Radiotherapy
for localized Prostate Cancer

Thomas Wiegel

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Radiotherapy for localized PCA

Structure

- Modern treatment technique
- Dose escalation - Hypofractionation
- Permanent seed implantation
- Combination with hormonal treatment
- (Intermediate and high-risk)
- Side effects
Radiotherapy for localized PCA

Radiation technique
Small field localization of the prostate

Moss and Cox, Textbook of Radiation Oncology 1990
Radiotherapy for localized PCA

3-D-(CT-)treatment planning - Dose wash

4-Fields
Radiotherapy for localized PCA

Rectal Bleeding (Laser-surgery, Transfusion) (3DCRT)

Peeters et al. IJROBP 61:1019, 2005
Radiotherapy for localized PCA

Fig. 25-4. A and B, Four-field technique for treating the pelvic lymph nodes and the prostate. (B, Bladder; FB, Foley bulb catheter with contrast; S, symphysis pubis; U, urethra; R, rectum.)
Radiotherapy for localized PCA

RT pelvic lymphatics a.p. and lat. (CTV)

Bladder Sparing

Presacral Nodes
Radiotherapy for localized PCA

Dose wash

- 3-D-Planning
- IMRT

5 Fields

6 Fields
Radiotherapy for localized PCA

„Fast“ IMRT – Rapid Arc/Volumetric Arc Technique

Bladder- and rectum sparing

Yoo et al., Int J Radiat Oncol Biol Phys 76 (2010)
Radiotherapy for localized PCA

Image guided RT (IGRT): In-Room 4D Tools

Accuray, BrainLAB, Elekta, Nomos, Resonant Medical, Siemens, TomoTherapy, Varian
Radiotherapy for localized PCA

Improved outcome with IGRT

- N=376, TD 86.4 Gy IMRT
- 186 with daily IGRT
- 190 without daily IGRT
- Med. FU: 2.8 years


Late GU Grade 2+ Toxicity Free Survival

10.4%  
P = 0.024  
20%

bNED
Radiotherapy for localized PCA

Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

Table 1. Baseline Demographic Characteristics for the IMRT vs CRT Comparison

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Before Propensity Weighting</th>
<th>After Propensity Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMRT (n = 6666)</td>
<td>CRT (n = 6310)</td>
</tr>
<tr>
<td>Year of radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>448 (6.7)</td>
<td>2402 (38.1)</td>
</tr>
<tr>
<td>2003</td>
<td>917 (13.8)</td>
<td>1846 (29.3)</td>
</tr>
<tr>
<td>2004</td>
<td>1334 (20.0)</td>
<td>1140 (18.2)</td>
</tr>
<tr>
<td>2005</td>
<td>1841 (27.6)</td>
<td>601 (9.5)</td>
</tr>
<tr>
<td>2006</td>
<td>2126 (31.9)</td>
<td>312 (4.9)</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>66-69</td>
<td>1338 (20.1)</td>
<td>1265 (20.1)</td>
</tr>
<tr>
<td>70-74</td>
<td>2415 (36.2)</td>
<td>2345 (37.2)</td>
</tr>
<tr>
<td>$\geq$75</td>
<td>2913 (43.7)</td>
<td>2700 (42.8)</td>
</tr>
</tbody>
</table>

SEER-Data-Base

Sheets et al., JAMA 307, 2012
Radiotherapy for localized PCA

Intensity-Modulated Radiation Therapy, Proton Therapy, or Conformal Radiation Therapy and Morbidity and Disease Control in Localized Prostate Cancer

Figure 1. Propensity Score-Adjusted Rates of Additional Cancer Treatment for Patients Treated With Intensity-Modulated Radiation Therapy vs Conformal Radiation Therapy

IMRT lower probability of new tumour-treatment

Sheets et al., JAMA 307, 2012
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Dose escalation
Radiotherapy for localized PCA

