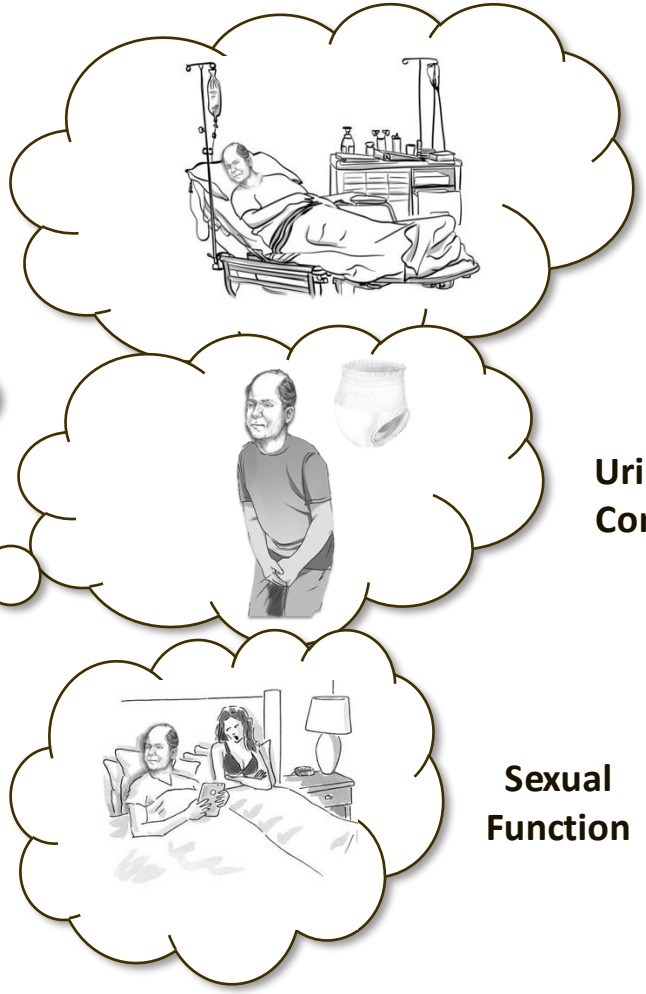
ST VINCENT'S HOSPITAL
SYDNEY

Professor Phillip Stricker

Focal Therapy For Prostate Cancer

Patient Priorities and Choice



Cancer Control

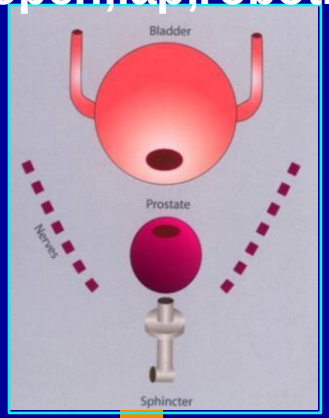
Urinary Control

Sexual Function

https://www.niddk.nih.gov/news/media-library/16433

What are the treatments?

Surgery
open,lap,robotic



Seeds

Radiotherapy

Wires

Focal Therapy

Active Surveillance

St Vincent's prostate cancer centre

Factors to consider when deciding

- Tumour factors
- Prostate factors
- Local factors
- Patient factors
- Institutional factors

St Vincent's prostate cancer centre

- **Patient Factors**
  - "Worrier" vs " Acceptor"
  - "Joint Decision" vs "Doctor decides"
  - "Wants it out" type
  - "Fear of surgery" type
  - "Pragmatic" type
  - "Thinks he'll live forever" type
  - "Punter" vs "Conservative"
  - "Natural therapy"
  - . Technophile

St Vincent's prostate cancer centre

Individualise Treatment

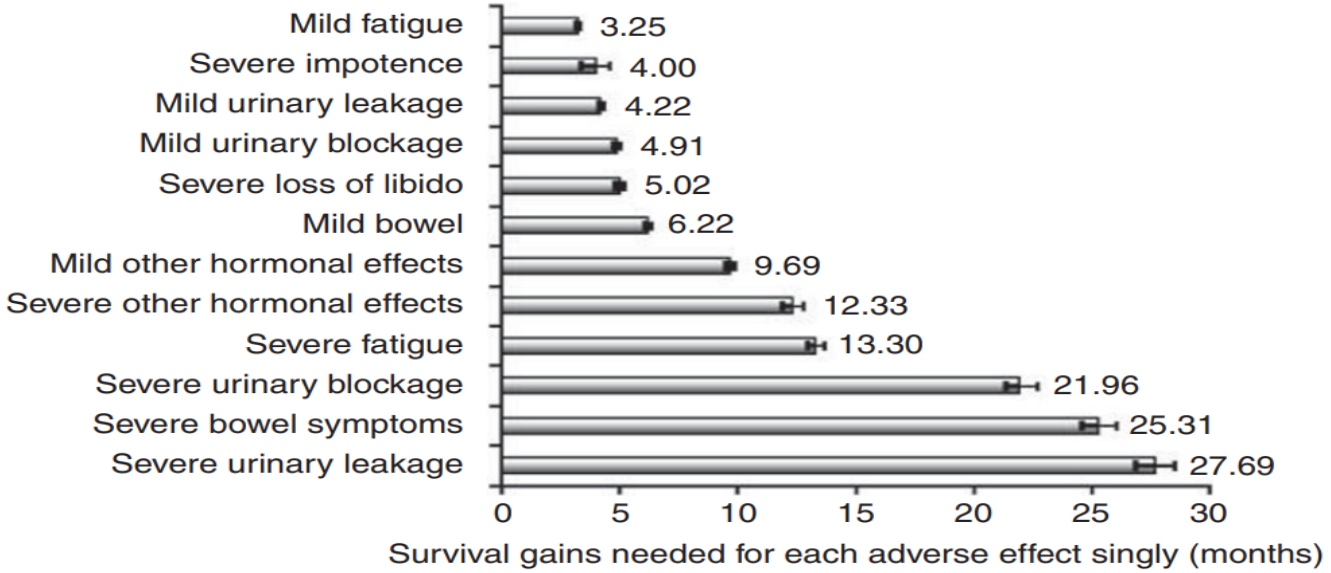
St Vincent's prostate cancer centre

Patients are Willing To Trade off Survival

Garvan Institute of Medical Research

Survival gains needed for localised prostate cancer

MT King *et al*



British Journal of Cancer (2012) 106, 638 – 645

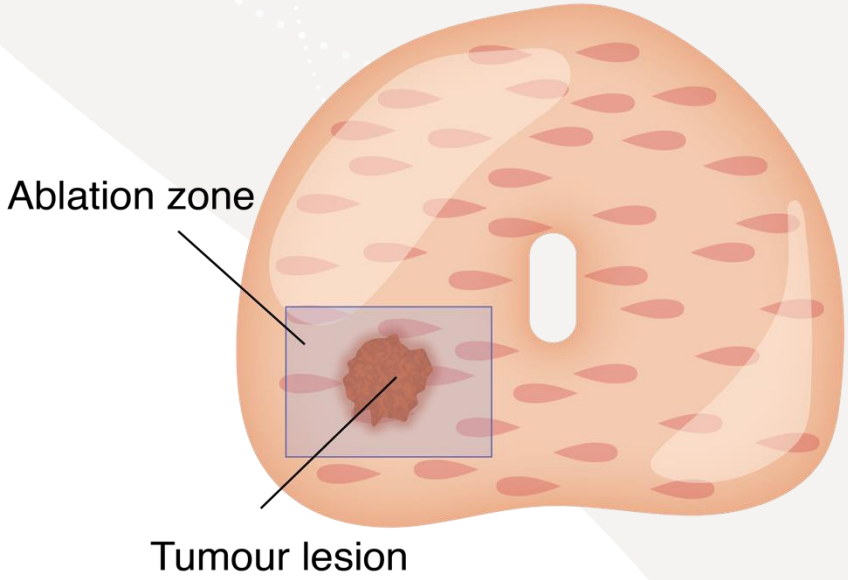
MT King*[,1,2], R Viney[2], DP Smith[3], I Hossain[2,4], D Street[2], E Savage[2], S Fowler[2], MP Berry[5], M Stockler[6,7,8], P Cozzi[9], P Stricker[10], J Ward[11] and BK Armstrong[8]

www.bjcancer.com

Focal Ablation for Prostate Cancer

Garvan Institute of Medical Research

- Focal ablation (FA) is an emerging option for localised PCa.
- Increased interest given improvements in disease localised with mpMRI and PSMA and better biopsy techniques.
- Whole-gland treatments (RP and RTx) provide excellent oncological control but still have significant impact of patient quality of life.



Emergence of Focal Therapy

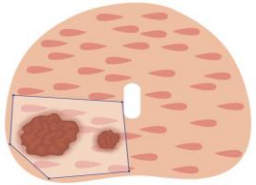
Garvan Institute of Medical Research

1. Ability to localise disease (MRI/PSMA PET /Template Biopsy)
2. Success in other organs → Breast, Kidney, Thyroid, Lung, Colon
3. Efficacy of Whole-gland treatment → ProtecT, PIVOT, SPCG-4---??Overtreatment in some patients and Side Effects
4. Index monoclonal origin (Liu et al,. *Nature* 2009 15:559)
5. Safety and Patient Preference

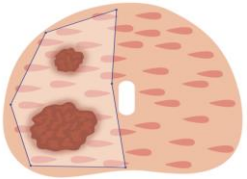
What areas can we treat with Focal ?

- **Energy**: IRE , HIFU , Cryo , Brachy , Laser
- **Template**: Quadrant or Hemiablation - ”region-ectomy” not “lesion-ectomy”
- **10 mm** added to the edge of mpMRI-visible lesion

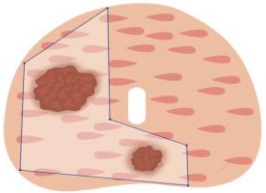
Quadrant Ablation – Index lesion with smaller significant lesion in the same quadrant



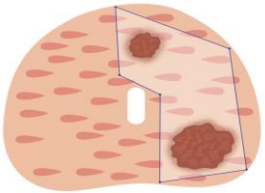
Hemiablation – Index lesion with small ipsilateral significant lesion



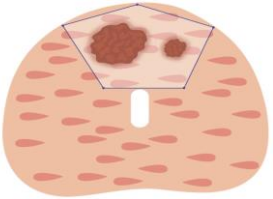
Wide Local Ablation – Index lesion with smaller significant posterior lesion



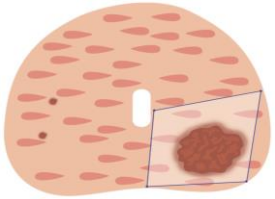
Wide Local Ablation – Index lesion with smaller significant anterior lesion



Anterior Ablation – Index lesion with smaller significant lesion both anterior



Wide Local Ablation – Index lesion with contralateral insignificant lesion

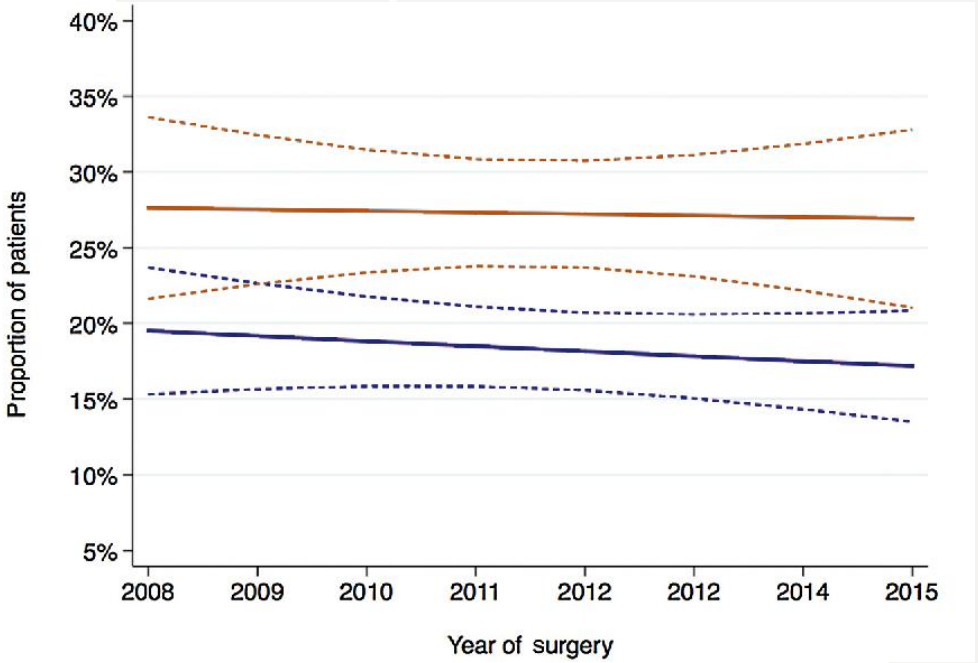


Side-effects from minimally invasive prostatectomy over time- still an issue

Trends in functional outcomes in Memorial Sloan Kettering Cancer Centre over time at 12 (blue) and 24 months (orange)

Erectile Function
RECOVERY

Capogrosso et al, European Urology, 2018



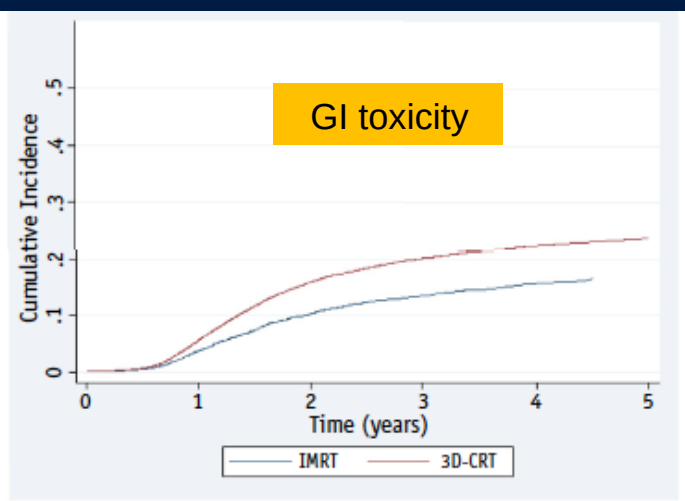
Real world UK data following radiotherapy – still significant side effects

International Journal of Radiation Oncology biology physics
www.redjournal.org

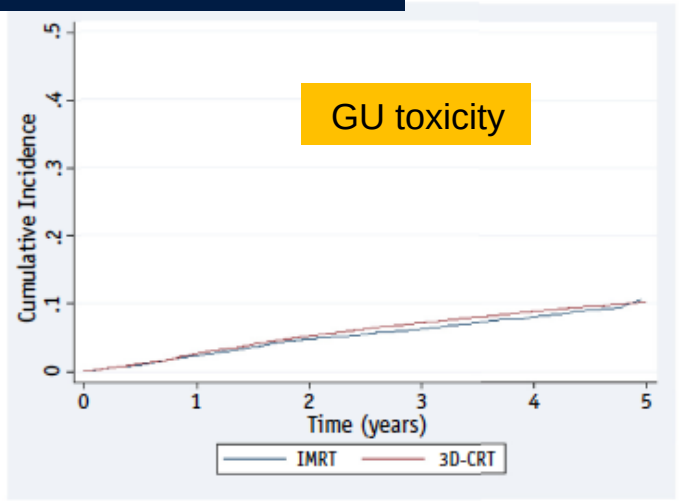
Clinical Investigation

National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer

Arunan Sujenthiran, MRCS,* Julie Nossiter, PhD,* Susan C. Charman, MSc,*,† Matthew Parry, MRCS,*,† Prokar Dasgupta, FRCS,‡ Jan van der Meulen, PhD,† Paul J. Cathcart, FRCS,§ Noel W. Clarke, FRCS,§ Heather Payne, FRCR,‖ and Ajay Aggarwal, FRCR‖,#



Numbers at risk						
Time (years)	0	1	2	3	4	5
3D-CRT	16,289	15,127	13,075	10,431	6,531	2,817
IMRT	6,933	6,598	6,010	1,997	649	170



Numbers at risk						
Time (years)	0	1	2	3	4	5
3D-CRT	16,289	15,640	14,923	12,276	7,834	3,373
IMRT	6,933	6,696	6,404	2,177	717	171

Fig. 2. Cumulative incidence curves for gastrointestinal toxicity (A) and genitourinary toxicity (B) after radical radiation therapy according to type of radiation therapy (intensity modulated radiation therapy [IMRT] vs 3-dimensional conformal radiation therapy [3D-CRT]).

