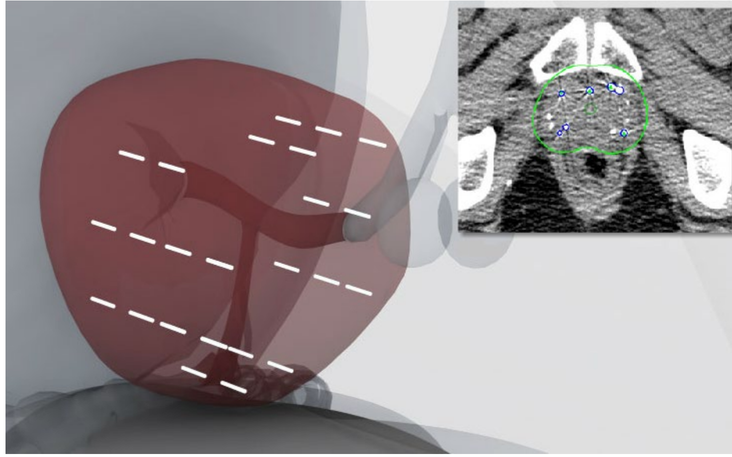

PKINS
N E

Focal therapy for prostate cancer

Daniel Song MD
Associate Professor
Johns Hopkins University School of Medicine

Disclosures

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- Research funding (current):
  - Bayer AG
  - Bristol-Myers Squibb
  - BioProtect
- Honoraria/ Prior funding:
  - Sanofi-Aventis
  - BrachySciences / Theragenics
  - GenomeDX
  - Augmenix
  - Bard Urology

‘Clinically Insignificant’ prostate cancer

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- Autopsies vehicular deaths (Rich, Franks)
  - Occult prostate cancer 30-45% of men age 40-50s
  - Vs 10% rate of clinically diagnosed PCa and 3% mortality rate
- Cystoprostatectomy specimens with small volume incidental cancers (Stamey)
- Patients with extremely low progression rates after radical prostatectomy (Epstein):
  - Volume < 0.5cc
  - No Gleason pattern 4 or 5
  - Organ confined
  - PSA density < 0.15 ng/mL per cc (Carter)

Active Surveillance – Rates of patient enrollment

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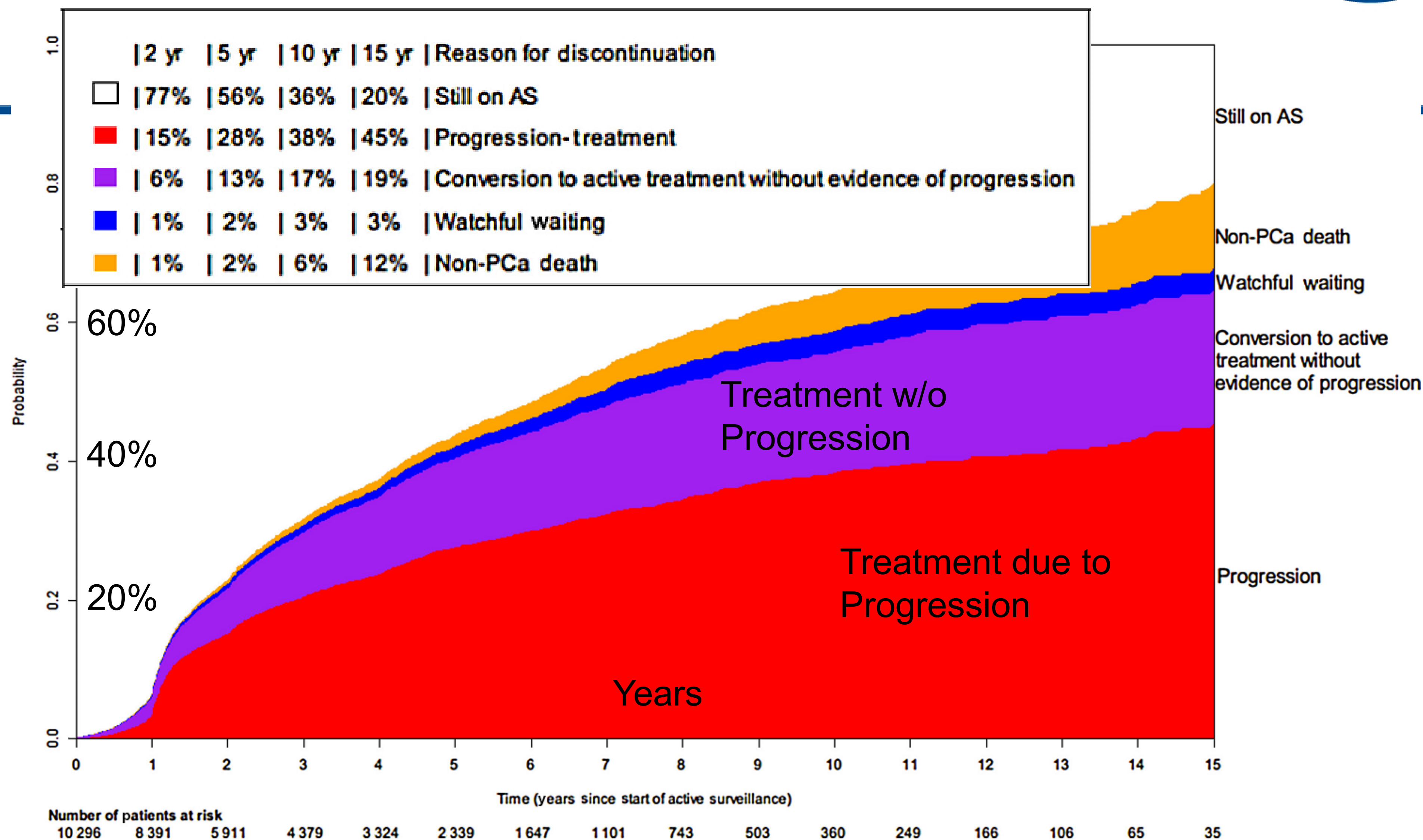
Author	Institution / Database	Risk group(s)	# patients	% Enrollment on Active Surveillance	Time Period
Sidana	Johns Hopkins	Low	493	5.3%	2001-2005
Anandadas	UK NW Uro-Oncology	Low, Intermediate	768	20%	2006
Weiner	SEER	Low	15,510	32%	2010
Weiner	NCDB	Low	28,028	20%	2010
Cooperberg	CaPSURE	Low	(10,472)	40.4%	2010-2013
Taylor	Kaiser N Cal	Low	1,140	39.3%	2012-2014
Loeb	Swedish Natl Registry	Very low / Low	(20,096)	93% / 79%	2014

Anandadas, BJU Int. 2011 Jun;107(11):1762-8. Sidana et al, Prostate. 2012 Jan;72(1):58-64. Taylor et al, Cancer Epidemiol Biomarkers Prev. 2016 Aug;25(8):1240-50. Loeb, JAMA Oncol 2017,3:1393-98. Cooperberg M, JAMA 314:80-82, 2015. Weiner AB, J Urol. 2015 Jan;193(1):95-102.

