Prostate Cancer

Hafidzul Jasman
Question

A 70-year-old gentleman with
• Good performance status
• LUTS with IPSS 10, QOL 3
• Qmax 12mls/sec, PVR 100cc
• Prostate volume 30cc
• PSA 6ng/ml
• Adenocarcinoma 3+4
• 4/6 cores right lobe
• T2a

Sexually active and concerned about incontinence.
How would you advise?
Background

• Age 70
  – Life expectancy >10 years
• Good performance status
• LUTS IPSS 10, QOL 3
  – Moderate (8-19), QOL mixed
• Prostate vol 30cc, Qmax 12mls/sec, PVR 100cc
  – Olmstead County Risk of progression AUR, BPH-related surgery
    • Prostate volume >30
    • Qmax <12
    • PVR >50
    • IPSS >7
    • PSA >1.4
• Sexually active, concern about incontinence
## Staging T2

<table>
<thead>
<tr>
<th>T2a</th>
<th>Tumour involves one half of one lobe or less</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2b</td>
<td>Tumour involves more than half of one lobe, but not both lobes</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumour involves both lobes</td>
</tr>
</tbody>
</table>
## D’Amico Pre-treatment prostate cancer risk stratification

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>T</th>
<th>PSA</th>
<th>GS</th>
<th>10 yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>T1-T2a</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>83%</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>T2b</td>
<td>10-20</td>
<td>7</td>
<td>46%</td>
</tr>
<tr>
<td>High risk</td>
<td>≥T2c</td>
<td>&gt;20</td>
<td>8-10</td>
<td>29%</td>
</tr>
</tbody>
</table>

Our patient: PSA 6
GS 3+4
T2a

D’Amico JAMA 1998
NCCN – Intermediate risk include T2C
Option

1. Radical prostatectomy
2. Radiotherapy
3. Brachytherapy?
4. Hormonal therapy?
5. Active surveillance?
NCCN Guidelines intermediate risk

• > 10 years life expectancy
  – RP +/- PLND
  – RT +/- short term neoadjuvant/ concomitant/ adjuvant ADT (4-6 mth) +/- bracytherapy

• < 10 years life expectancy
  – Active surveillance
  – RT +/- short term neoadjuvant/ concomitant/ adjuvant ADT (4-6 mth) +/- bracytherapy
Radical Prostatectomy

• Removal of the entire prostate gland, resection of both seminal vesicles, bilateral pelvic lymph node dissection

• Aim:
  – Eradicate disease
  – Preserve continence & potency

• Concept:
  – No age limit for RP
  – More comorbidities are assoc with higher risk of dying from non-CaP related cause
  – Based on life expectancy 10 yrs
• **Surgical approach**
  – Open radical retropubic prostatectomy (RRP)
  – Lap radical prostatectomy (LRP)
  – Robot-assisted radical prostatectomy (RARP)

• **Studies**
  – SPCG4
  – PIVOT
Scandinavian Prostate Cancer Group-4 (SPCG4)

- Bill-Axelson 2011 Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer
  - Age <75, life expectancy >10 years, T1-T2, PSA <50, bone negative
  - 695 Localized CaP, RP (n = 347) vs WW (n = 348)
  - 75% T2, 84% GS≤7

<table>
<thead>
<tr>
<th></th>
<th>RRP</th>
<th>WW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died of CaP at median 10 years follow up</td>
<td>13.5%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Diagnosed with distant metastases at 12 years</td>
<td>19.3%</td>
<td>26%</td>
</tr>
</tbody>
</table>

- 15 year cancer-specific survival 85%
- RP reduces CaP mortality and risk of metastases with little or no further increase in benefit ≥10 years after surgery
- Benefit on overall survival and metastasis-free survival being seen only in those <65
- PSA and Gleason score not modified
PIVOT

- Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group.
- Wilt TJ NEJM 2012 Radical prostatectomy versus observation for localized prostate cancer.
  - 731 men with localized prostate cancer (mean age 67 years; median PSA 7.8)
  - In intermediate risk group, RP had better all-cause mortality vs observation (hazard ratio, 0.69; 95% CI, 0.49 to 0.98)
  - RP associated with reduced all-cause mortality among men with a PSA >10
Lymph node dissection?

