THE MANITOBA PROSTATE CANCER SUPPORT GROUP NEWSLETTER

Prostate Cancer Canada Network Winnipeg

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New AUA Guideline for Castration-Resistant Prostate Cancer

Nick Mulcahy May 09, 2013 Medscape Medical News

The American Urological Association (AUA) has issued a new guideline for the management of castration-resistant prostate cancer (CRPC) that provides a "rational basis" for treatment decisions.

Those decisions are now "complex" because a group of treatment options for metastatic disease has emerged in a short period of time, according to a press release issued at AUA 2013 Annual Scientific Meeting, held in San Diego, California.

The treatment options in metastatic CRPC (mCRPC) include 4 new therapies that have been approved since 2010: sipuleucel-T (Provenge, Dendreon), cabazitaxel (Jevtana, sanofi-aventis), abiraterone (Zytiga, Janssen), and enzalutamide (Xtandi, Astellas/Medivation). These therapies, along with docetaxel (approved in 2004), have all been shown to improve overall survival in metastatic disease.

"Prior to 2004, once patients failed primary androgen deprivation, treatments were administered solely for palliation," write the guideline authors, led by Michael S. Cookson, MD, from Vanderbilt-Ingram Cancer Center in Nashville, Tennessee.

The guidelines are much needed, according to a clinician not involved with their writing. "There is a lack of clarity as to the best method for treating castration-resistant prostate cancer," said Willie Underwood III, MD, MPH, from the Roswell Park Cancer Institute in Buffalo, New York.

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Medical Advisors

Paul Daeninck M.D.
Pain Management

Darryl Drachenberg
M.D. Urologist

Graham Glezerson
M.D. Urologist

Ross MacMahon
M.D. Urologist

John Milner
M.D. Urologist

Jeff Sisler M.D.
Family Practitioner

Thanks!

Next Meeting: Tuesday September 17, 2013

Our annual
"Prostate Health Awareness Evening"
Dr. Jeff Sisler, Family Physician
Dr. Jeff Saranchuk, Urologist
Location: Caboto Centre,
1055 Wilkes Ave.
Time: 7 to 9 p.m. Free parking
Note: *No meeting*
at Seven Oaks Hospital on Sept. 19

SHARING IS CARING

The Manitoba Prostate Cancer Support Group does not recommend treatment modalities, medications, or physicians.

Thought Of The Day

Cross country skiing is fine ..... if you live in a small country!

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The guidance is especially important given the publicity that has accompanied the new therapies, as well as their cost, he told Medscape Medical News in an interview. "When a drug comes out with a lot of hype, every patient wants that drug."

A large part of the new guideline is recommendations for 6 different types of patients. These "index" patients represent the most common clinical scenarios in men whose prostate cancer is not responsive to traditional androgen-deprivation therapy.

The profiles of the index patients comprise symptoms, performance status, the presence or absence of metastases, and whether or not docetaxel has been administered.

The guideline authors acknowledge that treatment is rapidly changing, and advise clinicians to use it in conjunction with the "current literature" and an individual patient's treatment goals.

The following are the index patients and the associated recommendations.

Index Patient 1: Asymptomatic Nonmetastatic CRPC

Profile
The typical patient has a rising prostate-specific antigen (PSA) level and no radiologic evidence of metastatic prostate cancer. He is also required to have castrate levels of testosterone (less than 50 ng/mL).
Treatment recommendations
=> Observation with continued androgen deprivation
=> First-generation antiandrogens (flutamide, bicalutamide, and nilutamide) or first-generation androgen-synthesis inhibitors (ketoconazole plus steroid) to patients unwilling to accept observation
Discussion
No treatment has been shown to improve overall survival in these men. "Since all agents have potential side effects...we must first do no harm," write the authors.

