Focal therapy: Uses and misuses

Brennpunkt Urologie

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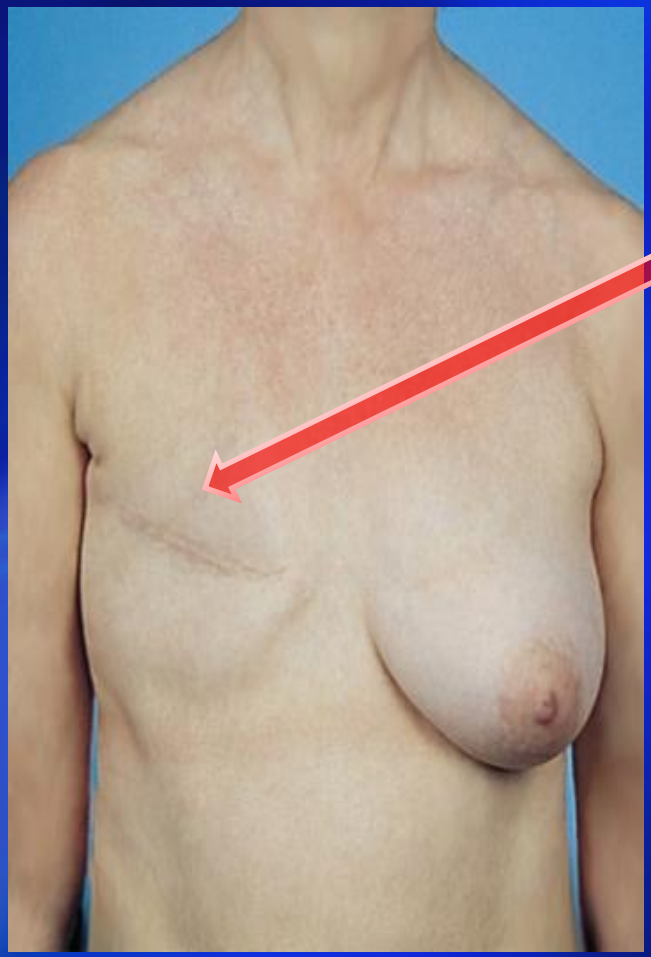
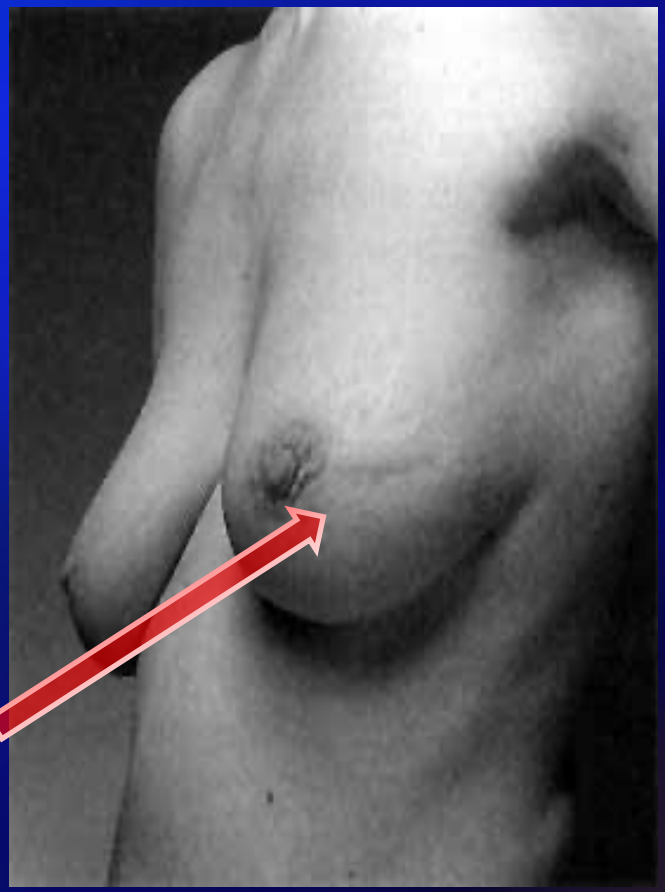
L. Klotz disclosures

- Consultant, miR Scientific
- Research funding, Exact Imaging
- Research funding, Profound Imaging



Current approach to localized Prostate Ca



Focal therapy

Uses/Appeal of Focal

- Many ‘clinically significant’ cancers are indolent—radical treatment risks overtreatment
- Little to lose (‘wiggle room’)
- Change the paradigm (male lumpectomy)
- Plenty of tissue to preserve--1-2 cc Ca vs 40 cc prostate
- Preserving prostate matters (functional outcome)
- Diagnostic pathway is changing (ie, MRI before biopsy)
- Improved ability to characterize cancer phenotype
- Profusion of methods

Misuses/Risks of Focal

- Tumour multifocality and heterogeneity
- Limitations of imaging and targeting
- Monitoring
- Biology of response of residual disease to injury
- ‘Effectiveness of ‘salvage’ treatment
- Lack of level 1 evidence (RCTs)
- Profusion of methods, approaches

A range of technologies are capable of destroyhing tissue in a predicxtable and reliable manner

- Extremes of temperature
  - Direct
  - Indirect
- High voltage current
- High dose rate radiotherapy
- Laser light
- Toxic direct injection

Failure free survival after FT (HIFU or Cryo):

