



Radiation for Prevention and Treatment of Brain Metastases in Lung Cancer, by Dr. Minesh Mehta

Dr. West:

Hi, this is Dr. Jack West, medical oncologist in Seattle and President & CEO of GRACE, the Global Resource for Advancing Cancer Education.

I'm happy to be here today with Dr. Minesh Mehta, who is a radiation oncologist and a Professor of Radiation Oncology at Northwestern University in Chicago. He's has an exquisite expertise in the management of brain metastases, which is a common complication in many cancers, with lung cancer actually being the leading underlying cause of brain metastases. I'm very happy to have him here to go over the evidence about the risks and potential benefits of radiation in lung cancer prophylaxis in high risk

Our program today with Dr. Mehta is sponsored by GRACE in partnership with the LUNGeivity Foundation.

With that, I'll turn it over to Dr. Mehta.

Dr. Mehta:

Well, Jack thank you very much. I'd like to welcome everyone to this webinar, which is entitled "Radiation for Prevention and Treatment of Brain Metastases in Lung Cancer." As Jack mentioned, I'm a radiation oncologist and I practice here at the Feinberg School of Medicine in the Lurie Cancer Center of the Northwestern University Hospital in Chicago. It's such a pleasure to have you both sharing this evening hour with me and with Jack on a topic that is very important to patients and families of patients who develop lung cancer.

What I hope to do over the next half an hour or so is to go over the problem, the issues of the problem and bring to our attention how we handle it, what the controversies are, and what we think that practices could be for this significant problem.

So let me start by showing my conflict of interest slide. I do have consulting roles as well as roles in several companies, and that's listed here in the conflict of interest disclosure, should you need to take a look at that.

I'm then going to go on and tell you what the theme of today's discussion is going to be about. I'm really going to focus on three points. I'm going to discuss the role of whole brain radiation therapy in preventing the development of metastasis in patients with two types of lung cancer: small cell lung cancer, as well as non-small cell lung cancer. I will also discuss the role of focal radiotherapy, very highly focused radiotherapy, known as radiosurgery in managing patients who have already developed brain metastasis from non-small cell lung cancer. And finally I will

discuss the role of whole brain radiotherapy in patients that have already had surgical resections of say, for example one or two brain metastases or the focused radiotherapy, known as radiosurgery, should we be following up with whole brain radiotherapy or not. So these are the thing things, the three objectives that I hope to be able to cover today.

So let me start first by talking about this concept of prophylactic cranial radiation. The use of radiation to prevent the development of metastasis. Now, in reality, we're not really preventing the development of brain metastasis. What we're doing is using whole brain radiotherapy to treat microscopic disease, small deposits of cells that may already have set up house in the brain that we typically cannot pick up and see with our imaging studies. So we assume that there are no brain metastases because we can't see them. But in reality, small colonies of cells might exist in the brain.

This is the concept that we first came to understand in children with leukemia and subsequently in small cell lung cancer. Now, small cell lung cancer is a disease that responds dramatically to chemotherapy. But because chemotherapy does not readily penetrate a sufficient amount into the brain, as a consequence of a barrier, known as the blood brain barrier, this results in the brain turning into a possible sanctuary site where microscopic disease can hang out and hide out without chemotherapy being efficiently able to kill it. As a consequence, even if the rest of the disease in the body appears to disappear, many patients with small cell lung cancer ultimately develop disease in the brain.

So, failure in the brain remains a common and a substantial issue in many of these patients. Small cell lung cancer is also intrinsically very sensitive to radiotherapy. And as a consequence, relatively low to moderate doses of radiation to the brain should be able to wipe out this small clone of tumor cells that hide out in the brain. As a consequence, we might be able to wipe out this microscopic sanctuary site and prevent the obvious development of brain metastasis.

This concept has been tested in numerous clinical trials. These clinical trials have in fact validated that we can indeed wipe about the microscopic deposits of cells. In 1999, a meta-analysis was published. This is large analysis of all the randomized trials that were done to address what the questions about prophylactic cranial radiation in small cell lung cancer. These trials, this meta-analysis clearly showed two things. First of all, the risk of developing brain metastasis was clearly reduced in patients who got the whole brain radiation. Secondly, the patients who got the whole brain radiation had a modest, but significant improvement in survival as a consequence of avoiding the development of brain metastasis.

