Q&A Session with Dr. Minesh Mehta on Prevention and Treatment of Brain Metastases in Lung Cancer

with Dr. H. Jack West

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Dr. West: I would like to take a moment to thank you for a remarkably comprehensive and very, very informative talk.

So one question is whether there might be any benefit from radiation for leptomeningeal carcinomatosis? Can you speak to whether there is any evidence to favor that?

Dr. Mehta: Thank you for asking that question. This is obviously an issue with did not address in the talk. So leptomeningeal carcinoma, just to bring everyone up to speed, is a very difficult and complex problem, because here we had disease that actually lines the surface and the inner lining of the brain and can sometimes extend out into the spinal cord. So the extent of the disease is quite substantial. Quite a significant volume of tissue becomes involved and this is the disease that creeps along the linings, the peel lining, the membrane of the brain. It's a very difficult problem to treat. We can produce symptomatic improvement in patients with leptomeningeal disease with non small cell lung cancer with open radiation. We do not substantially prolong survival. We probably do not make much of a difference in the natural history of the disease other than helping with the symptoms. In particular the symptoms that appear to have benefited most are deficits of the cranial nerves, the nerves that come out of the brain because the nerves are a considerable risk of getting coated with this leptomeningeal disease and then not functioning well. So the leptomeningeal carcinomatosis problem results in what we call cranial neuropathies, and these cranial neuropathies can be helped by whole brain radiotherapy.

But it is clearly a palliative approach. People have also tried systemic chemotherapy options for this using a variety of different approaches, either using intrathecal drugs or intravenous drugs or even oral drugs. Most of these have not really shown huge improvements in the outcome of patients. So this remains a vexing problem for which we don't have a solution to date.

Dr. West: Thank you. Can you speak to your general conclusions about whether at this point you think the data are strong enough to recommend prophylactic cranial irradiation for locally advanced non-small cell lung cancer after completion of chemo and

radiation, perhaps with surgery, and how you would approach a patient coming to you asking you about this after completed treatment for their disease in the chest?

Dr. Mehta: Absolutely. This is obviously a very crucial question. Let's start first with sharing you first what a party line is. So the data that I showed you from the RTOG trial were presented at a national meeting the radiation doctors go to. This meeting is known as the ASTRO meeting and Dr. Movsas was the investigator that presented the data there. I happen to be the moderator at that meeting so I got to editorialize that talk. So Dr. Movsas's conclusions were very clear. His conclusions were that whole brain radiotherapy decreases the likelihood of developing brain metastasis. It does not lengthen survival and it is associated with a decline in the Hopkins Verbal Learning Test, especially in early time points.

And therefore, these data would be interpreted to mean that routine use of whole brain radiotherapy should not be considered in these patients. However, that does not preclude the possibility of selective use in individual patients. Now, selective use can take many forms. One can look at a specific patient and try to estimate whether that patient has a higher risk of developing brain metastasis. So, for example, if we looked at a patient with squamous cell histology versus adenocarcinoma histology, the patient with adenocarcinoma would more than likely be at greater risk. There are emerging data that are not fully conclusive that show, for example, that patients that have greater bulk of disease, if they are significantly more, stage III or IIIB disease than someone with less voluminous disease, then patients with more voluminous disease may have a greater risk of developing brain metastasis.

An intriguing set of data that are emerging now are beginning to show that if we look at the PET scan that patients had at the time of diagnosis, if the PET scan is very hot in the primary tumor, then that patient might be at greater risk of subsequently developing a brain metastasis. So in a given patient, if we can take these different parameters and put them together and come up with a gestalt if a particular patient might be at a higher risk, and if that patient is also concerned with the risk of developing brain metastasis, then thinking about whole brain radiotherapy for that patient might be reasonable. In my practice, I have faced this situation on more than one occasion, and what we have done is have a very frank discussion with patients about the risk and benefit of whole brain radiotherapy. We have attempted to use this technique of hippocampal sparing whole brain radiotherapy, where we try to spare the region of the brain where think the stem cells reside that might be instrumental in forming memories and try to avoid that region when we do the whole brain radiotherapy.

We do not have conclusive data that this is necessarily a good thing to do or that it categorically spares memory. So this is what we've done in some patients. We've done the prophylactic cranial irradiation if we agree that this is a high risk situation, that the patient understands that this is a treatment that can be offered with the potential for some cognitive loss and that if we try to attempt to minimize that loss. So it's a lengthy answer, but it's a highly individualized answer depending on the patient's status.

