Local Salvage Therapies After Failed Radiation for Prostate Cancer

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Biochemical Failure after Radiation

- ASTRO criteria
  - 3 consecutive rises in PSA levels at least 6 months apart
  - Nadir + 2
  - High specificity but low sensitivity
- Confounding factors
  - PSA bounce (about 15% of patients)
  - Expected PSA rise after stopping ADT
- PSA nadir
Local versus Systemic Recurrence after XRT

• Local recurrence:
  – rising PSA confirmed on repeat evaluation
  – positive prostate biopsy at least 18 months after XRT
  – negative metastatic evaluation

• Systemic disease
  – Rapid PSA DT (< 3 months)
    • Only about 10% of patients
  – Positive metastatic evaluation

Treatment Options for Local Recurrence after Radiation Therapy

• Observation with delayed use of ADT
• Immediate hormonal therapy

• Salvage radical prostatectomy
• Salvage cryotherapy
• Salvage HIFU
• Salvage brachytherapy/HDR
Evaluation for salvage local therapy

1. Is the cancer potentially curable?
   • Initial cancer (before radiation) curable: T1-3a N0 M0
   • Current cancer T1-3a, PSA < 10, no evidence of metastases: bone scan, CT or MRI of abdomen and pelvic LN, ProstaScint monoclonal antibody or PET/CT scan

2. Is the patient appropriate?
   • Good health, life expectancy >10 years
   • Highly motivated, willing to accept risks of salvage therapy

3. Would the treatment be safe?
   • No evidence of severe radiation cystitis or proctitis

Why is salvage radical prostatectomy not widely accepted?

• Historically high peri-operative morbidity

• Doubts about long term oncologic efficacy
### Salvage RP: Surgical Details

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1984-1992 n=40</th>
<th>1993-2003 n=60</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean operative time, hours (range)</td>
<td>4.4 (2.8-7)</td>
<td>3.7 (2.2-6.3)</td>
<td></td>
</tr>
<tr>
<td>Operative approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard retropubic</td>
<td>19 (48%)</td>
<td>56 (93%)</td>
<td></td>
</tr>
<tr>
<td>Antegrade retropubic</td>
<td>10 (25%)</td>
<td>4 (7%)</td>
<td></td>
</tr>
<tr>
<td>Abdominoperineal</td>
<td>11 (28%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median blood loss, mL (range)</td>
<td>1000 (100-2400)</td>
<td>1000 (350-4000)</td>
<td></td>
</tr>
<tr>
<td>Median length of stay, days (range)</td>
<td>10 (6-16)</td>
<td>3 (2-7)</td>
<td></td>
</tr>
<tr>
<td>Readmission (%)</td>
<td>5 (13)</td>
<td>8 (13)</td>
<td></td>
</tr>
</tbody>
</table>


### Salvage RP: Intraoperative Complications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1984-1992 n=40</th>
<th>1993-2003 n=60</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectotomy (%)</td>
<td>6 (15)</td>
<td>1 (1.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Diverting colostomy (%)</td>
<td>2 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ureteral injury (%)</td>
<td>2 (5)</td>
<td>3 (5)</td>
<td></td>
</tr>
<tr>
<td>Obturator nerve injury (%)</td>
<td>0</td>
<td>1 (1.6)</td>
<td></td>
</tr>
</tbody>
</table>

### Salvage RP: Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>1984-1992 n=40</th>
<th>1993-2003 n=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-exploration for bleeding (%)</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocele (%)</td>
<td>0</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>1 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>UTI (%)</td>
<td>1 (2.5)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Thrombophlebitis (%)</td>
<td>1 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>Fistula-delayed cystectomy (%)</td>
<td>1 (2.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Ureteral stricture-reimplant (%)</td>
<td>1 (2.5)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Anastomatic stricture (%)</td>
<td>12 (30)</td>
<td>17 (28)</td>
</tr>
</tbody>
</table>


### Salvage RP: Recovery of Continence

- **OVERALL:** 62% (49-74)
- **1984-1992:** 45% (26-64)
- **1993-2003:** 66% (49-84)

