

# FOREFRONT

A Prostate Centre Update



Princess Margaret Hospital  
University Health Network



## A Message from Dr. Robert Bristow, Head of the PMH Prostate Program:

“Another issue of the Forefront continues to highlight internationally renowned research in prostate cancer prevention and novel treatments. The work of Dr. Fleshner is important as it may give valuable information and new strategies on how to prevent or delay prostate cancer in patients at high risk for the disease. The clinical trial and precision-guided radiotherapy research of Dr. Catton and his team provides a glimpse into state-of-the-art targeted therapies being developed within PMH as one of the world’s largest radiotherapy centres. Enjoy!”

## Winter 2007

### Inside This Issue

Message From the Head of PMHPP  
[Cover Story](#)

Chemoprevention of  
Prostate Cancer  
[Cover Story](#)

Study examines benefits of  
Hypofractionated Radiotherapy  
[Page Three](#)

**Princess Margaret Hospital has achieved an international reputation as a global leader in the fight against cancer and is considered one of the top five comprehensive cancer treatment and research centres in the world.**

## Chemoprevention of Prostate Cancer



Dr. Neil Fleshner  
Head, Division  
of Urology

Chemoprevention often refers to the use of drugs or dietary factors (e.g., micronutrients) to help prevent cancer growth. Over the past 6 to 7 years, interest in the prevention of prostate cancer has grown dramatically. The value of

chemoprevention has been emphasized in:

- the prevention of new cancer growth and;
- slowing the growth of an existing cancer or minimizing the risk of recurrence after cancer therapy (e.g., radical prostatectomy, radiation).

### Rationale behind the role for chemoprevention

In 2007, according to Canadian Cancer Statistics, prostate cancer continues to be the leading type of cancer diagnosed in Canadian men, with an estimated 22,300 newly diagnosed cases. A diagnosis of prostate cancer may not only affect the lifespan, but also the quality of life

(e.g., sexual and urinary function) of the individual that has been diagnosed.

Genetics are believed to play a role in the risk of prostate cancer, but they alone cannot completely explain the varying incidences of clinically diagnosed prostate cancer around the world.

For example, studies have shown that a large number of undiagnosed tumours are often found post mortem. This prevalence of “latent” prostate cancer increases markedly with age, and although latent or clinically insignificant prostate cancer occurs in large but relatively equal rates in autopsy studies among men in Asian countries and the United States, the rate of *clinically significant* prostate cancer has been documented to be much higher in the United States. This contrasting international pattern for latent versus clinically significant prostate cancer suggests that although initiation factors for prostate cancer may be similar around the

world, promotion and progression factors may differ between countries and reflect unique geographic exposure to external factors that drive tumour aggression.

Furthermore, men living in China and Japan have been shown to have the lowest rates of prostate cancer in the world. However, several studies have shown that Chinese and Japanese immigrants to the United States subsequently acquire increased risk and mortality from prostate cancer when compared to their countrymen that remained in their native countries.

Given that diet and other supplements are external factors that vary among geographic areas and that can change dramatically in migrants, the role of these factors in chemoprevention has been the focus of considerable research interest.

Recent studies have suggested that nutritional supplements and certain drugs may play an important role in the prevention of prostate

...continued on page 2

## Chemoprevention of Prostate Cancer... *continued from page 1*

cancer. One individual who has had extensive involvement and who has spearheaded much of the research in chemoprevention is Dr. Neil Fleshner, Head of the Division of Urology at the Princess Margaret Hospital and University Health Network. Dr. Fleshner was also instrumental in authoring a guide to prostate cancer nutrition entitled "Eating Right for Life", available through the Prostate Centre website: <http://www.prostatecentre.ca>. Dr. Neil Fleshner and his team are currently investigating the potential of certain nutrient



combinations to prevent precancerous cells in the prostate from developing into prostate cancer. They are also examining risk factors to determine their relation to prostate cancer development. Their research may significantly improve the ability to identify risk factors specific to an individual and to target these risk factors through chemoprevention. This clinical approach could prevent prostate cancer or slow its growth to the extent that it may no longer be clinically significant.

### Current research in chemoprevention

At this time, the capacity to prevent prostate cancer involves preventing cancer in men with a family history of prostate cancer and following them closely when they have evidence of pre-cancerous lesions (e.g., PIN), an initially elevated prostatic specific antigen (PSA) value or a rapidly-rising PSA value. The literature suggests that a variety of substances may be beneficial at preventing prostate cancer and many of these are actively being studied in pre-clinical and clinical settings. Certain chemopreventative substances are showing potential and work through different biological mechanisms. They include vitamin E (an antioxidant), selenium, lycopene, soy, dutasteride (a prescription medication – e.g., "Avodart") and finasteride (a prescription medication, e.g., "Proscar"). For example, in animal models, the combination of vitamin E, selenium and lycopene has been shown to be effective in preventing the growth of prostate tumours. However, with all the potential chemopreventative agents, more conclusive evidence of their effectiveness and safety (e.g., there is some concern regarding the use of very high doses of antioxidants) awaits the results of several ongoing major chemoprevention clinical trials.

