Biophysics, Mechanics and Technique of Irreversible Electroporation (IRE) of Prostate Cancer – Why and How We Do It Differently from (Almost) Everybody Else

Michael K. Stehling, MD, PhD
Director, Institut für Bildgebende Diagnostik and Prostata Center, Frankfurt/Offenbach, Germany
Visiting Scholar, University of California, Berkeley, USA

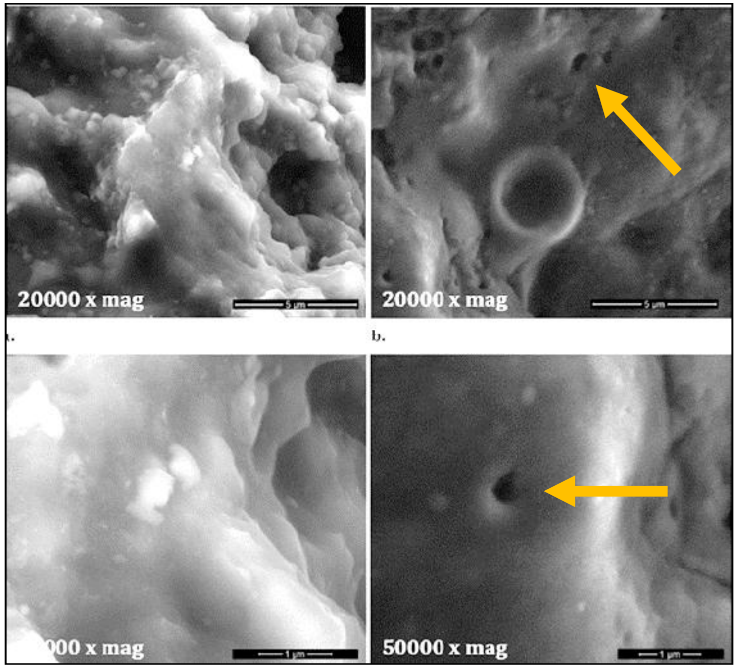
Enric Günther, Dipl. phys., Stefan Zapf, MD, Nina Klein, MSc Biophysics,
Institut für Bildgebende Diagnostik and Prostata Center, Frankfurt/Offenbach, Germany
Boris Rubinsky, PhD
Department of Mechnical Engineering, University of California, Berkeley, USA

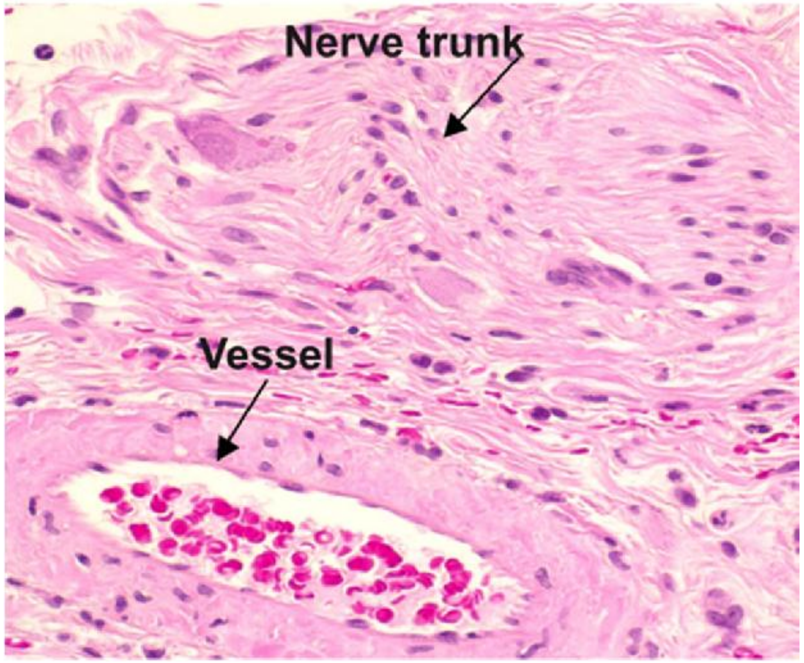
Disclosures:

MKSt is the owner and medical director of the Institut für Bildgebende Diagnostik and the Prostata Center, Frankfurt/Offenbach, Germany

Irreversible Electroporation (IRE):
Common Perception of Tissue Ablation/Cell Death

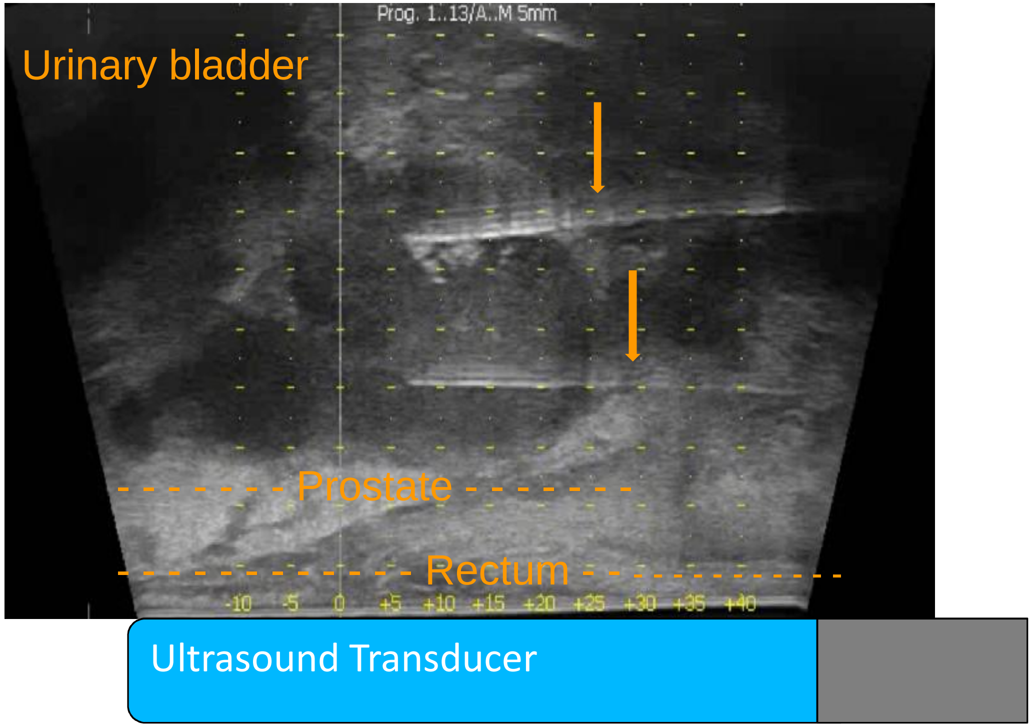
- Non-thermal tissue ablation by ultrashort (microsec.) strong electrical pulses
- Induction of cell death by pore formation in cell membranes
- Preservation of tissue infrastructure -> vessels, ducts, and nerves

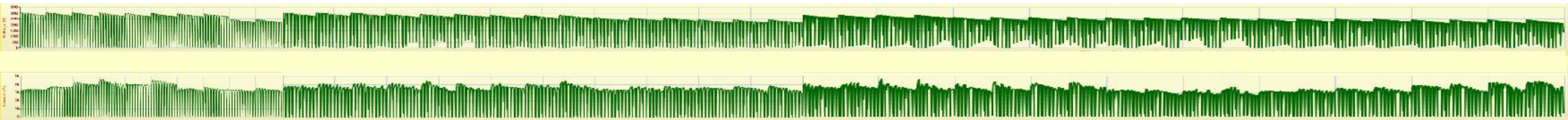




What Do We Expect to See when Cells are Electroporated?