Index Patient 2: Asymptomatic or Minimally Symptomatic mCRPC Without Previous Docetaxel Chemotherapy

Profile
These patients have "a rising PSA in the setting of castrate levels of testosterone" and metastatic disease documented on radiographic imaging.
Treatment recommendations
=> Abiraterone plus prednisone, docetaxel, or sipuleucel-T
=> First-generation antiandrogen therapy or ketoconazole plus steroid or observation to patients who do not want or cannot have one of the standard therapies
Discussion
The 3 standard therapies are approved by the US Food and Drug Administration for this indication and improved overall survival in randomized clinical trials. There are no direct comparison studies to inform optimal sequencing. "As a general principle, it is preferable to give the least toxic agent first," the authors note.

Index Patient 3: Symptomatic mCRPC With Good Performance Status and No Previous Chemotherapy

Profile
These patients have a rising PSA level in the setting of castrate levels of testosterone. Their symptoms should be related to prostate cancer alone (and not other conditions), and might include pain.
Treatment recommendations
=> Docetaxel
=> Abiraterone plus prednisone
=> Ketoconazole plus steroid, mitoxantrone, or radionuclide therapy for patients who do not want or cannot have one of the standard therapies
Discussion
Sipuleucel-T immunotherapy is not recommended in symptomatic disease, the authors note.

Index Patient 4: Symptomatic mCRPC With Poor Performance Status and No Previous Docetaxel Chemotherapy

Profile
Clinical trials have generally excluded patients with a poor performance status (ECOG 3 or 4); as a result, data guiding their management are extrapolated from randomized trials of healthier patients.
Treatment recommendations
=> Abiraterone plus prednisone
=> Ketoconazole plus steroid or radionuclide therapy to patients who are unable or unwilling to receive abiraterone plus prednisone
=> Docetaxel or mitoxantrone chemotherapy in select cases, specifically when performance status is directly related to the cancer

Patient 5: Symptomatic mCRPC With Good Performance Status and Previous Docetaxel Chemotherapy

Profile
A focus of therapy should be to maintain the excellent performance status without significant toxicity from additional therapy.
Treatment recommendations
=> Abiraterone plus prednisone, cabazitaxel, or enzalutamide
=> If the patient received abiraterone plus prednisone prior to docetaxel chemotherapy, offer cabazitaxel or enzalutamide
=> Ketoconazole plus steroid if abiraterone plus prednisone, cabazitaxel, or enzalutamide is unavailable
=> Retreatment with docetaxel for patients who were benefiting from but discontinued treatment with docetaxel because of reversible adverse effects
(Continued on page 3)

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Discussion

Abiraterone plus prednisone and enzalutamide appear to provide clinical benefit equivalent to (if not superior to) additional intravenous chemotherapy with an agent such as cabazitaxel. These 2 therapies have "significantly less acute toxicity and no apparent cumulative toxicity" over prolonged periods, say the authors.

Index Patient 6: Symptomatic mCRPC With Poor Performance Status and Previous Docetaxel Chemotherapy

Profile

"Treatment given in the last months of life may delay access to end-of-life care, increase costs, and add unnecessary symptom management. Patients with poor performance status (ECOG 3 or 4) should not be offered further treatment," write the authors.

Treatment recommendations

=> Palliative care

=> For selected patients, offer treatment with abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid, or radionuclide therapy

Discussion

There is insufficient evidence demonstrating a treatment benefit in this patient population.

Because the skeletal system is the most common site for prostate cancer metastasis, the guideline also makes recommendations regarding bone health.

Bone Health

Treatment recommendations

=> Offer preventative treatment (e.g., supplemental calcium, vitamin D) for fractures

=> Choose either denosumab or zoledronic acid as preventative treatment for skeletal-related events

"Prostate cancer deaths are typically the result of mCRPC, a painful disease," said Dr. Cookson in a press statement. "In recent years, a number of new treatments and therapeutic agents have entered the market that have been shown to minimize adverse effects and pain and prolong survival in some patients, but the fact remains that mCRPC is the terminal stage of prostate cancer."

