Focal Irreversible Electropororation as salvage treatment for prostate cancer: A prospective pilot study

FIRE

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Disclosures

- Rob Sutherland Urology research fellow for 2017 under supervision of Prof P. Stricker

- No conflict of interest to disclose
What is IRE?
How does electroporation work?

- When an electrical field is applied across a cell it creates hole or “pores” in cell membrane. This was named “electroporation” in the 1980s¹.

2. Figure of electroporation courtesy of AngioDynamics Image
Electroporation

- Once a certain electric field threshold is achieved, "holes" in the cell membrane becomes irreversible
- This leads to apoptosis of the cell unique to IRE (compare to necrosis of other modalities of FT)

Figure from AngioDynamics
Electroporation & Nanopores


![Normal Liver vs. IRE with Nanopores](image)
Advantages of IRE

- Reliable ablation
- Relatively quick day surgery procedure
- Repeatable
- Potential preservation of structures
- Salvage RP still possible
Who is the Ideal Candidate

- Unifocal OR single index lesion
- Perfect co-registration of MRI and TTMB
- Selective alternative to WGT (not AS)
- Low - Intermediate risk disease
- Refuses or unsuitable for WGT
- Primary or salvage
- New lesions on AS
- Consensus – PSA<15, T1c-T2a, Gl 7
- >60 years and >10 life expectancy
- Must accept ongoing AS

Must accept ongoing AS
Focal Therapy

- Always more than you can see – need 1 cm margin
Safety Margin

- Assessment of PCa extent on MRI and RP using detailed software-assisted co-registration
- $n = 46$ cancer lesions
- A 9mm treatment margin around an MRI-visible lesion ensures complete tumour Rx

- MRI underestimates histologically determined tumor boundaries
- A 9mm treatment margin around a lesion visible on MRI would consistently ensure treatment of the entire histological tumor volume

*Le Nobin et al, J Urol 2015; 194-2 (364-370)*
Pre-clinical IRE in the prostate

- Tsivian et al. (n=12) & Onik et al. (n=6)

- No damage to adjacent structures, no urinary incontinence.
- And no erectile dysfunction: methods????

Cellular vs. Non-Cellular

All cells in ablation zone are affected by electrical field.

**Fibrous and Collagen Structures are not affected.**

- Intact adventitia and laminae visible at 2 days with no smooth muscle cells present
- Endothelium largely repopulates at 2 day
- Smooth muscle repopulated at 2 weeks

1. ARC 991-1 Safety of Irreversible Electroporation of the Pancreas in a Porcine Model
2. Image @ Blue Histology, School of Anat. and Human Biology - The U. of W. Australia
3. http://www.lab.anhb.uwa.edu.au/mb140/Core\Pages\Vascular/Vascular.htm#ARTER
Histopathology results

Electrode configuration – Histology results

Focal ablation $\leq 3$ electrodes

Extended ablation $\geq 4$ electrodes

Van den Bos et al. WJU 2015
First phase 1-2 trials

Valerio et al. 2014 (n=34)  
No biopsy data (n=1)

Ting et al. 2014 (n=25)  
Biopsy (n=21)

Murray et al. 2014 (n=25)  
Biopsy (n=25)

Valerio et al. 2017 (n=19)  
Biopsy (n=16)

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Fig. 1 – Focal therapy scenarios. Red: neurovascular bundles. White: urethra. Dotted line: tumour lesions. Blue: ablation zone.
Anterior Lesion Pre & Post IRE
Nanoknife procedure
St Vincent’s cohort (n=200)

Cohort definitions (>6 months follow-up)

• **Primary Nanoknife treatment (n=63)**
  – Stage: pT1c – pT2c (based on Bx/mpMRI results)
  – Gleason score 6-7
  – Previous template biopsies performed & MRI

• **Salvage Nanoknife treatment (n=12)**
  – Radio-recurrent PCa (LDR/HDR/EBRT)
  – Organ-confined disease on baseline imaging
  – Any Gleason Score on template biopsies
  – No androgen deprivation therapy
Prostate segments & risk factors
Anterior vs Posterior

- Urinary
- Bowel
- Sexual
- Physical
- Mental
- AUA

Box plots showing comparisons between Anterior, Posterior, and NA groups for different categories.
Apex vs Base vs Apex-to-Base
Bilateral vs Unilateral

[Box plots showing comparisons between Bilateral and Unilateral groups for Urinary, Bowel, Sexual, Physical, Mental, and AUA categories.]
Salvage IRE outcomes

At 6 months salvage patients experienced a decline in:

- EPIC sexual domain (median of 38 to 24, \( p=0.028 \))
- Urinary domain (median of 96 to 92, \( p=0.074 \)).

