

**Interview with Dr. Vivek Mehta, Radiation Oncologist
on Radiation for Early Stage and Locally Advanced NSCLC
by Dr. Howard (Jack) West
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Dr. West: Hello, this is Dr. Jack West, medical oncologist at Swedish Cancer Institute and the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. I'm here with Dr. Vivek Mehta who is a radiation oncologist and the Director of the Center for Advanced Targeted Radiotherapy at Swedish Cancer Institute. And we're here to discuss several key issues in radiation oncology especially those relating to lung cancer.

So, Vivek, what are the leading approaches for patients now who have early stage non-small cell lung cancer, but who don't have the lung function to pursue surgery.

Dr. Mehta: Jack, I think there are a lot of non-surgical approaches for this cohort of patients. The traditional approach has been to do conventionally fractionated radiotherapy and we've been doing this approach for several decades and we've been improving and improving on that approach by various different technologies. Conventionally fractionated radiotherapy is based on the principle of delivering a very small dose of radiation each day, Monday through Friday, over a period of about 7 to 7 ½ weeks. The radiotherapy fields are designed to encompass the tumor volume and its extent of motion. So a lot of people today are doing 40-treatment planning which involves studying the tumor's trajectory and motion during a breathing cycle, customizing and individualizing the fields for that particular patient's tumor trajectory. The rationale behind giving a very small dose of radiation each day is that that dose is enough to cause damage but not actually cell death. Cancer cells since they're growing so rapidly, don't have the ability to repair that damage. Normal tissues because they are not cancer, have the ability to repair that DNA damage.

So the concept is that you selectively kill more cancer cells, you injure the normal cells, the normal cells repair themselves during that 24-hour healing period. When you look at sort of *in vitro* studies, it only takes about four hours for normal cells to repair that damage. Hence, the idea of fractionated radiotherapy.

Now if you look at the data for fractionated radiotherapy in this population, we do pretty well. But when you compare it to sort of the gold standard of surgery, across the board, retrospective studies from

large institutions, we're probably about 10% worse. Now part of the reason that we're a little bit worse than surgery is an issue with how the data is defined. When you use radiation data sets, you're often using the tumor size based on the CT scan. Okay. And a portion of those CT scans are either going underestimate or overestimate the extent of tumor disease.

When a surgeon compares his data set, he's comparing it based on pathologic specimens. So he's going to actually report the actual size of that tumor which may have been larger or smaller than the CT scan data. So there's going to be a little disconnect when you compare it to surgery.

The other issue is that as patients get upstaged because of the pathologic data, they get put into a different group. And that doesn't happen when you compare radiotherapy series because you don't have an upstaging phenomenon -- you have simply the CT data.

Also, if you're looking back at past data and comparing these two approaches, the radiotherapy population tended to be less well, less healthy than the surgery population that under the surgery. I would say that that's sort of still *de facto* standard in the community to do fractionated radiotherapy for about 7 or 7 ½ weeks for these small lesions in the surgically unresectable population.

In the last decade, there's been an emerging approach. In generic words, this is the idea of giving stereotactic radiosurgery to try to ablate these lesions. Stereotactic radiosurgery in general terms is to deliver a very high dose of radiation just to the tumor site. Okay. Instead of giving 30 or 35 fractions, you might be giving somewhere in the neighborhood of 3-5 fractions. Some people might actually just give one fraction depending on the size or location. The difference between three and five fractions tends to be the location in the lung and the adjacent proximity to surrounding normal tissues. You're giving a very high dose of radiation that biologically actually translates to the equivalent of giving 10-11 weeks of fractionated radiotherapy. So its actually biologically more powerful than even the 7-week course of radiation that we typically did.

The concept behind this is that you're delivering a very, very high dose of radiation just to the tumor bed and you're actually killing the cancer cells. You're not damaging DNA. You're simply killing them because they're getting such a high dose.

The other concept here is that you're delivering the dose with such precision and such accuracy that there's very little surrounding dose to

the normal lung tissue, so you're killing very little normal lung. The way you're able to do this is by identifying where the tumor is, then angling the beams from thousands of different angles so that they overlap on that particular target. There's very minimal entry dose, there's maximal dose right at that area.

Now, there's two approaches for knowing where the target is at any given instant. One is to do similar planning, that I talked to you about before, where you understand the tumor motion and trajectory by doing 4-D planning, and then based on that extent of motion, you try to suppress the motion either immobilizing the patient, actually maybe them wearing a band around the chest or around the abdomen so that the extent of motion is suppressed and then you carefully image just prior to treatment to make sure that you've got the patient set up accurately. So that would sort of be stereotactic radiosurgery, using an image-guided or motion encompassing strategy.

