2017 PCRI Annual Conference

LAX Marriott

Sept. 8 -10, 2017

http://pcri.org/2017-conference#speakers-topics

Main Topics

Topic	Presenter
• Prostatitis and Inflammation	J. Curtis Nickel MD
• Advanced PCa and Clinical Trials	Luke Nordquist MD
• High Dose Brachytherapy (HDR BT)	Jeffrey Demanes MD
• Axumin PET Scans	Jennifer Kujak MD
• Testosterone Therapy	John Mulhall MD
• The Pathology Report	Jonathan Epstein MD
• Durable Remission	Charles Snuffy Myers
• PET CT Imaging and Prostate MRI	Fabio Almeida MD
• Active Surveillance	Bela Denes MD
• Immune Therapy	Richard Lam MD
• Radiation Therapy	Michael Steinberg MD

Conference Leaders

Mark Moyad MD
Director of Preventive & Alternative Medicine
Michigan U.

Mark Scholz MD
Medical Director of PROS, founder of PCRI, author of Invasion of the Prostate Snatchers and The Key to Prostate Cancer

Prostatitis and Inflammation

J. Curtis Nickel MD

- Ongoing cannabis clinical trial in Canada – outcomes to be presented at next AUA conference
- Prostatitis (P) – no effective diagnosis or treatment to date. Only 8% due to infection.
- Inflammation is diagnosed by histology. 5 categories: I – acute; II – chronic; III – chronic +pain; IV –
- REDUCE trial demonstrated inflammation does not lead to PCa. Patients with P. should not have RT.
- Recommends 2 supplements for P: quercetin and rye pollen extract (Cernilton)

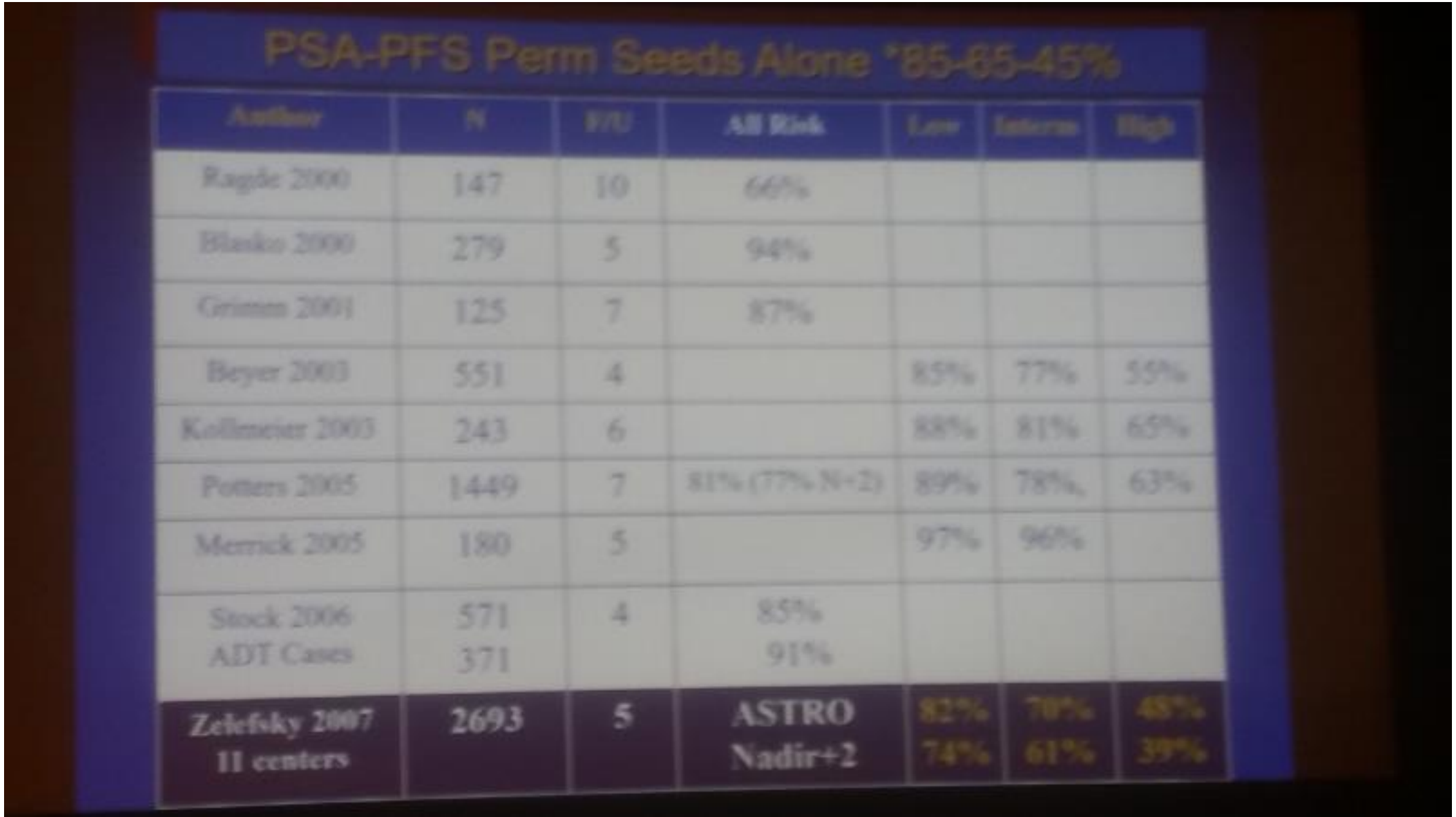
Advanced PCa and Clinical Trials

Luke Nordquist MD

High Dose Brachytherapy (HDR BT) Jeffrey Demanes MD

- Method involves temporary (20 min) insertion of seeds via catheters.
- Iridium 192 seeds - location can be optimized with visualization tools.
- Deliver high dose to target minimizing radiation to surrounding tissue without expanding treatment volume.
- Very high cure rates with added dose of EBRT. Very low toxicities.
- Sexual function comparable to normal decline.
- Uses SpaceOar infrequently as the EBRT dose is relatively low.
- Only 48% of HDR BT procedures received “excellent” score => patient needs to find the best provider. Recommends Dr. Greg Merrick in W. Va, Dr. Shu (UCSF).
- Dr. Demanes will provide a 2-hr consult.

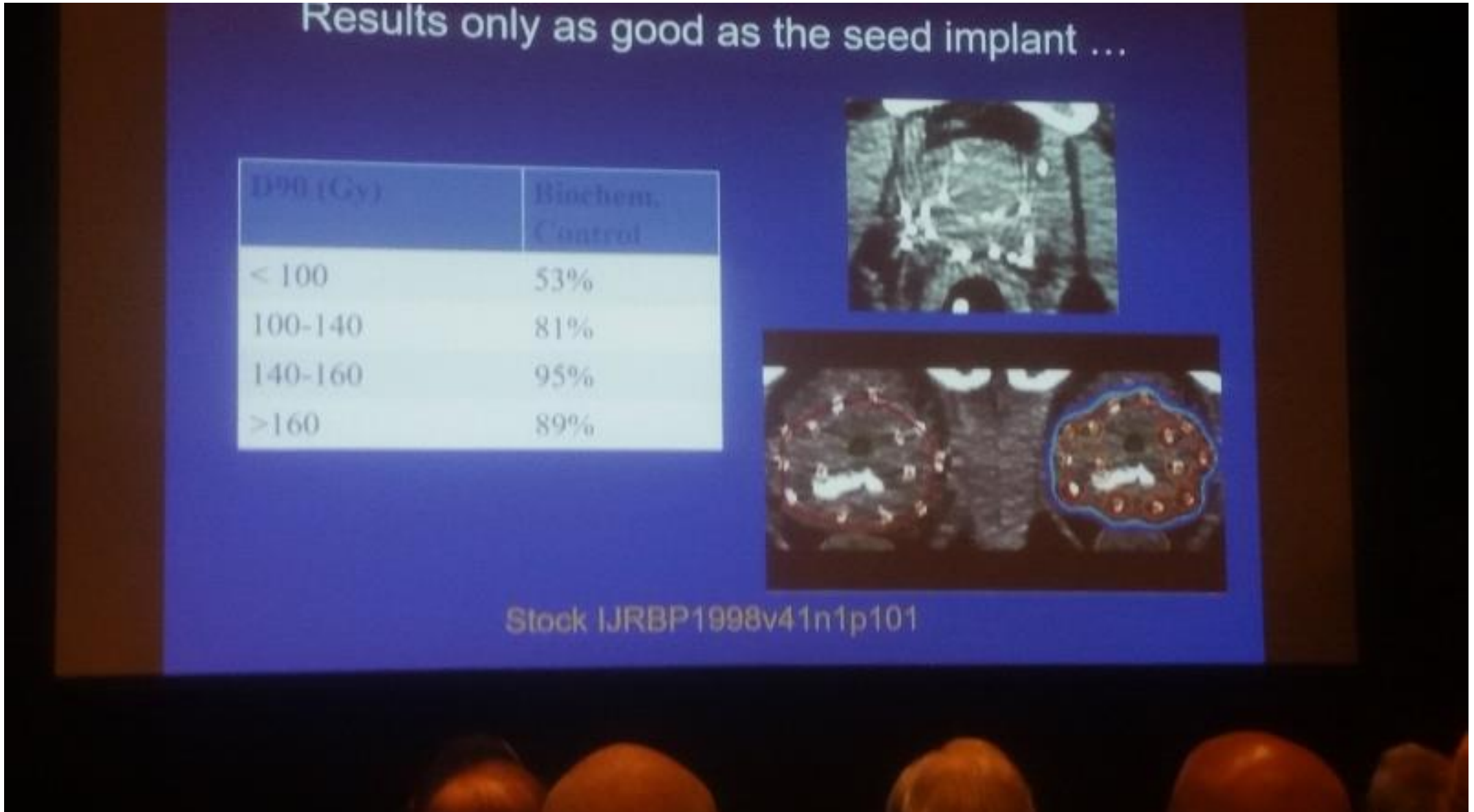
5-year Progression-free Survival – Seeds alone

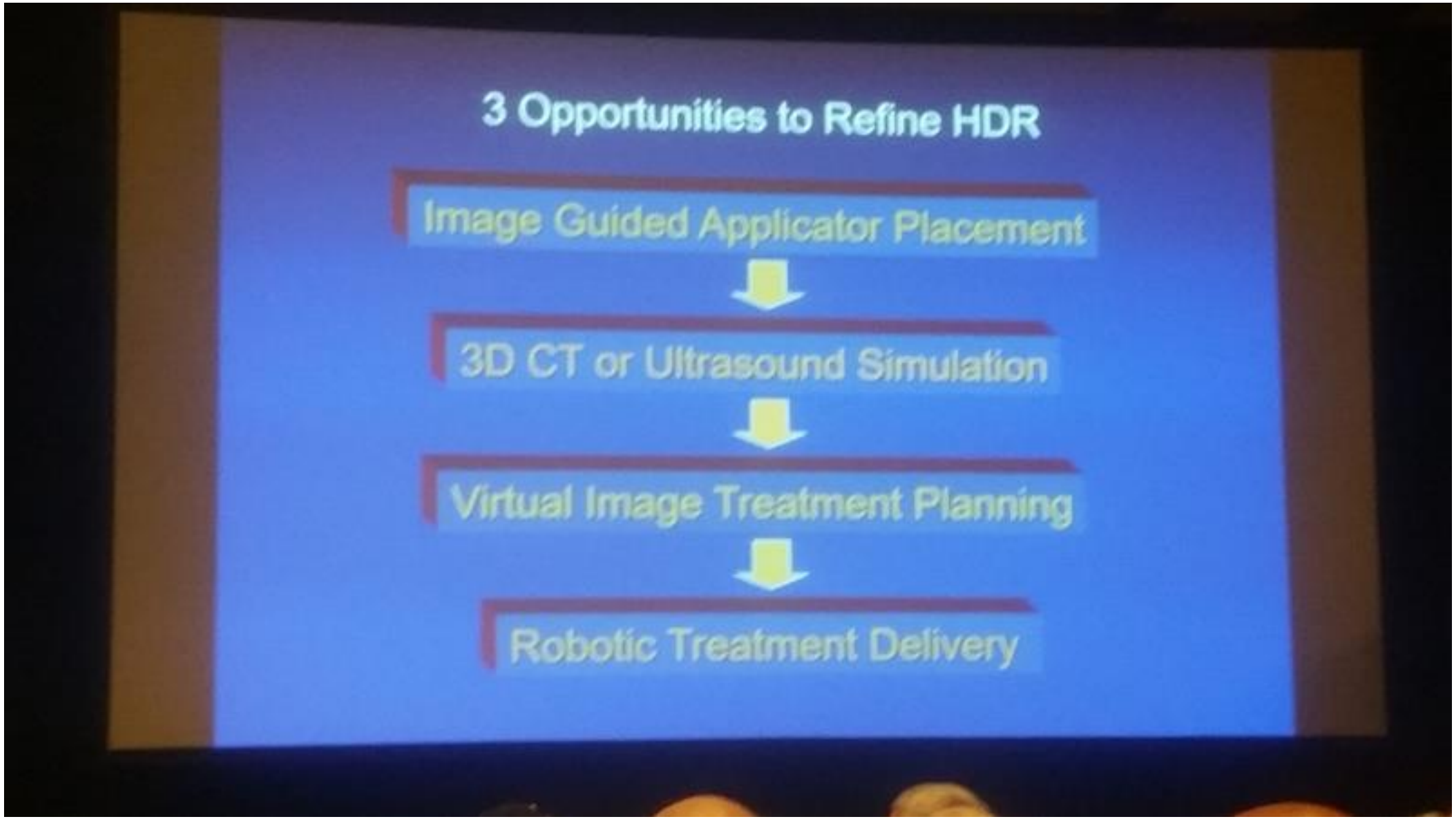


PSA-PFS Perm Seeds Alone '85-65-45%

Author	N	F/U	All Risk	Low	Interm	High
Ragde 2000	147	10	66%			
Blasko 2000	279	5	94%			
Grimm 2001	125	7	87%			
Beyer 2003	551	4		85%	77%	55%
Kollmeier 2003	243	6		88%	81%	65%
Potters 2005	1449	7	81% (77% N+2)	89%	78%	63%
Merrick 2005	180	5		97%	96%	
Stock 2006 ADT Cases	571 371	4	85% 91%			
Zelefsky 2007 11 centers	**2693**	**5**	**ASTRO Nadir+2**	**82% 74%**	**70% 61%**	**48% 39%**

