The New PCRI Website:
Access to Pertinent Knowledge, Not Just Information

By Peter Scholz, PCRI’s Web Content Manager

PCRI specializes in empowering the patient and the advocate through education. Nowadays there is access to almost an infinite amount of prostate cancer information on the internet. But, one cannot become educated by simply learning as many facts as possible; one becomes educated by learning how all the facts relate to one another. To the learned patient or advocate, new information is an empowering tool that builds upon a framework of existing knowledge. But without this pre-existing foundation, information can be intimidating and unmanageable.

Here at PCRI it is part of our mission statement that becoming educated about prostate cancer leads to empowerment and better medical care for the patient. Over the years PCRI has been amassing great amounts of relevant, cutting edge information and making it accessible to the people who need it through our annual conferences, helpline, website, and Insights newsletter.

But our focus is not just to provide the most accurate and up to date information about the changing world of prostate cancer; there is an even more important goal that needs to be achieved. We help you the patient (or advocate), build a mental landscape of the prostate cancer world, a useful framework that enables you to sort and filter through all the facts you find and put them within the context of your own specific needs. We don’t just tell you what you need to know, we also help you identify what you don’t need to know.

At the end of 2013, we launched our new website. Apart from the updates to the look and feel, we have made it easier to search for the information related to your topic of interest. For example, we have restructured the site to make more content quickly available on the home-page so you get to the important information faster. We have also added better video integration allowing us to present video content that we already have. The biggest improvement is that it is now managed completely in house so that maintenance and updates are more rapid and our information stays on the cutting edge of prostate cancer care.

The new website, in tandem with the possibility now to expand into visual education, is a platform that amplifies what we do best to a larger scale, broadening our reach, and making a more comprehensive knowledge base available. We believe this will expand the reach of PCRI’s message and enable more patients and advocates to educate themselves, become empowered, and get better outcomes.
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The Prolaris Test for Prostate Cancer:  

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In 2013, the American actress Angelina Jolie made a life-altering decision that fascinated the public and made the cover of *Time* magazine [1]. Based upon her family history and a genetic blood test for the BRCA1 gene, she was counseled that she had an 87% chance of developing breast cancer. This led to her decision to undergo a preventive double mastectomy. The *Time* article was titled “The Angelina Effect” and focused on the power of genomic medicine to guide clinical decision making. A family history can be considered part of “clinical information” and would certainly increase the odds of developing breast cancer, but only the genomic test increased those odds such that a preventive procedure became a reasonable strategy.

Where are we with genomic medicine in prostate cancer? The situation is distinct from the breast cancer scenario in that the inheritance pattern in prostate cancer relates to incidence of the disease, but not the biologic behavior of a tumor. Therefore we are looking to genomics to refine an individual’s risk of prostate cancer progression. In fact, prostate cancer has its unique qualities, in that the simple diagnosis of prostate cancer does not carry a significant risk of cancer mortality unless it is at the higher end of the Gleason scale [2]. Cancers that are small in volume, clinically contained, and low in Gleason grade have very small progression rates and cancer-specific mortality and can often be observed [3]. In contrast, there are lethal versions of prostate cancer that may require combination therapies to avoid progression and death [4]. So let us explore this topic further by defining two common decision points for men with prostate cancer and demonstrate the role of genomic testing. In this part I article, we will explore the biopsy-related indications for genomic testing.

**Diagnosis: Favorable Risk Prostate Cancer. Choice: Observe or Treat.**

First, let us review the nomenclature used for “clinical information” so we can set that apart from genomic testing. There are two clinical settings where prostate cancer may be considered: 1) screening, meaning they have no complaints, but they meet common guidelines for testing with a digital rectal exam (DRE) and serum Prostate Specific Antigen (PSA), or 2) clinical evaluation, meaning they have a symptom or complaint that makes their doctor want to test them for prostate cancer. In either scenario, an abnormality of the DRE or PSA may lead to the recommendation to undergo a biopsy of the prostate. Of course, you could stop here and write an entire article about the pros and cons of PSA screening, but for this article we will just make the point that once a biopsy is performed that shows cancer, it really does “take over” the majority of the “clinical information” compared to the DRE and/or PSA that were the initial concerns (unless the DRE shows bulky disease or the PSA is > 10 ng/mL or rapidly doubling). A biopsy of the prostate (often abbreviated TRUS-BX for transrectal guided ultrasound biopsy) often includes 10-12 individual needle biopsies performed under ultrasound guidance. The size of each needle biopsy core may be up to 15mm. Therefore you have 3 very powerful pieces of information from a TRUS-BX: 1) Gleason Grade, 2) number of positive cores, and 3) % involvement of positive cores. Used together, we can now define a common clinical condition of the man who was either screened or evaluated for a symptom and as a result found to have “low grade-low volume” prostate cancer [5-6]:

