BC CANCER
Provincial Health Services Authority

Focal Brachytherapy

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Disclosures

- Advisory Board/honoraria: Varian
- Advisory Board: Breast Microseed
- Speaker Honoraria: Abbvie
- Speaker Honoraria: Sanofi
- Research Funding: Ferring

Learning objectives

- Reasons to consider focal therapy
- Patient selection
- Technical issues
- Efficacy????
- Monitoring post focal therapy

Why focal therapy?

- Screening frequently diagnoses favourable risk with a low disease burden
- Appropriate for active surveillance but still not widely accepted
  - Overall ~6% in 2000, 10% in 2005, 40% in 2013 *
- Whole gland definitive treatment may be excessive and associated with toxicity
- Improved imaging modalities to define disease burden
- Natural history is driven by index lesion (largest lesion; highest grade)

*National Reviews Urology 2016

Choice of modality

- Proven efficacy in whole gland treatment
- Capacity to monitor accuracy of treatment delivery
- Well-established dose response relationship
- Options:
  - LDR or HDR brachytherapy
  - Cryotherapy
  - HIFU
  - PDT, IEP, RFA, laser

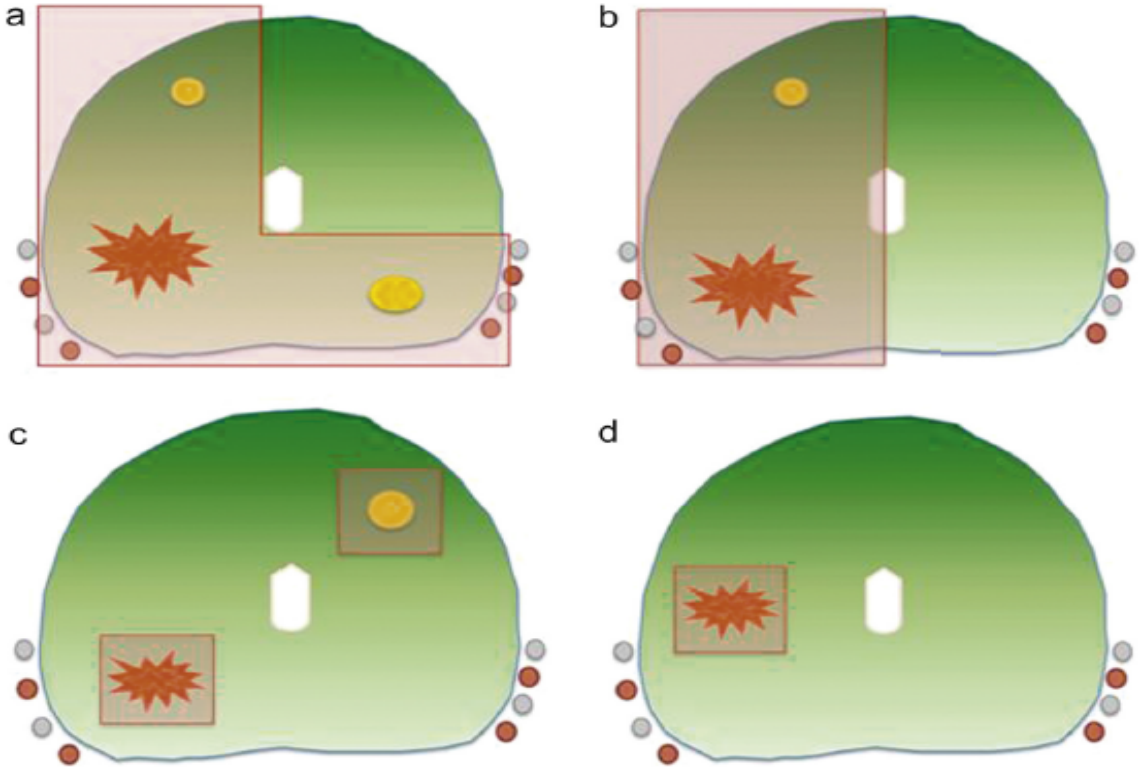
Focal treatment planning

- PCa is multifocal in ~ 80% of cases
- Up to 1/3 are unilateral
- Not all tumours require treatment (clinically insignificant)
- Dominant lesion drives the natural history
- Target volume may be focal, hemi-gland, dog-leg, etc
- Most series have attempted to treat all known disease
- Required margin is unknown

Target volume definitions (radiotherapy)

- F-GTV: clinically demonstrated disease
  - Fusion of T2 hypo intense lesion, with ADC and DCE
- F-CTV: F-GTV + clinically insignificant disease (if treated)
- F-PTV: need to add margin to F-GTV for uncertainty in image identification, image registration and dose delivery
- Restrict boundaries because of OAR (no margin posteriorly b/o rectum, no overlap with urethra)

