

# Irreversible Electroporation for Patients with Localised Prostate Cancer: Expert Opinion on this Versatile Therapeutic Approach

<b>Interviewees:</b>	Olivier Cussenot, <sup>1</sup> Phillip Stricker <sup>2,3,4</sup> <ol style="list-style-type: none"><li>1. Department of Urology, APHP-Sorbonne University, Tenon Hospital, Paris, France</li><li>2. Department of Urology, St Vincent's Private Hospital and Clinic, Sydney, Australia</li><li>3. Garvan Institute of Medical Research, Sydney, Australia</li><li>4. Australian PC Centre, Sydney, Australia</li></ol>
<b>Disclosure:</b>	Cussenot is an expert for INCa (French National Cancer Institute) and ANSES (French Agency for Food, Environmental and Occupational Health & Safety); he performs workshops on irreversible electroporation (IRE) in partnership with AngioDynamics; he is not receiving any grants from AngioDynamics and is not a paid consultant for the company. Stricker received fees from AngioDynamics for consultancy work.
<b>Acknowledgements:</b>	AngioDynamics and NanoKnife are trademarks and/or registered trademarks of AngioDynamics, Inc., an affiliate, or a subsidiary. Medical writing assistance was provided by Jennifer Taylor, London, UK.
<b>Disclaimer:</b>	The opinions expressed in this article belong solely to the named interviewees.
<b>Support:</b>	The publication of this feature interview was supported and reviewed by AngioDynamics.
<b>Citation:</b>	EMJ Urol. 2021;9[1]:56-62.



## Interview Summary

Irreversible electroporation (IRE) is emerging as a new method of soft tissue ablation, with applications including focal therapy in patients with prostate cancer. IRE can be delivered using the NanoKnife system. To better understand the extent to which the technology can be utilised in the treatment of prostate cancer, the EMJ interviewed two leading figures in urology who have extensive experience with the procedure. These were Olivier Cussenot, Head of the Department of Urology, APHP-Sorbonne University, Tenon Hospital, Paris, France, and Phillip Stricker, Chair of the Department of Urology, St Vincent's Private Hospital, and Clinic and Emeritus Fellow, Garvan Institute of Medical Research, Sydney, Australia.

The article begins with an overview of the current treatment options for prostate cancer and the role of focal therapies, including the NanoKnife system in clinical practice. Research on the NanoKnife system was discussed, followed by clinical experience including patient selection, outcomes, and follow-up. Technical aspects were reviewed such as the skill sets required and the nature of the tissue after the procedure. Finally, the experts provided future perspectives on the use of the NanoKnife system for the management of patients with prostate cancer.

## INTRODUCTION

### Treatment Options for Localised Prostate Cancer

Localised prostate cancers are classified as at low, intermediate, and high risk of progression. Low risk cancers are usually candidates for active surveillance or superactive surveillance (which adds focal therapy to active surveillance). Intermediate risk cancers are considered for active surveillance, superactive surveillance, or curative treatments including radical prostatectomy or radiotherapy. Males without benign prostatic hyperplasia (BPH) criteria could also be treated with brachytherapy at low and intermediate stages. High risk cancers require prostatectomy or radiotherapy with androgen deprivation, or a combination of both.

### Role of Focal Therapy in the Treatment of Prostate Cancer

Focal therapy could be discussed in cases of localised prostate cancers with significant low or intermediate risk of progression, when MRI shows circumscribed lesions. Cussenot said: “Radical treatment is required in about 30–40% of patients under active surveillance because of the potential for tumour growth and/or patient anxiety. Focal therapy aims to reduce the use of radical therapies and its adverse effects.”

### What Is Irreversible Electroporation?

IRE is a non-thermal tissue ablation modality based on the apoptotic effect of an electric field which changes the permeability of the exposed cells. Only targeted tissue is destroyed, while sparing critical structures including blood vessels, nerves, and ducts. “It ensures that the architecture of the tissue is respected,” explained Cussenot, adding that “NanoKnife is a smart and emerging tool for focal therapy with IRE ablation.” It does not rely on heat to achieve cell death, which allows treatment of peripheral or juxta-urethral lesions with maximum safety (including prostate cancer in the distal apex) in contrast to other focal ablation technologies. Moreover, IRE does not prevent iterative local treatment, in cases of asynchronous multifocality. A meta-analysis published this year demonstrated that cryoablation (CA), high-intensity focused ultrasound (HIFU), IRE, and vascular-targeted

photodynamic therapy (VTP) for prostate cancer patients have similar clinical outcomes.<sup>1</sup>