Tourinho-Barbosa RR, J Urol. 2020 Feb;203(2):320-330

N=309, 72% GG1, 27% GG2, 1% GG3

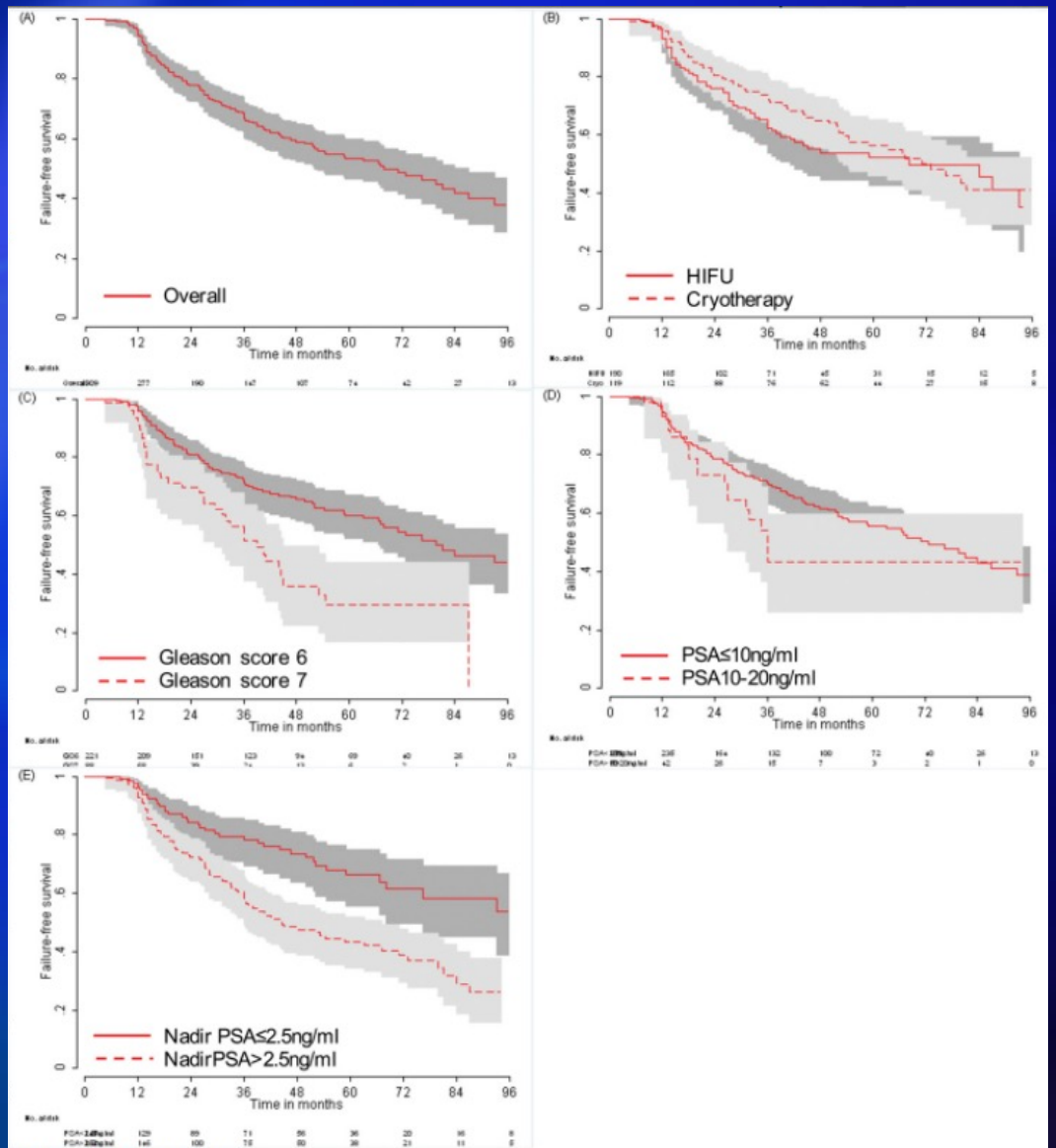
Overall

By treatment

By Gleason

By baseline PSA

By Nadir PSA



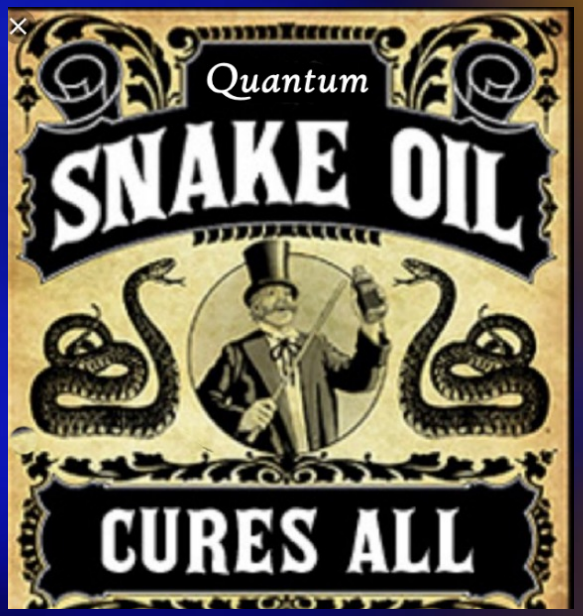
Germline genetic testing for PCa

Gene	Pca susceptibility	Risk for Aggressive Disease	Prevalence in Met dis	Other Ca risks	AS decision making	Metastatic RX options
ATM	+	++	++	Breast, Pancreas	+	++
BRCA1	++	+/-	+	Breast, ovarian		+++
BRCA2	+++	+++	+++	Male/femaie breast, ovarian, pancreas, melanoma	+++	+++
HOXB13	+++	-	-			
CHCK2	++	+	++	Female Breast, colon		
MSH2/6	++	+	+	Colon, ovarian, uterine, gastric, panc, UT urothelial, RCC		++
MLH1/ PMS2						++

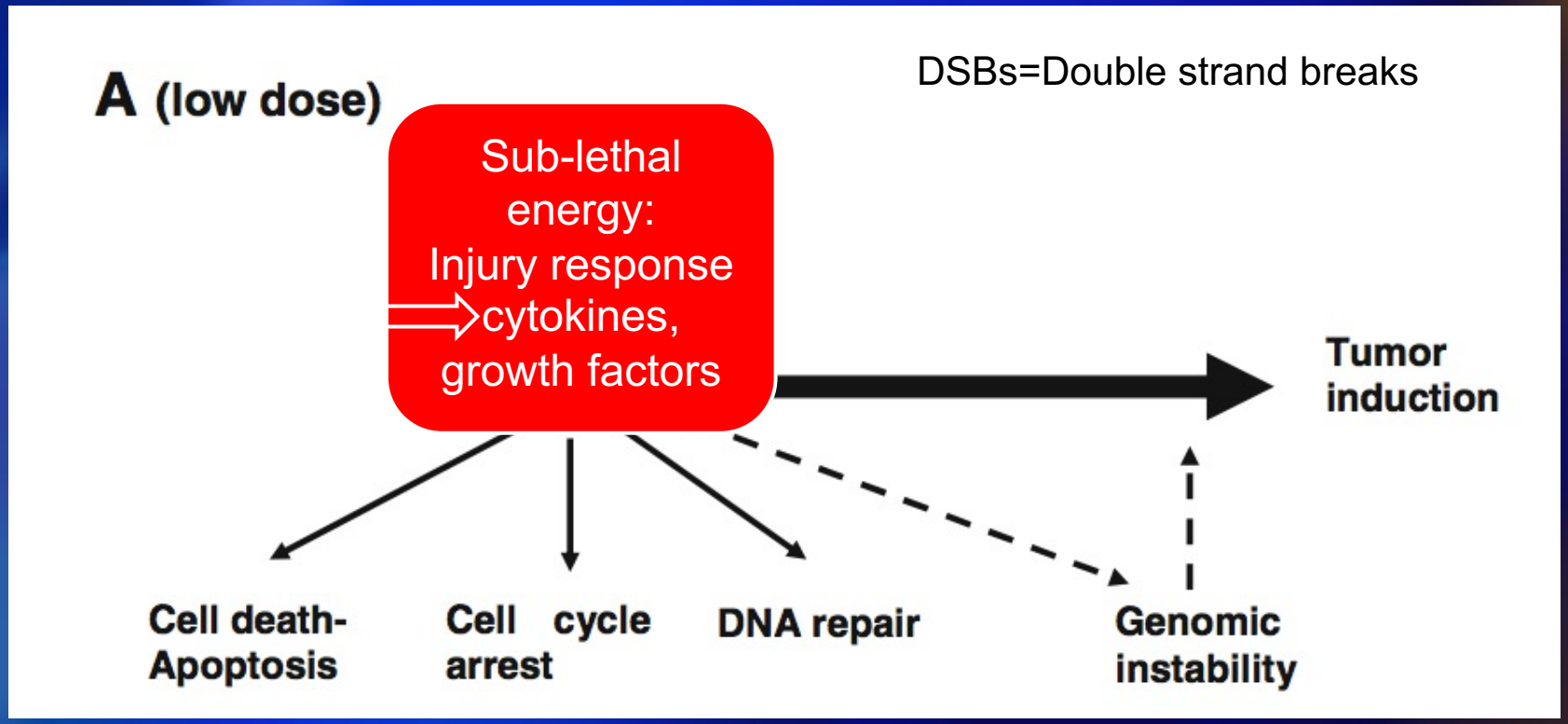
Adapted from Giri et al 2019

Concerns about focal therapy

- Focal therapy as snake oil medicine (ineffective treatment for a self-limited or clinically insignificant disease)
  - Risk of false reassurance of ineffective therapy for aggressive disease



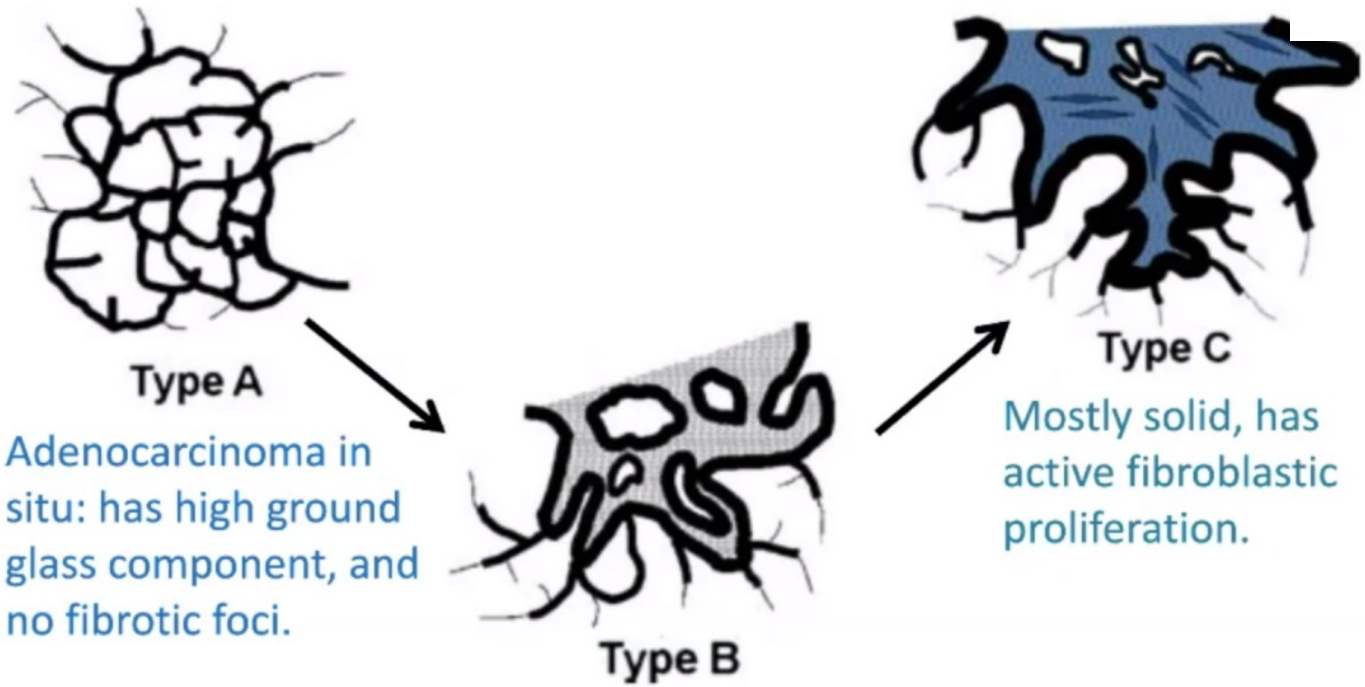
Model of accelerated carcinogenesis based on proliferative stress and inflammation for doses relevant to radiotherapy. Schneider U Radiat Environ Biophys. 2012 Nov;51(4):451-6.



