Intermediate, High Risk and Oligometastatic Disease: Radiation Options

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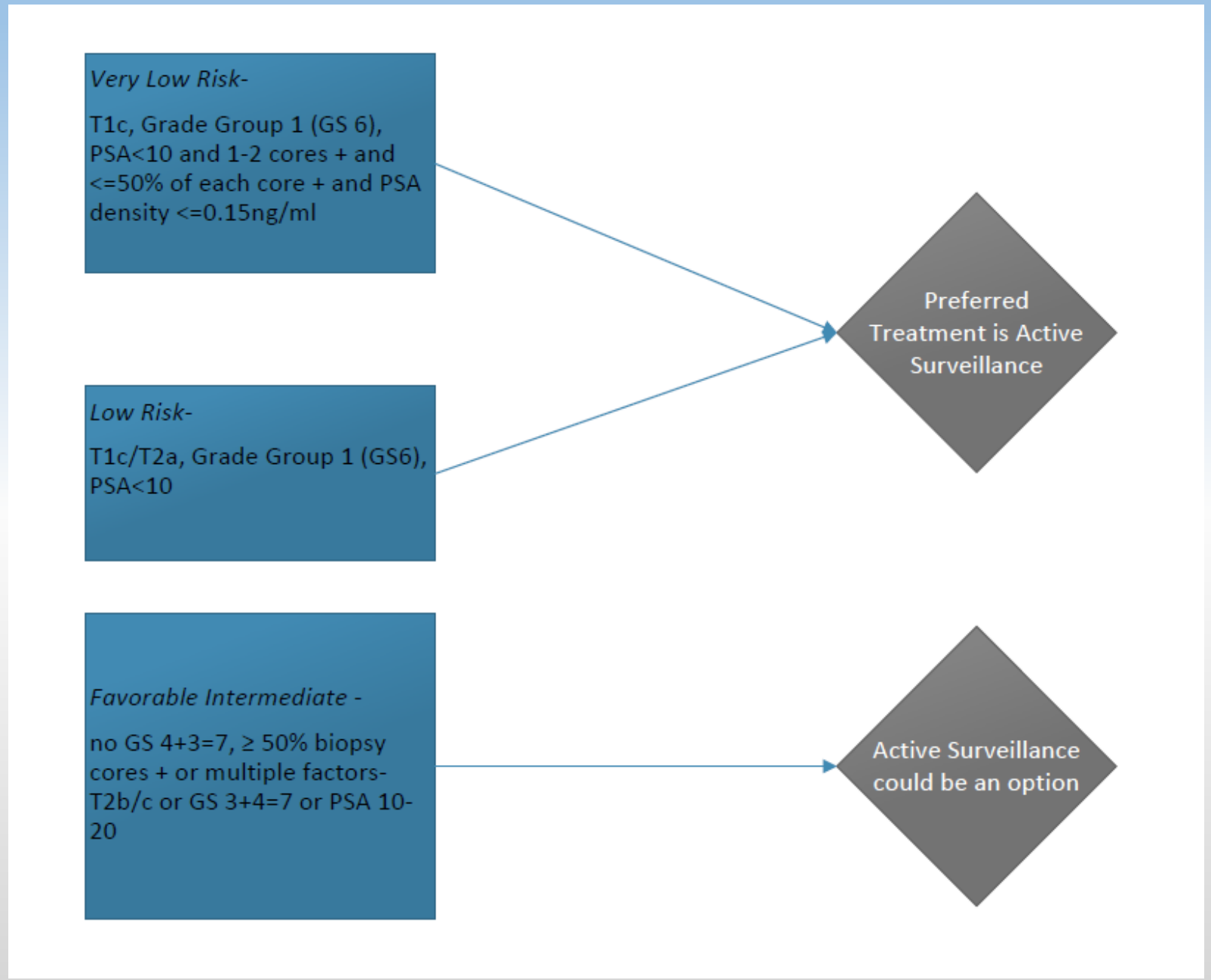
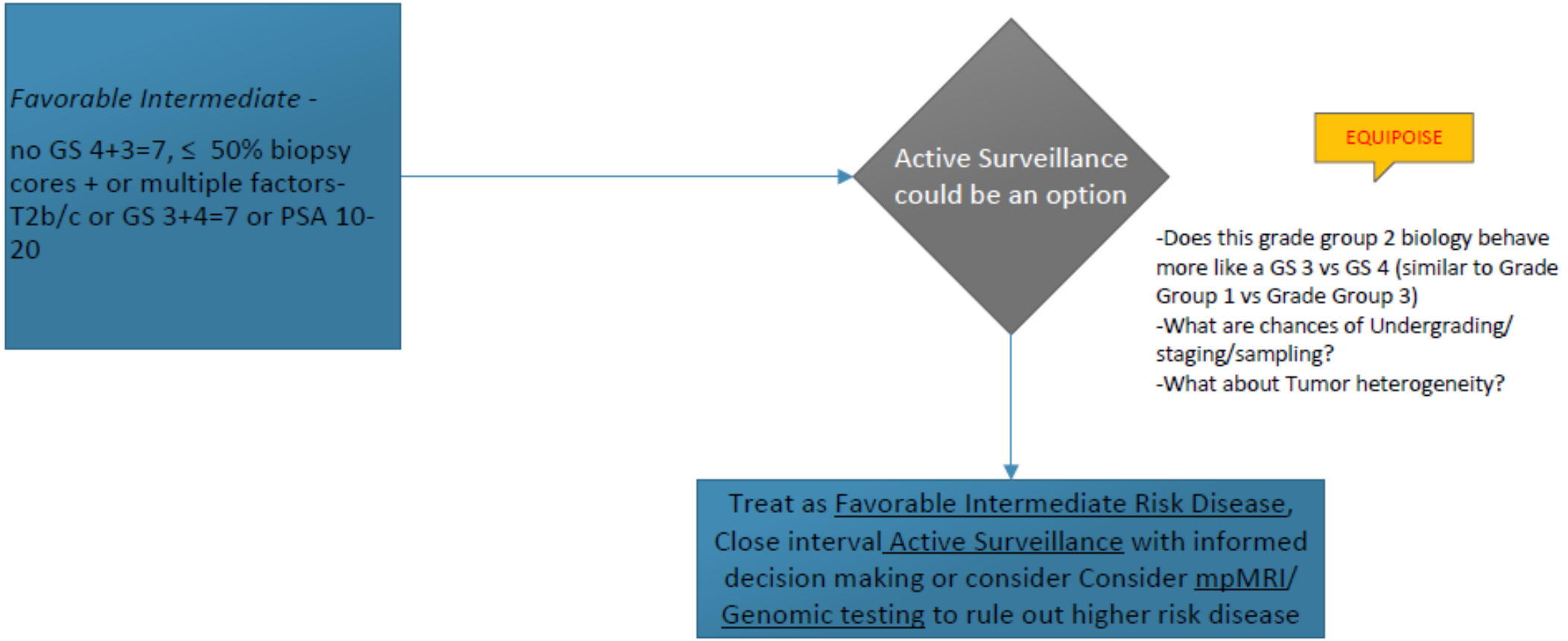
- I have no disclosures. This presentation represents my opinions and the views expressed do not necessarily represent the Armed Forces Radiobiology Research Institute, Uniformed Services University, U.S. Department of Defense or the U.S. government.

