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Brachytherapy for Prostate Cancer

14-16 June 2018 – Avignon, France

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Speakers

Course Director

- Peter Hoskin PH

Faculty

- Bashar Al-Qaisieh BAQ
- Stefan Machtens SM
- Carl Salembier CS
- Frank-Andre' Siebert FAS

Local organiser

- Nicolas Pourel

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Programme

Day 1		Thursday 14 June	
09:00	09:10	Welcome and introduction	PH
09:10	09:30	Prostate anatomy for brachytherapy	SM
09:30	10:00	Patient Selection for LDR seed brachytherapy	CS
10:00	10:30	Patient Selection for HDR seed brachytherapy	PH
10:30	11:00	Coffee break	
11:00	11:30	Imaging for prostate brachytherapy	SM
11:30	12:00	QA for brachytherapy	BAQ
12:00	13:00	LDR seed techniques and video demonstrations	CS/SM/BAQ
12:30	13:30	Lunch	
13:30	14:30	HDR techniques and video demonstrations	PH/FAS
14:30	15:30	CTV definition and Falcon exercise review	CS
15:30	16:00	Coffee break	
16:00	16:30	Radiation protection and incidents	BAQ
16:30	17:00	Adjuvant treatment in brachytherapy	CS
17:00	17:30	Review and interactive session	All

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Programme

Day 2		Friday 15 June	
09:00	10:15	Clinical results of LDR	CS
10:15	11:00	Clinical results of HDR	PH
11:00	11:30	Coffee break	
11:30	12:15	Image registration	FAS/BAQ
12:15	13:00	Planning principles and solution HDR & LDR	FAS/BAQ
13:00	14:00	Lunch	
14:00	14:30	Post-treatment evaluation	FAS/CS
14:30	15:30	Complications of prostate brachytherapy	SM
15:30	16:00	Coffee break	
16:00	17:00	Management of toxicity and complications	SM
17:00	17:30	Review and interactive session	All
Day 3		**Saturday 16 June**	
09:00	10:00	Focal therapy: concepts and LDR	SM
10:00	10:30	Focal therapy: HDR	PH
10:30	11:00	Coffee break	
11:00	11:30	Brachytherapy for salvage	CS
11:30	12:00	Prostate brachytherapy: LDR, HDR, surgery or IMRT	PH
12:00	12:30	Final discussion session	All

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WELCOME TO ESTRO PROSTATE BRACHYTHERAPY IN AVIGNON

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Your teachers ……..

- Peter Hoskin: Mount Vernon, UK
- Bashar AlQaisieh: Leeds
- Stefan Machtens: Bergisch Gladbach,DE
- Carl Salembier: Brussels, BE
- Frank Andre Siebert: Kiel, DE

For ESTRO ……..

- Elena Giusti

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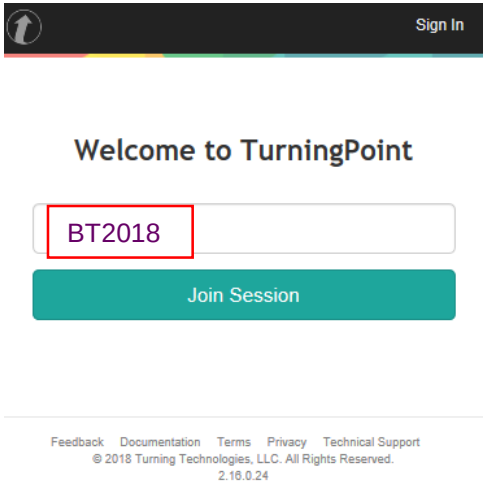
INTERACTIVE SESSION

Network: **cha13**

Password: **estro2018**



For live voting please go to

www.responseware.eu

Session ID: **BT2018**

Click on **Join Session**

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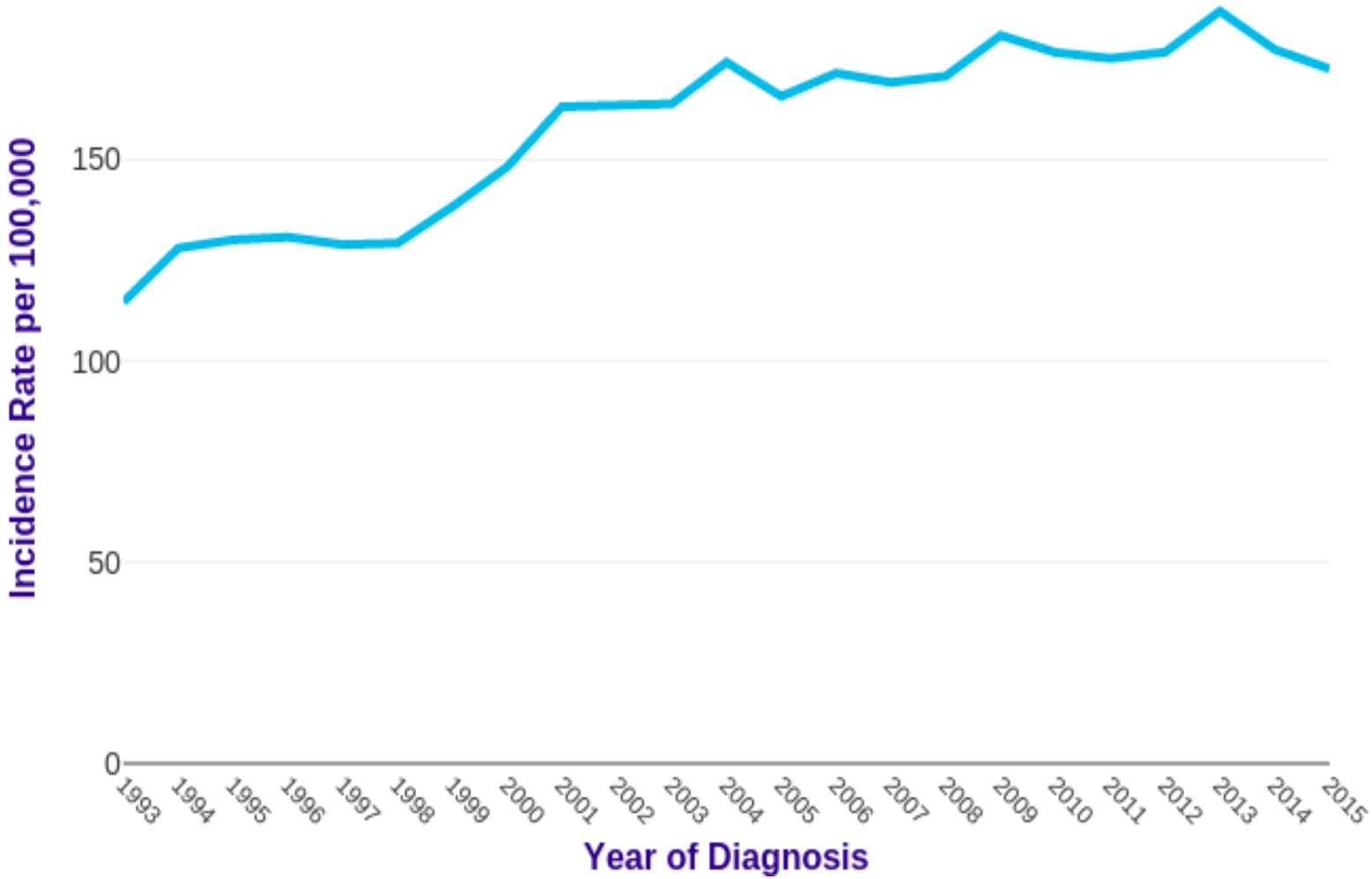
Our exhibitors

- Eckert and Ziegler
- Elekta
- Varian

http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer

Age-Standardised Incidence Rates, UK, 1993-2015



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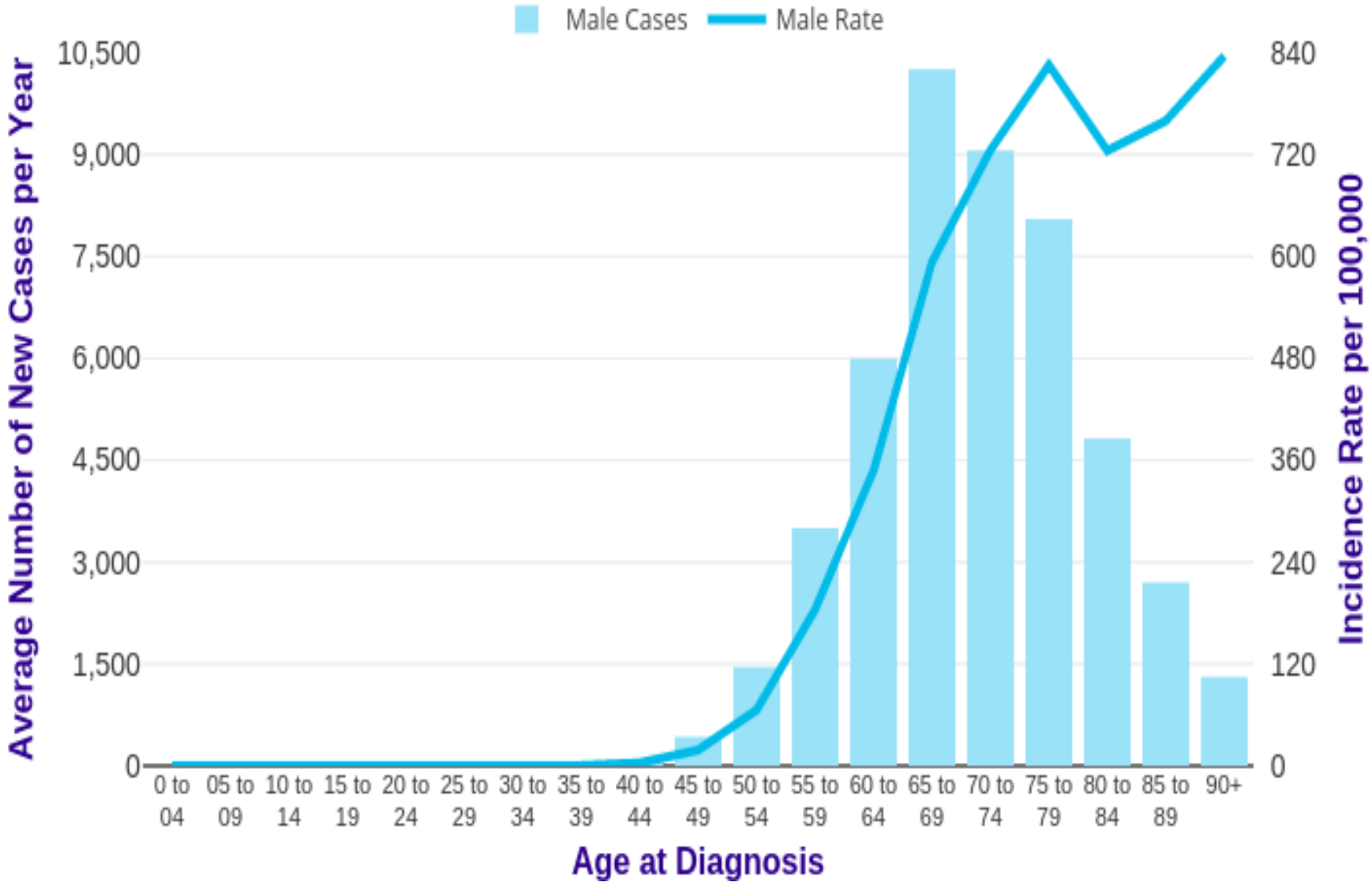
Age specific incidence rates UK 2013/15



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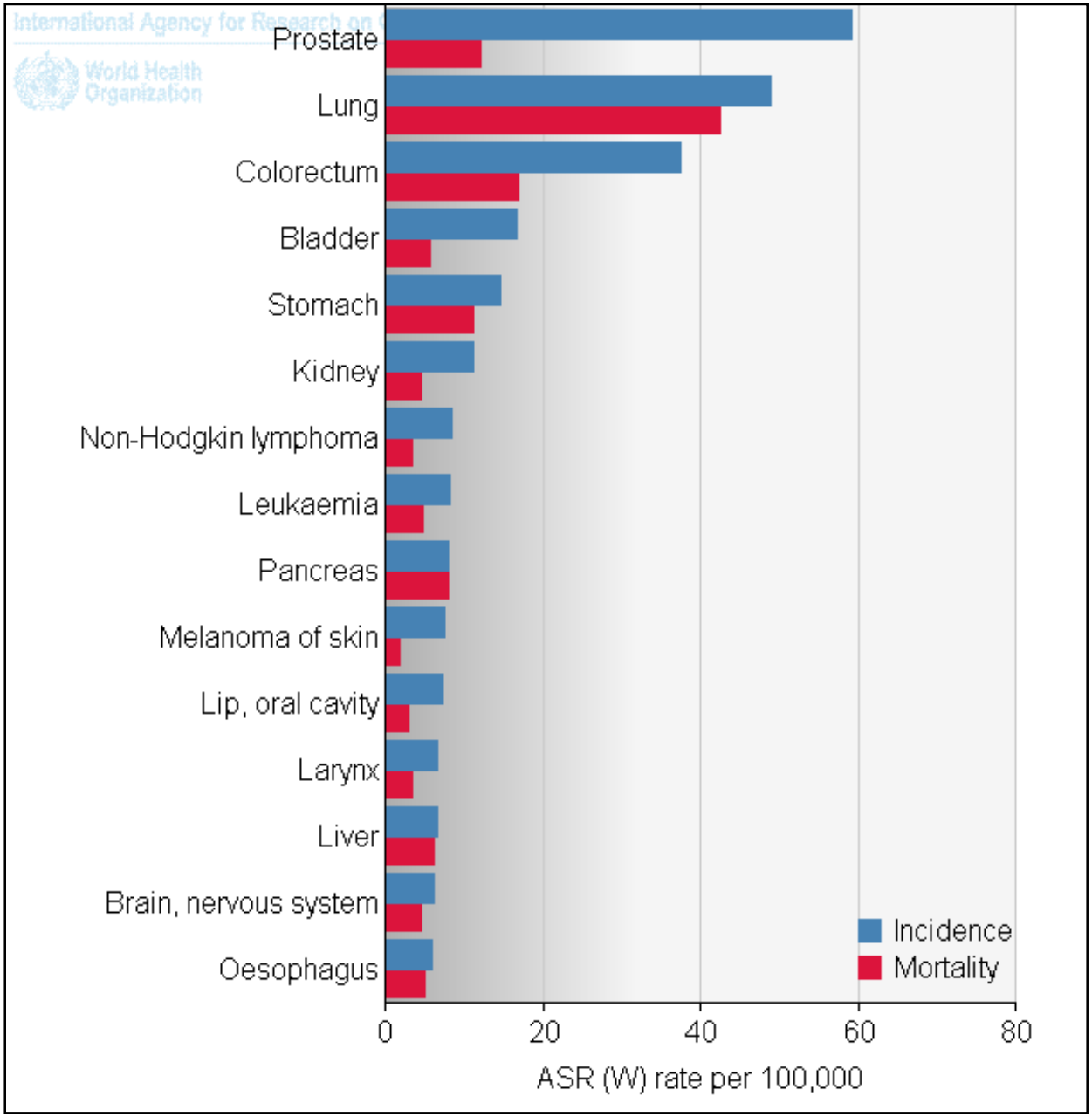
Cancer incidence and mortality, males, Europe: 2010



IARC

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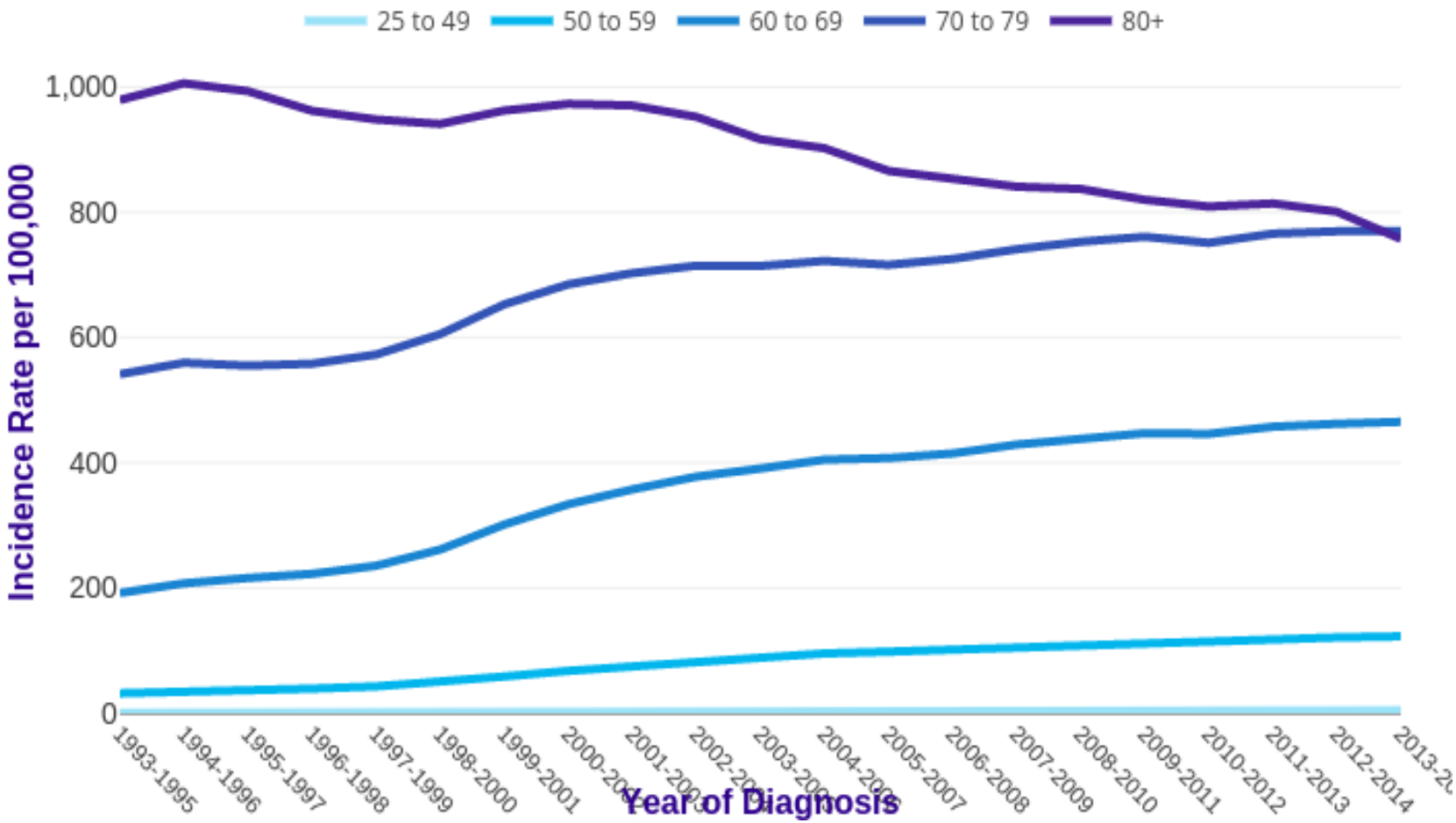
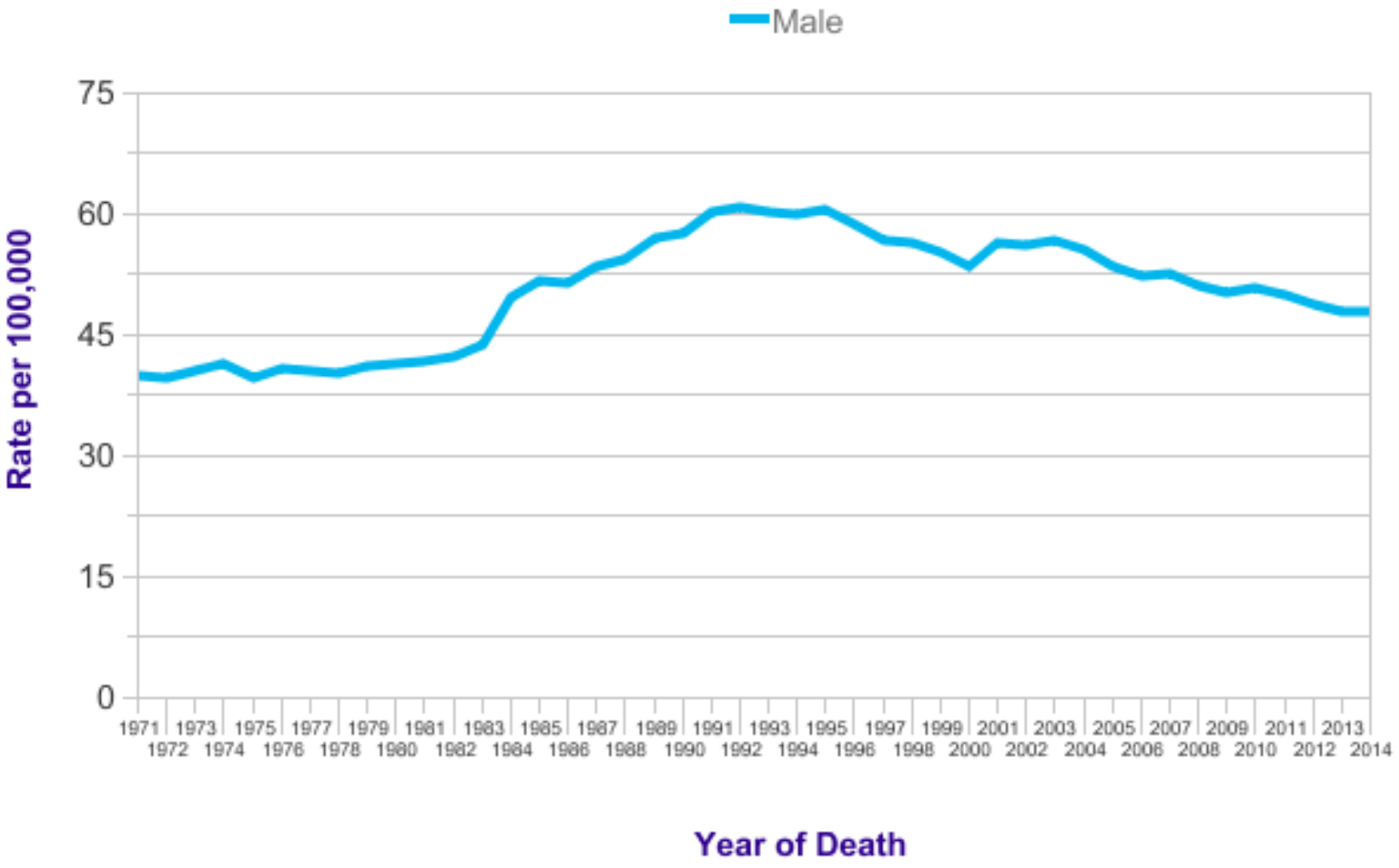
European Age-Standardised Incidence Rates, By Age, Males, UK, 1993-2015



European Age-Standardised Mortality Rates per 100,000 Population, Males, UK



Source: cruk.org/cancerstats

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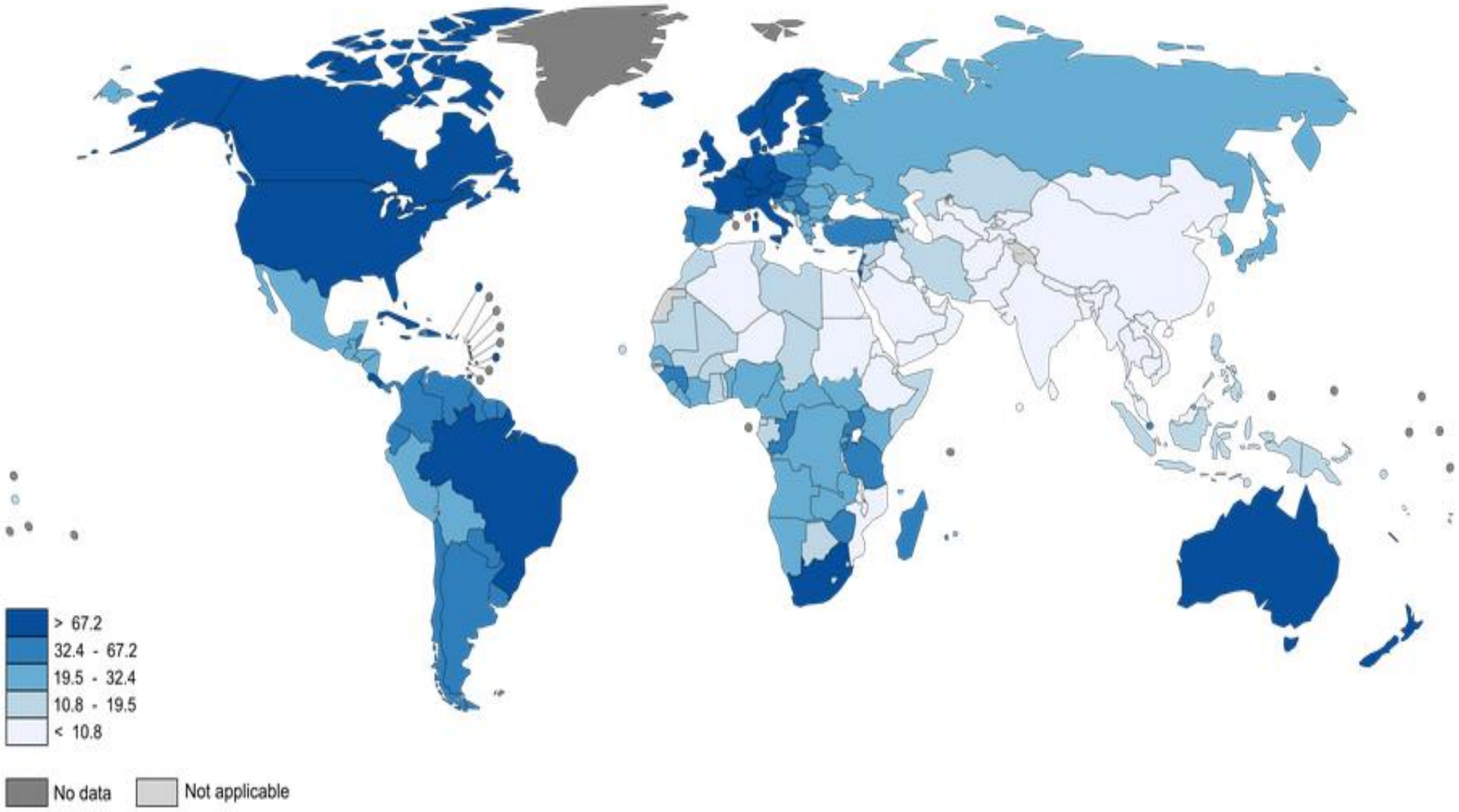
Estimated Prostate Cancer Incidence Worldwide in 2012



Data source: GLOBOCAN 2012
Map production: IARC
World Health Organization

World Health Organization

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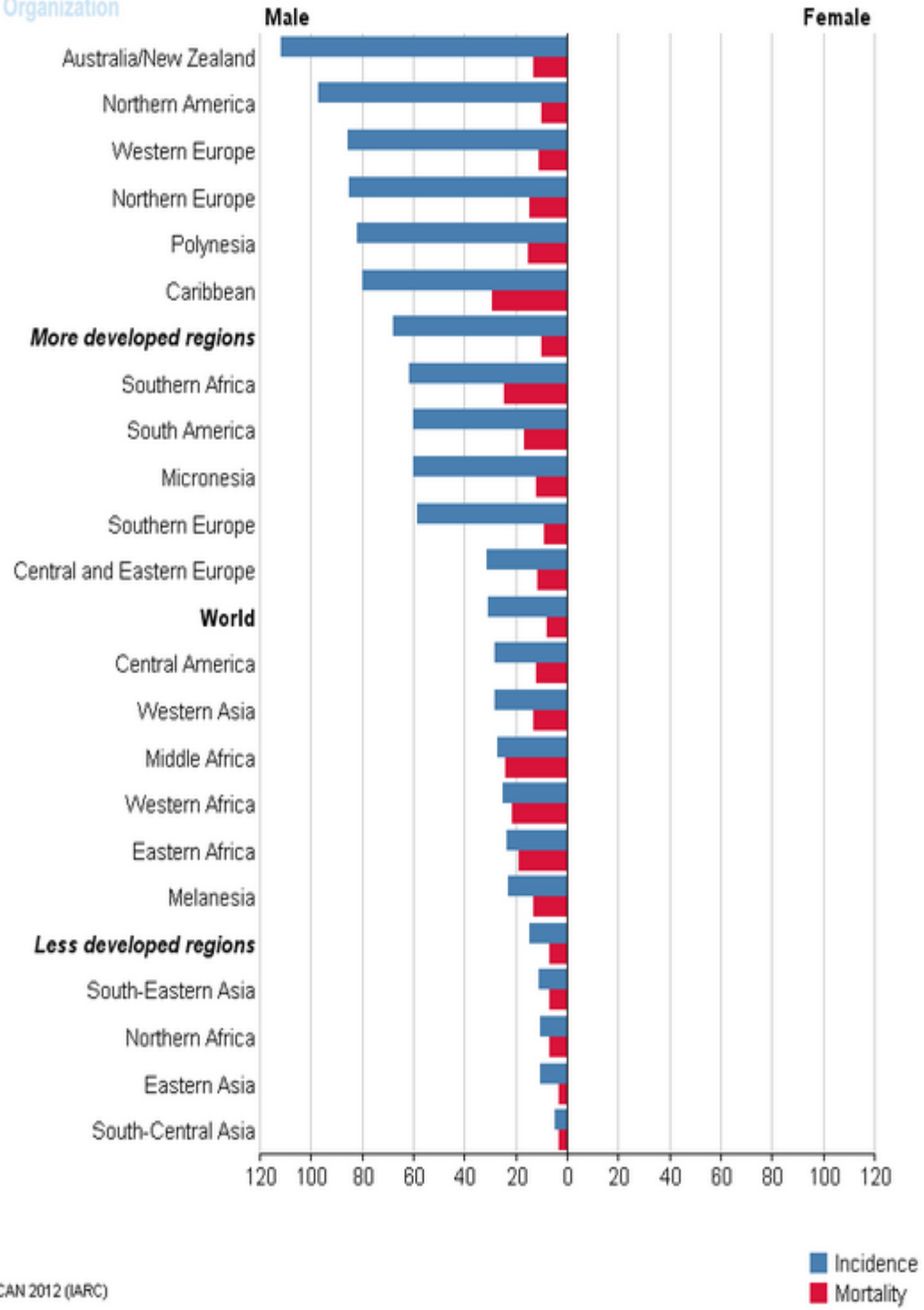

GLOBOCAN 2012 (IARC)

Worldwide
Age standardised incidence and mortality rates 2012

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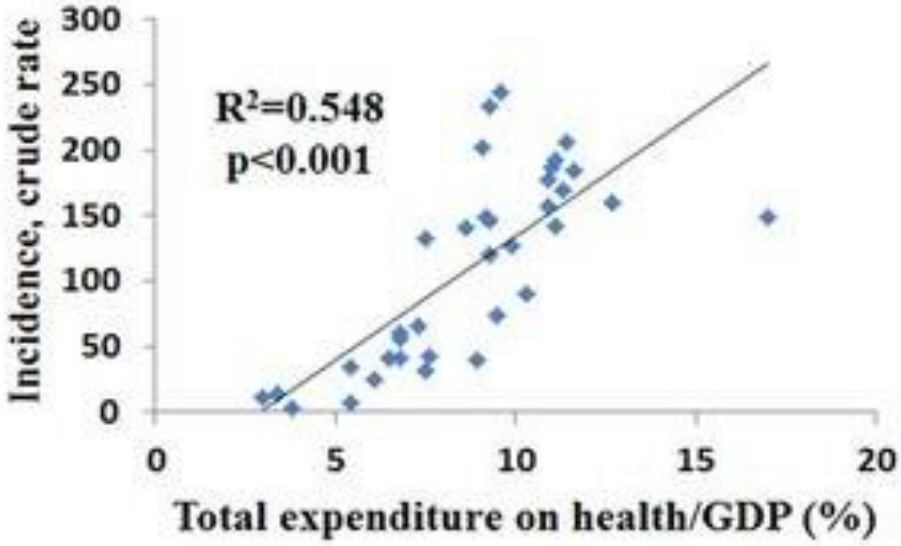
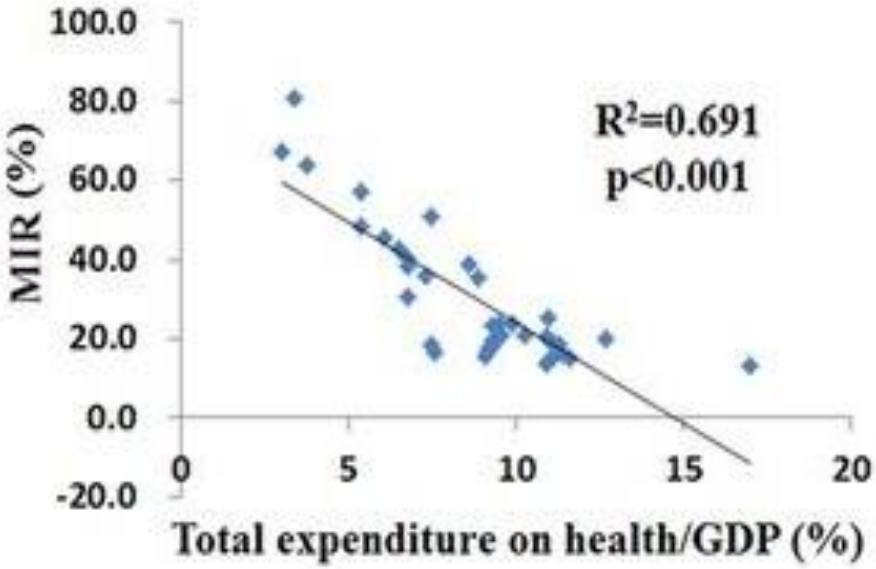
Prostate Cancer Mortality-To-Incidence Ratios Are Associated with Cancer Care Disparities in 35 Countries