Seeds planted v. well on Right…

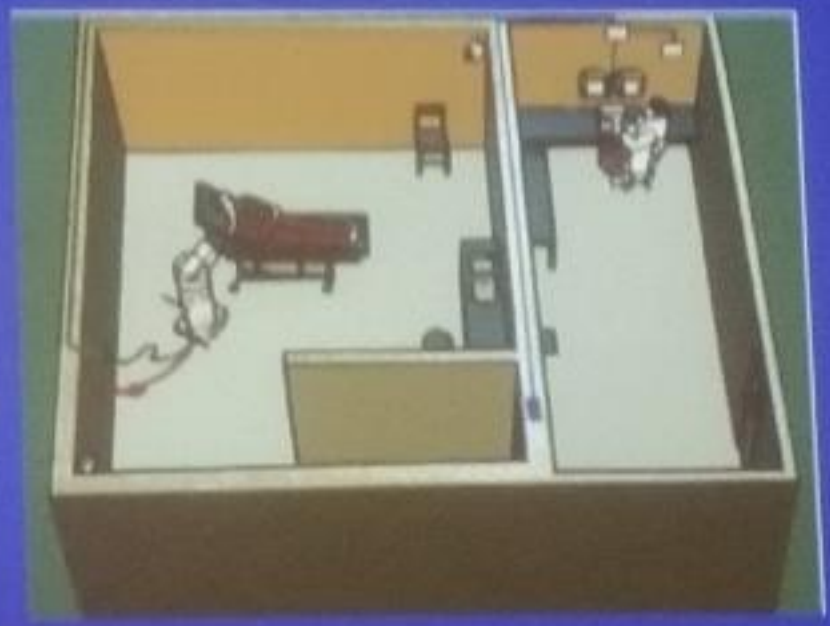


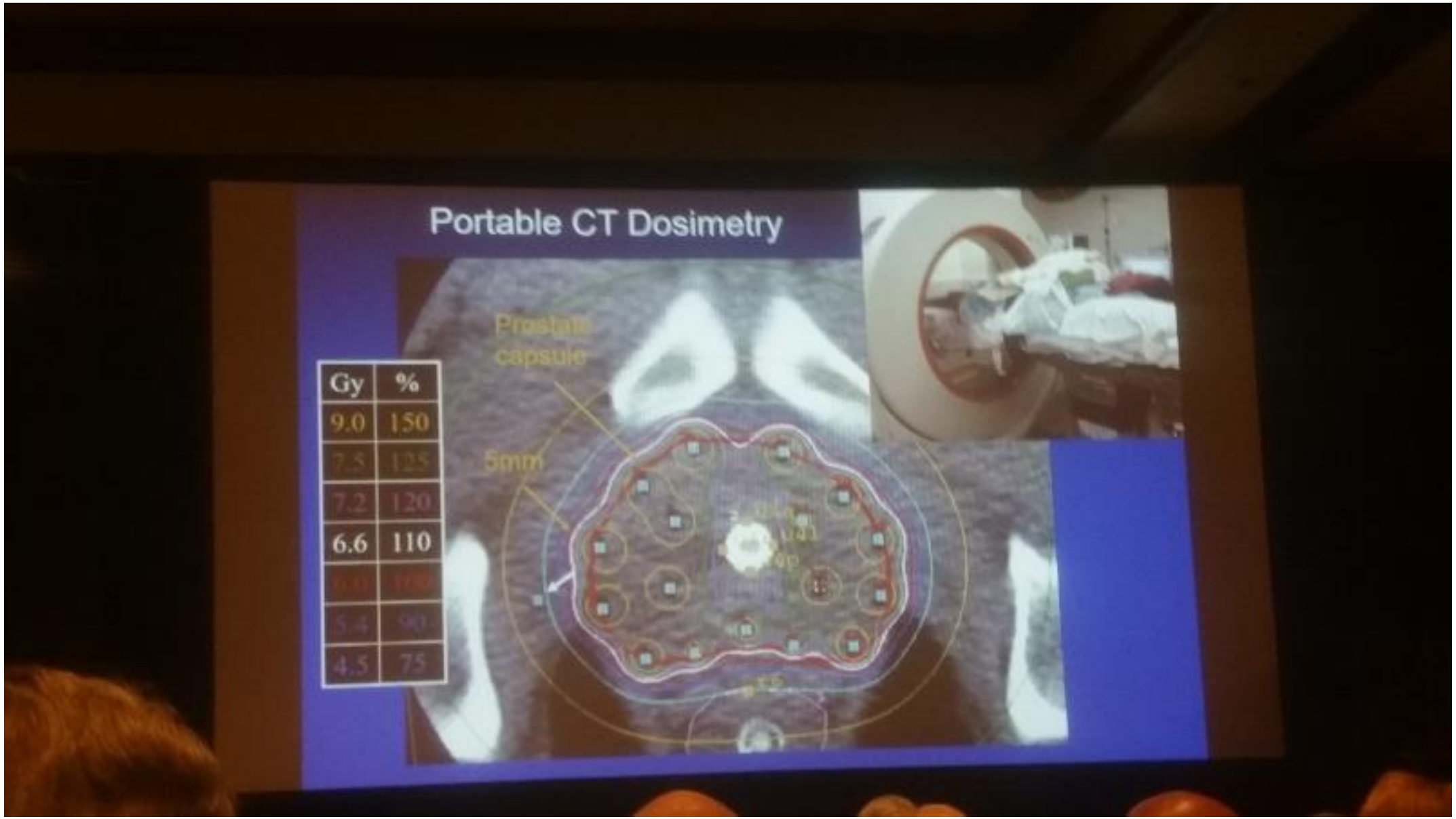

3 Opportunities to Refine HDR
Image Guided Applicator Placement
3D CT or Ultrasound Simulation
Virtual Image Treatment Planning
Robotic Treatment Delivery

HDR Temporary Robotic Source Insertion

Precise and Reliable

Multi-use Iridium-192



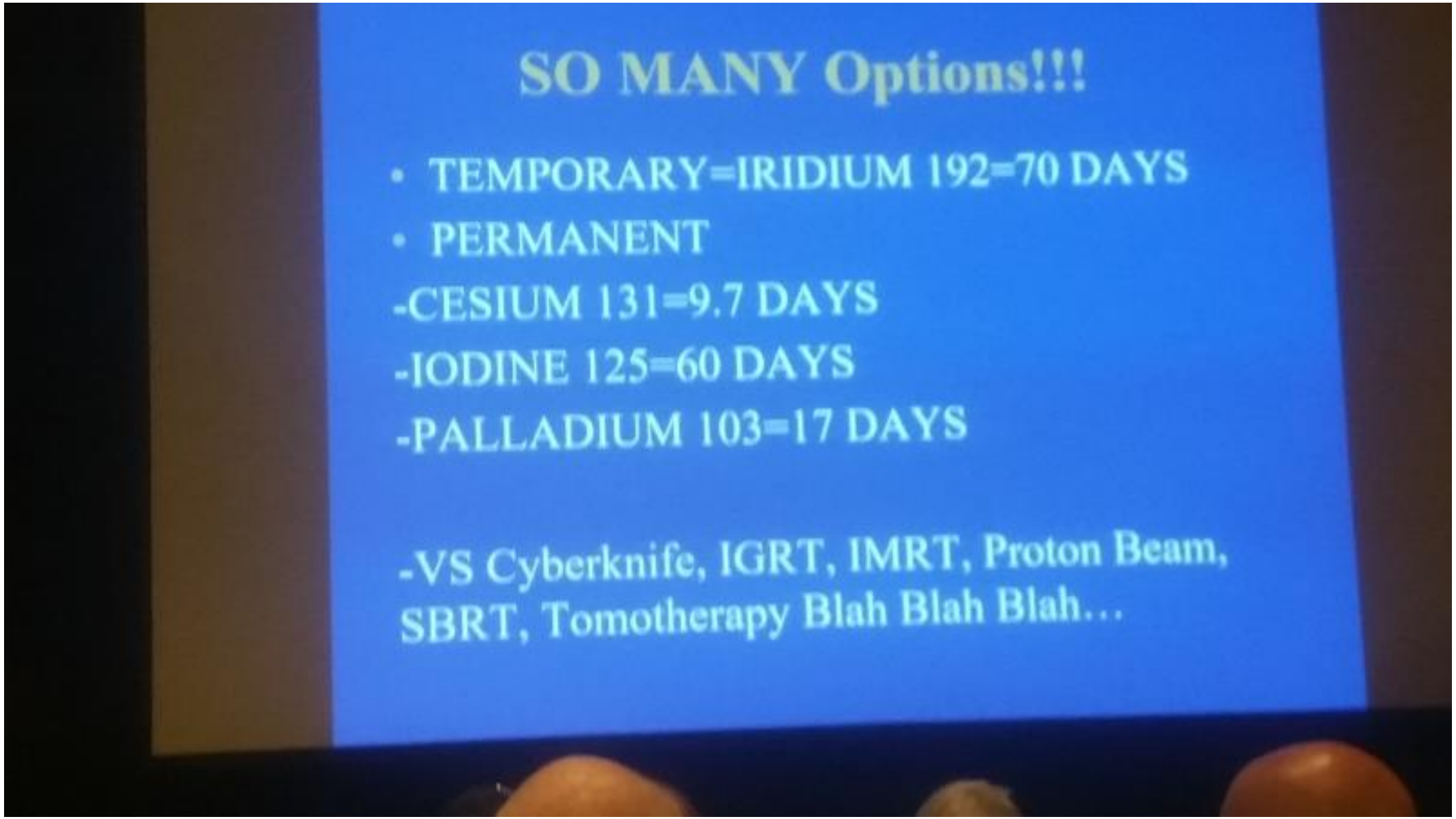

Portable CT Dosimetry
Prostate capsule
5mm
Gy
%
9.0
150
7.5
125
7.2
120
6.6
110
5.4
90
4.5
75

UCLA - HDR Monotherapy
10-year (Late)Toxicity

GI		GU		
Gr. 1-2	Gr. 3-4	Gr.1-2	Gr. 3/4	Gr. 4
2%	0%	10%	4.3%	0.2%

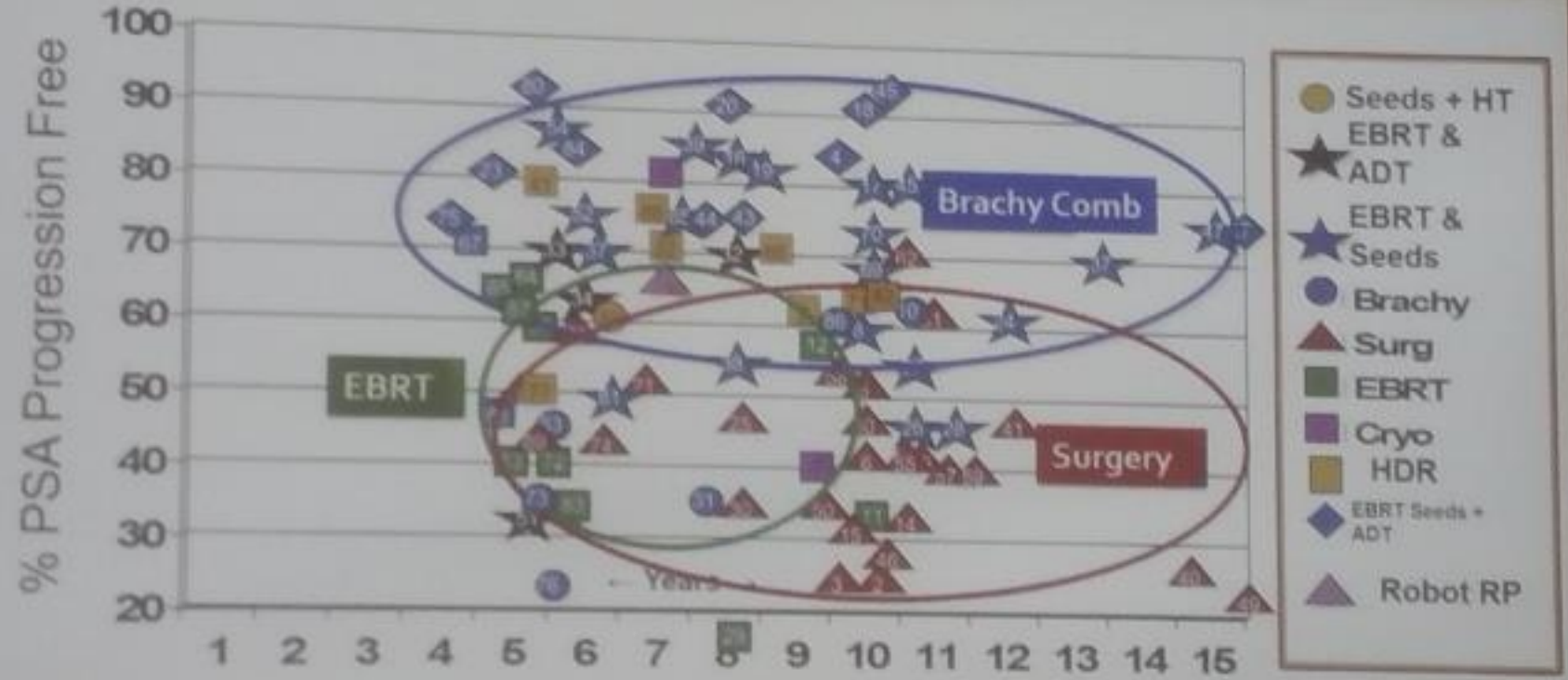
G3/4 90% TUR (often for marginal indications)

Hauswald IJRBP2013v85n3p672


SO MANY Options!!!
• TEMPORARY=IRIDIUM 192=70 DAYS
• PERMANENT
-CESIUM 131=9.7 DAYS
-IODINE 125=60 DAYS
-PALLADIUM 103=17 DAYS
-VS Cyberknife, IGRT, IMRT, Proton Beam, SBRT, Tomotherapy Blah Blah Blah…

High Risk Results – Grimm et al

Prostate Cancer Treatment Center Seattle



- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

9/9/2017

studymanager

Axumin PET Scans

Jennifer Kujak MD

- Works for RadNet, largest imaging company in US.
- The radioisotope is 18F.
- Axumin can detect down to 2 mm lesions.
- Not specific for liver and pancreas because of normal cell uptake.
- Sensitivity tied to PSA level.
- May be difficult to administer successfully due to uptake by muscles.
- Advantage of Axumin is relatively long half life (110 minutes).
- Disadvantage: not covered by all insurance plans.
- Copay could be high (~$1600).

18F-Fludeoxyglucose (FDG)

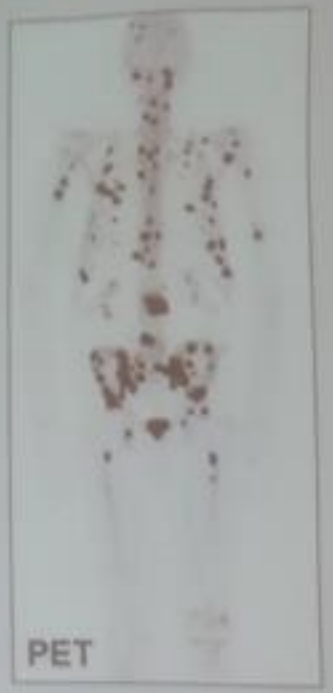
BLUE EARTH

- FDA approved
- Radioactive half-life of 110 minutes
- Readily available
- Commonly used for wide range of cancers
- Limited with prostate cancer
  - Most prostate cancers use non-glucose metabolic pathways, such as fatty acids
- Medicare reimburses for restaging of prostate cancer

18F-Sodium Fluoride (NaF)

BLUE EARTH

- FDA approved
- Radioactive half-life of 110 minutes
- Readily available
- Sensitive but not specific for bone mets
- Does not evaluate soft tissues well
- Medicare reimburses through National Oncologic PET Registry (NOPR); few private payers reimburse



C11-Choline

BLUE EARTH

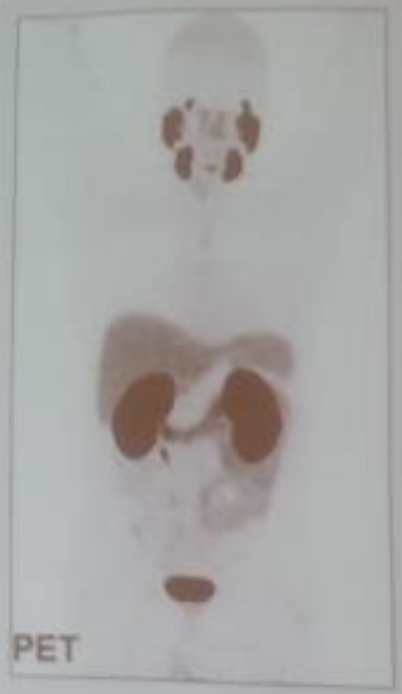
- FDA approved for recurrent prostate cancer
- Not readily available
  - C11-Choline has short half-life of 20 minutes
  - Limited to use at centers with on-site cyclotron
- Choline metabolized in cells by choline kinase, which is overexpressed in prostate cancer
- Can be positive in benign conditions and other cancers
- Findings are non-specific in the prostate gland
- Medicare reimburses for recurrent prostate cancer after negative bone scan, CT, or MR