- Accelerated repopulation well recognized in the XRT setting
- Analagous to focal therapy?

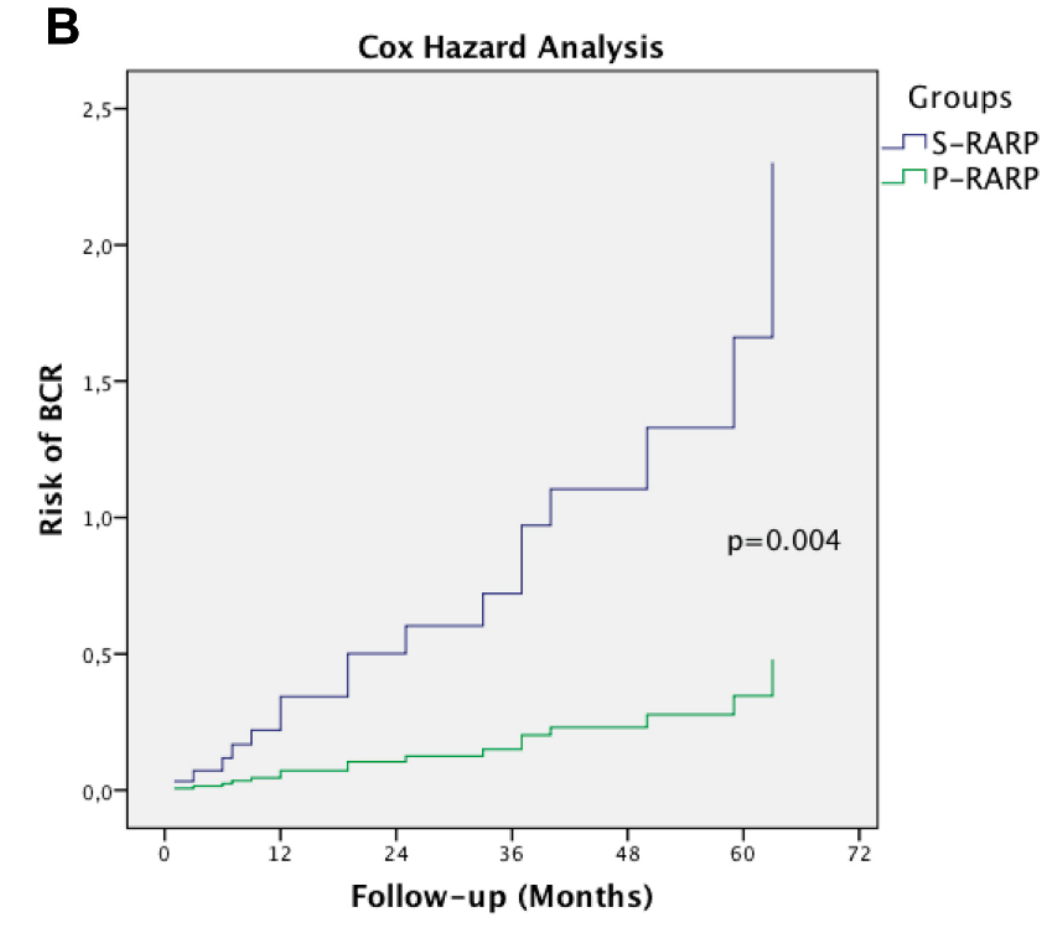
Injury induced fibrosis may alter cancer biologic phenotype

Noguchi Criterion for Stepwise Progression of Lung Adenocarcinoma



M. Noguchi, *Cancer Metastasis Rev* (2010); 29(1):15-21

Effect of Prior Focal Therapy on Outcomes of Salvage Robotic RP Nunes-Silva I, Sanchez-Salas R et al, J Urol. 2017 Nov;198(5):1069-1076



Post focal HIFU salvage RP (N=22) vs Primary RP (N=2750) outcome:

- Worse ED
- Worse bNED rate: 56.3% vs 92.4% at 2 yrs
- HR for PSA recurrence 4.8, p = 0.004).

If we use MRI to map disease, what are we missing?

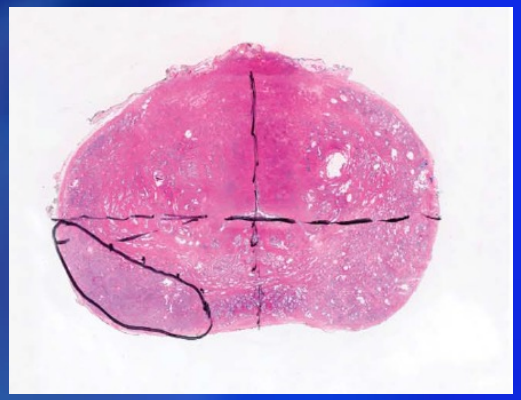
- 5-15% will have GG ≥ 2 on systematic biopsy
- 25% on Transperineal template bx (PROMIS)
- On whole mount studies from RP:
  - MRI detected 86% of solitary, 77% of index lesions
  - 39% of high grade tumors missed (usually < 1 cm)
  - Spatial relationship to the index tumor unclear

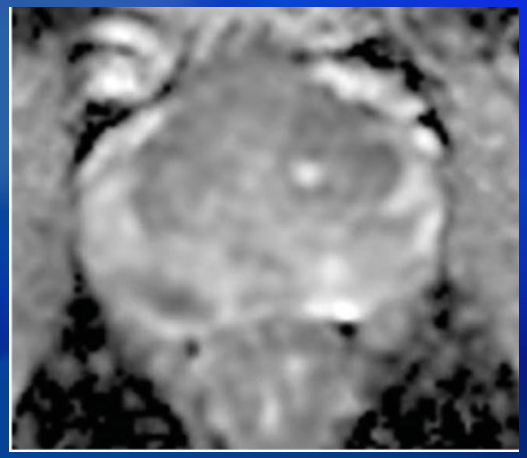
Wysock et al, BJU Int 2016; Filson et al, Cancer 2016; Ahmed et al, Lancet 2017