RT01 Dose escalation trial
843 patients
N=421: 64 Gy - 32 Fx
N=422: 74 Gy - 37 Fx
T1 – T3a N0 M0
PSA< 50 ng/ml
Neoadjuvant ADT 6-9 months
Med. FU 10 years

Dearnaley et al., Lancet Oncol. 15, 2014
Radiotherapy for localized PCA

RTO 01

- OS: No difference
- bNED: 20%

Figure 2: Primary analysis of overall survival and biochemical progression-free survival
(A) Overall survival, predicted from Kaplan-Meier function and flexible parametric model. (B) Absolute difference in overall survival, from flexible parametric model. (C) Biochemical progression-free survival, predicted by Kaplan-Meier function and flexible parametric model. (D) Absolute difference in biochemical progression-free survival, from flexible parametric model.
Radiotherapy for localized PCA

Metaanalysis of 7 RCT’s

![Graphs showing the relationship between radiotherapy total dose and biochemical control.](image-url)

**Higher dose – better bNED**

Heidenreich et al., Eur. Urol. 67, 2014

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Hypofractionation

a/b - What means - Value?

- Radiobiological description (for radiation sensitivity)
- Estimated on the basis of experimental and clinical data
- Normal: is high (>8) for tumours
- For PCA: probably <2
- Then lower than for Rectum and bladder
- Then: suggesting significant fractionation sensitivity
- Then: higher single doses (>2 Gy) better

What is when it is not 1-2 but 8-10?
Radiotherapy for localized PCA

Running Phase-III-Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>$\text{NTD}_{2\text{Gy}}$ if $a/b$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔ Fox Chase</td>
<td>Intermediate/high risk</td>
<td>76 Gy a 2.0 vs. 70.2 Gy a 2.7</td>
<td>76</td>
<td>84.3/77.2/74.3</td>
<td>300</td>
</tr>
<tr>
<td>MRC</td>
<td>Low/intermediate risk</td>
<td>70 Gy a 2.0 vs. 57 Gy a 3.0 60 Gy a 3.0</td>
<td>70</td>
<td>73.3/65.1/61.8 77.2/68.6/65</td>
<td>2100</td>
</tr>
<tr>
<td>NCIC</td>
<td>Intermediate risk</td>
<td>78 Gy a 2.0 vs. 60 Gy a 3.0</td>
<td>78</td>
<td>77.2/68.6/65</td>
<td>1204</td>
</tr>
<tr>
<td>RTOG 0415</td>
<td>Low risk</td>
<td>73.8 Gy a 1.8 vs. 70 Gy a 2.5</td>
<td>70.1</td>
<td>80/75/72.9</td>
<td>1067</td>
</tr>
</tbody>
</table>
Radiotherapy for localized PCA

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Treatment</th>
<th>NTD$_{2Gy}$ if a/b 1.5/5/10</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox Chase</td>
<td>Intermediate/high risk</td>
<td>76 Gy a 2.0 vs. 70.2 Gy a 2.7</td>
<td>76 84.3/77.2/74.3</td>
<td>300</td>
</tr>
</tbody>
</table>

N= 303 assessable pts.
Median FU: 68 months
Daily IGRT (ultrasound image guidance)

Primary Endpoint:
BCDF improvement (Hypofractionation)
Expected: 30% vs. 15% (HIMRT) at 4 years

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Fox Chase CC-Trial

Results:

Endpoint failed
No significant difference:
BCDF (ASTRO/Phoenix)
Overall survival

Alpha-beta estimation of 1.5 correct?

Radiotherapy for localized PCA

Fox Chase CC-Trial

Late side effects >=2

Results:

No significant differences

Radiotherapy for localized PCA

Fox Chase CC Hypofractionation - Trial

Cave HIMRT for pts. with IPSS > 12

Radiotherapy for localized PCA

Stereotactic Body Irradiation (including Cyberknife)
Radiotherapy for localized PCA

8 Institutions, 2003-2011
1100 pts. localized PCA
SBRT using Cyberknife system
Med. dose 36.25 Gy, 4-5 fractions
Med. FU 36 months

King et al, Radiother. Oncol. 2013
Radiotherapy for localized PCA

Multi-institutional phase-II trial with SBRT- Cyberknife

Very early results
5-year data questionable with 36 months median FU
Side effects second paper

Table 1
Patient and treatment characteristics (n = 1100).