PET

Ga68-PSMA

BLUE EARTH

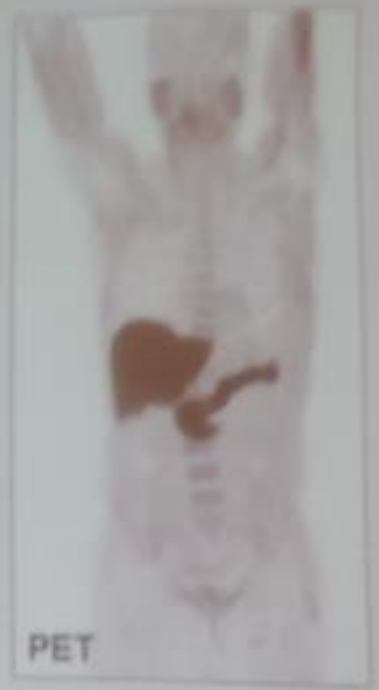
- Not FDA approved
- Not readily available
  - Half-life 68 minutes
- Large transmembrane glycoprotein increased 100-1000 times in prostate cancer
- Excreted in the urine which limits evaluation within the pelvis
- Available only through a clinical trial



Fluciclovine F 18 (Axumin®)

BLUE EARTH

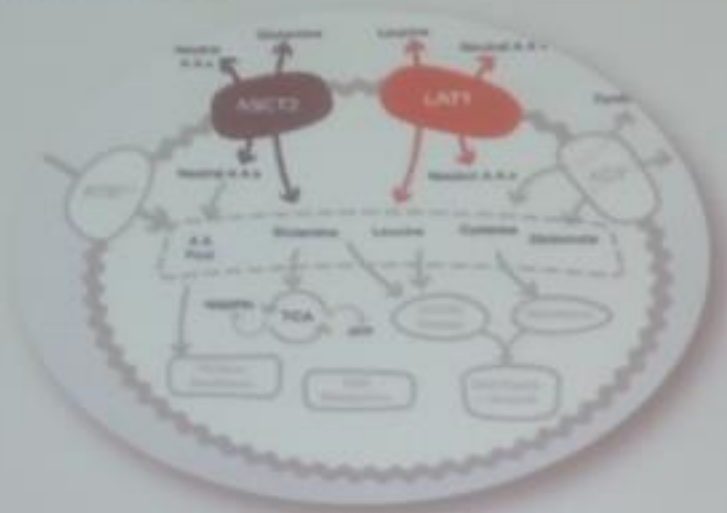
- FDA approved
- Readily available
- Radioactive half-life of 110 minutes
- Amino acid transporters overexpressed in prostate cancer cells
- 18F-Fluciclovine and Ga-PMSA not directly compared yet
- Medicare reimbursed very few private payers

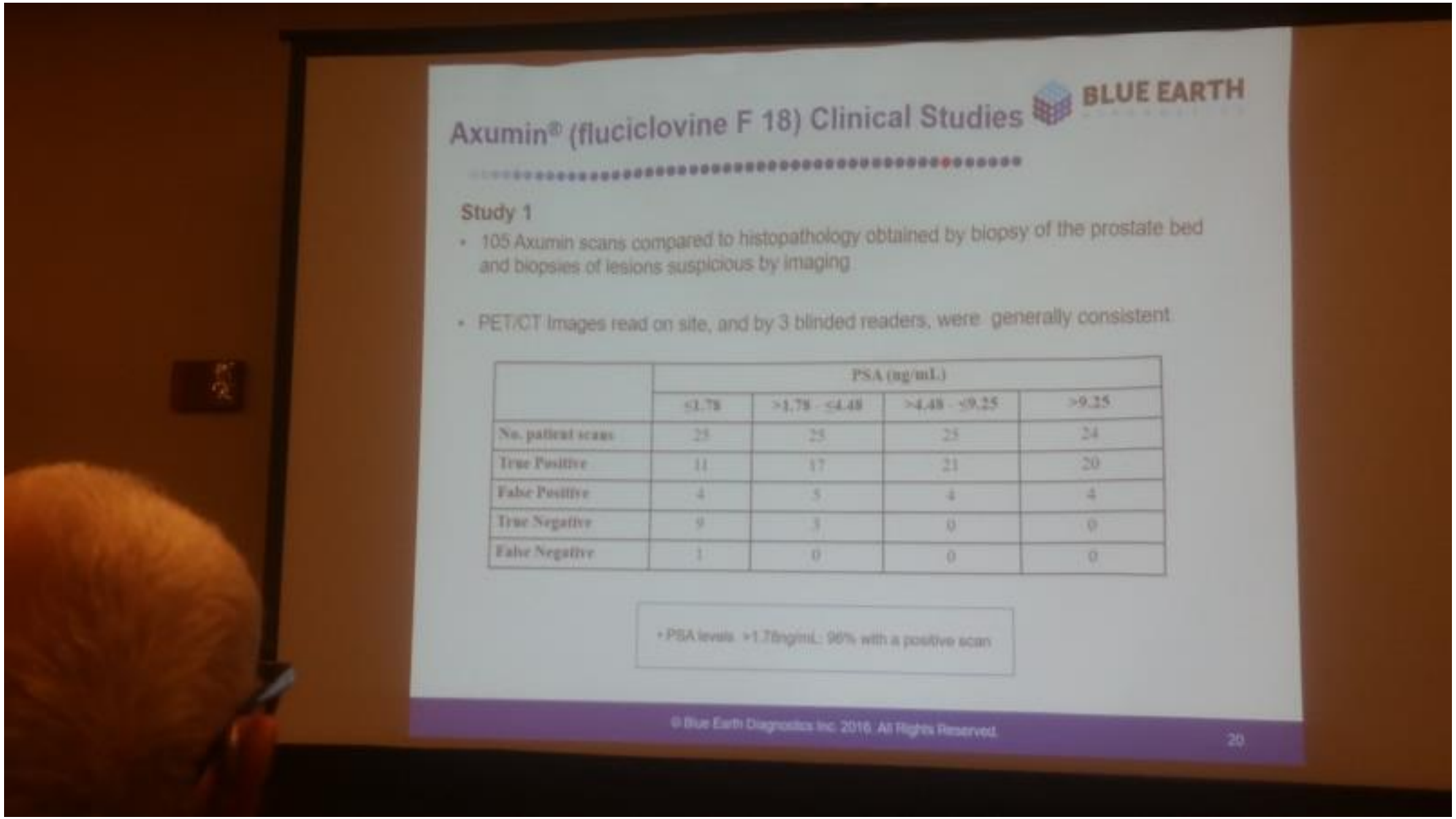


Axumin: How Does It Work?

BLUE EARTH

- Fluciclovine F 18 is a synthetic amino acid PET imaging agent labelled with ^{18}F
- Recognized and taken up by amino acid transporters that are upregulated in many cancer cells, including prostate cancer.




Axumin® (fluciclovine F 18) Clinical Studies
BLUE EARTH
Study 1
• 105 Axumin scans compared to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging
• PET/CT images read on site, and by 3 blinded readers, were generally consistent
PSA (ng/mL)
≤1.78
>1.78 - ≤4.48
>4.48 - ≤9.25
>9.25
No. patient scans 25 25 25 24
True Positive 11 17 21 20
False Positive 4 5 4 4
True Negative 9 3 0 0
False Negative 1 0 0 0
• PSA levels >1.78ng/mL: 96% with a positive scan
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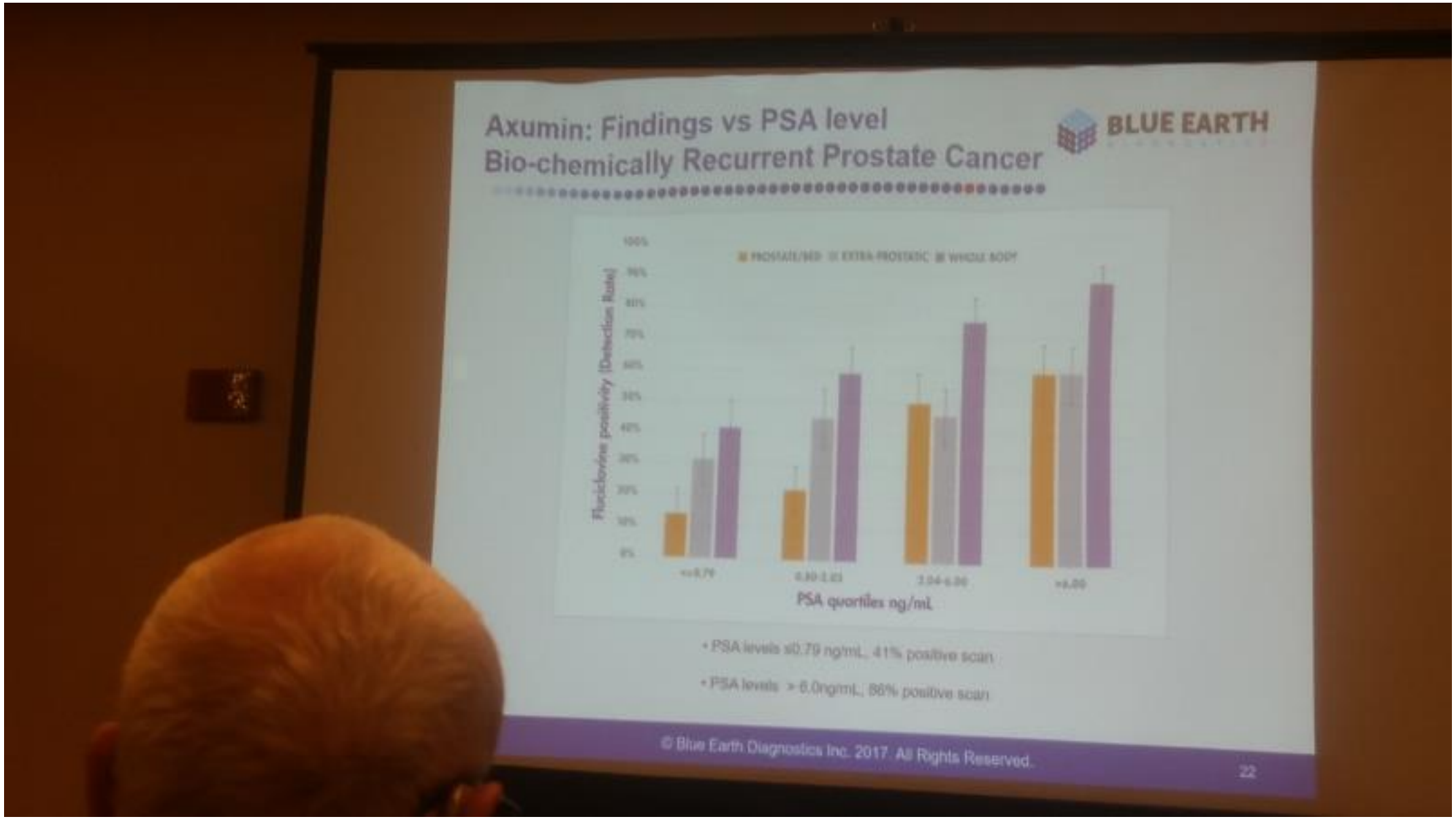
Axumin: Findings vs PSA level
Bio-chemically Recurrent Prostate Cancer
BLUE EARTH
PROSTATE/BED
EXTRA-PROSTATIC
WHOLE BODY
Fluciclovine positivity (Detection Rate)
PSA quartiles ng/mL
• PSA levels ≤0.79 ng/mL: 41% positive scan
• PSA levels > 6.0ng/mL: 86% positive scan
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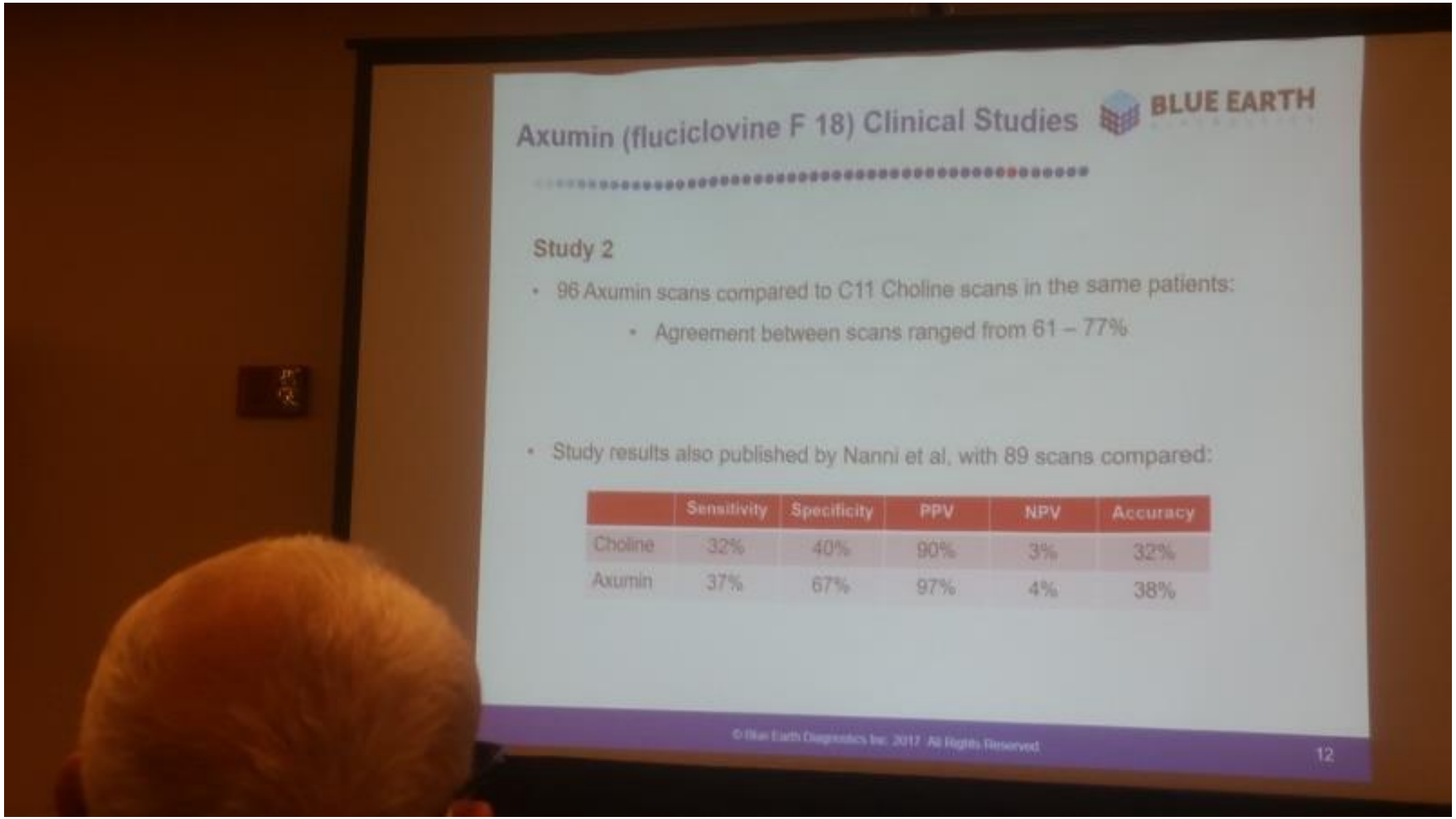
Axumin (fluciclovine F 18) Clinical Studies
BLUE EARTH
Study 2
• 96 Axumin scans compared to C11 Choline scans in the same patients:
• Agreement between scans ranged from 61 – 77%
• Study results also published by Nanni et al, with 89 scans compared:
Sensitivity Specificity PPV NPV Accuracy
Choline 32% 40% 90% 3% 32%
Axumin 37% 67% 97% 4% 38%
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Testosterone Therapy

