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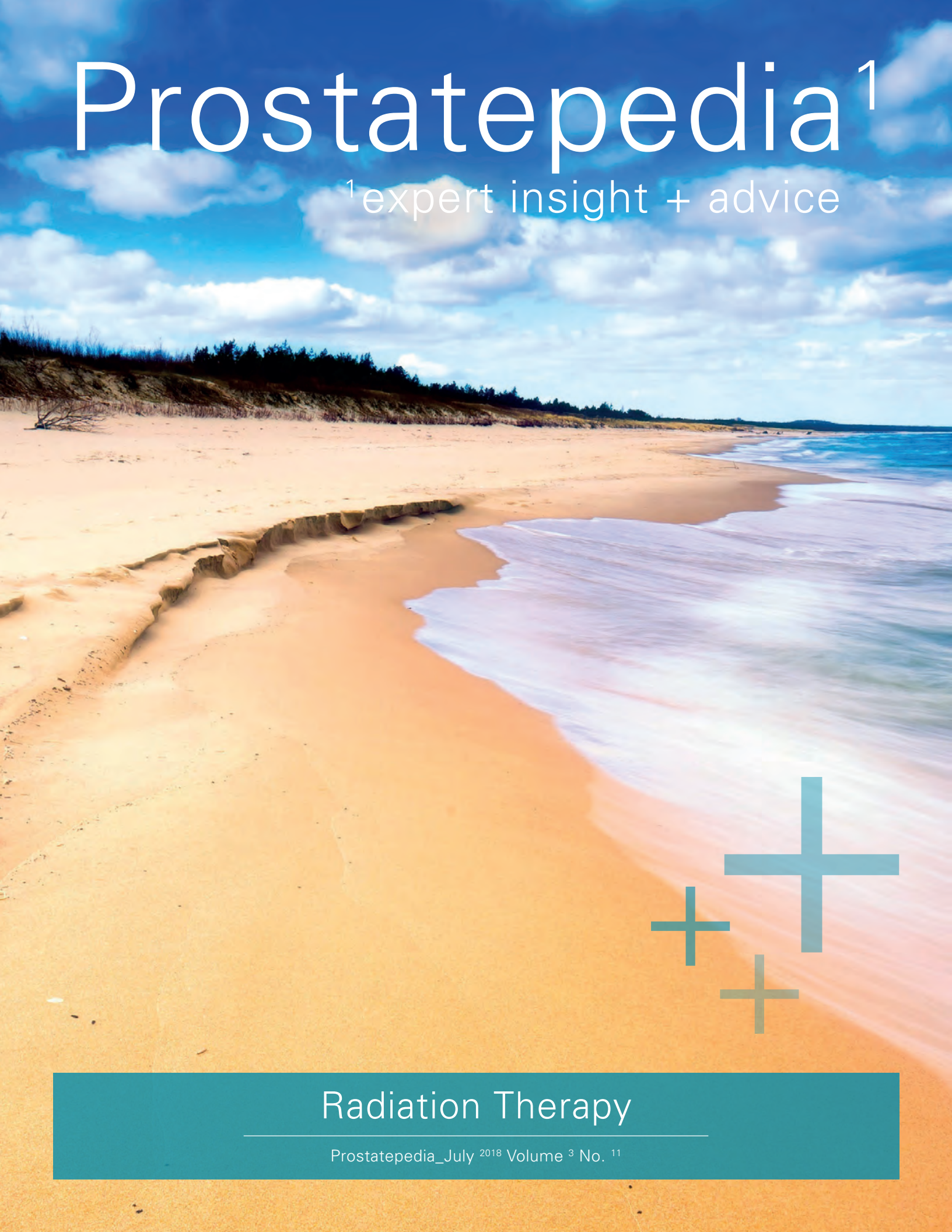

Radiation Therapy

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In this issue....

This issue focuses on the interaction between radiation therapy and immunotherapy for prostate cancer. This interaction has been extensively documented in laboratory models where the combined treatment can show benefit even in metastatic prostate cancer.

In the laboratory models, it appears that cancer cells damaged or killed by radiation trigger an immune response. This response can be enhanced by additional agents.

The most promising situation to test this approach is in patients with oligometastatic prostate cancer. These patients have 5 or fewer metastatic lesions that can be targeted by radiation therapy. In this setting, all detectable prostate metastases receive a radiation dose sufficient to treat the cancer.

The hope is that triggering an immune response will enhance the ability of radiation to kill all cancer in the irradiated lesions. There is also a hope that this immune response might suppress the growth of cancer metastases that are present but not radiated because the lesions are too small to be detected. This would act to delay the appearance of new metastatic lesions and possibly extend survival.

There are several unresolved issues in this area of research. First and foremost, immunotherapeutic agents with activity against prostate cancer are of limited effectiveness currently. For example, while the Provenge (sipuleucel-T) vaccine is FDA-approved to treat prostate cancer, it extends survival by only months. Immune checkpoint inhibitors, such as those that target PD1/PD1L, can cause dramatic responses, but they do so in only a small proportion of patients. Nevertheless, prostate cancer immunotherapy is a very active area of investigation with a number of promising concepts at various stages of testing.

Another unresolved issue is when is the best time to administer immunotherapy with regard to radiation treatment—before, during, or after. Radiation dose may also be critical as extensive radiation can dramatically suppress immune system function.

Despite these limitations, this is a research area worthy of investigation. The ultimate goal of cancer treatment is a durable complete remission. As it is unlikely that patients with metastatic cancer will ever be cancer-free, a more reasonable goal is to place remaining cancer cells in a state of dormancy. In laboratory models, immunotherapy is one of the most successful approaches to achieve cancer dormancy.

Charles E. Myers, Jr., MD Pp1

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Frontiers in Radiation Therapy

When you're diagnosed with prostate cancer, you're usually offered three options: monitor the cancer to see if it progresses, elect to have your prostate surgically removed, or elect to have the cancer treated with radiation therapy. Radiation is also used after surgery or in the event that the cancer comes back after that initial treatment.

Most of you are familiar with radiation therapy for prostate cancer—how it works, potential side effects, and special considerations. Even if you have not had radiation, chances are you've got a friend of relative who has.

This month, however, we're delving into less often discussed aspects of radiation therapy: the role genomics will play in radiation therapy, why we might consider combining radiation with immunotherapy, the impact imaging has on radiation therapy, and the role radiopharmaceuticals play.

Dr. Robert Bristow of the University of Manchester gives us a sweeping overview of precision radiation therapy—from functional imaging to genomics—as well as a run-down of molecularly-targeted agents.

Dr. Charles Drake of the New York-Presbyterian/Columbia University Medical Center discusses radiation therapy and the elusive but intriguing abscopal effect.

Dr. William Hall of the Medical College of Wisconsin talks to us about the precision radiotherapy movement and how it will revolutionize patient care.

Dr. Daniel Spratt of the University of Michigan Health System talks about a clinical trial he's working on with Dr. Felix Feng from the University of California, San Francisco (UCSF) that uses genomics to determine which patients will receive a combination of radiation therapy and Erleada (apalutamide) and which will get a placebo.

From Dr. Ralph Weischelbaum of the University of Chicago we hear about the thinking behind combining radiation therapy with immunotherapeutic agents—with a cautionary note.

Dr. Johannes Czernin from the University of California, Los Angeles (UCLA) talks about a clinical trial he's running on a radiopharmaceutical agent—a PSMA targeted lutetium-177. He is looking for patients to join, so if you think you might be a fit, please reach out to him at the email address included at the end of his conversation.

Ms. Merel Nissenberg offers the National Alliance of State Prostate Cancer Coalition's stance on hypofractionated radiation therapy.

Finally, Ron B. tells us about his experiences with stereotactic body radiation therapy. He has some advice for those of you in a similar situation to the one in which he found himself.

We suggest you read through this month's conversations and then send the issue to your health care team so that you can discuss the contents with them. Po

Anthony D'Amico, MD
Guest Commentary

Dr. Anthony D'Amico is Professor of Radiation Oncology at Harvard Medical School and Chief of the Division of Genitourinary Radiation Oncology at Brigham and Women's Hospital and Dana-Farber Cancer Institute in Boston, Massachusetts. He frames this month's conversations for us.

Dr. Charles Drake and others have done an outstanding job of describing all of the knowledge that has been assembled to date about the potential role of radiation in the immune-oncology setting.

We know that immune therapy works by removing immunologic breaks. That is, they remove the body's inability to fight against the cancer because the cancer itself has put a break on the immune system. That is what drugs like Keytruda (pembrolizumab) and others do. These drugs activate a T cell response against specific antigens that exist on the surface of cancer cells.

Everyone knows now that tumors are heterogeneous. They don't have only one antigen on their surface, so if you made only one antibody against it, it won't kill every tumor cell. Tumors can have many hundreds of different antigens that the immune system has to find, bind to, and connect with to kill. Radiation has the opportunity to make this happen if you irradiate the primary prostate cancer tumor. You ignite the immune T cell response against the antigens that live in the primary tumor as many people have discussed doing.

But that may not be sufficient. If a tumor has, say, a hundred antigens, but there are already cells in circulation that have escaped, then sometimes we can't detect them with imaging because they're below the level of resolution of our scans. Those cells developed different antigens (or mutations) that give them the ability to get away from the primary tumor, and they're continuing to mutate and develop new antigens. If all of that occurs, then those cells can go on eventually to metastasize. The immune system won't recognize them because the antigen(s) on their surface are different from the antigen(s) that are in the primary tumor.

To circumvent this issue, people are now combining radiation with immunotherapy. They irradiate the primary tumor in select men who have a couple of metastases—the so-called oligometastatic state—and then they irradiate those as well. By doing so, you potentially capture the antigens on the cells that have escaped the primary tumor and metastasized. This increases the probability of capturing all of the antigens and eliciting an immune response with T cells being activated against all the possible antigens that this tumor might carry.