<table>
<thead>
<tr>
<th>Risk group</th>
<th>N</th>
<th>35 Gy</th>
<th>36.25 Gy</th>
<th>38–40 Gy</th>
<th>ADT use</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>641 (58%)</td>
<td>254 (40%)</td>
<td>319 (50%)</td>
<td>68 (11%)</td>
<td>50 (8%)</td>
<td>36</td>
</tr>
<tr>
<td>Intermediate</td>
<td>334 (30%)</td>
<td>108 (32%)</td>
<td>188 (56%)</td>
<td>38 (11%)</td>
<td>49 (15%)</td>
<td>30.5</td>
</tr>
<tr>
<td>High</td>
<td>125 (11%)</td>
<td>23 (18%)</td>
<td>82 (66%)</td>
<td>20 (16%)</td>
<td>48 (38%)</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>1100</td>
<td>385 (35%)</td>
<td>589 (54%)</td>
<td>126 (11%)</td>
<td>147 (14%)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. PSA relapse-free survival Kaplan–Meier curves stratified by risk group. The 5-year actuarial PSA relapse-free survival rates are 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively (p < 0.0001). Censoring is indicated by tick marks on the curves and the number of patients at risk is given for the time intervals indicated.

King et al, Radiother. Oncol. 2013
A Systematic Review of Hypofractionation for Primary Management of Prostate Cancer

Bridget F. Koontz, Alberto Bossi, Cesare Cozzarini, Thomas Wiegel, Anthony D'Amico

Department of Radiation Oncology, Duke Cancer Institute, Durham, NC, USA; Department of Radiation Oncology, Institut Gustave Roussy, Villejuif, France; Department of Radiotherapy, San Raffaele Scientific Institute, Milan, Italy; Department of Radiation Oncology, University Hospital Ulm, Ulm, Germany; Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA

Review – Prostate Cancer

Radiotherapy for localized PCA

radiation per treatment. Prospective studies support the safety of moderate hypofractionation, while extreme fractionation may have greater toxicity. Both show promising cancer control but long-term results of noninferiority studies of both methods are required before use in routine treatment outside of clinical protocols.
Radiotherapy for localized PCA

RP or RT?

- Retrospective comparison
- RP vs. RT
- MSKCC 1993-2002
- N= 2500 pts
- Median FU: 5 vs. 5.1 years


### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Surgery (n = 1,316)</th>
<th>Radiation (n = 1,062)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at surgery, years</td>
<td>60</td>
<td>69</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>55-65</td>
<td>64-73</td>
</tr>
<tr>
<td>Median total PSA, ng/mL</td>
<td>6.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4.5-8.7</td>
<td>5.1-12</td>
</tr>
<tr>
<td>Median preoperative 5-year Kattan nomogram progression-free probability</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>73-90</td>
<td>63-89</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>574</td>
<td>527</td>
</tr>
<tr>
<td>(n = 1,316)</td>
<td>44%</td>
<td>50%</td>
</tr>
<tr>
<td>T2a</td>
<td>379</td>
<td>267</td>
</tr>
<tr>
<td>(n = 1,316)</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>T2b</td>
<td>191</td>
<td>114</td>
</tr>
<tr>
<td>(n = 1,316)</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>T2c</td>
<td>122</td>
<td>59</td>
</tr>
<tr>
<td>(n = 1,316)</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>T3a</td>
<td>51</td>
<td>55</td>
</tr>
<tr>
<td>(n = 1,316)</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>T3b</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>(n = 1,316)</td>
<td>0.1%</td>
<td>4%</td>
</tr>
<tr>
<td>Biopsy Gleason score*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>906</td>
<td>516</td>
</tr>
<tr>
<td>66%</td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>7</td>
<td>394</td>
<td>406</td>
</tr>
<tr>
<td>4%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>≥ 8</td>
<td>59</td>
<td>140</td>
</tr>
<tr>
<td>4%</td>
<td>12%</td>
<td>13%</td>
</tr>
</tbody>
</table>

