NanoKnife© IRE

FOCAL ABLATION OF THE PROSTATE

Introduction

Prostate cancer is one of the most commonly diagnosed cancers in men. It is now recognised that some cancers are "insignificant" (do not pose a threat to the patient even in the long term usually Gleason 6), whilst other patients with prostate cancer have "significant" cancers (these pose a threat to the patient in the intermediate to long term, generally > Gleason 6). The majority of men diagnosed with a low grade prostate cancer or an "insignificant cancer" (e.g. Gleason 6) live without symptoms and without it spreading and becoming life threatening. These patients are monitored on an active surveillance program with regular PSA testing, MRI and the occasional biopsy. Whilst other men with prostate cancer have a "significant cancer" that pose a threat in the intermediate or long term and do require treatment such as surgery or radiotherapy or occasionally even a combination of both.

Most cancers of the prostate are what we call multi-focal. This means that the cancer involves several areas of the prostate and therefore require therapy that treats the whole prostate or what is called whole gland therapy. Increasingly, there is evidence that there is a subgroup of patients who have prostate cancer where only a small area of the prostate is occupied by a significant cancer which does not require whole gland therapy but only the cancerous area to be treated and leave the rest of the prostate alone (similar to a lumpectomy in breast cancer). This would have the benefit of a simpler procedure, less complications and less side effects. Urologists are still determining how to decide who is suitable for such focal therapy and what the best follow-up is for these patients should they undergo this treatment.

Potential Energy Sources For Focal Therapy

Focal therapy involves the destruction of the small area of localised cancer and the preservation of the rest of the prostate. Focal therapy has become possible because of improved assessment of the prostate with imaging such as multiparametric MRI and thorough biopsy sampling often with transperineal template biopsying techniques.

The various forms of focal therapy include cryotherapy (freezing), high-intensity focused ultrasound (HIFU), laser ablation, TOOKAD (light stimulated destruction of tumour), focal brachytherapy using radioactive seeds and irreversible electroporation (NanoKnife therapy). All of these treatments aim to destroy the significant localised prostate cancer and a margin of tissue around it, sometimes incorporating half of the prostate but preserving the rest of the prostate. Each of these energy sources have their benefits and disadvantages.

What Is Focal NanoKnife© IRE Ablation?

NanoKnife© IRE (irreversible electroporation) focal ablation is the use of high-powered pulsed electricity to destroy the small section of the prostate involved with the cancer. As with all other forms of focal therapy, it aims to preserve the remainder of the prostate decreasing treatment side effects such as impotence and incontinence. As it does not rely on heat or freezing it has the unique potential to preserve adjacent structures thus improving the likelihood of preservation of continence and potency.

NanoKnife or irreversible electroporation was developed in 2007 by a team of biomedical engineers in Virginia Technikon and the University of California in Berkeley. It was FDA approved in 2008 and has been used around the world to treat liver, kidney, pancreas and more recently prostate cancer. It is especially useful in liver and pancreatic tumours that are deemed inoperable and in prostate cancer tumours which cannot be reached by other minimally invasive techniques (such as HIFU) or in certain salvage cases (where previous treatment has taken place) and more recently in all focal prostate cancer cases.

The NanoKnife uses an electrical field that can be precisely targeted to create tiny holes in tumour cells while not affecting adjacent organs. Ultra-precision allows treatment of particular areas within the prostate that are difficult to reach by other minimally invasive techniques. Better treatment appears to be produced in small tumours. It has the particular benefit that it does not rely on heat or freezing to destroy tissue but relies on the electrical current.

What Are The Risks And Benefits Of Focal NanoKnife© IRE Therapy?

As with all focal therapies there are less side effects compared to radical prostatectomy surgery and radiotherapy. In particular there is a much lower chance of incontinence, impotence, bowel damage and other complications often associated with surgery or radiotherapy. The treatment is much simpler to perform and is generally performed as a day only procedure.

The particular advantages of NanoKnife therapy over other energy sources appears to be its non-reliance on thermal energy therefore its relative preservation of adjacent structures such as the erection nerves and the urethra.

Other advantages of focal NanoKnife is that it can be repeated, that it does not rely on heat or freezing and that it appears to have less effect on nerve tissue than all the other modalities.