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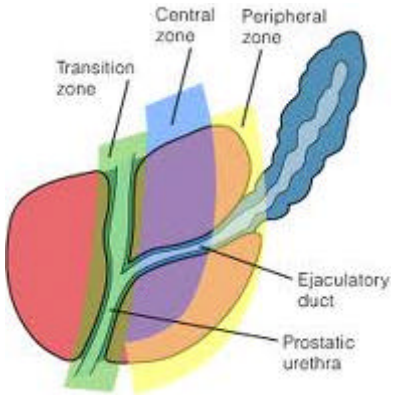
Primer on Prostate Anatomy

Many men are not aware of the location and function of their prostate gland until it begins to cause health problems. The prostate gland is chestnut shaped and sits at the base of the bladder, in front of the rectum and behind the base of the penis. It produces prostatic fluid (a component of semen), functions as a valve to keep urine and sperm flowing in the proper direction, and pumps semen into the urethra during orgasm.



The prostate gland is about the size of a pea at birth and grows until it reaches its normal adult size (roughly 1.5 inches in diameter) in a man's early 20s. When a man reaches his mid-40s or later, the inner portion of the prostate tends to enlarge, a condition called benign prostatic hyperplasia (BPH).

Physicians usually divide the prostate into three main zones:

- The peripheral zone comprises the outermost portion of the prostate gland and accounts for about 70 percent of its volume. Because prostate cancer is most likely to develop in this area, doctors usually sample tissue from this section during a biopsy. Since much of the peripheral zone sits adjacent to the rectum, doctors can often detect prostate cancer with a digital rectal exam.
- The transition zone is the innermost section of the prostate gland and accounts for roughly 5 percent of its volume in a healthy man. This zone surrounds the urethra, which passes from the bladder to the penis through the prostate. BPE begins in the tissues of the transition zone. Enlargement of this zone constricts the urethra and leads to the urination problems that are common in men with BPH.
- The central zone, which sits between the peripheral and transition zones, makes up about 25 percent of the prostate gland's volume. The ejaculatory ducts, through which semen enters the urethra, pass through this zone. Prostate cancer and BPH are unlikely to develop in the central zone.

Source: Johns Hopkins Health Alert.

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An interesting look at the PROS and CONS of Active Surveillance – Part 2

(This is the 2nd part of our article on treating prostate cancer using active surveillance. In our August newsletter Dr. Laurence Klotz talked about the PRO approach. This month Dr. Oliver Sartor will use the CON argument.)

Surveillance for Prostate Cancer: Are the Proceduralists Running Amok?

By A. Oliver Sartor, MD
June 11, 2013

Dept. of Medicine and Urology, Tulane University School of Medicine, New Orleans, Louisiana

Debating Dr. Laurence Klotz on active surveillance is a daunting task. He is one of this world's leading urologists, and certainly one of the best informed on surveillance. Why quibble with Dr. Klotz? All leading academic institutions now have large active surveillance cohorts, and well-attended symposia publically discuss the overtreatment problem in prostate cancer. Brave souls like Dr. Klotz have taken many arrows for leading the charge.

Despite academic leadership, uptake of surveillance among community urologists is hard to discern. In my experience, being treated for low-volume Gleason 6 tumors is the norm, not the exception, for men in the United States. Surveillance may be discussed as an option, but it is not taken seriously. In a recent discussion at a urology group practice, the question was raised, "How many of your prostate cancer patients are under surveillance?" Despite being a busy practice (dominated by robotic surgery), the answer was "nobody." Why so?

Much discussed by urologic proceduralists is the concept of focal therapy. Why not eradicate the tumor focally and avoid the side effects associated with radical surgery? Good concept, but I am not sure that the discussions are being focused on the right patients. Many discussions focus on procedures (freezing, burning, etc) that eradicate tumors of little clinical consequence. It is hard to leave the prostate alone, especially if you are well armed and trained to attack.