- Year of treatment
  - 1993-1995: 349 (26%)
  - 1996-1997: 427 (18%)
  - 1998-2000: 522 (20%)
  - 2001-2002: 317 (13%)

- Positive surgical margins: 155 (12%)
- Extracapsular extension: 336 (26%)
- Seminal vesicle invasion: 97 (7%)
- Lymph node involvement: 52 (4%)

Note: All differences in clinical characteristics between treatment groups were statistically significant (P < .001).

Abbreviations: PSA, prostate-specific antigen; NA, not applicable.

*Biopsy Gleason score was missing for 189 surgery patients. For these patients, we estimated biopsy Gleason score using pathologic Gleason score.
Radiotherapy for localized PCA

No difference low vs intermediate
Radiotherapy for localized PCA

For external radiotherapy, a dose of at least 74 Gy is recommended for the management of low-risk PCa because biochemical disease-free survival is significantly higher when compared with a dose <72 Gy (69% vs 63%; p = 0.046) [71].

For intermediate-risk PCa, many series have shown a significant impact of dose escalation on 5-yr progression-free survival in cT1c–T3 PCa, with a dose ranging from 76 to 81 Gy [72].
Radiotherapy for localized PCA

Permanent Seed Implantation (PSI)
Radiotherapy for localized PCA

Multi-Institutional analysis stage T1-2 with PSI

I-125 dose > 130 Gy D90: 8 years bNED 93% vs. 76% (p<.001)

Quality of Implantation important

Radiotherapy for localized PCA

Permanent Seed Implantation
„15 –year results“ – Lakewood Ranch

Table 1. Fifteen-year monotherapy overall breakdown

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70</td>
</tr>
<tr>
<td>Preimplant PSA</td>
<td>7.5 (0.2–74.6)</td>
</tr>
<tr>
<td>Gleason score, count (%)</td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>173 (100)</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>8–10</td>
<td>0</td>
</tr>
<tr>
<td>Clinical stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>T1b</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>T1c</td>
<td>31 (17.8)</td>
</tr>
<tr>
<td>T2a</td>
<td>113 (64.9)</td>
</tr>
<tr>
<td>T2b</td>
<td>16 (9.1)</td>
</tr>
<tr>
<td>T2c</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>T3</td>
<td>0</td>
</tr>
<tr>
<td>Initial PSA, n (%)</td>
<td></td>
</tr>
<tr>
<td>0–4 ng/mL</td>
<td>61 (35.0)</td>
</tr>
<tr>
<td>4.1–10.0 ng/mL</td>
<td>79 (45.4)</td>
</tr>
<tr>
<td>10.1–20.0 ng/mL</td>
<td>26 (14.9)</td>
</tr>
<tr>
<td>&gt;20.0 ng/mL</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>D’Amico risk groups, n (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>128 (73.5)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36 (20.6)</td>
</tr>
<tr>
<td>High</td>
<td>9 (5.1)</td>
</tr>
</tbody>
</table>


1988-1992
D90: 145 Gy
Med. NB: 11.7 years
Med. NB bNED: 15.4 years
Radiotherapy for localized PCA

PSI – „15-year results“ – Lakewood Ranch

Fig. 2. Fifteen-year Kaplan-Meier curves for biochemical progression-free survival using the nadir + 2 definition. Stratified by group using the D’Amico method of risk classification. BRFS = biochemical relapse free survival.