Intermediate Risk

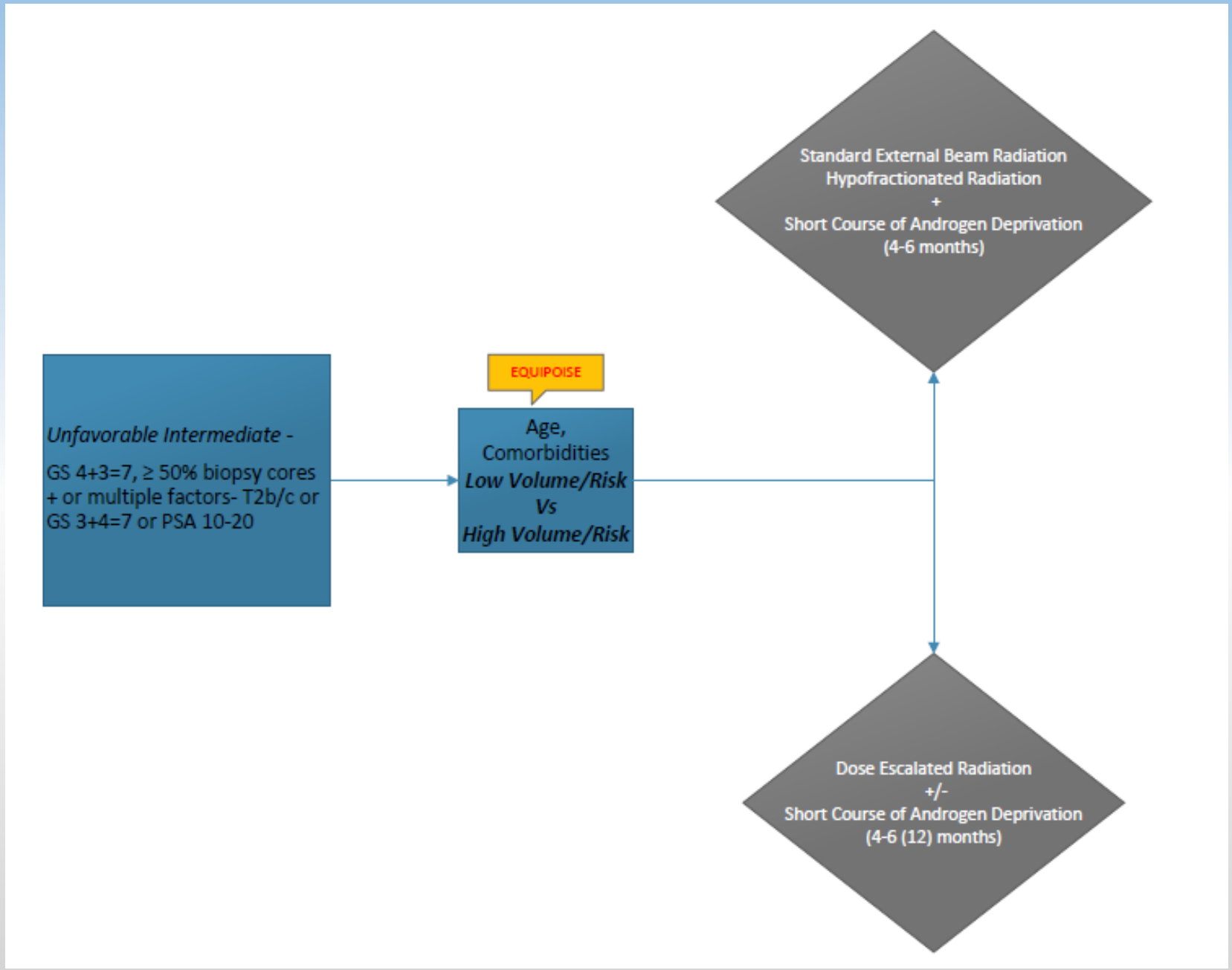
- Take home points
  - Favorable intermediate may behave more like low risk
    - More disease progression and metastases with active surveillance than treatment
  - Unfavorable intermediate get “treatment intensification”
    - “at least 2 modalities”
  - Uncertainty in use of MRI to upstage


Very Low Risk-
T1c, Grade Group 1 (GS 6), PSA<10 and 1-2 cores + and <=50% of each core + and PSA density <=0.15ng/ml
Low Risk-
T1c/T2a, Grade Group 1 (GS6), PSA<10
Preferred Treatment is Active Surveillance
Favorable Intermediate -
no GS 4+3=7, ≥ 50% biopsy cores + or multiple factors- T2b/c or GS 3+4=7 or PSA 10-20
Active Surveillance could be an option


Favorable Intermediate -
no GS 4+3=7, ≤ 50% biopsy cores + or multiple factors- T2b/c or GS 3+4=7 or PSA 10-20
Active Surveillance could be an option
EQUIPOISE
-Does this grade group 2 biology behave more like a GS 3 vs GS 4 (similar to Grade Group 1 vs Grade Group 3)
-What are chances of Undergrading/ staging/sampling?
-What about Tumor heterogeneity?
Treat as Favorable Intermediate Risk Disease, Close interval Active Surveillance with informed decision making or consider Consider mpMRI/ Genomic testing to rule out higher risk disease