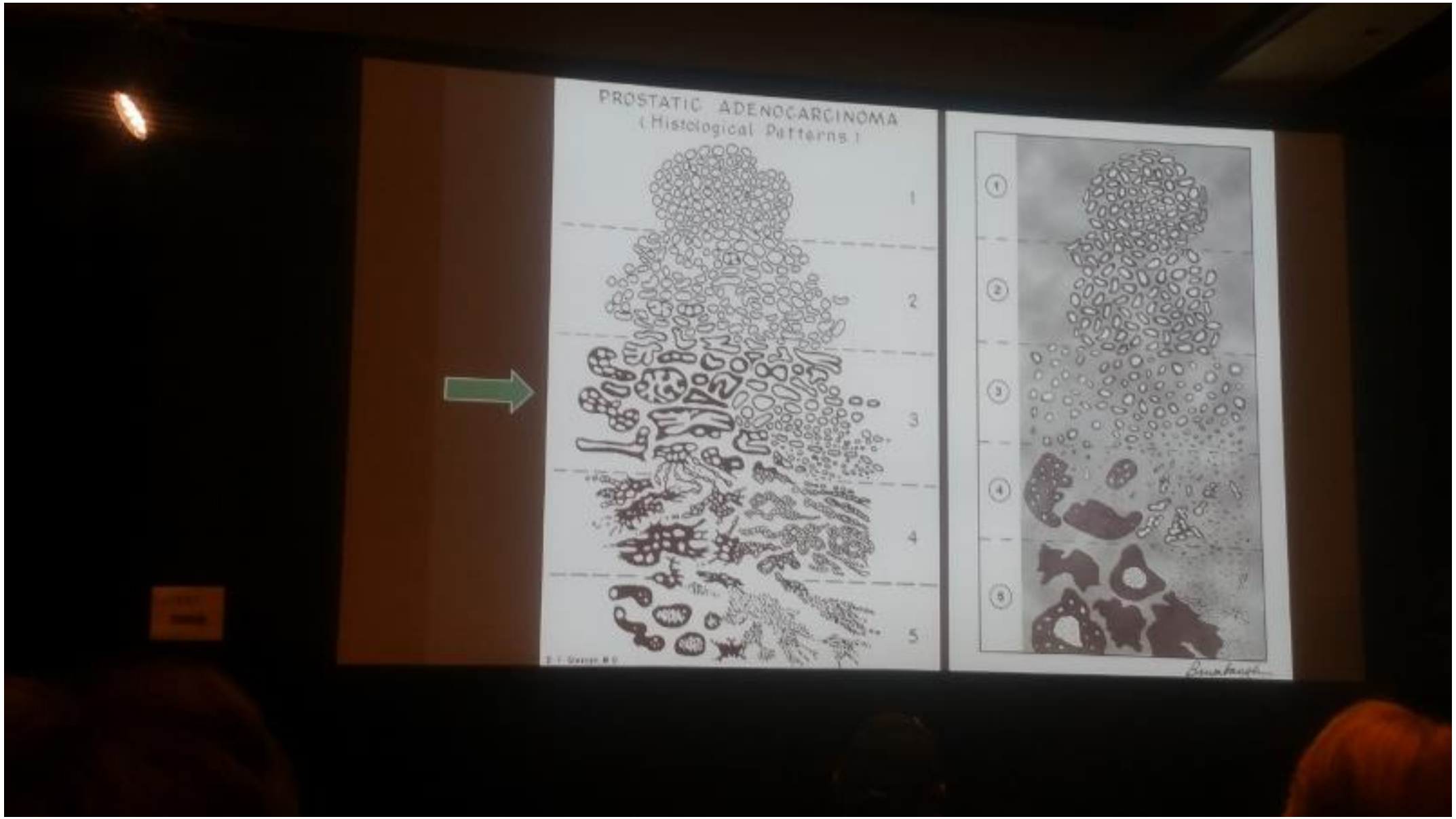
John Mulhall MD

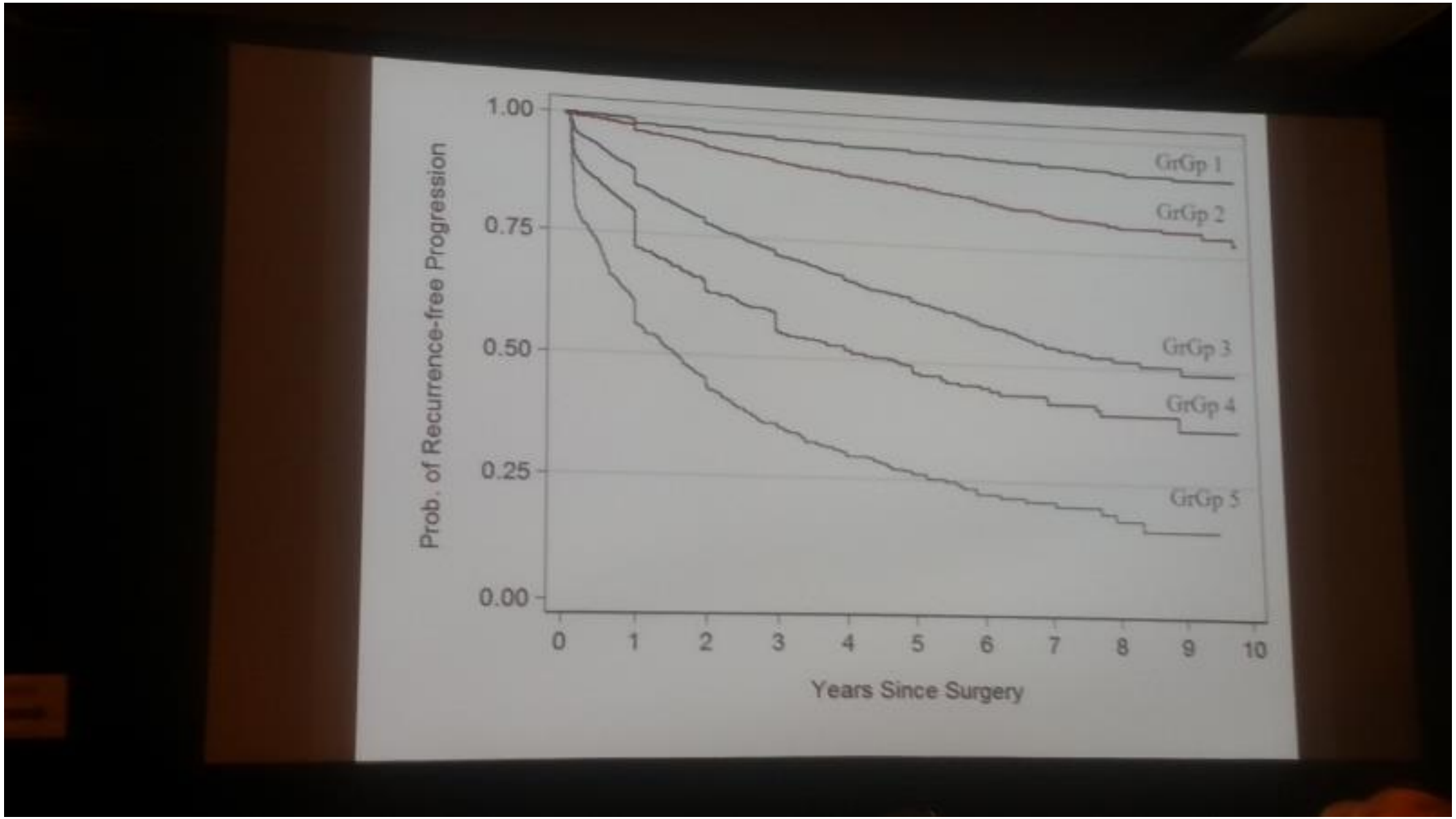
- Very concerned about side effects of ADT on bone density, glucose control and CVD.
- Anything longer than 18 months could lead to permanent damage.
  - Patients shd consider not only time on Lupron but also recovery time (4 months) to normal levels.
- As long as PCa is organ confined – no benefit to ADT.
- T-levels: PCa cells are saturated at 150 ng/ml so any level higher doesn't influence disease.
- Free T: level has to be checked with correct assay. Try Quest Diagnosis.
- Erectile function: very important to have erections to maintain blood flow to penis.

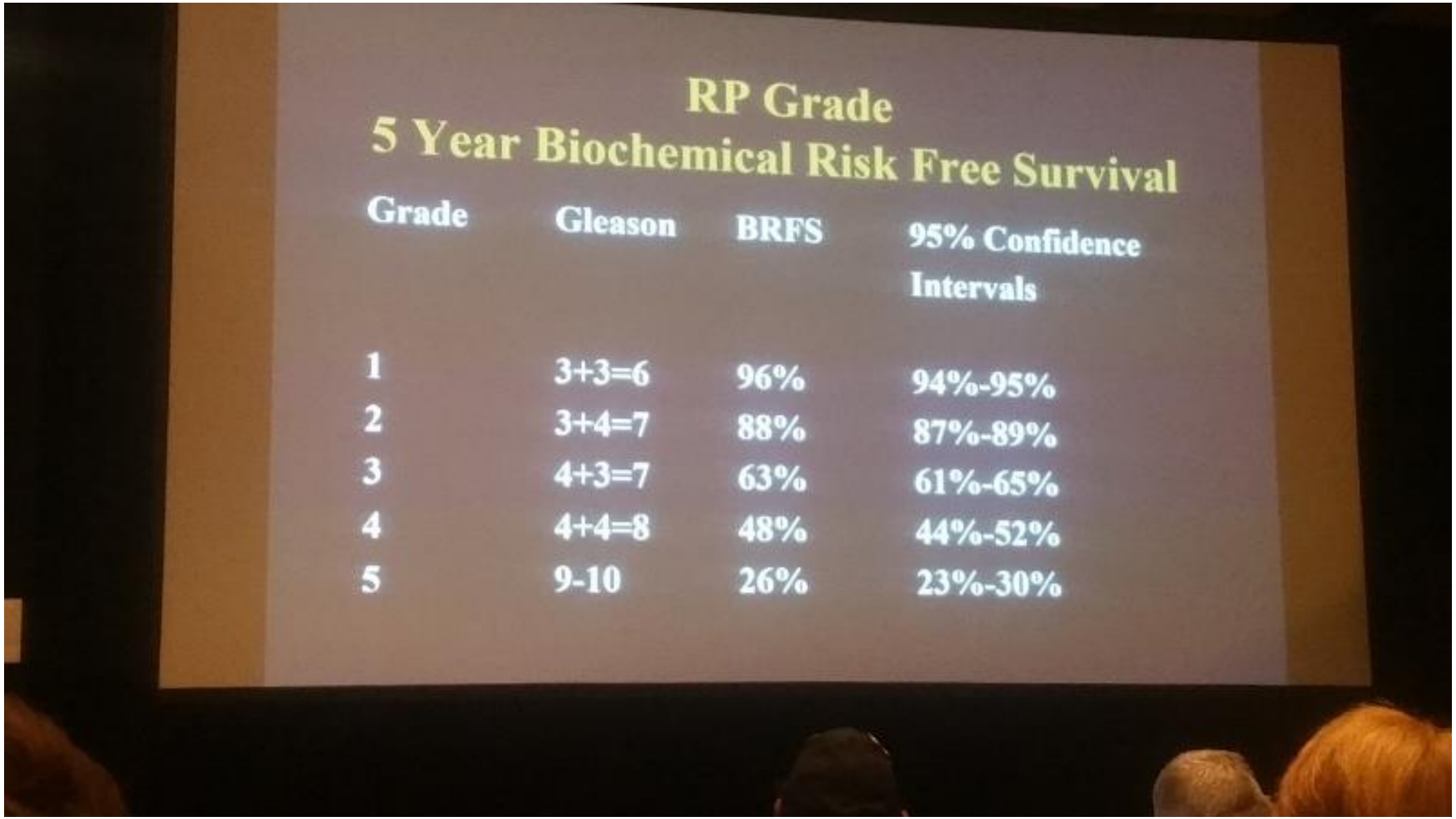
The Pathology Report

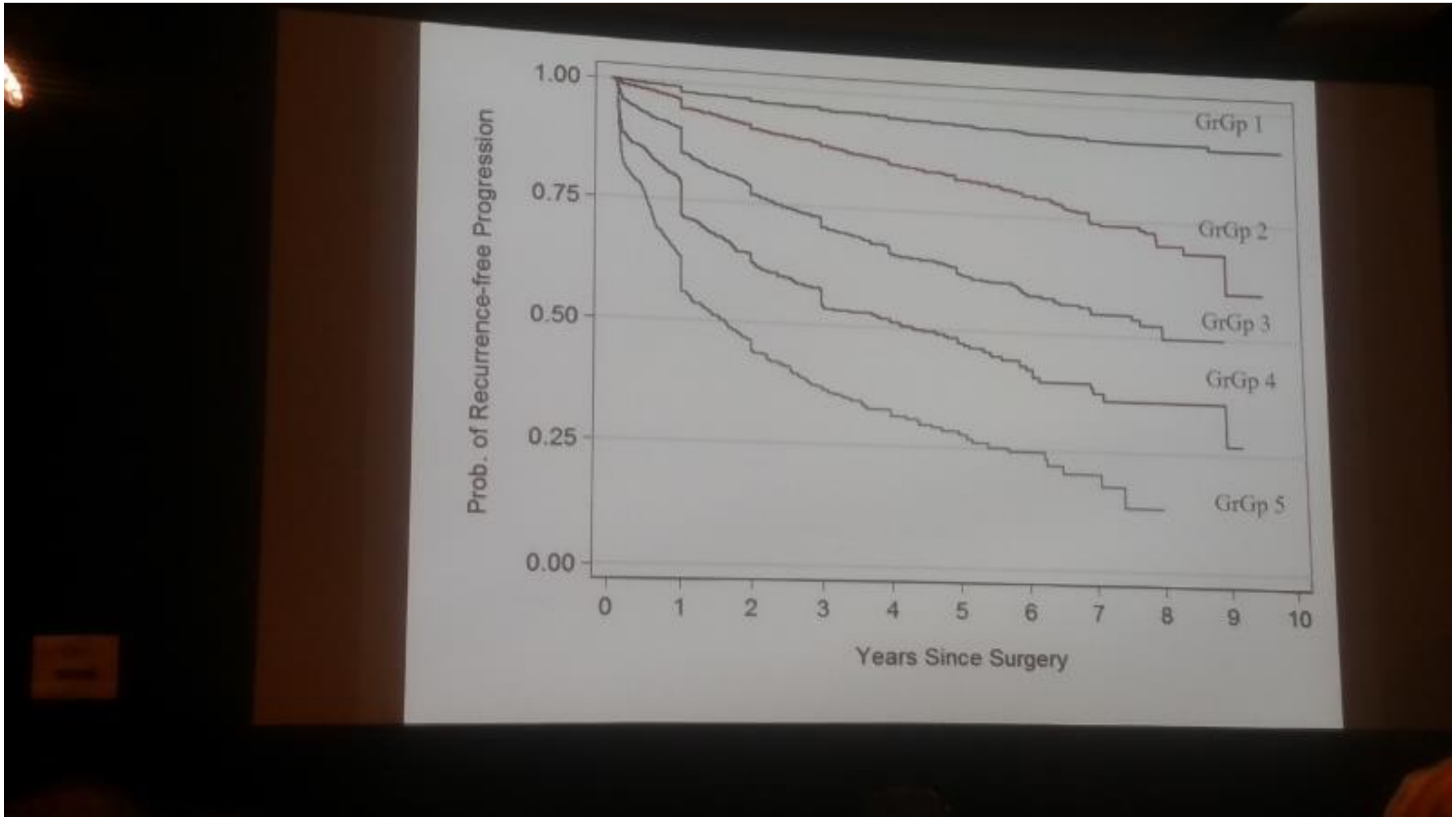
Jonathan Epstein MD

- Evolution of Gleason grading: in 2005 G system was changed so some pre-2005 G3 are now considered G4, thus G3 diagnosed before 2005 could be invasive.
- New grading system since 2014 replaces 2-digit score with single digit: G1 = 3=3, G2 = 3+4, G3 = 4+3, G4 =4+4, G5 = G9/G10.
- Note: new G5 is 2x more aggressive than G4.
- Errors in diagnosis: very few pathologists specialize in PCa. Therefore ~20% of results are either upgraded or downgraded at 2nd opinion.
- Low grade and high grade PIN can be ignored.
- “Intraductile carcinoma” is a sign of poor prognosis.