- **Biopsy Grade: Gleason 3+3**
- **Number of involved cores:** 1 or 2
- **Percentage of involved cores:** < 50%
- **PSA:** < 4 or similar with enlarged gland
- **DRE:** normal or very minimal findings
What happens when men undergo immediate treatment for this condition? They certainly can have favorable cancer control, but increasing evidence questions how much threat there was to begin with [4, 7]. Therefore, any long-lasting side effects they may experience from surgery or radiation would not be well balanced by a gain in cancer control. What happens when we recommend active surveillance? In general, we are correct in our decisions in approximately 70%, while the remaining 30% may be found to have higher volumes or grades of tumor on repeat TRUS-BX or a rapidly rising PSA that would trigger a delayed treatment. The majority of delayed treatments are based upon incremental changes in these features with favorable treatment outcomes, but there are occasional delayed findings showing significant upgrading or upstaging that cause concern [8-9].

So how can genomic testing such as Prolaris help? Prolaris is a test that looks at features of rapid cell turnover called Cell Cycle Progression (CCP) Genes [10]. These are the genes that tell the cell to divide into two. The lack of regulation of cell division is a hallmark of all cancer. The test looks at the average expression of 31 CCP genes to generate a unique scaled result that can be yet another number to consider, but more usefully grouped into a descriptor such as “much more aggressive than average risk,” “equal to clinical risk,” or “much less aggressive than average risk.” Therefore if a man is unsure about whether or not to choose immediate treatment or active surveillance, the Prolaris test can give an estimate as to his 10-year cancer specific mortality if left untreated. The good news is that to have the test performed, the necessary materials are all in the biopsy tissue, and therefore no more invasive procedures are required. The bad news is that the test is expensive—around $3400—but not unreasonable compared to the cost of the biopsy itself or advanced imaging such as an MRI or PET scan. [PCR note – Insurance coverage can vary with different insurance policies. See http://www.ProlarisTest.com or call (801) 584-1175 for more information.]

In my practice, I have found Prolaris helpful in some very young men who are considering active surveillance or just want maximum available information. I have found it even more useful in men who are interested in active surveillance but do not meet the above criteria for low-grade, low volume disease. See the following examples:

Example A: A 74 year old man with 3 positive cores of Gleason 3+4, normal DRE (T1c), and PSA 4.5 was evaluated and based upon his own research wanted a radical prostatectomy. However he had significant medical problems including heart disease, previous blood clots from surgery, and diabetes. Based upon the known clinical features of his cancer and overall health, we could make a reasonable prediction that he is unlikely to die of prostate cancer, unless the biology of his disease is much more aggressive than what we are seeing. His Prolaris score was in the “much less aggressive than average risk” category and a <2% chance of dying of prostate cancer in the next 10 years without definitive treatment. Therefore he changed his preference to active surveillance.

Example B: A 50 year old man was diagnosed with 3 small cores of Gleason 3+3 prostate cancer, normal DRE (T1c), and PSA 3.5. He would commonly be considered for a radical prostatectomy based upon this combination of multiple cores and young age. However he was extremely overweight to a degree that surgical complications and functional outcomes were a real concern. His Prolaris score was also in the “much less aggressive than average risk.” Therefore we have recommended an active surveillance plan with a major effort for him to lose weight in the event that future testing changes and he needs surgery.

Example C: A 55-year old healthy man has already been on active surveillance for 2 years with 1 core of Gleason 3+3, normal DRE (T1c), and PSA of 3.4. However at year 2, the repeat biopsy showed 1 small 1mm core of Gleason 4+3 and a second 1mm core of 3+3. For personal reasons and fear of side effects, he was just not ready to undergo definitive treatment, even though the Gleason 4+3 at his age is a significant concern. An MRI of the prostate was favorable—organ confined. His PSA levels and DRE have never changed. Six months later he requested another biopsy which showed 3 positive cores, but all Gleason 3+4 and less than 2mm. In aggregate, as his physician I would say that he has significant cancer that should be treated for cure with surgery or radiation. However, he still is adverse to side effects risk. A Prolaris score was ordered on the most recent biopsy, which returned “less aggressive than average risk;” and he remains on active surveillance. He realizes that he may need therapy one day, but is satisfied with his risk/reward decision to wait until repeat testing shows a more concerning finding.
Conclusions:
Genomic testing is now a reality in prostate cancer, and can be used to refine calculations of risk that can improve what we know from clinical features alone. The biopsy testing for Prolaris can specifically help define the risk of cancer-related mortality if left untreated—a calculation of particular interest to older patients with other risks of mortality. Future studies will certainly focus on how such genomic testing can help reduce the over-treatment problem associated with PSA screening and early detection. In part II of this article, we will examine the post-prostatectomy use of Prolaris, introduce some of the alternate genomic tests in the commercial marketplace, and critique our current position in genomic testing.