Sung-Lang Chen[1,2,3,*], Shao-Chuan Wang[1,2,3,*], Cheng-Ju Ho[2,4], Yu-Lin Kao[1,2,3], Tzuo-Yi Hsieh[1,2,3], Wen-Jung Chen[1,2,3], Chih-Jung Chen[2,5,6], Pei-Ru Wu[5], Jiunn-Liang Ko[3], Huei Lee[7] & Wen-Wei Sung[1,2,3,4,6]





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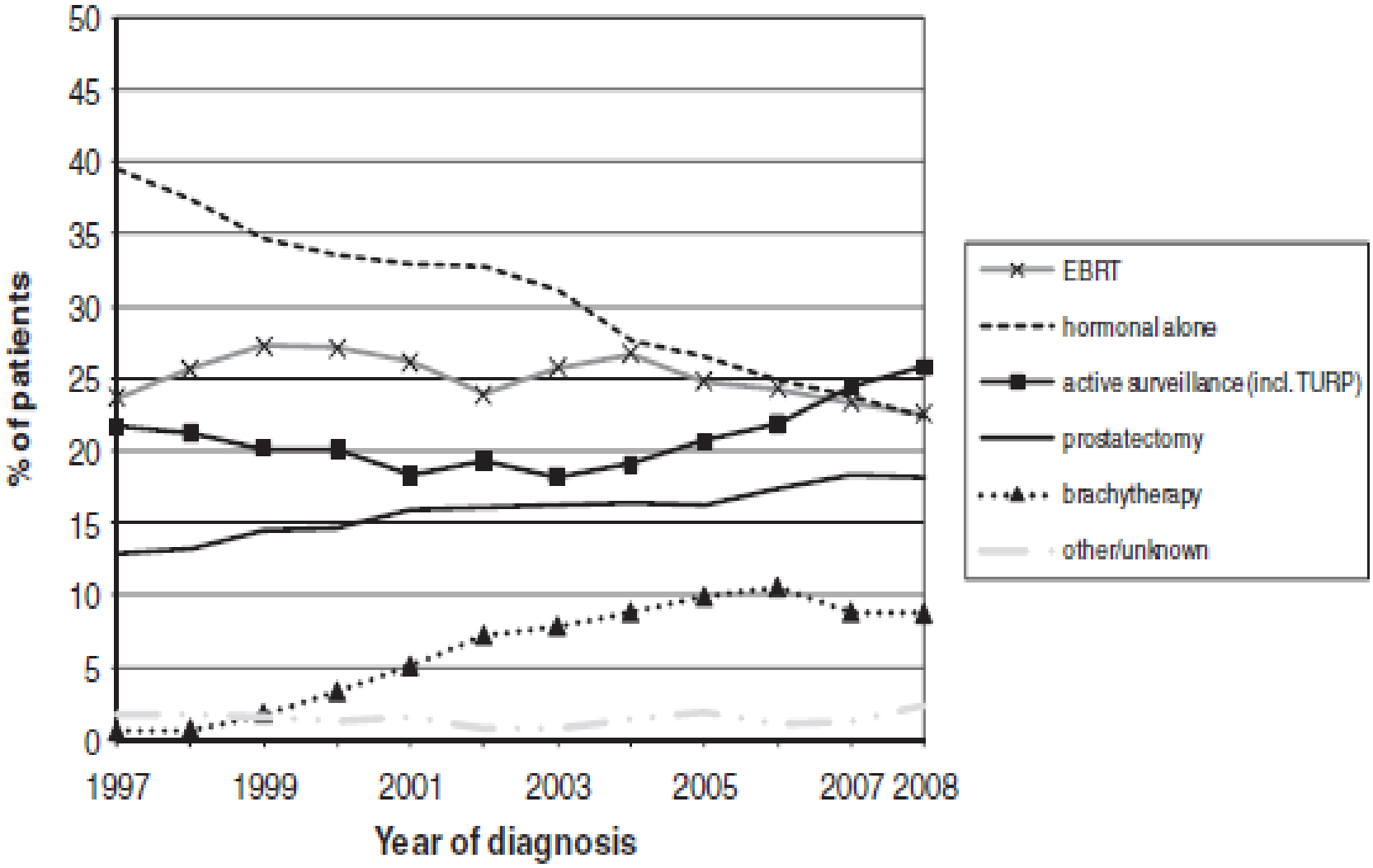
A population-based study on the utilisation rate of primary radiotherapy for prostate cancer in 4 regions in the Netherlands, 1997–2008

P.M.P. Poortmans [a], M.J. Aarts [b], J.J. Jobsen [c], C.C.E. Koning [d], M.L.M. Lybeert [e], H. Struikmans [f], J.C.M. Vulto [a], W.J. Louwman [b], J.W.W. Coebergh [b,g,*], E.L. Koldewijn [h]

Radiotherapy and Oncology 99 (2011) 207–213



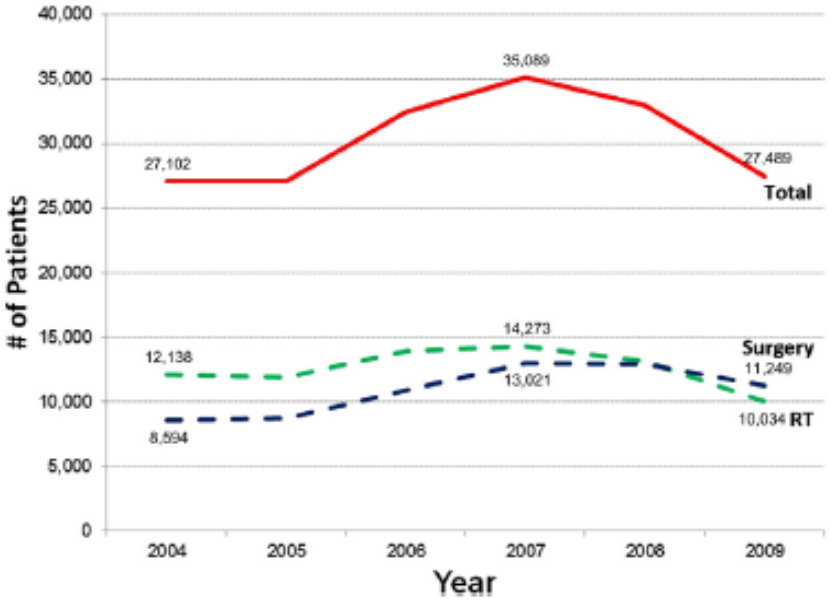
Declining use of brachytherapy for the treatment of prostate cancer

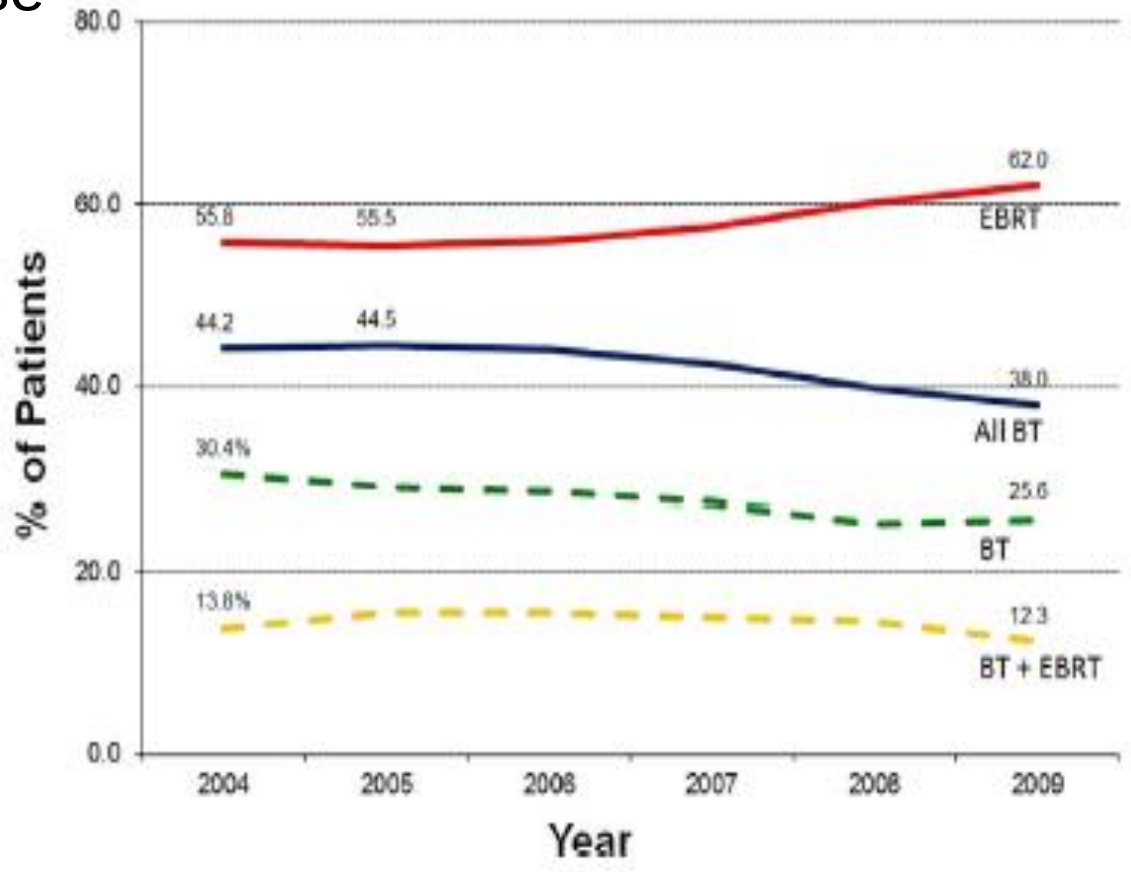
Usama Mahmood[1,*], Thomas Pugh[1], Steven Frank[1], Lawrence Levy[1], Gary Walker[1], Waqar Haque[1], Matthew Koshy[2], William Graber[3], David Swanson[3], Karen Hoffman[1], Deborah Kuban[1], Andrew Lee[1]

[1]*Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*
[2]*Department of Cellular and Radiation Oncology, University of Chicago, Chicago, IL*
[3]*Department of Urology, University of Texas MD Anderson Cancer Center, Houston, TX*

Brachytherapy 13 (2014) 157–162

182,123 men in SEER database





Estimation of the optimal utilisation rates of radical prostatectomy, external beam radiotherapy and brachytherapy in the treatment of prostate cancer by a review of clinical practice guidelines

Stephen R. Thompson [a,b,c,*], Geoff P. Delaney [a,c,d], Susannah Jacob [a,c], Jesmin Shafiq [a,c], Karen Wong [a,c], Timothy P. Hanna [e], Gabriel S. Gabriel [a,c], Michael B. Barton [a,c]

Radiotherapy and Oncology 118 (2016) 118–121

[a] Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Ingham Institute for Applied Medical Research, Liverpool Hospital, UNSW; [b] Department of Radiation Oncology, Prince of Wales Hospital; [c] University of New South Wales, Sydney; [d] University of Western Sydney, Australia; and [e] Division of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Kingston, Canada

- Peer review evidence based trees estimate:

RP: 24% (15-30)
EBRT: 58% (54-64%)
BT: 9.6% (6-17.9%)

- Actual utilisations rates:

RP: 13-44%
EBRT: 43-56%
BT: 1.8-10.9%

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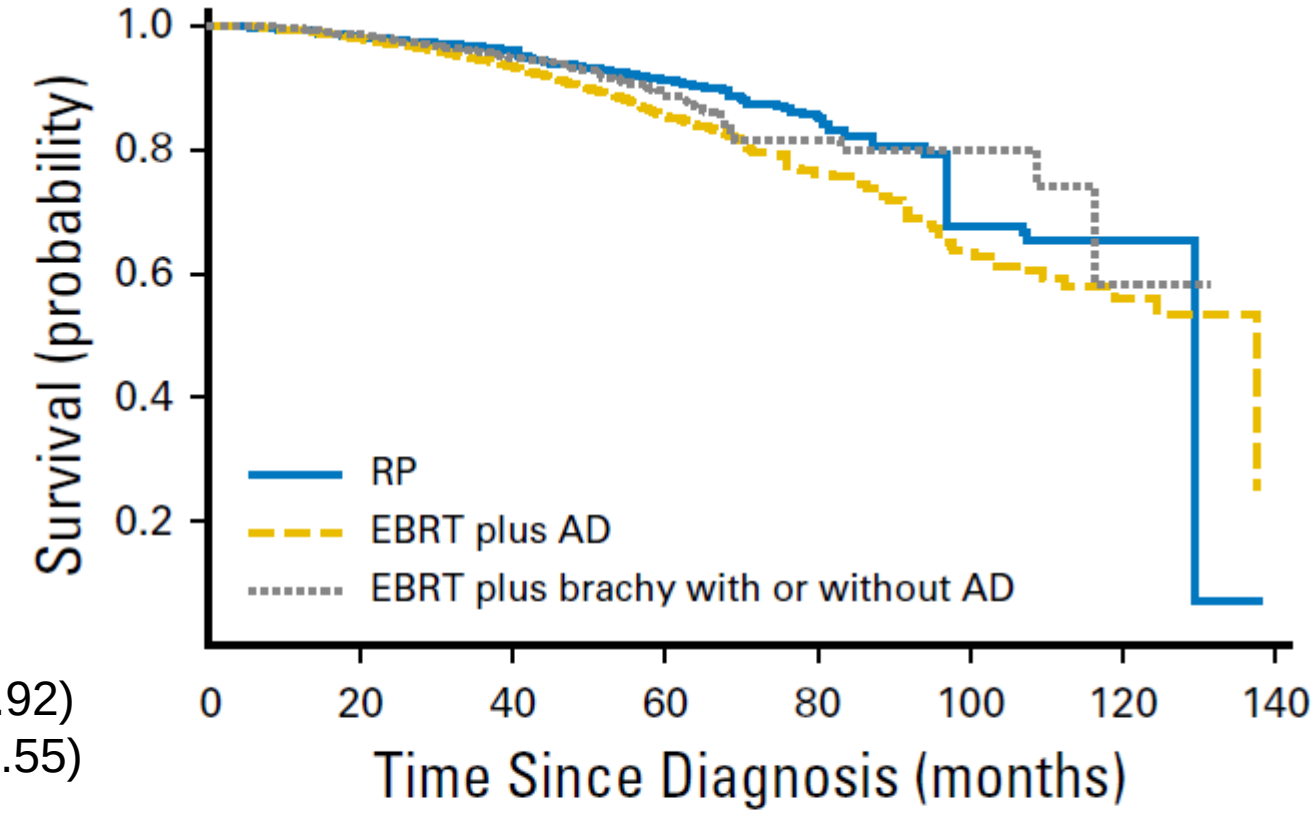
Brachytherapy-Based Radiotherapy and Radical Prostatectomy Are Associated With Similar Survival in High-Risk Localized Prostate Cancer

J Clin Oncol 36:1192-1198. © 2018

Ronald D. Ennis, Liangyuan Hu, Shannon N. Ryemon, Joyce Lin, and Madhu Mazumdar



Hazard ratios
RP vs EBRT + ADT: 1.53 (1.22-1.92)
RP vs EBRT + BT: 1.17 (0.88-1.55)

Weighted No. at risk:

RP	44,217	36,000	18,547	4,126	353	159	80	0
EBRT plus AD	41,897	35,163	17,938	3,804	301	123	33	0
EBRT plus brachy with or without AD	43,143	36,375	17,687	3,852	309	185	77	0

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Researchers identify optimal treatment for aggressive prostate cancer

Show Citation

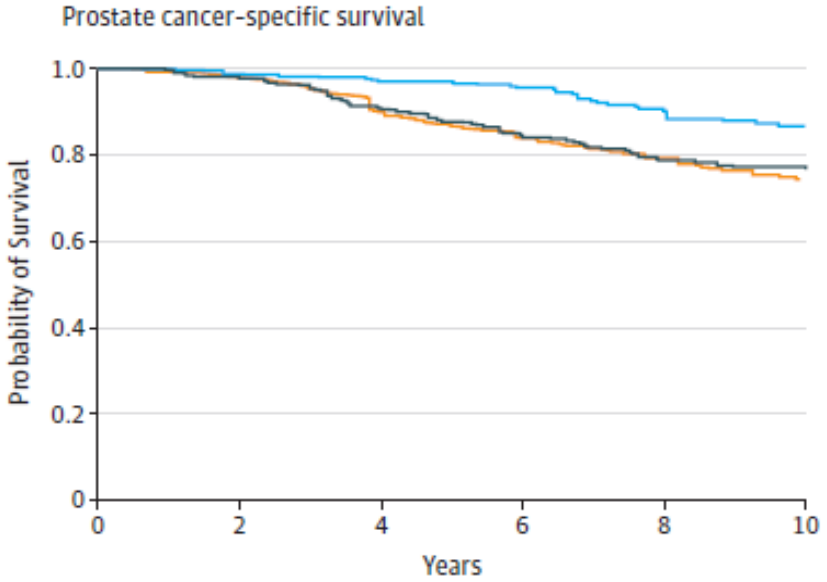
Kishan AU, et al. *JAMA*. 2018;doi:10.1001/jama.2018.0587.

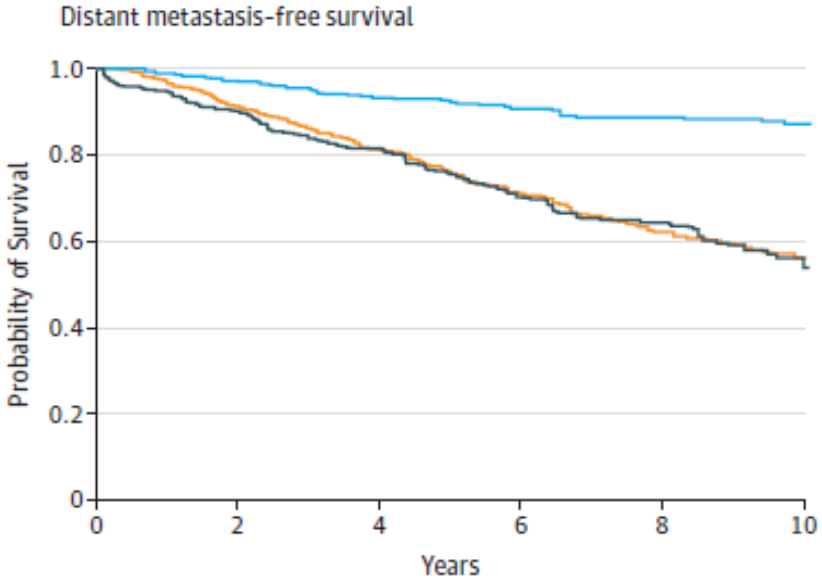
JAMA | Original Investigation

Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

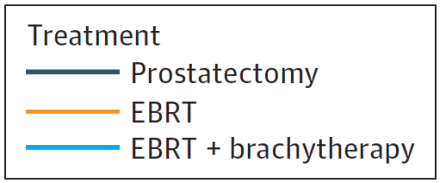
JAMA. 2018;319(9):896-905

Retrospective cohort study; 12 centres: 1809 men





No. at risk												
Prostatectomy	634	530	346	211	131	81	634	495	315	184	111	61
EBRT	725	635	457	288	172	102	734	595	407	235	133	77
EBRT + brachytherapy	431	397	317	222	159	87	436	393	307	210	156	86



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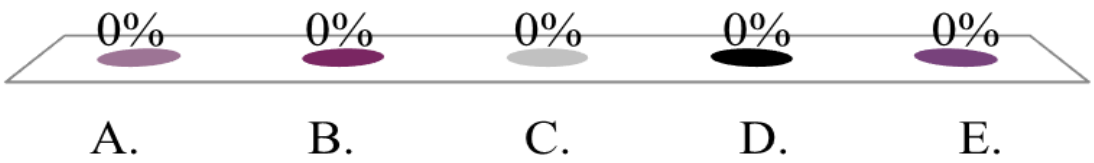
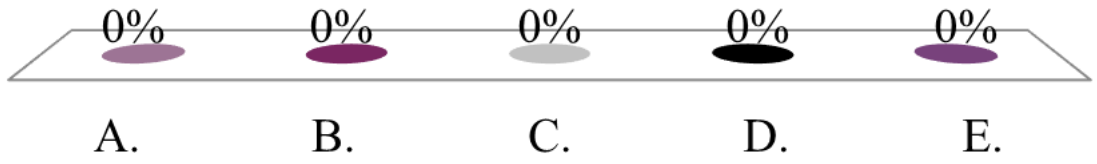
What is your role in your department?

A. Physicist
B. RTT / Radiographer
C. Physician
D. Nurse
E. Administrator



What is your experience of prostate brachytherapy?

A. None
B. Observed but not personally performed
C. Have undertaken (or planned independently) <5 implants
D. Have undertaken (or planned independently) <5 – 20 implants
E. Regularly undertake (or plan independently) implants



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Prostate Brachytherapy: Anatomy

S. Machtens

Director of the

Department of Urology and Paediatric Urology

Academic Teaching Hospital

Marien-Hospital Bergisch Gladbach

ESTRO Teaching Course on Brachytherapy for Prostate Cancer
Avignon, June 14th-16th2018

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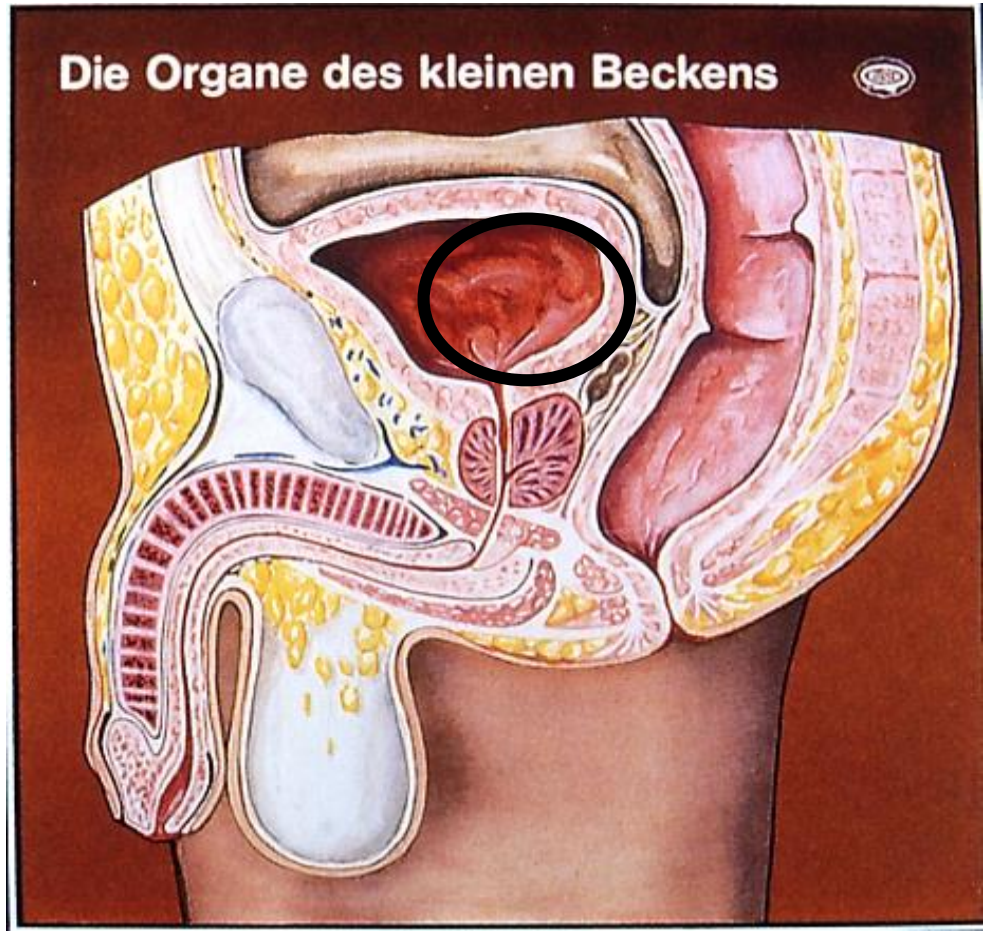
The prostate surrounds the urethra and is situated below the bladder.

The prostate produces fluid that is needed by sperms to move.



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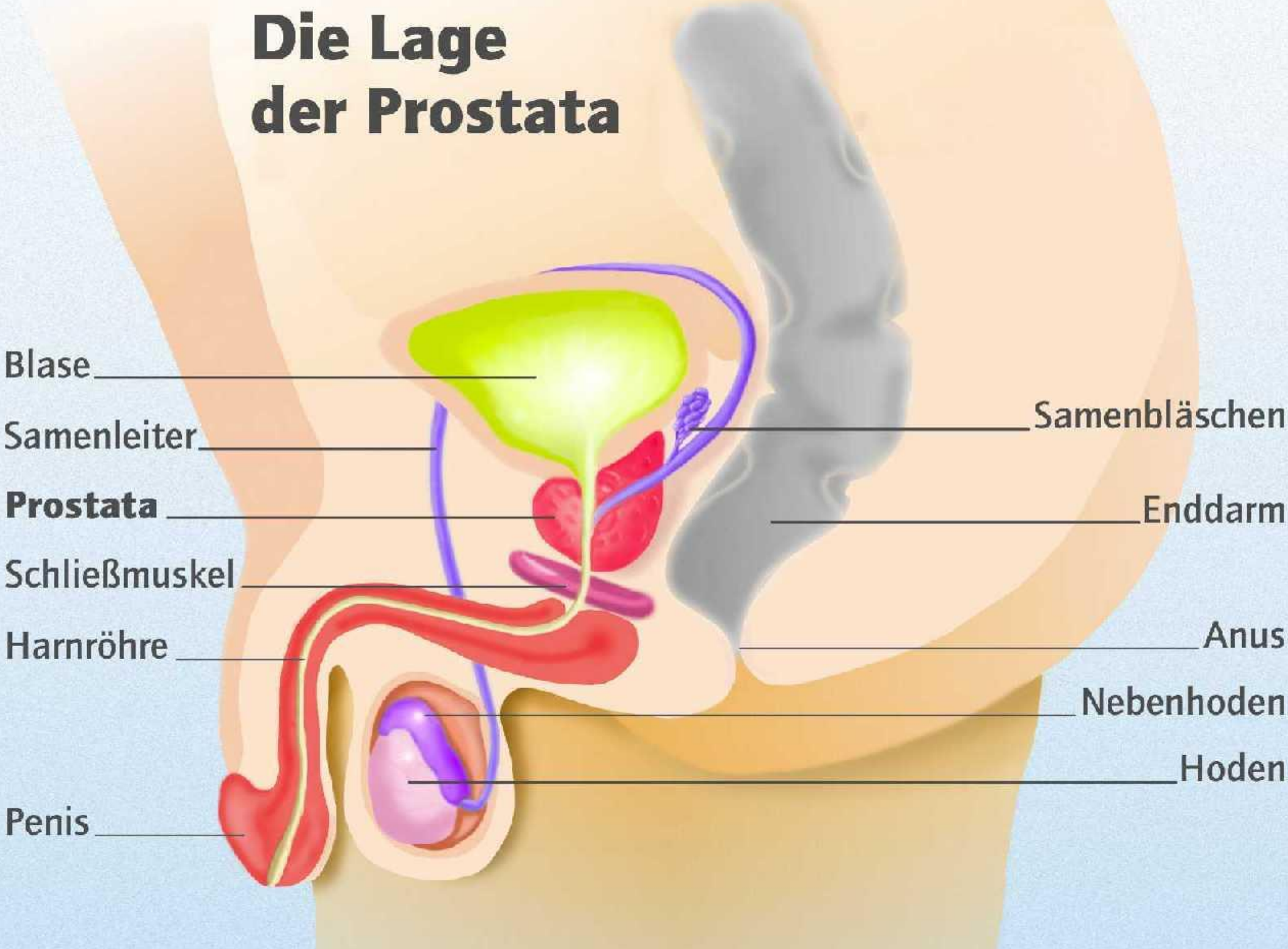
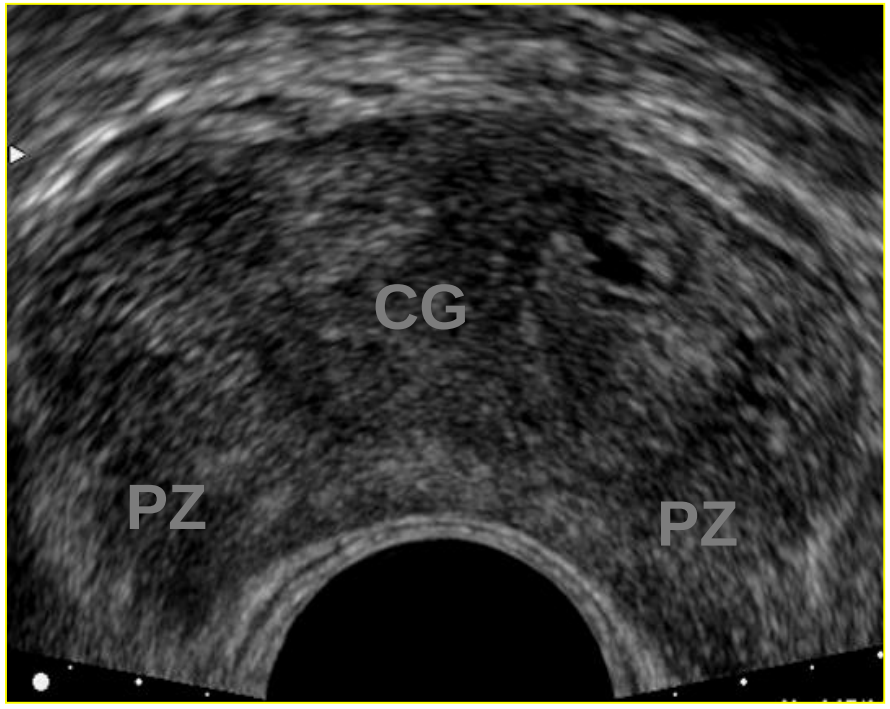
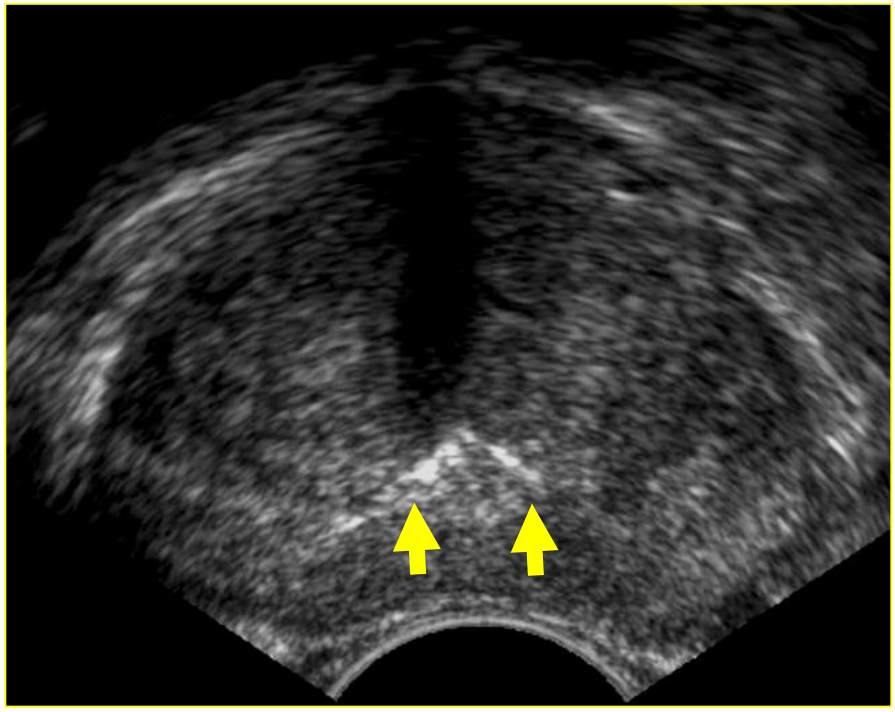
Die Lage der Prostata