When is active surveillance an option for GS 3+4

- PROTECT- Low/Favorable Intermediate Risk has <1% prostate cancer specific mortality at 10 years.
  - Criteria for localized disease by clinical exam, bone scan for PSA 10-19, ineligible if PSA>20, ability to receive RT or surgery.
  - GS 6~77%, GS=7~21%, GS=8-10~3% median PSA~4.8 ng/ml
- Higher risk of metastases compared with definitive treatment
  - Role of MRI and genomics in decision making
  - May result in treating with more intensification
    - Tumor stage shifts in up to 50% with 30% potentially in higher risk group

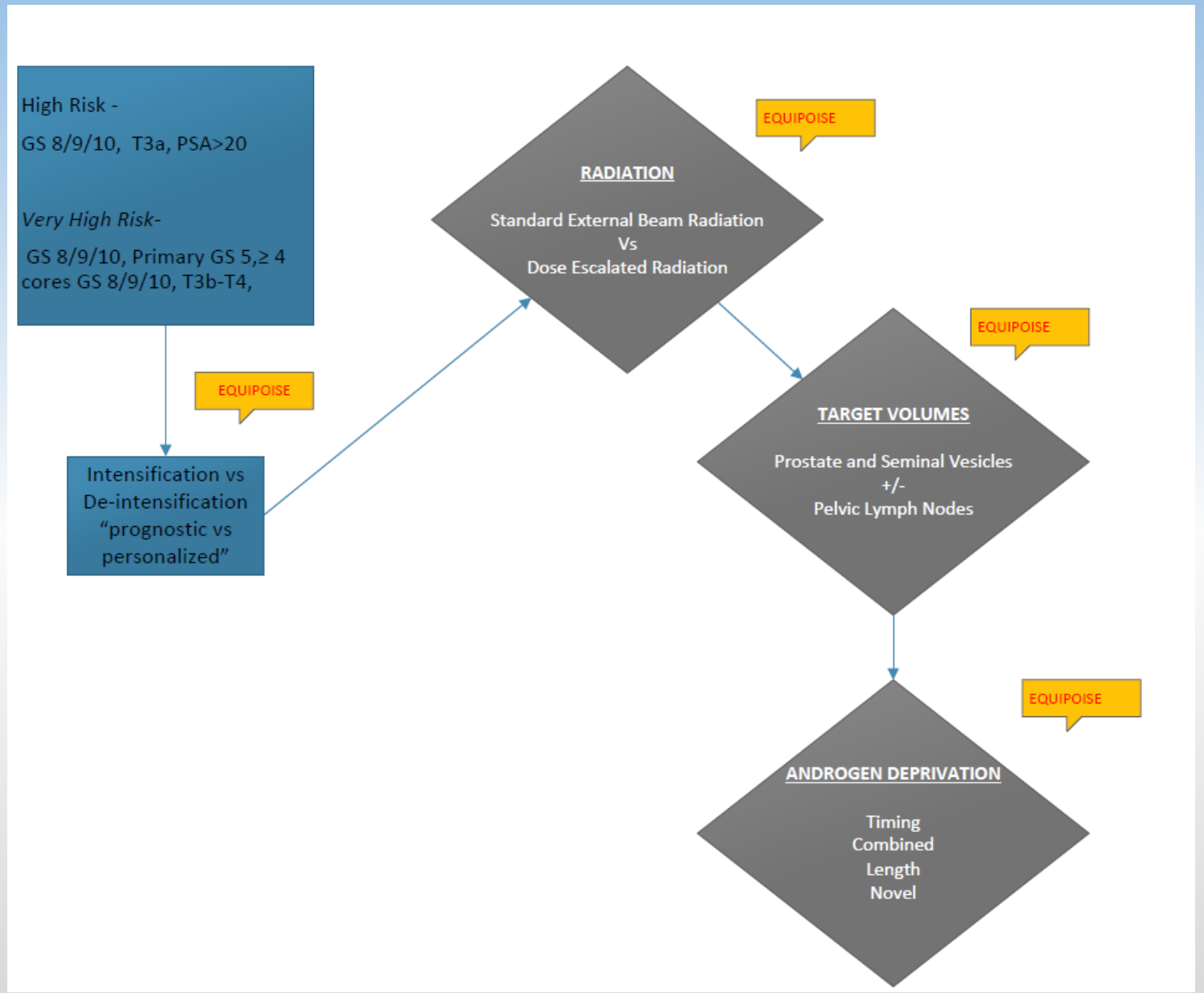

Standard External Beam Radiation
Hypofractionated Radiation
+
Short Course of Androgen Deprivation
(4-6 months)
EQUIPOISE
Unfavorable Intermediate -
GS 4+3=7, ≥ 50% biopsy cores + or multiple factors- T2b/c or GS 3+4=7 or PSA 10-20
Age, Comorbidities
Low Volume/Risk
Vs
High Volume/Risk
Dose Escalated Radiation
+/-
Short Course of Androgen Deprivation
(4-6 (12) months)

When does unfavorable intermediate risk need dose intensification?

- All options available- surgery , EBRT and brachytherapy
- Recommend short course of androgen deprivation
- Brachytherapy may provide dose escalation without need for androgen deprivation- select patients could receive monotherapy
- Results of mpMRI may show upstaging or potential undersampling
  - Tumor stage shifts in up to 50% with 30% potentially in higher risk group
    - bGS 4+3=7 upgraded to pGS 8~40%, downgraded to pGS=6~23%

High Risk and Very High Risk

- Take home points
  - More extensive disease
  - Worse prognosis (GS 9-10>GS 8)
  - Multimodal approach
    - Uncertainty in optimal approach to local disease (micrometastatic)
      - MAX RT vs MAX Surgery
      - Dose escalation
      - Target
      - Androgen Deprivation
      - Novel Agents


High Risk -
GS 8/9/10, T3a, PSA>20
Very High Risk-
GS 8/9/10, Primary GS 5,≥ 4 cores GS 8/9/10, T3b-T4,
EQUIPOISE
Intensification vs De-intensification "prognostic vs personalized"
RADIATION
Standard External Beam Radiation
Vs
Dose Escalated Radiation
EQUIPOISE
TARGET VOLUMES
Prostate and Seminal Vesicles
+/-
Pelvic Lymph Nodes
EQUIPOISE
ANDROGEN DEPRIVATION
Timing
Combined
Length
Novel
EQUIPOISE

When does high risk need radiation treatment intensification?