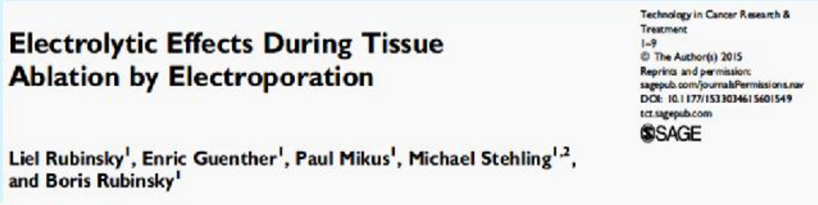
Sagittal US view of the prostate during IRE





(Bio)Physics of IRE:

Electric Currents in Tissue Cause Electrolysis

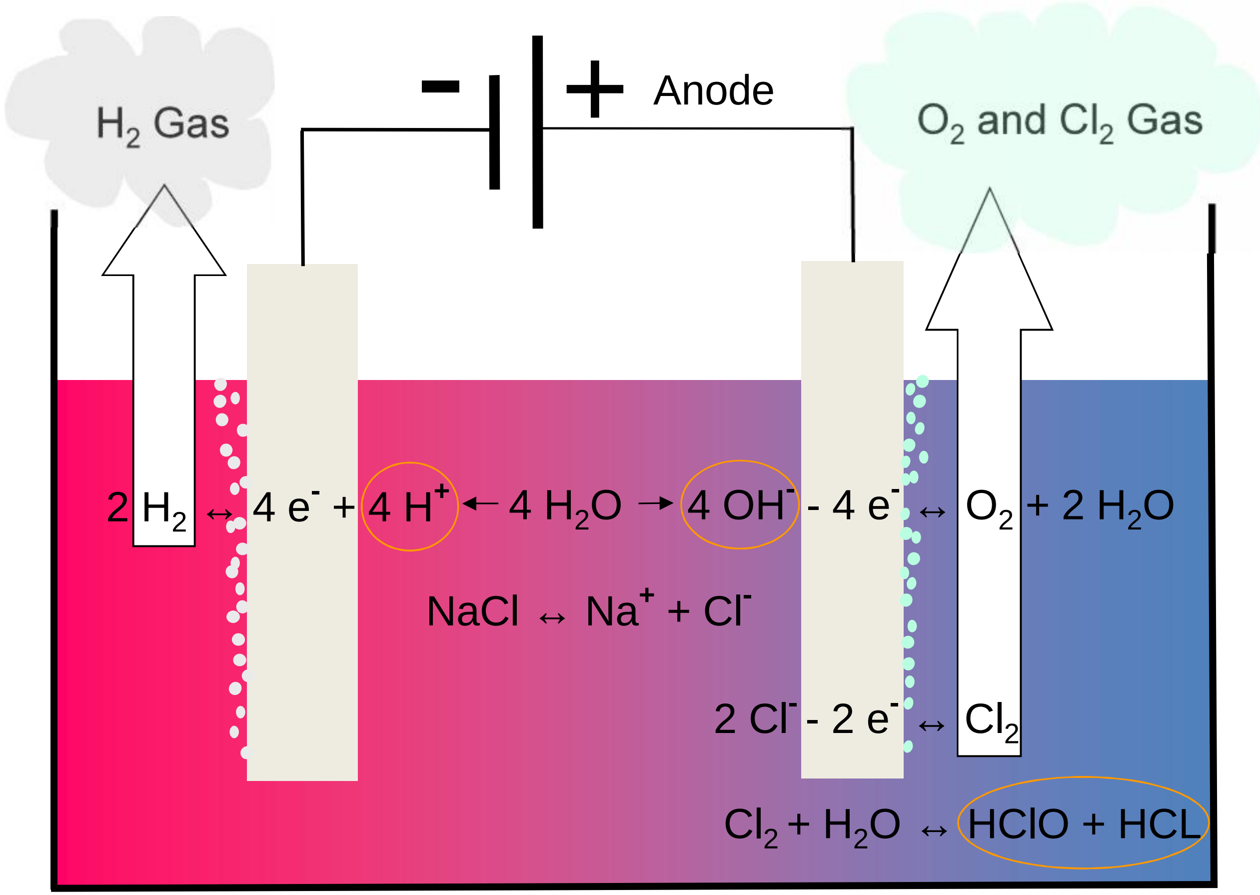


Technology in Cancer Research & Treatment
1–9
DOI: 10.1177/1533034615601549
tct.sagepub.com

SAGE

Electrolytic Effects During Tissue Ablation by Electroporation

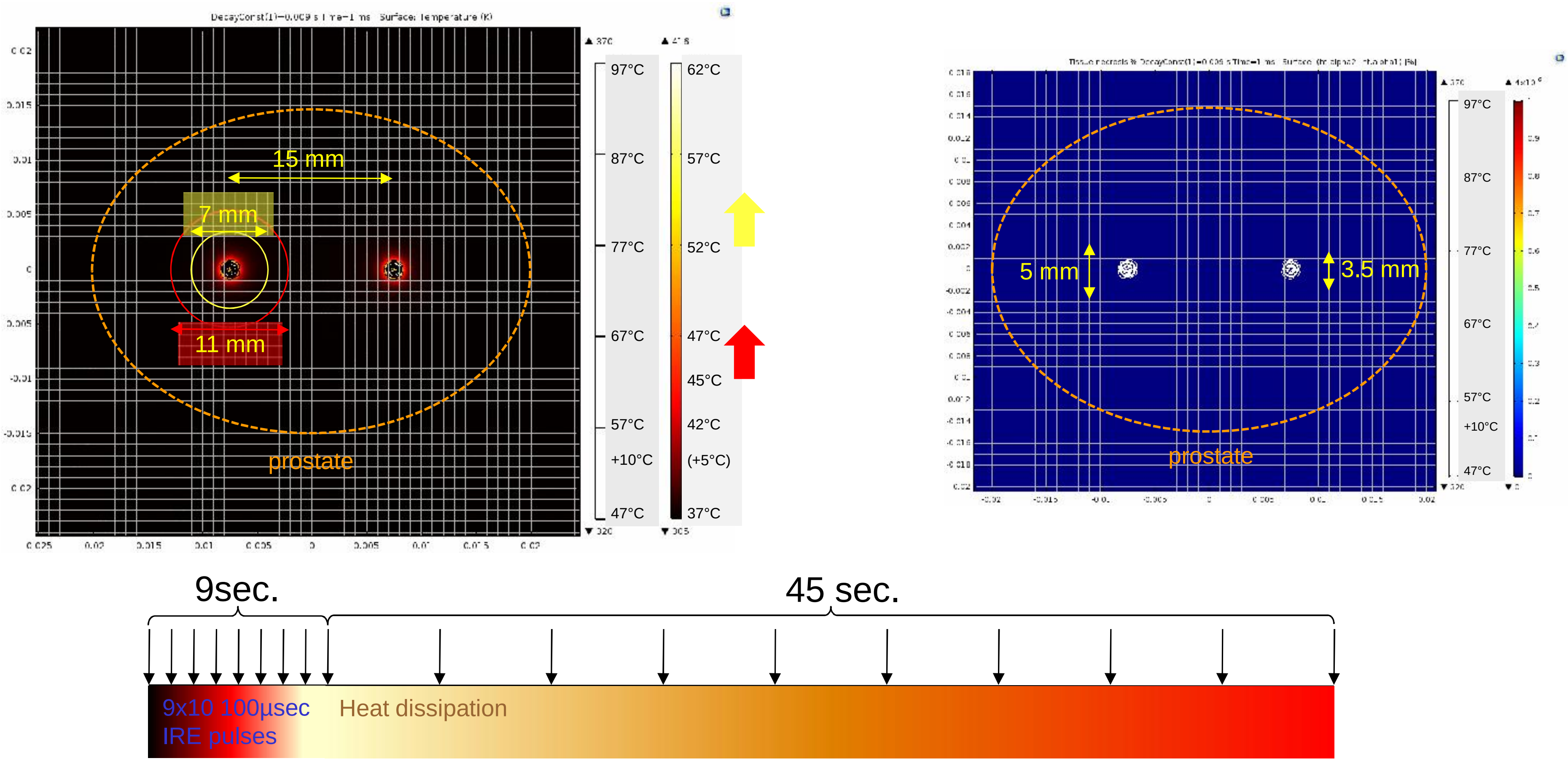
Liel Rubinsky[1], Enric Guenther[1], Paul Mikus[1], Michael Stehling[1,2], and Boris Rubinsky[1]



Rubinsky B, Onik G, Mikus P. Irreversible electroporation: a new ablation modality – clinical implications. Technol Cancer Res Treat. 2007;6(1):37-48.
Onik G, Mikus P, Rubinsky B. Irreversible electroporation: implications for prostate cancer ablation. Technol Cancer Treat. 2007;6(4):295-300.

