PCRI Insights

Patient & Physician in Co-Partnership

New Developments in Prostate Cancer Treatment

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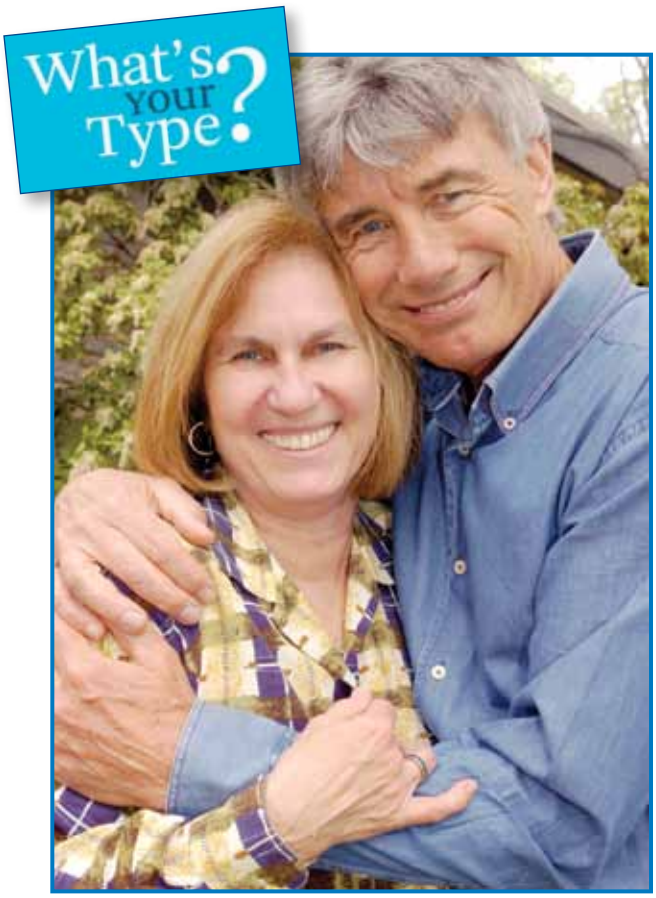


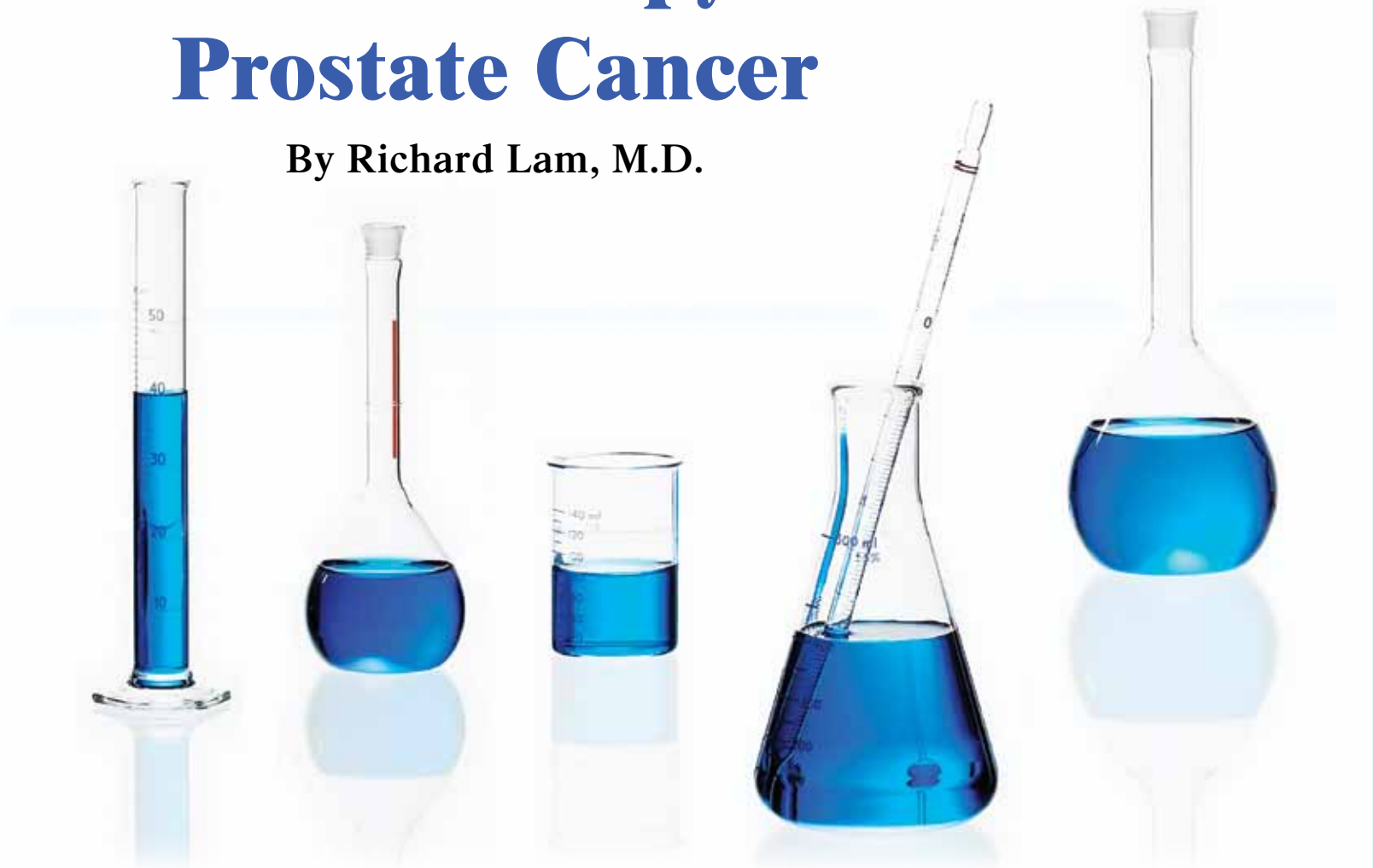
ATTENTION ALL NEWLY DIAGNOSED PC PATIENTS

At the 2008 Prostate Cancer Conference, the PCRI launched a new initiative and pamphlet developed by Dr. Mark Scholz to emphasize the need for a patient to fully evaluate his risk factors in determining whether (and when) treatment is in his best interest. The paper beginning on page 12 contains the text of that pamphlet with references to articles in PCRI Papers available on our web site (www.pcri.org). These articles [many from previous issues of ***Insights***], written by Dr. Scholz and other experts in the prostate cancer field, significantly expand on the concepts presented in the following paragraphs. We call this initiative "***What's Your Type?".***

(Continued on Page 12.)

Chemotherapy in Prostate Cancer

By Richard Lam, M.D.



