Prostate cancer treatment with Irreversible Electroporation (IRE): Safety, efficacy and clinical experience in 471 treatments

a summary of the scientific publication:

https://doi.org/10.1371/journal.pone.0215093
Irreversible Electroporation of the prostate
> 900 treated men – 429 evaluated patients

<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>83</td>
<td>226 (160/66)</td>
<td>111 (69/36/6)</td>
<td>9</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>25</td>
<td>88</td>
<td>312</td>
<td>4</td>
</tr>
</tbody>
</table>

Our cohort included cancer patients at all stages, including patients with recurrences and advanced stages of disease (including metastasis).

<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>Patient Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a - T1c</td>
<td>32</td>
</tr>
<tr>
<td>T2a - T2c</td>
<td>282</td>
</tr>
<tr>
<td>T3a - T3b</td>
<td>54</td>
</tr>
<tr>
<td>T1-T3 N1 or M1</td>
<td>19</td>
</tr>
<tr>
<td>T4 N0 M0</td>
<td>18</td>
</tr>
<tr>
<td>T4 N1 M0 / T4 N0 M1 / T4 N1 M1</td>
<td>24</td>
</tr>
</tbody>
</table>
Toxicity profile of IRE: treatment-related adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>% affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>19.7%</td>
</tr>
<tr>
<td>Only clinical or diagnostic observation; intervention not indicated</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3.7%</td>
</tr>
<tr>
<td>Minimal, local or non-invasive intervention indicated; limited age-appropriate activities of daily life</td>
<td></td>
</tr>
<tr>
<td>Severe or medically significant</td>
<td>1.4%</td>
</tr>
<tr>
<td>However, not immediately life threatening; Hospitalization or extension of existing hospitalization indicated; Disability; limits self-sufficiency in daily life</td>
<td></td>
</tr>
<tr>
<td>Lifte-threatening consequences</td>
<td>0%</td>
</tr>
<tr>
<td>Intervention urgently indicated</td>
<td></td>
</tr>
<tr>
<td>Death related to adverse events</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IRE-related Adverse Event</th>
<th>% affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria</td>
<td>6.8%</td>
</tr>
<tr>
<td>Transient Urinary Retention</td>
<td>9.1%</td>
</tr>
<tr>
<td>Milde Hematuria</td>
<td>3.8%</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>0.2%</td>
</tr>
<tr>
<td>Proctitis (Unclear genesis)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Epididymiditis</td>
<td>0.6%</td>
</tr>
<tr>
<td>Pseudo post vasectomy syndrome</td>
<td>0.2%</td>
</tr>
<tr>
<td>Permanent Urinary Retention (TURP necessary)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Recto-Prostatic Fistula (closed spontaneously after a few weeks)</td>
<td>0.2%</td>
</tr>
<tr>
<td>Severe prostatitis</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catheter-related Adverse Event</th>
<th>% affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Urinary Tract Infection (Catheter remained longer than 14d)</td>
<td>2.5%</td>
</tr>
<tr>
<td>Bladder perforation by catheter</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
Results on urinary and sexual function: erectile function

What is the IIEF-5 Score?

The International Index of Erectile Dysfunction (IIEF5) is a common diagnostic tool for studying the prevalence of erectile dysfunction (ED).

The difficulty with IIEF-5

Due to the interaction of physiological and psychological effects, ED is usually difficult to assess. As the IIEF-5 Score is a standard in urology, we still included its evaluation in this study. Although frequently used, assessment of treatment toxicity on EF by standard criteria (i.e. severe ED defined by IIEF-5 <7) does not provide the full picture. Evaluation of the changes in the IIEF-5-Score as a function of time and ablation volume provides a more accurate picture, which is what we opted for her. Additionally, we included the results of subjective assessment of ED through our own questions.
Results on urinary and sexual function: erectile function

What does this data show in detail?

Figure A shows that smaller ablation volumes (<50% of the prostate) resulted in a mean IIEF5-Score reduction of 17.7% (-5.3 points), in whole-gland ablations (100% ablation volume) it was twice as high (37%, -11.1 points).

Figure B shows that neurovascular bundle (NVB) involvement also correlates positively with ED.

Figure C shows a statistically significant improvement (p=0.045) of Erectile Function (EF) over time (>18m post IRE): from a mean reduction of the IIEF5-Score of 33% (-8.72 points) during the first year after IRE, to 15% (-3.88 points) after 18 months. Thus, data shows a recovery of Erectile Function after IRE.

Subjective assessment revealed no reduction of EF in 52% and transient reduction of EF in approximately 45% of all IRE treated patients (Figure D).
Results on urinary and sexual function: erectile function

What does this data show? The Summary

Overall Occurrence of ED (erectile dysfunction) after IRE in this series was rare, but not zero. Standard evaluation of ED by IIEF questionnaires revealed IRE-related severe ED in 11.3% of evaluated patients during the first year (transiently), and in 3% 12 months after IRE.

As assessment of erectile function is difficult due to co-factors such as the nocebo effect, we also used our own subjective assessment.

The results confirm the transient nature of ED after IRE, with 45% of men experiencing transient ED (up to 12 months), but only 3% persistent severe ED, whilst 52% experiencing no ED at all.

NWB = Neurovascular Bundle
Results on urinary and sexual function: continence

What is the IPSS Score?

The International Prostate Symptom Score (IPSS) is based on answering seven questions about urinary tract symptoms, plus one related to quality of life. For every question about urinary symptoms, the patient can choose from 5 possible answers that best describe the severity of his symptoms. The answers are assigned with scores 0 to 5. The total score thus ranges from 0 to 35 points (asymptomatic to very symptomatic).

