PROSTATE CANCER: LOCAL CONTROL, SURVIVAL AND HIGH DOSE RADIATION THERAPY

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Rome
Problems: the “epidemic” prostate cancer and its implications

USA 1999

# 60,000 patients underwent radical radiation therapy for prostate cancer

# About 25% of these were diagnosed with very limited disease (T1b - T1c)

JAMA, 281: 1598-604, 1999
Fig. 1. Yearly accrual of patients treated radically for prostate cancer in the centers with archives active since 1980 (number and trend, total n = 1057).
Patients to be treated with radical Radiation therapy: problems to be solved:

1. *Control of subclinical metastatic disease* (and *local control*) in locally advanced ones and in those with unfavourable "biological" features ("high" PSA, "high" Gleason score)

2. *Local control* in clinically localized disease, with favourable "biological" features
Attempting to solve these problems, the main proposals might be:

1. Association of prostate RT with hormonal manipulation (local control and control of subclinical metastatic disease)

2. Development of high dose radiation therapy to the prostate volume (local control and, maybe, survival)
Surgery and radiotherapy obtain substantially similar results in early stage prostate cancer; RT is generally preferred for locally advanced cases.

# Cleveland Clinic (1997): 607 T1-T2 patients:
  - 354 underwent surgery,
  - 253 radiation therapy;
  - 5 yr bNED 76% vs 75%;

5 and 10 yr NED survival rate for T3 pts undergoing RT is:
  - 55 - 75 % 5 yr
  - 35 - 60 % 10 yr;

Surgical data based on clinical stage are scarce and generally not equivalent to the RT series.
RT treatment of clinically negative pelvic and/or PA nodes gave conflicting and mostly negative results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Stage</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 7506</td>
<td>+/- RT to pelvic and PA nodes</td>
<td>B2-C</td>
<td>Random</td>
<td>N.S.</td>
</tr>
<tr>
<td>RTOG 7706</td>
<td>+/- RT to pelvic nodes</td>
<td>A2-B</td>
<td>Random</td>
<td>N.S.</td>
</tr>
<tr>
<td>McGowan</td>
<td>Retrospective, no overall survival gain, RFS better</td>
<td>(1981), 185 T2- T3 pts</td>
<td>+/- RT to pelvic nodes</td>
<td>No overall survival gain, RFS better</td>
</tr>
</tbody>
</table>
Some encouraging results come from **hormonal adjuvant** treatment trials in RT treated pts.

<table>
<thead>
<tr>
<th>Study</th>
<th>Approach</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC (1997)</td>
<td>3 YEAR TAS POST RT (PROSTATE PELVIS) VS RT</td>
<td>INCREASED L.C., +DIST.METS FREE &amp; OVERALL SURVIVAL</td>
</tr>
<tr>
<td>&gt; 400 T2-3 PTS RANDOM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 8610</td>
<td>&quot;NEOADJUVANT&quot; TAS + RT VS RT</td>
<td>LESS PSA &amp; LOCAL FAILURES, NO SURV. EFFECT</td>
</tr>
<tr>
<td>471 T2-4 PTS RANDOM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 8531</td>
<td>RT + GOSERELIN VS RT</td>
<td>LESS PSA &amp; LOCAL FAILURES &amp; DIST. METS, NO SURV. EFFECT</td>
</tr>
<tr>
<td>T3 &amp; NODE +VE PTS RANDOM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
THE EFFECT OF RADIATION DOSE ON SURVIVAL
HANKS (1988): 1348 stage B and C patients:

The higher the dose the higher the local control rates in stage C patients:

<table>
<thead>
<tr>
<th>Dose to the prostate (Gy)</th>
<th>&lt;60</th>
<th>60-64.9</th>
<th>65-69.9</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local failure rates</td>
<td>37%</td>
<td>36%</td>
<td>29%</td>
<td>19%</td>
</tr>
</tbody>
</table>

NO DISEASE SPECIFIC OR UNCORRECTED SURVIVAL ADVANTAGE WAS DESCRIBED
Nine Radiation Oncology Centers in Central and Northern Italy have pooled their prostate cancer databases in an unified format, to allow a retrospective survey of patterns of care in the last two decades:

* Arezzo  
* Brescia  
* Como  
* Firenze  
* Mantova  
* Milano  
* Perugia  
* Pistoia

