

FOREFRONT

A Prostate Centre Update



Princess Margaret Hospital
University Health Network



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

“The PMH Prostate Cancer Program continues to support leading edge prostate cancer treatment and research. In this issue of the Forefront, Dr. Tony Finelli explains the latest laparoscopic and robotic approaches to surgery for prostate cancer, which may reduce side-effects and the length of hospital stay. In another story, Dr. Michael Milosevic describes how identifying low oxygen levels in prostate cancers may lead to new ways to predict the behaviour and treatment of the most aggressive prostate cancers.”

The Prostate Centre cycles forward: congratulations to the numerous Prostate Centre staff members riding in the Princess Margaret Hospital Foundation’s Ride to Conquer Cancer.

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Embracing new technology in prostate cancer surgery



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While dealing with a prostate cancer diagnosis is difficult, the process of investigating and deciding on the most appropriate treatment option can make that difficult experience even more stressful.

For instance, in choosing a surgical technique, there are many issues to consider and ultimately, the decision is a personal one. Should the patient proceed with the latest and greatest technology or go with a tried and true approach? Of course, the primary concern will be to ensure the treatment is as effective as possible in controlling the cancer. Continued potency and continence are also critical. But what about the length of the hospital stay, the potential blood loss, and how long it will take for a return to normal activities?

Each of these factors – and others – may play a role in the decision-making process.

As a result, choosing the most appropriate from a range of options can be confusing for patients. That’s why it’s best to gather as much information as possible about the alternatives before deciding.

Laparoscopic Radical Prostatectomy (LRP) and Robot Assisted Laparoscopic Radical Prostatectomy (RALRP) are two of the surgical treatment choices prostate cancer patients currently have. In an effort to help educate patients and make sure they’re as informed as possible prior to making a decision about their treatment options, clinicians at Princess Margaret Hospital have been examining these two relatively new surgical techniques to determine their efficacy as well as the impact they may have on patient outcomes, on wait times, and on prostate cancer treatment in general.

The procedures

The conventional open surgery for a radical prostatectomy requires the surgeon to make a 10 cm midline incision in the patient’s

lower abdomen. The abdominal wall is then retracted to allow exposure and access to the prostate for removal. With the laparoscopic approach, the surgeon gains access to the abdomen and infuses CO₂ gas to distend the abdomen and create space. A series of five 5-10 mm incisions are then made and ports introduced (Figure 1). The benefits of this method include enhanced visualization through a magnified view as well as a relatively bloodless field.

Robot Assisted Laparoscopic Radical Prostatectomy is essentially an LRP with the added advantage of robotics. With this approach, a robot – developed by the company Intuitive Surgical and named *da Vinci*[®] Surgical System – holds on to the instruments that are inserted through the five ports. The surgeon sits at a console several feet away and controls the movement of the arms inside the patient remotely.

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Proponents of RALRP appreciate the depth perception the approach affords, as well as the tremor filtration that reduces the amount of movement in the instruments and the degrees of freedom available through the *EndoWrist*® technology that allows the robotic wrist to rotate fully. Plus, surgeons are generally more comfortable sitting at the console than standing throughout the operation. However, as with any procedure, there are drawbacks associated with RALRP as well. For instance, tactile feedback is virtually non-existent in RALRP, making it more difficult for the surgeon to perceive tissue resistance and trauma. In addition, some educators have expressed concern about a consequent over-reliance on technology and question whether more recent graduates would be able to perform the traditional open operation in the event of a technology failure.

Overall, however, when considering the effectiveness of one approach over another – from the perspective of both the patient and the health care system – surgeon experience remains an overwhelmingly important factor.

Examining the implications

Any time a new surgical technique is introduced, there are several issues to be considered: What impact will it have on patient outcomes? How much of a hospital's resources will it consume? And what effect will it have on wait times for treatment?

Regardless of the surgeon's experience, the initial LRP and RALRP procedures he or she performs will take longer than the conventional open operation – and that means fewer patients can be treated until the surgeon becomes efficient in the new technique. Plus, working with the latest technology often involves additional and/or disposable equipment, and this use of resources is particularly relevant in a universal health care system like the one we have in Canada. Finally, there is a learning curve associated with most new

techniques and studies suggest that a surgeon's results plateau after he or she performs 200-250 radical prostatectomies. Statistics like these can pose a dilemma to surgeons who are keen to maintain excellent patient outcomes while performing a procedure that is new to them.

But does that mean surgeons and their hospitals should shy away from the new technology? Not at all. In fact, RALRP is being performed in North America and worldwide with greater frequency and there is evidence to suggest that there are advantages with this approach. However, a head-to-head controlled study comparing outcomes of patients who underwent a RALRP to those of patients who underwent an LRP or the open operation has never been undertaken. And as researchers at Princess Margaret Hospital recently discovered, conducting such a trial would be very challenging.