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References:
What are you doing June 21st?

Join PCRI for the third annual ZERO Prostate Cancer Run/Walk!

PCRI is committed to bringing generations together for our ZERO Prostate Cancer 15K/5K Run in Los Angeles!

This fun-filled event will help support prostate cancer research and education. Get involved in promoting awareness this year by joining PCRI and ZERO for this exciting event!

When: June 21st, 2014
Where: Long Beach, California

If you will be in the Los Angeles area the weekend of June 21st, don’t miss out on the fun! Whether you are a seasoned athlete or a casual walker, this event is a fantastic opportunity to raise awareness for prostate cancer. There will be food, prizes (including a chance to win an iPad mini) and fun for the whole family!

Visit http://losangeles.zeroprostatecancerrun.org/ for more information and to register today!

Interested in volunteering on race day? E-mail info@pcri.org to learn how you can help!
Over the years, as the pace of scientific advancement accelerates, the new science being presented becomes even more hopeful and innovative. The best meeting each year is hosted in October by the Prostate Cancer Foundation (PCF). The meeting is put together by Howard Soule, the PCF director of research. This year was the PCF’s 20th annual meeting. It consisted of two full days of presentations, each averaging about fifteen minutes long. The sheer volume of new information is delightfully overwhelming.

A good number of presentations are at the basic science level and therefore have little relevance to the average reader of Insights. Research into basic science is designed to elucidate the fundamental biology and biochemistry of tumor cells. It is a laborious and expensive process designed to work out the “basic blueprints” of cancer function. The idea is to build a scientific foundation for the future discovery and rational design of new drugs. I’ll try to summarize the presentations that may be of greater interest to our readers.

A Retrospective on Surgery

Historically the PCF has focused on developing treatments for advanced disease. However, this year they hosted a 45-minute panel session of five famous prostate doctors to discuss the modern role of surgery. Dr. Holden, the medical director of the PCF moderated a discussion with Patrick Walsh, Phil Kantoff, Chris Logothetis, and Eric Klein (three urologists and two medical oncologists). Howard Sandler, a radiation therapist was asked to chime in from the audience.

In light of the acknowledged fact that surgery is unnecessary for low-risk prostate cancer it was fascinating to hear Dr. Klein and Dr. Walsh (the two surgeons on the panel) talk about the great research benefits and wonderful pathologic information we have obtained from actual prostates, the same ones that have been surgically removed over the last 20 years. As if this somehow gave purpose and meaning to the millions of men who have been treated with radical surgery! Patients in the audience must have felt a chill run up their spines at the cold blooded disregard for all the unnecessary, surgically-induced human suffering.

During the panel discussion both Dr. Kantoff, a medical oncologist, and Dr. Sandler, a radiation oncologist, were unwilling to make any remarks that could be construed as disagreement with Dr. Walsh. Therefore I apparently risk repercussions by disagreeing with a sweeping statement made by Dr. Walsh, “Men with high-risk disease treated with surgery don’t need hormonal therapy.” To be fair, I agree with Dr. Walsh that some favorable types of high-risk disease can forgo hormonal therapy. However, there is at least one piece of compelling evidence that men in the high-risk category treated with adjuvant hormone therapy experience lower relapse rates according to a large prospective study published in the Journal of Clinical Oncology by Dr. Tanya Dorff from USC.
My favorite quote from the panel discussion was from Chris Logothetis, the medical oncologist from MD Anderson. He said, “If surgery was a new drug under evaluation for approval by the FDA to treat low-risk prostate cancer—it would never be FDA approved.”

On another note, Dr. Klein, the urologist from the Cleveland Clinic expressed the optimistic belief that all the new genetic tests that help confirm that low-risk prostate cancer is really low-risk such as Prolaris and OncotypeDX, will lead doctors to restrain themselves from the overuse of surgery and radiation. Personally, I am not so optimistic that the ingrained systematic overtreatment of men with low-risk disease will be so easily revolutionized.

**New Immune Therapy**

I am particularly excited about new treatments with the potential for harnessing the immune system to fight cancer. The immune system is very complex with many moving parts. The T-cells are a component of the immune system that is utilized to attack cancer cells directly. However, cancers often “cloak” themselves from the immune system using mechanisms to “blind” the T-cells to their presence.

