Differences in dosimetry, treatment planning and equieffective dose

LDR vs HDR monotherapy

Presented by

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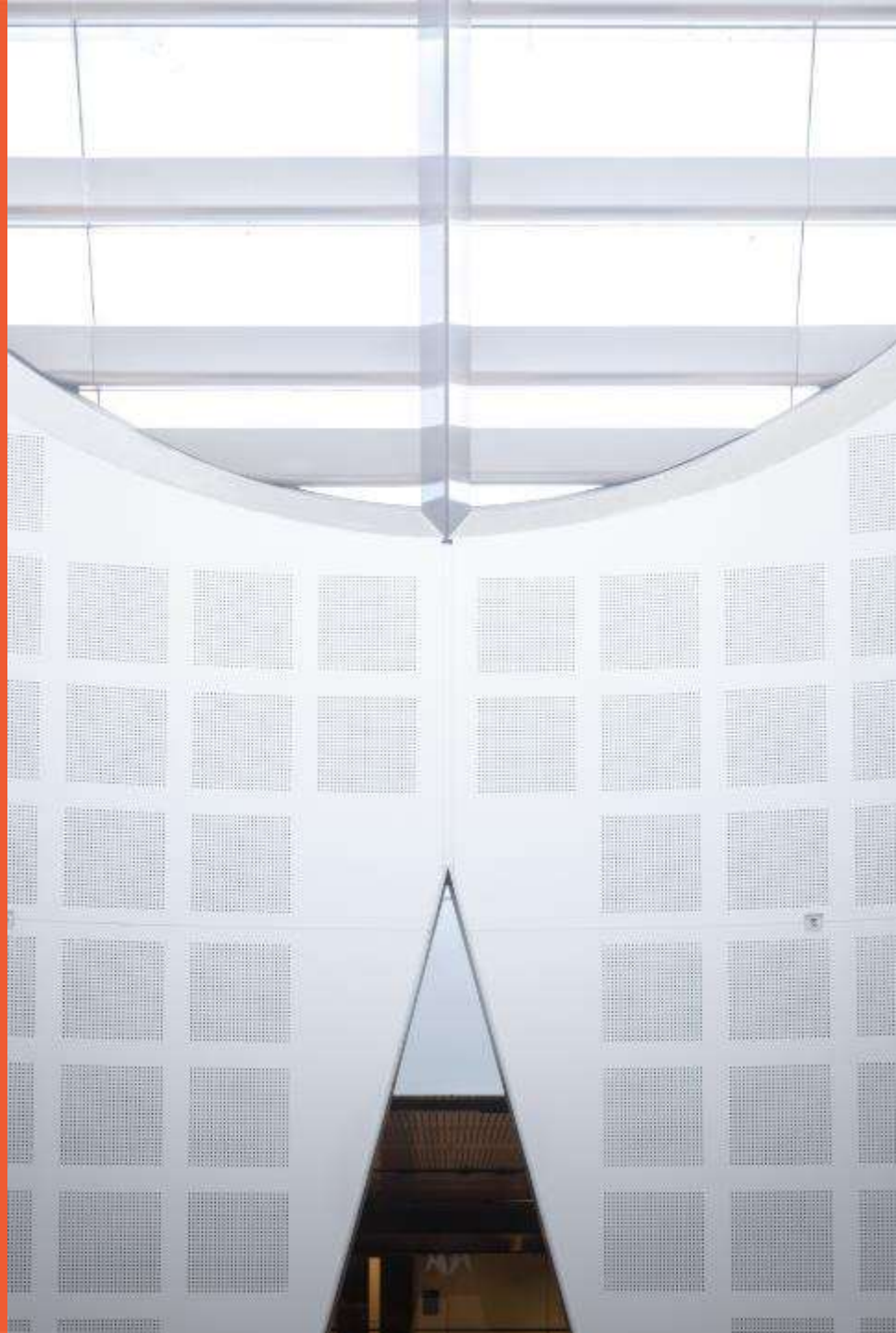


LDR vs HDR monotherapy

Both are safe and effective treatments in appropriately selected patients

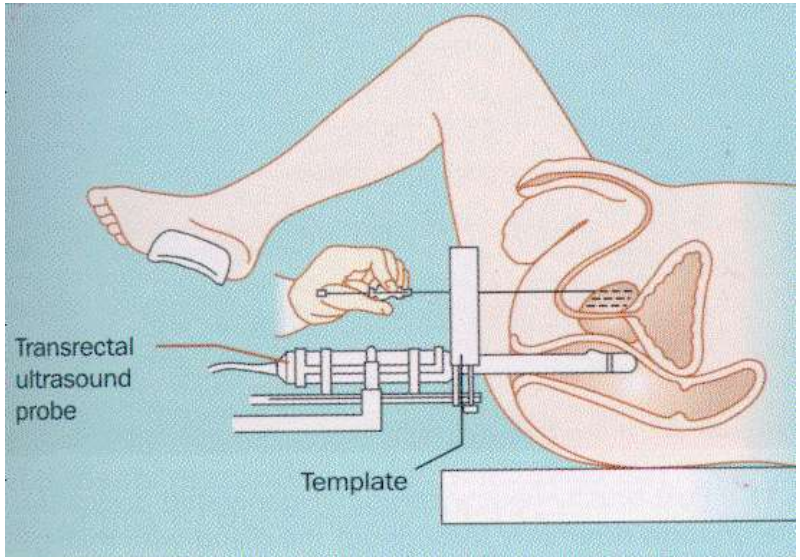
So which treatment would you choose for yourself / relative?

What are we trying to achieve? i.e. what is the comparator?

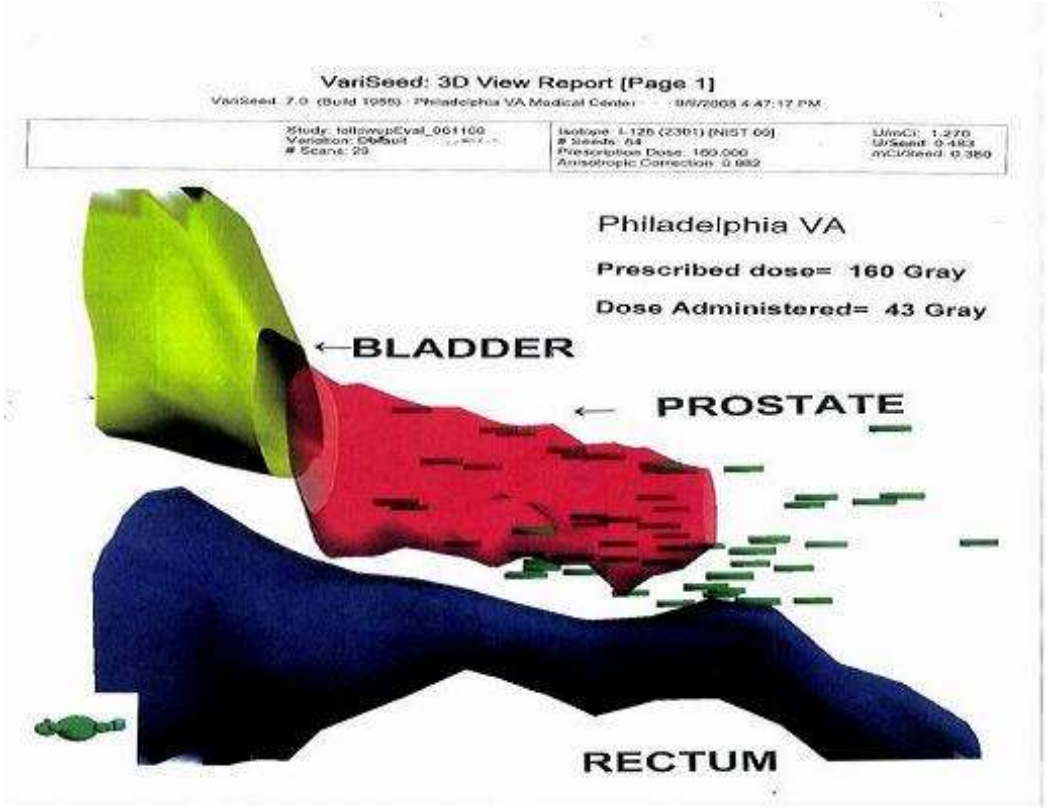
- Reduce the dose to OARs
  - Good for low risk disease
  - where Active Surveillance is now mostly indicated
- Dose escalation of the dominant lesion
  - Good for intermediate/ high risk disease
  - Where dose escalation has shown to benefit local control
- Improve the therapeutic ratio
  - i.e. maximise tumour control & minimise toxicity
- Maximise patient comfort/ convenience
- Cost?