When surveillance is actually practiced today, various entry criteria and algorithms are being utilized. Is a man with three cancerous cores eligible, or should only men with two positive cores be allowed? Some algorithms involve yearly biopsies and some do not, some involve complicated imaging and some do not, some involve lots of prostate-specific antigen (PSA) testing and some do not. What is the best technique? No consensus is apparent; furthermore, there is little consensus on who has "progression" and who does not.

For a brief moment, let us discuss data rather than opinions. There are prospective trials concerning localized prostate cancer. One noteworthy study was SPCG-4, a European study of radical surgery vs observation conducted in patients with disease detected by symptoms (not PSA elevation). Everyone understands radical surgery, but what about observation? Men in the "watchful waiting" group with signs of obstructive voiding were treated by TURP. Bone scan–detected metastases were managed with hormones. Hormonal treatment was also allowed later in the trial if there were "signs of tumor progression" (including elevated PSA level). After a median follow-up of 12.8 years, in patients over age 65, no benefit to surgery was seen in overall survival or prostate cancer–specific survival. Note that complicated surveillance schemes were not used; treatments in the watchful waiting group were typically initiated simply when symptoms were present.

Another prospective trial is PIVOT. There is much to hate about PIVOT, including the fact that the life-expectancy in the enrolled population was suboptimal. Mean age at entry was 67, and recruitment mainly occurred in Veterans Administration hospitals, not the healthiest of populations. In this trial of observation vs radical surgery, "observation" meant that patients were offered various forms of palliative therapy when indicated. After a median follow-up of 10 years, not surprisingly, no differences were seen in overall mortality or prostate cancer–specific mortality in this population. Among those with low-risk disease (PSA < 10 and Gleason score of 6 or less, and clinical stage T1c or T2a), there was no trend toward benefit. Other groups trended toward benefit from surgery, but subset analyses were terribly underpowered.

Contrast the observation arms in these prospective randomized trials with how surveillance is being done today: poking, probing, and testing are rampant, while treating for symptoms is viewed as anachronistic. My thesis is that we currently make surveillance too complicated. We do too many biopsies and have unnecessarily complicated algorithms. Too many people are excluded from surveillance in our protocols. Should the vast majority of patients with low-risk prostate cancer simply be followed for symptoms and our procedures held at bay?

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Erectile Dysfunction Patient Information Fact Sheet

What tests confirm a diagnosis of erectile dysfunction?
If appropriate, your doctor will prescribe medication for erectile dysfunction. If drug treatment is successful, there may be no need for further referral. Some men may be referred to a urologist for further tests to define the cause of the erectile dysfunction before treatment is started. A blood sample may be taken in order to measure testosterone levels. If a problem concerning the blood supply is suspected, x-rays of the arteries and measurement of the pressure inside the penis may be necessary.

How is erectile dysfunction treated?
If erectile dysfunction is the result of psychological factors, the cause needs to be addressed. Psychosexual or relationship counseling may be appropriate. Methods of coping with stress may also be helpful; sometimes reducing stress may solve sexual problems.
If erectile dysfunction is a side effect of medication, changing to an alternative treatment may solve the problem.

In a small proportion of men, erectile dysfunction is caused by a reduced level of testosterone. This can be corrected by androgen replacement therapy, which may be given in the form of testosterone supplied as skin patches (Androderm), tablets (Methitest), or capsules (Android). Testosterone may also be given as regular injections or as implants under the skin. It is also available as a gel (Testim, Androgel). Alprostadil is a drug that can be injected directly into the shaft of the penis and usually causes an erection within 15 minutes. The administration technique, called intracavernosal injection, is quite easy to teach most men. Alprostadil injection may be prescribed as Caverject. Alprostadil can also be given directly into the urethra (the tube that runs through the penis) in a suppository form known as Muse. Muse suppositories cause an erection within five to 10 minutes and are available in different strengths. Alprostadil may cause erections that are prolonged and painful and advice should be given about what action to take if this happens, as there is a risk of damage to the penile nerves.