Ultrasound
Normal Anatomy



Isoechoic PZ
Hypo/hyperechoic CG



Corpora Amylacea

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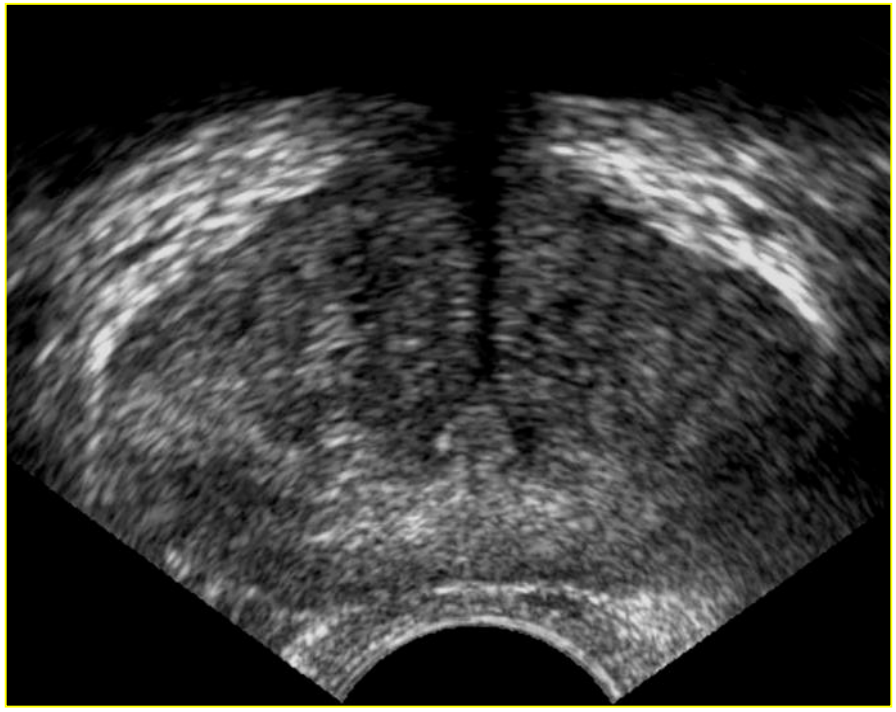
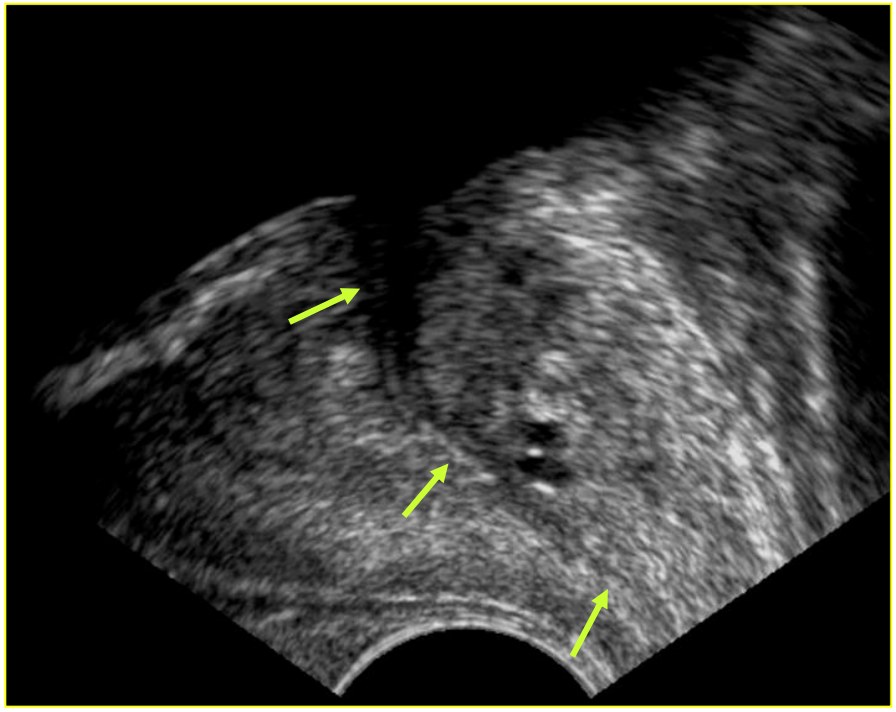
Ultrasound
Normal Anatomy



Urethra



Urethra
Sagittal

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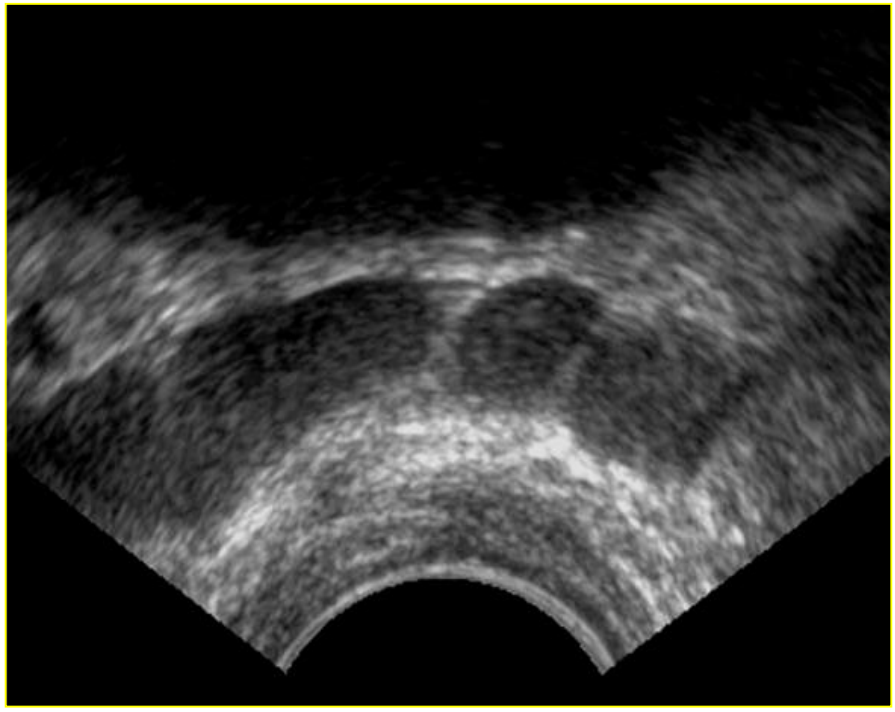
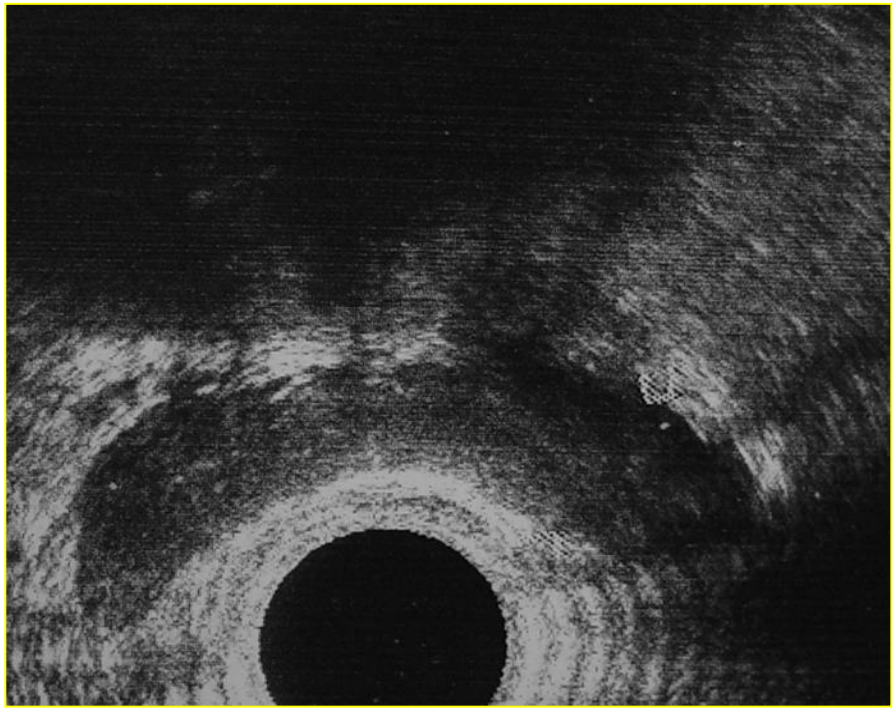
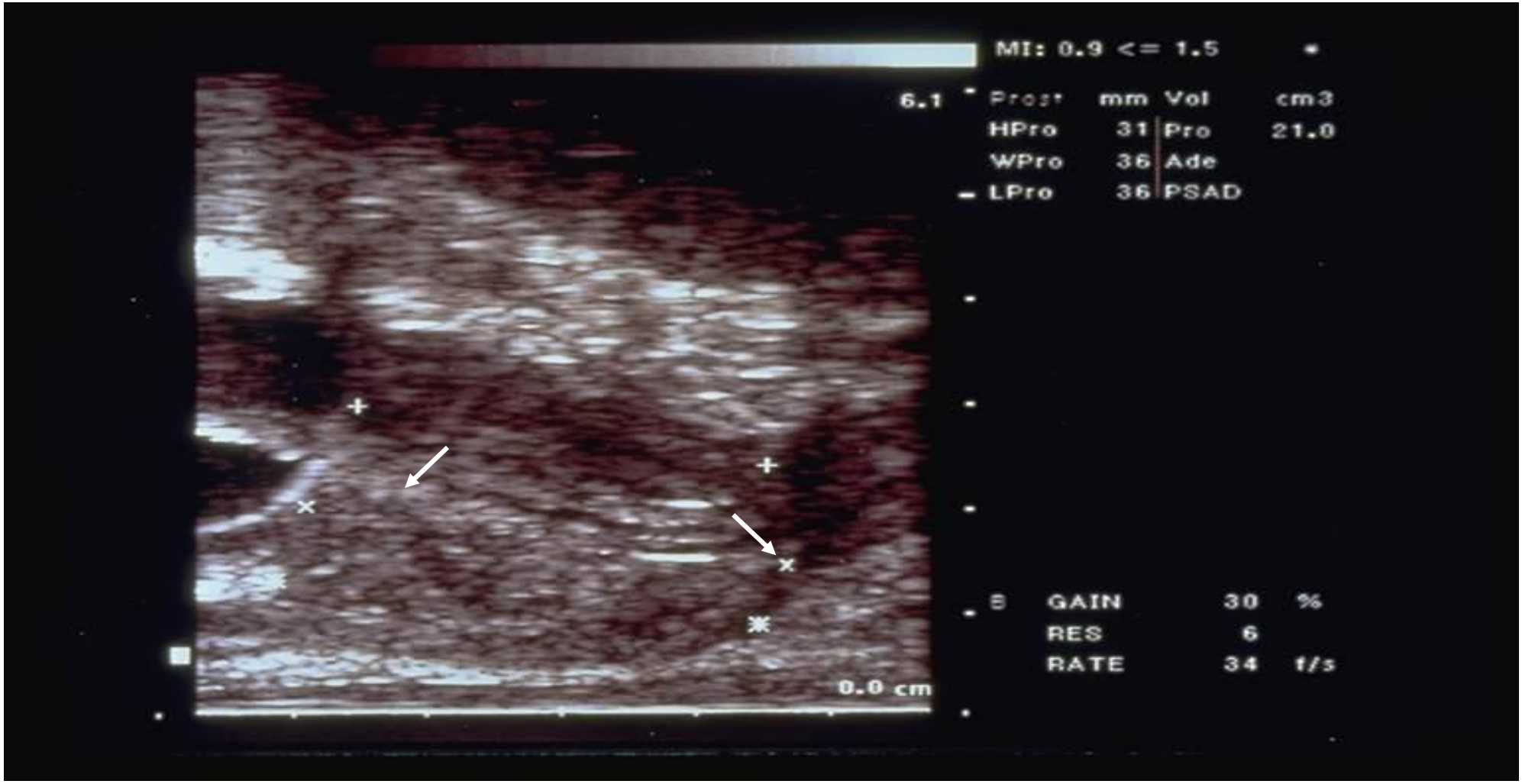
Ultrasound
Normal Anatomy



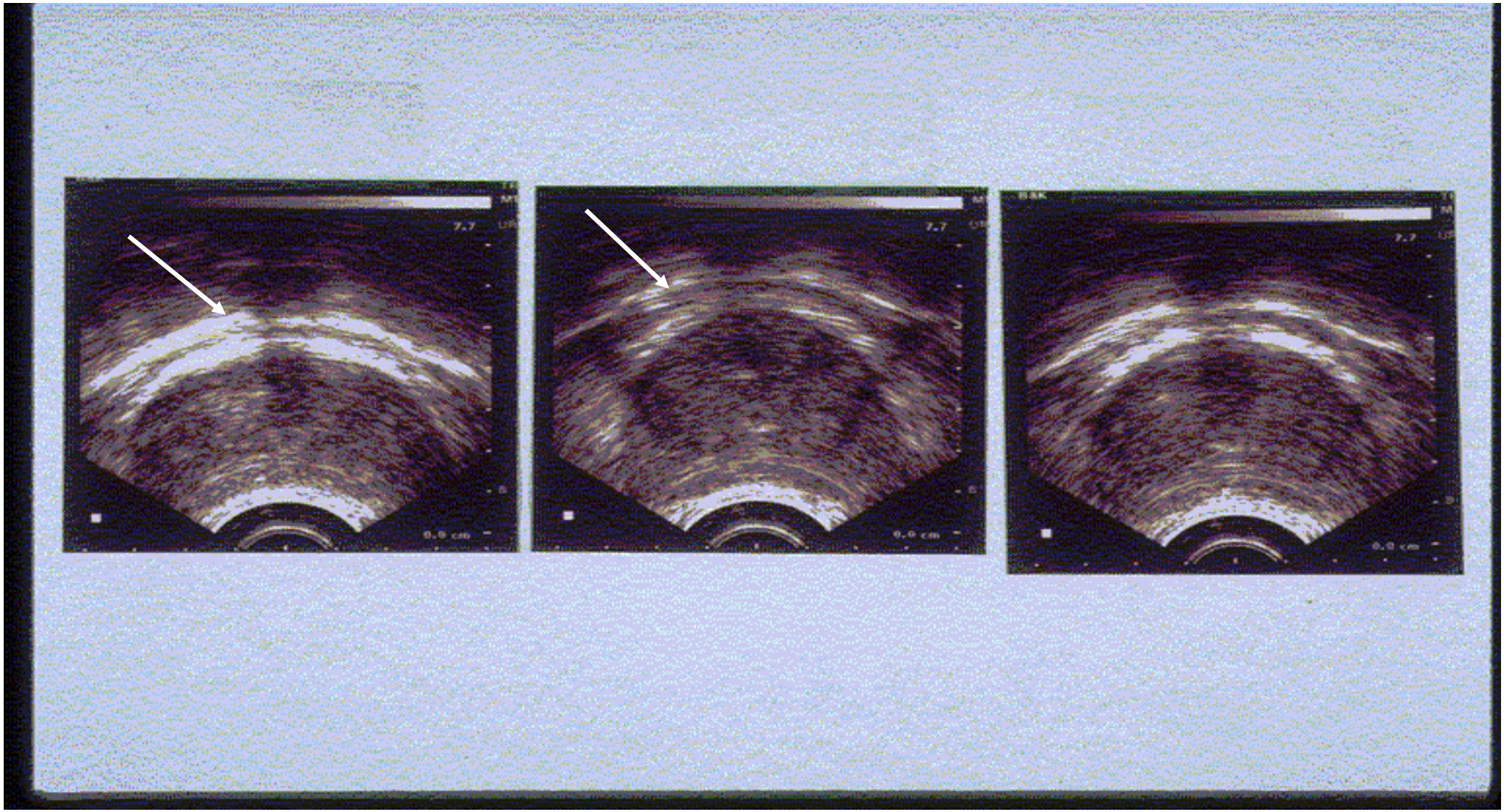


Seminal Vesicles
Convoluted Hypoechoic Cystic Structures

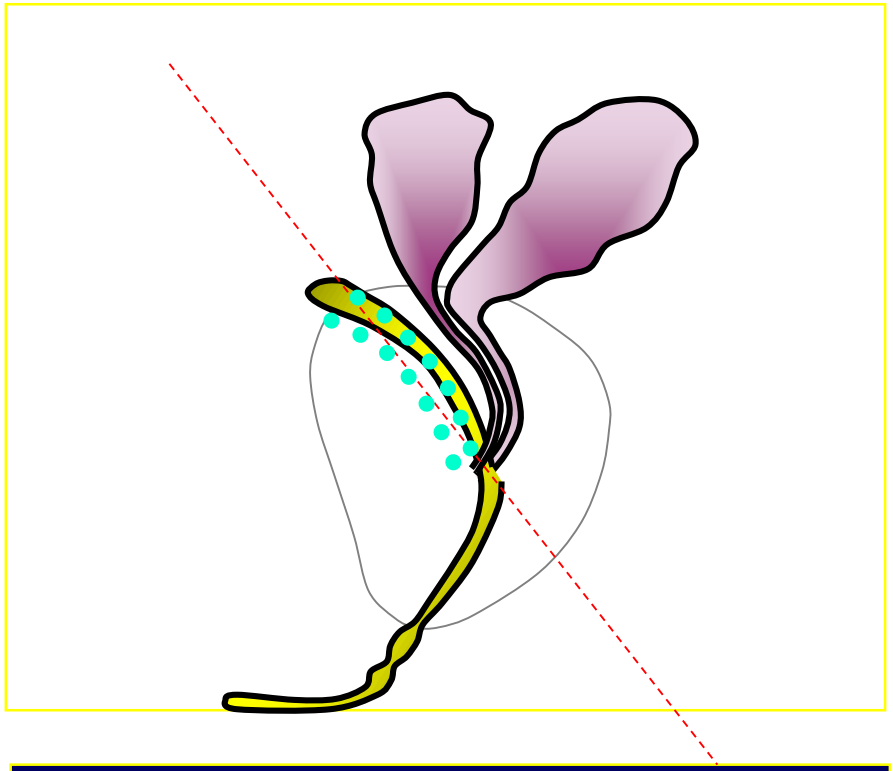
Ultrasound
Sagittal: urethral measurements



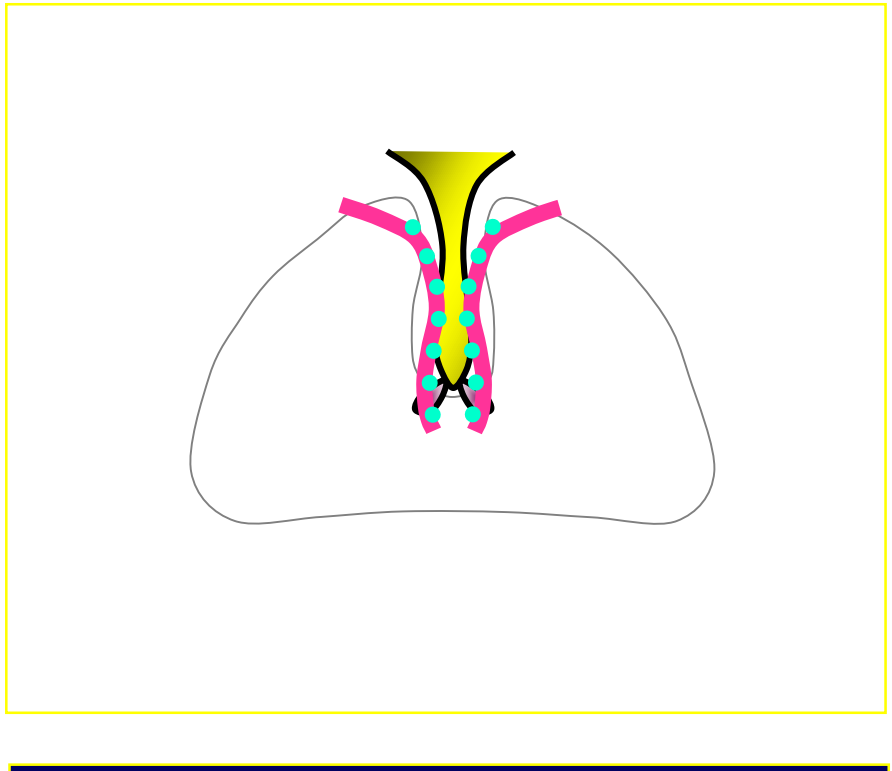
ULTRASOUND – Dorsal vein plexus



Zonal Anatomy
Central Gland



Periurethral Glands



Periurethral Glands
(paracoronal view)

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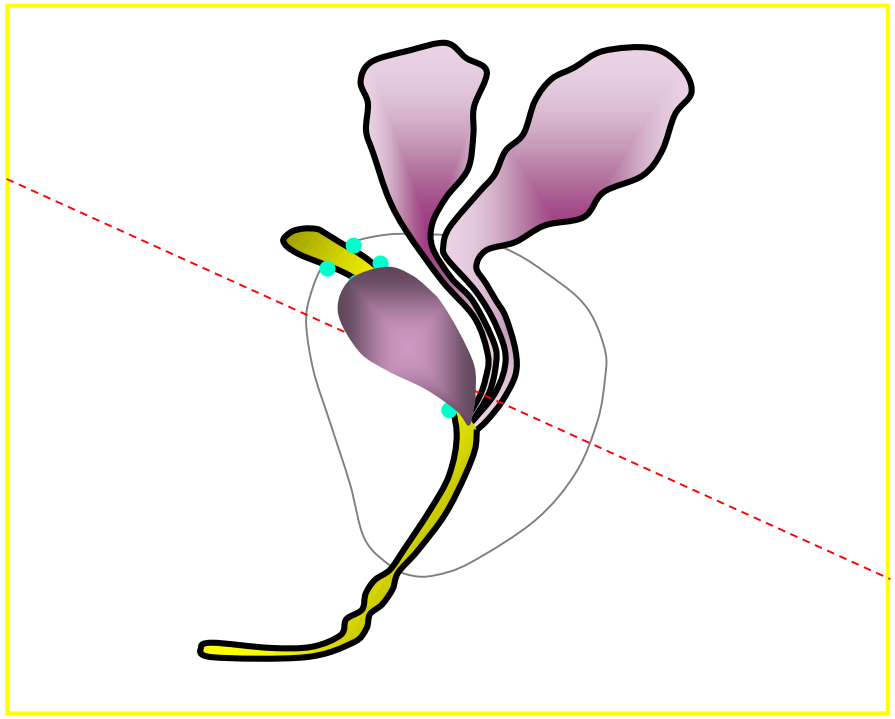
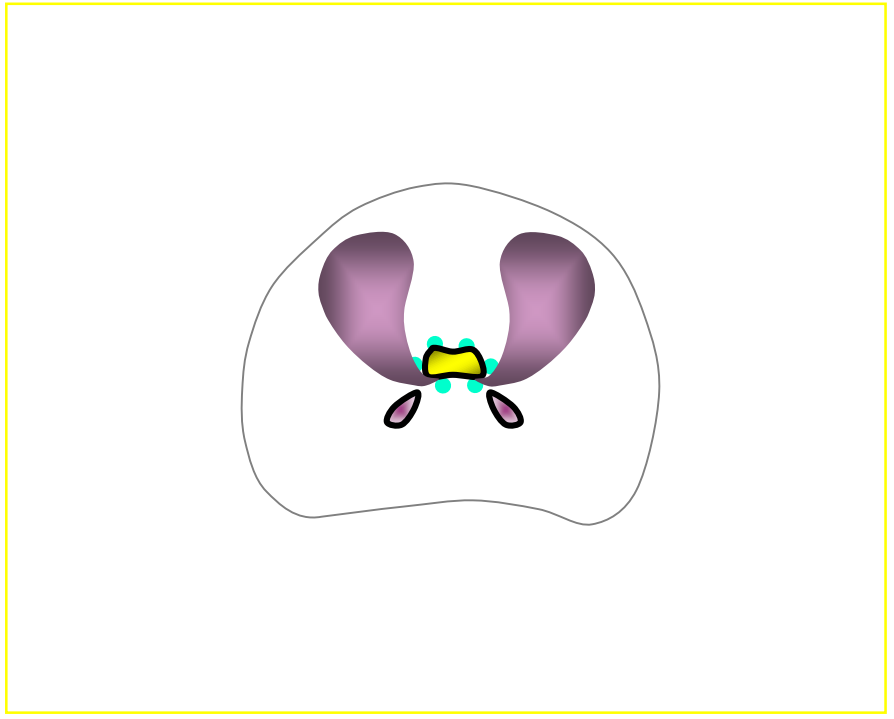
Zonal Anatomy
Central Gland



Transition Zone



Transition Zone
(transverse view)

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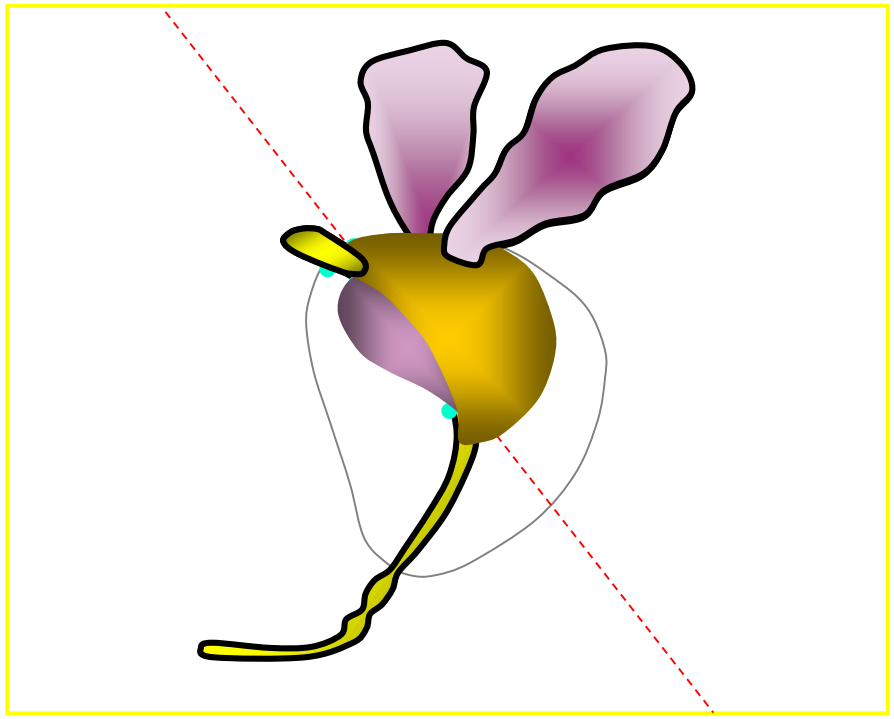
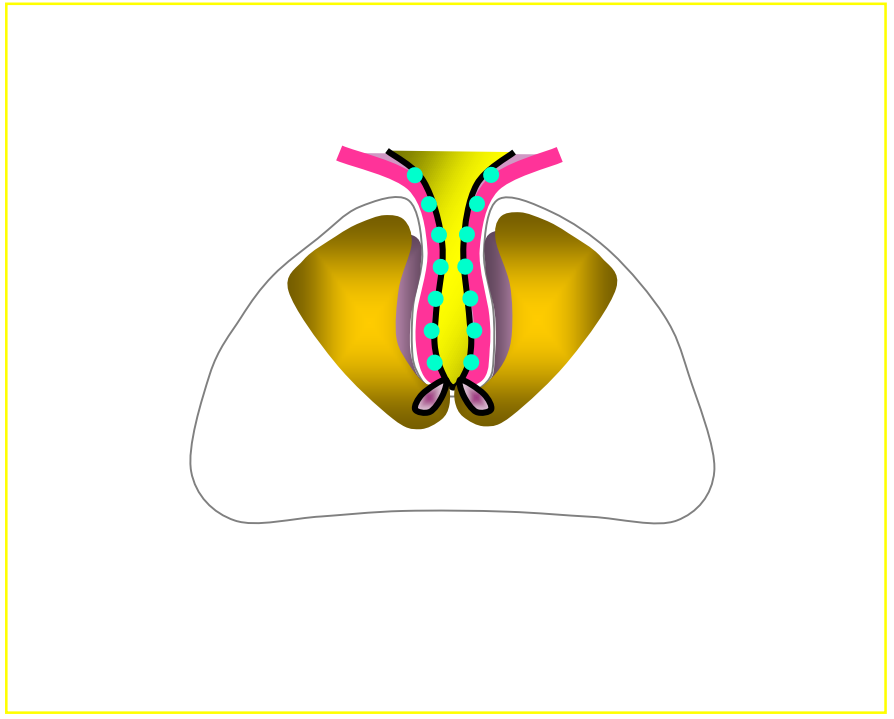
Zonal Anatomy
Central Gland



Central Zone



Central Zone
(paracoronal view)

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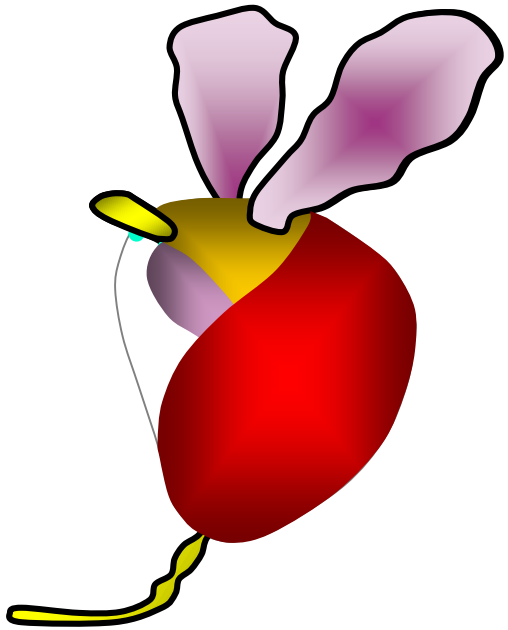
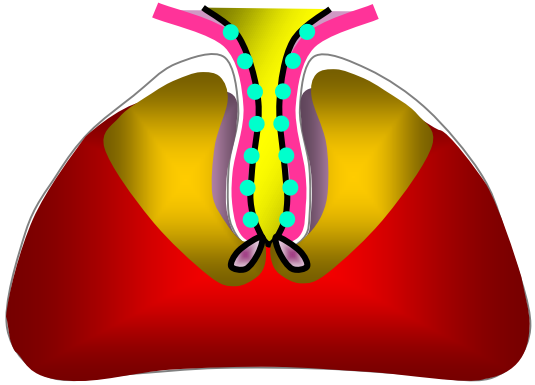
Zonal Anatomy
Overview



Peripheral Zone



Peripheral Zone
(paracoronal view)

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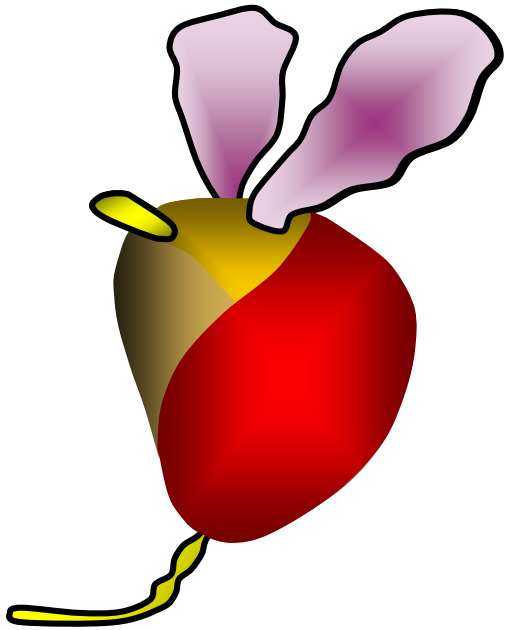
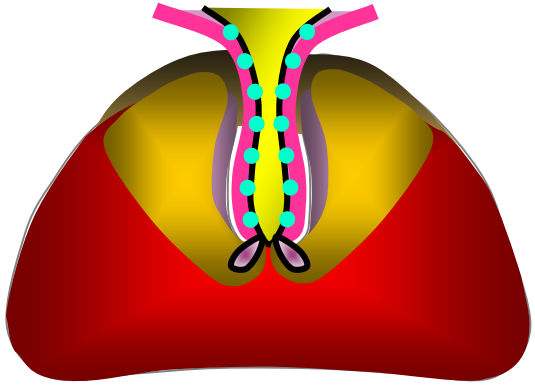
Zonal Anatomy
Overview



Anterior Fibromuscular Stroma



AFS (paracoronal view)

Zonal anatomy in MRI and Ultrasound

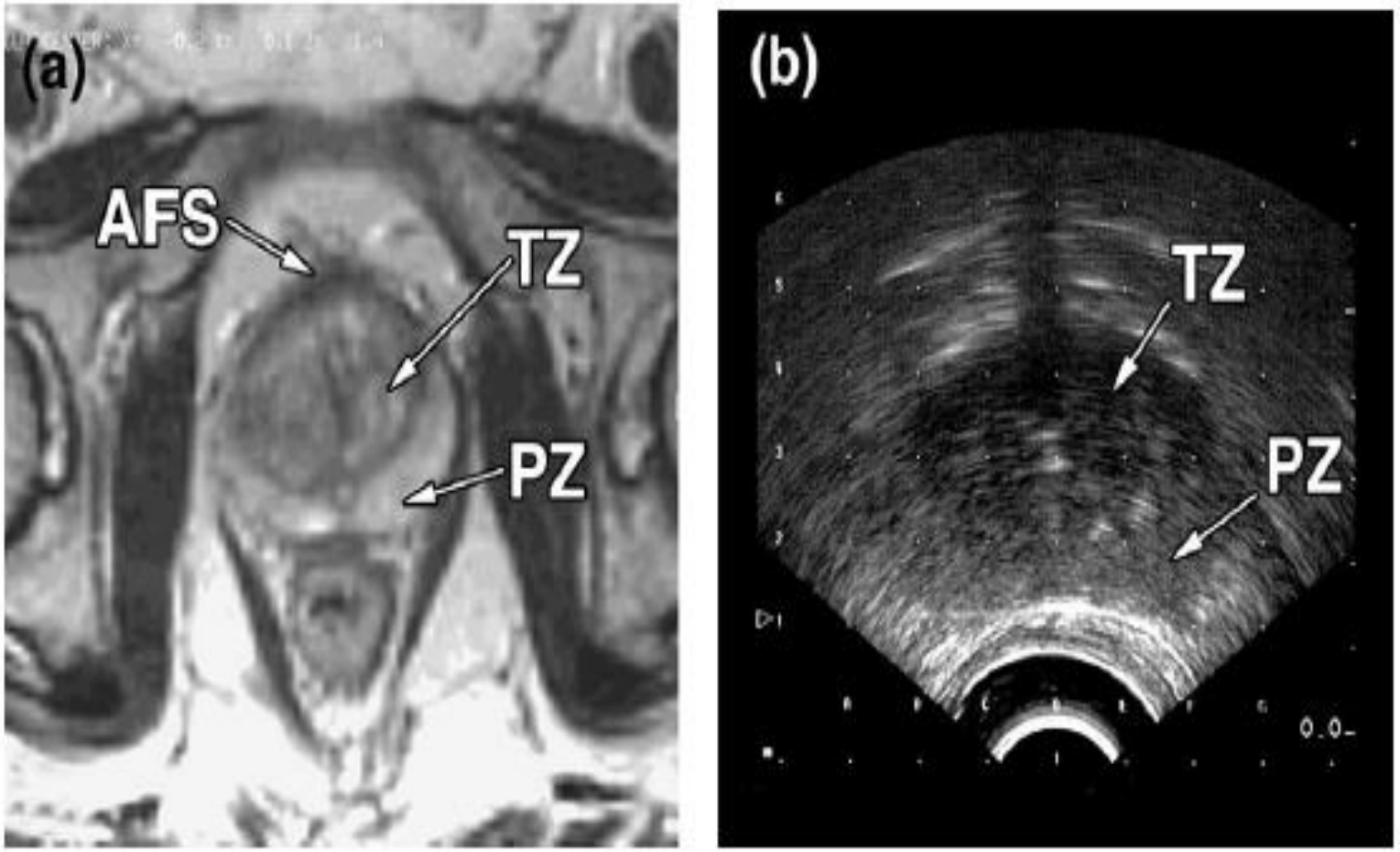


Fig. 2. Zonal anatomy of the prostate. Transition zone and peripheral zone on (a) T2 magnetic resonance imaging and (b) ultrasound. AFS = anterior fibromuscular stroma; PZ = peripheral zone; TZ = transition zone.