So what do we know: LDR

- Long experience (> 20 years)
- 145 Gy (I-125) monotherapy
- US guided planning and treatment
- Post implant dosimetry day 0,1 or 30
- AAPM, ESTRO & ABS guidelines
- Outcomes are great (FFbF typically > 90%)

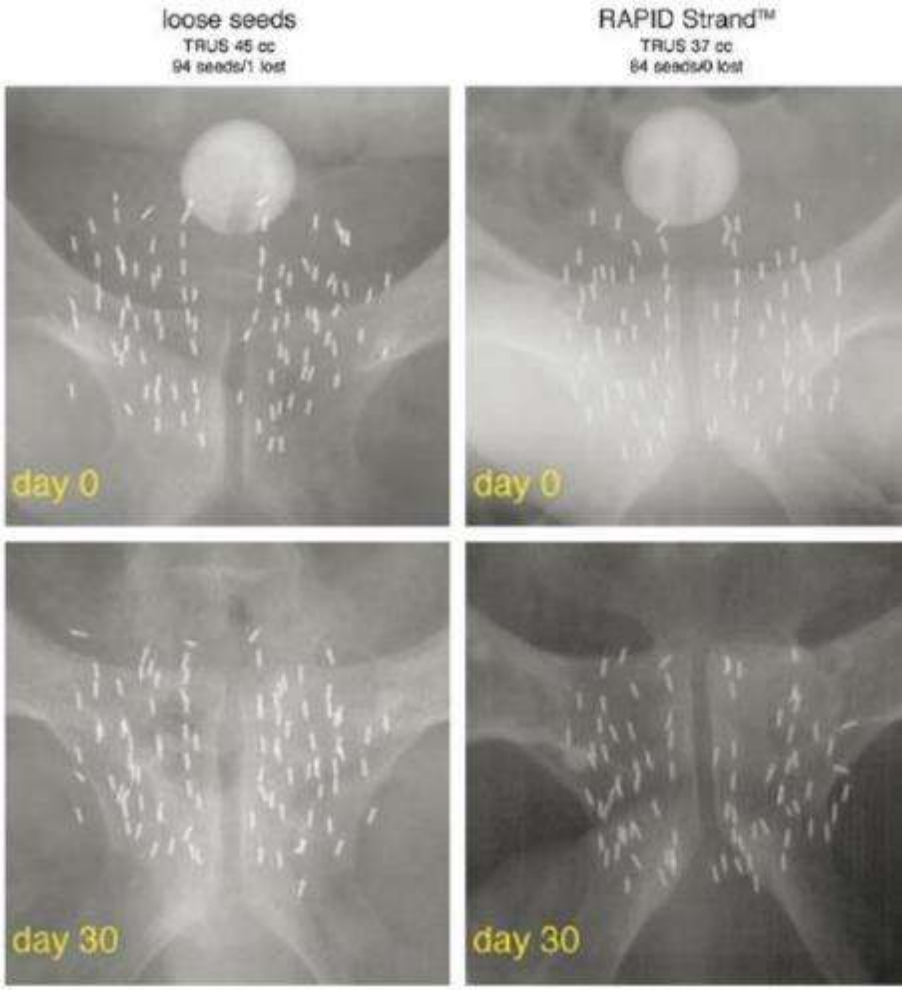


What can go wrong?



But to be fair…. This sort of thing could happen with HDR too…

What can go wrong?



R Reed, et al *Brachytherapy* 2007

Seed displacement / migration

When is an LDR implant quality unacceptable? The D90 debate

Brachytherapy 9 (2010) 299

Point/Counterpoint

Rebuttal to Dr. Stock

W. James Morris[1,*], Ross Halperin[2], Ingrid Spadinger[1]

[1]*Department of Radiation Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada*
[2]*Department of Radiation Oncology, British Columbia Cancer Agency, Kelowna, BC, Canada*

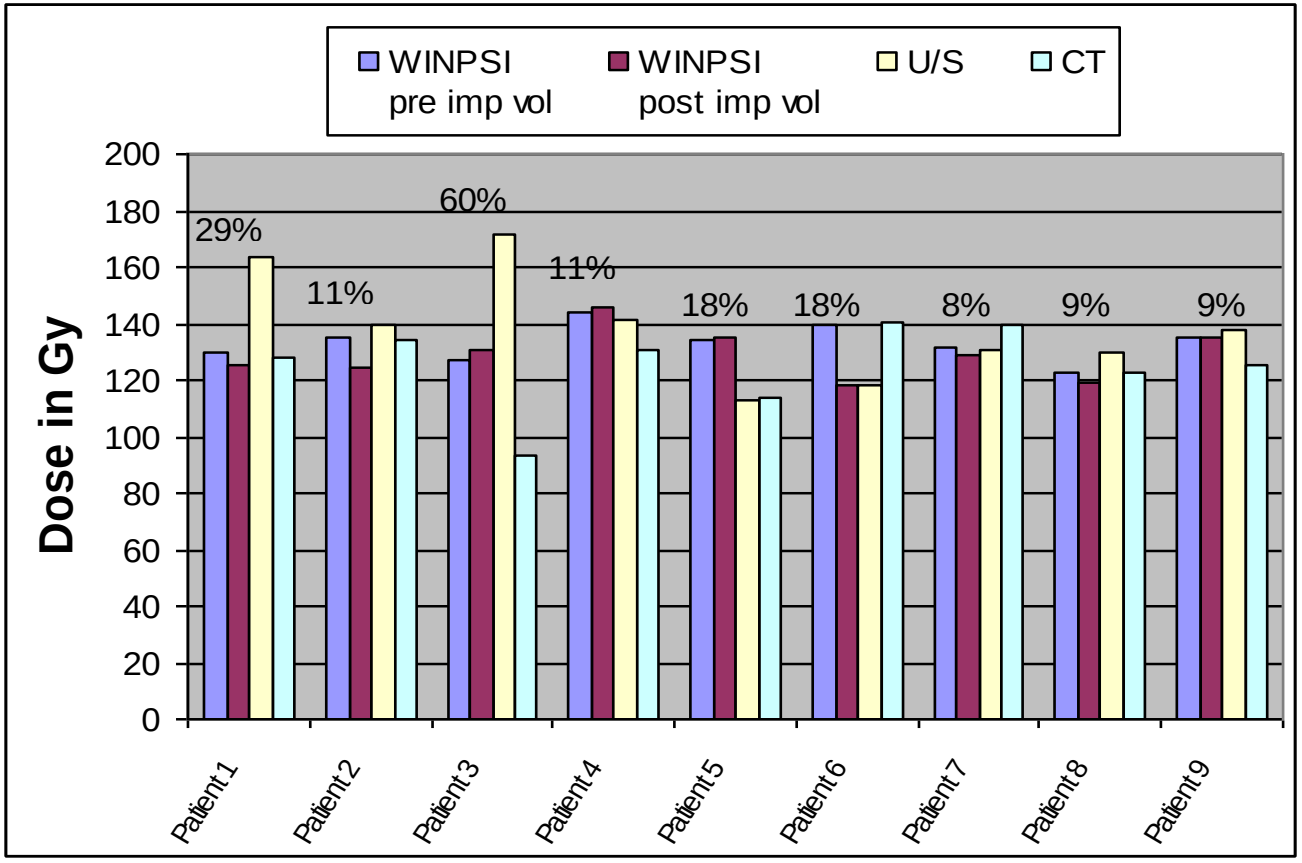
"….. Steep dose gradients at the periphery ….substantial uncertainty in D90 & V100……D90 & V100 capture no information on dose distribution……."

