EDUCATIONAL FORUM 3

CASE BASED APPROACH IN THE MANAGEMENT OF LOW VOLUME INTERMEDIATE RISK PROSTATE CANCER

PANEL MEMBERS

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LAST MINUTE SUBSTITUTION

- Role of Dr Taneja will be played by

- **Dr Joe Chin**

OUTLINE

- Case based approach
- Brief presentation from each panel member
- Meant to be very interactive

OBJECTIVES

- Role of Active Surveillance in Intermediate Grade Prostate Cancer
- Focal Therapy and its use in Intermediate Risk Prostate Cancer
- When to use newer radiotherapy modalities in Prostate Cancer

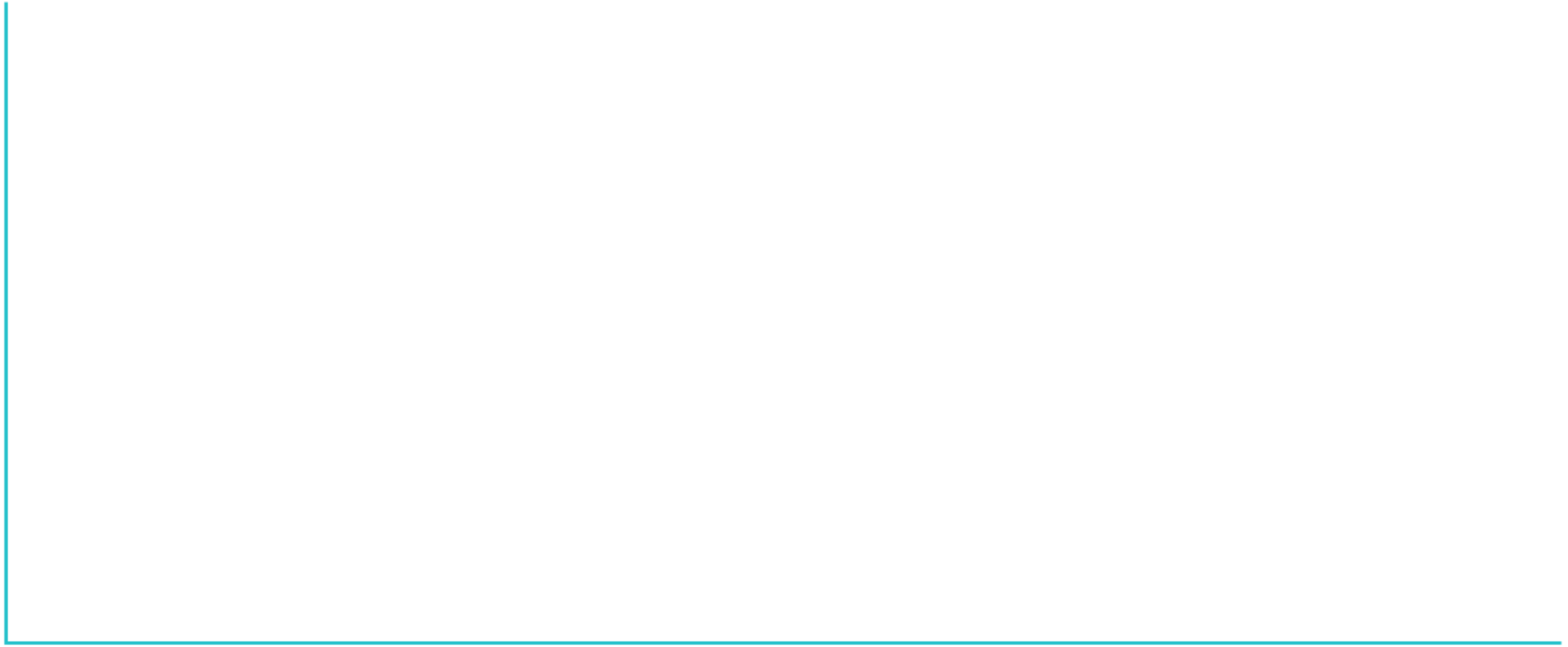
CASE 1

- 52 yo male who presents with PSA 4.2, which is the same on repeat 1 week later. Clinically benign exam but family history of PCa. Takes an antihypertensive and a lipid lowering agent. History bilateral laparoscopic hernia repair.

1. What is Your Next Step?

- Urinalysis and Culture
- Repeat PSA in a few months
- Prostate MRI
- Prostate Biopsy

1. What is Your Next Step?



1. What is Your Next Step?

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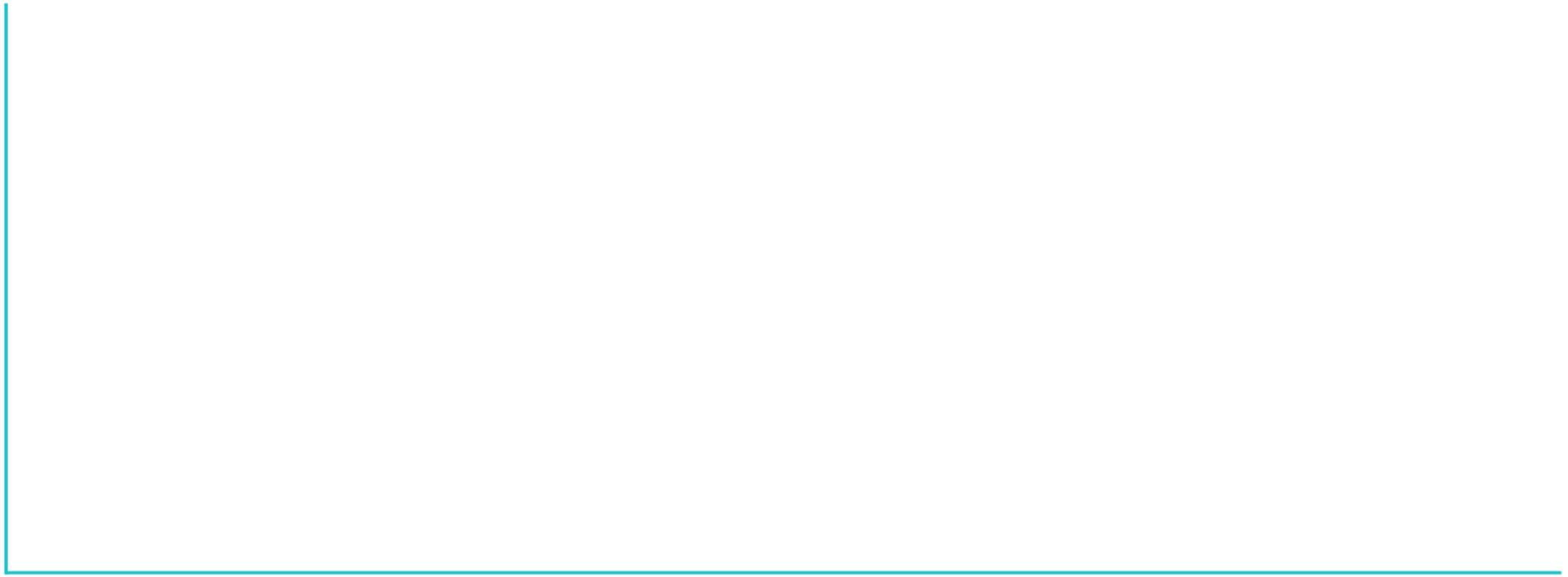
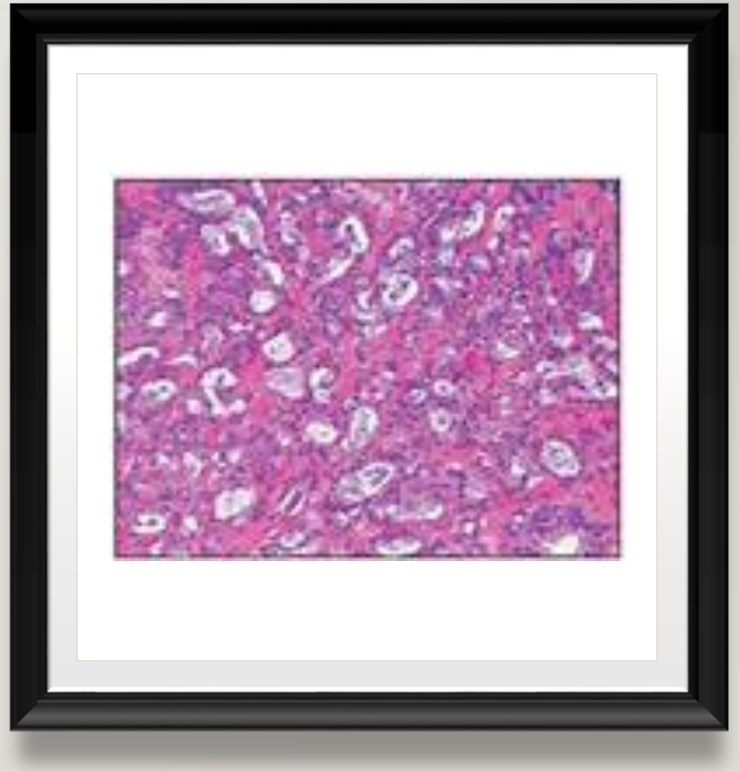


CASE 1

- Elects to undergo Prostate Biopsy. It comes back showing 1/12 cores Gleason GG 2. He has excellent pre op potency and continence with no LUTS.



2. What is Your Next Step?

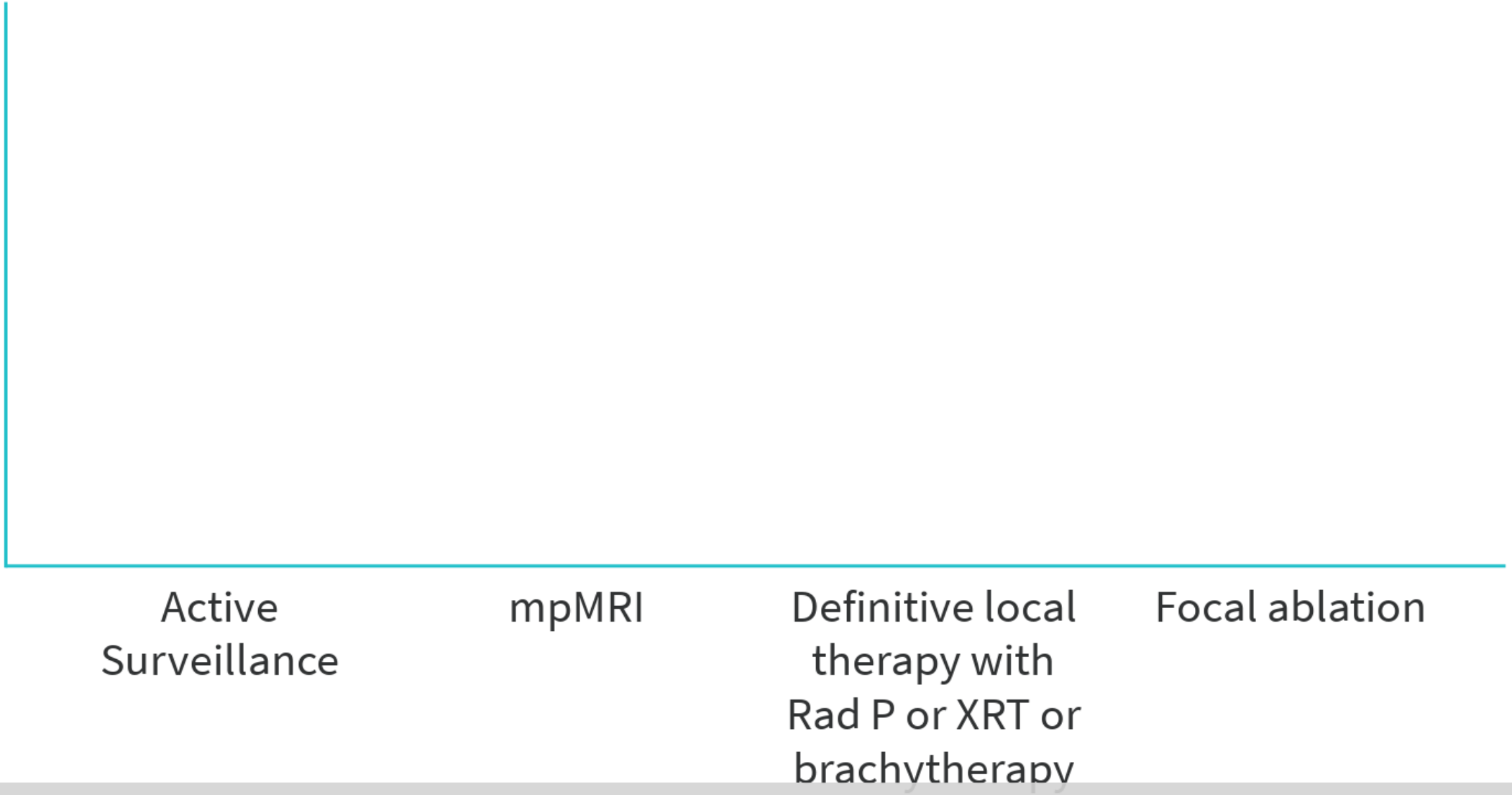
Active Surveillance

mpMRI

Definitive local therapy with
Rad P or XRT or brachytherapy

Focal ablation

2. What is Your Next Step?



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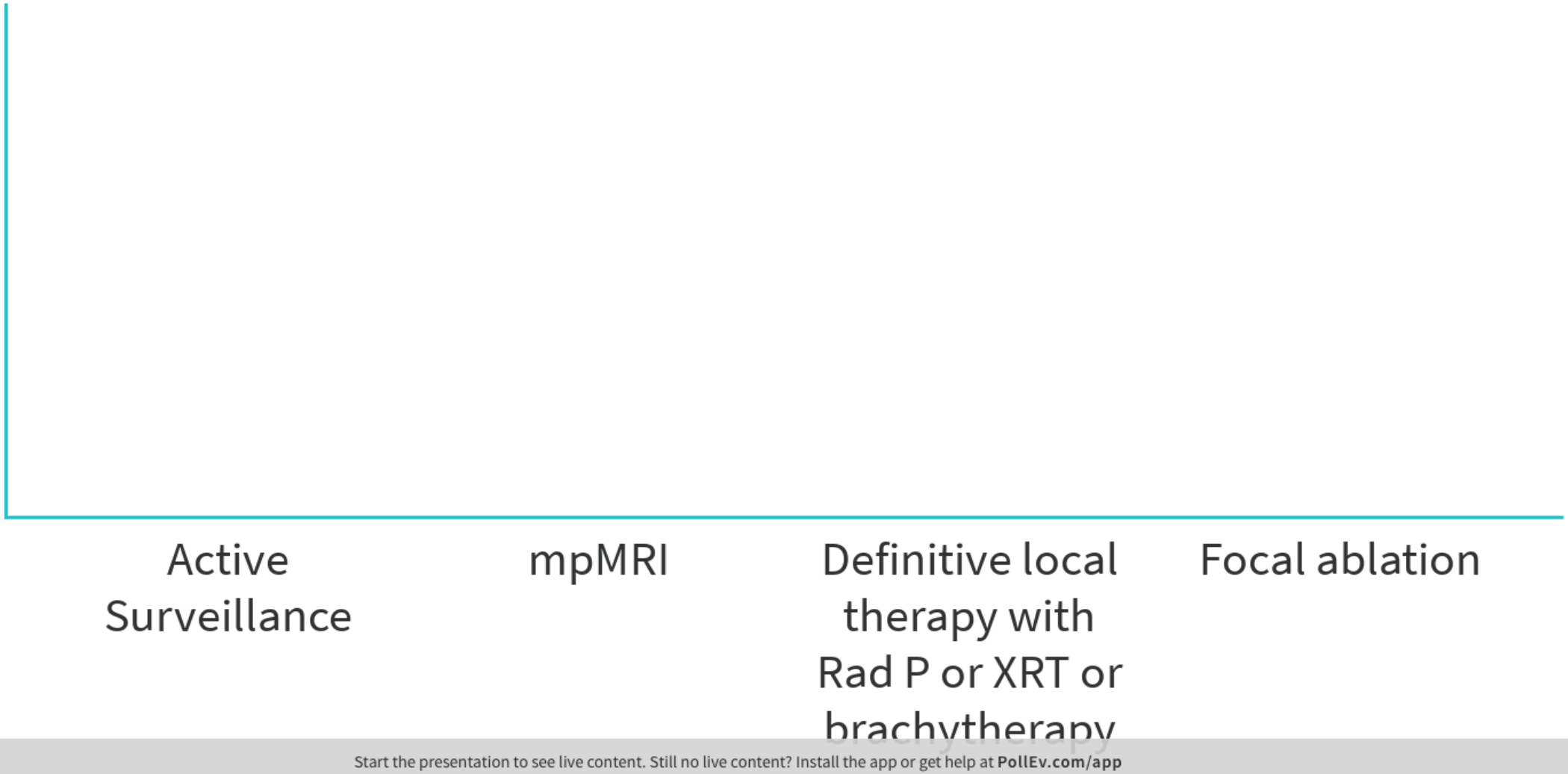


ACTIVE SURVEILLANCE

Active surveillance for intermediate risk prostate cancer

Luke T. Lavallée
Urologic Oncologist
Associate Scientist
Ottawa Hospital Research Institute
The University of Ottawa

Disclosures

- No financial related to this talk
- Ad boards/grants Sanofi, Janssen
- Perform robotic prostatectomy

Index patient

- 52M
- PSA 4.2
- 1/12 core + Gleason 7

Question:

1. AS
2. MRI
3. RP or XRT
4. Ablation

????

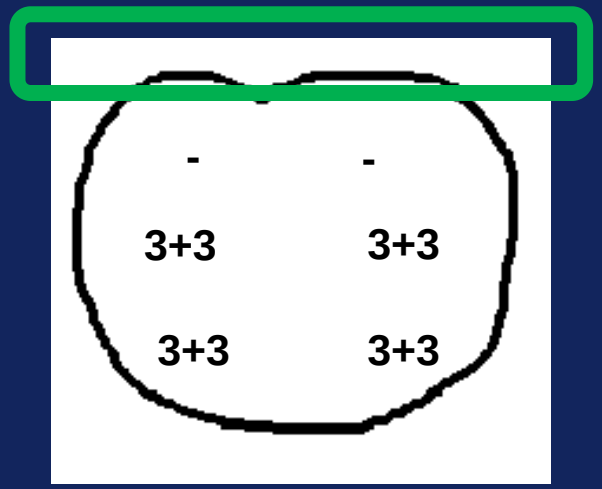
TRADITIONAL GLEASON SCORE	NEW GRADING SYSTEM GROUP 1
GLEASON 3+3=6 Only individual discrete well-formed glands	GRADE 1
GLEASON 3+4=7 Predominantly well-formed glands with a lesser component of poorly-formed/fused/cribiform glands.	GRADE 2
GLEASON 4+3=7 Predominantly poorly-formed/ fused/cribriform glands with a lesser component of well-formed glands.	GRADE 3
GLEASON 4+4=8 Only poorly-formed/fused/cribriform glands or -Predominantly well-formed glands with a lesser component lacking or -Predominantly lacking glands with a lesser component of well-formed glands.	GRADE 4
GLEASON 9-10 Lacks gland formation (or with necrosis) with or without poorly-formed/fused/cribriform gland.	GRADE 5

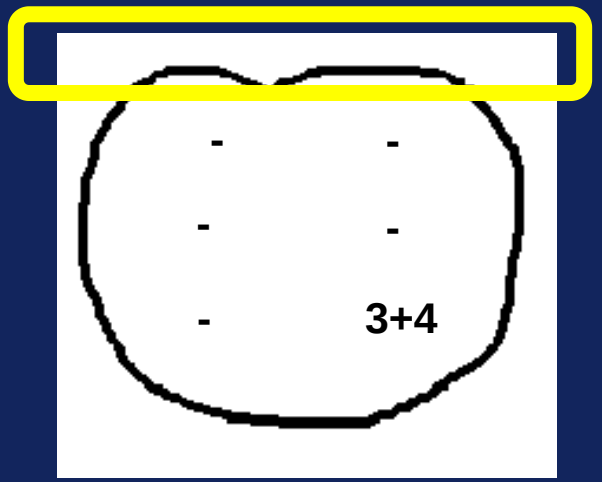
Definition of intermediate risk

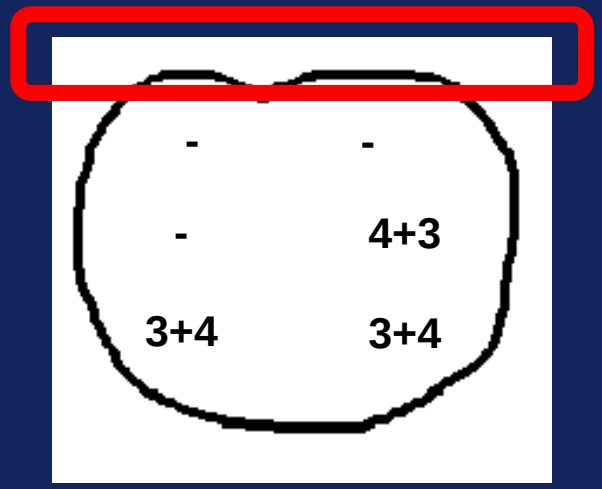
- Intermediate = heterogenous population
  - PSA, stage, Gleason grade / grade group

- Today: Intermediate risk focused on Gleason 7 (3+4 / GG2)

- Surveillance preferred for most Gleason 6







Goals of Active Surveillance

- Maintain quality of life
- Avoid risks of radical intervention
- Identify worse pathology (misclassified or progress)
- Don’t miss window of curability

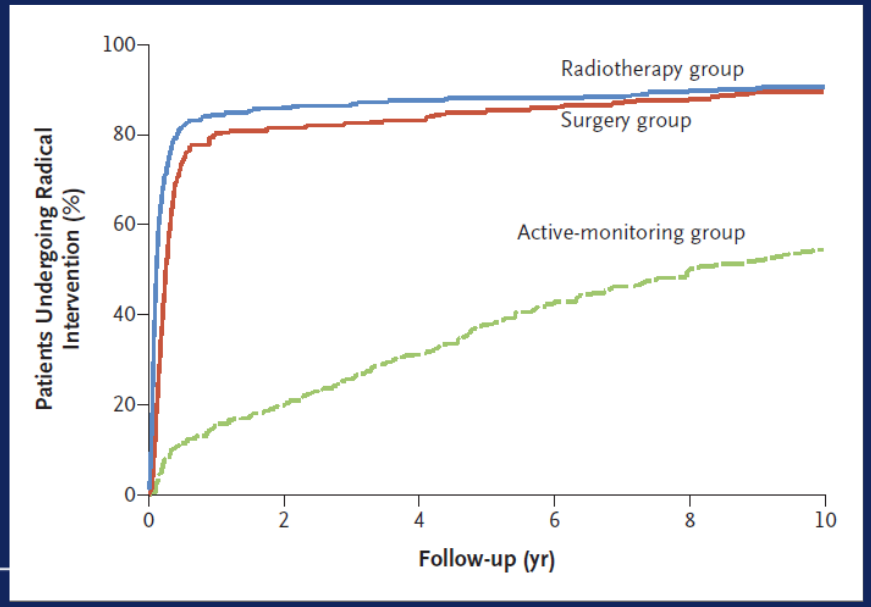
Outcomes Gleason 7 Surveillance

ProTect trial (Hamdy 2016)

