

#### Prostate Cancer: GET THE FACTS



# NEWSLETTER

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## PROSTATE CANCER—2 WORDS, NOT A SENTENCE What We Are About

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

## Join the IPCSG TEAM

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Bill Lewis @ (619) 591 -8670 "<u>bill@prostatecancerhelp.info</u>"; or **Director** Gene Van Vleet @ 619-890-8447.

## From the Editor

### In this issue:

Bill Lewis produced a summary of the talks last meeting. For further articles see the blog at https:// ipcsg.blogspot.com/ . Many new advanced topics are covered in articles linked in the blog for further reading.This month we've covered general introduction and overview of the disease in one longer article.:

1. Prostate cancer: definition, causes, symptoms, diagnosis and treatment By Cristiano Antonino .

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Topics discussed:

- The history of biopsy strategies
- Evolution of mpMRI
- Technical aspects of MRI-guided biopsies
- Rationale for MRI-guided laser focal therapy of PCa
- Update on NCT #02243033 (Phase II clinical trial)
- Tissue-based genomics
- PET/CT for staging, Radioligand Therapy

I. The history of biopsy strategies: As breast MRI's (magnetic resonance imaging scans) have long complemented mammograms and ultrasonic scans, MRI's of the prostate now complement PSA testing, digital rectal exams and TRUS (trans-rectal ultrasound) scans. It is now recommended by the American Urologic Association (since Oct. 2019) to do MRI before biopsy in cases of elevated PSA. It is appropriate for most men to start with a targeted biopsy under MRI guidance (in-bore MRI guidance developed in 2004) or MRI/US fusion biopsy (overlaying a prior MRI scan on the imaging done by ultrasonics during the biopsy). After the targeted biopsy, the patient has options of various types of focal therapy vs. whole-gland treatment (i.e., radical prostatectomy, radiation or ADT (anti -testosterone hormone therapy)).

The first biopsies were done in the 1920's via an incision in the perineum (the skin between the scrotum and the rectum), feeling around for the prostate, to take samples! Improvements came with trans-rectal ultrasound guidance (1960's), the PSA test (1986) and "systematic" biopsy grids (1989). Even with subsequent development of "saturation" biopsies using very many needles, they still miss significant tumors, especially since the depth of needle penetration is limited. Up through 2009, the NCCN (national comprehensive cancer care) guidelines still focused on repeating biopsies as often as annually. MRI guidance for biopsies was finally acknowledged/recognized in 2012, with standardization (PI-RADS guidelines) now worked out. Note that whereas some complain about the cost of MRI scans, the pathology reading on biopsy samples costs \$2-300 each, so that total cost exceeds the MRI cost.

A recent article argues "PSA density is superior than PSA and Gleason score for adverse pathological features prediction in patients with clinically localized prostate cancer." So men should be aware of their prostate volume, and calculate PSA density (PSA value divided by the prostate volume in cc).

In 2016, the NCCN updated their guidelines for prostate cancer early detection, recommending "<u>mpMRI</u> (multiparametric MRI; usually shortened to just "MRI") <u>followed by lesion targeting may maximize the detection of higher risk disease</u>, and limit the detection of lower risk disease." In October 2019, the American Urologic Association agreed with that philosophy, as noted above. Studies by the group Bernadette is in, and by a group at Yale found a "negative predictive value" for mpMRI of 91-96%, meaning a very high percentage of men with significant tumors were correctly identified.

Some people argue that an MRI machine needs to have a "3T" magnet (magnetic field strength in Tesla units) for best imaging. In the US, 71% of machines have 1.5T magnets, and 19% have lower field strength. Only 10% have 3T magnets. But Bernadette argues that equal or better images can be obtained with a 1.5T machine, if the operator is a credentialed, experienced mpMRI technologist, the software is modern / state-of-the-art, a high channel-count surface coil is used, the patient is properly prepared (fasting, using glucagon injection to decrease bowel motion, etc.), and the interpreter of the scans is an experienced radiologist. Slides were shown with clearly better results using 1.5T vs. 3T.