So we learned two things. We learned that we can prevent the obvious occurrence of diseases of the brain. We also learned that patients could potentially live longer as a consequence of this.

Let me show you this interesting paper. This was a paper that was published in the *Journal of Clinical Oncology* 2006. This is a trial where investigators speculated that small cell lung cancer is a very chemosensitive disease. If it's chemosensitive, it's quite likely that patients had a

metastasis to the brain, that this blood brain barrier might not be as intact as it would be in a normal brain. Then perhaps that second chemotherapy might be sufficient to wipe out the disease and get rid of it. So, patients with brain metastasis received chemotherapy, first line chemotherapy. So in other words, they were coming in with a new diagnosis of small cell lung cancer and brain metastasis and they were asymptomatic. They were treated a regimen of chemotherapy using three drugs: Cytosin, or cyclophosphamide, Adriamycin, or doxorubicin, and a drug a drug call VP16.

The systemic response rate, the response rate in the body, the likelihood of the tumor responding to chemotherapy by shrinking 50% or greater, was 73%. So almost three quarters of the patients responded to this chemotherapy. So we know this disease is very sensitive to chemotherapy. But in the brain, the response was only 27%, so only a fourth of the patients responded. So even when obvious disease exists in the brain and the blood brain barrier might be partially disrupted, it's not sufficiently disrupted to allow enough chemotherapy to get in to produce a high 70-75% response rate that we would like to see.

That's why radiotherapy makes sense in this disease. The meta-analysis that I talked to you about, the one that was published in 1999, was a very elegant study that was done. In this study, they looked at seven randomized trials, with almost a thousand patients. These patients had all undergone chemotherapy previously, with or without radiation to the chest. All of them had obtained what we would call a complete response. In other words, all known visible disease had disappeared. So effectively, we would've said these patients have no more disease. However, we did suspect that disease would be hiding out in the brain, and so that's why these patients were randomly assigned to receive whole brain radiation or not.

What I show you on this slide, which shows both the risk of death and the risk of developing brain metastasis, is a reduction -- a shift from a central bar, which is labeled at the point marked 1.0. If everything lined up at 1.0, it would imply that the experimental treatment is no different than the standard of care, which is no treatment at this point in time. Any shift to the left implies a reduction in the risk of death and a reduction in the risk of developing brain metastases. Any shift to the right would imply worsening of the results. So we see here, categorically, both for the risk of death and the risk of developing brain metastasis, there is a reduction across the board. In fact the risk reduction for brain metastasis is 54%, which is quite substantial.

The benefit in terms of reducing death is positive and substantial, but not as large as the reduction in the risk of developing brain metastasis but still a positive effect. Given that these patients off mostly with what we would call limited stage lung cancer, in other words the disease was limited to the chest, we have excluded the significant majority of patients that develop disease outside the chest. We call these patients extensive stage small cell lung cancer.

In 2007, a trial was published that was done primarily in Europe. In this trial, they took patients with extensive stage small cell lung cancer' on this slide I show you the design of the study. Patients received chemotherapy and if they responded, if they had any response whatsoever, in other words the restriction was quite a bit lax here. They didn't have to achieve a complete

response. They just needed to have some response. If they got into a response, they either received prophylactic radiation to the brain or not. The idea here was to look for a risk reduction in terms of the development of brain metastasis.

As you can see from this graph, the line in white represents the patients who did not get radiation to the brain. So this is sort of a natural history in terms of the risk of developing brain metastasis. Over a period of time, on the x-axis the time is shown in four month increments, from four to eight to twelve months and so on. The white line keeps on going up to about 16 to about 20 months when almost 45-50% of the patients end up developing metastasis to the brain. The line in yellow represents the patients who received whole brain radiation therapy. That line is consistently below the white line implying a reduction in the risk of developing brain metastasis. This reduction is quite significant. We express this in terms of a ratio that we call a hazard ratio. A hazard ratio of .27 is a very dramatic reduction in the risk of developing brain metastases.

This trial, like most trials, has some flaws in its design. But in spite of that, it clearly showed a reduction in the risk of developing brain metastases.