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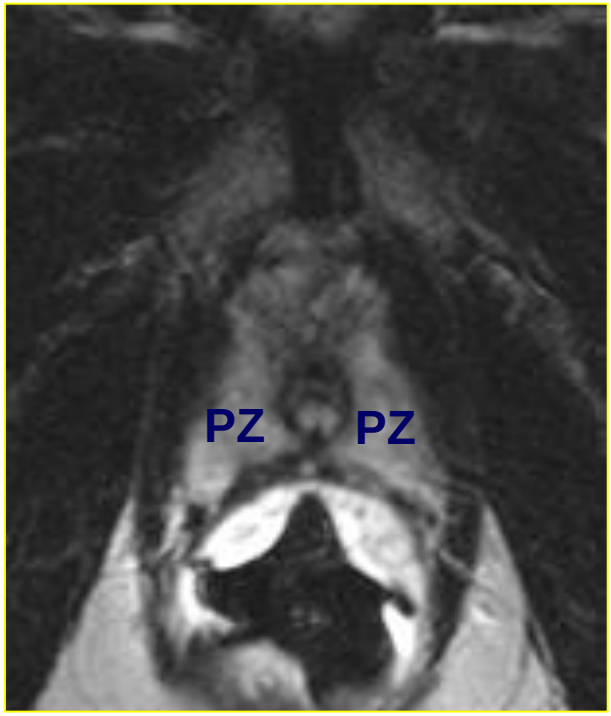
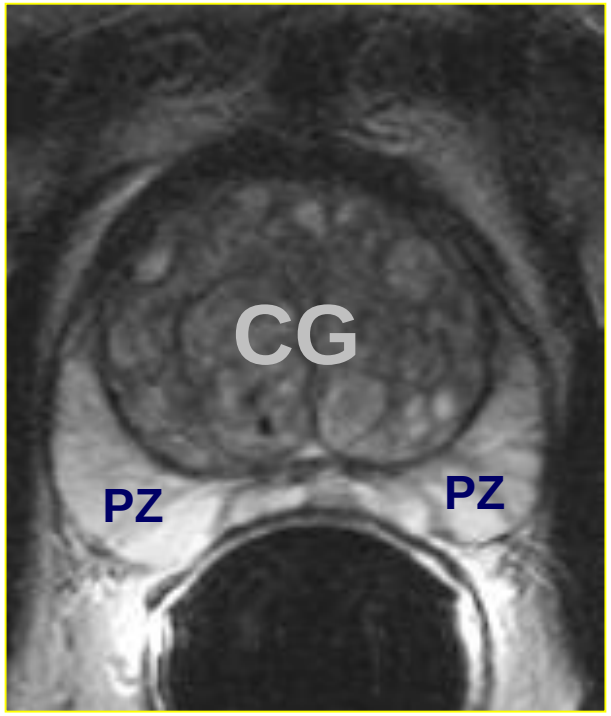
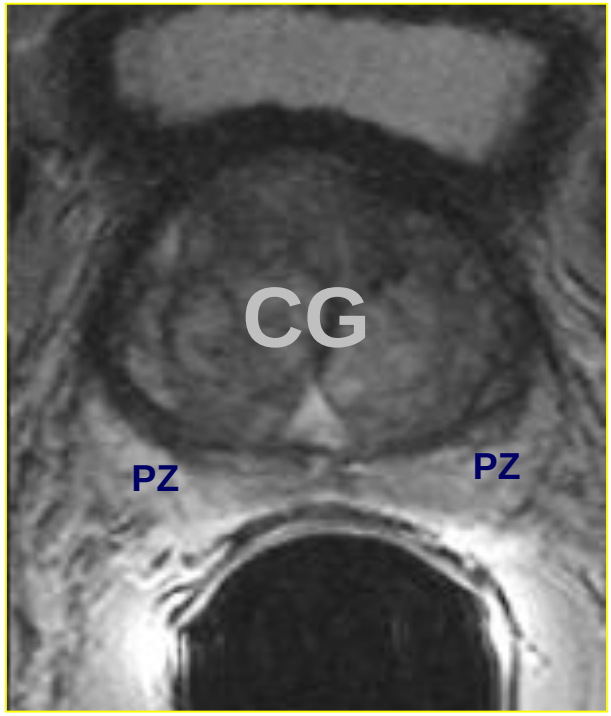
Anatomy
Prostate



Prostatic Apex



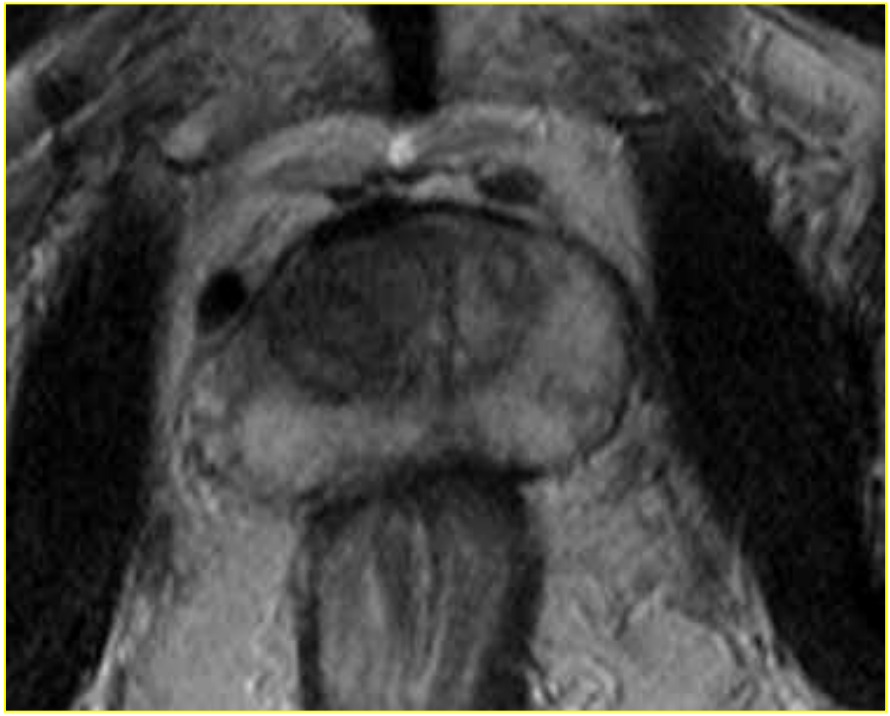
Midprostate



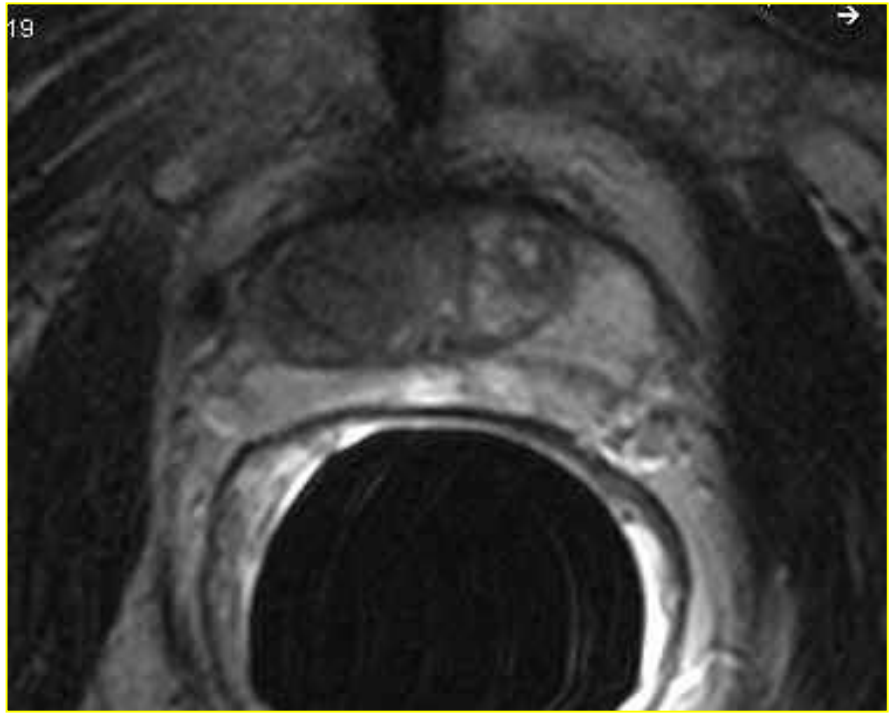
Prostatic Base

ESTRO School

Imaging of Prostate Cancer
Body coil versus Endorectal coil



Normal Prostate with Body Coil



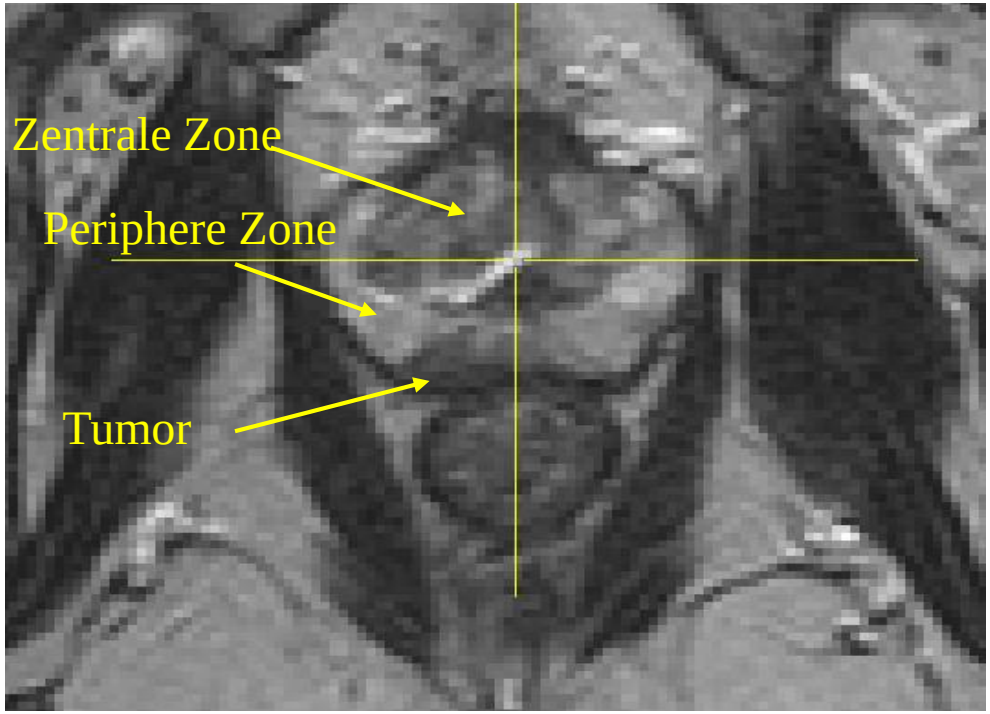
Normal Prostate with Endorectal Coil

ESTRO School

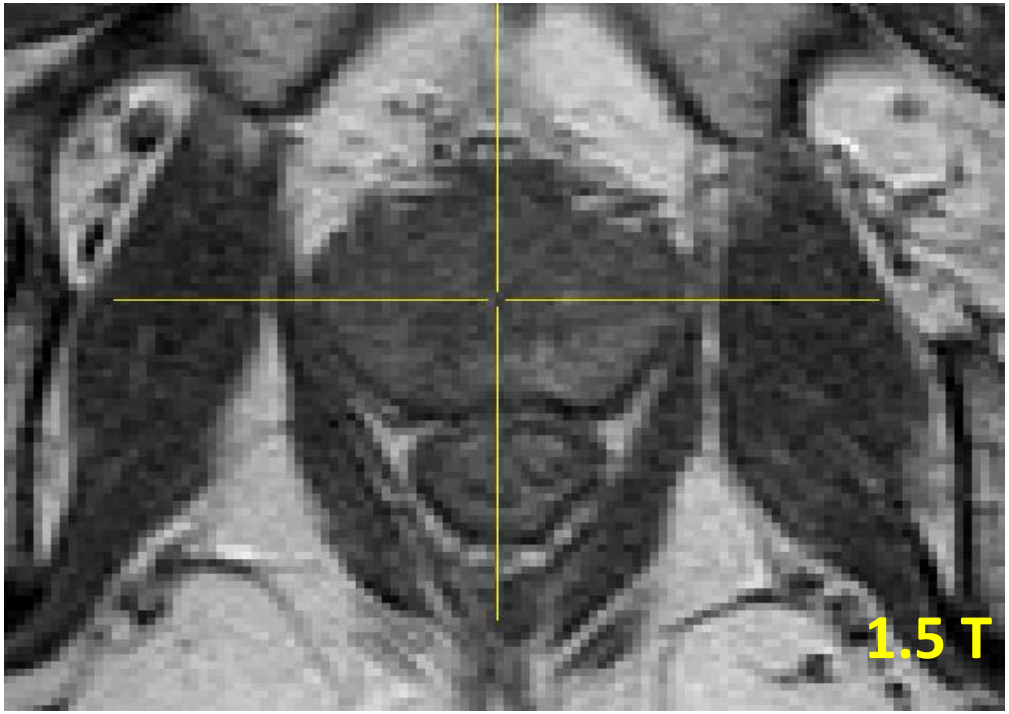
1.5 Tesla MRI

MRI:

- **Resolution: good**
- **Contrast: good, especially soft tissue contrast**

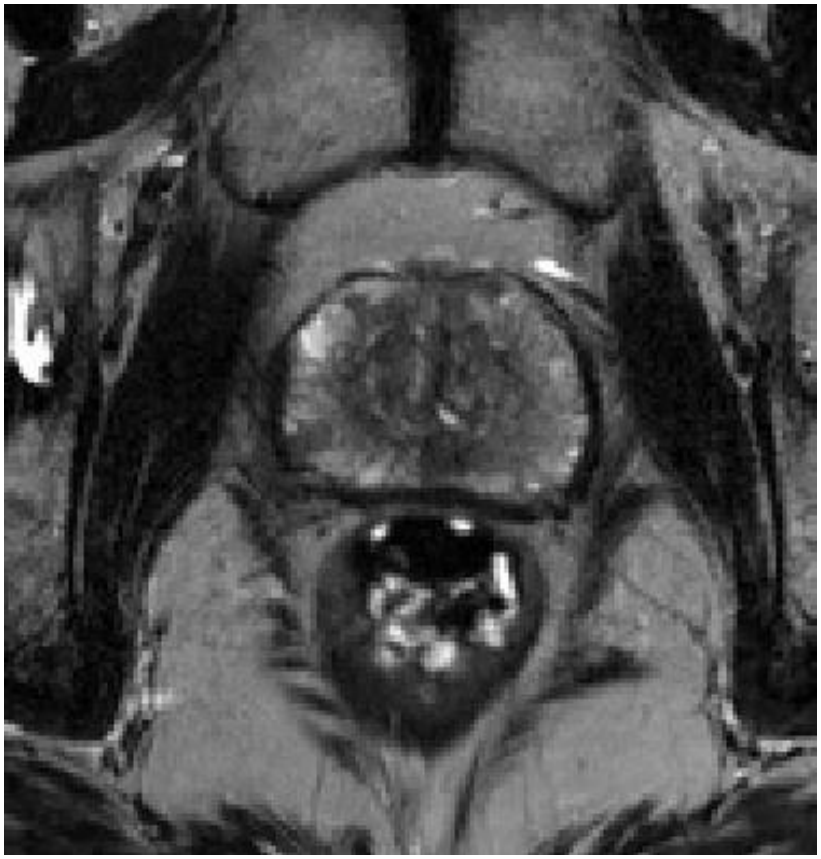


T2-weigthed

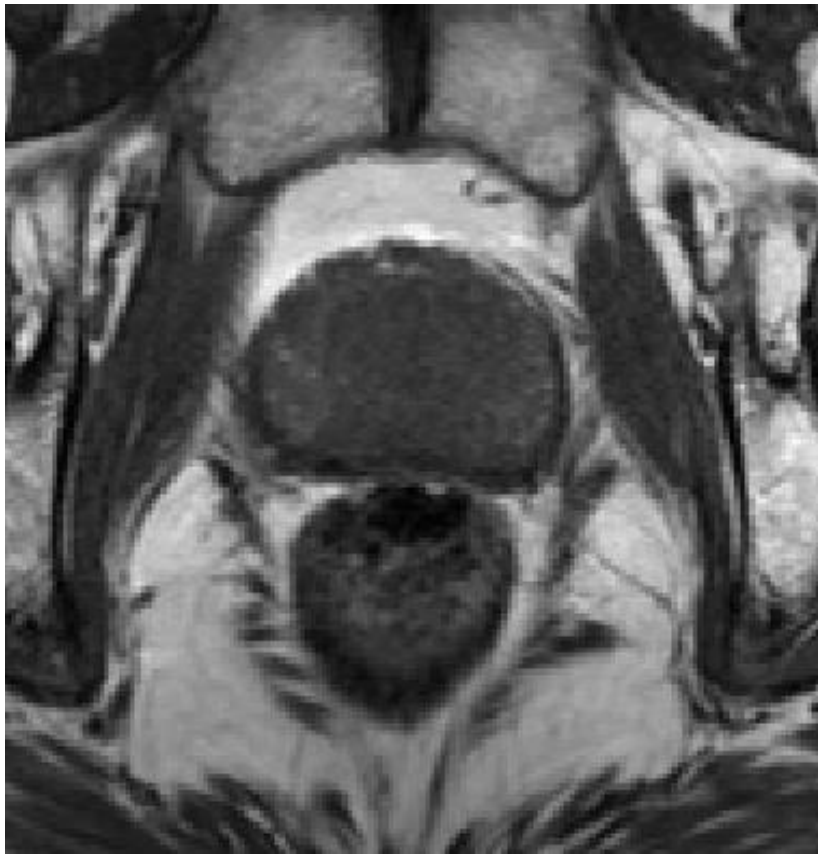


T1-weighted

3.0 Tesla MRI

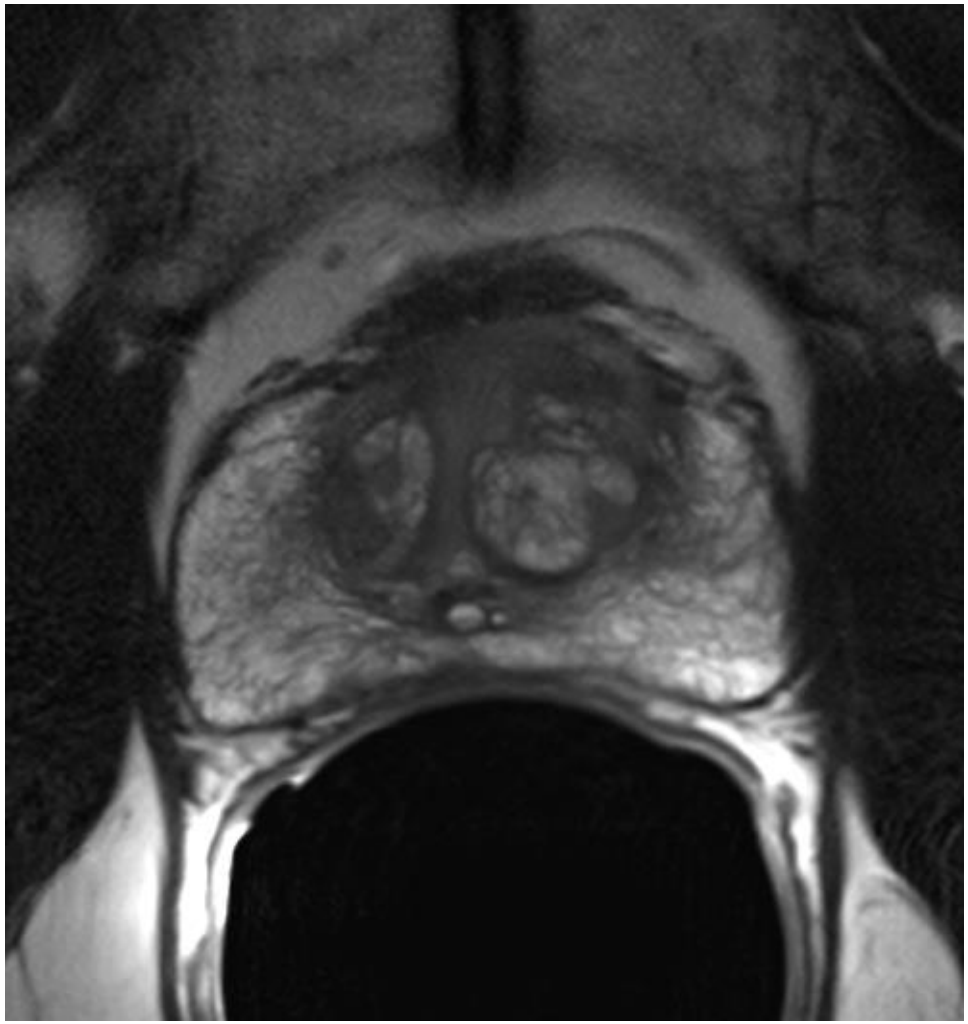


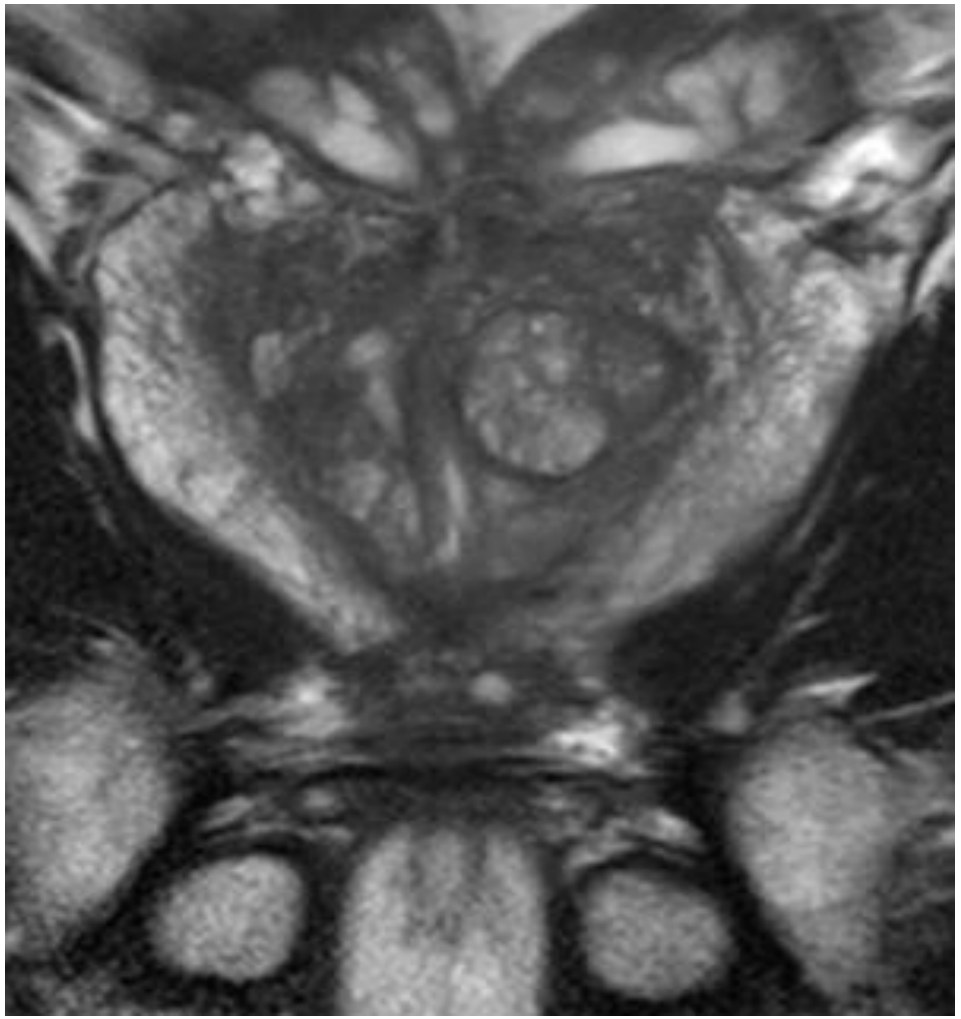
T2 -weighted



T1 weighted

3.0 Tesla MRI + Endorectal coil





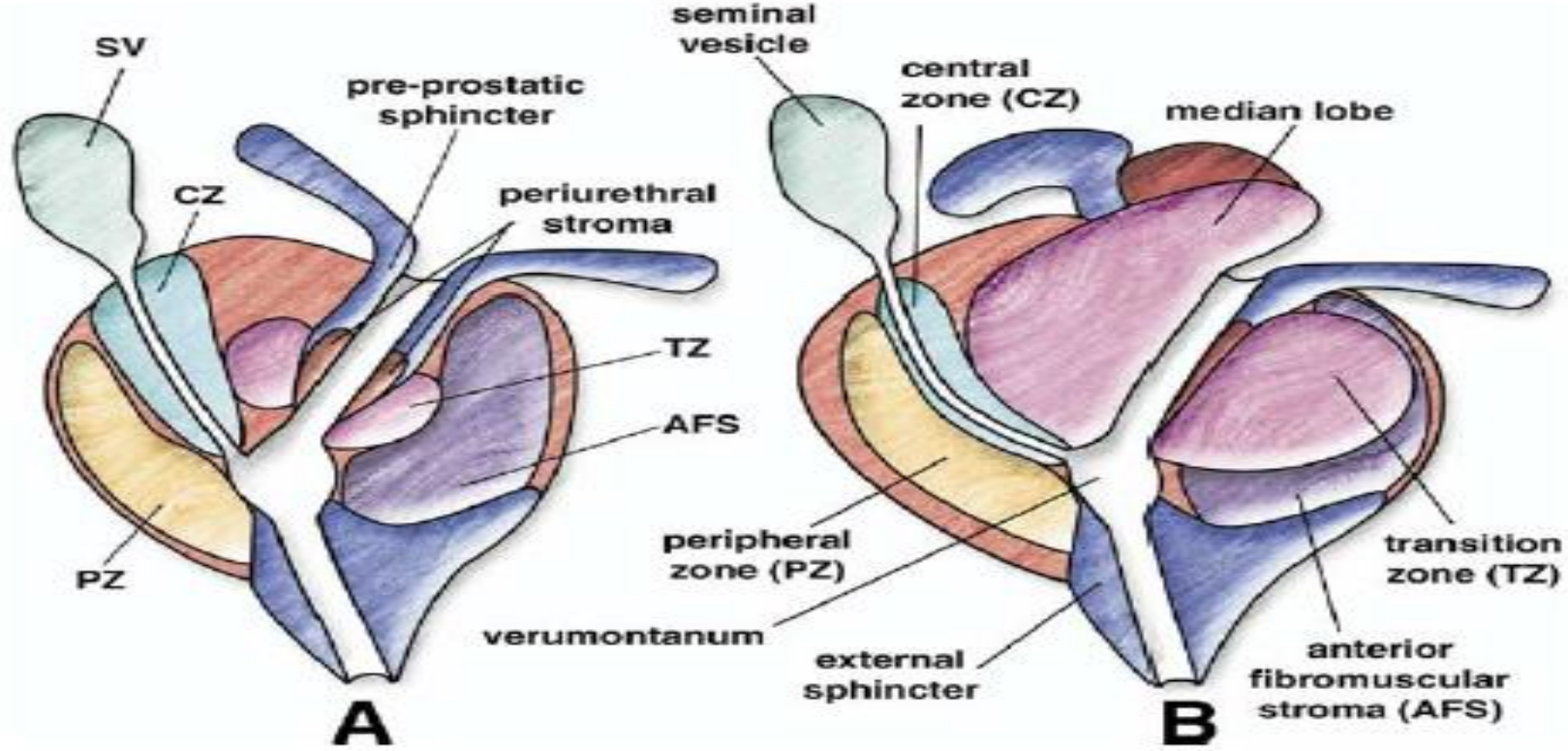
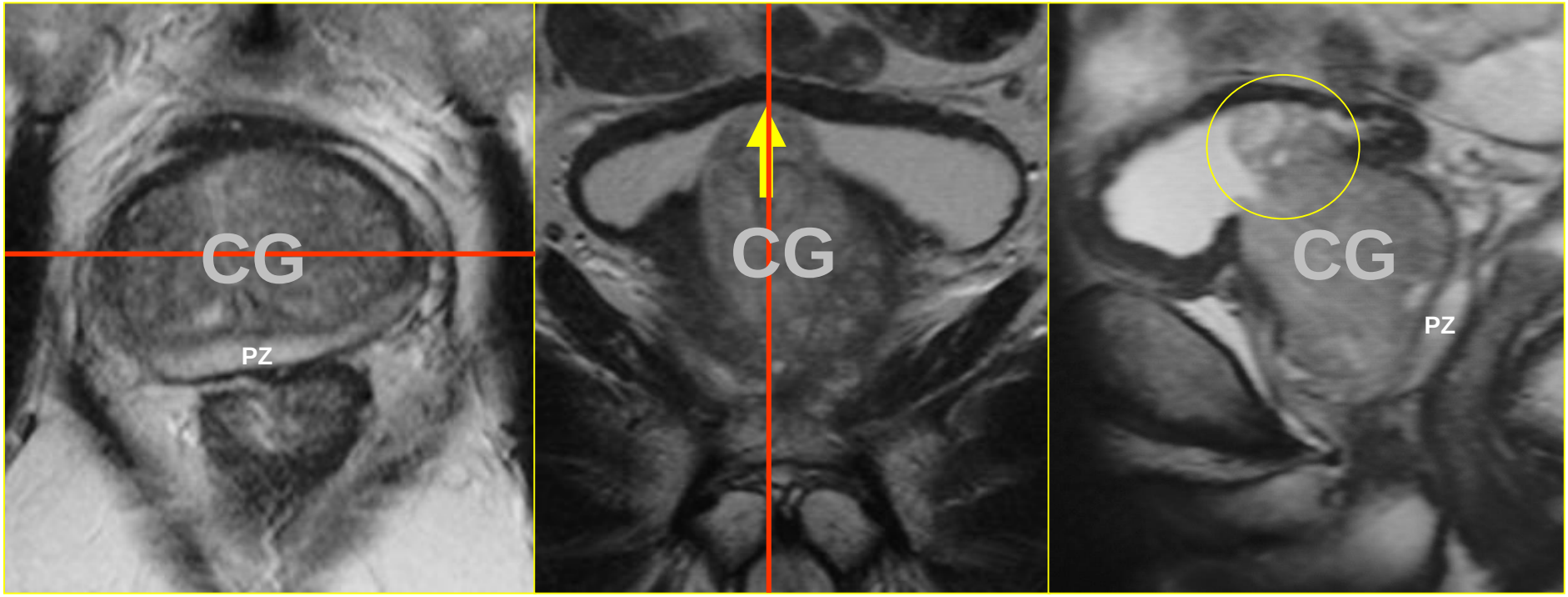


Fig. 1. Zonal anatomy of the prostate. (A) Young male with minimal transition zone hypertrophy. Note preprostatic sphincter and peri-ejaculatory duct zone (central zone of McLean) are clearly defined. (B) Older male with transition zone hypertrophy, which effaces the preprostatic sphincter and compresses the peri-ejaculatory duct zone. AFS = anterior fibromuscular stroma; CZ = central zone; PZ = peripheral zone; SV = seminal vesicle; TZ = transition zone.