- ASCENDE-RT (8 months neoadjuvant + 4 months concurrent/adjuvant with dose escalated whole pelvis EBRT+ EBRT boost and whole pelvis EBRT+brachytherapy)
  - 9 year biochemical recurrence
    - 24% improvement for intermediate risk (mostly unfavorable)
    - 20% improvement for high risk disease
    - No survival advantage (yet)
- High Volume vs Low Volume
  - Number of cores positive (impact of MRI guided on upstaging)
  - GS 4 % of core
  - GS 5 (impact of primary, secondary, tertiary)
  - Perineural invasion
  - Integrate with mpMRI

What is the radiation dose and fractionation?

- Standard/Hypofractionation (EQD2~78Gy)
  - 2-3 Gy fractions for 60-80 Gy
  - 45-50.4 Gy to elective lymph nodes (60-70 Gy to + lymph nodes)

- Dose Escalation (EQD2~90-95 Gy)
  - EBRT + brachytherapy
    - 45-50.4 Gy in 1.8-2 Gy fractions externally + isotope specific boost dose
  - Stereotactic (Ablative) Body Radiation Therapy: SBRT/SABR
    - 7-8 Gy per fraction for 5 treatments, every other day
    - 6-7 Gy per fractions for boost
    - On clinical trial or registry only

What are the acceptable target volumes?

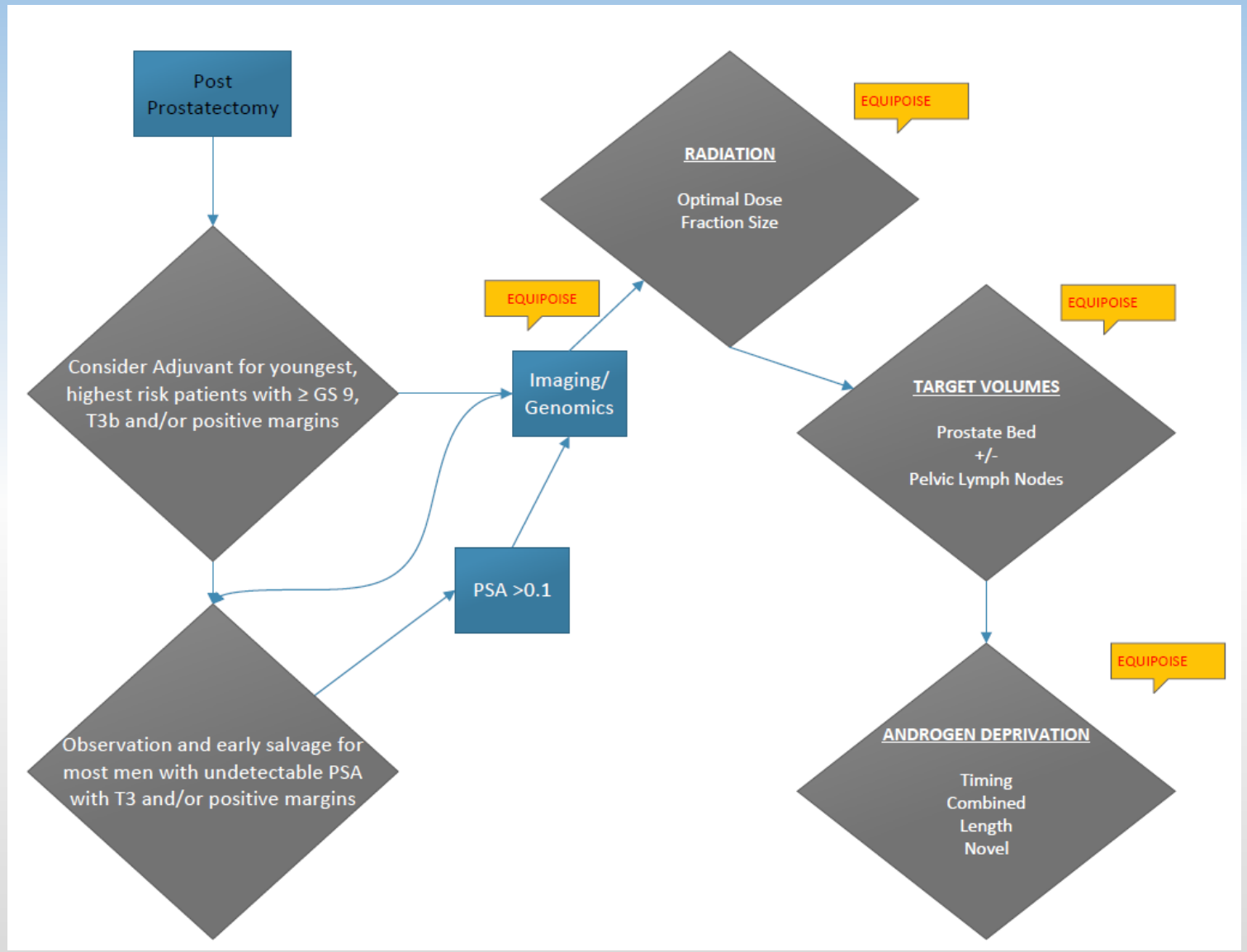
- Prostate and seminal vesicles (proximal 1 cm)
- Target margins to accommodate movement based on treatment techniques (3mm posterior to 8 mm)
- When to add the pelvic lymph nodes?
  - 2 randomized trials show no advantage to pelvic nodal irradiation
  - Reasonable for high enough risk (LN risk calculator)

What are the optimal androgen deprivation protocols?