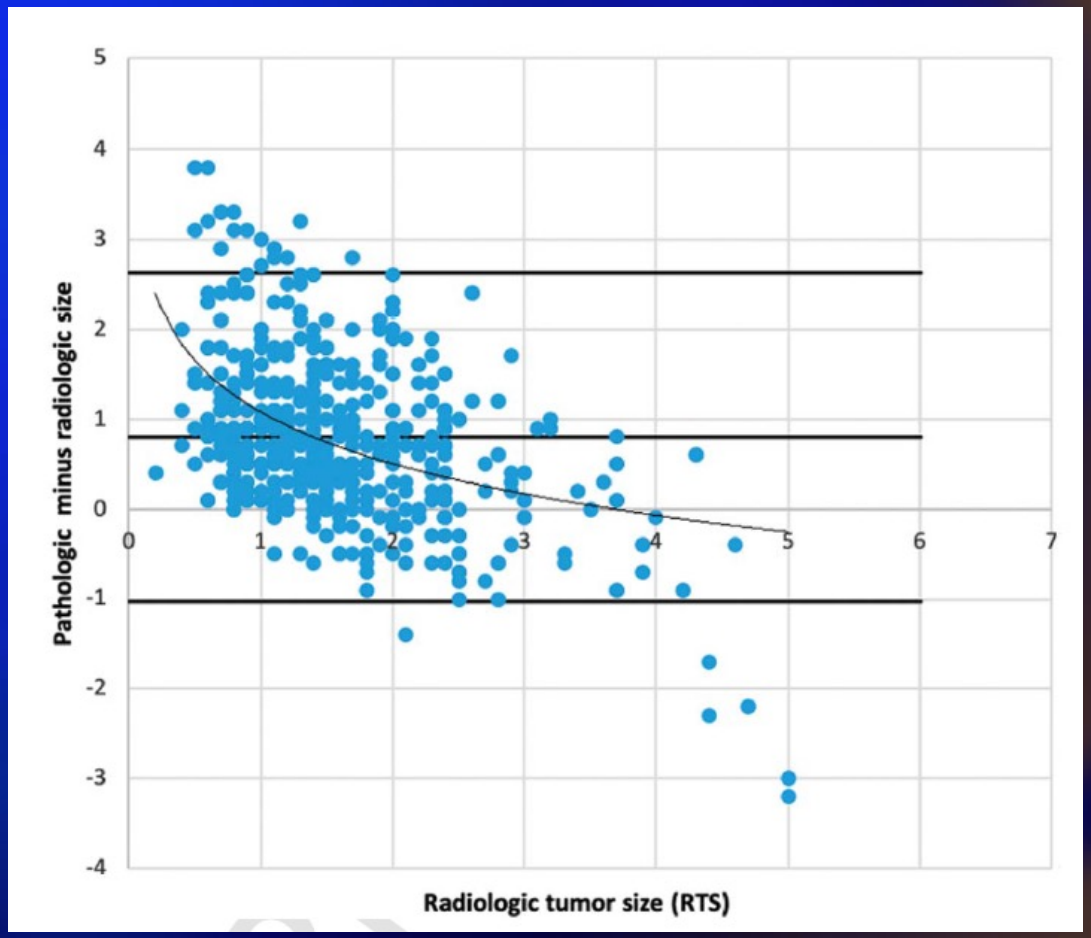
Predicting Pathological Tumor Size Based on MRI