Anatomy
Hyperplasia



Benign Prostatic Hyperplasia

ESTRO School

Variation of bladder neck according to BPH

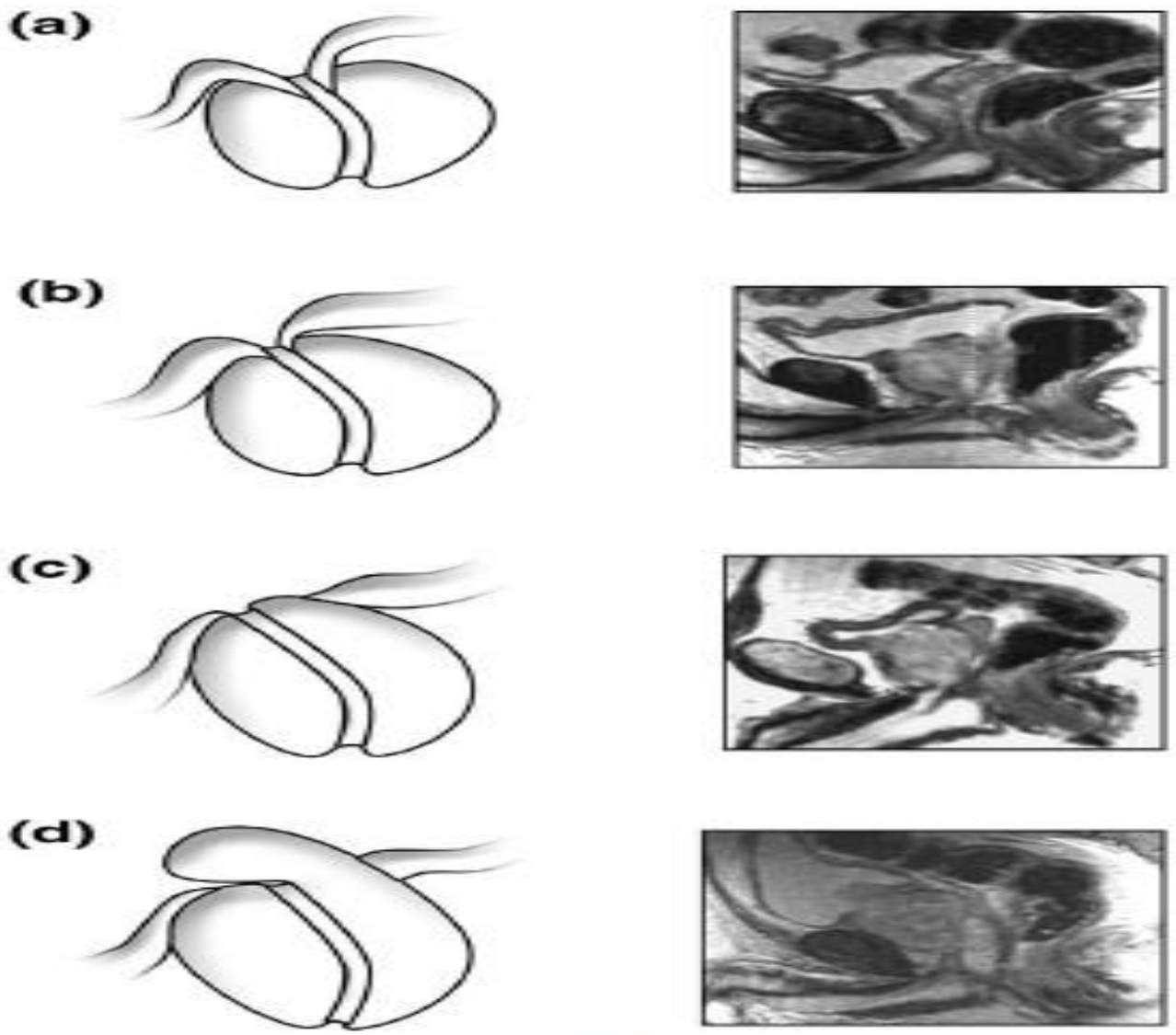


Fig. 4. Change in base anatomy with transition zone (TZ) enlargement. (a) A distinct bladder neck is apparent. With progressive TZ enlargement, the bladder neck is effaced by TZ enlargement (b, c). The most extreme change is median lobe enlargement (d) with associated ball valve obstruction.

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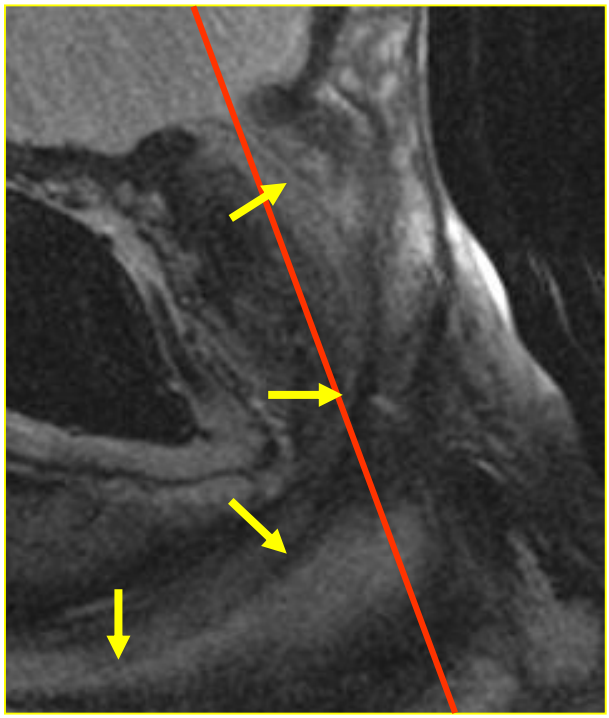
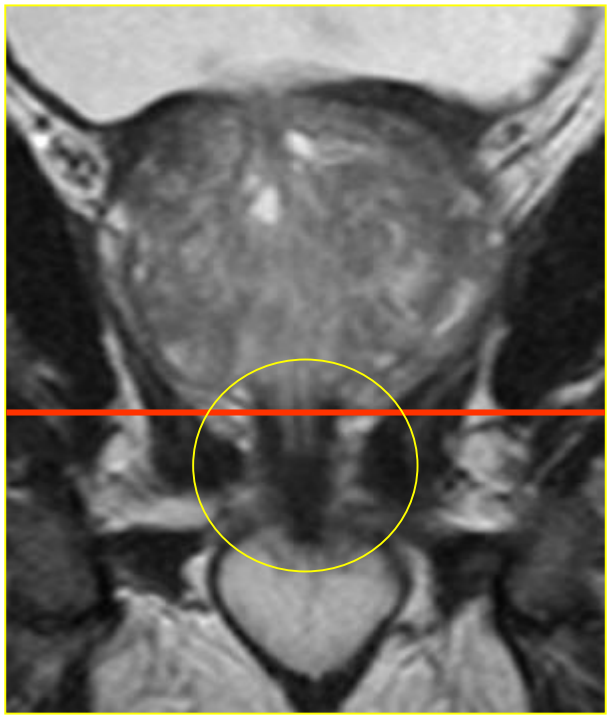
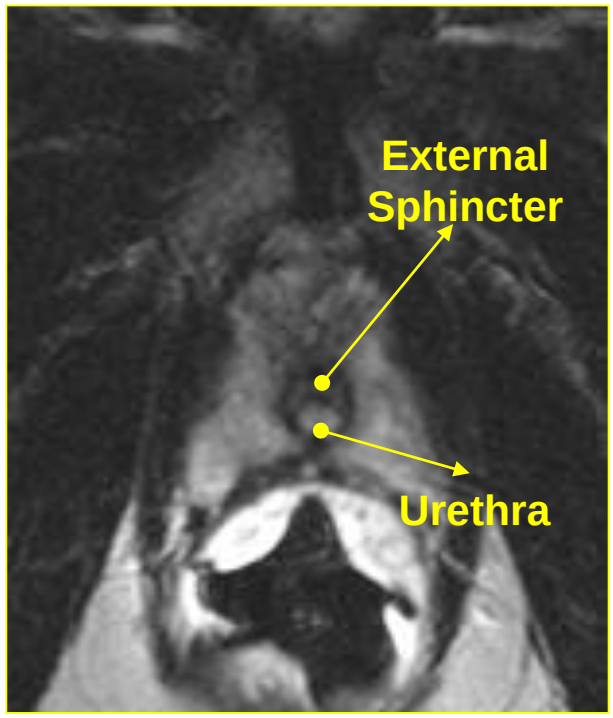
Anatomy
Urethra



Sagittal



Coronal

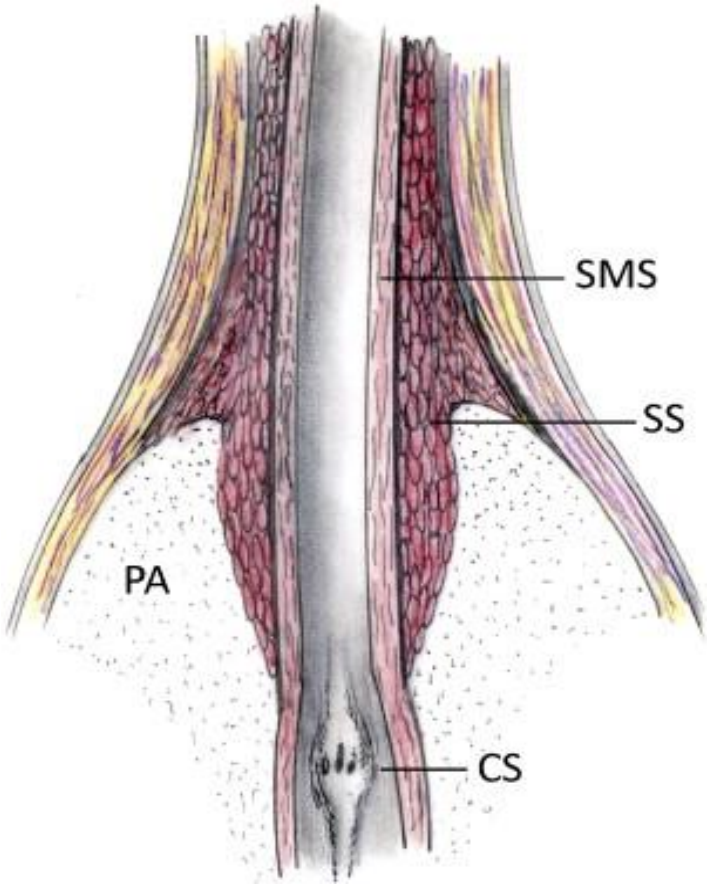


Transverse

Platinum Slide Series

EUROPEAN UROLOGY
A CUT ABOVE THE REST

Transversal section of the prostatic apex. A considerable part of the urethral sphincter is located intraprostatically between the prostatic apex and the colliculus seminalis.SMS = smooth muscle sphincter; SS = striated sphincter (rhabdosphincter); CS = colliculus seminalis; PA = prostatic apex.



ESTRO School

Thorsten Schlomm et al. Eur Urol 2011;2:320-329

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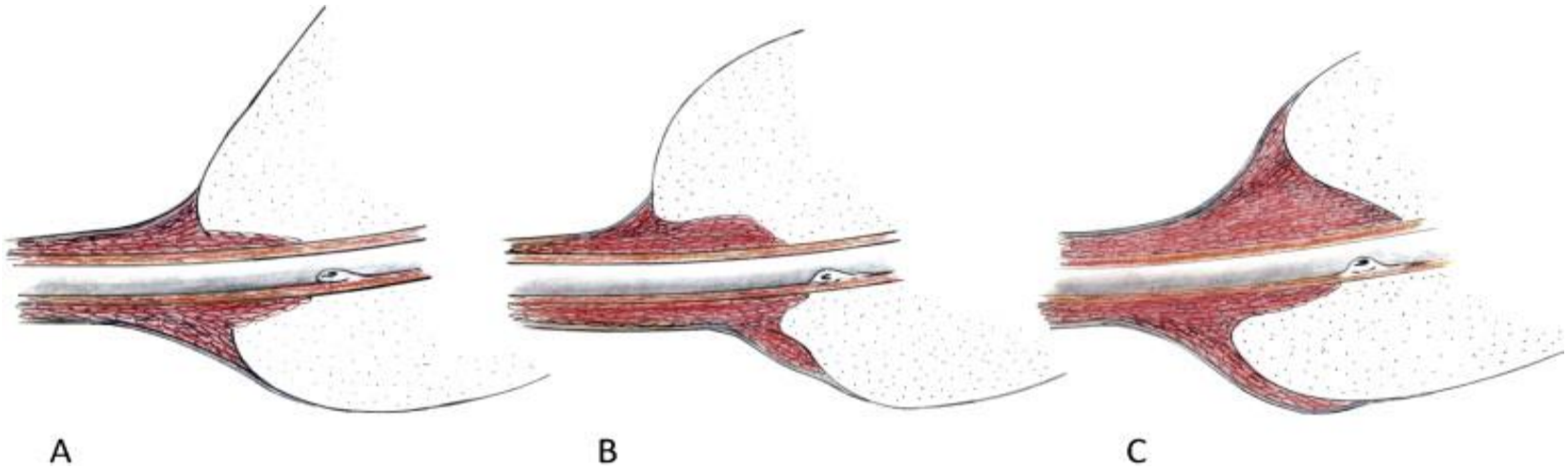
EUROPEAN UROLOGY
A CUT ABOVE THE REST

Anatomic variability of the prostatic apex. Depending on the individual apex shape, between 10% and 40% of the functional urethra is covered by parenchymal apex tissue. Otherwise, the prostatic apex is covered by some muscular tissue on the ventral and rectal aspects as rudiments of embryonic and adolescent prostatic development.



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Thorsten Schlomm et al. Eur Urol 2011;2:320-329

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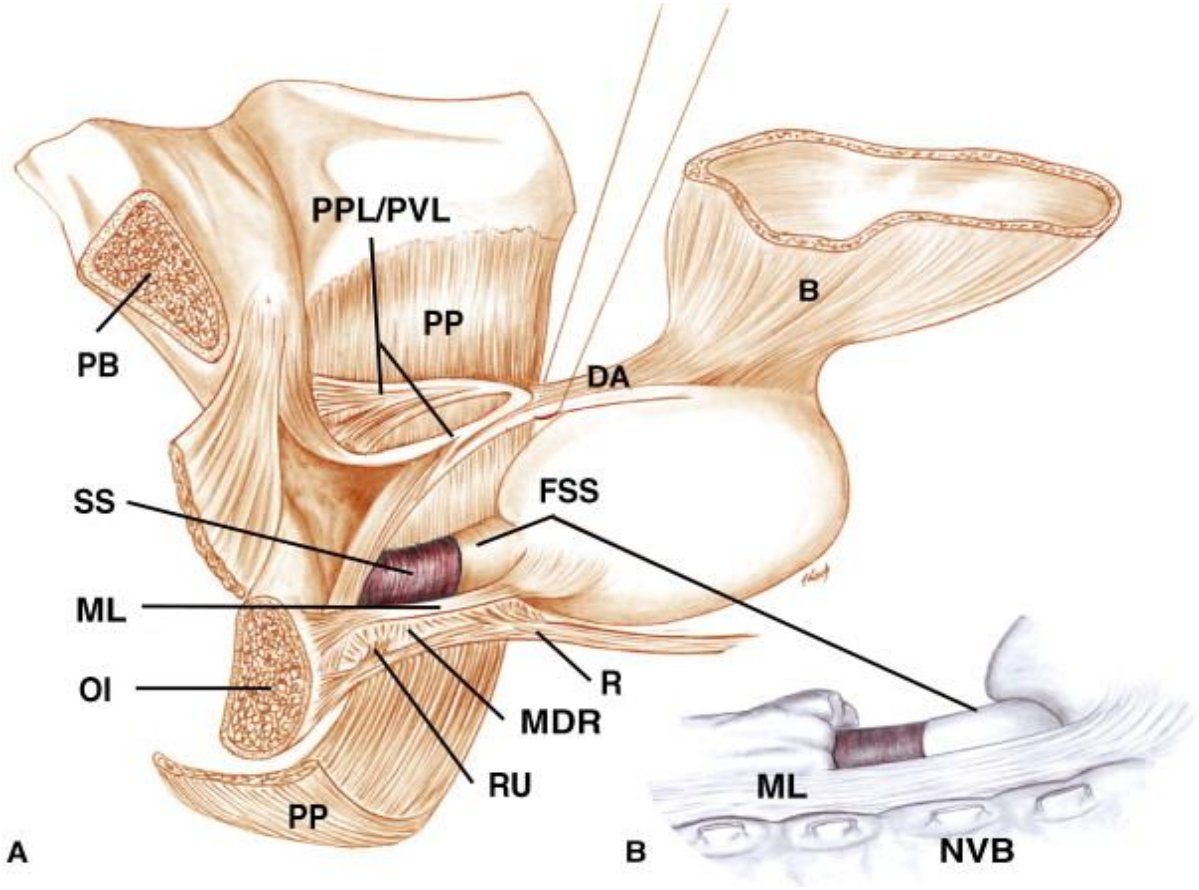
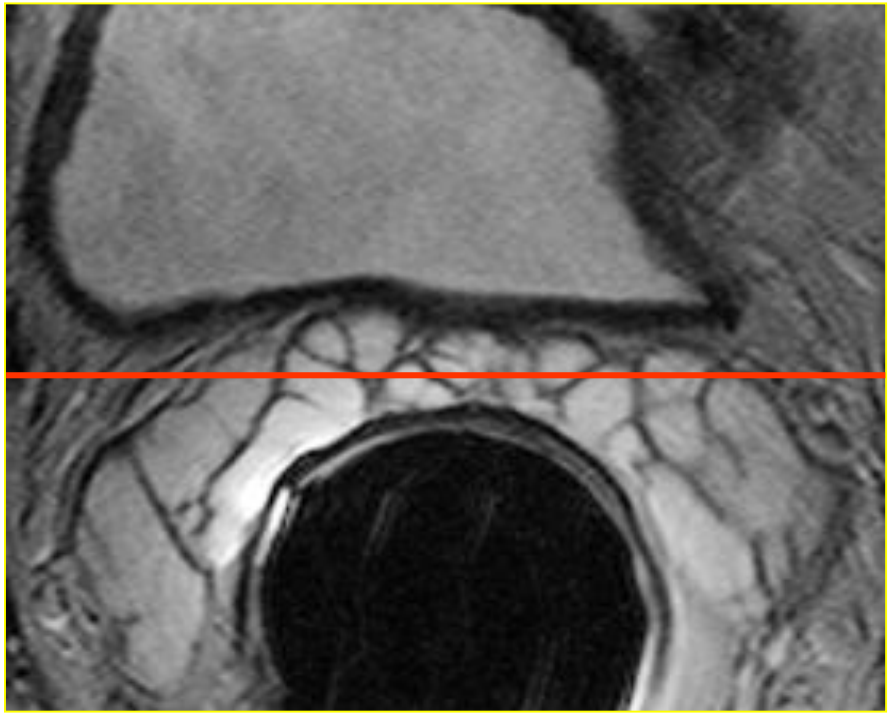
EUROPEAN UROLOGY
A CUT ABOVE THE REST

Surgical anatomy of the urethral sphincter complex. (A) Fixation of the urethral sphincter (modified from Luschka [16]). (B) Lateral aspect of the urethral sphincter after nerve sparing.PPL = puboprostatic ligament; PVL = pubovesicalis ligament; PP = puboperinealis muscle; DA = detrusor apron; B = bladder; FSS = fascia of the striated sphincter; ML = Mueller's ligaments (ischioprostatic ligaments); NVB = neurovascular bundle; R = rectum; MDR = medial dorsal raphe; RU = rectourethralis muscle; OI = Os ischiadicum; SS = striated sphincter (rhabdosphincter); PB = pubis bone.

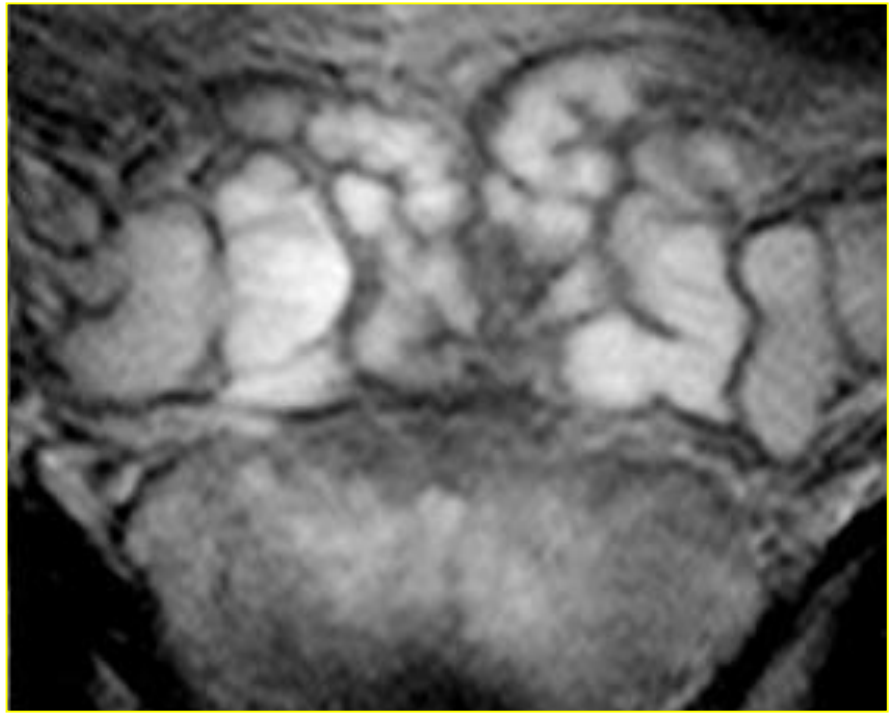


Thorsten Schlomm et al. Eur Urol 2011;2:320-329

Anatomy
Seminal Vesicles



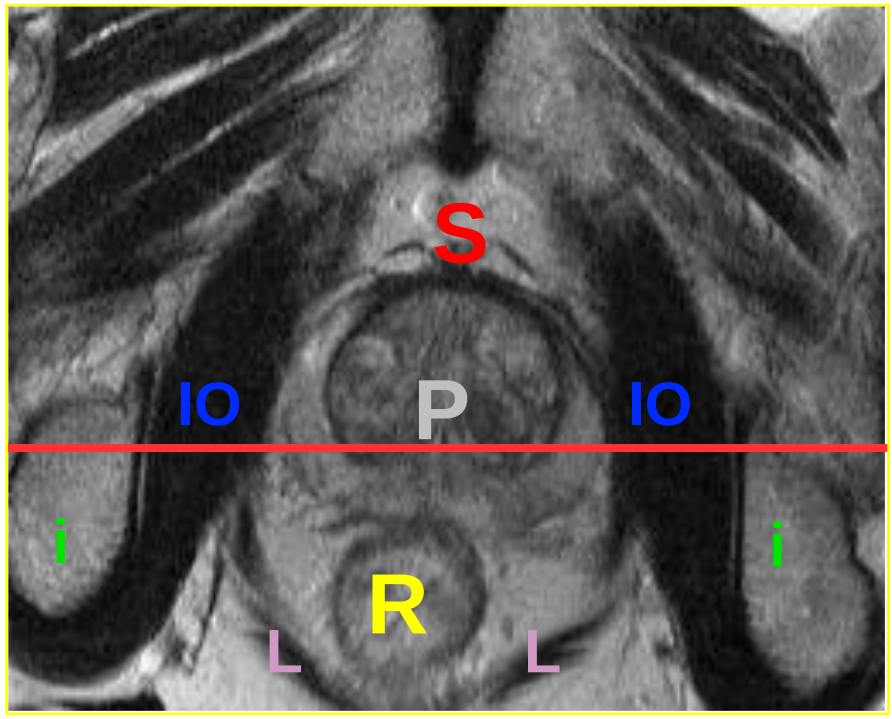
Transverse



Coronal

ESTRO School

Anatomy
Periprostatic Structures



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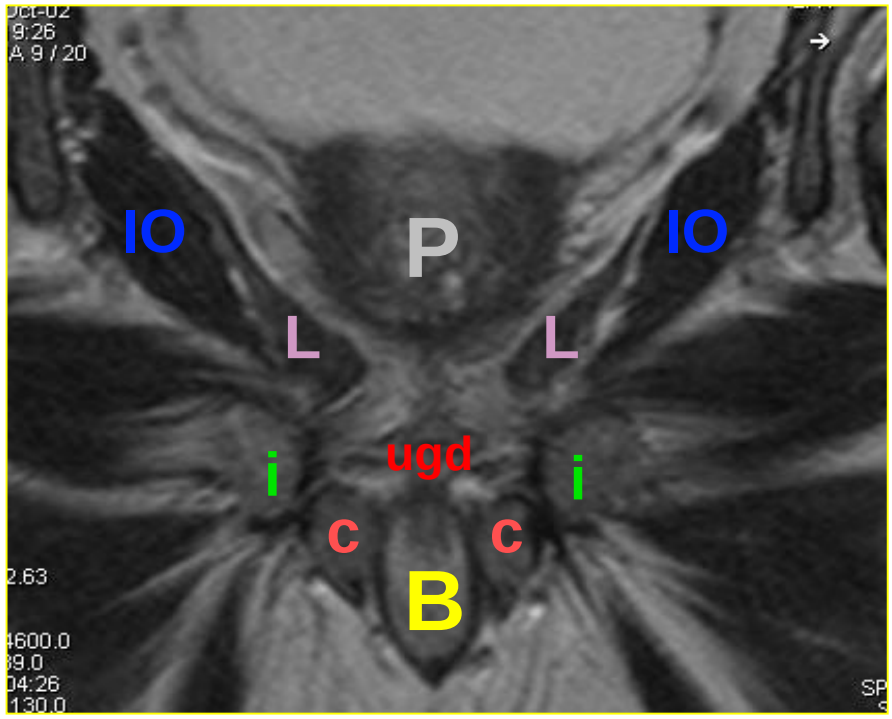

Coronal

Variation in Genitourinary diaphragm

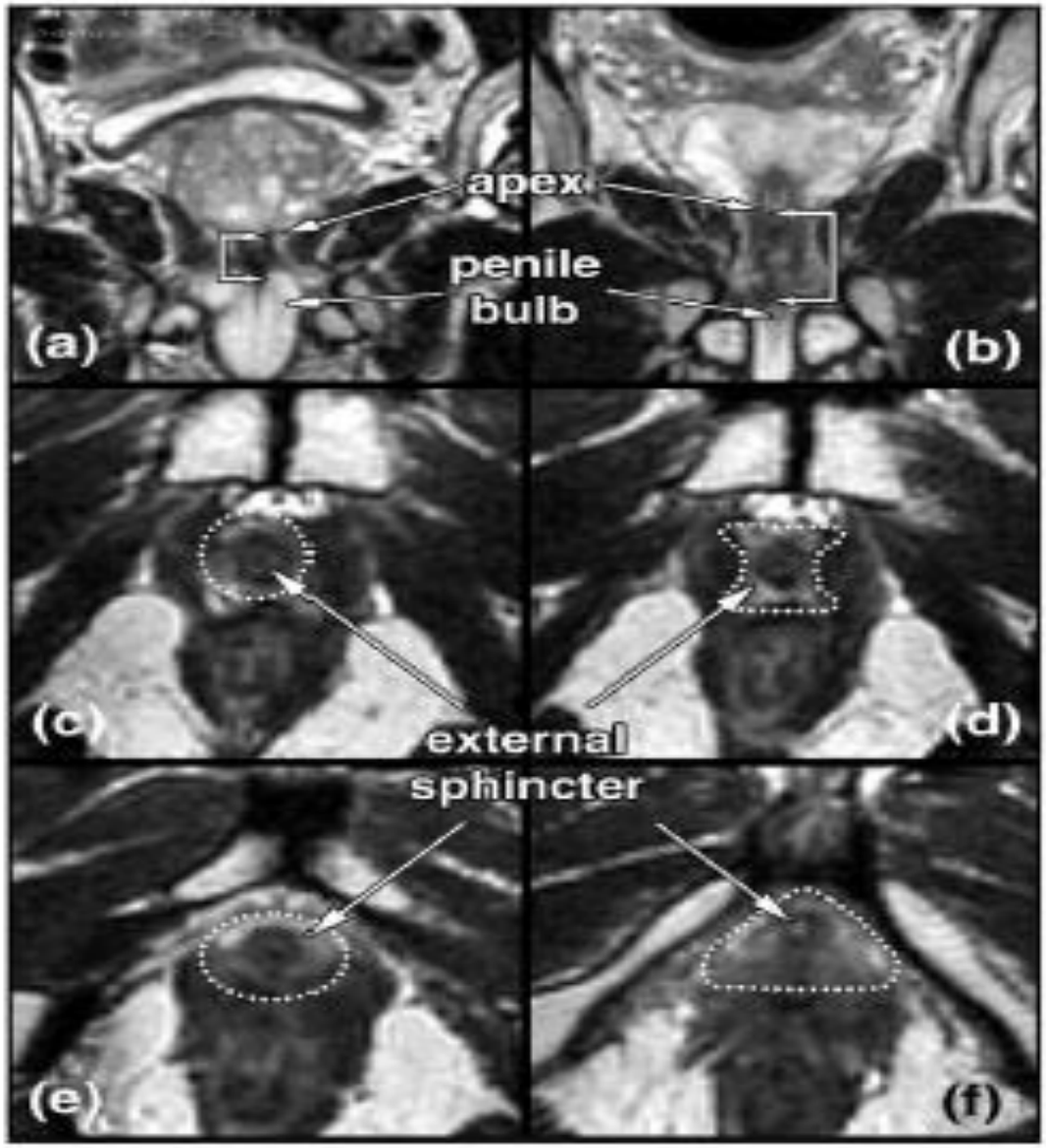

Fig. 5. Genitourinary diaphragm. Variation in thickness of the genitourinary diaphragm (GUD) (a, b). Levels of GUD from apex to penile bulb (c–f).

