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Emerging Technologies for Treating Non-Small Cell Lung Cancer

Announcer:
Welcome to *Closing the Gaps in Non-Small Cell Lung Cancer* on ReachMD, sponsored by Lilly.

Dr. Nacinovich:
Non-small cell lung cancer accounts for 84% of all lung cancer diagnoses, making it the most common type of lung cancer, but there is hope on the horizon as emerging technologies aim to address this very real threat in our patients. What those technologies are and how they have the potential to change our treatment approach will be the focus of today's discussion.

Welcome to Closing the Gaps in Non-small Cell Lung Cancer on ReachMD. I'm Mario Nacinovich, and joining me here is Dr. Gregory Kubicek, Associate Professor of Radiation Oncology at Rowan University and staff radiation oncologist at the MD Anderson Cooper Cancer Center.

Dr. Kubicek, welcome to the program.

Dr. Kubicek:
Thank you. I'm very honored to be here. Oncology has been a challenging but very rewarding career choice for me.

Dr. Nacinovich:
So, Dr. Kubicek, to start us off, can you give us a brief overview of the current directions and outlook for radiation oncology as a whole? just because this field has always been among the first to adopt new technologies for cancer care.

Dr. Kubicek:
Yes, absolutely. So, while we have a lot of work to do, there have been continued improvements in our ability to treat lung cancer. As you know, most of the excitement has come from the medical oncology side with immunotherapy, targeted therapy, liquid biopsy, but there have been some great innovations and advances in radiation oncology. Basically, the better computer technology gets, the better our ability to deliver precise radiation. This has led to radiosurgery, which entails high dose of radiation given with millimeter degree of precision. As opposed to conventional radiation, the doses in radiosurgery are so high that the cancer cell repair mechanisms are overwhelmed, and this results in more efficient cancer cell kill. While radiosurgery has been around for a while, the machines today are faster and precise. And again, this has allowed us to use radiosurgery in new and exciting ways in the treatment of lung cancer, including the results of using radiosurgery for locally advanced stage III lung cancer.

Another innovation that we'll talk about is called the MRI-LINAC. This is an MRI scanner built into a linear accelerator, and a linear accelerator is a machine that delivers the radiation, so using the MRI capabilities alongside the radiation delivery is another way to further improve our ability to deliver radiation in some really fascinating ways.

Dr. Nacinovich:
For patients who have just been diagnosed with non-small cell lung cancer, what factors do you take into consideration when making treatment decisions, especially when chemotherapy isn't the best treatment for some patients?

Dr. Kubicek:
Therapies are becoming much more individualized. While stage is still important, there are now more and more nuances in deciding the best treatment. For early-stage disease, the big decision is whether or not the patient is a surgical candidate. For patients in whom surgery is too risky, radiosurgery is a great option. As I mentioned, radiosurgery uses high-dose, pinpoint radiation. This allows us to treat early-stage lung cancer with minimal toxicity and high control rates all in less than a week of treatment. While radiosurgery has

been around for a while, the technology has steadily improved, and this has allowed us to use radiosurgery in an increasing number of settings. For example, the initial data for early-stage lung cancer found that radiosurgery was good for small and peripheral lung lesions. Myself and others have published on radiosurgery for early-stage but larger tumors. For example, I treated one patient with a lung cancer that was over 12 centimeters. Our results collaborated by others showed that as long as normal tissue constraints are met, the size is no longer a limit to the use of radiosurgery. This allows us to use the benefits of radiosurgery on a wider population of early-stage disease.

On the other side of the stage spectrum, for metastatic disease the paradigms are also changing. While we used to view all stage IV as the same as incurable disease, the field of oncology has begun to recognize that a subset of patients has limited metastatic burden and can enjoy long-term, disease-free survival. These patients are referred to as oligometastatic. And we now have 2 randomized phase II studies in lung cancer showing a survival improvement to aggressive local therapy for these patients.