What was more interesting about this particular trial was a secondary publication that came out of it in the *Journal of Clinical Oncology* in 2009. I'm showing you this very, very busy slide. On this busy slide there are again two lines for every graph. There is a yellow or gold line and a blue line, the dotted line. The gold line represents patients that received radiation to the brain and the blue line represents patients who did not. And here, what they were looking at was a change in patient-reported quality of life parameters. So, for example, let's look at the panel marked B. This is a panel where they look at hair loss. Clearly the line in yellow sits on top of the line marked blue. In other words, patients who got the radiation are more likely to lose hair than the ones that do not. That's obvious. You'd expect that. But I would like to point your attention to is the graph marked E. This is the graph looking at something called cognitive functioning.

How well do patients think? Now the reason that I'm showing you this slide is that we know that whole brain radiotherapy decreases the risk of developing metastasis in the brain. But the concern is the possibility of side effects from radiation to the brain. Can radiation cause decline in memory function in function of the brain? One way to measure that is to look at cognitive function. If you look at these bars, there is, indeed a small difference. The orange or yellow gold line is slightly lower, especially in the first four to six to eight months compared to the blue line. So there seems to be a small, early initial decline. But then it catches up. It seems to parallel the functioning of the patients that did not get the whole brain radiation. So, yes, there probably is some reduction in cognitive functioning. It's not very large. And it's sustained over time.

It seems to occur in an early phase and then both groups of patients appear to be doing quite the same. I will keep on coming back to this point a couple of times in my next few slides.

Let's summarize so far what we've talked about in terms of the role of prophylactic radiation in extensive stage small cell lung cancer. This radiation reduces the risk of developing brain metastasis in patients with extensive phase disease. But there is no difference in time to progress of the disease outside of the brain and there's actually the data for that. It also prolonged the period of time patients remained free of failure. We call that failure free survival. It's actually also prolonged overall survival. So even this group of patients benefited in terms of survival prolongation.

So it's reasonable to conclude that in both cohorts of patients, extensive stage as well as limited stage, if the patients respond to the initial therapy, there is possibly a role for prophylactic cranial radiation for these patients. If this works for small cell lung cancer, could it work for other diseases? In fact this interest was stimulated in recognition of the fact that as patients with non-small cell lung cancer have started to live longer, their risk of developing metastasis to the brain has also increased over time.

To try and address this issue, a clinical trial cooperative group, known as the Radiation Therapy Oncology Group, or RTOG, launched a prospective randomized trial which was comparing prophylactic cranioradiation versus no radiation to the brain in patients with advanced non-small cell lung cancer.

This trial was originally designed to randomize these patients to 30 Gray irradiation, which essentially takes fifteen days to deliver, or observation. The schema is illustrated on the slide I have up right now. This study ran from 2001 to 2007.

The target accrual, the study was designed to answer the question, a little more than 1,100 patients, that's a little more than 1,000 patients who would have been enrolled on the trial. Unfortunately in this almost six year time period, the accrual was only a third of what was expected. Only 356 patients were accrued, so the trial ran very very slowly. And of these 356, only 340 patients had enough data and had met the requirements to be considered evaluable for analysis for this particular trial. So unfortunately, we never completed the trial.

As a consequence, not surprisingly, we find in this graph looking at overall survival that there is no difference in overall survival. The red and blue curves are superimposed directly on top of each other. So survival was unchanged with additional prophylactic cranial irradiation.

Well how about the parameter of disease-free survival? The prophylactic cranial irradiation arm illustrated in red is consistently above the blue line. So these patients did better in terms of failure-free survival. And the reason that it's better is that they developed less brain metastasis, as shown on this particular slide.

The line in blue are the control patients who did not receive whole brain radiation, compared to the line in red which is the group of patients who had done whole brain radiation. They had a lower risk of developing brain metastasis. So clearly the risk of developing brain metastasis was

reduced and was statistically significant even though the trial did not reach the accrual that was necessary to establish this.

What was very interesting about this trial was that they also tested brain functioning, through a simple test called a mini mental status examination. This is somewhat of a crude test. This test detects big changes. Patients with significant changes in the brain, this would be picked up with the mini mental status examination. And what we see here, let's just focus on the green and the red lines that you see at the bottom. The green and the red lines at the bottom represent what we call the change in score over time.