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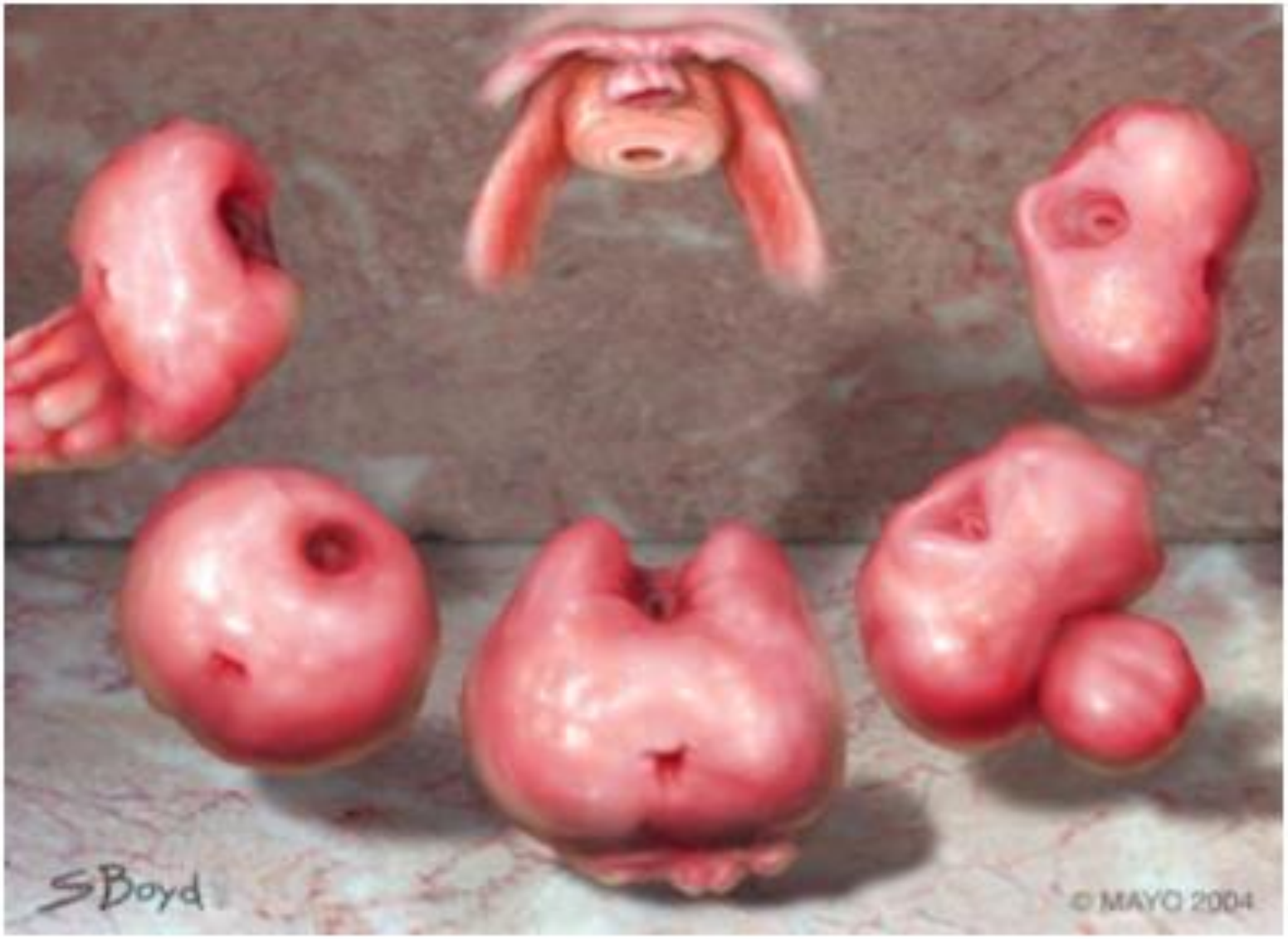
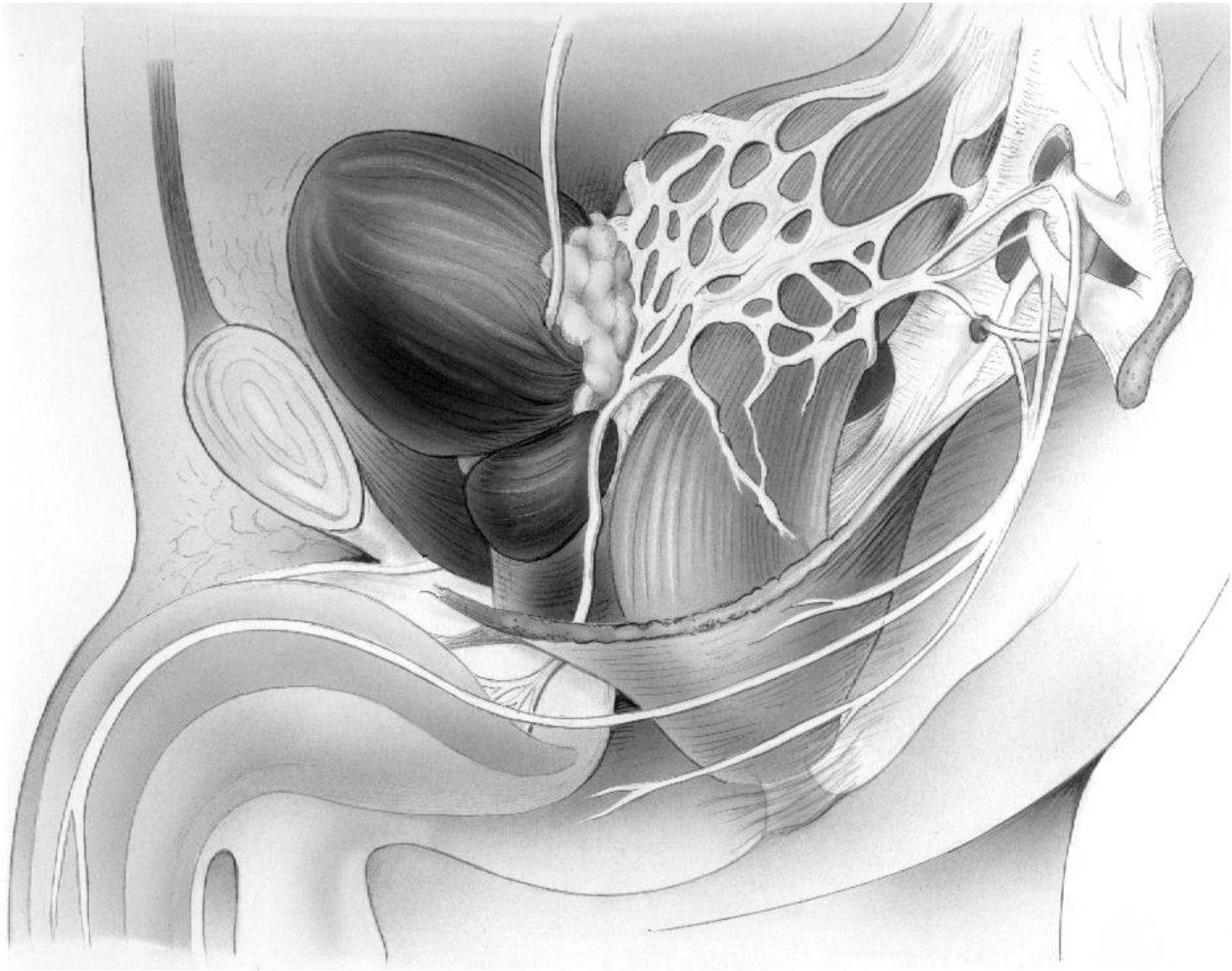
Apex: Anatomische Variabilität



Walz et al, Eur Urol, 2010

Parasympathic nerves



Course of neurovascular bundle

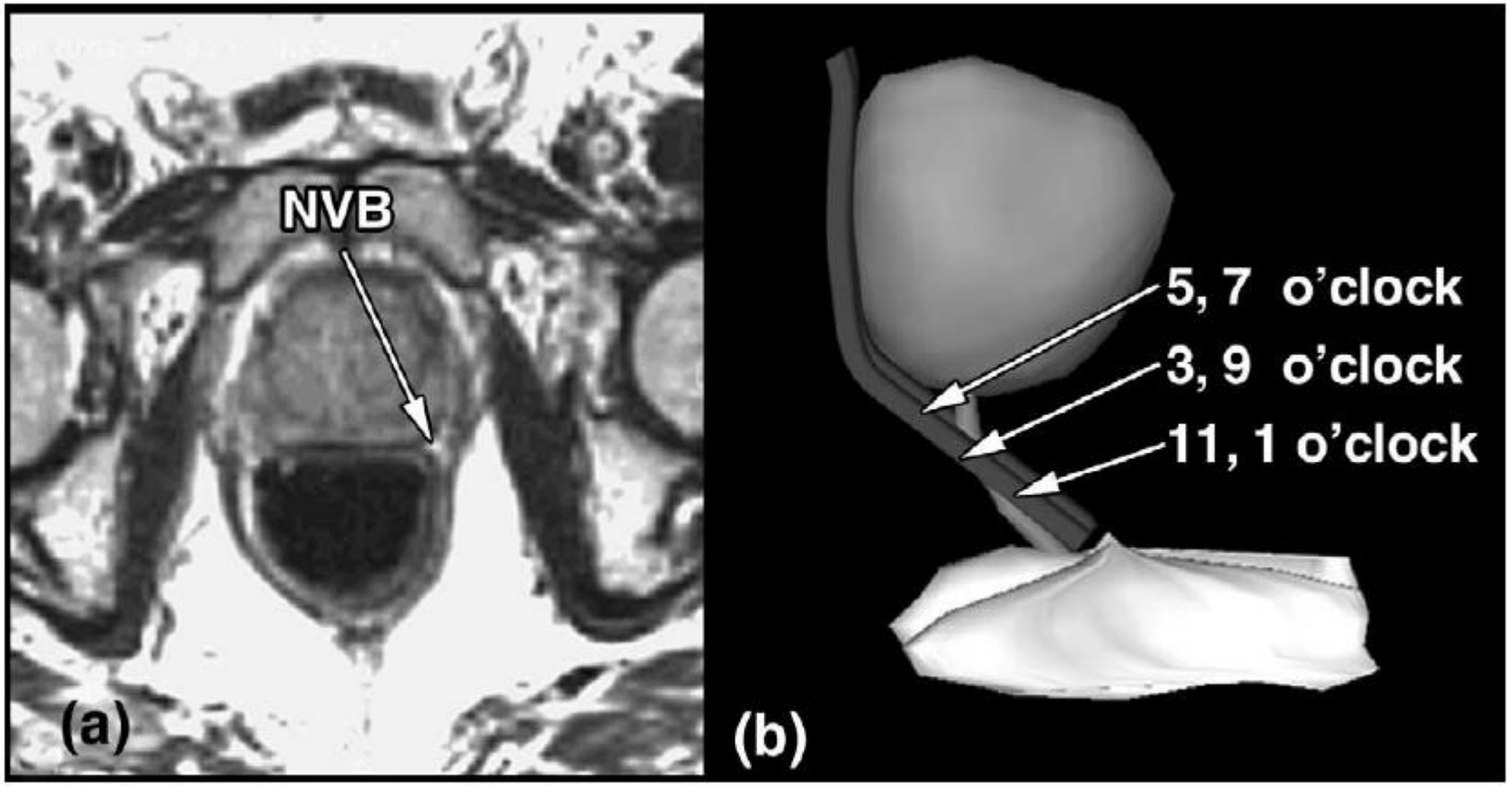


Fig. 7. Neurovascular bundle (NVB) and terminal branches. (a) Axial magnetic resonance imaging. (b) Three-dimensional reconstruction with cavernosal nerve defined by relationship to membranous urethra.

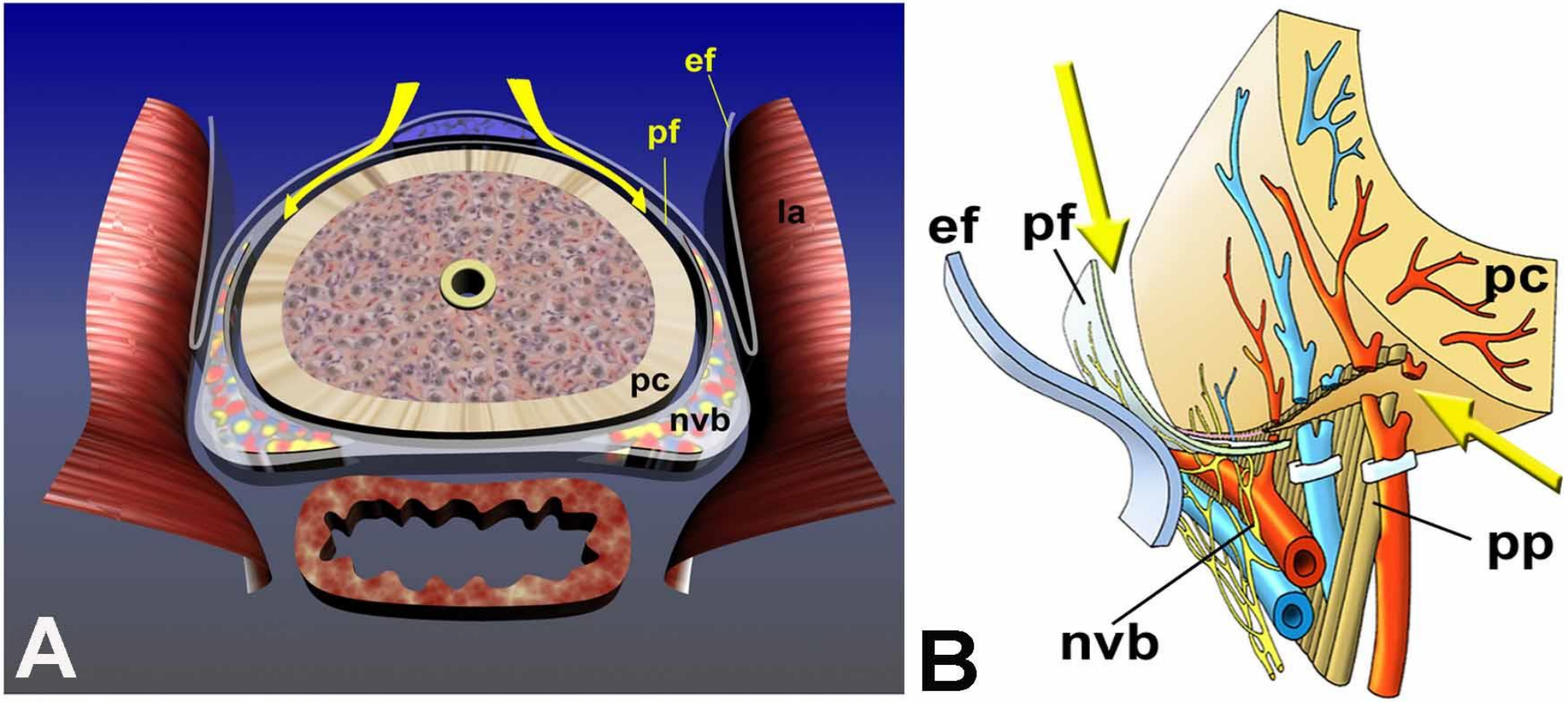
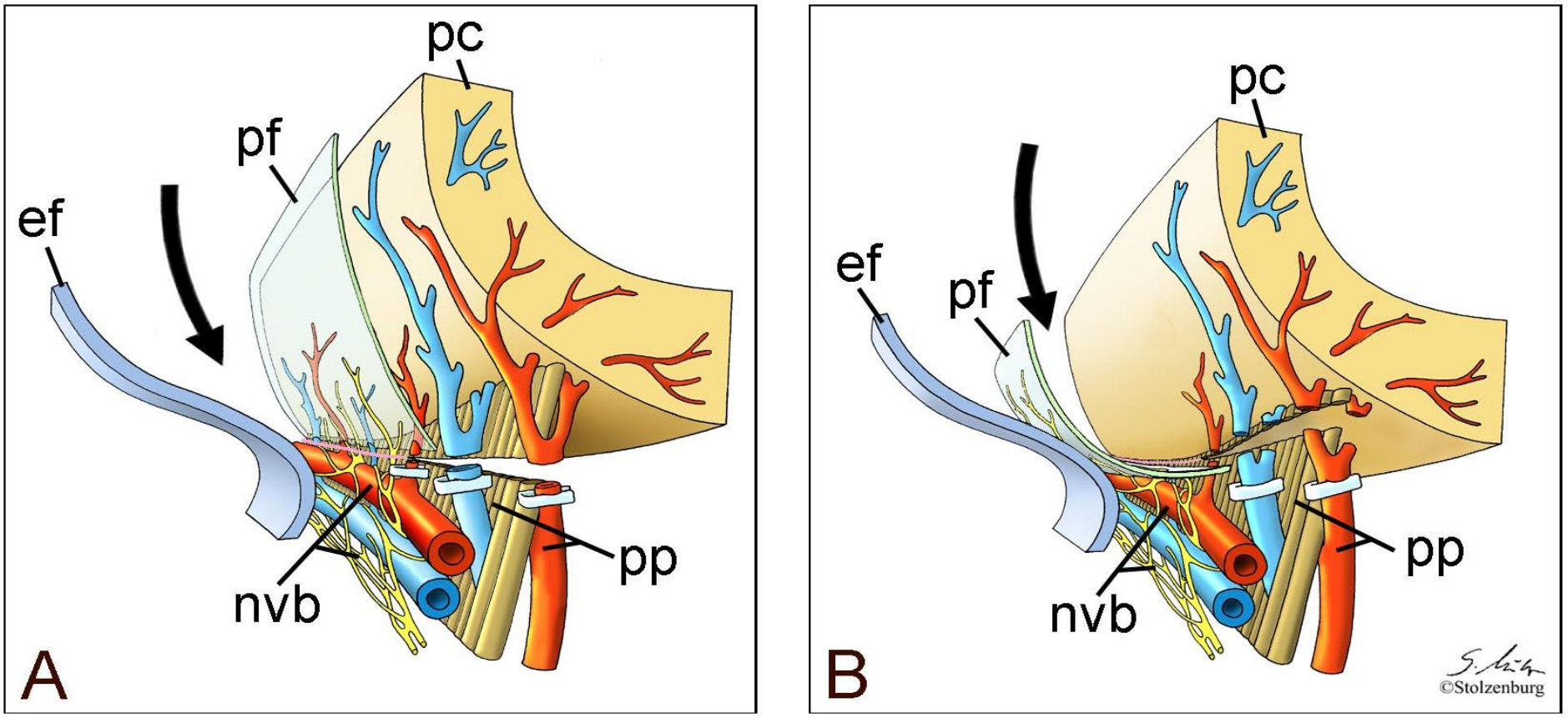


Abb.: 5

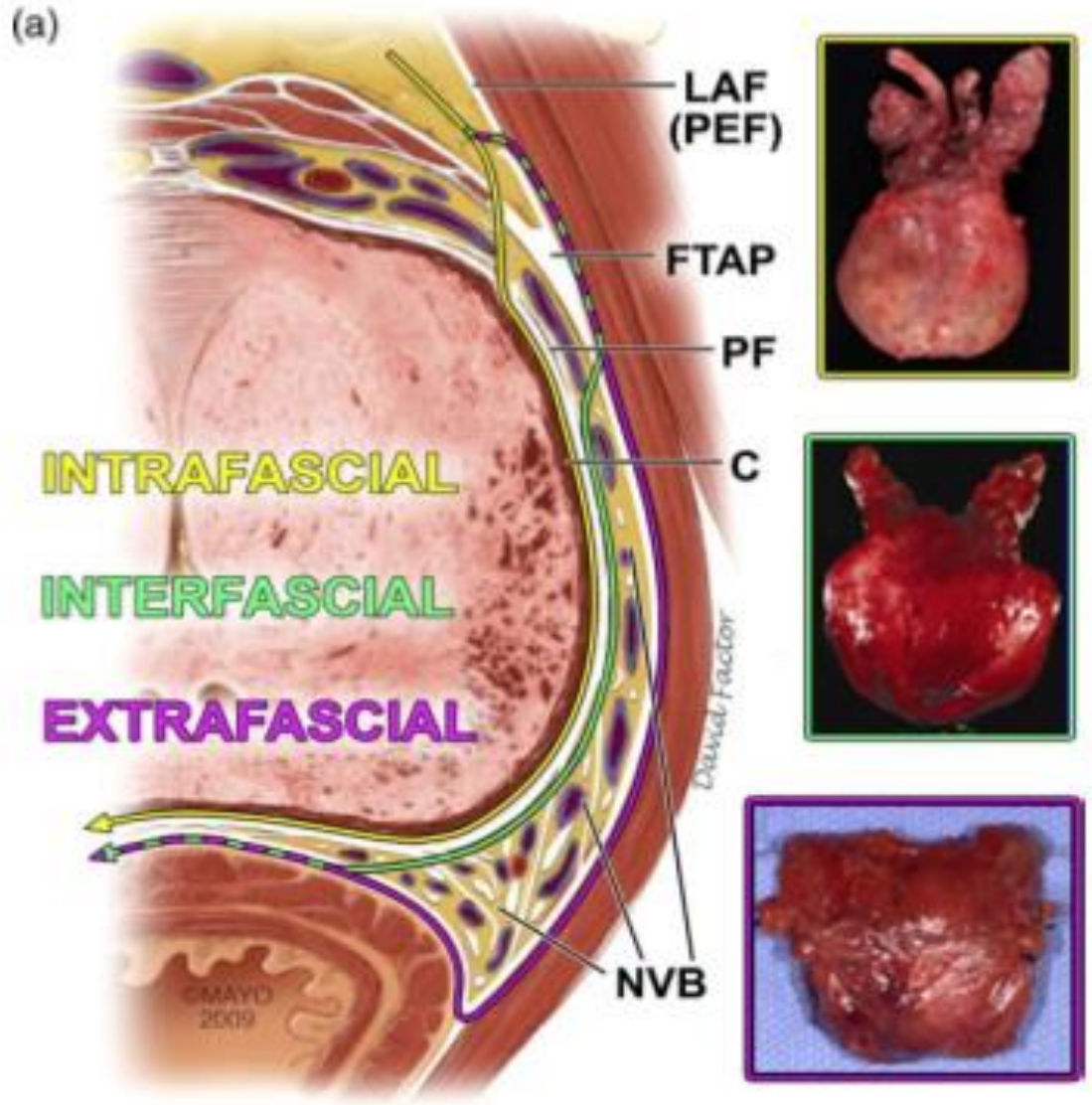
Stolzenburg et al, Eur Urol, 2007



Standardtechnik intrafasziale Technik

Abb.: 6

Stolzenburg et al, Eur Urol, 2007



Walz et al, Eur Urol, 2010

Prostate Brachytherapy Course

"Selection of patients for prostate cancer permanent implant brachytherapy"

C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

EUROPE EUROPA
2 Alice St-Michel St-Elisabeth
Cliniques - Ziekenhuizen

Patient selection:

- do we have recommendations ?
- if yes, what do they learn us ?

BRIEF HISTORY

- The initial ABS recommendations (1999)
- The ESTRO recommendations (2000)

- The 2012 ABS recommendations

- Int. J. Radiation Oncology Biol. Phys., Vol. 44, No. 4, pp. 789–799, 1999

- **AMERICAN BRACHYTHERAPY SOCIETY (ABS) RECOMMENDATIONS FOR TRANSPERINEAL PERMANENT BRACHYTHERAPY OF PROSTATE CANCER**

- *SUBIR NAG, M.D.,*† DAVID BEYER, M.D.,*‡ JAY FRIEDLAND, M.D.,* § PETER GRIMM, D.O.,*\ AND RAVINDER NATH, PH.D.*¶*

1999 AMERICAN BRACHYTHERAPY SOCIETY (ABS) RECOMMENDATIONS FOR TRANSPERINEAL PERMANENT BRACHYTHERAPY OF PROSTATE CANCER

- **Brachytherapy as Monotherapy:**
- Stage T1 to T2a and
- Grade Gleason sum 2–6 and
- PSA < 10 ng/ml
- *(i.e , Low-risk patients)*

1999 AMERICAN BRACHYTHERAPY SOCIETY (ABS) RECOMMENDATIONS FOR TRANSPERINEAL PERMANENT BRACHYTHERAPY OF PROSTATE CANCER

- **Clinical Exclusion Criteria:**
- Life expectancy < 5 years
- Large or poorly healed TURP defect
- Unacceptable operative risks
- Distant metastases

- **Relative Contraindications for Brachytherapy (1) :**
- *These patients are not ideal candidates for brachytherapy, but have nevertheless been successfully implanted. Beginners should not implant these patients.*
- Patients at increased risk of developing complications
- Large median lobes
- Previous pelvic irradiation
- High AUA score
- History of multiple pelvic surgeries
- Severe diabetes with healing problems

- **Relative Contraindications for Brachytherapy (2) :**
- *Technical difficulties which may result in inadequate dose coverage*
- Previous *(large ?)* transurethral resection of prostate (TURP)
- Gland size > 60 cc at time of implantation
- Prominent median lobe
- Positive seminal vesicles

- **Brachytherapy as a Boost to EBRT:**
- Stage Clinical T2b, T2c *or*
- Grade: Gleason sum 8–10 *or*
- PSA > 20 ng/ml
- **Other possible indications for Brachytherapy as a Boost to EBRT:**
- Perineural invasion
- Multiple positive biopsies
- Bilateral positive biopsies
- MRI positive for capsular penetration

The ESTRO recommendations

ELSEVIER

Radiotherapy and Oncology 57 (2000) 315–321

RADIOTHERAPY & ONCOLOGY
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ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer

Daniel Ash[a,*], Anthony Flynn[a], Jan Battermann[b], Theodorous de Reijke[c], Paulo Lavagnini[d], Leo Blank[e]

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[b]*Department of Radiotherapy, Academisch Ziekenhuis, Utrecht, Germany*
[c]*Department of Urology, Academisch Medisch Centrum, Amsterdam, The Netherlands*
[d]*Instituto Tumori, Genoa, Italy*
[e]*Department of Radiotherapy, Free University, Amsterdam, The Netherlands*

Received 18 September 2000; accepted 27 September 2000

Indication for prostate brachytherapy

	Recommended Do well	Optional Fair	Investigational Do poorly
PSA (ng/ml)	<10	10–20	>20
Gleason score	5–6	7	8–10
Stage	T1c–T2a	T2b–T2c	T3
IPSS	0–8	9–19	>20
Prostate volume (g)	<40	40–60	>60
Q_{max} ml/s	>15	15–10	<10
Residual volume cm^3			>200
TURP ±			+

Clinical exclusion criteria :

- **Life expectancy < 5 years**
- **Large or poorly healed TURP defect**
- **Unacceptable operative risks**
- **Bleeding disorder or anticoagulation that cannot be stopped**
- **Distant metastases**
- **Prostate volume greater than 50 cc (60 ?) at the time of implantation**

Relative contra-indications :

- **Large median lobes**
- **Previous pelvic irradiation**
- **High AUA score (IPSS > 15)**
- **History of multiple pelvic surgery**

ABS 1999

ESTRO 2000

Actually only minor differences with the ABS paper ...


12 YEARS OF SILENCE
a lot of literature
but
no new recommendations
until …. 2012

- **The 2012 ABS recommendations**

ELSEVIER

BRACHYTHERAPY

Brachytherapy 11 (2012) 6–19

American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy

Brian J. Davis[1,*], Eric M. Horwitz[2], W. Robert Lee[3], Juanita M. Crook[4], Richard G. Stock[5], Gregory S. Merrick[6], Wayne M. Butler[6], Peter D. Grimm[7], Nelson N. Stone[8], Louis Potters[9], Anthony L. Zietman[10], Michael J. Zelefsky[11]

[1]*Department of Radiation Oncology, Mayo Clinic, Rochester, MN*
[2]*Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA*
[3]*Department of Radiation Oncology, Duke University, Durham, NC*
[4]*British Columbia Cancer Agency, Kelowna, British Columbia, Canada*
[5]*Department or Radiation Oncology, Mt. Sinai Medical Center, New York, NY*
[6]*Schiffler Cancer Center and Wheeling Jesuit University, Wheeling Hospital, Wheeling, WV*
[7]*Prostate Cancer Treatment Center, Seattle, WA*
[8]*Department of Urology, Mt. Sinai Medical Center, New York, NY*
[9]*Department of Radiation Medicine, North Shore-LIJ Health System, New Hyde Park, Oceanside, NY*
[10]*Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA*
[11]*Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY*

Table 1
Elements of patient history for permanent prostate brachytherapy

1. Urologic history including:
   a. Prior transurethral or open resection of the prostate or other surgery on the urethra
   b. Prior procedure for benign prostatic hyperplasia such as transurethral needle ablation (30) or microwave therapy
   c. Medications for treatment of urinary obstructive symptoms
   d. Erectile function
2. Prior diagnosis of cancer, especially bladder or rectal
3. Prior pelvic radiotherapy, surgery, or fracture
4. Inflammatory bowel disease
5. Connective tissue disorders
6. Documentation of International Prostate Symptom Score
7. Documentation of erectile function, International Index of Erectile function score preferred

Table 2
Minimum required elements of workup for permanent prostate brachytherapy

1. Prostate biopsy indicating adenocarcinoma within the preceding 12 months of planned permanent prostate brachytherapy. Additional synoptic information is required and includes the Gleason grading and percent cancer in the biopsy specimen.
2. Pretherapy serum prostate-specific antigen
3. Digital rectal exam with clinical tumor classification, "T stage"
4. Prostate volume determination, transrectal ultrasound preferred
5. Determination of a patient's ability to tolerate an extended dorsal lithotomy position
6. Determination of suitability for general or spinal anesthesia

Table 3a
Absolute contraindications to TRUS-guided PPB

Limited life expectancy
Unacceptable operative risks
Distant metastases
Absence of rectum such that TRUS guidance is precluded
Large TURP defects, which preclude seed placement and acceptable radiation dosimetry
Ataxia telangiectasia

TRUS = transrectal ultrasound; PPB = permanent prostate brachytherapy; TURP = transurethral resection of the prostate.

Table 3b
Relative contraindications for TRUS-guided PPB

The items listed below are considered as essential elements of the history in determining eligibility, but the criteria by themselves do not necessarily preclude therapy. They should, however, be considered closely in electing to proceed with PPB. Published experience demonstrates that patients with such conditions may undergo PPB if appropriately evaluated by an experienced team.
High IPSS (typically defined as >20)
History of prior pelvic radiotherapy
Transurethral resection defects
Large median lobes
Gland size >60 cm^3 at time of implantation
Inflammatory bowel disease

TRUS = transrectal ultrasound; PPB = permanent prostate brachytherapy; IPSS = International Prostate Symptom Score.

Table 4
Suggested treatment schema for low-, intermediate-, and high-risk disease for PPB

Risk group per NCCN	Brachytherapy alone?	Combined with EBRT?	Combined with androgen deprivation?
Low	Yes	Not favored	Not favored
Intermediate	Optional	Optional	Optional
High	No	Yes	Favored

NCCN = National Comprehensive Cancer Network; EBRT = external beam radiation therapy; PPB = permanent prostate brachytherapy.

Indication for prostate brachytherapy

	Recommended Do well	Optional Fair	Investigational Do poorly
PSA (ng/ml)	<10	10–20	>20
Gleason score	5–6	7	8–10
Stage	T1c–T2a	T2b–T2c	T3
IPSS	0–8	9–19	>20
Prostate volume (g)	<40	40–60	>60
Q_{max} ml/s	>15	15–10	<10
Residual volume cm^3			>200
TURP ±			+

1999

2000

2012

Suggested treatment schema for low-, intermediate-, and high-risk disease for PPB

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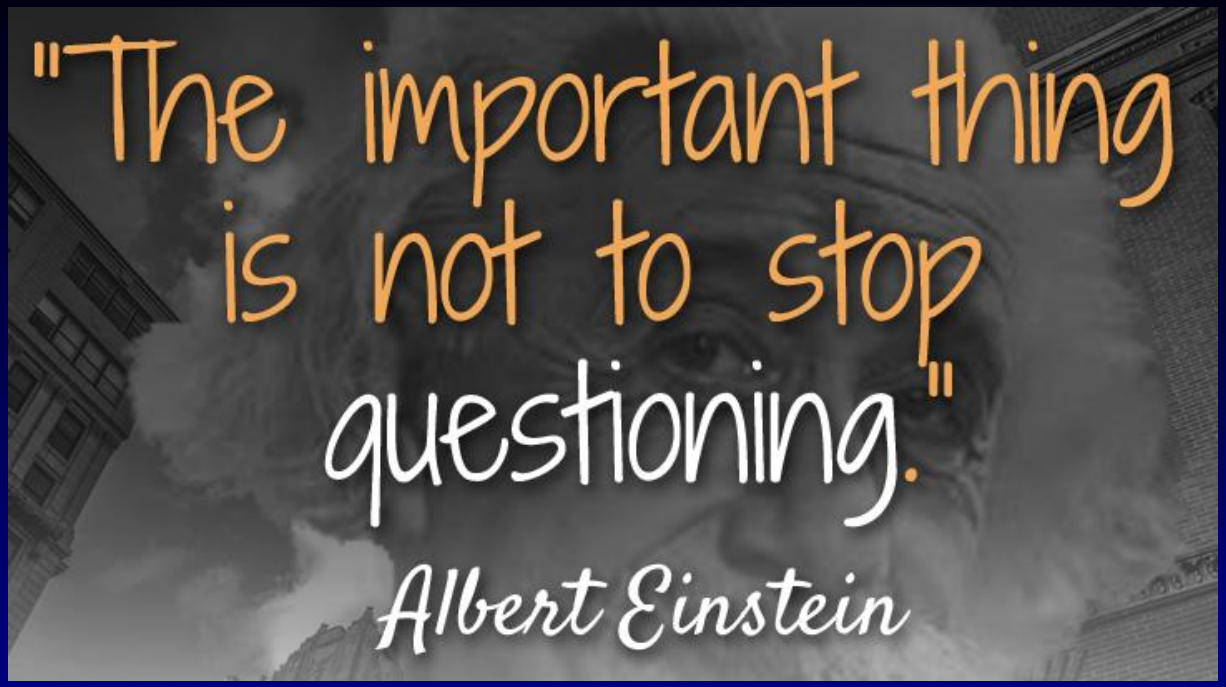


Patient selection for prostate LDR brachytherapy …. Do we have all the answers reading these recommendations ?