- Androgen Deprivation potentiates radiation damage by blocking DNA repair
- Improvement in survival in intermediate and high risk patients
  - In little vs none
  - In little vs lot in high risk patients
  - External beam dose escalation ADT still benefits
- Should optimal androgen deprivation include anti-androgen?
  - RTOG trials included combined androgen blockade
  - Additional agents- docetaxel, second generation anti-androgens, PARP inhibitors
- How long should ADT
  - **4-6 months** for intermediate
  - **24-36 months for high** risk~**18 months** may be not inferior
  - With Brachytherapy **6-12 months** may be reasonable for high risk (maybe just **4 months** if not doing whole pelvis)

Post-Prostatectomy Radiation

- Take Home Points
  - High Quality Surgery vs High Quality Radiation data not easy to compare
  - Most patients can delay immediate adjuvant radiation (treat young GS≥9 and SV and positive margins)
  - Need to **monitor closely** with early initiation of salvage radiation when PSA rises above 0.1
  - Addition of androgen deprivation and pelvic lymph nodes becoming more common
  - Low utilization- **ROOM for Improvement**
    - Prostatectomy only with higher prostate cancer specific mortality and metastases
    - Prostatectomy with appropriate post-surgery treatment (radiation, hormones)=no difference
    - 10-30% utilization of MAX Surgery

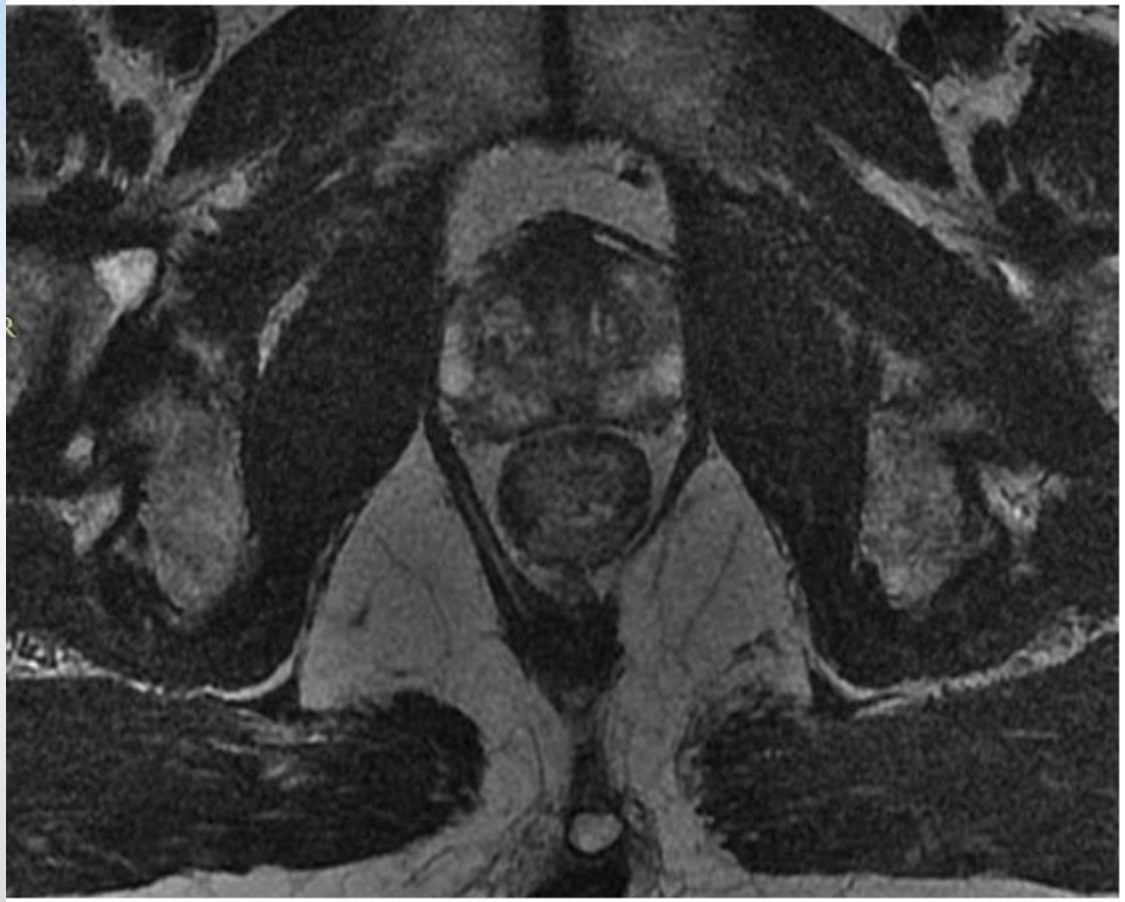

Post Prostatectomy
Consider Adjuvant for youngest, highest risk patients with ≥ GS 9, T3b and/or positive margins
Observation and early salvage for most men with undetectable PSA with T3 and/or positive margins
Imaging/ Genomics
PSA >0.1
EQUIPOISE
RADIATION
Optimal Dose
Fraction Size
EQUIPOISE
TARGET VOLUMES
Prostate Bed
+/-
Pelvic Lymph Nodes
EQUIPOISE
ANDROGEN DEPRIVATION
Timing
Combined
Length
Novel
EQUIPOISE

How can we reduce radiation side effects?

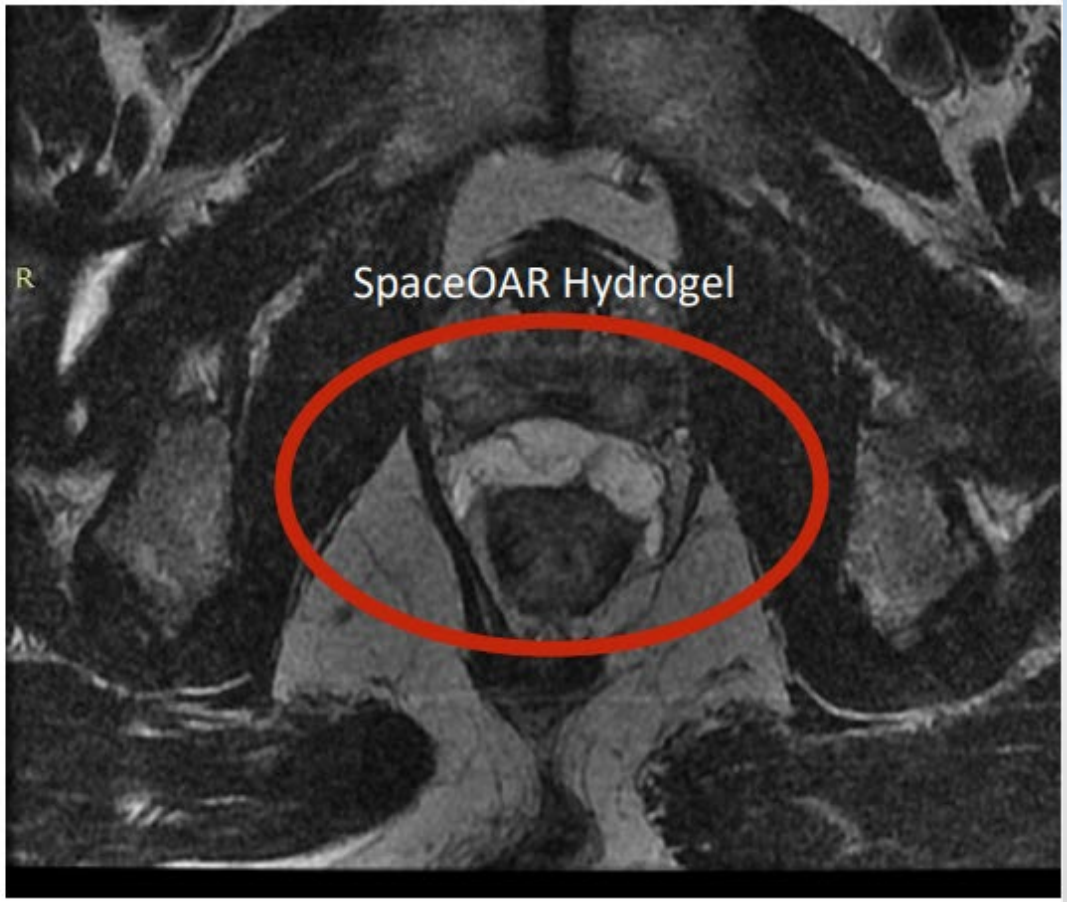
- Technology
  - Intensity Modulated Radiation Therapy
  - Image Guided Radiation Therapy
  - Proton Radiotherapy
  - Stereotactic Body Radiation Therapy
- Physical
  - Space OAR- pegylated hydrogel injected between prostate and rectum

