Management of node positive prostate cancer

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Disclosure

• I have no relevant conflicts of interest to disclose.

• This presentation will NOT discuss investigational or off-label use of drugs or therapies.
2009 AJCC Staging/Prognostic GROUPS
7th Edition

- **Group I** (Low risk)
  - T1a-2a, Gleason 6, PSA <10
  - T1-2a, Gleason X, PSA X

- **Group IIA** (Intermediate)
  - T2b or Gleason 7 or PSA 10-20

- **Group IIB** (High)
  - T2c or Gleason 8-10 or PSA ≥ 20

- **Group III** (Locally-advanced, T3a-b)

- **Group IV** (Mets T4, N1, M1)
Regional vs. Distant Mets

**REGIONAL** (below bifurcation of common iliacs)
- Hypogastric
- Obturator
- Iliac
- Sacral
- Peri-rectal

**DISTANT** (M1)
- Aortic
- Common iliac
- Inguinal
- Retroperitoneum
- Above diagphragm
Node positive prostate cancer

- Bad prognostic factor
- Competing risk of distant metastasis
- Node-only mets is rare phenotype

- Data on optimal management is sparse
- Hormone therapy is main therapy
- Uncontrolled primary is bad
Clinical situations of **regional** node (+)

- Path node (+) after prostatectomy & lymph node dissection
  - Adjuvant HT (ECOG RCT)
- Path node (+) but prostate intact
  - HT + Prostate (pelvic) RT
  - HT alone
- Clinically node (+) on imaging
  - HT + Pelvic RT
- Recurrent
  - Usually HT alone
ECOG Randomized Trial:
Immediate vs. Deferred HT for node positive after RP & lymphadenectomy

- 98 men w/ clinical T1-2 randomized to immediate or delayed HT @ time of mets (1988-1993)
  Median 2 nodes (+) [1-20] out of 11 [2-39]
  70% and 61% M (+), respectively
  ~80% postop PSA <0.2

- Median FU 11.9 years
- Immediate HT group had benefit in overall survival, PC-specific survival, and progression free survival

Messing et al. Lancet Oncol 2006;7
Majority of deaths (25/28) in deferred HT group were from prostate cancer

Messing et al. Lancet Oncol 2006;7
RTOG 85-31
Planned adjuvant HT > Salvage HT

977 pt (1987-1992)
27.8% Node positive
Pelvic RT 44-46 Gy; prostate 65-70 Gy
Median f/up 7.6 years
ADT: Goserelin

10 year PC-mortality: 16% 22% (SS)
10 year OS: 49% 39% (SS)
RTOG subset analysis of 173 men with path node (+)

- No radical prostatectomy (RP) = 131 and RP = 42 men
- Median FU 6.5 years

- RT + Immediate HT was better than RT + Delayed HT for OS, PFS, DMFS
- RP on multivariable analysis showed benefit on DMFS and PSA control

- Exploratory analysis
- Does not inform us on role of RT w/ HT vs. HT

Lawton et al. J Clin Oncol 2005;23
Clinical situations of **regional node (+)**

- Path node (+) after prostatectomy & lymph node dissection
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- Clinically node (+) on imaging
  - HT + Pelvic RT

- Recurrent
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Path node (+) but prostate intact

- Rationale for treating primary is that region of most disease may continue to be source of mets & may yield androgen-resistant clones

- Retrospective data supports treating the primary

- Including pelvic LN in field should be individualized based on extent of LND and clinical presentation
MDACC retrospective data to treat local RT field for path N (+)

- N=255 men w/ (+) N on LND and prostate left intact (1984-1998)

- 183 early androgen ablation, 72 AA + RT (68Gy, 11 x 11cm)

- AA alone had more T3 and higher PSA

- RT group had improved PFS and OS

Zagars et al. Urology 2001;58
Zagars et al. Urology 2001;58
Conventional RT – AP and LAT
## Updated results