Planning scenarios *Valerio, M. Europ Urol 2014*



Margin definition Mason et al, Brachytherapy 2013

- 15 patients treated with focal boost HDR
- mpMRI (1.5 T, T2W, DWI, DCE)
- Rigid registration of T2, ADC map and DCE
- Contoured by 2 radiologists and repeated (4 sets of contours)
- GTV taken as Boolean sum of abnormalities on T2, ADC and DCE
- T2 with GTV info registered to intra op TRUS with HDR needles

Quantification of uncertainties to determine margin

- Contours:
  - Left/right: 3.7 mm/3.4 mm
  - Ant/post: 4.9 mm/2.1 mm
  - Sup/inf: 3.8 mm/3.8 mm
- Image registration:
  - L-R: 1.6 mm
  - A-P: 1.6 mm
  - S-I: 2.8 mm
- F-PTV: single isotropic margin of 4.5 mm

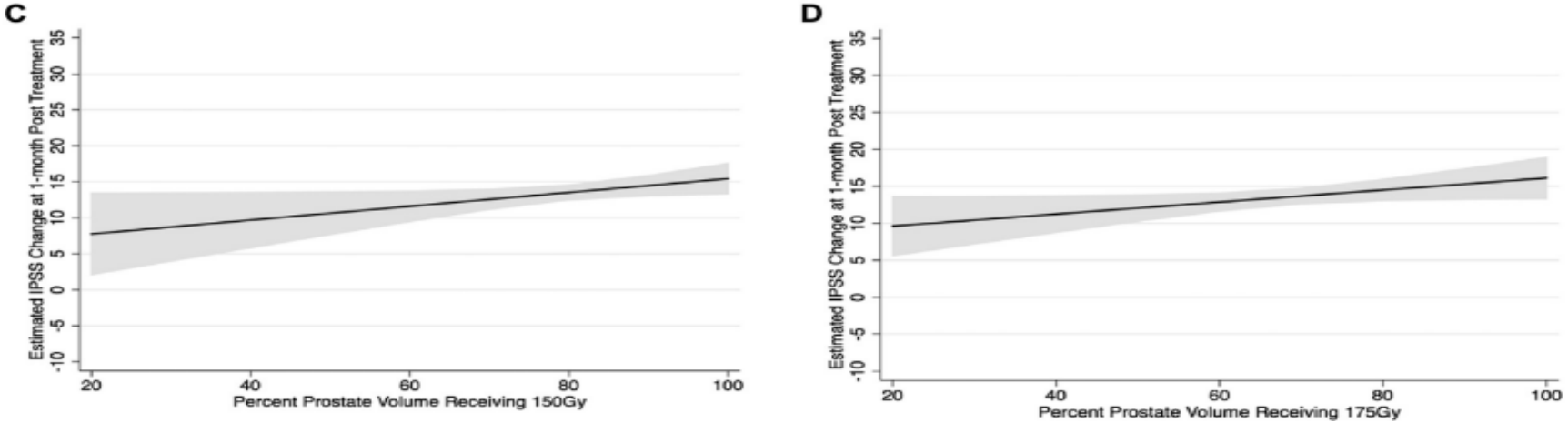
WHY FOCAL TREATMENT?

Reduction in acute morbidity

Ferro et al Brachytherapy 2017

- Compared 1 month post implant IPSS for full dose (n=191) vs. boost dose (n=41) Pd -103
- Adjusted for pre-implant IPSS and prostate volume
- Boost dose assoc with 4.5 point lower average increase in 1 month IPSS