• Partin’s table (updated 2013)
  – (The James Buchanan Brady Urological Institute, Johns Hopkins)
  – Parameters
    • Clinical T stage (T2a)
    • PSA (6)
    • Gleason (3+4)
  – Results
    • Organ confined 56%
    • Extraprostatic extension 38%
    • Seminal vesicle involvement 4%
    • Lymph node involvement 2%

• Conclusion: Not for LND because risk is <5%

• EAU: eLND should be performed in intermediate-risk PCa if the estimated risk for positive lymph nodes exceeds 5%

Our patient:
IPSS 10, QOL 3
Qmax 12mls/sec
PVR 100cc
Prostate volume 30cc
PSA 6ng/ml
Gleason 3+4
4/6 cores right lobe
T2a
eLND

• Which nodes?
  – overlying external iliac artery and vein
  – within obturator fossa located cranially and caudally to the obturator nerve
  – medial and lateral to the internal iliac artery
  – common iliac lymph nodes up to the ureteric crossing

• Adjuvant ADT needed when >2 nodes positive
### Complications (BAUS consent form)

<table>
<thead>
<tr>
<th>Mortality</th>
<th>0-1.5%</th>
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<tbody>
<tr>
<td>Infection</td>
<td>5-10%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5-10%</td>
</tr>
<tr>
<td>Rectal injury</td>
<td>5%</td>
</tr>
<tr>
<td>Impotence</td>
<td>40-60%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>50% (5-10% long term)</td>
</tr>
<tr>
<td>BN stricture</td>
<td>5%</td>
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</tbody>
</table>
• Post-RP incontinence and erectile dysfunction are common problems

• Systematic review Ficarra Eur Urol 2012

<table>
<thead>
<tr>
<th></th>
<th>RALP</th>
<th>RRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean continence rate at 12 mth</td>
<td>89-100%</td>
<td>80-97%</td>
</tr>
<tr>
<td>Mean potency recovery rate at 12 mth</td>
<td>55-81%</td>
<td>26-63%</td>
</tr>
</tbody>
</table>

– Better 12 month urinary continence recovery after RARP compared to RRP (OR 1.53, p=0.03) or LRP (OR 2.39, p=0.006)

– Better 12 month potency rates after RARP compared to RRP (OR 2.84, p=0.002) and not statistically significant with LRP (OR 1.89, p=0.21)

– Data supports cauterity-free dissection or use of pinpointed low-energy cauterization
Will continence get better?

- Lepor Kaci J Urol 2004
- Continence after RRP
- AUA symptom index

<table>
<thead>
<tr>
<th>Baseline</th>
<th>98.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mth</td>
<td>80.6%</td>
</tr>
<tr>
<td>6 mth</td>
<td>91.2%</td>
</tr>
<tr>
<td>12 mth</td>
<td>95.2%</td>
</tr>
<tr>
<td>24 mth</td>
<td>98.5%</td>
</tr>
</tbody>
</table>
  • improved continence by minimizing manipulation of the urethra and preserving all periurethral tissue distal to the apex
• Nerve-sparing RP can be performed safely in most men with localized Pca
• Contraindications
  – high risk of extracapsular disease eg cT2c or cT3
  – any GS > 7
  – more than one biopsy > 6 at the ipsilateral side
• Role of MRI for proper case selection
• If any doubt regarding residual tumour, should remove the neurovascular bundle
• Intra-op frozen section for lesion close to capsule
• Briganti 2010 PDE5 inhibitors had significantly higher 3-year erectile function recovery rate compared with patients who did not use any postoperative PDE5 inhibitors (73% vs. 37%, P < 0.001)

