PSA Recurrent $M_0$ Prostate Cancer: The Who, When and How of ADT Monotherapy

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Disclosure of Conflicts of Interest
None Related to Content of this Presentation
Defining PSA Recurrent Prostate Cancer (BCR)

- No consensus for post surgery BCR
  - Confounded by emergence of hypersensitive assays (<0.2; <0.02; <0.008)

- Met-free survival decreases as PSA limit increases from 0.2–0.4 uM
  - BCR with PSA levels of 0.2, 0.3, and 0.4 ng/mL associated with rising PSA in 49%, 62%, and 72% of patients respectively (Amling et al J Urol 2001;165:1146–51)

- Post surgery definitions of BCR include:
  - 3 successive PSA rises (final >0.2), single PSA >0.4, or use of secondary therapy for detectable PSA >0.1 (Stephenson et al Eur Urol 2014)

- RTOG-ASTRO Phoenix Consensus definition of BCR after RT
  - any PSA increase >2 ng/mL higher than PSA nadir (regardless of nadir)
Clinical course highly variable
- 5-year risk of clinical progression from 27–60% (Pound et al)
- Some rapidly progress to metastases, others have negligible threat to longevity

Poor surrogate for PCa specific mortality 10 yrs post-RP (88% vs 93%)
- 15 yr after BCR, ~1/3 are alive, 1/3 dead from Pca, and 1/3 dead from other causes

Need to assess individual risk to longevity or quality of life
- based on life expectancy
- pace of progression
- local or regional (eg. salvagable) or systemic (eg. palliative) disease
ADT in PSA Recurrent Prostate Cancer

- **Who needs ADT monotherapy?**
  - Those not candidates for salvage Rx
  - Those at risk of met progression (need risk stratify)

- **When to treat with ADT?**
  - Non-curative but prolongs OS in high risk disease
  - Impairs QoL, and longevity in low risk disease

- **How to treat with ADT?**
  - Continuous vs intermittent?
  - Future combinations of MAB, chemo-ADT
Risk stratification in BCR
Clinico-Pathologic Features

- Met-free survival after PSA recurrence is most strongly influenced by PSA doubling time and high Gleason score (and N status)
  - Independent of the type of local therapy (RP or RT)
  - PSADT <3 months as a surrogate for 5 yr PCSM (31% vs 1%), but most men dying with BCR have PSADT > 3 months

- Optimal PSADT cut-points for stratification remain uncertain
  - Cut-points of ≤ 3 vs > 3 mos, ≤ 6 vs > 6 mos, ≤ 10 vs > 10 mos and ≤ 12 vs > 12 mos.

**PSAdt**
Zhou et al, J Clin Oncol 2005; 23: 6992-8
D’amico AV, Cancer 1993; 72: 2638-43
Zagars GK, Radiother Oncol 1997; 44: 213 – 21
Freedland SJ JAMA 2005 ; 294 : 433 – 9

**Gleason Grade**
Okotie OT et al J Urol; 171: 2260 – 4, 2004
Kim-Sing C,. Int J Radiat Oncol Biol Phys 2004 ; 60 : 463 – 9
GS and PSAdt independent predictors of MFS in multivariate analysis:

- PSAdt < 3.0 vs 3.0 – 8.9 vs 9.0 – 14.9 vs ≥ 15.0 months
- Gleason score ≤ 6 vs 7 vs 8 – 10
BC data on intervention after EBRT failure

Those with PSAdt < 3 months do very poorly

Factors predicting death on MVA
PSAdt \( p = 0.007 \)
Gleason \( p = 0.018 \)
Intervention time \( p = 0.0006 \)
Intervention PSA n.s.
iPSA n.s.
T stage n.s.

Nomogram predicting PCSM for all patients had an internally validated c-index of 0.774

Use of PSADT added modest prognostic information
  - short PSADT correlated with higher PSA levels at BCR, shorter time to BCR, and adverse pathology

Web-based versions are available for free use at http://www.r-calc.com
Signatures and Sequencing

Can we better classify cancers more or less likely to respond to salvage RT post-RP?