Average diffusion coefficient (ADC) values provide a good (though not perfect) indication of disease aggressiveness. Examples were shown of a Gleason 3+3 case (ADC= 1240), a Gleason 3+4 case (ADC=990), and a Gleason 4+5 case (ADC=660). In the associated images, the suspected tumor area was darker (less diffusion) the lower the ADC value. The area of lowest ADC value is the spot to target in the subsequent biopsy, and moving the cursor on the computer-generated image shows that often the best spot to target is quite small. A few pixels away, the ADC value may be a lot higher. So in-bore biopsy (in the MRI machine) or fusion biopsy (overlaying the prior MRI image on ultrasound imaging) is needed for accurate targeting of the suspicious area.

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Ordinary TRUS biopsy needles only reach about 1.8 cm into the prostate. So the needles may not reach a significant tumor, may instead find a clinically insignificant tumor, or may only catch the edge of a significant tumor, where the cells show less aggressiveness than in the center. In 2010 study, it was shown that for Gleason >=7 tumors, MRI-guided biopsy found well over 90% of the tumors, but 10-core TRUS biopsy found only about half. With additional evidence mounting up over the years, we say good-bye to the days of TRUS biopsy.

What is Gleason score? It is the sum of two Gleason "grades," which are numerical rankings of how abnormal the cells in a biopsy sample are. Grades I & 2 are near-normal cells; relatively organized and benign-looking. 3 is somewhat abnormal, and a "cartoon" drawing of cells showing a certain degree of abnormality in shape and clustering is used as a standard for grading. Grades 4 and 5 are stepwise more abnormal – very much different from normal prostate cells – disorganized and scary-looking. The first number used in the sum that makes up the Gleason score is the grade of the most prevalent pattern of cells in the sample. If a (smaller) group of cells show a different pattern, that grade is added to the first number. So 3+3 means all the cells in the sample are "somewhat" abnormal, and 3+4 means that there are some cells of greater abnormality (at the "4" abnormality level). A Gleason score of 4+3 means that the predominant pattern is of the 4 grade, but some cells of grade 3 are also present. Although 3+4 and 4+3 both add up to a Gleason score of 7, the latter patient is considered to have a more aggressive/ dangerous cancer, consistent with the greater prevalence of grade 4 cells.

When patients are seen by Bernadette and her urologist partner, they are always referred to the NCCN (National Comprehensive Cancer Network) guidelines, which lay out the various potential cancer treatments, from active surveillance to surgery, radiation, cryo treatment, high-intensity focused ultrasound, hormone therapy, immunotherapy, chemotherapy, radiopharmaceuticals, clinical trials, and "understudied" treatments. Thus the patients are able to be fully informed before deciding what treatment approach they want to choose.

**2. Laser Focal Therapy.** A clinical trial (NCT02243033) is underway of the laser focal therapy procedure that Bernadette and colleagues developed. 201 men are enrolled in the trial, and will be followed for 20 years. The procedure is now offered commercially, for others who may choose the treatment.

The procedure involves the same equipment used for endorectal biopsies, but inserting a water-cooled 15-Watt laser probe (a 1.65mm fiber) with a heat-diffusing tip instead of a biopsy needle. The laser workstation is integrated with the MRI scanning machine (up to 1.5T) via Ethernet, and the software provides real-time responsiveness, including temperature measurement using the MRI, and safety control features (to protect the neurovascular bundle - which controls erection; the external urethral sphincter; and the rectal wall). The equipment was cleared by the FDA in September 2008. It was initially used in the brains of children to control epilepsy, so Bernadette considered it safe enough to use in prostate treatment. Initial work was done with colleagues at MDAnderson on dogs and pigs. It was difficult to get approval to bring the machine to an "ivory tower" academic hospital, so instead she brought it to Desert Medical Imaging (now Halo Diagnostics), and treated the first patient in May 2010.