ELSEVIER

Brachytherapy 4 (2005) 146–153

Impact of selection of post-implant technique on dosimetry parameters for permanent prostate implants

Annette Haworth[1,2,*], Martin Ebert[3,4], Shaun St. Clair[5], Brendan M. Carey[5], Anthony Flynn[5], David M. Bottomley[5], Gillian M. Duchesne[6], David Joseph[1], Daniel Ash[5]



D90

- Range as % of mean
- Ave variation is 19%
- (14% excluding patient #3)

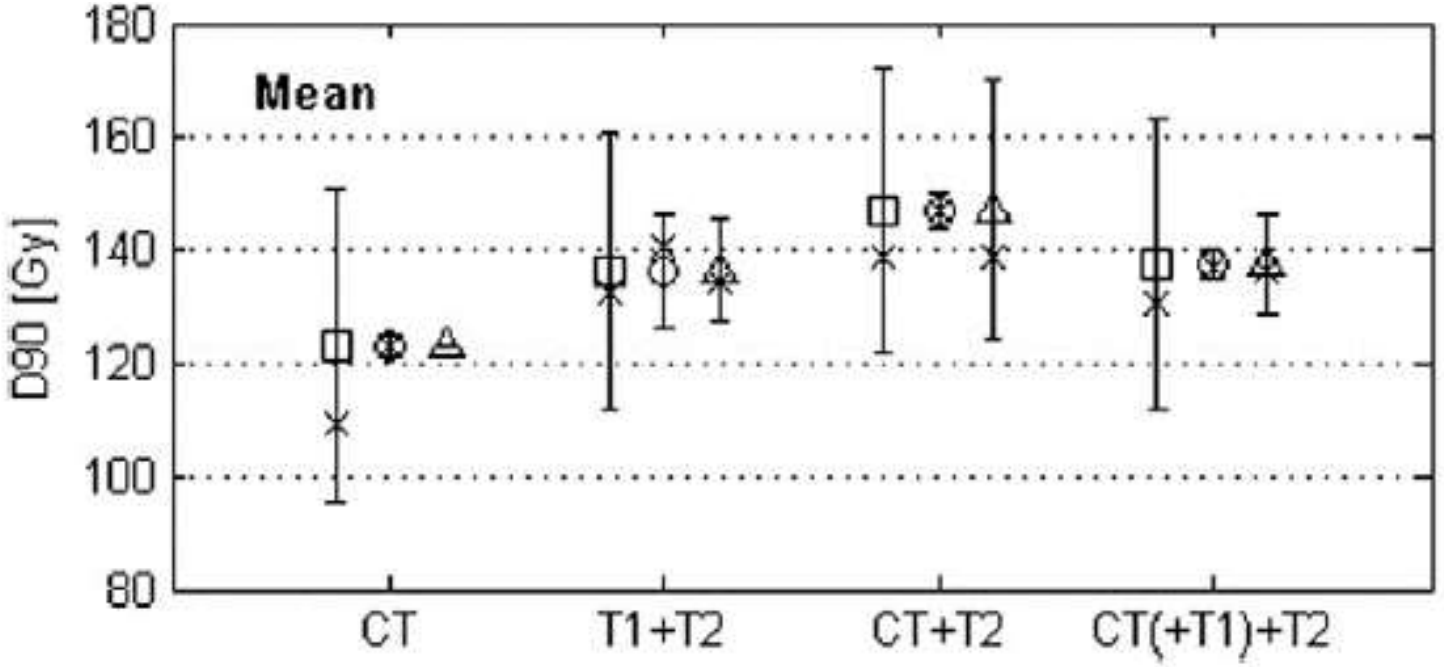
Using MR and CT, does this help?

Prostate post-implant dosimetry: Interobserver variability in seed localisation, contouring and fusion

Marisol De Brabandere [a,*], Peter Hoskin [b], Karin Haustermans [a], Frank Van den Heuvel [a], Frank-André Siebert [c]

