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**SPEAKER 1:** Thank you for joining us today for the Solomon Berson Award in Lectureship, given to the physician, scientist, or research who demonstrates excellence in their field. Dr. Solomon Berson, along with his friend and colleague, Dr. Yalow, developed many groundbreaking antigen assays for different disease processes and peptide hormones. Their work included developing assays for Type 2 diabetes, parathyroid hormone, ACTH, and growth hormones. Their contributions were later adapted as the base measure for hundreds of additional protocols.

Despite their incredible success, neither scientist patented these processes nor profited commercially from their discoveries. The work in the development of radioimmunoassays as well has been credited as being the precursor to modern nuclear medicine.

Doctor Berson later served as the chair for the Department of Medicine here at Mount Sinai prior to his passing away in 1972. In 1977, Dr. Yalow received the Nobel Prize for their work on the development of these radioimmunoassays. At her request, their laboratory that they shared was designated the Solomon Berson Research Library in order to memorialize their contributions to modern medicine.

It gives us great pleasure to present this award to Dr. Juan Wisnivesky, whose accomplishments as a physician scientist truly exemplifies the qualities that Dr. Berson had demonstrated in his career. Dr. Wisnivesky completed his residency in internal medicine at Montefiore and his fellowship in pulmonary at New York Presbyterian Hospital, Cornell University.

Dr. Wisnivesky did additional training and an additional doctorate at Columbia University. As a physician scientist he has published several manuscripts using population-based center registries to address screening, diagnosis, treatment disparities in care and outcomes in patients with lung cancer. In his previous role as vice chair for research for the Department of Medicine, Dr. Wisnivesky developed a comprehensive and highly regarded mentoring program for junior research faculty. Dr. Wisnivesky continues to be active as a physician scientist and mentor and currently serves as chief of the Division of General Internal Medicine here at Mount Sinai.

Please join me in congratulating this year's recipient of the Solomon Berson Award, Dr. Juan Wisnivesky.

[APPLAUSE]

**SPEAKER 2:** Beautiful. Look this way.

**DR. JUAN WISNIVESKY:** Well, thank you very much. I'm really honored speaking in a lecture honoring such a prestige physician scientist. And I want to thank Barbara and David and the [INAUDIBLE] for inviting me to give this presentation.

So I'm going to talk about lung cancer screening, what is the evidence supporting this new technique, and also what other type of information that we still need to translate all these research findings into improved patient outcomes. So these are my conflicts of interest.

I'm going to talk first a bit about the evidence supporting screening; and then what are the factors that may influence current adoption of screening at the national level; then talk about what are the issues that we need to really be aware when we are implementing screening to ensure that there's equitable access and benefits from it; and finally, talk a bit about lung cancer treatment, given that treatment is the ultimate stage so for that patients can benefit from screening.

So why screening is important? Lung cancer, as you probably know, is the second most common cancer in the United States, and the most common cause of cancer mortality, accounting for approximately quarter of all cancer death. And also as you probably know, the main risk factor for lung cancer is smoking, here showing rates of tobacco consumption in the population and lagging 10 to 15 years later incidence in mortality of lung cancer both in men and women.

But you are a hardcore scientist as Dr. Berson, and you want hard evidence for the association, here you clearly have the lung cancer and the cigarettes in the same picture.

[LAUGHTER]

So everybody knows about the NLST and that medication of the results for lung cancer screening. But actually, this work started many years earlier with the seminal work of Dr. [INAUDIBLE], which is sitting here and works at Mount Sinai and was my first mentor, who published a result and observational study of lung cancer screening, a cohort of 1,000 smokers, and showed not only that smoking is feasible, but that 85% of lung cancers diagnosed with screening are early stage compared in stark contrast what more than half of the cases that are advanced stage in the clinical practice.

10 year later as the NLST was published, this was a large randomized controlled trial of over 53,000 patients and smokers, 55 to 74 years with 35 years of smoking. And the participants underwent three rounds of low dose CT versus chest X-ray.