So, what we can clearly see if that the green line is consistently on top of the red line. The green line represents patients who did not get prophylactic cranioradiation. The red lines represents patients who received prophylactic cranial irradiation. There is very little separation between these lines. If we look at the actual score, which is shown on top of the red and the blue lines, there is very little separation. So this crude test, a test that looks for very obvious changes in brain functioning showed no difference. So that's good news. However, when we look at a more sophisticated test, as shown in this slide. -- this is a test known as the Hopkins Verbal Learning test, which looks at the ability to retain words and reproduce those words at a later point in time -- we see that the line in red at the bottom is consistently below the line in green, implying that patients do, in fact, have a reduction in their ability to memorize and reproduce words as early as three months. But then it starts catching up. In fact, you can see that in the upper two lines. The blue line that represents the patients that did not get prophylactic cranial irradiation, the red line represents patients who did. And you see a dip at three months, which tends to come back a little bit. Remember, we saw the same thing in the cognitive decline slide of the small cell lung cancer patients. There seems to be a small dip, and it seems to recover somewhat over time. It's not a huge dip: it's not a huge loss in terms of ability to recall words, and it does seem to bounce back, at least a little bit, with time.

Now, let's put this RTOG trial in context with the other trials that have looked at the same question. On this slide, I have listed a total of five different clinical series, randomized trials, and then I have summed them up in the bottom in row that is marked, cumulative experience. So this now includes over a thousand patients. If you look at the first two columns, whether they received the prophylactic radiation to the brain or not, there is indeed a significant reduction from about 13 to about 27% without the radiation, down to single digits, 4 to 9% with the radiation.

So we clearly have every trial done in this disease showing a benefit in terms of the reduction in the rate of developing brain metastasis. But obviously this appears to come at a price. There is some decline that can be measured using sophisticated tests such as the Hopkins Verbal Learning test.

So we have to ask ourselves, where is the balance? We know that neocognitive decline occurs in patients that get radiation. It may occur relative early, as early as three or four months. In a separate study that we did in my institution, we looked at the time course of neocognitive

decline in 212 patients who had received whole brain radiotherapy. We made two observations. We found that the time to decline was longer, in other words patients remained free of declining in their cognitive function, if the disease responded.

So if you control the disease, their cognitive function was maintained better, which would imply that the disease itself also contributed to decline in cognitive function. The second thing that we learned is that, of the many different cognitive functions that we can test, the one that was most susceptible to early decline, the one that would go down earliest was in fact memory, something that the Hopkins Verbal Learning Test actually measures. This becomes intriguing. This becomes intriguing because it brings in the potential for doing trials that would try and spare memory. We'll talk about that in a little bit.

Let's look at this group of patients with non-small cell lung cancer and try to make some sense out of this. We have about 300+ patients who got either whole brain radiation or not with a clear decline in the occurrence of brain metastasis, which comes at a price: early reduction in memory, some of which bounces back with time. Obviously, this would be a good thing in patients who are at very high risk of developing brain metastasis. Patients that have adenocarcinoma or large cell carcinoma, something the we call non-squamous non-small cell lung cancer, have more than a quarter risk, more than 27% risk of developing brain metastasis. These patients could be potentially better served by looking at the possibility of prophylactic cranial irradiation.

What about the neurological decline, the cognitive decline? Can we do something about it? There are many options. One option is to give drugs that spare cognitive function. One is a drug that came out from the Alzheimer's work, the drug known as Memantine. The RTOG has just completed a very large trial, upwards of 600 patients, a trial known as RTOG 0614, where half the patients used Memantine with whole brain radiation, and half the patients did not, the goal being to identify if Memantine actually protects memory. We don't have the results of this trial yet -- it's expected that before the year is out we will have results. So we are quite excited to find out if this drug helps to reduce the likelihood of developing cognitive decline when whole brain radiation is given. As you can imagine, if it does that, it would be a game-changing event, and this would be something that would become very common practice.

The other option is to look at technology to try and identify a region of the brain that we think are most likely to be positive for this memory decline. One of the theories that is out there is the stem cell theory that suggests that there are neural progenitor stem cells in the brain that live in and around an area of the brain known as the hippocampus.