A major advantage of laser focal therapy over other types of focal therapy such as cryotherapy (freezing), HIFU (high-intensity focused ultrasound), electroporation (nanoknife) and RF (radiofrequency ablation), is that the treatment zone can be controlled very precisely, with a very crisp boundary (about a millimeter) separating destroyed tissue from living tissue. The boundary can be 5-10 mm in cryo, HIFU or RF treatments.

A "test dose" is first given at 4W power, which heats tissue at the laser tip to about 100 degrees F – just to verify where the tip is. Then the treatment dose is 12W for 90 seconds.

Patients include "treatment naïve" patients (no prior treatment for their cancer), and "salvage" patients (after surgery or radiation -- i.e., Xray, proton or brachytherapy -- has not eliminated the cancer entirely). Most are 60-70 years old. Most of the treatment naïve patients have Gleason 7 tumors in the peripheral zone. Salvage patients may have tumors anywhere in/around the prostate, including the various zones, the seminal vesicles, the bladder wall, etc., and may have any Gleason score. The group also does "large volume" Gleason 3+3 tumors, that are MRI visible. The PSA typically declines about 40%. Sexual function, urologic function and emotional well-being, measured at 12 months, all show no significant decline in either group of patients. That is, laser focal therapy gives none of the morbidity (side effects) associated with either surgery or radiation!

The clinically significant cancer recurrence rate, based on 10-year biopsy results, is about 21%. The literature reports that prostatectomy and radiation both have more that 20% recurrence rate after only five years, and more than 30% after ten years. Over 90% if her patients with recurrence chose to have laser focal therapy again. Six percent of patients ended up "converting" to whole-gland therapy, but the other 94% avoided the associated morbidity

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(side effects). At ten years, there has been only one case of metastasis (i.e., 99% metastasis-free survival), and no deaths due to prostate cancer. Five patients have died, but in every case it was from some other cause than prostate cancer, such as metastatic melanoma, esophageal cancer, Parkinson's disease or a different cancer. The patients who do the best are those who educate themselves and "stay on top of it." That is, whether in active surveillance before any treatment, or later, it is important to get regular tests and scans as guided by the oncologist, and not slip into denial.

How recurrence rates after laser focal therapy might be reduced: Better treatment planning (3D mapping biopsy or tracking biopsy), Increasing treatment area (but can lead to some morbidity), Better risk stratification (whom to treat; based on PSA density, tissue-based genomics or liquid biopsies such as circulating tumor cells or circulating tumor DNA, molecular imaging such as by Axumin or PSMA PET/CT scanning, and/or combination treatments such as laser focal therapy with immunotherapy or oncolytic virus therapy or radiopharmaceuticals). Remember that it is possible to retreat with laser focal therapy as needed, and that "all options remain on the table" – the patient can still go for surgery or radiation or hormone therapy or whatever. If the cancer comes back, simultaneously appearing at several sites, she calls this "Whac-a-mole," and turns these patients over to whole-gland therapy.

In summary, laser focal therapy is safe, it's precise, and it's outpatient feasible. The treatment can be "sculpted" to fully treat areas of concern. The transition between treatment area and unaffected surrounding tissue is 1 mm, in contrast to 5-10 mm for HIFU, Cryo, radiation and other energy sources. Thermometry via the MRI software with safety cursors placed to protect sensitive areas is in real time. It is particularly useful for treating tumors in large-volume prostates, and for treating apex cancers (narrow/tricky area at the bottom of the prostate, treated while using urethral cooling catheter and continuous bladder irrigation).

#### **Conclusions & Next Steps**

13-year interim data in 200 research participants (and  $\sim$ 1000 commercial patients, TX + CA) indicates outpatient MR-guided trans-rectal laser focal therapy is both safe and feasible.

No statistically significant erectile dysfunction, or incontinence.

Favorable results for quality of life without eliminating the possibility of whole-gland therapy or additional laser focal therapy in patient's future.

Short term and intermediate term oncologic control is achievable in over 75% of patients.

Minimally invasive outpatient laser focal therapy of prostate cancer may be an attractive option for specific patient populations.

"Nothing ruins good results like follow-up." >>> 20-year Phase 2 study ongoing.