… no … after reading the literature some questions remain …

The main question :

- **The intermediate risk group :**
- **suitable for brachytherapy as monotherapy ?**

Oncology (Williston Park). 2016 Mar;30(3):229-36.

Favorable vs Unfavorable Intermediate-Risk Prostate Cancer: A Review of the New Classification System and Its Impact on Treatment Recommendations.

Serrano NA, Fastro MS.

Table 1. Proposed Intermediate-Risk Reclassification Schemes

Memorial Sloan Kettering Reclassification[26]		
Clinical Characteristics	**Favorable Intermediate-Risk[a]**	**Unfavorable Intermediate-Risk[b]**
	1 intermediate-risk factor[c]	> 1 intermediate-risk factor
	GS 3+4=7 or less	GS 4+3=7
	< 50% positive biopsy cores	≥ 50% positive biopsy cores

MD Anderson Reclassification[41]			
Clinical Characteristics	**Favorable[a]**	**Marginal[a]**	**Unfavorable[b]**
	GS 3+3=6	GS 3+4=7	GS 4+3=7
	≤ T2b	T2a/b	T2c

[a]*All* criteria must be met. [b]*Any* of these criteria can be met. [c]Based on the NCCN classification scheme.[5]
GS = Gleason score; NCCN = National Comprehensive Cancer Network.

2008 Genito-urinary symposium, ASC0-ASTRO,SUO Congress, February 2008

- Abstract 238, Linstadt et al (USA);
- Intermediate-risk patients; brachytherapy alone :
- 5-year bNED 96 %
- *« This series clinical success compares favorably with the results reported using other modalities ... »*

SELECTING PATIENTS FOR EXCLUSIVE PERMANENT IMPLANT PROSTATE BRACHYTHERAPY: THE EXPERIENCE OF THE PARIS INSTITUT CURIE/COCHIN HOSPITAL/NECKER HOSPITAL GROUP ON 809 PATIENTS

JEAN-MARC COSSET, M.D.,* THIERRY FLAM, M.D.,† NICOLAS THIOUNN, PH.D., M.D.,‡ STEPHANIE GOMME,* JEAN-CLAUDE ROSENWALD, PH.D.,* BERNARD ASSELAIN, M.D., PH.D.,* DOMINIQUE PONTVERT, M.D.,* MEHDI HENNI, M.D.,* BERNARD DEBRE, M.D.,† AND LAURENT CHAUVEINC, M.D., PH.D.*

*Institut Curie, Paris, France; †Cochin Hospital, Paris, France; and ‡Necker Hospital, Paris, France

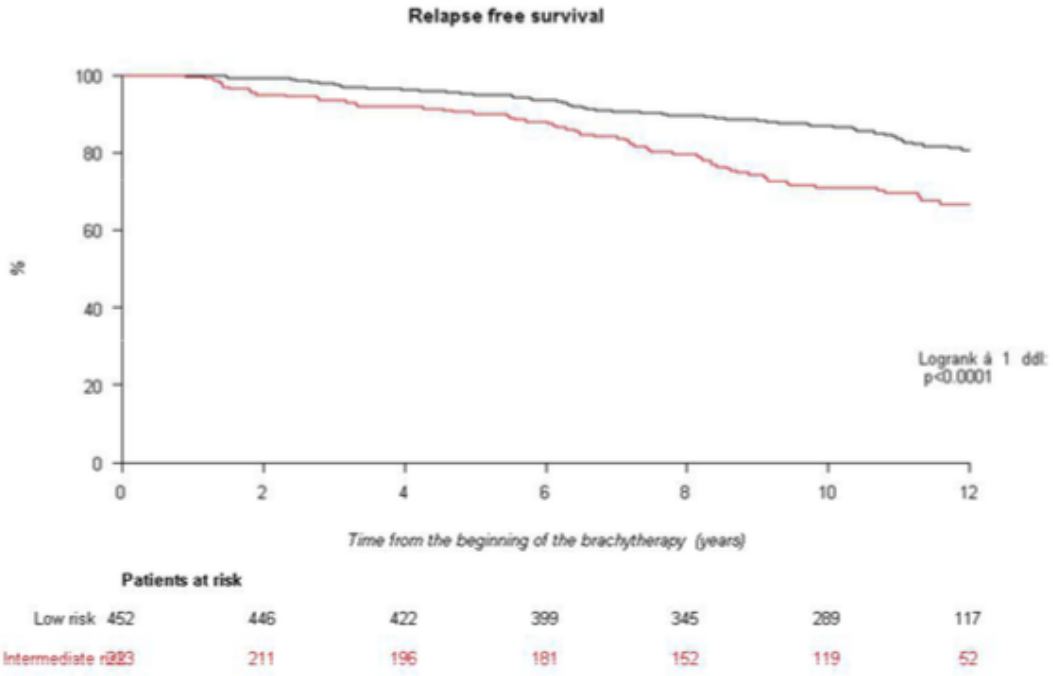
*Institut Curie, Paris, France; †Cochin Hospital, Paris, France; and ‡Necker Hospital, Paris, France

- IJRO 2008
- Purpose: The aim of this study was to analyze overall and relapse-free survivals in a cohort of 809 patients, 34% of whom corresponded to a higher risk group than ABS criteria.

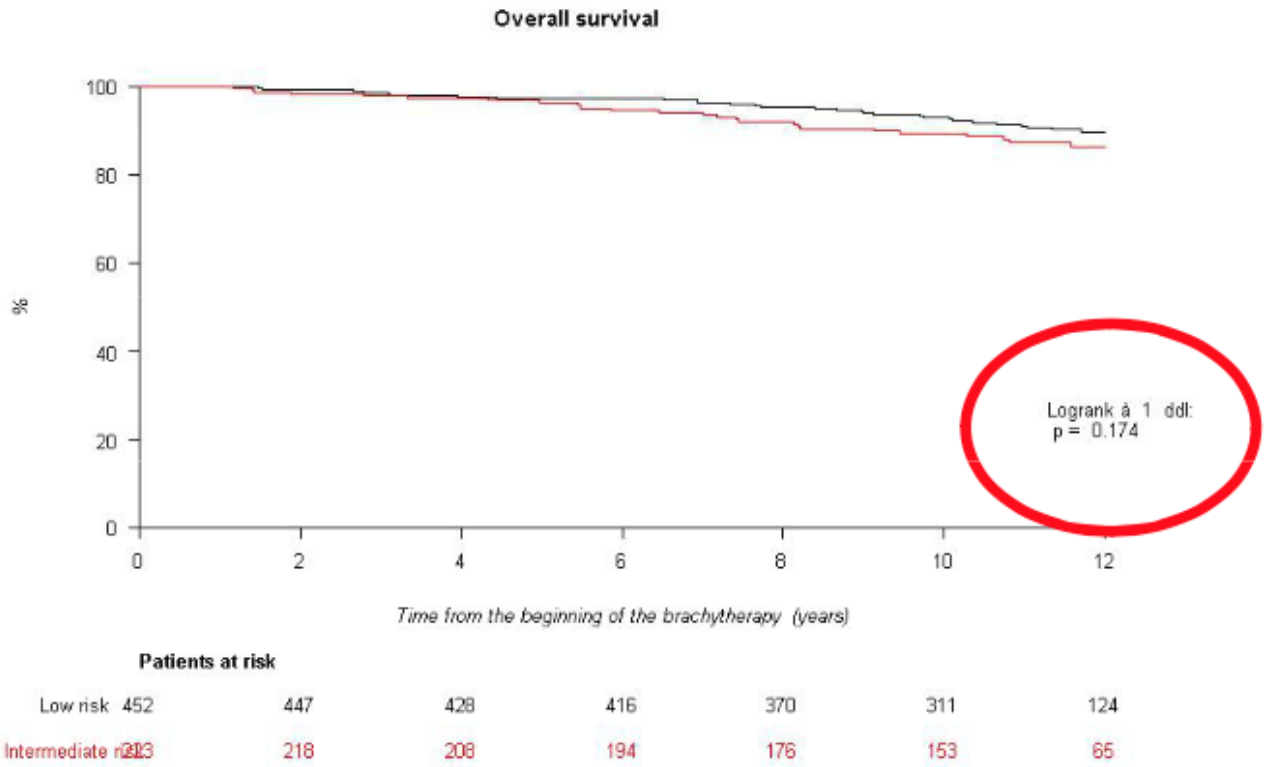
- For this Institut Curie series ;
- Low-risk patients
- and
- « Favorable intermediate » patients ;
- PSA between 10, and 15 and all other low-risk criteria
- Or ;
- Gleason 7, and all other low-risk criteria

The 2016 Institut Curie experience

- **Update on 675 patients, all with a follow-up of more than 10 years**



No difference in long-term overall survival …



Initial Report of NRG Oncology/RTOG 0232: A Phase III Study Comparing Combined External Beam Radiation and Transperineal Interstitial Permanent Brachytherapy with Brachytherapy Alone for Selected Patients with Intermediate Risk Prostatic Carcinoma

B. R. Prestidge[1], K. Winter[2], M. G. Sanda[3], M. Amin[4], W. S. Bice Jr[5], J. Michalski[6], G. S. Ibbott[7], J. M. Crook[8], C. N. Catton[9], H. A. Gay[6], V. Donavanik[10], D. C. Beyer[11], S. J. Frank[12], M. A. Papagikos[13], S. A. Rosenthal[14], H. J. J. Barthold II[15], M. Roach III[16], and H. M. Sandler[17]

[1]DePaul Medical Center, Bon Secours Cancer Institute, Norfolk, VA, [2]NRG Oncology Statistice and Data Management Center, Philadelphia, PA, [3]Emory University, Atlanta, GA, [4]Cedars-Sinai, Los Angeles, CA, [5]John Muir Medical Center, Walnut Creek, CA, [6]Washington University School of Medicine, St. Louis, MO, [7]MD Anderson Cancer Center, Houston, TX, [8]BC Cancer Agency, Kelowna, BC, Canada, [9]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [10]Christiana Care Health Services, Inc. CCOP, Newark, DE, [11]Cancer Centers of Northern Arizona, Sedona, AZ, [12]University of Texas MD Anderson Cancer Center, Division of Radiation Oncology, Houston, TX, [13]Coastal Carolina Radiation Oncology, Wilmington, NC, [14]Radiation Oncology Center, Sacramento, CA, [15]South Suburban Oncology Center, Quincy, MA, [16]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, [17]Cedars-Sinai Medical Center, Los Angeles, CA

Conclusions

- Among men with intermediate risk (IR) prostate cancer, the addition of external beam therapy to brachytherapy did not result in superior freedom from progression compared to brachytherapy alone at 5 years in this initial report.
- Toxicity in both groups was limited, but there were fewer late effects, mostly GU, noted in the brachytherapy alone arm.
- Implications for clinical practice: Men with intermediate risk prostate cancer may be well managed with brachytherapy alone.
- Further subset analysis will be required to determine if the unfavorable IR patients do as well as those with favorable IR disease.

favourable

- **The intermediate risk group :**
- **suitable for brachytherapy as monotherapy ?**


age
is just a
number

- **What about age ?**

- In the early years, most groups were reluctant to propose brachytherapy alone to « young » (< 60 years ?) patients,
- Mostly because of the lack of long follow-up …

- Cancer J. 2006 Jul-Aug;12(4):305-8.
- **The effect of age on prostate implantation results.**
- Peschel RE, Khan A, Colberg J, Wilson LD.

- **CONCLUSIONS:**
- Patients who are 60 years of age or younger who are treated with ultrasound-guided transperineal prostate implantation can expect 5-year biochemical disease-free survival rates similar to those of older patients treated with ultrasound-guided transperineal prostate implantation therapy.

- Am J Clin Oncol. 2008 Dec;31(6):539-44.
- **Biochemical and functional outcomes following brachytherapy with or without supplemental therapies in men < or = 50 years of age with clinically organ-confined prostate cancer.**
- Merrick GS, Wallner KE, Galbreath RW, Butler WM, Brammer SG, Allen ZA, Lief JH, Adamovich E.

- **CONCLUSIONS:**
- Men < or =50 years of age have favorable biochemical and functional outcomes following brachytherapy. Depending on risk group assignment, brachytherapy with or without supplemental therapies should be considered a viable option for all healthy men regardless of age.

- Int J Radiat Oncol Biol Phys. 2010 Aug 1;77(5):1315-21.
- **Young men have equivalent biochemical outcomes compared with older men after treatment with brachytherapy for prostate cancer.**
- Burri RJ, Ho AY, Forsythe K, Cesaretti JA, Stone NN, Stock RG.
- Department of Radiation Oncology, Mount Sinai School of Medicine, New York, New York, USA.
- **CONCLUSION:**
- Young men achieve excellent 5- and 8-year biochemical control rates that are comparable to those of older men after prostate brachytherapy.

- **In CONCLUSION (Burri 2010):**
- **"Young age should not be a deterrent when considering brachytherapy as a primary treatment option for clinically localized prostate cancer".**

Urological Oncology

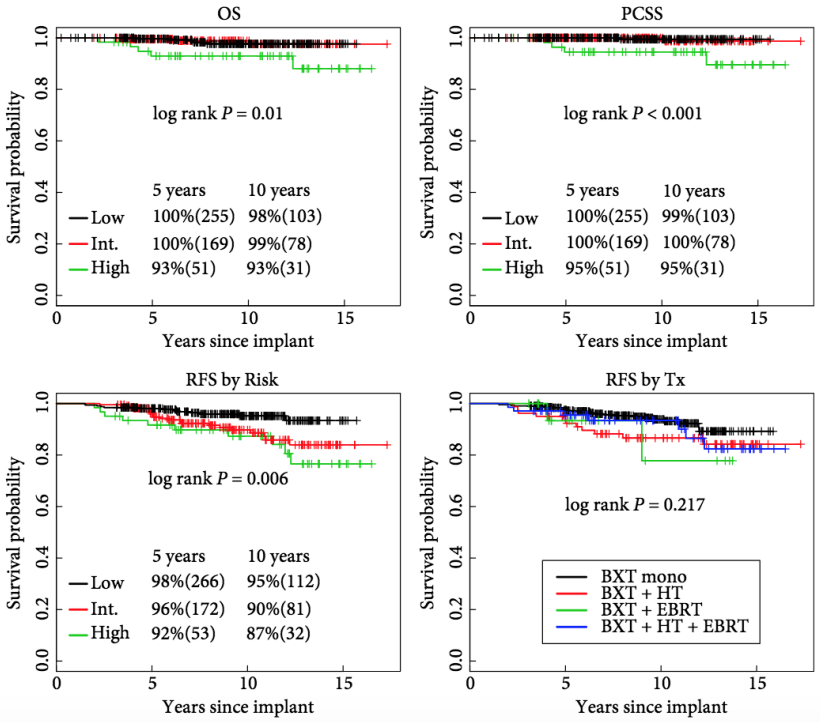
BJUI
BJU International

Long-term oncological outcomes and toxicity in 597 men aged ≤60 years at time of low-dose-rate brachytherapy for localised prostate cancer

Stephen E. M. Langley, Ricardo Soares, Jennifer Uribe, Santiago Uribe-Lewis, Julian Money-Kyrle, Carla Perna, Sara Khaksar and Robert Laing

St Luke's Cancer Centre, Guildford, Surrey, UK

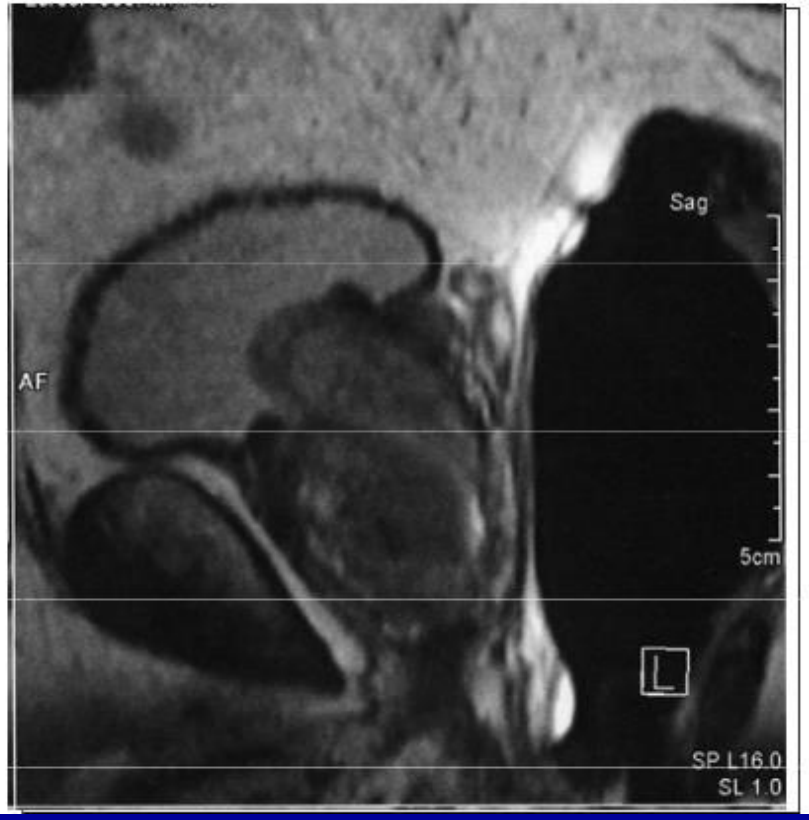
Fig. 1 Survival analyses. Top panels: Kaplan–Meier curves for overall survival (OS) and prostate cancer-specific survival (PCSS) by disease risk. Bottom panels: Kaplan–Meier curves for RFS by disease risk and by treatment type (Tx). Percentage survival estimates (*n* at risk) at 5 and 10 years after implantation by disease risk categories are indicated. Int., intermediate; BXT, brachytherapy; Mono, brachytherapy monotherapy.



Conclusion

LDR brachytherapy is an effective treatment with long-term control of prostate cancer in men aged ≤60 years at time of treatment. It was associated with low rates of treatment-related toxicity and can be considered a first-line treatment for prostate cancer in this patient group.

- **What about median lobes and obstructive syndroms ?**



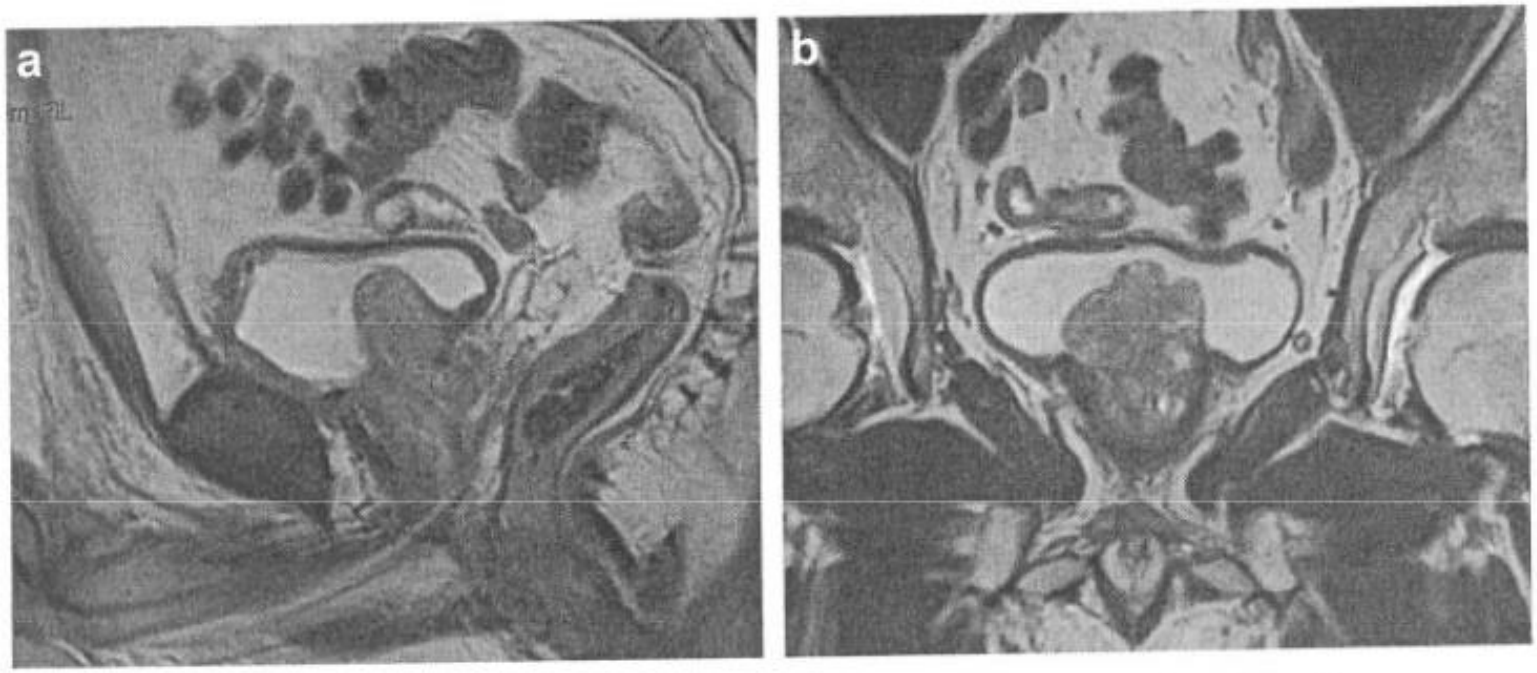


Fig. 1. (a and b) Example of a "very prominent" (+++) median lobe (Case $N = 19$).

- Brachytherapy. 2011 Jan-Feb;10(1):29-34.

- **One-step customized transurethral resection of the prostate and permanent implant brachytherapy for selected prostate cancer patients: technically feasible but too toxic.**

- Cosset JM, Barret E, Castro-Pena P, Cathelineau X, Galiano M, Rozet F, Pierrat N, Timbert M, Vallancien G
- Department of Radiotherapy, Institut Curie, 26 rue d France.

Two-step TURP and brachytherapy

- Now almost a standard ;
- See :
- Abstracts PO37 and PO38 , ABS 2011
- PO37 ; bladder neck resection 6 weeks before implant
- PO38 ; vaporization of obstructive prostate tissue by 100W holmium laser

OTHER THINGS

- **Brachytherapy « boost » after EBRT**
- **Salvage brachytherapy after failure of EBRT (or even brachytherapy)**
- **Focal brachytherapy**
- **(see ad hoc presentations)**

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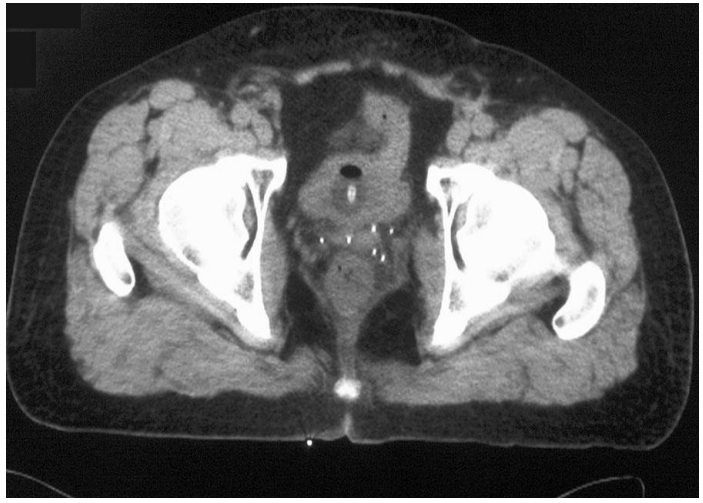
WWW.ESTRO.ORG/SCHOOL

High dose rate brachytherapy for prostate cancer: PATIENT SELECTION

HDR prostate brachytherapy

- Practical
  - Existing source, afterloading

- Physical
  - Greater implant volume
  - including seminal vesicles



- Biological
  - Low α/β tumour; greater biological dose with high dose per fraction

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Advantages of temporary HDR prostate brachytherapy

Radioprotection

- no free live sources
- no risk of source loss
- no radioprotection issues after discharge

Cheap: utilises existing HDR source and equipment

Day case procedure

Disadvantages of temporary HDR prostate brachytherapy

High dose rate radiation requires fractionation

- no longer!?

- logistics:
  - Quality assurance

Selection for HDR prostate brachytherapy

- Boost with external beam
- Monotherapy

Pre treatment investigations

- General medical assessment
- Prostate biopsy
- PSA
- IPSS
- IEFS
- Flow rate
- Pelvic MRI
- Staging investigations
  - PSA
  - Bone scan
  - (Whole body MRI)
  - (Choline PET)
  - (PSMA PET)

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GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update

Peter J. Hoskin[a,*,1], Alessandro Colombo[b,1], Ann Henry[c,1], Peter Niehoff[d,1], Taran Paulsen Hellebust[e,1], Frank-Andre Siebert[f,1], Gyorgy Kovacs[g,1]

[a] Mount Vernon Cancer Centre, Northwood, UK; [b] Department of Radiotherapy, Manzoni Hospital, Lecco, Italy; [c] St. James Institute for Oncology, Leeds, UK; [d] Department of Radiotherapy, City Hospital Cologne, Germany; [e] DNR Norwegian Radium Hospital, Oslo, Norway; [f] Universitätsklinikum Schleswig-Holstein, Kiel; and [g] University Hospital Schleswig-Holstein Campus Lübeck, Germany

Radiotherapy and Oncology xxx (2013)

Inclusion criteria

- Stages T1b–T3b
- Any Gleason score
- Any PSA level

Exclusion criteria

- TURP within 3–6 months
- Maximum urinary flow rate (Qmax) <10 ml/s
- IPSS > 20
- Pubic arch interference
- Lithotomy position or anaesthesia not possible
- Rectal fistula

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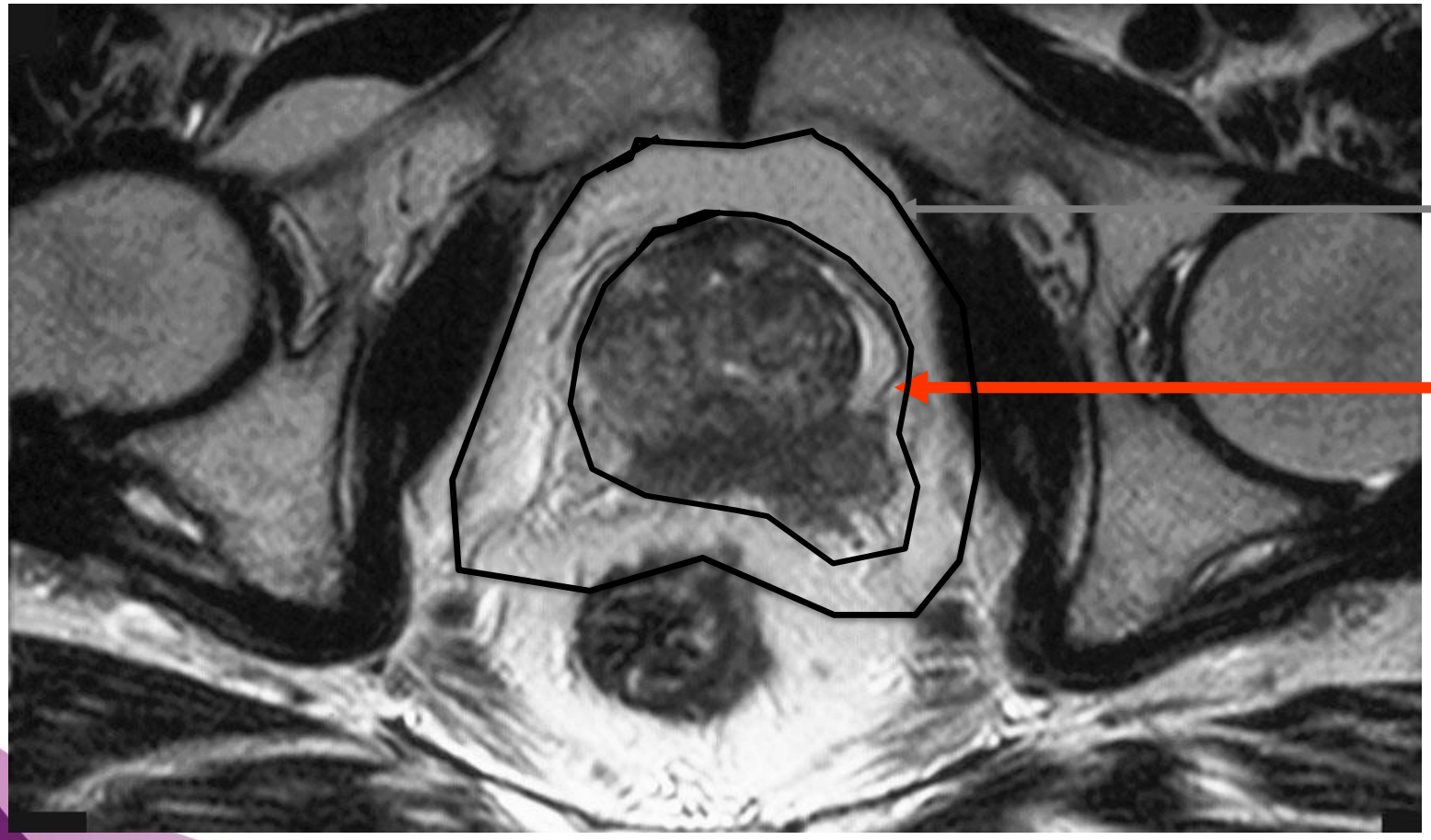
Indications for HDR prostate brachytherapy BOOST

Where there is a significant predictive risk of extracapsular or seminal vesical involvement:



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Indications for HDR prostate brachytherapy BOOST

Where there is a significant predictive risk of extracapsular or seminal vesical involvement:

T3a

T3b

?T2c

Gleason 8 – 10

?Gleason 4+3

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Probability of organ confined disease

[Partin 2001]

PSA 6.1-10.0

Gleason	T1c	T2a	T2b	T2c
3+4	54%(49-59)	35%(30-40)	26%(22-31)	24%(17-32)
4+3	43%(35-51)	25%(19-32)	19%(14-25)	16%(10-24)
8-10	37%(28-48)	21%(15-28)	15%(10-21)	13%(8-20)

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Probability of organ confined disease

[Partin 2001]

PSA >10.0

Gleason	T1c	T2a	T2b	T2c
3+4	37%(32-42)	20%(17-24)	14%(11-17)	11%(7-17)
4+3	27%(21-34)	14%(10-18)	9%(8-13)	7%(4-12)
8-10	22%(16-30)	11%(7-15)	7%(4-10)	6%(3-10)

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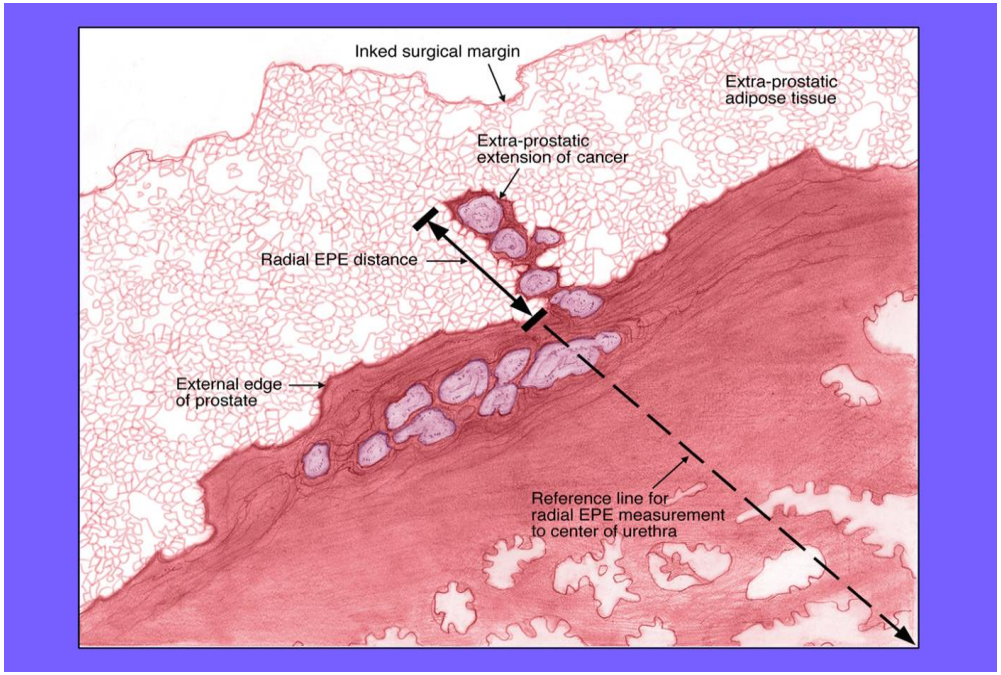
Ext beam/HDR boost for prostate

?The low risk patient

- PSA<10ng/ml
- Gleason 6 or below (?3+4)
- T2a or less

…….what is the risk of ECE or seminal vesicle invasion??.....