Therefore, radiation therapy may have its biggest impact in the immune-oncology setting in a patient with oligometastatic disease. For diffuse metastatic disease, it may be too overwhelming to radiate all sites safely.

In summary, I'm concerned that if we just treat local, regional disease, the tumor volume that you're radiating may not be expressing all of the mutations or all of the antigens that the T cells need to be directed towards. There could be cells already in circulation that have new mutations and new antigens that the primary just doesn't have.

I'd like to make a point about Zytiga, (abiraterone), Xtandi (enzalutamide), and Erleada (apalutamide), which are mentioned in several conversations in this issue of *Prostatepedia*.

When a man is diagnosed with high-risk prostate cancer, the usual treatment is radiation followed by 18 months to 3 years of hormonal therapy.

After radiation therapy, and after about six months of hormonal treatment, the nadir value of the PSA is a very important value. It can predict the future. Many studies show that, at that point, a PSA value over 0.5 ng/ml portends a bad prognosis. Many of those men will die of prostate cancer. If that nadir value of PSA is above 0.1, they won't do as badly, but they still do more poorly than those whose PSA becomes undetectable.

It is thought that this is because people who still have a persistently elevated PSA after being on standard hormonal therapy like Lupron (leuprolide) and Casodex (bicalutamide) already have evidence of castrate-resistant disease. Even thoughit may not be visible on staging scans, it appears to be refractory to the hormonal therapy they're receiving.

The novel thought is that using drugs like Zytiga (abiraterone), Xtandi (enzaludamide), and Erleada (apalutamide) at an earlier time will improve outcomes.

Specifically, if we intervene earlier, i.e. before the person is declared a PSA failure—PSA failure is defined as his nadir, or lowest, PSA plus 2 points—we have a chance to do better. Currently, if the nadir value is 0.2, you'd be called a PSA failure at a PSA level of 2.2 or higher. That could take months or years to happen after the nadir. So, if we know someone is destined to do poorly based on their nadir value, we can intervene earlier.

To that end, we have created a randomized trial in which men with high risk prostate cancer, who are on track to receive at least 18 months of hormonal therapy, are entered at the time of PSA nadir. This is usually six to eight months into the radiation and hormonal treatment plan, while their remaining hormonal therapy is still ongoing. We then randomize them to either standard of care, which is continuing the standard hormonal therapy for their intended 18-month to 3-year course, or to the rest of their hormonal therapy (supplemented by both Zytiga (abiraterone) and Erleada (apalutamide).

"The cancer itself has put a break on the immune system."

This concept was recently approved. The trial will launch in 2019 as an international, randomized study.

This trial is quite exciting because, while the doctors in this issue of *Prostatepedia* discuss the current and future use of these drugs, nobody has studied them in this particular setting. This unique setting captures people who have a poor prognosis and are very likely to die of the disease.

This concept is also novel because we catch them at a time when intervention with these novel agents may have a higher likelihood of success. We're not waiting months and years for that formal definition of PSA failure to happen before we intervene.

Finally, I'd like to add that it's an absolute privilege to work clinically and do research in the field of prostate cancer in this day and age. I've never seen so many opportunities and new discoveries in such a short period of time. I believe that, given all the ongoing research, it will continue.

Robert Bristow, MD, PhD, FRCPC
Precision Radiotherapy

Dr. Robert G. Bristow is the Director of the Manchester Cancer Research Centre (MCRC) at the University of Manchester in the United Kingdom.

Prostatepedia spoke with him about precision radiation therapy and combining radiation therapy with both molecularly targeted agents and immunotherapies.

Why did you become a doctor?

Dr. Bristow: I was very interested in doing a PhD to understand how cancer cells actually divided. As part of my graduate studies, one of my mentors, a clinician-scientist, invited me to the clinic so that I would understand the implications of my research with respect to real patients undergoing real therapy. This was when I was in Toronto training at the University of Toronto.

From that experience, I realized three things. One is that the models that I'm using to try to understand how patient tumors respond to radiation and chemotherapy can be quite limited. Finding new ways to study cancer directly in patients would be profound.

The second is the reality that every patient is different and has a different story to tell; therefore, the impact of the cancer, as well as the impact of the cancer treatment on the patient can be very different, even if the biology might be exactly the same. That was a really important lesson to learn.

As I attended more and more of the clinics with my mentor, I saw that there really was a satisfaction in a career as a clinician-scientist; having the benefits of both worlds for basic and clinical research. You can ask clinical questions in collaboration with patients, but at the same time you can interrogate tumor resistance or side effects back in the lab and bring the information into the clinic. That is the real truth. I started off as a scientist, and I became a physician after meeting patients in real clinics with real clinical problems.

You're saying that your role as a physician and your role as a scientist have a push-and-pull: each informs the other?

Dr. Bristow: That's exactly right. Most days are terrific as they both feed off each other. But sometimes the laboratory studies do not go as well as planned as your experimental hypotheses are proven incorrect or the funding for studies is not optimal. Even with those setbacks, the reality is that when you go into the clinical realm, it's just so rewarding and challenging.

The second part, of course, is that your favorite patients may, despite all of the best treatments that you try, not do well. In fact, some will even die of their disease. That really is an upsetting moment. The first

"I started off as a scientist and I became a physician after meeting patients."

time you're a physician and that happens even though you think you've done everything right for that patient, just as you did the same for others, suggests that we don't have all of the precise answers for an individual patient.

You've got to go back into the lab and work harder. It absolutely is a push/pull, but also it's so rewarding to go back and forth. There's a real challenge in terms of getting it right: to feed each area with the best ideas that will maximally impact on patients.

What is meant by precision radiotherapy? Terms like precision medicine and precision oncology are thrown around a lot in mainstream media, but few really understand what that means.

Dr. Bristow: There are at least two aspects to precision radiotherapy. The first is the "physical precision" of radiotherapy; the actual targeting of the radiation beams or radioactive compounds to the specific tumor tissues that you want to treat, with maximum protection to the normal tissues that surround that particular tumor. For example, external precision radiotherapy uses intensity modulated radiotherapy or proton therapy where you then deliver the radiation in very precise defined volumes.

The other type of physical precision in radiotherapy uses brachytherapy, actually placing seeds or catheters with radioactivity directly in the prostate and being able to conform the dose tightly to the prostate gland, with that dose falling off rapidly around the surrounding normal tissues that could acquire side effects (e.g. the bladder or rectum).
The concept of physical precision has allowed us to increase the total dose to the prostate cancer and yet maximally spare the normal tissues from side effects.

Another aspect of precision radiotherapy is "biological precision" whereby we think about the entire treatment using radiotherapy based on the innate characteristics of a particular patient's tumor.
This includes information about the genetics and microenvironment of the tumor cells within the cancer that make it uniquely suited to be cured by radiotherapy alone, or in combination with drugs that modify biology or the immune system.
This can have the effect of increasing the chance that the cancer is cured locally and also attack cancer throughout the entire body to kill what we call occult, or hidden, metastases.

Precision radiation therapy therefore now means both an understanding of the biology of the tumor in a specific patient as well as physics to optimally deliver that radiotherapy.

What role does functional imaging play?

Dr. Bristow: Imaging is a cornerstone for staging cancer and understanding its biology. It is absolutely required for staging patients to understand the anatomy of their cancer—not only where the local tumor is, but also the spread to the pelvic lymph nodes and beyond that to the bone, for example.

Anatomic imaging therefore gives us the geography of where those tumors are in the body. Functional imaging adds further components to start to understand the biology of those tumors. For example, by using functional imaging with MRI, we can look at differences in tumor blood flow, oxygen levels, or metabolically active versus metabolically inactive tumors.

"There are at least 50 trials in this area."

For PET scanning, we can use specific radioactive tracers that will tell us about the glucose in the tumor, the amount of the tumor that has low oxygen status (called hypoxia), and the relative growth rate of tumors. So imaging can now give us both anatomy and biology.

Totally different world, right?

Dr. Bristow: It is. If you understand the biology from the imaging and where things are, you can certainly target specifically those areas with precision radiotherapy using novel biological agents, which we call molecular targeted agents.

What are molecularly targeted agents? What is the thinking behind combining them with radiation therapy?

Dr. Bristow: One of the general success stories for cancer is the fact that when we think about the use of radiation therapy in a curative setting, the reality is that many of the gains in curing patients have come from combining radiotherapy with other types of treatments to improve local tumor kill and kill metastases. Classically, this means combining radiotherapy with surgery or radiotherapy with chemotherapy using drugs such as cisplatin, for example. We also combine radiotherapy with androgen deprivation therapy (e.g hormone therapy) in many prostate cancer patients.

But now when we talk about precision radiotherapy and the understanding of the biology of the cancer, we know that some tumors will have specific genetic changes or defects that make them more resistant to radiation and increase their ability to spread through the body, and these are associated with differences in the immune response to radiotherapy. Understanding these biological differences allows us to target that abnormal biology with specific drugs that take advantage of these aggressive genetic defects and, therefore, kill cells based on their biology. Doing that in combination with radiation therapy may do a better job than either agent alone.

Molecular targeted drugs are therefore based on targeting the pathways and molecules that are abnormal in cancer cells versus normal cells; these drugs take advantage of those differences.

When you combine treatments in this way, are the side effects synergistic?

Dr. Bristow: Not necessarily and when we design what we call *combined modality* therapy where we combine radiotherapy treatments with the molecular targeted agent, we have to be very careful that we don't combine the side effects. Then we lose the ability to kill more tumor cells than normal cells, which is called the *therapeutic ratio*.

