Hormone Therapy In High Risk Prostate Cancer

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Disclosures

• None
Before Anything Else..

• The most critical force in the equation in treating high risk is screening
• Screening can detect high risk early
• Earlier high risk is highly curable
• The TF directive is hurting men’s chances
• My practice - 8-12 AA at all times for 30 years
• AA - twice the mortality, twice the incidence, a decade earlier
Tipping Their Hand – TF Response to AA

• We need more AA on studies

• We are concerned there is a high biopsy infection rate

• We cannot make a recommendation on screening in AA
Observing the natural history of a lethal condition in the AA community without providing available curative treatment.
The Response

- ASCO
- AUA
- ASTRO
- ABS

No Comment
The Response

• American Cancer Society – strong rebuke
Complicit
Wisdom

• In an apparently hopeless situation, pursue the most hopeful scenario

• In an apparently hopeful situation, pursue the most hopeless scenario
In an apparently hopeless prostate cancer.

- 63
  - PSA 143
  - T3b
  - 10/12 cores positive Gleason 8

- 53
  - PSA 180
  - T2c
  - 12/12 + Gleason 8
  - Multiple grossly positive pelvic nodes
In an apparently hopeful prostate cancer.

- 55
  - Gleason 3+4 in 6/12 cores
  - PSA 5
  - Vague nodule
  - MRI unilateral no ece
Defining Success in 2019

- Cure
- Quality of Life
- Cure with Quality of Life
  - ADT impacts both
Beam + ADT

CMRT + ADT

Minimalist
The Tally

• How can we define the best global (Cure and Quality of Life) treatment?
• By traditional metrics more GU and GI toxicity with CMRT
• If full spectrum QOL is included CMRT + STADT wins over Beam plus LTADT
• Minimizing ADT critical ot the Cure/ QOL standard
The Good, Bad, and Ugly

• The Good
  – OS advantage with beam
  – Remarkable local tumor response

• The Bad
  – A litany of temporary side effects
  – Loss of libido, sexual dysfunction
  – Cognitive dysfunction, 23% mental illness
  – Loss of muscle mass, metabolic syndrome

• The Ugly
  – CV death
  – Alzheimer’s
  – Personality change
  – Personality annihilation
A Success Story

• 77 treated ADT plus beam

• At fu at 1 year PSA <0.03

• No complaints
Google This American Life Testosterone

https://www.thisamericanlife.org/220/testosterone
Consent

• Ted Slolarus MD Chief of Urology AA VA
  – A big push to insist man are fully informed and consent
  – It is increasingly common that men read about ADT and turn it down, even in the face of survival benefit
  – One key piece is that 30% never recover their baseline testosterone
    • Most do get back to normal levels
ADT in High Risk

• Straightforward = Beam + ADT

• Complex = Combination + ADT
Straightforward?

CSS : 6 versus 18 months
Straightforward?

CSS Advantage: 4 %
Straightforward?

CSS 0 versus 6 mo

12%
Straightforward?

Summation 0 6 18

12%
4%
Overall Survival

HR 0.83 (95% CI 0.68-1.02), p = 0.081

Adjusted cumulative incidence of all-cause mortality (%)
Favorable High Risk (20% of HR)

- I high risk factor (not G9,10)
- PSA >20 Gleason 6
- PSA <10 Gleason 8

6-12 months sufficient
Lethal High Risk

- Hamstra
- Kishan

Lifetime ADT?
CMRT + ADT

• What is missing are hard to find?

• ADT detrimental

• ADT adds nothing

• ADT essential
What is not there

• There is nothing easier than plotting beam alone versus beam plus ADT to demonstrate ADT value

• There is nothing harder than plotting CMRT alone versus CMRT plus ADT to demonstrate value

• No only do we not have randomized trials, we have a strange mix of Combination plus “HUNCH” ADT
ADT Detrimental

Matched 3 High Risk Factors HR + or - ADT
+ ADT No Better in G8<15

Variable ADT

No diff in

bNED

CSS

OS

Fig. 1. Overall survival (OS), cause-specific survival (CSS), and biochemical progression-free survival (BPFS) for all patients at 7 and 10 years.
OS

• In a massive database dive Harvard reports no overall survival advantage with CMRT
High Risk ADT

FHR  UHR  LHR

MERRICK  RADAR  UM  MERRICK ASCENDE  RADAR  UM  KISHAN
High Risk ADT
Radical School 6 and Out

- FHR
- UHR
- LHR

4-6
ECE
on
MRI
Dan Hamstra Device
CMRT / ADT in High Risk

- Favorable high risk 0
- Mid High risk 6
- Lethal high risk - probably 12 CMRT a must
KISHAN Gleason 9,10 Mets Free
UM Gleason 9,10 Prostate Cancer Death
Cure with Quality of Life: The Functional Anatomy Approach

Lancet Oncology May 2016
Cure and QOL

• Vessel Sparing
  – 2/3 combination
  – At 5 years 90% self report ability to be sexually active
  – No difference between combo, beam and ADT
  – Very low Grade 3 GU GI
Head to Head

ADT

DERT

COMBINATION
Tally

• Cure and QOL is the modern definition of success
• ADT should be minimized
• ADT essential with beam, limited role with CMRT
• If the full QOL impact of therapy is measured CMRT with STADT better than Beam plus LTADT
• MRI is not optional - it is essential in high risk
Prognosis Spectrum