MD Anderson in Houston published a randomized phase II study looking at stage IV lung cancer patients with 3 or fewer sites of metastatic disease who did not have progression after 3 months of initial systemic therapy. The patients were randomized to either maintenance therapy or local therapy to all areas of active disease, and the local therapy could include either surgery, radiation or a combination, although the vast majority of patients happened to have radiation. The study closed on the interim analysis on a massive benefit to local therapy. The median survival in patients in the maintenance arm was 17 months as compared to 41 months in patients getting aggressive local therapy. These results are pretty amazing that the median survival for stage IV traditionally incurable disease treated with local aggressive therapy is almost 3½ years. What this means is that not all stage IV is the same and that some patients appear to benefit from aggressive local therapy potentially with curative intent. The oncology community is in the process of replicating the results and a larger randomized phase III study, and we are actively participating in 1 study at MD Anderson at Cooper.

Dr. Nacinovich:
And since you started practicing radiation oncology, what type of advances have you seen in the treatment of non-small cell lung cancer?

Dr. Kubicek:
We've seen steady improvements both in cancer outcome and also in preserving quality of life. The outcome for locally advanced disease as well as metastatic disease has continued to improve. This is the result of a number of parallel evolving processes involving both better systemic therapy, such as immunotherapy, but also better local therapy, such as radiosurgery. Part of the better therapy but equally important is in deciding which patients to use which therapies for.

Dr. Nacinovich:
For those just joining us, this is Closing the Gaps in Non-small Cell Lung Cancer on ReachMD. I'm Mario Nacinovich, and today I'm speaking with Dr. Gregory Kubicek about new and emerging approaches for treating non-small cell lung cancer.

So, Dr. Kubicek, let's continue to look at these advances from your vantage point as a radiation oncologist. A big focus in your field and also a perpetual challenge is finding ways to deliver radiotherapy as safely and as localized as possible. So, can you tell us what the latest efforts have been to help advance those aims?

Dr. Kubicek:
Yes, happy to. It's amazing how technology continuously evolves, which in turn improves our ability to use radiation with greater accuracy and precision. The same advances that have allowed cell phones to evolve from flip phones to the iPhone 10 have done wonders for the delivery of therapeutic radiation. We can safely deliver higher doses of radiation in ever shorter periods of time. This allows us for better tumor control but also makes it easier for patients since they don't have the same time commitment for treatment. At ASCO 2020, we're presenting our data on radiosurgery for locally advanced disease.

Now, while radiosurgery has been used successfully in early-stage disease, we expanded this concept to include stage III disease, so this is part of a clinical study where we ask the question of whether a modified radiosurgery approach using high-dose precision radiation over 3 to 5 treatments delivered in between full-dose chemotherapy cycles could improve outcomes for unresectable stage II and stage III non-small cell lung cancer. The current standard of care for these patients is 6 weeks of daily treatment along with lower doses of chemo because when chemotherapy and radiation are given on the same day, it's too toxic to give full-dose chemotherapy, but because radiosurgery is completed so quickly, we can complete the entire radiosurgery course in between the 3-week cycles.

Our thoughts were that full-dose chemotherapy could reduce the metastatic disease burden and that radiosurgery would improve local control, and I have to say we're very happy with our results. We found a median survival of over 27 months, which is the same outcome as recent cooperative group studies found for the same patient population, but they used the traditional 6 weeks of daily treatment. We found that our local and regional failure rate as well as toxicity rates were better than historical norms. Furthermore, we collected quality

of life scores on our patients, and at 1 year the quality of life was unchanged compared to baseline. What this means is that patients who had previously been treated with 6 weeks of radiation and low-dose chemo can potentially be treated with just 1 week of radiation and with high doses of chemotherapy all while maintaining good quality of life without compromising on cancer outcome.

Another advantage of this method is that it would allow treatment for patients with curable disease but who are either elderly or frail and may not be able to tolerate a full 6 weeks of treatment. The prospect that they can be treated in 1 week could allow patients who would outside decline treatment to get the equal survival benefit of treatment but in a much shorter time span. For example, one of the patients in our study was 91 years of old… One of the patients in our study was 91 years old, and as you would imagine, logistics were a problem. It would have been very difficult for him to get back and forth for 6 weeks of treatment, not to mention the increased toxicity with the 6-week treatment approach. On the clinical protocol, he completed the radiation in just 1 week. He had a great disease response with treatment and had no side effects from the radiation. Now, our results do need to be replicated by other institutions or perhaps a cooperative group study, but we're very excited with the results of this phase II study.