## RECENT STUDIES WITH THE NANOKNIFE SYSTEM

### Safety and Clinical Feasibility of the NanoKnife System as First-Line Treatment

Stricker described his first study on the NanoKnife system in 2014, which examined the safety and clinical feasibility of the technology for the focal treatment of prostate cancer.<sup>2</sup> A total of 34 patients with a mean age of 65 years and a median prostate-specific antigen (PSA) of 6.1 ng/mL were included. Nine (26%), 24 (71%), and one (3%) patients had low, intermediate, and high-risk disease, respectively. After a median follow-up of 6 months, 12 Grade 1 and 10 Grade 2 complications occurred, with no Grade  $\geq 3$  events. Regarding functional outcomes, 100% (24/24) of patients were continent, and potency was preserved in 95% (19/20) of males potent before treatment.

“We showed that the NanoKnife procedure is safe in the primary setting,” said Stricker. “We had no major complications and quality of life was excellent. It was a much simpler treatment than radical prostatectomy and radiotherapy, with fewer side effects, done as a day procedure in almost every patient.”

### Safety and Feasibility of the NanoKnife System after Previous Failed Radiation

A subsequent study investigated the feasibility and safety of the NanoKnife system as salvage treatment for localised recurrent prostate cancer after previous radiotherapy.<sup>3</sup> A total of 18 patients with median baseline PSA 8.6  $\mu\text{g/L}$  were followed-up for a median of 21 months. Rates of recurrences and side effects were low. The multiparametric MRI (mpMRI) was clear in 11/13 patients, and 8/10 patients were clear of any prostate cancer on follow-up biopsy. Pad-free continence and erections sufficient for intercourse were preserved in 8/11 patients and 2/6 patients at 6 months, respectively.

“The options of treatment after failed radiotherapy are incredibly limited,” noted Stricker. “And whilst people do offer salvage surgery in that setting, the side effect profile is incredibly high, with up

to 50% of people being completely incontinent, a small incidence of rectal fistula and almost 100% impotence, with only a 50% cure rate. To find a therapy with a remarkably low side effect profile which could offer these patients a second chance of cure when radiotherapy has failed, which is not uncommon (20–30% of patients), was a real breakthrough.”

## The Importance of Follow-Up

Stricker then highlighted a study with up to 6 years’ follow-up. All 123 patients had an MRI at 6 months and a biopsy at 1 year to assess the control rate of focal ablation with the NanoKnife system as primary treatment.<sup>4</sup> The follow-up biopsy was clear of residual disease in 90.2–97.3% of patients. “The recurrence rate during the ensuing 5 years was 15%,” said Stricker. “These were very good results compared with the focal therapy literature. And I must emphasise that they were accurate because biopsy was a requirement during the follow-up. It suggests that NanoKnife is very successful in getting rid of the primary tumour, but there is some recurrence always in the outfield, so it does mandate regular long-term monitoring, usually with PSA and MRI.”

From a quality of life point of view, the incontinence rate was close to 0% and the impotence rate was initially around 10%, dropping to less than 5% after 1 year. Stricker commented: “This recovery of potency is unique to NanoKnife compared to cryotherapy and HIFU. IRE causes less damage to the erectile nerves because it preserves that type of collateral tissue as long as the cell nucleus is not inside the ablation zone. This study really put NanoKnife on the map as one of the options, alongside cryotherapy and HIFU, to treat focal lesions. There were no major complications, good oncological and functional outcomes, and it was performed as a day procedure in all cases.”

## The NanoKnife System Is a Treatment for Any Area of the Prostate

Stricker noted that, unlike other focal therapies, the NanoKnife system is a treatment which can be used in any area of the prostate. “With other technologies you have to be very careful at the apex because you can destroy the sphincter, which can lead to total incontinence, and you may need to have a safety margin at the apex

which often leaves some cancer behind,” he said. “But we showed that this is not the case with NanoKnife, which can be used around the urethra, in the front of the prostate, at the apex of the prostate, and posteriorly.”<sup>5</sup>

## Quality of Life with the NanoKnife System

“The quality-of-life outcomes with NanoKnife are one of the major reasons to choose the technology for suitable patients, while accepting the need for follow-up,” said Stricker. This was further demonstrated in a study evaluating the effect of robot-assisted radical prostatectomy (RARP) versus focal IRE with the NanoKnife system on patient-reported quality of life and early oncological control.<sup>6</sup> A total of 50 IRE patients were matched to 50 RARP patients by propensity score. IRE patients experienced more early oncological failure than RARP patients. But IRE was significantly superior to RARP in preserving pad-free continence and erections sufficient for intercourse up to 12 months after treatment.