**Clinical Investigation**

**Practice Patterns for Prostate Cancer in Nine Central and Northern Italy Radiation Oncology Centers: A Survey Including 1759 Patients Treated During Two Decades (1980–1998)**

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Sergio Villa, M.D.,‡ Emanuela Cagna, M.D.,§ Ernesto Maranzano, M.D.,‖  
Maurizio Perlì, M.D.,* Renato Pradea, M.D.,* Massimo Alcide Sperdaci, M.D.,**  
Andrea Chiavacci, M.D.,†† Enrica Ambrosi, M.D.,* Lorenzo Livi, M.D.,*  
Alessandro Magli, M.D.,* Rita Bellavita, M.D.,‖ Alberto Bossi, M.D.,§ and  
Gianpaolo Bitti, M.D.,†
RADIATION THERAPY OF PROSTATE CANCER

<table>
<thead>
<tr>
<th>Dose to prostate</th>
<th>OS (%)</th>
<th>DSS (%)</th>
<th>RFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>38±10</td>
<td>50±11</td>
<td>28±9</td>
</tr>
<tr>
<td>60-65</td>
<td>63±3</td>
<td>73±3</td>
<td>57±3</td>
</tr>
<tr>
<td>66-69</td>
<td>85±2</td>
<td>90±1</td>
<td>72±2</td>
</tr>
<tr>
<td>70</td>
<td>84±3</td>
<td>90±1</td>
<td>70±3</td>
</tr>
<tr>
<td>&gt;70</td>
<td>71±3</td>
<td>82±3</td>
<td>73±3</td>
</tr>
<tr>
<td>“P”</td>
<td>0.003</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

These results hold true also when considering, separately, only pts treated before 1989 (pre-PSA “era”), pts not treated with hormonal therapy, pts with Stage B and C.

These results and similar reports by other Authors represent the main reason to the widespread use of high dose RT (70 Gy and over) during the recent years.
# Radiation Therapy of Prostate Cancer

<table>
<thead>
<tr>
<th>Groups</th>
<th>OS (%)</th>
<th>DSS (%)</th>
<th>RFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associated HT(*)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT only</td>
<td>74+2</td>
<td>84+2</td>
<td>67+2</td>
</tr>
<tr>
<td>HT before RT</td>
<td>75+3</td>
<td>80+3</td>
<td>61+4</td>
</tr>
<tr>
<td>HT after RT</td>
<td>80+3</td>
<td>89+2</td>
<td>80+3</td>
</tr>
<tr>
<td>HT before+after</td>
<td>79+2</td>
<td>85+2</td>
<td>68+2</td>
</tr>
<tr>
<td>&quot;P&quot;</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Accrual period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980-1990</td>
<td>66+2</td>
<td>75+2</td>
<td>60+2</td>
</tr>
<tr>
<td>1991-1994</td>
<td>83+2</td>
<td>90+1</td>
<td>74+2</td>
</tr>
<tr>
<td>1995-1998</td>
<td>79+5</td>
<td>90+2</td>
<td>67+5</td>
</tr>
<tr>
<td>&quot;P&quot;</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

(*) HT=Hormonal Therapy

## Radiation Therapy of Prostate Cancer

<table>
<thead>
<tr>
<th>Groups</th>
<th>OS (%)</th>
<th>DSS (%)</th>
<th>RFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>84±2</td>
<td>91±1</td>
<td>77±2</td>
</tr>
<tr>
<td>II</td>
<td>79±2</td>
<td>86±1</td>
<td>67±2</td>
</tr>
<tr>
<td>III</td>
<td>67±3</td>
<td>76±3</td>
<td>58±4</td>
</tr>
<tr>
<td>“p”</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline PSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>84±4</td>
<td>88±4</td>
<td>77±5</td>
</tr>
<tr>
<td>6-10</td>
<td>84±4</td>
<td>94±2</td>
<td>79±4</td>
</tr>
<tr>
<td>11-20</td>
<td>87±3</td>
<td>92±2</td>
<td>72±5</td>
</tr>
<tr>
<td>&gt;20</td>
<td>77±3</td>
<td>86±2</td>
<td>61±4</td>
</tr>
<tr>
<td>“p”</td>
<td>ns</td>
<td>ns</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial.

