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

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

Comment:
This presentation was given by Professor Michael K. Stehling at the annual RSNA meeting in 2016. The world’s largest medical scientific conference on radiology.

Comments in this red box were added retrospectively for online publication.
This document is based on the presentation which was given on the RSNA 2016 by Michael K. Stehling MD PhD
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For the online publication of this document the slides has been edited and comments have been added
The statistics shown in this document will not be updated

Comment:
This page was added retrospectivly for online publication and was not part of the talk.
Irreversible electroporation has “potential to become new standard of care” in prostate cancer treatment
Non-Thermal Irreversible Electroporation (NT-IRE): Tissue Ablation by Strong Electric Pulses

Joule Heating in IRE ($H \sim I^2 \cdot R \cdot t$)

1500 V/cm
100 µsec

Mit Stromstößen gegen Krebs.
Stehling MK, Günther E, Rubinsky B. Spektrum der Wissenschaft, April, 2014

What Makes IRE Unique:
Selective Destruction of Cells - Preservation of Tissue Scaffold - Regeneration

Tissue, a composition of cells and non-cellular scaffold (collagen, elstin, reticular fibres, basal membranes and interstitial matrix)

7 days after IRE
Tissue scaffold without cells

28 days after IRE
Repopulation of tissue scaffold with cells

- endothelium
- smooth muscle cells
- cell free tunica media
IRE of the Prostate with the NanoKnife® (Angiodynamics Inc., USA)
The Way it is Commonly Used

[Image of the NanoKnife® system and settings table]

<table>
<thead>
<tr>
<th>Probe +</th>
<th>Probe -</th>
<th>Voltage</th>
<th>Pulse Length</th>
<th>N. Pulses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>2500 V</td>
<td>100 μSec</td>
<td>90</td>
</tr>
</tbody>
</table>
IRE of the Prostate: What Do We Expect to See When Cells Are Electroporated?

Sagittal US view of the prostate during IRE

Comment:
Loss of visibility is something that would not be expected from pure electroporation theory. This initial question sparked our interest in the details of what is really happening when applying IRE.
(Bio)Physics of IRE: Electric Currents in Tissue Cause Electrolysis

Comment:
Electrolysis is a major part of the physiologically relevant processes during IRE.
Electric Currents in Tissue Cause Joule Heating in IRE (H ~ I^2 R t) – and Resulting Tissue Damage

Comment: Joule Heating is another parameter that needs to be respected.
Standard Technique for Electrode Positioning with Grid: Potential Damage to Neuro-Vascular Bundle
Reasons Why We Prefer Manual Electrode Placement w/o Grid: Adaptation of Ablation Field to Tumour/Prostate Size and Shape
Clinical Application: IRE of Prostate Cancer
Our Experience in More Than 450 Patients Over 6 Years

Comment:

In the following, clinical experience is reported. This is not a prospective clinical trial with a strictly defined patient selection, treatment protocol or endpoint. All therapies were planned on an individual basis to the best of the current knowledge and respecting patient wishes.
Motivation for Treating PCa with IRE


Group 1:
Radical Prostatectomy

Time of Diagnosis

10 Years Later

Group 2:
No Treatment Observation Only

Comment:
Motivation: Default treatment provides little survival benefit for the patients but the patients pay a high price in terms of high probability for severe and permanent side effects.
Our Patient Selection for IRE of PCa

Inclusion Criteria

- **Patients with PCa who refused standard therapies** (surgery, Rx, ADT)
  - Main goal: preservation of erectile function and/or urinary continence
- PCa T1 – T4, any N and M

Exclusion Criteria

- Patients unfit for general anaesthesia
- Patients with cardiac defibrillators (and pacemakers)
**IRE of Prostate Cancer > 450 Men over 6 Years – 377 Evaluated**