### Selected studies that Dr. Fleshner and his team are involved with include:

1. Collaborative efforts with Dr. Robert Bristow demonstrating the effects of chemoprevention agents on the response to radiotherapy and determining when chemoprevention should be resumed after completion of radiation treatments.
2. Whether pre-surgical exposure of men to vitamin E, selenium and lycopene will slow cancer cell growth and lead to better surgical results.
3. Investigation of whether dutasteride, a 5 alpha reductase inhibitor, will be able to delay the progression of low-risk prostate cancer or extend the time before starting aggressive therapy. A clinical trial (also known as the REDEEM trial) will observe three hundred participants (designated for expectant management with biopsy-

proven, low-risk, localized prostate cancer) who will be exposed to either dutasteride or placebo for 3 years. These participants will be followed to observe time-to-disease progression (i.e., time elapsed until primary therapy for prostate cancer or pathologic progression), number of positive biopsy cores, change in Gleason score, and Quality of Life (QOL) assessments. Since PSA is an important monitoring tool in expectant management that may impact patients' comfort levels, PSA values will be provided to physicians and subjects over the course of the study, scheduled to be completed in 2010. It is hoped that this REDEEM study will evaluate the potential for dutasteride to delay disease progression in men with low-risk prostate cancer and better define which patients with prostate cancer can be managed with less invasive and debilitating therapies.



## Chemoprevention of Prostate Cancer... *continued from page 2*

A study that Dr. Fleshner is particularly proud of is a large cross-Canada clinical trial that is currently in its final analysis. This was a double-blinded, placebo-controlled, randomized study of a nutritional supplement (containing soy protein, vitamin E and a mineral called selenium) in patients with high-grade prostatic intraepithelial neoplasia (PIN), a precancerous prostate cell condition. Over 300 men with biopsy-confirmed PIN from 16 different hospitals were participants, as of July 2000. They were randomly assigned to receive either the nutritional supplement or an inactive powder that looked and tasted the same, and they endured additional biopsies at 6, 12, 24 and 36 months in order to monitor their conditions. All the men were monitored for three years for the development of prostate cancer. The trial will determine if patients who took the nutritional supplement developed fewer cancers.

### Future directions

After determining which chemopreventative agents are effective and understanding how they function, the next logical step will be to identify men in whom these agents will make a positive impact. In addition, through this research, identifying individuals at higher risk of prostate cancer and especially those at higher risk of aggressive prostate cancer will enable the clinician to individualize the prognosis of prostate cancer in each patient and to subsequently tailor an effective nutritional or supplemental approach to complement current treatments.

In the meantime, amidst these exciting developments, healthy caution should be exercised while awaiting the definitive results of the large clinical studies. It is extremely important to be mindful of the fact that chemoprevention is still currently viewed by physicians as a form of “complementary” versus “alternative”

therapy. It is also crucial that individuals interested in pursuing options in chemoprevention should consult with their treating physicians.

With the generosity of participants who donate their time and their dedication to clinical research trials, it is hoped that the study of chemoprevention will one day lead to more targeted treatments, to the prevention or delay of clinically significant cancers, to minimizing the invasive and morbid nature of conventional therapies, and to increasing the survival and the quality of life of those men diagnosed with prostate cancer.



## Study examines benefits of Hypofractionated Radiotherapy



Dr. Charles Catton  
GU site leader,  
Department of  
Radiation Oncology

Clinicians and researchers are constantly looking for ways to improve the treatment options available to patients diagnosed with prostate cancer. One of the areas that the team at the Prostate Centre at Princess Margaret Hospital is currently investigating is hypofractionated image guided intensity modulated radiotherapy.

### Leveraging technology

The traditional way of delivering external beam radiation is to break it down into small fragments called fractions, which are then administered over several weeks – usually six to eight. One of the goals of external beam radiation is to direct it as precisely as possible onto the tumour in the prostate while avoiding the rectum and the bladder. This approach not only maximizes the effectiveness of the therapy in eradicating the cancer, but also minimizes the side effects on the surrounding tissue.

Over time, technological advances have enabled us to improve the accuracy of the radiation delivery, and this has allowed us to give more radiation over more weeks. The resulting benefit, of course,

is an increased effectiveness in the treatment overall. However, the corresponding disadvantage is that the longer treatment period is more of a burden – on both the patient and the health care system at large.

To address this issue, a team of researchers recently undertook a study that examined the possibility of leveraging these advances to compress the traditional eight-week course of treatment into a shorter period of time. In other words, by relying on the technology, can we give more radiation in a fewer number of total increments, and have the treatment over and done with sooner?

