Optimizing the Radiotherapeutic Management of High Risk Prostate Cancer

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External Beam Radiotherapy 2016 for High Risk Disease

• High dose radiotherapy as a critical ingredient for long term tumor control in high risk prostate cancer.

• More precise and accurate ways of delivering high radiation doses such as IMRT and IGRT have resulted in ability to deliver high doses more safely.

• Use of androgen deprivation therapy for high risk disease has further improved long-term tumor control outcomes.
Impact of Dose for Gleason 8-10 Disease
(Pahlajni et al IJROBP 2012)
Outcome of 1002 Patients Treated with 86.4 Gy IMRT (Spratt & Zelefsky et al IJROBP 2012)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk*</td>
<td>97.70</td>
<td>93.40</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>89.10</td>
<td>75.50</td>
</tr>
<tr>
<td>High risk</td>
<td>76.10</td>
<td>65.80</td>
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</tbody>
</table>
High Risk Prostate Cancer Treated RP-
by one Surgeon at JHH
(*Loeb et al Urology 2010)
Modes of Dose Escalation

- IMRT High Dose
- LDR+ IMRT
- HDR+ IMRT
- HDR Monotherapy
PSA-Relapse Free Survival for Intermediate Risk
(Spratt et al BJU 2014)

Probability of Biochemical Control

IMRT

Combo

P = 0.00005
Distant Metastasis-Free Survival

- IMRT: 93.0%
- Combo-RT: 97.2%

P = 0.044
Multi-institutional Outcome of LDR Brachytherapy in 3928 Patients
(Stone et al 2007)
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Median F/U</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merrick (2016)</td>
<td>EBRT+ LDR</td>
<td>8 yrs</td>
<td>89%</td>
</tr>
<tr>
<td>Dattoli</td>
<td>EBRT+ LDR</td>
<td>9.5 Yrs</td>
<td>74%</td>
</tr>
<tr>
<td>Galalae 2014</td>
<td>HDR</td>
<td>9.6yrs</td>
<td>67%</td>
</tr>
<tr>
<td>Yanomoto 2012</td>
<td>Surgery</td>
<td>8.1 yrs</td>
<td>48%</td>
</tr>
<tr>
<td>Loeb 2010</td>
<td>Surgery-JHH</td>
<td>8 Yrs</td>
<td>68%</td>
</tr>
<tr>
<td>Diaz 2016</td>
<td>Robotic Surgery</td>
<td>10 yrs</td>
<td>42%</td>
</tr>
</tbody>
</table>

* Adapted from Crook et al Brachytherapy 2015
Optimizing the Use of Androgen Deprivation Therapy for High Risk Disease

• Based on randomized trials, ADT combined with RT is standard of care throughout the world for the management of high risk disease.

• It is our practice to utilize several months of neo-adjuvant and concurrent ADT.

• Longer courses of adjuvant ADT associated with survival benefits for high risk patients.

• All such patients should be on supplemental Vitamin D and calcium and recommended to have a baseline bone density examination.
Overall survival 6 months vs 36 months

- Long ADT
  - 85.3%
  - (98.2% CI: 80.5-89.0)
- Short ADT
  - 80.6%
  - (98.2% CI: 75.4-84.8)

HR(SADT/LADT): 1.43
(96.4% CI: 1.04-1.98)

P-Value: 0.6543
(H1: SADT non inferior)

P-value: 0.0191
(H1: LADT superior)

<table>
<thead>
<tr>
<th>Q</th>
<th>N</th>
<th>Number of patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>483</td>
<td>470 452 409 332 235 122 37 4</td>
</tr>
<tr>
<td>73</td>
<td>487</td>
<td>476 450 414 354 239 130 52 17</td>
</tr>
</tbody>
</table>
Shorter courses of treatment demonstrated a 21% reduction in the risk of mortality (HR 0.79, 95% CI 0.69-0.90, \(P = 0.0003\)), longer treatment durations provided benefits of an even greater magnitude (HR 0.61, 95% CI 0.47-0.81, \(P = 0.0005\))
Potential Important Ingredients to Improve Outcome with Radiotherapy for High Risk Disease

- Need to deliver escalated radiation dose levels
- Deliver and adequate duration of adjuvant androgen deprivation therapy
- Need to include regional nodes within the treatment portal
- To consider exploring in study settings the use of novel second generation anti-androgens or systemic therapy in conjunction with local therapy
RTOG 0521
High Risk Patients (n=600)

2 mo neoad ADT
+72-76 Gy 3D-CRT/IMRT
+ 2 Yrs LH-RH

neoad ADT+72-76 Gy IMRT
+ 2 Yrs LH-RH
6 cycles docetaxel+prednisone
Beginning 28 days post RT
AbiRT: Study Design

- Phase II single arm open-label study
- Target enrollment of 37 patients
- Protocol will be open at Duke Cancer Institute and MD Anderson Cancer Center
- Six months of ADT and abiraterone acetate and once daily prednisone concurrent with definitive RT to the prostate and seminal vesicles.
  - RT will start week 9 of Abiraterone acetate/prednisone

Unfavorable* Localized Prostate Cancer

Abiraterone acetate 1000mg PO daily x 6mo
Prednisone 5mg PO daily x 6mo
LHRH-Agonist x 6 mo

RT x 2 mo 75-80 Gy

1° Endpoint: Undetectable PSA @ 1yr

*Unfavorable =
- GS 7 PSA < 20 ng/ml T1-2b
- GS 8-10 PSA < 20 ng/ml T1
- GS < 6 PSA 10.1-40 ng/ml T1
- cT3 GS < 7 PSA <10 ng/ml
Abiraterone & ARN-509
Mechanism of Action = complete

CYP17 lyase inhibitor (abiraterone acetate): Decreases synthesis of androgens and estrogens

- CYP17 hydroxylase
- 17OH-Progesterone
- CYP17 lyase
- 17OH-Progesterone

Pregnenolone

Progesterone (upstream steroids)

Aldosterone (mineralocorticoids)

Cortisol (glucocorticoids)

Androgens

Estrogens

CYP19

Androgen Receptor (AR)

AR Antagonist (ARN-509): Prevents AR activation through selective competitive binding
MSKCC High Risk Phase II Study Comparing 2 Second Generation Anti-Androgens with SBRT (N=66)

- RT: hypo=fractionated RT starting 3 months after initiation of ADT: 5 Gy x 5 to Pelvis and 8 Gy x 5 to Prostate

- Arm 1: Abiraterone and Leuprolide x 6 months

- Arm 2: Abiraterone, ARN-509, and Leuprolide x 6 months with hypofractionated RT starting 3 months after initiation of ADT: 5 Gy x 5 to Pelvis and 8 Gy x 5 to prostate

- ENDPOINTS: PSA Relapse Free Survival @ 3 years 2 year biopsy outcomes
Conclusions

• High dose IGRT to the prostate and nodes + long-course adjuvant ADT represents a standard of care in the management of high risk prostate cancer.

• High quality MRI helpful in defining extent of disease and for targeting therapy.

• Dose intensification with brachytherapy combined with IGRT and de-escalation to normal tissues may be appropriate with emerging molecular imaging tools.

• Novel targeted and biologic agents are being tested in conjunction with radiotherapy to further improve outcomes in this cohort.