Pooli A, Reiter R J Urol. 2020 Oct 7:101097

- N=441
- Mean MRI size 1.6 cm^2; mean path. size 2.4 cm^2

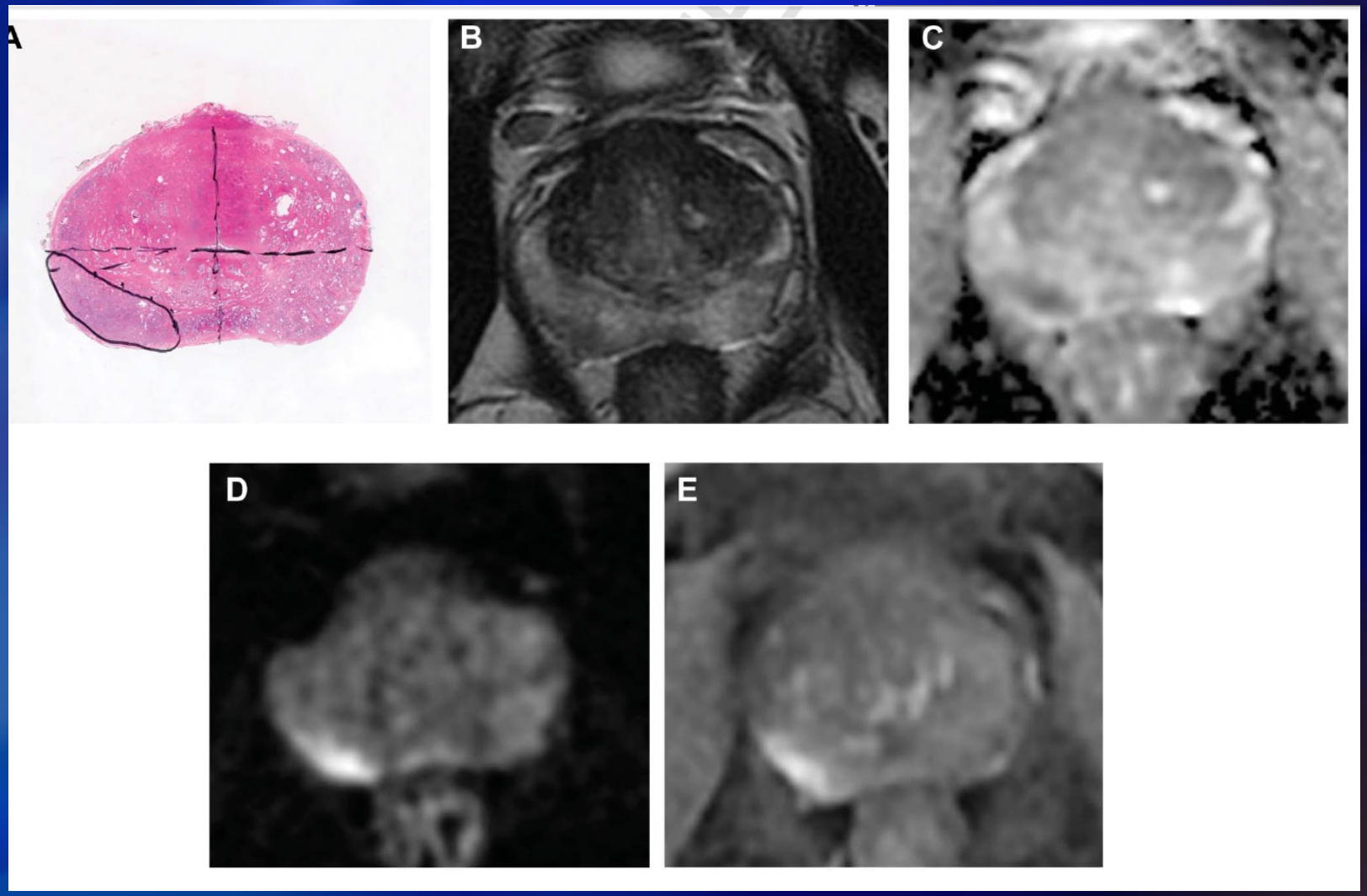






MRI lesion 1.6 cm^2; Surg path 2.7 cm^2

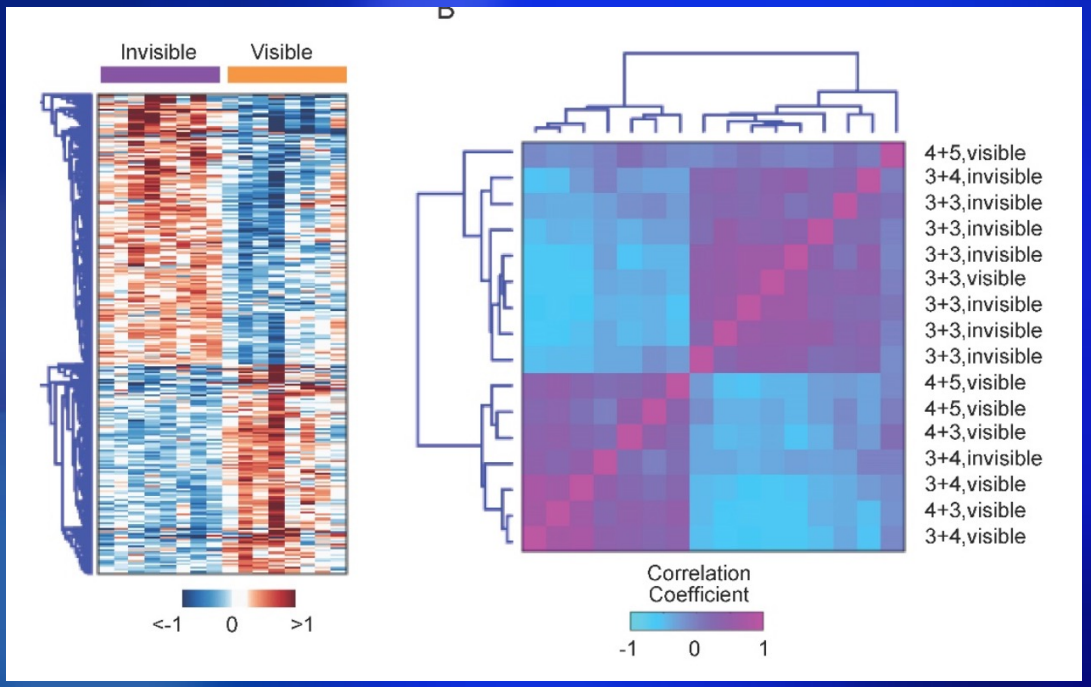
Courtesy of R Reiter, UCLA

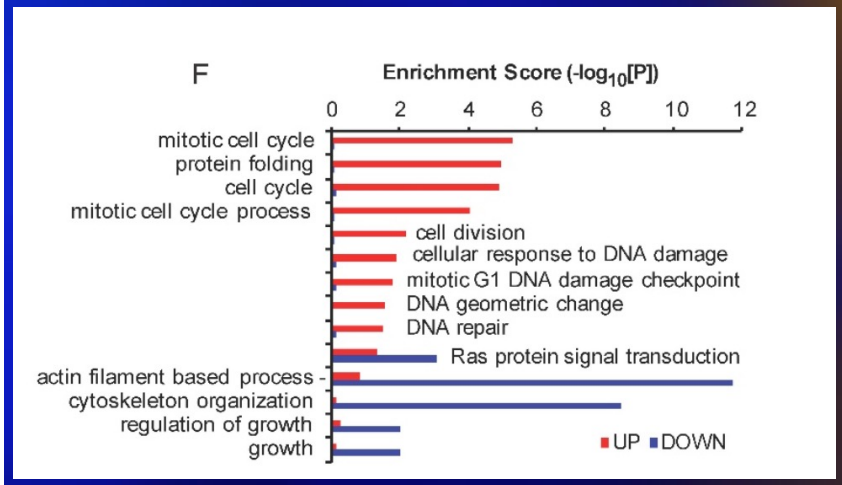


What is the biological significance of non-visible cancers?

- 15-25%
- MRI visibility a function of size and conspicuity
- Determined by tightness of cellular packing, quality of lumen; correlates with grade
- Some subtypes (mucin secreting) associated with lower conspicuity
- Invisible tumors have more favorable genetic featuresIn most cases, invisible lesions have more favorable biology
- ‘Image based’ management
- Wibmer et al
  - 1449 patients having RP for CS Pca

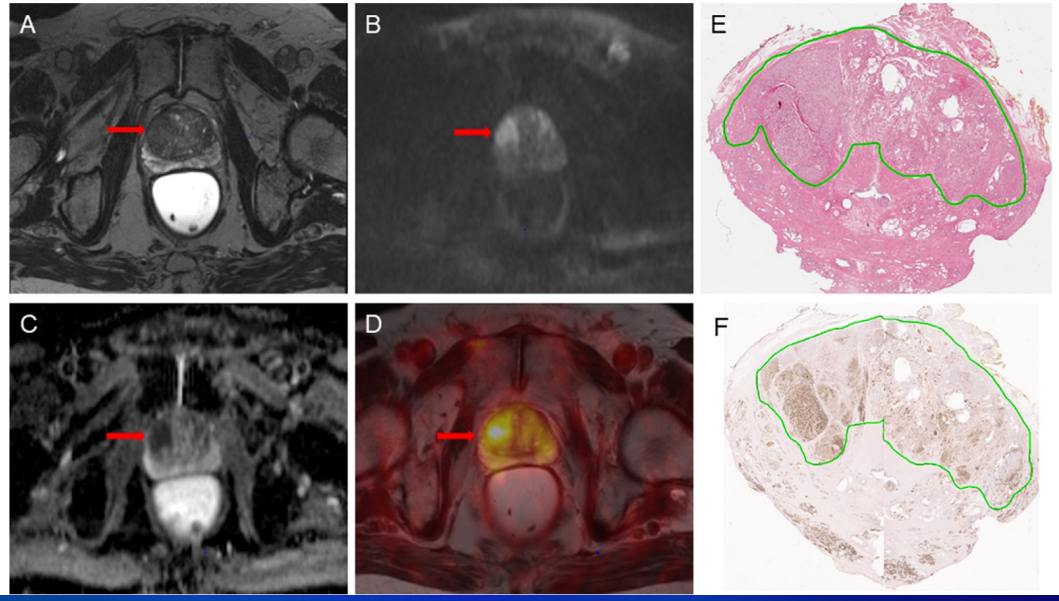
Genes involved in Pca progression determine MRI visibility. Li P,Theranostics. 2018 Feb 12;8(7):1752-1765





Radical Prostatectomy Without Prior Biopsy Following mpMRI and PSMA. Meissner H et al, EUROPEAN UROLOGY 82 (2022) 156–160

- 25 cases had RP based on positive MRI and PSMA PET only
- All had CS Pca (GG ≥ 2)



Age at surgery (yr), median (IQR)	70.9 (68.1–74.3)
PSA at diagnosis (ng/ml), median (IQR)	7.3 (3.9–13.0)
Lesions in mpMRI, PI-RADS v2, *n* (%)	
3	3 (7.5)
4	23 (58)
5	14 (35)
Lesions in PSMA-PET, *n* (%)	
3	2 (5.0)
4	10 (25)
5	28 (70)
Patient-based SUVmax, median (IQR)	9.5 (6.4–19.3)
SUVmax (all lesions), median (IQR)	6.4 (4.5–10.2)
Postoperative characteristics	
Pathological tumor stage, *n* (%)	
pT2a	1 (4.0)
pT2c	14 (56)
pT3a	6 (24)
pT3b	4 (16)
Pathological node stage, *n* (%)	
pN0	21 (84)
pN1	4 (16)
Pathological ISUP grade, *n* (%)	
2	8 (32)
3	15 (60)
4	0
5	2 (8.0)
Surgical margin, *n* (%)	
R0	20 (80)
R1	5 (20)

Principles of MRI targeted biopsy focal ablation

- Targeted and systematic biopsy
- Ablation with 10 mm intraprostatic margin, 3 mm extraprostatic margin if abutting capsule
- Choice of energy selection:
  - Size, extent of tumor and ablation zone
    - Image detected—more focal; systematic biopsy detected, wider
  - Location:
    - Proximity to NV bundle, apex
    - Anterior vs prosterior
    - Distance from rectum
- Follow up with PSA, MRI and targeted biopsy

Matching therapy and disease factors

- Anterior tumors:
  - Larger tumor volume acceptable
  - Wide margins feasible, safe
  - Needle based ablation reasonable
- Postero-medial cancers
  - Limited by rectal proximity/bladder/catheter
- Postero-lateral
  - Risk of NVB injury
- Apical
  - Most challenging due to risk of sphincter injury
- Calcifications
  - Disperse U/S energy