For example, radiotherapy causes DNA breaks in cancer cells and these breaks can lead to cancer cell death. If we used a molecular drug that targeted and inhibited the repair of these DNA breaks (e.g. a PARP inhibitor), then you might kill more cancer cells with radiotherapy. But you'd have to have exquisite physics within the radiotherapy to make sure that you didn't also have an increase in DNA breaks within the surrounding normal tissue and cause more harm than good to the rectum or bladder, for example. But if we know a cancer cell has a DNA repair defect itself, you might use the DNA repair inhibitor to kill cells upfront by taking advantage of the other DNA repair defects, a so-called Achilles' heel of the cancer cell. In this case, we could first use the DNA repair inhibitors alone to kill cancer cells and then separately come in with radiotherapy afterwards, so that the total cell *kill* is increased, but the two agents aren't given at the same time because it would be too much toxicity. So it's always important to utilize a molecularly targeted drug with radiation so that there is no summation of the toxicity when you give them together.

One of the straightforward examples of this is using a compound that targets low oxygen in cells, called *hypoxic cells*. These cells are resistant to radiotherapy and uniformly found in tumor cells, relative to normal tissues.

The use of a hypoxic cell targeting agent plus radiation should give a summated effect on the tumor but not a summated effect on the normal tissues because the hypoxic target drug would not affect normal tissue. You would only get the increased radiation effect by reducing those resistant cancer cells. It's those sorts of clever combinations that we need to think about going forward.

All of this comes back full circle to your previous point about functional imaging. If we were to use a hypoxic-targeted agent with radiotherapy, you'd really only want to use it in patients in whom functional imaging showed low oxygen in their tumor. Otherwise, there would not be a differential effect with using a hypoxia-targeted agent in a precise manner, and we lose the concept of precision radiotherapy.

In one tumor, you might have low oxygen, and in another tumor, you may not. You might consider targeting that first tumor with radiotherapy plus a hypoxia-targeted agent. In the second tumor, because there's no hypoxia, there's no point in using the hypoxia-targeted agent; there isn't a target. But maybe that tumor has changes in the way that cells are signaling, so we might use a signaling inhibitor.

Or, to come back to a big area of research these days, it might have specific markers that suggest it would respond to immunotherapy.

We might think of radiotherapy plus immunotherapy for those patients.

Let's talk about combining immunotherapeutic agents with radiation. Which immunotherapies look the most promising in combination with radiation therapy.

Dr. Bristow: When we're talking about radiotherapy, we're looking for anything that might increase the tumor cell kill within the local tumors in the prostate. But radiotherapy might have an added advantage. We don't totally understand the biology of this yet, but if you irradiate one part of the body, it might affect disease in another part of the body. This is called the *abscopal* effect.

In general, tumors hide from the immune system. They're very clever in doing this. There are a number of molecules such as PD-1, PD-L1, and CTLA-4 that basically control whether or not the normal tissues are seen by the immune system. In tumors it's the same sort of thing. Tumors acquire the ability to hide from the immune system. Sometimes they have high levels of PD-1 and PD-L1 that allow them to hide from the T cell responses that normally would have gotten rid of that cancer.

What we know now is that radiotherapy in some patients can actually make the tumor less evasive so that it can now be seen by the immune system. This allows the T cells to attack the cancer cells in combination with the radiotherapy.

In a perfect world, you would always unmask the tumor with radiotherapy and allow a patient's own immune system to also attack the tumor. That would allow the immune system to hit the cancer with the added effect of radiotherapy. But some tumors need help to do this and in order to unmask the cancer, we now *use immune checkpoint inhibitors* to release the evasive checkpoint and allow the immune T cell response to increase the effect of radiotherapy on the cancers.

There are other reasons why radiotherapy might work better locally with immunotherapy in taking that particular approach, such as the abscopal effect.

In the abscopal effect you irradiate a metastatic lesion. Specific cytokines and T cell responses associated with the irradiation in that one spot activate an immune response in other lesions in the body that hadn't been irradiated.

The abscopal effect is an exciting concept but is rarely seen in the clinic. There was a randomized trial in metastatic castrate-resistant prostate cancer where patients were treated with radiotherapy and then either with an immune checkpoint inhibitor or not. Overall, there wasn't a difference in survival. But in a sub-analysis, there was a suggestion that those patients with working immune systems might have benefited from such a checkpoint inhibitor.

There are lots of questions right now such as how can we predict which patients might respond to immunotherapy and which will not. One way to predict response is to potentially measure the PD-1 and PD-L1 levels on the outside of the cell. We also think that cancer cells that have more mutations might be more easily seen by the immune system than others. The mutation rate or cancers that have defects in DNA repair might be more amenable to immunotherapy than those cancers that have normal DNA repair.

All of this is under study, particularly with metastatic castrate-resistant prostate cancer. There are now clinical trials looking at whether or not those patients will respond to immunotherapy either alone or with radiation treatment.

In localized disease, there also is real interest in using PD-1 and PD-L1 checkpoint inhibitors with radiation to see in what percentage of patients do you see tumor unmasking and increased local control.

For prostate cancer, we do not yet have a biomarker that confidently tells us which patients will respond and which patients won't respond. This is why you'll see a number of clinical trials using different radiation doses and different types of immunotherapy before, during, or after radiotherapy.

There are at least 50 trials in this area all trying to understand how best to use immunotherapy and radiation therapy combinations with prostate cancer patients.

Let's step back a bit and talk about genomics because you have touched on it in almost every question. Do we have a way of predicting who will respond to radiation? And who will have severe side effects?

Dr. Bristow: The short answer is no. My work with my colleagues in Canada involved a huge effort to sequence the entire genome, or the entire DNA network within prostate cancer in patients in the localized setting. What we know in localized disease is that there are a number of patients that under the microscope look like they have the same Gleason score. When we do whole genome sequencing, we see that about a quarter of these actually have a number of genetic rearrangements and mutations within their tumor.

It's quite clear that the patients who have more aggressive mutations and increased number of mutations actually do worse. The way that they do worse is that they actually fail radiotherapy quite quickly after treatment. We therefore think that genetic instability, or the increased burden of mutation, is associated with hidden metastases as opposed to information about responding to surgery versus radiotherapy.

We've looked very hard in the Canadian study for a predictor of who would respond to radiotherapy versus who would respond to surgery. Although some early leads suggested one gene or another, I'm not confident right now that we actually have a marker so that when a patient comes into the clinic, we could do a quick test to say whether his disease was more or less sensitive to radiotherapy.

We hope that will change, of course, with further data. But we don't have it yet.

The other aspect that you pointed out is whether or not radiation side effects are associated with germline or blood DNA. Some data suggests there are specific gene mutations associated with cell growth, the way the cells contact each other, or DNA repair that might put patients at risk for erectile dysfunction or rectal bleeding. A lot of validation studies still need to be completed. It is also not ready for prime time.

Something that has come up in the last two to three years is that patients can have defects in genes associated with DNA repair. Your readers will have heard about the BRCA1 and BRCA2 genes normally associated with ovarian and breast cancer. We now know if you are a male BRCA2 carrier you have an increased risk for prostate cancer and an increased risk of *aggressive* prostate cancer.

One Canadian study suggested that some of these localized cancers in BRCA carriers already had acquired resistance patterns to hormone therapy and other types of therapy even though they had never seen the therapy. They are almost *primed* for resistance.

We also know that maybe up to 15% of patients with metastatic castrate-resistance prostate cancer have DNA repair defects.

This is important because it speaks to mechanisms of resistance and aggressiveness based on genes in your bloodline. The other important thing we've learned in the last five years is that prostate cancer patients with BRCA1 and BRCA2 DNA repair defects respond to PARP inhibitors.

This is a very exciting area of precision oncology using genomics to predict those patients that might respond to a molecular-targeted therapy in this case.

One can only assume that there might be other stories like the DNA repair defect story that would give us more information about different types of tumors.

Dr. Bristow: This comes back to what we were talking about before: carefully designing clinical trials to compare one treatment versus another in large numbers of patients in which there is high content information about the immune landscape, genetics of the tumor, genetics of their bloodline, and functional imaging of the tumors. This will allow us to start to put this information together to come up with a more precise way of treating our patients.

Cancer is complex. The complexities of cancer are for us to discover, but also for us to develop a number of tests that give us a sense of that complexity so that we can use the right treatment for the right patient at the right time.

"The promise of genomics in the last decade is now leading to novel treatment for patients."

Is there anything else you'd like patients to know about precision radiotherapy?

Dr. Bristow: The promise of genomics in the last decade is now leading to novel treatment for patients. There are still situations for which we don't know the best treatments. In those cases, patients need to demand from their healthcare givers information about which clinical trials are available to them so that we can solve these questions together. The reality is that we do require clinical trials to answer them. Pp[1]

Charles Drake, MD
Radiation, Immunotherapy + the Abscopal Effect

Dr. Charles G. Drake is the Director of Genitourinary Oncology, Co-Director of the Cancer Immunotherapy Program, and Associate Director for Clinical Research at the Herbert Irving Comprehensive Cancer Center, New York-Presbyterian/Columbia University Medical Center.

Dr. Drake discusses the thinking behind combining radiation therapy with immunotherapy as well as the rare but intriguing abscopal effect.

Have you had a particular patient who changed how you approach your work?

Dr. Charles Drake: Absolutely. I had a gentleman who had metastatic, castrate-resistant prostate cancer. He had been treated with hormonal therapy. He was about to go on chemotherapy. He had progression in his bone lesions, but he developed hematuria.

On CT scan, there was a fairly clear lesion in his bladder. We couldn't tell what it was just by the scans, and his PSA was doubling quickly, it had reached 30 or so in less than a couple of months. We sent him to Dr. Ronald Rodriguez, who was at Johns Hopkins at the time, and he thought it looked like this was probably metastatic prostate cancer invading the gentleman's bladder.

Dr. Rodriguez did a transurethral fulguration, meaning he *burned* all of the tumor he could find in the bladder. After the procedure, he told me that there was a fair amount of prostate cancer left behind. While the procedure went well, and he got most of the tumor, he didn't get all of it.