As you can see, oh. Sorry. Lung cancer incidence was higher in the CT arm compared to the chest X-ray arm. But more importantly, lung cancer mortality was significantly lower among those who underwent low does Ct. This translated approximately 20% reduction in lung cancer mortality and a 7% reduction in all cause mortality with the number needed to screen to avoid one lung cancer death being 308.

So the results of the NLST are important and highly internally valid. But they may not be generalizable to some special populations. So in our group we're interested in understanding and studying how lung cancer screening may apply to these groups. One of these groups are patients with HIV.

Patients with HIV have a higher risk of lung cancer both from increased rates of smoking, but also because of HIV itself. But also, this data showing that they may have also cancers may have higher aggressiveness, which are two factors that may suggest screening would be more beneficial.

Conversely, there was concerns that lung cancer may find more false positives in patients with HIV given the prior history of lung disease, as well as clearly, patients with HIV have lower life expectancy from competing causes of death, and that may add in with the benefit to screen.

So in order to solve these issues we conducted research using sophisticated simulation model, which is lung cancer policy model. And in using this data, we first-- in collaboration with a group [INAUDIBLE] first showed that more clearly replicated them in [INAUDIBLE] results with approximate 20% reduction in lung cancer mortality, and that eight patients with HIV with well controlled disease could also benefit in a similar fashion, with approximately 10% mortality reduction.

Moreover, we also evaluated different screening regimens because HIV patients get lung cancer and lower smoking exposure at a younger age. And while the current recommendations were beneficial, we show that screening regimens that are started at an earlier age could translate into a higher overall improvement in survival.

Another group that may also potentially benefit from screening is patients with COPD. Also, patients with COPD are different from NLST. First, they have increased risk of lung cancer, which has been quite shown in the literature, but also may have higher risk or harms from screening, including more complications from diagnostic workup, increased perioperative mortality, and also decreased life expectancy from COPD.

So [INAUDIBLE], which is a faculty at our division as part of [INAUDIBLE], she developed another simulation model to look at screening in patients with COPD. And she found that compared to patients in NLST, lung cancer screening could also lead to significant reductions in lung cancer mortality of around 20% to 30%. So even potentially higher than in the general population.

After the results of NLST there has been a lot of interest in optimizing eligibility criteria so that the best patients can be selected for screening and get the maximum benefit. One strategy that's been commonly used is trying to use prediction models to assess individual patients' rates of lung cancer and select candidates based on these criteria.

In this study published in the *New England Journal of Medicine,* investigators did exactly that with NLST participants. And they classify the estimated each person's risk of lung cancer and then divided patients in five quintiles from those with the highest risk to those with the lowest risk. And what they show is that if you screen the three higher risk quintiles, you can prevent almost 90% of the deaths that you will prevent with screening, with the other two only accounted for around 10%.

Similarly, that's reflected in the number underneath the screen that it goes from only 160 to prevent one dead among those at the higher risk to 300 in the higher cohort, suggesting that potentially you can reduce the number of screening the population with still achieving a lot of the benefit.

We were also interested in assessing what other information the first CT could tell you about the future risk of lung cancer and how that can be used to optimize additional rounds of screening. So in this study we also used NLST data. And we focused on the patients who underwent CT, and furthermore, on those who have two negative CTs, which do require further rounds of screening.

So we used the same models I described before to estimate patients' risk of lung cancer, and then stratified the sample into quartiles based on lung cancer increase to assess the additional contribution of [INAUDIBLE].

What we show is that for example, here in the dashed red is the cumulative number of cancers in NLST among patients who had a higher risk of lung cancer and did not have emphysema. And this was significantly lower than the same group with emphysema. And this was true across the four quartiles, again suggesting that the absence of emphysema could be a criteria to determine further screening.