Discontinuation rates on AS



Hemelrijck MV, Eur Urol 2018 Oct 29 (epub; in press)

Rationale for Focal Therapy

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- Advances in imaging and staging
  - multi-parametric MRI (mpMRI) + targeted biopsy technique
  - Systematic and/or saturation biopsies
- Index lesion concept
- Reduced morbidity of active surveillance for uninvolved regions
- Treatment while preserving quality of life

Trends in # of cancer foci in prostatectomy specimens

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Reference	Time Period	# of RP Cases	# of Distinct PCa Foci
Bastacky *et al.*	**1982-1991**	81	**7.3 (4.1-60)**
Wise *et al.*	**1992-1996**	559	**3.92**
Muezzinoglu *et al.*	**1983-1998**	974	**2.24**
Ward *et al.*	**1997-2006**	180	**3 (1-8)**
Yoon *et al.*	**2005-2006**	100	**2.9 (1-9)**
Haffner *et al.*	**2005-2007**	106	**2.43 (1-7)**

‘Index Lesion’ concept

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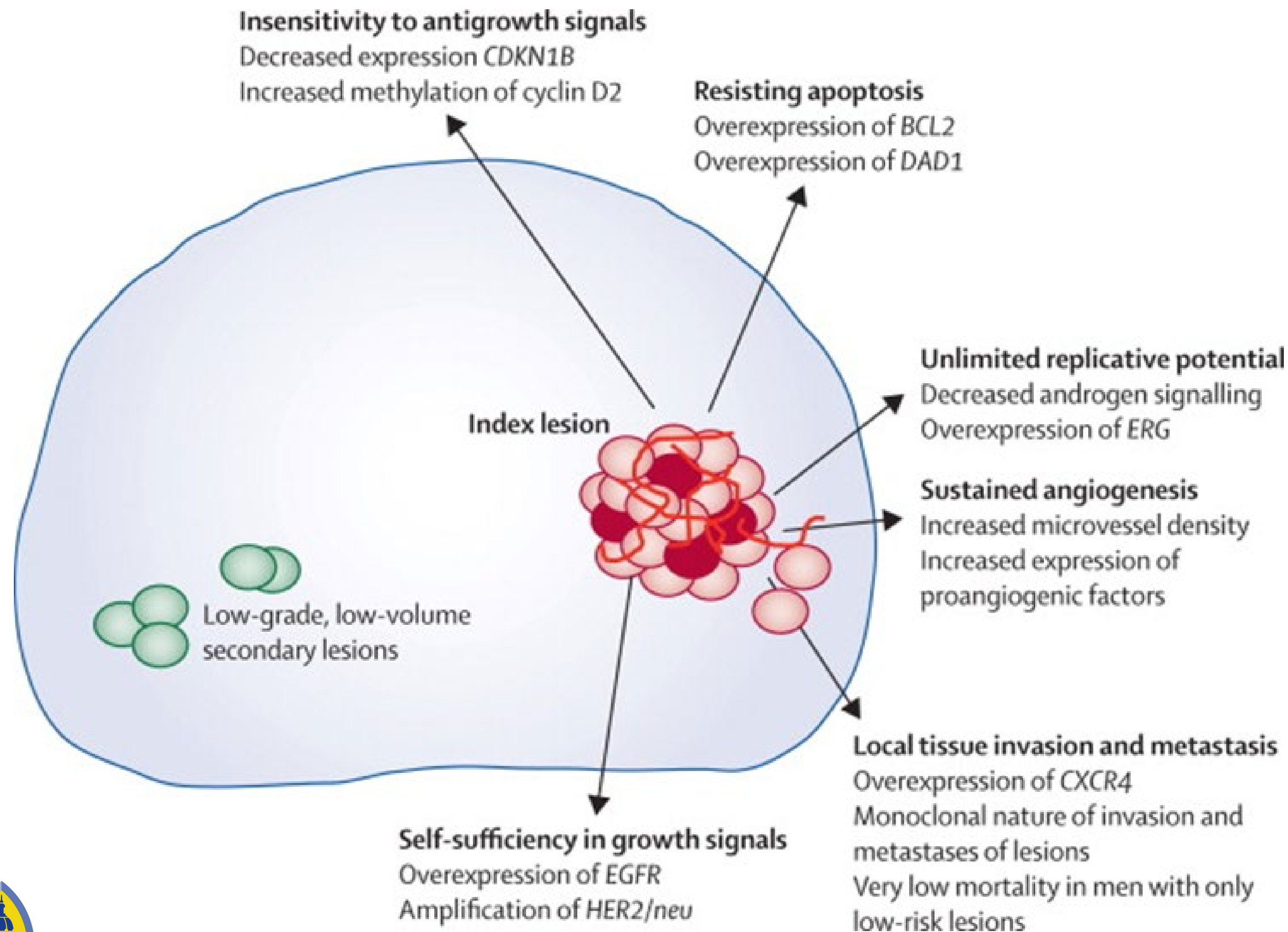
- 78% prostatectomies multifocal
  - Poor prognosis factors (e.g. extraprostatic extension) associated with largest (Index) lesion
  - Satellite foci: 87% < 0.5cc; 99% Gleason ≤ 6

- 83% of prostatectomies multifocal
  - Index lesion: median 2.78 cc
  - Satellite lesions: median 0.18 cc
  - ~ 85% of total tumor volume within Index lesion
  - PSA failure similar for Index vs Total tumor volume

Karavitakis, Nat Rev Clin Oncol. 2011; Wise et al, Urology. 2002.