Some of the new immune-based therapies work by awakening the immune system to “see” the cancer cell and attack it. Provenge is one such example, a FDA approved treatment for prostate cancer that sensitizes the immune system to the PAP antigen. At the meeting, new research was presented describing a newly created antibody that focuses T-cells on a different target, the PSMA antigen, a protein located on the surface of cancer cells. This new therapy uses a uniquely designed cancer-specific antibody that has been chemically altered to guide activated T-cells directly to the surface of the cancer cell.

**Improving the Identification of High-Risk Prostate Cancer**

Another important area of development in cancer therapy is what I call the reconnaissance aspect of cancer treatment. In military terms, you can’t fight the enemy if you don’t know the strength of his forces and their specific location. New research presented at the meeting gave details about the discovery of a new gene product called SCHLAP-1 that helps predict the likelihood of future metastases. SCHLAP-1 appears to have predictive power on the same order as Gleason score or possibly, even better. Most of you are already familiar with cancer grading using Gleason and how it is critically important in distinguishing low-grade from high-grade disease. The availability of a new predictive factor of this stature would be a wonderful addition to our clinical armamentarium.

**Promiscuous Hormones**

It has long been suspected that when the androgen receptor gets blocked, the cancer cell’s lack of access to testosterone stimulates a switch in the cancer cell to start using other hormones like progesterone or cortisol as a substitute to feed itself. Research presented at the meeting seems to confirm this. However, these findings are preliminary as the studies were laboratory based rather than clinical studies in humans. We will have to wait to find out if these new discoveries are clinically factual or just an artifact of an artificial lab environment.
Getting a Leg Up on The FDA for Approving New Drugs

One of the biggest factors slowing down the new-drug FDA approval process is the requirement that all new medications demonstrate a *survival advantage* in a clinical trial. Ironically, this immutable demand from the FDA becomes harder to fulfill as the number of effective drugs increases. Just in the last few years Provenge, Zytiga, Xtandi, Xefigo, and Jevtana have become available. Many experts believe that it is not ethical to study new, unproven drugs until all the proven drugs have been tried and found to be ineffective. So as more and more effective drugs get approved, fewer and fewer patients will be available for participation in clinical trials and the ones who are eligible to participate will have very advanced, treatment-resistant disease. A percentage drop in PSA after treatment has been repeatedly proposed as a measure of treatment effectiveness rather than survival. PSA actually works well in some situations such as with chemotherapy or hormonal therapy. However, PSA can be notably inaccurate as has clearly been demonstrated with Provenge and Xefigo as neither causes a consistent decline in PSA though both have shown to improve survival.

At the meeting Dr. Howard Scher presented some hopeful information about ongoing studies that rely on measuring a decline in circulating tumor cells (CTC) in response to therapy as an accurate method for the early prediction of long term survival. The actual protocol proposed by Dr. Scher used CTC levels in combination with a measurement of an enzyme in the blood called lactate dehydrogenase (LDH). Using this proposed system, patients with advanced disease were divided into three risk categories. “Low-risk” patients had normal CTC and LDH levels. “High-risk” patients had a CTC count above five. “Intermediate-risk” patients had an elevated LDH with a normal CTC count. What’s exciting is that this system has already been tested and validated to predict survival. Dr. Sher is planning to propose this new system for evaluating new drugs to the FDA in the near future. If successful, substituting the measurement of CTC for the existing system of measuring survival could really speed up the new-drug approval process.

Finally, A Way to Detect Microscopic Metastases?

Victor Velculecu from Johns Hopkins presented his work which suggests that the presence or absence of microscopic residual disease can be detected with new genetic tests called genomic analysis. If this work is confirmed it could revolutionize the way we treat cancer. For example, right now many men are treated with long term hormonal therapy after radiation because of the possibility that microscopic metastases are present. If an accurate test were available that could confirm that a patient is totally free of metastases, that patient could safely be advised that long-term hormonal therapy is unnecessary!

Reducing the Side Effects of Xefigo?

Dr. Morris presented some fascinating information about the function of injectable Radium (Xefigo) which was recently approved by the FDA. Xefigo is generally well tolerated but the most common side effect, if a side effect occurs, is GI related. This appears to occur because after the Xefigo is injected into the blood stream it lands in the bone and attacks the cancer. However, some of the Xefigo is not taken up by the bone and gets excreted through the small intestine. Therefore, the excess radioactivity passes sequentially through both the small bowel and the large bowel. Apparently the dose of radiation is too small for most men to feel it.
However, some men are more sensitive and experience nausea or diarrhea as a result. Men who have GI symptoms from Xofigo (since the side effects caused by radiation are related to both dosage and duration of exposure) might want to consider taking a laxative to accelerate the bowel transit time.