## CLINICAL EXPERIENCE WITH IRREVERSIBLE ELECTROPORATION

### Patient Selection, Outcomes, and Follow-Up

#### Patient selection

For Cussenot, patients are candidates for focal ablation using IRE if they have localised prostate cancer, International Society of Urological Pathology (ISUP) Grade 1 or 2, and an index tumour diameter <15 mm.

Stricker noted that advances in imaging, in particular MRI and more recently prostate specific membrane antigen (PSMA)-positron emission tomography (PET) scans, and the technique of transperineal mapping biopsies and MRI/ultrasound fusion have allowed better prediction of suitability for focal therapy than was possible in the past.

“With really high-grade cancers, such as Gleason 8 to 10, most people still feel that a more aggressive approach is needed because the recurrence and metastatic rates are quite high,” he said. “The ideal candidates for IRE have a Gleason 7 tumour on an MRI or PSMA-PET scan

and pathological concordance confirmed with a transperineal template biopsy. In addition, the patient is keen to avoid the side effects of surgery, radiotherapy, or brachytherapy but very happy to be followed-up carefully.”

When Stricker first started using IRE, his age cut-off was about 60 years, but he has since moved towards treating younger patients. “Having done almost 400 procedures now, I’m happy to perform IRE in patients 55 years and over and extremely select patients 50 years and over, with the understanding that they will be monitored for cancer for many, many years,” he said. “We also have to acknowledge that we’re not really sure whether they truly have a focal problem or whether that’s just the presenting edge of a multifocal condition. The ability to confirm the unifocal nature of some tumours should improve as we find more accurate markers (e.g., epigenetic markers) showing that the cancer is truly focal and the rest of the prostate has no abnormalities (i.e., no field defect).”

### **Follow-up after irreversible electroporation**

Regarding follow-up after IRE, Cussenot uses PSA and MRI at 6 and 12 months; if either suggests recurrence, then a biopsy is performed.

Stricker advocates more aggressive follow-up in the first year, with PSA measurements every 3 months, an MRI at 6 months, and a biopsy at 12 months. “The biopsy at 12 months is not universally agreed by the focal therapy pundits because it’s invasive. But MRI and PSA are only about 85% accurate, while 15% of recurrent cancers are found by the biopsy alone, so I personally think an aggressive initial assessment is needed. After you’ve got clearance at 1 year, you can follow-up with PSA and MRI, with a biopsy only if one of those becomes abnormal.”

The biopsy at 12 months detects recurrences early and gives the patient an opportunity of early curative whole gland therapy or redo therapy with the NanoKnife system, noted Stricker. “The chance of needing salvage surgery after one or two NanoKnife procedures is only about 5%. We have achieved over 90% negative margin rates with salvage surgery in those cases and I think that is because of our intensive follow-up.”

### **Quality of life with focal therapy versus radical prostatectomy**

Cussenot noted that “potentially 70% of localised prostate cancer treated by radical therapies exposes patients to unjustified urinary or sexual side effects. Erectile function and urinary incontinence are preserved with IRE; however, the volume of sperm ejaculation is usually reduced.”

Stricker highlighted the findings of a pair-matched comparison of focal IRE versus RARP.<sup>6</sup> “This study showed very clearly that general health, potency, and continence were markedly better with focal therapy compared to even the best nerve-sparing surgery,” he said. “The trade-off is that, after surgery in an earlier cancer, there’s no need for invasive follow-up. There’s always a possibility of a recurrence after focal therapy, and follow-up is essential.”

### **Distinguishing features of irreversible electroporation compared with other focal therapies**

Stricker said all focal therapies have similar procedural and recovery times. “The difference is the chance that you get rid of all the cancer,” he said. “One of the weaknesses of HIFU is that, because it’s a sound wave, it’s highly influenced by blood vessels and calcification in the prostate and the position in the prostate which could decrease the chance of clearing the cancer. This is particularly so in the front of the prostate.”

The disadvantage with cryotherapy is the need to ensure protection of the urethra and the neurovascular bundles. “That means you protect some of the tissue around the urethra and if there’s cancer there, then of course it will recur,” he said. “Whereas with NanoKnife therapy you can go right up to the edge of the urethra. And whilst you’ll get some swelling, you won’t end up getting necrosis of the urethra or a stricture; it will recover. So that’s a distinguishing feature.”

When comparing brachytherapy and IRE, Stricker said the one big disadvantage of radiation therapy of any type is that it cannot be repeated. “If the cancer recurred in another part of the prostate after focal brachytherapy, you couldn’t do another brachytherapy treatment. Whereas NanoKnife therapy is repeatable; I will redo NanoKnife once and if the cancer comes back another time, I think it’s time for whole gland treatment.”