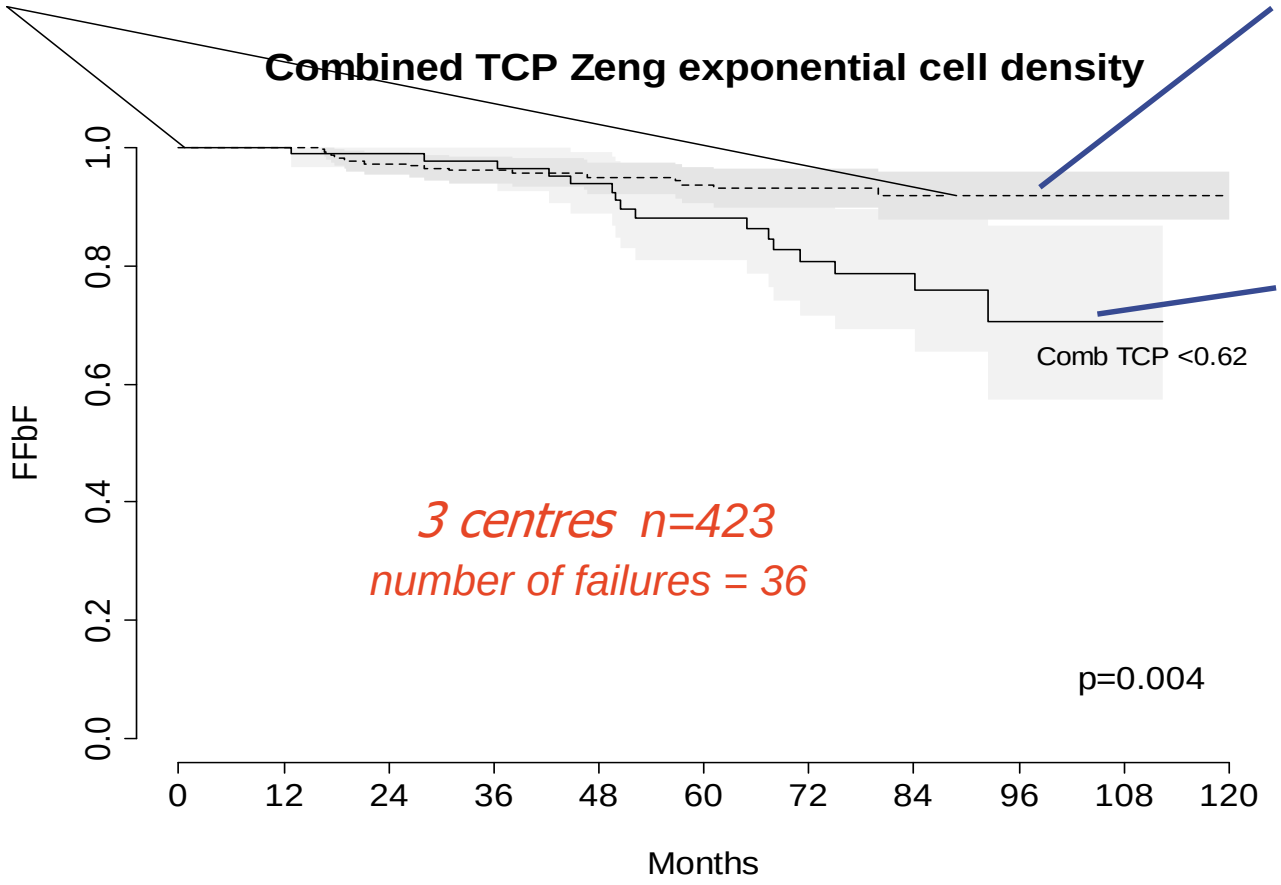
Radiother Oncol 2012

Contouring and image fusion are the 'weak links' in the procedure.



Contouring Seed reconstruction Image fusion

What TCP value predicts for treatment failure?



High TCP_{comb}
FFbF 93.7%
(95% CI 90.4-96.4%)

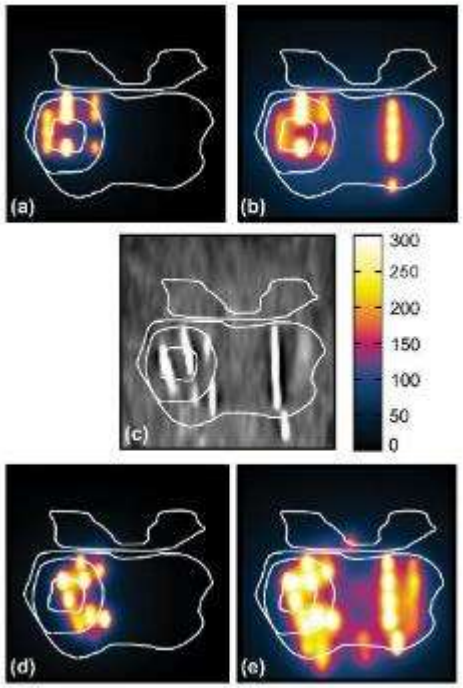
Low TCP_{comb}
FFbF 88.8%
(95% CI 81.3-94.5%)

Haworth et al *Brachytherapy* 2013

Can we make our plans robust to seed displacement?

Planned focal / total dose distribution

4-weeks post focal / total dose distribution

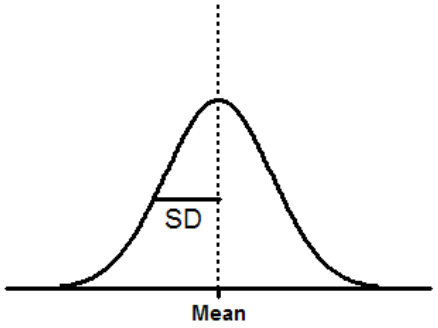


a <u>uniform margin of 0.5 cm</u> was necessary to cover 95% of the delineated F-GTV for all patients.

Polders et al 2015

OR

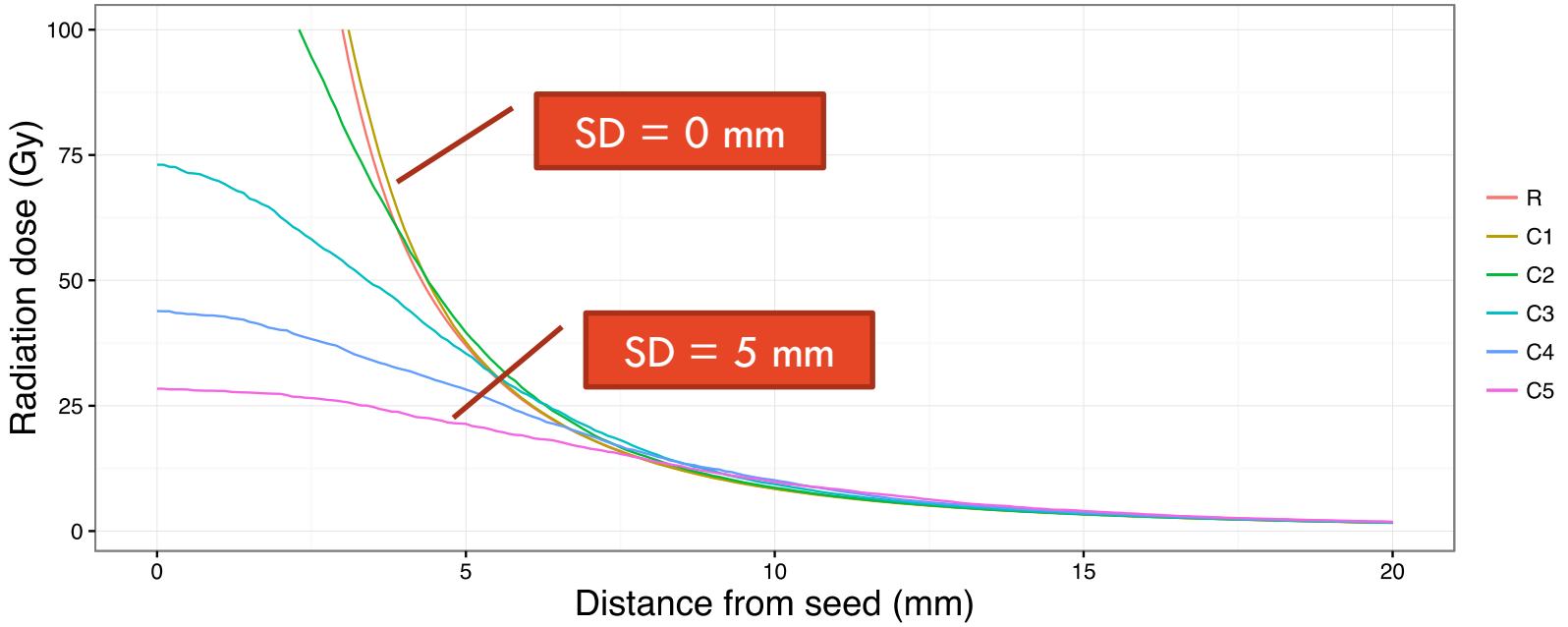
Apply a convolved dose rate model



Compared pre- and post-planned positions, calc SD

Convolved dose rate model

Original dose rate function (*R*) and convolved dose rate function for *SD = 1, ... ,5mm*.



Betts et al Procedia Computer Science 108C (2017) 1522–1531

Summing uncertainties in quadrature

Table 4
Example 4 – LDR ^{125}I sources for permanent prostate BT.

Category	Typical level (%)	Assumptions
Source strength	3	PSDL traceable calibrations
Treatment planning	4	Reference data with the appropriate bin width
Medium dosimetric corrections	5	No consideration is given for calcifications or their composition in the patient
Inter-seed attenuation	4	An advanced dose calculation formalism may indicate source models and orientations cause the largest effects
Treatment delivery imaging	2	US QA performed according to AAPM TG-128
Target contouring uncertainty	2	Using CT or CT + T2 imaging
Anatomy changes between dose delivery and post-implant imaging	7*	Post-implant imaging using CT, with a scalar correction factor for edema correction
Total dosimetric uncertainty ($k = 1$)	**11**	For treatment delivered without excreted seeds

* Estimated value based on expert discussion.