**Botox for Prostate Cancer?**

At the meeting some fascinating data showed the dependence prostate cancer cells have on growth factors secreted by the nerves in the prostate. One of the possible culprits is a hormone called vasointestinal peptide. A study was performed by injecting Botox into half of the prostate of men with known bilateral cancer. The other side of the prostate was injected with an inactive salt solution. A month later the men underwent radical prostatectomy. After surgery it was confirmed that the cancer regressed on the side of the prostate that was injected with Botox. The physician presenting went on to theorize that the development of neuroendocrine prostate cancer, a feature that is common in advanced hormone refractory prostate cancer, is really nothing more than cancer evolving its own “nerves” so it has plenty of nerve growth factors to feed on. A paraphrased quote from him would perhaps read as follows, “Under stress [of hormonal therapy] the cancer makes its own nerves.”

**Conclusion**

The little snippets of information I have shared with you in this short article do no justice whatsoever to the absolute deluge of quality science that was presented at the two-day meeting. The PCF is doing a wonderful job of raising money and distributing it wisely to the best researchers in the world. Howard Soule and his excellent team should be greatly commended for the wonderful work they are doing to encourage the development of effective new prostate cancer treatments. It’s hard to believe the PCF had called this meeting a “retreat.” The way things are going I would recommend renaming it an "advance." Happily, the development of new treatments for prostate cancer is moving forward at a furious pace.
Why Screen for Prostate Cancer?
Screening finds earlier stage cancers, allows for simpler treatments with fewer side effects, and saves lives. For example, in 1985, prior to PSA screening, the prostate cancer five-year survival rate was 69% compared to 99% in 2006. It’s unclear whether this dramatic survival increase is entirely due to PSA screening. Other factors, such as improved therapy have also contributed.

Why Is There A Controversy about Screening?
Prostate cancer can be very slow growing. If a man already has a short life expectancy, the cancer may never affect him. Therefore, the side effects of treatment may be worse than the disease. In addition, two studies evaluating the usefulness of PSA screening failed to show a benefit, perhaps because too many men in the comparative group who were supposed to forgo PSA screening ended up getting PSA testing outside the study. In a third study from Europe, in which the unscreened comparative group had a much lower exposure to outside PSA testing, the study showed an improvement in ten-year survival.

Is Immediate Biopsy Appropriate?
As medicine is presently being practiced in the United States, an elevated PSA almost always leads to an immediate 12-core, random needle biopsy. Over a million men get biopsied every year. Unfortunately, few people realize that low-grade prostate cancer is so common in the general population that a biopsy will be positive 20% of the time, even in men with normal PSA! The majority of cancers found on random biopsy are small and do not require treatment. However, consider the emotional devastation of a cancer diagnosis. Men can be literally frightened to death. Studies have shown that there is a sharp increase in suicides and heart attacks after a cancer diagnosis.

Stop PSA Screening Altogether?
Due to concerns about over-diagnosis and serious side effects from unnecessary treatments, the U.S. Preventative Services Task Force has come out recommending against routine PSA testing. Unfortunately, the Task Force is missing the point. PSA is not the main concern. The problem is the prevailing medical policy in which doctors routinely refer men with high PSA for immediate random biopsy leading to over diagnosis of low grade cancers.

Role of New Imaging Technology?
Rather than doing an immediate biopsy, doctors should consider prostate imaging with multiparametric MRI or Color Doppler Ultrasound. In experienced hands with state-of-the-art equipment, high-grade cancer can be ruled out with 95 to 98% accuracy. And when imaging detects a high-grade lesion, a targeted biopsy directed specifically at the area of abnormality can be performed. If the scans show that no high-grade disease is present, the patient can forgo biopsy and simply monitor the situation with further PSA testing and if necessary, consider additional imaging in six to twelve months.
The Frequency of PSA Testing is Affected by Various Factors:

Annual PSA testing and a digital rectal examination are the foundation of screening. Men with increased risk due to family history or because of African-American race should consider starting at age 40. Otherwise, men can begin PSA screening at age 50. It is reasonable however, for all men to get a baseline PSA between 40 and 50 years old, and then decide about further testing based on that initial reading.

- Begin PSA testing age 40-45 if a relative had prostate cancer before the age of 60.
- Begin PSA testing age 45-50 if you have a father, brother, or uncle who had prostate cancer at any age or if you are an African American.
- Yearly PSA for men age 50-75 if your PSA 1-2ng/ml then every 2 years is okay.

After age 75 general health factors are the most important consideration. When overall health status is good it’s reasonable to continue screening past age 75.

If the PSA is higher than 2.5ng/ml or if there is an abnormality detected on digital rectal examination, further evaluation with imaging is needed.