Laser ablation can be performed within the MRI machine, which is an advantage in terms of accuracy, but like HIFU and cryotherapy it is thermal-based. “That heat or freezing is not selective in its effect on tissues,” said Stricker. “Whereas the NanoKnife is selective, and so it tends to preserve adjacent structures like nerves, and particularly the erectile nerves, and it tends to preserve the blood vessels within the tissue, which the other focal therapies do not do. If you get a nerve inside a cryofield, laser field, or HIFU field, the patient will be impotent. Whereas if you get an erectile nerve in the IRE ablation zone, the patient might become impotent, although it is not inevitable.”

Another focal therapy is TOOKAD, which uses an injected chemical that is activated by light. Stricker said: “It is not a thermal based treatment, but it’s cumbersome; the patient becomes photosensitive and must be wrapped in foil for a couple of hours to protect their skin.” A prospective randomised Phase III study compared VTP with padeliporfin (TOOKAD) versus active surveillance in 413 patients with low-risk prostate cancer.<sup>7</sup> After an average follow-up of 2 years, 6% of patients undergoing VTP required radiotherapy or surgery, compared to 29% of patients who received active surveillance ( $p < 0.0001$ ). But Stricker commented: “The trial’s weakness was that many of the patients didn’t need treatment (Grade Group 1). The advantage of NanoKnife compared to TOOKAD is that we’ve shown that we can treat significant cancers (Grade Group 2).”

### **Irreversible electroporation as a primary focal treatment for prostate cancer**

Stricker estimated that about 15% of patients might be suitable for IRE therapy. “The old paradigm was either active surveillance or whole gland therapy with surgery or radiotherapy. I think the new paradigm is active surveillance for low grade tumours, focal therapy for some intermediate grade tumours, and whole gland therapy for the remainder. Focal therapy is filling a niche for patients who aren’t prepared to accept the side effect profile of whole gland therapy when they’ve got a tumour which, on consensus opinion, would suggest that focal therapy might be appropriate.”

Patient views regarding quality of life, invasiveness of treatment, and need for follow-up play a big role in this disease, noted Stricker. “Prostate cancer has a long natural history and slow time to recurrence, while the potential side effects of whole gland therapy, such as incontinence, impotence, and rectal damage, are quite devastating, so that type of discussion has to be had with patients.”

### **Questions that still need to be answered in future studies**

A randomised study comparing surgery and focal ablation would be definitive, but is unlikely to be conducted, said Stricker. Another study that would be worthwhile would be to compare focal therapy versus monitoring only in patients with intermediate grade cancer of the prostate, ending with radical prostatectomy if appropriate. “At that point you would analyse whether the radical prostatectomy was curative or not. In other words, does focal therapy add anything beyond active surveillance in these patients?” An ongoing randomised trial comparing hemiablation with HIFU versus radical prostatectomy will provide important answers on the role of focal therapy compared with whole gland therapy. Regarding patient selection, studies are needed to define better markers of a truly unifocal tumour versus more widespread tumours.

Cussenot would like to see long-term follow-up (over 10 years) data quantifying the quality-adjusted life-year benefit of focal therapies including IRE.

### **The Irreversible Electroporation Procedure**

#### **Duration of the procedure**

Cussenot and Stricker agreed that the NanoKnife prostate treatment typically takes 1 hour, from the time patients are sedated until they regain consciousness. Within that timeframe, the passage of energy takes 20–30 minutes. Skills are required in transperineal biopsy, transrectal ultrasound, and interpretation of imaging, including MRI/ultrasound fusion imaging. “Most urologists worldwide now have those skill sets,” said Stricker. “The procedure takes 2–3 hours initially and the learning curve is around 10–20 patients unless you pick tricky cases, which I don’t recommend in the first 50 cases.”

## IRE as a salvage technique

“IRE can be used as a salvage technique for intraprostatic recurrence, after histological confirmation of the recurrence,” said Cussenot. Selection criteria should be localised recurrence and preferably PSA <4, noted Stricker. “The lower the PSA, the greater the success in eradicating the cancer, so monitoring after radiotherapy, radical prostatectomy, or NanoKnife therapy is equally important to preserve the opportunity for a second cure.”

## Nature of the tissue following irreversible electroporation and the impact on subsequent treatments

One of the distinguishing features of the NanoKnife procedure is that it is non-thermal, and this means that subsequent therapies remain a possibility. “Other treatments including radical prostatectomy could be performed after IRE,” said Cussenot. “The absence of a thermal effect drastically reduces retractile fibrosis, which is observed after HIFU or cryotherapy.”

