Active Surveillance for Intermediate Risk Prostate Cancer

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• Disclosures: None
Objectives

– Understand active surveillance goals
– Review (and consider expanding) AS indications
– Appreciate heterogeneity of disease factors in Gleason 3+4 cancers
– Understand patient QOL concerns in treatment decisions
– Understand tools that help decision-making
Goals of AS: Timing is Everything

- Avoid or delay the costs of treatment
  - symptomatic
  - functional
  - financial
  - ...without compromising longevity/curability
  - Based on assumptions
    - Assessment of disease is reasonably accurate
    - Monitoring is effective
      - identifies change in risk when treatment options remain available
    - “no bridges are burned”
  - ...allows patient to process beyond early alarm period and educate more completely – informed decisions
Case

- 68 yr old man, retired PA
  - Well controlled DM2, HTN, hyperlipidemia
  - PSA 6.2
  - SHIM 21/25, IPSS 7 bother 1
  - Estimated u/s prostate volume 73 cc
  - Systematic TRUS/bx showed PCa in 1/12
    - 4 mm 3+4 LM
    - 11 negative biopsies
  - mpMRI showed no PIRADS 3/4/5 lesions

- Defined as favorable intermediate risk by NCCN 2018
- Options include RP, XRT and active surveillance
MSKCC Pre-RP Nomogram

Primary Treatment Outcomes

- Probability of cancer-specific survival after radical prostatectomy
  - 10 YR: 99%
  - 15 YR: 99%

- Progression-free probability after radical prostatectomy
  - 5 YR: 89%
  - 10 YR: 81%

Extent of Disease Probability

- Organ-confined disease: 57%
- Extracapsular extension: 42%
- Lymph node involvement: 2%
- Seminal vesicle invasion: 2%

Each extent of disease probability percentage is an independent prediction. We therefore would not expect these percentages to equal 100.
MSKCC Life Expectancy Calculator: +DM

At 10 Years
- 55 men would be alive
- 7 men would have died of untreated prostate cancer
- 38 men would have died of other causes

At 15 Years
- 29 men would be alive
- 10 men would have died of untreated prostate cancer
- 61 men would have died of other causes
DM + 20 pk yr cigs

At 10 Years
- 46 men would be alive
- 6 men would have died of untreated prostate cancer
- 48 men would have died of other causes

At 15 Years
- 22 men would be alive
- 8 men would have died of untreated prostate cancer
- 70 men would have died of other causes
DM + smoking + h/o MI

At 10 Years
- 36 men would be alive
- 5 men would have died of untreated prostate cancer
- 59 men would have died of other causes

At 15 Years
- 15 men would be alive
- 6 men would have died of untreated prostate cancer
- 79 men would have died of other causes
AS for 3+4 in recent guidelines

- **NCCN 2018**
  - AS is an option for patients with 3+4 and <50% positive biopsy cores

- **AUA/ASTRO/SUO**
  - “C” level option for favorable risk 3+4
Risk of metastasis/mortality increased but not high in low volume intermediate risk on AS

Metastasis free survival difference between patients with 3+3 and 3+4 on AS at 10 years – increased, but still low (Klotz)

ProtecT: 20% IR patients

JU 196: 1651 (Klotz group)
Current Tools to Assess Suitability for AS

- Epstein, D’Amico
  - Very low risk
  - Low risk
- CAPRA
  - Can still be low risk with low volume 3+4 disease
- PSAD
  - Better than PSA for reclassification and treatment
  - PSAD < .10 appears to be safe for AS
  - PSAD .10 - .15 may be safe too
AS: Triggers for Treatment

- Conventional triggers, though imperfect, are
  - Higher Gleason on subsequent biopsy
  - Increased tumor volume
  - PSA concerns: velocity, density

- These may expose patients to early treatment OR miss chance to cure

- Related to sampling error and/or PSA issues
  - What else can help? Tools that address concerns for “bad biology” and minimize risk of sampling error
Newer Tools: Genomic Tests

- OncoType DX prostate (GPS)
  - Biopsy tissue only
  - Predicts high grade disease, BCR, mets
- Prolaris
  - Biopsy or RP tissue
  - Predicts BCR and mets
- Decipher
  - Biopsy or RP tissue
  - Predicts mets, 10 yr survival
- PTEN
  - Add some value in decision-making, relatively expensive
    (note: Medicare covers these, commercial payors vary a lot)
Next Generation Genomics are Coming and Will Further Refine Risk
Role of mpMRI in AS

- UCSF series (n=1500)
  - Baseline multiparametric MRI
    - “negative”
      - 92% no Gleason upgrade on AS bx 3 yr
      - 84% no Gleason upgrade at 5 yr
    - “positive”
      - 53% no Gleason upgrade 3 yr
      - 35% no Gleason upgrade at 5 yr

- Remember that systematic biopsy alone still identifies 10-15% of upgrades after MRI

Peter Carroll, personal communication
Low biopsy volumes of Gleason 3+4 behave like Gleason 3+3

Michigan group

Adverse path = T3, 4+3

Suggests 20% threshold of Gleason 4 in total biopsy volume imparts higher risk of BCR and AVP

(Short f/u)
Should ALL men with 3+4 be treated immediately? NO!

- PIVOT and SPCG4 show small benefit to treatment, mainly in PSA>10, high risk, and palpable disease

- Delayed surgery does not affect mortality (ProtecT) and mildly affects rate of metastasis

- 3+4 alone adds little risk (1 CAPRA point); use multiple variables instead

- Volume of disease rather than grade alone is a better predictor of adverse pathology; single core confers no increased risk
  - If 3+4 is <33% core volume or <50% single core, no upgrade to adverse path seen
Should ALL men with 3+4 be treated immediately? NO!

- ProtecT PRO QOL demonstrated that far more patients have side effects than benefit from treatment
Should SOME men with 3+4 be treated immediately? YES!

- **Who?**
  - PSAD > 0.15
  - PIRADS-5 on mpMRI
  - High core volume
  - Adverse genomic evaluation
  - Certain histology (intraductal, cribiform)
AUA 2018: Hot topic!

- Multiple debates about the controversy AS vs intervention in 3+4 disease
- Abstracts supporting AS for favorable intermediate risk disease from MSKCC and Australian registry
- Abstracts supporting use of genomic testing to determine AS suitability
- Abstracts showing that delayed treatment does not lead to increase in biochemical recurrence
AS for 3+4 PCa: Recommendations

- Refined risk allows selected patients to be on AS
  - Low PSAD, low volume 3+4, low risk genomics, favorable MRI, [favorable confirmatory bx]
- Build a portfolio of info (i.e. a retirement portfolio)
  - Base decisions on the whole, not any one parameter
- Counsel patients on QOL
- Patients have varying tolerance of risk – be sensitive to this (the glass is more than half full)
• Remember, AS means delayed treatment remains an option without a significant increase in risk of progression/death
  – Oncologic risk is small and therapeutic benefit is modest

• Realize that disrupters are coming (or here)
  • Decreased detection due to policy in place
  • Imaging is increasingly helpful (mpMRI)
  • Focal therapy
  • Whole exome/genome sequencing for tumors/patients
“Medicine is a science of uncertainty and an art of probability”

Sir William Osler