Low grade/volume cancers lack hallmarks of malignancy



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Ahmed, Lancet Oncol, Volume 13, Issue 11, 2012, e509–e517

Grade Progression within Tracked Lesions on Repeat Mapping Biopsy

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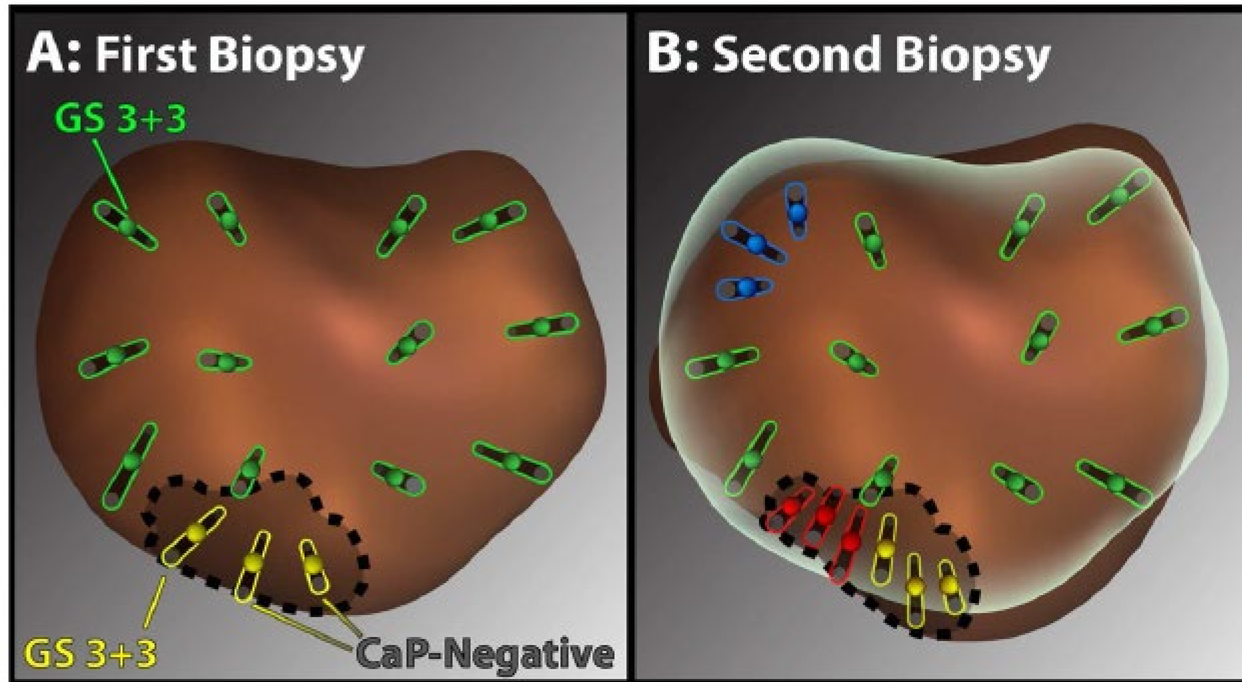

- Yellow – MRI-targeted cores
- Green – systematic cores
- MRI/TRUS fusion biopsy with mapping

- 26% with grade progression on follow-up biopsy for active surveillance (n=352)

Chang E et al, J Urol 2018

Grade Progression within Tracked Lesions on Repeat Mapping Biopsy

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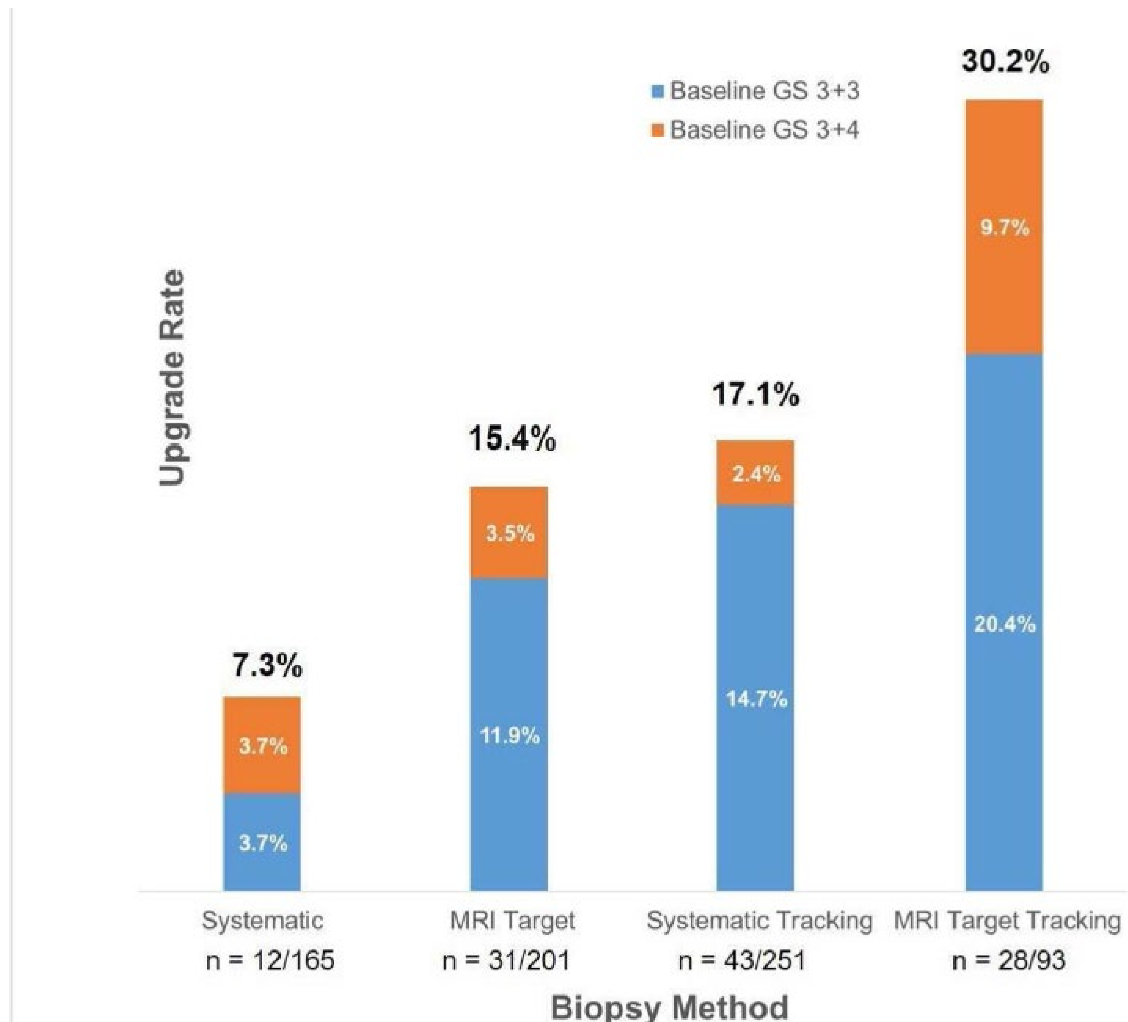

