

Forefront

A PROSTATE CENTRE UPDATE

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About The Prostate Centre

The Prostate Centre at Princess Margaret Hospital is the largest and busiest multi-disciplinary prostate-focused clinic in Canada. Its aim is to offer the best of medical care to men with prostate disease in a holistic, people-focused manner. In 2003 over 14,000 patient visits were registered with over 1,500 new patients with prostate disease seen. Clearly, this is a reflection of both the enormous need for prostate care and the recognition by our community of the special treatment afforded to men and their families at the Prostate Centre.

Our Centre continues to make great progress both in the timely delivery of world-class medical care of prostate disease (both physical and psychosocial)

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Promising New Treatments Being Investigated

Two new approaches to the treatment of prostate cancer are in the early stages of investigation by researchers at the University Health Network.

Dr. Jeffrey Medin and his colleagues are looking at a novel form of immunotherapy to help the body's immune defense system recognize the prostate tumor as a foreign body and then mount a targeted response against that tumor but not against other healthy tissue.

Some tumors produce specific proteins that normal cells do not. By developing these proteins as antigens (substances that trigger an immune response) it may be possible to overcome the body's tolerance of the tumor.

The technique being followed is to genetically modify certain cells called dendritic cells to become antigens which are then presented as peptides to the T cells—a form of white blood cells that are key to the body's immune response. These T cells are then activated with the expectation that they will attack the prostate tumor.

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The technique has been successfully applied in animals and Dr. Medin's group is now experimenting on human cells in culture.

Dr. Josh Silvertown, in Dr. Medin's laboratory, is exploring another potential treatment method involving the hormone H2-relaxin. This is a reproductive hormone predominately produced in the ovaries of women but is also produced in the male prostate. Since cancers can be sensitive to hormones, Dr. Silvertown decided to determine whether H2-relaxin had any influence on prostate tumor development.

In his study, human prostate cancer tumors producing extra H2-relaxin hormone were implanted into immuno-deficient mice. Mice producing more H2 had larger and faster growing tumors. It is hypothesized that H2-relaxin stimulated the tumors to grow blood vessels. The increased blood flow resulting from the development of extra blood vessels is thought to have supplied more nutrients to the tumors, hence encouraging and stimulating growth.

Now that a link between H2-relaxin and tumor growth has been established, along with the potential mechanism showing how tumor growth is encouraged, follow-up studies are currently being conducted to see how the tumors are affected when H2-relaxin is blocked.

Preventing Osteoporosis in Men Undergoing Hormonal Therapy



PATIENT RECEIVING A BONE DENSITY TEST

Dr. Shabbir Alibhai feels that evidence based guidelines are needed to help doctors deal effectively with the prevention of osteoporosis (OP) in men receiving androgen deprivation therapy (ADT) for their prostate cancer. Long-term use of ADT is associated with a loss of bone mineral density and an increased risk of fractures, but few guidelines exist for the prevention and management of OP.

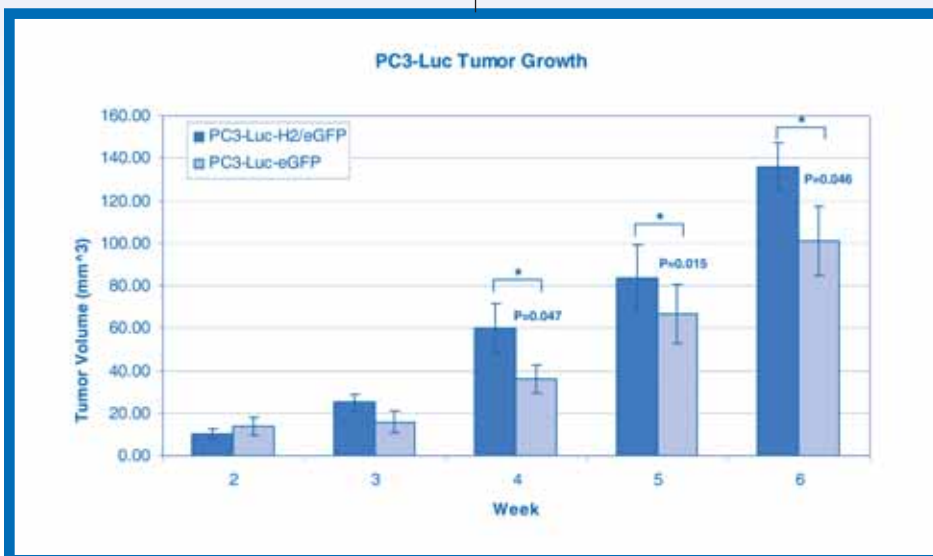
As current practices by doctors were not known, Dr. Alibhai sent out questionnaires to 312 Canadian urologists and radiation oncologists. The survey was designed to find out about the use of bone mineral density testing for men beginning ADT, the treatment options, referral patterns, and the oncologists' perceptions of the patient risk of developing OP.