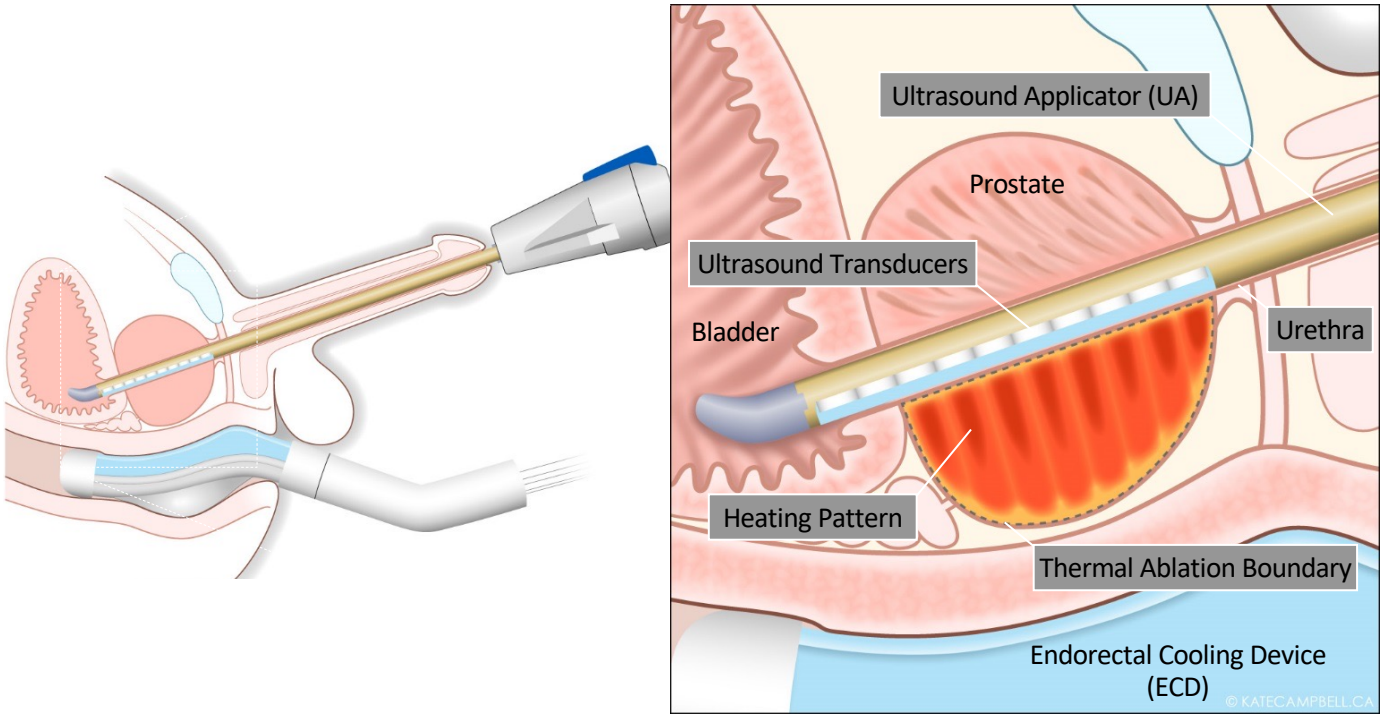
Level of evidence and focal therapy

- Challenging to demonstrate level one evidence for benefit with new technologies
- Benefits tend to be incremental, gradual (vs quantum improvements with new drugs)
  - Thousands of patients required to demonstrate small differences; such trials typically unfeasible.
- Important confounders of technical skill, experience, site variation
- Da Vinci Robot an important example
- FDA has acknowledged this in approving HIFU, TULSA (for tissue ablation)
- Unmet need: Robust end point for focal therapy trials

Focal therapy: Some key concepts

- Recurrences are an intrinsic component of a focal therapy management strategy
  - Risk is mitigated by careful tumour assessment, margin planning, and choice of therapy
- Careful follow up, allowing early identification of significant recurrence facilitates re-treatment in most
  - MRI the mainstay of follow up
  - PSA kinetics relevant
- Margin failures most common cause, and often amenable to repeat ablation
- Attention to disease biology, and nature and timing of recurrence relevant to decision re radical salvage
- Rare metastatic recurrences may reflect sub-optimal baseline staging

TULSA


Ultrasound Applicator (UA)
Prostate
Ultrasound Transducers
Bladder
Urethra
Heating Pattern
Thermal Ablation Boundary
Endorectal Cooling Device
(ECD)
© KATECAMPBELL.CA

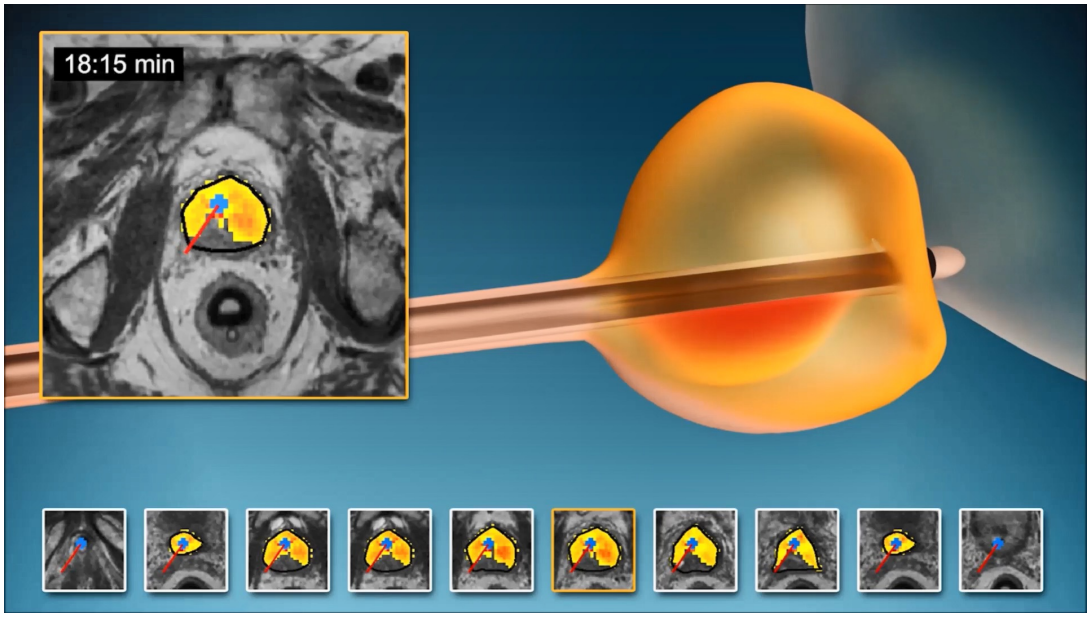
MR-Guided Transurethral Ablation of Prostate (TULSA)

The key concept: Closed loop temperature feedback control

1. Transurethral directional ultrasound ablation
   - Incision and radiation free ablation
   - No energy through rectum
   - Sweeping ultrasound, continuous rotation (no risk of cold spots between discrete sonications)
   - Small and large prostate volume (90+ cc)

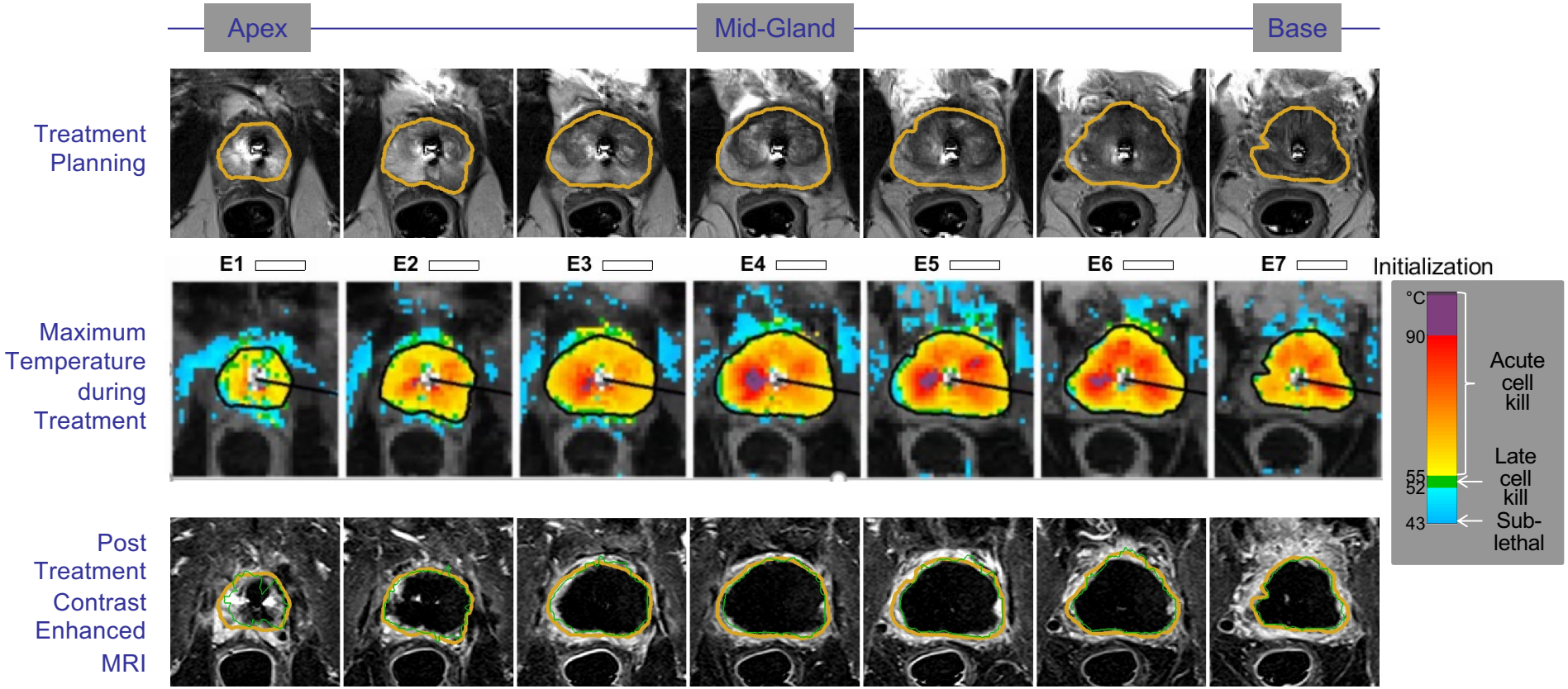
2. Real-time MRI thermal dosimetry & ablation control
   - Delivering a thermal therapy, while measuring temperature effect in real time, and automatically adjusting the energy delivered accordingly
   - Temperature feedback provides millimeter precision
   - Actively compensates for tissue and blood flow changes during treatment