And this is reflected in the number needed to screen to detect one lung cancer. While for the whole cohort was 166 CTs to detect lung cancer. And this went up after two negative CTs to 227, there was a huge difference among patients with or without emphysema. Those without emphysema, you needed to screen 367 patients to detect one lung cancer. And this dropped to only 86 among those with emphysema. Again, this information could be used to target and optimize further rounds of screening among those who have negative baseline CTs.

Another interesting finding on baseline CT is the presence or absence of interstitial lung disease. It is well known that several interstitial lung diseases, such as asbestosis or IPF, are associated with increased risk of lung cancer. However, less is known about what is called interstitial lung abnormalities. Milder findings are more in asymptomatic patients.

So Stacy Brown, which was a former fellow now starting as a faculty pulmonary, used also NLST data. And she looked at baseline CTs and compared those who had versus did not have interstitial abnormalities, and showed that the cumulative risk of cancer was significantly higher among those with ILS.

Moreover, in adjusting analysis she showed that the risk of lung cancer was approximately 50% to 60% higher among those who have ILS and baseline CT, suggesting that this may be a new independent risk factor for lung cancer, which also can help further optimize in additional rounds of screening.

So the evidence is pretty strong. How are we doing in terms of adoption of these new potentially lifesaving strategies? Well, unfortunately not that great. This is a population they studied from the National Health Interview Survey, which weighted sample of approximately 70 million US patients from the population. And it showed that only between 4% and 5% of high-risk smokers are currently screened for lung cancer.

Even more worrisome, approximately 1% to 2% of never smokers which never been screened are receiving screening. So that's pretty dismal.

So what other factors? What potential issues may be a barrier to adopting screening? Well, one is concern of all false positives. As shown in these slides and across many studies, approximately 20% to 30% of baseline CT will find non-calcified nodules.

And most of these patients do not have cancer. So this generates a long list of tests that could be done to work out these patients. While most of these patients can be workup noninvasively or with imaging. And also, data consistently showed that very few need unnecessary biopsies or resection. This is a concern for both patients and physicians.

And not only that, remember, primary carers are ordering these tests, and then have to deal with the results. And as you see, the guidelines for working these nodules are not light. And you learn the NCCA guidelines, and then maybe you need the [INAUDIBLE]. And if not the inflationary criteria and maybe the [INAUDIBLE] criteria.

There's a lot of agreement. But can you see how primary care doctors can be a bit overwhelmed by these guidelines? And I just want to clarify that many screening programs, such as the one here, will do this work for you and handle the management of these nodules. However, remember also that most of the United States is providing community in the community and not in advanced tertiary care centers. So this could be a significant barrier.

So machine learning may help in this issue. And there's been a lot of research to try to use artificial intelligence to try to further stratify these lesions and automatically identify those who need additional tests. In this study recently published in *Nature,* investigators used deep learning, which is a type of machine learning approach, to try to differentiate between solid, semi-solid, part solid, and calcified screen-detected nodules.

And the investigators showed that the computer-based algorithm had pretty good agreement, and it was almost as good as expert radiologists, suggesting that maybe these automatic approaches in the future may help managing these nodules. Or maybe not.

[LAUGHTER]

So an alternative approach is to use biomarkers to try to further identify patients who need nodules that need further workup. And this research, which is a collaboration between Charles Powell, here also at Mount Sinai, and a group in China. They used a mixture of clinical factors and blood biomarkers to try to identify which nodules may be malignant and need further workup.

And they show in the duration cohort that these combination of biomarkers have a high accuracy-- approximately 92% accuracy-- in identifying nodules that were malignant. And that was better than the current chest guidance to identify malignant nodules. However, and unfortunately something that commonly happens in studies in the validation setting, these results were not as strong.

Another concern about lung cancer screening is overdiagnosis. And by that we mean screen-detected cancers that are considered malignant but that either never progress or they are so slowly that will never be clinically detected or cause a patient death. And this is considered potential harm in screening because these patients will undergo resection but really do not benefit from that treatment.