Currently, there are three oral treatments for erectile dysfunction that can be prescribed for men who meet certain criteria: sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra). These treatments are intended for use only by men with erectile dysfunction. These medicines are not suitable for everyone, for example, men with recent stroke, severe heart disease or angina being treated with nitrates. These medicines should not be used in conjunction with other treatments for erectile dysfunction.

If drug treatment is unsuccessful, vacuum constriction devices are available. These draw blood into the penis and create an erection that can be maintained for up to 30 minutes by a tension band slipped around the base of the penis. A range of vacuum constriction devices is now available for men who meet certain criteria. Alternatively, a prosthesis can be surgically inserted. This should not be considered until all other treatment options have been tried as the insertion destroys the erectile tissue. One option is a semi-rigid splint, which creates a permanent erection but allows the penis to be bent out of the way. Another option involves the insertion of a small pump in the groin, which activates a hydraulic device causing an erection when required. If there is an abnormality in the blood supply to the penis, surgical correction of the problem may be possible in some cases.

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Thanks to **The Canadian Bridge Federation Charitable Foundation**
for a recent donation to the Manitoba Prostate Cancer Support Group.

The CBF disperses money raised each year
by Canadian Bridge Club players to various charities.
Their focus for 2013 is on seniors –
especially those organizations that assist and improve the life of seniors.

We appreciate they have considered us as worthy recipients for this year.
Many thanks to all the bridge players for their kindness.

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PCa: New Treatments

The next decade should do for prostate cancer what the past one has done for breast cancer

Mar 10th 2012 | PARIS | from the print edition of The Economist

MOST cancers are equal-opportunity killers. Some, though, are perforce sex-specific. Breast cancer is rare in men. And prostate cancer is obviously absent from women. Recent years have seen a plethora of new drugs—starting in 1998 with Herceptin—for treating breast tumours that are threatening to get out of control. No such breakthrough has happened with prostate cancer. Though easily treated if caught early, late-stage prostate cancer is serious and often fatal. But that may be about to change.

Better understanding of the biology of the disease, and particularly of the role of testosterone in promoting it, has stimulated a new era of drug development, reminiscent of the revolution that ushered in Herceptin. These novel treatments, which are now undergoing clinical trials, were one of the main topics of conversation at the Congress of the European Association of Urology, which took place in Paris on February 24th-28th.

Some of the therapies discussed remain conceptual almost to the point of fantasy: a genetically engineered virus that could destroy prostate-cancer cells from within, for example. Several, though, are already available, or are just about to be.

Cabazitaxel, made by Sanofi, a French firm, is one. It is a relative of taxol, a drug used to treat breast and ovarian cancer. It works by preventing the formation of structures called microtubules, which pull the chromosomes apart in dividing cells (such as cancer cells). It was approved for use in 2010 after trials showed that it could prolong the lives of men with late-stage disease. A second drug, abiraterone, made by Johnson & Johnson, an American company, was approved in 2011 after a trial was stopped because it had been so successful that the organizers deemed it unfair on those in the control group that they were not receiving the medicine too.

Abiraterone works by interfering with an enzyme involved in the production of testosterone. Crucially, it does so in all testosterone-producing tissues, particularly including the adrenal glands, not just the testes. A common change that occurs when prostate cells turn cancerous is that they become extremely sensitive to testosterone—so much so that late-stage prostate cancer is often referred to as being "castration-resistant", because even that drastic testosterone-reducing treatment cannot halt it. But abiraterone can.

Testosterone poisoning

Cutting off the testosterone supply is not, however, the only approach possible. MDV3100, made by Astellas, a Japanese firm, and Medivation, an American one, reduces the cancer's sensitivity to what testosterone is already there. This drug, not yet approved for prescription, works by gumming up testosterone receptors on the cancer cells' surfaces, so they cannot react to the hormone. It also cuts the lines of communication between any receptors which are still activated and the cell nucleus, so that the nucleus cannot take instructions from the hormone.