It's these cells that replicate and reproduce consistently and produce neurons that help us develop new memories. But these stem cells are quite sensitive to radiation and when patients get whole brain radiation, these stem cells are decreased, and this might be part of the reason that memory deficits occurs. So perhaps if we could spare these stem cells that live in and around the hippocampus, then we might be able to reduce the occurrence of memory decline. To test that, the RTOG just last week launched a clinical trial of hippocampal avoidance, or

“hippocampal sparing”, in patients receiving whole brain radiotherapy. It will be interesting to see what the results of that trial are. The trial is still whole brain, so it’ll probably be a year or so before accrual is completed on that trial.

I’m now going to shift gears and talk to you not about prevention, but about actual treatment of metastasis in the brain. This is something that we refer to as definitive whole brain radiotherapy. So whole brain radiotherapy that is used to try and treat metastases in the brain.

The RTOG, again, has done many, many clinical trials with thousands of patients. We can go back and look at these patients who got whole brain radiotherapy. What we find is that patients with brain metastasis don’t do very well. Many of these patients have relatively short survival. As you can see from this table, the median survival can range from as little as 2.3 months to 7.1 or longer. But it’s short survival, it’s measured in months.

But even in this group of patients with brain metastasis, there are different tiers, or different categories. Some, labeled as class three patients on this table, have very poor survival, only a couple of months. The other group, class one, relatively speaking, has better survival compared to class three. So we know that these patients are different. Whole brain radiotherapy produced perhaps different effect in different groups of patients with brain metastases.

To try and further answer that question, Dr. Sperduto, who works out of Minneapolis, has gathered a large database of brain metastasis patients from ten institutions and has been publishing a number of clinical papers on this particular data set. Let me show you two slides to illustrate to you how this data can be useful in determining the role of whole brain radiotherapy. One of the first questions that Dr. Sperduto and his colleagues asked was whether the type of cancer actually makes a difference. In this slide you can see, in this database, there were over 4,000 patients.

Almost 2,000 of them, 1,800 or so had non-small cell lung cancer, about 600 plus had breast cancer and almost 500 -- just under -- had melanoma.

When we look at these patients with different histologies, different types of tumors, we find that their survival is different. On this table in this slide, if you focus your attention on the first two tables, you see that by two more times, the survival is different. So, for example, breast cancer patients appear to live longer when they develop brain metastases compared with patients with melanoma or non-small cell lung cancer. So the type of cancer might make a difference of patients who are treated with whole brain radiotherapy.

More importantly, what we have recently observed is that if we treat patients with brain metastases with whole brain radiation, we come back and look at their brain with an MRI scan, we identify that the reduction in the size of the brain metastases, regression of the brain metastasis, is in fact suggestive of improved survival as well as improved cognitive function. This latter aspect is quite intriguing.

So, let me just show you the data from this analysis. This was a cohort of 135 patients who were still alive at two months after radiation therapy, who were divided in terms of so called good responders or poor responders based on the amount of reduction in the disease in the brain at the two month measurement point in time.

What we see here is the green line versus the blue line -- the good responders actually live longer than the poor responders. So controlling the disease in the brain appears to have an influence in the overall survival of patients which implied that we should really maximize our efforts to control the disease in the brain and not minimize those efforts.

Obviously we would want to minimize the efforts if the effort was deleterious. So if whole brain radiation was producing terrible side effects, we'd want to hold off on doing that. But as you can see on this graph, which is a graph of neurocognitive function, this is a graph that actually measures motor skills, how fast someone can operate something, the green line is better than the blue line. The green line is the good responder patients, the blue line are the poor responder patients. Remember that both patients received whole brain radiotherapy.

Obviously the ones where the disease is controlled do better. So controlling the disease is important who is going to live longer and who is also going to be doing better in terms of cognitive function. So this is an important point to bear in mind.

I'm now going to shift to a different type of radiotherapy, a technology known as radiosurgery, which is highly focal treatment of only the visible metastasis, not the whole brain. We're not treating microscopic disease of the brain, but essentially spot treating one or more lesions.

This concept was tested, again in a clinical trial by the RTOG, in a paper that was published in a journal known as *The Lancet* in 2004. This is the survival of patients with a single brain metastasis. The blue line represents patients who got whole brain radiotherapy and radiosurgery. The yellow line represents patients who got whole brain radiotherapy alone. Clearly the addition of radiosurgery prolongs survival in patients with a single brain metastasis. The majority of these patients had non-small cell lung cancer.