In the last decade, the role of chemotherapy has evolved significantly. The first approved chemotherapy agents, mitoxantrone (Mitoxantrone) and estramustine (Emcyt), were utilized for prostate cancer patients to help control pain and to relieve symptoms associated with their metastatic disease. Because of the drugs' inherent side effects, doctors were reluctant to prescribe chemotherapy unless patients were experiencing problems from the cancer. Understandably, even in the face of cancer progression, patients who had a good quality of life were not offered chemotherapy. More recently, as a result of two landmark phase 3 trials that demonstrated an overall survival benefit, the FDA approved docetaxel (Taxotere) for the treatment of metastatic prostate cancer. This article reviews the evolution of chemotherapy for prostate cancer, from the early role of mitoxantrone and Taxotere to the most up-to-date research on Taxotere-based regimens. Finally, a brief overview of new drugs and new indications of chemotherapy will be presented.

For prostate cancer, chemotherapy is administered after the development of hormone-refractory (also known as androgen-independent) disease. Hormone-refractory prostate cancer is defined by cancer growth despite castrate testosterone levels. Cancer growth can be demonstrated by (1) a rising PSA level, (2) new changes on radiographic studies, and (3) worsening symptoms such as pain. Oftentimes, physicians will prescribe secondary hormonal medications, such as nilutamide, ketoconazole, or estrogen, prior to starting chemotherapy. However none of these agents have any proven benefit in terms of overall survival.

In 1996, mitoxantrone was cleared by the FDA for the treatment of metastatic prostate cancer because this chemotherapy agent decreased pain and improved the quality of life of men suffering from prostate cancer. Mitoxantrone is administered intravenously every three weeks and is usually well tolerated. Possible side effects include mild nausea, fatigue, hair loss, and occasionally heart problems. However, because of its lack of benefit in prolonging survival, mitoxantrone was relegated to the palliative setting. Usually, patients were only referred by their urologist to a medical oncologist for mitoxantrone if they were having significant bone pain and were unable to tolerate narcotics.

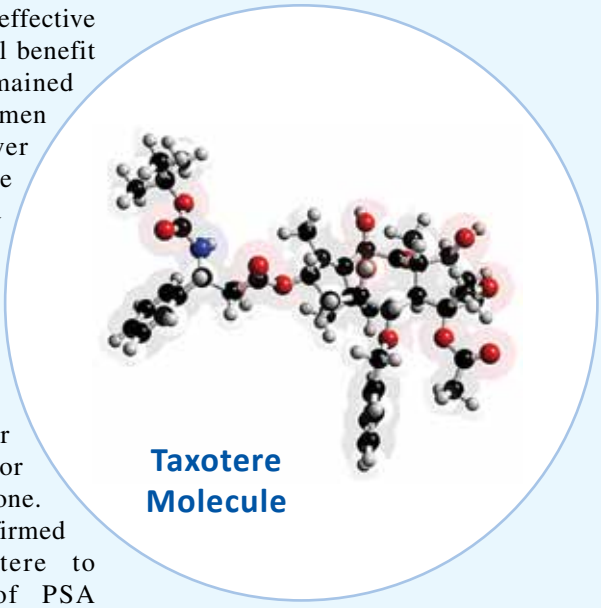
The Emergence of Taxotere

In 2004, these two important studies ushered in a new role for chemotherapy. For the first time, there was a drug, Taxotere, which actually helped prostate cancer sufferers live longer. The first study, TAX 327, randomized 1006 men with metastatic hormone refractory prostate cancer, to either Taxotere administered every three weeks, Taxotere administered weekly, or mitoxantrone. All three groups received prednisone. The median PSA was 115. Compared to the mitoxantrone group, the two groups that received Taxotere had a higher PSA response rate (45-48% vs. 32%) and better quality of life scores. More importantly, the every three-week Taxotere cohort had a statistically significant improvement in overall survival (19 vs. 16 months).

Of note, at least 30% of patients who were randomized to the mitoxantrone arm also received Taxotere after failure on mitoxantrone. This crossover effect probably decreased the apparent difference in overall survival between the two treatment groups. Despite this confounding effect of second-line treatment with the more effective therapy (Taxotere), a survival benefit associated with Taxotere remained apparent. In other words, if men on the mitoxantrone arm never received Taxotere, then the survival difference would likely have been larger.

The second study, SWOG 99-16, randomized 679 men with metastatic disease to either Taxotere plus estramustine (an older oral chemotherapy agent) or mitoxantrone plus prednisone. This study essentially confirmed the superiority of Taxotere to mitoxantrone in terms of PSA response, duration of response, and overall survival. However, the addition of estramustine to Taxotere resulted in more nausea/vomiting and cardiovascular side effects, without any apparent survival benefit. Therefore, estramustine is not commonly combined with Taxotere in the first-line setting.

Overall, Taxotere is well tolerated, and its side effects are usually very manageable. Many of the most reviled toxicities associated with chemotherapy (i.e. nausea and vomiting, blood transfusions, and weakening of the immune system) are generally not observed with Taxotere. One can expect to experience mild fatigue, mild loss of appetite, hair loss, skin and fingernail changes. Infections are uncommon. For details, please refer to the PCRI *Insights* article "Dealing with Taxotere Side Effects" from the May 2007 issue.



(Continued on Page 4.)

Richard Y. Lam, M.D.

Research Director, Prostate Oncology Specialists, Inc.

A board-certified internist and oncologist, Dr. Richard Lam has been specializing full time in the treatment of prostate cancer since 2001. He is director of clinical research at Prostate Oncology Specialists, Inc. and is currently researching the side effects of testosterone inactivating pharmaceuticals, especially its effects on bone integrity. He is an active member of the American Society of Clinical Oncology and the American Society of Hematology.

Dr. Lam continues to promote prostate cancer awareness and education by giving lectures at various medical conferences and prostate support groups. He also provides free prostate cancer management advice to patients at "Patient to Physician," which can be found via the Resources on the PCRI website. Dr. Lam received his undergraduate degree in biology, magma cum laude, at UCLA. He then went on to earn his medical degree at UCLA School of Medicine before completing his residency training in the specialty of Internal Medicine at UCLA Center of Health Sciences. He completed his oncology and hematology fellowship at Harbor-UCLA Medical Center.

Improving Taxotere-based Chemotherapy

The next phase of research for chemotherapy is to find ways to make Taxotere-based chemotherapy better. One such promising agent, bevacizumab (Avastin), appears to do just that. Avastin is a monoclonal antibody that targets the VEGF receptor; its main mechanism of action is via anti-angiogenesis. Anti-angiogenesis essentially means shutting down the blood supply, and thereby starving the cancer. For breast, colon and lung cancer, adding Avastin to chemotherapy improves clinical outcomes. As a result, Avastin is FDA-approved for these cancers.