The other approach would be to try to track the moving target, and the way you do tracking would be to implant some sort of marker into the target and then follow the marker. So the Cyberknife radiosurgery platform means that you would implant gold fiducial markers in and around the tumor and then the robot would track that moving target, turning the beam on and off based on what it sees, where those markers are. Early data suggests that you can get control rates of 85%-95% using these approaches in carefully selected patients. The idea of doing stereotactic radiosurgery as an alternative to surgery in even healthy patients is actually being studied in one open trial right now, and it's also the subject of another study as a single-arm phase II trial.

Dr. West: Are these trials distinguishing between patients who are considered medically unfit and with limited lung function or significant other medical problems, and other patients who for whatever reason don't want surgery because those patients probably have very different outcomes.

Dr. Mehta: So I think that the world has sort of come to the idea that the medically unfit, the patients that can't have surgery, can be treated with radiotherapy as an alternative. These two trials, one is a randomized trial of actually healthy patients that could have surgery because they have adequate lung function and its comparing the stereotactic approach to the actual surgery; the other trial takes those same healthy patients, but it's a single-arm phase II and treats them with stereotactic radiosurgery. So patients are obviously opting in to a trial that is an alternative to surgery even if they had been surgical candidates. So it's a little bit cleaner population for us to get a sense of how we do.

I will say one other thing, and that is these trials are not open everywhere because in order to participate in the trials, the treating radiation oncology facility needs to go through a lot of training and quality assurance to validate that they can actually do these treatments. So it's only a limited subset of radiation oncology facilities that are available to participate in these trials.

Dr. West: That was another question that I had, which is, what is the availability of these kind of approaches? Is this something that is available fairly broadly nowadays or is this something that you're lucky to have one or two places in your state that can do this kind of work?

Dr. Mehta: Well, I think it's an emerging treatment approach that is becoming more widely available. But I think you're probably still looking at only a handful of places of any given geography that have enough experience to approach this. It's such a high dose of radiation and there is this issue of movement and immobilization. It takes a lot more time on the machine. So I think you want to go to a center that's had experience in doing this.

Now, I guess, Jack, another question that just sort of popped into my mind is that there are some patients that are probably candidates for surgery, but they're not considered candidates for the classic lung cancer surgery. When we talk about the classic surgery, we're often talking about a lobectomy, so removing the tumor and the entire lobe that the tumor was in. Some of these patients could actually have a more limited surgery, like a wedge-resection, but that's not considered a classic tumor surgery. When we look at the people that have had sub-lobar resections, or wedge resections, that's a very heterogeneous population as well because how big a wedge or how big a sub-lobar resection is open to the surgeon, and it's open to the ability of that patient to sustain that surgery. And so, we see in some series recurrence rates that range from 20%-40% after that type of surgery.

Dr. West: Local recurrence...

Dr. Mehta: Local recurrence. And we've done studies in this population where we've tried to give external beam after that limited surgery, and we've had no success in reducing the recurrence rate. And part of the reason we think that's true is because when you do a sub-lobar resection and then the lung is reattached and fills with air, you actually can't visualize where that surgical margin was, where that high risk of having microscopic disease is. And it's constantly moving because you can't visualize it, you can't see it, you're not actually sure if your external beam field is encompassing the critical areas or not. At least that's the explanation for why we fail to show a reduction in risk.

There are a couple of centers now that have published really interesting work where they have gone into the operating room with the surgeons and lined that limited surgical resection with radioactive BBs, or radioactive pellets. And the idea is that you're treating just the area that's at most risk. And when they do that, they've seen a reduction in the risk of local recurrence. Now that approach used to be to take a number of pellets, somewhere in the neighborhood of 50 to 100 radioactive pellets, and sew them in individually, which is a burdensome thing to do. Now, that these pellets are actually come pre-sewn into a mesh, it's become an easier procedure to do with less time in the operating room.

Dr. West: And you're written a post about that really recently.

Dr. Mehta: We did write a post on the GRACE website about that.

Dr. West: So one of the very common situations that we face now is patients with locally advanced but potentially curable non-small cell lung cancer, stage III disease, and they're not, say, being treated with a plan for surgery afterwards. We standardly recommend concurrent chemotherapy and chest radiation. It's a pretty challenging thing for patients to go through. What do you tell patients about what to expect in terms of practically how it goes, and side effect profile for undertaking that kind of concurrent chemoradiation approach.