3. Urethra and rectum cooled
   - Thermal protection of important anatomy



TACT Case Study: Ablation on Treatment Day MRI

Treatment: 44 cc, 38 min, Thermal accuracy 0.1 ± 1.2 mm



TULSA-PRO Ablation Clinical Trial (TACT)

Clinically Significant Study Population

- 115 patients, 13 institutions, 5 countries
- Intermediate-risk (67%) and Low-risk (33%) PCa
- PSA ≤15 ng/ml, Gleason ≤3+4, age 45-80 years

Primary Endpoints (12 months)

- Safety: Frequency/severity of adverse events
- Efficacy: PSA reduction ≥ 75% in >50% of patients

Secondary Endpoints (to 5 years)

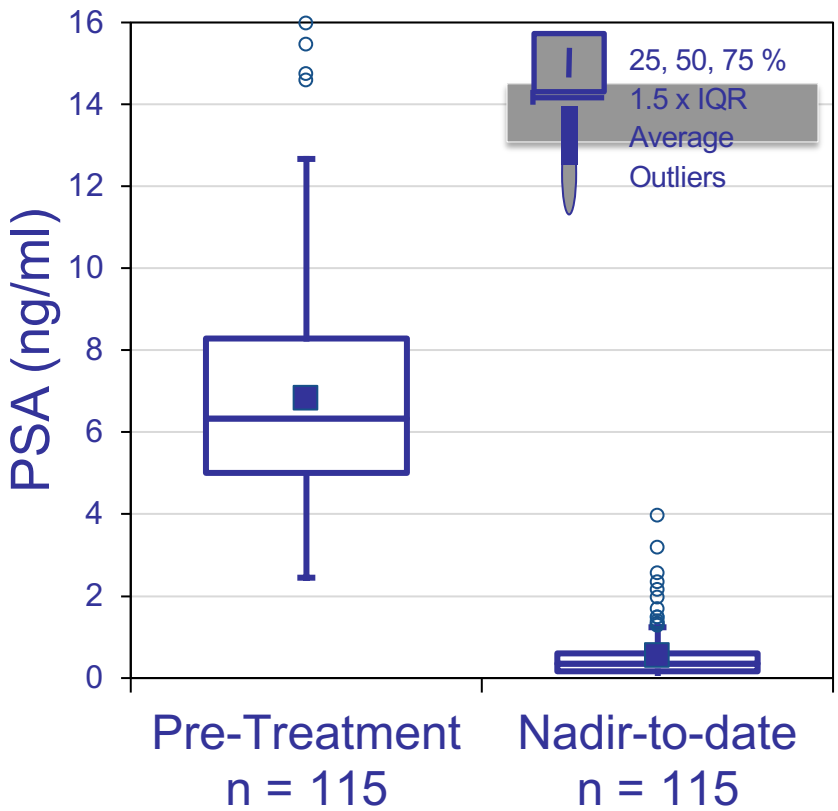
- 12 month volume reduction and biopsy
- 12 month mpMRI (central radiology lab)
- EPIC, IIEF, IPSS

Baseline Disease

Clinically significant GG2+

High volume GG1 (≥3 cores or ≥ 50% of a core)

Primary Efficacy Endpoint: PSA



PSA Primary Endpoint:

- PSA nadir ≤ 25% of baseline in ≥ 50% of patients

PSA Results:

- **PSA reduction ≥ 75% in 110 of 115 (96%)**
- Median PSA reduction 95% (IQR: 91 - 98%)
- Median PSA nadir 0.34 ng/ml (IQR: 0.12 - 0.56)

12 month MRI:

- Median prostate volume decreased from 41 to 4 cc (90%)

Efficacy: Biopsy Outcomes at 1 Year

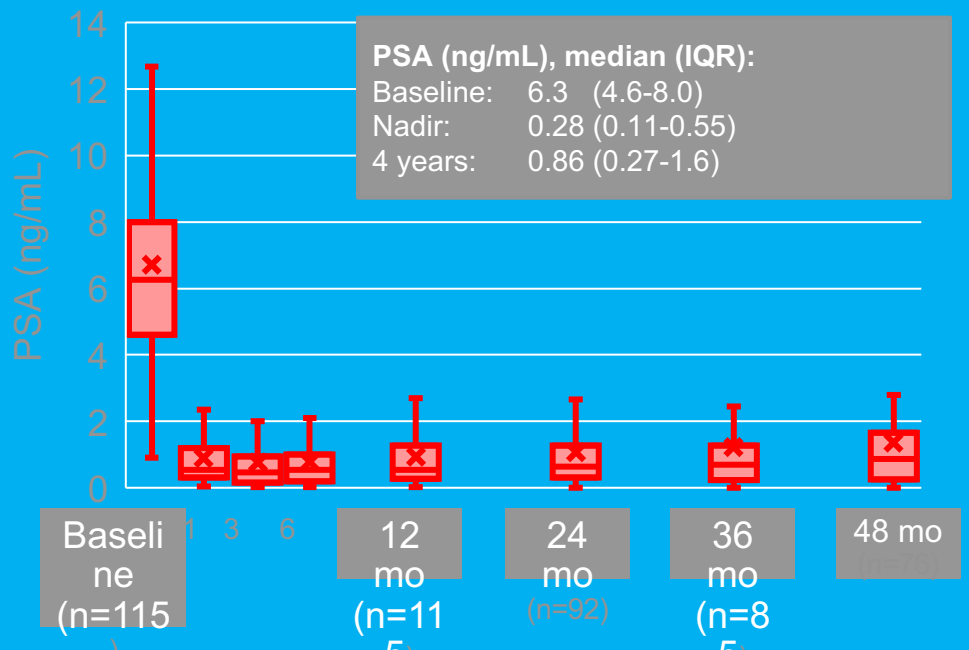
10-core Biopsy with High Sampling Density (median prostate volume = 4 cc)

- 111 biopsies (n=4; patient refusal)
- Among men with pre-treatment GG2, **54 of 68 (79%)** were free of GG2 disease
- Complete histological response and free of disease in 72 of 111 (65%)
- Of 39 positive biopsies, 16 (41%) were clinically insignificant (very low risk criteria)

TACT Biopsy Status (n=115)

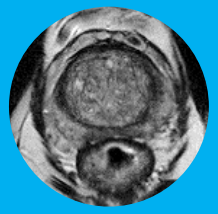
TULSA ablation efficacy endpoints to 4 years

- **PSA reduction durable to 4 years**
- **Median PSA reduction 96% to nadir, sustained 86% reduction to 4 yrs.**



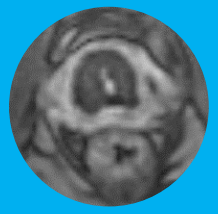
- Prostate volume significantly decreased
- Median volume reduction of 92% from 38 to 3 cc on 1-year MRI