Now, Phase 2 and 3 trials involving Avastin for prostate cancer are underway. One of the most exciting studies combines Avastin with Taxotere and thalidomide, an oral anti-angiogenesis agent. Researchers at the National Cancer Institute and the FDA treated 60 men with this combination regimen. All men had metastatic disease. The median PSA was 99, with a PSA doubling time of 1.5 months. These men had widespread, rapidly growing cancers. The preliminary findings appear to be significantly better than single-agent Taxotere. See Figure 1. 90% of the men had a PSA decline of over 50%, and for 76% of the men, their PSA levels declined more than 75%. At the time the data was presented, the median overall survival had not been reached, but the progression-free survival was 19 months, which means the overall survival must be at least that long. The main downside to this combination therapy is its toxicity profile. This combination therapy has side effects not commonly seen with single agent Taxotere; included are severe infections, bleeding and blood clots. To accurately assess whether or not the likely clinical superiority outweighs the extra side effects, further studies are required. Currently a large multinational Phase 3 trial comparing Taxotere to Taxotere plus Avastin is rapidly accruing patients. Other promising compounds that may enhance the clinical benefit of Taxotere are capecitabine (Xeloda), custirsen, sunitinib, and 5,6-dimethylxanthenone-4-acetic acid (DMXAA).

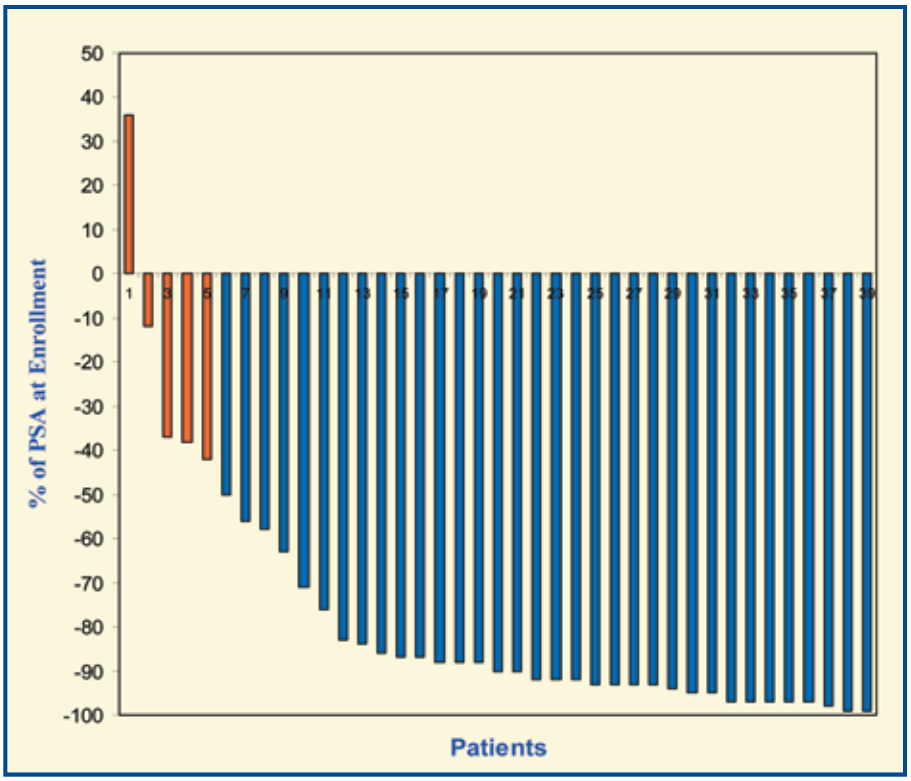


Figure 1 Courtesy of Yang-min Ning NCI/NIH

Figure 1: PSA reduction (%) while on **Taxotere, Avastin** and **Thalidomide**

Approaches When Taxotere Loses its Effects

Another clinical dilemma encountered by physicians and their patients is what to do when first-line Taxotere loses its effect. Few trials have been conducted in the second line setting. Therefore, there are no standard approaches. Researchers have reported modest response rates with single agent mitoxantrone, cyclophosphamide, ixabepilone, and capecitabine. At Prostate Oncology Specialists, we have observed an encouraging response rate (40%) using the combination of carboplatin, paclitaxel, and estramustine. In some cases, this response has been very durable, lasting over 12 months. Also, PSA responses have been observed by simply adding Avastin or Xeloda to Taxotere, even when single-agent Taxotere fails. Finally, a non-chemotherapy compound, abiraterone has generated a great deal of interest as a second line agent for men who have progressed on Taxotere. In early Phase 1/2 studies, abiraterone resulted in fairly high PSA response rates of 50% or more. The multinational Phase 3 trial comparing abiraterone to placebo is rapidly accruing. Preliminary clinical results should be available in mid-2009.

Multi-Modality Approaches

As in other cancers where chemotherapy was initially approved in the metastatic setting but has subsequently been shown to be beneficial in earlier settings, chemotherapy, mainly Taxotere, is being evaluated in the non-metastatic setting. Patients who may benefit from chemotherapy are men with cancers that have high-risk features, such as a rapid PSA doubling time, a high baseline PSA, a

Commonly Prescribed and Newer Novel Chemotherapy Regimens
Estramustine 140mg-280mg PO, three times daily
Cyclophosphamide 25-50mg PO, twice daily
Mitoxantrone 12mg/m2 IV, every 3 wks + **Prednisone** 5mg PO, twice daily
Docetaxel 60-75mg/m2 IV, every 3 wks + **Prednisone** 5mg PO, twice daily
Docetaxel 30mg/m2 IV, weekly x3, then 1 wk off + **Thalidomide** 200mg PO, daily
Docetaxel 75mg/m2 IV + **Bevacizumab** 15mg/kg IV every 3 wks + **Thalidomide** 200mg PO daily
Docetaxel 35mg/m2 IV weekly x3, then 1 wk off + **Capecitabine** 625mg/m2 PO on day 5-18
Carboplatin AUC 5 IV + **Paclitaxel** 175mg/m2 IV, every 3 weeks

IV=intravenous; PO=taken by mouth

high Gleason grade, and a high tumor volume. For these cases, Taxotere is being studied as part of a multimodality approach, where the drug is combined with surgery, radiation, and hormone therapy. The goal with such an approach is to increase the cure rate for patients who have a high risk of relapsing. Another clinical setting where Taxotere is being studied is for patients who have relapsed rapidly after local therapy (surgery or radiation) and who may develop hormone resistance soon. Usually, the goal of using chemotherapy in this setting is to prolong hormone-sensitive disease and possibly allow patients to be off salvage treatment for longer periods of time.

Chemotherapy is now administered to prolong the duration and quality of life.

In summary, the role of chemotherapy is gaining acceptance for men with high risk or metastatic prostate cancer. Initially used as a palliative treatment for men who wanted to avoid narcotic medications, chemotherapy is now administered to prolong the duration and quality of life. As newer compounds and newer drug combinations become available, more clinical benefit will be seen. Furthermore, researchers are studying ways to incorporate chemotherapy in early-stage high-risk disease to improve clinical outcomes as well.