Dr. West: Fair enough. A practical question comes in and that is, is there any practical difference between prophylactic cranial irradiation and whole brain radiation therapy except whether you are treating the potential for brain metastases or visible brain metastases? Or is it the exact same procedure for both?

Dr. Mehta: It's very similar for both but they are quite different. The technique is similar: you are creating the same volume. You are fractioning the radiation, so you are treating on a daily basis. What is different is the actual dose. So when a patient has obvious metastasis in the brain, we tend to use slightly higher dose of radiation compared to when we are using this in the preventive or prophylactic setting when the biological equivalent dose is a little bit lower. So we tend to use a little less dose each day because we know that one way to cause cognitive decline in the brain is to use a large dose in a very short period of time. So if we pack in a high dose in a short period of time, the brain is more likely to suffer memory defects and other cognitive decline. So that's the difference between the two.

Dr. West: Are you less inclined to recommend whole brain radiation in an immediate way for patients that have smaller and asymptomatic brain metastases, or if there is someone who has even subcentimeter several lesions, you're inclined to treat them sooner rather than later?

Dr. Mehta: So the answer to that question is a lukewarm yes, and let me tell you why it's a lukewarm yes. Intuitively, if a patient comes in with asymptomatic disease, they have no symptoms, and the scan shows that the disease is small, it's not very large, and if this patient also had disease elsewhere, there is a need to get going with chemotherapy quickly to control the disease elsewhere. Then we might say, it's asymptomatic, it's kind of small, let's just go ahead and start the chemotherapy or wait on the whole brain radiation or repeat the scan in a month and see what's going on. Sometimes we can get away with this. There are some patients where the chemotherapy works on the systemic disease and on the brain disease. But the

brain disease might be slower and might remain stable, and you can continue the systemic therapy and the patients benefit from this approach.

However, in all honesty, this has never been studied in a clinical trial. And, for every patient where I've seen where I'm encouraged that this is a good thing to do, I've seen more patients where I've been discouraged in the sense that a month or two later, the small disease in the brain and it's almost like we have interrupt the chemotherapy because the disease is growing in the brain. We're not going to be able to get away with this for too long. Let's go ahead and do the radiation to the brain. So really we don't have a good handle on who are the best patients in which this approach can be used when we delay the whole brain radiotherapy, so that the systemic therapy gets a chance to come in quickly. I think it's a great idea; we just need to find out who are the patients that really benefit from it.

Dr. West: A couple of questions about people who have progression of metastases after whole brain radiation, and that is: If someone has a single or a few lesions, do you routinely recommend stereotactic radiosurgery after whole brain radiation? And what can you say about the feasibility of repeating whole brain radiation in people who have multiple brain metastases? Or would you recommend not doing that and trying to manage this with systemic therapy or any other approach you might think of?

Dr. Mehta: So let's first start by defining which patients are most likely to benefit from radiosurgery. We know that patients with a single brain metastasis benefit from improved local control in terms of lengthening their survival. So whether we improve local control by removing the tumor surgically or treating it with radiosurgery, these patients actually live longer by getting more aggressive with their single brain metastases.

So most patients with one brain metastasis should be considered for radiosurgery or surgery. Now when we go to more than one brain metastasis, things change a little bit. We have not shown a survival benefit in patients with two or three or more brain metastases with more aggressive therapies such as radiosurgery or surgery. However, we have shown an improvement in local control, in randomized trials for patients with up to four brain metastases when radiosurgery is added. So, in practice, it's not uncommon to use a number of around four as a practical number to consider the cut off point for radiosurgery. Now this number shifts based on the center and the area of the country. In some places they say, well it works with four, five is pretty close -- we'll use five.

And also, if you know, radiosurgery is often done by applying a frame to the patients head on the day of the procedure, which is a minimally invasive procedure. Then an MRI scan is repeated. You may have obtained the MRI scan a week or two before that showed you four lesions and you think, well I'm going to do radiosurgery for four. But on the day of the treatment, you repeat the scan and you see six. Now you have a bit of dilemma: "what do I do? Do I treat four and call it a day? Do I take the frame off and not do radiosurgery? Or do I treat all six? Depending on your approach and your beliefs in the value of radiosurgery, some people do it, and some people don't. That's why I showed you the example of the paper where they were treating patients with up to ten brain metastases or to ten brain metastases. This is not a randomized trial. This is just the experience of a single institution. They go on to contend that they get better control rates in the brain by doing radiosurgery. We have nothing to compare with. So it's hard to know if the data are real or simply a function of selection bias. So that I hope helps define the role of radiosurgery.