Fig. 5. Fifteen-year overall survival outcomes of entire treatment cohort compared with that of the typical 70-year-old man based on United States vital statistics from 1989 (Vital statistics of the United States 1989, Life tables, Volume II Section 6. U.S. Department of Health and Human Services [41]).
Guidelines

**EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent—Update 2013**

Axel Heidenreich a,*, Patrick J. Bastian b, Joaquim Bellmunt c, Michel Bolla d, Steven Joniau e, Theodor van der Kwast f, Malcolm Mason g, Vsevolod Matveev h, Thomas Wiegel i, F. Zattoni j, Nicolas Mottet k

<table>
<thead>
<tr>
<th>Guideline/recommendation</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In localized PCa (T1c–T2cN0M0), 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>For high-risk patients, long-term ADT before and during RT is recommended, as it results in increased overall survival.</td>
<td>2a</td>
<td>B</td>
</tr>
<tr>
<td>In patients with locally advanced PCa (T3–T4N0M0) who are fit enough to receive EBRT, the recommended treatment is EBRT plus long-term ADT. The use of ADT alone is inappropriate.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td><strong>Transperineal interstitial brachytherapy with permanent implants is an option for patients with cT1–T2a, Gleason score ≤7a, PSA ≤10 ng/mL, prostate volume ≤50 mL without a previous TURP and with a good IPSS.</strong></td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Immediate postoperative external irradiation after RP for patients with pathologic tumor stage T3N0M0 improves biochemical and clinical disease-free survival.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>In patients with pathologic tumor stage T3N0M0, immediate postoperative external irradiation after RP may improve biochemical and disease-free survival, with the highest impact in cases with positive surgical margins.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In patients with pathologic tumor stage T2–T3N0M0, salvage irradiation is indicated in cases of persisting PSA or biochemical failure with rising PSA levels ≤0.5 ng/mL. Salvage RT might be initiated, even at low PSA levels of 0.1–0.2 ng/mL, if a continuous PSA increase has been documented.</td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td>In patients with locally advanced PCa, T3–T4N0M0, concomitant and adjuvant hormonal therapy for a total duration of 3 yr, with external-beam radiation for patients with WHO 0–2 performance status, is recommended, as it improves overall survival.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In a subset of patients with T2–T3N0M0 and Gleason score 2–6, short-term ADT before and during RT can be recommended, as it may favorably influence overall survival.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>In patients with very-high-risk PCa, c–pN1M0, and no severe comorbidities, the therapeutic role of pelvic external irradiation and immediate long-term ADT is unclear; the adjuvant treatment options have to be discussed on an individual basis, taking into consideration the age of the patient, comorbidities, and biology of the cancer.</td>
<td>3b</td>
<td>B</td>
</tr>
</tbody>
</table>

ADT = androgen deprivation therapy; 3D-CRT = three-dimensional conformal radiation therapy; EBRT = external-beam radiation therapy; GR = grade of recommendation; IMRT = intensity-modulated radiation therapy; IPSS = International Prostate Symptom Score; LE = level of evidence; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; TURP = transurethral resection of the prostate; WHO = World Health Organization.

Heidenreich et al., Eur. Urol. 65, 2014
Radiotherapy for localized PCA

Combination with Androgen Deprivation Therapy
Radiotherapy for localized PCA

(Neo)adjuvant HT- + Radiotherapy

- Reduction prostate mass (20-30%)
- Reduction clonogene tumour cells

- Part Bladder/Rectum high dose level ↓
- D95 Bladder: 40-50% ↓
- D95 Rectum: 15-20% ↓

Conclusion: Rate Late side effects ↓
Tumour Control Rate ↑

Zelefsky et al., Urology 1997
Radiotherapy for localized PCA

Neoadjuvant + adjuvant HT + RT

- Prospective randomised Phase-III-Study
- 206 Pts. 70 Gy vs. 70 Gy + 2+2+2 Months HT
- Randomisation: 1995-2001
- Med. FU.: 7.6 years

5-year OS: 88% vs. 78% (p<0.05)
7 years: HR 1.8 (p=0.01)
low Co-Morbidity-Rate: HR 4.2

D’Amico et al., JAMA 299, 2008
Phase-III-Trial
70 Gy vs. 70 + 6 mo HT

Elder men (>73 years) with low comorbidity profit from combination treatment - improved OS-

---

**Table 2.** Cox regression for all-cause mortality among men with no or minimal comorbidity older than the median age (72.4 y).