HARRY PINCHOT Awardee: Phil Olsen
By: Jan Manarite

I loved hearing Dr. Lurvey speak of how he knew Harry Pinchot, as he presented the award to Phil Olsen, PCRI’s 2013 winner at the September Conference. An award which bears a person’s name should represent that person well. Phil Olsen does. I also knew Harry, who lost his PC battle in 2008. I believe he would have been proud of Phil for receiving this award. They were fellow-advocates and friends.

The list of Phil’s contributions to the world of prostate cancer is almost too long to list. His journey started with a misdiagnosis in 1989, before the PCRI existed. He was declared metastatic in 1993. His zeal for learning turned his battle into a meaningful journey that would both extend his life and change it for the better. In 1998, Phil joined and led an UstoO Support group in Hawaii which continues to this day. In 1999 he began attending PCRI’s annual conferences – possibly making him our most frequent attendee. That same year, he was appointed Regional Director of UstoO in Hawaii. From 2001 to 2006, Phil traveled the state to help initiate many other support groups. In 2005, he went on to found the Hawaii Prostate Cancer Coalition, part of the NASPCC.

My favorite memory of Phil is when he showed up in Washington DC on June 4th, 2007 to participate in a march on Capitol Hill which involved multiple prostate cancer organizations. We were known that day as Raise A Voice. I organized this march, and I still remember seeing him and realizing he came from Hawaii, and I thought to myself...do I have a gold star? Twelve hours of flying – really? I remember the smile on his face, and the hat he was wearing. He was simply proud to be there. Funny – because I wish I would have had an award to give him then, for being the person who traveled the farthest to be part of a march in DC.

Phil’s contributions have not ceased. They include public speaking, spearheading Hawaii’s recognition of PC Awareness Month, participating in DOD funding reviews, and engaging Hawaii’s Congressional delegation in important discussions about the United States Preventative Service Task Force’s recommendation against PSA screening.

Now at age 83, his involvement, and contributions continue. He is a prime representation of tireless advocacy, and of Harry Pinchot’s own work. Congratulations Phil – from all of us at PCRI.

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THE ABSCOPAL EFFECT:
The Effect of Radiation on the Immune System

By: Mark Scholz, M.D.

In general, the word “radiation” has very negative connotations. Many people therefore, will surprised to hear that some forms of radiation actually stimulate the immune system. Yes, I said stimulate. You probably thought I meant to say suppress. Of course, radiation to the whole body, such as what Japanese people were exposed to at Nagasaki, does suppress the immune system, sometimes to a fatal degree. Allow me to use a clinical story to illustrate how radiation may actually stimulate the immune system.

Clinical Case Study

A 54-year-old physician was diagnosed February 2011 with a PSA of 233. His scans were positive for bone and lymph node metastases. He immediately started Casodex and Lupron and his PSA briefly dropped down to 2 but subsequently rose to 10.8 in July of 2011. A prostatectomy in September showed 25 of 71 nodes with cancer. After his surgery the PSA continued to rise to 20 and another scan showed extensive cancer in almost every bone. At that point he underwent treatment with Provenge, the FDA approved immunotherapy for prostate cancer. At the same time he was also administered spot radiation to two small areas of cancer in his backbone. Afterwards, by January of 2012, his PSA dropped down to 0.47! Even so, six months later the PSA started rising again, up to 6. So he began Nilutamide, a feeble hormone medicine we rarely use anymore. Surprisingly his PSA again dropped to 0.8 and another scan showed that his previously enlarged lymph nodes had shrunk back to normal size.

Subsequently, when his PSA started to rise again and he began taking a combination of Xtandi and Zytiga, also with good results. However, by January of 2013 his bone pain started to return. Therefore, he elected to try a second cycle of Provenge given in combination with spot radiation. All the bone pain resolved.

To this day he continues to fight his disease with all available means including new agents such as Xofigo, an injectable form of radiation and XL-184, a medication that was recently FDA approved to treat thyroid cancer. As of the time of this article being written he continues to work fulltime with a PSA that hovers around 7.

In my experience dramatic cancer reversals like this with Provenge therapy alone are rare. Immune treatment is expected to retard the progression of the cancer, not cause a dramatic reversal. When something unexpected like this happens it leads one to consider that the results in this case are partially attributable to the addition of the spot radiation. This possibility is not as farfetched as you might think. Immuno-stimulatory effects from radiation have been reported frequently enough to garner a specific name—the Abscopal effect.

The Abscopal Effect

The Abscopal effect works as follows. When radiation incites direct damage to tumor cells, the immune cells in the blood are drawn toward the radiation-damaged cells. This close approximation of immune cells with tumor cells enables the immune cells to “detect” new tumor antigens being released from the dying cancer cells. Once the immune cells, “get the scent” of the cancer, the immune cells can then travel and attack cancer tumors outside the radiation field in other parts of the body.
Of course, radiation therapy kills cancer cells directly, inducing DNA damage to the neoplastic cells. The accumulation of DNA breakdown, and consequent insufficient DNA repair, inside the cancer cell is what triggers the irradiated cells to die. But this direct radiation effect only occurs to the cancer cells in the pathway of the radiation beam. The Abscopal effect is the observation that cancerous tumors in non-radiated areas of the body also shrink, presumably by means of newly activated immune cells.