305 stage T1-T3 pts., Follow-up 60 months
150 pts  70 Gy
151 pts  78 Gy

Freedom from failure (FFF)
70 Gy 64%
78 Gy 70% \( p = 0.003 \)

Conclusion: An increase of 8 Gy resulted in a highly significant improvement in FFF for patients at intermediate to high risk, although the rectal reactions were also increased. Dose escalation techniques that limit the rectal volume that receives $\geq$ 70 Gy to < 25% should be used.

A. Pollack et al., Int J Radiat Oncol Biol Phys 53, 1097-1105, 2002

264 stage T1-T2a pts., Follow-up 35 months
Gleason grade ≤ 6

Freedom from failure (FFF)
- <66 Gy 79.2
- 66 Gy 78.4
- > 66 84.5

Conclusion: Within a range of doses considered standard for treatment of low-risk clinically localized prostate ca. during an 8 y. period, no improvement in biochemical FFF was noted with the higher doses. The overall 5 y. rate of freedom from biochemical failure is consistent with that reported by others with standard and escalated EBRT doses. Prospective randomization is necessary.

M. Hurwitz et al., Int J Radiat Oncol Biol Phys 53, 1106-1110, 2002
High-dose intensity modulated RT for prostate ca.: early toxicity and biochemical outcome in 772 pts.

772 stage T1c, T2a, T2b, T3 pts., Follow-up 24 months
698 pts. 81 Gy 74 pts. 84.6 Gy

• 3 y. actuarial likelihood of ≥ late grade II rectal toxicity 4%
• 3 y. actuarial likelihood of ≥ late grade II urinary toxicity 15%

Conclusion: Data demonstrate feasibility of high dose IMRT. Acute and late rectal toxicities seem to be significantly reduced compared with conventional 3D RT. Short-term PSA control rates compare with 3D RT. At Memorial Sloan Kettering Institute IMRT is standard treatment.

M. J. Zelefsky et al., Int J Radiat Oncol Biol Phys 53, 1111-1116, 2002
Preliminary observations on bRelapse-free survival rates after short-course IMRT (70 Gy, 25 Gy/day) for localized prostate ca.

282 stage T1/T3 pts., Follow-up 25 months
70 Gy, 2.5 Gy/day, 5 IMRT fields 166 pts
78 Gy, 2.0 Gy/day, 3D conformal 116 pts

bRFS (30 months)
3D 88%
IMRT 94% (p ns)

Conclusion: The IMRT schedule had a comparable bRFS with the 3D CRT schedule. Grade 3 late rectal toxicity occurred in a total of 10 pts. Actuarial grade 3 late rectal toxicity rate (30 m.) was 2% for IMRT and 8% in the 3D group.

RADIATION THERAPY OF PROSTATE CANCER: EXPECTANCIES OF IMPROVEMENT WITH CONFORMAL TECHNIQUES
The aims of conformal RT (CRT) are twofolds:

• To allow a more homogeneous dose distribution across the target volume (CTV, PTV);

• To reduce the complication rate (critical organs sparing), thereby allowing the escalation of the dose to the tumor.
**IMRT Intensity Modulated Radiation Therapy.**

**IMRT** – Intensity Modulated Radiation Therapy: Newer type of irradiation based on the use of optimized non-uniform radiation beam intensities incident on the patient.

IMRT techniques are significantly more complex than many other conventional forms of RT including conventional 3D-CRT.
**IMRT and Inverse Planning or Automated Optimization 3D-RTP**

Inverse planning or Automated Optimization 3D-RTP uses the computer optimization techniques to modify the Beam intensities across the target volume.

To optimize the shape of dose distributions to generate complex volumes is not only a problem of using beam modifiers such as compensators or wedges, but the central problem of IMRT is to determine the physically deliverable Beam Fluence Profiles resulting in a dose distribution matching the desired one.
New irradiation modalities: Intensity-modulated radiation therapy

Potentiality to achieve a much higher degree of target Conformity and/or normal tissue sparing effect than most other treatment techniques, especially for target volumes and/or organs at risk with complex shapes and/or concave regions.

