PROSTATE CANCER
Clinical Case Presentation

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The Royal Marsden NHS Trust, Sutton, United Kingdom
Disclosure

Funding from AAA, Bayer, Janssen, Steba
PROSTATE CANCER
Guidelines Session

- Systemic treatment for node positive disease
- Local treatment for node positive disease
- Management of PSA failure after radiotherapy
- Treatment of low volume metastatic disease
- Bone health management on ADT

ADT, androgen deprivation therapy; PSA, prostate-specific antigen
Systemic treatment for node positive disease

- ADT alone
- ADT + docetaxel
- ADT + abiraterone
- Other
Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Effect of addition of docetaxel to standard of care on survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Control</th>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GETUG-12&lt;sup&gt;25&lt;/sup&gt;</td>
<td>49/206</td>
<td>42/207</td>
<td>0.94 (0.60–1.48)</td>
</tr>
<tr>
<td>RTOG 0521&lt;sup&gt;28&lt;/sup&gt;</td>
<td>59/281</td>
<td>43/282</td>
<td>0.70 (0.47–1.04)</td>
</tr>
<tr>
<td>STAMPEDE&lt;sup&gt;8&lt;/sup&gt; (SOC +/− Doc)</td>
<td>65/460</td>
<td>31/230</td>
<td>0.95 (0.62–1.46)</td>
</tr>
<tr>
<td>STAMPEDE&lt;sup&gt;8&lt;/sup&gt; (SOC + ZA +/− Doc)</td>
<td>31/227</td>
<td>20/228</td>
<td>1.05 (0.57–1.95)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.87 (0.69–1.09)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.80; \text{df}=3; p=0.614; I^2=0\%$
### Abiraterone for prostate cancer not previously treated with hormone therapy

<table>
<thead>
<tr>
<th>B Failure-free Survival</th>
<th>Hazard Ratio with Combination Therapy (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmetastatic</td>
<td>0.21 (0.15–0.31)</td>
<td>0.08</td>
</tr>
<tr>
<td>Metastatic</td>
<td>0.31 (0.26–0.37)</td>
<td></td>
</tr>
</tbody>
</table>

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<tr>
<th>A Overall Survival</th>
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<tr>
<td>Metastatic status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmetastatic</td>
<td>0.75 (0.48–1.18)</td>
<td>0.37</td>
</tr>
<tr>
<td>Metastatic</td>
<td>0.61 (0.49–0.75)</td>
<td></td>
</tr>
</tbody>
</table>

Local treatment for node positive disease

- No local treatment
- Surgery
- Radiotherapy
- Other
Local treatment for node positive disease

Androgen Deprivation With or Without Radiation Therapy for Clinically Node-Positive Prostate Cancer
Chun Chieh Lin*, Phillip J. Gray*, Ahmedin Jemal, Jason A. Efstathiou
Local treatment for node positive disease

Failure-Free Survival and Radiotherapy in Patients With Newly Diagnosed Nonmetastatic Prostate Cancer for the STAMPEDE Investigators

*JAMA Oncology*  March 2016  Volume 2, Number 3

![Graph showing failure-free survival and radiotherapy outcomes](image-url)
Local treatment for node positive disease

- Radiotherapy improves survival in N0 M0 disease (MRC PR07, SPCG7)
- If radiotherapy also improves survival in N0/1 M1 disease (HORRAD, STAMPEDE)…. 
- then it would be safe to conclude that radiotherapy also improves survival in N1 M0 disease
Management of PSA failure

- Early ADT above PSA threshold (e.g. PSA > 10 ng/mL)
- Early ADT below PSA doubling time threshold (e.g. < 4 months)
- Observation until site of recurrence identified on imaging
- Other
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, Catherine D’Este, Mark Frydenberg, Madeleine King, Leo Ledwich, Andrew Loblaw, Shawn Malone, Jeremy Millar, Roger Milne, Rosemary G Smith, Nigel Spry, Martin Stockler, Rodney A Syme*, Keen Hun Tai, Sandra Turner