Reduction in acute morbidity
Ferro et al Brachytherapy 2017



As % of prostate receiving 150 Gy and 175 Gy increases, so does the 1 month IPSS

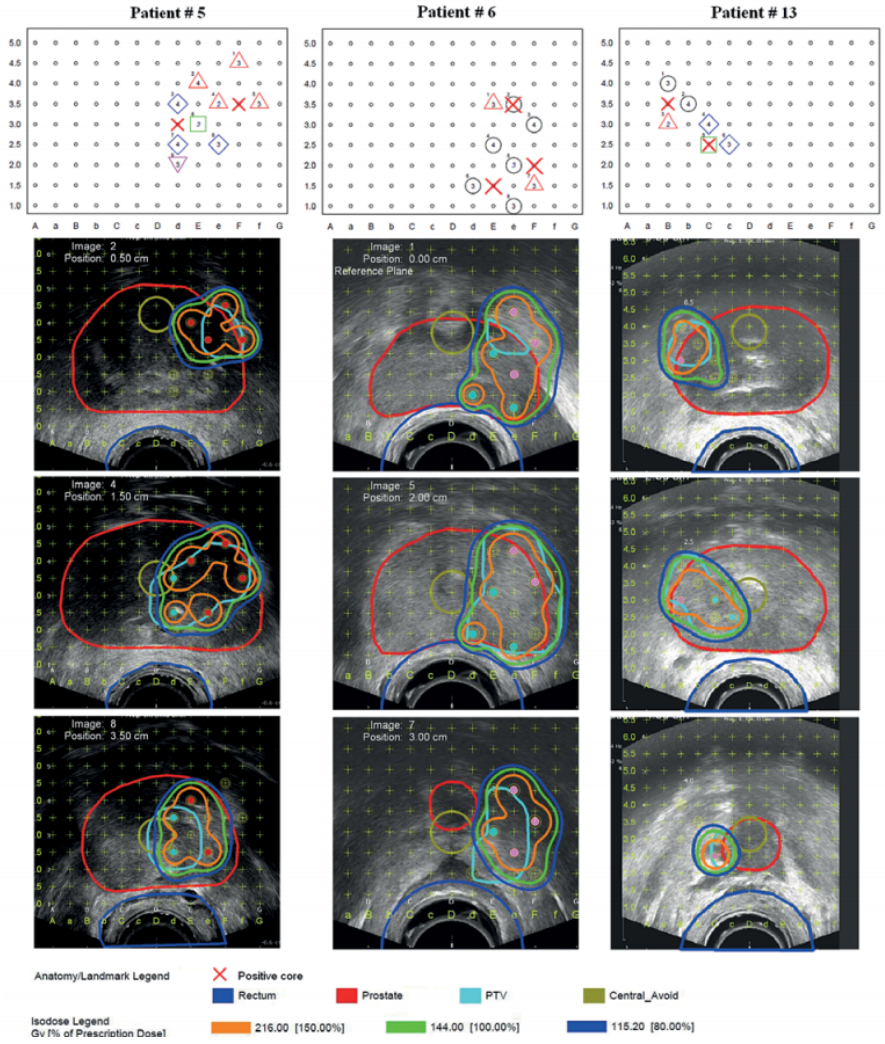
Urinary toxicity of focal BT depends on target location *Srougi et al Brachytherapy 2017*

- Focal BT for 28 patients (apical) and 13 (base)
- Target defined with MRI, TMB, + 1 cm margin
- I-125
- 6 month IPSS 6.4 (apical) vs. 10.6 (base) p=0.02
- No difference at 12 or 24 months
- No difference in continence or potency
- Recommend appropriate advice for patient expectations

Focal LDR

Mahdavi et al J Contemp Brachy 2017

- 17 eligible pts underwent mpMRI
- 14 went on the TMB
- 7 eligible for focal BT(unilat): 5 implanted
- Focal PTV 5.5 - 12.9 cc (16-43% P volume)
- 15-29 seeds, 6-9 needles
- Post implant dosimetry V100 88-94% f-PTV
- RD1cc 39-81 Gy/ UV125: 0
- 12 mo mpMRI either no susp lesion or PiRADS 3 (n=1)


Patient # 5
Patient # 6
Patient # 13
Image: 2
Position: 0.50 cm
Image: 1
Position: 0.00 cm
Reference Plane
Image: 4
Position: 1.50 cm
Image: 5
Position: 2.00 cm
Image: 8
Position: 3.50 cm
Image: 7
Position: 3.00 cm
Anatomy/Landmark Legend
Positive core
Rectum
Prostate
PTV
Central_Avoid
Isodose Legend
Gy [% of Prescription Dose]
216.00 [150.00%]
144.00 [100.00%]
115.20 [80.00%]