Dr. Mehta: You know, Jack, it is a tough treatment to go through. It may not be the toughest thing that we do to patients with lung cancer, but its close. These patients can get really sick, really worn out. They can have problems with eating and drinking and swallowing. We call a lot of that esophagitis which is sort of a glorified word for a sunburn in the esophagus.

I've seen patients from many medical oncologists and when the patients come from a medical oncologist first, they often tell me, so you're the guy that's going to burn my throat; you're the guy that's going to burn my esophagus. And I like to remind them that that's actually not true, although it's partly true. When we've treated patients with lung cancer in the past with radiation alone, if you go back two decades, the incidents of really bad radiation burns in the esophagus that would require a PEG tub or IV hydration was somewhere in the neighborhood of about 2% or 3%. When we treated patients with chemotherapy and then we followed it with radiation, the incidence went up to 3%-4%. Now when you overlie the chemotherapy and the radiation together, that's when you see about a six-fold jump. You see a about a quarter of these patients getting about grade 3 radiation esophagitis.

It's a tough thing to go through. It's not everybody going through it and the length of the severity of this and the duration of severity and how bad it is is variable. But I think keeping these patients adequately hydrated, keeping their nutritional status up and creating that expectation that it might happen to them is important. One of the things that we don't want to happen is these patients get sick and then we interrupt their treatment. We don't really want to interrupt their chemotherapy. We don't want to delay their chemotherapy. We don't want to dose reduce their chemotherapy. We don't want to interrupt or delay their radiotherapy. Both of those things basically subtract from the intensity of the treatment.

Now, the magnitude of benefit of doing concurrent chemoradiotherapy over sequential chemoradiotherapy is not particularly high. Okay. But it's real, and it's been proven in multiple studies now and if our goal is to try to cure and eradicate this disease, we're going to cure more people if we do it concurrently. So, I think it's an open and honest discussion with these patients.

Now there are some things that have happened over the years on the radiotherapy side of things that have helped to try to mitigate some of these side effects. If you go back to when these trials were designed about a decade ago, oftentimes the radiotherapy fields were far bigger than they are today. The sort of the rapid development or availability of PET and PET-CT, this allows us to identify patients that are at risk for having lymph nodes that are in the mediastinum high or low or intermediate areas, and the radiotherapy fields are more tailored to that. And so I think that's help reduce some of the esophagitis risk.

Dr. West: Which patients now would you recommend a sequential instead of a concurrent approach for if you're trying still to cure locally advanced stage III non-small cell lung cancer.

Dr. Mehta: It's more of a case-by-case basis when we start to think about those patients. Some of these patients may not appear as robust as others and we may want to approach them with a sequential approach. Some of them on their imaging studies, they're questionable whether they're locally advanced or actually metastatic and we might to test out their responsiveness to chemotherapy. And there are still others that while they may be able to tolerate this, they lack the social infrastructure and support. If you're going to go with a concurrent approach, it's nice to have that support around those patients. So I think we have to tailor our decision making to the patient that we seen in front of us.

Dr. West: How about any role for medications, these radio-protectants, have any of these proven to be valuable for esophagitis? And also, do they reduce any of the activity against the cancer?

Dr. Mehta: Those are great questions. When you think about a drug that is supposed to protect normal tissues, you worry that it might protect cancer. So the idea of using a radio-protectant is a compelling idea. The challenge is that you want an agent that's going to protect normal tissues and not protect the tumor. I think the community of radiation oncologists and medical oncologists today is waiting to hear more about a drug called palifermin made by Amgen, which is basically a KGF-like agent that protects the epithelial cell lining. It's being tested in the setting of patients getting radiation and chemotherapy for lung cancer. It's meant to reduce the incidence and risk of esophagitis. And we're waiting to see how that data pans out; and it should be out shortly. This drug actually got approved by the FDA in the setting of bone marrow transplant where patients were getting total body irradiation as well as high dose chemotherapy and in a randomized phase III, it significantly reduced the risk of esophagitis. It also significantly reduced a series of other sort of toxicities associated with that.

Now, bone marrow transplant, we often talk about that as being sort of liquid diseases. And so the risk of protecting epithelial cells in a sort of liquid disease is different than protecting epithelial cells in a solid tumor-like setting, head and neck cancer or lung cancer. The other drugs that have been tested out there haven't really panned out. Amifostine is a drug that is supposed to reduce the risk of mucositis. The mucositis data for amifostine is a bit questionable. It clearly protects the parotid gland from xerostomia in the setting of old fashioned or 3-D conformal radiation. Whether that benefit is still real in the setting of IMRT has never been studied. So we don't have a lot of really good radiation protectors out there.