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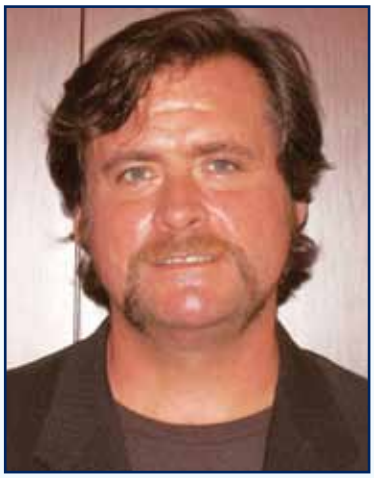
The Abscopal Effect and the Prospect of Using Cancer Against Itself

By William Cavanagh



William Cavanagh

William Cavanagh formerly served as Chief Scientific Officer of Sangretech Biomedical, LLC. His mission there was to provide patients with better treatment options by researching, developing, and commercializing cellular therapies for cancer and other medical conditions. Mr. Cavanagh has also been Director of the Haakon Ragde Foundation for Advanced Cancer and was previously a Manager of Informatics of the Seattle Prostate Institute, a Research Consultant at the University of Washington Department of Radiation Oncology and a Director of the Pacific Northwest Cancer Foundation.

Mr. Cavanagh graduated *magna cum laude* from the University of Portland and was a graduate student in Medicine at the University of Washington School of Medicine. He is the author of numerous articles about prostate cancer.

As discussed in the February 2008 issue of *Insights*, several clinical investigations are ongoing in the field of cancer (including prostate cancer) treatment. These investigations seek to mobilize the immune system and its highly specific destructive capability in order to impact cancer. In this article, I will highlight some further basic scientific findings that may subsequently provide evidence to use cancer as part of anti-cancer therapy. That is to say, someday we may "use cancer against itself".

In order to try and make sense of this seeming conundrum, let's consider a study[1] published in 2004 by Dr. Sandra Demaria and others. Using four groups of experimental mice, they injected two tumors into each mouse, one injection on the left side and one on the right side. Under ordinary circumstances, both tumors will grow unabated on the mice, and ultimately will lead to the death of the animals.

As depicted in Figure 1, four different groups of mice were involved in the experiment. Group A. had no treatment Group B. received immune stimulation only; Group C. received radiation to the right-sided tumor only, and Group D. received both radiation to the right-sided tumor AND immune stimulation. (Immune stimulation in this study was achieved with Flt3 ligand, a growth factor that stimulates cells of the immune system).

When the investigators irradiated the right-sided tumors in Groups C. and D, they were very careful to block the rest of the mouse with lead shielding so that the radiation only reached the single tumor. As noted above, Groups B. and D. received an immune system stimulant (Flt3 ligand) that is known to increase the number of immune cells, and specifically a type of immune cell called a dendritic cell.

In Group A., where no treatment was delivered, both tumors grew at a fast rate (see Figure 1). The tumors in the Group B mice – those that underwent immune stimulation only – grew at about the same rate.

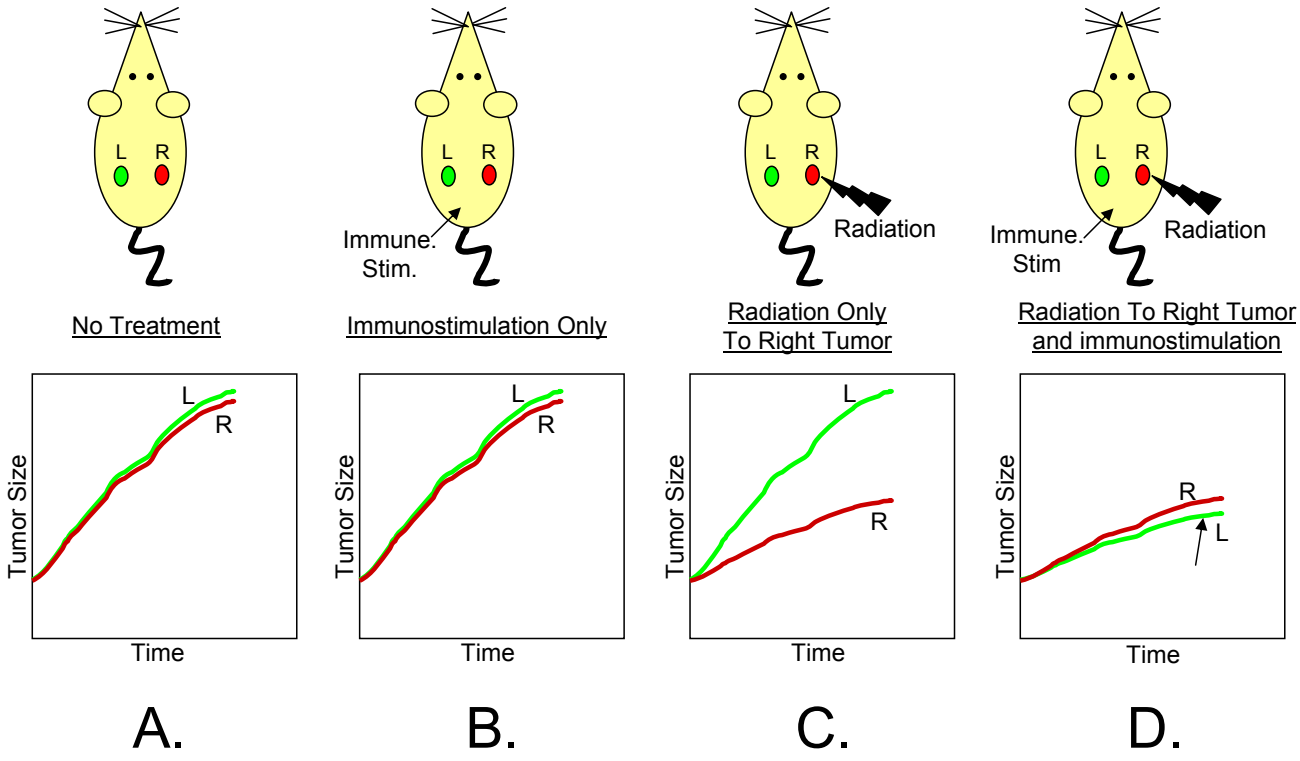


Figure 1. Schematized illustration of the Demaria experiment described in the text. Arrow indicates significant slowing of the untreated tumor in Group D.

In the mice that received radiation-only (Group C), the radiation was successful in impeding the growth of the right-sided tumor, which was the one that was radiated. The second tumor continued to grow as expected. But in the mice that received both radiation and the immune system stimulant (Group D), not only did the irradiated tumor slow its growth, but the growth rate of the second tumor slowed as well (arrow in Figure 1). Of the various groups of mice treated, only those that received radiation and immune stimulation showed this effect.

The Abscopal Effect

What Dr. Demaria and her colleagues demonstrated in this experiment is known as the "abscopal effect", "ab-" being the Latin prefix for "away from", and "scopus" being the Latin noun for "target". In cancer treatment, an abscopal effect occurs when a particular treatment has an impact on a tumor that was not treated. The term is best known in radiation oncology[2], wherein anecdotal observations have been collected for some years describing the regression of tumors in a patient who undergoes radiation treatments – but where the regressing tumors were not irradiated.