Prostata-Center
innovativ - interdisziplinär - international

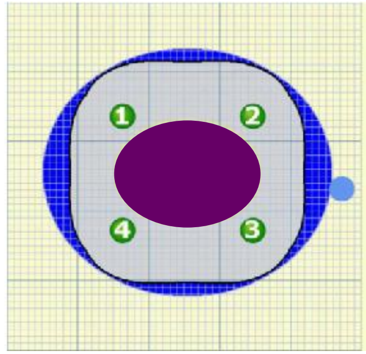
(Bio)Physics of IRE:
Electric Currents in Tissue Cause …
… Joule Heating in IRE ($H \sim I^2 \cdot R \cdot t$) – and Resulting Tissue Damage



van Gemert, Martin JC, et al. "Irreversible electroporation: just another form of thermal therapy?." *The Prostate* 75.3 (2015): 332-335.
Davalos, Rafael V., Suyashree Bhonsle, and Robert E. Neal. "Implications and considerations of thermal effects when applying irreversible electroporation tissue ablation therapy." *The Prostate* 75.10 (2015): 1114-1118.

Prostata-Center
innovativ - interdisziplinär - international

Commonly Employed Technique for IRE of the Prostate – Why and How We Do It Differently from (Almost) Everybody Else



Electrode Insertion:

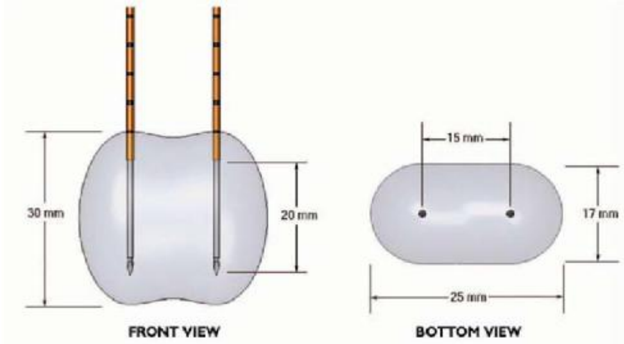
- Transperineal US-guided electrode insertion with
- stepper and brachy-therapy grid for guidance

Electrode Geometry:

- Electrode placement encompassing the tumour

Electrode Parameters:

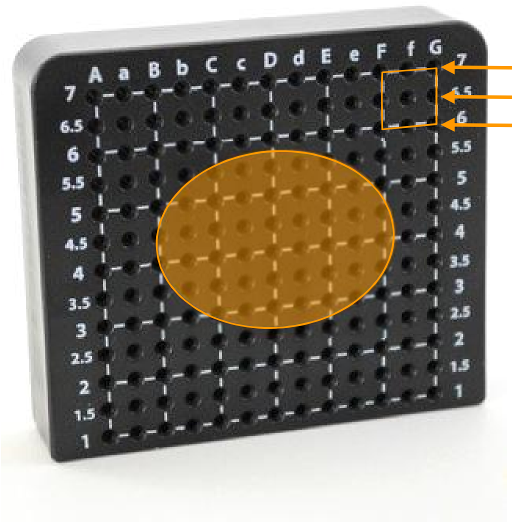
- Parallel positioning of electrodes
- Equal length of conducting electrode tips
- Maximum length of conducting electrode section 15 mm at 20 mm distance or 20 mm at 15 mm distance

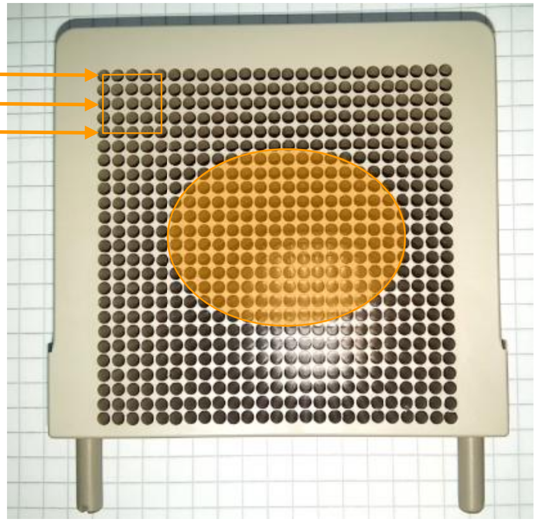


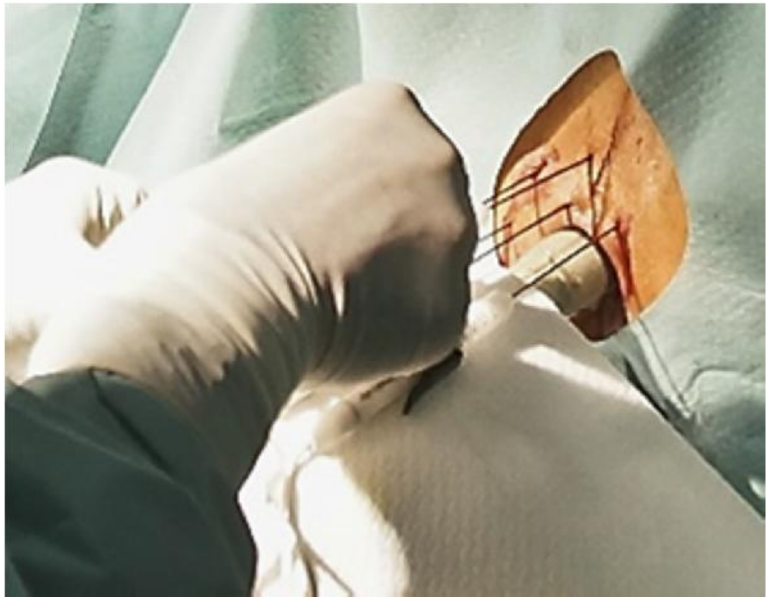
Generator Settings

Probe +	Probe -	Voltage	Pulse Length	N. Pulses
1	2	2500 V	100 μSec	90

Reasons Why We Prefer Manual Electrode Placement w/o Grid (1): Higher Accuracy



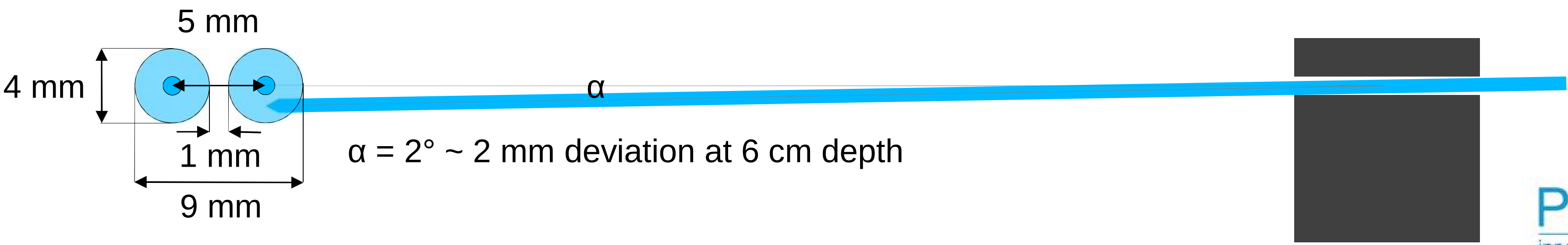




Standard brachytherapy grid:
5 mm spacing: ~ 9 mm accuracy

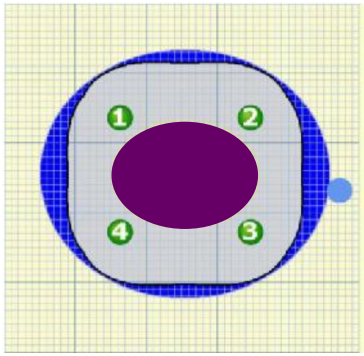
Custom made grid:
2.5 mm spacing: ~ 6.5 mm accuracy