- No urethral-recto fistula or high-grade AE’s
Primary Oncological control

Initial Oncological Control primary patients

• In-field oncological control;
  – 84% (38/45)

• Whole-gland oncological control;
  – 76% (34/45)
## Comparison of peri-operative parameters of patients free of in-field significant PCa compared with patients with in-field significant cancer on FU biopsy

<table>
<thead>
<tr>
<th>Median, IQR</th>
<th>No significant PCa on biopsy ($n = 34$)</th>
<th>Significant in-field cancer on biopsy ($n = 7$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum (mm) interelectrode distance</td>
<td>9 (8-10)</td>
<td>8.5 (8-9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Maximum (mm) interelectrode distance</td>
<td>18 (17-19)</td>
<td>18 (16-20)</td>
<td>1.0</td>
</tr>
<tr>
<td>Minimum voltage</td>
<td>1500 (1350-1780)</td>
<td>1480 (1200-1620)</td>
<td>0.4</td>
</tr>
<tr>
<td>Maximum voltage</td>
<td>2550 (2400-2850)</td>
<td>2550 (2400-2700)</td>
<td>0.6</td>
</tr>
<tr>
<td>Minimum amperage</td>
<td>23 (20-28)</td>
<td>20 (17-26)</td>
<td>0.3</td>
</tr>
<tr>
<td>Average amperage of lowest pulse set</td>
<td>26 (22-30)</td>
<td>21 (17-28)</td>
<td>0.2</td>
</tr>
<tr>
<td>Maximum amperage</td>
<td>41 (37-47)</td>
<td>39 (35-50)</td>
<td>0.6</td>
</tr>
<tr>
<td>Safety margin (mm)</td>
<td>10 (10-10)</td>
<td>5 (5-10)</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>System errors</td>
<td>8.8% (3/34)</td>
<td>57% (4/7)</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>
Primary Oncological control

With adequate safety margin and no errors

• In-field oncological control;
  – 97% (38/39)

• Whole-gland oncological control;
  – 87% (34/39)
Salvage oncological control

Salvage oncological control (n=12)

- A total of 3 and 4 patients experienced biochemical failure using the Phoenix and Stuttgart definitions of biochemical failure (all true positive)
- 80% (n=8/10) of the patients were clear of any PCa on follow-up biopsy
- 2 patients had significant PCa on follow-up biopsy (ISUP 5).
- Metastases developed in 2 patients; bone and solitary pelvic lymph node disease.
<table>
<thead>
<tr>
<th>PCa definition</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS ≥ 4+3 or ≥ 6mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infield</td>
<td>43 (10-82)</td>
<td>86 (73-95)</td>
<td>33 (14-61)</td>
<td>90 (83-95)</td>
</tr>
<tr>
<td>Outfield</td>
<td>33 (4-78)</td>
<td>82 (68-92)</td>
<td>20 (6-48)</td>
<td>90 (84-94)</td>
</tr>
<tr>
<td>Whole-gland</td>
<td>46 (19-75)</td>
<td>71 (54-85)</td>
<td>35 (20-54)</td>
<td>79 (69-87)</td>
</tr>
<tr>
<td>GS ≥ 3+4 or ≥ 4mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infield</td>
<td>38 (9-76)</td>
<td>86 (72-95)</td>
<td>33 (14-62)</td>
<td>88 (81-93)</td>
</tr>
<tr>
<td>Outfield</td>
<td>38 (14-68)</td>
<td>87 (72-96)</td>
<td>50 (26-74)</td>
<td>80 (73-87)</td>
</tr>
<tr>
<td>Whole-gland</td>
<td>44 (22-69)</td>
<td>73 (54-87)</td>
<td>47 (29-66)</td>
<td>71 (60-79)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence intervals; GS, Gleason Score
80% (12/15) of the lesions missed by mpMRI contained low-volume (<4mm MCCL) or high-volume Gleason 3+3=6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Nadir PSA (µg/L)</td>
<td>1.9 (1.1 – 4.7)</td>
</tr>
<tr>
<td>PSA density (µg/L per cc)</td>
<td>0.0572 (0.0354 – 0.0913)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up biopsy lesions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No or insig. PCa</td>
<td>32</td>
</tr>
<tr>
<td>GS 3+3, ≥4mm*</td>
<td>7</td>
</tr>
<tr>
<td>GS 3+3, ≥6mm*</td>
<td>4</td>
</tr>
<tr>
<td>GS 3+4, any*</td>
<td>8</td>
</tr>
<tr>
<td>GS 3+4, ≥6mm*</td>
<td>2</td>
</tr>
<tr>
<td>GS 4+3, any*†</td>
<td>5</td>
</tr>
<tr>
<td>GS ≥4+4, any*†</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mpMRI results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No ROI</td>
<td>33</td>
</tr>
<tr>
<td>Infield ROI</td>
<td>9</td>
</tr>
<tr>
<td>Outfield PI-RADS 3</td>
<td>8</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>5</td>
</tr>
<tr>
<td>Transition zone</td>
<td>3</td>
</tr>
<tr>
<td>Outfield PI-RADS 4</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>1</td>
</tr>
<tr>
<td>Outfield PI-RADS 5</td>
<td>0</td>
</tr>
</tbody>
</table>
FIRE Study