Screening: 58 cc
PSA 5.5 ng/ml



Immediate Post
PSA 6.0 ng/ml

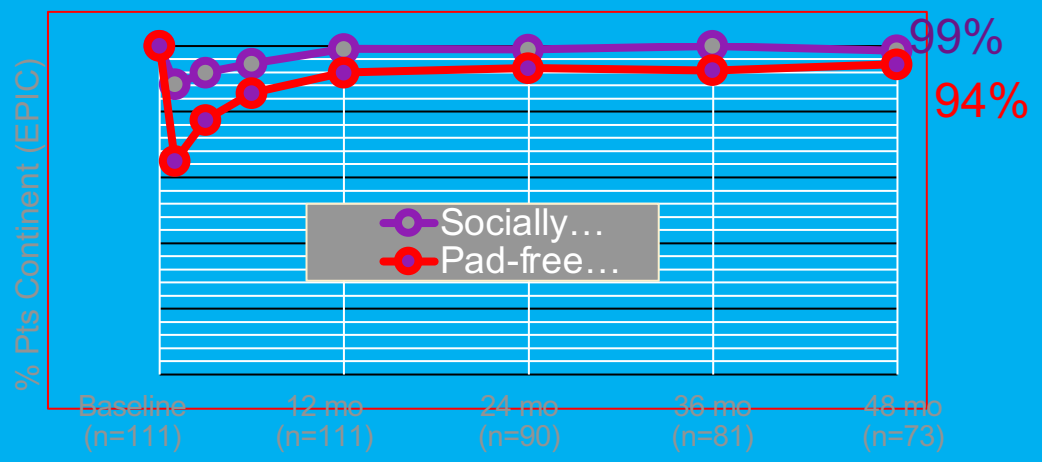
3-months Post
PSA < 0.1 ng/ml

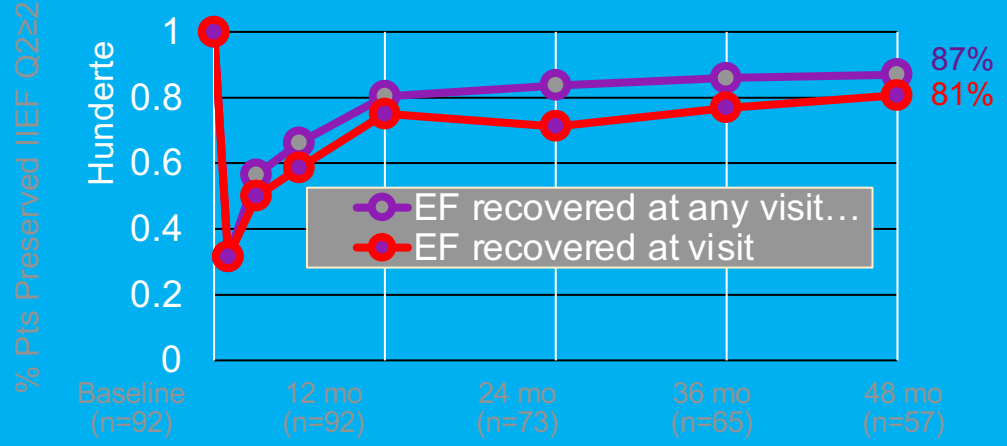


12-months Post: 0.5 cc
PSA < 0.1 ng/ml

PROFOUND MEDICAL Inc.

TACT safety and quality of life to 4 years





Adverse events to 4 years:

- No grade 4 events, no rectal fistula, no intraoperative complications
- 8% serious (SAE) or severe (G3) events:
  5 GU infections, 4 endoscopic resection for retention or stenosis, all resolved by 1 year

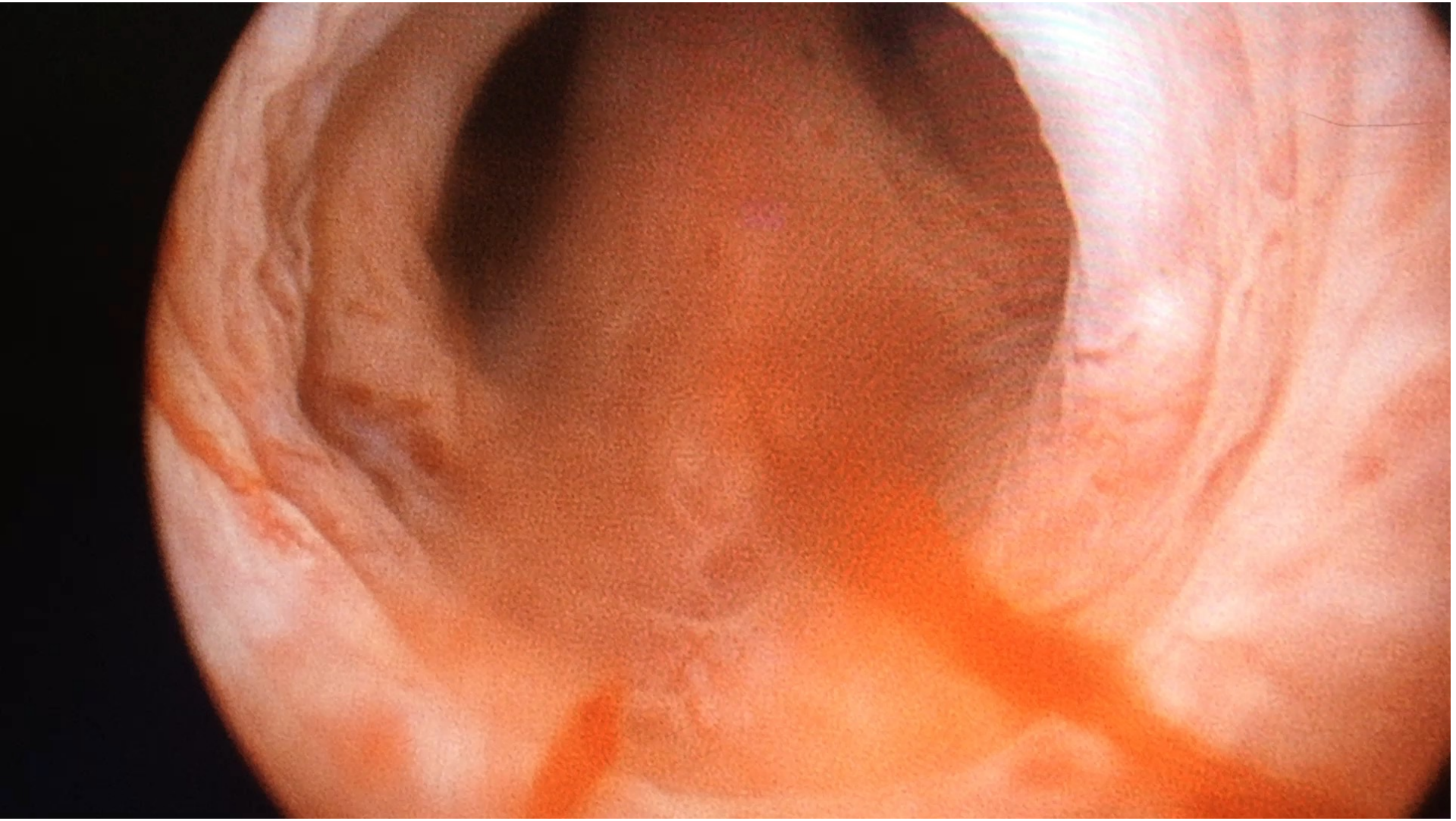
Urinary continence to 4 years:

- 99% socially continent (0 or 1 pad/day)
- 94% pad-free

Erectile function to 4 years:

- 0% severe ED (medication not helpful)
- 87% previously potent patients reported erection firmness sufficient for penetration
  by 4 years after TULSA

TULSA Ablation & Urethra Preservation



Remaining controversies in focal Rx

- How to define the index lesion
  - MRI/Gleason GG/Size or tumour length
- Significance of disease left behind
  - Impact of injury response on tumour biology
- On whole mount correlative studies from RP:
  - MRI detected only 77% of index lesions
  - 44% of non-index lesions
  - High grade tumours missed by MRI in 35%
    - Typically small
  - Can non-visible lesions be followed until they ‘show up’?

The future of focal therapy:

- Patients will increasingly demand this
- Increasing role of molecular biomarkers into patient selection
- Matching of lesion to energy type--
  - Electroporation/for anterior cancers
  - Cryo for apical
  - HIFU for PZ lesions
  - TULSA for large glands
- Improved outcome and follow up; reduced reliance on biopsy
- Mandate to confirm oncologic effectiveness and safety
- Determining which is 'best' a major challenge (large scale registry)
- Molecular therapy in symbiosis—immunotherapy/AR pathway targeted short term therapy, etc.
- THE SHIP HAS SAILED—FOCAL IS 'THE NEW BLACK'

FOCAL THERAPY SOCIETY