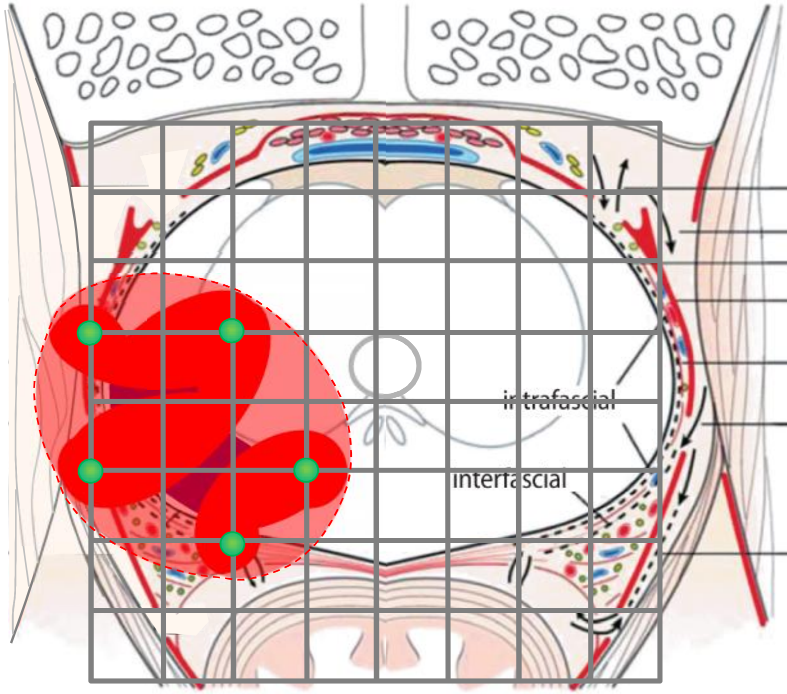
Manual electrode placement:
~ 1-2 mm accuracy



Prostata-Center
innovativ - interdisziplinär - international

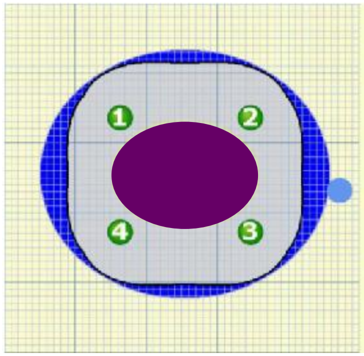
Standard Technique for Electrode Positioning with Grid: Excessive Damage to Neuro-Vascular Bundle

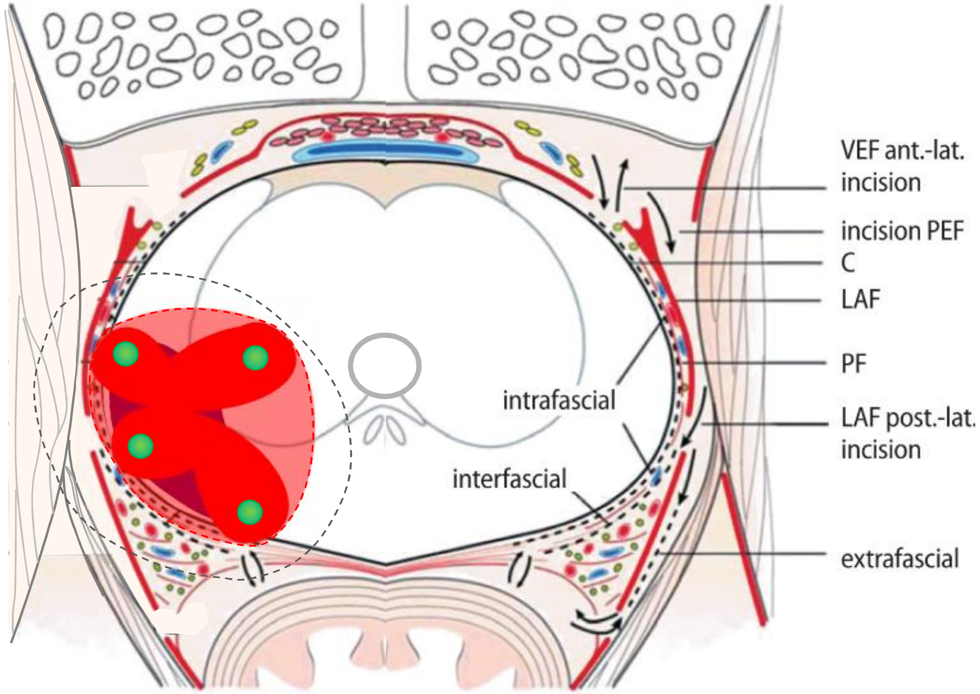




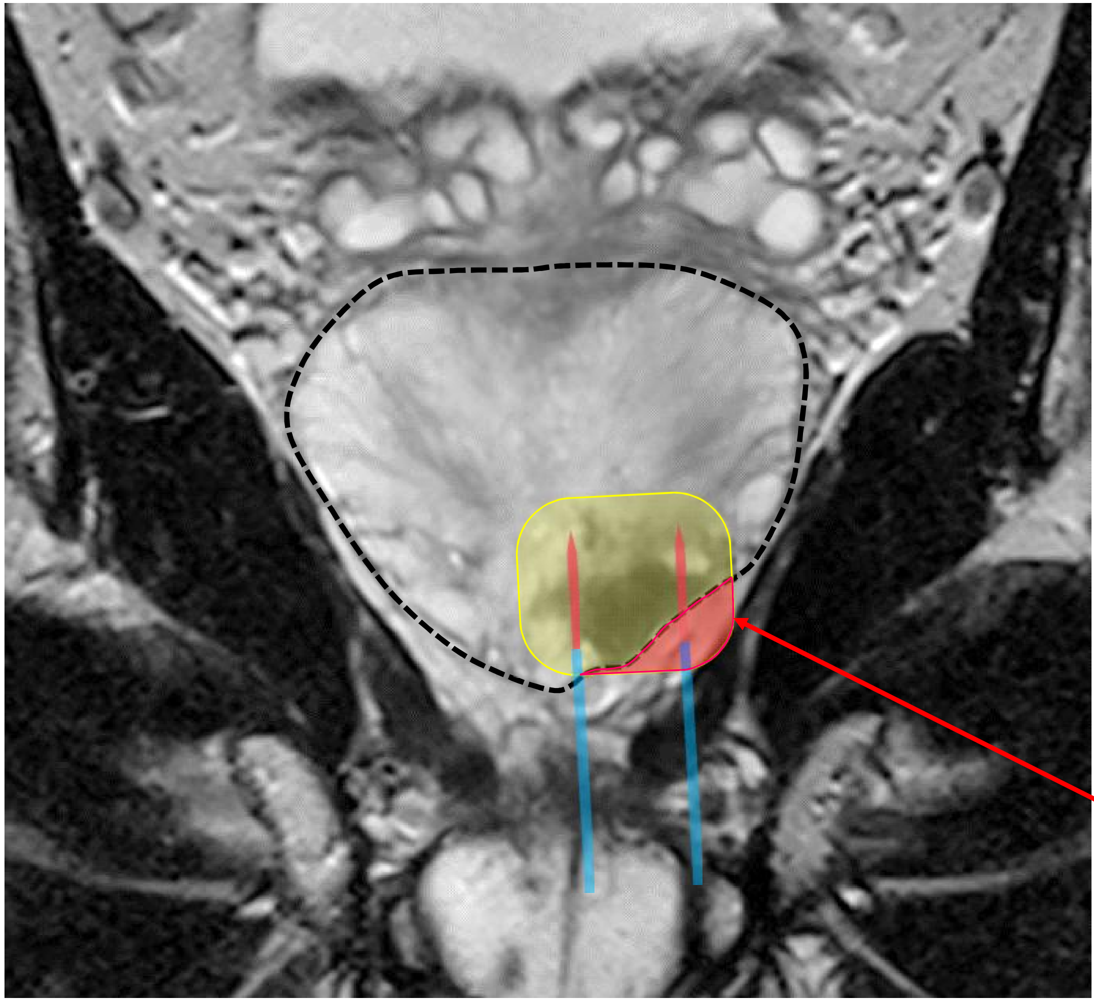
Prostata-Center
innovativ - interdisziplinär - international