• Nandipati 2006 Early combination therapy: intracavernosal alprostadil + sildenafil after bilateral nerve sparing RP
  – Sexually active in 57% injection alone, 42.9% combination

• Early administration of intracavernous injection therapy could improve the definitive potency rates

• Early use of PDE5 inhibitors in penile rehabilitation remains controversial
  – No benefit from daily early administration vs on-demand
### EAU recommendation on RP

<table>
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<tr>
<th>Indications</th>
<th>LE</th>
<th>GR</th>
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<tbody>
<tr>
<td>In patients with low and intermediate risk localized PCa (cT1a-T2b and GS 2-7 and PSA &lt; 20 ng/mL) and life-expectancy &gt; 10 years.</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td><strong>Optional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selected patients with low-volume, high-risk, localized PCa (cT3a or GS 8-10 or PSA &gt; 20 ng/mL), often in a multimodality setting.</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Highly selected patients with very-high-risk, localized PCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Short-term (3 months) or long-term (9 months) neoadjuvant therapy with gonadotrophin-releasing hormone analogues is NOT recommended for the treatment of stage T1-T2 disease.</td>
<td>1a</td>
<td>A</td>
</tr>
<tr>
<td>Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS &lt; 7 and PSA &lt; 10 ng/mL, or refer to Partin tables/nomograms).</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Multiparametric MRI can help in deciding when to perform nerve-sparing procedures in intermediate- and high-risk disease.</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
Radiotherapy

- No randomized studies comparing RP with either EBRT or brachytherapy for localized CaP
- Gold standard: Intensity-modulated radiotherapy (IMRT) +/- image-guided radiotherapy (IGRT)
- 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated external-beam radiotherapy (IMRT)
EORTC 22863 Bolla 2010

- 415 patients, either T1-2 G3 or T3-4 N0 M0 and any histological grade (high risk)
- RT + ADT vs RT alone
- Androcur then Zoladex 3 years
- Follow up 66 months (Survival 78% vs 62%)
- Follow up 9 years (OS 58.1% vs 39.8%)
- 10 year CaP mortality (11.1% vs 31%)
- Apply to intermediate risk?
RTOG 94-08 Jones 2011

- 1979 patients T1b-T2b PSA <20
- Complete ADT 2 months before & 2 months during conventional lower dose RT (66Gy) significantly improved 10-year OS rate (62% vs 57%)
• Combined dose-escalated RT + ADT
• 1074 Intermediate risk CaP
  – RT to prostate & seminal ves
    • Dose 64.8-86.4 Gy
    • Dose >81 Gy last 10 years using IMRT
  – Complete ADT (LHRH agonist + antiandrogen)
    • 456 intermediate risk
    • Started 3 months before RT, continuing during RT, total 6 months
  – 10 year PSA-RFS (relapse free survival)
    • 76% (>81Gy), 57% (lower doses)
  – 10 year Distant mets free survival
    • 87% (>81Gy), 81% (lower doses)
  – 10 year CaP mortality 3.6%
  – 10 year OS 76%
  – No survival advantage of 6-month course of ADT seen
• Bolla 2009 NEJM – longer ADT course better than 6 months
Proposed ERBT in intermediate risk

• Patient suitable for ADT:
  – combine IMRT + short term ADT 4-6 months

• Patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health)
  – IMRT at an escalated dose (80 Gy) or a combination of IMRT and brachytherapy
RT toxicity

- EORTC 22863 Bolla
  - Incontinence 5.3%
  - Cystitis 5.3%
  - Proctitis 8.2%
  - Hematuria 4.7%
  - Stricture 7.1%
  - Leg edema 1.5%

- Robinson 2002 meta-analysis 1-year probability rates for maintaining erectile function
  - 0.76 after brachytherapy
  - 0.60 after brachytherapy + external irradiation
  - 0.55 after external irradiation
  - 0.34 after nerve-sparing radical prostatectomy
  - 0.25 after standard RP
Brachytherapy