International multi-institutional Phase 2 trial through the International Laser Network awaiting IRB approval. Ongoing IRB approved clinical trial exploring tissue genomics for risk stratification.

IND submission completed to FDA for combination therapy awaiting approval.

**3. Genomic testing**: Bernadette prefers Prostavysion (2 genes – ERG and PTEN) and Decipher (22 genes). In tumors, the ERG gene may be overexpressed, which is bad. PTEN normally occurs in 2 alleles (ie, specific variations of the gene). If one allele is missing, it is called hemizygous deletion. If both, homozygous. Loss of one, or especially both, results in reduced immunosuppressive ability. So Prostavysion ranks the cancer aggressiveness based on the possible combinations of these three negative genetic factors.

#### [Sidebar on genetic science: See June 2021 IPCSG Newsletter]

The Decipher test was developed to analyze RNA in prostatectomy pathology samples, to determine whether the patient should receive follow-on radiation. About seven years ago, Bernadette proposed to the test inventor that the test could also be run on biopsy samples, and that it would make sense to do so if the samples were of the high quality that can be obtained using MRI-guided biopsy – to be sure that the sample was taken in the heart of the most tumor-suspicious area. He thought about it, and Decipher for Biopsy was released in 2016. Commercially, it measures 22 genes and predicts the potential for metastases. But on a research basis, they measure up to 1.4 million genes and provide access to their evolving database of genetic variations vs. disease progression. Bernadette has gotten this data for her cohort of patients under a research protocol.

Value of Decipher: It can accurately predict PCSM (prostate cancer specific mortality). Decipher results can

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provide much faster results than PSAdt (PSA doubling time) and can be used to predict clinically significant events (including BCR; i.e., recurrence) before all other methods. CAPRA-S and Decipher provide complementary information and together can identify very high-risk patients and provide improved risk prediction.

#### [Sidebar on the CAPRA-S score: See June 2021 IPCSG Newsletter]

Several case studies were discussed in the video by Bernadette and by Dr. Aaron Harman.

The video is available on YouTube at https://www.youtube.com/watch?v=GSoiFYNtOC8

As noted above, Bernadette's email is Bernadette@halodx.com.



## ON THE LIGHTER SIDE

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#### **Items of Interest**

### Prostate cancer: definition, causes, symptoms, diagnosis and treatment

#### By Cristiano Antonino Last updated Jun 20, 2023

Adenocarcinoma, a particular type of prostate cancer, is a malignant growth that develops in the gland of the same name, an integral part of the male reproductive system

The prostate is a gland, the size of a walnut, which is located between the rectum and the bladder, directly including the first part of the male urethra, that thin "tube" that carries urine towards the outside of the body.

The prostate, in addition to being an active part in the production of seminal fluid, also constantly secretes a particular type of protein called prostate specific antigen (PSA) into the blood.

When the prostate becomes enlarged and the blood levels of this protein are too high, cancer can be suspected. Fortunately, prostate growths are not always malignant.

In fact, there are many cases of benign formations that do not require special care.

The prostate is a gland found only in men and prostate cancer is one of the most common among these individuals.

Data in hand, it is estimated that in Italy there are about 40,000 cases a year: among the most affected ethnic groups we find those of North America, north-western Europe (of which our country is part), the Caribbean islands and of Australia.

#### Seniority is also a risk factor that should not be underestimated.

Prostate cancer remains the most common type of cancer among patients over the age of 80

The course of prostate cancer is usually slow and rarely affects areas outside the gland with metastases.

For this reason the person, assuming the appropriate therapies in any case, can live with it for a long time.

Cases in which the carcinoma is aggressive, particularly malignant and with a rapid course are rarer, but still exist, because the tumor cells, transported by the blood and the lymphatic system, extend beyond the prostate gland, creating metastases in the body.

Prostate cancer: the causes

Modern medicine is still engaged in identifying the causes that lead to the development of this particular type of tumor.

To date, unfortunately, a precise reason has not yet been identified.