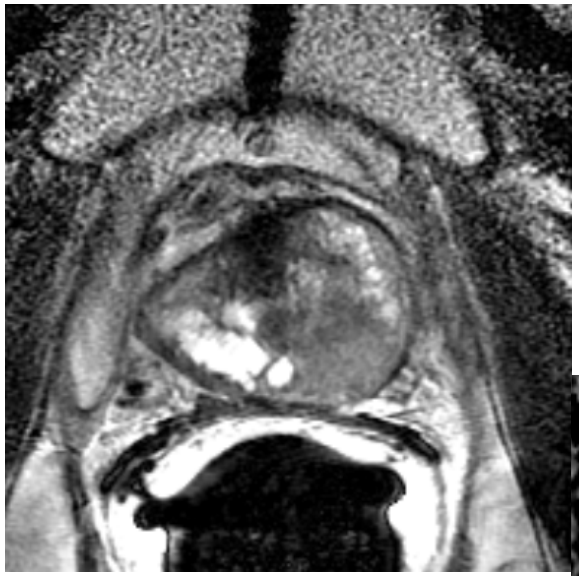
Focal salvage

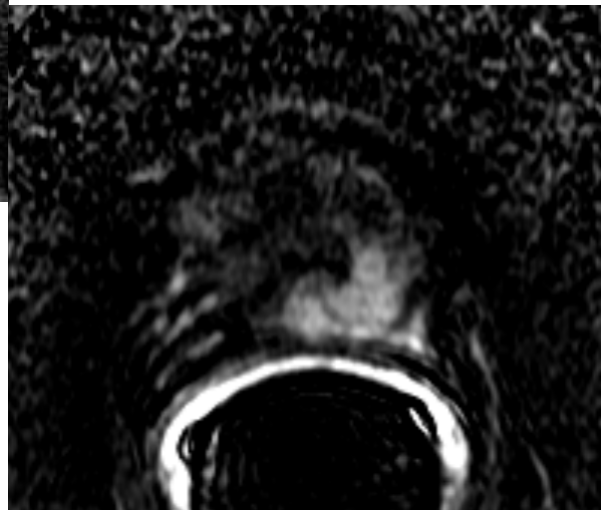
74 Gy in 2007, GS 8, PSA 4.9

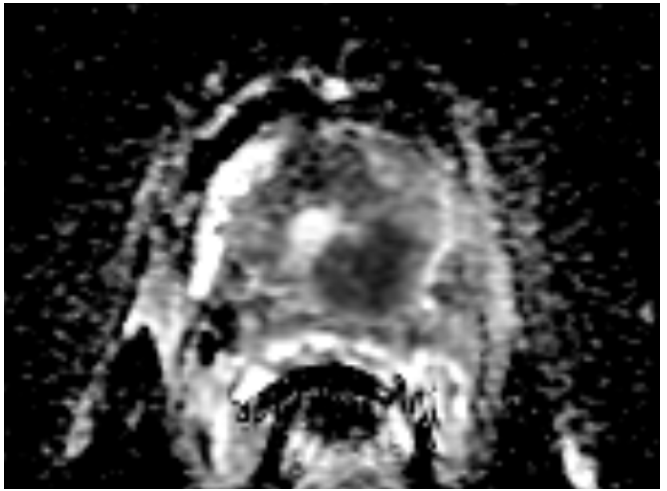
Current PSA 3.1, DT 12 mo

Bone scan/CT negative

MR-guided biopsies Gleason pattern 4



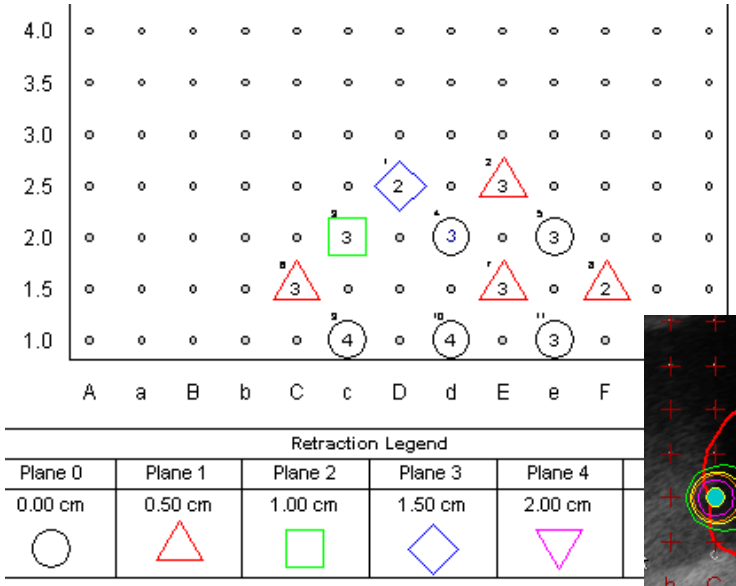


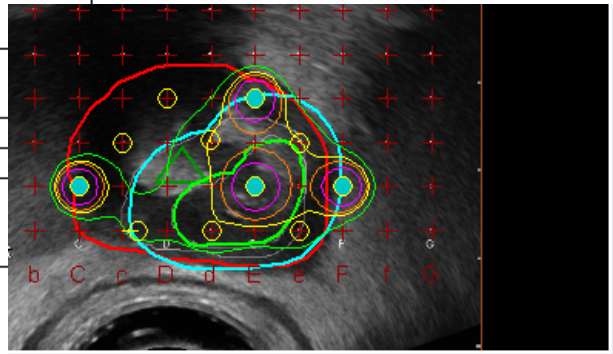


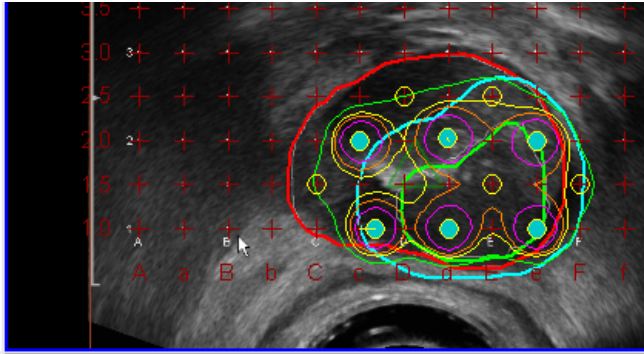
LDR focal

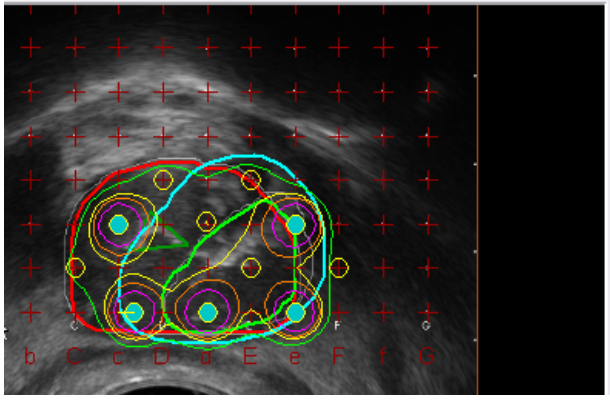
11 needles, 33 seeds

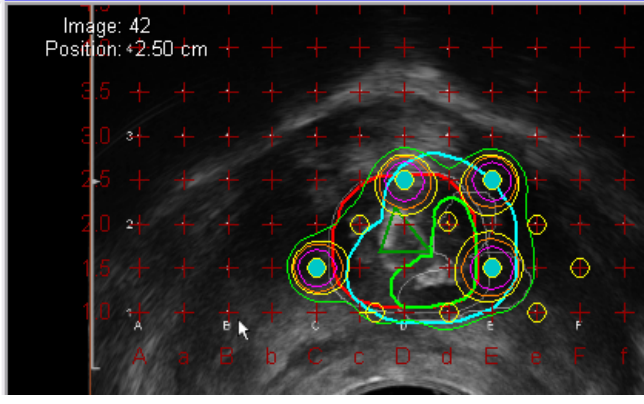
Prostate volume 15 cc











F-GTV 3.1 cc

F-PTV 11 cc

LDR reports: *Laing Radiother and Oncology 2016*

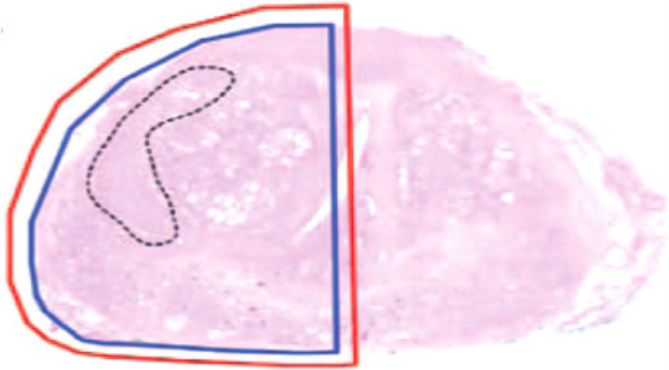
- n=22, Hemi-gland LDR BT