- Level 1 evidence

- AS vs RP vs XRT (AS monitoring less intense)
  - n = ~550 per arm
  - 54% of AS had intervention

- PCa survival >98% at 10yrs



Gleason 7 in ProTect

- n = 111 Gleason 7 in AS (20%)
  - Stratified data not reported

- 2-3x increased mets and progression in AS group
  - 6.3 vs 2.4 mets / 1000 person years (low event rate)

Gleason 7 on Surveillance
Cohort studies

- Sunnybrook series (Klotz JCO 2015)
  - n=993
  - 132 (13%) Gleason 7
  - 28 (2.8%) developed mets
    - 16/861 (1.8%) Gleason 6
    - 12/132 (9.1%) Gleason 7
  - Mean time to mets 7.3 years

Intermediate risk and AS

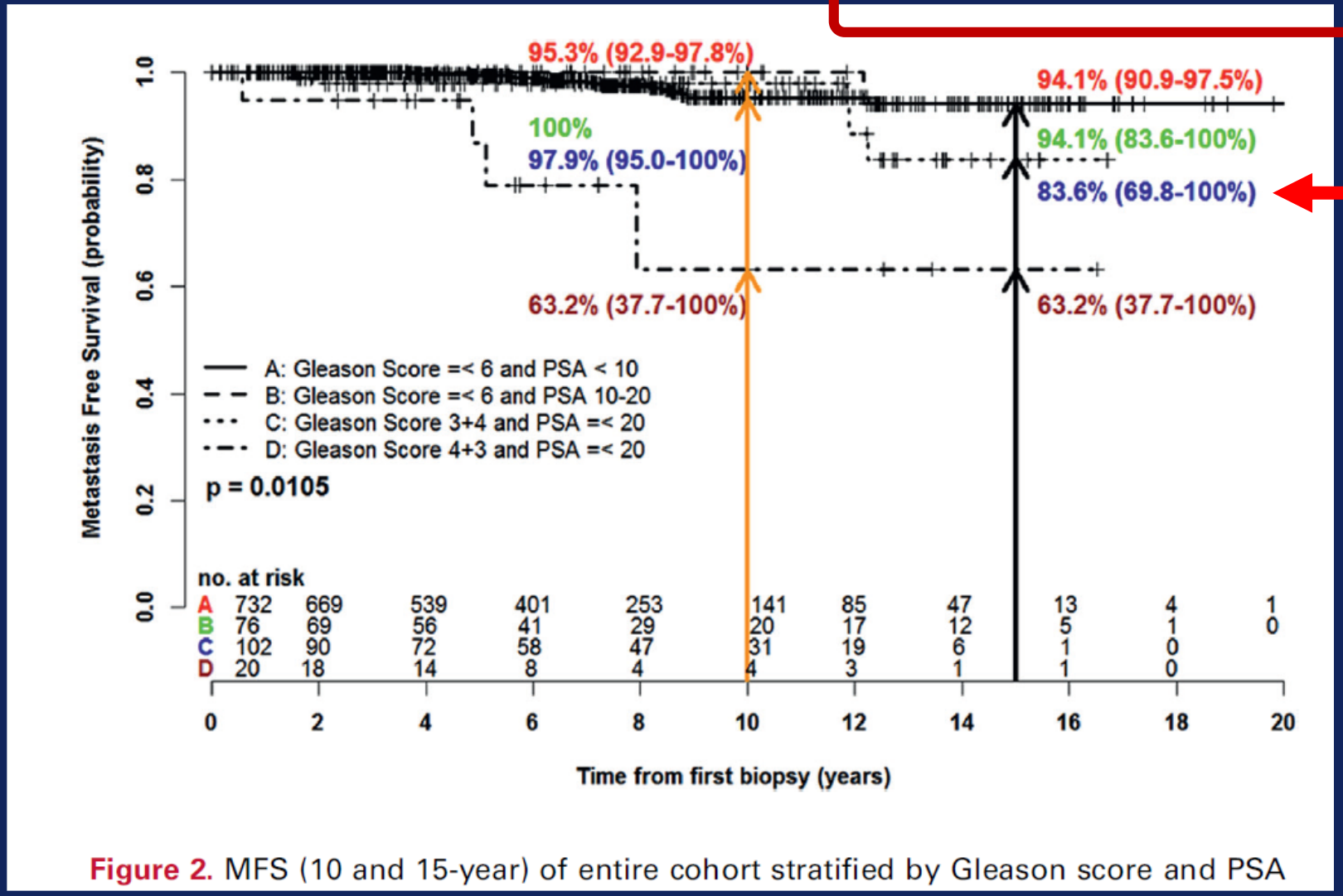


Figure 2. MFS (10 and 15-year) of entire cohort stratified by Gleason score and PSA

Surveillance for intermediate risk

- Conclusions
  - Mets more common
  - Change btwn 10 and 15 year f/u

Questions remain

1. Will longer f/u show worse outcomes in AS?

2. Selection bias to enter studies, trigger treatment?
   - Where these patients followed/treated the way we would treat a healthy Gleason 7 on AS?

3. Could MRI/biomarkers help select/monitor?

Cancer Care Ontario Guideline

- CUAJ Morash et al. 2015

> **RECOMMENDATION 2:** Active treatment (RP or RT) is appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume Gleason 3+4=7 localized prostate cancer, AS can be considered.

- <10% pattern 4
  - Assumes 12 core biopsy/standardized reporting

NICE Guideline (UK 2019)

1.3.12 For people with intermediate-risk localised prostate cancer:

- offer radical prostatectomy or radical radiotherapy **and**
- consider active surveillance (in line with recommendation 1.3.9) for people who choose not to have immediate radical treatment.

How to perform AS in Gleason 7

- PSA – trend more than number
- DRE
- MRI – early if not done before biopsy
- Repeat biopsy early
- Genomic testing, biomarkers??
  - I do not use at this time

NICE 2019 – AS protocol

Table 4 Protocol for active surveillance

Timing	Tests[†]
Year 1 of active surveillance	Every 3 to 4 months: measure prostate-specific antigen (PSA)[‡] Throughout active surveillance: monitor PSA kinetics[§] At 12 months: digital rectal examination (DRE)[¶] At 12 to 18 months: multiparametric MRI
Year 2 and every year thereafter until active surveillance ends	Every 6 months: measure PSA[‡] Throughout active surveillance: monitor PSA kinetics[§] Every 12 months: DRE[¶]

[†]If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re-biopsy. [‡]Could be carried out in primary care if there are agreed shared-care protocols and recall systems. [§]Could include PSA density and velocity. [¶]Should be performed by a healthcare professional with expertise and confidence in performing DRE. In a large UK trial that informed this protocol, DREs were carried out by a urologist or a nurse specialist.

Eligibility Criteria - Key concept

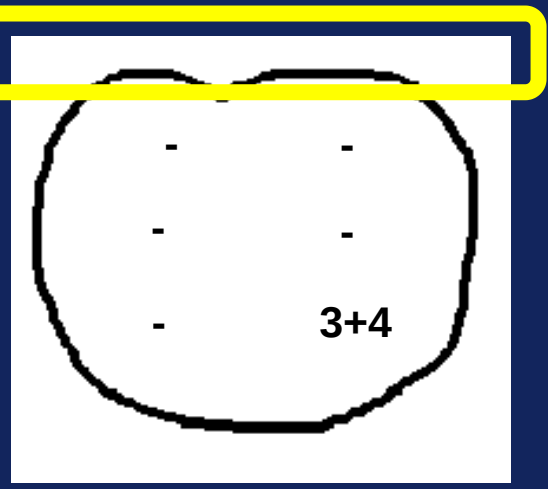
- Eligibility criteria represent a spectrum of risk

  - Restrictive criteria → less progress to treatment
  - Inclusive criteria → more progress to treatment

Match intensity to patient/disease characteristics

Take Home Messages

- Surveillance is standard for Gleason 6



- Gleason 7
  - Short term outcomes good
  - Long term, higher risk mets

- My opinion:
  - Period of surveillance acceptable for some Gleason 7
  - Need research to:
    - Define eligible patients
    - Determine best monitoring plan

Thank you

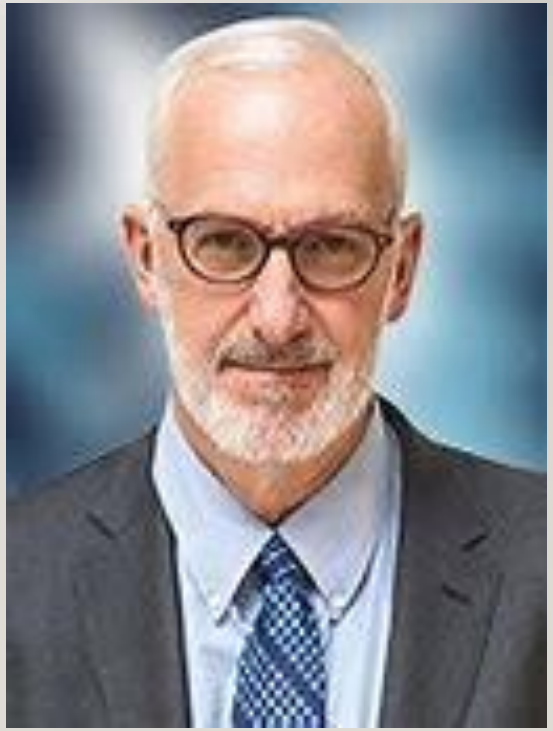
- Luke Lavallée
- lulavallee@toh.ca

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

SURVEILLANCE TAKE AWAYS

CASE 2

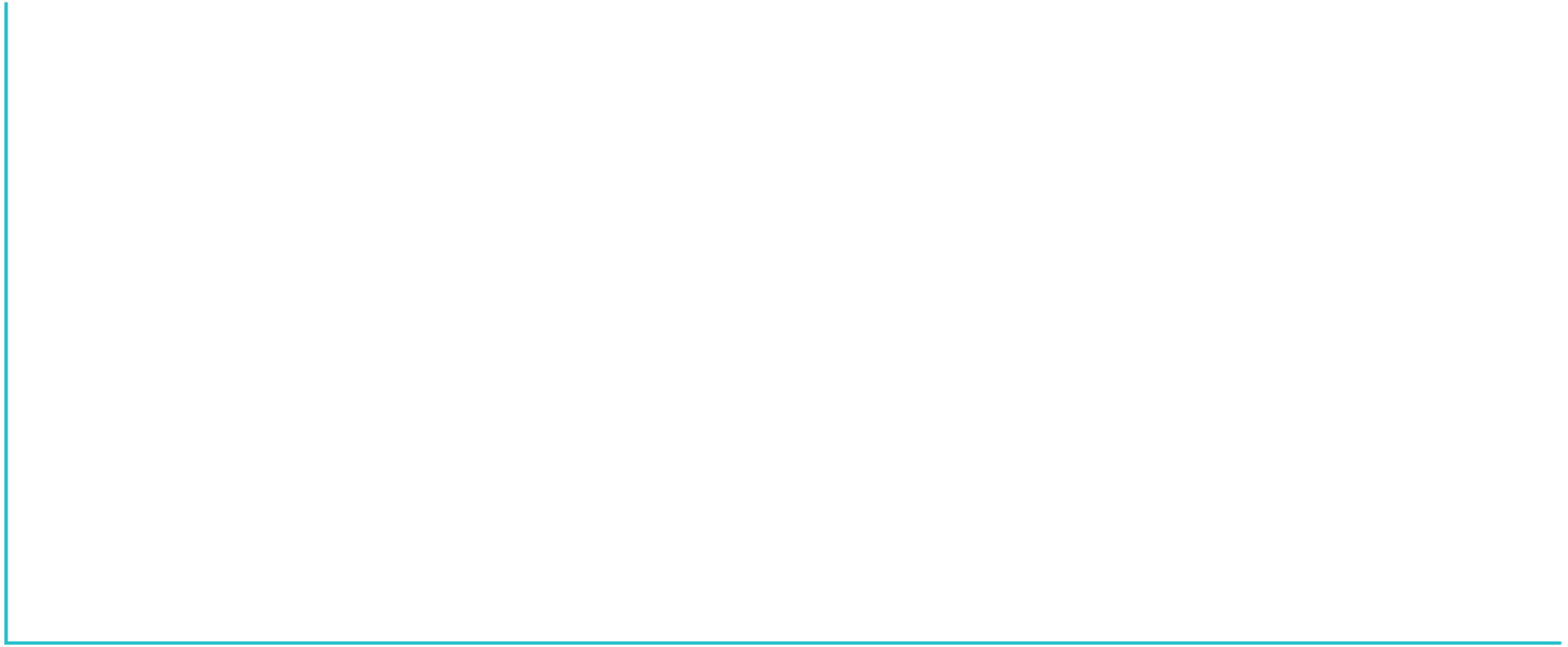
- 67 yo male referred with PSA 8, DRE reveals a benign feeling prostate of about 40cc. Minimal LUTS, has HTN and hypercholesterolemia, previous appendectomy. Last year his PSA was 4.
- He elects to undergo a prostate Biopsy and it shows 3/12 cores positive with most of the cores showing 10-15% volume. Gleason Grade Group 1.



3. What is Your Next Step?

- Initiate Active surveillance
- mpMRI prostate
- Arrange for definitive Treatment
- Arrange CT scan and Bone scan

3. What is Your Next Step?



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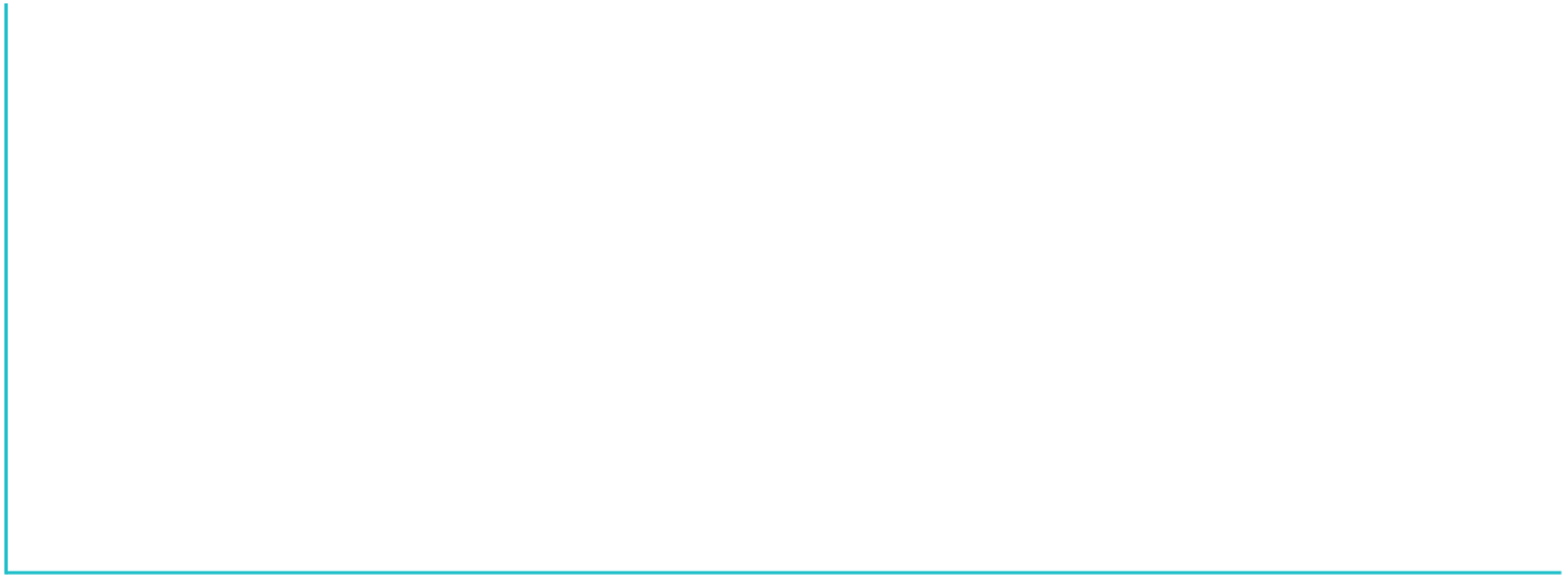


CASE 2

- On confirmatory Biopsy it shows 3/12 cores + with one core showing GG2 with 70% of that core positive and the remaining GG1

4. What is Your Next Step?

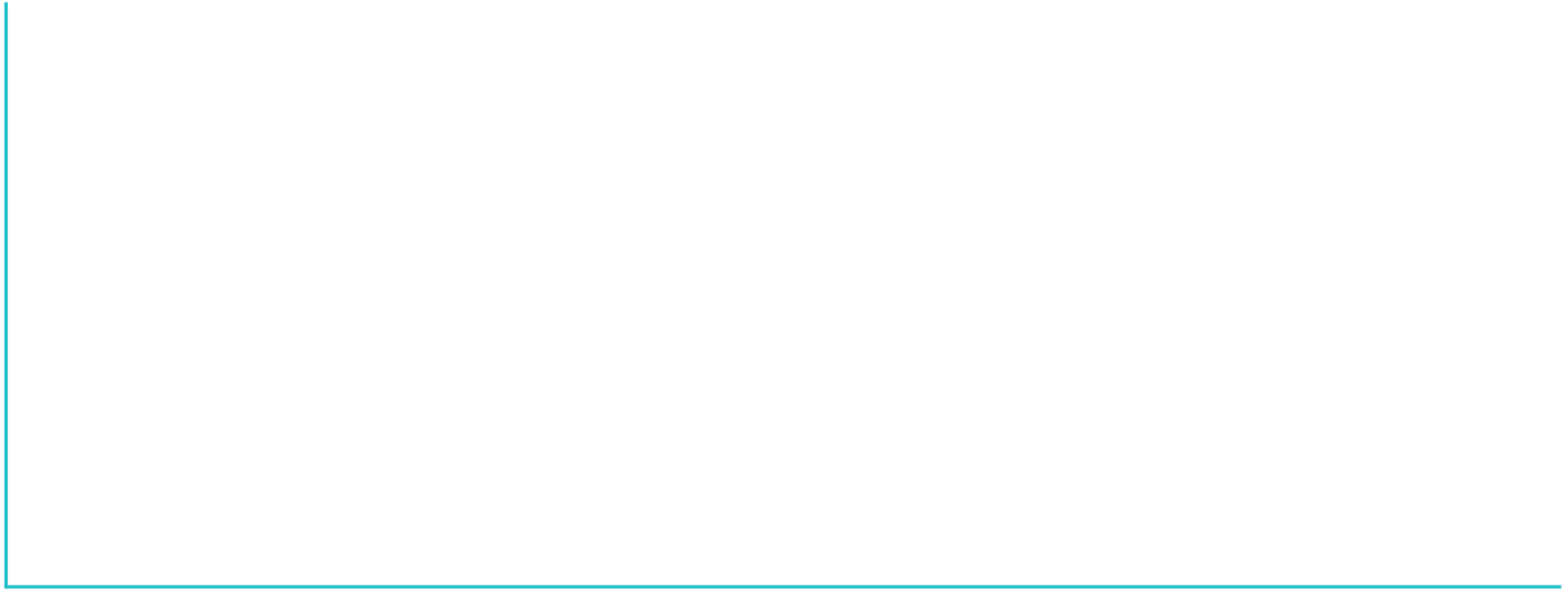
Continue Active surveillance

MRI prostate

Arrange for definitive Tx with focal therapy

Arrange for definitive Tx with XRT or
Radical Prostatectomy

4. What is Your Next Step?



4. What is Your Next Step?

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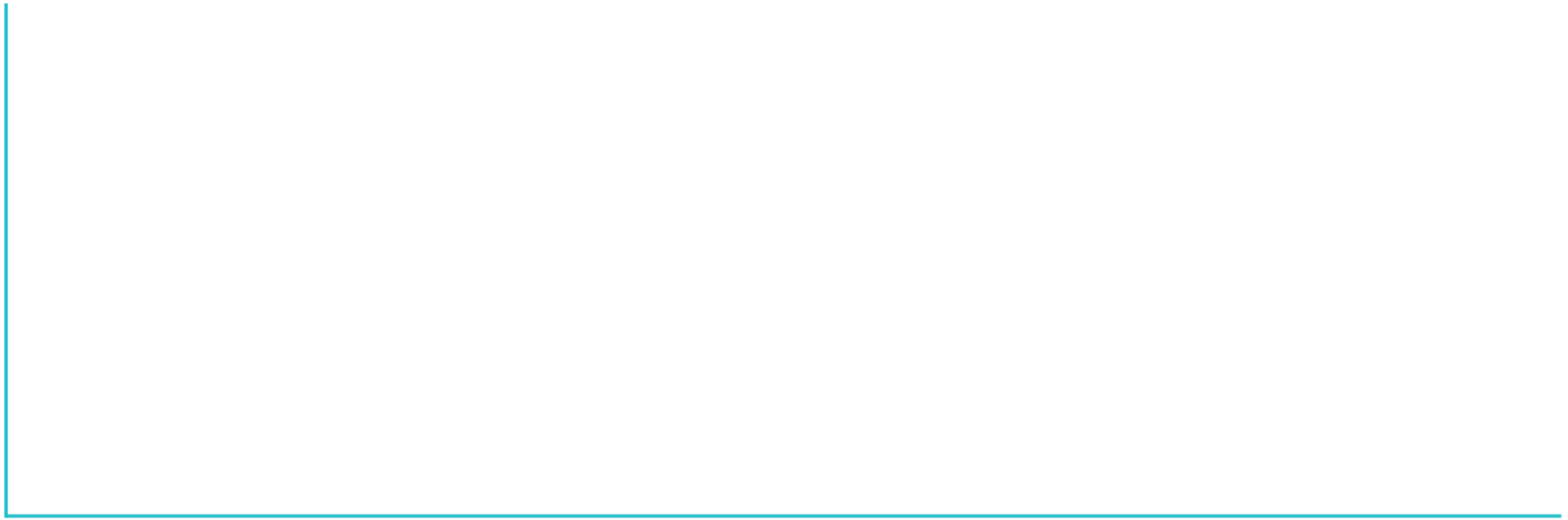


FOCAL THERAPY

IMPLEMENTATION OF FOCAL THERAPY IN PRACTICE :CRITICAL CONCEPTS AND OBSTACLES

Samir S. Taneja, MD

The James M. and Janet Riha Neissa Professor of Urologic Oncology

Professor of Urology, Radiology, and Biomedical Engineering

Director, Division of Urologic Oncology

GU Program Leader, NYU Perlmutter Cancer Center

J.L. Chin, M.D.

