcinoma is clearly the most prevalent of histologic types in lung cancer. But if you're a pulmonologist, about ten percent of the time, you're going to see small cell. For me, it seems to come in runs; we might not see it for a few months, and then we'll see two or three cases. Is that your feeling, Dr. Alexander?

Dr. Alexander:
Oh, yes. That has certainly been my experience—we don't see cases for several months, and then we suddenly see an onslaught of patients coming into the hospital, and they end up having small cell lung cancer.

Dr. Silvestri:
And staying with you just for another moment, Dr. Fox, can you walk us through why tumor board review is such a critical early step for patients with limited stage small cell lung cancer?

Dr. Fox:
Absolutely. Tumor board is a critical tool for our patients with small cell lung cancer, and I would hedge to guess that almost all of my patients, especially with limited stage, are reviewed at our tumor board. The reason for that is that we need quality and expedient multidisciplinary care, especially in these patients for whom the stage is a little bit questionable. We need to have radiology—and, in particular, radiation oncology—review the images and the extent of the disease that we can see on imaging to help make that determination. In part, what can be irradiated safely helps determine whether we treat patients as if they are limited or extensive stage. And so having that review where everyone gets together to decide what the stage is can be really helpful.

And additionally, while it's quite rare and usually unintentional, there is some evidence for surgery in small cell. Usually, we find out after the fact, but it does come up sometimes when a single focus of small cell is found, perhaps on a biopsy with no evidence of spread. It's certainly at least considered. And I think tumor board is the right place to do that. One person making that decision doesn't make a lot of sense to me. I think having all parties really weigh in on their experience can really help that.

And then, there's the other component of speed—the expedited care that we hope to have for these patients. For instance, if we ballpark the volume-doubling time for non-small cell lung cancer—what most of us see more commonly in about 350 to 400 days—then we have time for many of those patients. The growth is not so rapid. A lot of estimates that I've found for small cell lung cancer put that at closer to 40 or 50 days to double the size of someone's tumor.

So this pace of disease that is so typical for small cell lung cancer makes us worried, especially in the limited stage, that if there's too many delays in biopsies, coordination of care, and getting patients to their appointments, that perhaps after treatment, we find out we've missed the ball. This is now no longer limited stage, and now it's moved on to the extensive stage, which has prognostic implications.

Dr. Silvestri:
Thanks, Adam. And I would agree—we want to get them through the work-up quickly, we want to get everyone weighing in who's going to be part of their care—generally, medical oncology and radiotherapy—and we want to get their staging scans done rapidly.

Now, Dr. Alexander, if we zero in on treatment strategies, we know that immunotherapy plays a major role in managing other forms—particularly non-small cell lung cancer—but it isn't helpful for patients with limited stage small cell lung cancer. So do we know why some patients respond and others don't?

Dr Alexander:
Yeah. So let me start by going over the pivotal trial for the benefit of immunotherapy in limited stage small cell lung cancer, which was the ADRIATIC clinical trial that recently reported. So this was the first study that showed that maintenance immunotherapy with the PD-L1 antibody durvalumab following concurrent chemoradiation actually improved progression-free survival and overall survival.

So this was a phase III, randomized, double-blind placebo-controlled trial where 730 patients were randomized to durvalumab versus placebo after concurrent chemoradiation as long as the cancer was stable or improved after that concurrent chemoradiation. So the patients in the durvalumab arm experienced almost a two-year prolongation in overall survival compared to placebo. So this makes this the new standard of care, with the FDA approving it in December 2024 for all patients after completion of concurrent chemo-RT who had not shown disease progression, and it's part of our NCCN guidelines.

When you look at specific subgroups, there were benefits seen regardless of the stage, receiving prophylactic cranial irradiation, the chemotherapy regimen, frequency of the radiation, or the timing of starting the durvalumab. The greater benefit was actually seen in patients where durvalumab was started close to completion of concurrent chemoradiation. But patients were only included in the study if their cancer was stable or improved after concurrent chemoradiation and as long as they did not have any Grade 2 or higher toxicities.