“The results of salvage radical prostatectomy after IRE are excellent as long as it is performed early,” added Stricker. “As soon as you know that there’s a recurrence and it’s not suitable for redo NanoKnife therapy, you should do early radical prostatectomy. Because you only ablate a small area of the prostate with NanoKnife and the remaining tissue is unaffected, the oncological and functional outcomes of salvage surgery are markedly better than after more extensive treatments such as radiotherapy, brachytherapy, and HIFU.”

## FUTURE PERSPECTIVES

### Vision for Incorporating Irreversible Electroporation into the Management of Patients with Prostate Cancer

“IRE could be discussed currently as an opportunity to adapt the risk-benefit ratio in the management of low and intermediate risk localised prostate cancers,” commented Cussenot.

Stricker sees the technology becoming commonplace. “I think that IRE will form part of the armamentarium of many urologists who offer all the treatment options. My vision is that it will

find a middle ground between active surveillance where patients don’t need treatment and whole gland therapy so that IRE is performed in people with localised Gleason 7 tumours.”

### What Role Could Irreversible Electroporation Play in Combination with Immunotherapy?

“Although immunological responses are enhanced after focal therapies such as VTP or IRE, it’s too early to conclude that combination IRE and immunotherapy could be used in clinical practice,” said Cussenot, adding that “IRE and immunologic management must also be explored for advanced disease.”

Stricker is embarking on two studies. One will investigate whether the NanoKnife system triggers an immune stimulatory effect. The second will examine whether immunotherapy combined with the NanoKnife system boosts the systemic effects of treatment. “It makes sense that if you can release tumour specific antigens with the NanoKnife and then give the appropriate stimulation of immunity, you might get some regression of secondary tumours. But at the moment it is hypothesis generating and there are no data.”

The immune studies are part of Stricker’s larger programme of research on the NanoKnife system, which is also evaluating the technology as salvage therapy. Another line of investigation is the selection of patients for focal therapy using epigenetic markers and imaging with MRI and PSMA-PET scanning. The value of these imaging modalities in the follow-up of patients after IRE is also being explored.

### Closing Remarks

Stricker said that international research on IRE, such as an Australian multicentre study and a U.S. Food and Drug Administration (FDA)-approved clinical trial, plus ongoing training in urology centres, are important steps towards adoption. “I think that will all go towards making this an established treatment that is eventually reimbursed and included in guidelines. While there are long-term data and experience with other focal therapies including HIFU, cryotherapy, and laser therapy, when urologists realise the simplicity of IRE and the potential advantages,

I think that it will organically replace the other technologies with time. Because IRE is not thermal based, it preserves collateral tissues, which is different to the other therapies. As we get better with selection, the results will speak for themselves.”

## Biographies

### Olivier Cussenot

Head, Department of Urology, APHP-Sorbonne University, Tenon Hospital, Paris, France

### Phillip Stricker

Chair, Department of Urology, St Vincent's Private Hospital and Clinic, Sydney, Australia

#### References

1. Guo RQ et al. Cryoablation, high-intensity focused ultrasound, irreversible electroporation, and vascular-targeted photodynamic therapy for prostate cancer: a systemic review and meta-analysis. *Int J Clin Oncol.* 2021;26(3):461-84.
2. Valerio M et al. Initial assessment of safety and clinical feasibility of irreversible electroporation in the focal treatment of prostate cancer. *Prostate Cancer Prostatic Dis.* 2014;17(4):343-7.
3. Scheltema MJ et al. Feasibility and safety of focal irreversible electroporation as salvage treatment for localized radio-recurrent prostate cancer. *BJU Int.* 2017;120(Suppl 3):51-8.
4. Blazevski A et al. Oncological and quality-of-life outcomes following focal irreversible electroporation as primary treatment for localised prostate cancer: a biopsy-monitored prospective cohort. *Eur Urol Oncol.* 2020;3(3):283-90.
5. Blazevski A et al. Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). *World J Urol.* 2021;39(4):1107-14.
6. Scheltema MJ et al. Pair-matched patient-reported quality of life and early oncological control following focal irreversible electroporation versus robot-assisted radical prostatectomy. *World J Urol.* 2018;36(9):1383-9.
7. Azzouzi AR et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. *Lancet Oncol.* 2017;18(2):181-91.

FOR REPRINT QUERIES PLEASE CONTACT: [INFO@EMJREVIEWS.COM](mailto:INFO@EMJREVIEWS.COM)