- Compared to 120 whole gland controls
- Target identified with mpMRi and TMB
- Low and intermediate risk PCa, unilateral
- PSA < 15, T1-T2B, GS $\leq$ 7 (3+4 or 4+3)
- Prostate vol < 60 cc (mean 29, range 13-46 cc)
- Seed activity 0.5 U
- Combination peripheral strands and Mick loose centrally

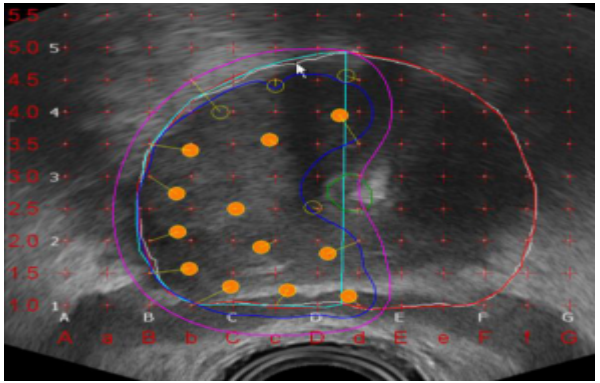
Laing: hemi gland 2016

	D90	UD10	UD30	RD2cc
Hemi Intra-op	175 Gy	180 Gy		85 Gy
Hemi Post-op	154 Gy	175 Gy	150 Gy	75 Gy
Whole	159 Gy		175 Gy	95 Gy

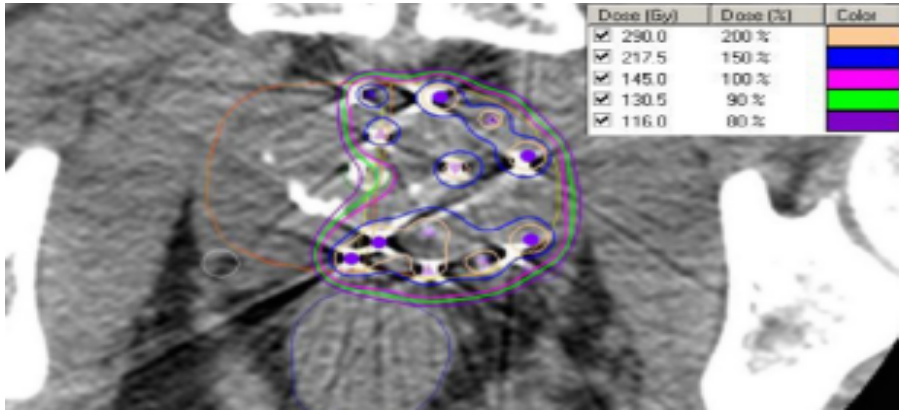
NVB ipsilateral 220 Gy, contra lateral 63 Gy

Laing et al: hemi gland LDR BT





Some seeds may be implanted in contralateral gland



Sounds straight forward and promising….