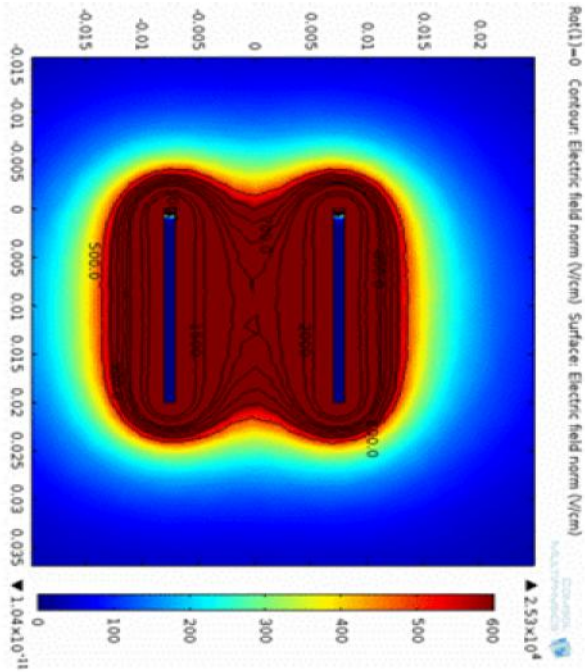
Reasons Why We Prefer Manual Electrode Placement w/o Grid (1): Adaptation to Tumour/Prostate Size and Shape





Standard Technique with Grid: Parallel Electrodes of Equal Exposure Length:
Mismatch of Ablation Field with Shape of Prostate





Unnecessary exposure to …

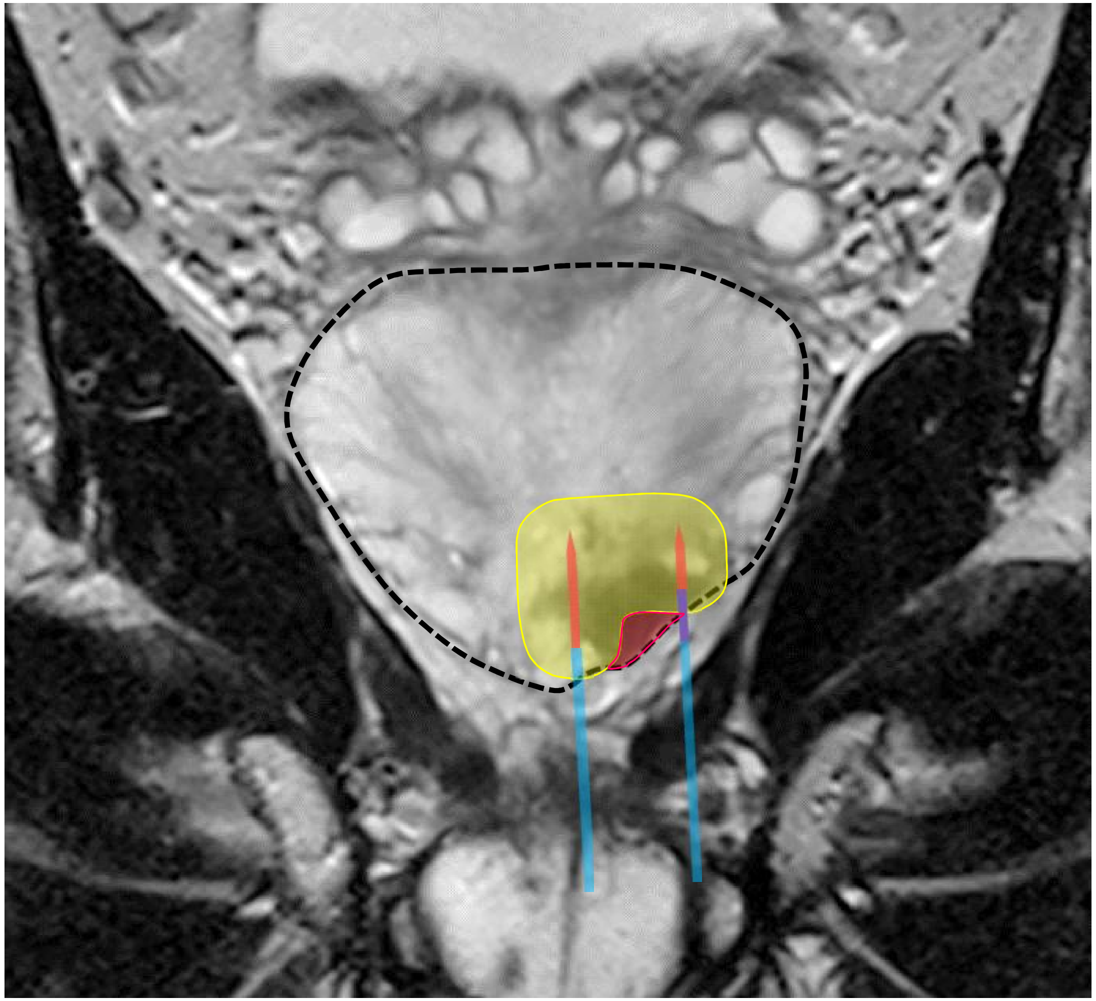
… irreversible electroporation

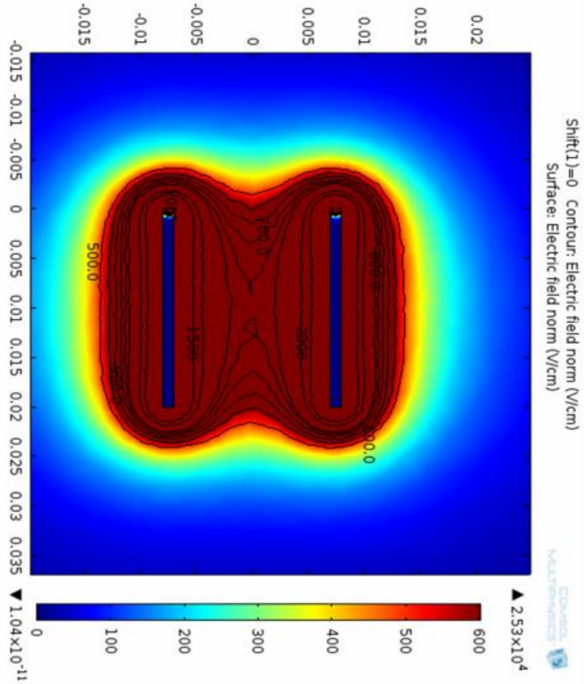
… acidity, alkaline and cytotoxic chemicals