What happened next was fascinating. The patient's PSA dropped. His PSA went from 30 to 20 to 10. It eventually nadired, or reached its lowest point, at less than 1 ng/ ml and he remained in remission for nearly two years.

Although clearly anecdotal, in my mind, there is almost no question that this was one of those anecdotal abscopal responses, which makes you believe that it can happen. Almost certainly that was what happened for this patient. I'll never forget it, frankly.

Interesting. An unexpected systemic response from local treatment, right?

Dr. Drake: Yes. It was brilliant. Just by treating the local disease in the bladder, this gentleman did well for over two years before it apparently progressed again, and he wound up getting chemotherapy. He also did very well with the chemo, so in my hopeful view, that suggests that maybe this fulguration procedure sparked a systemic immune response.

What's the thinking behind combining radiation therapy with immunotherapy? Why take that approach?

Dr. Drake: The basic idea is that radiation, and perhaps other local modalities like cryotherapy, leads to destruction of tumor cells. If they're destroyed in a way that's immunogenic or pro-immunogenic, then the dying cells are taken up by resident antigen-presenting cells. These antigen-presenting cells get activated; they traffic to the draining lymph node, if you're lucky. If they traffic to the draining lymph nodes, and then activate a systemic immune response (T cells), then maybe you can turn a local therapy into a systemic therapy. When that happens, it's called the abscopal effect. We can demonstrate this in mice fairly readily, but it's quite hard to demonstrate in humans.

In the literature, it's not that common. There's a review paper that reports around 60 total cases in the world that are clearly documented. But if you talk to people who take care of patients, everybody has one or two that they can talk about.

Are some radiotherapy and immunotherapy combinations synergistic while some are not?

Dr. Drake: We published on this topic in collaboration with a neurosurgeon named Dr. Michael Lim. We modeled the additive effects of radiation therapy and immunotherapy first in models of glioblastoma (GBM) brain tumors in mice. We showed that anti-PD-1 was synergistic with radiation therapy in the GBM models.

In the clinic, the last time I counted, there were somewhere around 40 or more trials trying to use radiation plus anti-PD-1 to induce an abscopal response in humans. So far though, this has not yet panned out to be a broadly applicable principle.

We now think that what's holding back an abscopal response might not be PD-1 but the presence of regulatory T cells. In the well-documented cases, two abscopal responses (one in lung cancer and one in melanoma) both occurred with anti-CTLA-4. Perhaps anti-CTLA-4 is a better partner in humans to produce an abscopal response.

There is also a trial in kidney cancer run by Dr. Hans Hammers, my former colleague from Johns Hopkins. He's looking at combining Yervoy (ipilimumab), Opdivo (nivolumab), and radiation in kidney cancer.

It was maybe too hopeful that we'd get a high incidence of abscopal responses when patients receive radiation plus anti-PD-1. I don't think it's panned out. We need to consider the regulatory T cells and maybe even some of the other suppressive elements in the tumor microenvironment.

Your group has shown that radiation therapy works by cross-presentation and not direct presentation. Can you explain what that means for patients?

Dr. Drake: Radiation does a lot of things, and one is that it makes tumors more immunogenic; it upregulates molecules called Class I major histocompatibility complex (MHC) molecules. This would make the tumor more recognizable to the immune system. This was pretty clear across multiple tumor types. It was shown quite nicely in prostate cancer by James Hodge at the National Institute of Health.

Radiation also does what I discussed before; it leads to the tracking of tumor antigens to the lymph nodes.

In a paper we published in *Cancer Immunology Research* in 2015 with Dr. Andrew Sharabi as the first author, we showed that almost all of the effect was cross-presentation. That means that the tumors are presented in a draining lymph node. In some plans, you radiate the lymph nodes. But we weren't sure if this was a good thing or a bad thing.

We recently completed a series of studies over about two years that carefully model whether it is good to radiate the lymph nodes. The answer is clear. If you radiate the lymph nodes, you ruin the combination effects of immunotherapy and radiation therapy. When combining radiation therapy with immunotherapy, you probably don't want to radiate the lymph nodes because that's where the antigens are presented. This paper, with Dr. Ari Mari Mariscano was recently accepted in *Clinical Cancer Research*. It's a great story.

You might want to remove those surgically?

Dr. Drake: Yes, that's true, but in the case of radiation therapy, you probably need them to present the antigen. And the mechanism is simple. When you radiate a tissue, the lymphocytes want to track there. If you radiate a tumor, the lymphocytes also want to go to the tumor. But if you radiate the lymph node, then you kill some of the lymph node cells that are being primed, and some of the immune cells that are being primed. You also create a gradient so that the lymphocytes want to go there. When you radiate both the lymph node and the tumor, it's like the lymphocytes get confused and can't decide which one to choose.

Wow, that's crazy.

Dr. Drake: I know. It's surprising. It could have gone one of three ways. It could have been good to radiate the lymph node; it could have been bad to radiate the lymph node; or it could have been neutral. In our animal models, it was clearly worse if you radiate the lymph nodes.

We talk about radiation therapy as if it's all one thing, but do different forms of radiation therapy have different immunogenic impacts or not?

Dr. Drake: That's a brilliant question. Even in pre-clinical models, which are supposed to be reductionist, there is a lot of disagreement. In fact, radiation oncologists disagree vehemently. Some groups suggest that a single large dose is optimal for immunological priming. Other groups suggest that fractionated (or multiple, smaller) doses are more immunogenic than a single large dose. For example, in some models my friend and colleague Dr. Silvia Formenti has shown that maybe five fractions are optimal.

In Dr. Sharabi's paper, we modeled this ourselves in mice, and we thought we were going to have a definitive answer. But our results were a little equivocal; we found that fractionation didn't seem to make that much of a difference. But it needs to be recognized that most mouse models use implants of fast-growing tumors,

and we don't quite know their relevance to human studies.

In a clever Phase I trial by Regeneron, they tested their PD-1 drug in combination with two different schedules of radiation therapy. We don't know the results yet, but the fact that they included two different doses and schedules in their Phase I shows that the field is still not quite certain about how to best combine radiation therapy with immunotherapy.

What about radiopharmaceuticals like Xofigo (radium-223)? Is that considered a form of radiation therapy?

Dr. Drake: Absolutely. Xofigo (radium-223) emits alpha particles, and some suggest that it's reasonably immunogenic.

Another former colleague at Johns Hopkins—Dr. Emmanuel Antonarakis—is running a trial with Dr. Oliver Sartor combining Xofigo (radium-223) with Provenge (sipuleucel-T). They are looking into whether the vaccine effect of Provenge (sipuleucel-T) will be amplified by killing tumor cells with the alpha particles from Xofigo (radium-223). It's an interesting idea. It's also important because Xofigo (radium-223) homes beautifully to the bones, where most prostate cancer metastases occur. They may be able to prime the immune system in the bone with this strategy. It's a clever trial that's been open for a while. There haven't been any preliminary results though.

It's worth mentioning that there are other radiopharmaceuticals, too. There's J591 anti-PSMA antibody, which has been labeled with Lutetium. [See page 28 to read about a clinical trial on lutetium-177 PSMA.] That might be another idea; can something like an immune checkpoint blockade or a vaccine prime or amplify local delivery of a radioisotope?

Is anyone combining those radiopharmaceuticals and checkpoint inhibitors?

Dr. Drake: In prostate cancer, it's a little early along. Dr. Scott Tagawa at Cornell has some of the tools to do those combinations eventually, but they're still getting through their Phase I and II trials of the radiopharmaceuticals.

What else should patients know about combining radiation with immunotherapy?

Dr. Drake: There was an article in the *New England Journal of Medicine* showing an abscopal response with Yervoy (ipilimumab) anti-CTLA-4 in a patient with melanoma. It was a beautifully done paper with nice immunological correlates. After that got published, we found that radiation oncologists and medical oncologists were giving people a combination of immunotherapy and radiation and were telling patients they would get abscopal responses. But that's a bit overly ambitious. In the clinic, it's not that easy. It's going to be a while before we understand what's needed therapeutically to be able to induce abscopal responses in the majority of patients. It's going to take a little more work before we can have that happen broadly. On the other hand, if we can make it work, it'll be fantastic. Dr. Hammers' trial combining anti-PD-1, anti-CTLA-4, and radiation in kidney cancer is perhaps a more clever approach. That may be what we need to do.

In other words, abscopal responses do happen, but we don't exactly know why or how and can't reproduce it?

Dr. Drake: Exactly. And it doesn't happen nearly as often as we'd like. Pp

William Hall, MD
Precision Radiotherapy

Dr. William Hall (@whallradonc) is an Assistant Professor in the Department of Radiation Oncology at the Medical College of Wisconsin.

Prostatepedia spoke to him about precision radiation therapy and the importance of including detailed radiation therapy data in large-scale genomic studies.

Why did you become a doctor?

Dr. William Hall: I never thought I was going to become a doctor. I was a biomedical engineer. I had a real passion for science, engineering, and programming. I also liked biology as a concept and as applied to helping people.

It wasn't until the beginning of my senior year in college that I started to think about medical school. And it wasn't until I began working as a biomedical engineer that I ultimately changed my career trajectory and went to medical school. I started my career as a biomedical engineer, and I pretty quickly realized that it didn't give me the direct human interaction or tangible benefits that I desired in my work.

I tremendously enjoy being a doctor because I love science, and I love the applications of science. I like cool new science, and I love interacting with patients. Those two things make my job tremendously rewarding and fun. That's really what got me here.

What role has next-generation imaging played in precisely targeting radiation therapy?

Dr. Hall: By next-generation imaging, are you referring to functional MR-based imaging, advanced CT-imaging, and those types?

Yes.

> *"Next-generation and advanced imaging sequences have completely revolutionized what we are able to do."*

Dr. Hall: Next-generation and advanced imaging sequences have completely revolutionized what we are able to do with radiotherapy. They have changed our ability to target, visualize, and understand exactly what we're treating in a completely different way.

