Local disease control in patients with oligometastases: the way forward?

Local disease control with radiotherapy

Prof David Dearnaley
Global Congress on Prostate Cancer
Vienna  June 2016
Should we treat the prostate with RT?
Local RT for a man with local and small volume metastatic disease?

**FOR**
- Might prevent local progression, need for catheter, TURP, defunctioning colostomy, nephrostomies
- Might improve survival

**AGAINST**
- Cost, time and morbidity of RT
- Could give RT later if needed
Local RT for a man with local and small volume metastatic disease?

FOR
• Might prevent local progression, need for catheter, TURP, defunctioning colectomy, nephrostomies
• Might improve survival

AGAINST
• Cost, time and morbidity of RT
• Could give RT later if needed
The use of radiotherapy to the prostate will retard progression of metastases in men presenting with metastatic prostate cancer
Factors elaborated by the primary tumour enter the circulation ..... and promote secondary tumours at specific distant sites

Bob Weinberg,
Professor of Biology
at the Massachusetts Institute of Technology
Some primary tumours release circulating factors which mobilise bone marrow cells and make distant sites more receptive to metastases.
Local radiotherapy in metastatic prostate cancer

- Data from other cancers
- Data from prostate cancer
- The RT comparison in STAMPEDE
Cytoreductive nephrectomy improves survival in metastatic renal cancer

SWOG 8949

EORTC 30947

Resection of the intact primary tumor in women with Stage IV breast cancer is associated with longer survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log (hazard ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio IV, random, 95% CI</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Khan 2002 R1</td>
<td>-0.286</td>
<td>0.028</td>
<td>10.1%</td>
<td>0.75 [0.71, 0.79]</td>
<td>2002</td>
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<tr>
<td>Khan 2002 R0</td>
<td>-0.491</td>
<td>0.027</td>
<td>10.1%</td>
<td>0.61 [0.58, 0.65]</td>
<td>2002</td>
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<tr>
<td>Rapiti 2006 R0</td>
<td>-0.511</td>
<td>0.261</td>
<td>2.8%</td>
<td>0.60 [0.36, 1.00]</td>
<td>2006</td>
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<tr>
<td>Rapiti 2006 R1</td>
<td>0.262</td>
<td>0.246</td>
<td>3.1%</td>
<td>1.30 [0.80, 2.10]</td>
<td>2006</td>
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<tr>
<td>Babiera 2006</td>
<td>-0.693</td>
<td>0.443</td>
<td>1.2%</td>
<td>0.50 [0.21, 1.19]</td>
<td>2006</td>
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<tr>
<td>Fields 2007</td>
<td>-0.635</td>
<td>0.119</td>
<td>6.7%</td>
<td>0.53 [0.42, 0.67]</td>
<td>2007</td>
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<tr>
<td>Gnerlich 2007</td>
<td>-0.478</td>
<td>0.032</td>
<td>10.0%</td>
<td>0.62 [0.58, 0.66]</td>
<td>2007</td>
</tr>
<tr>
<td>Blanchard 2008</td>
<td>-0.342</td>
<td>0.125</td>
<td>6.4%</td>
<td>0.71 [0.56, 0.91]</td>
<td>2008</td>
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<tr>
<td>Hazard 2008</td>
<td>-0.226</td>
<td>0.354</td>
<td>1.8%</td>
<td>0.80 [0.40, 1.60]</td>
<td>2008</td>
</tr>
<tr>
<td>Ruiterkamp 2009</td>
<td>-0.478</td>
<td>0.102</td>
<td>7.4%</td>
<td>0.62 [0.51, 0.76]</td>
<td>2009</td>
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<tr>
<td>Bafford 2009</td>
<td>-0.75</td>
<td>0.25</td>
<td>3.0%</td>
<td>0.47 [0.29, 0.77]</td>
<td>2009</td>
</tr>
<tr>
<td>Shien 2009</td>
<td>-0.117</td>
<td>0.06</td>
<td>9.1%</td>
<td>0.89 [0.79, 1.00]</td>
<td>2009</td>
</tr>
<tr>
<td>Neuman 2010</td>
<td>-0.342</td>
<td>0.217</td>
<td>3.7%</td>
<td>0.71 [0.46, 1.09]</td>
<td>2010</td>
</tr>
<tr>
<td>Perez-Fidalgo 2011</td>
<td>0.654</td>
<td>0.202</td>
<td>4.0%</td>
<td>0.52 [0.35, 0.77]</td>
<td>2011</td>
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<tr>
<td>Dominici 2011</td>
<td>-0.062</td>
<td>0.057</td>
<td>9.2%</td>
<td>0.94 [0.84, 1.05]</td>
<td>2011</td>
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<tr>
<td>Booh Pathy 2011</td>
<td>-0.545</td>
<td>0.093</td>
<td>7.8%</td>
<td>0.58 [0.48, 0.70]</td>
<td>2011</td>
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<tr>
<td>Rashan 2012</td>
<td>-0.105</td>
<td>0.216</td>
<td>3.7%</td>
<td>0.90 [0.59, 1.37]</td>
<td>2012</td>
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<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.69 [0.63, 0.77]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; Chi² = 110.08, df = 16 (P<0.00001); I² = 85%
Test for overall effect: Z = 7.15 (P<0.00001)