- Artificial urinary sphincter in 23 patients
  - All require ≤ 1 pad per day after AUS
  - Only one has required AUS revision

Stephenson AJ et al J Urol 2004;172:2239-2243
Pathologic Outcomes after Salvage RP

<table>
<thead>
<tr>
<th></th>
<th>Overall N=100</th>
<th>1984-92 N=40</th>
<th>1993-2003 N=60</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ-confined</td>
<td>32%</td>
<td>17%</td>
<td>46%</td>
<td>0.002</td>
</tr>
<tr>
<td>EPE</td>
<td>45%</td>
<td>67%</td>
<td>25%</td>
<td>0.005</td>
</tr>
<tr>
<td>SVI</td>
<td>38%</td>
<td>50%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Positive margin</td>
<td>29%</td>
<td>31%</td>
<td>8%</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive node</td>
<td>9%</td>
<td>4%</td>
<td>14%</td>
<td>0.02</td>
</tr>
</tbody>
</table>


Progression Free Probability (PFP) after Salvage RP

5-year PFP: 54%

Number at risk: 148 02 51 35 24 11

Log-Rank Test:
1 vs. 2: \( p = 0.02 \)
1 vs. 3: \( p = 0.014 \)
2 vs. 3: \( p = 0.79 \)

Progression by Preoperative PSA level
<4 vs. >4 and <10 vs. >10 ng/mL

For pre-salvage RP PSA < 4 ng/ml:
PFP at 5 and 10 years: 82% and 69%, respectively

Progression Free Probability (PFP) after Salvage RP
Biopsy Gleason Score

Clinical Local Recurrence after Salvage RP

- Recent update includes 124 patients
  - 75 free of BCR
  - 49 with BCR
- Only 1 patient experienced clinical local recurrence (hormone refractory with bone mets)
  - Urinary obstruction; TURP 30 months after salvage RP
  - Specimen demonstrated Gleason 5+5=10

Death after Salvage RP

- Death from prostate cancer at 5 years: 4%
- Death from prostate cancer at 10 years: 18%

Cumulative incidence

Death from prostate cancer
Death from other causes

Time from salvage prostatectomy (years)

Salvage Radical Prostatectomy for Radiation-Recurrent Prostate Cancer: A Multi-Institutional Collaboration

- Mayo Clinic, Rochester, MN, USA, (Drs Karnes and Blute)
- Vita-Salute San Raffaele University, Milan, Italy, (Drs Briganti and Montorsi)
- Netherlands Cancer Institute, Amsterdam, The Netherlands, (Dr van der Poel)
- Katholieke Universiteit Leuven, Belgium, (Drs Van Poppel and Joniau)
- The Prostate Centre, Vancouver General Hospital, (Drs Coll and Gleave)
- University of Sao Paulo, Brazil, (Drs Chade, Dall’Oglio, and Srougi)

Patients

- SRP performed on 404 men with radiation-recurrent prostate cancer from 1985 to 2009
- Median age at SRP was 65 years
- Median pre-SRP PSA was 4.5 ng/mL
- BCR after SRP was defined as a serum prostate-specific antigen (PSA) ≥ 0.1 ng/mL
Results

- 195 patients experienced BCR
- 64 developed metastasis
- 40 died from prostate cancer
- At 10 years after SRP
  - BCR-free: 37% (95% CI: 31%-43%)
  - Metastasis-free: 77% (95% CI: 71%-82%)
  - PCSS: 83% (95% CI: 76%-88%)

Salvage RP: Lessons Learned

- Modern salvage radical prostatectomy is safe and major complications are less common
  - Patients had had fewer pelvic procedures
  - Surgeons have gained experience
  - Radiation therapy is better targeted
- Long-term progression-free probability, by pathologic stage, is comparable to standard RP
- Continuing challenges:
  - High rate of incontinence, strictures
  - Long lag time between radiotherapy and salvage RP leads to high recurrence rate
Treatment Options for Local Recurrence after Radiation Therapy

