Salvage Cryotherapy

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1. Mechanisms of action and limitations (geometry)
2. Adverse effects (historical series)
3. Guidelines on radiorecurrent PCa
4. Pre-operative management
5. Efficacy
6. Prognostic factors
Cryotherapy addresses cancer simultaneously at the cellular (membranes, organites) and the stromal support (microvasculature) levels.

It then engages the cascade of apoptosis in injured but surviving cells.

There is no known -possible- mechanisms of resistance to cryotherapy when the appropriate temperature was reached for a sufficient length of time.
two cycles of -20°C for 10 minutes at the outer limit of the target, interspersed by passive thaw
Freezing point of a 0.9% w/v solution (saline solution) is -3.3°C. That is the temperature reached at the outer limit of the iceball.

Laboratory testing was performed in room temperature (21°C) gel; measurements were made after two 10-minute Freeze cycles separated by a 5-minute passive Thaw cycle. Accuracy is ±3 mm width, ±4 mm length.

<table>
<thead>
<tr>
<th>ISOTHERM DATA</th>
<th>IceSeed® 1.5 1.5 mm (17G)</th>
<th>IceSphere® 1.5 1.5 mm (17G)</th>
<th>IceRod® 1.5 1.5 mm (17G)</th>
<th>IceRod® 1.5 PLUS 1.5 mm (17G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0° C</td>
<td>33 mm x 38 mm</td>
<td>39 mm x 45 mm</td>
<td>41 mm x 60 mm</td>
<td>43 mm x 60 mm</td>
</tr>
<tr>
<td>-20° C</td>
<td>20 mm x 27 mm</td>
<td>26 mm x 32 mm</td>
<td>27 mm x 50 mm</td>
<td>30 mm x 48 mm</td>
</tr>
<tr>
<td>-40° C</td>
<td>11 mm x 20 mm</td>
<td>16 mm x 24 mm</td>
<td>16 mm x 41 mm</td>
<td>18 mm x 42 mm</td>
</tr>
</tbody>
</table>

Ice Sphere: 11 mL/-20°C
Ice Rod: 19 mL/-20°C
Limitations therefore pertain to our ability to extend the ice ball beyond the tumor margins

Porcine Kidney, 1 week after CA
The Dutch experience (4 centers) and review of the literature

Table 4  Comparison with results from previous literature—toxicity

<table>
<thead>
<tr>
<th>Salvage procedure</th>
<th>Radical prostatectomy</th>
<th>125-I implantation</th>
<th>Cryosurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Literature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>308</td>
<td>66</td>
<td>707</td>
</tr>
<tr>
<td>% GU toxicity</td>
<td>20–68 % incontinence</td>
<td>12 % grade 1–2</td>
<td>4–83 % incontinence</td>
</tr>
<tr>
<td></td>
<td>22–41 % bladder neck</td>
<td>38 % grade 3–4</td>
<td>7–55 % bladder neck stricture/retention</td>
</tr>
<tr>
<td>stricture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% GI toxicity</td>
<td>2–7 % rectal injury</td>
<td>0–12 % grade 1–2</td>
<td>6–37 % perineal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–2 % grade 3–4</td>
<td>1–11 % fistula</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>72 %—Nearly uniform</td>
<td>NA</td>
<td>72–86 %</td>
</tr>
</tbody>
</table>

**Present study**

| % GU toxicity | 23 % grade 3 | 23 % grade 3 | 22 % grade 3 |
| % GI toxicity | 9 % grade 3  | 6 % grade 3  | 7 % grade 3  |
| Erectile dysfunction | 86 %         | 45 %         | 93 %a        |

*GU* genitourinary; *GI* gastrointestinal; NA not available

a 44 % of patients had pre-existent erectile dysfunction
Urethral warmer is instrumental in reducing the risks of fistula but may promote recurrence in the close vicinity of the urethra.
PRad: PSA <10, PSAdT>12M, GS<7

Table 3 – Guidelines on treatment options for prostate-specific antigen relapse following local treatment

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrences are best treated by salvage RT with 64–66 Gy at a PSA serum level ≤0.5 ng/ml.</td>
<td>B</td>
</tr>
<tr>
<td>Expectant management is an option for patients with presumed local recurrence who are too unfit or unwilling to undergo RT.</td>
<td>B</td>
</tr>
<tr>
<td>PSA recurrence indicative of systemic relapse is best treated by early ADT, resulting in decreased frequency of clinical metastases if poor prognostic risk factors such as PSA DT &lt;12 mo or Gleason score 8–10 are present.</td>
<td>B</td>
</tr>
<tr>
<td>Luteinising hormone-releasing hormone analogues/antagonists/orchiectomy or bicalutamide 150 mg/d when hormonal therapy is indicated.</td>
<td>A</td>
</tr>
<tr>
<td>Local recurrences can be treated with salvage RP in carefully selected patients, who presumably have organ-confined disease, that is, PSA &lt;10 ng/ml, PSA DT &gt;12 mo, low-dose brachytherapy, biopsy Gleason score &lt;7.</td>
<td>B</td>
</tr>
<tr>
<td>Cryosurgical ablation of the prostate and interstitial brachytherapy are alternative procedures in patients not suitable for surgery.</td>
<td>B</td>
</tr>
<tr>
<td>HIFU may be an alternative option. However, patients must be informed about the experimental nature of this treatment modality due to the short follow-up periods reported.</td>
<td>B</td>
</tr>
<tr>
<td>In patients with presumed systemic relapse, ADT may be offered.</td>
<td>C</td>
</tr>
</tbody>
</table>