HDR?

- Long history when HDR is combined with EBRT (boost)
- Growing number of monotherapy studies
- Promising FFbF (too soon for OS, metastasis free survival etc?)
- Promising toxicity

HDR: what dose & what fractionation?

Table 3
Oncological results of high dose rate monotherapy for localised prostate cancer

Reference	n	High dose rate protocol			Median follow-up (years)	Biochemical control*	BED (Gy)	EQD2 (Gy)
		Gy/fraction	Fractions (implants)	Total				
[7]	190	6.0 Gy	8 (1 implant)	48.0 Gy	7.6	93% IR, 81% HR at 5 years	240–270	103–116
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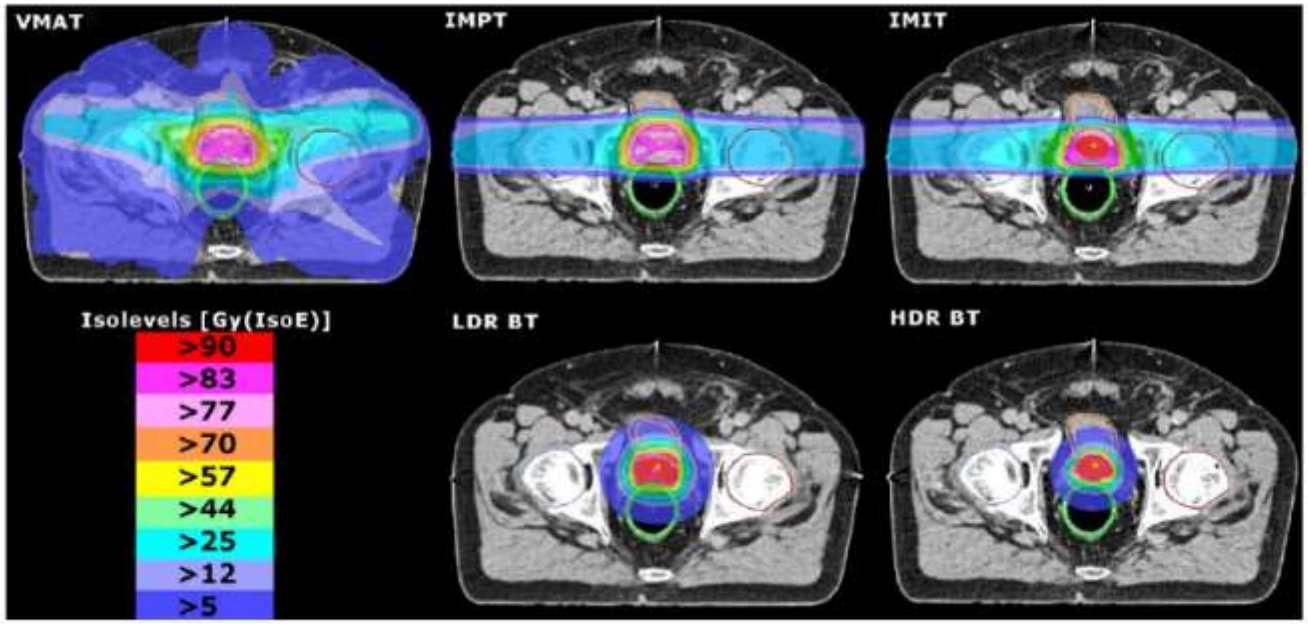
LR, low-risk group; IR, intermediate-risk group; HR, high-risk group; BED, biologically effective dose considering an a/β ratio for prostate cancer of 1.5 Gy; EQD2, equieffective dose administered in 2.0 Gy fractions considering an a/β ratio for prostate cancer of 1.5 Gy.
* Biochemical failure defined by the Phoenix definition [59].

HDR monotherapy

- > 2 or 3 fractions
  - Undesirable due to cost, convenience etc
- 1-2 fractions: highly desirable
  - But how many implants?
  - 1 or 2?

Dose distribution: Which is best?



Representative dose distributions for a selected patient for all 5 treatment techniques after radiobiological conversion.

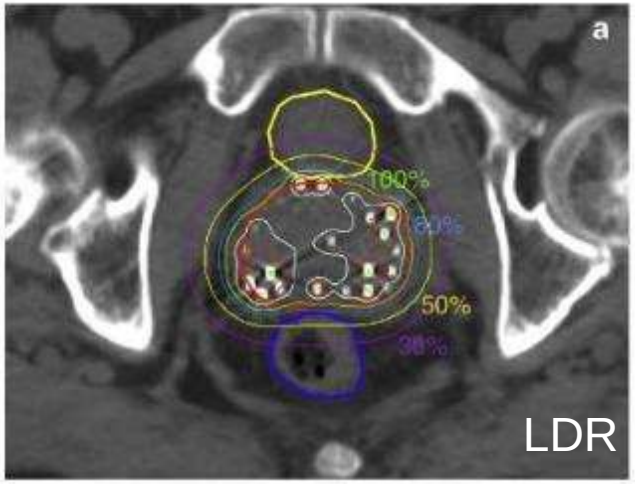
Urethral doses:

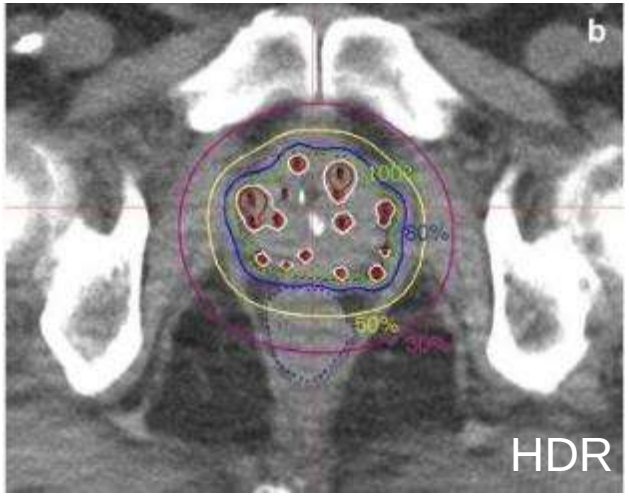
VMAT, IMPT, IMIT ~ 74Gy(IsoE)

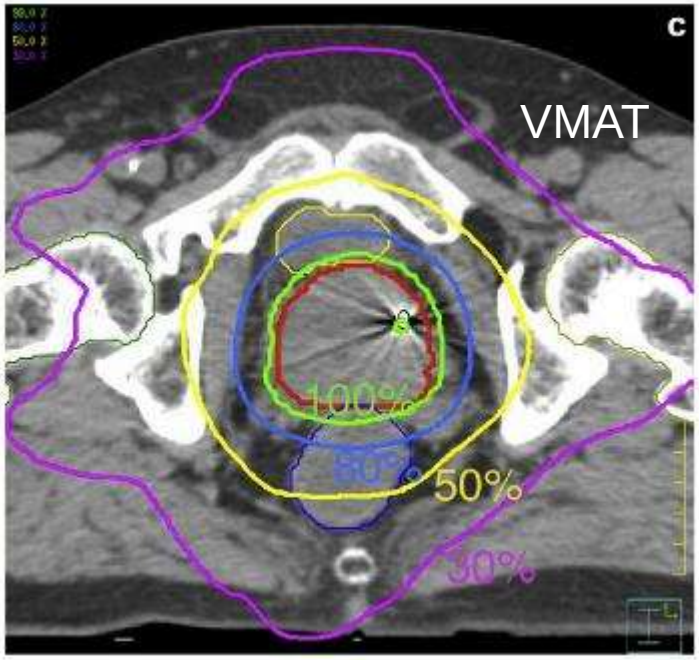
LDR ~ 30Gy(IsoE) HDR ~ 10Gy(IsoE)

Georg IJROBP 2014

Dose distribution: Which is best?