Intermediate Risk

FIR  UIR  HRIR  FHR  UHR  LHR

Favorable  Unfavorable  High Risk  Favorable  Unfavorable  Lethal

High Risk
# Intermediate Risk

<table>
<thead>
<tr>
<th></th>
<th>FIR</th>
<th>UIR</th>
<th>HRIR</th>
</tr>
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<tbody>
<tr>
<td>FAVORABLE</td>
<td>T2b/c OR Gleason 7 OR PSA 10 - 20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNFAVORABLE</td>
<td>&gt;1 int. risk factor OR Gleason 4+3 OR &gt;50% biopsies +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIGH RISK</td>
<td>2 or 3 int. risk + &gt;50% biopsies +</td>
<td></td>
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</tr>
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</table>

- **FAVORABLE**
  - 1 int. risk factor
  - Gleason 3+4 Or less
  - < 50% Bx. +

- **UNFAVORABLE**
  - >1 int. risk factor
  - Gleason 4+3
  - >50% biopsies +

- **HIGH RISK**
  - 2 or 3 int. risk + >50% biopsies +
Intermediate Risk

T2b/c  OR  Gleason 7  OR  PSA 10 -20

FIR  UIR  HRIR

HARVARD  6  HARVARD  ASCENDE  DART
# High Risk

<table>
<thead>
<tr>
<th>FHR</th>
<th>UHR</th>
<th>LHR</th>
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<tbody>
<tr>
<td><strong>Favorable</strong></td>
<td><strong>Unfavorable</strong></td>
<td><strong>Lethal</strong></td>
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<tr>
<td>Gleason 8</td>
<td>Gleason 8-10</td>
<td>Gleason Grade 5</td>
</tr>
<tr>
<td>single core</td>
<td>or</td>
<td>GS 9, 10 or tertiary</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>Hamstra - XRT</td>
</tr>
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<td></td>
<td>or</td>
<td>Partin - surgery</td>
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<td></td>
<td>PSA &gt;20</td>
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Lethal PCa

• Conforms to a sequential model of metastasis, not horse is out of the barn
• There is a window of opportunity, when intensive local therapy is life saving
• Lethal Pca must be ablated, not treated
• They do not require more ADT, they require verified dose escalation
ADT/Brachytherapy

• Must reckon with great results with short course ADT

• Must reckon with great results with no ADT

• MDs who do high quality brachytherapy see ADT sparing as a major advantage

• (cure and QOL)
Fig. 2. A dose–response comparison between radiation dose escalation subgroups of men treated with 6 months neo-adjuvant AS versus 6 months neo-adjuvant AS followed by 12 months adjuvant AS (i.e. 18 months in total) at 6.5 years post randomisation. The error bars represent standard errors. See the electronic supplement for comment regarding the 74 Gy group.
Intermediate Risk

T2b/c       OR       Gleason 7       OR       PSA 10-20

FIR       UIR       HRIR
Head to Head

ADT a much bigger advantage than DERT
  DERT advantage 5\%bNED
  ADT advantage 20\%bNED
  (Stoyanova)

ADT is critical to outcomes with Beam in any form of aggressive Pca
  Never treat aggressive PCa with beam alone
  Exception: Old age and comorbidity

Combination + limited ADT can accomplish more than ADT plus beam
Head to Head

ADT

COMBINATION

DERT
Cure with Quality of Life: The Functional Anatomy Approach

Lancet Oncology May 2016
Cure and QOL

• Vessel Sparing
  – 2/3 combination
  – At 5 years 90% self report ability to be sexually active
  – No difference between combo, beam and ADT
  – Very low Grade 3 GU GI
Humanity

• Refusing hormones with high risk disease
  – Case 1
  – Case 2
Alright doc you made the case
The only way we can erase
You say in time I’ll do the mojo dance
With fire in the belly and in my pants
The reaper lives on Mr T
If we want to beat him. Ill agree
Pull the plug to save my life
And the Reaper will put don his knife
Doc doc doc doc doc doc please don’t make me do this
Doc doc doc doc doc please don’t put me through this

You’re gonna knock this king from my throne
You’re gonna take the wind out of my cyclone
I’ll have a B cup all my own
You’ll take away my funnin’ bone
I’ll lose all my muscle tone
And all the manly hair I’ve grown
And I can hear myself just piss and moan
Cause you took away took away
Testosterone Testosterone
Best drug I’ve ever know
I’ve tried a few
I’m here to say
Testosterone
Can make my day and night
It’ll make my day and night
Summary

• ADT is a critical tool in the treatment of high risk prostate cancer
  – More important than dose escalated RT, less important than Combination therapy

• It is possible the dominant mechanism is local tumor response

• Should be limited to minimum due to profound side effects and toxicities
Could This Possible Be True?

- QOL the same for end stage, palliative and curative stage prostate cancer
- Major sexual dysfunction not addressed
- ADT is more prevalent in localized
Sexual Function

A

Men (%)

Sexual function

- Poor or very poor erections
- Poor or very poor orgasm ability
- Erections not firm
- Erections not reliable
- Poor or very poor sexual function
- Overall sexual problem

Stage I or II
Stage III
Stage IV
General Well Being

A graph illustrates the mean scores for General Well Being across different age groups (55, 55-64, 65-74, 75-84, >85) for stages I or II, III, and IV. The mean scores are represented as bars with error bars indicating variability.
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