Prostate IMRT plan

5-field to 81 Gy
RADIATION THERAPY OF PROSTATE CANCER
RADIATION THERAPY OF PROSTATE CANCER
RADIATION THERAPY OF PROSTATE CANCER
Some data are available to support the hypothesis of better bRFS rates with CRT due to higher doses and better “coverage” of the target volumes.

**MIR (1998):** 257 pts, T1c-T2

3 yrs bRFS advantage
90% vs 80%, p=0.01

for: CRT and slightly higher doses (68-74 Gy) vs standard and lower doses (68-70 Gy).
Some data are available to support the hypothesis of a reduction of RT toxicity with CRT.

The RMH experience (1999):
225 randomised pts

Grade 2 rectal toxicity at 2 yrs:
- CRT 5%
- "Standard" box 15%
- p=0.01
Some data are available to support the hypothesis of a reduction of RT toxicity with CRT.

The Rotterdam experience (1999):

- 266 pts
- Random CRT
- 3-field standard technique
- rectal toxicity 32% vs 19%  p=0.02
At the RT Department of the University of Florence a program to develop CRT for prostate cancer started during 1996. Since then patients have been treated with CRT. A comparison of the dose distributions obtained in a first series of patients with two CRT techniques (4-field; 6-fields) and with the “standard” box technique has been performed.
RESULTS

“Standard” box technique, a significantly larger bladder volume and larger volume of rectum were included in the 95% isodose curve.

PTV “coverage” was also better with the two CRT techniques, without significant differences between them.
RADIATION THERAPY OF PROSTATE CANCER

% OF PTV WITHIN THE 95 % ISODOSE

CONFO4
CONFO6
STANDARD

±1.96* Std. Dev.
±1.00* Std. Dev.
Mean

P<0.001

RADIATION THERAPY OF PROSTATE CANCER
RADIATION THERAPY OF PROSTATE CANCER

% OF BLADDER VOLUME WITHIN THE 95% ISODOSE

P<0.001

CONFO4
STANDARD
CONFO6

±1.96*Dev.Std.
±1.00*Dev.Std.
Mean

RADIATION THERAPY OF PROSTATE CANCER
TIME TO HAVE A PATIENT READY TO BE TREATED WITH CRT IS MUCH LONGER THAN WITH THE STANDARD "BOX" TECHNIQUE

12 patients CRT - average time to the completion of the planning procedure: 586 min (including 191 min for dose computation).

Corresponding times averaged 65 min for the standard box technique.
CT and MR studies after registration
Body fix to secure comfortable position and daily reproducibility of position.
Fiducial Markers

Repeated CT's

- week 0
- week 3
- week 6
POSITION VERIFICATION

- No pv: error 4.9 mm
- Pv bone: error 2.8 mm
- Pv marker: error -0.1 mm

Marker-pv: the systematic error is near to zero.

Displacement (mm) vs. fraction.
Marker migration within prostate

Dehna d et al. (2002)

Data from 10 patients, 239 treatment fractions
### Conclusions

5 y. bDFS for patients with favourable, intermediate and poor prognosis patients

<table>
<thead>
<tr>
<th>Pts Group</th>
<th>Low Dose</th>
<th>High Dose</th>
<th>Brachy</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>80%</td>
<td>85%</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53%</td>
<td>75%</td>
<td>75%</td>
<td>67%</td>
</tr>
<tr>
<td>Poor</td>
<td>29%</td>
<td>54%</td>
<td>60%</td>
<td>50%</td>
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</table>

Acute and late urinary and rectal toxicity from 81 Gy by IMRT

<table>
<thead>
<tr>
<th></th>
<th>Urinary</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Late</td>
</tr>
<tr>
<td>None</td>
<td>17%</td>
<td>83%</td>
</tr>
<tr>
<td>Grade I</td>
<td>46%</td>
<td>8%</td>
</tr>
<tr>
<td>Grade II</td>
<td>36%</td>
<td>9%</td>
</tr>
<tr>
<td>Grade III</td>
<td>0.5%</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusions - II

Acute and late urinary toxicity from $^{125}$I Brachytherapy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute (&lt;3 mos)</th>
<th>Late (1 y.)</th>
<th>Late (2 y.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>20%</td>
<td>86%</td>
<td>95%</td>
</tr>
<tr>
<td>Grade I</td>
<td>37%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Grade II</td>
<td>40%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Grade III</td>
<td>3%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>