However, the extent of overdiagnosis is unclear. So it's interesting that you can learn about overdiagnosis from actually untreated lung cancer patients. Because if you think about it, if you simulate here as we do here a group of untreated patients with lung cancer, and you look at lung cancer specific survival, basically you take away [INAUDIBLE] from other diseases. Then if a group of these patients is [INAUDIBLE], meaning that after a certain point these untreated lung cancer patients do not die from disease progression, this is culturally the definition of overdiagnosis-- cases that are untreated but are not progressing.

So you can use the point where the curve plateau as an estimate of overdiagnosis. So in a study with [INAUDIBLE] and Keith, also from the division, we look at SEER Medicare at large national registry, and a study over 2,000 patients with untreated stage 1 lung cancer. And we show that both among men and women, overdiagnosis was common around only 2%. However, that changed significantly with size, where for smaller tumors, less than 15 millimeters, abruptly 10% of the cases could be overdiagnosed. And for tumors that are larger, over 4.5 centimeters, rates of overdiagnosis were 0.

Radiation is another issue related to screening. Again, you're gonna put patients-- smoker-- through at least three, but maybe 10 to 20 years of screening. And here it shows the exposure of [INAUDIBLE], which is approximate equivalent to 14 chest x-rays or three mammograms. And then half of a third of the [INAUDIBLE] exposure in the US.

However, in the data from a large screen cohort from Italy showed that the attributed number of cancer cases to radiation exposures even after 10 years of screening is pretty low-- less than 0.05%, suggesting that this is not a major concern.

What about the primary care providers? As I said, primary care doctors are the one implementing and requesting the screening. So Dr. Lin, which is also a faculty here, conducted this study at Sinai, where she asked primary care doctors about their attitudes and beliefs about screening.

As you can see here, most providers-- almost 99% of them felt familiar with guidelines for breast, colorectal, or cervical cancer screening. However, only half of the providers were knowledgeable of lung cancer screening guidelines.

Moreover, several providers have attitudes that were less favorable lung cancer screening. There were only 14% feeling that they have sufficient time to counsel their patients about screening, or 90% of them feeling worry about false positives in the workup of those.

And this is important because there is an additional burden to primary care doctors, which is that current CMS recommendations mandate that before screening is ordered, providers or some other nurse as part of a screening program that's a shared decision-making session using an official decision aid. And while obviously shared decision-making, it is something that is beneficial for both smokers in terms of making the decisions, this adds additional time and burden for screening, and is not required for any other screening test.

To further complicate things, this shows you a list of Medicare-mandated core measures for primary care doctor. This is what Medicare tells our primary care doctors they should do for their patients, and are held accountable for. As you can see, several cancer screening strategies are mandated. However, lung cancer screening is missing from this. Therefore, primary care doctors are not held accountable for how much screening for lung cancer they do.

So those are some of the barriers. But how do we implement screening-- adopt screening-- so that everybody equally benefit from them? Well, unfortunately, the burden of lung cancer in the United States affects more significantly minorities, particularly blacks. And while the NLST was a large study and highly generalizable, the number of African-Americans and Hispanic patients are underrepresented compared to the general population, which is a common theme in many studies.

And this is important because there is data that show that blacks are maybe more susceptible to the effects of smoking than other populations, particularly whites. In this large study from California it shows higher incidence from both men and women which were black. And while this is self-reported [INAUDIBLE] and a social construct and may not reflect actually true biological differences, could be related to smoking patterns, the type of cigarette smoke, this is still important because current guidelines for screening do not take into account the susceptibility by race, and may leave many black patients with a higher risk of lung cancer non-eligible for screening.

Moreover, it should be noted that Medicaid does not cover screening. And because many minorities are in low socioeconomic status, they do not have good access to screening test.