Historically, radiation therapy was delivered using relatively crude techniques. It was delivered using plain film X-rays, similar to what you'd see for a chest X-ray. More recently, it's been delivered using CT, which gives us some better delineation of where neural structures are located. But it doesn't do a ton with regard to exquisitely detailed locations of tumors versus normal soft tissues or potentially even more aggressive regions of tumors.

Our ability to understand which part of a tumor is the most aggressive and how aggressively we need to treat that tumor is rapidly expanding. Cancer will soon be identified more accurately with advanced imaging techniques, and we will be able to target the areas of cancer that really need high doses of radiation to control it. That should result in better cancer control rates and fewer side effects.

We're beginning to understand how these new technologies will impact cancer control. To really understand prostate cancer control rates requires a lot of patience and a lengthy follow-up, anywhere from seven to ten years. Innovative medical imaging technologies are just beginning to enter a time when we're going to be able to watch patients for five to ten years after they're treated.

How is genomics impacting radiation therapy?

Dr. Hall: There exists a wide heterogeneity of genomic profiles of tumors, some of which are very resistant to radiation, others of which are very susceptible to radiation-induced damage. Currently, our ability to measure and clinically use that information is relatively limited.

We don't have a lot of tests that have been robustly explored and validated to prove that they can be used on patients with genomic-type information. Without that proof, we currently treat patients based on traditional cancer metrics of aggressivity, such as Gleason Score, PSA, and digital rectal exam. Those metrics still dictate when we are going to do treatment with radiation. When we do select treatment with radiation, most patients get similar types of doses. We don't really take into account genomic information or stratify patients' radiation dose based on genomic data. That goes for both the tumor and normal tissues.

Some patients have tissues that are extremely susceptible to radiation-induced injury while some may have extremely resistant tissues. We don't yet know the best way to identify those patients, but we're getting there. We have open clinical trials. We have promising research studies that tell us these groups of patients exist. We just have to figure out the genomic metrics that can point us in the right direction.

We will be there hopefully within the next ten years. We will be at a place where radiation oncologists are using genetic data to direct radiotherapy doses, so we can select a dose based on genomic susceptibility and adapt our dose based on a patient's intrinsic sensitivity to radiotherapy.

We need to integrate genomics into treatment planning in radiation therapy within the next 10 to 15 years. We are currently not doing enough of that.

Is it just a matter of getting the clinical trials done?

Dr. Hall: Yes. The biggest challenges for these trials is that they require a tremendous number of patients, a very long follow-up, and the design of logistical methods by which that data can be collected and used in a clinical setting. When it comes to this type of genomic data, acquiring, measuring, and using it is actually quite difficult.

> *"We need to integrate genomics into treatment planning in radiation therapy within the next 10 to 15 years."*

Assuring the accuracy of genomic data acquisition and knowing whether it can be applied clinically or not is quite complex. It takes years of clinical trials and years of validated metrics until we feel it's acceptable to change our treatment recommendations.

Many men with prostate cancer are going to be successfully cured with current treatment methods. Most of them will come out of treatment with few serious side effects. When you have a cancer that you're doing well with, you hesitate changing any of your standard treatments. That's why cancer doctors who treat a fair number of patients with prostate cancer —particularly radiation oncologists— are cautious about changing what we're doing because right now we're doing okay. That's perhaps why genomic data is slowly integrating into radiotherapy.

There are a bunch of big data genomic studies underway. Are they including information about radiation therapy? If not, why not?

Dr. Hall: Yes. Several big data genomic studies are attempting to get more radiotherapy information. That is expanding.

Radiation oncology is a field that most cancer specialists, medical oncologists, and surgical oncologists know little about. It is really amazing how little many of our colleagues know about the granular details of radiotherapy—the nuanced types of information that we deal with on a daily basis. When these big databases are created, radiation oncologists need to be engaged and involved in their creation at an early point in their inception. We have to be able to collect the source of data that we need.

I'll give you an example. Some databases will include the fact that the patient receives radiotherapy. Those will include maybe a total dose of radiation, but they won't include the number of treatments that a patient had. That actually makes a huge difference in radiation oncology literature. To a non-radiation oncologist it might sound like a very minor detail if a patient received 70 Gy over 28 treatments or 70 Gy over 35 treatments. But it actually makes a huge difference.

We have trials now that include over 1,500 patients that have focused on very small variations in total radiation dose. We need to include that level of granularity of data so that we can

really identify the types of genomic metrics of response that we need.

Do you think it's odd that radiation therapists aren't being included in the initial design of these studies? Most patients must initially choose between surgery and radiation.

Dr. Hall: Yes, it is. It depends on the big data genomic study. There certainly could be some that do focus on granular radiotherapy data. But a lot of these big data-type efforts often don't place much of an emphasis on very granular radiotherapy data. That's been my limited experience.

There are some wonderful consortium-type activities. There's one called the Radiogenomics Consortium (RGC), which is a phenomenal big data effort underway among many radiation groups extremely focused on radiotherapy data.

The other challenge with collecting radiotherapy data is that there is so much complexity to pulling out different data points from a given radiation treatment plan. Those types of details make a big difference, and they take a huge amount of effort.

For example, there's a huge amount of effort required to go into an individual patient's radiotherapy plan and pull out detailed data about exactly the types of doses they received in their rectum or bladder and how that changed over the course of their treatment. If their treatment took place over five or six weeks, did they consistently fill their bladder over five or six weeks or did they frequently get treated with an empty bladder? Whether and when a patient was able to fill their bladder well could impact the rates of toxicity substantially.

If you enter that type of data into a big data genomic set, and you don't have that level of detailed information, you may not know whether the patient had bladder toxicity because they had the following genomic alterations or if they have bladder toxicity because they simply didn't fill their bladder well every day.

> *"Several big data genomic studies are attempting to get more radiotherapy information."*

That's another big challenge that we face. Getting that data from each treatment course is hard. It's different than, say, extracting chemotherapy data, where you can say this patient had two and a half cycles of chemotherapy. You can see the infusion data, you know when they got it, and you know the dose that they received. It's different because there is so much variability in how a patient can be treated with radiation.

What else should patients know about radiotherapy?

Dr. Hall: Radiation therapy is an extremely technical specialty that is rapidly evolving. Many patients think that radiation therapy is the same, regardless of where they receive it. That is not so. Expertise, delivery methods, and the unique methods of radiation therapy administration can vary tremendously from hospital to hospital. That's extremely valuable for patients to understand

You should seek a radiation oncologist who specializes in your type of cancer, someone who focuses their research and clinical efforts on a few types of cancer. In larger academic centers, radiation oncologists tend to do that.

There are many opportunities for clinical research trials. In fact, we have two that are ongoing at our institution, in which patients who are interested in contributing to the advancement of genomic data integration with radiotherapy planning or advanced imaging integration into radiotherapy planning can participate. Patients, in many cases, get a tremendous reward from participating in these types of trials. They get as much personal satisfaction from helping themselves as they do others.

We have a couple of clinical trials in which we're imaging patients weekly with advanced MRI while they are undergoing radiotherapy treatment. We also have a trial in which we take a bunch of genomic information and correlate it with the toxicity that develops during and after radiotherapy.

I assume that for the imaging study patients would need to come to you weekly. What about the genomic study?

Dr. Hall: The genomic study would be available to them if they're being treated here or at the University of Rochester in New York. This study entails obtaining a blood sample before treatment and after treatments starts, it also involves a lot of detailed questionnaires, and we provide a scoring of toxicity. We pull out a lot of really detailed information about their radiotherapy delivery. This study is a very exciting collaboration with the University of Rochester in New York, and we feel fortunate to be able to participate in the study. Pp1

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Daniel Spratt, MD
Radiation Therapy Combinations

Dr. Daniel Spratt is a radiation oncologist and the Chair of the Genitourinary Division of Clinical Research at the University of Michigan Health System.

He is keenly interested in the interaction of androgen signaling and DNA repair in prostate cancer as well as methods of overcoming resistance to radiation therapy.

Why did you become a doctor?

Dr. Daniel Spratt: There are no physicians or healthcare workers in my family. I took an unconventional path to becoming a doctor.

I started working as a personal trainer when I turned 18. I was always involved in fitness and exercise. I took some time off from going to college and worked one-on-one with clients. At that time, I noticed that I liked being able to help change people's lives and have that unique interaction. But there are limitations to what a personal trainer can do for a person. That inspired me to go back to college, focus on the research, and go to medical school to become a radiation oncologist.

How did you make your way to radiation oncology versus urology?

Dr. Spratt: In medical school, we rotate through a bunch of different specialties. All along, I thought I was going to be a neurosurgeon; that was my focus and my research. But I started to realize that I love to connect, to have the time and flexibility to discuss how patients are doing. I care more than just about the technical treatment. I enjoy emotionally connecting with patients.

The radiation oncology industry is a unique specialty in that a machine delivers our treatments, and then we get to see the patient. I almost do two things at once. If a surgeon is operating all day, they can't see anyone other than the one patient in front of them. I get to see and treat dozens of patients a day.

Are you still involved in the exercise world?

Dr. Spratt: Definitely. It is not as strong, but if you spoke to any of my patients, they'd tell you that I prescribe exercise to all of them.

The side effect profile for my patients who are inactive versus the ones who are active is like night and day. It's amazing how patients undergoing prostate cancer treatment, including radiation and especially hormone therapy, are improved by exercise. It doesn't need to be joining a gym —just being active in some way.

The guys who are active have much fewer side effects during treatment. I jokingly prescribe exercise while I prescribe radiation to them.

Maybe you shouldn't joke and really do it!

Dr. Spratt: Exactly. I don't think a pharmacy can fill that.

Can you talk to us a bit about the thinking behind your trial combining radiation therapy and Erleada (apalutamide)?