  - Stage T1b-T2a N0M0
  - Gleason ≤ 6
  - PSA ≤10
  - ≤ 50% biopsy cores involved
  - Prostate volume <50
  - IPSS ≤12

Our patient:
- IPSS 10, QOL 3
- Qmax 12mls/sec
- PVR 100cc
- Prostate volume 30cc
- PSA 6ng/ml
- Gleason 3+4
- 4/6 cores right lobe
- T2a

In patients with cT1-T2a, Gleason score < 7 (or 3+4), PSA ≤ 10 ng/mL, prostate volume ≤ 50 mL, without a previous TURP and with a good IPSS, transperineal interstitial brachytherapy with permanent implants can be an alternative.
• Complication:
  – AUR 15%, micturation resumes within 2 weeks
  – Erectile morbidity 16.7% (D’Amico 2006)

• Kupelian 2004
  – 2991 patients T1-2 Cleveland MSKCC, follow up 1 year
  – 5-year Biochem disease free rates are similar for brachytherapy, high-dose (> 72 Gy) external radiation, combination seed/external irradiation, and radical prostatectomy
Active surveillance

- Van As 2008 Gleason $\leq 3+4$, PSA $< 15$ ng/mL, T1-T2a, N0-Nx, M0-Mx, $< T2a$, $< 50\%$ biopsies +
- Klotz 2010 Gleason $< 6$, PSA $< 10$ ng/mL (up to 1999: Gleason $\leq 3+4$, PSA $< 15$ ng/mL), $< 3$ biopsies +, $< 50\%$ each core
- NCCN intermediate risk (for life expectancy $< 10$ years) PSA 6 monthly, DRE yearly

<table>
<thead>
<tr>
<th>Recommendations - active surveillance</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active surveillance is an option in patients with the lowest risk of cancer progression: over 10</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>years of life-expectancy, cT1-2, PSA $\leq 10$ ng/mL, biopsy Gleason score $\leq 6$ (at least 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scores), $\leq 2$ positive biopsies, minimal biopsy core involvement ($\leq 50%$ cancer per biopsy).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up should be based on DRE, PSA and repeated biopsies.</td>
<td>2a</td>
<td>A</td>
</tr>
<tr>
<td>The optimal timing for follow-up is still unclear.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with biopsy progressions should be recommended to undergo active treatment.</td>
<td>2a</td>
<td>A</td>
</tr>
</tbody>
</table>
Cryosurgery

- Indication:
  - Intermediate risk whose condition prohibits radiotherapy or surgery
  - Prostate size <40cc
- No longterm data
- Long et al 2001
  - Intermediate risk: 5 year Biochemical disease free survival at mean follow up 24 months
  - PSA threshold 1.0 (71%) <0.5 (45%)
- Bahn 2002
  - 7 year BDFS intermediate PSA <0.5 (68%)
- Cryo OnLine Data Levy 2009
  - PSA nadir >0.6 associated with risk of biochemical failure within 2 years (46% intermediate)
- Complications: ED 80% (Onik 2002) Incontinence 4.4% (De La Taille 2000)
HIFU

• No long term data

• Crouzet 2013
  – n=1002, median follow up 6.4 years
  – Biochemical recurrence free for intermediate 63%
  – Overall DFS at 10yrs 97%, mets free 94%

• Complications
  – Impotence 55-70%, Stress incontinence 12%
    (Poissonnier 2007)
Conclusion

• Option:
  1. Radical prostatectomy without eLND but needs counseling on complications
  2. High dose ERBT + ADT (4-6 months)

Our patient:
IPSS 10, QOL 3
Qmax 12mls/sec
PVR 100cc
Prostate volume 30cc
PSA 6ng/ml
Gleason 3+4
4/6 cores right lobe
T2a
References

• Ficarra et al. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012 Sep;62(3):405-17
• van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. Eur Urol 2008 Dec;54(6):1297-305
• Bolla et al. Duration of androgen suppression in treatment of prostate cancer. NEJM 2009;360:2516-27