The optimal method for inducing an Abscopal effect is yet unknown. But now new advances in radiation technology enable doctors to safely administer large doses of radiation to small, sensitive areas of the body without causing serious collateral damage to the normal cells that surround the tumor. So new technology, rather than needing long sequences of daily radiation extended over many weeks, can increase necrotic damage to tumors and further enrich the immune system with cancerous antigenic material with a single dose of radiation.

Researching How Often the Abscopal Effect Occurs

Considering that radiation seems to enhance the anti-tumor immune response, boosting this immune response even further with an immunotherapy like Provenge* is an attractive idea to test in a larger group of patients in a formal clinical trial. It’s logical to consider that that radiation and Provenge together will cause a greater anti-cancer immune effect than either method by itself.

Presently, very little is known about how anti-cancer therapies like radiation interact with immunotherapy in a clinical setting. However, 21st Century Oncology, based in Phoenix, is going to be opening an interesting clinical trial designed to determine if tumor cell death occasioned by radiation therapy augments the anti-tumor responses from Provenge. In this study, patients treated with spot radiation and Provenge in combination will have their tumor responses tracked with the latest scanning technology using C11-acetate PET scans. (See below for information on these clinical trials).

“As I have worked on the concept of combining radiation therapy and immunotherapy since 1999, we believe clinical trials in this area provides an opportunity to share the latest, state-of-the-art advances with the oncology community,” said Steven E. Finkelstein, M.D. Dr. Finkelstein is a board-certified radiation therapist and the National Director of the Translational Research Consortium, the research arm of 21st Century Oncology. “We are confident that the information we learn from clinical trials and research we conduct today will improve outcomes for patients with cancer moving forward.”

Dendreon, the manufacturer of Provenge, and 21st Century Oncology should be commended for designing and implementing a visionary new clinical trial that incorporates a variety of innovative ideas in the area of immunology, radiation therapy and imaging. This trial will benefit patients by giving them access to state-of-the-art technology while at the same time advancing our understanding of how immunotherapy works.

For information on these clinical trials go to our website http://prostate-cancer.org/ or give us a call at (310) 743-2116
WHAT’S NEW IN PROSTATE CANCER: A Clinical Perspective
From Dr. Brosman

There are over 150,000 prostate cancer articles and abstracts published each year. Trying to select which are the most important is impossible. These are just a few new developments that are changing the way that prostate cancer is diagnosed and managed.

DIAGNOSTICS:
A new genetic test has been developed that can predict the most aggressive types of prostate cancer. A prostate biopsy pathology report is assigned a Gleason grade of 3, 4 or 5 by the pathologist (2 grades are added to create the Gleason Score.) Grade 3 (Score 6) cancer cells are considered to be the slow growing variety and these men are often assigned to a program of Active Surveillance. But as many as 30% of these men will be found to actually have more aggressive disease and require therapy at a later time [1]. The ability to understand the behavior of these grade 3 tumors would separate those who really have a more aggressive tumor from those that do not. The OncotypeDx Genomic Prostate score uses a panel of 17 genes that have been associated with prostate cancer gives us that ability.

In one study, biopsy samples were analyzed in a group of 400 men who subsequently had prostate surgery and initially, they were all thought to be of low risk for cancer recurrence. Dr. Peter Carroll and his associates found that the risk category was changed in 23%. [2] The implication is that not all grade 3 or even some grade 4 tumors may not behave as expected. A test to clarify the potential aggressiveness of these cancers can spare more men from unnecessary treatment and treat those who would derive the most benefit from treatment. The test results are likely to be helpful in half of the patients and highly significant in a quarter of the patients who participated in this study.

IMAGING:
The use of MRI in prostate cancer management is being done with increasing frequency. The specific name for this is a multiparametric-MRI, or mp-MRI. This imaging study used to be done with a probe in the rectum (endorectal coil) and after 45 minutes of experiencing the probe and the loud pounding of the machine, most men did not want to return. Now, the probe is not usually necessary but the pounding noise remains.

Mp-MRI allows us to see abnormalities in the prostate that are suspicious for aggressive prostate cancer. The test does not detect every small, aggressive tumor. It tends to miss cancers that are considered to be insignificant or low grade, which actually is a good thing. No test is perfect but in experienced hands, the ability to detect Gleason score 7 and 8 tumors was accurate in 98% and the ability to predict the absence of aggressive tumors was 91%. [3] Pretty good!