**RNA expression assays:** Oncotype (Genome Health); Polaris (Myriad); GC (GenomeDx)

**DNA sequencing assays:** Copy number; percent genome alterations; germline BRCA?
Meta-analysis of 852 patients from five cohorts shows Decipher is a significant predictor of metastasis across all clinical subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>730</td>
<td>1.46 (1.31-1.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>African-American</td>
<td>106</td>
<td>1.43 (0.95-2.15)</td>
<td>0.087</td>
</tr>
<tr>
<td>Preoperative PSA (ng/mL)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;5</td>
<td>457</td>
<td>1.91 (1.29-2.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>5-10</td>
<td>277</td>
<td>1.42 (1.19-1.7)</td>
<td></td>
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<tr>
<td>&gt;10</td>
<td>457</td>
<td>1.47 (1.25-1.72)</td>
<td></td>
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<tr>
<td>RP Gleason Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3+4</td>
<td>459</td>
<td>1.43 (1.11-1.85)</td>
<td>0.007</td>
</tr>
<tr>
<td>4+3</td>
<td>171</td>
<td>1.46 (1.15-1.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥8</td>
<td>222</td>
<td>1.24 (1.06-1.45)</td>
<td>0.008</td>
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<tr>
<td>Surgical Margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>356</td>
<td>1.45 (1.21-1.73)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>499</td>
<td>1.44 (1.25-1.66)</td>
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<tr>
<td>Extraprostatic Extension</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absent</td>
<td>492</td>
<td>1.44 (1.16-1.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Present</td>
<td>359</td>
<td>1.42 (1.24-1.63)</td>
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<tr>
<td>Seminal Vesicle Invasion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Absent</td>
<td>614</td>
<td>1.48 (1.27-1.72)</td>
<td>&lt;0.001</td>
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<tr>
<td>Present</td>
<td>238</td>
<td>1.37 (1.15-1.64)</td>
<td>0.001</td>
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<tr>
<td>Lymph Node Invasion</td>
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<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>805</td>
<td>1.45 (1.28-1.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>49</td>
<td>1.36 (1.06-1.76)</td>
<td>0.016</td>
</tr>
<tr>
<td>Treatment Modality</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Partial Prostatectomy alone</td>
<td>421</td>
<td>1.47 (1.24-1.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adj. RT</td>
<td>140</td>
<td>1.86 (0.92-3.76)</td>
<td>0.085</td>
</tr>
<tr>
<td>Salvage RT</td>
<td>213</td>
<td>1.44 (1.19-1.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adj. ADT</td>
<td>44</td>
<td>1.52 (0.97-2.39)</td>
<td>0.068</td>
</tr>
<tr>
<td>Salvage ADT</td>
<td>116</td>
<td>1.27 (1.02-1.59)</td>
<td>0.035</td>
</tr>
<tr>
<td>ADT</td>
<td>160</td>
<td>1.33 (1.11-1.61)</td>
<td>0.002</td>
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</tbody>
</table>

- Hazard ratio per 0.1 (10% increase) in Decipher score
- Decipher improved the ability to predict the cumulative incidence of metastases in nearly all subgroups based on clinicopathologic factors, treatment factors, and demographic factors

Implication: high scores = systemic disease ⇒ need for ADT

Spratt et al., in press J Clin Onc
Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy


*Department of Surgery, Division of Urology, Center for Integrative Research on Cancer and Lifestyle, Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; ‡Surgery Section, Durham Veterans Affairs Medical Center, Durham, NC, USA; §Genentech Resolutions Inc, Vancouver, BC, Canada; ¶Department of Histopathology and Nephrology, Duke University, Durham, NC, USA; ¶San Diego Pathologists Medical Group, San Diego, CA, USA; †Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA; ‡Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI, USA; *University of Michigan, Ann Arbor, MI, USA; ‡Department of Urology, Mayo Clinic, Rochester, MN, USA

• c-index for GC was 0.85 vs 0.63–0.65 for clinico-pathologic risk models;
• GC is most significant predictor of mets post SRT on MVA
• May reclassify high risk by CAPRA into low risk by GC
• High GC pts may help guide when to treat with combined ADT + SRT
Patients with high PORTOS have lower rates of metastasis with post-operative radiation

High PORTOS Score (top quartile) = 7 fold better response to radiation after RP
PORTOS is NOT prognostic of metastasis in patients NOT treated by radiation
PSA Recurrent CaP – Who are candidates for Intervention?

Imaging Work-up

6.10.4.6 Guidelines for imaging and second-line therapy after treatment with curative intent

<table>
<thead>
<tr>
<th>Biochemical recurrence (BCR) after RP</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the case of BCR, bone scan and abdominopelvic CT should be performed only in patients</td>
<td>3</td>
<td>A</td>
</tr>
<tr>
<td>with a PSA level &gt; 10 ng/mL, or with high PSA kinetics (PSA-DT &lt; 6 mo or a PSA velocity &gt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ng/mL/mo) or in patients with symptoms of bone disease.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Choline PET/CT is not recommended in patients with BCR and a PSA-level &lt; 1 ng/mL</td>
<td>3</td>
<td>A</td>
</tr>
</tbody>
</table>

Biochemical recurrence after RT

In patients with BCR who are candidates for local salvage therapy, prostate mpMRI may be used to
localise abnormal areas and guide biopsy. 3 C

Newer more sensitive Imaging modalities:
- NaF PET bone scan
- PSMA PET imaging
PET Imaging to Identify and Target Oligometastases

- 65-yr-old man had RP 11 yrs ago
- In 2014, PSA increased to 2 and then 5 in 2015.
- Started on ADT by local urologist

PSMA PET

Salvage right PLND 2016

PSA 6 months post op < 0.008
This 50-year-old had RP 2012 for Gleason 4+5=9, pT2, margin negative, N1 Pca.

