Radical Prostatectomy: Management of the Primary From Localized to Oligometastatic Disease
Disclosures

I do not have anything to disclose
Sexual function causes moderate to severe distress 2 years after RP in what percentage of men:

1. 10-20%
2. 20-30%
3. 40-50%
4. 70-80%
Which of the following statements are true:

1. Neoadjuvant docetaxel + ADT followed by RP results in a survival advantage over RP alone
2. Adjuvant ADT improves survival in men after RP who are lymph node positive compared to delayed ADT
3. SEER registry data suggest that men presenting with metastatic prostate cancer who have their primary cancer treated with RP or XRT survive longer than men who do not have their primary cancer treated
4. All are correct
5. 2 and 3 are correct
Surgery for Prostate Cancer

- RP should rarely be used for low-risk prostate cancer
  - Restage with MRI and repeat biopsy to rule out an aggressive cancer, then monitor on an AS protocol
- RP with PLND works well for intermediate- and high-risk clinically localized prostate cancer
- Cancer control is excellent, and long-term cancer-specific survival is very good with early salvage radiation for PSA recurrence
- But complication rates are relatively high, and urinary and sexual side effects troublesome to patients and their partners
Cancer Control (freedom from BCR) with RP alone: MSKCC series

All Patients

By AUA risk group

<table>
<thead>
<tr>
<th>Incidence or Risk</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>96%</td>
<td>93%</td>
<td>91%</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>83%</td>
<td>83%</td>
<td>80%</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>High Risk</td>
<td>63%</td>
<td>61%</td>
<td>57%</td>
<td>53%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Time (years) from Radical Prostatectomy

Freedom from PSA Progression

Memorial Sloan Kettering Cancer Center
Quality of Life and Satisfaction with Outcome among Prostate-Cancer Survivors

Martin G. Sanda, M.D., Rodney L. Dunn, M.S., Jeff Michalski, M.D.,

NEJM2008;358:1250-61

- Sexual function caused moderate or severe distress after 2 years in 43% of men after RP, 37% after EBRT and 30% after brachytherapy
  - ED caused distress in 44%, 22% and 13% of partners
- Urinary function led to moderate or severe distress after 1 yr in 7% of patients after RP, 11% after EBRT and 18% after brachytherapy and in 4-5% of partners
- GI symptoms caused moderate or severe distress in 9% of patients and 4-5% of partners 1 year after radiation (EBRT or brachytherapy)
The Changing Role of Surgery

With the advent of more effective systemic therapy (antiandrogens, immunotherapy, chemotherapy), RP is being explored for locally advanced and oligometastatic prostate cancer as part of a multimodality approach.
Clinically Localized, High Risk Prostate Cancer

- Clinical Stage T2c-T3a  OR
- PSA > 20 ng/ml  OR
- Biopsy Gleason score 8-10
- No evidence of metastatic disease

- Patients are at increased risk of treatment failure if managed with single treatment modalities
Why Not Surgery?

• Concerns about QOL
  – Higher rates of intra-operative complications
  – Higher rates of incontinence
  – Higher rates of erectile dysfunction

• High rates of biochemical recurrence
Why Not Surgery?

- Concerns about QOL
  - Higher rates of intra-operative complications: **NO**
  - Higher rates of incontinence: **NO**
  - Higher rates of erectile dysfunction

- High rates of biochemical recurrence
Why Not Surgery?

- Concerns about QOL
  - Higher rates of intra-operative complications: NO
  - Higher rates of incontinence: NO
  - Higher rates of erectile dysfunction: YES

- High rates of biochemical recurrence
Potency after RP in High-Risk Prostate Cancer

- Radical prostatectomy performed in men with one or more high risk features

- Potency was defined as IIEF score ≥ 21

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Surgical Margins (N=515)</td>
<td>24% (21%, 28%)</td>
</tr>
<tr>
<td>Potent at baseline and 24 months follow-up</td>
<td></td>
</tr>
<tr>
<td>Potency at 12 months (N=181)</td>
<td>32% (25%, 39%)</td>
</tr>
<tr>
<td>Potency at 24 months (N=160)</td>
<td>47% (39%, 55%)</td>
</tr>
</tbody>
</table>
Why Not Surgery?