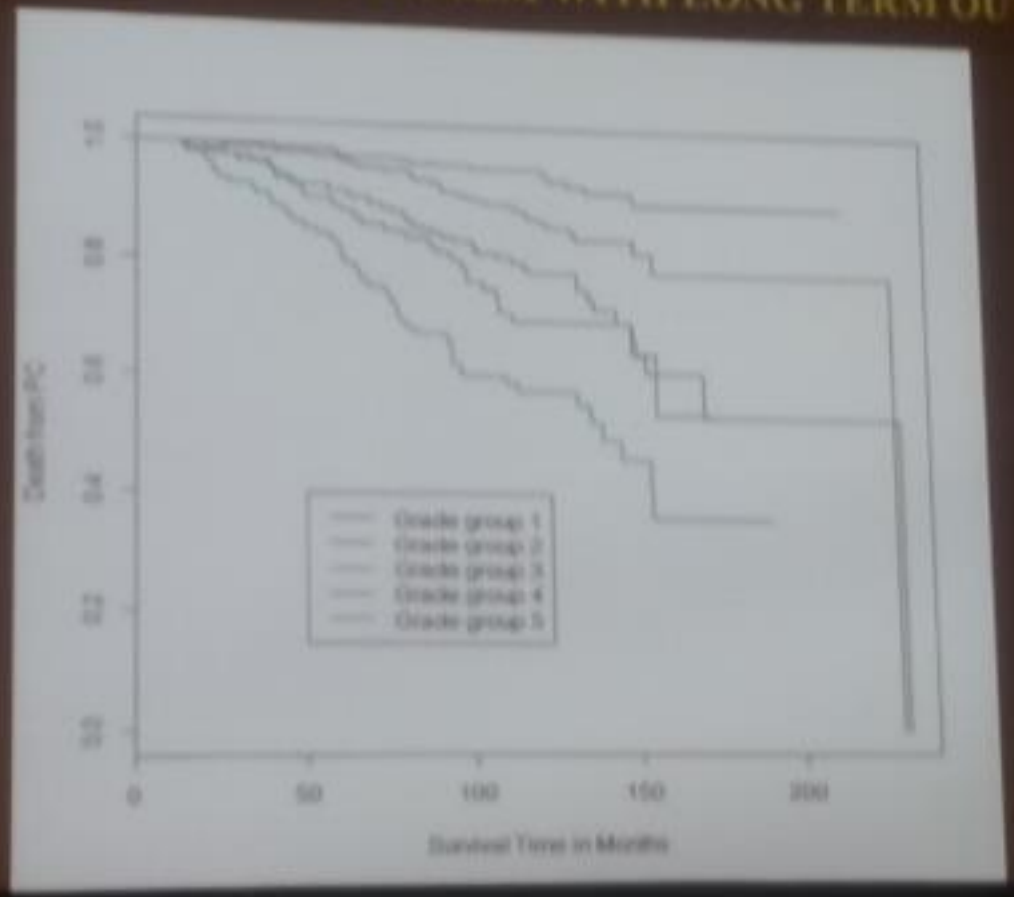

PROSTATIC ADENOCARCINOMA
(Histological Patterns)
1
2
3
4
5
1
2
3
4
5


Prob. of Recurrence-free Progression
1.00
0.75
0.50
0.25
0.00
GrGp 1
GrGp 2
GrGp 3
GrGp 4
GrGp 5
0
1
2
3
4
5
6
7
8
9
10
Years Since Surgery

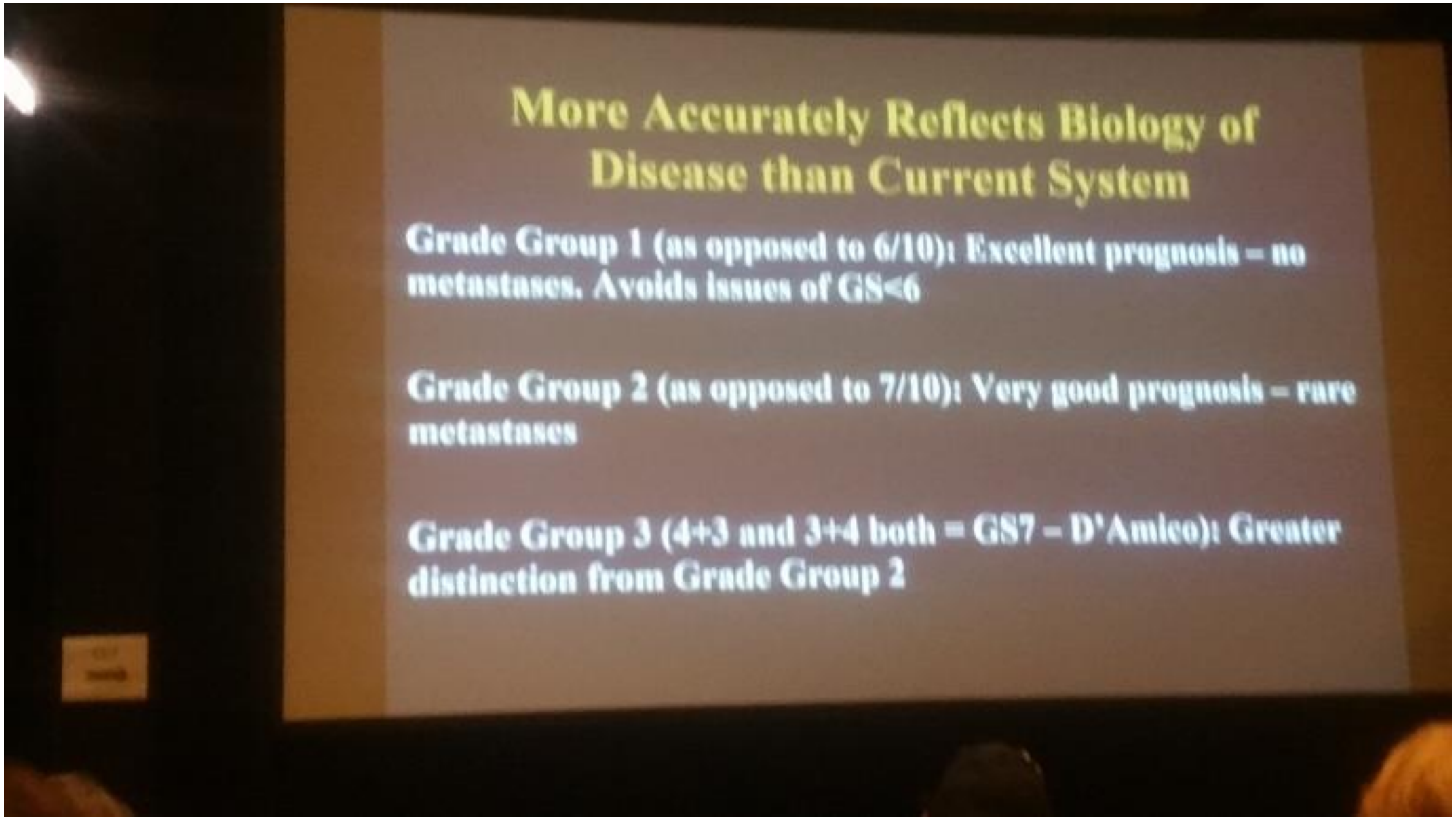

RP Grade
5 Year Biochemical Risk Free Survival
Grade Gleason BRFS 95% Confidence Intervals
1 3+3=6 96% 94%-95%
2 3+4=7 88% 87%-89%
3 4+3=7 63% 61%-65%
4 4+4=8 48% 44%-52%
5 9-10 26% 23%-30%

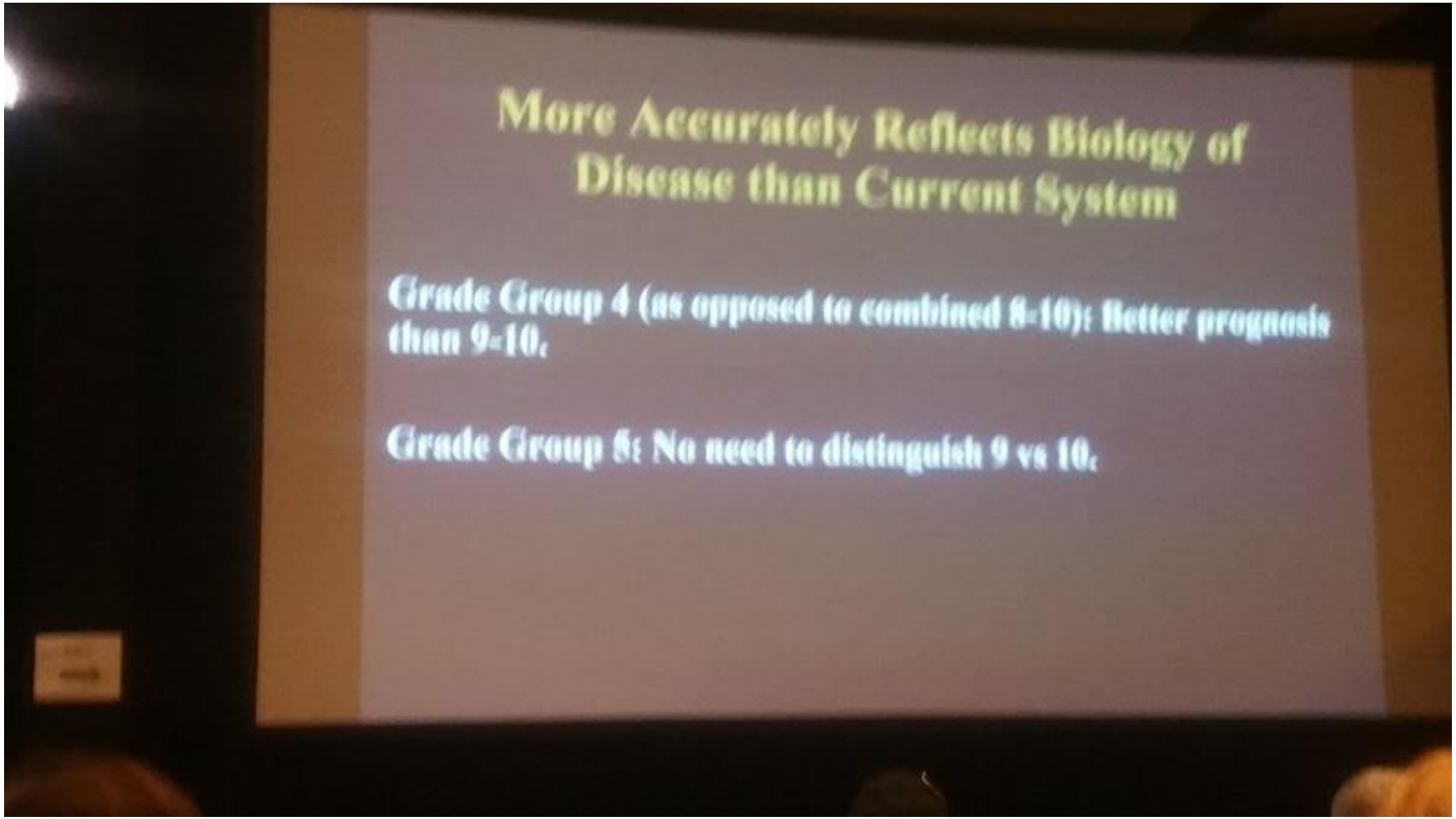

Prob. of Recurrence-free Progression
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
Years Since Surgery
GrGp 1
GrGp 2
GrGp 3
GrGp 4
GrGp 5

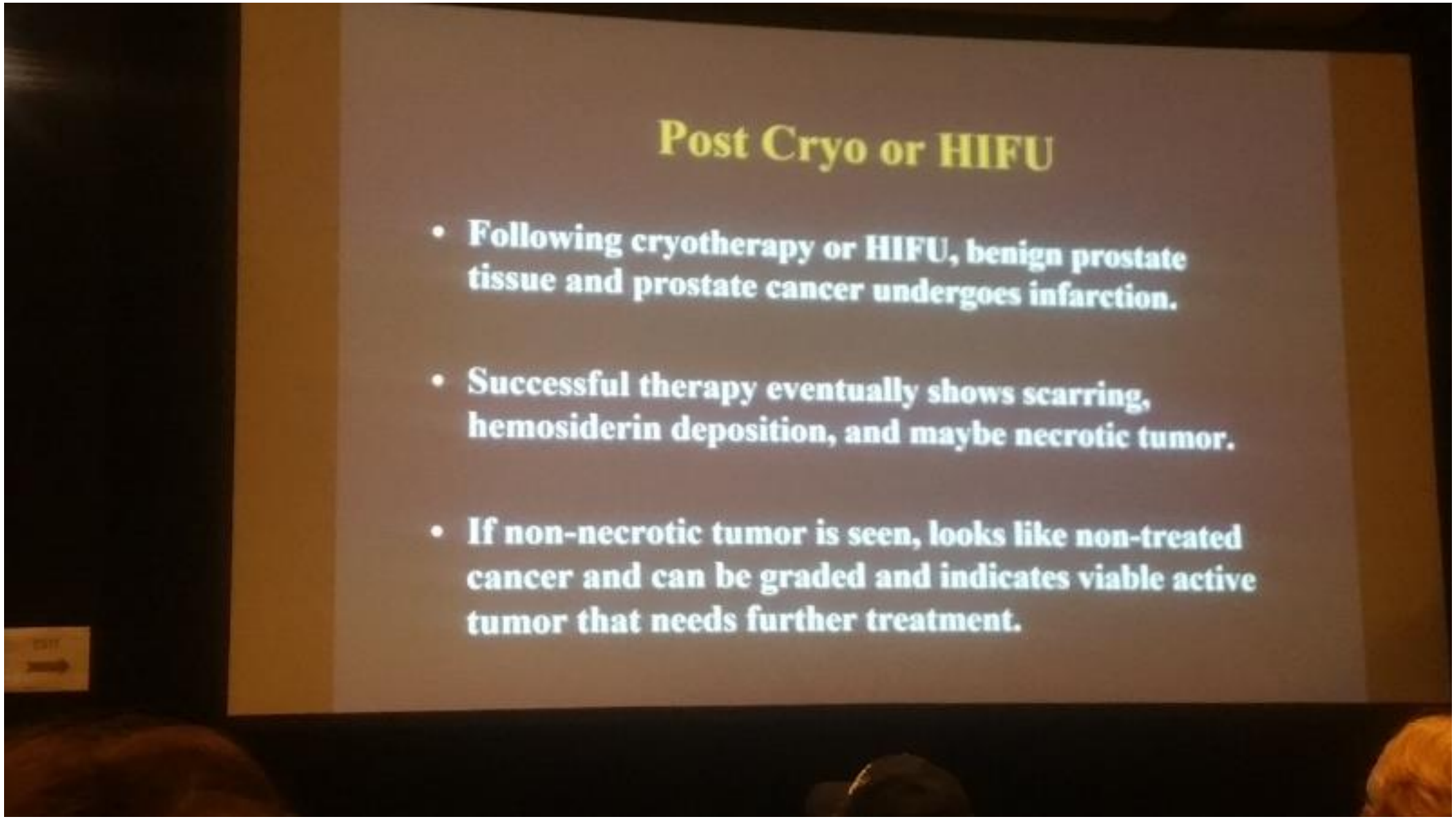
VALIDATION OF A CONTEMPORARY PROSTATE CANCER GRADING SYSTEM WITH LONG TERM OUTCOME