- Grade progression on 2nd biopsy in both systematic (non-MRI visible) and MRI-tracked regions

Chang E et al, J Urol 2018

Clonality of prostate cancer metastases

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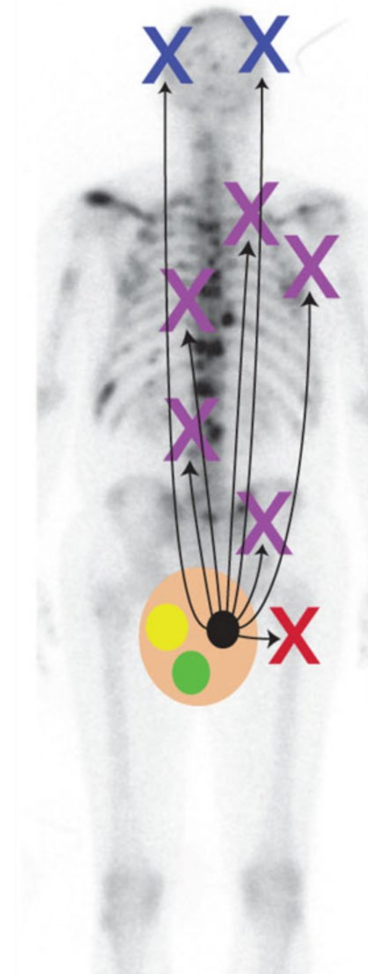
- Do multi-focal / multi-clonal cancers in prostate result in multi-clonal vs mono-clonal metastases?

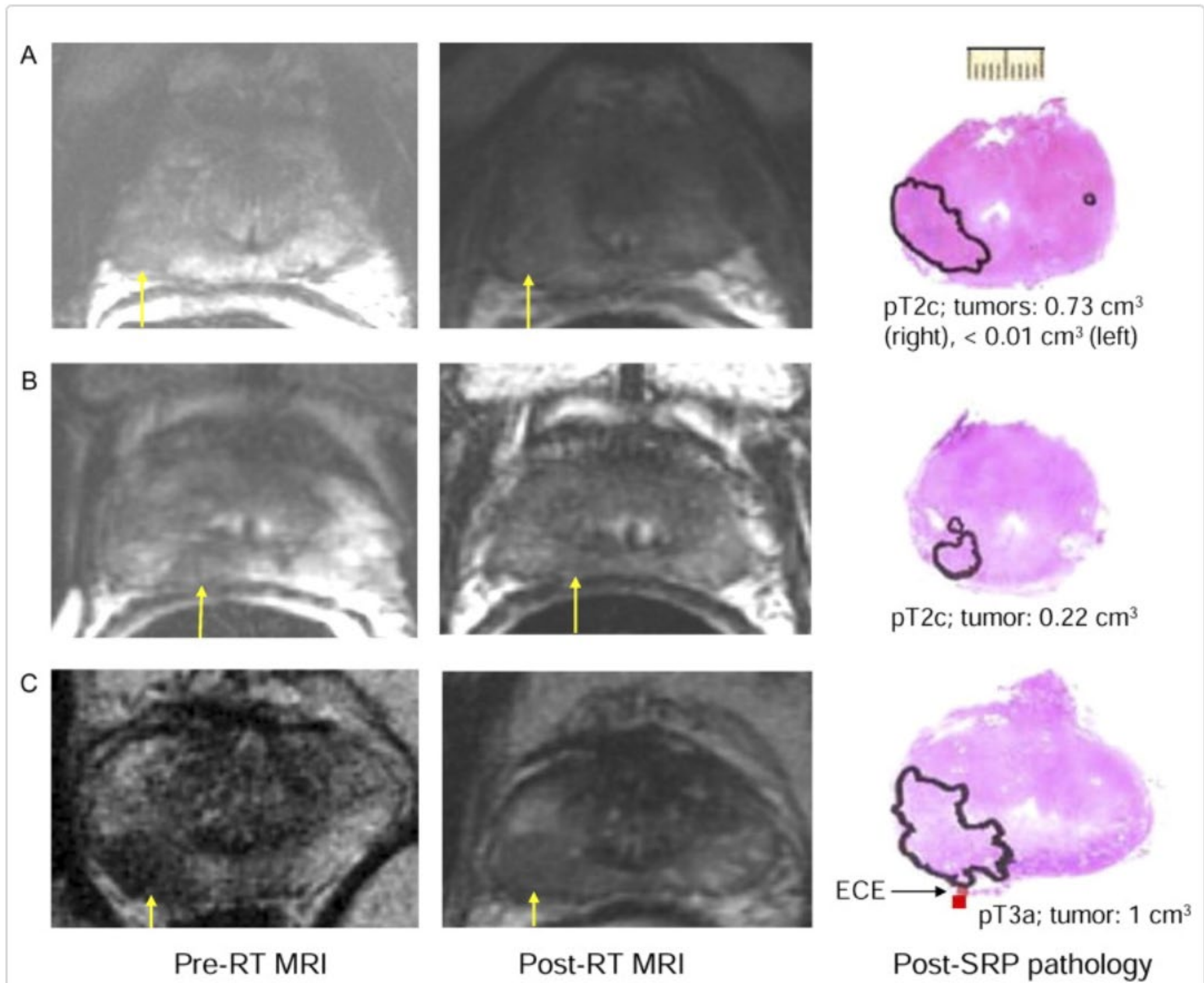
- 94 metastases from 30 patient autopsies
- Comparative Genomic Hybridization and Single-Nucleotide Polymorphism assays

- Highly variable genetic profiles of metastases between patients
- Highly uniform profiles of metastases within a given patient



Liu W et al, Nature Med 15, 559-565, 2009.