<table>
<thead>
<tr>
<th></th>
<th>AA alone (%)</th>
<th>AA + RT (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8-yr OS</strong></td>
<td>56.8</td>
<td>80.0</td>
<td>P=0.001</td>
</tr>
<tr>
<td><strong>12-yr OS</strong></td>
<td>31.9</td>
<td>65.9</td>
<td></td>
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<tr>
<td><strong>8-yr FFDM</strong></td>
<td>65.5</td>
<td>86.4</td>
<td>P=0.001</td>
</tr>
<tr>
<td><strong>12-yr FFDM</strong></td>
<td>47.0</td>
<td>83.5</td>
<td></td>
</tr>
<tr>
<td><strong>8-yr PSA FFS</strong></td>
<td>49.4</td>
<td>79.5</td>
<td>P=0.001</td>
</tr>
<tr>
<td><strong>12-yr PSA FFS</strong></td>
<td>46.6</td>
<td>73.8</td>
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</tbody>
</table>

Lee et al. ASTRO 2005
Overall survival

Overall survival

TIME (months)

Overall survival

AA+RT

AA
AA+RT: 8-year OS 89% vs. 66% (p=0.01) stratified by % positive lymph nodes
Path node (+) but prostate intact

- Consider other clinical factors (e.g. T-stage, PSA, Gleason) and expected longevity of patient

- Consider level of LND and # nodes (+)

- MDACC historically has treated AA + local RT (Prostate & SV)

- Consider pelvic nodal RT in select cases (e.g. limited LN sampling, >15% N +)
Clinical situations of regional node (+)

- Path node (+) after prostatectomy & lymph node dissection
  
  Adjuvant HT (ECOG RCT)

- Path node (+) but prostate intact
  
  HT + Prostate (pelvic) RT
  
  HT alone

- Clinically node (+) on imaging
  
  HT + Pelvic RT

- Recurrent
  
  Usually HT alone
Clinically node (+) on imaging

- Rationale for treating primary is that region of most disease may continue to be source of mets & may yield androgen-resistant clones
- Retrospective data supports RT
- Extrapolation of randomized data support RT
- HT + Pelvic nodal RT
- Boosting nodal disease largely un-tested
Extrapolating from SPCG-7: HT +/- XRT

875 pt (1996-2002)
LN dissection for PSA ≥ 11
(pN+ ineligible)
Prostate RT 70 Gy
Median f/up 7.6 years
ADT: flutamide

T1b-T2, G2-3 or any T3
PSA < 70 and N0

RT + ADT lifelong
ADT lifelong

10 year bPFS: 25.3% 74.1% (SS)
10 year DSM: 23.9% 11.9% (SS)
10 year OS: 61.6% 71.4% (SS)

Windmark et al. Lancet 2009; 373: 301–08
Randomized trials have shown a survival benefit to radiation therapy

Multi-center study 875 men randomized between hormone therapy (HT) vs. HT + EBRT (1996-2002)

<table>
<thead>
<tr>
<th>10-year Endpoints</th>
<th>HT vs. HT+RT</th>
<th>Absolute Reduction</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dz-specific mortality</td>
<td>23.9 vs. 11.9%</td>
<td>12%</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>39.4 vs. 29.6%</td>
<td>9.8%</td>
<td>0.68*</td>
<td>0.004</td>
</tr>
<tr>
<td>PSA recurrence</td>
<td>74.7 vs. 25.9%</td>
<td>48.8%</td>
<td>0.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Lancet 2009:373

*This is significantly better risk reduction than used to justify chemotherapy for early stage breast cancer
SPCG-7/SFUO-3
PSA-FFS and DSS improved w/RT

Widmark et al. Lancet 373, 2009
NCIC CTG PR.3/MRC

No pelvic LN path staging
Pelvic RT 45Gy; Prostate 60-69 Gy
Median f/up 6 years
ADT: LHRH agonist (92%); orchiectomy (8%)