It's reasonable to conclude that in a patient with a single brain metastasis, the addition of radiosurgery to whole brain radiotherapy improves the survival and should be strongly considered. In patients with more than one brain metastasis, if we look at all comers there are three different trials we are looking at here. All of these trials had a design where patients did either whole brain radiation or whole brain radiation plus the technique of stereotactic radiosurgery. The third box, colored black, shows the local control rate of the brain metastasis in patients who had both treatments, whole brain radiation and stereotactic radiosurgery. The box to the left shows patients who received only whole brain radiotherapy, but no radiosurgery.

Consistently the numbers in the black box are superior to the numbers in the blue box over to the left, implying that even in patients with multiple brain metastases, the addition of radiosurgery improves local control. But there is no evidence of improvement of survival in

these patients. So, yes -- we can improve local control by adding radiosurgery, but not in fact survival in patients with more than one brain metastasis.

Now, the study that I showed you typically included patients with one, two, three, or four brain metastases. But there are people who have published their experience with patients with more than four brain metastases. This is a paper that was published in a journal, *The International Journal of Radiation Oncology* in 2006. In this particular paper, there were 205 patients with various malignancies who received radiosurgery for their disease. It also went on to conclude that patients did quite well. The problem, of course, here is that we don't have a group to compare with. All of these patients were treated, and they were selected to be treated with this particular modality. So we don't really know whether any improvement or so-called improvement that we might see is genuinely because of the treatment or is a consequence of only selected patients being chosen for this particular treatment.

So, now let's look at the impact of whole brain radiotherapy that get such local therapy such as radiosurgery or surgery. Because there is an increasing practice of reserving whole brain radiotherapy patients to get surgery or radiosurgery, and whole brain radiotherapy is withheld. So let's look at the impact of that. What happens?

In this table, I'm showing you results from a surgical trial. In this surgical trial, patients with a single brain metastasis were resected and afterwards received whole brain radiotherapy or not. If we look at the first three columns in this slide, on the left you can see we are looking at two groups of patients: patients that have failure anywhere in the brain, or in the second row, patients that had failure only at the original site only where the tumor had been removed. The second column represents the 46 patients who did not get radiation to the brain. The third column represents the 49 patients who did receive radiation to the brain. The rate of failing in the brain in the absence of whole brain radiotherapy is 70%, without whole brain radiotherapy. This is reduced three fold, down to 18%, with the addition of whole brain radiotherapy. The risk of failing at the original site where the tumor is removed from approaches 50% without whole brain radiotherapy and drops down to 10% with the addition of whole brain radiotherapy. So clearly whole brain radiotherapy after resection is beneficial.

This is a busy slide, a busy table, where I have taken now five different cohorts of patients. They are similar in the sense that these are all randomized trials where patients had resection of their brain metastasis or radiosurgery. Half of them did not get whole brain radiotherapy; half of them did.

Let's get down to the very bottom row, which is the range that we see here. So if we take all of these patients and add them up, what do we see?

Let's first look at failure anywhere in the brain in the absence of whole brain radiotherapy. So go over to your right and look at the third column that is entitled, "No WBRT", and go down to the bottom number that's marked range. You can see that the likelihood of the patients

developing disease in the brain if they do not get whole brain radiotherapy approaches 80% -- it's 70 to 80%.

If they get whole brain radiotherapy -- I would like you to go over to the sixth row that is marked "WBRT" -- that says any brain failure, go to the bottom, that risk is effectively halved or reduced down to one quarter. It goes down to 22-47% with the addition of whole brain radiotherapy. So clearly the use of radiosurgery alone or surgery alone is associated with a very high risk of failing in the brain -- 70 to 80% -- and this can be substantially reduced down to 22-47% with the addition of whole brain radiotherapy.

Now we talked about the impact of whole brain radiotherapy on the Mini Mental Status Examination in the prophylactic cranial irradiation group when we talked about the non-small cell trial. What about patients that actually have brain metastasis? Do they do worse in terms of their brain functioning if we add the whole brain radiation?