Additionally, we conducted a study several years ago showing that there are differences in the beliefs about screening and lung cancer among different racial ethnic groups. And black and Hispanic patients have a different perceptions about the risk of lung cancer, fatalism, attitudes toward cancer, as well as increased worries about the potential side effects of screening. Obviously, all of these need to be taken into consideration in discussion about lung cancer screening with minority patients.

Finally, as I mentioned before, and I will discuss in the second half of the lecture, for screening to be beneficial there should be optimal [INAUDIBLE]. And this is data which has been clearly shown in many studies that black patients in the United States with early stage lung cancer have worse outcomes. And this is explained by lower rates of resection. So another barrier for minorities to benefit from screening.

So this is a lot of evidence that things may be different for minorities in terms of screening. I think we may want to implement screening a different way. The typical approach for new interventions for screening tests is that we roll them out, and then 10, 15 years later we look and study where disparities [INAUDIBLE] with findings.

So I think maybe with lung cancer screening we need to reverse things and really consider all these issues that I mentioned, and include it in the option of screening so that when the screening is rolled out, minorities really have [INAUDIBLE] rates and been equally benefit from these potentially life-saving tests.

So what about treatment? How we can make sure that early diagnosis, which is the main [INAUDIBLE] shift introduced with screening translate into improved survival?

Well, unfortunately, there's a lot of gaps in terms of the knowledge we have about the optimal treatment of early stage lung cancer. First, prior to screening, less than 20% of lung cancers were early stage. Therefore, this was not a major focus of research.

Second, lung cancer screening, as I said, detect smaller cases and some that may have less aggressiveness. So the approaches that were used for clinically detecting cancers may not fully apply to this population. So therefore, all these factors create gaps in knowledge.

So what is a standard management of early stage lung cancer? Well, surgery is the preferred approach, mostly lobectomy, but there is data suggesting that I want to share with you that limited resection may have a role for some patients.

Patients with first stage 1 are followed with observation. However, patients with stage 1 disease which have positive pulmonary or [INAUDIBLE] nodes are recommended adjuvant chemotherapy.

Approximately 20% of patients with early stage lung cancer are either unresectable or have preference against resections. And those usually treated with SBRT, and for tumors more than 5 centimeters, they usually receive standard radiation.

So what is the evidence in supporting these treatments? Well, this is it. There's been very few randomized controlled trials.

There are some. All trials that I shared with you are surgery from my team, but conducted over 50 years ago. And then a single trial in the mid-80s compared limited resection with full resection for lung cancer. The rest of the therapies are completely unstudied.

And this is a stark contrast with other oncological procedures, particularly chemotherapy. As you probably know, immunotherapy has been recently adopted for advanced stage lung cancer. And this is a number of studies that have been recently completed in evaluating the potential effectiveness of immunotherapy. And the list probably is incomplete and growing. And this is a list of ongoing studies. Clearly, a huge difference compared with interventions for lung cancers that are rapidly adopted without much evidence.

So as I say, surgery is considered the standard of care. Nobody-- if you go to a tumor ward, nobody will doubt that the patient with early stage lung cancer should be resected. However, if you look at the evidence supporting a surgery, it's less clear. This, as I said, were studies conducted many, many years ago comparing surgery to radiation therapy-- types of radiation therapy that have been long abandoned and that were very, very simple.

And as you can see, the risk of death following radiation therapy was higher compared to surgery. However, all the confidence intervals include 1, suggesting that surgery was not better than these really simple now considered useless forms of radiation. So maybe we're going to institute new surgery.

Well, let's take you to this very interesting study that was published in the *BMJ* a few years ago looking at the evidence for using parachutes to prevent death when you jump from an airplane. And actually, investigators really-- and this is a true paper, it was published, it's very funny-- really did a systematic review and could find no randomized trials. And then they concluded that maybe the basis for the effectiveness of using parachutes is actually due to a healthy core effect. Maybe these patients also smoke less, have a better diet and exercise. No?