Garvan Institute of Medical Research

Focal Therapy…treating the Index Lesion

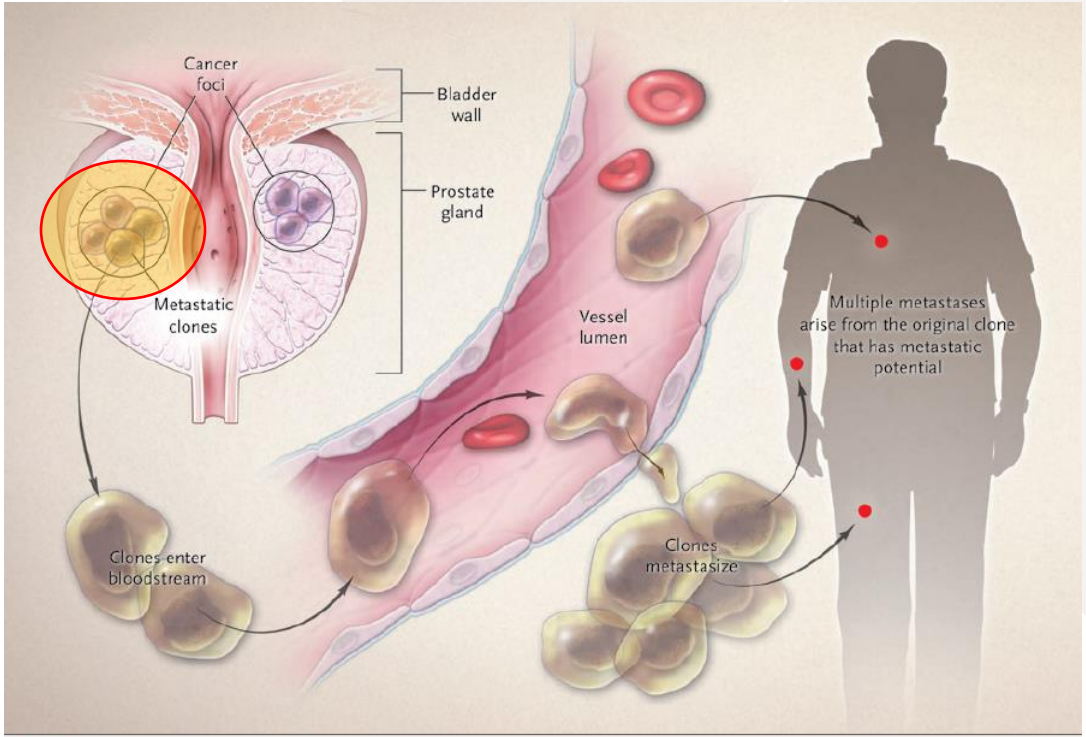
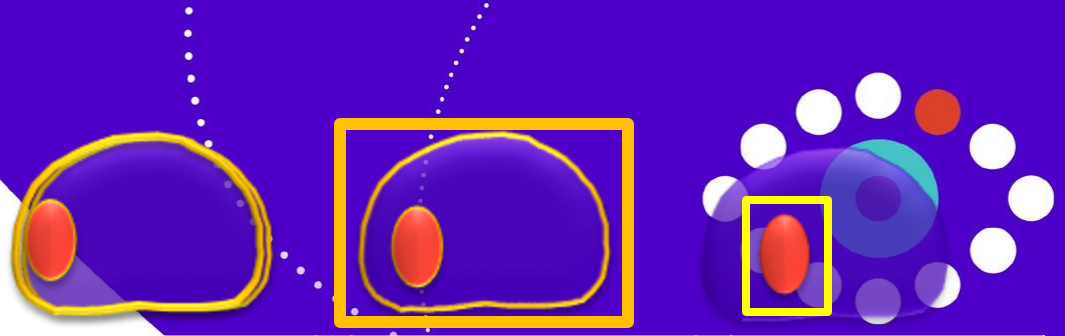


Figure 1. Monoclonal Origin of Prostate Cancer Metastases.

Ahmed HU, NEJM, 2009

Garvan Institute
of Medical Research

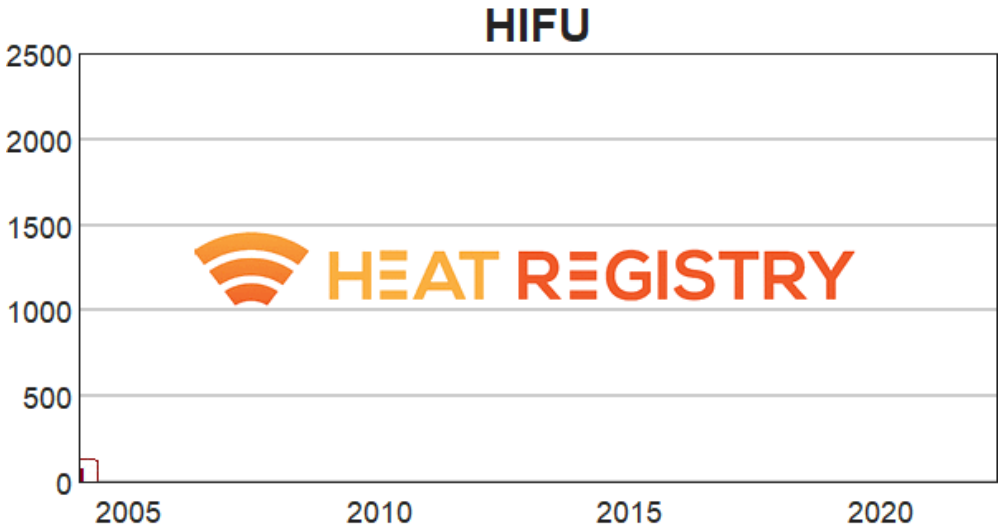


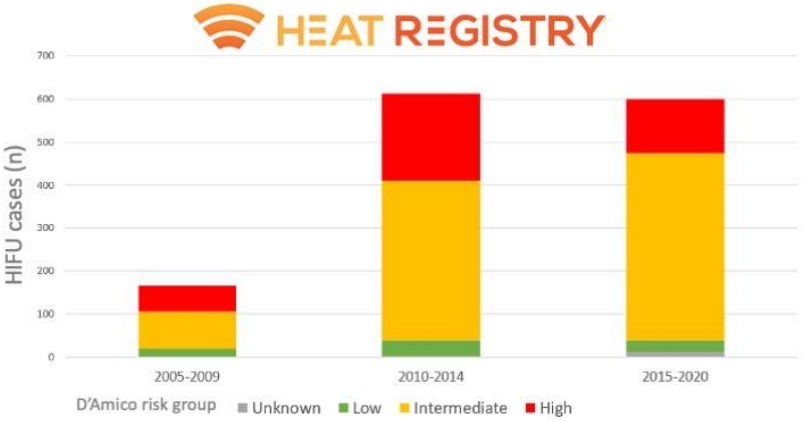
	Radical Surgery	Radical Radiotherapy	Focal Therapy
Urinary issues	5%	10-20%	1%
Incontinence	10-25%	5%	0-1%
Impotence	40-60%	50-60%	5-15%
Ejaculation	0%	0%	60%
Rectal toxicity	0.1%	5-15%	0.1%
Salvage at 5-10 years	10-15%	10-15%	15-20%
Survival at 5-10 years	99%	99%	99%

Is Focal Therapy Increasing?

Garvan Institute of Medical Research

UK HEAT HIFU focal therapy registry





HIFI Trial: HIFU vs Radical Prostatectomy for Localised Prostate Cancer

- Non-inferiority, prospective, non-randomized, nationwide study in 46 French centers
- Inclusion criteria:
  - > 69 years in HIFU arm
  - Low and intermediate risk Pca (cT1-2 NxM0, GG 1 or 2, PSA <15 ng/ml)
  - Not eligible for AS
  - Maximum 4/6 positive sextants at post mpMRI systematic biopsies
- Primary endpoint: salvage treatment-free survival (STFS)
  - Any salvage treatment including RP, RT and/or androgen blockage
- Secondary endpoints: metastasis, specific and overall survival, safety and functional outcomes

American Urological Association
THE JOURNAL of UROLOGY
Official Journal of the American Urological Association

Rischmann, P. J., Coloby, P., Chevallier, T., Houede, N., Villers, A., & Ploussard, G. (2024). P2-06 HIFI TRIAL: HIFU VS RADICAL PROSTATECTOMY FOR LOCALIZED PROSTATE CANCER IN 3328 CASES. FINAL RESULTS. Journal of Urology, 211(5S2), e4. https://doi.org/10.1097/01.JU.0001015816.87470.c9.06 (Original work published May 1, 2024)

HIFI Trial: HIFU vs Radical Prostatectomy for Localised Prostate Cancer

3328 patients

- 1967 HIFU
- 1361 RP

GG2 50% in both arms

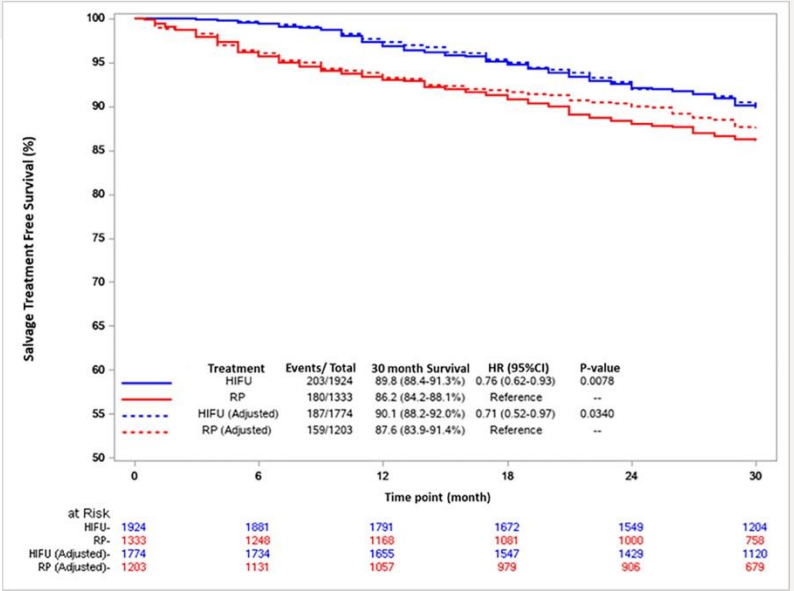
30-month STFS rate was significantly higher in the HIFU arm (89.8%) compared with the RP arm (86.2%; HR 0.76; p = 0.008)

No distant metastasis or PCa-specific death reported

No OS difference between groups when adjusted on age (HR=2.53; 95%CI 0.95-6.73; p = 0.06)

At 12 months, urinary continence was better in HIFU group

IIEF-5 score decreased significantly less after HIFU compared to RP (median Δ = -4 vs -9, p<0.001)



Conclusion: Salvage therapy-free survival after HIFU was NOT inferior to RP at 30 month follow up

Current Treatment Paradigm

Garvan Institute of Medical Research

	Low-Risk	Intermediate-Risk	High-Risk
Gleason Score	GS 6	GS7	GS >7
PSA	PSA ≤ 10 n	PSA 10-20 ng/mL	PSA ≥ 20 ng/mL
TNM	cT1-T2a	cT2b-2c	>cT3a

Active Surveillance

Whole-Gland Treatment

New Paradigm??

Garvan Institute of Medical Research

	Low-Risk	Intermed e Risk	High-Risk
Gleason Score	GS 6	GS7	GS >7
PSA	PSA ≤ 10 ng/mL	PSA 10- g mL	PSA ≥ 20 ng/mL
TNM	cT1-T2a	cT2b-2c	>cT3a

Active Surveillance

Focal Therapy

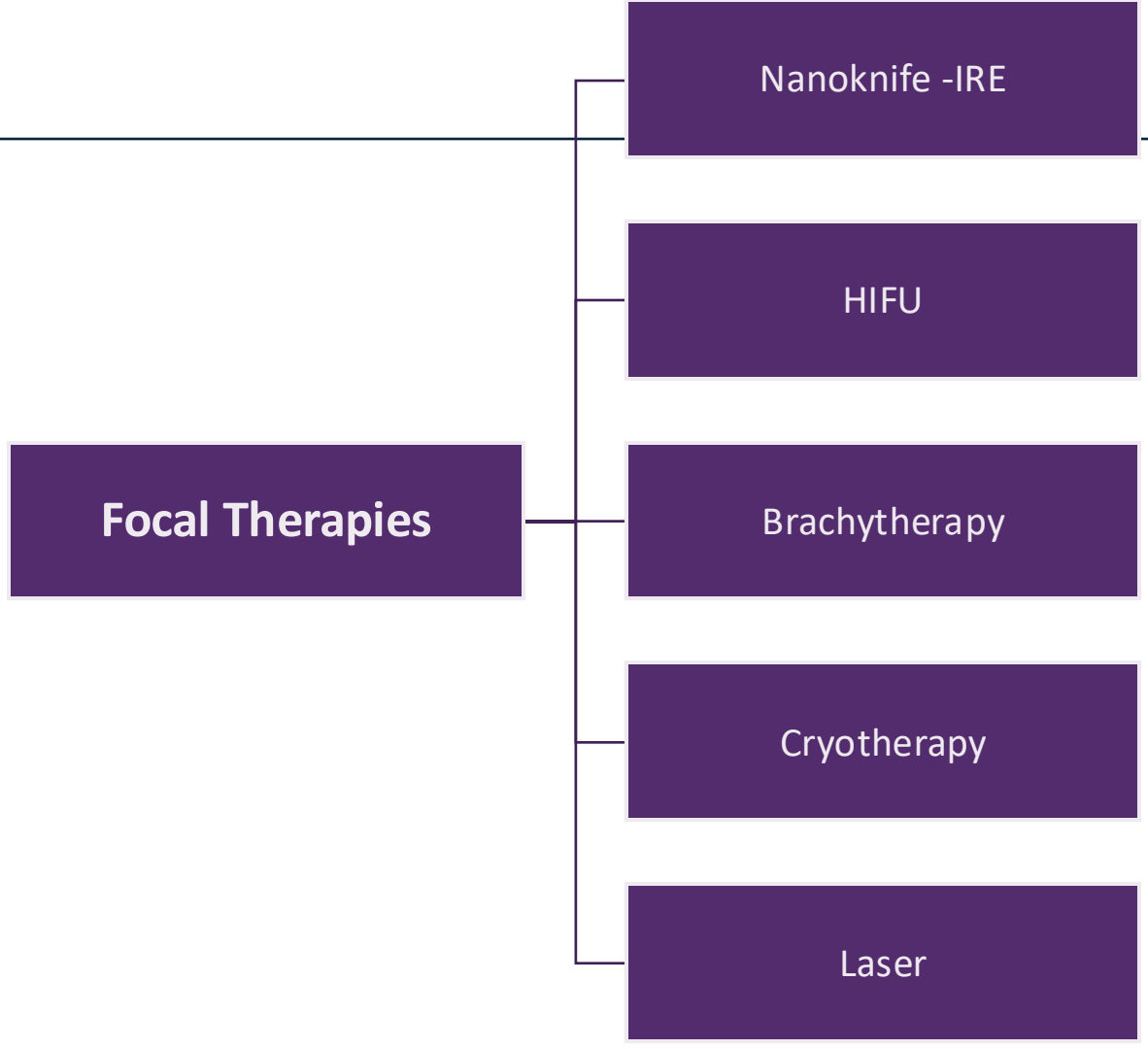
Whole-Gland Treatment

Focal Therapy for Prostate Cancer

- Not all patients are candidates for FA of PCa (<20%)