It is assumed that it may derive from mutations in the DNA of cells that induce disordered and uncontrolled replication, eventually forming tumor masses, but the causes of these mutations are still not completely clarified.

By carefully studying the affected patients, it has been possible to define a series of risk factors that contribute to increasing the probability of developing the disease:

Age of the individual. This type of cancer is very rare in people under the age of 45. The number of patients increases proportionally with advancing age. At present, the most affected group is the one between 60 and 70 years old.

*Genetics.* Hereditary factors, including ethnicity, increase the likelihood of having the disease. Having a father or a sibling who developed this cancer increases people's risk. Similarly, African American groups are statistically the most affected for some genetic reason, still unclear.

Diet. Some studies show that diets too rich in protein and saturated fat can increase the risk of developing prostate cancer.

Obesity and overweight.

Then there are some diseases and inflammations of the prostate that act on the state of health of the gland, increasing the risk of malignant transformation.

Intraepithelial prostatic neoplasia is a dysplasia, most of the time mild but to be checked periodically, as it could evolve into prostate cancer.

The same happens in patients with proliferative inflammatory atrophy, a condition in which cells in the prostate are smaller than normal.

Prostate cells can also be weakened when prostatitis is present, a bacterial inflammation that can be very intense.

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Finally, all subjects with atypical microacinar proliferation are at risk of prostate cancer.

That is, when the result of the biopsy is uncertain and it is not clear whether the tumor is benign or malignant, it must be kept under control.

It should be remembered that an enlarged prostate is not necessarily a symptom of malignancy.

There are many cases in which prostatic hyperplasia is benign, and the neoformation is practically harmless.

#### Prostate cancer: symptoms

When prostate cancer is in its early stages, the disease is almost totally asymptomatic, both because it affects a limited anatomical area and because, in most cases, its course is very slow.

However, it can happen (fortunately in very rare cases) that this type of tumor presents itself immediately as aggressive, affecting not only the prostate area, but also spreading to other areas of the body with the development of metastases.

It usually happens when the blood and lymph vessels that carry the cancer cells are also affected.

Typical symptoms are classified into two large macro-categories.

Disorders of urination and ejaculation include:

frequent urination even during the night;

urinary incontinence;

painful urination. The difficulty and pain in urination are given by the fact that, by enlarging, the prostate gland occludes a part of the urethra;

difficulty maintaining a steady stream of urine (feeling like you are not emptying your bladder completely); blood in the urine;

painful ejaculation;

erectile dysfunction;

constant pressure and discomfort in the pelvic area and lower abdomen;

In the most serious stages, the disease evolves affecting the skeleton and lymph nodes:

bone pain, especially in the trunk and pelvis (spine, femur, ribs, hipbones). In most cases, the pain felt is directly related to the presence of localized metastases;

when the tumor compresses the bone marrow, there may be numbress in the lower limbs, urinary and fecal incontinence;

frequent bone fractures even without having suffered major trauma.

Some of these symptoms are also associated with benign tumors, which is why it is always necessary to consult a specialist from the first signs.

Routine check-ups are also essential because prostate cancer is often discovered accidentally when you go to the doctor to investigate the origin of the aforementioned symptoms.

Prostate cancer: the diagnosis

Prostate cancer prevention is essential to avoid a late diagnosis and to ensure that the disease remains localized, lowering the risk of incurring more serious complications.

For this purpose, it is recommended that you periodically visit your doctor or a urologist.

Routine checks must become good practice especially for those who are part of the age group most at risk, that of the over 60s.

Blocking the disease from its onset guarantees a better prognosis.

The visit begins with the collection of the subject's medical history and continues with an objective examination carried out by the specialist, who will take care to investigate not only the present symptoms, but also the past clinical history, in order to have a 360-degree view.

A fundamental step in the diagnostic process is the blood sample to check the PSA values which, as we have seen, if too high can be a sign of an alteration at the glandular level.

Its presence, however, is not specific for the presence of a malignant tumor, but can also highlight the presence of other prostatic pathologies such as prostatitis and prostatic hypertrophy.