Preliminary results of the survey were presented at the first international

prostate cancer symposium recently held in Orlando, Florida. Almost half of the surveys (46%) had been returned at that point, and it was found that only 13% of doctors would obtain a baseline bone mineral density for their patients. Furthermore, less than one third would order this test after starting ADT if the baseline bone density test was normal or unknown. In cases where the baseline bone density indicated OP, more than two thirds of the oncologists would order testing.

For men with normal bone densities starting ADT, the surveys indicated that doctors recommended weight bearing exercises (58%), calcium supplements (50%), vitamin D supplements (47%), and bisphosphonate drugs as a preventative tactics (6%). For men identified as having OP at the start of ADT therapy, use of non-prescription therapies increased only slightly, but the use of bisphosphonate drugs increased to 44%.

This is the first survey to examine physician practices related to the prevention of OP in patients receiving ADT. Based on the survey results, Dr. Alibhai recommends the establishment of practice guidelines. This recommendation is based on the observation that few doctors order baseline bone density tests in healthy men and few doctors would prescribe prescription OP preventative medications, despite the fact that half would consider prescribing drugs to treat existing OP in men starting ADT. Guidelines are necessary as there is wide variation in doctors' perceptions of the risk of developing OP secondary to ADT.



TUMORS OVEREXPRESSING H2-RELAXIN (IN BLUE) HAVE AN INCREASED TUMOR VOLUME STARTING AT WEEK 4 UNTIL THE END OF THE STUDY AT WEEK 6

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and in forging new scientific initiatives to prevent and treat these diseases.

The Centre, although multidisciplinary in focus, is organizationally divided into several working groups. They include Radiation Oncology, Surgical Oncology, Medical Oncology, Psychosocial Oncology, and a newly formed Preventive Oncology group. These activities are closely linked to a prostate-directed basic and translational science program funded by The Princess Margaret Hospital Foundation.

Brachytherapy:

A WELL TOLERATED AND EFFECTIVE OPTION FOR EARLY STAGE PROSTATE CANCER

Brachytherapy is a popular and highly effective treatment for men with early stage prostate cancer and a favorable prognosis. Available at Princess Margaret Hospital since 1999, the treatment involves placing radioactive iodine 125 directly into the prostate so that the radiation is more effectively targeted against the malignant tissue and less damaging to the surrounding healthy tissue.

509 men have undergone this treatment from the time it began in March 1999 to February 2004. Their average age was 65 years, and 20% of the men had a short course of hormone therapy to shrink the prostate before implantation. The details of the implant were predetermined using trans rectal ultrasound (TRUS) viewing of the prostate and the tumor. The iodine was placed while the patient was under general anesthesia, using TRUS and fluoroscopy for accurate placement. The men were discharged the same day, and returned 1 month later for a CT scan and MRI to verify the quality of the implant.

Urinary function after implant has been evaluated, and long-term results demonstrate no difference from the pre-implant status. Irritative urinary symptoms were resolved in about 6-9 months. Only 16% of the men needed a temporary catheter after the procedure, 1% developed a narrowing of the urethra, and 3% had a mild inflammation of the rectum (1 patient had a moderate inflammation). Only 1 man died of cancer while 10 died from other causes.