<table>
<thead>
<tr>
<th>Adj. hazard ratio</th>
<th>95% Confidence interval</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+AST</td>
<td>0.36</td>
<td>0.13 - 0.98</td>
</tr>
<tr>
<td>Age (y)</td>
<td>1.22</td>
<td>0.99 - 1.58</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>0.57</td>
<td>0.18 - 1.82</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>1.02</td>
<td>0.27 - 3.92</td>
</tr>
<tr>
<td>Clinical T2</td>
<td>0.80</td>
<td>0.31 - 2.02</td>
</tr>
<tr>
<td>Log (PSA)</td>
<td>1.22</td>
<td>0.46 - 3.22</td>
</tr>
</tbody>
</table>

*Abbreviations: RT+AST = radiation therapy plus androgen suppression therapy; PSA = prostate-specific antigen.*

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**Fig. 1.** All-cause mortality among men with no to minimal comorbidity who were older than the median age, stratified by treatment (\( p = 0.01 \)).
Radiotherapy for localized PCA

Phase-III-Trial
70 Gy vs. 70 + 6 mo HT

<table>
<thead>
<tr>
<th>Adj. hazard ratio</th>
<th>95% Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+AST</td>
<td>5.16</td>
<td>1.32</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>0.80</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>0.11</td>
<td>0.02</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>0.44</td>
<td>0.11</td>
</tr>
<tr>
<td>Clinical T2</td>
<td>0.30</td>
<td>0.07</td>
</tr>
<tr>
<td>Log (PSA)</td>
<td>0.55</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Abbreviations: RT+AST = radiation therapy plus androgen suppression therapy; PSA = prostate-specific antigen.

Elder men (>73 years) with high comorbidity do not profit from combination treatment
- OS worse -

Radiotherapy for localized PCA

Increased mortality with Androgen Deprivation Therapy?

**Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer**

A Meta-analysis of Randomized Trials

---

**Figure 2. Relative Risk of Cardiovascular Deaths Associated With ADT Among Patients With Prostate Cancer**

<table>
<thead>
<tr>
<th>Source</th>
<th>ADT</th>
<th>Control</th>
<th>Relative Risk (95% CI)</th>
<th>Favors ADT</th>
<th>Favors Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Amco et al., 2008 (DFCI 95-069)</td>
<td>15/102</td>
<td>13/104</td>
<td>1.02 (0.50-2.09)</td>
<td></td>
<td></td>
<td>.96</td>
</tr>
<tr>
<td>Messing et al., 2006 (ECOG/EST 3886)</td>
<td>3/47</td>
<td>1/51</td>
<td>3.25 (0.35-30.2)</td>
<td></td>
<td></td>
<td>.30</td>
</tr>
<tr>
<td>Bolla et al., 2010 (EORTC 22853)</td>
<td>22/207</td>
<td>17/208</td>
<td>2.30 (0.71-7.68)</td>
<td></td>
<td></td>
<td>.94</td>
</tr>
<tr>
<td>Schroder et al., 2009 (EORTC 30945)</td>
<td>10/119</td>
<td>10/115</td>
<td>0.97 (0.42-2.23)</td>
<td></td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>Studer et al., 2006 (ECOG/EST 3891)</td>
<td>264/492</td>
<td>97/493</td>
<td>0.91 (0.70-1.18)</td>
<td></td>
<td></td>
<td>.47</td>
</tr>
<tr>
<td>Elsathari et al., 2009 (RTOG 85-31)</td>
<td>52/477</td>
<td>65/468</td>
<td>0.78 (0.56-1.10)</td>
<td></td>
<td></td>
<td>.17</td>
</tr>
<tr>
<td>Roach et al., 2008 (RTOG 80-10)</td>
<td>31/224</td>
<td>29/222</td>
<td>1.23 (0.76-2.01)</td>
<td></td>
<td></td>
<td>.40</td>
</tr>
<tr>
<td>Denham et al., 2011 (RTOG 06-11)</td>
<td>36/632</td>
<td>23/270</td>
<td>0.70 (0.48-1.31)</td>
<td></td>
<td></td>
<td>.37</td>
</tr>
<tr>
<td>Overall</td>
<td>255/2200</td>
<td>252/1941</td>
<td>0.93 (0.79-1.10)</td>
<td></td>
<td></td>
<td>.61</td>
</tr>
</tbody>
</table>