Dr. Tony Finelli and a team of Princess Margaret Hospital clinicians conducted a survey of their Canadian and American urologic colleagues to determine what they feel are clinically significant differences in outcomes. In other words, what aspects of a patient's outcome must

be considered (e.g. length of procedure, amount of blood loss, length of hospital stay) and how extensive does the difference have to be in order for it to be considered significant? After polling these specialists across North America and asking what type of clinical significance would determine whether one surgical technique was more effective than another, it became clear that undertaking a trial to compare outcomes under the various techniques and to demonstrate what is clinically relevant on statistical grounds would require thousands of volunteer men – rendering the likelihood of the study actually taking place impractical at best and impossible at worst.

Where does this leave us? While there appear to be advantages to RALRP, issues of feasibility will prevent us from confirming those benefits in a trial setting. Though it may not be clearly superior at this point, RALRP is definitely the way of the future. Rather than resist the changes that technology inevitably brings, we must embrace it, strive to validate its purported advantages, and continue to improve on the existing platform to realize better outcomes in prostate cancer care.



Figure 1. Laparoscopic Radical Prostatectomy

Investigating the effect of oxygen levels in prostate cancer



Dr. Michael Milosevic
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Prostate cancer is the most common form of cancer among North American men: In 2008 alone, an estimated 24,700 Canadian men will be diagnosed with the disease. Though

much progress has been made in understanding the intricacies of prostate cancer, many questions remain to be explored. Currently, Dr. Michael Milosevic and a team of researchers at Princess Margaret Hospital are working to learn more about the effect the level of oxygen in prostate cancer has on how these tumours behave and react to treatment.

Does the microenvironment matter?

Clinicians have known for many years that a number of factors come into play when trying to determine how a malignant tumour is going to behave. That is, will the cancer cells spread or stay local? How aggressive will they be? Will they be resistant to treatment like radiation, chemotherapy, and hormonal therapy? Until recently, investigations into these questions have focused primarily on the cancer cells themselves and genetic mutations. However, scientists are now discovering that the microenvironment of the cells – including stromal elements and blood vessels – may also be relevant and have a significant role to play in both recommending treatments and predicting outcomes.

In particular, a team of researchers from Princess Margaret Hospital and the

University of Toronto has been examining the connection between the oxygenation levels in tumours and patients' response to treatment and their ultimate outcomes. Hypoxia – or low oxygenation levels – in tumours has been identified in a range of human cancers, including cervical and head-and-neck, and has been shown to determine which genes get switched on or off, with the resulting genetic instability influencing the behaviour of tumour cells. As a result, links have been found between the degree of hypoxia and the recurrence and spread of those cancers.

Now, hypoxia is starting to emerge as an important factor in prostate cancer as well and researchers are exploring not only the extent of its relevance, but also how to translate what they learn into practical information that can improve patients' response to treatment as well as their outcomes.

The hypoxia connection

As part of the recent body of research, clinical-translational investigators at Princess Margaret Hospital studied approximately 300 men who had been diagnosed with a localized tumour in their prostate. Before these patients began their radiation treatment, oxygen level measurements were taken in a series of locations throughout the prostate gland using a special electrode process.

Many of the prostate tumours that were tested contained low levels of oxygen. The results from this study are significant primarily because they establish that hypoxia is present in many men who have been diagnosed with prostate cancer. Interestingly, the study

results also revealed that the hypoxia was at times present in regions of the prostate gland that did not contain cancer.

Though still speculative at this point, this may be relevant to our continued quest to understand prostate cancer evolution and development, and the role played by altered gene expression.

The men who participated in this study are in the process of being followed and monitored for five years post-radiotherapy to determine whether hypoxia influences the rates of recurrence, metastasis, and survival. Those data could prove invaluable in our bid to better manage cancer treatment in general – whether chemotherapy, surgery, radiation, hormonal therapy, or a combination thereof.

Angiogenesis and androgens

This ever-expanding body of research is also looking at angiogenesis in prostate tumours and its connection to hypoxia. Angiogenesis is the growth of new blood vessels, and it occurs in both healthy and cancerous tissue. Angiogenesis in normal tissue performs functions like promoting healing and takes place in an organized, efficient fashion. However, in cancerous tissue, the process looks quite different. As tumours grow, they require a source of nutrients. As a result, they induce a blood supply to grow and they draw in blood vessels from whatever tissue they're already growing in. This angiogenesis is far from organized. Instead, it's chaotic – the blood vessels that form are full of holes and are very inefficient. Because these vessels are not doing their job properly, the oxygen the tumour needs to grow does not reach the cells, making

them hypoxic. This hypoxia, in turn, may stimulate further angiogenesis.