Quality of Life	Potentially Less side effects
Rectal Issues	Surgery
Erections	Radiation
Incontinence	Radiation
Urinary Bother	Surgery

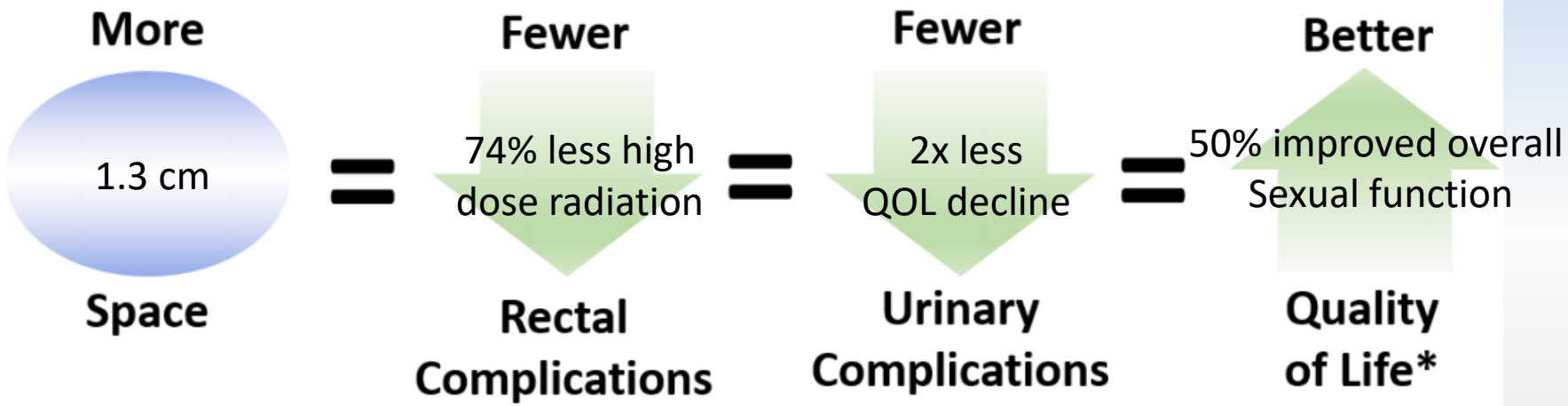
Anatomy Pre-Implant



Anatomy Post-Implant

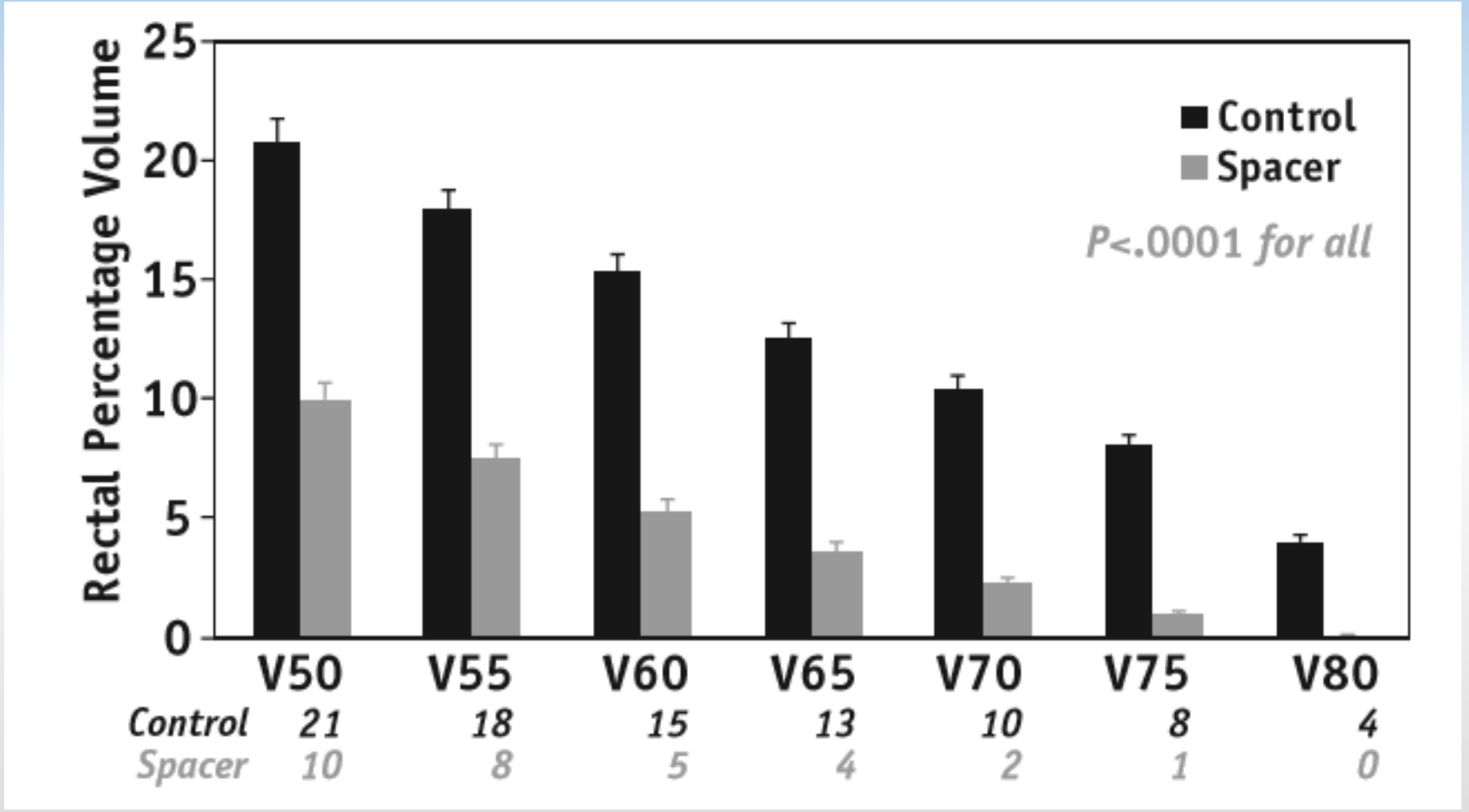