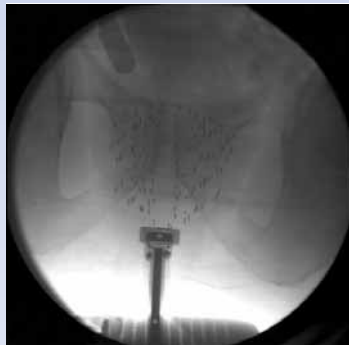
So far, there have only been 7 failures of treatment—including 3 distant occurrences of cancer (bone or lymph nodes), 1 recurrence in the prostate, and 3 increased PSAs. Of the 509 men treated, 259 have been followed for more than 30 months since implant: their mean PSAs are 0.3, 0.18, 0.06, and <0.05 at 30, 36, 48, and 60 months respectively.

About one third of the men experienced what is referred to as a PSA bounce. This is a temporary rise in the PSA followed by a spontaneous decrease without any additional treatment. It usually occurs between 12-36 months post implant and can last for about 8 months.

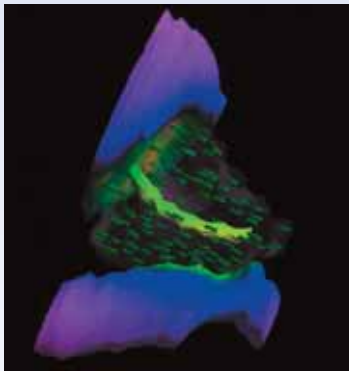
Before their brachytherapy treatment, 85% of the men reported that they were potent and 16% used erectile dysfunction (ED) drugs like Viagra. At follow up averaging 19 months post implant and extending out to 5 years, 85% of the men who were potent before treatment still reported satisfactory potency. During this time, ED drug use had increased to 34%, and for men whose

time since treatment was 3 years or more, ED drug use had increased to approximately 65% and was considered effective.

Brachytherapy is very well tolerated and effective for treating early stage prostate cancer. When compared to radical prostatectomy however, there is a longer period of uncertainty while the men and their families wait for the radiation to work. It often takes 4-5 years for PSA to reach undetectable levels.



FLOUROSCOPY PICTURE INTRA-OPERATIVELY OF COMPLETED IMPLANT

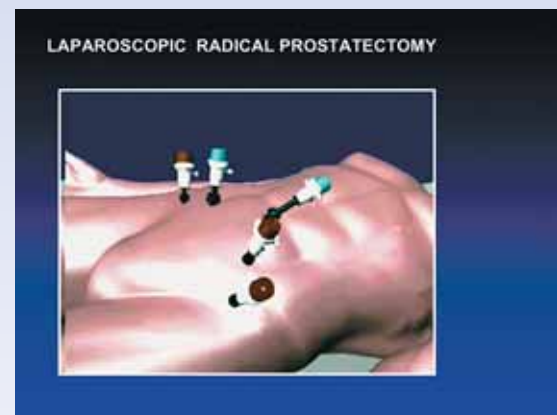


ONE MONTH EVALUATION SHOWING SEEDS IN PROSTATE. (BLADDER AND RECTUM, ARE SHOWN ABOVE AND BELOW).

Radical Prostatectomy:

SURGICAL OPTIONS AVAILABLE

Patients at Princess Margaret who require a radical prostatectomy now have a choice between the conventional open technique, and the minimally invasive laparoscopic procedure (LRP), which is considered to be one of the most technically advanced laparoscopic procedures available. The laparoscopic procedure involves placing a needle into the abdomen at the navel, and infusing the abdomen with carbon dioxide in order to create a working space. Surgical instruments are then inserted at other points into the abdomen (see diagram). The surgeon then proceeds in a similar fashion as in an open procedure.



The surgeon at PMH who is currently performing LRP prostatectomies, Dr. Tony Finelli, reports that the operation takes about 3 1/2 hours to complete and is slightly longer than the open technique. On average blood loss is 300 ml (less than a can of soda) and less than 1% of patients require a transfusion. Other benefits of this surgery are diminished pain (most patients do not require morphine), diminished length of stay in hospital (an average of 1-2 days only), diminished time to catheter removal (7 days), and a lower rate of bladder neck stricture or contracture. In experienced hands, results with LRP are equivalent to open surgery in respect to surgical margin rates, continence, and potency.