- Ideal Patient (Consensus Group)
  - Not Insignificant cancers→ Need AS
  - Gleason 3+4= 7 (ISUP 2) – With good prognosis – Helps avoid overtreatment and Excess Side effects of WGT
  - Focal (localised or unilateral)
  - Thoroughly evaluated with Transperineal Biopsy and High quality Imaging
  - Visible on Imaging (MRI or PSMA)
  - Co-registration between imaging and tissue biopsy
  - Must accept invasive/intensive follow-up Monitoring
  - High utility for preserving genito-urinary function
  - Awareness and acceptance of the uncertainties
  - Awareness and acceptance of salvage strategies

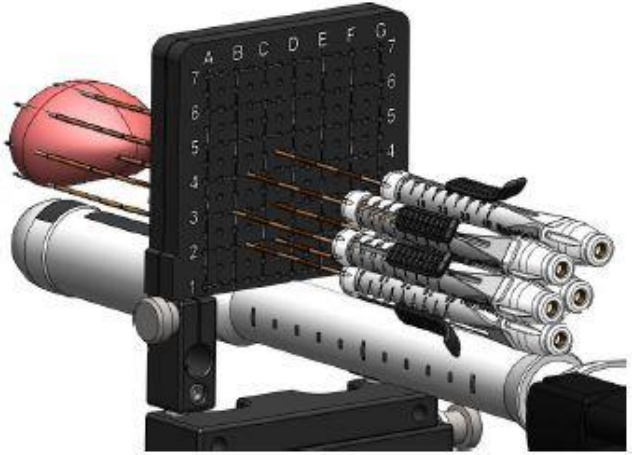
Guidelines of guidelines: focal therapy for prostate cancer, is it time for consensus?
Sean Ong, Kenneth Chen , Jeremy Grummet, John Yaxley, Matthijs J. Scheltema,Phillip Stricker , Kae Jack Tay and Nathan Lawrentschuk
BJU Int 2022 doi:10.1111/bju.15883


Focal Therapies
Nanoknife -IRE
HIFU
Brachytherapy
Cryotherapy
Laser

Irreversible Electroporation
Overview

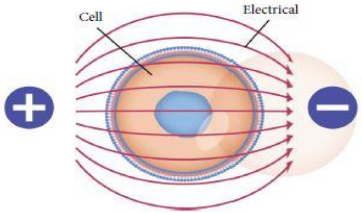
Mechanism of Action

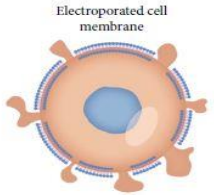
- Cell disruption through direct electric current



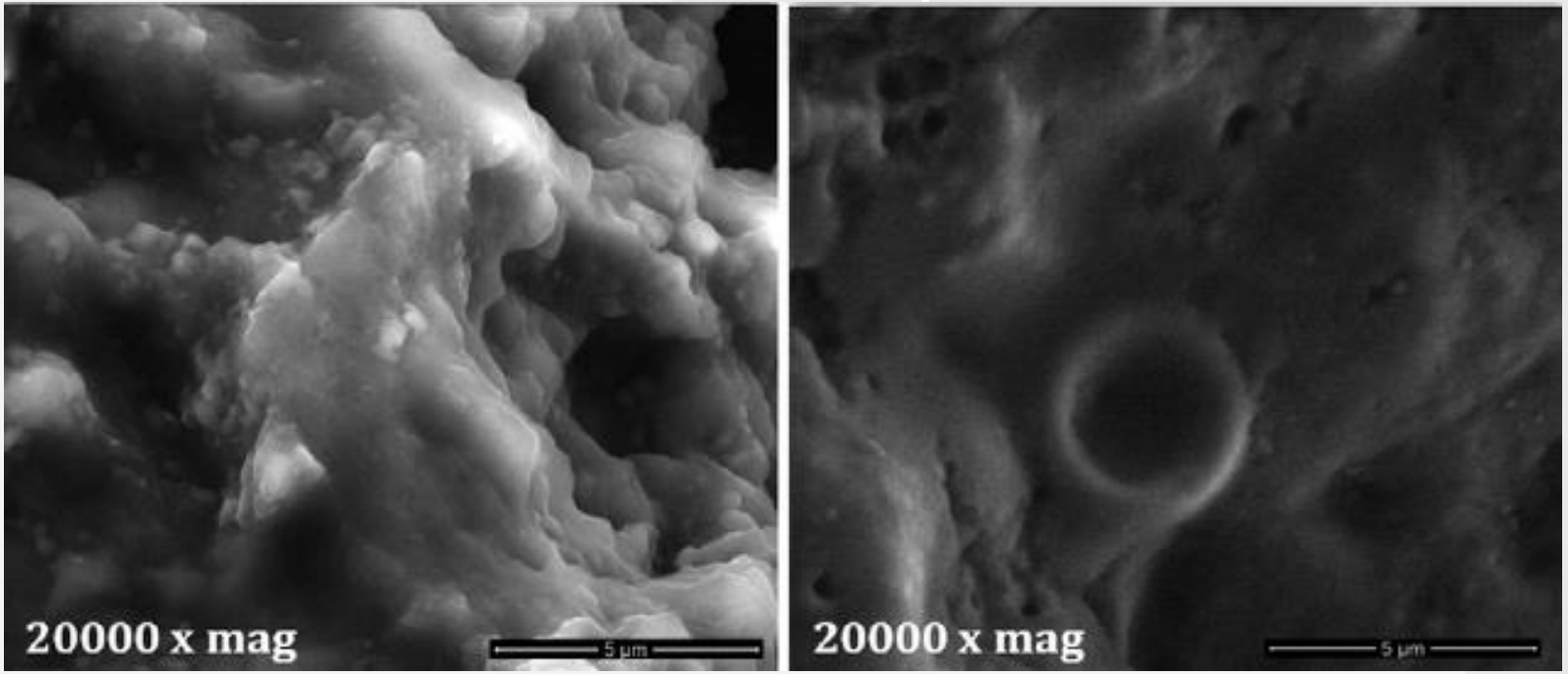
Location/methods

- Administered by transperineal application with patient in operating theatre

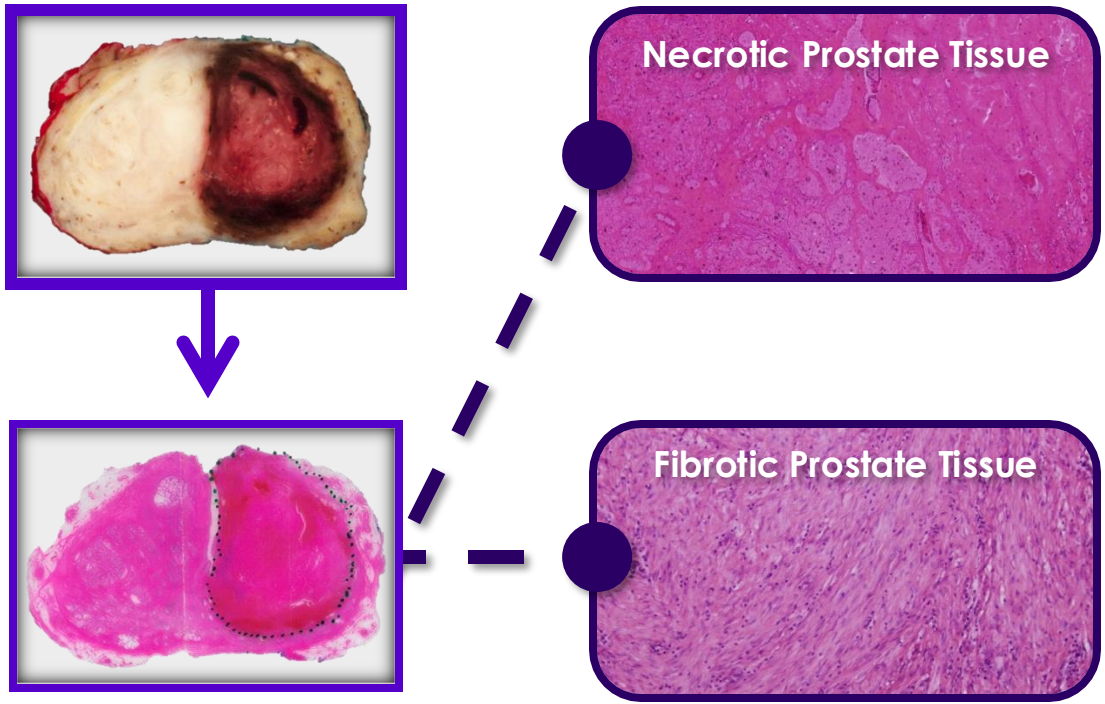




Irreversible Electroporation



IRE Provides Reliable Ablations



16 Patients
IRE & RP 4w later
No In-field viable tissue

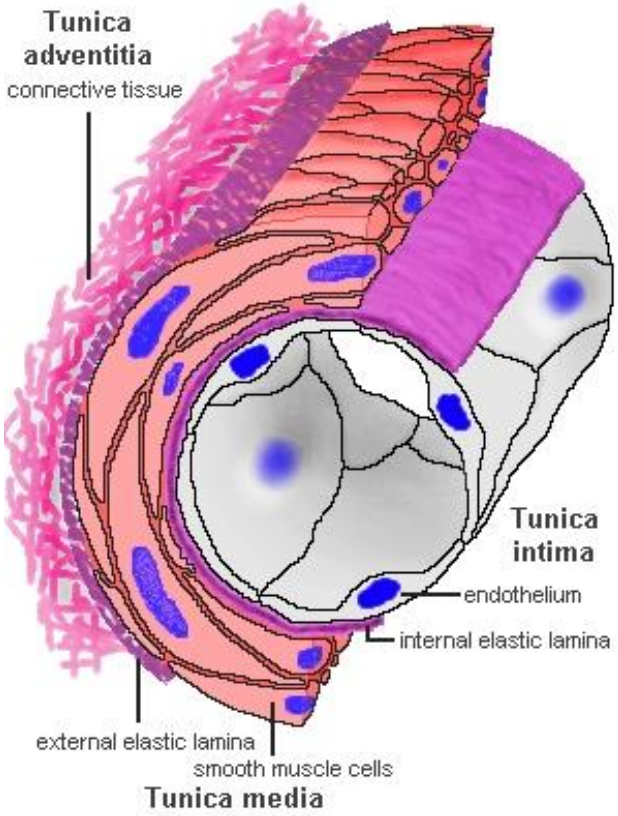
Histopathological Outcomes after Irreversible Electroporation for Prostate Cancer: Results of an Ablate and Resect Study

W. van den Bos,* R. R. Jurhill, D. M. de Bruin, C. D. Savci-Heijink, A. W. Postema, P. G. K. Wagstaff, B. G. Muller, I. M. Varkarakis, A. Skolarikos, P. J. Zondervan, M. P. Laguna Pes, T. M. de Reijke and J. J. M. C. H. de la Rosette†

From the Department of Urology (WvdB, DMdB, AWP, PGKW, BGM, PJZ, MPLP, TMdR, JJMCHdlR), Department of Pathology (RRJ, CDS-H), and Department of Biomedical Engineering & Physics (DMdB), Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, and 2nd Department of Urology, Athens Medical University, University of Athens, Athens, Greece (IMV, AS)

Van den Bos et al. J Urol 2016

IRE – Preservation of Tubular Structures



All cells in ablation zone are affected by electrical field while 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

Advantages of IRE

- Reliable ablation

- Relatively quick day surgery procedure

- Repeatable

- Potential preservation of structures

- Salvage RP still possible

IRE Has Minimal Limitations

- **Location** = Suitable in all segments *(Anterior, Apex, Posterior)*
- **Calcification or metal** = No effect
- **Peri-urethral** = Reliable ablation and no sloughing or strictures
- **ECE** = Able to extend extracapsular with less collateral damage
- **Non-Thermal** = Greater chance of erection recovery

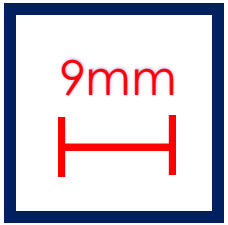
Short Procedure – 620 cases over 11 years

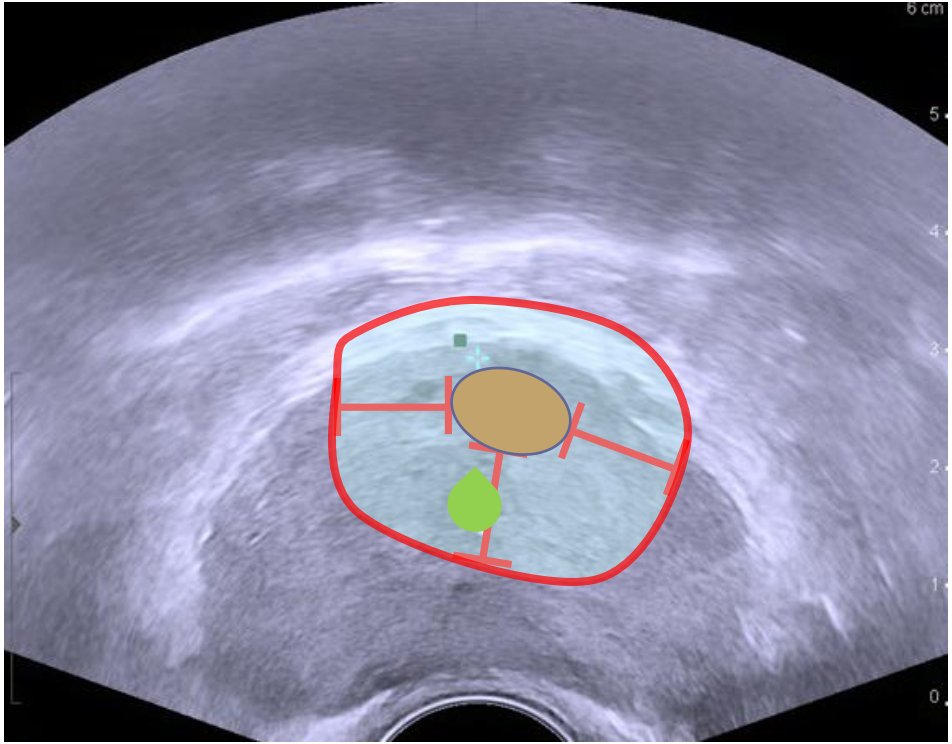
Within a urologist's skill set.
~45 to 60 minutes~