The next question was, do we actually add radiosurgery to whole brain radiotherapy, or do we actually add whole brain radiotherapy to radiosurgery? These are two different things. My bias is to add radiosurgery to whole brain radiotherapy, because that is how all the studies have been done. That's where we have the evidence. However, I must state that there is quite a voluminous practice out there of patients who get radiosurgery, and whole brain radiotherapy is withheld. And the intention here is that I'll come back and do a scan in a couple of months. And if you do a scan in a couple of months and you see more disease, then you treat with radiosurgery. Then we'll come back again in a couple of months and do a scan and if there is more disease, we'll come back and treat that with radiosurgery. You could argue that that's fine, and it might be fine to do that. But we don't really have any good evidence to support it. It's definitely much more expensive to do it that way. The concern is that we are allowing the disease to actually occur. We know from the data that recurring disease in the brain is a bad idea -- that people do worse cognitively. So are these patients actually doing worse because we allowed the disease to come back? That's actually never been studied. So because of all these ifs and buts, my personal bias is to recommend addition of aggressive local therapy on top of whole brain radiotherapy for most patients.

Even in my practice, I have patients that don't get whole brain radiotherapy because they have major concerns and hesitations. They say, I've heard everything you've told me, I'm still concerned about the cognitive deficit. I'm not going to do the whole brain radiotherapy. That's ok. We obviously want the

patient to make an informed choice. Jack, I don't know if there's another aspect of the question that I missed?

Dr. West: It was really what happens if someone has multiple additional metastases after having previously received whole brain radiation months or a year before?

Dr. Mehta: A very, very difficult situation. So, there are only a handful of retrospective reports in the literature. A bunch of patients were treated and someone went back and said, ok what happened? This is not a clinical trial. And these reports show really very limited to no gain with retreatment of radiation to the brain. And they say that it is not uncommon to retreat patients with whole brain radiotherapy in selected situations.

So, let me give you some examples. If a patient was treated with whole brain radiotherapy, quite a while ago, many months ago or a year or two ago, and now they have metastasis in the brain, and during that time you've seen that the metastasis that the patient originally had has shrunk or disappeared. Now you are seeing new ones that are popping up. It's reasonable to conclude that this is a patient that has radioresponsive disease that went away. The patient benefited -- they lived long. Now there is a second occurrence, and there is a possibility that they might respond again. That kind of a patient would possibly be a good patient to retreat with open radiation. You have to be careful, because the risk of damaging the brain goes up when you use it a second time. So you have to be ginger with the dose of radiation, and we haven't quite defined what the appropriate parameters are, but most people cut down the dose by 20% or 25% in terms of the second time around.

Dr. West: Thank you. A question about whether there might be interventions which can decrease the risk of longer term problems, radionecrosis in the brain, for instance. Whether an intervention like hyperbaric oxygen or Avastin (bevacizumab) might be beneficial. Do you have any sense, or are there any data that speaks to the potential benefit to either of these in terms of improving the safety of the intervention?

Dr. Mehta: So radiation necrosis is a challenging and difficult problem and is more frequently associated with options that give large doses of radiation to the brain, such as radiosurgery. It is almost unheard of with standard whole-brain radiotherapy. Not zero but single digits -- 1% or less. With stereotactic radiosurgery the number is larger. By imaging studies it could be anywhere from 10 to 30%, depending on the

parameters that you use to define radiation necrosis. But clinically symptomatic radiation necrosis, where a patient has symptoms, is typically less than 10%.

So this is a situation where normal brain tissues surrounding the tissues start dying off start an inflammatory response in the brain that is attempted to control with steroids at first, and this may work for a period of time. But for some patients, inflammatory response takes over and causes lots and lots of problems and symptoms and can't be controlled with steroids. The gold standard for these patients has been resection, going in and removing the necrotic tissue. And for the most part, that helps the majority of patients. It is also helps for the diagnosis: are we dealing with progressive disease are we dealing with radiation necrosis? People have tried many drugs to try and reverse radiation necrosis, prevent it, get rid of it.