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>6</th>
<th>7 (a/b)</th>
<th>&gt; 7 (8/9/10)</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75</td>
<td>178 (134/44)</td>
<td>91 (54/31/6)</td>
<td>33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D'Amico Risk Classification</th>
<th>low</th>
<th>intermediate</th>
<th>high</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>83</td>
<td>250</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a - T1c</td>
<td>32</td>
</tr>
<tr>
<td>T2a - T2c</td>
<td>226</td>
</tr>
<tr>
<td>T3a - T3b</td>
<td>54</td>
</tr>
<tr>
<td>T4 N0 M0</td>
<td>29</td>
</tr>
<tr>
<td>T4 N1 M0 / T4 N0 M1 / T4 N1 M1</td>
<td>30</td>
</tr>
<tr>
<td>N/A (BPH treatment)</td>
<td>6</td>
</tr>
</tbody>
</table>

Comment:
Evaluation cut off date was 6/2016.
Our Diagnostic Work-Up for IRE of PCa

Ideal (the way we prefer to do it)

- **Endo-rectal coil mpMRI** (and 3D-biopsy) generally 1.5 T more robust than 3.0 T. 3.0 T needs endo-rectal coil and experts!
- **3D-mapping biopsy** important when MRI is suboptimal, e.g. chronic prostatitis or motion artifacts

Suboptimal (outside and/or incomplete data):

- Outside transrectal biopsy and e-mpMRI at PC
- No biopsy (refused any) and e-mpMRI at PC
- Outside (any) MRI and 3D-biopsy at PC
- Outside transrectal biopsy and (any) MRI

<table>
<thead>
<tr>
<th>1.5 Tesla</th>
<th>DWI (b=0)</th>
<th>3.0 Tesla</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>SNR</td>
<td>100</td>
</tr>
<tr>
<td>7.77</td>
<td>Voxel size/ mm³</td>
<td>12.1</td>
</tr>
<tr>
<td>13.3</td>
<td>SNR/ mm³</td>
<td>8.26</td>
</tr>
</tbody>
</table>
IRE of PCa: Minimally-invasive Interventional Image Guided Procedure

IRE 24 Hour Treatment Schedule

Day 1:
- Arrival and preparation in the morning
- Approx. 2 h procedure room
- Full anaesthesia
- Foley catheter
- US guided transperineal IRE-electrode placement (no grid!)
- Deep muscle relaxation to suppress IRE-induced muscle contractions
- Approx. 2 h recovery room
- Overnight hotel or clinic

Day 2:
- Follow-up MRI
- Discharge (Foley remains 5–14d)
263/377 Focal Ablations

53 y, T2b N0 M0, Gleason 7b
PSA before IRE = 5.2 ng/ml
PSA 3m post IRE = 2.3 ng/ml
114/377 Whole Gland Ablations

63 y, T2c N0 M0, PSA 11 ng/ml, Gleason 8

BEFORE IRE

1 DAY AFTER

3 MONTHS AFTER IRE
PSA : 0.0 ng/ml
Patient Follow-Up After IRE

REQUESTED:
- MRI at 3, 6 and 12 m after IRE, then yearly
- PSA at 3, 6 and 12 m after IRE, then 3 – 6 m
- Request for immediate feedback from patients on procedure related complications
- Urinary Incontinence (ICIQ) and Impotence Questionaire (IIEF-5) (subgroup)

OTHER:
- Telephone follow-up for adverse effects, impotence, incontinence
- Re-biopsies only in cases where PSA and MRI or PSMA-PET suggested recuccent PCa

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

Recurrences N=24/377 (max 60 months follow-up)

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a-T2b=8</th>
<th>T2c=6</th>
<th>T3a-T4=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Gl. 6 = 0</td>
<td>Gl. 7 = 7</td>
<td>Gl.&gt;7 = 17</td>
</tr>
<tr>
<td>Location</td>
<td>inside IRE field=6</td>
<td>adjacent to IRE field=11</td>
<td>outside IRE field = 7</td>
</tr>
<tr>
<td>3D-Biopsy</td>
<td>Yes = 10</td>
<td></td>
<td>No = 14</td>
</tr>
</tbody>
</table>

Recurrence rates after radical PE (data from Han tables)

Gl > 7
T1 - T2c, PSA 10-20 (organ confined disease)

Gl > 7
T3 + T4, PSA 10-20 (non-organ confined disease)
Recurrence Free Survival after IRE for PCa (max. 60 months follow-up): Only TRUE Recurrences IN or ADJACENT TO the IRE Treatment Field