Lancet Oncol 2016; 17: 727–37
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<tr>
<th></th>
<th>Delayed ADT</th>
<th>Immediate ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Ca deaths</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Other deaths</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Total deaths</td>
<td>26</td>
<td>14</td>
</tr>
</tbody>
</table>
Timing of ADT after radiation: planned analysis of two RCTs

- 339 patients, median 5 year follow up
- Immediate versus delayed ADT
- Overall survival HR 0.75, 95% CI: 0.4-1.4; p=0.37

RCT, randomised clinical trial

Loblaw et al. JCO 36, 2018 (suppl: abstr 5018)
ESMO Guidelines – PSA failure

Early ADT is **not routinely recommended** for men with biochemical relapse unless they have symptomatic local disease, or proven metastases, or a PSA doubling time < 3 months.
Treatment of low volume metastatic disease

- ADT alone
- ADT + docetaxel
- ADT + abiraterone
- Other

ADT, androgen deprivation therapy
What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis


Annals of Oncology 29: 1249–1257, 2018

- Doc+ADT vs ADT
  - CHAARTED: 0.73 (0.59, 0.90)
  - GETUG 15: 0.88 (0.68, 1.14)
  - STAMPEDE: 0.76 (0.62, 0.93)
  - Network: 0.77 (0.68, 0.87)
  - Pairwise ($I^2=0\%$; Heterogeneity $p=0.52$): 0.77 (0.68, 0.88)

- AAP+ADT vs ADT
  - LATITUDE: 0.62 (0.51, 0.76)
  - STAMPEDE: 0.61 (0.49, 0.75)
  - Network: 0.61 (0.53, 0.71)
  - Pairwise ($I^2=0\%$; Heterogeneity $p=0.91$): 0.62 (0.53, 0.71)
Credibility of claims of subgroup effects in RCTs: systematic review

- Was the subgroup variable a baseline characteristic?
- Was the subgroup variable a stratification factor?
- Was the subgroup hypothesis specified a priori?
- Was the analysis one of a small number of subgroups tested?
- Was the test of interaction significant?
- Was the significant interaction effect independent?
- Was the direction of the subgroup effect correctly pre-specified?
- Was the effect consistent with previous studies?
- Was the effect consistent across related outcomes?
- Indirect supportive evidence e.g. biological rationale?
ESMO Guidelines – Metastatic disease

ADT plus docetaxel may be considered as first-line treatment for metastatic, hormone-naive disease.
Bone health management

- Monthly zoledronate/denosumab
- 6-12 monthly zoledronate/denosumab
- Oral bisphosphonates (eg alendronate 70 mg weekly)
- None unless bone density scan shows osteopenia/osteoporosis
Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data

Effect of addition of bisphosphonates to standard of care on survival

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<td>CALGB 90202&lt;sup&gt;30&lt;/sup&gt;</td>
<td>151/322</td>
<td>134/323</td>
<td>0.88 (0.70-1.11)</td>
</tr>
<tr>
<td>STAMPEDE&lt;sup&gt;8&lt;/sup&gt; (SOC+/-ZA)</td>
<td>350/724</td>
<td>170/366</td>
<td>0.93 (0.78-1.12)</td>
</tr>
<tr>
<td>STAMPEDE&lt;sup&gt;8&lt;/sup&gt; (SOC+Doc+/-ZA)</td>
<td>144/362</td>
<td>158/365</td>
<td>1.04 (0.79-1.37)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.94 (0.83-1.07)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=0.84; \text{df}=2; p=0.656; I^2=0\%$

Favours SOC+zoledronic acid  Favour's SOC
ESMO Guidelines – Bone health

Men on long-term ADT should be monitored for side-effects including osteoporosis (using bone densitometry)
National osteoporosis guideline group (2017)
www.shef.ac.uk/NOGG

- Assess fracture risk (FRAX)
- Lifestyle measures
  - Regular weight-bearing exercise
  - 800 IU cholecalciferal + 700-1200mg calcium intake daily
- Intervention threshold based on risk of major fracture (FRAX)
- Alendronate/risedronate are first line treatments
Prostate cancer

Guidelines Session

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