And it's all bias. You know? Well, this is kind of a very nicely written paper, but kind of goes to the point that unfortunately, medicine does many things that we cannot base our practice on randomized trials. And what randomized trials provide the best level of evidence, many times we need to make decisions based on other types of data.

So how do we use these data for early stage lung cancer? Well, first, as I mentioned before, there are different types of surgeries you can do. The standard of care is lobectomy, which is the resection of a full lung. However, alternative approaches include segmentectomy, which is the resection of anatomical segment, or wedge resection, which is reception of the tumor with the smallest leave of parenchima around it.

Lobectomy is a preferred approach. However, this is based on a single RCT more than 30 years old now, and that provided actually mixed results with not really clear advantage of full resection. As I say, this may be too much of a resection for small, screen-detected tumors that may be less aggressive.

So we were interested in addressing this issue with observation and data given the lack of randomized trials. And in this study we use SEER, which is a large national cancer registry, to evaluate patients with stage 1 lung cancer less than 2 centimeters-- the typical size of screen-detected cancers. And we compared those who underwent limited resection with those who underwent lobectomy.

The challenge with this-- oh. Sorry. SEER, as I say, which uses registry linked to Medicare claims, is a national registry that includes all new cases of cancer in several states and with metropolitan area and represents approximately a quarter of the US population.

So the problem is that when you do these types of conversation study, is they have bias. The patients that receive one treatment may or may not be comparable to the others. So bias, bias, bias-- I hope you get the point, didn't fit anymore on this slide-- is a huge issue.

So how can you address this issue? Well, before that, I think the best example of bias-- this type of selection bias-- comes actually from history. And this is a true story. During World War II, the British would send planes to Germany. And up to a third of the planes were not returned. And there was a huge problem particularly because they were losing a lot of the pilots.

So the RFA conducted a survey of the planes returning to try to identify where were the areas that received more bullets in order to apply reinforcement breaks in those areas to have less planes shot down. And then they did a map like this. And I copied this from from Wikipedia. It is the best source of knowledge, even better than the *New England Journal.* And you know, have something like that.

So if you were doing this survey, would you put plates in part A, part B, or part C? Who say Part A? Raise your hand. One person there. Few? More? More? OK. Sorry. Whoops.

What about B? C? A Lot. Why C? Anybody.

**AUDIENCE:** [INAUDIBLE]

**DR. JUAN WISNIVESKY:** Yeah. These are the planes-- they were sampling the planes that came back. Those areas that received no bullets-- in again, all those planes were still back in Germany because they weren't shut down. OK?

And here, clearly, the usual selection bias completely turn your data around. And if you include that, you'd make the wrong association. Actually, the RFA wanted to put the plates in the areas that received more bullets. And there was a very sophisticated mathematical unit that had a major role in the war that told them, no, no, no. Guys, you are thinking this all wrong.

And then they actually put the plates on the areas that had less bullets. And it did significantly drop the number of planes that were dropped in Germany. But this tells you the power of selection bias. And if you don't properly consider it, your results can be completely biased.

So let me just get a small technical explanation here. But you can really skip the next slide without loss of continuity. So this is time to use your sleeping tie if you were smart enough to get one and deploy it.

So how do we try to address selection bias with observation and data? Well, a randomized controlled trial is easy. You have a group of patients with stage 1 lung cancer. And they are randomized with equal chance to get lobectomy with limited resection. And then obviously, the two populations are well balanced. And then you can compare us in terms of survival.

In an observation study you start backwards. You have patients, some got lobectomy, and some got limited resection. So what you need to do is first build a statistical model that predicts type of risk of surgery, for example, lobectomy. From the data based on patient characteristics at the time of presentations-- age, comorbidity, et cetera, et cetera.