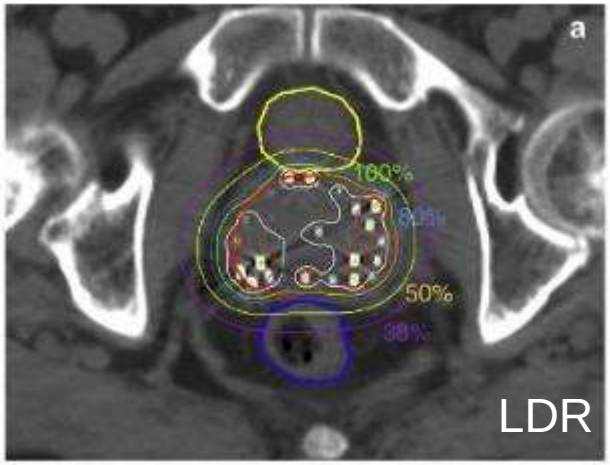


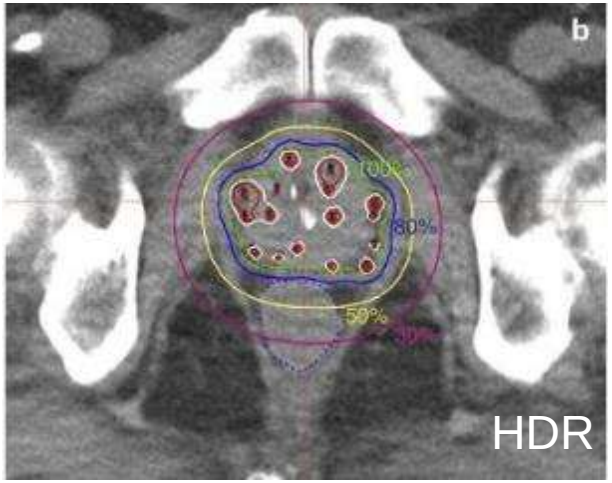


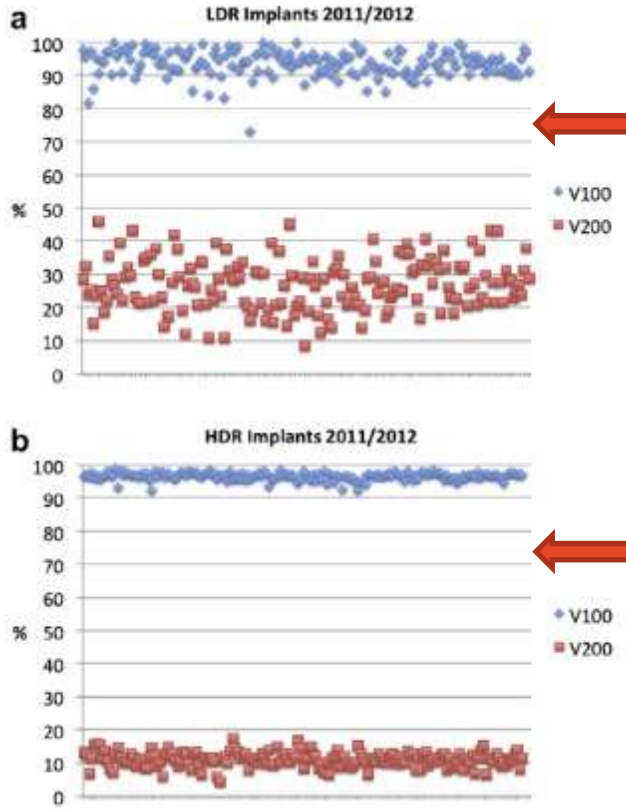
Morton & Hoskin 2013

C.C. Morton, P.J. Hoskin / Clinical Oncology 25 (2013) 474–482

Dose distribution: Which is best?







What was actually delivered

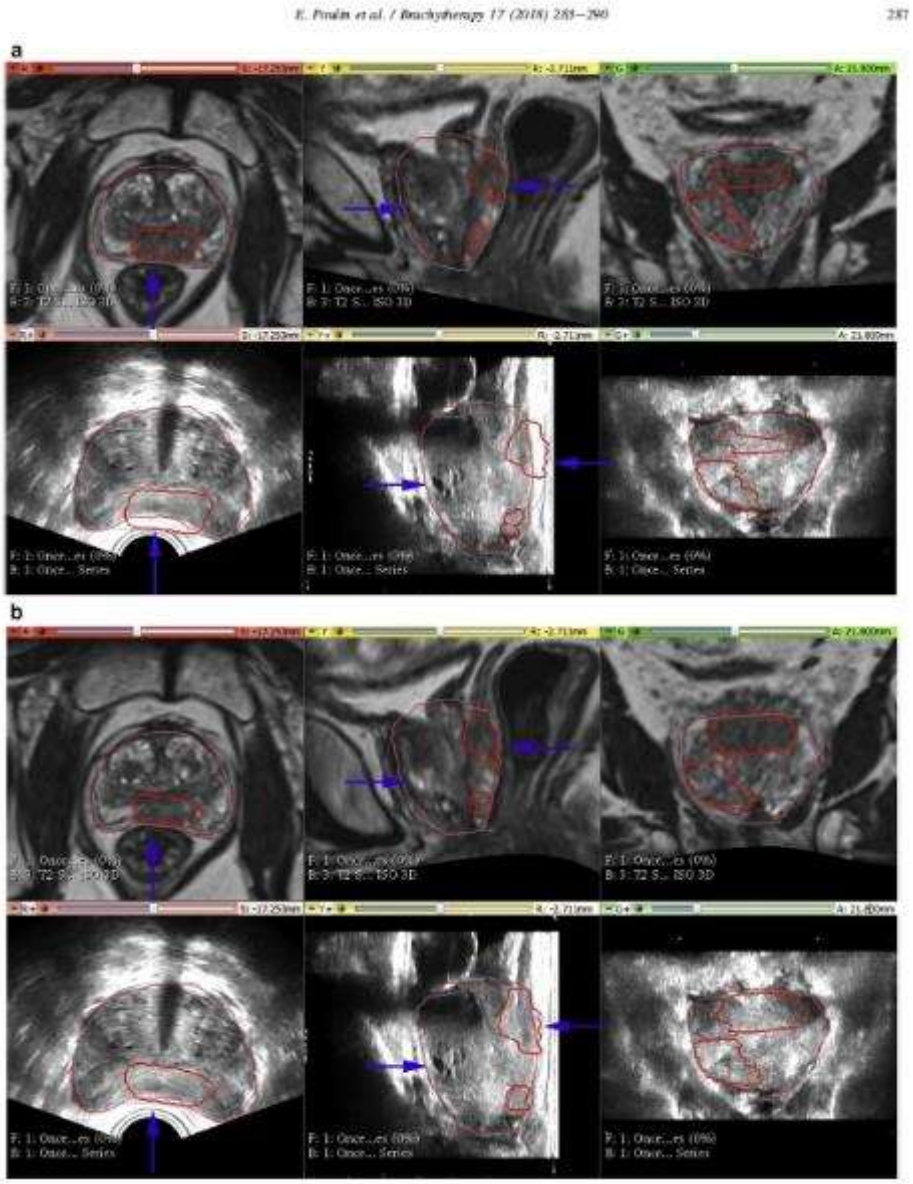
What we assume was delivered

Probably ok in real-time US-guided HDR

Morton & Hoskin 2013

C.C. Morton, P.J. Hoskin / Clinical Oncology 25 (2013) 474–482

Use of deformable image registration software for MR + US: Promising results



Rigid registration

Deformable registration

Use of deformable image registration software for MR + US: Promising results

Table 1
Summary analysis results generated between STAPLE and each of ROs (average) and the three autogenerated DIL contours