Local recurrences occur in original tumor foci after radiotherapy



- 9/9 recurrences in same location as original tumor (based on salvage prostatectomy)

Pucar, Int J Radiat Oncol Biol Phys 69(1), 2007

Proposed criteria for focal therapy

ITF-FLP
Intl Task Force on Prostate Cancer and Focal Lesion Paradigm

- ≤ T2 (radiologic ≤ T2c)
- PSA < 10 ng/ml
- PSA Density < 0.15 ng/mL/cc
- PSA velocity < 2 ng/ml/yr
- Gleason ≤ 6
  - ≤ 20%, ≤ 7mm cancer per core
  - ≤ 33% cores positive
  - Single lesion ≤ 12 mm
  - ≤ 10 mm capsular contact

IWFTI
Intl Workshop on Focal Therapy and Imaging

- ≤ T2a (radiologic ≤ T2b)
- PSA < 20 ng/ml
- Life expectancy > 10 y
- Transperineal mapping biopsy
- Gleason ≤ 4+3
  - Not primarily anterior or apical location

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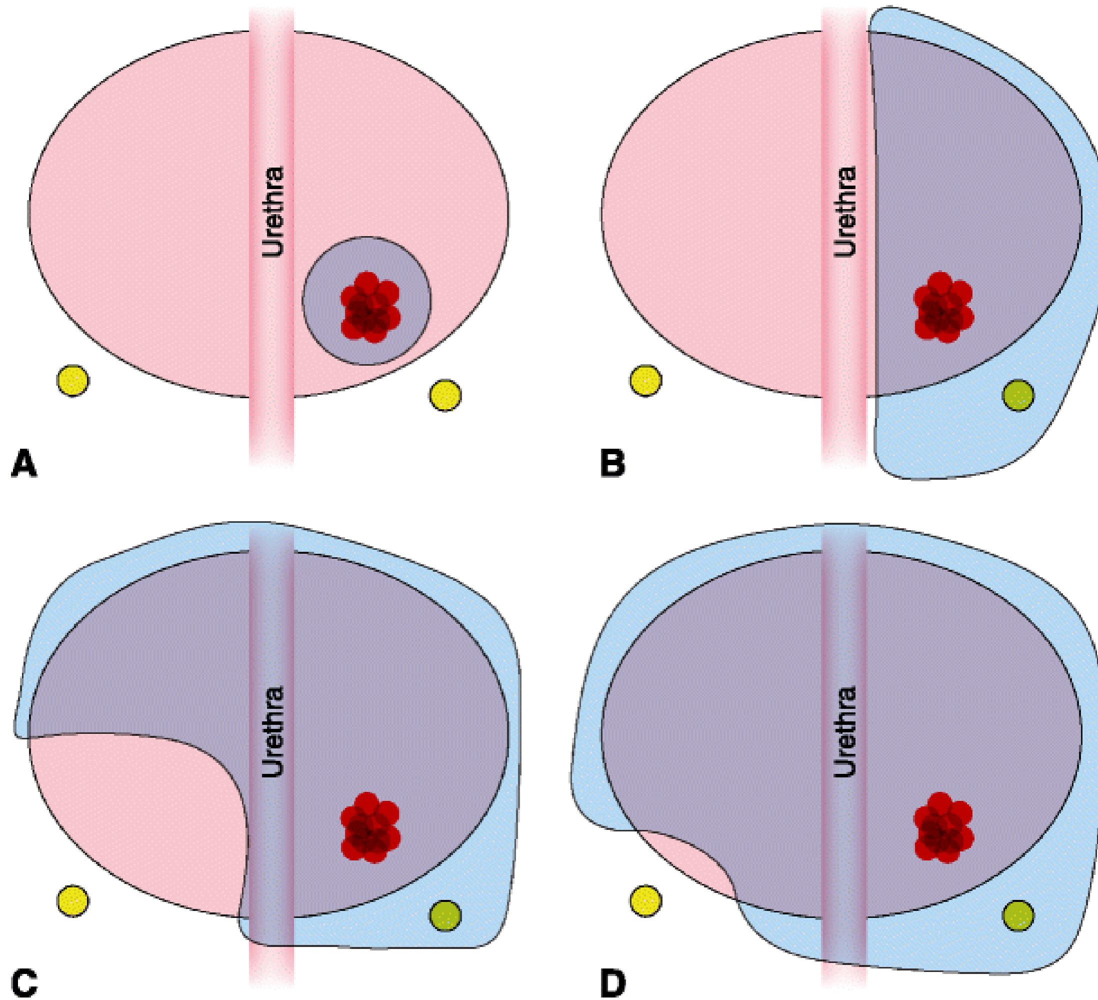
Varying strategies for focal therapy



A Lesion + margin

B Hemiablation

C Template ablation

D Subtotal ablation

Tsivian M, Polascik TJ. Curr Urol Rep. 2010;11(3):147–51

Focal therapy modalities

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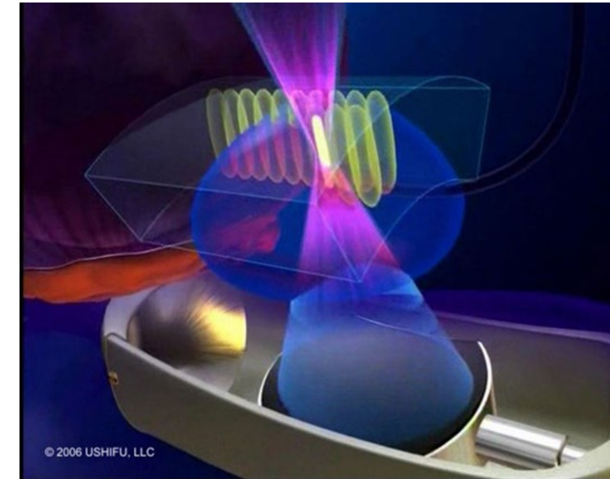
Acronym	Description	Effect	# Published Reports (2017)
HIFU	High Intensity Focused Ultrasound	Thermal energy → 60° C tissue ablation	13
Cryo	Cryotherapy	Thermal energy → -40° C	11
PDT	Photodynamic Therapy	Vascular photosensitizer → Reactive oxygen species	3
LITT	Laser Interstitial Thermotherapy	Direct thermal energy	4
Brachy	Brachytherapy	Radiotherapy	2*
IRE	Irreversible Electroporation	High voltage, low energy current	3
RFA	Radiofrequency Ablation	Alternating electrical current	1