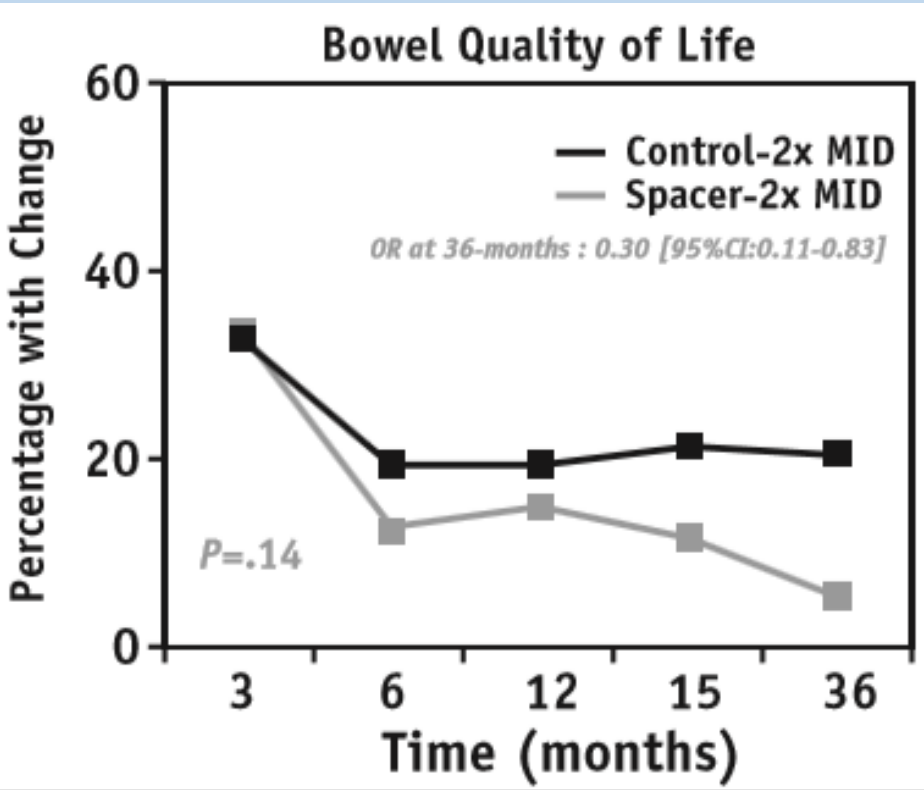
Space OAR

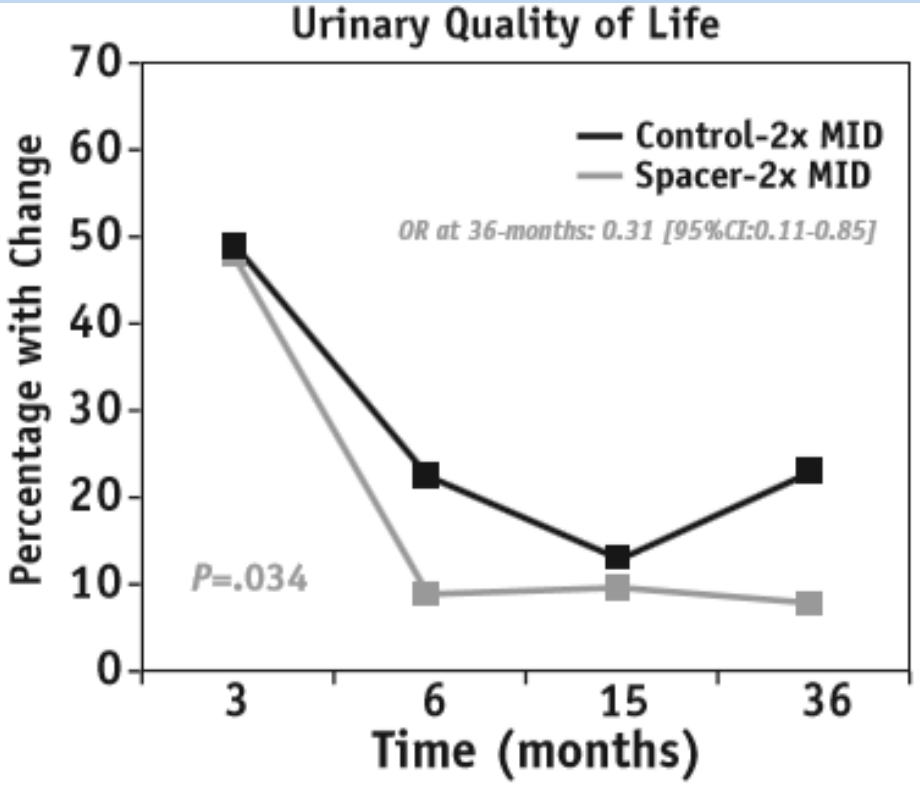


*After radiotherapy was complete, control patients experienced a clinically significant (1X MID) decline in bowel, urinary and sexual QOL 8 times more often than SpaceOAR patients.[1,2]