A fourth drug, alpharadin, developed by Algeta, a Norwegian firm, has a completely different mechanism of action. It works not on the primary cancer but on one of its most dangerous consequences, secondary bone tumours. Ironically, its active ingredient is radium, a substance more usually thought of as a cause of cancer than as a treatment. But one reason radium is dangerous is that, as a glance at the periodic table will show, it is chemically similar to calcium, a principal ingredient of bone. It therefore gets absorbed by bones if ingested, rather than being excreted.

Algeta's researchers have exploited this to produce a drug that is taken up by bones. In someone who already has cancer that is a good thing, because the radiation produced kills the cancer cells, and the drug gets concentrated where it is needed most.

It sounds desperate, and it is. But it seems to work. A trial at the Royal Marsden Hospital, in London, was stopped last year for the same reasons that the abiraterone trial was stopped: the treatment was too successful to deny it to the control group. Alpharadin is now, therefore, awaiting approval by the authorities. The final proven approach to castration-resistant prostate cancer is a vaccine. This is not a prevention, in the way that most vaccines are, but a treatment for existing disease. Sipuleucel-T, as the vaccine in

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question is known, is made by Dendreon, an American firm. The starting point is a culture of human dendritic cells. These are part of the immune system and, if suitably treated with a substance called a fusion protein, can be used to make prostate-cancer cells vulnerable to immune attack.

Sipuleucel-T's main drawback is that each treatment has to be handcrafted to the individual receiving it, using dendritic cells from his own body. This is hugely expensive—almost $100,000 a course. That is a sum which insurance companies and government health services might understandably be reluctant to fork out.

Cost, indeed, is a consideration for others among the new anti-prostate-cancer treatments. Britain's National Institute for Health and Clinical Excellence, which assesses the cost-effectiveness of new medicines that might be paid for by the country's National Health Service, reckons, for example, that abiraterone is too expensive to justify the extra months of life it brings. But Herceptin, too, was subject to scrutiny about its cost at the beginning. Now Herceptin treatment is routine, and many women's lives are the better (and longer) for it. With luck, in a few years' time, men will be able to say the same

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How do I make a decision about whether or not to have a PSA test?

Having a PSA test may lead to further decisions after the test results are back, especially if the blood PSA level is raised. So, there are several things to think about before having a PSA test for prostate cancer:

=> your age
=> your level of concern about having prostate cancer
=> your risk of having prostate cancer (is there a family history of the disease?)
=> the risk and benefits of early detection.

The benefit of a PSA test is that it may find PCa when it is small and able to be cured.

The risks include having unnecessary and possibly harmful effects of treatment with surgery or radiotherapy if a cancer is found that may not have caused problems if left untreated. However, the option of active surveillance, whereby a low risk cancer is watched closely instead of being treated, helps to lower these risks.

The side-effects of treatments include erectile problems (difficulty having erections, impotence) and urinary incontinence (inability to hold urine, urine leakage, having to wear urine pads).

Most prostate cancers tend to progress slowly and men may die of other age-related illnesses first rather than their prostate cancer.

Source: Australian Prostate Cancer Foundation.