So these are the results from a Japanese trial that looked at 82 patients on whom they've measure the Mini Mental Status Exam score, and they looked at two parameters. They looked at how long it took for patients to drop three points on this score. A three point drop is considered significant. If you drop three points, that's quite a bit of loss of memory function. The patients who did not get whole brain radiotherapy on average dropped three points in less than eight months; 7.6 months, they dropped three points. Remember that they had not received whole brain radiation, and yet half of them dropped three points in less than eight months. We expect that whole brain radiation therapy patients might do *worse* because of the impact of radiation on the brain, but surprisingly the patients in this study that had done whole brain radiotherapy took longer -- they took over sixteen months -- to drop their score by three points or more.

We see the same trend when we look at what we call landmark analysis, different time points, at twelve months or twenty four months, we found that the patients that got the whole brain radiotherapy were less likely to have cognitive or neurologic deficits in their brains compared to patients who did not get whole brain radiation.

So what's going on here? There can only be one logical conclusion. The logical conclusion is that yes, indeed, whole brain radiotherapy can cause a decline in cognitive function. *But recurrence of disease in the brain is a far more efficient way of causing decline in memory function than whole brain radiotherapy.* In other words, progressive disease in the brain is worse than whole brain radiotherapy alone.

One other study bears consideration. This is a small study that came out of MD Anderson Hospital. In this study, they looked at this fancier test, the HVLT, the Hopkins Verbal Learning Test, that I mentioned to you earlier as well. Here they looked at a group of patients that had received radiosurgery only or radiosurgery plus whole brain radiotherapy. And if we look at the four month time point, at four months the likelihood of decline of this memory function is greater for the patients that received whole brain radiotherapy: 49% compared to 24% for patients who

did not get the whole brain radiotherapy. But these data are very consistent with the other graphs I showed you, that cognitive decline can come up early at three or four months, but then bounces back. In part this is a reflection in when you chose to measure it. If you chose you to measure it at a point where it's most likely to be down, then you can see it. If you were to come back a few months later, this difference would probably have become much more narrow; it might be statistically significant.

So this is a good point for me to conclude. Let's summarize what we have discussed so far. We've talked about the role of whole brain radiotherapy in patients with metastases both in small cell lung cancer and in non-small cell lung cancer. We've talked about the preventive role in patients with small cell lung cancer, which is well established. It reduces the likelihood of developing disease in the brain and prolongs survival, both for patients with limited stage and extensive stage disease.

In non-small cell lung cancer, we have almost 1,000 plus patients that have now been randomized to preventive or prophylactic trials and they consistently show a reduction in the risk of developing brain metastases, but do not categorically show a survival improvement; and in the RTOG study, although the Mini Mental Status Examination was not changed between the two arms, the Hopkins Verbal Learning Test, which measures the ability to memorize and retain words, did show an early decline with whole brain radiotherapy, with some regain of function over time.

We talked about the therapeutic use of whole brain radiotherapy which is used primarily for patients with multiple brain metastases and results in regression of disease. And we have learned that regression of disease is a good thing because it is associated with longer survival and better preservation of cognitive functioning.

We discussed what we called the adjunctive role, or the additional role, of whole brain radiotherapy either after surgery or stereotactic radiosurgery. We saw that the addition of whole brain radiotherapy reduces both local failure in the tumor bed, or the targeted area, and also reduces the likelihood of developing metastasis in the rest of the brain. In fact, if we look at the data collectively, the likelihood of developing more metastases in the brain approaches 80% if whole brain radiotherapy is withheld. This can be reduced down by half or a fourth with the addition of whole brain radiotherapy.

Finally, we must also address toxicities. We have talked about memory changes, and we've talked about the fact that when we used tools like the Mini Mental Status Exam, which looks for significant large changes, we find only minor changes. They seem to occur early, and in fact it seems that it's worse as the tumor progresses and the tumor in fact may be more nefarious than the effects of the whole brain radiotherapy.

When we use finer tools, like the Hopkins Verbal Learning Test, we pick up some early decline in memory changes, especially around the three or four month time period, but with some rebound thereafter. We've seen that in small cell lung cancer patients. In the European trials,

the Slotman trial. We've seen that in non-small cell lung cancer, preventive trial that Dr. Movsas has presented. And we've seen that also in patients that have been treated for brain metastasis. So this is now a consistent finding in many trials, suggesting the potential for preventing dysfunction either with the use of drugs such as Memantine, with which a clinical trial has been completed, or with technological innovations that spare the areas where these stem cells live, such as in and around the hippocampus. And those trials are ongoing.

I'd like to thank you for your attention.