Overall hazard ratio: 0.69 (95% CI 0.63, 0.77)
Randomised phase 3 trial evaluating resection of primary tumour in Stage 4 Breast cancer: MF07 study
Soran et al ASCO 2016 Turkish Federation of Societies fro Breast Diseases

Local surgery + systemic treatment vs systemic treatment alone

- No. 274 Median FU 40m
- 5 year OS: 42% S +ST vs 24% ST only   HR 0.67 p=0.005
- In unplanned subgroup analysis favourable features eg ER+, HER2neu(-), solitary bone mets and age<55yrs
Local surgery (+/-RT) + systemic treatment vs systemic treatment alone

- No. 350 Stage 4 BrCa with resectable primary (+/-LN) pre/post chemotherapy
- Median FU 23m
- 2 year OS: 42% S +ST vs 43% ST only  HR 1.04 p=0.8
Local radiotherapy in metastatic prostate cancer

- Data from other cancers
- Data from prostate cancer
- The RT comparison in STAMPEDE
Local and Systemic Therapy for Patients with Metastatic Prostate Cancer: Should the Primary Tumor Be Treated?

Edith D. Canby-Hagino, MD*, Gregory P. Swanson, MD, E. David Crawford, MD, Joseph W. Basler, PhD, MD, Javier Hernandez, MD, and Ian M. Thompson, MD

Metastatic Prostate Cancer—Does Treatment of the Primary Tumor Matter?

Gregory Swanson,† Ian Thompson, Joseph Basler and E. David Crawford

From the Departments of Radiation Oncology and Urology, University of Texas Health Science Center at San Antonio and Cancer Therapy and Research Center, San Antonio, Texas, and University of Colorado Health Science Center, Denver, Colorado

Purpose: In recent years there has been increased interest in adjuvant therapy for prostate cancer. This trend has engendered a tendency toward overlooking the issue of therapy to the primary tumor in advanced disease. We reviewed the effect of treating the principal disease bulk on overall treatment outcome in patients with advanced and metastatic cancer. Specifically we evaluated the role of surgical tumor cytoreduction.

Materials and Methods: We performed a comprehensive literature review to evaluate the role of surgical debulking on the outcome of advanced cancer, including any published evidence supporting a benefit of this therapy for prostate cancer.

Results: Even in cancers for which adjuvant chemotherapy and radiation are used liberally there is a clear benefit to optimal surgical debulking for local control and survival. The beneficial role of maximal surgical cytoreduction has been clearly demonstrated in advanced ovarian cancer and gastrointestinal carcinomas. Maximal debulking of brain, liver and lung metastasis has translated into longer survival. Removal of the primary tumor has been proven to increase survival in randomized trials of metastatic renal cell cancer. It appears that patients with node positive and possibly metastatic prostate cancer have a better response to androgen ablation with surgical removal of the gland.

Conclusions: Surgical cytoreduction of cancer results in a more favorable and durable response to systemic therapy. It is reasonable to explore aggressive surgical therapy for advanced prostate cancer.

Key Words: prostate, prostatic neoplasms

0022-5347/06/1784-1292©
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Vol. 176, 1292-1298, October 2006
Printed in U.S.A.
DOI:10.1016/j.juro.2006.06.069
Might Men Diagnosed with Metastatic Prostate Cancer Benefit from Definitive Treatment of the Primary Tumor? A SEER-Based Study

Stephen H. Culp\textsuperscript{a,*}, Paul F. Schellhammer\textsuperscript{b}, Michael B. Williams\textsuperscript{b}

![Graph showing cumulative incidence of prostate cancer-specific mortality over time from initial diagnosis (months) with different treatment groups: NSR, BT, and RP.]

- N=7811
- N=129
- N=245

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
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<tr>
<td>NSR</td>
<td>7811</td>
<td>3299</td>
<td>1252</td>
<td>426</td>
<td>52</td>
<td></td>
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<tr>
<td>BT</td>
<td>245</td>
<td>160</td>
<td>76</td>
<td>34</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>129</td>
<td>84</td>
<td>47</td>
<td>14</td>
<td>2</td>
<td></td>
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</table>
Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Rusthoven et al JCO June 2016,

Retrospective review from National Cancer Data Base

![Graph showing overall survival comparison between different treatment groups](chart.png)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ADT alone</th>
<th>Radiation &lt; 65 Gy + ADT</th>
<th>Radiation ≥ 65 Gy + ADT</th>
<th>Prostatectomy + ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>5,844</td>
<td>163</td>
<td>324</td>
<td>69</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>3,034</td>
<td>73</td>
<td>254</td>
<td>56</td>
</tr>
<tr>
<td>Survival Rate at 120 months (%)</td>
<td>51</td>
<td>78</td>
<td>50</td>
<td>46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT alone</td>
<td>Ref</td>
<td>1</td>
<td>.874</td>
</tr>
<tr>
<td>Radiation &lt; 65 Gy + ADT</td>
<td>1.02</td>
<td>0.84 to 1.23</td>
<td>.874</td>
</tr>
<tr>
<td>Radiation ≥ 65 Gy + ADT</td>
<td>0.45</td>
<td>0.38 to 0.54</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Prostatectomy + ADT</td>
<td>0.38</td>
<td>0.25 to 0.58</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>
Which type of local treatment?