The results are mixed, but generally discouraging. Most of the drugs have not really shown good results, and a variety of different drugs have been used, including hyperbaric oxygen, which really hasn't shown that much benefit to radiation necrosis in the brain, although it has shown benefit in terms of radiation necrosis of the jaw bone or ulceration of the lining of the mouth when patients get radiation to the head and neck region. Most recently, the use of bevacizumab has cast some interesting questions about the use of drug for reversing radiation necrosis. The study that was done was conducted at MD Anderson Hospital in Houston, and they took a group of patients that had developed radiation necrosis because they had radiation to the skull base area. None of these patients had brain tumors. All of these patients, in fact, had skull-based tumors, so we knew that the brain was not the organ at risk in terms of disease coming back. So what we were seeing was clearly necrosis and not recurrence of disease.

These patients were treated with bevacizumab, and in fact it was a randomized trial, so some were treated with bevacizumab, and some were treated with placebo. A group of patients responded. The ones that did not respond, they went back and checked what they were receiving, and they were all receiving the placebo and then they switched over to receive the bevacizumab, and then they responded at that time. So necrosis of the brain in the absence of actual tumor in the brain has been shown to respond nicely to Avastin (bevacizumab).

However, we don't have a similar trial that's been done for tumors that are in the brain, either primary tumors or metastases. But based on this trial, there is increasing use of bevacizumab in the face of radiation necrosis. There are clearly

reports -- individual reports -- of patients responding. So this is clearly an area that needs further study but could be promising.

Dr. West: Thanks -- great. Another question is, if you do have a patient who experiences a significant neurologic decline after radiation to the brain, are there any specific recommendations that you have or you could know of that could be effective in reducing that or reversing it?

Dr. Mehta: So once again we are now dealing in the realm of limited evidence for this particular situation. We sort of have to extrapolate from experiences in other diseases of the brain. For example, there was a European trial in patients with low grade glioma. In this trial, patients were randomly assigned to what's called cognitive rehabilitation, which is just observation after the treatment. So a deliberate attempt was made to try and help patient keep their memory intact. And the cognitive rehabilitation group did much better. So trying to work on preventing this could be beneficial. How does one prevent it? What are the things that you can do?

There are actually simple tricks that one could try. For example, keeping the mind alert and active by forcing it to do tasks that require association between words and letters. Sudoku, crossword puzzles, repeating words, mnemonics, looking at calendars, repeating events -- things of this sort -- even substantial reading could be beneficial. So, cognitive rehab could have a role, even though this has never been studied for brain metastases.

For patients that have already developed cognitive decline, sometimes steroids will reverse some of the symptoms. And the reason for this is that they have swelling in the brain, and steroids might be able to reverse it, at least temporarily. In other patients, there could be other situations that are contributing to this. For example, some patients that were put on steroid medications, the most notorious being phenytoin (Dilantin). This is a drug that can cause significant cognitive decline, and sometimes patients don't actually need it. They've been on it a while, and we tend to forget that they are on this drug. Taking away the drug can also result in significant improvement of the memory.

So looking at the patient as a whole can help. We've found that many of these patients are often hypothyroid and if you check their thyroid function, their hypothyroid and if you replace Synthroid, or thyroid hormone, their memory improves. When you've done all of this, you've ruled out other causes, you've checked all these things and you still have a patient that has cognitive decline, are

there drugs that work? Once again, the clinical trials are not very good in this regard.

The RTOG trial is one of the best ones that has looked at the drug Memantine -- the Alzheimer's drug. We don't have the results yet. But in my practice, we have used Memantine on some of these patients and it appears that it has worked in some patients. But that is really what you'd call anecdotal experience and anecdotal experience is only so valuable. It's really not categorically good evidence. There are other drugs in early testing that appear to do the same thing. Drugs called ACE inhibitors for example. ACE inhibitors are used to manage of high blood pressure. There are animal models and preclinical data that show that ACE inhibitors might in fact prevent the development of cognitive deficits. So there are clinical trials being developed for that. There are other drugs beyond that which are also being tested. So, a series of drugs are being looked at for potentially reversing the cognitive decline. But we don't have conclusive data on any of these yet.