More importantly, Dr. Demaria's group illustrated that this controversial effect is more than likely due to, or is mediated by, the immune system. The mice that underwent only irradiation of the first tumor had their second tumors grow as usual; the results were the same with the mice that underwent immune stimulation only. The mice that underwent both treatments exhibited this surprising impact on the untreated tumor.

How Does It Work?

Given these observations, it seems that both the radiation and the immune stimulation played a role in the abscopal effect seen in this experiment. Let's examine the role each likely played, because it would be a tremendous advancement were we able to understand what was happening in these mice and to make it happen in cancer patients.

What appears to be occurring is that the radiation directed at the Group C. tumors caused cells from the tumor to die. When cells die (and I'm going to oversimplify for the sake of illustration), their contents scatter. The contents of cells are proteins, and as described in the earlier article on immunotherapy in the February 2008 issue of *Insights*, protein is what makes cells "do what they do". It is very likely that cancer cells make certain proteins that allow them to grow without restraint, and to spread to different organs and grow there. The destructive nature of ionizing radiation can cause proteins to become separated from the cells that contain them, whereas a living cell holds on to its proteins pretty tightly. *(Continued on Page 8.)*

Proteins are by and large the target of the immune system. Our immune systems keep us, for the most part, free from invaders (i.e. viruses, bacteria) because "their" protein differs from "our" protein. The immune system can detect this difference and can unleash an impressive display of force to eliminate the threat inside our bodies.

Because cancer in all likelihood also differs from our normal cells in terms of its protein, numerous groups of people around the world are trying to train the immune system to set upon cancer in the way it tears apart other undesirable organisms that attempt to cohabitate in the organs and tissues of humans. The difficulty has been, and continues to be, finding those proteins that differentiate cancer from our normal, well-behaved cells, with the idea that we can "train" an individual's immune system to attack those proteins, and therefore the cancer.

This task turns out to be tougher than it sounds (and it sounds pretty tough to begin with). Each cell among the trillions in our bodies is mind-bogglingly complex. The search continues for these "tumor-specific" proteins, and it will likely go on for some time.

But, as Dr. Demaria's work shows, maybe we need look no further than the cancer that has already revealed itself – in this case the tumors that were implanted and were growing in the mice in the study. The radiation directed at the targeted tumor seems to have caused some of the tumor mass to die, causing the protein from this tumor to become separated from the cells that comprised the tumor.

But recall that the radiation by itself was insufficient to provoke an effect on the second tumor. However, where the immune system was stimulated at about the same time – voilà – the second tumor shows an abscopal effect. What is it that the immune stimulant was able to accomplish?

The Effects of the Immune Stimulation

The immune stimulation employed in this study is known to be very effective at causing a substantial increase in the number of circulating dendritic cells (DCs). DCs are truly impressive components of our immune systems (and those of mice too). DCs can be thought of as part of the intricate sensory apparatus of the immune system. Very simply stated, DCs can pick up protein, examine it, and cause other, more aggressive, components of the immune system to attack anything that has that particular protein attached to it.

So in boosting the number of DCs in some of the mice – while destroying part of the first tumor with radiation – the immune systems in those animals were able to activate against that particular tumor, and retard the growth of the second tumor. Hence the title of Dr. Demaria's journal article that describes these results: "Ionizing Radiation Inhibition of Distant Untreated Tumors (Abscopal Effect) is Immune Mediated". It all makes sense now, right?

Recent Studies

In the past few years, in fact, several other studies have appeared that continue to support the idea that treatments can be designed that involve the immune system in significantly impeding the progress of cancer outside of the directly treated area. These studies all use a methodology similar to that of Dr. Demaria's group, that is, they implant two tumors, treat one of them, and observe the effect on a tumor implanted at some distance from the treated tumor.

But rather than use an immune stimulant that increases the number of DCs throughout the mouse's body, recent studies report a methodology that goes straight to the source: they make DCs and flood the treated (first) tumor with them. I won't go into how one "makes" DCs, but dramatic progress these past few decades has allowed immunologists to very reliably grow millions of DCs in the laboratory.

In order to observe the abscopal effect in experimental mice, we seem to need two things: (1) we need some sort of cancer-killing (tumoricidal) treatment, and (2) we need DCs that can process what's left of the cancer cells after they have been (at least somewhat) destroyed. As I mentioned, DCs can be provided by the millions via modern technology. But how best to disrupt the "first" cancer in order to see the effect on the "second" cancer? According to published studies, the tumoricidal treatment to the first cancer in the mouse can be radiation therapy, chemotherapy[3], or cryotherapy[4].

Where DCs are injected into the treated cancer, all three have demonstrated results very similar to those of Dr. Demaria. That is, where the treatments – disruption and DC – are combined optimally, a clear and undeniable abscopal effect is observed. There are most certainly other factors that are involved in getting the immune system mobilized enough to inhibit the growth of cancer, but the disruption/DC combination seems to repeatedly result in an abscopal effect on cancer in the mouse.

This would appear to be a very interesting development. As we are all aware, cancer poses its most lethal threat when it spreads to sites that are difficult to reach with anti-cancer therapy. In the case of prostate cancer, its spread to the lymph nodes, bones, and other sites serves as a devastating blow to attempts to eradicate it through any means. If we were able to employ the immune system to provoke the kind of abscopal effect observed in the mice in the above-mentioned studies, we might be able to "reach" these disseminated, or metastatic, sites by focusing on some of the cancer that we can reach with tumoricidal or cancer-disruptive treatments.

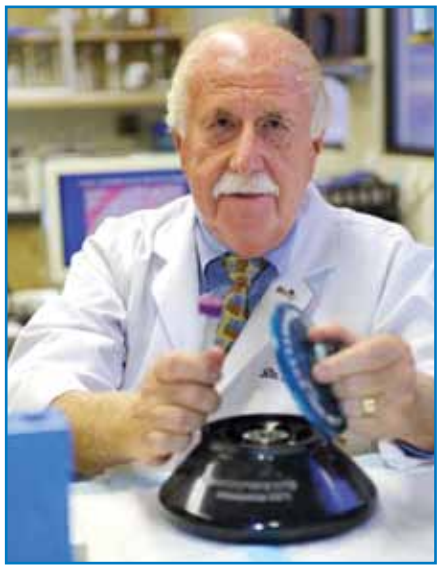


Figure 2: Dr. Richard Ablin

Déjà Vu?

While this idea may sound novel and promising, a young immunologist explored this notion some 40 years ago. In the late 1960s, Dr. Richard Ablin, shown in Figure 2, was consulted by prostate cancer specialists in order to explore a set of truly unusual findings: it was found that some patients with metastatic prostate cancer experienced remarkable changes in the course of their disease following cryo treatment of their prostate cancers. As you might guess, only the prostate was treated in these patients. However, known lesions involving the lungs and skeleton were observed to regress or stop growing following the treatment of the prostate. (Abscopal effect, anyone?).