WHAT ARE THE LONG TERM OUTCOMES?

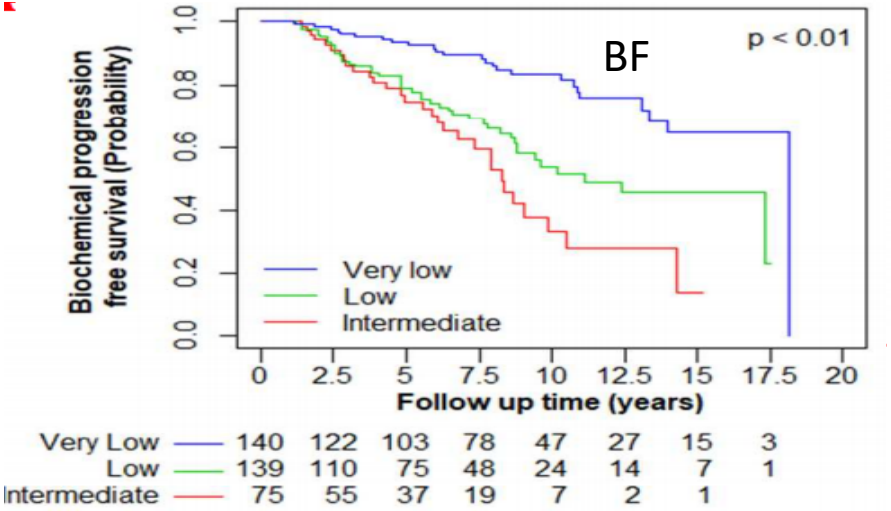
Long term outcomes of MR-guided partial prostate LDR BT *King, Nguyen et al, Ca 2018*

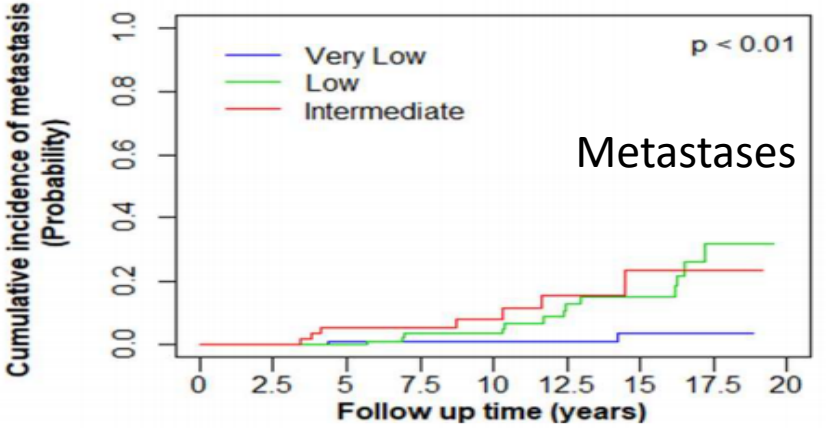
- 1997-2007, 354 T1c, GS 3+3 or 3+4
- Implanted to MR-defined peripheral zone
- Med follow up 8.6 yrs
- 10-year bNED for vLR 83%, LR: 54%, IR: 33%
- Modified definition of bNED nadir+2 + velocity
  - vLR: 90%, LR: 75%, IR:55%
- 10-year LF 22% (expect <3%)
- 12-year DM for IR 16%

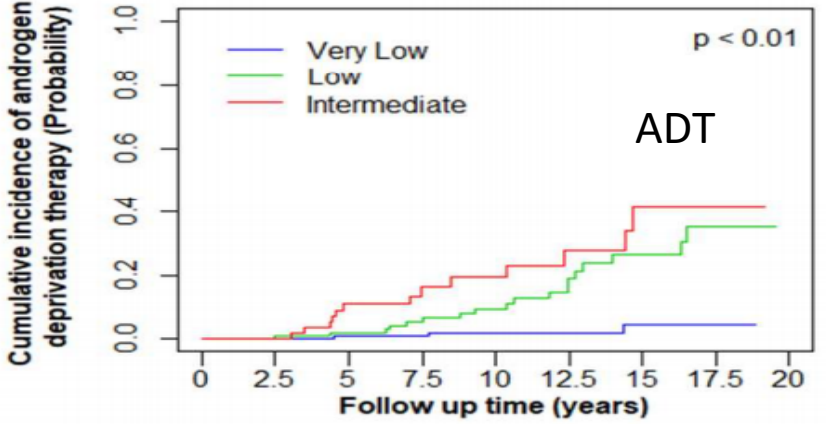
Cautionary tale

- LDR and HDR brachytherapy provide highly effective treatment with very low rates of serious morbidity and acceptable QOL
- Surveillance of non-lethal prostate cancer is widely accepted and increasing
- Must be very careful in de-escalating treatment for those who require cure
- Nguyen's study used 0.5T MRI to treat PZ and would have missed ant lesions and those straddling TZ
- Current protocols with mpMRI should do better in target definition but long term follow up lacking

King, Nguyen et al. Ca 2018







WHAT LEVEL OF ACCURACY IS ACHIEVABLE?