… heat

-> potential damage to the NVB

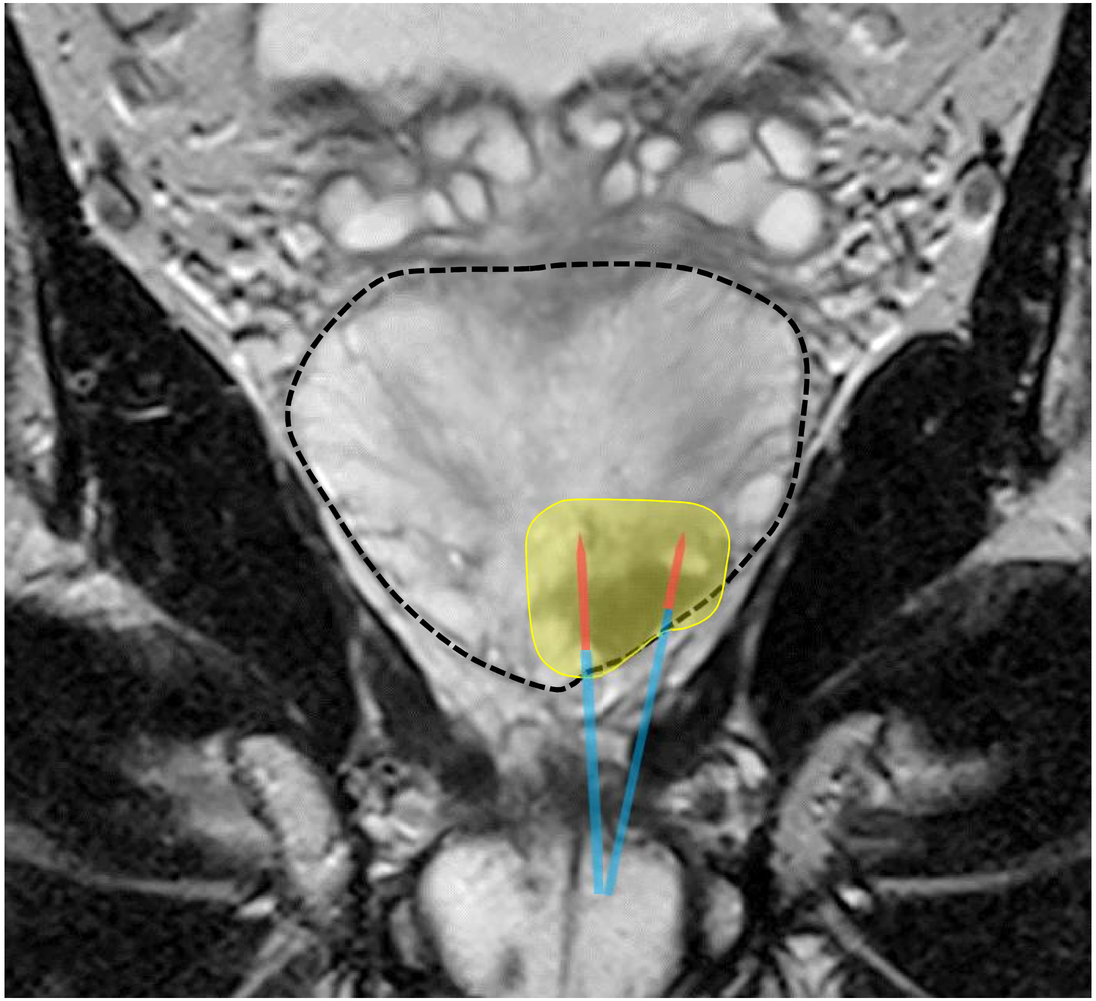
Parallel Electrodes with Unequal Exposure Length: Better Adaptation of Ablation Field to Shape of Prostate

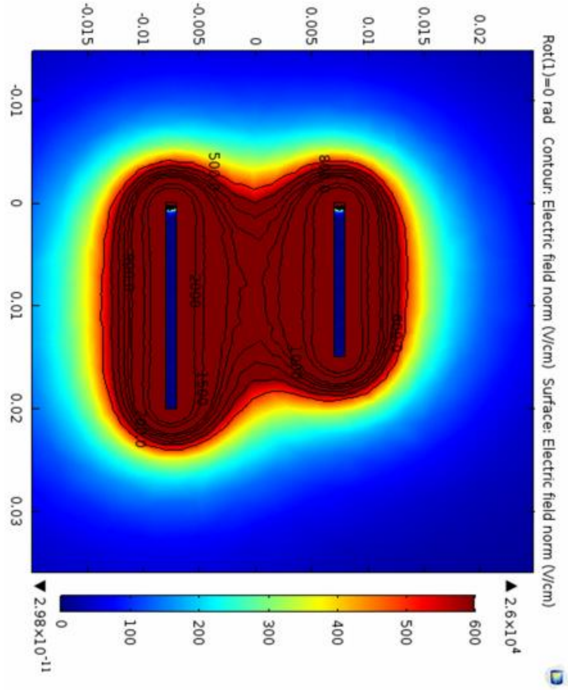




Prostata-Center
innovativ - interdisziplinär - international

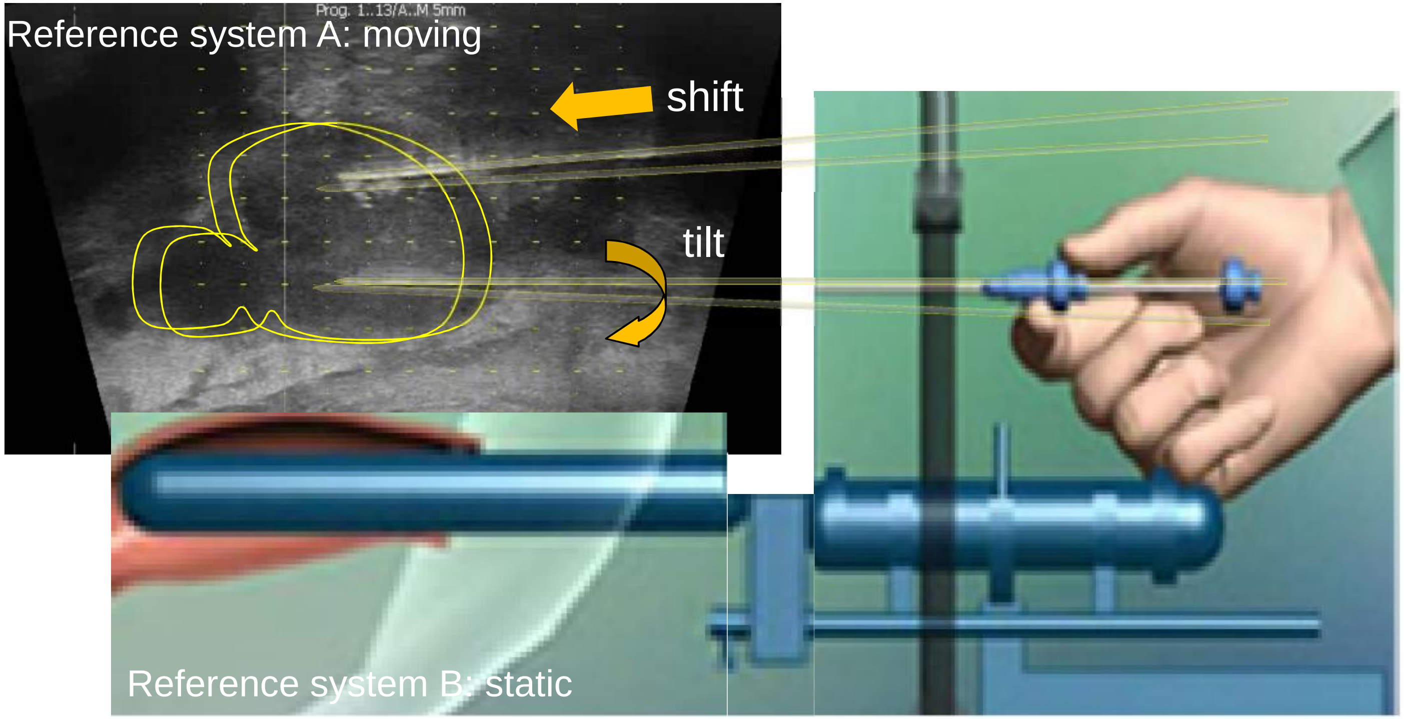
Highest Accuracy w/o Grid: Angulated Electrodes with Unequal Exposure Length
Best Adaptation of Ablation Field to Shape of Prostate