Recurrence rates after radical PE (data from Han tables)

Gl > 7
T1 - T2c, PSA 10 - 20 (organ confined disease)

Gl > 7
T3 + T4, PSA 10 - 20 (non-organ confined disease)

13/24 TRUE recurrent PCa Gleason > 7
All stages (T1-T4, organ confined and non-confined PCa), all PSA

Percent

Time elapsed/months

0 20 40 60
Comment regarding the two previous Kaplan Meier curves

- Based on all patients including T3 and T4
- Including patients with additional therapies (i.e. ADT)
- Dotted lines indicate ci95 to the according Gleason Score
- Dashed blue and purple line indicate virtual corridor of radical prostatectomy recurrence rate according to Han Tables (linearly connecting mean 3 and 5 year recurrence rate of the organ-confined and non-confined group, respectively)
- Follow-up periods were not in all cases in accordance with our recommendation and some patients have very limited follow-up data.
- However, „lost“ patients are respected in Kaplan Meier curves (or do not change the percentage) as long as there is no reason to think that recurrence-free patients and recurrent patients get „lost“ unequally frequently (but effects ci95)
- A recurrence was noted when EITHER:
  - PSA values were significantly rising 3 measurements in a row
  - MRI showed a suspicions change (Pi-Rads ≥ 4) relative to previous scans
  - positive PSMA-PET/CT
  - Positive biopsy
  - This leaves margin for both false-positive and false-negative (random biopsies would hypothetically have more false-negative but no false-positive)
  - To that point in time systematic re-biopsy was not performed, since not all patients accept a re-biopsy without suspicion.
## Procedure Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild clinical or diagnostic observations only; intervention not indicated</td>
<td>43/377 (11.4%)</td>
</tr>
<tr>
<td><strong>Moderate</strong> minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living</td>
<td>8/377 (2.1%)</td>
</tr>
<tr>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare activities of daily living</td>
<td>5/377 (1.3%)</td>
</tr>
<tr>
<td>Life-threatening consequences urgent intervention indicated</td>
<td>0</td>
</tr>
<tr>
<td>Death related to adverse event</td>
<td>0</td>
</tr>
</tbody>
</table>

## IRE-related adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient urinary retention catheter longer than 14</td>
<td>30/377 (8.0%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>28/377 (7.4%)</td>
</tr>
<tr>
<td>Mild haematuria no drop in hematocrit</td>
<td>13/377 (3.4%)</td>
</tr>
<tr>
<td>Permanent urinary retention requiring TURP</td>
<td>3/377 (0.8%)</td>
</tr>
<tr>
<td>Recto-prostatic fistula closure without surgery</td>
<td>1/377 (0.3%)</td>
</tr>
<tr>
<td><strong>Catheter related problems</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection requiring antibiotic therapy</td>
<td>8/377 (2.1%)</td>
</tr>
<tr>
<td>Bladder perforation by catheter self-healed</td>
<td>1/377 (0.3%)</td>
</tr>
</tbody>
</table>
IRE of PCa with Rectal Infiltration

79 y, initially Gl. 6, T4 N0 M0, refused AHT, had 2 previous „hyperthermias“ (48°C, 3 hours)

Before IRE:
PSA=10.6 ng/ml
Rectal infiltration

9m after IRE:
PSA=77 ng/ml
Recurrent PCa:
T4 N1 M1b
Re-biopsy: Gl. 8
Subjective Assessment of Urinary Continence

Patients were asked at the time of Foley catheter removal, during follow-up visits and/or by telephone whether they had „normal urinary bladder function or were losing urine in an uncontrolled way“. Slight „urge incontinence“ within the first 3 months after IRE was considered normal. Patients with incontinence before IRE were excluded.