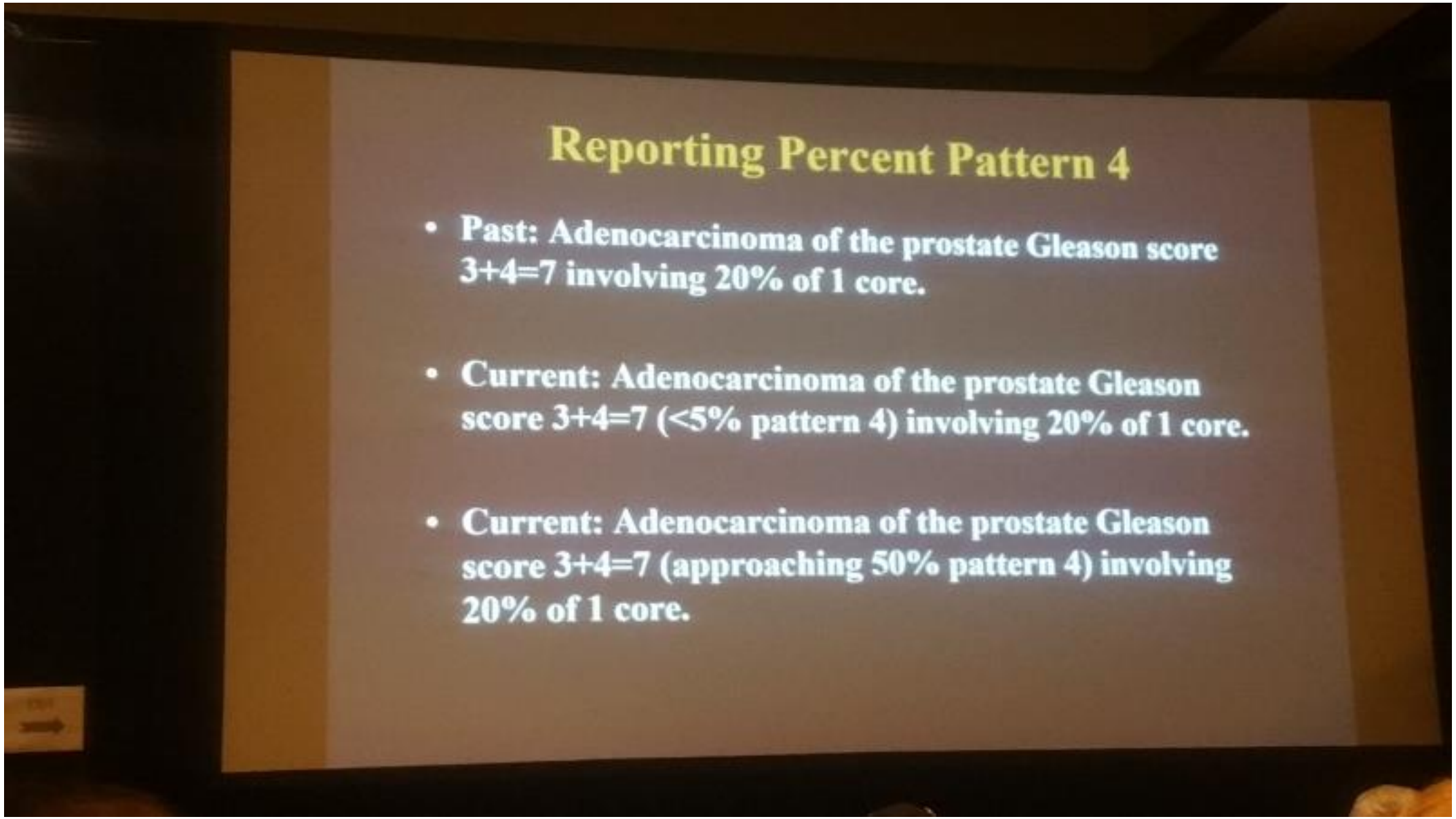


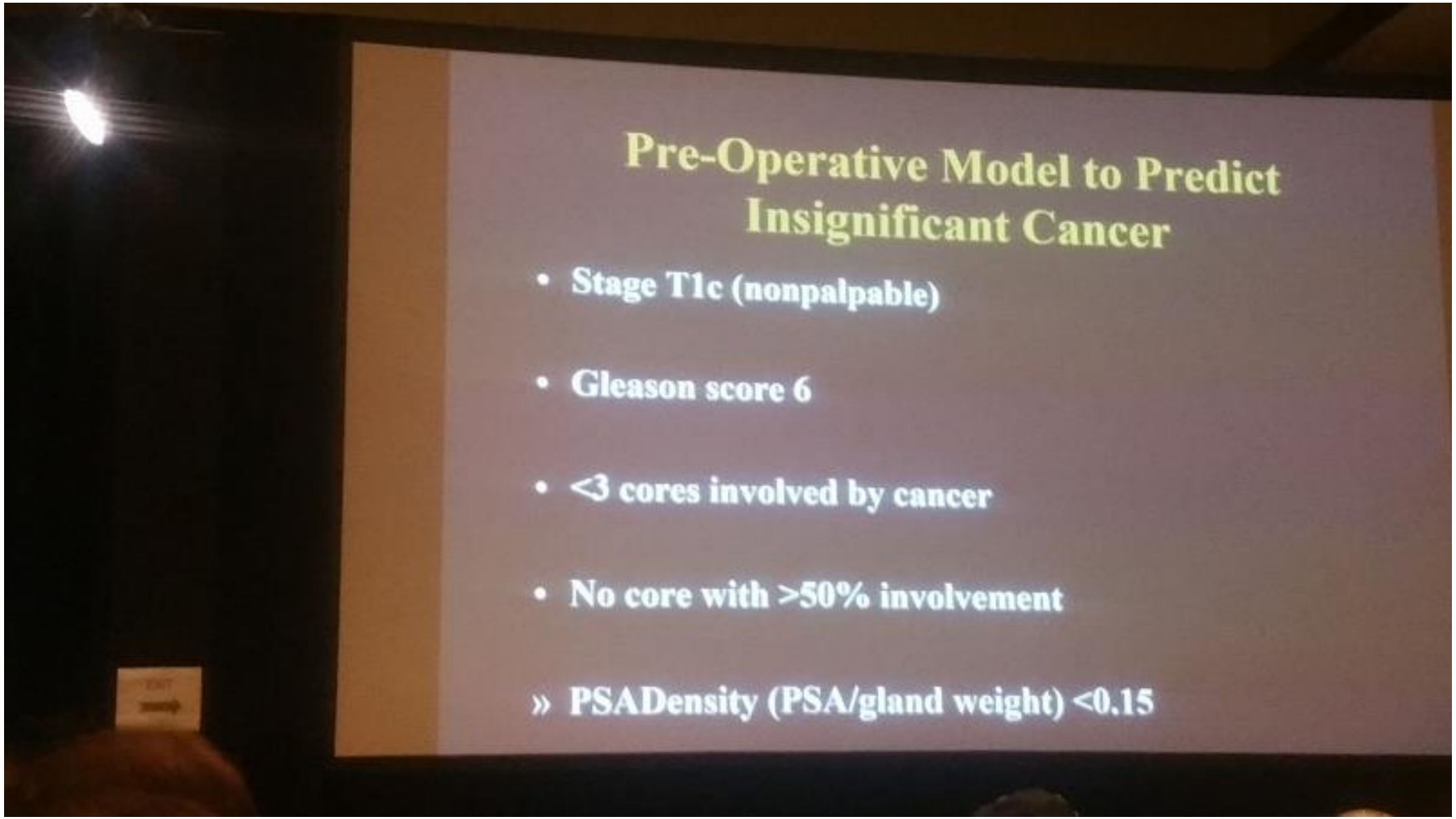
B J Cancer
Berney D., et al.
2016


More Accurately Reflects Biology of Disease than Current System
Grade Group 1 (as opposed to 6/10): Excellent prognosis = no metastases. Avoids issues of GS<6
Grade Group 2 (as opposed to 7/10): Very good prognosis = rare metastases
Grade Group 3 (4+3 and 3+4 both = GS7 – D'Amico): Greater distinction from Grade Group 2


More Accurately Reflects Biology of Disease than Current System
Grade Group 4 (as opposed to combined 8-10): Better prognosis than 9-10.
Grade Group 5: No need to distinguish 9 vs 10.


Post Cryo or HIFU
• Following cryotherapy or HIFU, benign prostate tissue and prostate cancer undergoes infarction.
• Successful therapy eventually shows scarring, hemosiderin deposition, and maybe necrotic tumor.
• If non-necrotic tumor is seen, looks like non-treated cancer and can be graded and indicates viable active tumor that needs further treatment.

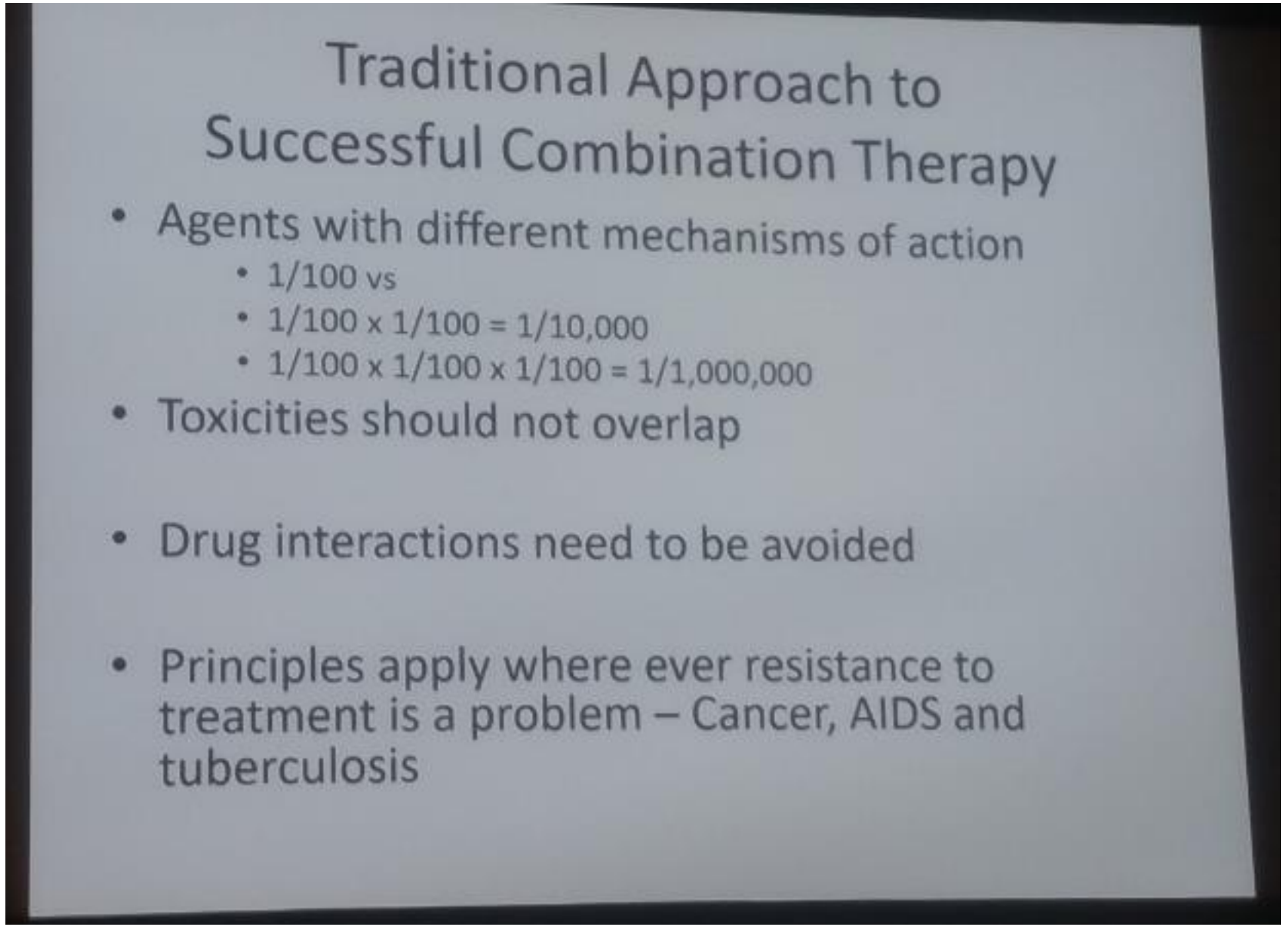

Reporting Percent Pattern 4
• Past: Adenocarcinoma of the prostate Gleason score 3+4=7 involving 20% of 1 core.
• Current: Adenocarcinoma of the prostate Gleason score 3+4=7 (<5% pattern 4) involving 20% of 1 core.
• Current: Adenocarcinoma of the prostate Gleason score 3+4=7 (approaching 50% pattern 4) involving 20% of 1 core.


Pre-Operative Model to Predict Insignificant Cancer
• Stage T1c (nonpalpable)
• Gleason score 6
• <3 cores involved by cancer
• No core with >50% involvement
» PSADensity (PSA/gland weight) <0.15

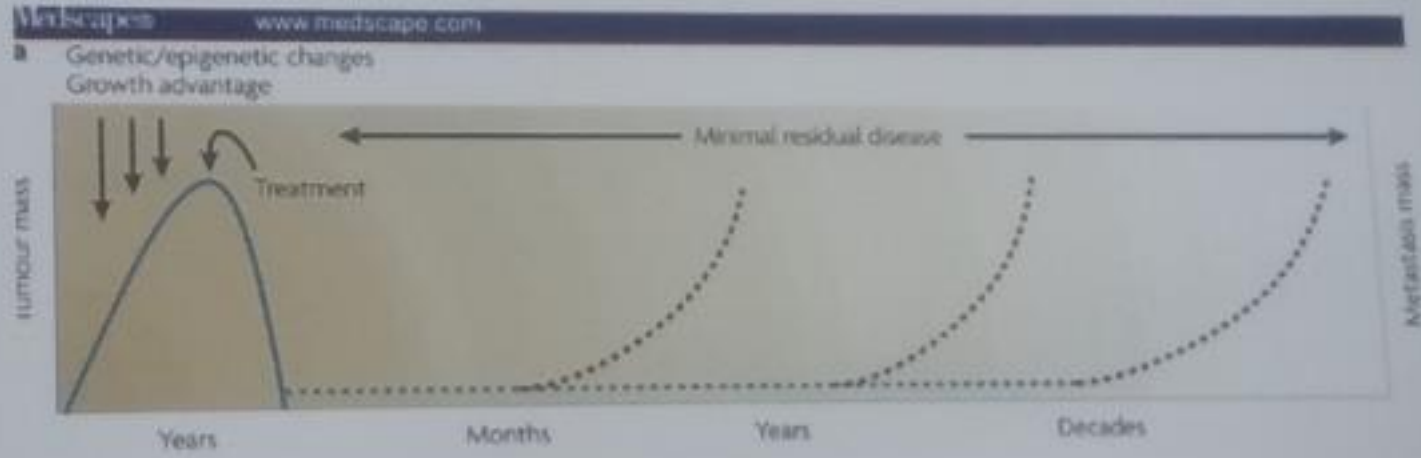
Durable Remission

Charles Snuffy Myers MD

- Snuffy is officially retiring Nov. 1. Will continue write, support Prostapedia.
- For his 850 patients he recommends Charles Drake (NYC), William Berry, Nick Vogelsang (Las Vegas), Mark Scholz (LA), Nancy Dawson, Philip Lemming (Cinti), Oliver Sorter (NO).
- Big fan of combination therapy based on liquid biopsy to monitor genetic changes that drive hormone resistance.
- Many examples of durable remission. Fan of intradermal estradiol to prevent EMT (epithelial-mesenchymal transition), metformin – activates AMPK, statins, dutasteride (Avodart), low glycemic index diet.
- Avoid corn and other food high in omega 6.
- Important to slow PSADT – can add years to disease progression.
- Once PSA stabilizes stop Avodart, let PSA rise then use one of new imaging tools to find tumors for irradiation.