Dr. Nacinovich:
How do you see the emergence of personalized medicine penetrating our therapeutic approaches to non-small cell lung cancer both from your specialty standpoint and the oncology field in general?

Dr. Kubicek:
Yes, this is an excellent question because we want to find patients who are most likely to benefit from any given therapy. For example, the typical response rate for second-line chemotherapy is around 10%. What that means is that only 1 in 10 patients will benefit from this therapy, but right now we have no way of knowing who the 1 is and who the 9 are, so we have no choice but to give the same chemotherapy to everyone.

A better approach, of course, is to find some biomarker to predict which patient will respond to which therapy, and we have this for targeted therapies. For example, we know that only patients with EGFR mutation will respond to an EGFR-targeted therapy, but we need to find better ways of finding more biomarkers. For example, a recent study found that KRAS mutations may predict for better response to radiosurgery. Now, this is fascinating because KRAS mutations will never have an actual mutation such as EGFR, ROS, etc., and so the possibility that they can respond well to radiosurgery is very intriguing. So one thought based on this is to use radiosurgery to all sites of metastatic disease in KRAS mutant patients since they don't have an actual mutation amenable to targeted therapy. By treating all these disease sites with radiosurgery, we could delay the use of cytologic chemotherapy for a year or so, maintain the patients with a good quality of life while controlling disease in a very excellent fashion. This is still very experimental and thought-provoking but may be the future of how we stratify some of these patients. And like I said, we still need more and better biomarkers. We discuss oligometastatic disease. This is a patient population that would be great to have some better predictive tools for. An ideal biomarker would predict which patients with limited metastatic disease can benefit from aggressive local therapy versus patients that will not benefit. And people are looking at circulating tumor cells as well as machine-learning analysis of diagnostic studies such as CT or PET scans. While there's not been any validated marker so far, we are certainly continuing to search for them.

On a more simple and big picture, we published results of looking at gait pace in predicting outcome. What we did was, on 3 separate phase II studies, all of which enrolled patients with locally advanced disease, we collected how long it took the patients to walk 6 meters. This is very simple, cheap and very reproducible. The beauty of it is that all it takes is a stopwatch. What we found was that this gait pace could predict for overall survival, that patients who took longer to walk 6 meters had worse survival. We feel that this could allow us to better stratify patients into who may benefit from some sort of aggressive therapy, such as radiation, chemotherapy, etc., versus patients that may be better served with either less aggressive therapy or perhaps best supportive care alone. While we do not want to withhold aggressive therapy to those who could benefit, we also do not want to impact quality of life in patients unlikely to benefit. Some combination of biomarkers, gait pace, etc., may allow us to pick the best type and level of therapy for every individual patient.

Dr. Nacinovich:
Finally, Dr. Kubicek, looking out months or even years down the road, what are some potential innovations being investigated for lung cancer that you're excited about?

Dr. Kubicek:
One breakthrough that I'm very excited to have is called MRI-LINAC, or magnetic resonance image-guided linear accelerator. This uses MRI technology together with radiotherapy to treat cancers anywhere in the body. The radiation delivery on an MRI-LINAC is fully integrated with the MRI. What this means is that the system can deliver therapeutic radiation beams and at the exact same time monitor the target with the anatomical precision of an MRI scan. The unique combination of technologies will allow us greater control over the delivery of radiation because we'll be able to see with great detail both the cancer and the normal tissue so we can use this information

to finetune the radiation treatment plan and personalize and adapt each treatment in unprecedented ways.

I'm very excited to use this technology in combination with our previous results on radiosurgery for locally advanced disease. The MRI ability to differentiate cancer from normal tissue and the ability to make adjustments in realtime can allow us to use high-dose precision radiosurgery for patients with advanced stage III disease. I'd like to imagine a world where no patient has to spend more than a week receiving radiation but at the same time has high rates of cancer control with minimal toxicity.

Dr. Nacinovich:
Well, I'm looking forward to catching up with you again when these advances within the field start to become the new norms for practice, but in the meantime I want to thank you for walking us through these new directions and opportunities in the non-small cell lung cancer treatment landscape. Dr. Kubicek, it was great having you on the program.

Dr. Kubicek:
Thank you again. I am very passionate about this and love talking about it.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes in this series, visit ReachMD.com/NSCLC, where you can Be Part of the Knowledge. Thanks for listening.