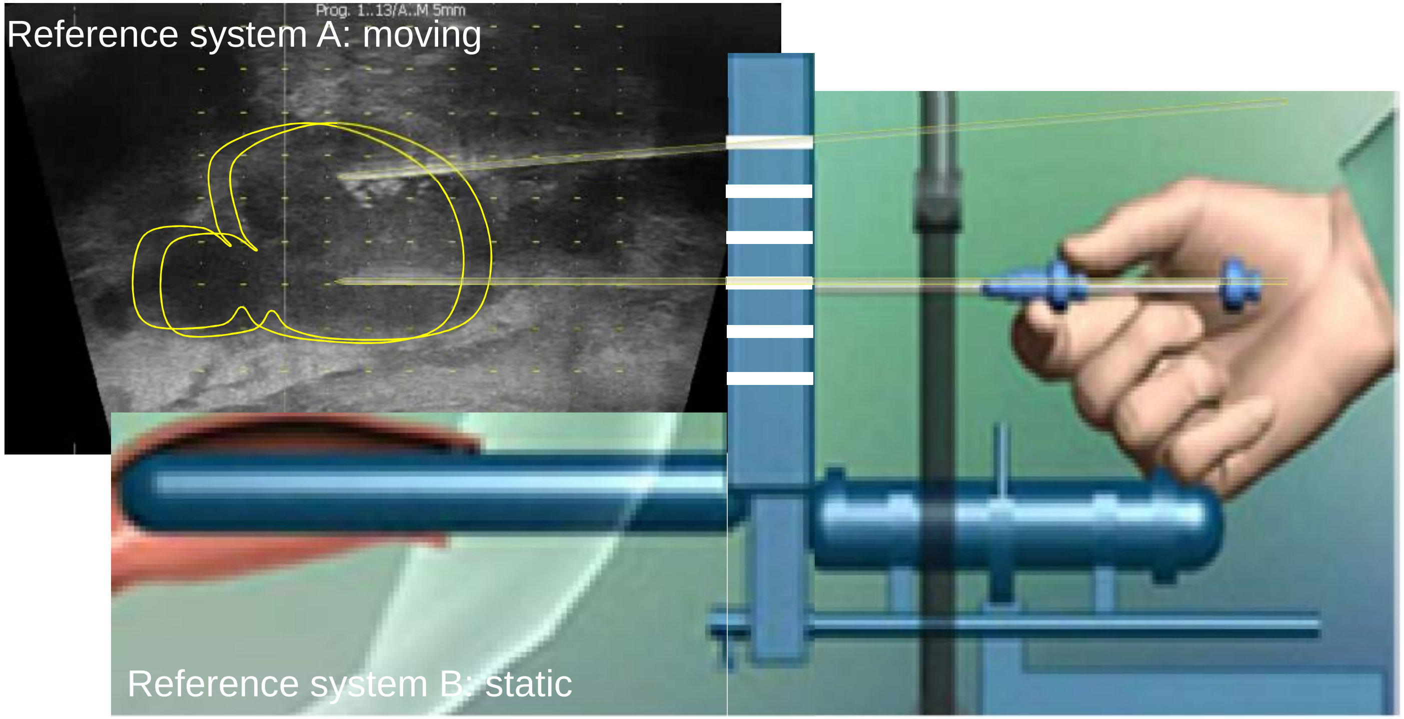
Prostata-Center
innovativ - interdisziplinär - international

Reasons Why We Prefer Manual Electrode Placement (2): Electrodes Shift and Tilt with Prostate due to Muscle Contractions



Prostata-Center
innovativ - interdisziplinär - international

Reasons Why We Prefer Manual Electrode Placement (2):
With Grid: Electrodes May Jam in Grid and Become Displaced in Prostate

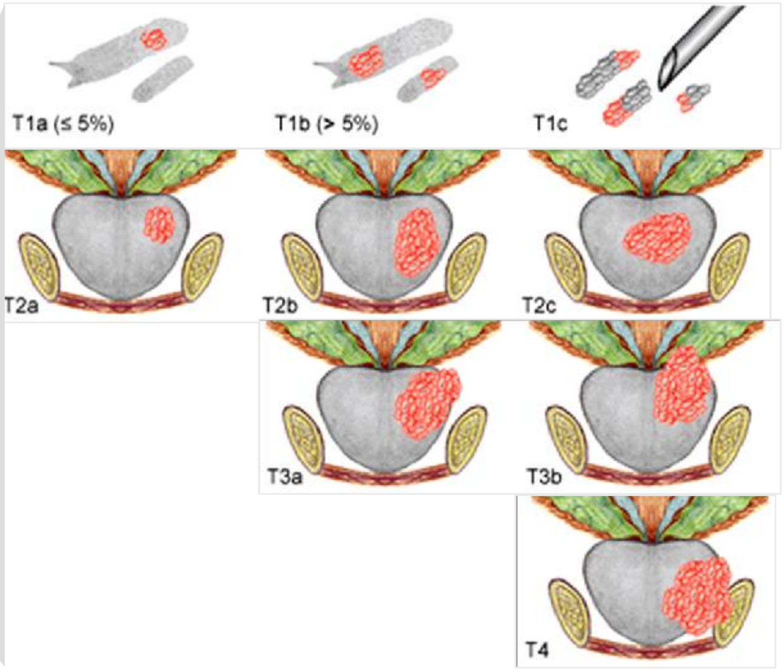


Prostata-Center
innovativ - interdisziplinär - international

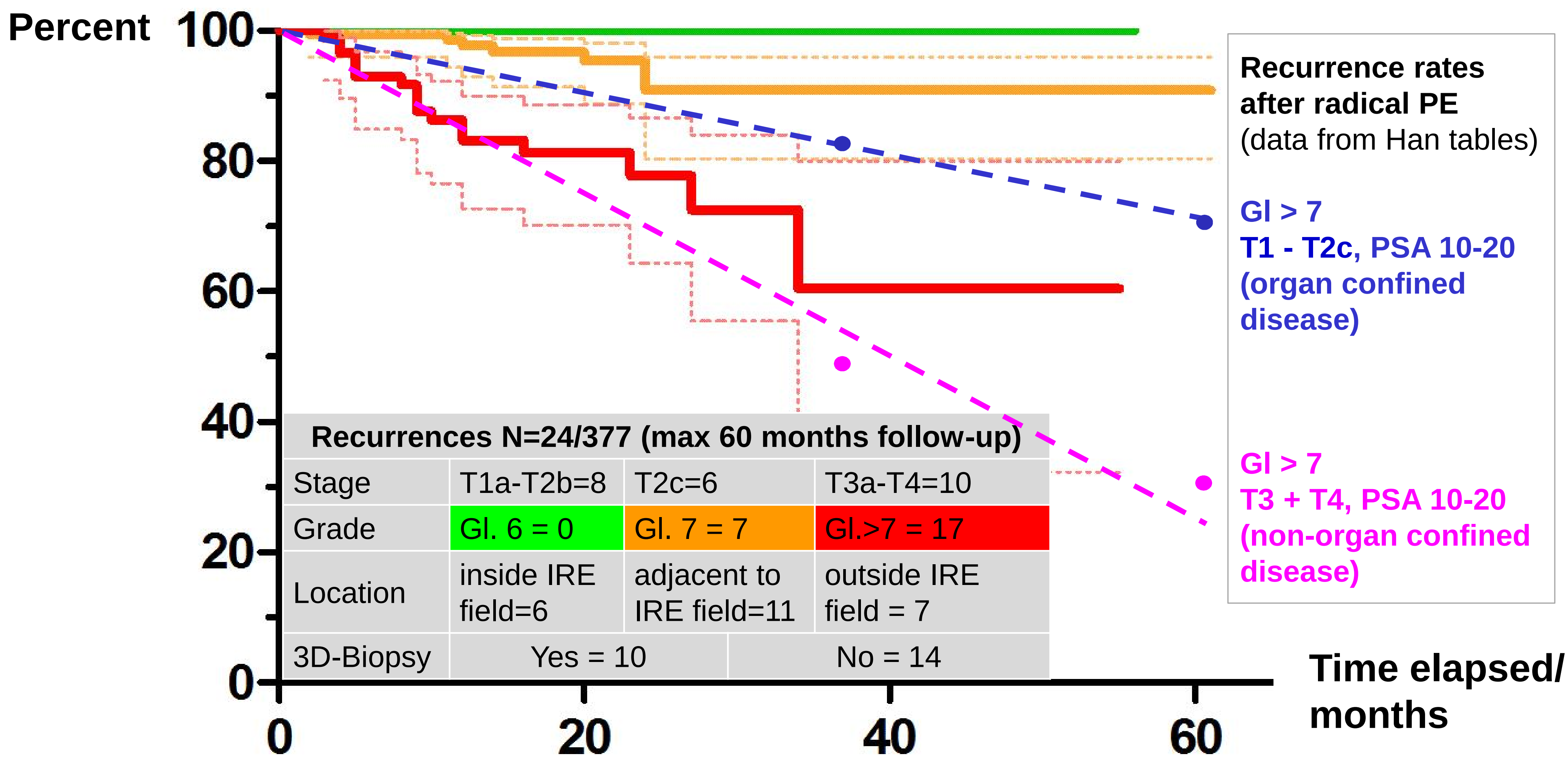
Our Results: IRE of Prostate Cancer > 450 Men over 6 Years – 377 Evaluated