Dr. Ablin set about exploring the possible link between the freezing of a cancerous prostate and the sudden remission of metastatic cancers that were not treated. Believing the immune system to be the conduit between local (prostate) and distant (metastatic) treatment effects observed in these patients, Dr. Ablin initiated a series of experiments designed to detect the involvement of the immune system in scenarios involving the freezing of tissues.

It is important to note that the science of tumor immunology was in its earliest infancy at that time. It could be argued that it hadn't even been born yet. The instruments and scientific capabilities that have made possible the contemporary understanding of the mammalian immune system had simply not yet been conceived.

Nonetheless, Dr. Ablin was able to generate and publish persuasive evidence from both human and animal studies that the immune system had responded to the freezing of the prostate. In experimental animals, he was able to show that auto-antibodies (immune protein) occurred in the serum of animals after freezing of the prostate and prostate-like glands. In other words, an immune response had occurred throughout the body following the freezing of a specific gland! Dr. Ablin termed this phenomenon the "cryo-immunologic response," and coined the term and concept of cryoimmunotherapy[5].

Unfortunately, the effect seen in humans was relatively rare and did not occur reliably following cryo treatment. At the time, Dr. Ablin postulated that the status of the immune system in a given patient – for instance a debilitated immune system in some cancer patients – could significantly influence the possibilities of seeing dramatic regressions based on the cryo-immunologic principle. He called this concept "immune-staging", and we now know that he was probably right. But given the primitive understanding and lack of technology designed to manipulate the human immune system (the dendritic cell as we know it was not yet discovered), further investigation of the cryo-immunologic response was essentially abandoned.

Recent developments and the kinds of studies described above have precipitated a renewed interest in cryoimmunology and its possible application to human cancer treatment. It is important to appreciate that the highly controlled nature of animal experiments (such as the mouse experiments described above) often results in the observations being poorly, if at all, translatable to successful human treatment. However, given what appears to be a strong underlying set of observations across several different studies, human studies are likely to follow in the near future.

A Contemporary Approach in Human Subjects

Bostwick Laboratories has designed and initiated one such study, and is currently seeking patients to participate in it. To qualify for this study, patients must have cancer diagnosed in their prostate glands as well as at a limited number (three or fewer) of metastatic sites.

Having read to this point, by now you will have surmised that the cancer in the prostate will be frozen and thawed using state-of-the-art cryotherapy technology. Between 25 and 100 million DCs will be injected into the prostate once it has been cryosurgically destroyed and thawed back to body temperature. Based on the principles outlined above, the study will seek to evaluate the possibility of an abscopal effect occurring under these circumstances.

The study treatment will also involve patients undergoing a course of low dose cyclophosphamide for six months. I encourage anyone interested in this aspect of treatment to read *Immunotherapy and Advanced Prostate Cancer* in the February 2008 issue of *Insights*. Taken together, all aspects of the study treatment are designed to take advantage of what we now know about the functioning of the immune system, and to employ and motivate the immune system in these patients to replicate the results explored by Dr. Ablin decades ago.

It is important to understand that this trial is designed to examine the safety of the study *(Continued on Page 10.)*

treatment that is described below (the "Phase I" part), and also to begin to explore the potential for this treatment have an impact on the outcome of the disease that is treated (the "Phase IIa" part). An outline of the study treatment appears in Figure 3, in which each step in the process is enumerated as follows.

The "CRITICAL" Study

Bostwick Laboratories – A Phase I/IIa Trial of Combined Cryotherapy and Intra-Tumoral Immunotherapy with Autologous Immature DCs (VDC2008) in Chemo-Naïve Men with Prostatic Adenocarcinoma and Limited Metastases to Lymph Nodes and/or Bone

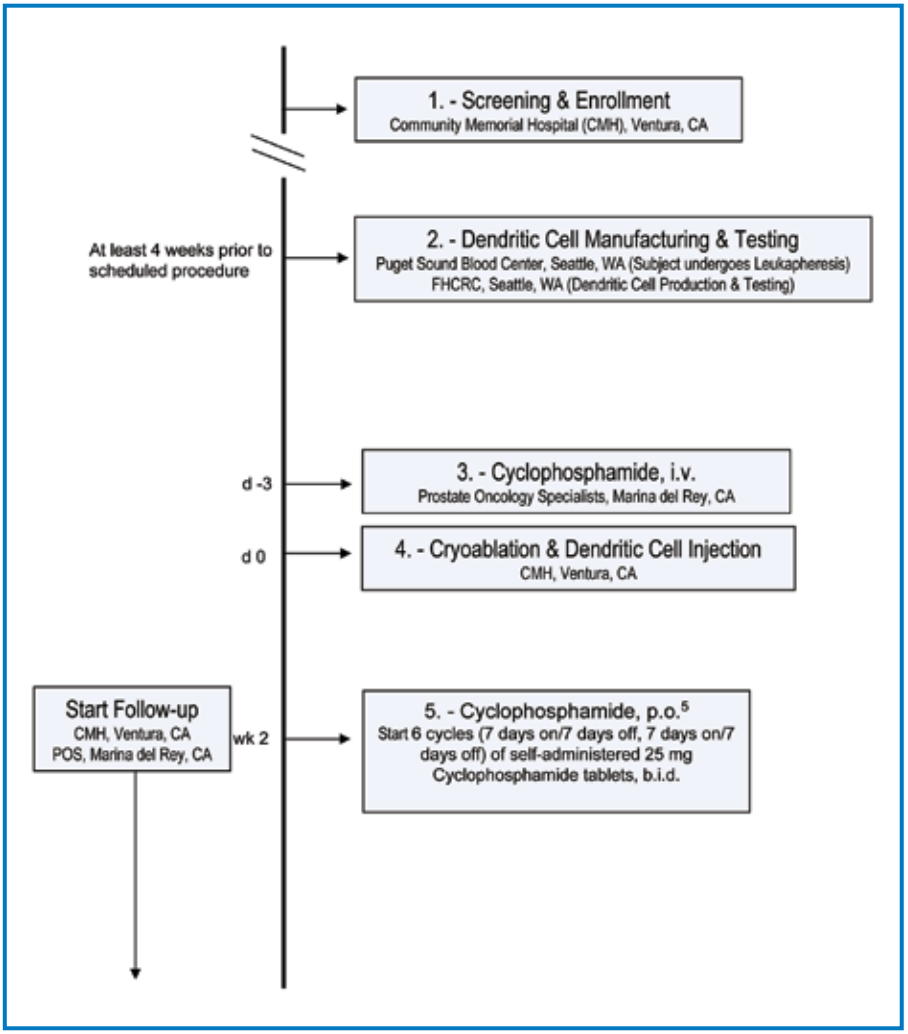
1.) Screening and Enrollment

This important first step involves the establishment of "eligibility" for this study. Only patients who meet a rigorous sent of "eligibility criteria" will be able to enter this trial and receive the study treatment. These criteria are fairly extensive, but, importantly, they require that cancer exist in both the prostate and at three or fewer sites outside the prostate and its local lymph nodes. The cancer must have become "androgen-independent" (a state also known as "hormone-refractory"), which means that the cancer has stopped being sensitive to hormonal therapy. Typically, such a state is determined when serum PSA measurements continue to climb even while combined hormonal blockade is being administered.