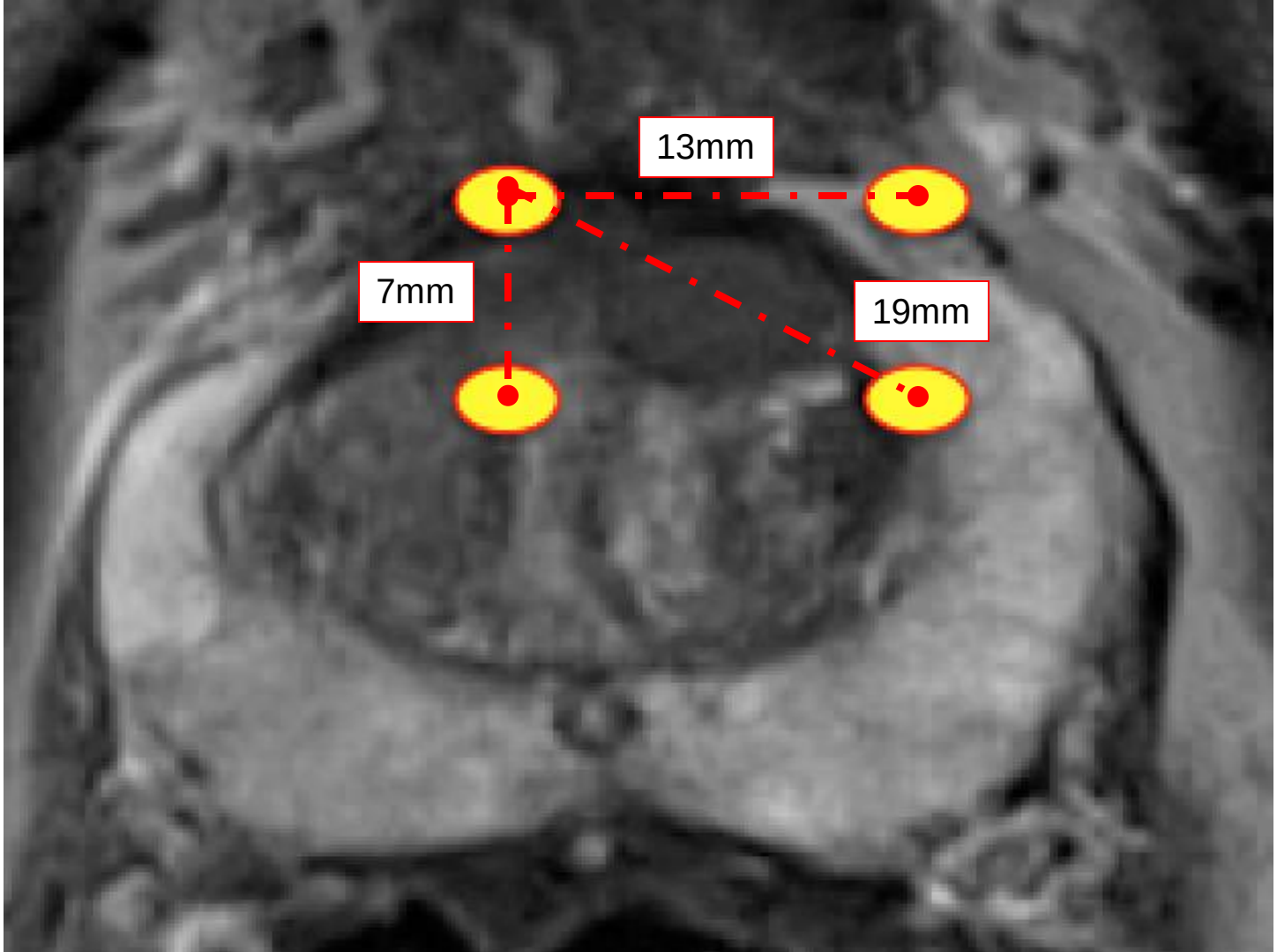
Ensuring Optimal Treatment Margin - Regionectomy

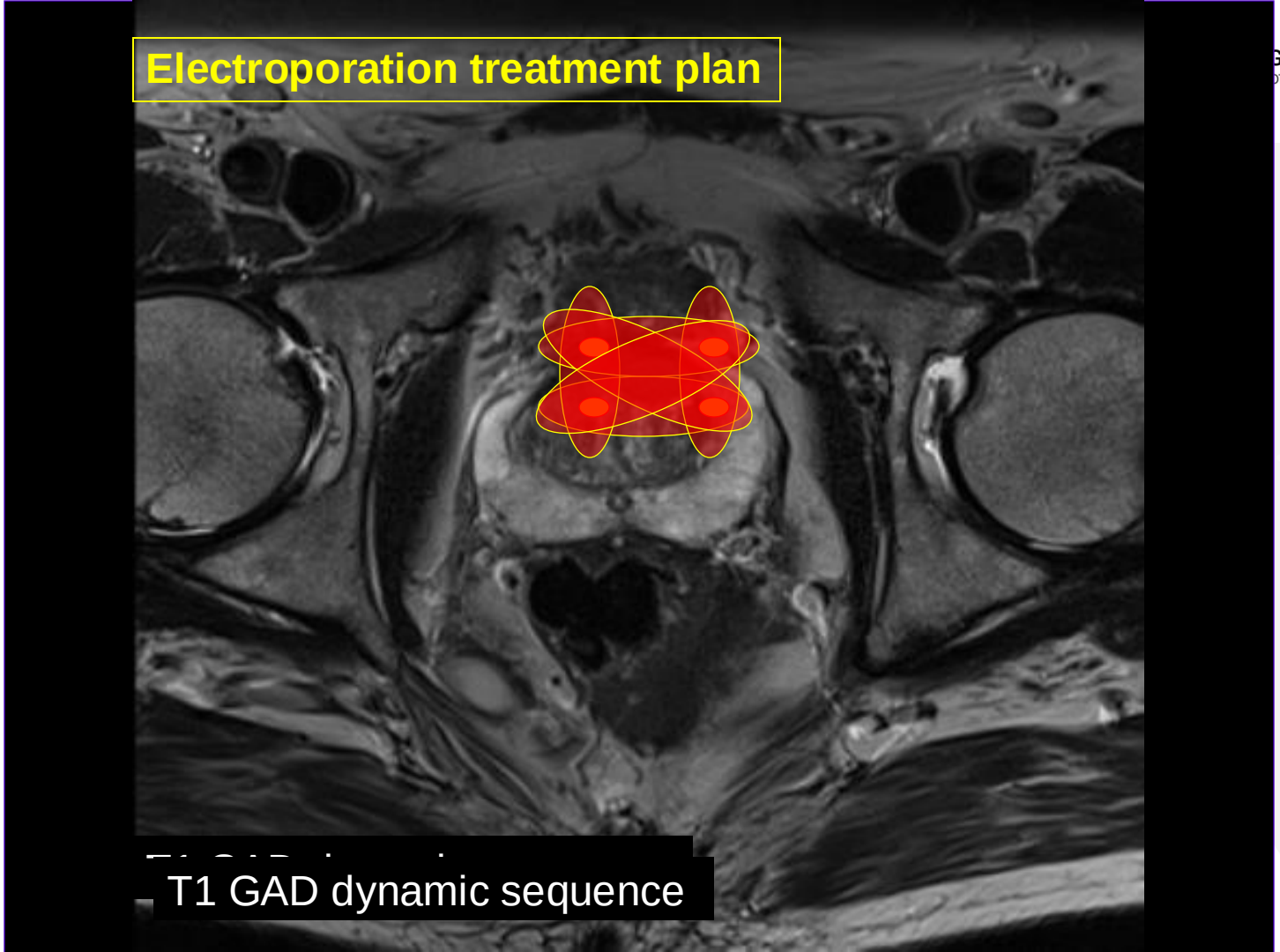
Nobin et al. 2015 overviewed mpMRI visible disease is an underestimation of true histological disease volume

Within prostatic tissue ≥9mm treatment margin should be applied to ensure optimal oncological control

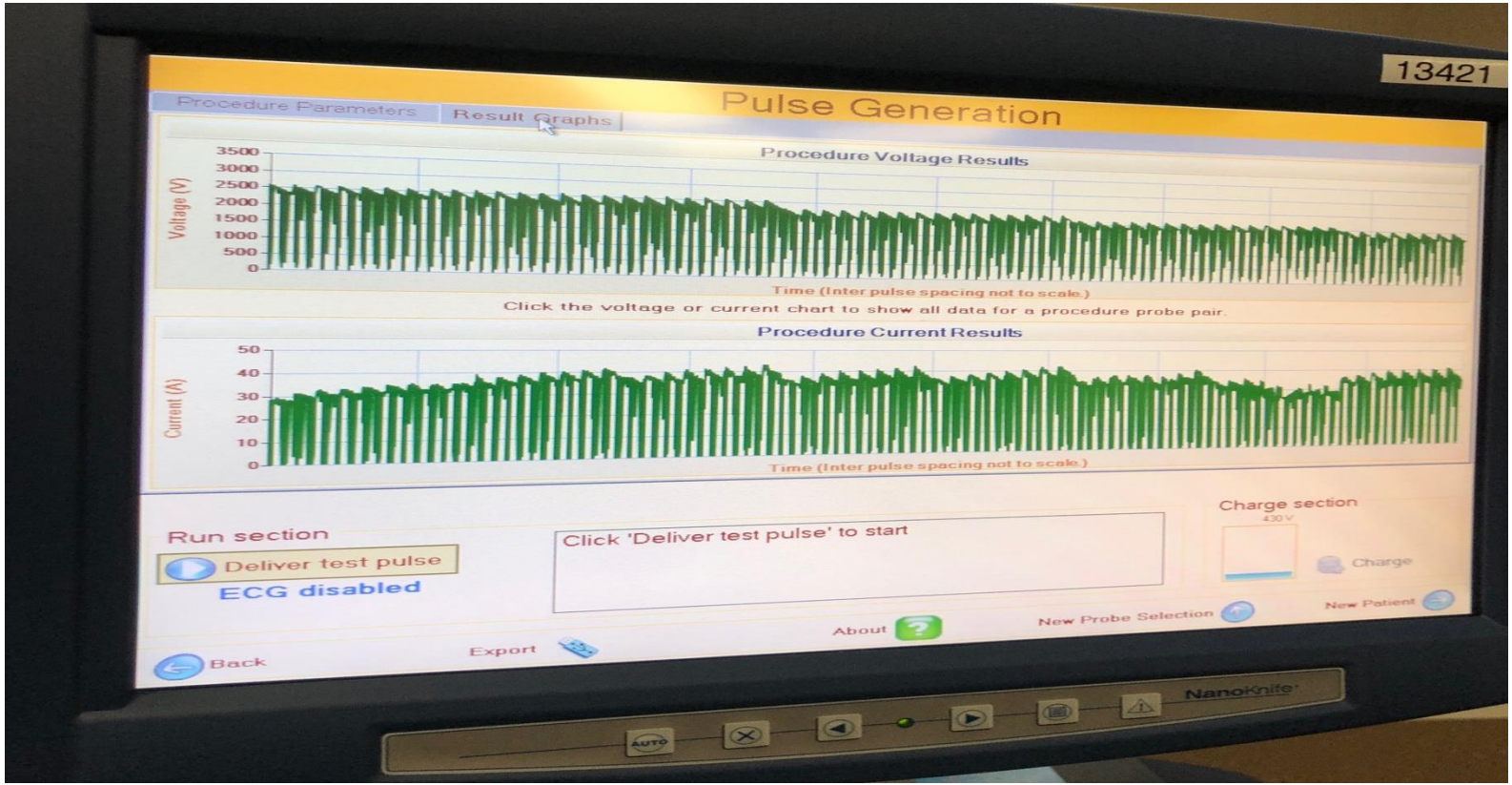




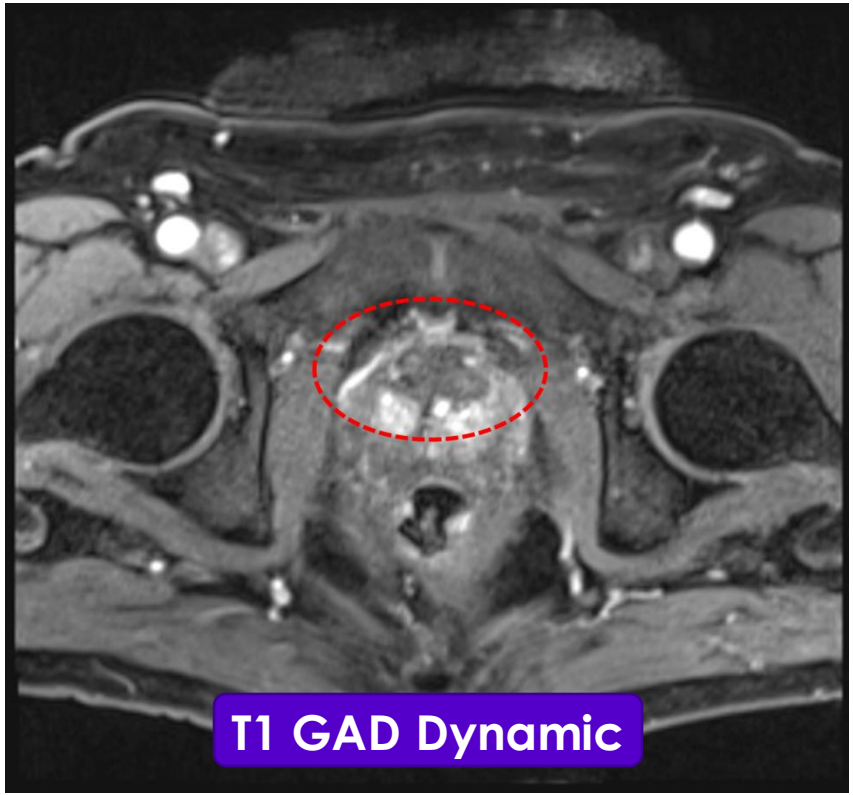

13mm
7mm
19mm


Electroporation treatment plan
T1 GAD dynamic sequence

NanoKnife Procedure



2-5 Days Post-Treatment limited MRI



Postoperative Monitoring

- PSA – every 3 months for the first year
- mpMRI – after 6 months (Initial limited MRI 2-7 days)
- QOL – Epic 6 monthly
- Per-protocol at 1 year (Only 80% agree) :
  Systematic transperineal biopsy + targeted biopsy (4-6 cores)

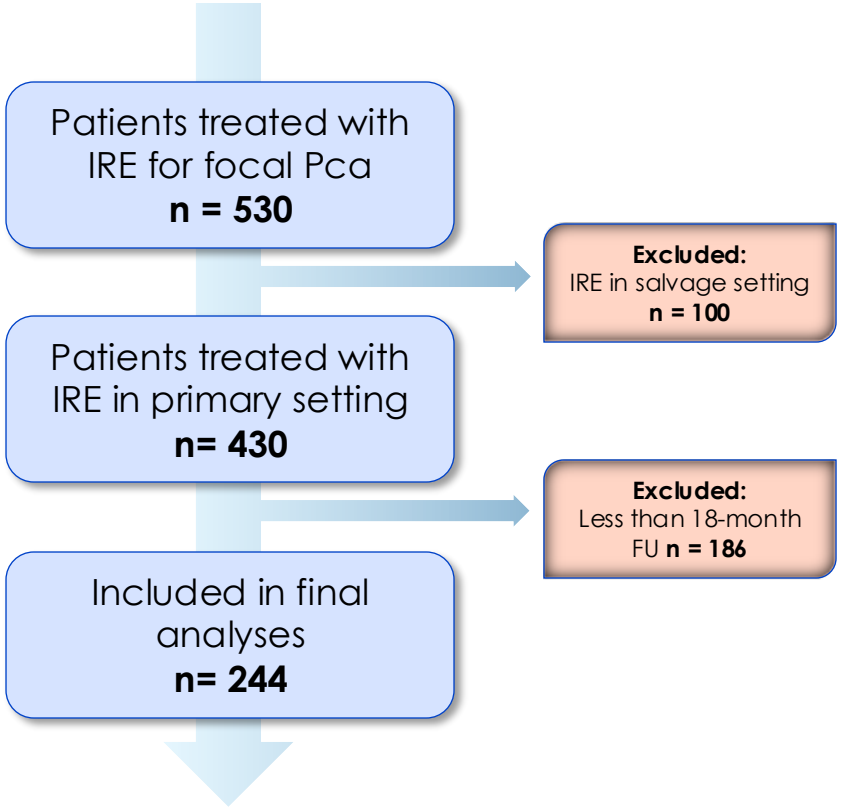
Primary IRE Results at SVH

Selection Criteria

- Patients with unifocal, localized prostate cancer
- ISUP grade 1–4
- Positive lesion on MRI
- Good co-registration biopsy/MRI
- PSA <15 ng/mL