The disadvantages of all focal therapy programs including NanoKnife therapy is that there is no long-term data on cancer outcomes and it requires much closer follow up. Guidelines are still being currently developed to correctly select the right patients for focal therapy treatments and as such there is always a risk that the cancer will reappear in another part of the prostate. Consensus papers how now been published to guide patient selection . In our St Vincent's program this has occurred in less than 20% of the patients treated to date. Also there is a theoretical concern that if subsequent surgery is required, the previous focal therapy may make that surgery more difficult. To date this has not been borne out in the 22 cases we have performed (out of 400 cases).

Who Is Suitable For Focal NanoKnife© IRE?

Ideal patients are those where less than a quarter of the prostate is involved with a significant prostate cancer as evidenced by an MRI and biopsies where there is good co-registration between the two modalities. The tumour is preferably visible on the MRI or on PSMA Pet/Ct Scanning so that the correct area can be targeted during the treatment. As it is in its early stages of development without long-term follow-up, it is generally reserved for an older group of people, preferably over 60 years of age. Furthermore as it only treats the prostate and not any of the regional lymph glands, it is generally reserved for intermediate grade or Gleason 7 tumours (3+4 or 4+3).

All patients must have had a thorough saturation biopsy as well as a targeted biopsy and a high quality multiparametric MRI performed. Sometimes a PSMA Pet Scan is also used .These must confirm that there is a significant prostate cancer (generally Gleason 7 tumour) that is limited to at most, a half of the prostate and preferably less than an eighth of the prostate. Professor Stricker feels that between 10 to 20% of patients with significant prostate cancer may be suitable for this program. No patients with Gleason 9 and 10 are accepted.

Patients must give a full and informed consent which includes the understanding there are no long-term results and that currently it is not a standard of care treatment such as surgery and radiotherapy. Internationally, focal NanoKnife therapy has only been used in the last 10 years. Other energy forms such as focal cryotherapy and HIFU have been used for 10 to 20 years.

Can Focal NanoKnife Ablation be used after previous failed radiotherapy?

To date Professor Stricker has treated approximately 80 patients with NanoKnife therapy following failed radiotherapy. Once again this is only suitable in selected patients with the extent of the tumour and Gleason score taken into consideration. The procedure is the same as for the standard NanoKnife focal ablation. This is a particularly unique group of patients as further treatment options of the prostate are very limited. A multicentre international trial (FIRE study) investigating 40 patients in this group commenced under Professor Stricker in 2017 is now completed and is submitted for publication.

The Procedure

The procedure is done under a general anaesthetic and takes approximately 45minutes to perform. Four to six electrodes are placed through the skin behind the scrotum (the perineum) into the prostate under ultrasound guidance. A pulsed high energy electricity current is then passed sequentially between each of the electrodes enabling the area of prostate mapped out to be destroyed. The extent of the treatment depends on the results of the MRI and biopsies but will always incorporate at least a 1 cm safety margin around the cancer. The electrodes are also placed to avoid damage to adjacent structures. You can google Professor Stricker's video of the procedure on doi.org/10.1016/j.jvir.2016.01.003.

Occasionally if a patient has pre-existing urinary symptoms such as a slow flow, it may be necessary for Professor Stricker to remove some of the benign prostate tissue that is obstructing the urinary tract at the same time as the NanoKnife procedure. If this is the case then this will require an overnight stay in hospital. This will be decided at the time of your prior consultation with Professor Stricker.

What Preparation Do I Need Before The Procedure?

❖ Informed consent. This includes a discussion with Professor Stricker regarding the procedure, oncological outcomes such as tumour clearance/eradication and recurrence, ongoing follow up as well as functional outcomes such as erectile dysfunction and urinary incontinence and retrograde ejaculation

❖ A general health assessment may sometimes be required if you have any pre-existing medical conditions. Please inform Professor Stricker of these at your consultation.

❖ The bowel must be emptied within 12 hours of the procedure. Use 2 Durolax suppositories (available at the Pharmacy) at 4 pm on the day prior to your procedure. If you do not open your bowels please inform the nursing staff on your admission to hospital and a small enema maybe required prior to your procedure.