Salvage cryotherapy when not suitable for surgery

Experimental nature of salvage HIFU
1990-2000: PSA recurrence in one patient out of three (Phoenix definition)

10% of good pronostic patients,

up to 60% in the poor prognostic group

Better results (DFSR) since IMRT and adjuvant ADT
Salvage Therapies for Radiorecurrent Prostate Cancer

Kamran Zargar-Shoshtari, Pranav Sharma and Julio Pow-Sang*

From the Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center, Tampa, Florida

Quite a few large series

<table>
<thead>
<tr>
<th>Radiation Therapy</th>
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<tbody>
<tr>
<td>Biochemical Recurrence PSA &gt; 2 ng/ml above Nadir</td>
</tr>
<tr>
<td>Repeat Staging Histological Confirmation</td>
</tr>
</tbody>
</table>

Local Recurrence and Candidate for Salvage Therapy

- Surgery
- Brachytherapy
- Cryotherapy
- HIFU

Systemic Recurrence or Not candidate for Salvage

- Androgen Deprivation
- Treatment for Oligometastatic disease

Key Words: prostatic neoplasms; radiotherapy; neoplasm recurrence, local; salvage therapy; prostate-specific antigen; biochemical recurrence.

No direct or indirect commercial incentive associated with this work. Submitted for publication August 10, 2014.

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* Correspondence: Genito-Urinary Oncology Program, H. Lee Moffitt Cancer Center, Tampa, Florida

No standard salvage therapy exists. Treatments are best administered at specialist centers where there is expertise with managing potential complications.

Conclusions:

These modalities have different side effect profiles, but the morbidity associated with SRP has limited widespread acceptance. No direct or indirect commercial incentive associated with this work. Submitted for publication August 10, 2014.

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No standard salvage therapy exists. Treatments are best administered at specialist centers where there is expertise with managing potential complications.
There was no evidence that salvage ablative therapy was either better or worse than salvage RP following primary EBRT for any outcomes.

**Summary and conclusions from the evidence of the comparative effectiveness of salvage ablative therapy**

This review considered data from 400 participants treated with salvage therapy following primary EBRT across nine studies, all of which were single-arm case series. Six studies involved salvage RP, two involved salvage cryotherapy and one involved salvage HIFU. All of the studies were considered as having a high risk of bias. Consequently, the findings should be interpreted cautiously to reflect the extremely poor quality of the evidence base and the heterogeneity of outcome definition, different time points of outcome measurement and different means of outcome reporting. Data on the long-term effectiveness of salvage therapy were limited, with the majority of studies reporting on short-term data only.

In the short term, there was no robust evidence that mortality or other cancer-specific outcomes (biochemical disease-free survival or failure) differed between salvage cryotherapy and salvage RP. There were no data on cancer-specific outcomes for salvage HIFU.

With regard to functional outcomes, including urinary and sexual dysfunction and quality of life outcomes, the limited data prevented any valid conclusions from being made.

For adverse event outcomes, there was a general trend for salvage cryotherapy to have fewer procedure-related complications, especially for bladder neck stenosis (up to 2% at a median of 18.6 months), in comparison with salvage HIFU (up to 17% at a median of 15 months) and salvage RP (up to 25% at a median of 20 months). However, the data limitations render these findings uncertain at best.

In conclusion, the results of this review on salvage therapies were associated with large uncertainty owing to the quality and quantity of the evidence base. There was a lack of long-term direct measures of effectiveness and a lack of prospective comparative studies. There was no evidence to suggest that salvage ablative therapy was either better or worse than salvage RP following primary EBRT for any outcomes.

**Fig. 4 – Kaplan-Meier curve for overall and disease-free survival with corresponding n values.**

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Overall Survival</th>
<th>Disease Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>36</td>
<td>70</td>
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<tr>
<td>48</td>
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<td>60</td>
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<tr>
<td>60</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>72</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>84</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>96</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>108</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

10 year Overall survival: 90%
10 year Disease-free survival: 40%
Two pre-salvage prognostic factors

**Pre-salvage PSA (5 or 10ng/mL)**

- **Pre Salvage PSA (5 or 10ng/mL)**

![Graph showing Kaplan-Meier curve for pre-salvage PSA nadir (nanograms per deciliter) with corresponding % Disease Free over time.]

**Pre Salva ge Bx Gleason score**

- **Pre Salvage Bx Gleason score**

![Graph showing Kaplan-Meier curve for pre-salvage Gleason scores with corresponding % Disease Free over time.]

*It’s therefore important to refer patients as early as possible after failure (Phoenix)*

Williams, Eur Urol 2011
No analysis was shown using the Phoenix definition of PSA nadir plus 2 ng/ml, and they described recurrence rates that are significantly higher than our series. From our experience, we have seen significantly higher biochemical recurrence rates in this cohort using the ASTRO definition that do not seem to translate to an increased recurrence rate under the Phoenix definition. This highlights the fact that with a lack of a validated standard definition of failure, long-term follow-up is required. Comparisons between treatment modalities can be heavily influenced by the definitions used. Regardless, we have demonstrated a significant overall recurrence-free survival that can be optimized with appropriate stringent patient selection. We acknowledge that we have not proven any survival benefit for this treatment given the absence of any control arm. A trial of salvage versus observation, however, is unlikely to...

Fig. 2 – Kaplan-Meier curve for prostate-specific antigen (PSA) nadir (nanograms per deciliter) with corresponding n values.

PSA nadir <1 ng/ml as post-salvage prognostic indicator.
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Thank You