<table>
<thead>
<tr>
<th>Incontinence</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/262 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Comment:
This is the most significant result from the case series as a) several cases with lower urinary sphincter infiltration were included b) the criteria is stricter than the standard ICIQ and IPSS criteria used by Urology to assess incontinence
IRE of PCa with Lower Urinary Sphincter Infiltration
73 y, T4 N0 M0, refused biopsy, no previous treatment, treatment in two consecutive sessions

<table>
<thead>
<tr>
<th>First Treatment</th>
<th>Second Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before IRE: PSA=15.8 ng/ml LUS infiltration</td>
<td>1d after IRECT: Fully continent, no retention, no pain</td>
</tr>
<tr>
<td>1m after IRE: PSA=6 ng/ml Fully continent, no retention, no pain</td>
<td>1m after IRECT: Fully continent, no retention, no pain</td>
</tr>
</tbody>
</table>

IRE: Irreversible Electroporation and Electrochemotherapy
Evaluation of Erectile Function after IRE: IIEF5 Questionnaire

Total Database N=405 patients

At least **one correctly** filled out IIEF5 before IRE: N=234

… AND at least **one correctly** filled out after IRE: N=92

… AND no previous therapies (i.e. ADT) OR adjuvant therapies: N=78

… AND IIEF5 score was above 6 (= severe ED) before IRE: N=73

… AND valid, readable dates on the IIEF5 forms: **N=68**

**IRE-induced severe ED (IIEF5 > 6 before < 6 after IRE)**

- Within 1st year after IRE: ~ **15%** (10 of 68 patients)
- More than 1 year after IRE: ~ **1.5%** (1 of 68 patients)

IIEF Score: 6-10: severe ED; 11-16: moderate ED; 17-21: slight to moderate ED; 22-25: slight ED; 26-30: no ED

Comment:

We used two methods. The standard IIEF-5 questionnaire (this slide) and subjective assessment in patient dialog (next slide) to further evaluate sexual function.
Evaluation of Erectile Function after IRE: „Subjective“ Assessment

### Subjective Assessment of Erectile Function

Patients were asked during their follow-up visits or via telephone ...

1. ... whether they had noticed any negative change in their erectile function after the IRE-treatment
   AND

2. ... whether they were unable to have normal sexual intercourse (even with the use of Viagra, Cialis, etc.) – and had no spontaneous nocturnal erection either

Patients who answered both questions with YES were diagnosed with an „IRE-induced significant erectile dysfunction“.

<table>
<thead>
<tr>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient (up to 12 months) significant erectile dysfunction</td>
</tr>
<tr>
<td>Persistent (longer than 12 months) significant erectile dysfunction</td>
</tr>
<tr>
<td>No erectile dysfunction</td>
</tr>
</tbody>
</table>
## Conclusions
### IRE versus Surgery

<table>
<thead>
<tr>
<th>Irreversible Electroporation</th>
<th>Surgery (Prostatectomy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimally invasive</td>
<td>Open surgery</td>
</tr>
<tr>
<td>24h (outpatient/overnight in-patient) procedure</td>
<td>7-10d, up to 3 weeks in hospital</td>
</tr>
<tr>
<td>5–14d Foley</td>
<td>7-14d Foley, additional suprapubic catheter</td>
</tr>
<tr>
<td>No rehabilitation</td>
<td>3-6w rehabilitation</td>
</tr>
<tr>
<td>No wound pain (!)</td>
<td>5-6d analgesia via peridural catheter</td>
</tr>
<tr>
<td>Zero incontinence rate</td>
<td>20 - 50% incontinence</td>
</tr>
<tr>
<td>Low (&lt; 10%) impotence rate</td>
<td>50 - 70% impotence</td>
</tr>
<tr>
<td>Low recurrence rate of 5% at 50 m (25% in Gl.&gt;8 group)</td>
<td>Depending on stage/grade 20-40 % at 60 m</td>
</tr>
<tr>
<td>Can be repeated as often as needed</td>
<td>Repeat surgery difficult</td>
</tr>
<tr>
<td>Suitable for recurrent PCa after surgery, Rx, HIFU, etc.</td>
<td>Repeat surgery difficult</td>
</tr>
<tr>
<td>Suitable for T4 PCa (rectal, sphincter, bladder infiltration)</td>
<td>Stage T4 problematic</td>
</tr>
<tr>
<td>Secondary (anti-tumoral) immunological effects</td>
<td>none</td>
</tr>
<tr>
<td>Patient satisfaction high</td>
<td>Patient satisfaction low</td>
</tr>
</tbody>
</table>
Without These Guys It Would Not Have Been Possible …