The value can also rise following trauma involving the prostate (for example, if the sample is taken after riding a bicycle).

If the blood tests are not very clear or show abnormal values, the doctor may decide to continue with the investigation, using biomedical imaging techniques.

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Digital transrectal ultrasound (DRE) allows to identify disorders of the prostate gland.

Similarly, an MRI helps provide a 3D image of the gland, highlighting any problems.

A prostate biopsy, although more invasive, allows a part of the diseased prostate tissue to be taken directly for its histological study.

Thanks to this technique it is possible to find out if the tumor is benign or malignant and at what stage it is in its evolution.

The surgery usually takes place in the clinic under local anesthesia and does not require hospitalization.

If the cancer is at an advanced stage and has metastasized, the specialist may decide to order tests that provide further details:

a chest x-ray can see if the cancer has already spread and metastasized to the lungs;

CT is the method of choice to investigate the health of the lymph nodes, in particular the pelvic and abdominal ones, the first to be affected by prostate cancer;

bone scintigraphy offers a precise view of the spread of the tumor to bone and soft tissue;

choline PET is a brand new test, currently the most accurate, to highlight this type of mass. A radiopharmaceutical is injected into the patient, which highlights the abnormal areas.

A thorough examination is always useful to exclude other pathologies that affect the prostate but are not cancerous.

An increase in prostate volume can, in fact, be associated with benign prostatic hyperplasia – therefore a harmless tumor of the gland – or prostatitis, a bacterial inflammation that affects this organ.

What happens if the doctor detects cancer during tests?

Whenever the results of the investigations suggest the presence of a tumor, it will be the doctor's job to try to understand its benign or malignant nature.

The grade of the tumor is also evaluated, i.e. at what stage it is, whether it is in the initial stage or has already formed metastases.

This is vital information that directly affects the patient's treatment and prognosis.

Treatments and cures for prostate cancer

The treatments provided for prostate cancer vary according to the intensity of the symptoms and the stage in which the disease is.

The most used for the treatment of localized and early stage cancer include, as an essential first step, a constant control of PSA levels in the blood, by sampling and studying the blood component.

To prevent the situation from getting worse by invading extra tissue, the urologist can recommend radical prostatectomy to the patient.

It is an invasive surgical therapy, which involves the removal of the prostate.

The new surgical engineering offers the patient a laparoscopic and robotic surgery, which guarantees shorter recovery times because it does not require direct access from the abdomen.

These are techniques that minimize the risk of future incontinence and erectile dysfunction.

This is because it reduces the risk of damaging surrounding structures.

It is an operation aimed only at the areas to be removed.

Normally surgery is the ideal way to treat limited cancer since it does not necessarily have to be followed by other radiological and chemotherapy treatments.

Often used instead of surgery, brachytherapy involves implanting radioactive sources in the prostate.

It is a type of radiotherapy that acts directly on the injured area, without involving the surrounding ones.

External beam radiotherapy, on the other hand, consists of direct irradiation of the prostate.

Cancer cells are more sensitive than healthy cells to X-rays and are damaged.

When the cancer is advanced and has already started to spread through the body, the following are ideal: androgen deprivation therapy or hormone therapy. These are hormonal treatments that reduce the level of androgens in the body which are currently considered one of the main causes of the multiplication of cancer cells. In general, early use of this type of therapy causes the growth of the cancer to slow down or even stop;

chemotherapy is a last resort, prescribed only for patients who do not respond to hormone treatments.

There are many cancer centers that are experimenting with new biological therapies based on the use of engineered immunity cells that selectively attack the diseased ones.

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#### NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Gene Van Vleet and Bill Lewis is available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcsg.org or Bill 619-591-8670 (<u>bill@prostatecancerhelp.info</u>) to coordinate.

Member John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcsg.org/personal-experience

#### **FINANCES**

We want to thank those of you who have made <u>special donations</u> to IPCSG. Remember that your gifts are <u>tax deductible</u> because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. <u>Corporate donors are welcome!</u>