7 year DSM: 19%
7 year OS: 66%

NCIC CTG PR.3/MRC
OS and PC-specific survival better w/RT

Warde et al. Lancet 2011
NCIC CTG PR.3/MRC Conclusions

- Improved 10 year bPFS, DFS, DSS, LC, OS
- Less favorable prognosis than in SPCG-7 trial
- Modern ADT w LHRH agonist (vs. flutamide in SPCG-7)
- RT included pelvic field (vs. prostate only in SPCG7)
- Low bowel toxicity (as in SPCG-7)
- These studies suggest a benefit to local therapy in advanced disease (Node +?)
Who would I consider pelvic nodal RT?

- “Very” high risk (e.g. T3 + GI 9 + PSA >20)
- Men w/ isolated radiographic lymphadenopathy who have responded well to HT
- Consider age and performance status of patient

- Use longer term neoadjuvant HT 6-12 months prior to RT and continue for >36 months
- VMAT 46-50 Gy to pelvis → 78 Gy P+SV
- Rarely dose-escalate LN w/ SIB
Contouring LN

- RTOG consensus guidelines are good starting point but may need to modify for own practice (*IJROBP* 2009;74:383-7)
- Start superiorly (L5) and move inferiorly (above femoral heads & top of pubic symphysis)
  - Distal common iliacs, presacral (S1-3), external & internal iliacs, obturators
  - CTV’s include vessels + 7mm margin
  - Do NOT include bone/bowel as part of CTV
  - Mobile bowel may need to be contoured over as part of CTV
  - Contouring too much of inferior external iliacs may impact femoral head DVH

Use adequate PTV on LN-CTV based on your practice
Do NOT under-dose the prostate to cover LN
DVH Consensus: Organs At Risk (OARs)

- Rectum: 2 data points:
  - 50 Gy ≤ 50%
  - 70 Gy ≤ 20%

- Bladder: 2 data points:
  - 55 Gy ≤ 50%
  - 70 Gy ≤ 30%

- Femoral Heads <5% @ 50Gy

- Small Bowel 0% @ 52Gy

- Large Bowel Same as Rectum

- Penile Bulb No Constraints

- Iliac Crests No Constraints
“Doctor, should we target the nodes or the prostate?”
Simultaneous integrated boost (SIB) of residual LN after HT
69yo T3c, Gleason 9, PSA 8.1 s/p HT + IMRT.

PSA failure 4 years later.

Salvage HT, but eventually hormone refractory

CT report:

“…..I do not see any retrocrural, retroperitoneal, pelvic, or inguinal lymphadenopathy. There is no evidence of mesenteric lymphadenopathy….,”
85-31 Post-hoc analysis: HT duration

ADT \(> 5 \text{ years} \) improved PFS, DMFS, OS
(Adjusting for age, prostatectomy, nodal status, GS, and stage)

Souhami et al. JCO 27, 2009.
*Hormone therapy is not benign nor conservative therapy

- Cardiac mortality, loss of bone density and muscle mass, aberrations in lipid profiles, increase in serum glucose, anemia, libido loss, sexual dysfunction, hot flashes, gynecomastia, etc.

- Side effects somewhat dependent upon duration
  (0 < 6 months < 2 years)

- Testosterone recovery after long-term HT is variable & typically low
Practical considerations of HT + RT

• Begin HT at least 2 mos prior to RT and longer for clinically node positive patients.
• Consider total androgen blockade prior to/concurrent with RT
  – Prostate volume may reduce >30% in first 2-3 months
  – Total androgen blockade results in faster volume reduction than LHRH agonist monotherapy
  – Want stable target volume through radiation course, decrease dose to rectum

• Consider pre-HT planning target volume for patients with locally-advanced (T3) disease
  – Prostate volume reduction may be concentric but tumor regression may not be
  – Neoadjuvant HT studies prior to RP
Possible role of abiraterone

Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): Results of a randomized phase II study.