HDR advantages over LDR?

- *Permanent Seed Implants (LDR)*
  - Seed loss/migration (even with strands!)
  - UF plans very sensitive to seed misplacement/displacement
  - Operator performance
  - Quality evaluated after the fact: correction difficult!
- *HDR*
  - Dose precisely controlled and delivered
  - No seed loss
  - No organ motion
  - No patient motion (if US-based planning)
  - Dose easily sculpted to target with avoidance of critical structures

Focal HDR protocol

- *mpMR*I; identification of DIL On T2, ADC and DCE
- Boolean addition of DIL's
- Contour prostate, urethra, DIL
- *Pre-op TRUS* with aerated gel in urethra
- Fuse mpMRI and TRUS for transposition of DIL
  - Rigid registration or deformable
- HDR procedure: fusion of intra-operative TRUS with catheters in position to pre-op TRUS with DIL
- Dose optimization
- Treatment delivery

HDR catheter displacement

Maenhout Brachytherapy 2018

- 17 pts enrolled in prospective trial of focal HDR BT
- Compared cath position on planning MRI to immediate post treatment MRI
- Technique involves self-anchoring umbrella catheters, single fraction, immediate treatment
- 3T diagnostic MRI, GTV + 5 mm margin
- US-guided catheter insertion

HDR catheter displacement

Maenhout Brachytherapy 2018

- BUT after catheter insertion, TRUS probe and template removed, wedges under knees for in-suite 1.5T MRI for planning. Repeat MRI pre treatment and post treatment to check catheter positions

- Catheters movement on average < 1 mm (1.3 mm in z-axis) but 20% of pts had z-axis shifts > 4 mm and up to 5.5 mm
- D90 CTV < 19 Gy in 6 patients, < 17 Gy in 2

Catheter displacement and D90's

Maenhout Brachytherapy 2018

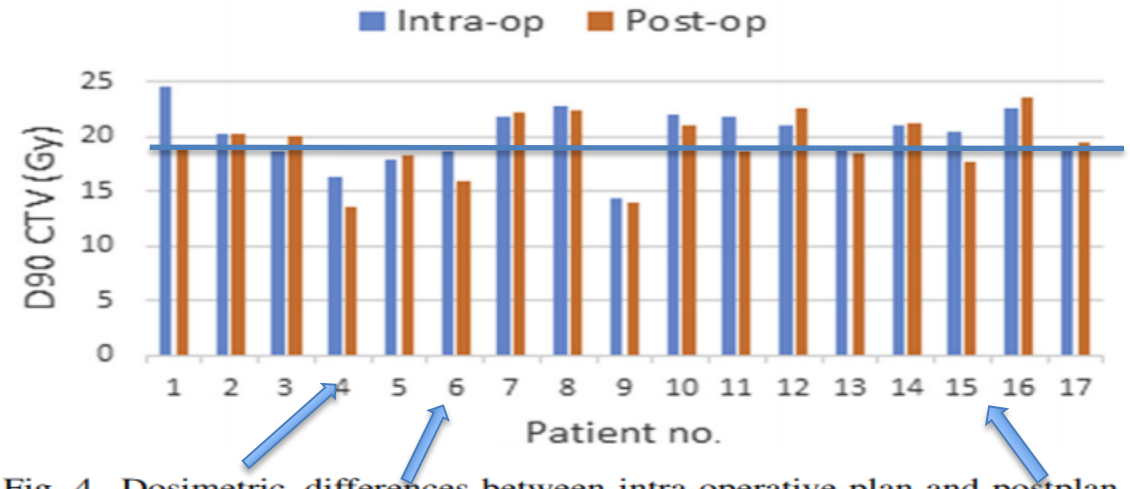


Fig. 4. Dosimetric differences between intra-operative plan and postplan for D95 and D90 of the CTV. CTV = clinical target volume.