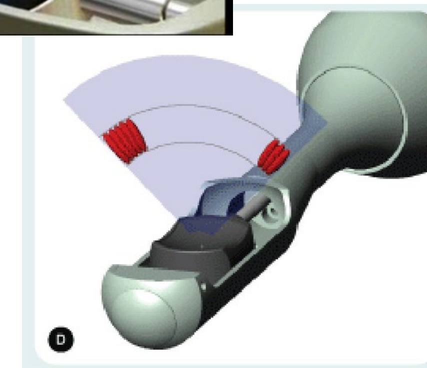
* ≥ 4 other studies since

Valerio M et al: Eur Urol 2017

High-Intensity Focused Ultrasound (HIFU)

- Transrectal probe with 2 transducers of varying focal lengths (30-50mm)
- Tissue heating in cigar-shaped focal band ~ 3x10mm
- Visualization of tissue changes monitored on US
- Cooling unit to keep rectal and probe temperatures low





- Sonablate® and Ablatherm® FDA approved under 510(k) for tissue ablation (not specific to prostate cancer)

5-year experience with focal HIFU

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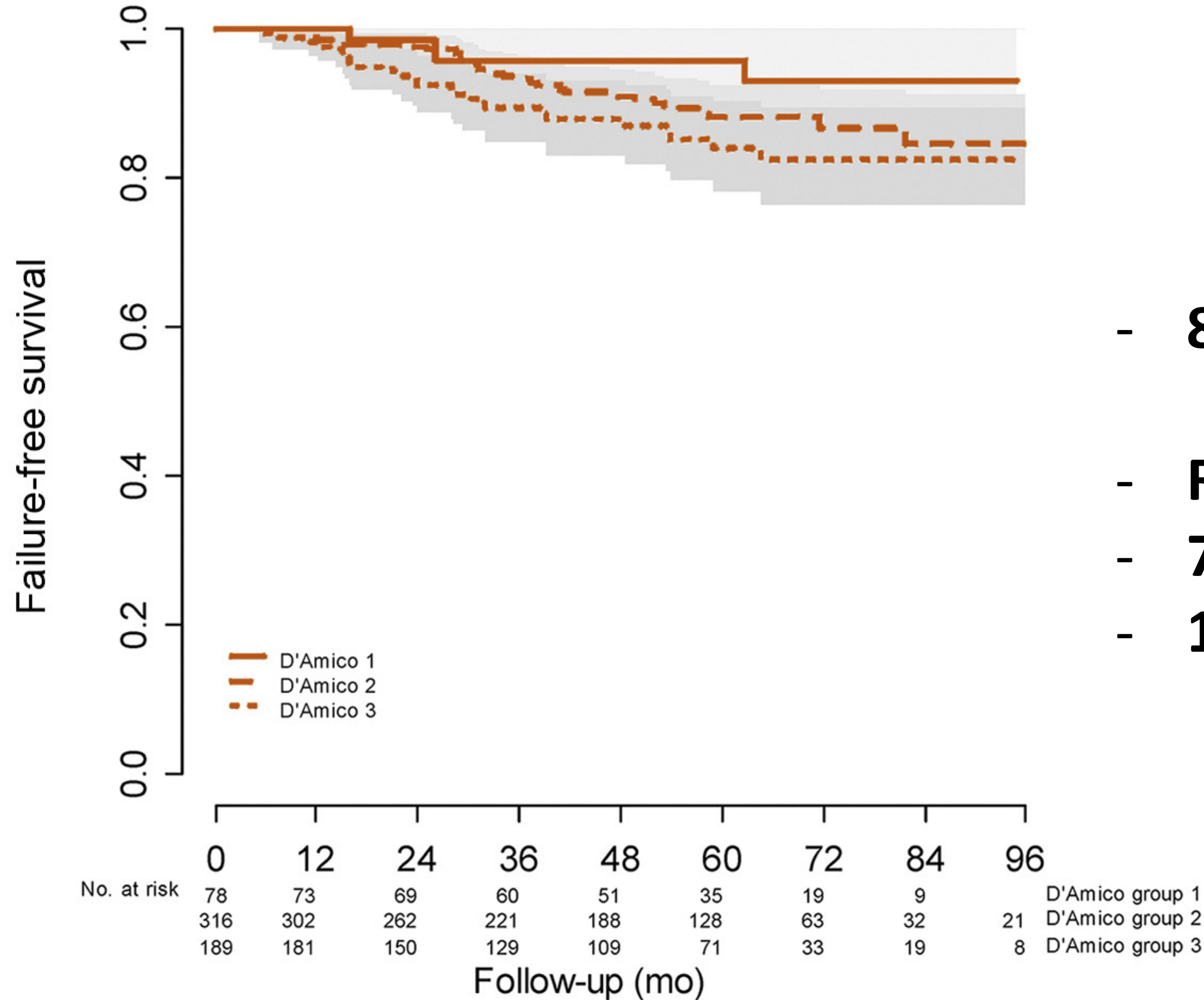
- 625 pts treated 2006 – 2013 (UK & Netherlands)
- MRI-targeted and systematic biopsies
- Gleason 6 (> 4mm), or Gleason 7-9 areas treated
- Post-treatment: →
  - PSA every 3-6 months + annual MRI
  - Two rises in PSA → Biopsy or mpMRI with biopsy of lesions
- Primary endpoint: Failure-free survival
  - Surgery/RT/systemic therapy, metastasis or prostate-cancer death
  - Up to 2 retreatments allowed without call as treatment failure

Guillamuier, Eur Urol 74 (2018):422-29

5-year experience with focal HIFU



Risk grouping:

- 13% low
- 53% intermediate
- 32% high

- **88% 5-year FFS**

- **Repeat HIFU in 20%**
- **7.5%** salvage RP or RT
- **1.7%** metastasis

Guillamuier, Eur Urol 74 (2018):422-29

Padeliporfin vascular-targeted photodynamic therapy

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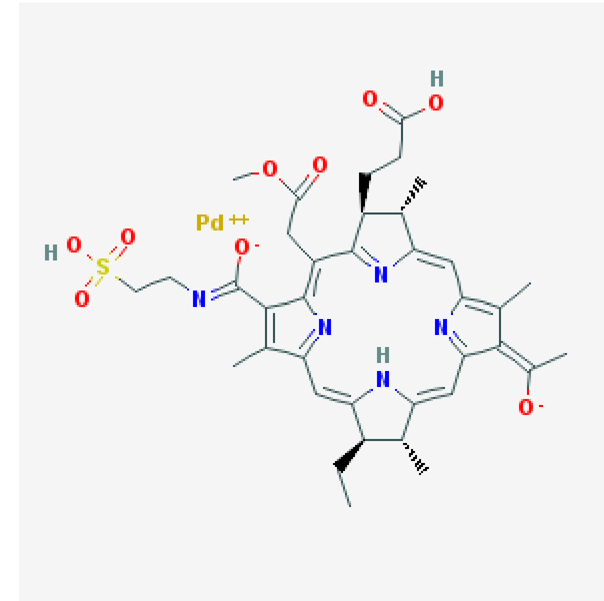
- Vascular-acting photosensitizing agent
  - Water-soluble, bacteriochlorophyll derivative
  - aka ‘**TOOKAD**’
- IV administration
- Activation via low-power laser (753 nm) from interstitial catheters
- Reactive oxygen species causing necrosis



Azzouzi A, Lancet Oncol 18:181-91, 2017.

Padeliporfin vascular-targeted photodynamic therapy vs AS

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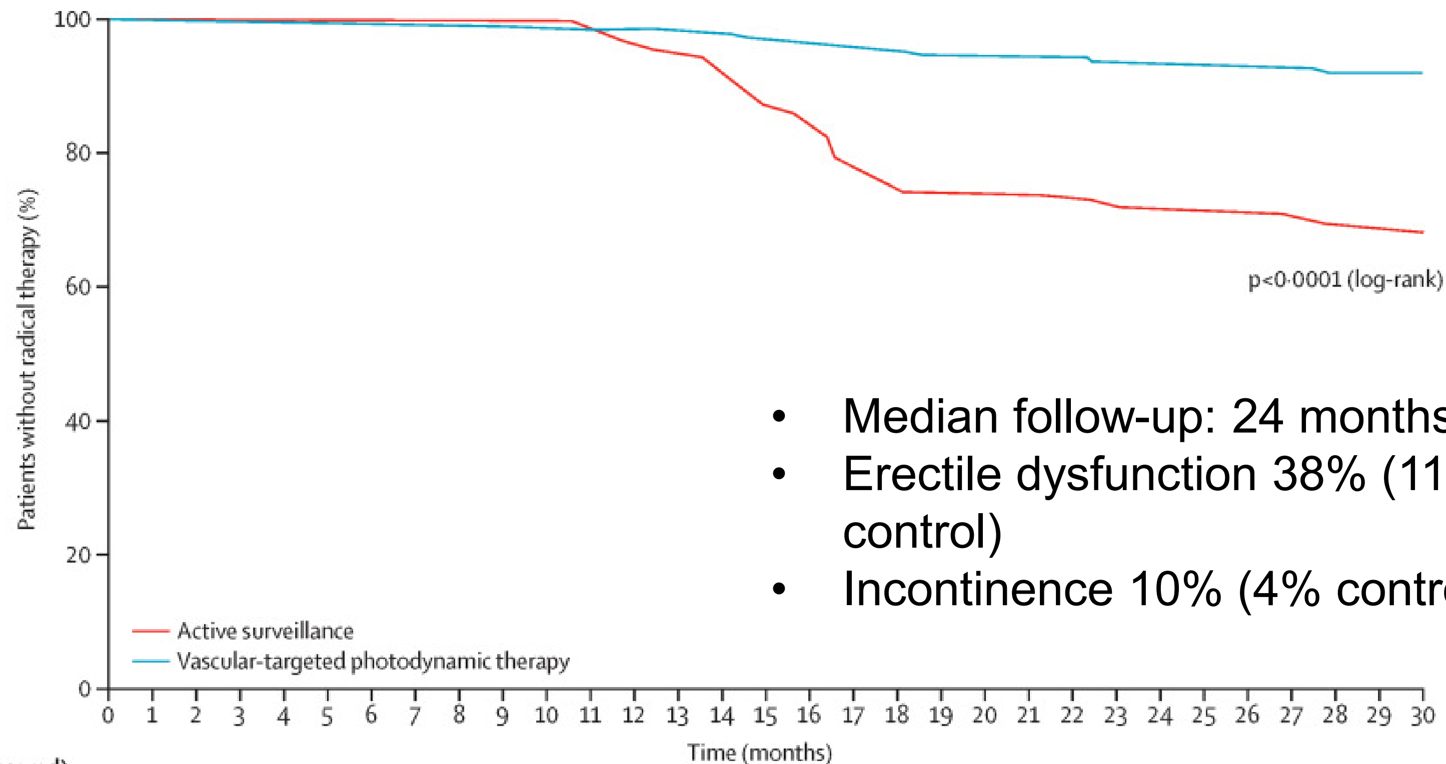