This data summarizes the data of all patients who completed the baseline and follow-up questionnaires correctly.

* ungepaarter t-test mit Welch Korrelation
Results on urinary and sexual function: continence

What does the data show in detail?

In patients fully continent before IRE, no urinary incontinence was observed 12 months post IRE or later during the observation period.

IPSS-Score analysis revealed that in 7.7% of the evaluated patients scores increased temporarily from below 8 to above 19 (severe symptoms) after IRE. In one case, the last included data point still showed a score above 20.

In terms of urinary symptoms, 72.8% of evaluated patients reported no change or an improvement in quality-of-life, 27.2% reported a decrease.

To the date of data acquisition cut-off, the last available data point only shows dissatisfaction (≥ 5 points) in one patient who was initially satisfied (≤ 2 points).
Results on urinary and sexual function: continence

What does the data show? The Summary

The data shows the complete preservation of urinary continence after IRE in all patients, despite the partial or total inclusion of the lower urinary sphincter in the IRE-field.

In terms of urinary symptoms, the majority of patients (72.8%) reported no change or an improvement in quality-of-life, while 27.2% reported a transient decrease.

Until data analysis cut off, only one patient out of 429 who was initially satisfied reported dissatisfaction with regards to urinary function.

* ungepaarter t-test mit Welch Korrelation
Functional long-term outcome after established treatments for localized PCa

<table>
<thead>
<tr>
<th>Result</th>
<th>2 years</th>
<th>5 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incontinence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE</td>
<td>9.6 %</td>
<td>13.4 %</td>
<td>18.3 %</td>
</tr>
<tr>
<td>RT</td>
<td>3.2 %</td>
<td>4.4 %</td>
<td>9.4 %</td>
</tr>
<tr>
<td><strong>Impotence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE</td>
<td>78.8 %</td>
<td>75.7 %</td>
<td>87.0 %</td>
</tr>
<tr>
<td>RT</td>
<td>60.8 %</td>
<td>71.9 %</td>
<td>93.9 %</td>
</tr>
<tr>
<td><strong>Disturbed bowel function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE</td>
<td>13.6 %</td>
<td>16.3 %</td>
<td>21.9 %</td>
</tr>
<tr>
<td>RT</td>
<td>34.0 %</td>
<td>31.3 %</td>
<td>35.8 %</td>
</tr>
</tbody>
</table>

RPE = Radical Prostatectomy  
RT = Radiation Therapy  

Direct comparison to established therapies  
By way of comparison, this table summarizes the results of an extended study that analyzed the data of 1655 men for the assessment of long-term urinary, bowel, and sexual function after radical prostatectomy or external radiotherapy.  
Although we compare the results of patients primarily treated with RPE and RT with those secondarily treated with IRE, the outcome of urinary, bowel and sexual function after IRE is still much better.

Treatment efficacy: recurrence-free survival rate

Kaplan-Meier curves are effective for the analysis of data with different survival times (times to event), especially if not all subjects continuously participate in the study.

Their purpose is to estimate survival over time, even if patients fail during the evaluation process. In this series, recurrences were diagnosed by an increase in PSA with corresponding findings in mpMRI and/or PSMA-PET / CT. Re-biopsies were performed on a few patients and as needed.

The dotted lines represent the confidence intervals (95%) in the colors of the corresponding Gleason Score.
Treatment efficacy: recurrence-free survival rate

What does this data show?

Number of recurrences after IRE:
- Gleason 6: 3 patients
- Gleason 7: 18 patients
- Gleason > 7: 26 patients

Recurrence-free survival rates thus were:
- Gleason 6: 94%
- Gleason 7: 85%
- Gleason > 7: 60%

For comparison:
- In this diagram, any tumor re-occurrence, including those outside the IRE treatment field, was included. Despite this conservative approach, the recurrence rates for high-grade (Gleason > 7) cancers fall inside the corridor of the recurrence rates after prostatectomy (obtained from the Han Tables of Johns-Hopkins) for comparable cancer stages and PSA-levels (blue and magenta dots, CI shown as bars for ease of perception).
Recurrence-free survival after IRE

What does this data show?

Number of recurrences after IRE
Gleason 6: 1 patients
Gleason 7: 10 patients
Gleason > 7: 16 patients

Recurrence-free survival rates thus were:
Gleason 6: 98%
Gleason 7: 93%
Gleason > 7: 75%

For comparison:
In this diagram, only the recurrences inside or at the margin of the IRE treatment field, excluding the 20 PCa which were located within residual prostate tissue and thus classified as out-of-field recurrence, were considered.
All recurrence rates are outside the corridor of the recurrence rates after prostatectomy (obtained from the Han Tables of Johns-Hopkins) for comparable cancer stages and PSA-levels (blue and magenta dots, CI shown as bars for ease of perception).
The retrospective evaluation of our data allows the conclusion that Irreversible Electroporation (IRE) is a safe, effective and suitable modality for the treatment of prostate cancer at all clinical stages and for recurrent disease. Initial local tumor control was achieved in all IRE-treated patients. Treatment fields included the lower urinary sphincter, seminal vesicles, neurovascular bundles and in some cases partially the rectum and bladder, yet overall toxicity was low. Continence was preserved in all cases. In terms of local tumor control the comparison of IRE with radical prostatectomy (RPE) revealed similar recurrence rates over time, suggesting similar effectiveness of IRE to RPE. Thus the data illustrates the feasibility of IRE for prostate cancer treatments, with similar functional outcomes and short to midterm efficacy to RPE, but much lower toxicity profile.