It will also be required that patients NOT have undergone chemotherapy in the past, and that several laboratory tests, including measurements of blood, liver, and kidney function, are all within normal range. These are just a few of the eligibility criteria to be used in determining study status.

It is highly recommended that anyone interested in determining his own status with regard to entry to this study contact one of the study investigators - Dr. Duke Bahn at the Prostate Institute of America (888.234.0004), or Dr. Mark Scholz at Prostate Oncology Specialists (310.827.7707). A complete list of study eligibility criteria are also located on the Internet at www.clinicaltrials.gov/ct2/results?term=NCT00753220.

Figure 3: Clinical Flow Chart



2.) Dendritic Cell Manufacturing and Testing

For a patient who has "passed" all the study eligibility criteria – and who has read and signed the Informed Consent Form for this study – the next step is a trip to Seattle, where the next study steps will take place. In Seattle, a process known as "leukapheresis" [loo-kuh'-fer-ee-sis] will take place. Leukapheresis is a bit like having your blood drawn (everybody knows what that is like) – except this blood draw can take upwards of four hours.

Given the length of the leukapheresis, you might guess that a whole lot of blood is drawn. In reality, blood is taken from the patient one "batch" at a time; the blood is processed in such a way that certain white blood cells are taken from each batch of blood, and the rest (the vast majority) of each batch goes right back into the circulation. When the process is finished, the processor has a very large number of white blood cells.

These white cells form the beginning point of the autologous (derived from self) dendritic cell product that will

comprise the cells that will be injected into the prostate at the study treatment. The process of making the DCs, as well as the testing that is required to make they are ready to be injected, is complicated. But if all goes according to plan, the result of the quick trip to Seattle will result in a number of vials of the patient's own DCs.

The reasons for the Seattle trip bear mentioning here. Basically, there are only a few places with laboratories where DCs can be manufactured. The sponsors of the study are evaluating facilities in Seattle to perform this manufacturing.

Also, recall that the leukapheresis procedure provides the beginning material for the dendritic cell manufacturing. Problem is, the cells in the leukapheresis "product" will start to die soon after they are drawn out the patient. By putting the leukapheresis process and the manufacturing process very close together, a high likelihood of generating a good dendritic cell product is ensured. the sponsors will of course pay for the trip to Seattle.

3.) Cyclophosphamide IV

This unwieldy looking word (Sigh-cloa-fos-fa'-mide) refers to a chemotherapy drug that has been used for many decades for many conditions. In this study, a very low dose of this drug will be administered into an arm vein three days before the "big" part of the treatment. The cyclophosphamide (let's call it Cy) is intended to prepare the patient's immune system for the treatment to follow, because Cy has been shown to reduce the numbers of an immune cell (the regulatory T cell or T-reg) that is thought to interfere with successful immunotherapy. In fact, several follow-up blood draws (the quick ones) will be performed in order to see how well this therapy is working in getting T-reg counts down.

This part of the treatment will be performed by Dr. Mark Scholz, at Prostate Oncology Specialists in Marina del Rey, California.

As you can see by skipping ahead to step 5, the Cy treatment will continue following the main study treatment, in the form of tablets that will be taken at home. The dose of Cy that is given, both before the study starts and in the tablet-based (p.o. = per orum = per mouth) therapy, is a dose that is not expected to result in the side effects that one usually thinks of when thinking about chemotherapy. However, one of the study objectives is an evaluation of how patients respond, side effect-wise, to this kind of treatment.

4.) Cryoablation and DC Injection

Now that all these preparations have been made, it is time to put the experimental treatment into action! Cryoablation of the prostate, performed by Dr. Duke Bahn, will be undertaken at Community Memorial Hospital in Ventura, California. The DCs will be shipped in their frozen state from Seattle right into the operating room, where they will be injected into a prostate cancer that has been frozen and thawed.

Drs. Bahn and Scholz will follow all study patients for approximately one year following the cryoablation/DC injection. There will be eight follow-up visits over that year, so it is important to understand the commitment made by the study patients.

If successful, the study will demonstrate that DCs made from an individual's blood can be safely given back in tandem with a disruptive cryo treatment against a known cancer. An evaluation of whether or not such a strategy can be shown to result in an "abscopal" effect against other, metastatic, cancers will have to wait for the successful completion of this – and probably other – studies. But forward-thinking and properly planned and executed clinical trials must incorporate the latest understanding of cancer; otherwise, we will not be able to break through to the prostate cancer treatments of the future.

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Prostate Cancer is Different from Other Cancers

Not all forms of prostate cancer are life-threatening. As a result, not all prostate cancer requires treatment. The need for treatment is determined by a man's "Risk Level." Men with the Low-Risk type of prostate cancer can safely be monitored without treatment. Men with Intermediate-Risk or High-Risk disease usually do require treatment.

Reference article: ***Newly-Diagnosed–the Very Basics*** Drs. Mark Scholz and Richard Lam, November, 2008

Good news: Even with High-Risk Prostate Cancer, Survival is Excellent

Compared to other cancers, prostate cancer has an excellent 10-year survival rate. With high-risk prostate cancer, 95 out of 100 men are still alive in 10 years.[1] Remarkably, men with low or intermediate-risk disease are not at any increased risk for dying of prostate cancer within the first 10 years after diagnosis.[2]

Reference article: ***Beating Prostate Cancer with Hormonal Therapy*** by Dr. Charles (Snuffy) Myers [May, 2007]

Take Time to Make the Best Choice – Don't Panic

Many men wrongly believe that they have to get treatment fast when they hear they have prostate cancer. Fear makes them leap without looking at their options. They don't realize that this disease tends to grow much more slowly than other cancers. Also, prostate cancer is usually found very early.

That means you have time to learn about your disease and your treatment options. Then you will be equipped to make the choices that are best for you.

Reference article: ***The Way to Find the Best Available Treatment for Your PC*** by Dr. Mark Scholz [August, 2004]

Sexual Performance Can be Affected by Treatment

Treatments for prostate cancer can have serious risks. Treatments can cause problems like difficulty of holding urine or trouble getting an erection. One study of over 1200 men showed that two years after surgery 78% of men were impotent and 10% were permanently incontinent.[3] These problems can make a big difference in your daily life.

