Phase II study of FFF-SBRT in 5 fractions for low and intermediate risk prostate cancer


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Background

• Combination of IGRT and IMRT: delivery of an increased dose to the target while limiting toxicity to normal tissues.

• Several studies suggest that prostate cancer may have a low alpha/beta ratio. The slow proliferating prostate cancer cells have high sensitivity to dose per fraction.
  Brenner et al., 2002; Dasu, 2007

• The linear/quadratic model suggests that SBRT is able to deliver the equivalent dose of a radical treatment in a few days schedule.
## Background

### GANTRY-BASED SYSTEMS

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th># of patients</th>
<th>Risk group(s)</th>
<th>Median follow-up (months)</th>
<th>Late Grade 3 GU Toxicity</th>
<th>Late Grade 3 GI Toxicity</th>
<th>FFBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madsen et al.</td>
<td>33.5 Gy in 5 fx</td>
<td>40</td>
<td>low</td>
<td>41</td>
<td>None</td>
<td>None</td>
<td>90% 4-years actuarial</td>
</tr>
<tr>
<td>Baske et al.</td>
<td>45-50 Gy in 5 fx *</td>
<td>45</td>
<td>low &amp; int</td>
<td>30, 18, 12</td>
<td>4%</td>
<td>2% plus 1 Grade 4</td>
<td>100%</td>
</tr>
<tr>
<td>Mantz et al.</td>
<td>40 Gy in 5 fx *</td>
<td>80</td>
<td>low</td>
<td>36</td>
<td>None</td>
<td>None</td>
<td>100%</td>
</tr>
</tbody>
</table>

### CYBERKNIIFE

<table>
<thead>
<tr>
<th>Study</th>
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<th># of patients</th>
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<th>Late Grade 3 GI Toxicity</th>
<th>FFBF</th>
</tr>
</thead>
<tbody>
<tr>
<td>King et al.</td>
<td>36.25 Gy in 5 fx †</td>
<td>67</td>
<td>low</td>
<td>32</td>
<td>3.5%</td>
<td>None</td>
<td>97%</td>
</tr>
<tr>
<td>Friedland et al.</td>
<td>35 Gy in 5 fx</td>
<td>112</td>
<td>low, int, &amp; high</td>
<td>24</td>
<td>&lt; 1%</td>
<td>None</td>
<td>98%</td>
</tr>
<tr>
<td>Katz et al.</td>
<td>35 – 36.25 Gy in 5 fx</td>
<td>304</td>
<td>low, int &amp; high</td>
<td>48</td>
<td>2%</td>
<td>None</td>
<td>97, 93, 95 4-year actuarial</td>
</tr>
<tr>
<td>Freeman et al.</td>
<td>7.7-25 Gy in 5 fx</td>
<td>41</td>
<td>low</td>
<td>60</td>
<td>&lt; 1%</td>
<td>None</td>
<td>93% 5-year actuarial</td>
</tr>
<tr>
<td>Bobicen et al.</td>
<td>35 Gy in 5 fx</td>
<td>46</td>
<td>low, int</td>
<td>20</td>
<td>None</td>
<td>2%</td>
<td>100%</td>
</tr>
<tr>
<td>Jabbari et al.</td>
<td>38 Gy in 4 fx †</td>
<td>38</td>
<td>low &amp; int</td>
<td>18</td>
<td>5%</td>
<td>None</td>
<td>100%</td>
</tr>
<tr>
<td>McBride et al.</td>
<td>36.25-37.5 Gy in 5 fx</td>
<td>45</td>
<td>low</td>
<td>44</td>
<td>&lt; 1%</td>
<td>None</td>
<td>100%</td>
</tr>
<tr>
<td>Fulke et al.</td>
<td>38 Gy in 4 fx †</td>
<td>54</td>
<td>low &amp; int</td>
<td>36</td>
<td>4%</td>
<td>None</td>
<td>98%</td>
</tr>
<tr>
<td>Kang et al.</td>
<td>32-36 Gy in 4 fx</td>
<td>44</td>
<td>low, int &amp; high</td>
<td>40</td>
<td>None</td>
<td>None</td>
<td>100%, 100%, 90.9%</td>
</tr>
</tbody>
</table>

## Objectives

**Prospective phase II pilot feasibility study**

### Primary end-points

- Acute and late toxicity *(criteria CT-CAE v4.0 2010)*
- Survival free from biochemical failure *(Phoenix’s definition 2005)*

### Secondary end-points

- Quality of life *(EPIC questionnaire)*

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Materials and methods

Inclusion criteria

- Age ≤ 80 years
- WHO performance status ≤ 2.
- Histologically proven prostate adenocarcinoma
  - Any case where prophylactic lymph node irradiation is not required (risk of microscopic involvement ≤ 15%)
  - PSA ≤ 20 ng/ml.
  - T1-T2 (localized)-stage
- No pathologic lymph nodes at CT/ MR and no distant metastases
- No previous prostate surgery other than TURP
- No malignant tumors in the previous 5 years
- IPSS 0-7
- Combined HT according to risk factors.
- Informed consent

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Radiotherapy schedule

- Totale dose 35 Gy
- 5 fractions of 7 Gy on alternate days
- VMAT technique with FFF beams
- EQD2 = between 70 – 85 Gy for α/β between 3 -1.5 Gy.
Simulation and Target definition

- Simulation CT
- Simulation MRI
- CT/MRI registration

**CTV:** prostate + SV, except for T1-T2 lesions with risk of SV involvement ≤ 15% in which case CTV is prostate only

**PTV:** CTV + 5 mm margin in each direction

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Treatment planning

Red: Target
Brown: Rectum
Green: Bladder
Blue: Femoral heads
Yellow: Penile bulb

2 arcs with FFF beam
Beam On Time = 120 sec
Prostate motion

Cone beam CT pre- and post-daily treatment for assessing geometrical and dosimetric intrafraction variability during radiotherapy of prostate cancer

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Prostate displacement

Treatment verification

Online registration and matching

Use of calcifications for repositioning

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Results

<table>
<thead>
<tr>
<th>N. of patients</th>
<th>75 *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>Dec 2011 – Apr 2014</td>
</tr>
<tr>
<td>Median Age [year]</td>
<td>70 [48 – 80]</td>
</tr>
<tr>
<td>Median Gleason Score</td>
<td>6 [6–7]</td>
</tr>
<tr>
<td>Initial PSA [ng/mL]</td>
<td>Median: 7.17 [0.5–17]</td>
</tr>
<tr>
<td>NCCN Low Risk Class</td>
<td>47</td>
</tr>
<tr>
<td>NCCN Intermediate Risk Class</td>
<td>28</td>
</tr>
<tr>
<td>CTV [cm³]</td>
<td>Mean: 58.4 [25,1–110,2]</td>
</tr>
<tr>
<td>PTV [cm³]</td>
<td>Mean: 108.6 [52.8–182.2]</td>
</tr>
</tbody>
</table>

* First 40 pts: Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: preliminary report of a phase II study.
Radiat Oncol. 2013 Jul 8;8:171

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Results

- Acute toxicity
- Late toxicity

Conclusions

- SBRT with RapidArc and FFF beams in 5 fractions for prostate cancer is well tolerated in acute and late settings.
- A longer follow-up is needed to assess definitive toxicity and outcome.
- Randomized clinical trials could clarify the role of SBRT in prostate cancer.