So in the real world, it is unclear if adding immunotherapy for these patients who've had toxicities to concurrent chemoradiation or had

some progression after chemoradiation would be beneficial. Also, unlike in non-small cell lung cancer, where the PD-L1 expression helps guide us in who's more likely to benefit, we do not have these specific biomarkers in small cell lung cancer. So PD-L1 has not predicted benefit so far.

So we currently recommend durvalumab consolidation for all patients as long as their cancer is stable after completion of concurrent chemoradiation, and a lot of future research is exploring the timing of the immunotherapy, various combination strategies of immunotherapy, and the specific patient populations that are more likely to benefit than others.

Dr. Silvestri:
I just want to summarize one thing. So, for decades—and I've been at this for 30 years—in lung cancer, we had nothing other than chemoradiotherapy for limited stage small cell. What you're telling me now, though, is that immunotherapy is really a breakthrough for small cell—the first in generations, if you will—and that it does make a difference when it's added to chemoradiotherapy in the appropriate population?

Dr. Alexander:
Yes. And the key point to make here is it's actually improving survival. It's not just progression-free survival, but overall survival has improved with the addition of immunotherapy.

Dr. Silvestri:
And turning to you, Dr. Singh, we often hear that twice-daily radiation is more effective in this population, but what are the practical hurdles for both clinicians and patients?

Dr. Singh:
So, you're absolutely right, Gerard. And in 1999, the INTERGROUP trial was published, and it established twice-daily radiation as the then standard of care. Since then, several studies have attempted to displace twice-daily radiation, and none have been found to be superior to twice-daily.

Now, that doesn't mean that they're not necessarily equivalent. The studies just weren't designed that way. And if you look at the survival curves, they do overlap. So effectively, patients have the option of getting twice-daily 4,500 units of radiation in 150-unit twice-daily fractions, or 6,600 to 7,000 units of radiation in 200-centigrade daily fraction, so over six to seven weeks.

Now, the obvious benefit of the twice-daily is that you're done in three weeks. The disadvantage is that you have to come in twice for treatment separated by six hours. And I don't know about you, but it's often difficult to get my patients in once for treatment, so having them come in for treatment, leave, and come back six hours later is just unfathomable for many patients. It's also very difficult for the logistics of our treatment delivery because our machines are often set up to treat the patient only once, and the quality assurance that we do is set up to treat the patient only once. So things like the checks and the double checks we do to make sure that the treatment was delivered appropriately aren't really set up for twice-daily radiation in a lot of clinics. And so those are the multitude of factors that result in most patients and physicians opting for once-daily radiation, even though it is a longer course.

Dr. Silvestri:
And as a percentage in your practice, 75 percent get once-daily? 80 percent? 90 percent?

Dr. Singh:
I would say, honestly, 95 percent. It is offered to patients, but most patients just flat out refuse.

Dr. Silvestri:
For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, and I'm speaking with Drs. Adam Fox, Mariam Alexander and Anu Singh about how we can better manage limited stage small cell lung cancer.

It's back to you, Mariam. Let's continue discussing the available treatment options. There's ongoing debate about adding immunotherapy during the chemoradiation phase, but what are your concerns around this approach?

Dr. Alexander:
So we found that in the ADRIATIC clinical trial, the toxicities were quite manageable, and it was good to see no significant differences in the higher-grade toxicities between the immunotherapy durvalumab arm versus the placebo arm. Very slight increase in the pneumonia—radiation pneumonitis—with the durvalumab arm with about 38.2 percent versus 30.2 percent in the placebo. It is important to note that patients were excluded if they had Grade 2 or higher toxicities after concurrent chemo-RT, unlike some of the older trials, like the CONVOY trial, where patients were randomized before radiation was started.

So there are some other studies that have incorporated immunotherapy during the concurrent chemo-RT portion, like the NRG-LU005

study. So this study added the immune checkpoint inhibitor atezolizumab during the concurrent chemo-RT portion and then as maintenance, and they compared that to placebo. In this study, there was no improvement in overall survival when immunotherapy was added, and there was a much higher degree of pneumonitis in the immunotherapy arm compared to placebo, with two patients having Grade 5 pneumonitis.

So this indicates that giving immunotherapy with chemoradiation rather than after radiation is completed reduces the activity of immunotherapy for unclear reasons. Maybe due to some immunosuppressive effects. We don't know. But what we do know is we need to allow the immune system some time to recover after radiation to see the benefits of adding immunotherapy.