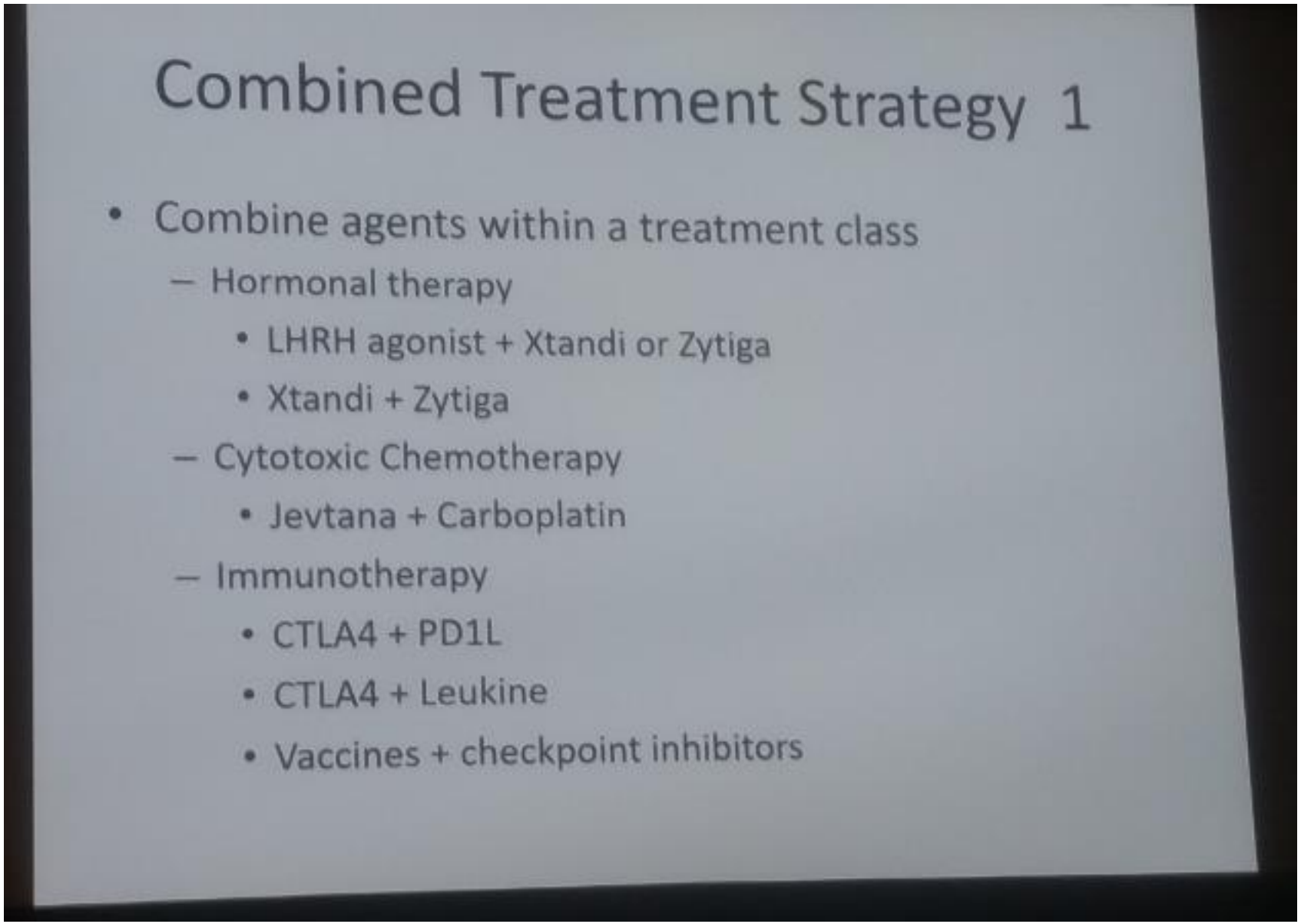

Traditional Approach to Successful Combination Therapy
• Agents with different mechanisms of action
• 1/100 vs
• 1/100 x 1/100 = 1/10,000
• 1/100 x 1/100 x 1/100 = 1/1,000,000
• Toxicities should not overlap
• Drug interactions need to be avoided
• Principles apply where ever resistance to treatment is a problem – Cancer, AIDS and tuberculosis

Complete Remissions
Variable Duration



Minimal residual disease = cancer cell clusters too small to detect

Cancer Dormancy = cancer survives for a time, but does not grow or spread


Combined Treatment Strategy 1
• Combine agents within a treatment class
– Hormonal therapy
• LHRH agonist + Xtandi or Zytiga
• Xtandi + Zytiga
– Cytotoxic Chemotherapy
• Jevtana + Carboplatin
– Immunotherapy
• CTLA4 + PD1L
• CTLA4 + Leukine
• Vaccines + checkpoint inhibitors

Combined Treatment Strategy 2

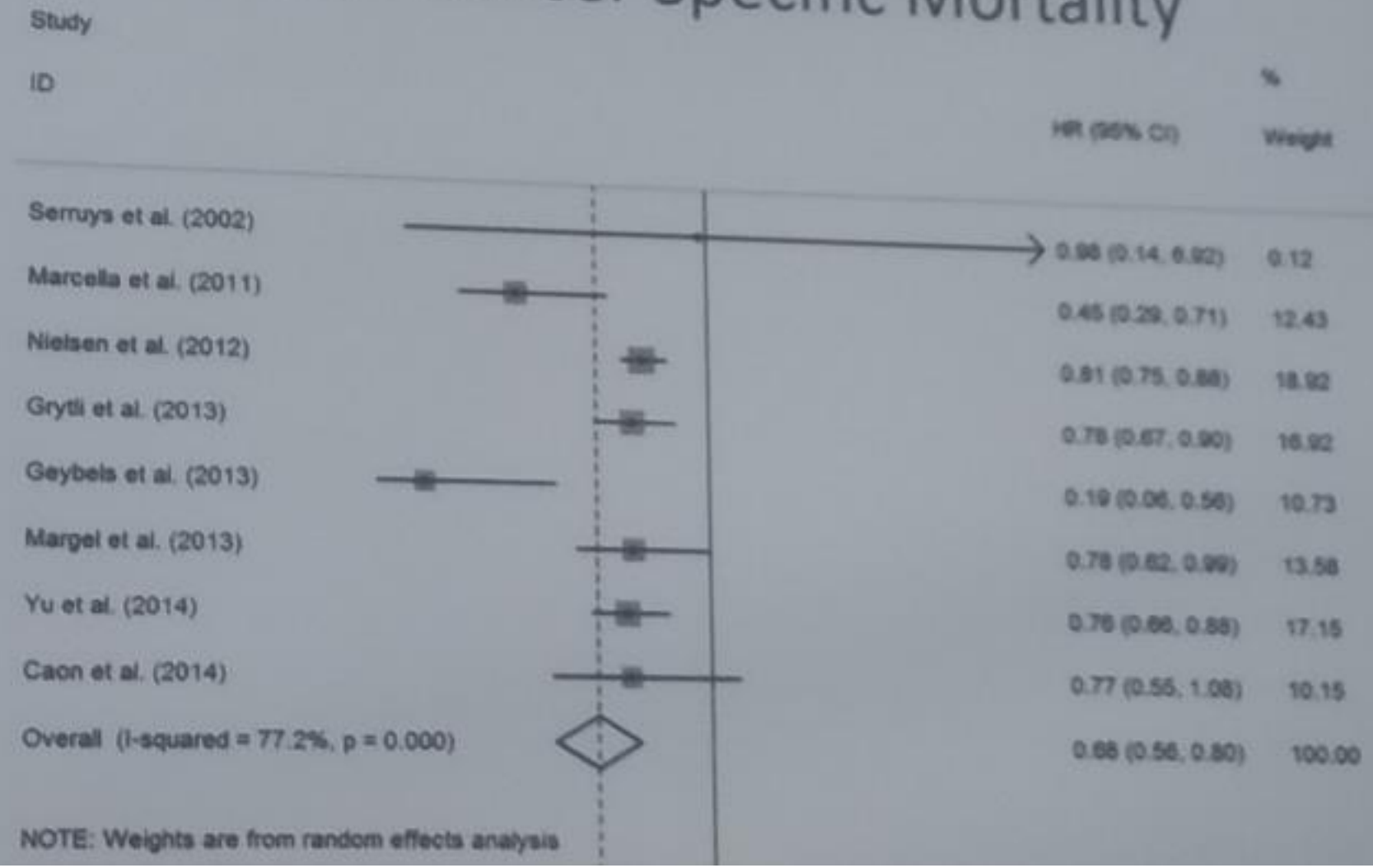
Combine treatment modalities

- Radiation for oligometastatic disease + systemic treatment
- Hormonal + cytotoxic chemotherapy
  - Lupron + taxotere
- Hormonal therapy + immunotherapy
  - Xtandi + Provenge
  - Ketoconazole + Leukine
- Xofigo+ hormonal therapy and/or immunotherapy
- Gene-targeting drugs with any of the above

MH

- Diagnosed in 9/2005, age 53, Gleason 4+4=8, PSA of 3,488. Before PSA reached 4,400
- Lymphoma-like disease distribution- wide spread massive lymph node disease
- Major academic prostate team gave him projected survival of less than 2 years
- Started Lupron, Casodex, Avodart
- At 6 months, PSA undetectable by PSA ultra sensitive assay
- At 9 months, he was in a radiologic complete remission
- October 2006, Lupron & Casodex stopped
- Remission maintenance: Avodart, Celebrex.

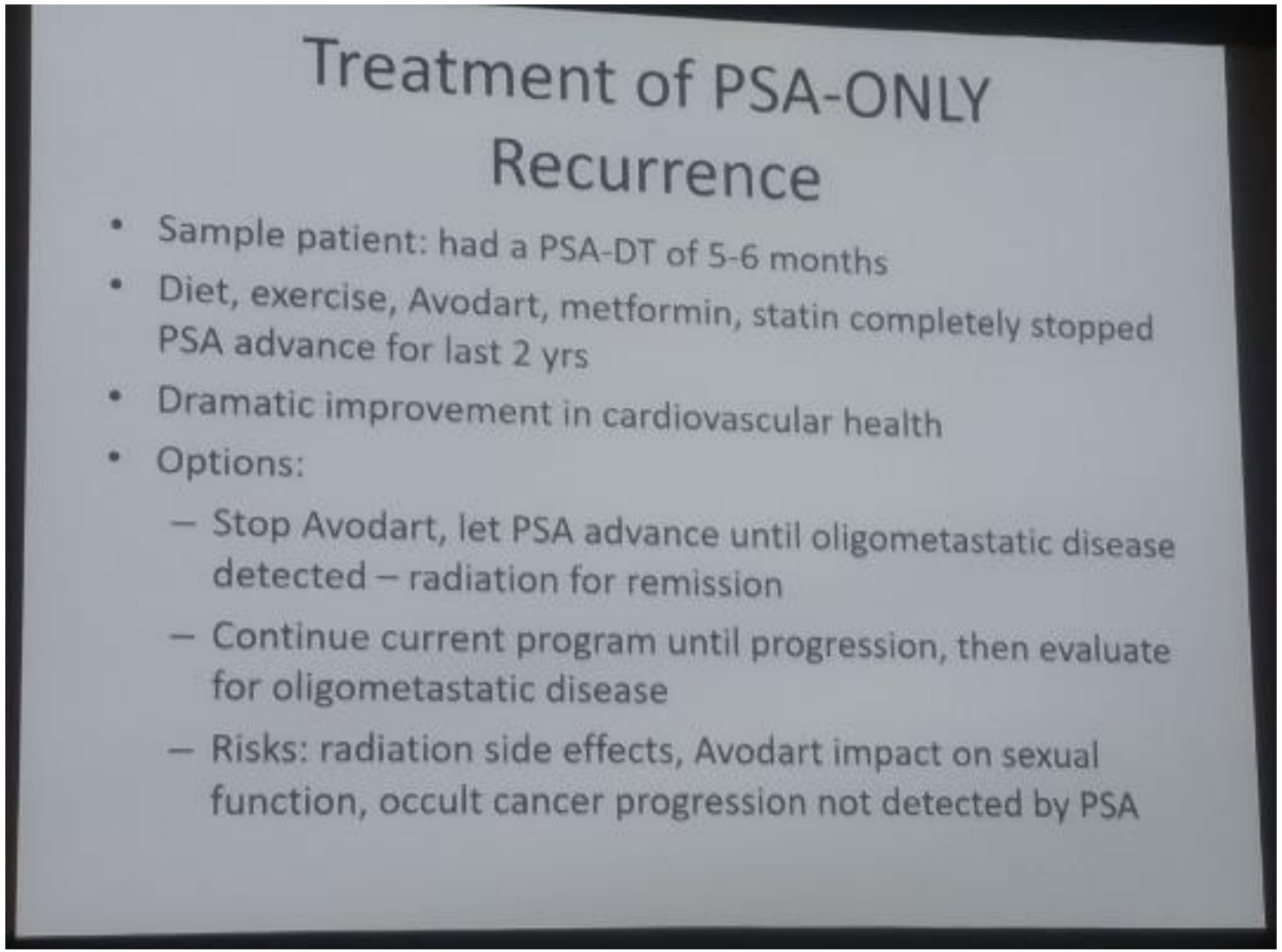
Impact of Statins on Aggressive PC: Prostate Cancer Specific Mortality



Avodart (dutasteride)

- ARTS randomized controlled trial
  - Dutasteride vs Placebo in men with PSA recurrence after radical prostatectomy
  - At two years, >50% reduction in metastatic disease requiring hormonal therapy

