Clinical Trial: Phuoc Tran, MD Salvage Radiation Clinical Trials

Dr. Phuoc Tran, the Clinical Director of Radiation Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, treats patients with genitourinary cancers. He uses stereotactic radiation techniques (such as SRS and SBRT/SABR) to treat patients with oligometastatic disease.

Prostatepedia spoke with him about two clinical trials he is running.

How did you come to focus on prostate cancer?

Dr. Phuoc Tran: I'm a physician/scientist: an MD/PhD with a focus on cancer biology. That interest stems all the way back from medical school through graduate school into

"Prostate cancer is a disease spectrum."

my residency training in radiation oncology and my postdoctoral fellowship training in cancer biology. Along the process of that training, I had a chance to interact with men who had prostate cancer, which influenced greatly my research interests in prostate cancer. Despite many recent advances, prostate cancer is still among the major causes of death.

What is the thinking behind your Movember-PCF-funded clinical trial looking at stereotactic body radiation therapy (SBRT) in oligometastatic disease?

Dr. Tran: Cancer is not one illness, as many people believe, but many. Prostate cancer is not unique in that regard. Prostate cancer is likely broken up into distinct molecular subsets with distinct biologies and possibly distinct clinical behaviors. However, clinically speaking, we prescribe treatments for men with prostate cancer as though prostate cancer presents in discrete clinical states: in one state are patients we believe to have purely localized disease and they are curable by surgery or radiation. In the other state are patients with metastatic disease and those patients are treatable but not curable with our current therapies.

In general, this old treatment paradigm says that patients who have localized disease benefit mostly from local therapies like surgery and radiation and very little from systemic treatment like hormones and chemotherapy.

Those who have metastatic disease benefit from treatments that go everywhere—hormone treatments and chemotherapy-type treatments. These patients don't benefit a lot, at least in a life-prolonging way, from radiation.

In reality, prostate cancer is a disease spectrum—with purely localized prostate cancer patients on one end and widely metastatic prostate cancer patients on the other. Within that spectrum are patients who have oligometastatic disease: low-volume metastatic disease, or just a few metastases. (Oligo is just a fancy word for *few*.) Using the same characteristics and rationale, it stands to reason that patients with limited metastatic disease might benefit from both systemic and *local* treatment. Systemic treatment to kill stray cells that may reside throughout the body, but also localized therapies to the few areas of disease that can be seen on imaging or physical exam. These oligometastatic patients actually may still be curable because some, myself included, believe that they are closer in disease biology to localized patients than widely metastatic patients. Right now, as I previously stated, the old way of thinking is that a patient is not curable whether he has one or 100 metastases.

There is some provocative data, but a lower level of evidence—what we call *retrospective* data—which suggests this approach of giving local therapy to those with only a few metastases may be true. If you treat not only the primary disease in the prostate or the pelvis, but also the few metastatic lesions, patients can actually live a long time without disease progression and/or be cured.

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In colorectal cancer, for instance, when just a few lesions have gone to the liver, the treatment paradigm is to give chemotherapy, surgery to remove the colorectal cancer, as well as intensive local therapy to those liver metastases. A fair number of patients can be cured. It's not that unreasonable to extend this idea to prostate cancer patients.

From a radiation oncology perspective, there has been a lot of technological growth over the last 15 to 20 years, which has culminated into an approach called stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation (SABR). SBRT and SABR are highly focused radiation given in an intense fashion. I tell patients it's like spot welding—small area, very intense, and theoretically ablative, meaning it kills all the cancer in that spot.

Armed with that new technology and with the idea that local therapies such as surgery, radiation, and other ablative therapies can be beneficial in oligometastatic patients, we wanted to test our idea in a rigorous way. There is data suggesting there may be a benefit from local therapies like surgery and radiation to oligometastatic patients, but there is not, at least in prostate cancer, good data from randomized clinical trials.

Our trial is a randomized trial of patients with oligometastatic prostate cancer defined as three or fewer metastases. They have to have received treatment for the primary prostate disease, so surgery or radiation, and have had no prior hormonal therapy for their metastatic disease. They can have had hormonal therapies in conjunction with treatment for their *primary* disease, but not for their *metastatic* disease.

Patients are randomized to either SABR to up to three sites or a short observation period of three to six months. The randomization is 2:1 to SABR versus observation.

Are there any other eligibility requirements?

Dr. Tran: Like I said, the number of lesions has to be three or less. The tumors have to be of a certain bulk or size—they can't be too large. Patients have to have a PSA doubling time of less than 15 months. (PSA doubling time is the time it takes for the PSA to double.) We chose less than 15 months because there are patients who have biochemical failure or low-volume metastatic disease with long doubling times, sometimes many years. Those patients, frankly, probably just won't ever need to be treated. We want to zero in on patients for whom this type of treatment can make a difference.

Why do you limit to three mets? I thought oligometastatic disease was defined as three to five?

Dr. Tran: The definition of oligometastatic disease depends on the histology, so it is different for prostate versus lung cancer versus other cancers. In general, the literature defines oligometastatic disease as three to five mets. In prostate cancer, there is not a terrific amount of good data. But because we're doing a randomized trial with an observation component, we wanted to limit the number of mets to three for safety reasons.

Do patients need to be in the Baltimore area to participate?

