Oligometastatic Prostate Cancer

A Radiation Oncologist perspective

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Instructor, Duke-NUS Graduate Medical School, Singapore

ESMO Advanced Course on Prostate Cancer, 21-22 Sep 2018, Singapore
Disclosures

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Advisory/Consultancy roles:
Varian
Evolution of a new disease paradigm

- High-risk vs Disseminated metastases vs Oligometastatic state (N+, limited M1)

Clinical evidence supporting local therapy in oligometastatic state

What the future holds… (Ongoing trials)
Evolution of high-risk prostate cancer

Locally Advanced

*(High risk of occult metastases)*

**Clinical:** cT3-4; GS 8-10; PSA > 20-50

**Molecular:** Genomic instability; SChLAP1+ve

**Treatment:** Long-term androgen deprivation (ADT) + Radiotherapy (IGRT vs IGRT + Brachytherapy boost); Radical Prostatectomy +/- Pelvic nodal dissection
Evolution of high-risk prostate cancer

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**Conventional Paradigm of Progression**

**Disseminated Hormone-sensitive**
Clinical: M1; high-volume disease (visceral or multiple bone); PSA >150
Treatment: ADT + Systemic agent (Docetaxel vs Zytiga)
Evolution of high-risk prostate cancer

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**Oligometastatic state**
(Limited systemic disease)
Clinical: cT2-4; GS 7-10; PSA>50-150
De novo vs Recurrent
Site-specific – LN vs Bone vs Visceral
Molecular Hallmarks: Genomic instability; SchLAP1+ve; BRCA2-mut
Treatment: Systemic vs Local?

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**Contemporary Paradigm of Progression**
ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
**Oligometastatic PCa:** Defining the disease

**PET-imaging**

**Bone**

**Lymph nodes**

**Types of Tracers**
- PSMA (Overall)
- F-Choline (LN)
- Na-F (Bone)
- Fluciclovine (Overall; newest)

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Oligometastatic PCa: Defining the disease

PET-imaging

Bone

Table 2: Summary of sensitivity and specificity of meta-analyses evaluating PSMA, choline, and fluciclovine PET/CT

<table>
<thead>
<tr>
<th>Systematic review and meta-analysis</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Sensitivity (per lesion) (95% CI)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>PSMA Perera 10</td>
<td>N = 16</td>
<td>N = 1309</td>
<td>80% (66-89)</td>
<td>97% (92-99)</td>
<td>86% (37-98)</td>
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<tr>
<td>Choline Fanti 14</td>
<td>N = 12</td>
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<td>86% (83-88)</td>
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<tr>
<td>Evangelista 55</td>
<td>N = 19</td>
<td>N = 1555</td>
<td>90% (74-97)</td>
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<tr>
<td>Umbehr 56</td>
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<td>Sher 57</td>
<td>N = 9</td>
<td>N = 423</td>
<td>87% (80-92)</td>
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<td></td>
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</tr>
<tr>
<td>Fluciclovine Ren 58</td>
<td>N = 6</td>
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ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
PSMA-PET

PET-imaging

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Pattern of nodal relapses detected by PSMA matched RT lymph node CTV contouring consensus

Janice Tan, M Chua, et al, under review

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**PSMA-PET as an ultrasensitive modality**

Pattern of nodal relapses detected by PSMA matched RT lymph node CTV.