Western University

London ON Canada

DISCLOSURES

Consultant: Insightec

Sophiris

Trod Medical

Francis Medical

Scientific Investigator: MDx Health

Sophiris

DISCLOSURES : J. CHIN

	Company/Organization
I am a member of an **Advisory Board or equivalent** with a commercial organization.	Profound Med Inc US HIFU Amgen, Janssen, Astellas , Ferring
I have **received payment from a commercial organization** (including gifts or other consideration or 'in kind' compensation)	Profound Med Inc. Amgen, Janssen, Astellas, Abbvie

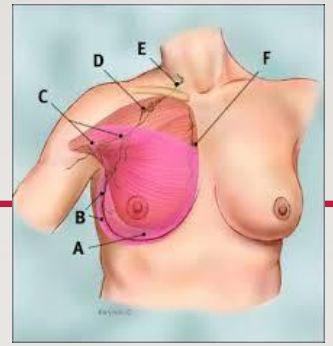
	Company/Organization
I have **received a grant(s)** or an honorarium from a commercial organization.	Profound Med Inc US HIFU Amgen, Janssen, Astellas, Abbvie
I **hold a patent** for a product referred to in the CME/CPD program or that is marketed by a commercial organization.	
I **hold investments** in a pharmaceutical organization, medical devices company or communications firm.	
I am currently participating in or have participated in a **clinical trial** within the past two years.	Profound, US HIFU, Astellas, Abbvie, Novartis, DiagnoCure, Amgen,SanofiAventis, AstraZeneca, Ferring

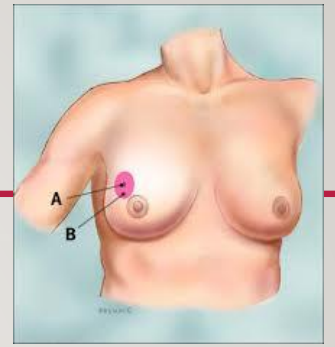
THERAPY FOR PROSTATE CANCER IS A CONCEPT, NOT A TECHNIQUE

Or …IS IT?

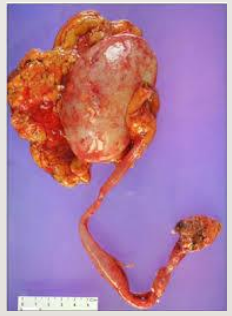
LESSONS FROM OTHER ORGAN SITES

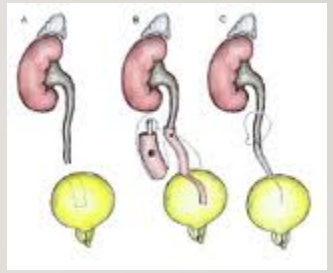
- Breast



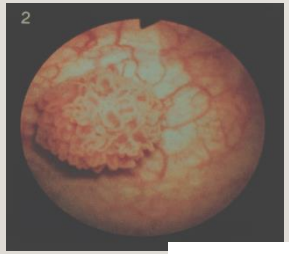


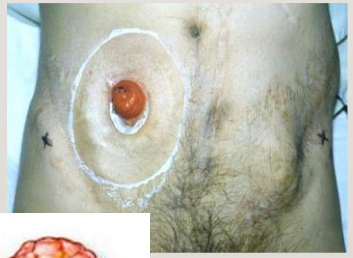
- Urothelial

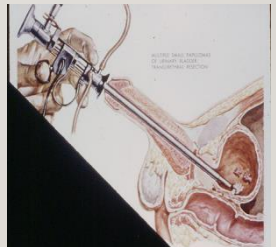




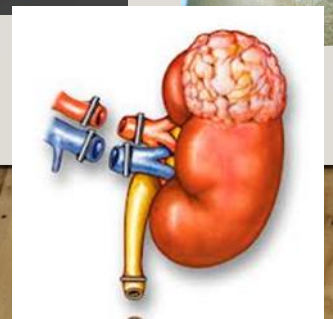
Low Risk Bladder

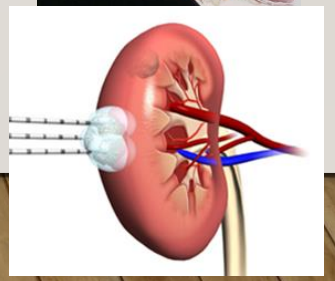




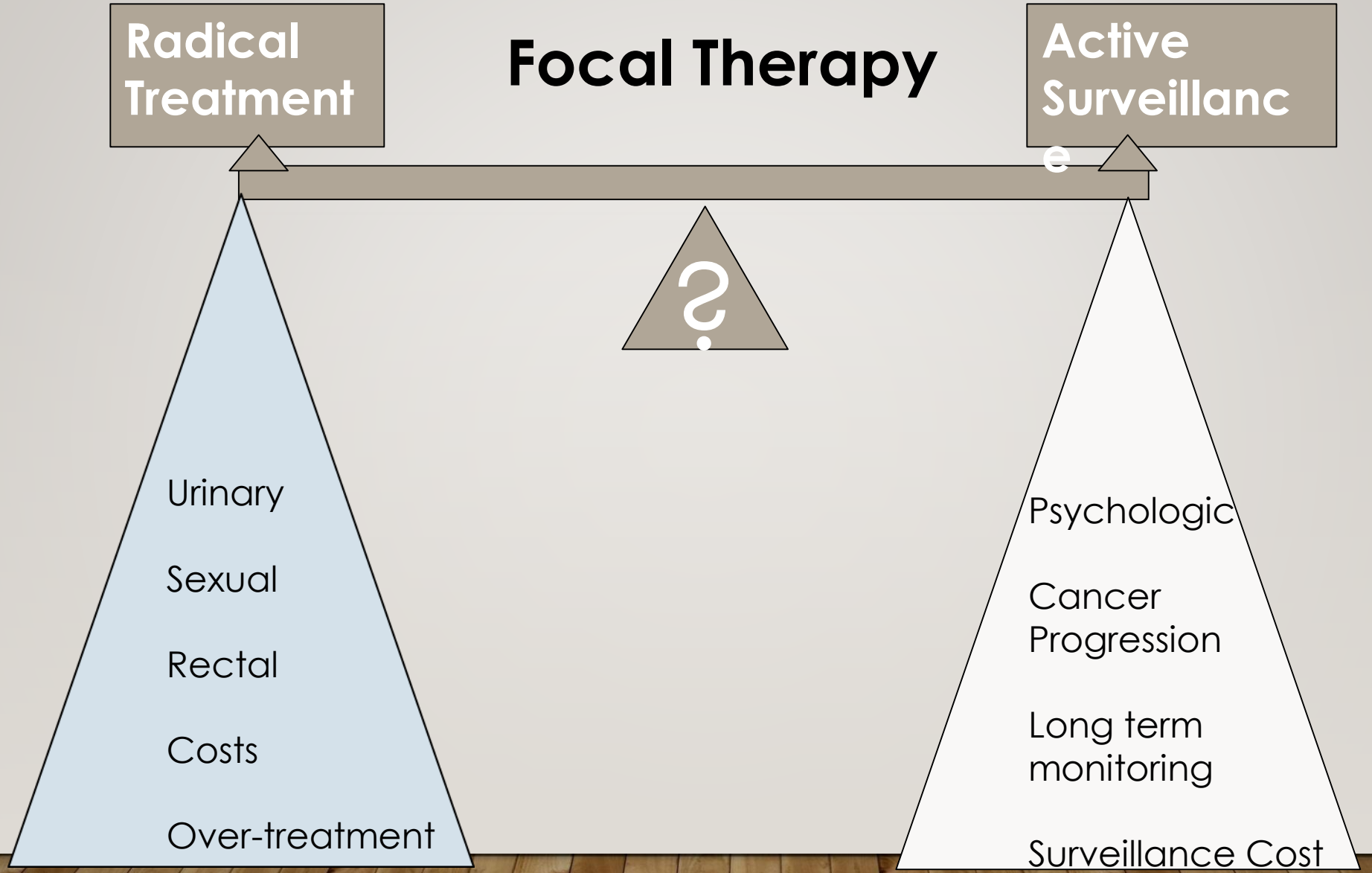


Renal





Options for Localised "Focal " Prostate Cancer

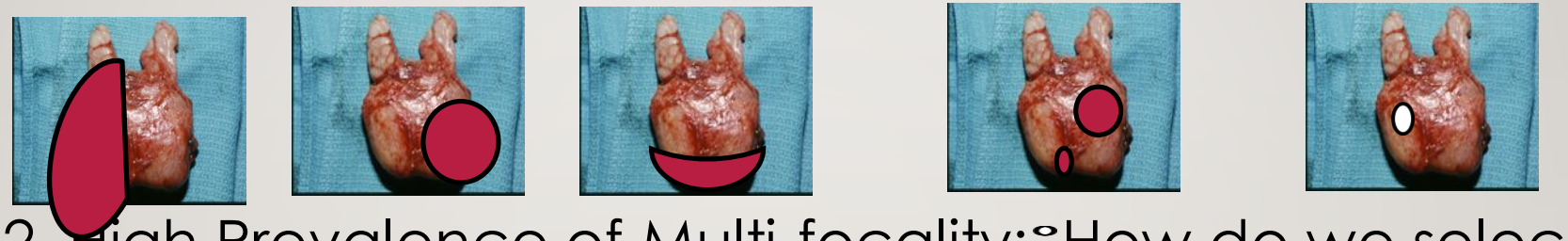


CRITICAL CONCEPTS YOU MUST ACCEPT TO ADOPT FOCAL THERAPEUTIC APPROACHES

- **Therapeutic goal is distinct from conventional therapy**
  - **high likelihood of residual cancer foci (>50%)**
  - **goal is prevention of metastasis/mortality**
  - **may allow reduced intensity of follow-up as compared to active surveillance**
- **Maximal treatment incorporates biopsy/MRI/3d conceptualization of tumor**
- **Follow-up may be inaccurate**
  - **relies on biopsy sampling efficiency/ image detection**
  - **PSA not as useful as in radical therapy**
- **The approach is investigational**
  - **no long term outcomes**
  - **No consensus on definitions of success**

CHALLENGES & TYPICAL CRITICISMS OF FOCAL THERAPY

- 1. Defining "Focal Ablation" Therapy
  - *Hemi-. Quadrant ab., Zonal ab., Index lesion ab.. ? "True Focal"*



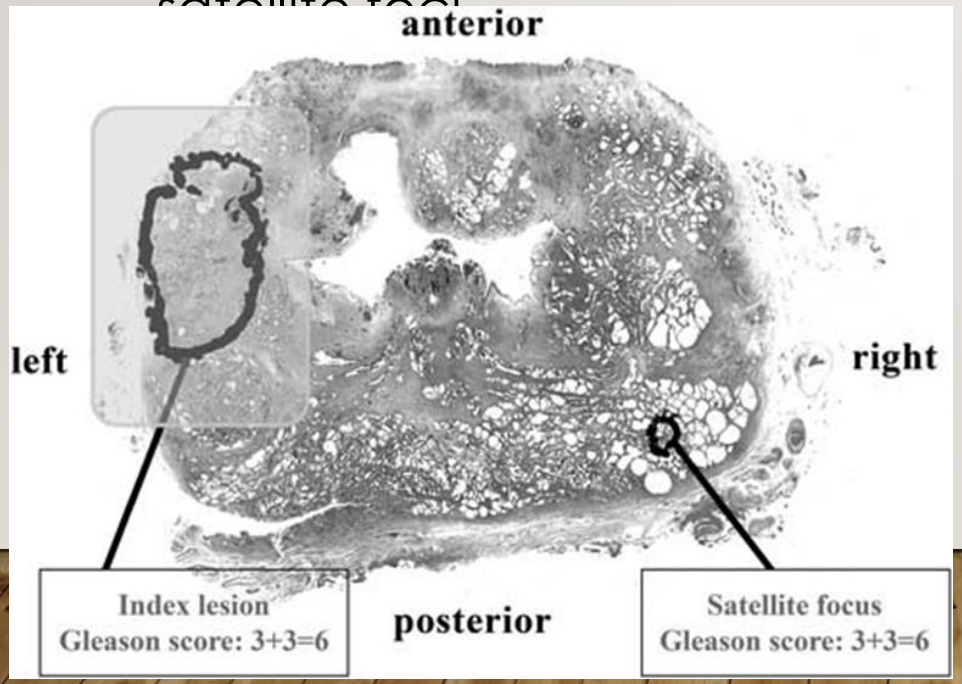
- 2. High Prevalence of Multi-focality: How do we select the right candidates?
  - → *"Index Lesion Hypothesis"*
- 3. Imaging, Biopsy & Access Challenges: accurate localization, sampling & targeting
  - → *Advanced Adjunctive Imaging and Localization Aids*
- 4. Effective Selective Ablation:
- 5. Assessing "Success"

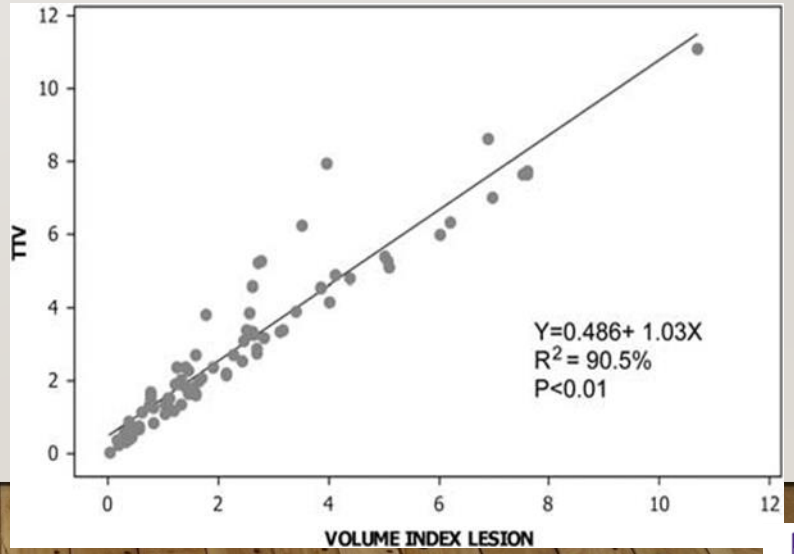
POSSIBLE ANSWER TO MULTIFOCALITY ISSUE "INDEX LESION HYPOTHESIS"

Villers, McNeal, Stamey; Cancer 1992

- ~~Disease progression and Natural History determined by Biology~~ and size of the Index Lesion

- ? Suffices to Ablate Index Lesion and Closely Follow-up smaller satellite foci





Prostate Cancer and Prostatic Diseases (2010), 1–7

1365-7852/10
www.nature.com/pcan

ORIGINAL ARTICLE

Histological characteristics of the index lesion in whole-mount radical prostatectomy specimens: implications for focal therapy

M Karavitakis[1,2], M Winkler[3], P Abel[1,3], N Livni[4], I Beckley[3] and HU Ahmed[5]

Index Lesion vs 2° Lesion : Different characteristics

Table 4 Histological characteristics of the individual tumour foci

Tumour type	*Total*	*Gleason ⩾7*		*Gleason ⩽6*		*Volume ⩾0.5 cm³*		*ECE*		*SVI*	
		N	%	N	%	N	%	N	%	N	%
Unifocal	22	7	31.8	15	68.2	18	81.8	5	22.7	7	31.9
Index lesions	78	24	30.7	54	69.3	66	84.6	13	16.6	5	6.4
Secondary lesions	170	1	0.6	169	99.4	22	12.9	2	1.1	0	0
Total	270	32		238		106		20		12	

Bott et al BJU Int 2010 374 foci

Median largest /Index tumor 0.95 ml

Median volume of largest 2^0 tumor 0.2 ml

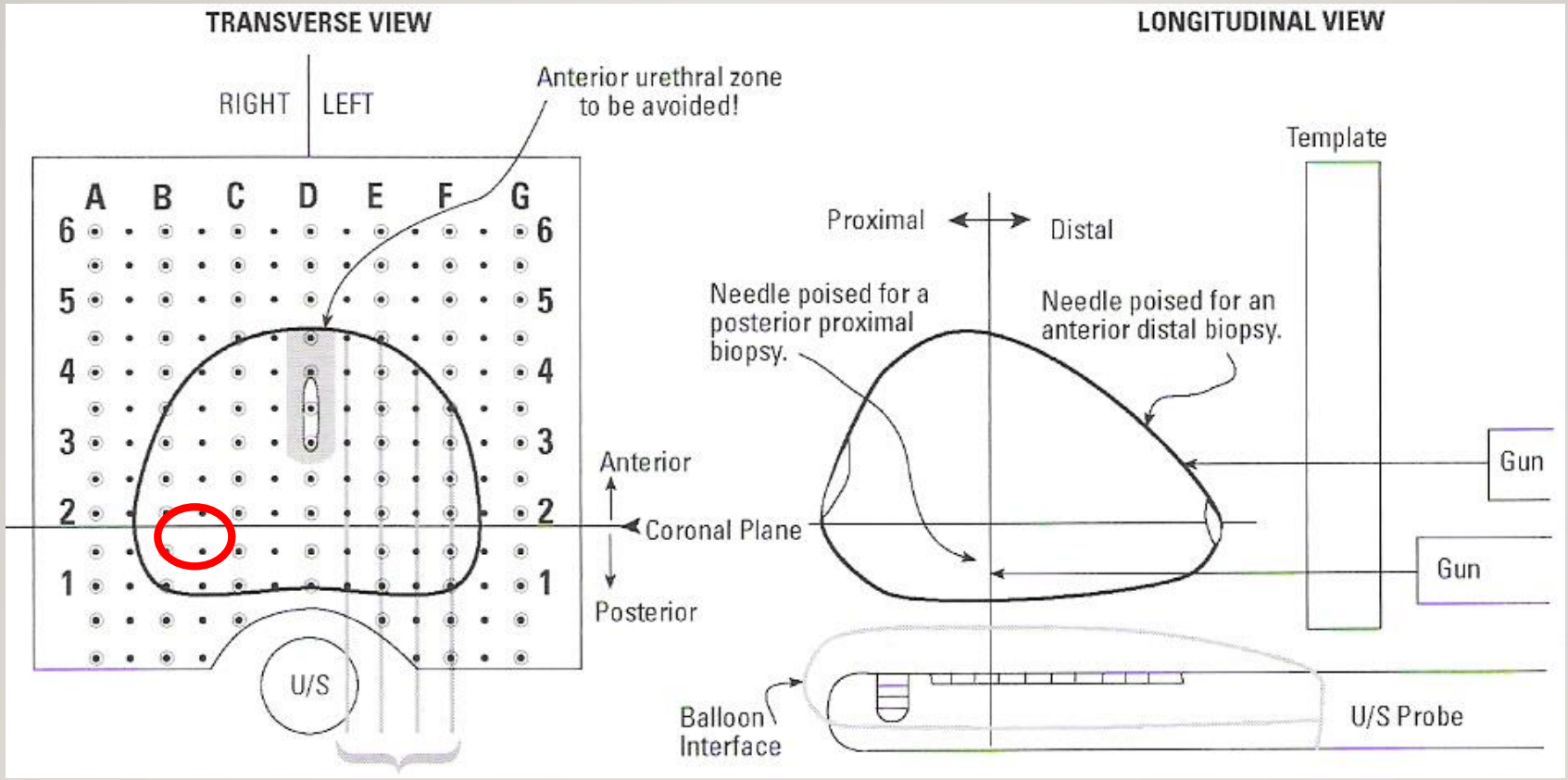
No pt with insignificant index lesion had significant (grade/EPE) 2^0 lesions

Molecular Evidence

Liu et al Nat Med

Western

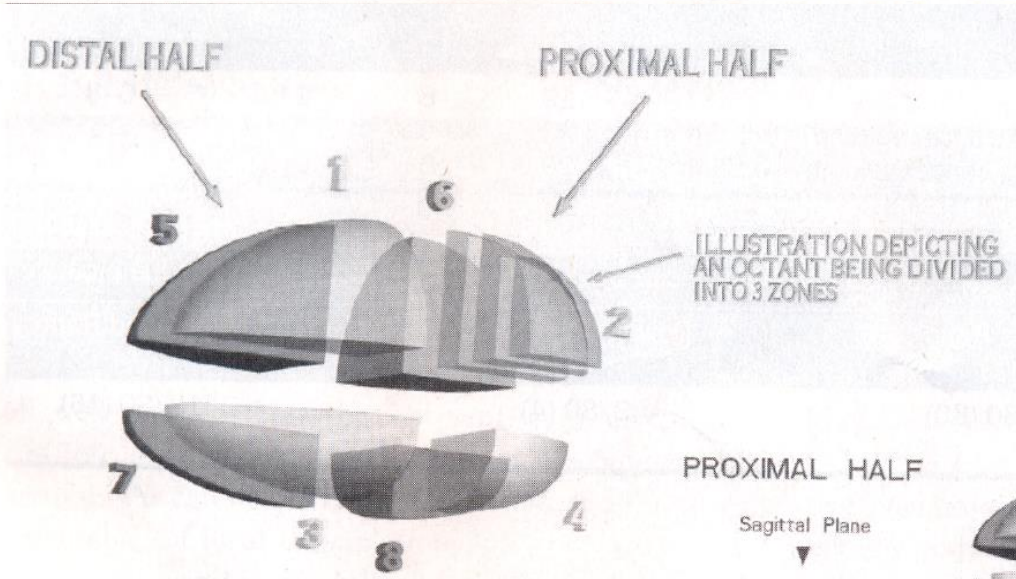
How to find the lesion(s)
PROSTATE MAPPING BIOPSIES