Then you take your population, and using this model for each patient in your groups, you estimate the specific patient probability of getting lumpectomy. If you're lucky and you have enough large sample, you have something like this where among patients treated with lobectomy, you have a group of maybe younger, healthy individuals that have a higher probability of getting lumpectomy, but also some patients are maybe older, have more comorbidities, poor function of [INAUDIBLE], but still got more aggressive surgery. And the same thing for limited resection.

So what you can do then is sample from each group 2 patients with the same probability of resection based on the characteristics at the time of treatment. And then you keep doing that until you have two groups that are well-balanced. And therefore, you can do meaningful comparisons of survival.

So this is what we did with these 2,000 patients in SEER. And what we found is that when you look at the risk of overall mortality, patients with limited resection have approximately 10% increase in overall mortality. But that was not statistically significant, suggesting that the two treatments may be equivalent in this population.

However, when you look at bigger tumors, when you go up to three centimeters, limited resection did worse than lobectomy, suggesting that a more aggressive approach is needed.

As I mentioned before, another evolving treatment for early stage lung cancer SBRT. And this is you know I decided I would use for brain tumors which provides a lot of radiation focus to a small size where the tumor is, therefore, potentially eradicating the disease.

And this was first introduced approximately 10 years ago with this publication of these two phase II study with treated unresected early stage cancer patients with SBRT and showed rates of survival that was considerably higher than those of observed in historical controls with standard radiation.

And these follow as in any new technique in the United States, particularly if it's potentially more expensive with a quick uptake. And you see how SBRT quickly replaced other types of therapies for early stage cancer, despite the lack of randomized trials. Actually, three RCTs were started in approximate 10 years ago. And they all were stopped because they failed to recruit. There's new ones ongoing, but I think they're still also having quite significant challenges.

So you're seeing this approach. And I mentioned before you see population of data tried to fill gaps in knowledge. We conducted this study with Nicole Ezer, which was a fellow from Canada. Then I was at McGill. And we used SEER data over 2,000 patients to look at survival of those who underwent SBRT versus limited resection.

And as you can see in the overall cohort, there was increased risk of death among those who underwent SBRT. However, that was not statistically significant.

However, SBRT fared worse than segmentectomy, which is the resection of an entire segment of the lung. So in a patient which may not be a candidate for full lobectomy, but could undergo segmentectomy, this probably should be the preferred approach.

Finally, the other potential treatment for early stage lung cancer is standard RT. This is data for a study we did now over 15 years ago, which was the first data to compare side by side in patients treated with standard radiation versus no radiotherapy. And this is the standard of care for unresected patients more than 5 centimeters.

In this study we showed that radiation therapy was associated with approximately six to seven month gain in life expectancy. And then we used, again, propensity score approaches. And we showed that they were translating approximately 20% reduction in lung cancer mortality.

However, what about unmeasured confounders? And this too, the physician is like, thinking maybe this patient may not do as well with radiation therapy. And what he's seeing is gestalt, may sometimes be hard to measure in a database with vials.

So can you really account for that with observation of data? Well, there is. There is a method called instrumental variable analysis, which is a technique that can simulate an RCT using observation of data and allows us to control-- seems magic-- but controls for both measured and unmeasured confounders, and has been used for many health-related questions and provides the best level of evidence or observation of data. Not quite as high as RCTs, but the next best standard.

So while I'm skipping all the technical details, and I have a couple of slides that you can certainly use if you have trouble sleeping at night, we did apply this technique to the SEER Medicare data. And we found that compared to those who-- this would be the standard approach. If you use a standard approach and you compare one year's survival, you would estimate that radiation therapy improves survival approximately 14%. And this, however, includes the potential [INAUDIBLE] and measured compounds.

However, when we apply the instrumental variable approach using geographic area as an instrument, we estimated that radiation therapy, it was associated with a 10% improvement in one year survival among unresected patients. And this, again, adjusting for all types of confounders.