**ESMO Advanced Course on PCa, 21 Sep 2018, Singapore**

*Janice Tan, M Chua, et al, under review*

**Table 3. Summary of additional lesions detected by $^{68}$Ga PSMA PET/CT, and the influence on subsequent treatment.**

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>Number of patients (n)</th>
<th>Number of additional lesions</th>
<th>Impact on management</th>
</tr>
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<tbody>
<tr>
<td>Prostate bed RT only to WPRT + HT</td>
<td>Overall 33 (of 44 patients with positive scan)</td>
<td>Overall 106 (of 175)</td>
<td>Overall PSA ≤2.0 PSA &gt;2.0 Switch to Palliative HT (Polymetastatic) SBRT to metastases (Oligometastatic; &lt;5 lesions)</td>
</tr>
<tr>
<td>Locoregional only</td>
<td></td>
<td></td>
<td>Overall PSA&lt;2.0 PSA&gt;2.0 SBRT&lt;2.0 SBRT&gt;2.0</td>
</tr>
<tr>
<td>Prostate bed</td>
<td>18</td>
<td>32</td>
<td>10 4 6</td>
</tr>
<tr>
<td>Nodes +/- prostate bed</td>
<td>8</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Distant</td>
<td></td>
<td></td>
<td>Overall PSA&lt;2.0 PSA&gt;2.0</td>
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<tr>
<td>Nodes only</td>
<td>15</td>
<td>74</td>
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<tr>
<td>Skeletal only</td>
<td>3</td>
<td>10</td>
<td>7 1</td>
</tr>
<tr>
<td>Nodes + skeletal</td>
<td>7</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>Visceral</td>
<td>2</td>
<td>19</td>
<td>1</td>
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Abbreviations: RT = radiotherapy, WPRT = whole pelvic radiotherapy, HT = hormonal therapy, SBRT = stereotactic body radiotherapy, PSA = prostate specific antigen.
Evolution of Management of HR PCa

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CT, Bone Scan, MRI, PSA

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
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PET imaging

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**Why local tx for a systemic disease?**

Targeting the bulk of the tumour clones in the prostate and other gross metastatic sites

*Scientific rationale: If imaging identified all regions of clinical disease, then targeting these regions will prevent future seeding of tumour clones*

**Metastatic progression in prostate cancer is a dynamic clonal process.**

*Clonal tracking reveals that local and regional tumours continue to “seed” future metastases.*

Lung Cancer: A Case Example

The Lancet Oncology

Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non-Small-Cell Lung Cancer

Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial

Long term survivors

Prevented new lesion occurrence!!!

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RT “the magic bullet”: targeting nodal mets

PET Contouring

RT plan

Daily matching – transverse

Coronal

Planning CT

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
RT “the magic bullet”: targeting spinal mets

RT plan – Dose plan & constraints

Dose constraints
- Thecal sac – D0.03cc = 17 Gy
- Bowel – D0.03cc = 20 Gy
- Great vessel – D0.03cc <30 Gy

Beam arrangements

Dose distribution

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
RT “the magic bullet”: targeting spinal mets

RT delivery techniques – VMAT (Arc) vs Multi-cone

**Pros and Cons**
- Single vs Multi-levels
- Speed of delivery – much faster with VMAT
- Dose for Single (24 Gy/2#) vs Multi-level (30-50 Gy/5#)

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Metastasis-directed therapy: **STOMP trial**

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

- BCR after radical RT or RadP
- ≤3 lesions on choline-PET
- SBRT (30Gy/3#) or metastatectomy

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
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Are patients truly “cured”???

2018

Long-term off ADT

Table 2. Indications for Starting Androgen Deprivation Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Surveillance (n=24)</th>
<th>Metastasis-Directed Therapy (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not started yet</td>
<td>6 (19)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Polymetastatic progression</td>
<td>16 (65)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Symptomatic progression</td>
<td>3 (10)*</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

PSA-DT at inclusion

<table>
<thead>
<tr>
<th></th>
<th>( \leq 3 ) months</th>
<th>( &gt; 3 ) months</th>
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<tbody>
<tr>
<td>No. of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (29.0)</td>
<td>18 (58.1)</td>
</tr>
<tr>
<td>2</td>
<td>10 (32.3)</td>
<td>6 (19.3)</td>
</tr>
<tr>
<td>3</td>
<td>12 (38.7)</td>
<td>7 (22.6)</td>
</tr>
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Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial

Shankar Siva, Mathias Bressel, Declan G. Murphy, Mark Shaw, Sarat Chander, John Violet, Keen Hun Tai, Cristian Udovicich, Andrew Lim, Lisa Selbie, Michael S. Hofman, Tomas Kron, Daniel Moon, Jeremy Goad, Nathan Lawrentschuk, Farshad Foroudi.

Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Detected via Prostate-specific Membrane Antigen Positron Emission Tomography

Andrew Kneebone, George Hruby, Hannah Ainsworth, Keelan Byrne, Chris Brown, Linxin Gao, Alexander Gaminski, Thomas Eade.

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Metastasis-directed therapy: **POPSTAR**

**Take home message:**
- Local ablative therapy is effective for target lesion
- Distant metastatic progression still dominates as pattern of relapse and **stratification for systemic tx is UNAVOIDABLE!!!**

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Metastasis-directed therapy: ORIOLE

Eligibility:
- ≤3 metastatic lesions (≤5 cm)
- Hormone-sensitive disease
- PSADT < 15 months
- ECOG ≤2

Randomization:
- Observation: 1:2
- SBRT

Day 1:
- PSA, LDH, AP, T, ctDNA, and rectal swab

Days 1-30:
- Observation

Day 90:
- PSA, LDH, AP, T, and ctDNA

Day 180:
- Bone scan, CT, PSA, LDH, AP, T, and ctDNA

Patients progressing on observation can be crossed over off-protocol to receive SBRT

SABR: 29% of pts have progressed @ 6-mos

Observation: 67% of pts have progressed @ 6-mos

P=0.049

Presented by Phuoc Tran (PI), ASCO GU 2018 and PCF retreat 2018
Metastasis-directed therapy: ORIOLE

Included systemic targeting

Observation: 67% of pts have progressed @ 6-mos
SABR: 29% of pts have progressed @ 6-mos

Presented by Phuoc Tran (PI), ASCO GU 2018 and PCF retreat 2018
Looking ahead.....

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<th>Ongoing trials</th>
<th>Number of sites IR</th>
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<tr>
<td>University of Florida (NCT018592221)</td>
<td>NS</td>
</tr>
<tr>
<td>CROP trial (Toronto; NCT02563691)</td>
<td>≤5</td>
</tr>
<tr>
<td>Sidney Kimmel CC (NCT02489357)</td>
<td>≤4</td>
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<td>Mayo clinic (NCT01777802)</td>
<td>≤3</td>
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<tr>
<td>Spain (NCT02192788)</td>
<td>≤4</td>
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<td>Ghent Uni (NCT01558427)</td>
<td>≤3</td>
</tr>
<tr>
<td>Dresden Uni (OncoRay; NCT02264379)</td>
<td>≤5</td>
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<tr>
<td>City of Hope (NCT00544830)</td>
<td>≤5</td>
</tr>
<tr>
<td>MSKCC (NCT02020070)</td>
<td>≤10</td>
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<tr>
<td>ORIOLE</td>
<td>≤3</td>
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<tr>
<td>GETUG P07 (NCT02274779)</td>
<td>≤5 (nodes only)</td>
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ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
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PET imaging

CT, Bone Scan, MRI, PSA

Local treatment intensification

Systemic intensification

ESMO Advanced Course on PCa, 21 Sep 2018, Singapore
Acute emergence of data “supporting” the value of intensive local therapy in advanced disease

- *Is RT the magic bullet to “catch them all”?*
- >70 Gy RT to primary and metastatic sites
- Data is stronger for *N+ & oligometas (≤5 sites)*

Understand the biology driving progression of advanced disease

- *True oligometastases vs occult poly-metastases*
- *Better patient selection for local tx -> Health economics and burden of over-tx*

*Optimising systemic therapy is still crucial to maximize therapeutic ratio for combinatorial systemic-RT*
Thank you!

Questions