Selection Method

- Transperineal saturation biopsies
- MRI-targeted biopsies if a lesion is seen



Median 5-year outcomes of primary focal irreversible electroporation for localised prostate cancer
Matthijs J. Scheltema , Bart Geboers , Alexandar Blazevski , Paul Doan, Athos Katelaris,Shikha Agrawal, Daniela Barreto, Ron Shnier, Warick Delprado, James E. Thompson and Phillip D. Stricker
BJU Int 2022 doi:10.1111/bju.15946

Primary IRE – Our 5-10 year Results

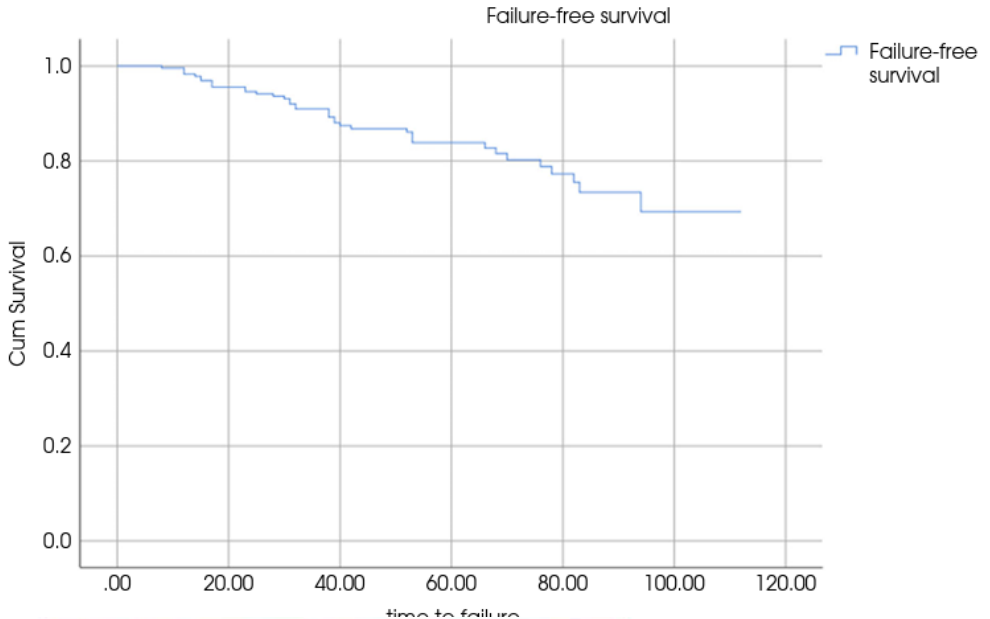
Oncological outcomes

- 12 month Btx: 3% infield recurrence, 14% outfield recurrence
- 5 year failure free survival of 83%
- 10 year estimated K-M failure free survival of 69%
- Metastasis free survival of 99,6% at 5 years

- <u>Radical treatment free survival;</u>

  83%

  - RP: 28
  - RT: 10
  - ADT: 1 → refused any FU



BJUI
BJU International

Original Article

Median 5-year outcomes of primary focal irreversible electroporation for localised prostate cancer

Matthijs J. Scheltema ✉ Bart Geboers, Alexandar Blazevski, Paul Doan, Athos Katelaris, Daniela Barreto, Ron Shnier, Warick Delprado, James E. Thompson, Phillip D. Stricker

Low In-Field Recurrence

European Association of Urology

Oncological and Quality-of-life Outcomes Following Focal Irreversible Electroporation as Primary Treatment for Localised Prostate Cancer: A Biopsy-monitored Prospective Cohort

Alexandar Blazevski[a,b,c,], Matthijs J. Scheltema[a,b,d], Brian Yuen[a,b], Natasha Masand[b,c], Tuan V. Nguyen[b,c,e], Warick Delprado[f], Ron Shnier[g], Anne-Maree Haynes[b], Thomas Cusick[b], James Thompson[a,b,c], Phillip Stricker[a,b,c]*

[a] St. Vincent's Prostate Cancer Centre, Darlinghurst, NSW, Australia; [b] Garvan Institute of Medical Research and Kinghorn Cancer Centre, Darlinghurst, NSW, Australia; [c] St Vincent's Clinical School, UNSW, Sydney, Australia; [d] Amsterdam UMC, Amsterdam, The Netherlands; [e] School of Biomedical Engineering, University of Technology, Sydney, NSW, Australia; [f] Douglas Hanly Moir Pathology, Macquarie Park, NSW, Australia; [g] I-MED Radiology, Sydney, NSW, Australia

	All patients	Excluding initial cohort
PSA nadir (IQR)	3.48 (1.43–5.67)	3.37 (1.04–5.7)
mpMRI at 6 mo (n = 112)		
Clear	90/112 (80%)	70/80 (87.5%)
In-field lesion	3/112 (2.6%)	1/80 (1.25%)
Adjacent to field (marginal)	6/112 (5.4%)	3/80 (3.75%)
Out-of-field lesion	11/112 (9.8%)	6/80 (7.5%)
In- and out-of-field lesion	6/112 (5.4%)	0
Biopsy results (n = 102)		
Median (IQR) number of cores taken	25 (22–31)	
Median (IQR) number of positive cores	1 (0–3)	2/74 (2.7)
Significant in-field disease, n (%)	10/102 (9.8)	9/74 (12.1)
Significant out-of-field disease, n (%)	13/102 (12.7)	63/74 (85.1)
Whole gland free of clinically significant cancer at 12 mo, n (%)	79/102 (77.5)	

IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; PSA = prostate-specific antigen.

In-field recurrence = **9.7%**

Out-of-Field recurrence =**12.7%**

In-field recurrence dropped to **2.7%** with refinement in technique and a including a 10 mm margin of ablation.

Functional Outcomes

- **Incontinence rate (≥1 pad/day)**
  - Baseline: 3/153 (2.0%)
  - Last follow-up (3-24 months): 3/130 (2.3%)

- **Erectile function sufficient for intercourse** **(with or without medication)**
  - Baseline: 105/151 (69.5%)
  - Last follow-up (3-24 months): 80/135 (59.3%)

- **Side Effects**
  - No Grade 3 or 4 complications
  - No rectal fistulas

Are These Results Translatable

IRE for focal therapy of prostate cancer – Brisbane results

Yaxley WJ et al. Investigative & Clinical Urology – accepted for publication March 2022

- 70 patients between August 2018 – August 2021
- Median follow up 23 months
- 50 primary IRE with > 12 months follow 40/50 proceeded to surveillance prostate biopsy
- Median ISUP grade 2, but 12/50 with ISUP grade 4-5
- Median PSA = 6.1 ug/L (0.77-25 ug/L)

	Wesley, Brisbane	SVH, Sydney
Total primary IRE patients	70	244
Median FU	23 months	50 months
% clear on TTMB	87.5%	83%
Sustained erections	85.7%	89.8%
Sustained continence	100%	97.7%

Teaching Programme 2018-24

USA - >40 centers
Australia – 8 centers
NZ – 2 centers
Europe - >40 Centers

Wesley,Royal
Brisbane
Brisbane

4 Masterclasses Yearly

Epworth,Cabrini
Melbourne

Is Salvage RP Succesful After IRE?

sRARP for primary IRE (sub-analysis)

RARP n=22 with median FU of 19 months

- Median time to RARP 39 months (IQR17-70)
- No major complications
- Negative margins 91% (20/22) (both GS3: 1.5mm/0.3mm)
- 45% pT2 disease; 55% pT3a disease, 0% pT3b
- 4% (1/22) In-field tumour on RARP specimen (GS3+4 left post apex)
- 4% (1/22) biochemical recurrence → Controlled after RT of prostate bed
- 100% continence (≤ 1 pad) by 6 months (96% (21/22) pad-free)
- 61% potent by 6 months

Van Riel et al. BJUI, 2022

10) Van Riel et al. BJUI, 2022;4:157-159 10.1016/j.euros.2022.02.012

Is IRE Repeatable ?

Redo-IRE in 10% (26/244) with median FU of 39 months

- Local control after 12 months 58% (15/26), overall 46% (12/26)
- No complications
- Progression to radical treatment in 54% (14/26) --> median time to Tx: 25 months
  - RARP: 38% (10/26)
  - RT: 15% (4/26)

IRE – Potential For Nerve Recovery

- Multicenter RCT
- Focal vs Extended IRE
- 106 Pts Low /Int Risk
- QOL Trial
- IIEF at <6m – Sig Diff

  >6m – No Sig Diff

IRE is associated with recovery of Sexual Function with time

RCT Trial Europe – Focal Vs Extended IRE

De La Rosette et al – J.Urol .2023 ;209(2):347-353

QoL Equal after Focal IRE in all Segments

DIR
Diagn Interv Radiol 2018; 24:268-275

INTERVENTIONAL RADIOLOGY
ORIGINAL ARTICLE

Impact on genitourinary function and quality of life following focal irreversible electroporation of different prostate segments

Matthijs J. Scheltema
John I. Chang
Willemien van den Bos
Ilan Gielchinsky
Tuan V. Nguyen
Theo M. de Reijke
Amila R. Siriwardana
Maret Böhm
Jean J. de la Rosette
Phillip D. Stricker

PURPOSE
We aimed to evaluate the genitourinary function and quality of life (QoL) following the ablation of different prostate segments with irreversible electroporation (IRE) for localized prostate cancer (PCa).

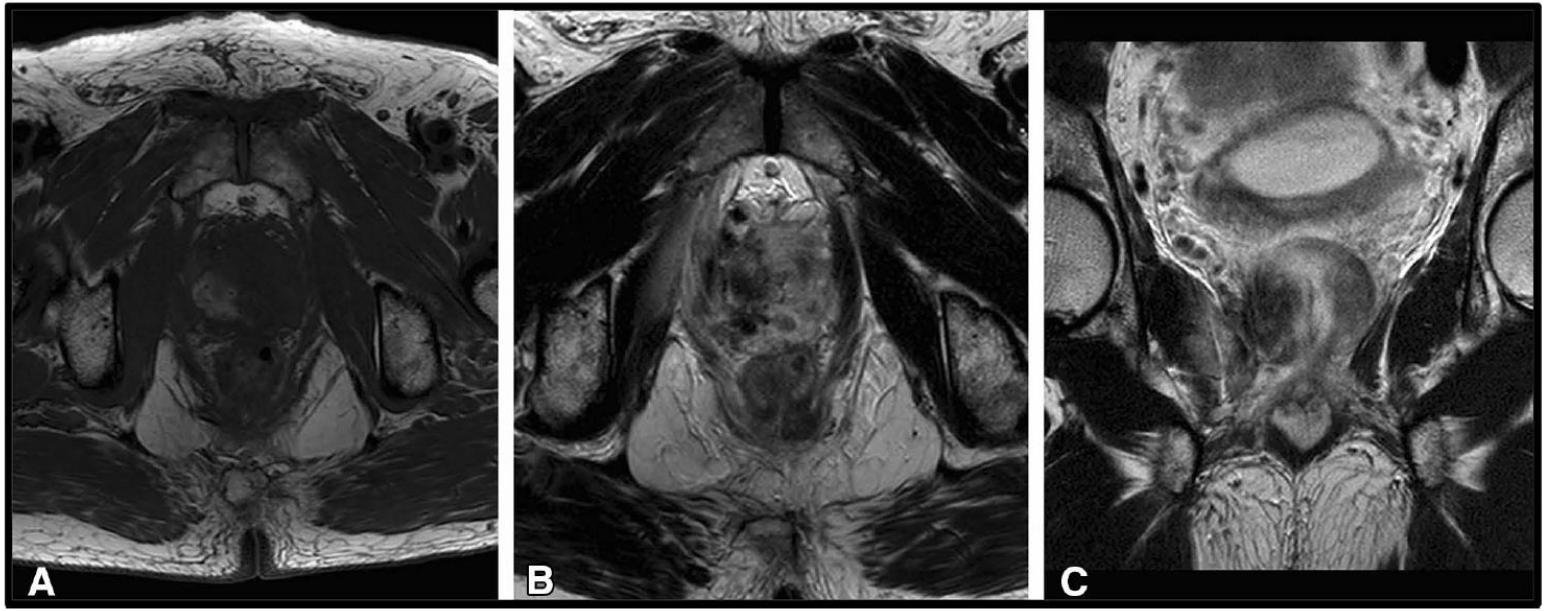
METHODS
Sixty patients who received primary focal IRE for organ-confined PCa were recruited for this study. Patients were evaluated for genitourinary function and QoL per prostate segment treated (anterior vs. posterior, apex vs. base vs. apex-to-base, unilateral vs. bilateral). IRE system settings and patient characteristics were compared between patients with preserved vs. those with impaired erectile function and urinary continence. Data were prospectively collected at baseline, 3, 6, and 12 months using the expanded prostate cancer index composite, American Urological Association symptom score, SF-12 physical and mental component summary surveys. Difference over time within segments per questionnaire was evaluated using the Wilcoxon's signed rank

IRE Is Suitable In All Prostate Segments

Apical Lesions; *50 patients*

Oncological infield recurrence 2.5%

2% incontinence rate at 12 months
0% at 24 months



Blazevski A, Amin A, Scheltema MJ, Balakrishnan A, Haynes AM, Barreto D, Cusick T, Thompson J, Stricker PD. Focal ablation of apical prostate cancer lesions with irreversible electroporation (IRE). World J Urol. 2021 Apr;39(4):1107-1114. doi: 10.1007/s00345-020-03275-z. Epub 2020 Jun 2. PMID: 32488359.