Structure	DIL			
Metric	ROs	MR2US	Rigid	B-Spline
DSC	0.80 ± 0.10	0.80 ± 0.13	0.65 ± 0.20	0.51 ± 0.30
MDA (mm)	1.24 ± 0.73	1.30 ± 0.53	1.71 ± 0.80	3.10 ± 2.00
Distance between centroids (mm)	6 ± 2	5 ± 2	7 ± 5	18 ± 11
Registration time (sec)	227 ± 27	11 ± 2	7 ± 1	199 ± 38
Volume (cc)	3.52 ± 2.00	3.31 ± 2.00	2.83 ± 1.74	2.30 ± 1.64
Difference between volumes (cc)[a]	0.86 ± 0.50	1.10 ± 0.50	1.50 ± 1.00	2.10 ± 1.20

ROs = radiation oncologists; DIL = dominant intraprostatic lesion; DSC = dice similarity coefficient; MDA = mean distance to agreement; STAPLE = simultaneous truth and performance level estimation.

[a] Absolute difference between STAPLE and each of ROs, rigid, and deformable registration methods.

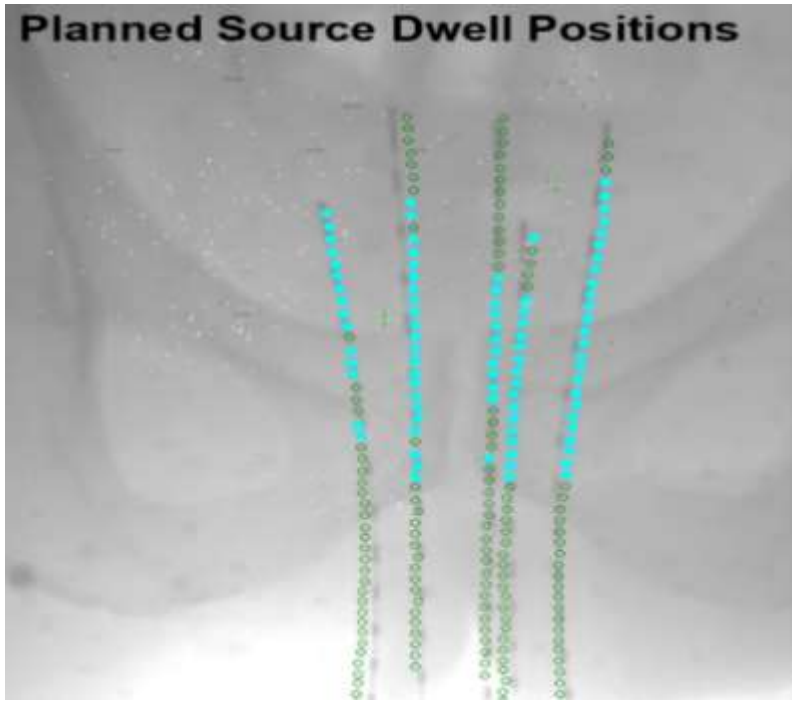
Use of real-time electromagnetic tracking for auto-catheter reconstruction

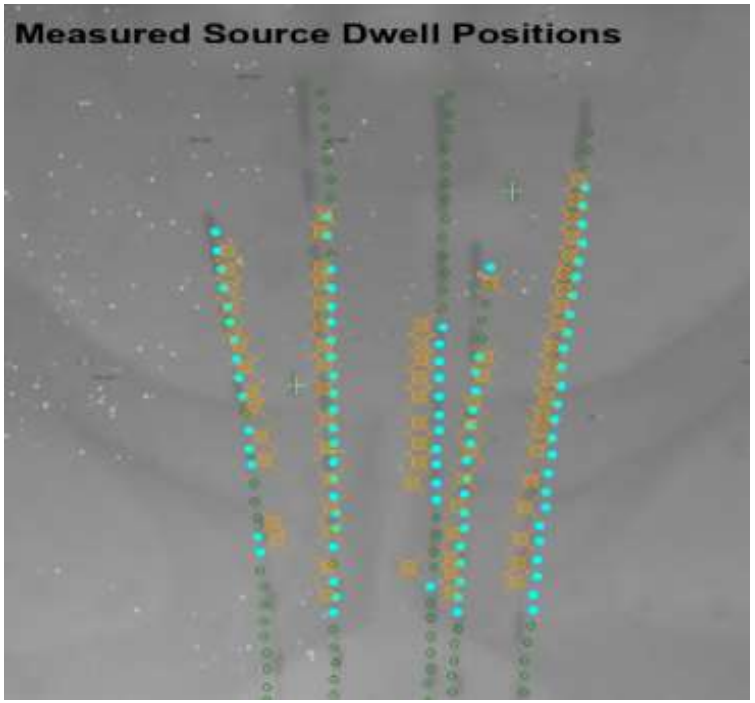
To achieve accurate and rapid catheter reconstruction during intra-operative procedures

Beaulieu, Brachytherapy 2018

Plan robustness: HDR

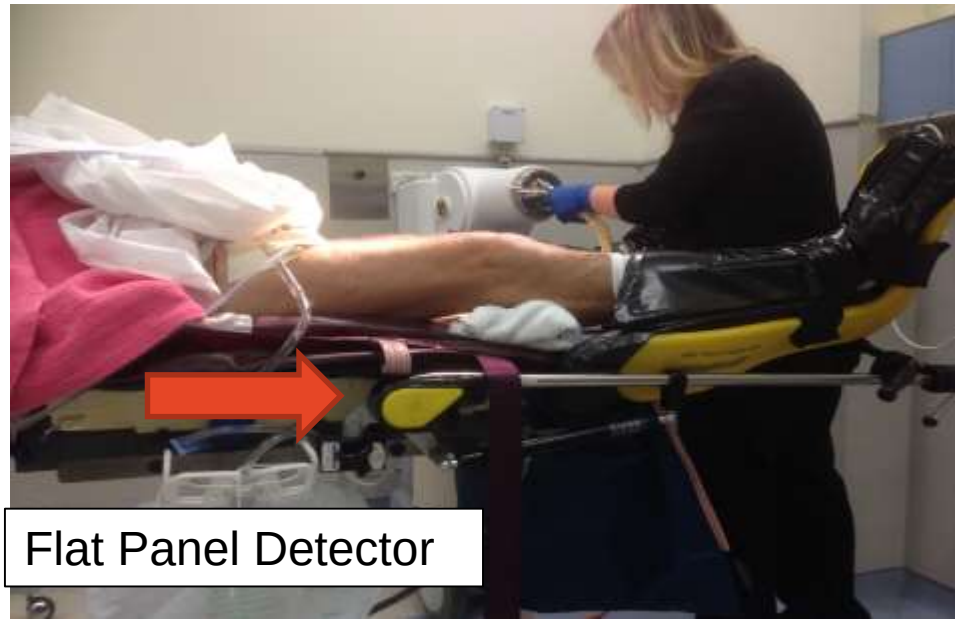
If the patient is transferred to CT or MRI for planning, needles can displace