D'Amico Risk Classification	low	intermediate	high	N/A
	30	83	250	14
Gleason Score	**6**	**7 (a/b)**	**> 7 (8/9/10)**	**N/A**
	75	178 (134/44)	91 (54/31/6)	33

TNM Stage	Number of patients	
T1a - T1c	32	258
T2a - T2c	226	
T3a - T3b	54	113
T4 N0 M0	29	
T4 N1 M0 / T4 N0 M1 / T4 N1 M1	30	
N/A (BPH treatment)	6	

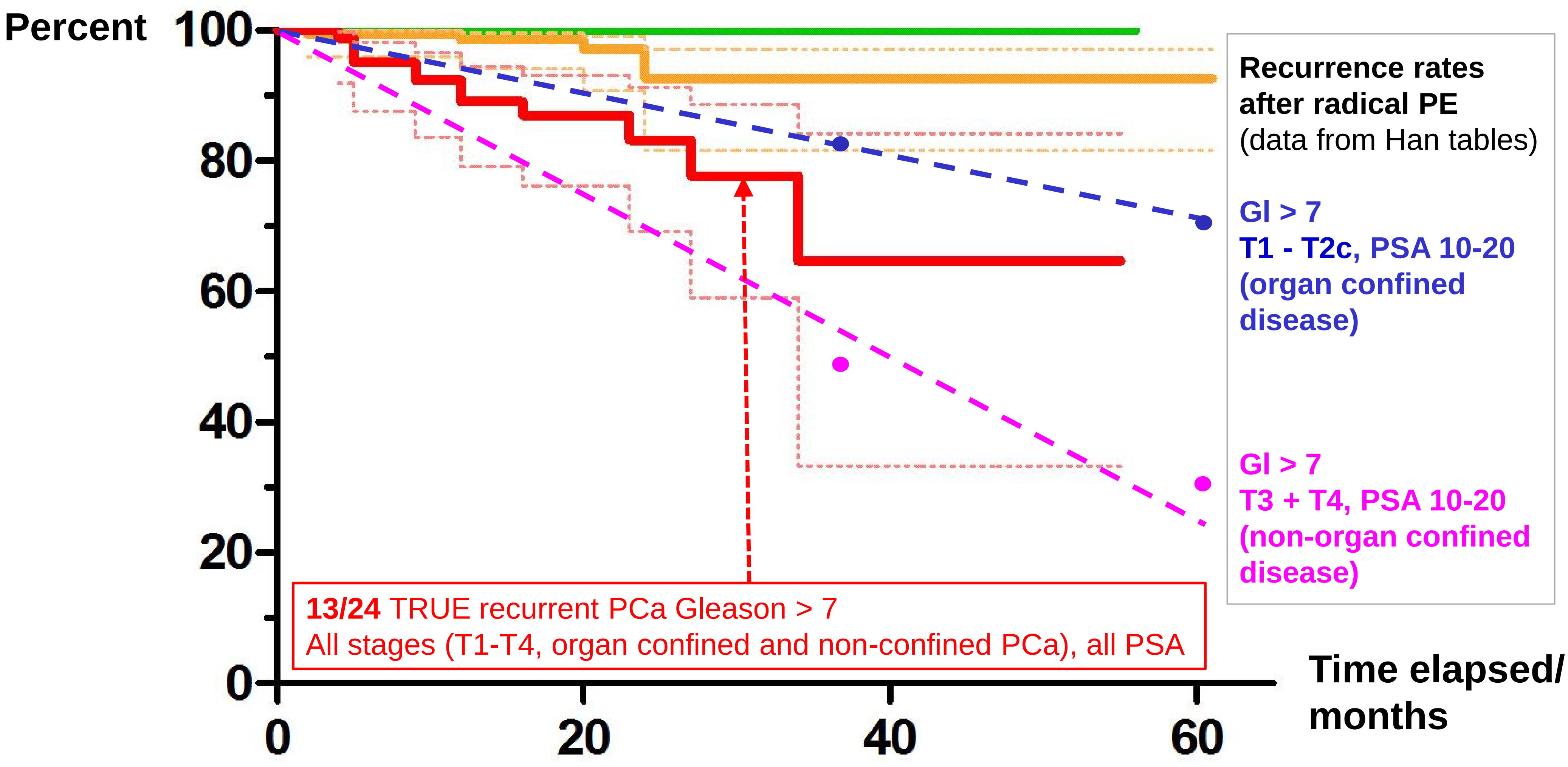


Recurrence Free Survival after IRE for PCa (max. 60 Months Follow-Up)



Recurrences N=24/377 (max 60 months follow-up)			
Stage	T1a-T2b=8	T2c=6	T3a-T4=10
Grade	Gl. 6 = 0	Gl. 7 = 7	Gl.>7 = 17
Location	inside IRE field=6	adjacent to IRE field=11	outside IRE field = 7
3D-Biopsy	Yes = 10	No = 14	

Recurrence Free Survival after IRE for PCa (max. 60 months follow-up): Only TRUE Recurrences IN or ADJACENT TO the IRE Treatment Field



Procedure Related Adverse Events

Adverse events	No. of patients
Mild	43/377 (11.4%)
Moderate	8/377 (2.1%)
Severe or medically significant	5/377 (1.3%)
Life-treatening consequences	0
Death related to adverse event	0

Erectile dysfunction	No. of patients
Transient (up to 1 year)	99/220 (45%)
Persistent (> 1 year)	6/220 (2.8%)
Urinary incontinence	
Other than urge incontinence during first 3 months after IRE	0/262 (0%)

IRE-related adverse events	No. of patients
Transient urinary retention catheter longer than 14 days	30/377 (8.0%)
Dysuria	28/377 (7.4%)
Mild haematuria no drop in hematocrit	13/377 (3.4%)
Permament urinary retention requiring TURP	3/377 (0.8%)
Recto-prostatic fistula closure without surgery	1/377 (0.3%)
Catheter related problems	
Urinary tract infection requiring antibiotic therapy	8/377 (2.1%)
Bladder perforation by catheter self-healed	1/377 (0.3%)

Prostata-Center
innovativ - interdisziplinär - international

Conclusions

IRE is an almost ideal method for treating prostate cancer:

- Effective local tumour control – recurrence rates comparable to prostataectomy
- Low toxicity – zero incontinence, << 10% impotence, no wound pain
- Suitable for T1 – T4 PCa, recurrent PCa after surgery, Rx, HiFU, etc.
- 24 hour procedure
- Can be repeated as often as needed

IRE is more than irreversible electroporation:

- Gas formation
- Formation of cytotoxic chemicals T
- Thermal effects close to electrodes

Effective use of IRE for the treatment of prostate cancer requires:

- Reliable diagnostic work-up: endorectal mp-MRI and 3D-mapping biopsy
- Understanding of the biopysics of IRE: gas formation, cytotoxic species, heat, etc.
- Optimised electrode placement – best achieved manually w/o grid

Prostata-Center
innovativ - interdisziplinär - international

Issues Not Addressed in this Presentation

- Optimised diagnostic work-up for IRE of PCa
- Longitudinal re-positioning of electrodes
- IRE pulse sequence optimisation
- Optimised electrode pairing and handling of electric discharges
- Electrode grouping for optimal fixation to the prostate
- Hydro-dissection of the rectum for protection
- IRE technique used for tumour infiltration of the sphincter, rectum, base of the bladder, etc.
- IRE-ECT (with bleomycin) for high-grade and recurrent prostate cancers
- IRE-ECT for lymph-node and bone metastases

If you are interested in learning more about IRE for the treatment of prostate cancer

or if you are interested in a scientific or clinical collaboration

-> contact me: **mstehling@t-online.de** (Michael K. Stehling)

Prostata-Center
innovativ - interdisziplinär - international

Without These Guys It Would Not Have Been Possible …

Dr. Stefan Zapf

Interventional Radiology

Dr. Rachid El Idrissi

Urology

Dr. Oliver Grohs

Anaesthesia

Enric Günther

Physics

Nina Klein

Physics

Alexandra Osei-Bonsu

Administration

Prof. Gary Onik

Interventional Radiology

Prof. Ducksoo Kim

Interventional Radiology

Boston University

Claudia Reckowski

Administration

Prostata-Center

innovativ - interdisziplinär - international