PSA increased to 1.7 and treated with ADT + salvage RT.

Second PSA relapse
Referred for PSMA PET

SBRT on COMET 2016

PSA 6 months < 0.01 on ADT
PSA Recurrent MO CaP - Who are candidates for ADT Monotherapy?

- Initial consideration given to candidacy for salvage Rx vs ADT monotherapy for men with M0 BCR deemed a risk for PCSM (life expectancy, PSAdt, grade, pN1)

**Multi-modal Salvage Therapy:**
- salvage ADT + RT standard of care
- Selective use of PSMA-PET detected oligomets for salvage LND, SBRT

**ADT monotherapy is an option for men**
- With rising PSA post salvage RT
- When RT is contraindicated (eg. prior RT, IBD, contracture)
- Less likely to benefit from post-surgery RT (*give most benefit of doubt*)
  - Unfavorable PSA kinetics (PSAdt< 6 mos; PSA >1);
  - pN+;
  - ? High Decipher, low PORTOS
Who needs ADT monotherapy?
- Those not candidates for salvage Rx
- Those at risk of metastatic progression

When to treat with ADT?
- Non-curative but prolongs OS in high risk disease
- Impairs QoL, and longevity in low risk disease

How to treat with ADT?
- Continuous vs intermittent?
- Future combinations of MAB, chemo-ADT
Optimal Timing of ADT - Immediate vs Delayed?

Phase III Studies Evidence Supporting Early Therapy

1. **EORTC**: improved survival with immediate HT post-RT (Bolla et al, NEJM 1995)

2. **ECOG**: 2% vs 30% PCa mortality with immediate vs delayed HT in N+ post-RP (Messing et al, NEJM 2000)

3. **MRC - improved OS M0** (Br J Urol 1997; 79: 235–46)

4. **EORTC 30891 in 985 M0 patients - improved OS with immediate ADT (HR 1.25)** (Studer et al. JCO. 2006 ;24(12):1868-76)

5. **EPC Data (Casodex monotherapy trial)** (McLeod DG et al. BJU Int 2005; 97: 247–54)
   - OS improved in Casodex arm in high risk CaP (HR 0.68) but reduced in low risk CaP (HR 1.47)

6. **TOAD Trial – Immediate ADT improved OS in men with M0 PSA relapsing PCA** (Lancet Oncology 2016)
At What PSA Level Should We Initiate ADT?

Conjecture From Messing, et al* Study of Immediate vs. Delayed Hormonal Therapy for D1 Disease After RP

1. 78% of patients in immediate ADT group had undetectable PSA when they started therapy
2. The median PSA level at the start of ADT in observation group was 14 ng/mL
3. Immediate ADT arm enjoyed a marked disease-specific survival advantage compared with those who were observed
4. Therefore, the “window of opportunity” may be between 0.2 and <14 ng/mL

Early ADT and Survival Among Patients with Localized Disease: EPC Programme

- reduces radiographic and biochemical time to progression
- OS adversely affected in Casodex arm in low risk CaP! (HR ~1.4)
- OS improved in Casodex arm in high risk CaP! (HR ~1.4)

McLeod DG et al. BJU Int 2005; 97: 247–54
Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial

Gillian M Duchesne, Henry H Woo, Julie K Bassett, Steven J Bowe, Catharine D’Este, Mark Frydenberg, Madeleine King, Leo Ledwich, Andrew Loblaw, Shawn Malone, Jeremy Millar, Roger Milne, Rosemary G Smith, Nigel Spry, Martin Stocklee, Rodney A Syme*, Keen Hui Tai, Sandra Turner


- **OS Entire population**
  
  16 (11%) died in immediate ADT arm vs 30 (20%) in delayed arm (P=0.047)

- **PCA Complication-free survival**
  
  Number at risk
  
<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Delayed ADT arm</th>
<th>Immediate ADT arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>151</td>
<td>142</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>138</td>
</tr>
<tr>
<td>2</td>
<td>135</td>
<td>127</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>113</td>
</tr>
<tr>
<td>4</td>
<td>101</td>
<td>98</td>
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<tr>
<td>5</td>
<td>70</td>
<td>76</td>
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<tr>
<td>6</td>
<td>50</td>
<td>50</td>
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<tr>
<td>7</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