Dr. Spratt: Three components inspired this trial. First, there was a 2017 study called RTOG 9601 by Dr. Bill Shipley published in the New England Journal of Medicine. The trial started almost 25 years ago and compared men who had recurrence after surgery—those whose PSA was rising—and looked into whether they should get radiation with or without two years of an older drug called Casodex (bicalutamide). Casodex (bicalutamide) is a type of anti-androgen therapy.

The trial showed that, overall, men who received this hormone therapy seemed to live longer and were cured more often. Most of the men on this trial had cancers which were much more aggressive and advanced than the ones we see today, which inspired me. We've learned over the past 20 years that, after you recur, you only need to check the PSA. When a patient's PSA is low, less than a value of about 0.6, the patients in that trial had no benefit at all from the hormone therapy; they just had side effects. However, we get excited when a big paper is published showing a benefit to patients and some people jumped to the conclusion to give hormone therapy to everyone. Unfortunately, there is no study that shows that adding hormone therapy will improve their survival or prevent the cancer from spreading, especially not this older form of hormone therapy.

Second, today we have a next generation hormone therapy. Erleada (apalutamide) is a hormone therapy pill that is much more targeted and selective. It's been shown to be much more effective than the older type of hormone therapy in men with more advanced disease. Men with a rising PSA after surgery have biochemically recurrent prostate cancer. But if we detect it early enough, when the PSA is still low, maybe we can improve outcomes with this newer hormone therapy.

The third component that motivated this trial is the need to personalize treatment to patients. We need to understand the biology of why some patients are intrinsically more likely to benefit from hormone therapy than others.

Dr. Felix Feng from the University of California San Francisco and I have worked to develop a gene signature. This is a gene signature that was developed for breast cancer patients to help sub-classify cancers into something called the *luminal type* and *basal type*. This is a type of cell that prostate cancer most looks like. In retrospective studies, we looked back at the outcomes of a variety of patients who had been treated. We showed that patients with a luminal subtype seemed to have a large benefit from hormone therapy whereas some of the other subtypes, like the basal subtype, did not.

We are not just interested in all-comers who benefit in our trial. While that's important, we're also layering in this gene signature to determine if we can identify which men benefited the most from this hormone therapy. This is the first time this has ever been done in a large national cooperative group trial; we built that in to the study to be one step closer to personalizing which men should receive this therapy.

So men interested in participating are first tested to determine whether they have luminal or basal subtypes of prostate cancer, and then get the radiation + Erleada (apalutamide) combination?

Dr. Spratt: Exactly. It's a test that is run on their prostatectomy specimen. After surgery, prostates are stored for many years in a pathology warehouse at almost every center. For the test, we take a piece of the tumor in that stored tissue sample and send it to a special laboratory that analyzes the tissue and returns the results.

Fascinating! It's like precision clinical trial design.

Dr. Spratt: Exactly.

After they get that test, and they know which type of cancer they have, then they get the radiation and Erleada (apalutamide). How does that happen?

Dr. Spratt: After a patient consents and enrolls in the study, the test is sent off. The patient is not given the results because this is not commercialized for prostate cancer. The purpose of this trial, in a way, is to validate that test. The trial coordinators will know the results and randomize the patients so that half will get a placebo pill and half will get Erleada (apalutamide).

They'll get radiation delivered over about 38 or 39 treatments. (Each center in the United States varies the exact number of treatments they give.) The hormone therapy will start on the same day as the radiation therapy. That is a standard Monday through Friday schedule, which adds up to about seven or eight weeks of radiation. They'll take one Erleada (apalutamide) or placebo pill every day and continue beyond the radiation for a total of six months from start to finish.

The type of radiation delivered is up to the institution. Most places in the United States recommend intensity modulated radiation therapy (IMRT) or image-guided radiation therapy (IGRT). That is conformal to keep radiation off of the rectum and parts of the bladder. There are still some centers that use 3D-conformal radiation, a slightly older technology. This achieves similar results, but it doesn't spare quite as much of the rectum and bladder.

What happens after they receive radiation and Erleada (apalutamide)? How do you monitor them?

Dr. Spratt: Just as if a patient were not on the trial. They're going to get serial PSA and testosterone measurements. The PSA will be tracked over time. In the beginning, it's tracked more frequently (approximately every three months), but rapidly transitions to every six months. As patients get a few years

out, they'll transition to getting tested once a year. Some physicians like to keep testing PSAs twice a year for five years; that's up to the discretion of the treating physician.

The best test to monitor treatment response is the PSA. If a man's PSA starts to rise, the treating physician will often get some type of scan. We hope this won't happen because the goal of the trial is for the PSA to go down, stay down, and go undetectable so there's no sign of cancer at all.

Is the scan up to the individual doctor or is that part of the study?

Dr. Spratt: That's up to the study doctor. This is a Phase II randomized study. We're looking for a strong signal that Erleada (apalutamide) improves outcomes, and if so, whether we can detect which patients benefited most from the Erleada (apalutamide). If that's identified, we'll proceed with a Phase III trial where we will potentially select only the patients who have that luminal subtype. They're the ones we think will benefit the most.

We will run that Phase III trial in those patients to prove that they are the ones who derived the most benefit from hormone therapy. We will look at other, long-term endpoints like development of metastases. These are the steps necessary to make this test an approved test so physicians around the world can determine who needs hormone therapy.

How long do you anticipate the trial lasting?

Dr. Spratt: For the Phase II trial, we're going to follow men for a minimum of three years. We're looking for a signal of efficacy of biochemical control, whether the patients' PSAs stay down or go up. Based on that signal, we'll either proceed to a Phase III trial, or if there's no signal of benefit, we'll stop.

After the three years, will you then tell patients whether they were a luminal subtype or not? Or will that information remain cloaked?

Dr. Spratt: That's a good question. It will depend on where the state of that assay is. This year, we're trying to get it added to a commercial clinical-grade report so it can be reported to patients. If that happens, and it goes through all the regulatory processes, we should be able to tell patients their subtype.

Are there any specific exclusion criteria patients should know about?

Dr. Spratt: Patients can't have a PSA higher than 1.0 at the time that they enroll on the study. We think that all patients with PSAs that high should get some form of hormone therapy. Given that half the patients in this trial are getting a placebo, we don't think they're the best candidates for this trial. There are other trials for which they'd be better candidates.

If someone reading this is interested in participating, can they contact you directly or is there somebody else that they should get in touch with?

Dr. Spratt: They can contact me directly. It's an IRB trial, and centers have to open the study, so it's available across the United States and Canada. Many centers are in the process of trying to open the trial because it just activated a week or two ago. I would encourage patients to ask their physicians whether they have it open or if they can open the study. Pp

Ralph Weichselbaum, MD
Combining Radiation + Immunotherapy

Dr. Ralph Weichselbaum is the Daniel K. Ludwig Distinguished Service Professor of Radiation and Cellular Oncology and Chair of the Department of Radiation and Cellular Oncology at the University of Chicago Medicine and Biological Sciences.

Dr. Weichselbaum is keenly interested in investigating how tumors spread and how we can use radiation therapy and immunotherapy to treat cancer.

Prostatepedia spoke with him about the potential for combining radiation therapy with immunotherapy.

Why did you become a doctor? What drew you to medicine in the first place?

Dr. Ralph Weichselbaum: I was interested in medicine and my father was a doctor, but at the time they were drafting people in Vietnam, and I think that was what pushed me over, to tell you the truth. But I'm very glad I did it.

What is oligometastatic disease?

Dr. Weichselbaum: Oligometastasis is not a very precise definition. Initially, Dr. Sam Hellman and I—he's been a collaborator and teacher of mine for a long time—said one to five metastatic sites in our initial paper. The idea was that that one could use an ablative intervention and cure some patients who didn't have widespread disease. I think the two trials that I'm familiar with in prostate cancer, the STOMP trial and the Oriole trial—which isn't published—define oligometastatic prostate cancer as one to three metastases.

The idea is that oligometastatic is an intermediate stage between widespread metastases and local disease?

Dr. Weichselbaum: Yes. It's like all processes; it's a spectrum of things.

What are some of the advantages to treating these oligomets with radiation therapy versus surgery? Is the cancer control similar? What about side effects?

Dr. Weichselbaum: All good questions. I think there are no Phase III randomized trials published as yet, but some are underway. For prostate cancer, I infer that if patients have positive lymph nodes, they're probably taken out. If they have bone metastases, they were irradiated. I think that's the most appropriate thing to do under both sets of circumstances, however, I do not know for sure.

I think in other oligomets, like colon to liver, if the patient is able to undergo an operation, I probably would recommend an operation because the results are quite good. For lung metastases, it's a little more complex due to morbidities. I think it depends on the situation. Probably for solitary metastasis, I would recommend taking them out. There's not a lot of data to suggest one is better than the other.

For prostate cancer, it makes good sense to take out the lymph nodes and radiate the bone mets because I think there are some significant side effects to operating on bone. There are also some significant side effects to radiating the pelvis at very high ablative doses. But, I can't say for sure that there is any data to support what I just said.

Some are exploring combining radiation therapy with immunotherapy. What is the thinking behind that?

Dr. Weichselbaum: Radiation was long thought to be immunosuppressive. That is it reduced white counts. In fact, wide-field radiation did depress immunity. Within the past 20 years, it's been recognized that radiation is an inflammatory stimulus and it seems to help anti-tumor immunity. There is speculation as to why this occurs. Part of it is likely because after radiation the tumor activates "danger signals" which alert the body to the fact there is something foreign there. It's a system that's conserved by evolution to get rid of viral infections. By using what's called the innate immune system, it recognizes these signals and then the innate immune system primes the adaptive immune system, the CD-8 cells.

Now, I think it's a little bit overdone, and perhaps I'm responsible for this in part. I think we need to add these immune-stimulatory drugs to this to fully actualize the effects of radiation and immunotherapy. I know it's still pretty primitive in terms of how these things are combined. Like anything, it's probably been a little bit overdone, although I do think there are some interesting signals out there. Nonetheless, it requires a lot more study.