IRE –A Systematic Review

- 19 Studies , 1452 pts
- IF SigPC – 0-33% , Overall 8.4%
- OF SigPC – 0-30% , Overall 13.5%
- Re-Rx – 8-36%
- FFS 3yr=90-96% , FFS 5yr IR 83-85%
- Pad free rate - 98-100%
- Grade 3 Complications – 1-8%
- Potency Preservation - 92-93%

Original Article
Prostate cancer

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https://doi.org/10.5534/wjmh.240012

The World Journal of MEN's HEALTH

Irreversible Electroporation for the Focal Treatment of Prostate Cancer: A Systematic Review

Kai Zhang[1], Jeremy Teoh[2], Gang Zhu[1], Chi-Fai Ng[2], Michel Suberville[3], Pilar Laguna[4], Jean de la Rosette[4]

Falcon Focal Therapy Consensus

IRE – Bottom Line

- Mature 5-10 year Data
- Suitable for 20% of Patients
- 85% avoid Surgery or RT
- No Major Side effects
- No Incontinence , Minimal Erection issues
- Day Procedure
- All options still open

Many Competing Energy Sources

Energy	Median reported rates of clinically significant cancer following ablation
HIFU	15% (range 0 to 22%)
Cryoablation	Up to 20%
IRE	8.5% (range 0 to 33%)
Laser	16.5% (range 4 to 40%)
Photodynamic	10 to 13%

Morgan et al.,(2024). Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part I: Introduction and Treatment Decision-Making at the Time of Suspected Biochemical Recurrence after Radical Prostatectomy. The Journal of urology, 211(4), 509–517. https://doi.org/10.1097/JU.0000000000003892

High-Intensity Focused Ultrasound - (HIFU)

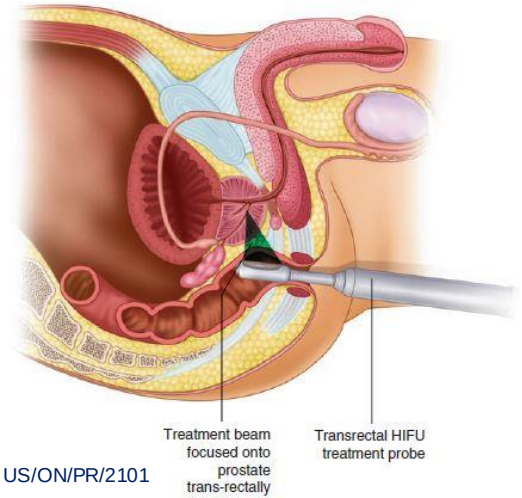
Overview

Mechanism of Action

- High Intensity US waves delivered by transrectal probe to a focal point [1]
- Immediate and irreversible coagulation necrosis with temperature >60ºC [1]

Location/methods

- Administered transrectally in operating theatre with patient under general [2]



Polascik TJ, ed. Imaging and Focal Therapy of Early Prostate Cancer. 2nd ed. Cham, Switzerland: Springer International Publishing; 2017 p. 45, 311.
Blazevski A, Scheltema MJ, Amin A, Thompson JE, Lawrentschuk N, Stricker PD. Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment. BJU Int. 2020 Mar;125(3):369-378. doi: 10.1111/bju.14951. Epub 2019 Dec 5. PMID: 31725935.

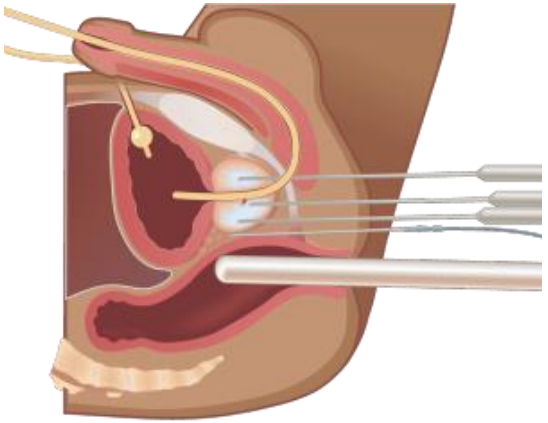
Cryoablation
Overview

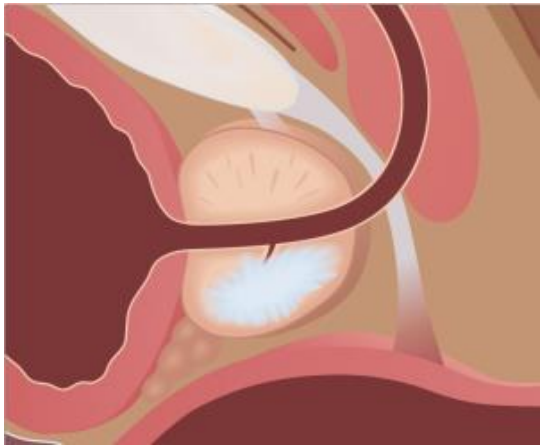
Mechanism of Action

- Freezing that leads to cell rupture by ice crystal formation, oedema and ischaemic apoptosis
- Application of cold temperature of less than -40°C and then thawing of at least 2 cycles

Location/methods

- Administered by transperineal application with patient in operating theatre





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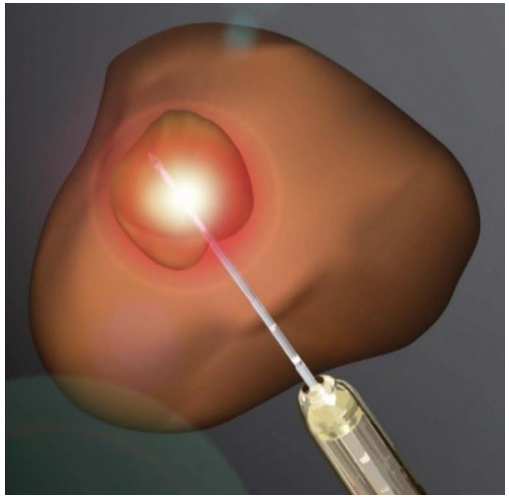
Focal Laser Ablation
Overview

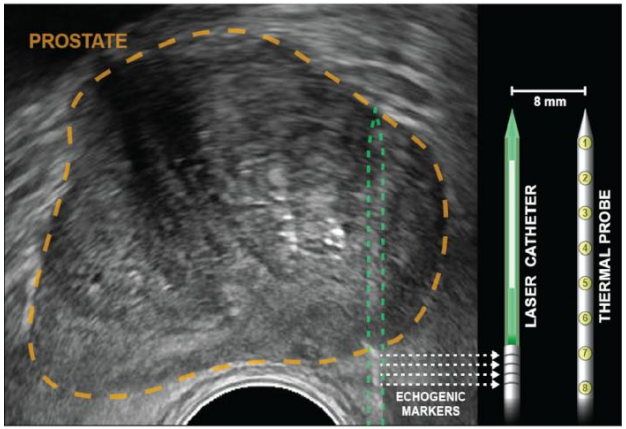


Mechanism of Action

- Photothermal injury through high-energy laser light

Location/methods

- In-bore transperineal or transrectal
- Or Ultrasound guided
- Under conscious sedation



Blazevski A, Scheltema MJ, Amin A, Thompson JE, Lawrentschuk N, Stricker PD. Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment. BJU Int. 2020 Mar;125(3):369-378. doi: 10.1111/bju.14951. Epub 2019 Dec 5. PMID: 31725935.

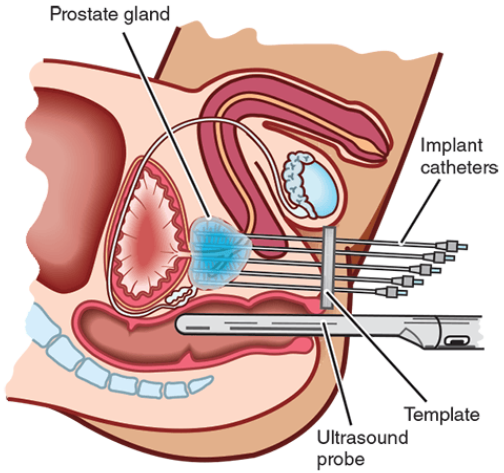
Focal Brachytherapy
Overview

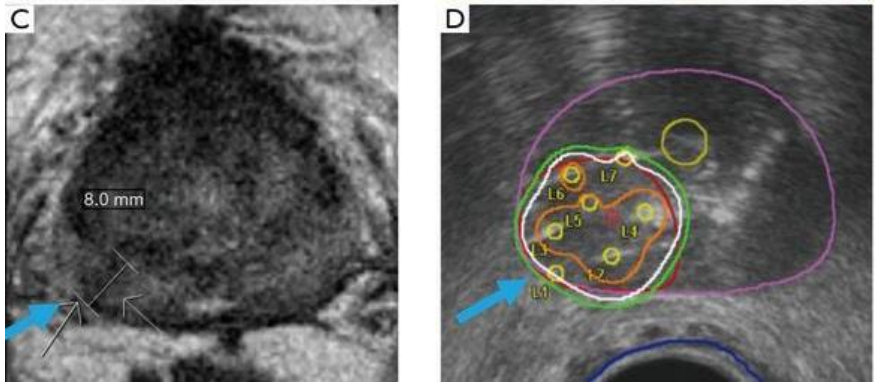
Mechanism of Action

- Radioactive sources are placed in the targeted area of the gland

Location/methods

- Administered by transperineal application with patient in operating theatre
- May also be completed in-bore





Blazevski A, Scheltema MJ, Amin A, Thompson JE, Lawrentschuk N, Stricker PD. Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment. BJU Int. 2020 Mar;125(3):369-378. doi: 10.1111/bju.14951. Epub 2019 Dec 5. PMID: 31725935.

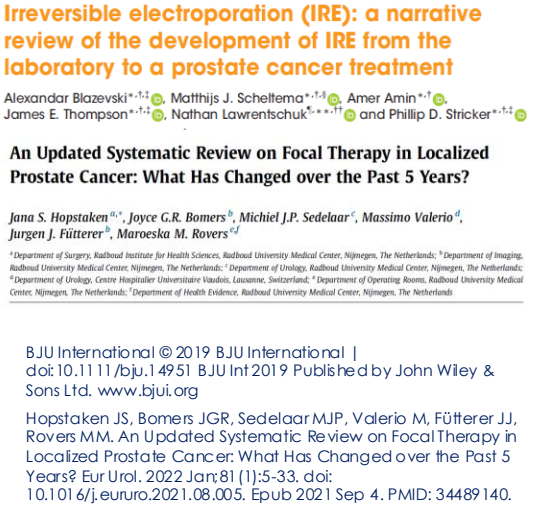
Functional Outcomes of Focal Therapies

Energy	Studies	Pad-free continence %	Worsening of EF%
HIFU	26 studies	93.3 - 100	0 - 75
Cryoablation	22 studies	92 - 100	3 – 94.4
IRE	14 studies	92 - 100	4 - 32
Focal Brachytherapy	11 studies	100	0 - 50
FLA	10 studies	100	0 – 22.2
PDT	8 studies	93.3 - 100	11 - 32
MWA	3 studies	100	0 - 6
Partial Prostatectomy	3 studies	92 - 100	17
RFA	2 studies	100	NR
PAE	1 study	100	NR

Nicoletti et al.,(2023). Functional outcomes and safety of focal therapy for prostate cancer: a systematic review on results and patient-reported outcome measures (PROMs). Prostate cancer and prostatic diseases, 10.1038/s41391-023-00698-8. Advance online publication. https://doi.org/10.1038/s41391-023-00698-8

Concerns About Other Energies

- **HIFU**
  - Prostate size, calcification and extreme apex
  - High Infield Recurrence in Salvage Series
- **Laser**
  - Extreme apex, ECE, Difficult to broaden field, Inbore
  - Short Followup
- **Cryo**
  - Limitations – Urethral sparing, ECE, Extreme Apex
- **Brachy**
  - Not Repeatable,
  - Unknown effect on Untreated zone



Irreversible electroporation (IRE): a narrative review of the development of IRE from the laboratory to a prostate cancer treatment

Alexandar Blazevski[*,†,‡], Matthijs J. Scheltema[*,†,§], Amer Amin[*,†], James E. Thompson[*,†,‡], Nathan Lawrentschuk[¶,**,††] and Phillip D. Stricker[*,†,‡]

An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years?

Jana S. Hopstaken[a,*], Joyce G.R. Bomers[b], Michiel J.P. Sedelaar[c], Massimo Valerio[d], Jurgen J. Fütterer[b], Maroeska M. Rovers[e,f]

[a]Department of Surgery, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; [b]Department of Imaging, Radboud University Medical Center, Nijmegen, The Netherlands; [c]Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands; [d]Department of Urology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; [e]Department of Operating Rooms, Radboud University Medical Center, Nijmegen, The Netherlands; [f]Department of Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

BJU International © 2019 BJU International | doi: 10.1111/bju.14951 BJU Int 2019 Published by John Wiley & Sons Ltd. www.bjui.org

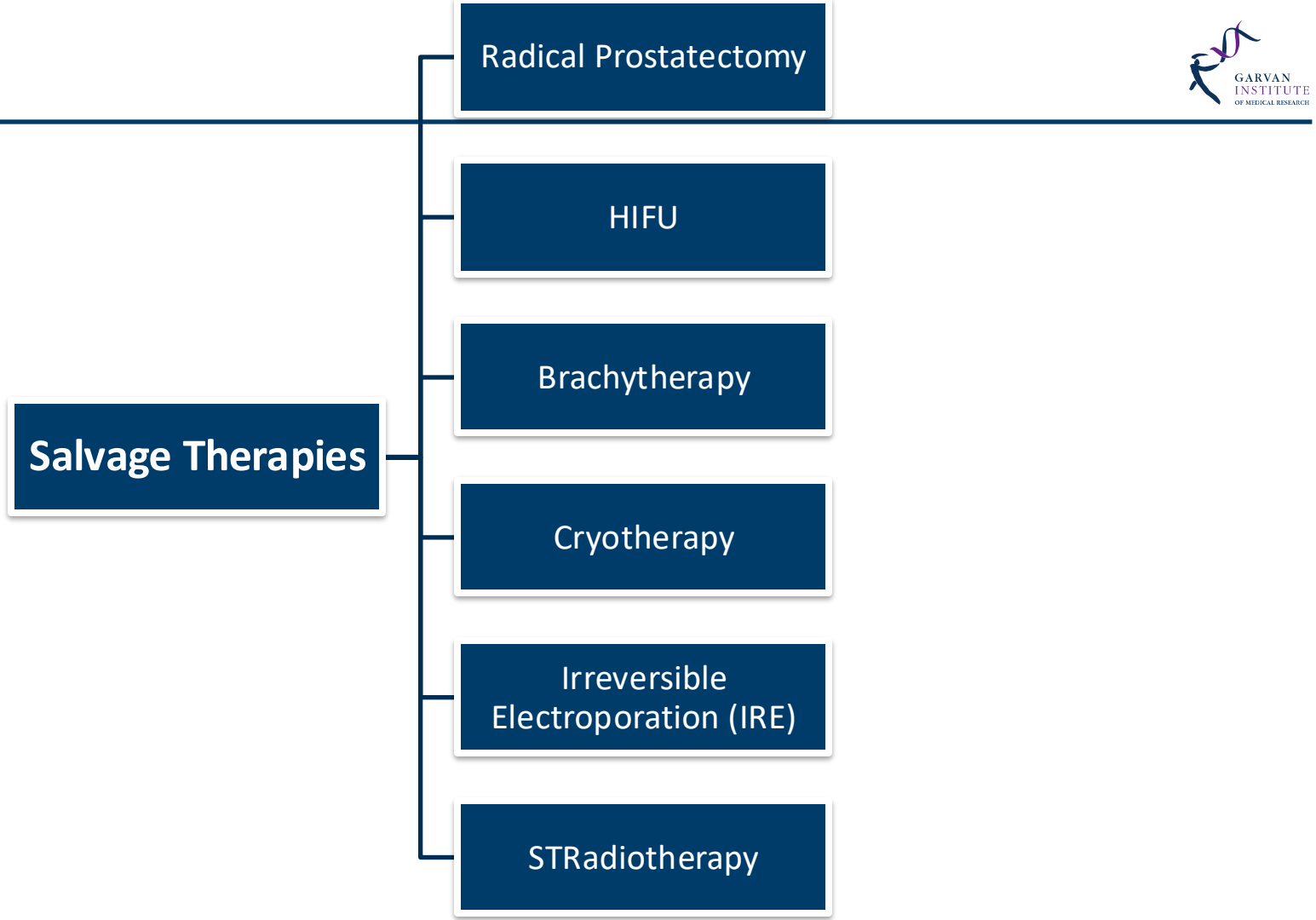
Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years? Eur Urol. 2022 Jan;81(1):5-33. doi: 10.1016/j.eururo.2021.08.005. Epub 2021 Sep 4. PMID: 34489140.