Dr. West: Do you think at this point brain MRIs should be part of standard follow up for patients that are longer term survivors of either non-small cell or small cell lung cancer, whether it is patients that are years out from surgery or treatment of locally advanced disease or for patients who are receiving ongoing treatment but for a period of months or years after their initial diagnosis for advanced disease? We don't usually do this, but do you recommend surveillance of the brain?

Dr. Mehta: So the honest answer to the question is, I don't know. I don't know because we haven't done this in a structured, constructive way that we can actually learn and see if this makes a difference. This has been done in some other diseases. There are small studies in the arena of breast cancer. In the small studies that are available in the breast cancer literature, it does not appear that detecting brain metastasis early through screening MRI studies results in prolongation of survival.

So we don't improve survival by doing surveillance MRI imaging studies in the small studies that are available in the world of breast cancer. In the world of lung cancer, we just don't have good data at all. I think it's less likely that we will see survival improvement unless we pick up a significant cohort of patients with just one brain metastasis. If we were to be so lucky, then we might in fact see a difference in survival by doing surveillance. The problem with surveillance is when, how often, and for whom? It's a tough question. We don't know whether it should every two months, every three, every four, every six. Should it change in

the second year compared to the first? Should it change in the third compared to the second?

I think these are very difficult questions. But I think what is very clear to me from clinical practice is if a patient has symptomatic change, even the vaguest of symptoms -- persistent headaches that don't go away, memory changes, gait changes, vision changes, balance problems, if they just stop being themselves -- it's certainly worth doing an MRI then, because quite often you might pick up brain metastases then.

So I don't know whether we should do surveillance. My gut feeling is that there might be a subset of patients that are considered high risk and if one were to do it, you couldn't be faulted for it. But there are no good guidelines. There's clearly potential to overuse and abuse it.

Dr. West: Fair enough, still far more questions than answers with that one**.** Then a final question is, what is your level of comfort and your recommendations in terms of administering whole brain radiation concurrently with chemotherapy or an EGFR inhibitor? Are you comfortable with that or do you prefer to avoid that if possible?

Dr. Mehta: It really depends on the drug. In general, if we don't know whether we are going to increase toxicity or not, we should avoid it, because one of the biggest fears that patients have from whole brain radiotherapy is the possibility of cognitive decline. And if we don't know whether a drug could potentially increase that in combination with radiation, we should try and avoid that.

So what do we know? What are the drugs that we know we can safely give with whole brain radiotherapy? There are some clinical trials where some drugs have been used. So for example the alkaloid agent temozolamide has been used in an RTOG study that has not been published -- we don't have the results yet. But for patients who were treated with whole brain radiation and temozolamide for non-small cell lung cancer with brain metastasis, we did not see any dramatic increase in obvious negative effects so it's reasonable to conclude that this could be safe.

Similarly, we have also looked at EGFR inhibitors. This is an interesting area. EGFR inhibitors in the laboratory, most of them can be shown to be radiation sensitizers for tumor cells. So here we could have the potential not only for an EGFR inhibitor to act on its own against an appropriate tumor that has the right characteristics for response from an EGFR inhibitor. But also the potential that it

could enhance the affects of radiation on the tumor. So the RTOG studies that I mentioned to you with temozolamide had a second arm where an oral EGFR inhibitor was combined, Tarceva and that was combined with whole brain radiation.

That particular study, again we don't know the results yet, did not show increase toxicity since Tarceva was combined with whole brain radiation. That problem is not drugs such as temozolamide or Tarceva. The problem really is the standard of care doublet chemotherapy that we use for most patients with metastatic non-small cell lung cancer. For example, if we were to use the gemcitabine-based regimen, or a pemetrexed-based regimen, or potentially even a paclitaxel-based regimen, there could be some concerns. These drugs are radiosensitizers and potentially also radiosensitizers of normal tissue. That's where the worry and the fear comes from when we use the combination of full dose chemotherapy especially used in a doublet context, where we might perhaps find more risk. There I try and avoid it.

Dr. West: Great. Dr. Mehta, thank you so much for your generosity with your time and the great answers that you've provided.

Let me say also, I'd like to thank the LUNGevity Foundation which worked in partnership with GRACE, the Global Resource for Advancing Cancer Education to have this program. Take care.

Dr. Mehta: Thank you everybody. It was a pleasure.