**Test for heterogeneity:** $Q = 5.12; P = .04; I^2 = 0$

ADT indicates androgen deprivation therapy. The summary relative risk of cardiovascular deaths was calculated using a fixed-effects model. The size of the squares indicates the weight of the study, which is the inverse variance of the effect estimate. The diamond indicates the summary relative risk.

---

None influence (?)

Nguyen et al., JAMA 306, 2011

University Hospital Ulm • Department of Radiation Oncology
## Radiotherapy for localized PCA

### Intermediate Risk – HT + RT

#### Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short-Term ADT plus Radiotherapy (N=987)</th>
<th>Radiotherapy Alone (N=992)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>70</td>
<td>71</td>
</tr>
<tr>
<td>Range</td>
<td>47–91</td>
<td>47–88</td>
</tr>
<tr>
<td>Karnofsky performance score — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100</td>
<td>905 (92)</td>
<td>920 (93)</td>
</tr>
<tr>
<td>70–80</td>
<td>82 (8)</td>
<td>72 (7)</td>
</tr>
<tr>
<td>Risk subgroup — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>351 (36)</td>
<td>134 (34)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>524 (53)</td>
<td>544 (55)</td>
</tr>
<tr>
<td>High risk</td>
<td>112 (11)</td>
<td>114 (11)</td>
</tr>
<tr>
<td>Gleason score — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>623 (63)</td>
<td>592 (60)</td>
</tr>
<tr>
<td>7</td>
<td>252 (26)</td>
<td>286 (29)</td>
</tr>
<tr>
<td>8–10</td>
<td>93 (9)</td>
<td>87 (9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>19 (2)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>PSA — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 ng/ml</td>
<td>109 (11)</td>
<td>100 (10)</td>
</tr>
<tr>
<td>4–20 ng/ml</td>
<td>878 (89)</td>
<td>892 (90)</td>
</tr>
</tbody>
</table>

*RTOG 94-08  
Med. FU: 9.1 years  
Jones et al., NEJM. 365, 2011
Radiotherapy for localized PCA

5% OS advantage
10 years
62% vs. 57%
(p<0.005)

Figure 2. Kaplan–Meier Estimates of Overall Survival.
ADT denotes androgen-deprivation therapy. Panels B, C, and D show post hoc analyses.

Jones et al., NEJM. 365, 2011
Radiotherapy for localized PCA

PCA-intermediate risk

Patients who are reluctant to accept short-term hormonal treatment can receive definitive radiotherapy alone provided that a dose escalation up to 78-80 Gy is proposed.

Radiotherapy for localized PCA

Side effects
Radiotherapy for localized PCA (IMRT) - Results MSKCC -

- MSKCC New York
- 81 Gy
- N=170
- Med. FU: 99 months

Erectile Dysfunction: 51%
GU-late side effects II-III: 9%/3% 11%/5%
GI-late side effects II–III: 2%/0.1% 2%/1%

Zelefsky et al., J. Urol. 176, 2006
Alikus et al., Cancer 2011
Radiotherapy for localized PCA

Risk GU late side effects

- Long duration possible, dose dependent
- Incidence 10 years: 10%
- Increased risk with severe acute side effects

Erectile Dysfunction after RT

- 5 years after RT: 30-60%
- 2 randomized trials
- Double-blind, placebo-controlled
- 60 Pts.
- Sildenafil and Tadalafil (20 mg)
- 50-60% significant improvement