How Does IRE Compare

Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An Updated Systematic Review on Focal Therapy in Localized Prostate Cancer: What Has Changed over the Past 5 Years? Eur Urol. 2022 Jan;81(1):5-33. doi: 10.1016/j.eururo.2021.08.005. Epub 2021 Sep 4. PMID: 34489140.

*7 recent publications not included in Systematic Review

Energy Source	# Studies	Patients (n)	Median Follow-up	In-field failure	SAEs > 2 DC	Pad free %	Erectile Dysfunction	Salvage
HIFU	27	75 (12-1032)	25 mo (6-45)	15.4% (0-22%)	(0-13.9%)	95%	20%	13.4% (6.0-31.3%)
Focal Laser Ablation	8	26 (7-120)	12 mo (3-34)	16.5% (4-40%)	<1%	100%	NS or NR	(1.7-14.3%)
Cryoablation	11	89 (17-317)	19 mo (6-58.3)	15% (0-20%)	(0-9%)	83%-100%	31%	11.5% (7.7-24.2%)
Focal Brachytherapy	8	30 (9-50)	24 mo (6-48)	(0-12%)		100%	0-50%	5.9%
***Irreversible Electroporation**	**15**	**55 (12-229)**	**21.5 mo (7-60)**	**7.0% (0-33%)**	**(0-4%)**	**100% (92-100%)**	**7.3% (0-16%)**	**11.4% (0-36.6%)**


Salvage Therapies
Radical Prostatectomy
HIFU
Brachytherapy
Cryotherapy
Irreversible Electroporation (IRE)
STRadiotherapy

Salvage IRE Post RT

BJU Int 2023 doi:10.1111/bju.15948

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Original Article

Median 4-year outcomes of salvage irreversible electroporation for localized radio-recurrent prostate cancer

Bart Geboers[1,2], Matthijs J. Scheltema[1,3], Alexandar Blazevski[1,2,3], Athos Katelaris[1,2], Paul Doan[1,2,3], Imran Ali[2], Shikha Agrawal[1,2], Daniela Barreto[1,2], Jayne Matthews[2], Anne-Maree Haynes[1,2], Warick Delprado[4], Ron Shnier[5], James E. Thompson[1,2,3] and Phillip D. Stricker[1,2,3]

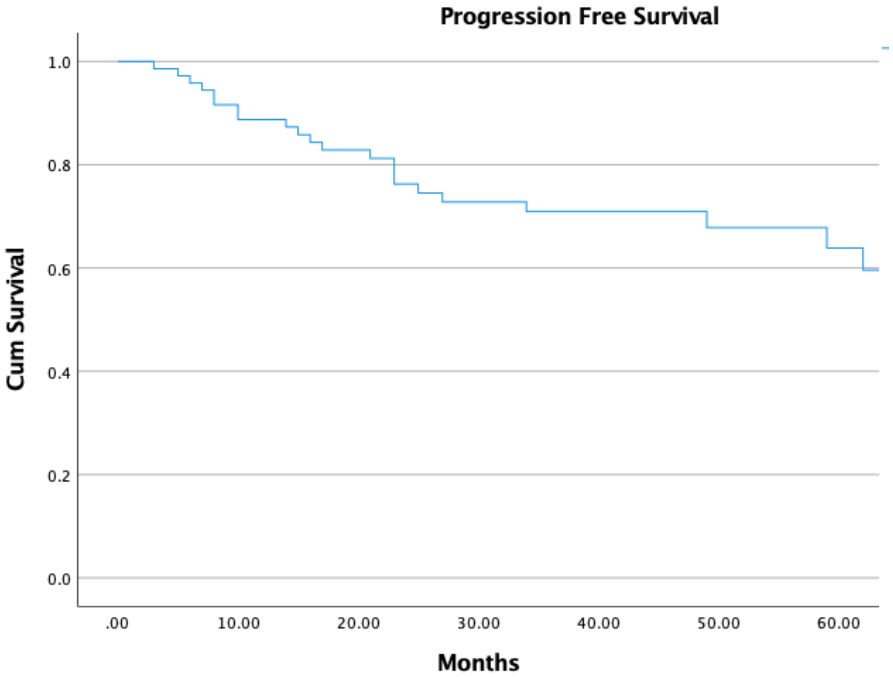
[1]Garvan Institute of Medical Research & The Kinghorn Cancer Centre, [2]Department of Urology, St. Vincent's Prostate Cancer Research Centre, Darlinghurst, Sydney, [3]St. Vincent's Clinical School, University of New South Wales, [4]Douglass Hanly Moir Pathology, and [5]I-MED Radiology, Sydney, NSW, Australia

Salvage IRE Outcomes SVH

Oncological outcomes

Total follow-up of 74 Patients

- **Median FU 32 months** (IQR 18-48)
- Disease progression occurred in 22 patients (29%)
- Overall median **Progression Free Survival 34 months** (IQR 37-54)



Median PFS: 34 months (IQR 16-52)

Kaplan-Meier curve on progression-free survival

(i.e. no signs of local / systemic disease after IRE)

BJU Int 2023 doi:10.1111/bju.15948

BJUI BJU International

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Median 4-year outcomes of salvage irreversible electroporation for localized radio-recurrent prostate cancer

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Conclusions

- 9% of patients require TURP in follow-up due to urethral sloughing
- 93% of patients preserved urinary continence
- Additional erectile disfunction in 15%
- Local control at 12 months was achieved in 91%
- 77% of patients required no salvage therapy

Salvage IRE is feasible, safe, and has minimal morbidity and acceptable early oncological outcomes

Geboers B et al. Median 4-year outcomes of salvage irreversible electroporation for localized radio-recurrent prostate cancer. BJU Int. 2023 Jun;131 Suppl 4:14-22. doi: 10.1111/bju.15948. Epub 2023 Jan 3. PMID: 36594205.

Comparison to published data

	WGT/Focal	2yr RFS	5yr RFS	Severe GU	Severe GI
Salvage RP	100/0	69%	54%	21%	1.9%
Cryotherapy	93/7	68%	50%	15%	1.7%
HIFU	86/14	54%	53%	23%	1.6%
IRE	0/100	80%	60%	9%	0%
HDR	85/15	77%	60%	8.0%	0.0%
LDR	92/8	81%	56%	8.1%	1.5%

Source: Valle et al. (2020). A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). European Urology, 80(3): 280-292.

IRE – Future Perspectives and Trials

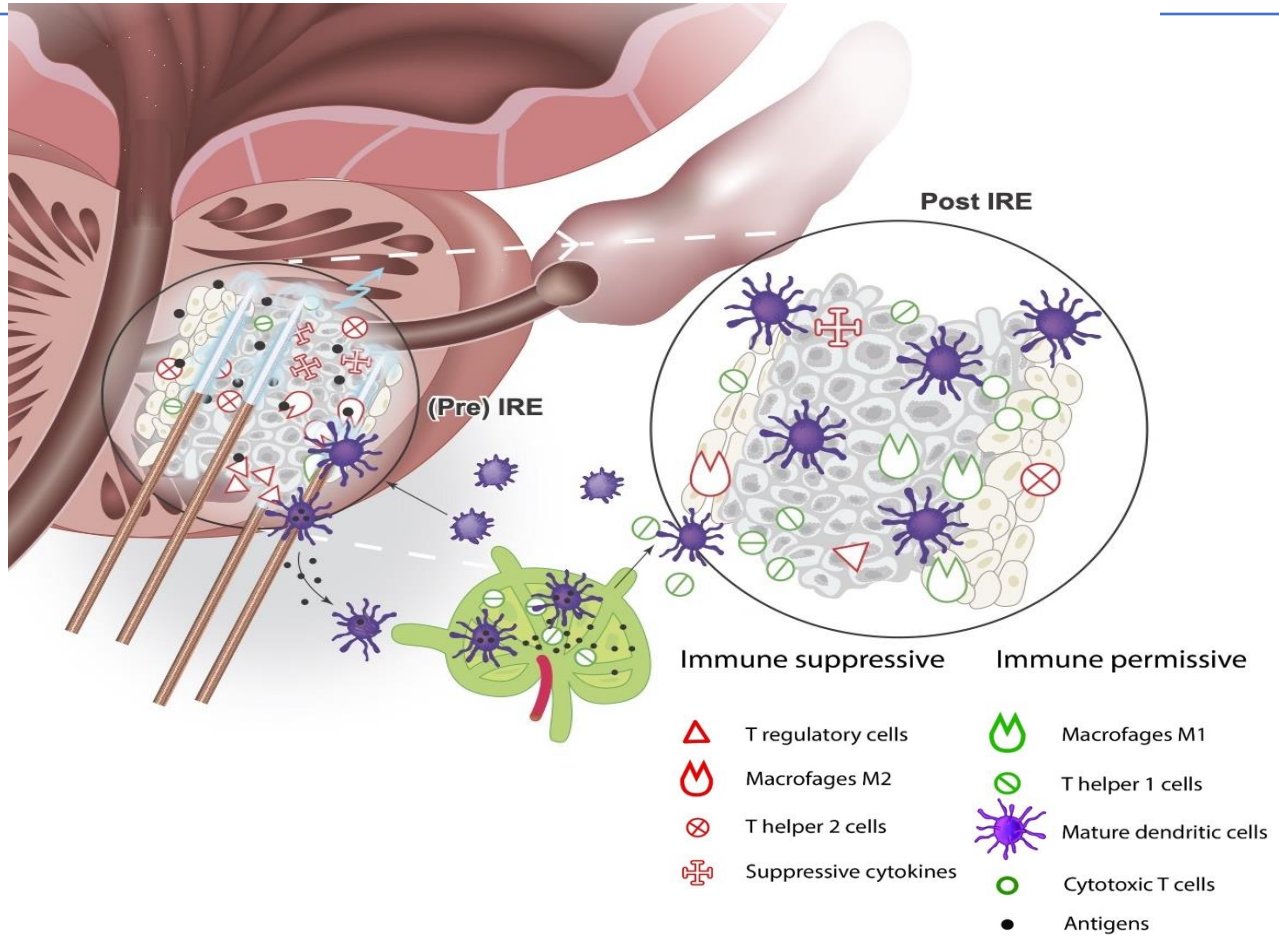
- Wider Acceptance
- Better Patient Selection - PSMA
- Immune effect
- Multicentre Registries
- RCTs
- FDA Preserve Trial Results

NICE Updates – July 5th, 2023

IRE no longer experimental.

IRE to be performed for PC with special arrangements for clinical governance, consent , and audit or research.

IRE – Potential Immune Effect



Can IRE Induce an Immune Response ? – B Geboers

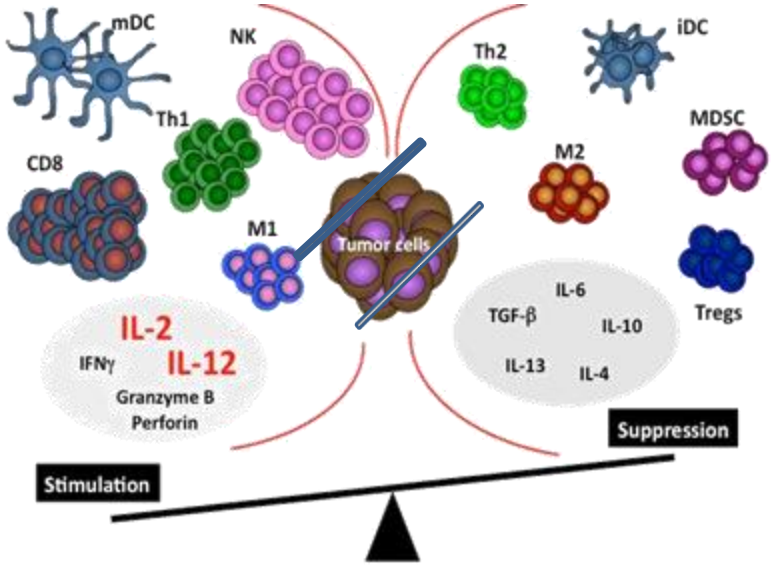
IRE → <u>in-vivo vaccination</u>

- Reduced tumour induced immune suppression
- Massive antigen release for effective tumour antigen presentation and T-cell activation
- Intact vasculature allows effective immune cell migration

+

Immunotherapy

May benefit Metastatic lesions ??



IRE – Prospective Multicenter Registries

Study Title:
Multi-Centre Registry for Oncological and Quality of Life Outcomes of Irreversible Electroporation (IRE) of Prostate Cancer

Short Title: Multi-Centre Registry IRE

This is a multi-Centre Registry to assess oncological outcomes defined by recurrence of prostate cancer and/or need for salvage treatment at 1,3, 5, and 10 years, after IRE, as well as the change in functional outcomes (e.g. incontinence or erectile function) from baseline, and to collect information on possible differences between centres.

Ongoing data will be collected in a central database at Baseline and up to 10 years post IRE Nanoknife® to include The Expanded Prostate Cancer Index Composite (EPIC) quality of life surveys.