• Concerns about QOL
  – Higher rates of intra-operative complications: NO
  – Higher rates of incontinence: NO
  – Higher rates of erectile dysfunction: YES

• High rates of biochemical recurrence: YES
Cancer Control (freedom from BCR) with RP alone: MSKCC series

All Patients

By AUA risk group

Memorial Sloan Kettering Cancer Center
Risk of Death from Prostate Cancer by AUA Risk Group

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Pts</th>
<th>PCa Death</th>
<th>15-yr PCSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1816 (19%)</td>
<td>108 (79%)</td>
<td>19%</td>
</tr>
<tr>
<td>Inter</td>
<td>3327 (35%)</td>
<td>10 (7%)</td>
<td>10%</td>
</tr>
<tr>
<td>Low</td>
<td>4338 (46%)</td>
<td>19 (14%)</td>
<td>2%</td>
</tr>
</tbody>
</table>

Majority of deaths were among high risk group, but the risk of death from PCa (19%) was still less than from other causes (31%).

P < .001
RP: Neoadjuvant or Adjuvant Treatment

• Neoadjuvant ADT for up to 8 months
  – Reduction in likelihood of a positive surgical margin
  – No difference in BCR, clinical recurrence, or survival

• Adjuvant XRT better than observation
  – Improves overall and metastasis-free survival
  – ? if better than early salvage XRT

• Adjuvant ADT improves survival if LN+
  – ? Role of adjuvant ADT is other high-risk groups

• Other systemic agents, including chemotherapy?

Thompson et al. J Urol. 2009;181:956
Current Considerations

- Role of non-hormonal based agents?
- Does “androgen annihilation” improve outcomes after surgery in clinically localized high-risk prostate cancer?
Current Considerations

• Role of non-hormonal based agents?

• Does “androgen annihilation” improve outcomes after surgery in clinically localized high-risk prostate cancer?
**SWOG 9916: Docetaxel Improves Overall Survival in CRPC**

![Survival Curve Graph]

<table>
<thead>
<tr>
<th></th>
<th># at Risk</th>
<th># of Deaths</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+E</td>
<td>338</td>
<td>217</td>
<td>18</td>
</tr>
<tr>
<td>M+P</td>
<td>336</td>
<td>235</td>
<td>16</td>
</tr>
</tbody>
</table>

HR: 0.80 (95% CI 0.67, 0.97), p = 0.01

Petrylak et al. ASCO 2004
Neoadjuvant Chemo-hormonal Therapy Prior to Radical Prostatectomy

**CALGB 90203**

- 6 cycles of chemohormonal therapy
  - Docetaxel 75 mg/m² IV every 21 days
  - LHRH agonist therapy (18-24 weeks)

- Surgical Intervention
  - Staging pelvic lymphadenectomy
  - Radical prostatectomy

**Eligibility:**
- Kattan Pre-operative nomogram prediction of < 60%
- OR
- Biopsy Gleason Sum 8-10

**Sample size:** 750
Current Considerations

- Role of non-hormonal based agents?
- Does “androgen annihilation” improve outcomes after surgery in clinically localized high-risk prostate cancer?
Neoadjuvant Abiraterone (A) plus LHRH Agonist (LHRHa) in Clinically Localized High-risk Prostate Cancer: A Randomized Phase II Study

- 28 men received 12 weeks A + 24 weeks LHRHa
- 30 men received 24 weeks A + 24 weeks LHRHa
- 1 patient from each arm refused RP

- 1/27 and 3/29 were pCR
- 3/27 and 7/29 were near pCR (tumor < 5 mm)

Establishing a Cure Paradigm Using an Undetectable PSA and Non-Castrate Testosterone as a Screening Endpoint

- A clean, binary value
- Avoids debate over “meaningful” post-treatment PSA declines and “response”
- Potentially acceptable as evidence of being disease free depending on durability
- Although survival is a “gold standard” primary endpoint in clinical trials, biochemical recurrence (a detectable PSA) indicates treatment failure after RP when the objective is disease eradication

Combining ADT and “Systemic Agent(s)” with RP to Improve Cure of Patients with High-Risk Prostate Cancer

ADT to maximize the apoptotic response: release of tumor antigens to enhance immune response