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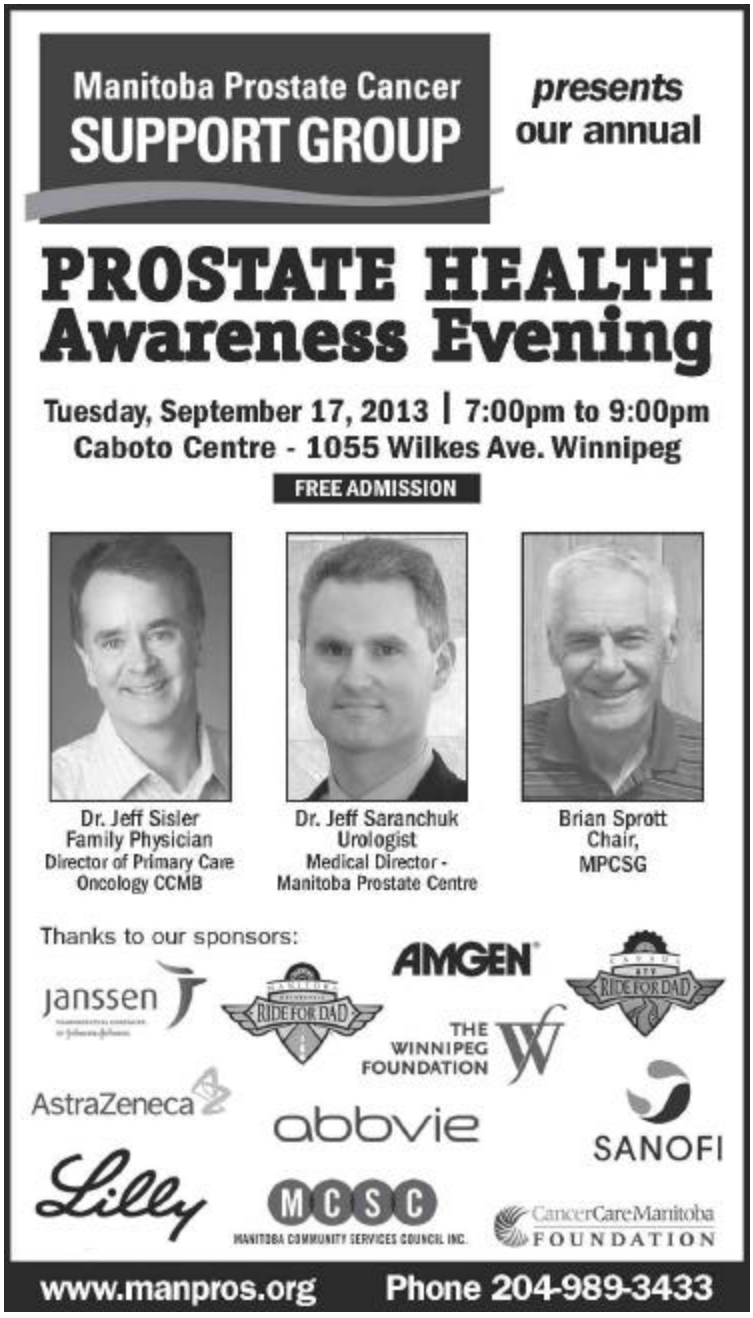

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The Board of the Manitoba Prostate Cancer Support Group would like to recognize a generous donation from the Winnipeg Foundation. The Winnipeg Foundation, Canada's first community foundation (established 1921), is a collection of endowment funds established by donors from all walks of life. Funds are pooled and invested with the income distributed as grants to registered charitable organizations. Their financial support assists us with our work, in particular, the provision of our newsletter. Their continued support is sincerely appreciated.

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MEETINGS

September 17, 2013 (Tuesday)
Prostate Health Awareness Evening
Caboto Centre, 1055 Wilkes Ave.
Presenters: Dr. Jeff Sisler, FP & Medical Lead, Primary Care Oncology Program.
Dr. Jeff Saranchuk, Urologist & Medical Director – CancerCare Manitoba.

Note: No meeting at Seven Oaks Hospital on Sept. 19, 2013

October 17, 2013
Pat Murphy, Clinical Ethicist
Health Care Directives – Do they provide the relief they promise?

November 21, 2013
Dr. Harvey Quon, Radiation Oncologist
Intimate Fire-side chat on Radiation Options and Fractionation in Winnipeg

All meetings are held at
Seven Oaks General Hospital Auditorium
7-9 p.m.
Everyone welcome

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