- Observation with delayed use of ADT
- Immediate hormonal therapy
- Salvage radical prostatectomy
- Salvage cryotherapy
- Salvage HIFU
- Salvage brachytherapy/HDR

The Anatomic and Pathologic Characteristics of Irradiated Prostate Cancers May Influence the Oncologic Efficacy of Salvage Therapies

William C Huang, Bobby Shayegan, Kentaro Kuroiwa, Peter T Scardino, James A Eastham

Huang et al, J Urol. 2007; 177(4): 1324-9
Methods

- 47 Salvage Prostatectomies @ MSKCC between 2000-2004
- Institutional Review Board approved study
  - 46 whole mount salvage prostatectomy specimens reviewed by a single uro-pathologist (KK).
  - Detailed analysis of pathologic features
    - Anatomic distribution
    - Cancer volume (computerized planimetric method)

Huang et al, J Urol. 2007; 177(4): 1324-9

Results

Huang et al, J Urol. 2007; 177(4): 1324-9
Results

<table>
<thead>
<tr>
<th>Tumor Location (N=70)</th>
<th>No. of foci</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>43</td>
<td>61.4%</td>
</tr>
<tr>
<td>Mid Gland</td>
<td>43</td>
<td>61.4%</td>
</tr>
<tr>
<td>Base</td>
<td>23</td>
<td>32.9%</td>
</tr>
<tr>
<td>Peripheral Zone (PZ)</td>
<td>70</td>
<td>100.0%</td>
</tr>
<tr>
<td>Transition Zone (TZ)</td>
<td>3</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Distance to Urethra (mm)</th>
<th>Value</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3.8</td>
<td>0.0-18.4</td>
</tr>
<tr>
<td>Apex</td>
<td>4.1</td>
<td>0.0-10.8</td>
</tr>
<tr>
<td>Mid</td>
<td>6.5</td>
<td>0.0-17.1</td>
</tr>
<tr>
<td>Base</td>
<td>13.8</td>
<td>1.3-22.3</td>
</tr>
</tbody>
</table>

| Median Tumor Volume (cc)       | 6.8   | <0.01 - 15.9|

Huang et al, J Urol. 2007; 177(4): 1324-9

Mapping Study: Conclusions

- Irradiated Prostate Tumors:
  - Pathologically advanced (Gleason 8, ECE, SVI)
  - Distributed in regions of the prostate which may be technically difficult to treat with salvage ablative therapies
    - Apex (62%)
    - Capsule
    - Periurethral (67%)
- These findings raise questions regarding the oncologic efficacy of locally ablative therapies

Huang et al, J Urol. 2007; 177(4): 1324-9
Salvage Cryotherapy

• Technical improvements have decreased morbidity
  – Urethral warmer
  – Smaller probes
  – Argon gas

• Long-term oncologic outcomes unclear
  – What is the definition of success?
    • Negative biopsy?
    • Post-cryotherapy PSA?

Salvage Cryoablation of the Prostate: Follow-up and Analysis of Predictive Factors for Outcome

• 187 patients with locally recurrent prostate cancer after radiotherapy underwent salvage cryoablation between 1995 and 2004
• 71% had 3 to 6 months of neoadjuvant hormonal therapy for downsizing
• Mean follow-up of 39 months
• Biochemical failure was defined as the serum PSA reaching 2 ng/ml above the nadir

Ng CK et al. J Urol 2007; 178(4): 1253-1257
For pre-salvage RP PSA < 4 ng/ml:
PFP at 5 and 10 years: 82% and 69%

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower urinary tract symptoms:</td>
<td></td>
</tr>
<tr>
<td>Transient</td>
<td>72 (39)</td>
</tr>
<tr>
<td>Persistent</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Incontinence:</td>
<td></td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>69 (37)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Urethreorectal fistulas</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Acute urinary retention</td>
<td>40 (21)</td>
</tr>
<tr>
<td>Perineal pain</td>
<td>25 (14)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Ng CK et al. J Urol 2007; 178(4): 1253-1257
Locally Recurrent Prostate Cancer After Initial Radiation Therapy: A Comparison of Salvage RP Versus Cryotherapy