F Schroder et al European Urology 63:779, 2013

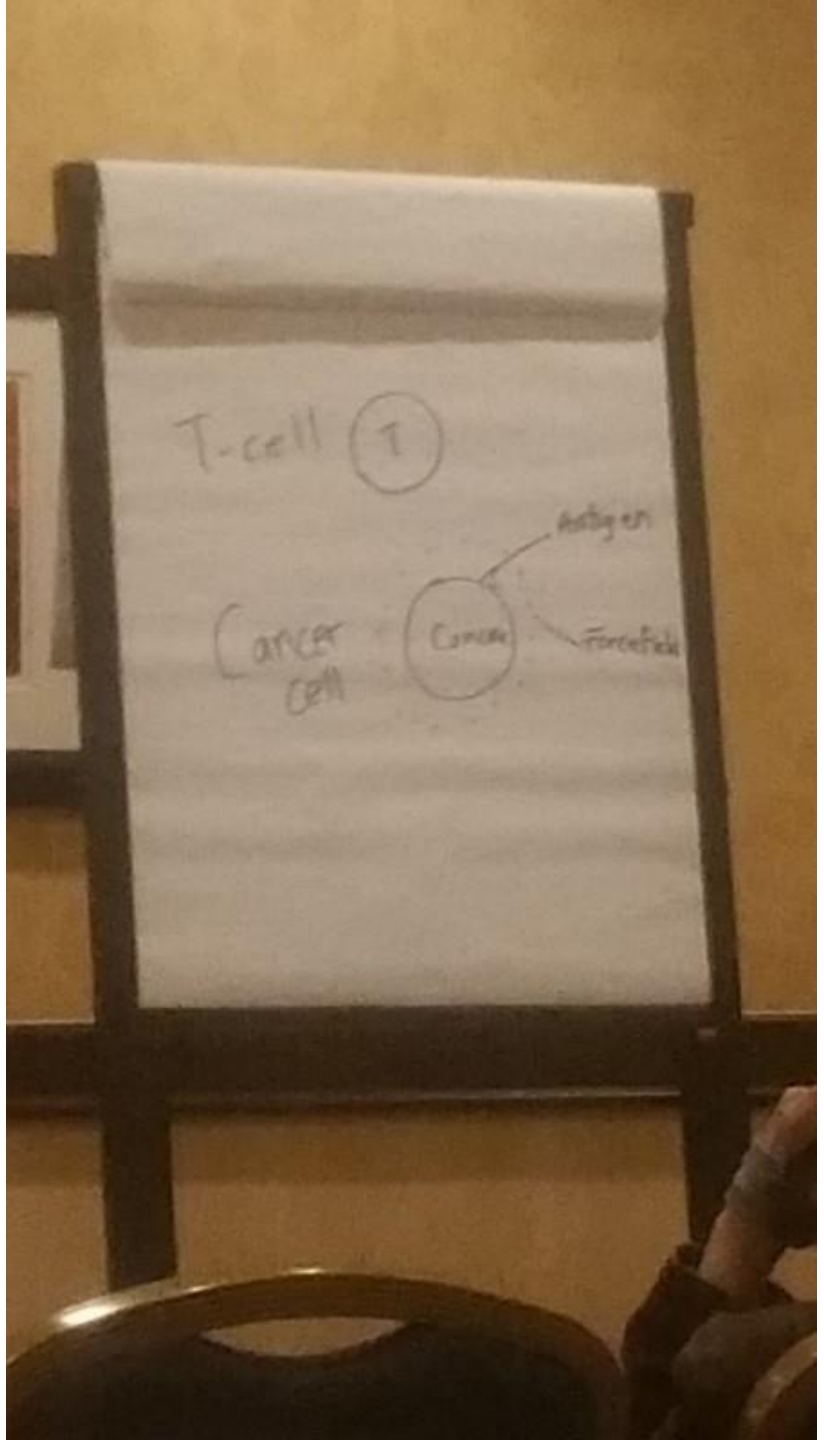

Treatment of PSA-ONLY Recurrence
• Sample patient: had a PSA-DT of 5-6 months
• Diet, exercise, Avodart, metformin, statin completely stopped PSA advance for last 2 yrs
• Dramatic improvement in cardiovascular health
• Options:
– Stop Avodart, let PSA advance until oligometastatic disease detected – radiation for remission
– Continue current program until progression, then evaluate for oligometastatic disease
– Risks: radiation side effects, Avodart impact on sexual function, occult cancer progression not detected by PSA

Immune Therapy

Richard Lam MD

- Reviewed latest developments. In general the challenge is to educate the immune system to find cancer, then to overcome the “force field” surrounding the cell.
- ProstVac: results of phase 3 clinical trial to be released shortly – may be a headliner. Immune checkpoint inhibitors (pembrolizumab- Keytruda and nivolumab, PD-1 inhibitors): only for CRPC because the side effects (including death) outweigh the benefits for men who are still hormone sensitive.
- Cryo + PD-1 release of tumor antigens into the bloodstream illicits a strong immune response.
- Guardant 360 liquid biopsy: only effective for metastatic disease.
- PARP inhibitors: effective when BCRA mutation is present (10-15% of men).


T-cell
T
Antigen
Cancer cell
Cancer
Forcefield


T-cell
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Antigen
Cancer cell
Cancer
Forcefield


Immuno-Oncology Luke Nordqusit, MD
General Immune Modulating Therapies (Interferon)
Vaccines (Provenge, Prostvac, Panacea, Inovio)
Check Point Inhibitors (Opdivo, Keytruda)
Vaccine Based Immune Regimen (VBIR)
CAR T Cells
PROSTATE CANCER
RESEARCH INSTITUTE

PET CT Imaging and Prostate MRI Fabio Almeida MD (Phoenix Molecular Imaging)

- Not much new about MRI except whole body diffusion is non-starter because of cost (3 hrs in machine) and toll on radiologist because of amount of scans to process also SE's on patient like audio trauma. However agrees it is extremely sensitive and precise as diagnostic tool.
- His typical process for whole body scan is 18F bone scan (1 mm resolution) and C11 acetate PET-CT. Advantage of C11 acetate is high sensitivity esp for pelvic area. Prefers C11 acetate or C11 choline over Axumin (PPV of Axumin only 62% with fair amount of false positives from one 600-patient study. Axumin tracer tends to migrate to muscle, rendering some studies unreadable.
- C11 acetate radiation dose greater for the CT imaging vs. the radiotracer, however new CT con-touring technology adjusts dose to area being scanned so total dose only 20-30 mS.
- C11 acetate not covered by insurance. $3000 fee. Foundation provides stipends based on need.
- 68Ga PSMA scans – many types of ligand and many competing institutions – who will win out?
- Choice of ligand limited to small molecules to reduce chance of allergic reactions. Two ligands (617 and R2) could be theranostic (agents for carrying therapeutic radiation dose). Problem: bladder uptake shrouds pelvis.
- PSMA is misnomer actually present in many different tissues. ~10% of PCa doesn't present PSMA which impacts statistical comparisons to other scanning techniques.
- Predictive value of any of the scans is highly PSA related. If PSA is 0 – 1.0, sensitivity is function of PSADT (must be <10 months) but for >1.0 very sensitive for any DT.

Axumin

THE JOURNAL OF UROLOGY
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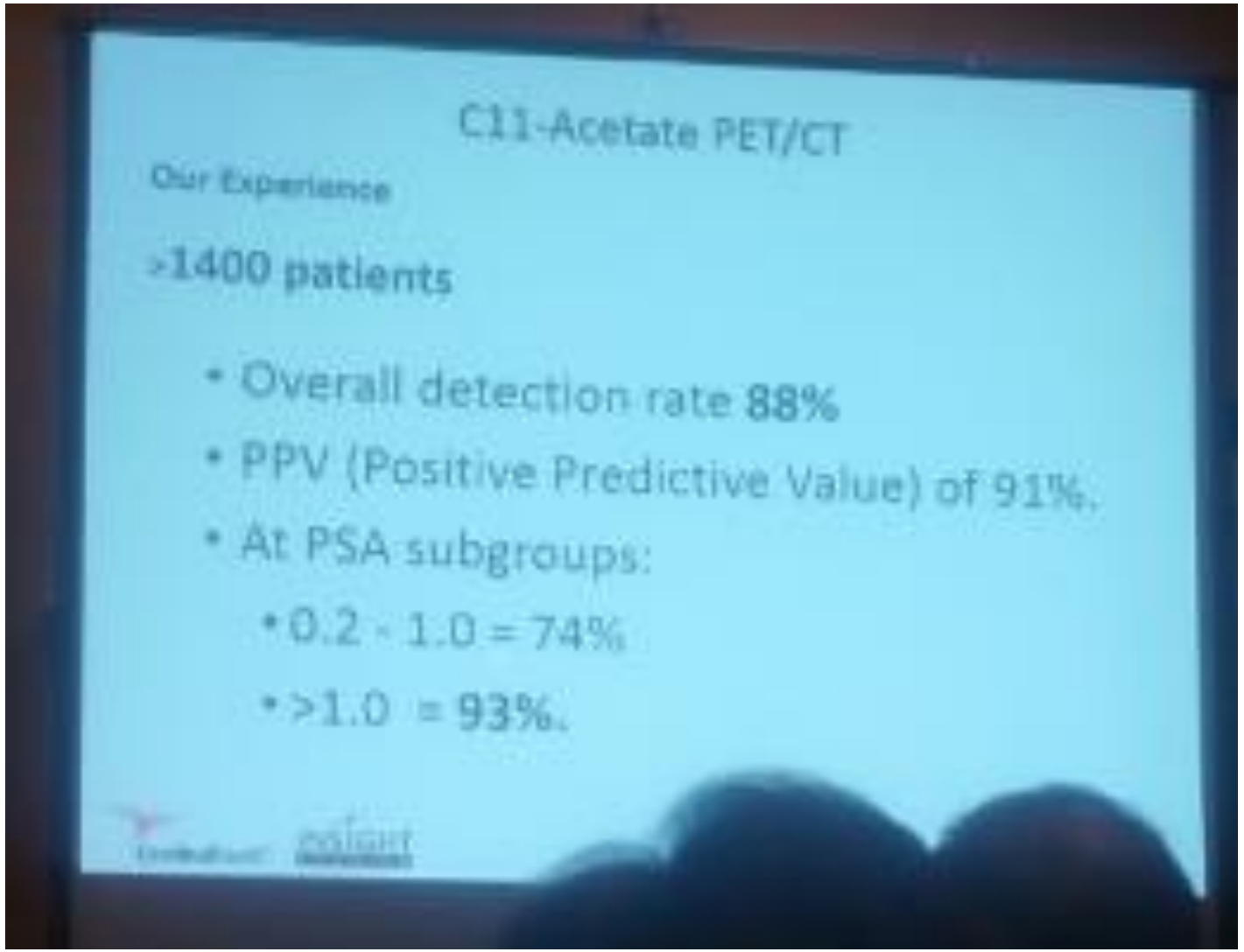
Multisite Experience of the Safety, Detection Rate and Diagnostic Performance of Fluciclovine (18F) Positron Emission Tomography/Computerized Tomography Imaging in the Staging of Biochemically Recurrent Prostate Cancer

Purpose: Sensitive detection of cancer foci in men experiencing biochemical recurrence following initial treatment of prostate cancer is of great clinical significance with a possible impact on subsequent treatment choice. We describe a multisite experience of the efficacy and safety of the positron emission tomography/computerized tomography agent fluciclovine (18F) after biochemical recurrence.

Materials and Methods: A total of 596 patients underwent fluciclovine (18F) positron emission tomography/computerized tomography at 4 clinical sites. Detection rate determinations were stratified by the baseline prostate specific antigen value. Diagnostic performance was assessed against a histological reference standard in 143 scans.

Results: The subject level fluciclovine (18F) positron emission tomography/ computer tomography detection rate was **67.7%** (403 of 595 scans). Positive findings were detected in the prostate/bed and pelvic lymph node regions in 38.7% (232 of 599) and 32.6% of scans (194 of 596), respectively. Metastatic involvement outside the pelvis was detected in 26.2% of scans (155 of 591). The subject level detection rate in patients in the lowest quartile for baseline prostate specific antigen (0.79 ng/ml or less) was 41.4% (53 of 128). Of these patients 13 had involvement in the prostate/bed only, 16 had pelvic lymph node involvement without distant disease and 24 had distant metastases. The positive predictive value of fluciclovine (18F) positron emission tomography/computerized tomography scanning for all sampled lesions was **62.2%**, and it was 92.3% and 71.8% for extraprostatic and prostate/bed involvement, respectively. Fluciclovine (18F) was well tolerated and the safety profile was not altered following repeat administration.

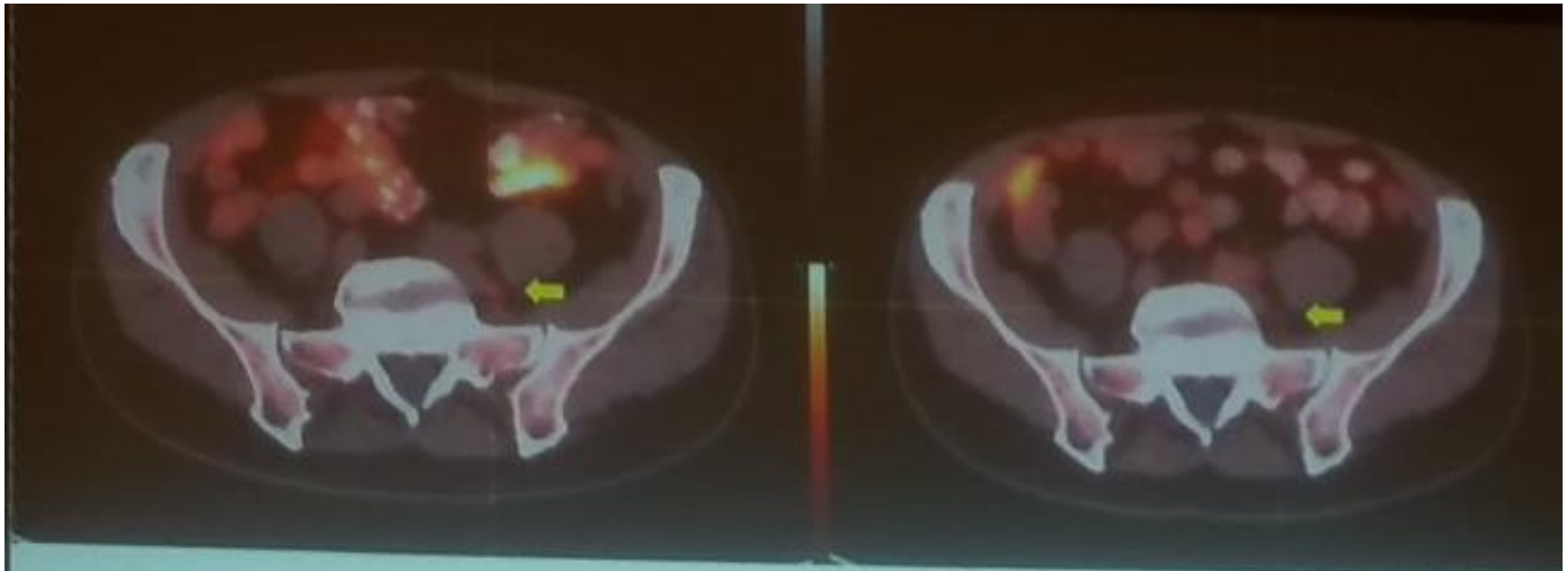

C11-Acetate PET/CT
Our Experience
>1400 patients
• Overall detection rate 88%
• PPV (Positive Predictive Value) of 91%.
• At PSA subgroups:
• 0.2 - 1.0 = 74%
• >1.0 = 93%.

C11-Acetate PET/CT

PSA & dT influence on detection

dT	PSA ≤ 1	PSA > 1
≤ 3 months	90%	92%
> 3 ≤ 10 months	72%	94%
> 10 months	50%	90%

CardinalHealth™ INSIGHT



69 y/o Gs 3+4 = 7, Rising PSA 0.7 ng/mL.
Left Imaging C11-Acetate, Positive left common iliac node.
Right, same pt, Axumin, minimally positive.

PSMA targeted molecules

Multiple radiolabels on various different small molecules currently under investigation

- Found in prostate, brain, kidney proximal tubules, intestinal brush border membranes
- Expression is increased in prostate cancer and tumor neovasculature
- Function of PSMA in the prostate cancer is unclear; believed to play a role in tumor invasiveness
- Detection rate 83-93%

68Ga-PSMA-11
68Ga-PSMA-617
68Ga-PSMA-I&T
68Ga-PSMA-R2
68Ga-PSMA-SR6
68Ga-NODAGA
68Ga-P16-093
64Cu-PSMA-617
64Cu-NODAGA

99mTc-MIP-1404
99mTc-HYNIC-PSMA
99mTc-J591
99mTc-EC0652
123I-MIP-1972
123I-MIP-1095
18F-DCFPyl
18F-DCFBC
18F-CTT1057
18F-PSMA-1007

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