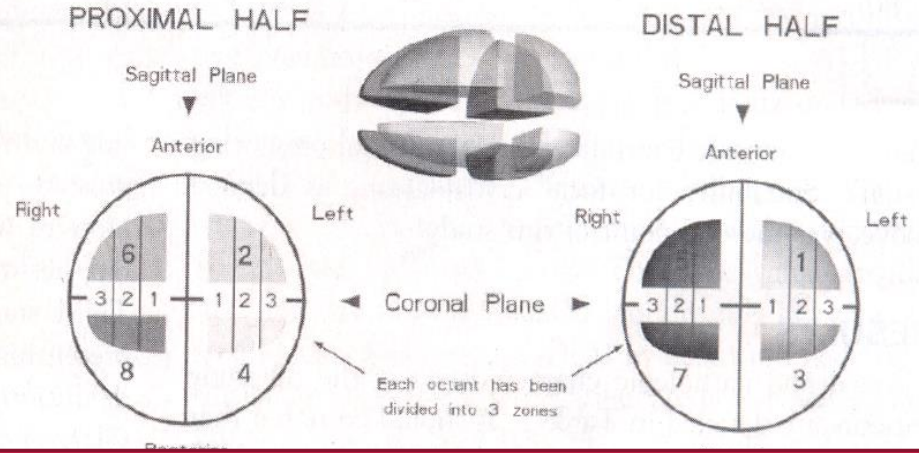
Barzell et al. Urology 2007; 70: S27
Onik et al. J Clin Oncol 2009; 27: 4321
Hara et al. Urology 2008; 71: 191

Appropriate Patient Selection in the Focal Treatment of Prostate Cancer: The Role of Transperineal 3-Dimensional Pathologic Mapping of the Prostate—A 4-Year Experience

Winston E. Barzell and Myron R. Melamed



Specimen jars:
24 Zones
2 Midline (proximal/distal)
2 to 8 TRUS
Total 28 to 34



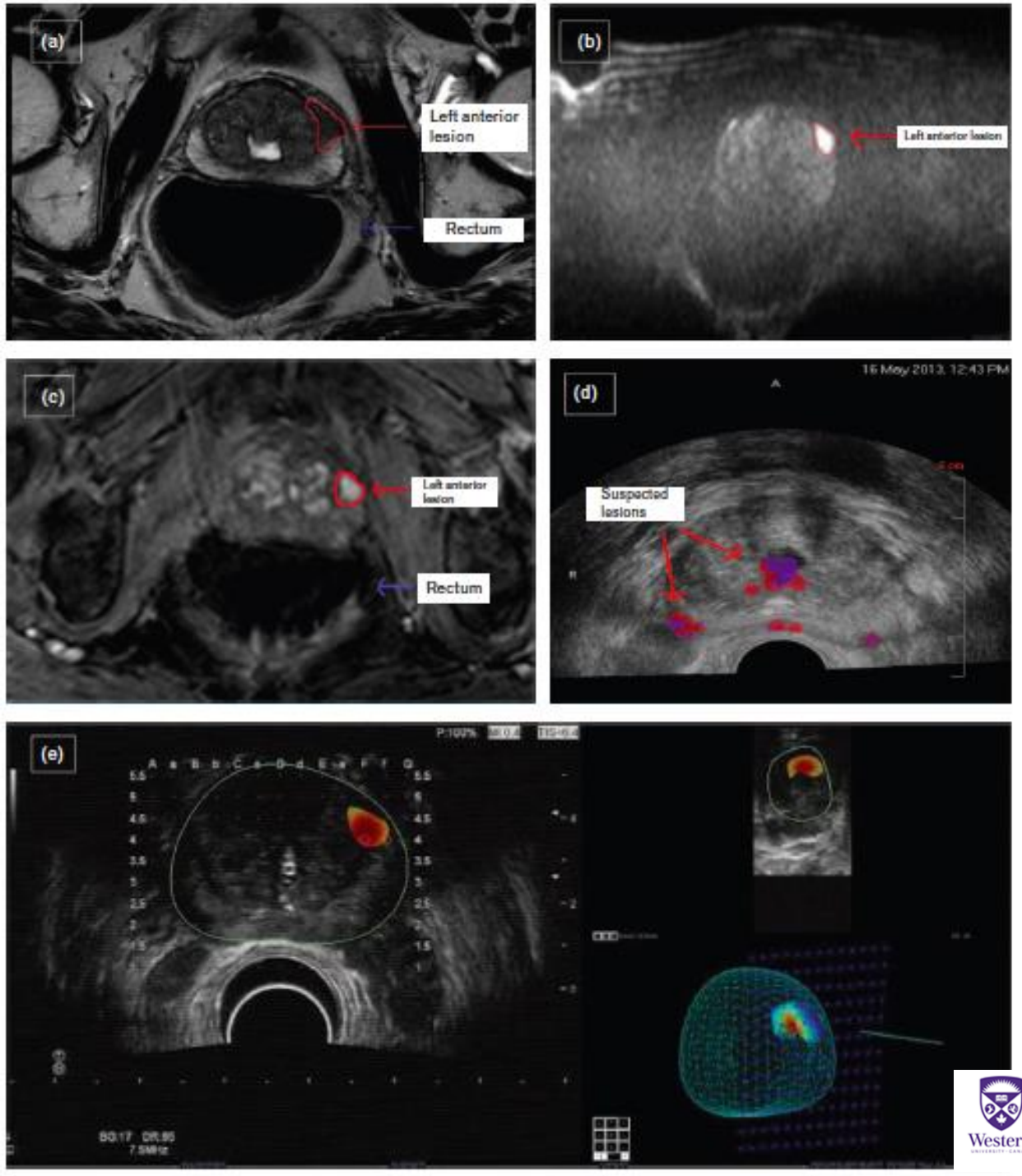
Do more extensive biopsies

Game Changer:

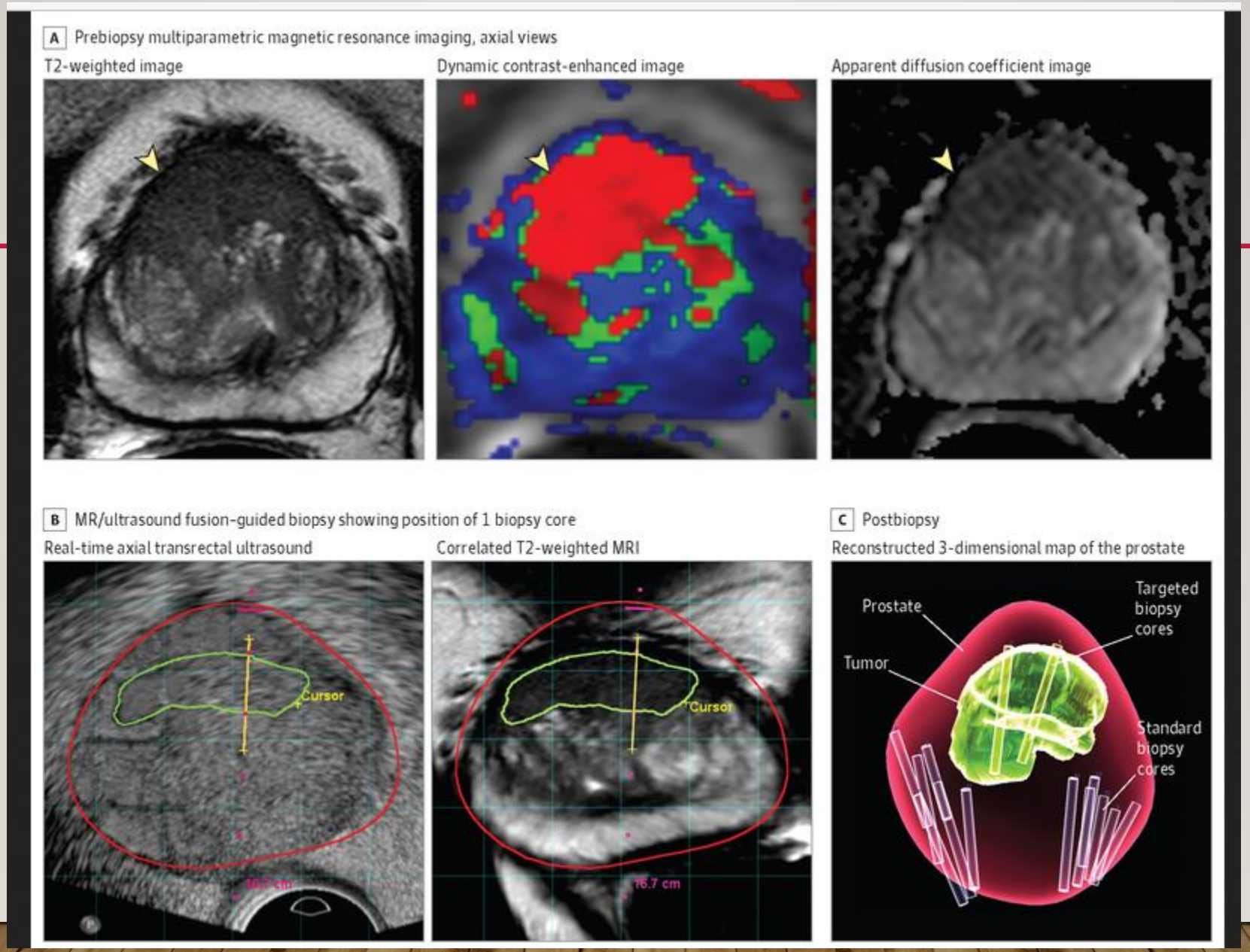
MPMRI, MRI-FUSION BIOPSY: REPORTED STUDIES (TO 2017)

Author	Site	Journal	Year	Study Type	Population Type	N	Other
Sonn et al.	UCLA	JUrol	2013	Prospective	Repeat & Active Surv.	171	Artemis
Sonn et al.	UCLA	EurUrol	2013	Retrospective	Repeat Biopsy	105	Artemis
Delongchamps	France	JUrol	2013	Prospective	No prior Bx	391	Koelis/ cognitive
Fiard et al.	France	Urology	2013	Prospective	First and repeat	30	Median F/U 6m
Kuru et al.	Germany	JUrol	2013	Prospective	First and repeat	347	BiopSee 3D system
Puech et al.	France	Radiol	2013	Prospective	+'ve MRI	96	Fusion vs. Cognitive
Siddiqui et al.	NIH	EurUrol	2013	Prospective	First and repeat	582	UroNav
Pinto et al.	NIH	Jurol	2011	Prospective	First, repeat, active surv,	101	UroNav
Pinto et al.	NIH	Jurol	2012	Retrospective	Negative previous biopsy	195	UroNav
Emberton et al.	UK	JUrol	2013	Retrospective	First & repeat	182	Transperineal
Anastasiadis	Germany	EurUrol	2006	Prospective	+'ve MRI Repeat	27	MR-GB
Hambrock et al.	Holland	EurUrol	2012	Retrospective	Prostatectomy	123	MR-GB
Hoeks et al.	Holland	EurUrol	2013	Retrospective	Repeat	438	MR-GB
Costa et al.	Beth Is.	JMRI	2013	Retrospective	Repeat Biopsy	38	Cognitive registration
Cool et al	UWO	JCUA	2017	Retrospective	Repeat Bx ASAP	100	Artemis

a) MRI T2W
b) DWI
c) DCE
d) Histoscanning
e) MRI – US fusion



Kanthabalan et al. Curr Opin Urol 2014



Siddiqui et al JAMA 2015

Precision study: Comparison of Cancer Detection

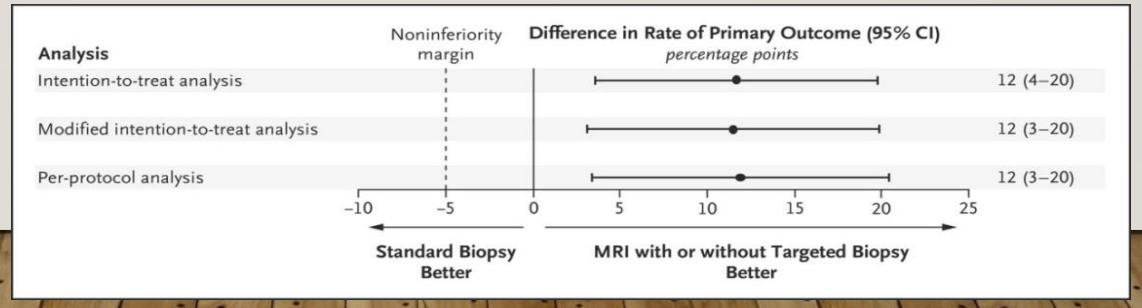
Table 2. Comparison of Cancer Detection between Groups.*

Outcome	MRI-Targeted Biopsy Group (N=252)	Standard-Biopsy Group (N=248)	Difference†	P Value
Biopsy outcome — no. (%)			—	—
No biopsy because of negative result on MRI	71 (28)	0		
Benign tissue	52 (21)	98 (40)		
Atypical small acinar proliferation	0	5 (2)		
High-grade prostatic intraepithelial neoplasia	4 (2)	10 (4)		
Gleason score				
3+3	23 (9)	55 (22)		
3+4	52 (21)	35 (14)		
3+5	2 (1)	1 (<1)		
4+3	18 (7)	19 (8)		
4+4	13 (5)	6 (2)		
4+5	7 (3)	2 (1)		
5+5	3 (1)	1 (<1)		
No biopsy‡	4 (2)	3 (1)		
Withdrawal from trial§	3 (1)	13 (5)		
Clinically significant cancer¶				
Intention-to-treat analysis — no. (%)	95 (38)	64 (26)	12 (4 to 20)	0.005
Modified intention-to-treat analysis — no./total no. (%)	95/245 (39)	64/235 (27)	12 (3 to 20)	0.007
Per-protocol analysis — no./total no. (%)	92/235 (39)	62/227 (27)	12 (3 to 20)	0.007
Clinically insignificant cancer — no. (%)	23 (9)	55 (22)	−13 (−19 to −7)	<0.001
Maximum cancer core length — mm	7.8±4.1	6.5±4.5	1.0 (0.0 to 2.1)	0.053
Core positive for cancer — no./total no. of cores (%)	422/967 (44)	515/2788 (18)	—	—
Men who did not undergo biopsy — no. (%)‖	78 (31)	16 (6)	—	

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 10, 2018 VOL. 378 NO. 19

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis

MR targeting bx results:
- More clinically significant ca
- Fewer clinically insignificant ca
- Max core length higher
- % +ve cores/total cores



KASIVISVANATHAN ET AL. NEJM 2018

CRITICAL DECISIONS IN FOCAL THERAPY IMPLEMENTATION

- **Candidate Selection**
- **Method of Disease Mapping/ Identification**
  - **Biopsy vs Imaging**
- **Choice of Energy**
- **Manner of Follow-up/ Verification of Efficacy**

CANDIDATE SELECTION: DISEASE RISK STRATIFICATION

- **Low risk men**
  - **Usually based upon high disease volume, young age**
  - **Not likely to improve survival relative to surveillance**
  - **Practical benefits of avoiding repetitive surveillance biopsies, cost**

To mitigate uncertainty & anxiety

- **Intermediate risk men**
  - **Usually based upon low disease volume, older age**
  - **In need of treatment**
  - **Long lead time provides reasonable salvageablity**

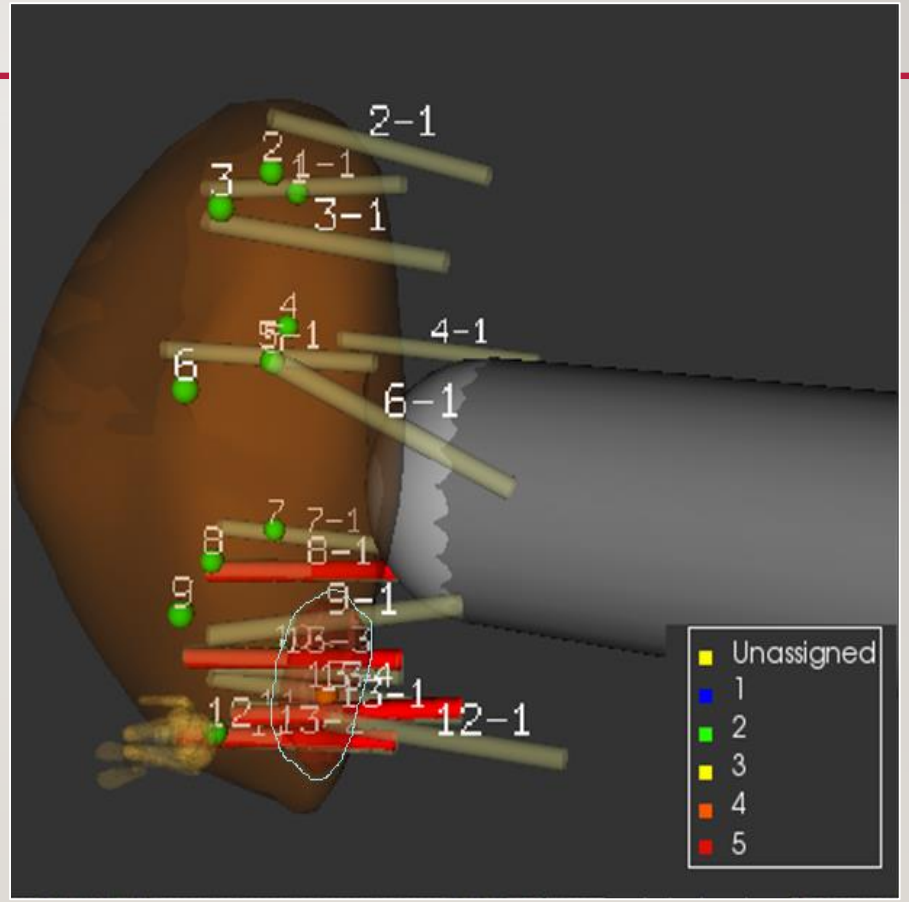
In place of Definitive Whole Gland Ablation
To mitigate/defer adverse effects

- **High risk men**
  - **As monotherapy in low volume disease**
  - **As adjunct to systemic therapy in high volume disease**
  - **Local failure risks loss of 'window of curability'**

Part of multi-modal therapy

CO-REGISTRATION GUIDED FOCAL ABLATION

- Biopsy targeting by fusion and systematic biopsy
  - Concordance of MRI, targeted biopsy, and systematic biopsy
- Ablation with 10 mm intraprostatic margin
- Ablation with 3 mm extraprostatic margin if abutting capsule
- Follow-up co-registered biopsy
  - Fusion using pre and post treatment MRI



CRITICAL DECISIONS IN FOCAL THERAPY IMPLEMENTATION

- Candidate Selection
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AVAILABLE ENERGY SOURCES FOR FOCAL ABLATION

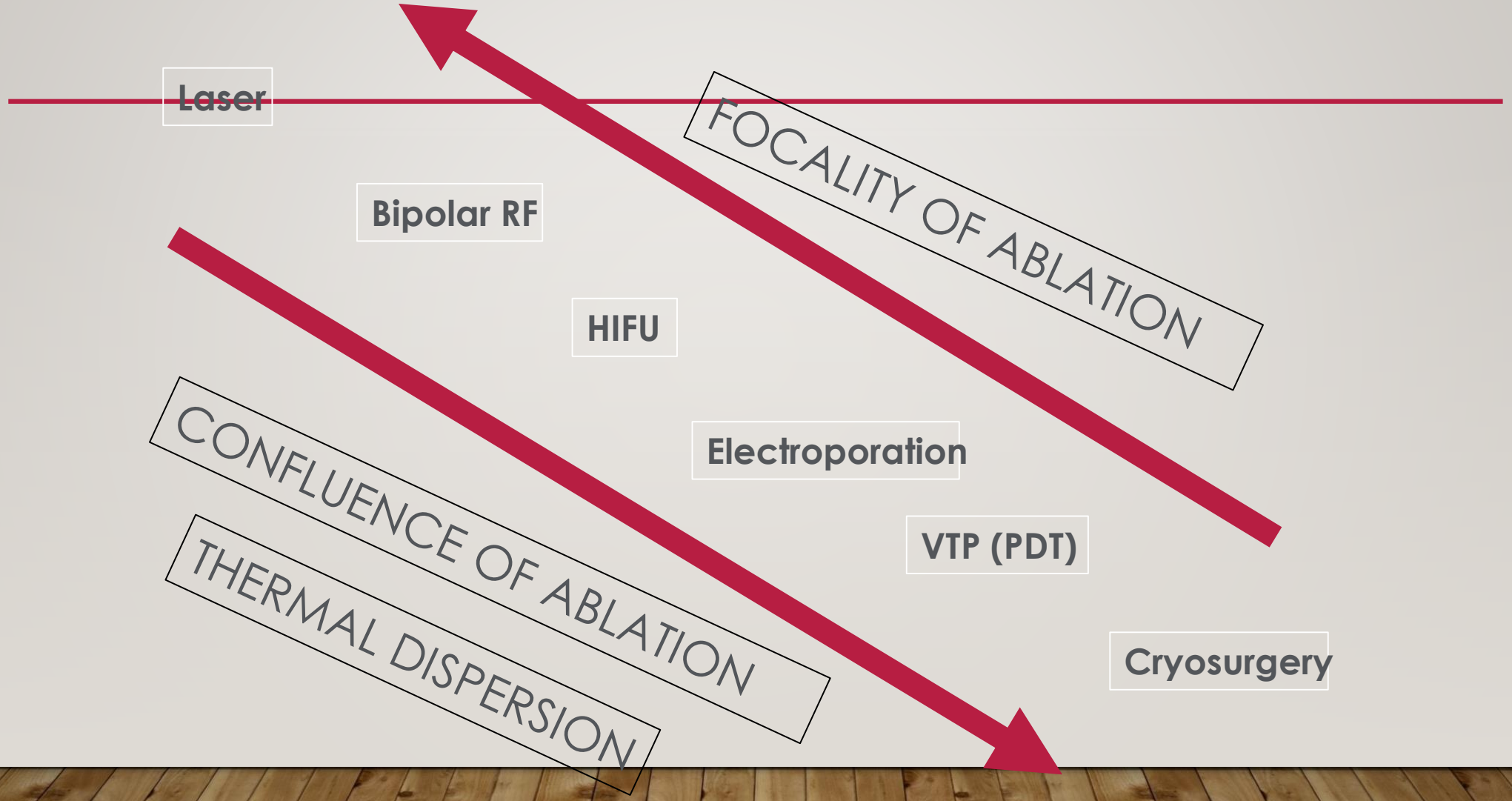
- Laser
- Electroporation
- Radiofrequency (bipolar)
- Photodynamic Therapy
- High-intensity Focused Ultrasc
- Cryosurgery
- Drugs/toxins
- Radiation (focal/interstitial)
- Surgery

Ablative Technologies Scorecard

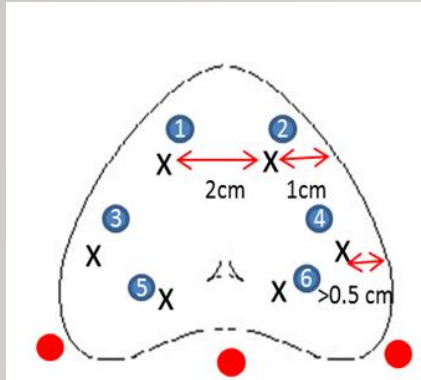
J. Chin, 2019

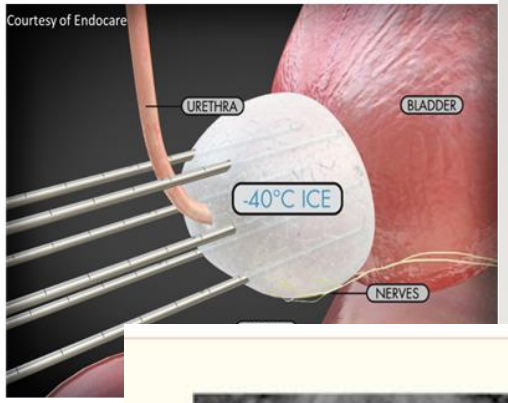
	Surgeon-Friendly?	Patient-Friendly?	Track Record / published data	Imaging	Imaging - Ablation Coupling	F / U of ablated area	Truly Focal ?
Cryo	++	++	++++	TRUS + Fusion ?	+/-	+/-	++
HIFU/ "FocalOne"	+++	++	+++	TRUS + Fusion ?	++ US or MR	+	+++
Vasc.	-	+/-?	-	TRUS	-	+/-	-?
Inters. Laser	--	++?	--	MR	++	+/-	+?
Brachy	+	+?	+ -	TRUS/MR	-	+	++?
Irrev EP	+	+	--	TRUS	?	+	+?
TULSA	+	+	---	MR	++	+	Segmental

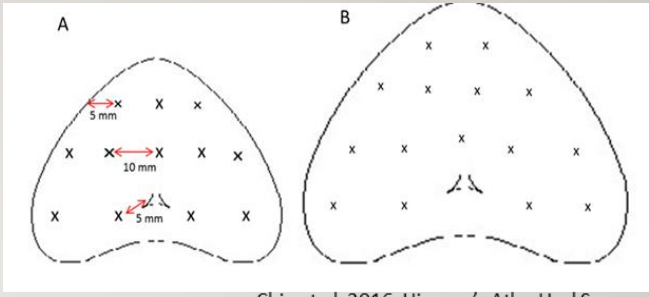
SPECTRUM OF ENERGY SOURCES



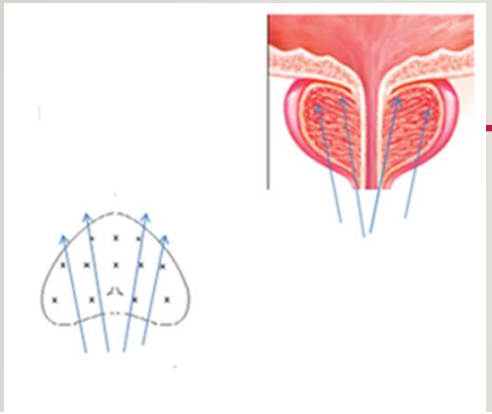
Cryoprobe Placement : Location! Location! Location!