Ohebshalom et al., J. Urol. 174, 2005
### Table 5. Total, early (1–5 y) and late (≥5 y) SPCs by location and treatment group

<table>
<thead>
<tr>
<th></th>
<th>No RT, no surgery</th>
<th>RT only</th>
<th>EBRT</th>
<th>Brachytherapy</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patients</strong></td>
<td>40,433</td>
<td>67,719</td>
<td>48,400</td>
<td>10,223</td>
<td>9,096</td>
</tr>
<tr>
<td><strong>Patients with SPC†</strong></td>
<td>3,208</td>
<td>5,993</td>
<td>4,997</td>
<td>480</td>
<td>516</td>
</tr>
</tbody>
</table>

**Patients without SPC**
- **All SPCs**: 3,208, 6,240, 6,240, 4,997, 480, 516
- **Pelvic area**: 586, 1,236, 20,6, 1,236, 20.6
- **Primary pelvic area**: 492, 1,084, 18.1
- **Secondary pelvic area**: 94, 2,512, 2.5
- **Nonpelvic area**: 626, 4,757, 79.4
- **Early SPC**: 2,293, 81.7
- **Late SPC**: 9,154, 37.5
- **Early SPCs**: 2,293, 100.0
- **Pelvic area**: 416, 2,741, 19.8
- **Primary pelvic area**: 348, 1,052, 27.4
- **Secondary pelvic area**: 69, 89, 3.0
- **Nonpelvic area**: 1,877, 81.9
- **Late SPCs**: 9,154, 100.0
- **Pelvic area**: 170, 1,866, 22.0
- **Primary pelvic area**: 144, 1,587, 19.4
- **Secondary pelvic area**: 26, 1,632, 23.8
- **Nonpelvic area**: 745, 1,750, 37.8

**Abbreviations as in Tables 1 and 2.**

**Differences in proportions might just reflect differences in follow-up; for example, EBRT group had more SPCs (10.3%) but also had longest follow-up (median, 5.2 y).**

*Comparison of proportion of SPC (all, early, or late) among four treatment groups (no RT, no surgery, EBRT, brachytherapy, and combination).*

† Adjusted p values for pairwise comparisons: EBRT vs. no RT, p < 0.0001; brachytherapy vs. no RT, p < 0.0001; combination vs. no RT, p < 0.0001; EBRT vs. brachytherapy, p < 0.0001; combination vs. no RT, p < 0.0001; brachytherapy vs. combination, p < 0.0001.

‡ Adjusted p values for pairwise comparisons: EBRT vs. no RT, p < 0.0001; brachytherapy vs. no RT, p < 0.0001; combination vs. no RT, p < 0.0001; EBRT vs. combination, p < 0.0001; brachytherapy vs. combination, p < 0.0001.

Radiotherapy for localized PCA

What is the risk?

CONCLUSION

Patients choosing EBRT might be at a greater absolute risk of developing a second malignancy—not just from the RT *per se*, but possibly related to other factors such as longer follow-up or older age, or more risk factors—an additional 207 cases of 100,000 patients or 0.2% can be expected. However, the incidence of second cancers that could possibly be RT-induced (RTSPC) was shown to be 162 of 100,000 or 0.16% in the present study—although it might actually be significantly lower if significant risk

Secondary tumours: 0.2% (207/100 000)

Real RT-induced Tumous: 0.16% (162/100 000)

Conclusions

- RT, RP, PSI and AS comparable for low risk PCA
- IMRT with IGRT standard, total dose >74 Gy<80 Gy
- Intermediate risk: 4-6 months ADT, RT alone dose 76-78 Gy
- High risk: selected cases 6 months ADT, usually 2-3 years, RT 76-78 Gy
- Severe side effects: GI>2%, GU more common, erectile dysfunction
Radiotherapy for localized PCA

Urologists and Radiation Oncologists still became friends.......

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