Finally, as you may know, immunotherapy has been increasingly used for particularly advanced stage lung cancer, and is now the standard of care for advanced tumors. And this recently published study evaluated the feasibility and safety of immunotherapy as new adjuvant therapy for early stage lung cancer before resection. And they show that if you look at percent regression, which 90% is the threshold for a significant response, approximately 50% of early stage lung cancer that got immunotherapy did show a response, suggesting a potential future role, particularly for among high risk patients that may recur after resection.

So finally, we are doing research again with [INAUDIBLE] where we are trying to evaluate what is the optimal management of early stage lung cancer patients with comorbidities, another group that are typically excluded for randomized controlled trials. And for these we're using the lung cancer policy model, which they say is a very sophisticated simulation model, which actually has been used to come up with the United States Preventive Services Task Force recommendations for lung cancer screening. And it includes 40 computer modules.

And this is a basic structure. But if you blow up in any of these, you will find something like this, which a lot of pathways that are all simulated and has been very well calibrated to existing cohorts. So we're using this model to assess the treatment on patients with comorbidity. And for example here, we have a stage 1 patient with coronary artery disease, and showing survival over time based on treatment with lobectomy, limited resection, or RSBRT.

And this is for a patient with group performance studies, which shows that both survival and [INAUDIBLE] survival and the rates of complications with each treatment. However, the model may show that for a patient with poor performance status, limited resection actually provides better outcome and less toxicity. So this is a way to explore and replicate randomized controlled trials from groups that could never be randomized.

So in summary, I think there is strong evidence supporting the benefit screening. This is equivalent to other cancers for which we do have established screening programs. And that higher adoption of lung cancer screening hopefully will translate to increase in survival of high rate smokers.

Second, I think screening criteria could be individualized based on additional risk beyond those who are currently included in recent smoking and age criteria, and potentially updated based on the findings of baseline CT to kind of really optimize the best screening regimen for further rounds of screening.

Also strongly feel that the issues that I mentioned about race should be taken into account when screening is implemented in the United States so that we take a preventive approach and we avoid disparities in screening and outcomes in the future.

And I think there is a lot of need to better understand what is the best optimal management of these patients, screening technique patients to maximize survival outcomes.

So this is a bit of a timeline of the different history of lung cancer in the United States. From the 1960s-- the 1970s when the first cases were recognized to whatever we view now. And Dr. Solomon, as we say, which we dedicate this lecture to, was born in 1918 at the height-- well, sorry. At that time where lung cancer was almost an unknown disease. There is a report from a surgeon, from one of the busiest surgeons from 1900, in 1908 where he wrote, like-- where he did his first anatomy pathology of a patient with lung cancer, his mentor told him that he should pay attention because we'll most likely not see another case in the rest of his life.

So that's where he was born. And then unfortunately, he died in 1872 when we were at the peak of the lung cancer epidemic. And the only potential screening test at that time was chest X-ray, which is shown to be not effective. And there were very few effective treatments.

So I dare to say that he may be excited about all the recent discoveries and maybe hopeful that with low dose CT screening and new mechanistic-based targeting therapies, we can really improve the outcomes of lung cancer patients in the future.

So these are my acknowledgment. Obviously, this is a huge team that participated in all these studies. And this is kind of the fun of doing this type of research. And I obviously think our funders. And I guess that's all. I'll be happy to take any questions.

[APPLAUSE]

**SPEAKER 3:** Questions.

**AUDIENCE:** [INAUDIBLE]

**DR. JUAN WISNIVESKY:** No. Either that was very clear or they don't understand what I say. I forgot to put the captions in. But anyway.

**SPEAKER 3:** I want to thank Juan for a fantastic lecture. And I also want to thank Juan for everything he's done for the department. In his role as division chief, and also in his role as a mentor, not only as the vice chair for research, but as his role as a mentor for his own lab and for his own division. He really is exemplary in what he does. So thank you very, very much.

**DR. JUAN WISNIVESKY:** Thank you.