Mary-Ellen Taplin, Robert B. Montgomery, Christopher Logothetis, Glenn J. Bubley, Jerome P. Richie, Bruce L. Dalkin, Martin G. Sanda, Massimo F. Loda, Lawrence D. True, Patricia Troncoso, Elizabeth M. Genega, Steven P. Balk, Peter Nelson, Wanling Xie, Christopher M. Haqq, Namphuong Tran, Cameron S. Liu, Thian San Kheoh, Arturo Molina, Philip Kantoff.

ASCO 2012 Abstract
Eligibility: patients with either GS≥7(4+3), T3, PSA≥20, or PSA velocity >2:
12 wks of LHRHa +/- Abiraterone → Prostate biopsy →
12 wks of LHRHa +/- Abiraterone → RP

ASC0 2012 Abstract

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 wks AA/</th>
<th>24 wks AA/</th>
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<tbody>
<tr>
<td></td>
<td>n=28</td>
<td>24 wks LHRHa</td>
<td>24 wks LHRHa</td>
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<tr>
<td>Gleason: 7/8/9/10</td>
<td></td>
<td>8/10/10/0</td>
<td>9/7/11/3</td>
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<tr>
<td>PSA (median)</td>
<td>10.6</td>
<td>6.8</td>
<td></td>
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<tr>
<td>PSA: &lt; 10/10-20/≥ 20</td>
<td>12/9/7</td>
<td>20/6/4</td>
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<tr>
<td>Elevated PSA velocity</td>
<td>6</td>
<td>3</td>
<td></td>
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<tr>
<td>Stage T3</td>
<td>8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Results n=27</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PSA: wk 4/8/12/16/20/24</td>
<td>4.34/1.35/1.06/0.20/0.09/0.06</td>
<td>0.65/0.17/0.10/0.09/0.06/0.05</td>
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<tr>
<td>12 wk nadir PSA ≤ 0.2</td>
<td>1/27 (4%)</td>
<td>26/29 (90%) p&lt;0.0001</td>
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<tr>
<td>24 wk nadir PSA ≤ 0.2</td>
<td>23/27 (85%)</td>
<td>25/29 (85%) p=0.9131</td>
<td></td>
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<tr>
<td>pCR</td>
<td>1/27 (4%)</td>
<td>3/29 (10%) p=0.3349</td>
<td></td>
</tr>
<tr>
<td>Near pCR (tumor ≤ 5mm)</td>
<td>3/27 (11%)</td>
<td>7/29 (24%) p=0.2034</td>
<td></td>
</tr>
<tr>
<td>Total pCR/near pCR</td>
<td>4/27 (15%)</td>
<td>10/29 (34%) p=0.0894</td>
<td></td>
</tr>
<tr>
<td>pT3</td>
<td>16/27</td>
<td>14/29</td>
<td></td>
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<tr>
<td>Positive nodes</td>
<td>3/27 (11%)</td>
<td>7/29 (24%)</td>
<td></td>
</tr>
<tr>
<td>Positive margins</td>
<td>5/27 (19%)</td>
<td>5/29 (17%)</td>
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</table>
**Future Directions**

**RTOG 1115**: Phase III Trial of Dose Escalated Radiation Therapy and Standard Androgen Deprivation Therapy (ADT) with a GnRH Agonist vs. Dose Escalated Radiation Therapy and Enhanced ADT with a GnRH Agonist and TAK-700 for Men with High Risk Prostate Cancer

- **Primary Objective:** To evaluate the difference in overall survival in men with clinically localized prostate cancer with unfavorable prognostic features between a) standard treatment (ADT + radiotherapy) and b) standard treatment with the addition of 24 months of TAK-700.

TAK-700 (orteronel): Androgen synthesis inhibitor...selectively inhibits the enzyme CYP17A1 which is expressed in testicular, adrenal, and prostatic tissues.
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Thank you