A growing body of evidence suggests that the presence of androgens (such as testosterone) may promote this angiogenesis-hypoxia cycle (Figure 1). The flipside, then, is to determine whether androgen withdrawal – through medical or surgical castration – can initiate an antiangiogenic response and a subsequent reduction in prostate cell hypoxia.

To that end, a subset of the study cohort of 300 men was treated with the androgen antagonist bicalutamide prior to radiation. Their oxygen levels were measured both before and after 30 to 145 days of being given the castrating drug. These measurements were noteworthy as they revealed that there was a significant reduction in tumour hypoxia with androgen withdrawal. These patients are also being followed for five years to determine whether there's a connection between the reduction in hypoxia and long-term outcomes.

Looking ahead

These new findings are important on several fronts and provide a solid foundation for further investigations moving forward. First, they offer some insight into the behaviour of tumours in individual patients. For instance, two patients might present with the exact same PSA levels, Gleason scores, and staging, but experience very different responses to treatment and outcomes. Developing a better understanding of the underlying biology of the tumour may

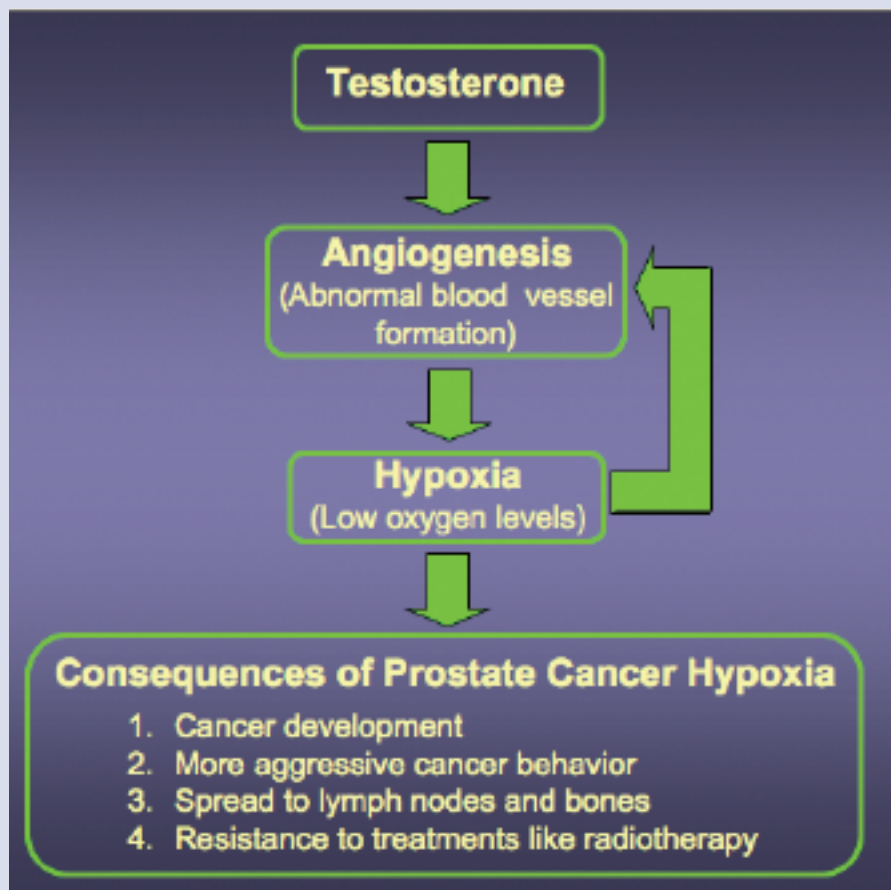


Figure 1. The angiogenesis-hypoxia cycle and related consequences of prostate cancer hypoxia.

help explain those differences. Clinicians will then be better equipped to customize the course of treatment that will be most effective for each patient. Second, if markers like hypoxia levels can help physicians predict whether, for instance, a patient is likely to have a recurrence of the disease, then attempts can be made to change the characteristics of the tumour before treatment is even started. That way, it may be possible to improve both the efficacy of the treatment and the patient's outcome. For example, by determining what induces

hypoxia in the cancer cells, drugs to target the hypoxia could be administered to offset it. Or, perhaps if the hypoxic region of the tumour can be identified, the radiation prescription could be tailored so that a higher dose is delivered to that particular region.

Though these approaches are still speculative, there remains enormous potential for advancements in treatment and improvements in outcomes. As more results become available, they will be featured in future editions of *Forefront*.