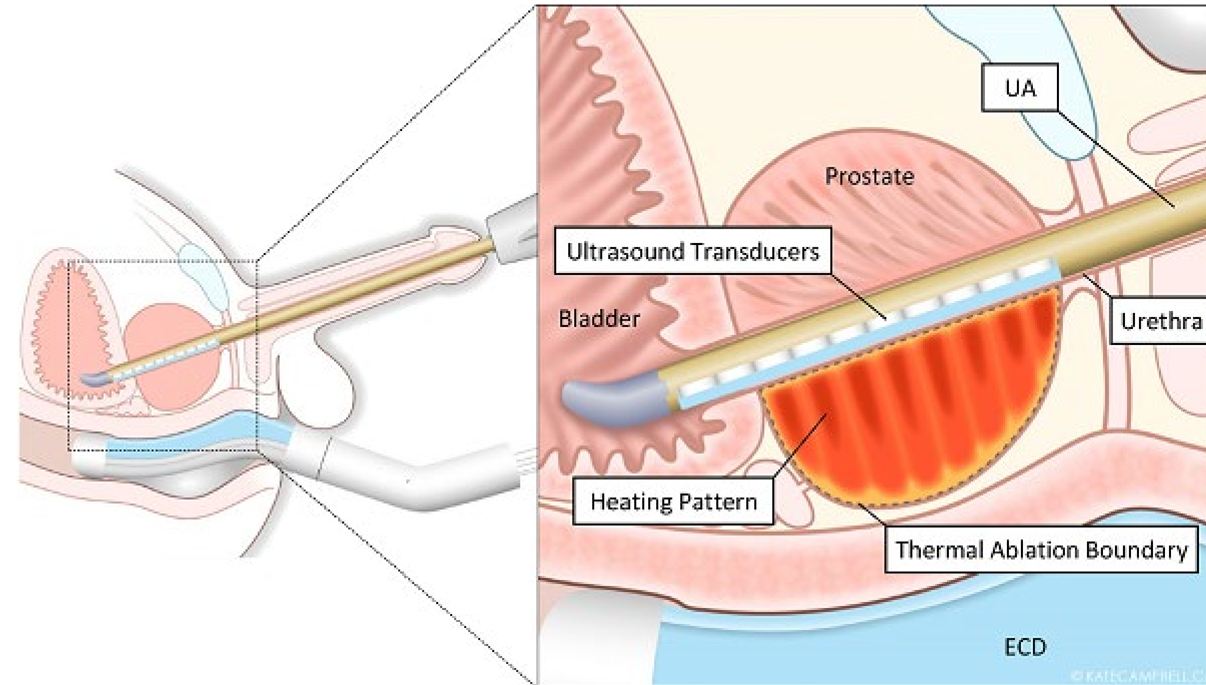
Number at risk (censored)											
Vascular-targeted photodynamic therapy	206 (9)	197 (9)	196 (10)	195 (12)	192 (14)	186 (14)	183 (15)	180 (38)	156 (186)	8 (193)	1 (194)
Active surveillance	206 (4)	202 (7)	199 (8)	197 (11)	188 (19)	162 (21)	136 (21)	133 (46)	103 (144)	4 (146)	1 (147)
Number of events											
Vascular-targeted photodynamic therapy	0	1	0	1	4	3	2	1	0	0	0
Active surveillance*	0	0	1	6	18	24	3	5	1	1	0

- Median follow-up: 24 months
- Erectile dysfunction 38% (11% control)
- Incontinence 10% (4% control)

Azzouzi A, Lancet Oncol 18:181-91, 2017.

MRI-Guided Transurethral US Ablation (MRI-TULSA)

- Rigid urethral applicator with 10-transducer U/S array
- Directional (not focused) U/S energy
  - Less risk of cold spots
- Cooling systems for urethra and rectum
- MRI thermometry-guided linear motion and energy of applicator



Chin et al, Eur Urol 70 (2016): 447-455

MRI-Guided Transurethral US Ablation (MRI-TULSA)

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- Phase I trial in low-, intermediate-risk
- ‘Whole-gland ablation’
  - 3-mm safety margin *within* prostatic capsule
  - Suprapubic catheter (2 weeks) in all patients
- Results (12-month)
  - Median 87% PSA decrease
  - Positive biopsies in 55%
    - Clinically significant disease in 31%
- Grade 2 events
  - UTI 33%; Urinary retention 17%
- Larger study in 110 pts with < 3mm safety margin

Chin et al, Eur Urol 70 (2016): 447-455

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Advantages of Brachytherapy as Focal Treatment Modality

- Well-known tumoricidal effect and dose-response
- Acceptable toxicity profile of whole-gland treatment
- Imaging validation of dose
- Validated method for pathologic evaluation of treated prostate cancer
- Identification of treated vs residual untreated prostate aided by presence of seeds (LDR)

Focal brachytherapy at Institut Mutualiste Montsouris

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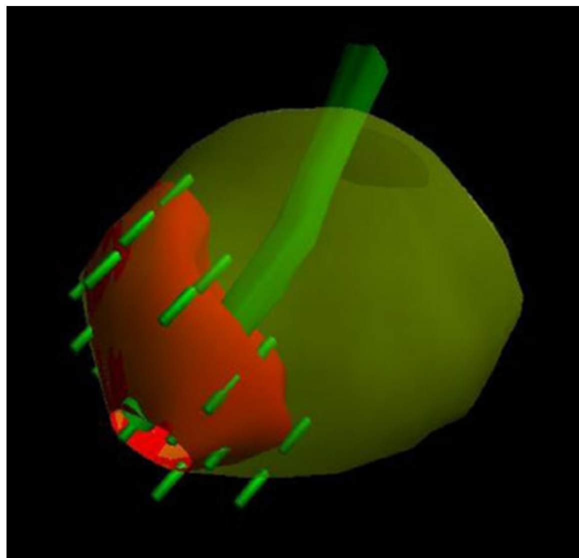
- 21 patients with low-risk, unilateral cancer
  - Declined active surveillance
- mpMRI staging
- 2-4 diagnostic biopsies, including transperineal saturation



- Lesion + margin
- 145 Gy I-125
- Mean 34% of total prostate treated

Cosset et al, Brachytherapy 12 (2013) 331-337

Institut Mutualiste Montsouris:
Urinary, Sexual morbidity with focal brachy

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	Urinary (IPSS, mean)	Sexual (IIEF-5, mean)
Initial	5.4	20.1
2 months	11.8	18.6
6 months	6.6	19.1
12 months	6.1	19.8

- Comparison vs 100 whole-gland patients:
  - Faster recovery in 6- and 12-month IIEF (vs whole-gland)
  - Borderline lower IPSS at 6-months
- Treatment of prostate base associated with higher IPSS

Cosset et al, Brachytherapy 12 (2013) 331-337; Srougi et al, Brachytherapy 16 (2017) 988-992.

JHU Focal Brachytherapy (NCT 03861676)

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- Very-low / Low / Intermediate-risk (declining AS)
- Multi-modality image fusion:
  - Transperineal mapping biopsies (Koelis)
  - mpMRI
  - PSMA (F18-DCFPyl)
- Focal brachytherapy with iRUF intraoperative dynamic dosimetry
- MRI years 1 & 2 with Targeted biopsy
- DCF-Pyl PSMA + Saturation biopsy at 2 years

NIH 2-R01CA151395, PIs: Song, Lee, Burdette

Focal therapy – Conclusions

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- Active surveillance effective, but with significant rates of progression and discontinuation
- Grade progression within lesion over time
- Dominant effect of index lesion on outcome
  - Focal treatment feasible despite multifocality / multiclonality
- Early data suggest:
  - Rates of progression and salvage manageable
  - Lower toxicity compared to whole-gland treatment
- Potential role for molecular assays to characterize lethal potential of index / non-index lesions

Thank you!

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