❖ If you have moderate to severe urinary symptoms such as difficulty passing urine, slow flow, hesitancy, frequency or urgency, it is important to inform Professor Stricker as medications such as Flomaxtra or Xatral may need to be commenced before the procedure or alternatively a resection of the obstructing tissue may need to be performed at the time of the NanoKnife treatment to avoid urinary retention post procedure.

❖ Inform Professor Stricker of all your medications (even herbal supplements) particularly blood thinning agents as these may need to be stopped prior to the procedure to minimise bleeding post procedure.

❖ You will be notified by the hospital the day prior to your procedure (Friday if your procedure is on a Monday) of your fasting time. Prior to this there are no dietary requirements.

Post Procedure

Catheter

A catheter will be placed into the bladder at the time of the procedure. This is a hollow tube that is inserted through the opening of the penis which allows urine to drain from the bladder to a bag attached to your leg. You will be instructed on the care and management of your catheter prior to discharge from hospital. The catheter will be left in place for two to five days. The time frame depends on the size and location of area treated, previous radiotherapy and pre-treatment urinary symptoms. Professor Stricker will discuss with you prior to discharge when the catheter is to be removed.

Occasionally you may experience slight leakage from around the catheter near the tip of the penis. This is due to spasm of the bladder due to irritation by the recent procedure and also having a foreign body i.e the catheter in the bladder. If this does occur you may need to wear a small pad in your underclothes. Professor Stricker may commence you on medication (Ditropan) to relax the bladder. This medication must be stopped 24 hours prior to the catheter being removed. Ensure your catheter is securely

taped to your leg to prevent it from pulling (allow a lot of "slack"). This will help to minimise bladder spasm and ensure the catheter is more comfortable when walking. Some men prefer to wear supportive underwear even with the catheter insitu as this may also help to minimise pulling however this is an individual preference. The catheter is generally left in place for 2 to 5 days .

The catheter is removed by Professor Stricker's Clinical Manager Jayne Matthews. Please ring Jayne (8382 6569) on discharge from hospital to arrange a time for the catheter to be removed. It is often recommended that the catheter be removed earlier in the day to ensure that you are passing urine adequately prior to leaving the clinic. If the patient does not live in Sydney then occasionally the catheter may be removed by their GP/Urologist. This would have been previously discussed/arranged with Professor Stricker. However, as an MRI is performed (in Sydney at IMed Radiology) within 5 days following the procedure it is recommended that the catheter be removed in Sydney.

Approximately 5-10% of patients are unable to pass urine on removal of the catheter and require recatheterisation for a further two to five days to allow any swelling in the prostate to subside. Medications called alpha blockers (Xatral or Flomaxtra) may be commenced to ensure that there will be no difficulty passing urine after the procedure and following the removal of the catheter.

Will I experience pain after the procedure?

Some patients may experience discomfort in the prostatic region for two to four hours after procedure. Analgesia will be administered by the nursing staff if you do have this level of discomfort. This discomfort is the response of the body to the inflammation induced by the NanoKnife ablation. This pain always settles but a more minor discomfort can continue for several days. Generally this can be controlled by Panadol or if more severe Targin, an anti inflammatory such as Voltaren or antispasmodic tablets such as Ditropan. If the major discomfort is an urgency to go to the toilet then the antispasmodic Ditropan is best used 5 mg three times a day. If the major discomfort is just a mild pelvic discomfort then Panadol or Voltaren is best used. Ensuring that your catheter id taped correctly without any pulling will also help to minimise discomfort.

Antibiotics

You will be on antibiotics following the procedure and for the duration of your catheter. Please ensure you have these prior to discharge from hospital.

Exercise

Walking is permitted even with the catheter. As the catheter bag is strapped to your leg there is no visible urine bag. Obviously long loose trousers are preferable. Once the catheter is removed you may resume your normal activities. Bike riding should be avoided for 6 weeks as this may cause discomfort and some bleeding.

Sexual Activity

Once the catheter is removed you may resume sexual activity when you feel comfortable. You may notice a decrease or absence in ejaculatory fluid (can be permanent). This is variable and unpredictable and may affect fertility. There may be some blood with orgasm which should settle by 6-8 weeks. Occasionally erections maybe affected by the treatment. Often this is temporary however sexual dysfunction can occur in 10%. The use of Viagra, Cialis or Levitra may help during this time.