Active Surveillance May Be Your Best Option

Studies now show that if you have low-risk disease, you only need regular checkups instead of having immediate surgery or radiation. Following the approach of monitoring rather than immediate treatment, more than half of men with low-risk tumors have not required treatment five years later.[4]

In another study of low-risk disease, men who received immediate treatment were compared with men who only got checkups until the cancer became higher risk. The outcome was the same in both groups.[5] However, the men who waited were able to avoid treatment (and its side effects) for years until they really needed it.

Waiting is not right for every man with prostate cancer, but it's a good option for men with low-risk disease.

Reference article: ***Active Surveillance For Favorable Risk Prostate Cancer: What Are The Results, and How Safe Is It?*** By Dr. Laurence Klotz [November, 2006]

Find Out Your Risk Level – "*Your Type*"

Before selecting treatment the first thing to learn is your personal "risk level".

The chart on the facing page (Table 1) shows the way doctors measure risk level. You can compare your own test results to this chart to understand your risk level.

- To be "low-risk", all your results must meet the low-risk standards in the green row in Table 1. Even one result outside the green means you are either intermediate-risk (yellow) or high-risk (red)

Table 1. How to Measure Your Risk Level

Cancer Risk Level Recommended Treatment	Gleason Score	% of Biopsy Cores with Cancer	PSA Levels	PSA Velocity*	PSA Density**	Digital Rectal Exam
Low-Risk No Immediate Treatment	Less Than 7	Less Than 34%	Less Than 10	Less Than 2	Less Than 0.15	No Nodule
Intermediate Risk Monotherapy	7	34% - 50%	10 - 20	**Less Than 2**	More Than 0.15	Small Nodule
High Risk Combination Therapy	More Than 7	More Than 50%	More Than 20	More Than 2		Large Nodule

* PSA Velocity: How many points the PSA went up in the previous a year
** PSA Density: The PSA divided by the size of the prostate in cubic centimeters (cc)

- Not all experts agree on the exact line between intermediate-risk and high-risk.
  - Some say that having two or more scores in the intermediate range raises the risk to high.
  - Others believe that you are not high-risk until you have one or more tests that are clearly in the high-risk range.

Reference article: ***Newly Diagnosed Prostate Cancer Part 1: Understanding the Diagnosis***
by Dr. Mark Scholz [February, 2003]

Many Types of Treatment

Systemic therapies (Treatments that affect the whole body including the prostate)

- Testosterone Inactivating Pharmaceuticals (TIP) also called "androgen blockade". These are drugs that keep the male hormone testosterone from stimulating prostate cancer growth.
- Chemotherapy (for treatment of high-risk disease)

Local therapies (Treatments that only affect the area near the prostate)

- External Radiation therapy
- Seed implants
- Surgery
- Cryotherapy

Reference article: ***Newly Diagnosed Prostate Cancer Part 2: Options for Low-Risk Disease***
by Dr. Mark Scholz [August, 2003]

Treatment Selection Based On Risk

Men who are in the low-risk category can forgo immediate treatment and simply monitor their situation in a program called Active Surveillance. This consists of regular PSA testing, prostate exams, and periodic repeat biopsies.

Men with intermediate-risk disease usually start with one kind of treatment, local or systemic. Doctors call this "monotherapy," which is Greek for "one treatment." Men with high-risk prostate cancer generally get two or more kinds of treatment. For instance, the doctor might use TIP and radiation. Doctors call this "combination therapy."

Reference article: ***Newly Diagnosed Prostate Cancer Part 3 – Options for Higher-Risk Disease***
by Dr. Mark Scholz [February, 2004]

Side Effects Matter

Since prostate cancer is not nearly as life-threatening as other cancers, it is important to focus on the possible side effects of treatment. All treatments can have side effects. Some of these effects never go away, even after you stop the treatment.

There is no convincing evidence of a difference in survival with the different monotherapies. Therefore, your concern about selecting the best type of treatment should be focused on which side effects you most want to avoid. Combination therapy should be reserved forhigh-risk disease because two treatments cause more side effects than one. *(Continued on Page 15.)*

DR. DONALD F. GLEASON DIES AT 88

Dr. Donald F. Gleason, the Minnesota pathologist who developed the Gleason score that is now used almost universally to define the aggressiveness of prostate cancers and predict the likely outcome, died December 28 of a heart attack at his home in Edina, Minn. He was 88.

Fifty years ago, there was no uniform system for determining the grade of prostate tumors. Each pathologist pretty much used his own system, which made comparing research results among different groups nearly impossible.

At that time, Gleason was an unknown, junior-grade pathologist at the Minneapolis VA Medical Center. Then, in 1962, the hospital's chief of urology, Dr. George Mellinger, asked him to develop a standardized rating system for tumors to ease communication between groups at 14 hospitals that Mellinger was administering in a cooperative research project on prostate cancer.

Gleason examined biopsy samples from more than 300 patients at the medical center and eventually defined five representative pictures that were characteristic of virtually all the patients. He then sent the pictures to the National Institute of Health statisticians who had all the information about the patients.

These statisticians found a surprisingly strong correlation between the pictures and the patients' death rates. The system was subsequently verified in a study of more than 4000 patients.

Despite this corroboration, the Gleason Score was not widely accepted until, in 1987, leading authorities in urology and urological oncology sent a letter to the editor of the *Journal of Urology* urging that the Gleason Score be applied uniformly in all publications on prostate cancer. Their recommendation was adopted, and the scale quickly came into widespread use.

Gleason, who spent his entire career at the University of Minnesota and the affiliated VA Hospital, formally retired a year later. However, his scientific interest continued, and in 2002, he and a colleague, Dr. Akhouri Sinha, developed an enzyme test that they hoped would help identify which prostate tumors would progress most rapidly.

In addition to Nancy, his wife of 62 years, Dr. Gleason is survived by three daughters, Donna O'Neill of Annandale, Va., Sue Anderson of Burnsville, MN, and Ginger Venable of Eden Prairie, MN.; a sister, Barbara Jarl of St. Paul, MN.; and nine grandchildren.

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Where to Learn More

Talk to your doctors. Visit a **support group**. Many men in support groups will gladly share their experiences and knowledge. Visit our website at www. pcri.org, or contact the PCRI helpline via email **help@pcri.org** or phone 800-641-PCRI to obtain copies of any of the referenced articles.

As you learn more, you can make better choices and feel more confident about them.

Reference article: ***E-Empowerment*** by Dr. Arthur Lurvey [November, 2004]

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Credit card donations can be made at **www.pcri.org** or by calling (310) 743-2116.

A Call to the PC Community

Advocates across the country are uniting to urge Congress to increase funding for prostate cancer research in 2009. More than 10 national, state and local organizations have joined in spearheading this effort.

Many federal funding decisions including funding for prostate cancer research are expected to take shape on Capitol Hill by the end of March. The effort to increase research funding is the first of many policy items that the prostate cancer groups will tackle this year in Washington and around the country.

To join this effort, log onto the ZERO's website (www.zero.org) and look for Advocacy Center under "Get Involved".

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