### The study

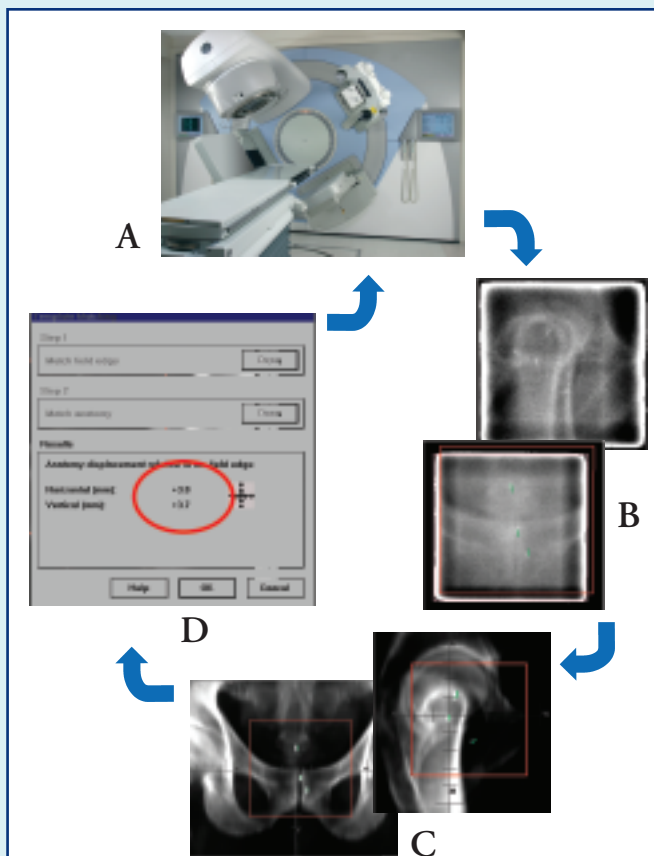
Between June 2001 and March 2004, 92 patients were treated with hypofractionated radiotherapy (HypoRT), receiving 60Gy in 20 fractions over four weeks – half of the traditional eight-week course. The group had a median Prostate Specific Antigen (PSA) of 7.06 and the majority had Gleason grade 5-6 or 7. Overall, 29 patients had low risk disease, 56 intermediate risk, and seven high risk.

The success of this Phase 2 study of the effects of HypoRT depended, in part, on maximizing the accuracy of the delivery of

...continued on page 4

the radiation – because more radiation was being given in fewer number of days, every treatment counted and not a single day could be lost to the radiation missing its target.

The team adopted two techniques to improve the accuracy of the radiation administration on the study participants. The first involved inserting gold seeds into the prostate using a needle under ultrasound guidance. These fiducial markers were visualized online every day immediately before treatment to ensure proper targeting of the radiation (*Figure 1*).

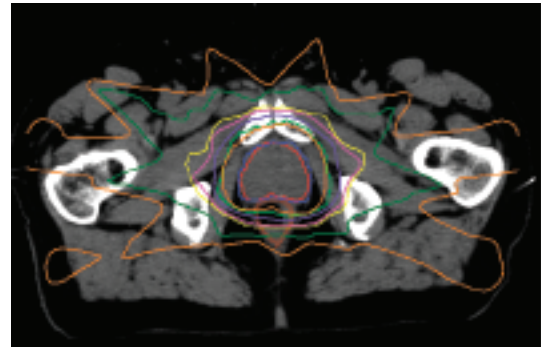


**Figure 1: Image guided radiotherapy**

The treatment unit (A) creates an image of the implanted gold seeds (B), which are then matched to reference images (C). The mismatch is calculated automatically (D), and corrections are then made before treatment starts.

The team also took advantage of the benefits inherent in Intensity Modulated Radiation Therapy (IMRT), a process that allows therapists to direct the radiation beams in a certain shape – in this case, that of the prostate gland (*Figure 2*). Using this image guided

IMRT, volunteers underwent treatment using radiation beams shaped like the prostate and directed precisely onto the gland over the four-week period.



**Figure 2: An IMRT treatment plan for prostate cancer**

The highest dose radiation region shown in blue is conformed very closely to the outline of the prostate shown in red.

Patients who participated in the study were monitored for outcomes and side effects throughout the treatment and for an average of 38 months afterwards. The side effects experienced by participants were very modest in terms of late bladder and rectal toxicity and were therefore in line with the lowest side effects reported for traditional prostate radiation. Similarly, the patients’ outcomes – as measured by the rate of biochemical control – were in keeping with what would be expected with an eight-week course of radiation.

### Encouraging results

These results are very encouraging as they indicate that patients may be able to undergo treatment for prostate cancer using HypoRT in combination with image-guided IMRT and experience the same results in half the time as compared to traditional radiation. This will result in a strategy for treatment that will be more convenient and more cost-effective – not only for patients but for the health care system.

Since the conclusion of this Phase 2 proof of principle study, the team is going on to a Phase 3 study which will involve testing the efficacy of the four-week HypoRT treatment against the traditional eight-week treatment. This controlled, multi-centre, international study will take place over several years and will eventually involve 1,200 participants. We will keep you posted on the progress of this next phase.