• Retrospectively reviewed the medical records of:
  – Patients who underwent salvage RP at the Mayo Clinic between 1990 and 1999
  – Patients who underwent salvage cryotherapy at M. D. Anderson Cancer Center between 1992 and 1995
• Eligibility criteria were:
  – PSA $\leq$ 10 ng/ml
  – Post-radiation therapy biopsy showing Gleason score $\leq$ 8
  – Prior radiation therapy alone without pre-salvage or post-salvage hormonal therapy

Results

• Mean follow-up was 7.8 years for the salvage RP group and 5.5 years for the salvage cryotherapy group.
• Salvage RP resulted in superior biochemical disease-free survival (61% versus 21% at 5 years, $p < 0.001$)
• Salvage RP resulted in superior overall survival (95% versus 85% at 5 years, $p = 0.001$)
• After adjusting for post-radiation therapy biopsy Gleason sum and pre-salvage treatment PSA on multivariate analysis salvage RP remained superior to salvage cryotherapy for biochemical recurrence and overall survival
Conclusion: Salvage RP vs Cryotherapy

Young, healthy patients with recurrent prostate cancer after radiation therapy should consider salvage RP as it offers superior biochemical disease-free survival and may potentially offer the best chance of cure.
HIFU
A therapy in which ultrasound energy is focused at a specific location in the body. At that location, or focal point, the temperature rapidly rises to almost 90°C (195°F). Any tissue at the focal point is destroyed.

The feasibility and safety of HIFU as salvage therapy for recurrent prostate cancer following EBRT

- 31 cases treated using the Sonablate® 500 HIFU device, between 2005 and 2007
- Mean follow-up of 7.4 (range 3–24) months

Zacharakis E et al. BJU Int. 2008;102(7):786-92
HIFU: Results

• Side-effects included:
  – stricture or intervention for necrotic tissue in 11 (36%)
  – Urinary tract infection or dysuria syndrome in 8 (26%)
  – Urinary incontinence in 2 (7%)
  – Recto-urethral fistula occurred in 2 (7%)

• Half of the patients had PSA levels of <0.2 ng/mL
• 71% were free of disease following salvage HIFU

Zacharakis E et al. BJU Int. 2008;102(7):786-92

Treatment Options for Local Recurrence after Radiation Therapy

• Observation with delayed use of ADT
• Immediate hormonal therapy

• Salvage radical prostatectomy
• Salvage cryotherapy
• Salvage HIFU
• Salvage brachytherapy/HDR
Salvage Brachytherapy

- 37 patients treated between 1994 and 2008
- Neoadjuvant/adjuvant hormonal therapy was used in 31 of the 37 men for an average of 6 months
- The median follow-up after salvage BT was 86 months (range, 2–156 months)
- Failure defined by Phoenix definition (nadir + 2)

Salvage Brachytherapy-Toxicity

- 17 of 37 patients did not develop any toxicity
- 3 patients developed Grade 1 urinary symptoms
- 13 patients developed Grade 2 toxicity requiring medications for symptom relief
- Three patients developed Grade 3 toxicity
  - 2 patients required TURP
  - 1 patient required fulguration for gross hematuria
- One patient developed Grade 4 toxicity, constituting a prostato-rectal fistula requiring urinary diversion


Salvage Brachytherapy-Outcomes

- 21 patients treated with salvage brachytherapy
- Median follow-up 36 months
- Failure was defined as three consecutive rises in prostate-specific antigen scored at the call date, initiation of hormone therapy, or clinical failure

Lee et al; Brachytherapy 2008: 7 (1): 17-21
Biochemical failure-free survival rates were:

- 3 years: 94%
- 5 years: 38%

Lee et al; Brachytherapy 2008: 7 (1): 17-21

Conclusions

- Salvage RP demonstrates the “best” long-term oncologic outcomes
- Salvage RP has high rates of incontinence and BNC
- Salvage thermal therapies can be given safely
  – Modest short-term oncologic outcomes
  – Side effect profile favors cryo rather than HIFU
- Salvage brachytherapy is being studied