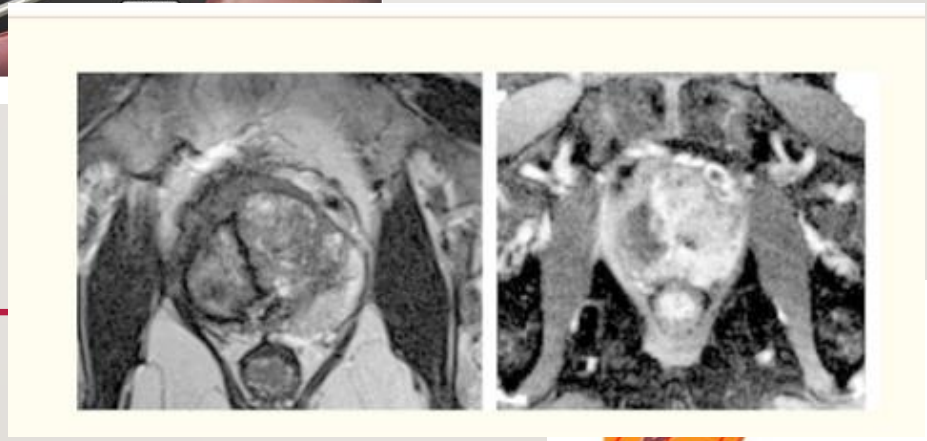


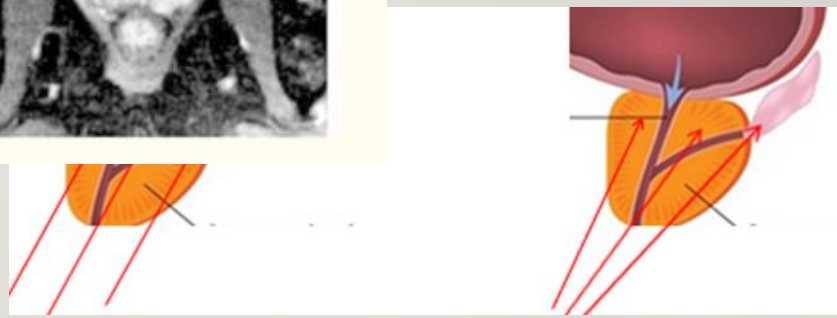


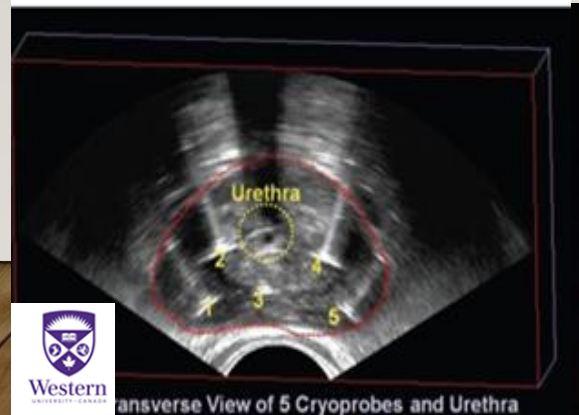


Chin et al, 2016, Hinman's Atlas Urol Surg

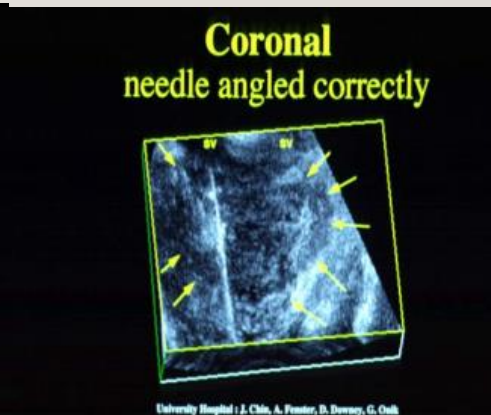


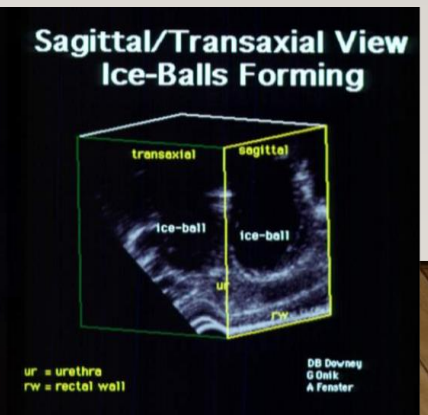




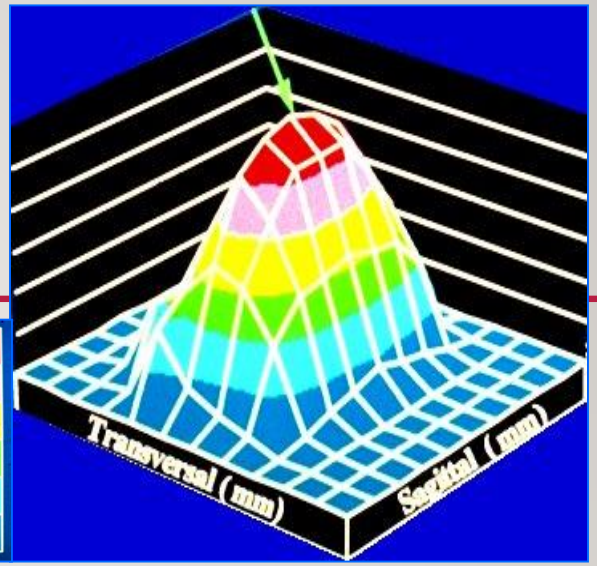


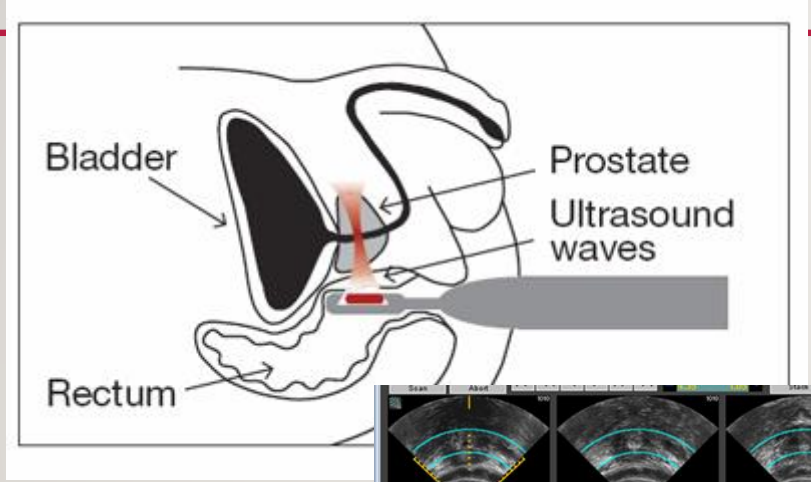
ansverse View of 5 Cryoprobes and Urethra

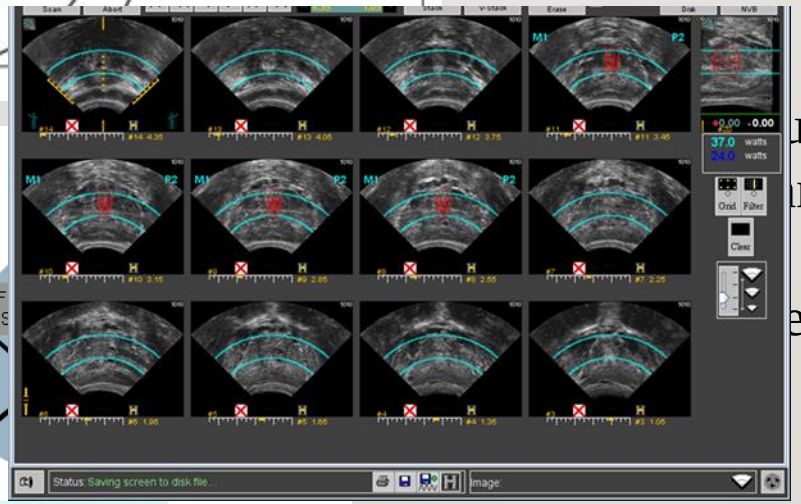




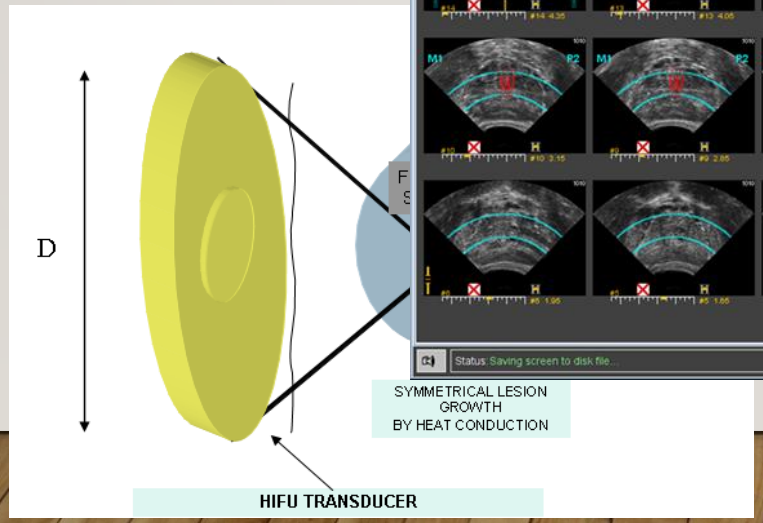
HIFU (Prostate)







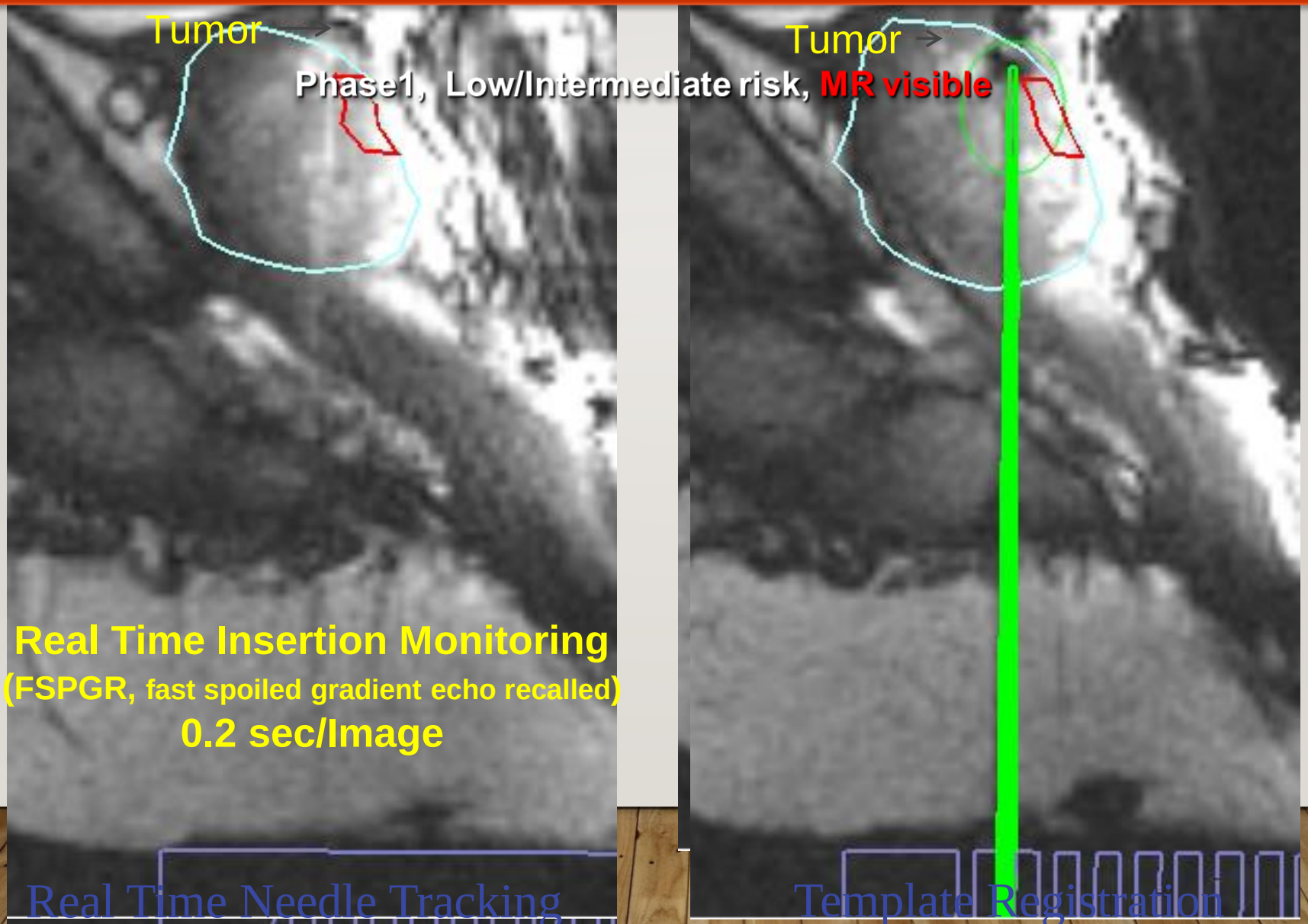
ulses
rget volume
3- 5 sec. delay
e of energy flow density



No damage to intervening

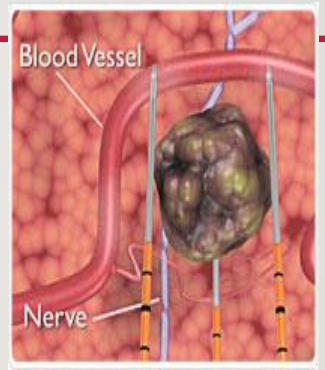
In Bore Robot Assisted MR Guided Focal Laser Ablation

Trachtenberg J et al 2013



IRREVERSIBLE ELECTROPORATION (IRE)

- Interstitial application of electrical energy to tissue using needles
- In Prostate: Transperineal needle insertion using brachytherapy equipment
- Utilizes ultrasound guidance
- Needle placement must be parallel and spacing between 10 - 20 mm apart
- Limited ability to



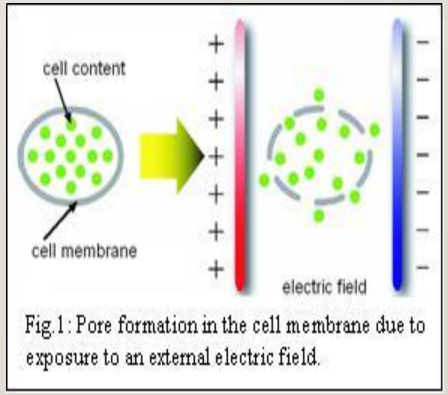
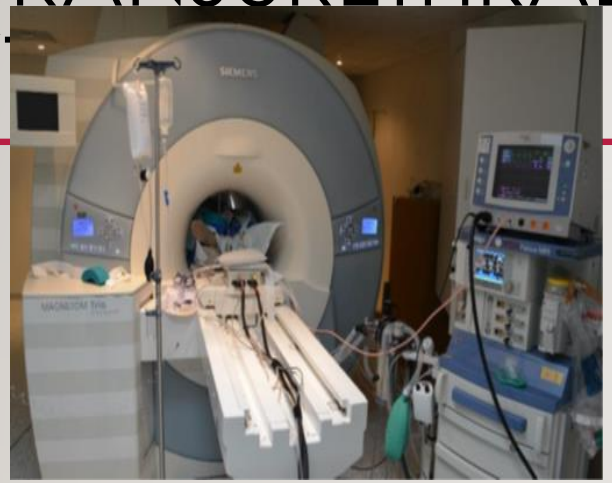


Fig.1: Pore formation in the cell membrane due to exposure to an external electric field.

Courtesy of Dr. Jonathan Coleman

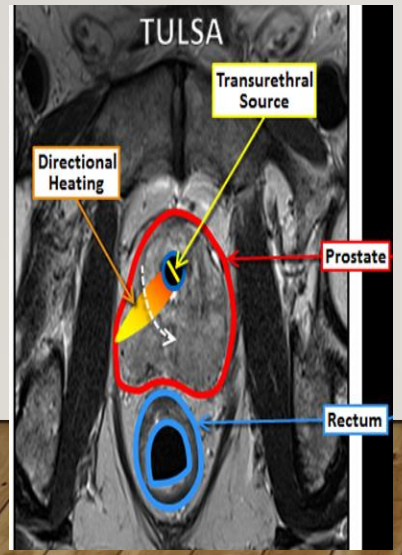
TRANSURETHRAL ULTRASOUND ABLATION (

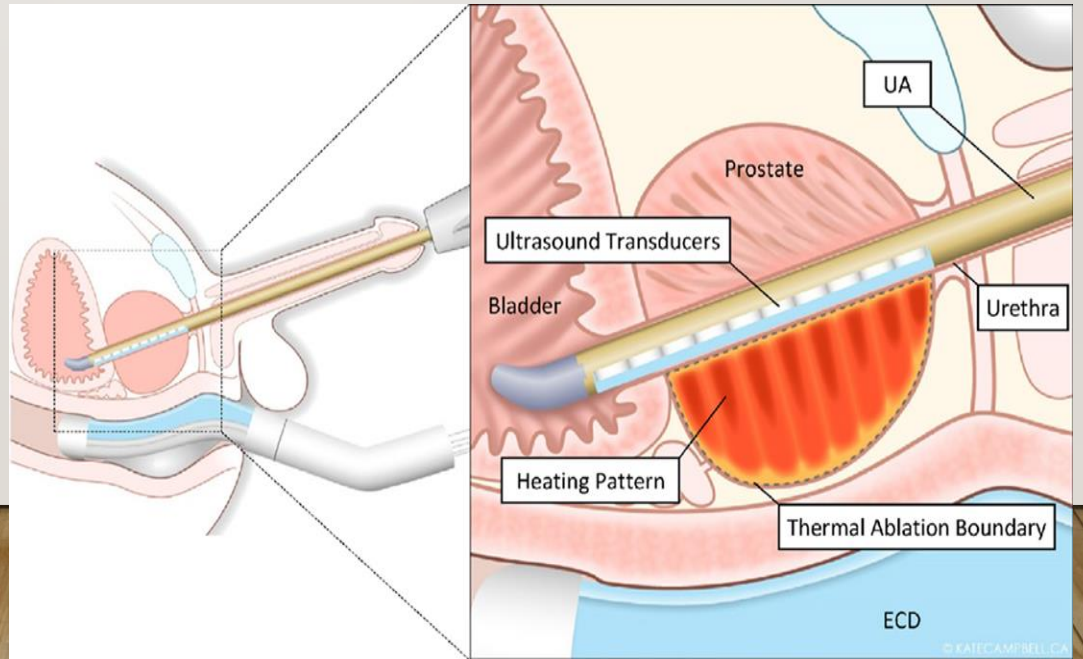


Magnetic Resonance Imaging–Guided Transurethral Ultrasound Ablation of Prostate Tissue in Patients with Localized Prostate Cancer: A Prospective Phase 1 Clinical Trial