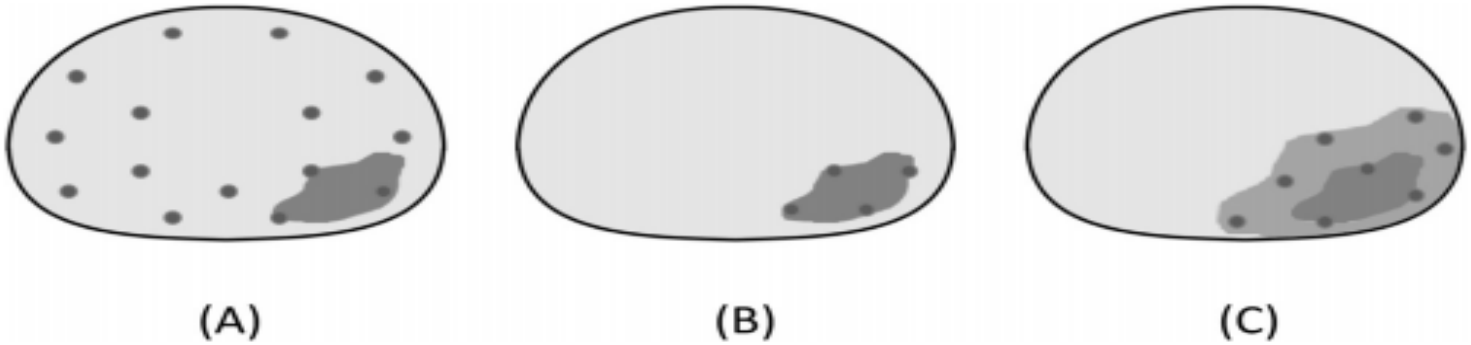
19 Gy

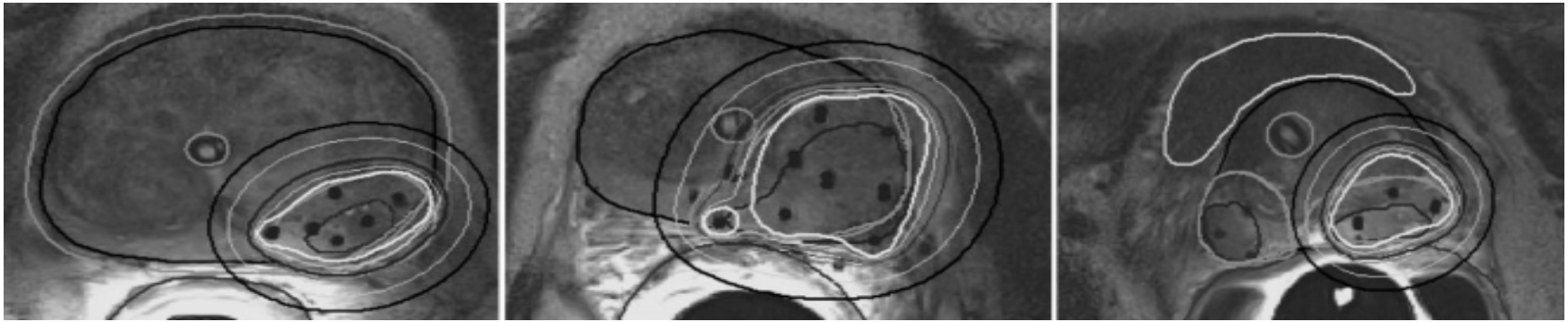
Focal HDR reports *Hosni Radiother Oncol 2017*

- MR-guided focal HDR BT
- Target defined on mpMRI and deformably registered onto post catheter insertion MRI
- PTV defined as GTV + 5mm margin except cranio-caudal: 9 mm margin
- Prescription aim: 16.5 Gy x 2 or 24 Gy x1
- 7/20 plans converted to single dose since 24 Gy achievable without exceeding OAR constraints

Focal HDR reports *Hosni Radiother Oncol 2017*

- Constraints:
  - D0.5 cc bladder/urethra <15 Gy
  - RD2cc < 10.8 Gy
- Inserted catheters 11 (1-19)
- Utilized catheters 4 (1-12)
- GTV: 0.7 cc (0.1-5.7)
- PTV: 5.6 cc (5.2-20)
- OAR doses UD0.5cc: 9.2 Gy (5.6-15)
  - RD2cc: 9.4 Gy (2.8-10.8)





1 fraction plan

2 fraction plan

Failed plan

Defining success

- No validated PSA outcome
- Active monitoring similar to that for Active Surveillance
  - Significant undetected disease
  - Residual disease in the treated area
  - Cancer progression

- Biopsy of treated and untreated areas mandatory
- Role for mpMRI but requires further validation

Focal brachtherapy

- mpMRI imperfect; expertise is evolving
- Reports are from largely high-volume centers and may not translate directly to community
- Focal LDR single brief out-patient procedure but implementation very sensitive to accurate seed deposition
- HDR easier to sculpt dose precisely but requires fractionation, and with limited margins very sensitive to catheter displacement

Recommendations: Focal Therapy

- Clinically significant disease in one area of the prostate (Clinically insignificant disease may be monitored by AS)
- Accurate localization essential (mpMRI and/or TTMB)
- Follow up and monitoring as per AS protocols including biopsy of treated and untreated areas
- Optimal technology for focal therapy TBD but both LDR and HDR appropriate
- Planning issues such as margin determination remain but 5-6 mm margin on mpMRI-defined GTV has been adopted
- Level of evidence still very low concerning disease control/survival