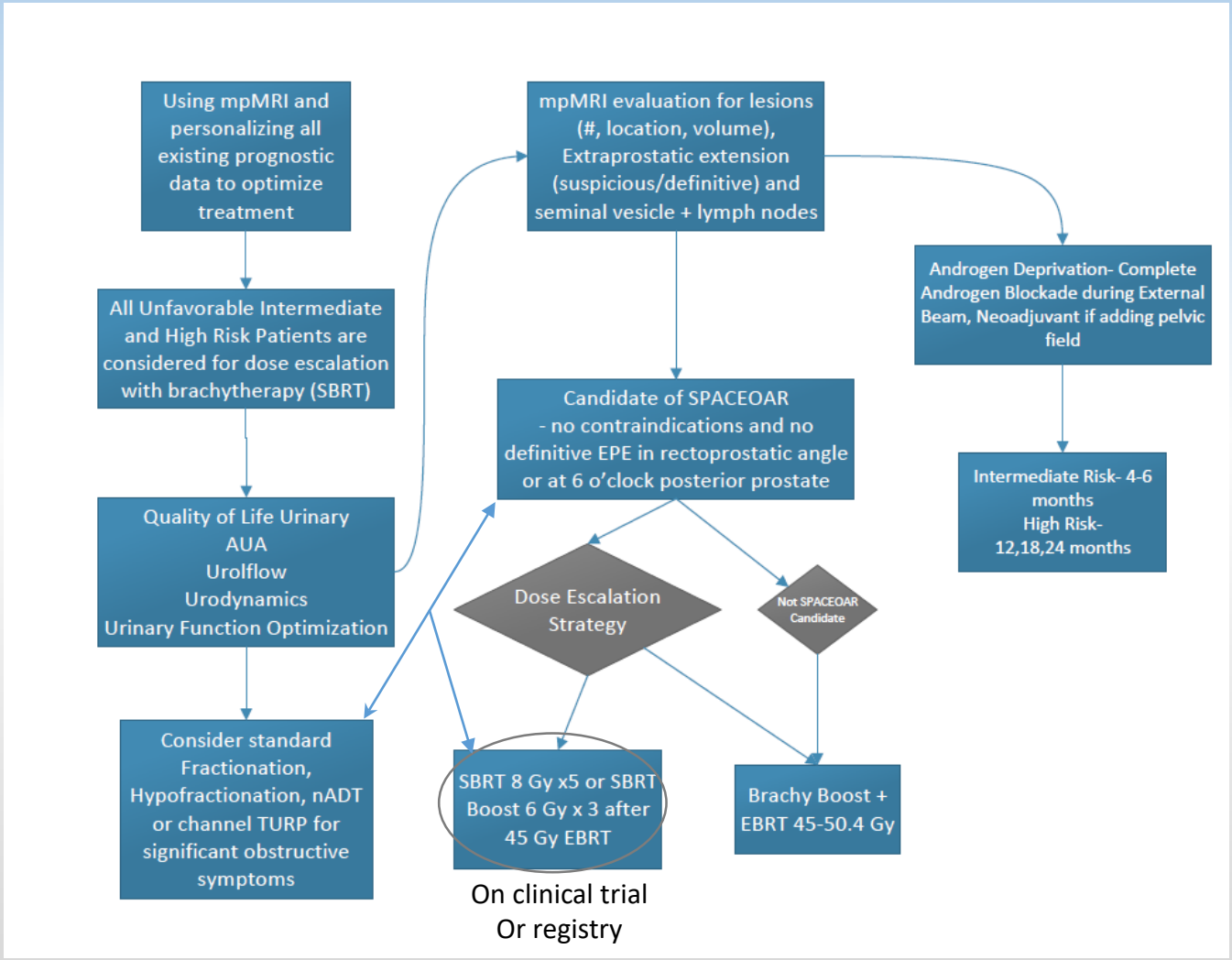
1) Hamstra D, et al. Continued Benefit to Rectal Separation for Prostate RT: Final Results of a Phase III Trial. Int J Radiation Oncol Biol Phys, Vol. 97, No. 5, pp. 976-985, 2017
2) Hamstra D, et al. Evaluation of sexual function on a randomized trial of a prostate rectal spacer. J Clin Oncol 35, 2017 (suppl 6S; abstract 69


Rectal Percentage Volume
25
20
15
10
5
0
Control
Spacer
P<.0001 for all
V50
V55
V60
V65
V70
V75
V80
Control 21 18 15 13 10 8 4
Spacer 10 8 5 4 2 1 0


Bowel Quality of Life
Percentage with Change
60
40
20
0
Control-2x MID
Spacer-2x MID
OR at 36-months : 0.30 [95%CI:0.11-0.83]
P=.14
3
6
12
15
36
Time (months)


Urinary Quality of Life
Percentage with Change
70
60
50
40
30
20
10
0
Control-2x MID
Spacer-2x MID
OR at 36-months: 0.31 [95%CI:0.11-0.85]
P=.034
3
6
15
36
Time (months)

Implementation of Space OAR into practice
Current: all non-extraprostatic radiation treatments



On clinical trial
Or registry

Oligometastatic Disease

- No high quality data on metastases directed treatment
  - Phase II randomized data
- Treatment decision need to be individualized
  - Site of metastases, disease free interval, age, comorbidity
- SBRT to oligometastatic prostate cancer (less than 3 metastases) “seems” to increase the time to needing androgen deprivation therapy and “may” improve progression free survival overall survival.

- Needs to be confirmed in larger trials and registries
  - Patient selection important- PSMA, mutations, biomarkers

Johns Hopkins Experience

- 156 oligometastatic patients treated with “definitive” radiation
- Assessed for biochemical failure and time to next intervention
  - Toxicity-
    - 35% acute grade 1, 5% acute grade 2, no grade 3, 9% late toxicity
  - Local Failure- cumulative incident at 2 years of 7.4%
  - Median biochemical freedom from progression 12.9 months, 52% at 1 year
  - Median time to next intervention 21.6 months
    - Hormone sensitive vs castrate resistant different outcomes
- Metastasis directed therapy has promise, patient selection will impact efficacy.