Dr. Silvestri:
Dr. Singh, as we consider the next steps for our patients, this would be after a complete response from chemoradiotherapy with or without immunotherapy. There's been long discussions for many years about prophylactic cranial irradiation—is that still a common option? How do you counsel patients on whether it's right for them?

Dr. Singh:
Yeah. So it is certainly a common option in that the discussion needs to be had with patients because we know that with small cell lung cancer, the brain is a substantial site of failure. And so it makes intuitive sense to use the prophylactic cranial irradiation. However, the data that support that approach really occurred at a time before we had routine use of very good imaging, and so the question becomes, is it the same population today as it was then?

And the answer is probably not because with today's MRIs, what you're saying is, you need to find a patient whose disease is too small to be seen by MRI yet present and able to be treated by the prophylactic cranial irradiation. And threading that needle is quite hard in the modern era. Also, we have alternatives for patients. So we have the alternative approach of imaging them frequently and then using stereotactic body radiation therapy to treat any metastases that do pop up, and that would have the theoretical benefit, at least, of avoiding irradiation of normal brain tissue. And that's something that we have an increasing appreciation of—that there are consequences to patients to having their normal brain irradiated—and they can be picked up in subtle and not so subtle ways, like questionnaires like the Hopkins Verbal Learning test. And so we know that there are real consequences. We have an appreciation for that, and it's a decision that the patient needs to be fully educated about, counseled on, and informed on how that institution usually approaches such patients.

Dr. Silvestri:
So I'm going to put you on the spot. Of your patients who have a complete response, with limited-stage small cell, to chemoradiotherapy, what proportion of yours go on to have a prophylactic cranial radiation?

Dr. Singh:
About 5 percent or less. You will have this conversation with people, and the odd person will say, “No, I definitely want everything done, and I'm really worried about it. If it's an option, I want to do it.” And in that case, if they're fully educated and understand the consequences, we will do it for them. But for everyone else, they see that our institutional approach is to do imaging with expectant management as necessary.

Dr. Silvestri:
And for our last question, I'm going to turn to you, Adam. What do you think the key takeaway is on how we can improve the therapeutic landscape for patients with limited stage small cell lung cancer? And there's a lot of nihilism around lung cancer. Can you tell us, particularly in limited stage small cell, whether we should be a bit more optimistic with our patient population?

Dr. Fox:
Well, let me try to address both of those things. So, in terms of the nihilism piece, especially in the limited stage, there is a chance for a cure and long-lasting survival in this stage. And with the aggressive nature of small cell lung cancer and potential for rapid progression, that's what gives everyone this clinical sense of urgency. I think that is certainly somewhat old news. I think most of our audience knows that small cell is a bad actor, and it’s fast. I hope they can appreciate that some patients do quite well with therapy. It's not the majority, but it is a significant proportion to consider if you were going through this process. And in terms of the way things are changing, hopefully this is the first of many advances in this area. That's one of the take-home points—this is really the first breakthrough in treatment that's affecting survival for small cell lung cancer in decades. That's definitely one of them.

I think many pulmonologists I've been speaking to—some of our pulmonary fellows at our institution—they were totally blown away that immunotherapy was being used in this disease. So they're learners, and they need to be. But the other perspective is many pulmonologists don't work in a multidisciplinary thoracic oncology clinic for their primary practice, and so many of our listeners may be surprised to learn that this is being more routinely used in small cell lung cancer.

And finally, the fact that small cell lung cancer is rare but common enough that most pulmonologists will continue to see this in their practice really highlights the need for expedient, and much like this panel, a multidisciplinary approach to align all of these potential things as quickly as possible.

Dr. Silvestri:
As those forward-looking insights bring us to the end of today's program, I want to thank Drs. Adam Fox, Mariam Alexander and Anu Singh for joining me to share their approach to managing small cell lung cancer. Dr. Fox, Dr. Alexander and Dr. Singh, it was great having you today.

Dr. Fox:
Thank you so much for having me.

Dr. Alexander:
Thanks for having me. It was a good discussion.

Dr. Singh:
Great to be here. Thank you.

Announcer:
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