Dr. West: One of the cooperative groups, the North Central Cancer Cooperative Group, or NCCTG, which is based out of Mayo Clinic, started a trial recently where patients are going to receive radiation to areas of residual disease if they have one or a few isolated spots of residual disease after first-line chemo. This certainly goes against the idea that if a cancer has already metastasized, there isn't a role for radiation except to palliate symptoms like bone pain or shrink a compressing tumor. Do you think that this idea of irradiating residual disease in one or a handful of spots immediately after first-line chemo makes much sense?

Dr. Mehta: You know, it's a changing paradigm. And there's no doubt that we're in a situation for lung cancer that's evolving. If we go back five years, six

years, ten years even, there really were no established fourth-line chemotherapy agents, no established third-line chemotherapy agents, no established second-line chemotherapy agents. And for metastatic lung cancer, we didn't do very well. Now what we're starting to see is that patients will respond to drug therapy but maybe not entirely. They will respond in some areas of their disease, but not all of their areas of disease. And that we can improve survival by altering the chemotherapy agents, changing the regimens, adding second-line, adding third-line.

So the idea of using radiation in a sort of spot-welding mode of treating bulk disease in some area or another using the chemotherapy to treat the micrometastatic disease and prolonging survival is theoretically attractive. Okay. Now whether that's going to pan out or not is hard to know.

Where is this sort of whole paradigm get some of its legs, if you will? It gets some of its legs from some of the physicians that we know, colleagues that we have that have been very aggressive in treating patients. Perhaps overly aggressive from the standard and have now reported that, look these patients seem to be doing better. That could all be a phenomenon of selection. I mean you could simply be having patients that do better would have done better anyway and by the fact that they were treated aggressively is not the determining factor. So I think studies like this are going to be important. Paradigms shift and paradigms change. And whether we have proof of this or whether this is going to pan out, it's hard to know. And I think that when we tackle local or multiple local sites with local therapy whether its surgery or radiation, the criticism is the same, that something else might pop up downstream. There are groups of patients though that we all see in the clinic where they have one or two isolated foci and they stay that way. Okay. And then we see patients that have two isolated foci and the next scan they have ten isolated foci. And then they have 20 isolated foci. We don't do a very good job of differentiating those two and we don't know if we wait too long on the people that have two, whether that's going to recede to somewhere else. And we don't know why our chemotherapy seems to sterilize everywhere else except in these isolated areas. So I think this is an open question.

I think that perhaps what is going to happen is that we're going to find out that these cancer cells, even though its lung cancer in a particular patient, are far more heterogeneous than we ever thought before. And, you know, perhaps the chemotherapy is working best on the cells that have the most metastatic potential. And the cells that are locally aggressive may not be responding to the chemotherapy; hence these isolated foci of disease where you're keeping the rest of the body

sterilized. There's a lot to be learned. And it makes the whole genomic space more complicated because you'll get one pattern of one cluster of cells which may not represent the entire biology of that particular patient's cancer cells.

Dr. West: Can you give more radiation to patients who have received prior chemo and radiation for, say, stage III locally advanced non-small cell or limited small cell for that matter and then have what appears to be a local recurrence in the radiation field?

Dr. Mehta: I think there's two aspects to your question. Can you, and should you? And what's the risk that the patient takes when you do that?

When we treated patients in prior eras, we didn't have as much technology and so we had exposed a lot of the normal tissues to a high enough dose that it caused some risk of complications. And we would go to that very threshold. And so the idea of retreating them was dangerous and challenging. And we did it when we had no other options. Today the technology allows you to come in from different beam angles, allows you to spread the dose around, so perhaps we're a little bit safer in retreating these patients than we were in the past. Now, the second part of that question is can you actually do some good when you retreat these patients and there are series and certain disease types. There's a lot more evidence in breast cancer when you retreat that you can actually get durable local control. In lung cancer there's sort of emerging data that it might be a useful option. The challenge in lung cancer is these patients sometimes fail outside of that field as well.

But there's an intellectual question and that is if you couldn't eradicate the cancer the first time around with conventionally fractionated radiation, what makes you think that you would be able to do it again with either the same approach or slightly less dose the second time around? So I think what people are now trying to do is consider giving stereotactic radiation approaches, so the big whopping doses, one to four times in those previously irradiated fields and they seem to be able to do that with minimal toxicity and good local control.

Dr. West: Great, thanks.