• Effectiveness
• Morbidity
• Biology?
Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial

Lancet 2009 373 301-8

- 875 men 1996-2002
- Initial PSA 19.8
- Follow up 7.6 years
- H.R 0.44
- 12% reduction in CaP deaths
- NNT 8.3 to prevent CaP death

Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial

Lancet 2011 378 2104-11

- 1057 men 1995-2005
- Initial PSA 27.5
- Follow up 6.0 years
- H.R 0.77
- 11% reduction in CaP deaths
- NNT 9.0 to prevent CaP death
Prostate RT improves OS in locally advanced prostate cancer

Cumulative incidence of death from prostate cancer (%)

Follow-up (years)

Cumulative incidence of death from any cause (%)

Follow-up (years)

Endocrine alone

Endocrine plus radiotherapy


10yr Prog. free survival 63% vs 27%  HR 0.31
CaP deaths 43% vs 52%  HR 0.46 p< 0.001
OS 10yr 55% vs 49%  HR 0.70 p<0.001

No.1205 1995-2005
Median 8 yr FU
Does radiotherapy get good (enough) local cancer control?

- PSA control is a proxy but potentially overestimates local failure
- Post treatment biopsy is rarely done in clinical practice
- Is tumour eradication rather than “control” required?
CHHiP Time to biochemical failure and prostate cancer recurrence
Primary analysis

CHHiP Time to biochemical failure and prostate cancer recurrence
Primary analysis

5 year disease control
Int. Risk 90%
High Risk 85%

HR_{60} = 0.83 90% CI: 0.68 to 1.02
HR_{57} = 1.19 90% CI: 0.99 to 1.44
A phase I/II IMRT dose escalation study to treat the prostate and pelvic nodes

No.460  Mean PSA 41  Gl ≥8 51%  Adj. ADT for 3yrs  
Prostate RT 74Gy or 60Gy   LN dose 50-60Gy or equiv.

- 5 year PSA control 71%
- 5 year local control 94%
- 5 year distant met free 83%
- 5 year DSS 92%
2 year positive biopsy rate

- Dose <70.2 Gy - no ADT 50% (of 78)
- Dose ≥75.6 Gy - no ADT 37% (of 128)

- Dose <70.2 Gy - with ADT 24% (of 17)
- Dose ≥75.6 Gy - with ADT 15% (of 116)
Which type of local treatment?

- Effectiveness
- Morbidity
- Biology?
CHHiP trial  PRO: Change from baseline to 2 years  Wilkins et al Lancet Oncol 2015

Overall bowel bother

Overall urinary bother
Which type of local treatment?

- Effectiveness
- Morbidity
- Biology?
Perioperative activation of disseminated tumour cells in bone marrow of patients with prostate cancer

Dorothea Weckermann, Bernhard Polzer, Thomas Ragg, Andreas Blana, Günter Schlimok, Hans Arnholdt, Simone Bertz, Rolf Harzmann, Cristoph A. Klein

Pre-op bone marrow

Post-op bone marrow

Weckermann JCO 2009; 27(10): 1549-56
Surgery, wound healing, and metastasis: Recent insights and clinical implications

Wim Ceelen a,*, Piet Pattyn a, Marc Mareel b

Critical Reviews in Oncology/Hematology 89 (2014) 16–26
HORRAD study: NTR271

A prospective, randomised study onto the effect on survival of hormonal treatment versus hormonal treatment plus local external radiotherapy in patients with primary metastatic (bone) prostate cancer.

Recruitment 2004–2012: 305

Local radiotherapy in metastatic prostate cancer

- Data from other cancers
- Data from prostate cancer
- The RT comparison in STAMPEDE
Failure-free and overall survival for newly-diagnosed M1 patients in the STAMPEDE trial

Clarke et al. ASCO (2013)
STAMPEDE trial design for M1 disease

Newly diagnosed M1 patients¹

Randomisation

A  ADT

H  ADT + RT to prostate

¹ except pts with a contra-indication to RT

http://www.stampedetrial.org/default.aspx
STAMPEDE: Population and sample size

Eligibility
● New, histologically diagnosed, metastatic prostate cancer
● No previous radical treatment to prostate
● No contraindication to prostate RT

Primary outcome measures
● Definitive: overall survival; target HR=0.75
● Intermediate: failure-free survival

Sample size
● ~1200 pts needed for this RT comparison

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http://www.stampedetrial.org/default.aspx
Stampede Arm A: SOC vs Arm H: SOC + Local RT
No. 1804 Jan 2013- June 2016
Should we treat the prostate with RT?
Making the discoveries that defeat cancer

One of the world’s most influential cancer research institutes