Which of these radiation-immunotherapy combinations and sequences look to be the most promising?

Dr. Weichselbaum: The most promising study was in lung cancer of chemotherapy-radiation followed by an anti-PDL-1. That was called the Pacific trial. It shows us that immunotherapy, like radiotherapy or chemotherapy or surgery, is effective against small-volume disease. The laboratory data suggests that it's the ratio of tumor cells to immune cells that really determines the outcome.

There are also combinations of the immune checkpoints anti-CTLA-4 and anti-PD-1 with radiation. The idea has been to shed tumor antigens, elicit danger signals and then increase T cell priming and take the off peripheral T cells. I think this needs a lot more work in the context of radiation although there are groundbreaking papers with the checkpoint inhibitors. Regarding radiotherapy there are very optimistic papers that I think are over-interpreted at the present time. There's an interesting signal, but there is no data that really demonstrate a clear benefit. I might get some pushback from colleagues on that, but I think it's probably the most conservative, realistic interpretation right now.

What are the side effects like with these combinations and sequences?

Dr. Weichselbaum: Right now these agents are given with focal radiation. The immunotherapy in this context probably has worse side effects than the radiation therapies. There are some side effects of the combined, but I don't think they're untoward more than immunotherapy alone or radiotherapy alone although I do worry about combined lung and bowel toxicity.

So there's not a synergistic effect in terms of side effects?

Dr. Weichselbaum: There may be in the long term. Most of the clinical trials with these combinations use limited radiation fields. That limits the contribution of the side effects from radiation.

Is there anything else that you think patients should know, either about treating oligometastases with radiation or about combining radiation with immunotherapy?

Dr. Weichselbaum: There is an interesting and rare effect called the abscopal effect, in which you irradiate one site and you get a response in another. This is very rare with radiation alone. When you add a checkpoint inhibitor, it seems to be more common. This converts, potentially, radiation from a local treatment to a systemic treatment, so that is very interesting. Again, the abscopal effect is over-interpreted, but it suggests that combining radiation with other kinds of immunotherapies may be helpful.

The other thing is that by doing multi-site radiation, radiation can be converted to a systemic agent. I think that these are new uses for radiotherapy, unlike the debate over radiotherapy or surgery for primary prostate cancer. This is a bit different.

I also think that there may be, in some men, a use for checkpoint inhibitors in radiation for local therapy. If we can combine radiotherapy with immunotherapies in local treatment, maybe we can reduce the dose of radiotherapy, and in the long run, get better cure rates with fewer side effects. This is quite important.

I think people tend not to think about that. Mostly people think about how are we going to cure metastatic disease, which of course is important. Nonetheless, I think we want to make these primary treatments more effective and less invasive.

Do you think that's because the clinical trial tends to focus on metastatic disease?

Dr. Weichselbaum: It's also much easier to get a FDA-approval in metastatic disease. If you try to do this in local prostate cancer, you'd be doing this forever.

Do you think that's just the way the clinical trial world and the approval process are structured?

Dr. Weichselbaum: Absolutely. That's a little speculative. If something bad happens to someone who has only got a one-month life expectancy, it's tragic but people can accept it. If something happens to somebody who's going to live 15 or 20 years, the risk-benefit is much different.

They've been robbed of more years, I guess.

Dr. Weichselbaum: Well, you can't take a great risk if one has a potentially curable disease. There is much more at stake. Pp1

Clinical Trial: PSMA + Radiopharmaceutical Lutetium-177

Dr. Johannes Czernin is the Chief of the Ahmanson Translational Imaging Division at the University of California, Los Angeles (UCLA) and the President of the Academy of Medical Imaging.

He spoke with *Prostatepedia* about a clinical trial he's running that looks at lutetium-177 targeted PSMA treatment for prostate cancer. Lutetium-177 is a radiopharmaceutical, or a radioactive drug.

"The trial will now be free-of-charge for 700 patients worldwide."

Why did you become a doctor? What is it about medicine that drew you in the first place?

Dr. Johannes Czernin: The answer to that question is complex. One becomes a physician by wanting to help people. I lost my father to cancer when I was very young, so that played a role in this decision. Also, I really found medicine very interesting in both the basic sciences and the clinic. So the initial motivation was good deeds, and then later on, what is meaningful changed for me. I really want to make a difference in patient outcomes from a translational science point of view, so really helping to implement things to help patients live better and longer.

Can you put your trial on lutetium-177 targeted PSMA treatment in context for my readers?

Dr. Czernin: We are conducting a Phase II trial at three sites in the United States, Radiomedix in Houston, Excel Diagnostics run by Dr. Ebrahim Delpassand in Houston, and Ahmanson Translational Imaging Division at UCLA. This approach labels a ligand of prostate-specific membrane antigen (PSMA) that sits on the surface of prostate cancer cells with lutetium-177.

We started doing this because we sent more and more patients to Europe for this specific treatment. Reports from Europe—mostly from Germany— showed that this treatment is quite effective in alleviating symptoms and reducing blood PSA levels significantly in about 50% of patients. We got really excited about that.

A group led by Dr. Michael S. Hofman published a prospective study in

June 2018 in The Lancet Oncology. They completed a Phase II trial that reported everything that was already reported from Germany. We see significant response rates in the study population by PSA reductions and symptom improvement. But in a Phase II trial, you cannot really comment on survival benefits because it's not a randomized trial.

We had to send some patients who had exhausted all therapeutic options to Europe for treatment. That is something that I didn't like because it puts hardship on patients, it's complicated to set up, and it's not feasible for all patients. That said, our trial is also costly for patients.

We submitted an Investigational New Drug (IND) application to the FDA together with the Houston site, which took two or three years of work. It was finally approved, but the only way we could get this done was through an IND with cost recovery, which means that the financial burden is put on the patient.

As this treatment comes in four cycles, eight weeks apart, each cycle costs an average of $11,000. That's about $50,000 total. It's very expensive.

We are fully aware that this raises some ethical questions, as only wealthy people can afford this trial. But as no one else is funding us—no private or public group or even the NIH would fund this kind of trial—we argued that at least if the wealthy patients get it started, we can then move to a stage that would lead to FDA approval and reimbursement for everyone. We're not there yet, but we will be soon.

We started treating our first patient in November 2017. We have now enrolled about 35 patients and are treating 28. The others are waiting for the first cycle. We know already that the PSA goes down in a substantial number of patients and the symptoms improve markedly. But we need to have the survival data.

Midway through this, a company called Endocyte acquired the rights to the compound and took over the trial as the responsible sponsor. This is good because after a Phase II trial, we need a Phase III clinical trial.

Endocyte is now setting up the Phase III trial, which will be a randomized trial with a 2:1 randomization that includes patients who have had everything, including toxin-based chemotherapy.

The trial will now be free-of-charge for 700 patients worldwide. Approximately 500 patients will be randomized for the treatment arm. That will give the definitive answer whether we improve progression-free survival and overall survival.

The Phase III trial is projected to end in early 2020 because recruitment will be very quick. After the appropriate follow-up time, this data will be used to submit a new drug application with the FDA and a Medicare reimbursement.

This is a trial with 40 sites in the United States and 40 sites in Europe.

The only drawback of the trial is that patients who enter the randomization will not get any treatment if they are randomized to the non-radioactive (no lutetium-177) treatment.

From a physician's point of view, I find this hard to digest, but it is the only way to get it done.

It's a strange recurrence in medicine that often we have good evidence that a treatment is effective, but we don't know the real degree of its effectiveness and we don't know whether the effectiveness is only random. That is where we are currently with these trials.

We will close our Phase II trial the moment we have approval to start the Phase III trial, which is bittersweet. We'll smile because more patients will get the benefit of the treatment. But we'll cry because some patients will not get the treatment due to the randomization.

What can patients who sign up for the Phase III trial expect to happen?

Dr. Czernin: Patients will be included if they meet certain blood criteria. Their hemoglobin, white blood cell count, and platelets need to be of a certain level. These are fairly mild inclusion criteria that are not at all prohibitive.

However, patients must have undergone toxin-based chemotherapy, which many patients have not had. But that's an inclusion criterion. We want to have patients who have exhausted everything so that this new treatment is ethically justified. It's a little bit different in our case with lutetium-177 because there is really so much non-structured experience from Europe. But still, I understand why Endocyte has to do this; it's an FDA requirement.

There's a time interval from last chemotherapy to the lutetium-177 treatment.

There is also an imaging entry. You have to be imaged with a PSMA PET/CT scan because we want to know whether all the tumor lesions express PSMA, which is the therapeutic target. Some people will drop out because not all their lesions express PSMA. I think that's a good thing because therapy will be ineffective if lesions do not express PSMA; the imaging target is the same target as the treatment target.

Other than that, it's going to be fairly straightforward. The randomization arm is not set up so that they get no treatment. They will get standard of care at the treating physician's discretion. They will go back to their urologist and will get whatever their urologist feels could be done, except for the lutetium-177 treatment.

What are the side effects of the treatment? Is there anything else you'd like patients to know either about this specific trial or about PSMA-directed therapies?

Dr. Czernin: This lutetieum-177 treatment is very well tolerated, but it has some side effects that can last for a few days: mild nausea and blood count can go down a little. Severe blood toxicity does not happen often; it's very rare, actually. Some people get a dry mouth from the salivary gland radiation. That is just because the radiation goes everywhere in the body and especially to the salivary glands. Patients will be informed about some side effects.

Other than that, it's an outpatient procedure that takes about two hours.

In the end, when all the noise of the trial, paperwork, and safety protocols are no longer needed, this treatment will be a lot like Xofigo (radium-223). You get an IV infusion that takes half an hour or so and then you are out again. You won't need any kidney protection. We know already that the kidneys don't get damaged. It's going to be a fairly easy treatment.