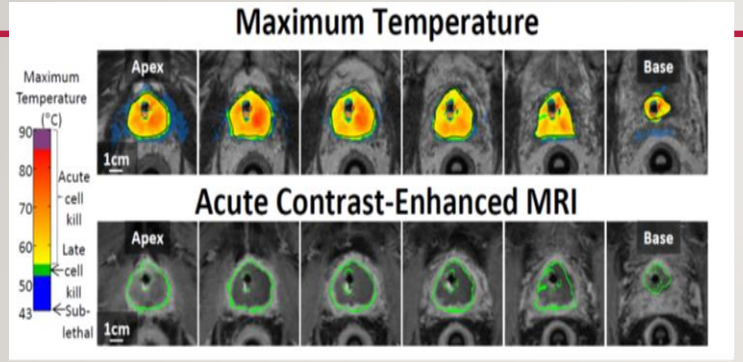
Joseph L. Chin [a,], Michele Billia [a], James Relle [b], Matthias C. Roethke [c], Ionel V. Popeneciu [d], Timur H. Kuru [d], Gencay Hatiboglu [d], Maya B. Mueller-Wolf [c], Johann Motsch [d],*

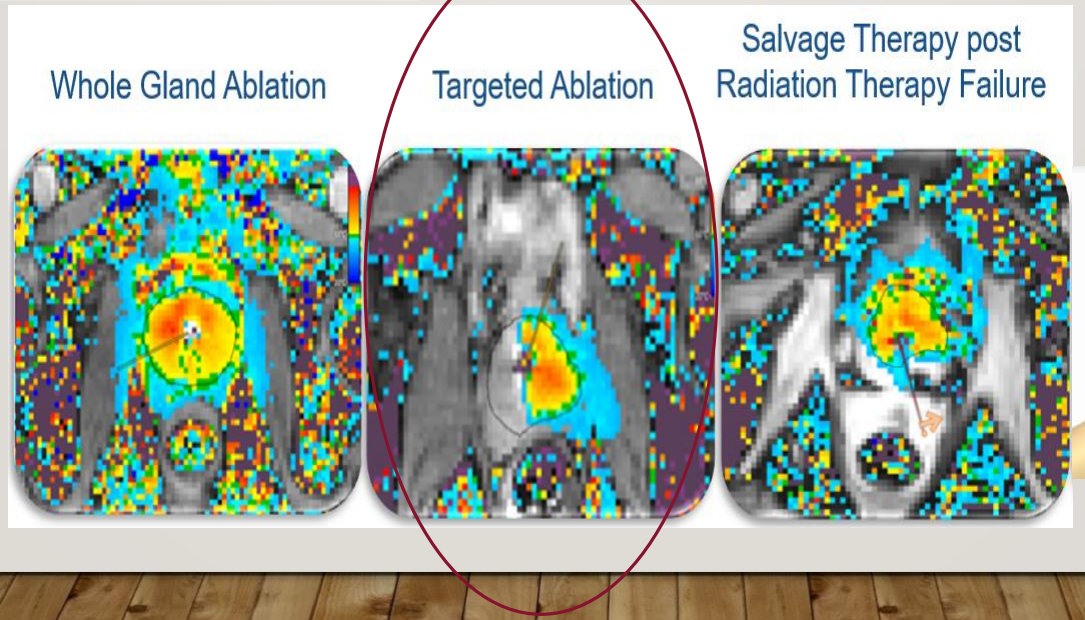
Eur Urol 2017

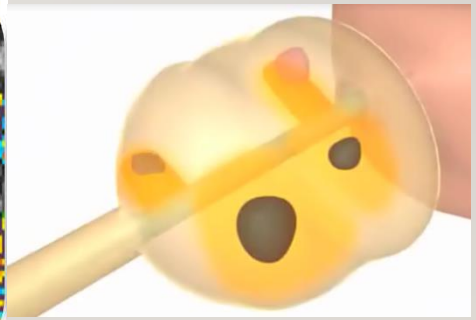




WHOLE- GLAND OR SEGMENTAL/FOCAL ABLATION







New and Established Technology in Focal Ablation of the Prostate: A Systematic Review

Massimo Valerio[a,b,c,†,*], *Yannick Cerantola*[c,†], *Scott E. Eggener*[d], *Herbert Lepor*[e], *Thomas J. Polascik*[f], *Arnauld Villers*[g], *Mark Emberton*[a,b]

Total # Focal Therapy studies	37
HIFU	13
Cryo	11
PDT	3
Laser interstitial	4
Brachy	2
IRE	3
RF	1

PUBLISHED FOCAL HIFU STUDIES

Nature of Trial	#
Stage I	6
Stage IIa	4
Stage IIb	3

Study Design

No RCT's
Retrospective
Prospective Proof of Concept
Developmental studies

Imaging

TRUS for Localization Targeting
- standard
- Extended
- Targeted
- Template

MR used in some manner mostly for localization (some In Bore)

Signif cancer	Insignif cancer	OS	DSS
0	23.3%	100%	100%
2^0 therapy	**SAE**	**Pad-free Cont.**	**Potency preserv.**
7.8%	1.5%	100%	88.6%

FOCAL CRYOABLATION – ONCOLOGICAL OUTCOMES

Study	N	Median follow-up (months)	Biochemical progression definition	BPFS	Biopsy Trigger	Total number biopsied	Biopsy Outcome	Mets.	Death
Lian et al 2016	41	63	Phoenix	95%	Mandatory	32	7 positive – 2 ipsi. (1 Gl. 7), 5 contra. (2 Gl. 7)	0	0
Durand et al 2014	48	13.2	Phoenix				2 positive - 5 ipsi. Gl. 7), 6 contra all Gl 6), 1 bilat. Gl 7)	0	0
Barqawi et al 2014	62	28	Increas above pre-operative level				2 positive - 7 ipsi, contra, 1 bilat. (all Gleason 6)	NR	NR
Hale et al 2013	26	19.1	0.5 over nadir	88%	PSA triggered	2	2 positive – both Gl. 6	0	0
Bahn et al 2012	73	44.4	NR	NR	Mandatory	48	12 positive - 1 ipsi. (Gl. 8), 11 contra.	0	0

Variable metrics used
Short f/u and small #s
Most are single centre case-series

COMPLICATIONS AND FUNCTIONAL OUTCOMES

Study	Complication	Definition of Continence	Continence	Definition of Potency	Potency
Lian et al 2016	Retention 3.4%	No pad	97.6% at 6 weeks (mild incontinence) 100% at 1 year	Ability to have intercourse	76.9% of those previously potent
Durand et al 2014	Retention 15% Recto-urethral fistula 2% Cavernous corpus necrosis 2% Urethral st 2%	No pad	100%	IIEF	Mild reduction in IIEF at 3 months then back to baseline at 6 months
Barqawi et al 2014	NR	AUA SS	decrease in AUA SS at 24 mo		ge at 24 mo
Hale et al 2013	4% (1 retention needing TURP), 1 UTI 4%	No pad	100%	Need for assistance/ IIEF	73% needed assistance No impotence

Not surprisingly,
Good functional outcome

FORMS OF FAILURE

- Treatment zone failure - RARE
  - Due to incomplete thermal effect
  - Due to non-confluence in treatment zor

Didn't see it
Didn't target properly
Didn't heat/freeze enough
Didn't plan properly

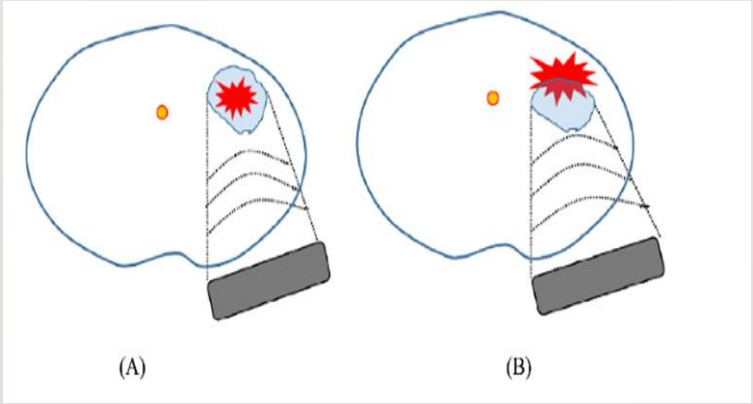
- Margin failure- **MOST COMMON**
  - Inadequate treatment margin
  - Underestimation of tumor size
  - Inadequate thermal effect at margin

- Failure outside the treatment zone – COMMON BUT QUESTIONABLY RELEVANT
  - Poor baseline staging
  - Generally indolent disease

Many Unanswered Questions…..
Still Investigational

Best Imaging? Best Targeting/coupling ? Best Ablative Modality???
Longer term results???
Best follow-up routine???
Salvageabilty??? Strategies???

?



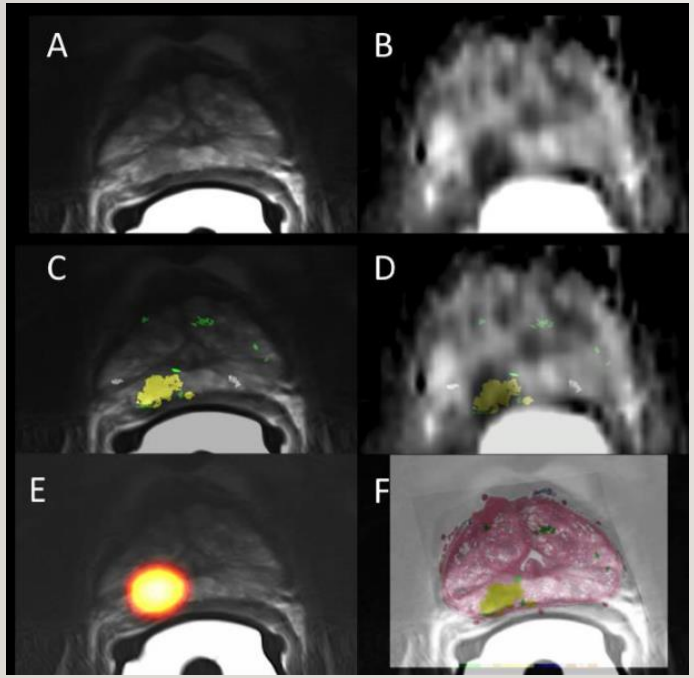
HIFU, Cryo, and Brachy for posterior, anterior, and apical tumors, respectively, to improve the overall outcome???

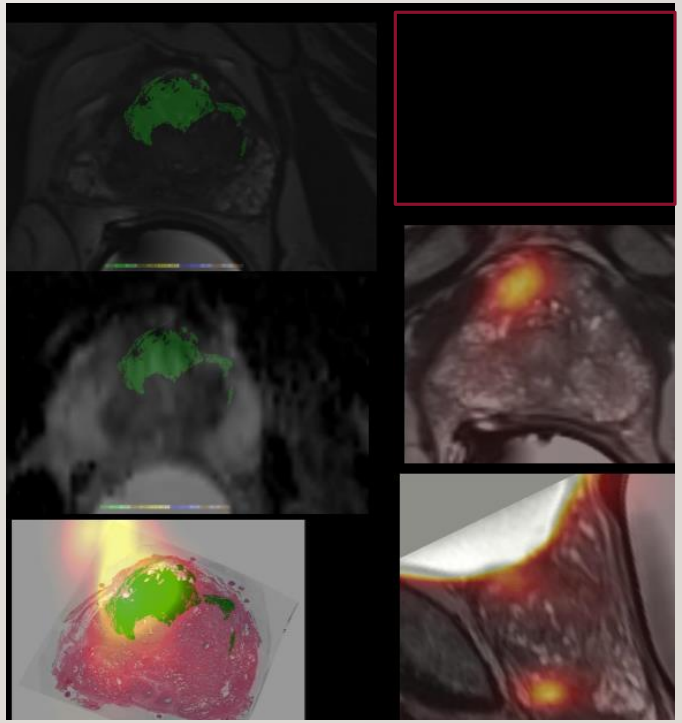
PSMA PET / MRI……PSMA PET / CT
….maybe very useful for Focal Therapy

Eur Urol Focus. 2016 Oct 26. pii: S2405-4569(16)30147-X. doi: 10.1016/j.euf.2016.10.002. [Epub ahead of print]

[18F]-DCFPyL Positron Emission Tomography/Magnetic Resonance Imaging for Localization of Dominant Intraprostatic Foci: First Experience.

Bauman G[1], Martin P[2], Thiessen JD[3], Taylor R[3], Moussa M[4], Gaed M[4], Rachinsky I[3], Kassam Z[5], Chin J[6], Pautler S[6], Lee TY[7], Valliant JF[8], Ward A[9].





WHAT IS NEEDED TO START A FOCAL THERAPY PROGRAM

- A shift of your thinking
- A good team
  - Radiologist
  - Pathologist
  - Data management
  - Care coordination
- Good tools
  - Biopsy tools
  - Imaging
  - Ablation
- A good plan for conduct
  - Biopsy guided
  - Image guided
- A good plan and resources for follow-up
  - Diligence from patients and staff in adherence to follow-up
  - Careful data recording
- QA initiatives to inform and re-define approach

SUMMARY: PROSTATE FOCAL ABLATION

It's here to stay!

- Dominant Lesion theory
- Imaging & Dx: mpMRI essential, ?PET
- Patient Selection: Patient and Tumor factors – Key to good oncological and functional outcome
  - "Best" candidate: Gl.3+4, solitary lesion favorable location & size, good life expectancy
- Metrics:
  - NO standardized defn for BCR,
  - Residual disease needs to be histologically confirmed
  - QOL & functional outcomes req validated instruments

Summary: Prostate Focal Ablation

- Published results to date: No Level 1 Evidence
  - Mostly Cryo and HIFU….variable reporting
  - Good ***SHORT-TERM*** oncologic results & excellent functional outcomes
  - High quality RCT's req'd
- F/U: mpMRI, Bx of treated area Yr. 1, 2 & 5
- PSA & functional assessment q3, then q 6m
- Salvage Strategies
  - individualized according to 1° focal therapy
  - Focal salvage recommended only if causes of initial failure identifiable and rectifiable

Remember: It's still investigational

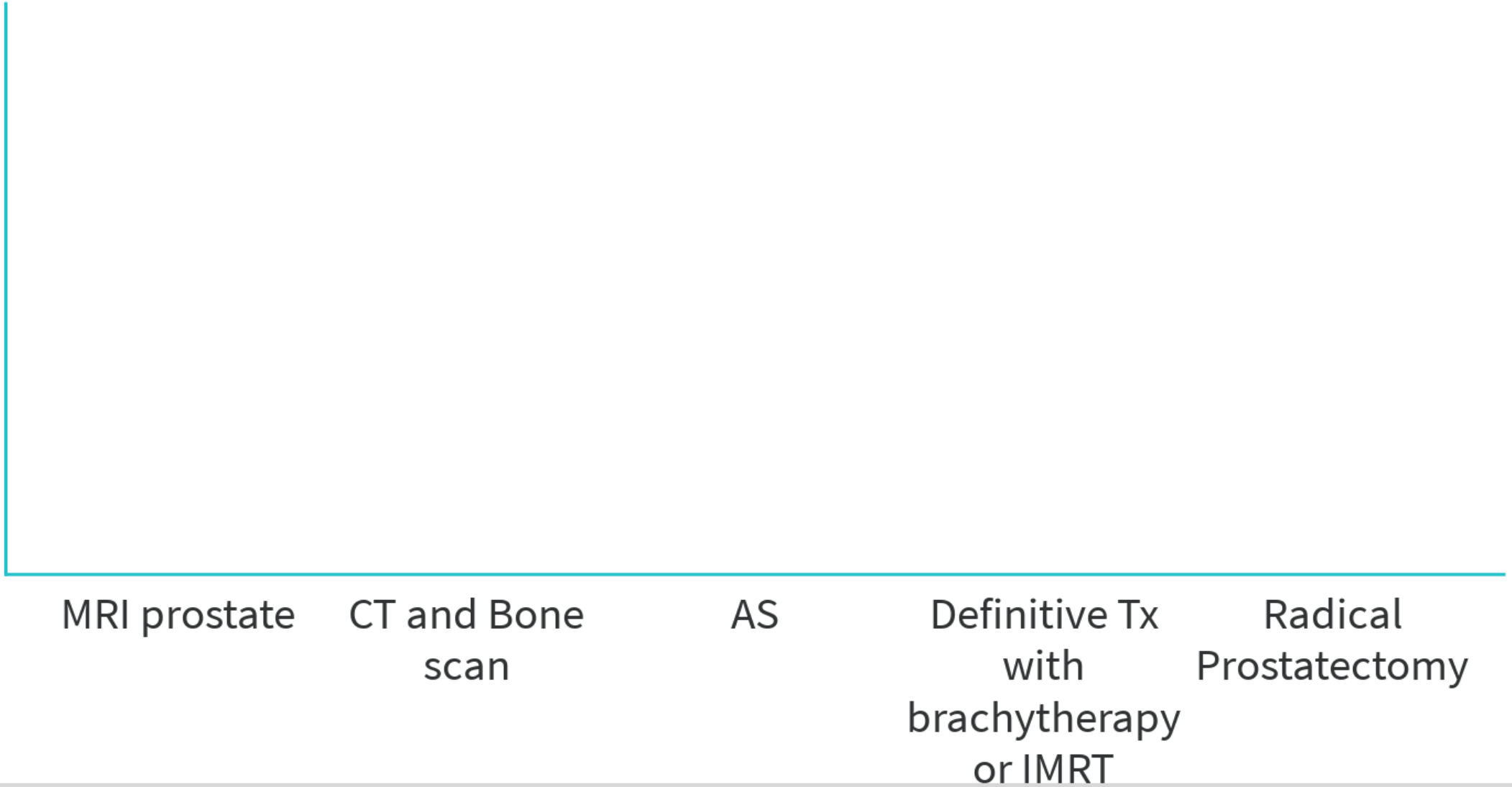
CASE 3

- 65 yo male who has recently been diagnosed with PCa. PSA 6.5 with 4/12 cores with 2 cores showing GG 2, and the others GG1. His past history is significant for GSW to abdomen as a young man and exploratory laparotomy as well as CABG 10 years ago but has good exercise tolerance now. BMI 38.

5. What is Your Next Step?

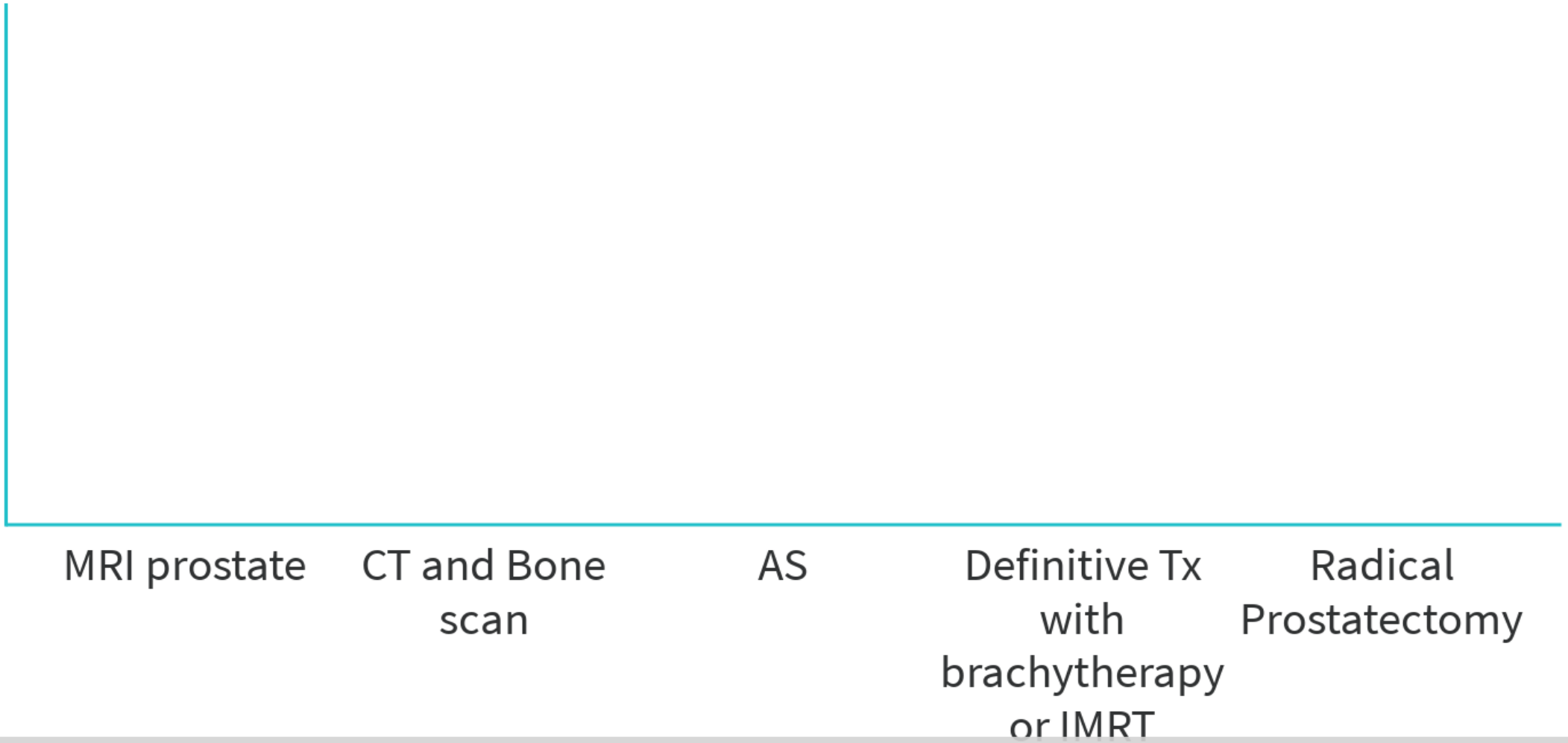
- MRI prostate
- CT and Bone scan
- AS
- Definitive Tx with brachytherapy or IMRT
- Radical Prostatectomy

5. What is Your Next Step?



5. What is Your Next Step?

Poll locked. Responses not accepted.