International and Australia-wide study Centres involved:

- St. Vincent's Prostate Cancer Research Centre (New South Wales, Australia)
- Wesley Medical Centre (Brisbane, Australia)
- Cabrini Malvern (Melbourne, Australia)
- Tel Aviv, Israel (Site TBC)
- Netherlands (Site TBC)

Currently Recruited 43 patients

BJU Int 2023 doi:10.1111/bju.16207

BJUI
BJU International

Original Article

Prostate-specific membrane antigen positron emission tomography in addition to multiparametric magnetic resonance imaging and biopsies to select prostate cancer patients for focal therapy

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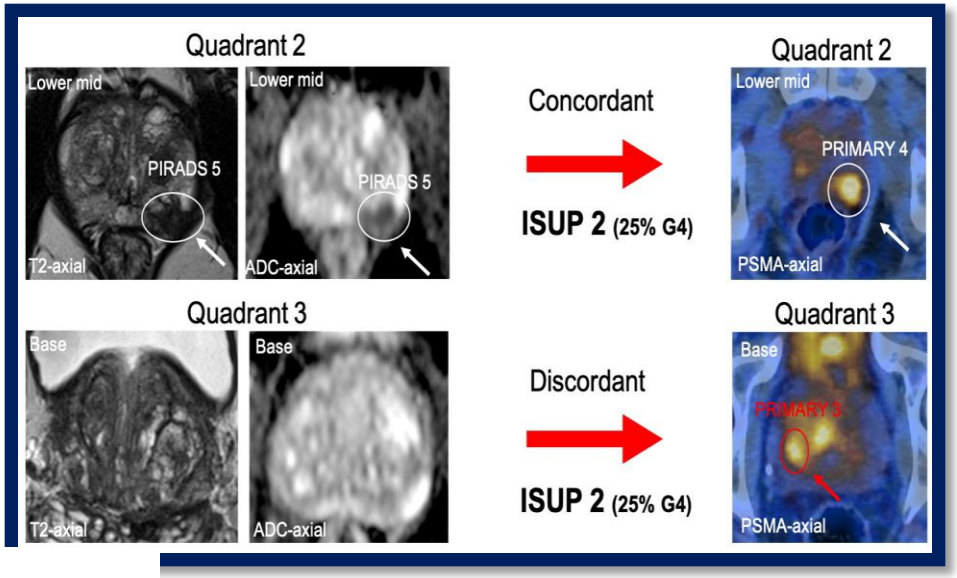
PSMA Improves Patient Selection

138 Patients – Retrospective

- MRI , PSMA, TPBX , RP
- Suitable for Focal Hemiablation
- PSMA – Found 26/46(57%) unsuitable Pts
  - 4/138 (3%) false Pos



BJU International

PSMA-PET in Addition to mpMRI and Biopsies to Select Prostate Cancer Patients for Focal Therapy

DOI: 10.1111/bju.16207

Status: In Production

PSMA in Patient Selection

In primary intermediate risk PCa patients that meet FT consensus criteria:

- Addition of PSMA-PET/CT has superior Diagnostic Accuracy to conventional combination of mpMRI and TMB

- Addition of PSMA-PET/CT correctly identifies +/- 50% of non-suitable FT patients

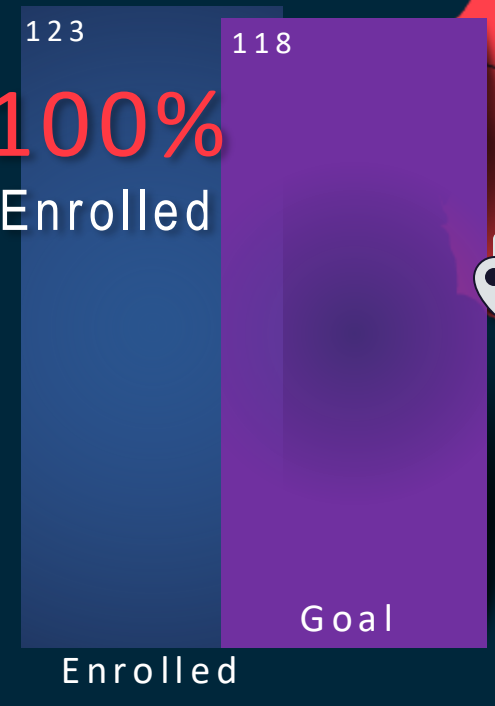
- Addition of PSMA-PET/CT might reduce outfield NanoKnife recurrences from 12% **to 6%**

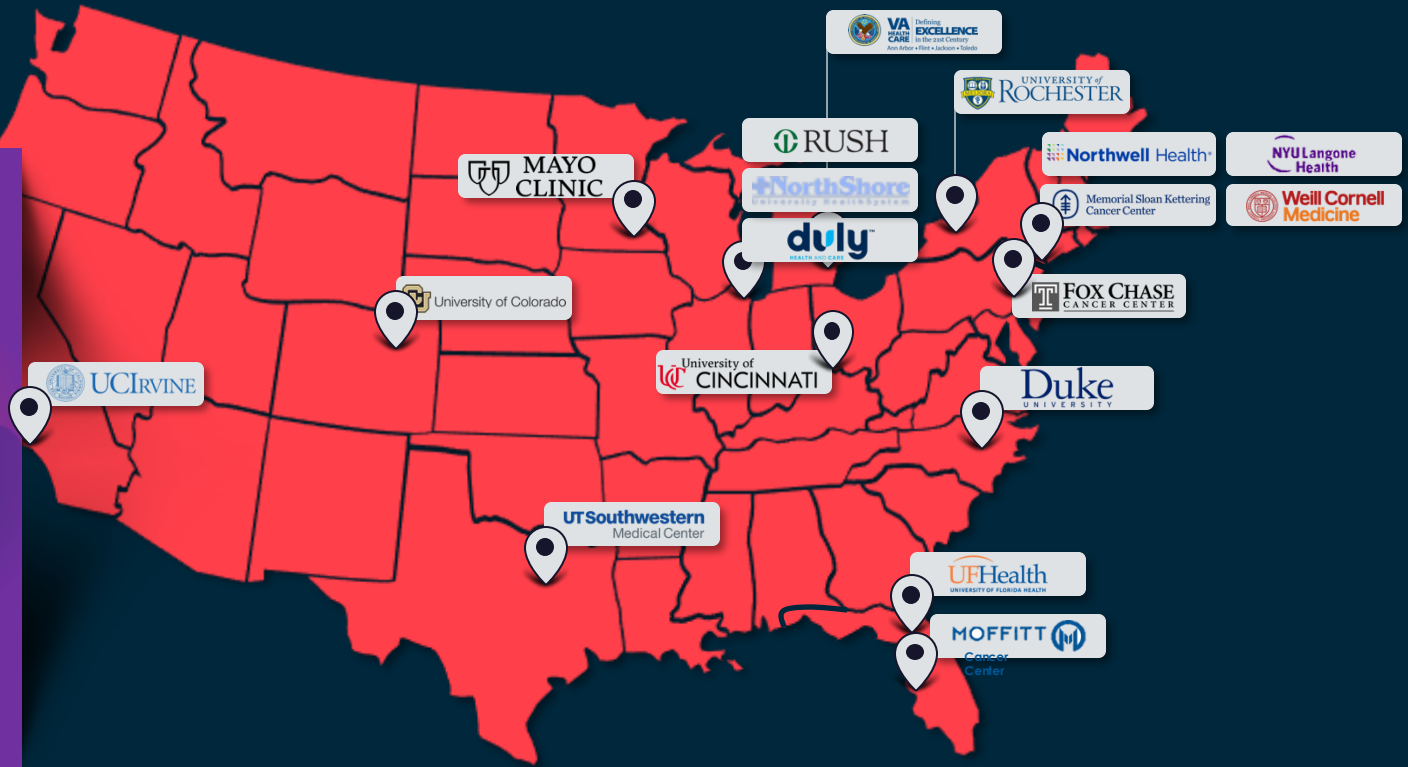
Addition of PSMA-PET/CT to workup could improve patient selection for FT
Prospective study is currently accruing

PRESERVE

ACTIVE SITES

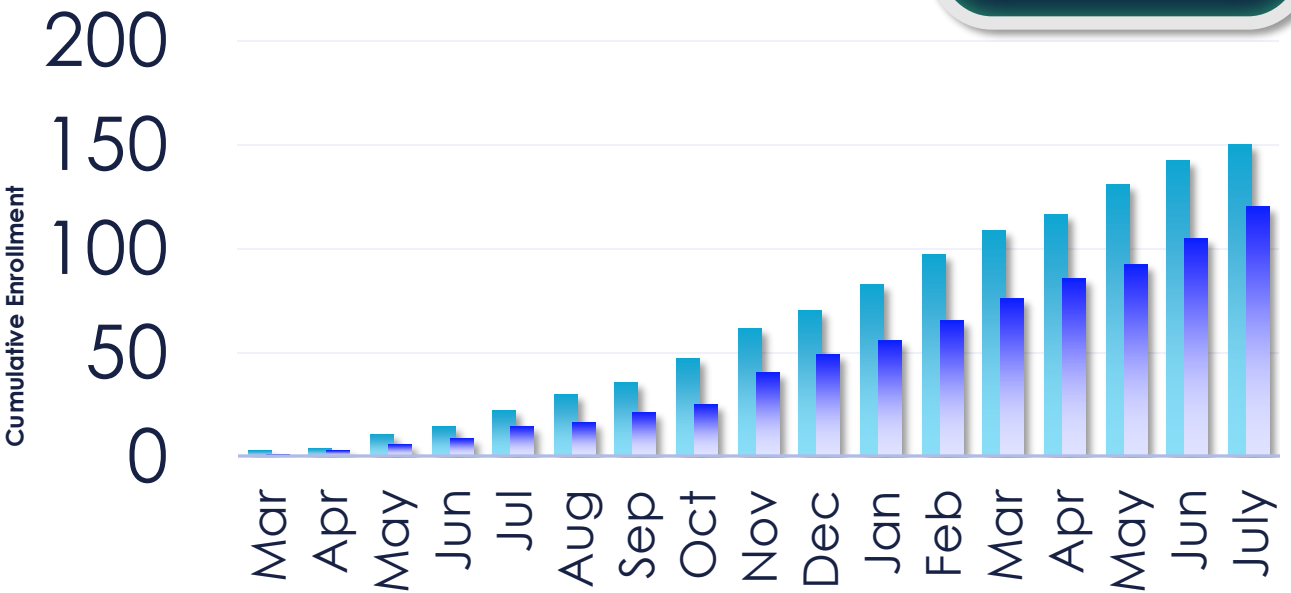
NanoKnife
Irreversible Electroporation (IRE)



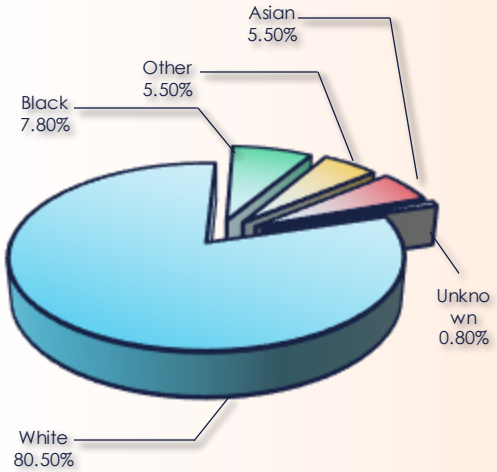


PRESERVE Update – Fully Enrolled

Consented: 151
Treated: 121



PRESERVE
Demographics



SITU
SURGICAL INTERVENTION TRIALS UNIT

PART

UNIVERSITY OF OXFORD

A randomised controlled trial of **P**artial prostate **A**blation versus **R**adical **T**reatment in intermediate risk, unilateral clinically localised prostate cancer

NUFFIELD DEPARTMENT OF SURGICAL SCIENCES
Medical Sciences Division

CI: Richard Bryant
Surgical Intervention Trials Unit (SITU)
Nuffield Department of Surgical Sciences, University of Oxford

FUNDED BY
NIHR | National Institute for Health and Care Research

PRIS Trial - IRE vs RP

Prostate Cancer IRE Study (PRIS): A Randomized Controlled Trial Comparing Focal Therapy to Radical Treatment in Localized Prostate Cancer

Anna Lantz[a,b,], Per Nordlund[c], Ugo Falagario[b,d], Fredrik Jäderling[b,e], Orhan Özbek[f], Mark Clements[a], Andrea Discacciati[a], Henrik Grönberg[a], Martin Eklund[a], Phillip Stricker[g], Mark Emberton[h], Markus Aly[b], Tobias Nordström[a,i]*

RCT – IRE vs RP or RT
184 Patients
Functional Outcomes
> 50 Randomised

https://doi.org/10.1016/j.euros.2023.03.003

Epigenetic Marker - GSTPi

Peters *et al. BMC Genomics* (2024) 25:251
https://doi.org/10.1186/s12864-024-10027-5

BMC Genomics

RESEARCH Open Access

Characterisation and reproducibility of the HumanMethylationEPIC v2.0 BeadChip for DNA methylation profiling

Timothy J. Peters[1,2], Braydon Meyer[1,2], Lauren Ryan[1,2], Joanna Achinger-Kawecka[1,2], Jenny Song[1], Elyssa M. Campbell[1,2], Wenjia Qu[1], Shalima Nair[1], Phuc Loi-Luu[1], Phillip Stricker[1,2,3], Elgene Lim[1,2], Clare Stirzaker[1,2], Susan J. Clark[1,2*†] and Ruth Pidsley[1,2*†]

How Does IRE Compare?

- Intermediate term data (up to 10 years)
- Safe and easily integrated
- Minimal collateral damage (urethra, sphincter, nerves)
- Oncological results at least equal to other technologies (high in-field clearance)
- Functional results equal or superior to other technologies
- Repeatable
- Applicable to all segments of the prostate
- Suitable for primary and salvage cases

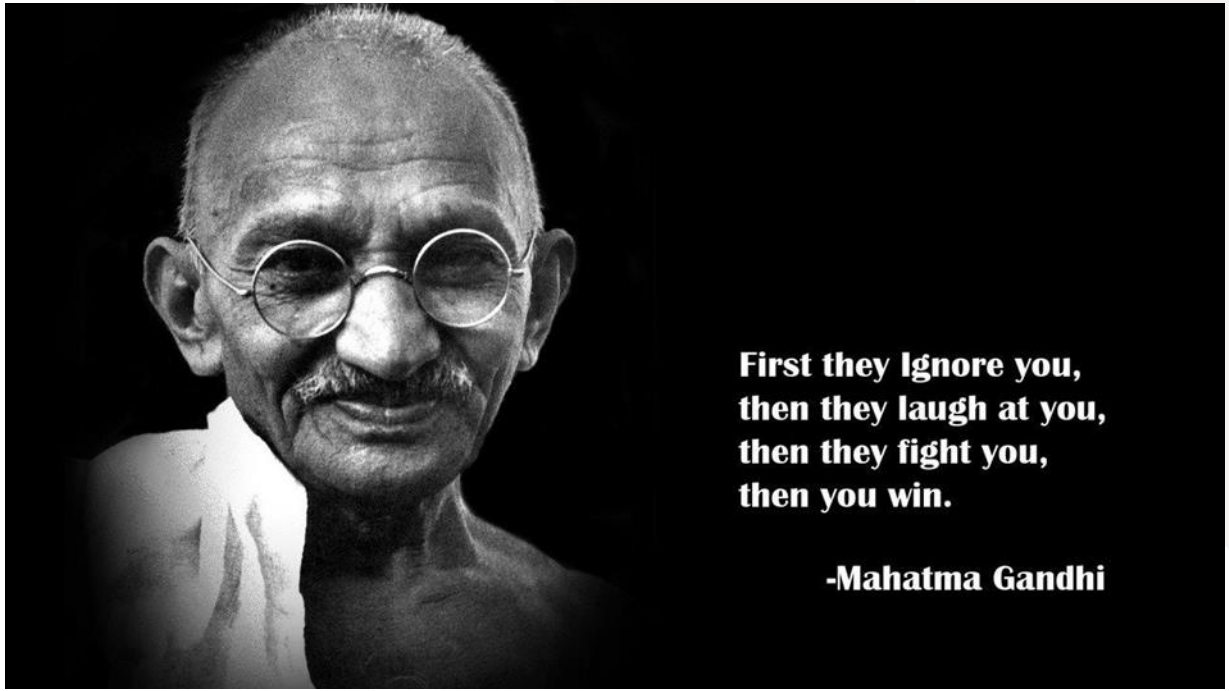
When will IRE be reimbursed ?

- MSAC application submission April 2024
- Aim for a Medicare item number
- Currently no focal therapy is reimbursed
- Multisite registry commenced based at Garvan
- 10 year data available , NICE approval in England and now reimbursed through NHS , FDA Preserve trial completed , Multiple centres now trained across Australia

Conclusions

- Focal Ablation with IRE(Primary and Salvage) is suitable for men with unilateral, localised intermediate risk prostate cancer
- Strict follow up is essential! (Imaging and Biopsy)
- IRE provides reliable in-field ablation with acceptable medium term oncological and functional outcomes
- Patient Selection needs to improve (? Epigenetics ?PSMA)
- Long Term Registries are essential and are underway

Focal prostate therapy is NOT THE FUTURE – it's THE PRESENT



A focal therapy programme has to embrace the most stringent quality control measures

Garvan Institute of Medical Research

- Exceptional imaging
- True partnership with radiology
- Near perfect risk stratification
  - No net upgrading at radical prostatectomy
  - High detection rates
- Expert management of energy sources
- Commitment to long term follow-up (registries)
- **A key (and possibly defining) component of high quality comprehensive cancer care**

ST VINCENT'S HOSPITAL
SYDNEY

Discussion