According to Dr. Finelli, open radical prostatectomy has also improved

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Vitamin E May Reduce Risk Of Prostate Cancer

BUT EXERCISE CAUTION WHEN TAKING SUPPLEMENTS

Vitamin E supplements are currently receiving a great deal of attention in the news as scientific studies have now indicated that they may increase the risk of heart failure. Many people take vitamin E and other supplements in the hope that they will strengthen their immune system and help to prevent diseases like cancer. Some health care professionals recommend vitamin E supplements for their antioxidant properties. Antioxidants reduce the damage from free radicals in the body. Free radicals are highly reactive chemicals that attack molecules by capturing electrons and damaging cells. In short, it is widely believed that supplementing with vitamin E (alone or in combination with other antioxidants like selenium and lycopene) reduces the risk of cancer.

Men concerned about prostate cancer prevention may wish to incorporate vitamin E into their dietary routine, but should be aware of the potential benefits and problems associated with taking these supplements.

The first study to identify a potential

role for vitamin E in the prevention of prostate cancer was conducted in 1998. In this study the effects of vitamin E and Beta Carotene on lung cancer were examined in more than 29,000 male smokers.

Although no relationship was identified between vitamin E and the prevention of lung cancer, the scientists did observe reductions in both the risk of and death from prostate cancer. Men taking 50 mg (or approximately 110 IUs) of vitamin E daily for 5-8 years were 32% less likely to be diagnosed with prostate cancer. Additionally, men diagnosed with prostate cancer while taking vitamin E

Vitamin E is not advisable for men with pre-existing heart conditions or diabetes mellitus.

The findings of the lung cancer study also led to the development of the Selenium and Vitamin E Cancer Prevention Trial (SELECT). This clinical trial was designed with the hope of discovering methods of preventing the onset of prostate cancer. SELECT is a multi-centre randomized, controlled trial that is studying the effects of long-term supplementation of vitamin E (400 IU) and/or Selenium (200 mcg) in healthy men.

The controversy regarding the benefit of vitamin E has been generated by studies connecting this supplement to an elevated risk of heart failure. In January of this year, a study reviewing results from 19 different scientific studies suggested that taking supplements of 400 IU or more per day might increase the risk of death. However, the participants in several of the reviewed studies had health conditions such as cardiovascular disease, coronary artery disease, Alzheimer's disease, and Parkinson disease, which may have contributed to the increased risk of death.

More recently, results from the international HOPE-TOO trial have also suggested that patients supplementing with 400 IU of natural vitamin E were at a greater risk of heart failure than patients receiving a placebo. In this study, participants included men with vascular disease or diabetes mellitus. Based on this information, it appears that supplementing with vitamin E is not advisable for men with pre-existing heart conditions or diabetes mellitus.

While lower doses of vitamin E may not be harmful and may reduce risk of prostate cancer, men interested in taking these supplements are advised to consult their family physician. It is important to determine whether an individual has a health condition that may place him at an increased risk for heart problems. Family physicians can also recommend appropriate dosages for individuals who are free of heart problems.



were 41% less likely to die from the disease. These findings prompted health care professionals to recommend vitamin E supplementation to men concerned about prostate cancer.

Since the release of the results from this study, other studies have attempted to replicate the findings of the protective effect of vitamin E against prostate cancer. Dr. Neil Fleshner and colleagues examined the influence of vitamin E on prostate cancer in mice that were injected with human prostate cancer cells. It was determined that tumor growth rates were slowest in mice receiving daily vitamin E. This included mice consuming both normal and high-fat diets.

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greatly over the past few years. This technique had previously been associated with significant morbidity, but contemporary outcomes demonstrate a marked reduction in blood loss, transfusion rates, and length of hospital stay.

However, Dr. Finelli states, "I believe that the long-term results of LRP will be equivalent and possibly superior to open RP." With LRP, the surgeon has the advantage of operating in a magnified bloodless field that facilitates precise dissection, nerve sparing, and reconstruction. Although no head-to-head comparisons of the two techniques have yet to be reported, patients tend to develop a strong preference for one form of treatment over the other.

Each of these two surgical techniques are continuing to be refined, and irrespective of the option patients choose, they can be assured of the hospital's objective of excellent patient outcomes.