BRACHYTHERAPY OR STEREOTACTIC RT

Stereotactic Body Radiotherapy (SBRT) vs Brachytherapy in the management of Low Intermediate Risk Prostate Cancer

Eric Vigneault MD,MSc

COI Disclosure

Advisory Board / Speaker

Sanofi	Tersera
Abbvie	Janssen
Ferring	Bayer

Learning Objectives

At the conclusion of this talk the participant will be able to:

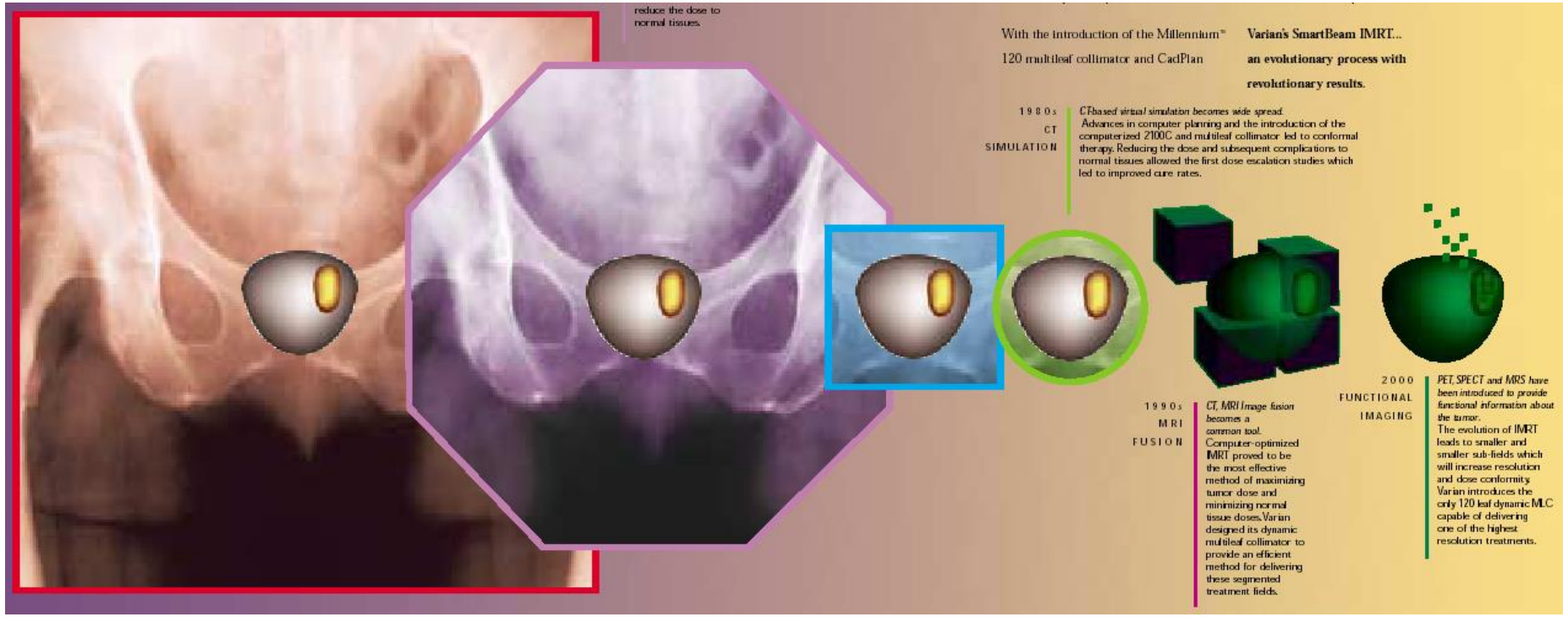
1. Describ the impact of technology in prostate cancer radiotherapy
2. Describ the role and evolution of SBRT in prostate cancer
3. Describ the role and evolution of brachytherapy in prostate cancer

Plan

- Introduction
- Progress in treatment technology
- SBRT the new kid on the block
- Evidence based data in favor of BT
- The Future
- Questions

Progress in treatment technology

Field size reduction and dose escalation



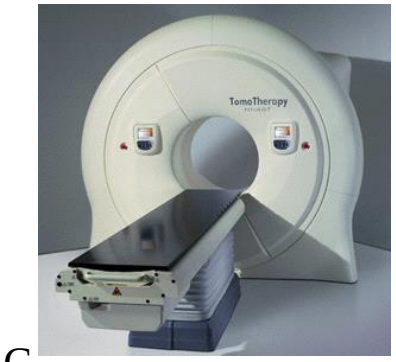
Hypofractionation and local intraprostatic targetting

Progress in treatment technology

Imaging

Portal Films | Skin Marks | EPID : Bone anatomy | EPID: Fiducial Marker | Isocentre positionning displacements | Cone/fan-Beam CT 3D data set

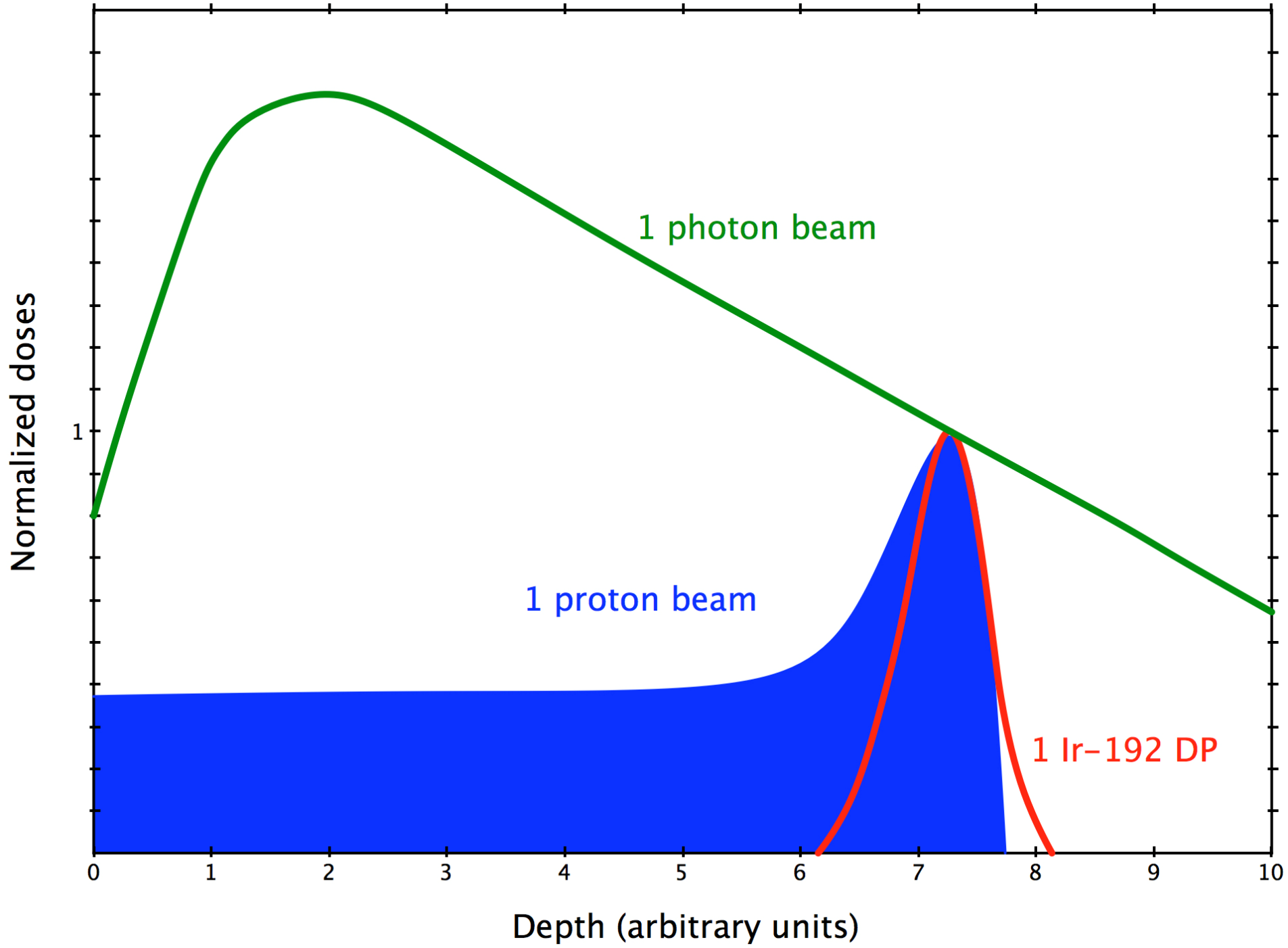
Films : orthogonal Xray | Simulator | Assym jaw, CT attachment | CT planning | CT-simulator | Fusion: PET-CT MRI-CT



Co-60 | Linac | Assymetric jaw Remote control | MLC | Dynamic *M*LC | MicroMLC linacs Tomotherapy CYberknife MR Linac *TEP linac*

… | 3D dose calculation Algorithm | Conformal 3D Dosimetry | IMRT, Inverse planning

RT technology


Normalized doses
1
1 photon beam
1 proton beam
1 Ir-192 DP
0
1
2
3
4
5
6
7
8
9
10
Depth (arbitrary units)

SBRT the new kid on the block

SBRT/SABR definition

- Stereotactic Body Radiotherapy = Stereotactic Ablative Radiotherapy
- Precise delivery of very high fractional doses with modern image-guided radiation therapy therapy devices
- To deliver brachytherapy-like doses while sparing adjacent normal tissues
- In order to improve relapses rates and reduced toxicity

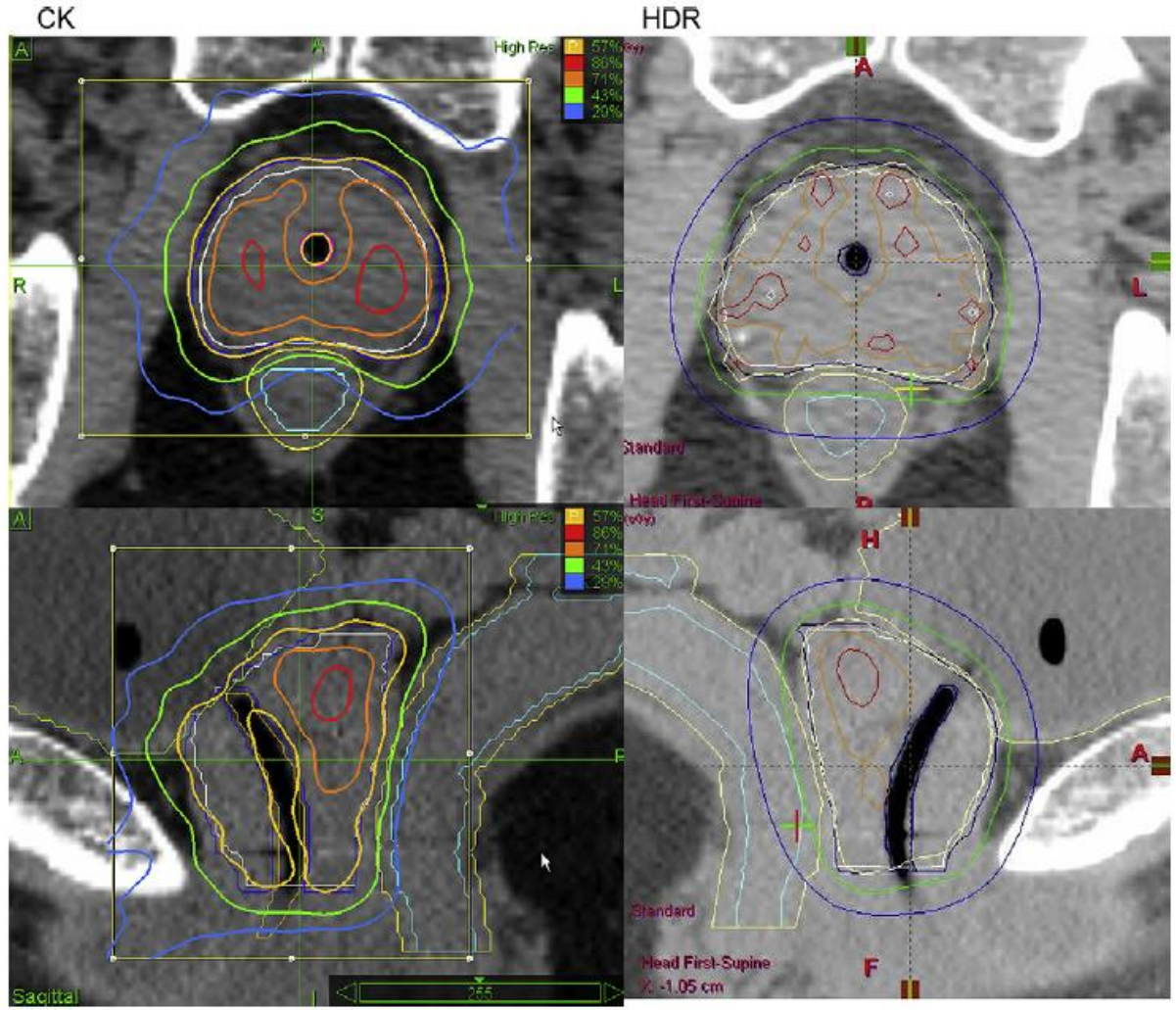


Fig. 4. Axial and sagittal comparison: CyberKnife (CK) vs. simulated high-dose-rate (HDR) dosimetry. White line = prostate contour; dark blue line = 2-mm planning target volume expansion. Isodose lines shown as follows: 150%, red; 125%, orange; 100%, yellow (very light on HDR image); 75%, green; and 50%, blue. Note similar morphologic characteristics of 100%, 125%, and 150% coverage lines, with partial exclusion of the urethra from 100% isodose volume coverage with CK (left) and lower rectal wall and mucosa 75% and 50% isodose volume with CK (left).

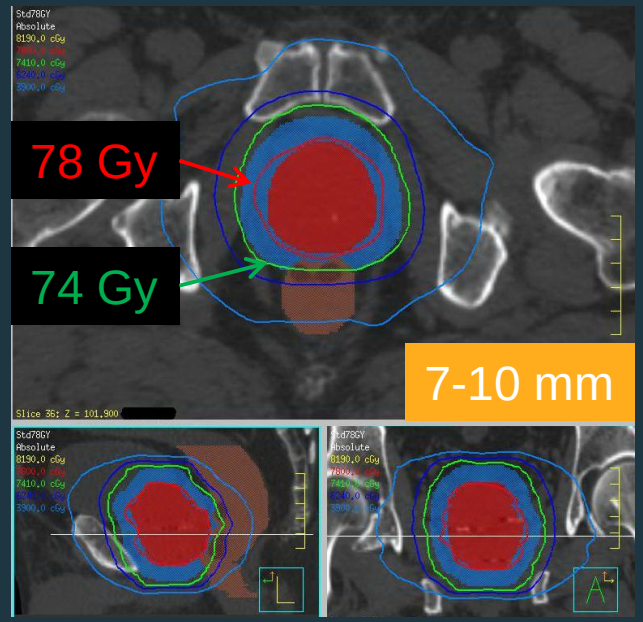
Standard EBRT vs SBRT

- 2-3 Gy / Fx
- Total Dose = 60-78 Gy
- PTV margin > 5 mm
- IGRT = optional
  - CBCT
  - Fiducial markers
  - US system
- Tx schedule = daily X 4-8 weeks
- No rectal devices

- 7-9 Gy / Fx
- Total Dose = 35-45 Gy
- PTV margin ≤ 5 mm
- IGRT = mandatory
  - Fiducial markers
  - Robotic tracking system
  - gating
- Tx schedule =1-2 /week X 2-4 weeks
- Rectal devices for high doses regimen

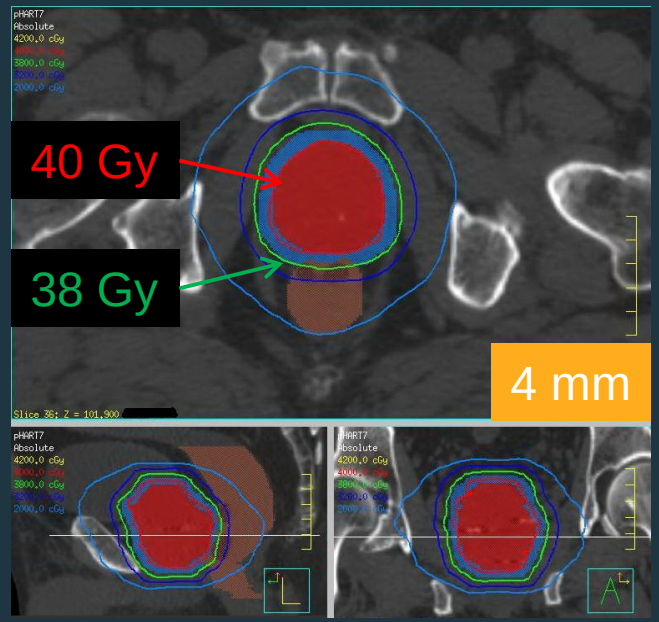
IGRT vs SABR vs 2STAR

RT Past



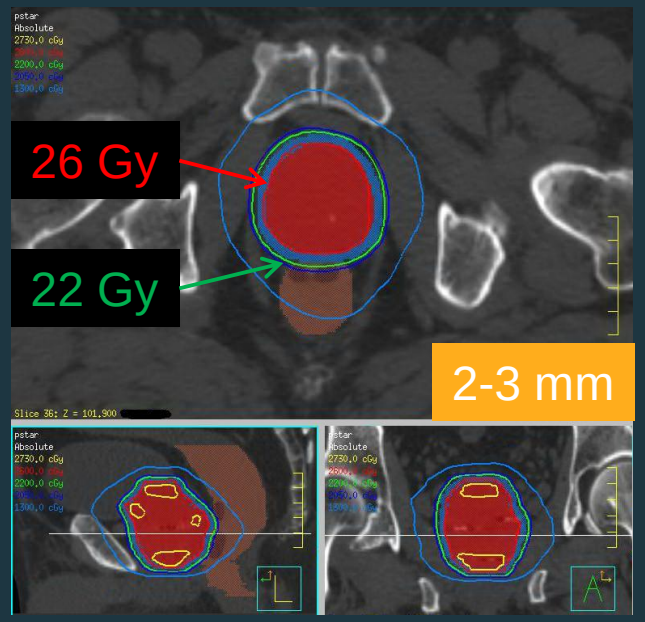
EQD2 tumor dose = 78 Gy
EQD2 rectal dose = 73 Gy
PTV-rectum overlap = 3.5cc

RT Present



EQD2 tumor dose = 110 Gy
EQD2 rectal dose = 73 Gy
PTV-rectum overlap = 1.3cc

RT Future



EQD2 tumor dose = 110 Gy
EQD2 rectal dose = 55 Gy
PTV-rectum overlap = 0.4cc

Courtesy of Andrew Loblaw MD

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ROJ Radiation Oncology Journal

Stereotactic radiotherapy of the prostate: fractionation and utilization in the United States

Joseph P. Weiner, MD[1,2], David Schwartz, MD[1,3], Meng Shao, MD[1,3], Virginia Osborn, MD[1,3], Kwang Choi, MD[3], David Schreiber, MD[1,3]

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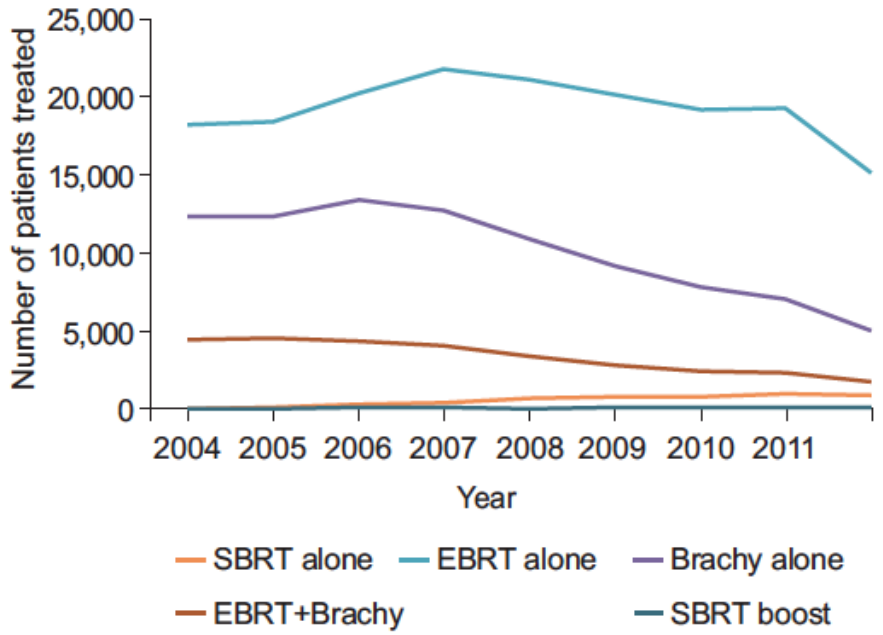


Fig. 1. Utilization of radiotherapy for treatment of prostate cancer over time. SBRT, stereotactic body radiotherapy; EBRT, external beam radiation therapy.

Table 1. Patient characteristics for those who received SBRT alone

Characteristic	SBRT (n = 4,962)
Age (yr)	
<60	751 (15.1)
60–70	2,348 (47.3)
>70	1,863 (37.5)
Race	
White	4,161 (83.9)
Black	657 (13.2)
Other	144 (2.9)
NCCN risk group	
Low	2,082 (42.0)
Intermediate	2,201 (44.4)
High	679 (13.7)
Facility type	
Community	2,311 (46.6)
Academic	2,651 (53.4)
Insurance	
Private	1,681 (33.9)
None	54 (1.1)
Medicaid	56 (1.1)
Medicare	3,024 (60.9)
Other government	58 (1.2)
Unknown	89 (1.8)
Hormones	
No	4,312 (86.9)
Yes	650 (13.1)
Fractionation	
700 cGy × 5	916 (18.5)
725 cGy × 5	2,147 (43.3)
750 cGy × 5	561 (11.3)
>750–1,000 cGy × 5	341 (6.9)
Other schemes [a)]	997 (20.1)

Values are presented as number (%).
SBRT, stereotactic body radiotherapy; NCCN, National Comprehensive Cancer Network.
[a)]Fewer than 5 fractions or missing data; the most common other fractionation scheme was 950 cGy × 4 for 164 patients.

SBRT review

Table 1 Medium term outcomes of SABR prostate

Study [year]	Dose (Gy)/F/ week	EQD2 (Gy)	n	G6 (%)	Med FU (mo)	5 y bDFS (%)	Acute G3 + (%)		Late G3 + (%)		
							GU	GI	GU	GI	ED
Pham *et al.* [2010] (32)	34/5/1	82	40	100	60	93	2	0	3	0	50
Katz *et al.* [2013] (33)	35–36.3/5/1	86.5–92.2	303	73	60	95	0	0	2	0	25
Kupelian *et al.* [2013] (34)	35–40/ 4–5/1–2	86.5–110.6	135	80	60	97	NR	NR	NR	NR	NR
Mantz [2014] (35)	40/5/2	110.6	102	69	>60	100	2	0	NR	0	NR
Hannan *et al.* [2016] (36)	45-50/5/2	138–168	91	47	54	99	0	2	5.4	6.8	26
Musunuru *et al.* [2016] (37)	35/5/4	86.5	84	100	74	97	1	0	0	1	43
Zimmerman *et al.* [2016] (38)	45/9/9	84.7	80	100	83	96	NR	NR	4	13%	NR
Total*	–	–	835	77	63	97	0.6	0.3	2.6	1.0	30

*, weighted average. SABR, stereotactic ablative body radiation; EQD2, equivalent dose in 2 Gy; GU, genitourinary; GI, gastrointestinal; ED, erectile dysfunction; NR, not reported; Med FU, median follow-up; mo, months; bDFS, biochemical disease-free survival.