- Focal Irreversible Electroporation as salvage treatment in radio-recurrent prostate cancer: a prospective multi-centre pilot study

- Centres:
  - Australia: St Vincent’s Private Hospital
  - Netherlands: Academic Medical Centre
  - USA: Memorial Sloan Kettering Cancer Center
  - New Zealand: Grace Hospital
• Prospective interventional pilot study
• Prospectively registered on ANZCTR (ACTRN12617000806369)
• Ethics approval (SVH16191)
• Study duration: 4 years

• Objectives

  – Primary:
    1. To assess the safety profile of salvage focal IRE in radiorecurrent disease
    2. To assess QoL and urinary and sexual functional outcomes up to 1 year post treatment

  – Secondary:
    1. To assess presence of cancer following salvage focal IRE in radio recurrent PCa
    2. To characterise the correlation between mpMRI and biopsy at 1 year post treatment
      – 10 participants recruited at each centre. (40 in total)
Selection criteria

- Radio-recurrent PCa ≥ 2 years post LDR/PDR/HDR brachytherapy or external beam radiotherapy
- Imaging negative for metastatic disease
- Radiological stage T1-T3a N0M0 disease
- Lesion visible on mpMRI with good biopsy co-registration
- Histologically proven Gleason 7-10 PCa
- PCa recurrence limited to a single lesion in the prostate as indicated by pre-operative biopsy
- PSA <10 ng/mL
- Fulfil Phoenix criteria (Nadir +2)
- Life expectancy of 10 years or more
- Able to proved written consent.
Exclusion criteria

- Biopsy proven lymph node involvement
- Metastatic disease
- Bowel disease (e.g. IBD)
- Previous transurethral resection of the prostate (TURP)
- Major medical or psychiatric illness, which in the investigator’s opinion, would prevent completion of treatment and/or follow-up
- Inability to undergo mpMRI
- Incompatible metallic implants
- Claustrophobia
- Men unable to tolerate transrectal ultrasound
- Men who have undergone previous focal therapy to the prostate (HIFU, IRE, cryosurgery, thermal, microwave, laser therapy)
- Men who have received androgen suppression/hormone treatment within the last 6 months
- Metallic implants or stents in urethra
- Histological evidence of any cancer in more than one area of the prostate
- Requires simultaneous urological procedure at time of salvage IRE (e.g. mini TUR)
Study timeline

Patient meeting selection criteria recruited

Base line EPIC QoL survey and VAS

Pre-treatment data collection (PSA etc.)

IRE procedure

1 week MRI

3 months EPIC QoL: survey + VAS + PSA + safety assessment

6 months EPIC QoL: survey + VAS + PSA + safety assessment + MRI

9 months PSA

12 months TTMB (≥ 18 cores)

12 months EPIC QoL survey + VAS + PSA + safety assessment
Acknowledgements

• Prof Phillip Stricker from St Vincent’s Prostate Cancer Centre
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• The Australian Commonwealth Department of Health, the St Vincent's Prostate Cancer Centre and the Cancer Institute New South Wales for financial support of the Australian Prostate Cancer Research Centre – NSW
• Jayne Matthews for clinical support
Questions?