The Phase III trial will include up to six cycles given at intervals of six weeks: it's a 36-week treatment. Currently, it's four cycles, but I think the company did the right thing in expanding it to six cycles because there's no reason not to. They will have certain criteria to define whether patients qualify for cycle five or six.

Isn't Xofigo (radium-223) also in six cycles?

Dr. Czernin: Yes, but Xofigo (radium-223) is in four-week intervals.

It sounds like an exciting trial.

Dr. Czernin: It's going to be really important. I'm not sure about the extent, but there will be a survival benefit just based on the experience we already have in Europe. Our benefit may be equally important for prostate cancer patients. The quality could really improve. Pp

How To Get Involved…

For more information, email Dr. Johannes Czernin at JCzernin@mednet.ucla.edu or Dr. Jeremy Calais at JCalais@medmed.ucla.edu.

Merel Nissenberg: Hypofractionated Radiotherapy

Ms. Merel Nissenberg is the President of the National Alliance of State Prostate Cancer Coalitions, a nation-wide organization comprised of state prostate cancer coalitions dedicated to saving men's lives and enhancing the quality of life of prostate cancer patients and their families through awareness, education, and the development of a public policy network.

She offers two views of hypofractionated radiotherapy for prostate cancer.

NASPCC supports the use of new treatments and therapies that good evidence shows help prostate cancer patients, but only those that do not have more risks than benefits as compared to conventional care. Consider radiation therapy in prostate cancer. As radiation therapists and medical oncologists consider future trends in radiation therapy for prostate cancer, there are two settings in which the idea of hypofractionated radiotherapy is being explored. It may not yet be ready for prime time.

The first setting is either the postoperative adjuvant period for prostate cancer patients with aggressive pathological features following radical prostatectomy or as salvage therapy for patients with biochemical recurrence after prostatectomy. Although there is now evidence from Phase III trials supporting the use of hypofractionation in terms of good biochemical control and favorable short-term toxicity, the role of such radiotherapy in these patients is still considered investigational due to conflicting results with long-term genitourinary late toxicity.

The second setting involves men with localized prostate cancer who are often treated with external beam radiation therapy (EBRT) as their primary treatment, with treatments given over the course of 8-9 weeks. For these types of localized prostate cancer patients, trials are now being conducted to ascertain the non-inferiority of hypofractionation. That is, can larger doses of radiation per treatment over a shorter time be just as effective as standard EBRT and with no increased toxicity?

In one such trial reported in Journal of Clinical Oncology in 2017 (V35, no. 17, 1884-1890), intermediate risk patients were randomized to either conventional radiotherapy of 78 Gy in 39 fractions over 8 weeks (598 patients) or to hypofractionated radiotherapy of 60 Gy in 20 fractions over 4 weeks (608 patients). No androgen deprivation was allowed during the trial.

The primary outcome was "biochemical-clinical failure" (BCF), defined as the first occurrence of any one of 4 outcomes: PSA failure, hormonal intervention, clinical evidence of local or distant failure, or death as a result of prostate cancer. Median follow-up was 6 years.

"the role of such radiotherapy in these patients is still considered investigational."

The five-year BCF disease-free survival was 85% in both arms of the trial, and there were no significant differences between the two arms in terms of grade 3 or worse late GU and GI toxicity. There were twelve deaths as a result of prostate cancer in the standard RT arm, and ten deaths as a result of prostate cancer in the hypofractionated arm.

The trial investigators concluded there is evidence to support the use of moderate hypofractionated RT in patients with intermediate-risk prostate cancer but not in high-risk disease.

"More studies are therefore needed"

For hypofractionated radiotherapy to be adopted as standard practice for patients with intermediate-risk disease, it must be shown to be equivalent or superior to conventional radiotherapy in terms of excessive toxicity, especially late radiation genitourinary and gastrointestinal toxicity. More studies are therefore needed, particularly because there has been conflicting evidence in terms of such toxicity.

While some reports from last year conclude that moderate hypofractionation is safe and effective for localized prostate cancer and further suggest it should be standard of care, it cannot be over-emphasized that caution is strongly urged.

"Caution is strongly urged"

Longer-term toxicities are not yet known from the increased dosage of radiation with the new modalities. NASPCC strongly supports more clinical trials and longer-term follow-up to answer the question of long-term toxicity with the use of hypofractionation. Pp[1]

Patients Speak
Ron B.: I Had Stereotactic Body Radiation Therapy

Mr. Ron B. had stereotactic body radiation therapy (SBRT) when his prostate cancer came back 6 years after initial surgery.

He spoke with *Prostatepedia* about his experiences.

How did you find out that you had prostate cancer?

Mr. Ron B.: I had a regular physical. The PSA came back elevated. I believe it was 4.3. The GP suggested that I have a re-test, of course. It came back about the same. Then he sent me to a local urologist. They did more PSA tests. It rose a little bit. Then the urologist suggested I get a biopsy, which I did. That came back 11 of 12 cores positive, and a Gleason of 7+8. Then it became a question of what to do next.

What was the first treatment you received?

Ron B.: The urologist recommended a radical prostatectomy. Given I was only 51 at the time, he thought that was the best route. I did a little bit of research with another doctor. It seemed like the best route was the surgery.

I ended up going to Memorial Sloan-Kettering in New York City and meeting with a surgeon there. Of course, he recommended surgery.

There weren't a whole lot of options in 2004 like there are today. There was robotic surgery, but it was new. Cryotherapy was new. I was a little uneasy about trying something new. I just opted to go with the prostatectomy. He suggested plastic surgery, also, to restore the nerves. So they did that.

Did it work, or did you have any side effects afterwards?

Ron B.: It sort of worked. It was only said to be 60% effective. I decided to go for it because it was an option that might work. It didn't really seem to have any risk to it.

The plastic surgery alone was not effective.

For six months after the surgery, I also had a regimen of erectile dysfunction pills and Trimix prostaglandin injections. Even so, my function today is not what it was prior to surgery. I avoid the pills if I can because of the side effects.

How were you monitored after surgery?

Ron B.: I had PSA tests every month for a while and then every three months. The PSA tests were fine for a period of six years almost. I had no detectable PSA.

Then, all of a sudden, around 2010, I suddenly had a rise in PSA. It rose to 0.13, then 0.49, and then 0.58. That's when they decided that I needed to get scanned. I got a PET scan, MRIs, and bone scans to try and figure out what was going on and locate the problem. That was in 2010, six years after the surgery.

Did they find any bone mets?

Ron B.: Yes. They found one lesion. It was in the pubic bone. I went to see an oncologist at Memorial. He gave me some options. Initially, they didn't sound too encouraging. One of them was hormone injections. The idea with that was that it probably would hold things down for a couple years. Then, ultimately, you run out of options.

Finally, the oncologist suggested SBRT, radiotherapy. He had a colleague there who evidently has had a lot of success with that therapy. I went to see that doctor and he explained the procedure to me. It was all in one treatment, which sounded pretty good. He said that they had a good deal of success with it, so I opted to go with the radiotherapy.

Did you have any side effects from the treatment?

Ron B.: The only side effect I had was a mild sunburn in the area that was irradiated. That went away in a couple of weeks. Other than that, I did not have any side effects at all.

How are you being monitored now?

Ron B.: Yes. Of course, after the radiotherapy, they did quite a bit of MRIs, bone scans, and so forth. They wanted to see if the radiated area was healing. Then there apparently was a pretty dramatic drop in PSA. I had the radiotherapy in June, and by August of 2010, two months later, my PSA went down to 0.13. By April, it was undetectable.

Even so, they continued to do scans to check everything. Ever since early 2011, I've been undetectable, which is not quite eight years.

That's a brief explanation, I guess, from what I can recall.

Now it's 14 years away from the beginning of the whole ordeal. I still don't know what to expect. I continue to get PSA tests on a yearly basis.

My oncologist told me, after a couple of visits, that he suggested I enter their regular patient monitoring. That's what I do. I go once a year. I get my PSA tested. I also go to my GP, and I have the regular exam there. That's where I'm at right now.

Do you have any thoughts for other men who might be in a similar situation?

Ron B.: There are a lot of different treatments. There are a lot of different drugs than they had in 2004. You don't have to make a hasty decision.

I remember when I first got the diagnosis, I wanted to get it taken care of right away. For some reason, I thought the earlier you paid attention to it the better off you would be. The sooner I could get something done, the better. That was my thought.

Later on, I learned that I could probably have continued to research and look for other types of treatments for a month or two before actually having to get something done. I just wanted to get it done right away. That was my thought at the time. I think for most men, from what I'm reading and hearing, they have time because it is a slow-moving cancer unless it's spread. Mine was negative on the surgical margins, but there was what they call some extracapsular extension. Right before I had the biopsy, they noticed with the digital rectal exam, that there was some extension. Nevertheless, after the surgery, it was all within the surgical margins. I felt like I had a pretty good prognosis. And I did until almost six years later. You never know. My oncologist told me I was one in a million after the radiotherapy. He said it was extremely rare to have that kind of result.

He said that normally, for someone with my situation, he would have expected to be giving me injections and so forth. It never came to that. I never had any hormone injections. That's where I'm at. I don't know if that helps anybody.

I would like to get some kind of a prognosis on the future, but I guess nobody seems to know after this kind of treatment. The only thing they tell you is you have to continually get checked, which I do. I guess prostate cancer is just something you're stuck with for the rest of your life.

It's not like you can rest easy because you never know. Even after the surgery, and so forth, you have to religiously have your PSA monitored. You can't just assume that you're five years out and home free. That's just not the case. You have to make sure you get your PSA monitored for the rest of your life.

That's just a once a year, though; it's not that difficult to do, right?

Ron B.: Once a year is fine. Actually, I've been doing it twice a year because I go to my general practitioner, and I have it done there as well. I have two readings on it. Maybe I'm being overly cautious. I don't know, but I'd rather get two opinions at this point. Pp[1]

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August:
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