SBRT vs EBRT

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson

- N = 1180
- 78 Gy/39 vs 42.7 / 7
- 89% IR and 11% HR
- No difference 5y FFS
- No difference in Toxicity
  - acute and late GU /GI
  - ED

- N = 874
- 78 Gy/39 or 62/20 vs 36.2 /5
- ≥ 91 % IR
- No difference in acute RTOG GU and GI toxicity
- Too early for other endpoints

SBRT vs I125

Acute toxicity appears to be lower after SBRT compared to brachytherapy (from 10 to 40 % versus 30 to 40 %, respectively). Conversely, acute and late gastrointestinal toxicity (from 0 to 21 % and from 0 to 10 % of grade 2, respectively) appears more frequent with SBRT. Late urinary toxicity seems identical between both techniques (from 20 to 30 % of grade 2), with a possible urinary flare syndrome. Both treatments have an impact on erectile dysfunction, although it is not possible to conclude that a technique is superior because of the limited data on SBRT. SBRT has better bowel and urinary (irritation or obstruction) quality of life scores than brachytherapy; while sexual and urinary incontinence remain the same. The absence of randomized trial comparing SBRT with brachytherapy for prostate cancers does not allow to conclude on the superiority of one technique over another, thus justifying a phase III medicoeconomic evaluation.

SBRT vs EBRT vs BT

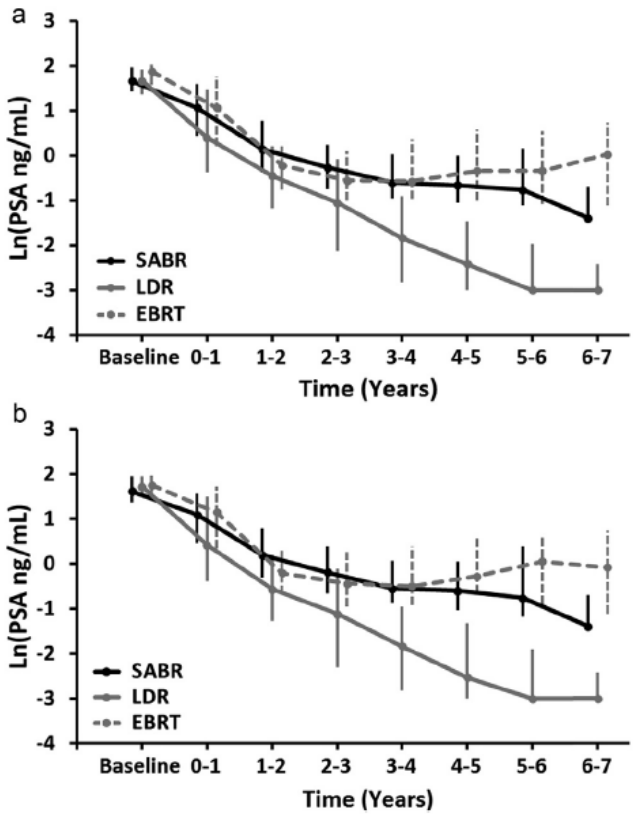


Fig 3. Semi-log plot of median prostate-specific antigen (PSA) follow-up profiles stratified by cohort (SABR, LDR, EBRT) for (a) all patients ($n = 602$) and (b) patients included in final propensity score matched cohorts only ($n = 324$). Mean ± mean 95% confidence intervals shown. SABR, stereotactic ablative radiotherapy; LDR, low dose rate brachytherapy; EBRT, external beam radiotherapy.

A. Loblaw et al. / Clinical Oncology 29 (2017) 161–170

Dirty Little Secret

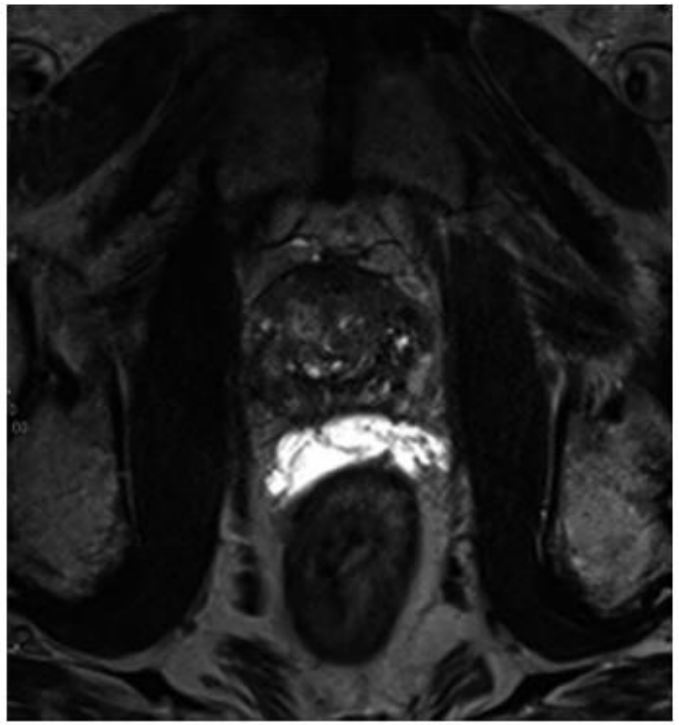


Figure 1. MRI image of SpaceOAR in situ. SpaceOAR appears bright on a T2-weighted sequence. Note the separation between the posterior prostate and anterior rectal wall.

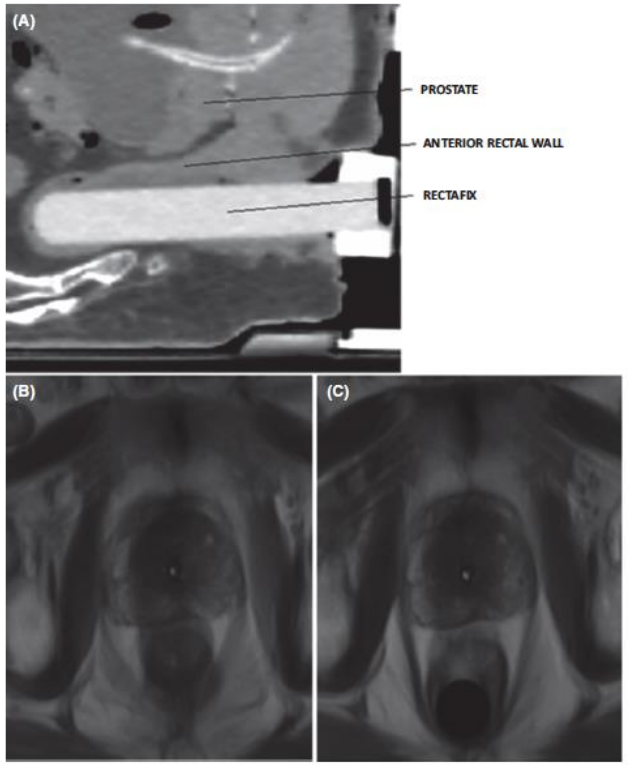


Figure 2. (A) Sagittal CT image of Rectafix RDD in situ with relevant structures identified, (B) MRI images of patient without Rectafix in situ and (C) with Rectafix in situ. Note the posterior displacement of the rectum.

Evidence based data in favor of BT

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

Joseph Chin, R. Bryan Rumble, Marisa Kollmeier, Elisabeth Heath, Jason Efstathiou, Tanya Dorff, Barry Berman, Andrew Feifer, Arthur Jacques,† and D. Andrew Loblaw

J Clin Oncol 35.

Table 1. Results

RCT	Treatment (dose)	No. Patients, Risk Group if Reported	Median Age (years)	Median Follow-Up Time (months)	Primary Outcome	OS Rate	PCSM (No., %)	MFSR (No., %)
Prestidge[15] RTOG 0232 2003-2012 (abstract)	EBRT LDR-B	287 292 Low-intermediate: 588		80.4	5-yr PFS: 85% (95% CI, 80% to 89%)† 5-yr PFS: 86% (95% CI, 81% to 90%)† HR, 1.02; $P < .001$ for futility			
Morris[5,6] ASCENDE-RT 2002-2011*	LDR-B	198	68	78†	bDFS: 3-yr, 94% 5-yr, 89% 7-yr, 86% 9-yr, 83%	3-yr, 91% 5-yr, 86% 7-yr, 78%	7 (3.5)	17 (8.5)
	DE-EBRT	200			bDFS: 3-yr, 94%; 5-yr, 84%; 7-yr, 75%; 9-yr, 62%	3-yr, 89% 5-yr, 82% 7-yr, 74%	11 (5.5)	18 (9)
		Low-intermediate: 2; high-intermediate: 120; high: 276			Log-rank $P < .001$	$P = .29$	$P = .32$	$P = .83$
Hoskin[12] 1997-2005*	EBRT-HDB EBRT	109 111 Low: 9; intermediate: 91; high: 116	68.9 (47-79)	30	bDFS: 5.1 yr (95% CI, 4.6 to 5.5) bDFS: 4.3 yr (95% CI, 3.8 to 4.8) $P = .04$	7-yr, 81% 7-yr, 88% $P = .2$	NR	NR
Sathya[13] 1992-1997	EBRT-B EBRT	51 53 Intermediate: 42; high: 62	65 (49-74) 66 (57-74)	98.4	BCF: 71% BCF: 39% HR, 0.42; 95% CI, 0.23 to 0.75; $P = .0024$	NR	NR	NR

Abbreviations: B, brachytherapy; BCF, biochemical failure; bDFS, biochemical disease-free survival; DE-EBRT, dose-escalated external beam radiotherapy; EBRT, external beam radiotherapy; EBRT-B, external beam radiotherapy plus brachytherapy; HDB, high-dose brachytherapy; HR, hazard ratio; LDR-B, low–dose rate brachytherapy; MFSR, metastasis-free survival rate; NR, not reported; OS, overall survival; PCSM, prostate cancer–specific mortality; PFS, progression-free survival; PSA, prostate-specific antigen; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group.

*Definitions of biochemical disease-free survival: Morris et al[5,6]: Phoenix nadir + 2 ng/mL; Hoskin et al[12]: ASTRO, defined as three consecutive PSA increases after a nadir with the date of failure as the point halfway between the nadir date and the first increase or any increase great enough to provoke initiation of therapy; Sathya et al[13]: ASTRO as above.

†Comprising clinic visits every 6 months until 5 years (yearly thereafter) for prospective collection of patient- and physician-reported adverse effects, complications, and quality of life; PSA and testosterone levels measured every 6 months to assess predefined primary end point of PFS standard nadir + 2 ng/mL (Phoenix) threshold.

Table 2. Adverse Effects

RCT	Treatment (dose)	No. of Patients	Genitourinary Toxicity		GI Toxicity	
			Grade 3	Grade 4	Grade 3	Grade 4
Prestidge[15]	LDR-B	292	3%		3%	
RTOG 0232	EBRT	287	7%		2%	
2003-2012 (abstract)			P = NR		P = NR	
Morris[5]	LDR-B	198	19%	1%	9%	1%
ACENDE-RT	DE-EBRT	200	5%	1%	4%	0
2002-2011 (abstract)			$P < .001$	$P = .547$	$P = .12$	P = NR
			5-year cumulative incidence (worst grade recorded)	5-year cumulative incidence (worst grade recorded)	5-year cumulative incidence (worst grade recorded)	5-year cumulative incidence (worst grade recorded)
Hoskin[12]	EBRT-HDB	109	31		7	
1997-2005	EBRT	111	30		6	
			$P = .5$		$P = .8$	
Sathya[13]	EBRT-B	51	13.7%		3.9%	
1992-1997	EBRT	53	3.8%		1.9%	
			$P = .09$		$P = .61$	
			> 18 months, any grade 3 or 4		> 18 months, any grade 3 or 4	

NOTE: Adverse effects scales used: Morris et al[5]: Late Effects Normal Tissue Task Force–Subjective, Objective, Management, Analytic; Hoskin et al[12]: RTOG and Common Toxicity Criteria Version 3.0; Sathya et al[13]: National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria.

Abbreviations: DE-EBRT, dose-escalated external beam radiotherapy; EBRT-B, external beam radiotherapy plus brachytherapy; HDB, high-dose brachytherapy; LDR-B, low-dose rate brachytherapy; NR, not reported; RCT, randomized controlled trial; RTOG, Radiation Therapy Oncology Group.

HDR monotherapy

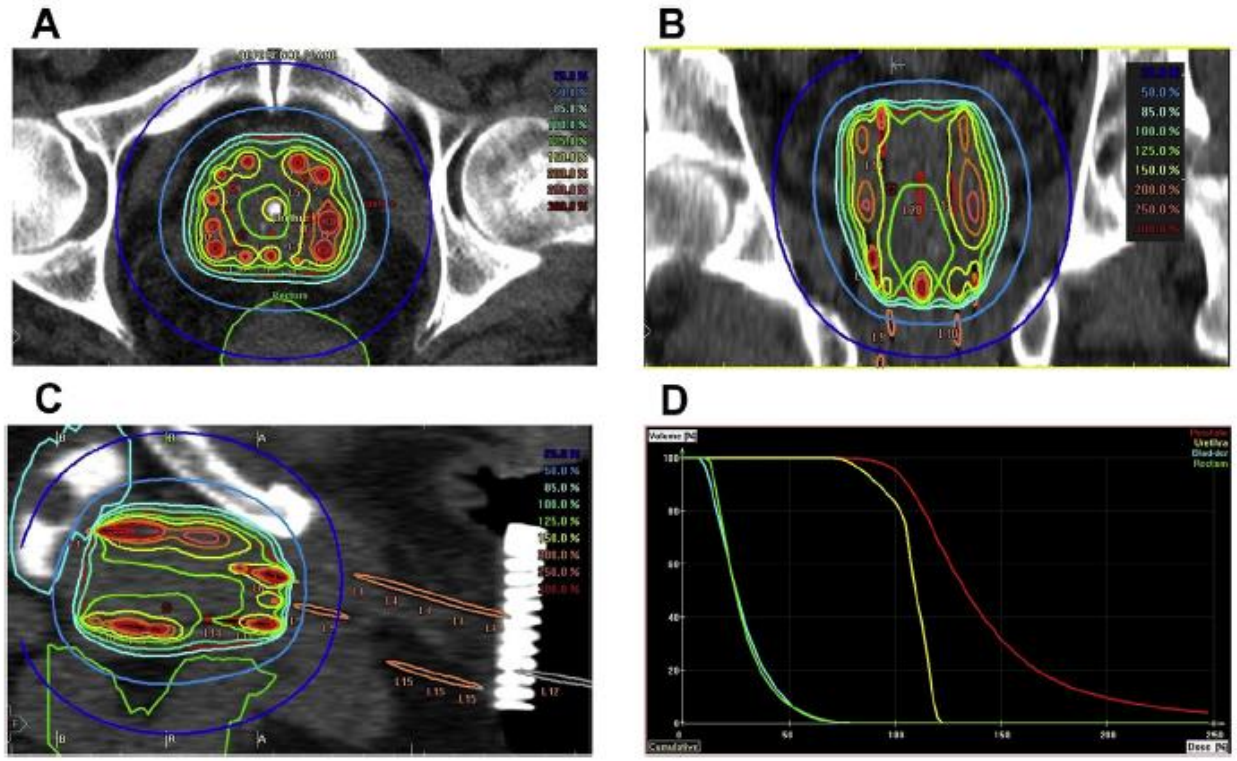


Fig 2. Results of inverse optimisation with Oncentra Prostate (Elekta-Brachytherapy, Elekta AB, Sweden) using hybrid inverse planning optimisation for a computed tomography-based treatment plan of high dose rate prostate brachytherapy. The isodose lines overlay to (a) the central axial plane (reference plane), (b) a coronal plane and (c) a representative sagittal plane. (d) shows the corresponding dose volume histogram curves for the planning target volume, urethra and rectum. One hundred per cent corresponds to the aimed dose prescription.

Table 2 Dose fractionation, late genito-urinary (GU) and Gastrointestinal (GI) toxicity, and biochemical disease-free survival (DFS) by risk groupings in HDR monotherapy series.

Author	N	Dose (Gy)/no. of fractions	Median FU (yrs)	Late Grade 3 toxicity (%)		Biochemical DFS (%)		
				GU	GI	Low	Intermediate	High
Yoshioka (55)	190	48/8	7.6	1	1	–	93	81
		54/9						
		45.5/7						
Hauswald (56)	448	42–43.5/6	6.5	5	0	99	95	–
Rogers (57)	284	39/6	2.7	1	0	–	94	–
Demanes (58)	157	42/6	5.2	3	0	97	–	–
Patel (59)	190	43.5/6	6.2	4	0	–	90	–
Zamboglou (60)	492	38/4	5–7.7	6	1	95	93	93
Barkati (61)	79	30–34.5/3	3.3	9	0	85	85	–
Strouthos (62)	450	34.5/3	4.7	1	0	96	96	92
Kukielka (63)	77	45/3	4.7	1	0	97	97	–
Jawad (64)	319	38/4	5.5	6	0	98	98	–
	79	24/2	3.5	0	0	92	92	
	96	27/2	2.9	8	0	100	100	
Hoskin (65)	30	34/4	5	3–16	1	–	99	91
	25	36/4	4.5					
	109	31.5/3	3					
Hoskin (66)	106	31.5/3	9	11	1	–	91	91
	138	26/2	5.25	2	0		93	93
	50	19–20/1	4.1	2	0		94	94
Krauss (67)	63	19/1	2.9	0	0		93 (3 yrs)	–
Prada (68)	60	19/1	6	0	0		66 (6 yrs)	–

FU, follow-up; HDR, high dose-rate.

The future ?

- Phase III study comparing 36 or 25 Gy in 5 over 1-2 weeks vs Conventional / Moderate HypoFx regimen
  - PACE
  - HEAT
  - NRG GU005
- Phase III study comparing 36 or 25 Gy in 5 over 1-2 weks vs BT
  - None so far
  - Pilot study CHU de Quebec ACURA grant 2019

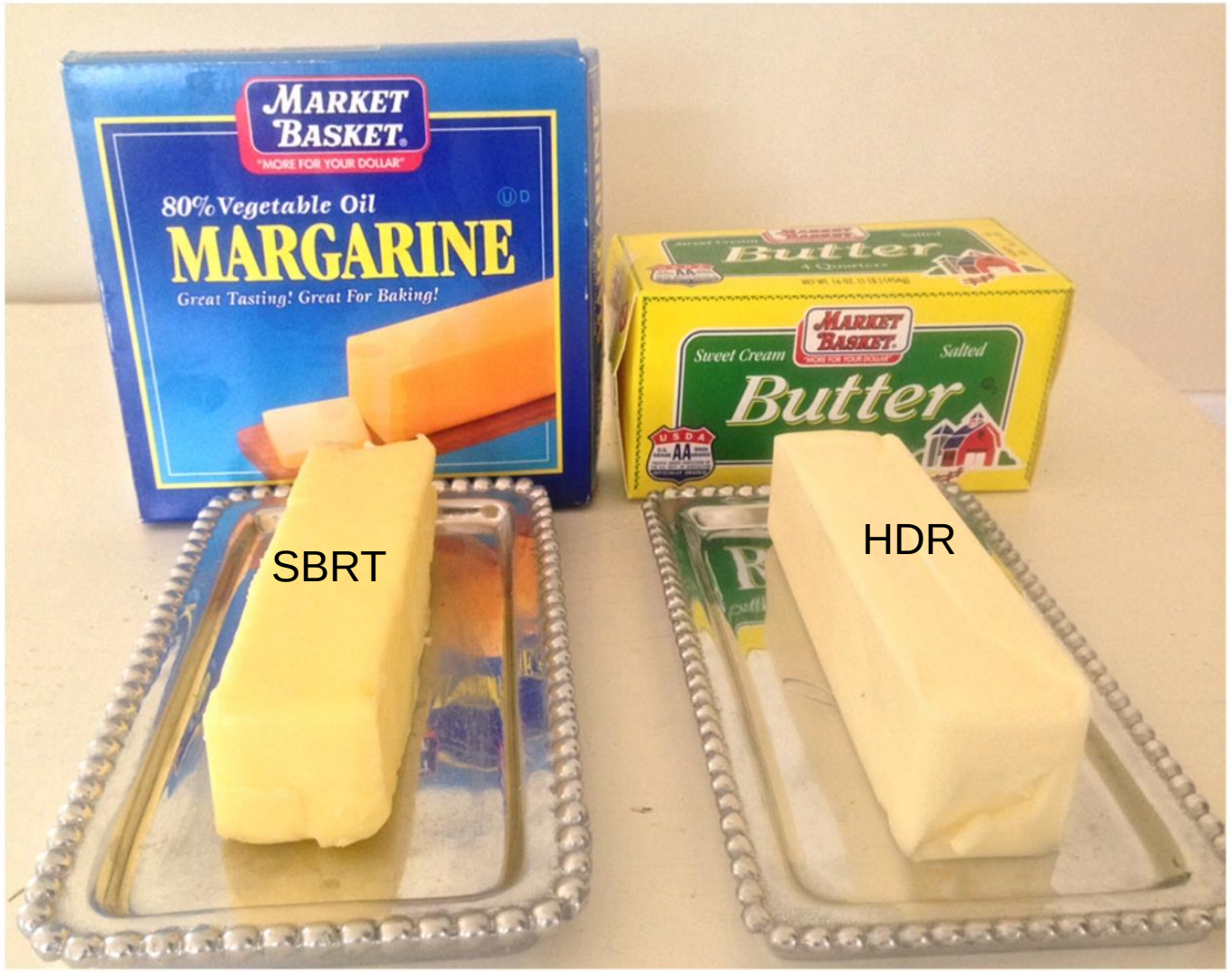
The future ?

- Better Patients Selection:
  - With biomarkers of tumor response and toxicity
  - Better staging M1 vs N1 vs Localized with Functional Imaging
- Better insertion / position of seeds / catheters
  - Image guided robotic BT
- Focal Therapy
- Local delivery of drugs/ radiosensitizer
- Immunotherapy and HypoFx

Conclusion

- SBRT appears equivalent to EBRT in LR, IR
- No comparative phase III study SBRT vs BT
- BT(LDR/HDR) >>> EBRT in IR, HR (phase III data)
- SBRT appears to present greater GI toxicity than BT
- SBRT lower GU toxicity than I125
- HDR lower GU/GI toxicity than I125
- The goal of SBRT is to replicate the dose distribution of HDR

Why the Substitute ?



Questions

Thank you

CLOSING REMARKS