Bleeding

It is not uncommon to notice blood in your urine following the procedure. This is often most noticeable at the beginning and end of urinating. Bleeding may take up to 6 weeks to settle completely with the occasional patient noticing it up to 3 months. This may be in patients that a larger area has been ablated.

Travel

If you are live in the country, interstate or overseas it is recommended to stay in Sydney for approximately a week after the procedure unless previously discussed with Professor Stricker. This allows time for catheter removal and follow up MRI as well as if there are any concerns eg with the catheter, that you are nearby.

Follow-up After Focal NanoKnife© IRE Therapy

A preliminary MRI is performed usually within one week following the procedure. This is to ensure that the tumour area has been adequately targeted. The MRI will be arranged by Professor Stricker's office and performed at IMed Radiology (no cost). You will be informed of the result of the MRI by Professor Stricker within 1-2 weeks following the test. This MRI is only for quality assurance and not diagnostic .

An appointment is required six weeks after the procedure. Please ring Professor Stricker's office on 8382 6971 to book the appointment. This may be done via the telephone for patients that live in the country, interstate or overseas.

PSA testing is required following treatment. It is recommended that you have your PSA every three months for the first year and then 6 monthly after that. These are to be arranged by your GP. Ensure copies of the result are always forwarded to Professor Stricker and where possible always have your PSA with the same pathology company to ensure consistency with testing. Remember the PSA with not fall to 0 as only an area of the prostate has been treated. The level of fall of PSA may vary depending on the amount of prostatic tissue that is ablated. On average there is a decrease in PSA level by 2 ngs from the preoperative level

An MRI is required at six months and a prostate biopsy at one year. This is to assess the success of the treatment. These tests will be arranged by Professor Stricker's office. Occasionally these tests are arranged through your local Urologist if you live interstate or overseas. This should be discussed with Professor Stricker as certain instructions may need to be given to the Urologist.

Professor Stricker should review or speak (if interstate or overseas) with you at least once a year. The reason for this is to maintain close follow-up of all PSA readings, functional outcomes, MRI's and biopsies to ensure no new tumours develop. In essence this means you are still on active surveillance for the remainder of the prostate, as having had a tumour in one part of the prostate, this puts you at increased risk of having a new tumour develop in another part of the prostate.

Quality of Life questionnaires will be sent to you periodically (baseline, 6weeks, 3 months, 6 months, 1 year & 2 years) by the prostate cancer research team at the Garvan Institute. It is important that you complete these as this helps to monitor your functional outcomes following treatment as well as monitoring the ongoing success and development of this emerging treatment.

Current Focal NanoKnife© IRE Results

Professor Stricker's results have been published and presented nationally and internationally . Furthermore he now teaches this technology both nationally and internationally . He has treated over 400 patients to date (primary)and has over 15 peer reviewed international publications The maximum follow up is 10 years . In addition, a further 80 patients have been treated after recurrence after previous unsuccessful radiation therapy (salvage).

Current results are as follows:

- Clearance of the targeted tumour: >97%.
- Recurrences outside of the treated area in other areas of the prostate: <20% in the primary group and 10% in the radiotherapy group.
- More serious complications: 0% in primary cases and 10% in the radiotherapy group (majority have resolved with time).
- Rectal Fistula: 0% in the primary cases and 2% in the salvage cases
- Incontinence: 0% in the primary setting (2% temporary) and <10% in the salvage setting
- Impotence: there has been approximately a 10% decline in erectile functioning which is more prominent in the failed radiotherapy group. This may improve and recover to some degree over a 12 month period

❖ Retrograde Ejaculation: this has occurred in up to 20% of cases often developing several months after the procedure

❖ It should be noted that this excludes Professor Stricker's first 20 patients where there was a lesser safety margin around the tumour and lower energy sources used. Since a more appropriate safety margin has been used and better energy parameters during the treatment, results have consistently improved.

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Please note that this patient guide may not cover all aspects of NanoKnife© IRE therapy.

Should you have any queries please contact Professor Stricker's office on 02 8382 6971.

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