The radiologist reading the MRI images of the prostate assigns a score on a 5 point scale to express the probability of high grade, aggressive cancer being present. If the score is 5/5, the possibility of an aggressive tumor is > 90%. If the score is 1/5 the probability of there being a high grade cancer is less than 10%. If there is a 4/5 abnormality the positive biopsy result for an aggressive tumor is > 75%. A 2/5 is associated with a low probability of there being an aggressive cancer and a 3/5 means that we don’t know what’s going on.
Here is how this information is being used. When a man visits a urologist because of an elevated or rapidly rising PSA, an mp-MRI can not only help determine the probability of an aggressive cancer but also where it is located within the prostate. This allows a more targeted approach to doing a needle biopsy. If the radiologist reports a 4/5 or a 5/5, a targeted biopsy is advised. A 1/5 or a 2/5 is usually adequate evidence that a biopsy is not necessary. A 3/5 means that you have to decide for yourself whether or not to have a biopsy based upon other factors. New biopsy techniques permit a prostate biopsy to be done at the same time that the mp-MRI is performed. Another method is to overlay the images on ultrasound in order to biopsy the most relevant areas. The mp-MRI is also very useful for following patients with prostate cancer who are on Active Surveillance. The number of follow-up biopsies can be reduced which makes everyone happier. Mp-MRI is also being used to assess the nerve bundles and any unusual anatomic features prior to surgery.

Here’s the problem. It takes the right kind of MRI, not all MRI’s are the same. Most experts argue that a 3-Tesla MRI is needed. Most important, a highly trained and experienced radiologist is critical to perform and interpret the study and there aren’t that many of them. There is also the issue of cost. This is an expensive test that is not always covered by insurance. Undoubtedly, the mp-MRI has an important role in the diagnosis and management of prostate cancer, but how it will be integrated into clinical practice will need further study.

**THERAPY:**

Medications to treat osteoporosis in men who are receiving “hormone therapy” have been used for years. But now we have learned that men who have bone metastases can have a stabilization and regression of the tumor with the use of these agents. Denosumab, also known as Prolia and XGEVA, are being used with good results. In fact, in a recent publication, Dr. Matthew Smith and his colleagues reported that the use of Denosumab can be a preventive agent and delay the onset of bone metastases in patients who are at high risk.[4]

Another agent that has recently been approved by the FDA called Xofigo is used to treat existing bone metastases in men who are having pain [5]. Xofigo consists of radium that is injected into the bloodstream. The radioactive radium has a special affinity for metastatic spots in the bone so when it localizes near the cancer it ends up delivering a high dose of radiation directly to the cancer. Xofigo is available at various sites throughout the country. There is low toxicity but high effectiveness.

The plan going forward for this column is to continue providing quarterly updates of the recent developments in scientific literature in future issues of Insights. In the next issue, we’ll enter the confusing world of “Alice in Dietland.” We’ll see if we can make some sense of the many confusing articles that have been published about the role of diet and prostate cancer.

Helpful links for further research:

Mark your calendars and plan to be with us this September in Los Angeles, California for the annual Prostate Cancer Conference. This unique 3-day patient conference has grown into the leading provider of education for prostate cancer patients in all stages of their treatment.

We will once again have a fully expanded program beginning on Friday afternoon and ending on Sunday afternoon. These programs will include the latest on treatments, diet & nutrition, supplements, sex-life and more!

Visit PCRI.org for early registration!
The PCRI is excited to announce the line-up* of our General Session speakers on Saturday, September 6th!

Laurence Klotz, M.D. Sunnybrook Health Science Centre, Toronto, Canada
Active Surveillance for Low-Risk Prostate Cancer

Maha Hussain, M.D. University of Michigan Medical Center
Advanced Prostate Cancer

Anthony Zietman, M.D. Massachusetts General Hospital
Intermediate and High Risk Disease

Eugene Kwon, M.D. Mayo Clinic Cancer Center
Treating Oligometastatic Disease with Multimodality Therapy

John Mulhall, M.D. Memorial Sloan-Kettering Cancer Institute
Sexual Complications of Treatment

Mark Moyad, M.D. University of Michigan Medical Center
Diet, Dietary Supplements and Prostate Health

Charles “Snuffy” Myers, M.D. American Institute for Diseases of The Prostate
Immune Therapy

Mark Scholz, M.D. Prostate Oncology Specialists
Treating PSA-Relapsed Disease

The LAX Marriott Airport Hotel is offering conference attendees a special reduced rate of $99/night!

Find more information and registration at http://pcri.org.

See you in Los Angeles this September!

*Subject to Change