Additional systemic agent(s) to promote durable anti-tumor responses

RP to control the primary tumor site and perhaps to further promote antigen release to enhance the immune response
Treatment Of High Risk Prostate Cancer: Conclusions

• Expanding role of RP in high-risk patients
  – Surgery is feasible/safe in high-risk prostate cancer
  – RP is curative in some and benefits most
• Adjuvant/salvage RT is a viable option with minimal impact on QOL
• Local therapy alone is often inadequate for patients with high-risk prostate cancer
  – Multimodal treatment strategies are being investigated

• Support clinical trials!!!!
Rationale for Removing the Primary Cancer in the Setting of Metastatic Disease
Cytoreduction is Effective in Metastatic Cancer
Combining cytoreductive surgery + systemic therapy improves overall survival for:

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Systemic Therapy</th>
<th>Systemic Therapy + Cytoreduction</th>
<th>Overall Survival</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell</td>
<td>Interferon-alpha</td>
<td>Interferon-alpha + Radical nephrectomy</td>
<td>7 vs. 17 mo</td>
<td>0.03</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Platinum + cytoreduction</td>
<td>Platinum + &gt;75% cytoreduction</td>
<td>23 vs. 34 mo</td>
<td>0.001</td>
</tr>
<tr>
<td>Colon</td>
<td>5-FU + leucovorin</td>
<td>5-FU + leucovorin + cytoreduction/HIPEC</td>
<td>13 vs. 22 mo</td>
<td>0.03</td>
</tr>
</tbody>
</table>
A Survival Benefit for Local Therapy was Suggested in Men With Documented Stage IV (M1a–c) PCa at Diagnosis in SEER

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>5-yr Overall Survival</th>
<th>5-yr Disease Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>245</td>
<td>67.4%</td>
<td>76%</td>
</tr>
<tr>
<td>Radiation</td>
<td>129</td>
<td>52.6%</td>
<td>61%</td>
</tr>
<tr>
<td>No Surgery or Radiotherapy</td>
<td>7811</td>
<td>22.5%</td>
<td>49%</td>
</tr>
</tbody>
</table>

…but RP was used in only 3% of the population

RP in Patients With Minimal Metastatic Disease (MMD) Who Respond to ADT Prolongs the Time to CRPC and Clinical Progression, Improves Cancer Specific Survival and Reduces the Need for Local Surgical Palliation

<table>
<thead>
<tr>
<th></th>
<th>RP</th>
<th>No RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>Age</td>
<td>61 (42-69)</td>
<td>64 (47-83)</td>
</tr>
<tr>
<td>Follow-up (mos)</td>
<td>35 (7-75)</td>
<td>47 (28-96)</td>
</tr>
<tr>
<td>Time to CRPC (mos)</td>
<td>40 (9-65)</td>
<td>29 (16-59)</td>
</tr>
<tr>
<td>Time to clinical progression (mos)</td>
<td>39</td>
<td>27</td>
</tr>
<tr>
<td>Cancer specific survival</td>
<td>96%</td>
<td>84%</td>
</tr>
<tr>
<td>Local surgical palliation</td>
<td>0%</td>
<td>29%</td>
</tr>
</tbody>
</table>

MMD: Clinically localized, ≤ 3 bone metastasis, no bulky adenopathy, and no visceral disease
Response to ADT: No evidence of cancer progression and PSA < 1.0 ng/ml at 6 months

Comparable: Clinical stage, Gleason score, PSA and extent of metastases
   but longer f/u in no RP group and patients were not randomized

Heidenreich et al: J Urol. 2015
Extended LN Dissection for Advanced PCa

In selected patients with pelvic and/or retroperitoneal lymphadenopathy with or without limited bone metastases, we have performed extended LN dissection up to the renal hilum in conjunction with systemic therapy (ADT +/- immunotherapy) and radiation of bone metastases in an effort to provide long-term cancer control in some patients otherwise considered incurable.
Treatment Of High Risk Prostate Cancer: Conclusions

- Expanding role of RP in high-risk patients
  - Surgery is feasible/safe in high-risk prostate cancer
  - RP is curative in some and benefits most
- Adjuvant/salvage RT is a viable option with minimal impact on QOL
- Local therapy alone is often inadequate for patients with high-risk prostate cancer
  - Multimodal treatment strategies are being investigated

- Support clinical trials!!!!