Dr. Tran: The fortunate thing with this trial is that because we're using SABR we can treat individual lesions in anywhere from one to five treatments, unlike traditional radiation that requires eight weeks. If patients come to Baltimore for treatment, it wouldn't have to be for as long as traditional conventional radiation.

We are thinking about opening up the trial at sites outside of the Baltimore/Washington area, but we haven't made that jump yet.

Is there anything else you think patients should know about this trial?

Dr. Tran: We're going to have a lot of really interesting correlative studies. Patients will have their blood drawn before treatment and at three and six months. We'll be using those blood samples to look at things like circulating tumor DNA and circulating tumor cells.

We're also going to look at the effect of radiation on the immune system, by looking at something known as T-cell receptor profiling, which is

a really advanced way to look at individual circulating T-cells.

We will also look at a new PSMA-based radiotracer called DCFPyL. PSMA is a marker commonly displayed on prostate cancer cells that allows us to employ a very sensitive type of imaging. Patients will get that as well so that we can evaluate how helpful that imaging is.

Our study is trying to answer whether or not we can change the natural history of oligometastatic disease with SABR while also evaluating cutting-edge correlative and translational science endpoints.

How many patients will you enroll?

Dr. Tran: This is a 54-patient trial: 36 patients will be randomized to the active treatment arm and 18 to the control arm. In the observation arm, if a patient progresses—typically measured by PSA—he can cross over and get SABR off-trial. Ultimately, all patients can be treated with SABR.

Do you have a second trial that combines salvage radiation therapy with Xtandi (enzalutamide)?

Dr. Tran: Yes. About 30,000 men die of metastatic castration-resistant prostate cancer every year. Only about a third, or 10,000, are diagnosed initially with metastatic prostate cancer. The majority of the patients who die every year had, at initial diagnosis, actually presented with localized disease that was potentially curable. They were treated with surgery or radiation, but these therapies, unfortunately, didn't work.

These men recur biochemically in most cases, meaning their PSA starts going up. Up to two-thirds of these men then progress farther and farther down this unfortunate pathway until they have metastatic castration-resistant prostate cancer. If we had something better in the way of salvage treatment, those men could potentially be spared that progression to metastatic castration-resistant prostate cancer and ultimately death.

Salvage radiation is standard of care for patients who have failed surgery and have biochemical failure. Unfortunately, for a number of reasons, it's not as effective as we'd like. In certain patients, salvage radiation can be quite effective, as high as 70 to 80%. But if we lump all the patients together whom we treat with salvage radiation, we only have about a 40 to 50% control, or success, rate. Bottom line: we need to improve that.

If we had much better salvage treatments, perhaps we could get the number of men who die every year down to as low as 10,000. Recall that the majority of men who die from prostate cancer each year originally had potentially curable disease. That is the basis of our study: trying to reach the biggest population of patients to whom we can potentially give a second chance at a cure.

We know from patients presenting with prostate cancer who are treated with radiation upfront that radiation can have a synergistic interaction with hormone deprivation or hormone therapy. There are many Phase III trials demonstrating this with excellent data. Some of the best data in prostate cancer in general shows that radiation combined with hormones cures more men.

Unfortunately, in the salvage setting—that is when men have biochemical failure after radical prostatectomy—there is very little in the way of good randomized data. As I said before, there are a huge

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number of men with prostate cancer who fall into that space. We want to improve outcomes of men in this space in a scientifically rigorous way.

A medical oncologist named Dr. Emmanuel Antonarakis and I led the design and activation of a trial called SALVENZA, which is a Phase II randomized trial of men with prostate cancer with biochemical failure following radical prostatectomy. Patients are given salvage radiation and receive either a placebo or Xtandi (enzalutamide).

Xtandi (enzalutamide) is, as I'm sure many of your readers know, a next-generation hormone blocker, which has been FDA approved for use in metastatic castration-resistant prostate cancer, both pre- and postchemotherapy. There are also some very promising new studies that are now being reported looking at Xtandi (enzalutamide) in the rising PSA castration-resistant prostate cancer space. Xtandi (enzalutamide) also has a very promising side effect profile compared to traditional castrating hormonal therapy, which knocks testosterone down to less than 20.

In that trial, the hope is that we'll be able to increase the ability of salvage radiation to cure more men by adding Xtandi (enzalutamide) and test this concept in the most rigorous way possible by randomizing men to Xtandi (enzalutamide) and placebo control.

Is that trial also Baltimore-based?

Dr. Tran: This is a multi-institutional trial open at Johns Hopkins University, as well as the University of Michigan, Wayne State University, the University of Chicago, the University of Utah, and Oregon Health Sciences University. We're trying to open at the University of Texas Southwestern in Dallas as well.

How To Get Involved…

Patients who are interested in participating should contact Dr. Tran on 410-502-8000 or tranp@jhmi.edu for more details.

Are there any eligibility criteria?

Dr. Tran: We're looking for men who have biochemical failure following radical prostatectomy. They have to have a Gleason 7 with positive margins or extracapsular extension following surgery or a Gleason 8 to 10. They have to have a detectable PSA, obviously, on two subsequent determinations, so a PSA of 0.1 twice.

How many patients will you enroll?

Dr. Tran: It is a 122-patient trial. We're about a third of the way there, but we need to finish enrolling in the next year or two. Pp