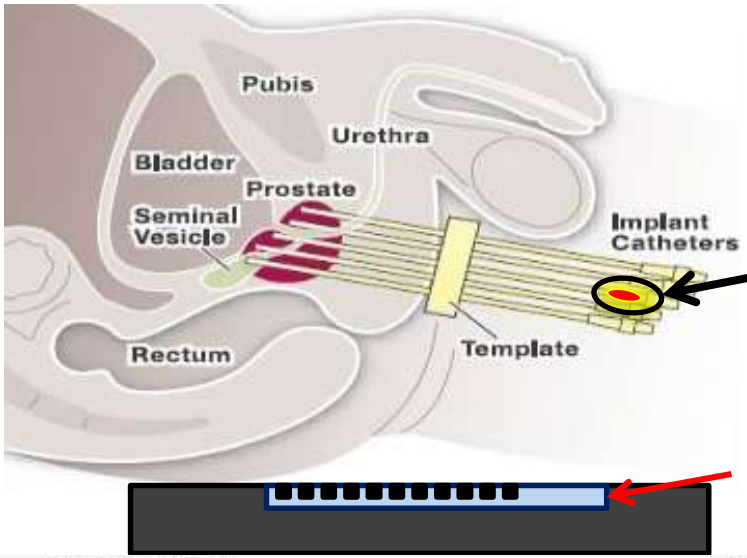


Images courtesy R Smith, Alfred Hospital, Melbourne

Dose delivery verification methods: Integrated Source Tracking and Imaging

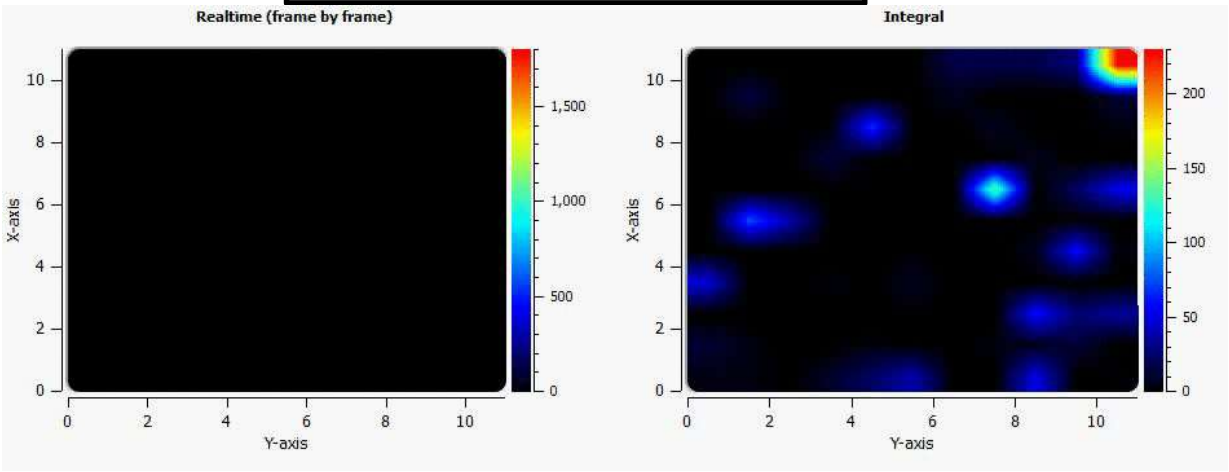


Slide courtesy R Smith, Alfred Hospital (Smith et al 2017)



Ir-192 HDR Source Activity - 10 Ci

Magic Plate Imbedded in Couch



Slides courtesy of Anatoly Rosenfeld, CMRP, UOW Australia

Summing uncertainties in quadrature

Table 5
Example 5 – HDR ^{192}Ir source for temporary prostate BT.

Category	Typical level (%)	Assumptions
Source strength	2	PSDL traceable calibrations
Treatment planning	3	Reference data with the appropriate bin width
Medium dosimetric corrections	1	Full scatter conditions in the pelvic region and for the prostate location are assumed
US-based Treatment planning and delivery: Catheter reconstruction and source positioning accuracy	2	Assuming usage of dedicated catheter reconstruction tools (catheter free-length measurement based methods) for an accurate (0.7 mm) reconstruction of catheter tip and 1.0 mm source positioning accuracy by the afterloader for straight catheters and transfer tubes
US-based 2D and 3D-imaging overall effect	2	US QA performed according to AAPM TG-128 report
Changes of catheter geometry relative to anatomy between intraoperative treatment planning and intraoperative treatment delivery	2	Assuming that new image acquisition and treatment plan calculation is done always before each fraction. It is also required that no manipulation of the implant and anatomy occurs, as it is the case when removing/manipulating the US-probe or moving the patient from the operation table before treatment delivery
Target contouring uncertainty	2	Using CT or CT + T2 imaging
Total dosimetric uncertainty ($k = 1$)	**5**	For treatment delivery without patient movement and changes in the lithotomic set-up and with the US probe at the position of the acquisition (transversal plane at the prostate base)

Kirisits et al Radiother Oncol 2014

Radiobiological Considerations

Table 3
Oncological results of high dose rate monotherapy for localised prostate cancer

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BED for LDR

- Depends on implant quality
- Typically >>100 Gy

Radiobiological Considerations

- α/β clear favours HDR
- Radiobiology uncertainties at high dose/ fraction
- Single fraction HDR:
  - ? Re-oxygenation
  - ? Redistribution

So potentially HDR (1 or 2 fractions) *may* be better than LDR?

- Plan robustness
- Dose to the urethra
- Radiobiological considerations

But what about the elephant in the room?

TOXICITY????

Toxicity

- Urinary toxicity:
  - LDR: Almost all patients experience irritative symptoms for up to 12 months
  - Martinez 2010:

	HDR*	LDR (Pd)
Acute Dysuria	39%	60%
Frequency/urgency	58%	90%
etc		

  - Morton et al 2017: 2 vs 1 fraction HDR monotherapy
    - 51% acute Gd 2 GU in first 3 months, falling to 31%

*38 Gy in 4, or 42 Gy in 6 fractions

But, bad things can happen….

Urethral strictures following high-dose-rate brachytherapy for prostate cancer: Analysis of risk factors

Benjamin R. Hindson[1,2,*], Jeremy L. Millar[1,3], Bronwyn Matheson[1,2]

[1]*William Buckland Radiation Oncology, Alfred Health, Melbourne, Victoria, Australia*
[2]*Department of Surgery, Monash University, Melbourne, Victoria, Australia*
[3]*Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Victoria, Australia*

CONCLUSIONS: In our patients, those who received 19 Gy/2 were at a significantly higher risk of stricture formation. Most of these strictures were mild, requiring only one intervention but a 2-year stricture risk of 31.6% was striking, and we have modified our protocol.

See also Barkati et al 2012

Future Work

- Dose to the urethra is an important consideration
  - Focal or boost focal approaches (LDR or HDR) should be considered (dose painting by numbers approach)
  - Use of MR is encouraged, but understand registration uncertainties
- HDR (1-2 fractions)
  - Pre-treatment verification / in vivo dosimetry urgently needed
  - Knowing what dose was delivered:
    - Better understanding of dose – response relationship (target & OAR)
    - Better modelling of radiobiology parameters at high dose/ fraction

Conclusions

- LDR monotherapy:
  - Convenient for the patient
  - There are ways to deal with random seed displacement
  - Long term results: we know what to expect
  - Patient selection is critical
- HDR monotherapy
  - 1 or 2 fraction schedules may offer similar convenience
  - Careful planning and pre-treatment verification essential
  - Radiobiological advantages
- Clinical trials are needed
  - Confirm results are translatable to other centres
  - Better understanding of radiobiology high dose/ fraction