- **Limitations** - accrual was slow; only 1/3 of screened subjects were randomized; f/u only to 5 yrs; few events

- **261 men with BCR after previous RP or RT, and 32 men not considered suitable for curative treatment**

- **Randomized 1:1 to immediate or deferred (>2 yrs) ADT of choice (most treated with intermittent ADT)**

- **41% of delayed arm did not require ADT during study; but those who did started after median of 1.58 yrs**
ADT in PSA Recurrent Prostate Cancer

- Who needs ADT therapy?
  - Who are not candidates for salvage Rx
  - Who are at risk of metastatic progression

- When to treat with ADT?
  - PSAdt <12 months, or PSA >4

- How to treat with ADT?
  - Continuous vs intermittent?
  - Future combinations of MAB, chemo-ADT (Tax 3503)
Types of intervention

• Castration therapy
  – LHRH agonist or antagonist, vs (orchiectomy)
    • +/- NSAA (bicalutamide)
  – Intermittent vs continuous

• Alternatives – not licensed in N America
  – 5-α reductase inhibitor +/- antiandrogen
  – Antiandrogen monotherapy
• Canadian NCIC study
  – SWOG, CTSU, MRC (UK)
  – 1999 - 2005
  – 1386 randomized

• Prior curative RT at least a year ago
  – Rising PSA level >3 ng/ml and >nadir
  – Serum testosterone >5 nmol/L (144 ng/dl)
  – Life expectancy >5 years, No evidence mets on bone scan

• Intermittent arm - 8-month treatment cycle
  – Off-cycle started if PSA <4 ng/ml, no evidence of clinical progression
  – During off-cycle:
    • PSA q2 months until 10 ng/ml, with no evidence of disease progression
NCIC PR.7 – CAS vs IAS in post-RT failures

- Median F/U 6.5 years
- Time to progression favours IAS (HR 0.83, p=0.06) but trial design may bias IAS arm
- **Overall survival with IAS non-inferior to CAS**
- Only 27% of time was spent on therapy

Crook et al NEJM 367: 2012
## Investigator-Reported Cause of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths in Intermittent ADT Group (n=268)</th>
<th>Deaths in Continuous ADT Group (n=256)</th>
<th>Total Deaths (n=524)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer or related causes</td>
<td>120</td>
<td>94</td>
<td>214</td>
<td>1.18 (0.90-1.55)</td>
<td>0.24</td>
</tr>
<tr>
<td>Unrelated to prostate cancer</td>
<td>148</td>
<td>162</td>
<td>310</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: Hazard ratio and p-value for deaths unrelated to prostate cancer were not reported.

Secondary Endpoint: Quality of Life

• IAS group had better QoL related to:
  – hot flashes (p<0.001)
  – desire for sexual activity (p<0.001)
  – urinary symptoms (p=0.006)
  – trend towards improved fatigue (p=0.07)

• No significant difference in functional domains

**Primary Objective**: To evaluate efficacy, as measured by metastasis-free survival (MFS)

**Secondary**: OS; treatment-free proportion; time to CRPC

**Primary Assessment**: Central radiographic imaging approximately every 6 months

**Key Inclusion Criteria**
- PSA doubling time ≤ 9 months as calculated by the sponsor
- Screening PSA ≥ 2.0 ng/mL post RP or ≥ 5.0 ng/mL and ≥ to nadir + 2 ng/mL post RT
Estimated % Patients on Treatment Holiday Due to Undetectable PSA*

*Based on internal enrollment projections
EMBARK Design Challenges

1:1:1 Randomization Stratification

Enzalutamide

Enzalutamide + Leuprolide

Placebo + Leuprolide

Informed Consent

Screening Day -28 to -1

N=1860

Primary Assessment: Radiographic imaging approximately every 6 months

Daily enzalutamide

Daily enzalutamide or placebo

Leuprolide

PSA < 0.2 ng/mL?

Yes

No

Treatment Suspension

Remain on Treatment

Treatment Re-start

Local PSA results leading to treatment discontinuation

Manageable ADT related AE Treatment Discontinuations

NO MFS Event
Summary: Who, When and How Regarding ADT Monotherapy for M0 BCR?

- Earlier, compared to deferred, ADT prolongs OS in men at high risk of dying of their disease
  - long life exp, PSAdt < 12 months, PSA > 4
  - Selection improves with genomic and imaging biomarkers

- Avoid ADT in low risk, slowly progressive disease

- IAS is equivalent to CAS in M0 or N+ disease, reduces AE’s associated with ADT, and is standard of care for this population of patients

- Reasonable to speculate that more potent AR pathway inhibition will prolong OS in appropriately selected men