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Probability of organ confined disease

[Partin 2001]

PSA 4.1-6.0

Gleason	T1c	T2a	T2b	T2c
2-4	90% (78-98)	81% (63-95)	75% (55-93)	73% (52-93)
5-6	80% (78-83)	66% (62-70)	57% (52-63)	55% (44-64)
3+4	63% (58-68)	44% (39-50)	35% (29-40)	31% (23-41)

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GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update

Peter J. Hoskin[a,*,1], Alessandro Colombo[b,1], Ann Henry[c,1], Peter Niehoff[d,1], Taran Paulsen Hellebust[e,1], Frank-Andre Siebert[f,1], Gyorgy Kovacs[g,1]

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Radiotherapy and Oncology xxx (2013)

Inclusion criteria

- Stages T1b–T3b
- Any Gleason score
- Any PSA level

Exclusion criteria

- TURP within 3–6 months
- Maximum urinary flow rate (Qmax) <10 ml/s
- IPSS > 20
- Pubic arch interference
- Lithotomy position or anaesthesia not possible
- Rectal fistula

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American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

Yoshiya Yamada[1,*], Leland Rogers[2], D. Jeffrey Demanes[3], Gerard Morton[4], Bradley R. Prestidge[5], Jean Pouliot[6], Gil'ad N. Cohen[7], Marco Zaider[7], Mihai Ghilezan[8], I-Chow Hsu[6]

Brachytherapy 11 (2012) 20–32

Absolute contraindications

Absolute contraindications for HDR brachytherapy include the following conditions:

1. Preexisting rectal fistula,
2. Medically unsuited for anesthesia, and
3. No proof of malignancy.

High-dose-rate brachytherapy for large prostate volumes (≥50 cc)—Uncompromised dosimetric coverage and acceptable toxicity

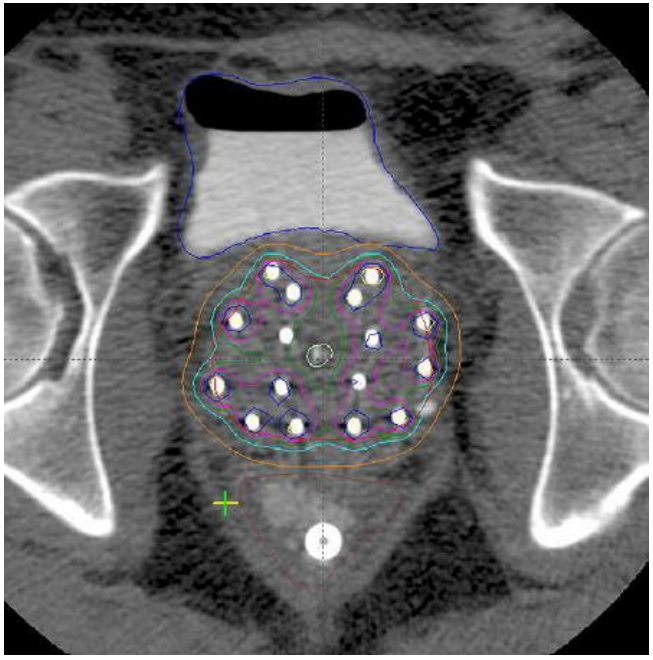
Alan T. Monroe*, Patrick O. Faricy, Scott B. Jennings, Robert D. Biggers, Gregory L. Gibbs, Anuj V. Peddada

Penrose Cancer Center, Department of Radiation Oncology, Colorado Springs, CO

Brachytherapy 7 (2008) 7–11

54 patients

Gland size median 57ml; range 50-97.3ml



All dosimetric goals achieved

Number of needles	
14	2 (4%)
15	1 (2%)
16	46 (85%)
18	4 (7%)
20	1 (2%)

Univariate analysis of factors associated with catheter placement and rise in AUA score of 3 and 5 points beyond baseline

Factor	Catheter	Three points (p-value)	Five points (p-value)
EBRT sequencing	0.667	**0.033**	0.137
Hormone use	0.365	0.156	0.298
Stage	0.999	0.081	**0.040**
Age	0.399	0.222	0.653
V_{100}	0.999	0.203	0.374
D_{90}	0.999	0.999	0.999
Ultrasound volume	0.668	0.999	0.999
V_{150}	0.999	0.999	0.999
5% Urethral dose	0.194	0.999	0.643
Baseline AUA score	0.999	0.425	0.632

ESTRO School

The Influence of Prostate Volume on Outcome After High-Dose-Rate Brachytherapy Alone for Localized Prostate Cancer

Hien Le, FRANZCR, Ana Rojas, PhD, Roberto Alonzi, FRCR, Robert Hughes, FRCR, Peter Ostler, FRCR, Gerry Lowe, MSc, Linda Bryant, DCR (T), and Peter Hoskin, MD

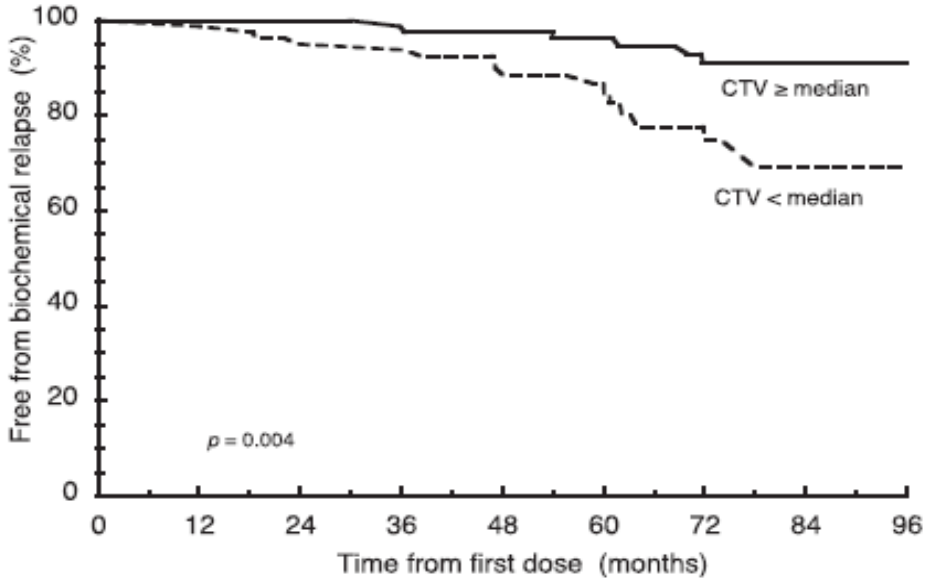
Mount Vernon Cancer Centre, Middlesex, UK

Int J Radiation Oncol Biol Phys, Vol. 87, No. 2, pp. 270–274, 2013

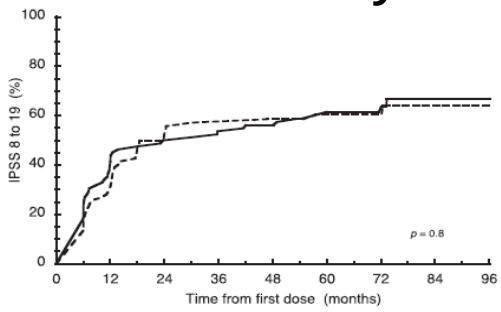
164 patients HDR monotherapy; median CTV volume 60mls (range 14-2

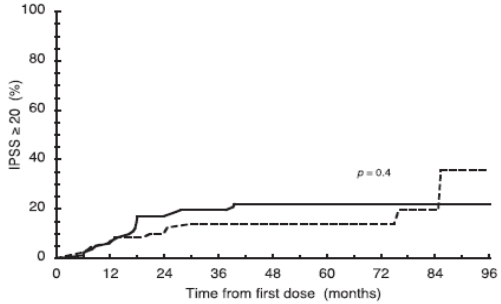
Volumes	V100 mean	*P* value	D90 mean	*P* value	V150 mean	*P* value	Urethral D30 mean	*P* value
≤Median	93	.24	103.7	.14	29.0	.97	11.2	<.0001
>Median	94	-	104.7	-	28.9	-	10.6	-

bRFS



Toxicity



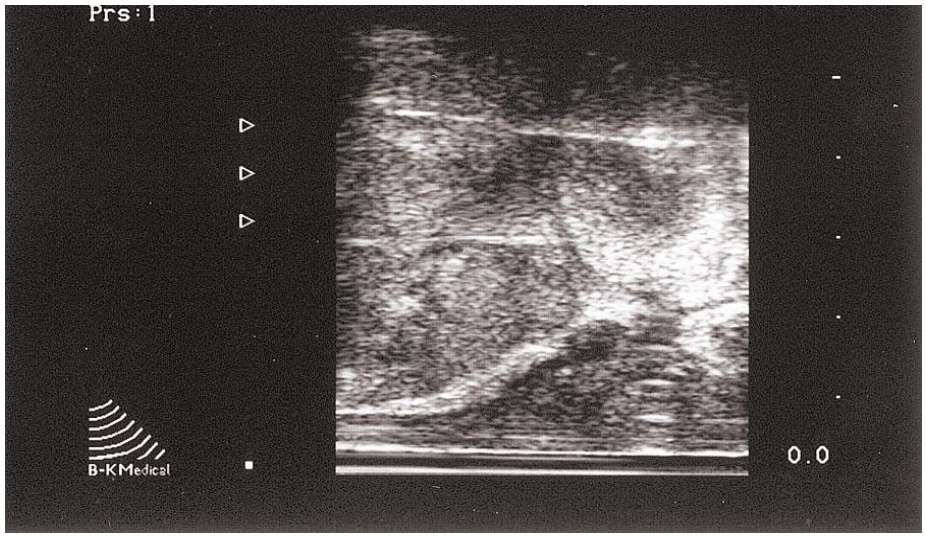


ESTRO School

Pubic arch interference

- Patient position:
  - Hyperextended vs standard
  - Plane of prostate vs pubic arch
  - Table / stand positions

- Needle insertion
  - Bend the needle?
  - Enter via adjacent co-ordinate



ESTRO School

HDR PROSTATE BRACHYTHERAPY INDICATIONS

- Boost with external beam therapy
  - Intermediate/high risk disease
  - ?Low risk disease

- Monotherapy
  - Phase II studies…..
  - Low/Intermediate/high risk disease

ESTRO School

HDR monotherapy for prostate

? low risk patient

Intermediate risk patient

High risk patient

HDR monotherapy; published series and risk groups

	LOW	INT	HIGH
Yoshioka et al MSKCC	X	X	X
Hoskin et al MVCC		X	X
Rogers et al		X	
Mark et al Texas	X	X	X
Prada et al Spain	X	X	
Martinez et al Michigan	X	X	
Demanes et al CET	X	X	
Zamboglu et al Offenbach	X	X	X

ESTRO School

HDR monotherapy: what the guidelines say……

GEC ESTRO

Long term outcome data are not yet available from these cohorts and it is recommended that this treatment is not undertaken outside a formal study.

ABS

HDR monotherapy has been reported by several institutions (see Table 1), largely for low-risk, but also for intermediate-risk patients. The reported outcomes for disease control and toxicity are favorable. Monotherapy demands a higher degree of technical and planning expertise than boost HDR therapy. Institutions should take the requirements of HDR monotherapy into consideration before embarking on a monotherapy program. Monotherapy for high-risk patients should be considered investigational.

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HDR for salvage?
GEC ESTRO guidelines 2013

HDR in recurrence

There is limited experience of HDR brachytherapy for locally recurrent prostate cancer after previous irradiation and this is not recommended outside a formal prospective study. OAR constraints are critical in this setting. Published schedules (planning aim) include the following:

36 Gy in 6 fractions [44].
21 Gy in 3 fractions [45].
30 Gy in 2 fractions to peripheral zone after 30–40 Gy external beam [46].

- Rectum: D2 cc $\leqslant$ 75 Gy EQD_2
- Urethra:
  - D0.1 cc = $\leqslant$120 Gy EQD_2
  - D10 $\leqslant$ 120 Gy EQD_2
  - D30 $\leqslant$ 105 Gy EQD_2

ESTRO School

HDR for salvage?
ABS guidelines 2013

There is a promising data describing the use of HDR monotherapy as salvage for localized recurrence after prior external beam radiation or permanent seed brachytherapy. The ABS recommends that the use of HDR as salvage therapy be limited to Institutional Review Board-approved protocols or specialty centers with appropriate expertise.

Selection for HDR prostate brachytherapy

Boost with external beam

Monotherapy

Salvage

Selection for HDR prostate brachytherapy ……whole gland or focal…….

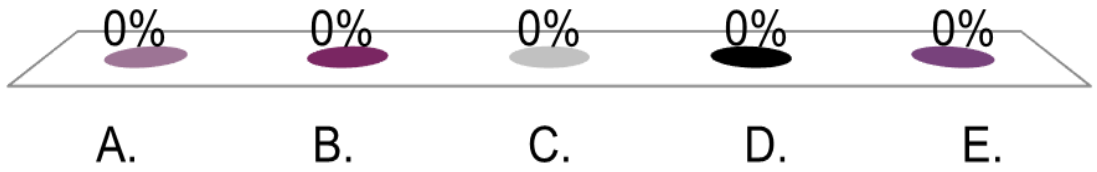
Indications for consideration of focal HDR BT

- HDR BT indicated
- Low and favourable intermediate risk
- Focal lesion identified by:
  - mpMRI ‘dominant’ lesion
  - Template biopsy mapping

- Salvage

Which of the following is a contraindication to HDR brachytherapy boost

A. Multifocal prostate cancer
B. PSA>20ng/ml
C. Prostate volume >70ml
D. Gleason score 9
E. Maximum flow rate <10ml/min



QUALITY ASSURANCE (QA) FOR PROSTATE BRACHYTHERAPY

Bashar Al-Qaisieh

The Leeds Teaching Hospitals NHS
NHS Trust

Overview

- ESTRO working parties
- Seed calibration
- Needle Check
- Template Calibration
- Ultrasound Machine Check
- Commissioning Planning System
- Treatment Plan Check
- Post Implant QA

ESTRO: BRAPHYQS projects

- WP12: QA for Brachytherapy ultrasound
- WP 18: Seed dosimetry
- WP 19: Commissioning and QA BT treatment planning systems.

BRAPHYQS WP 18

Chair Jose Perez-Calatayud: European Guidelines

- Calibration of seeds at hospital level
- What to do when discrepancies occur between certificate and measurement ?
- Seed afterloader
- Recalibration of dosemeters
- Multi-seed inserts

In close cooperation with seed vendors and European standard laboratories (as consultants)

Seed Calibration-Well chamber

- Calibration every two years. Med. Phys. 18, 1991.
- Consistency check.

  Cs-137, Co-60

Guidelines

"The activity of all sources should be measured, and *compared* with the calibration certificate supplied by the supplier, before being administered to a patient"…..Medical and Dental Guidance Notes, IPEM

Seed Calibration

•Sterile sources located in MICK magazine

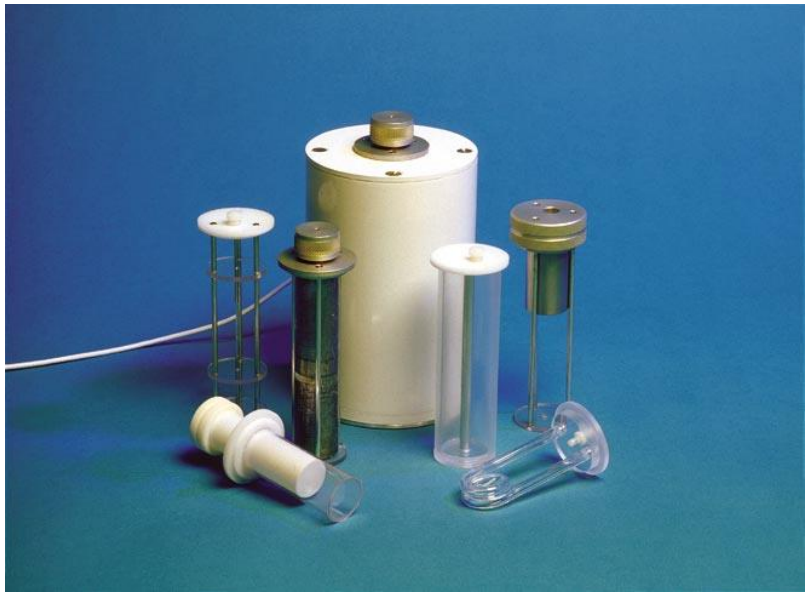
- a minimum of 10% of the total or two magazine cartridges of 15 seeds, whichever is greater.

• Sterile stranded sources.

- a minimum of 10% of the total or two strands of 10 seeds, whichever is greater.

• Loose seeds

- a minimum of 10% of the total or 20 seeds, whichever is greater.



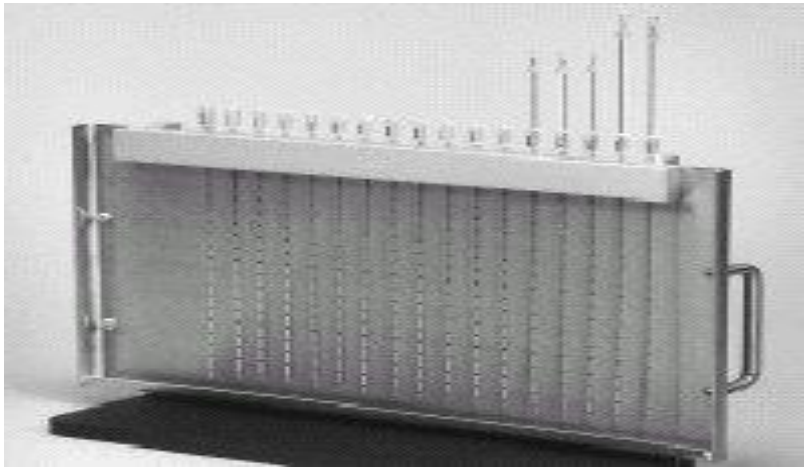
Action level if seeds are out of tolerance

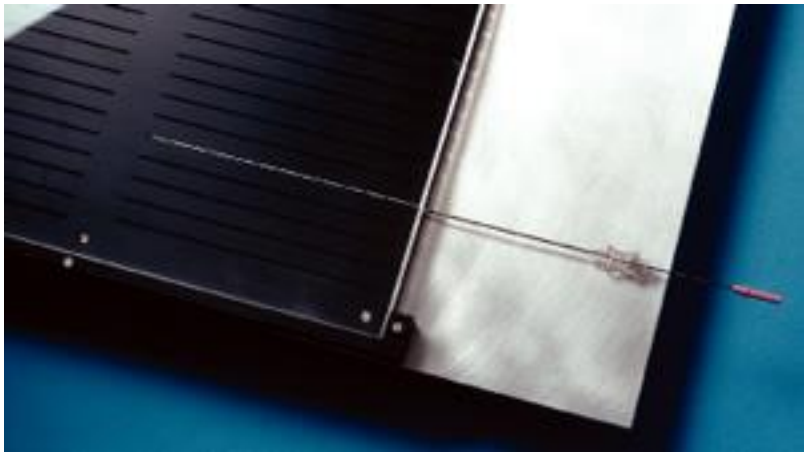
- If the mean source strength of the measured sources agrees within 3% of the manufacturer's stated source strength and the absolute difference of all the individual source/strand measurements are within the quoted calibration uncertainty on the manufacturer's certificate, the sources can be used clinically.
- If the mean difference is greater than 3%, the first step of investigation of the discrepancy should be to increase the sample size.
- After increasing the sample size, if the mean difference is still greater than 3%, further action must be taken to resolve the differences.
- If the mean difference is greater than a 5% action limit, the manufacturer should be consulted, if possible, to assist in resolving the differences. For measurements performed in the OR with the patient anaesthetised, discussions between the radiation oncologist and the MPE should take place regarding the consequences of proceeding with the implant using the measured source strength.

Clinical Oncology
The Royal College of Radiologists

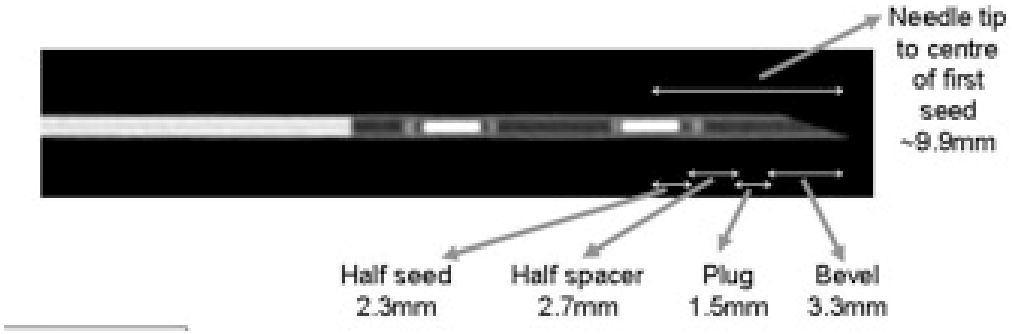
Needles Check

- Verification of loaded brachytherapy needles.
- Place a film on top of the needles. The radiation from the loaded needles exposes an image in the film.
- The film will verify correct loading of seeds and spacers within each needle, or indicate any discrepancies or missing seeds.

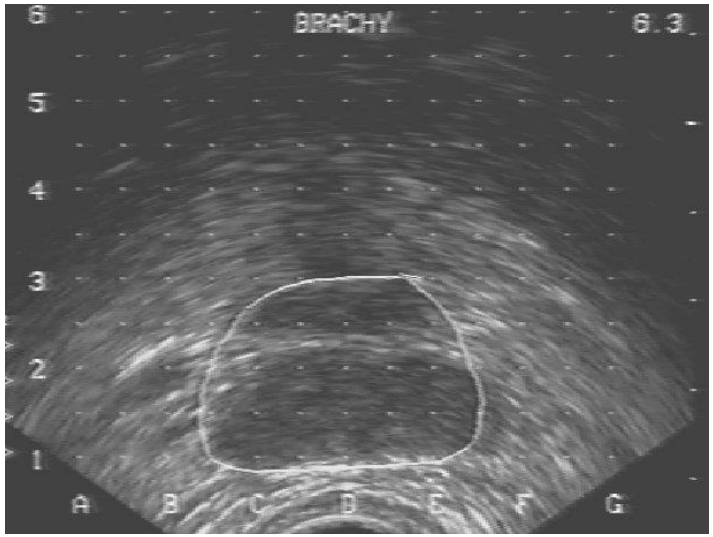




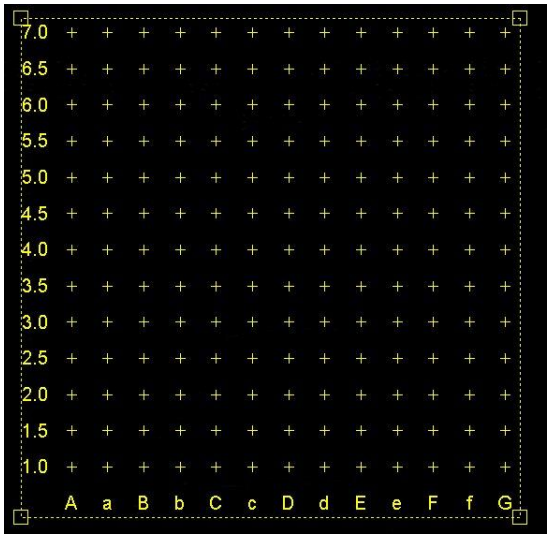
Needles Check



Template Calibration



Ultrasound Template

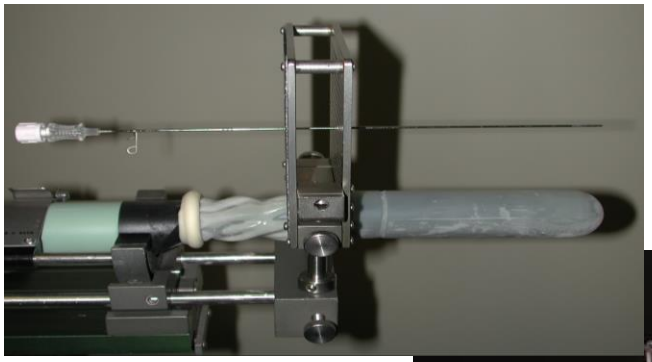


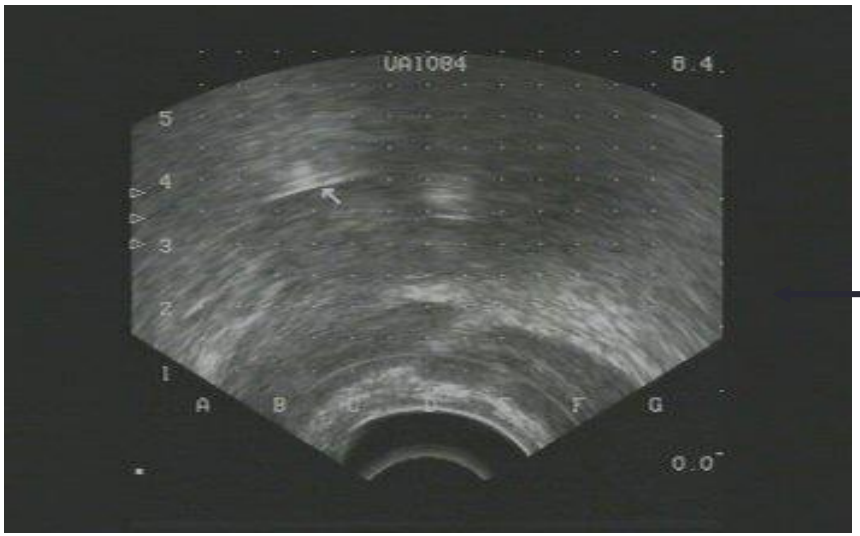
Guidance Template

Level of tolerance is ± 1mm

Planning Template

Template Calibration





Ultrasound Machine Check

- Assurance of Mechanical and Electrical Safety
- Distance Accuracy (vertical and horizontal)
- Contrast and Brightness (Gray bar visualization)
- Image Uniformity
- Penetration
- Lateral Resolution

-IPEM report 71: Price R et al. 1995/2002

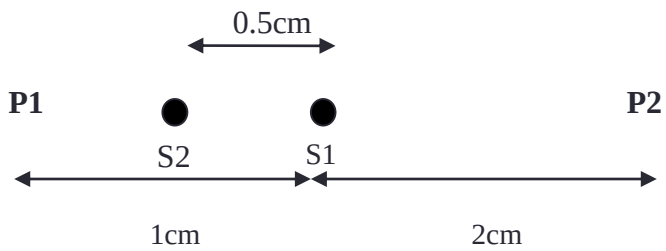
-TG –1: Goodsitt et al. Med Physics 25(8) 1998.

Clinical Commissioning of Planning System

- Test 1: Dose Point Calculation-TG 43-U1
- Test 2: Isodose Level-TG 43-U1
- Test 3: Volume and Dose Volume-TG 43-U1
- Test 4: Anisotropy Function/Line Source Calculation-TG43-U1
- Test 5: Data transfer and handling
- Test 6: Stepper Depth and Angle Tracking and Accuracy Tests

Dose Point Calculation Test

- This dose calculation verification test uses a dose point(s) to verify the calculations of the planning system. Discrepancy should be within 1%.

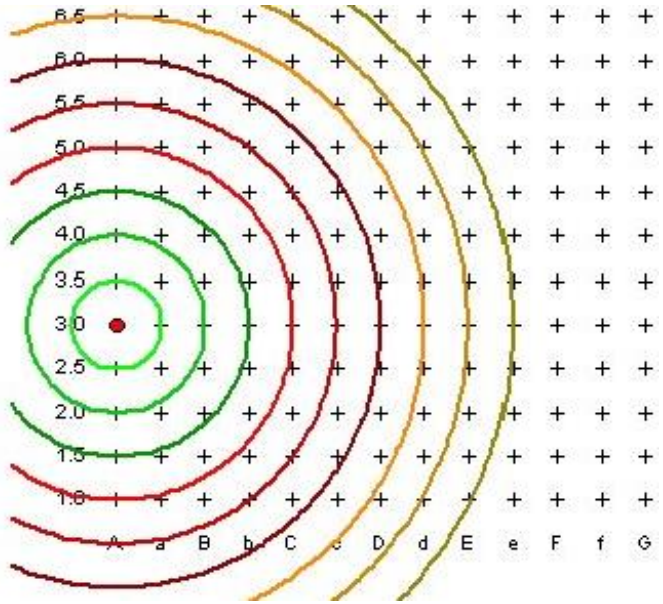


Dose rates (cGy h^{-1} U^{-1}) as a function of distance

r (cm)	Amersham model 6711
0.5	3.937
1.0	0.911
1.5	0.368
2.0	0.186
3.0	0.0643
4.0	0.0284
5.0	0.0134
6.0	0.00688
7.0	0.00373

Isodose Level Test

- This test is to verify the display of isodose levels
- The distance discrepancy of contours and template should be within ± 2 mm

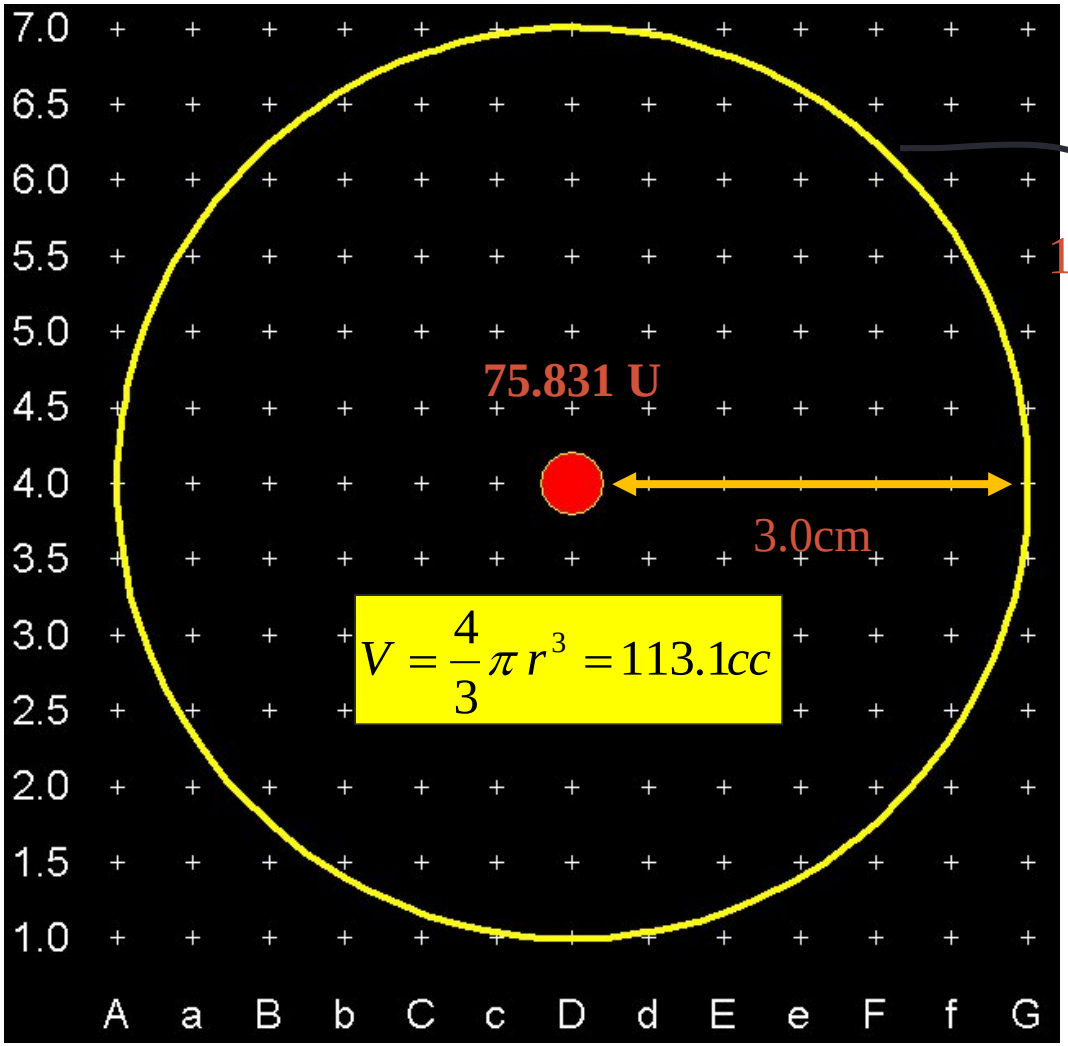


Dose Volume Test

- This test uses DVH values to verify the dose volume calculation of the planning system.

- Discrepancy should not exceed 5%.

Dose Volume Test-Example



Dose Volume Test

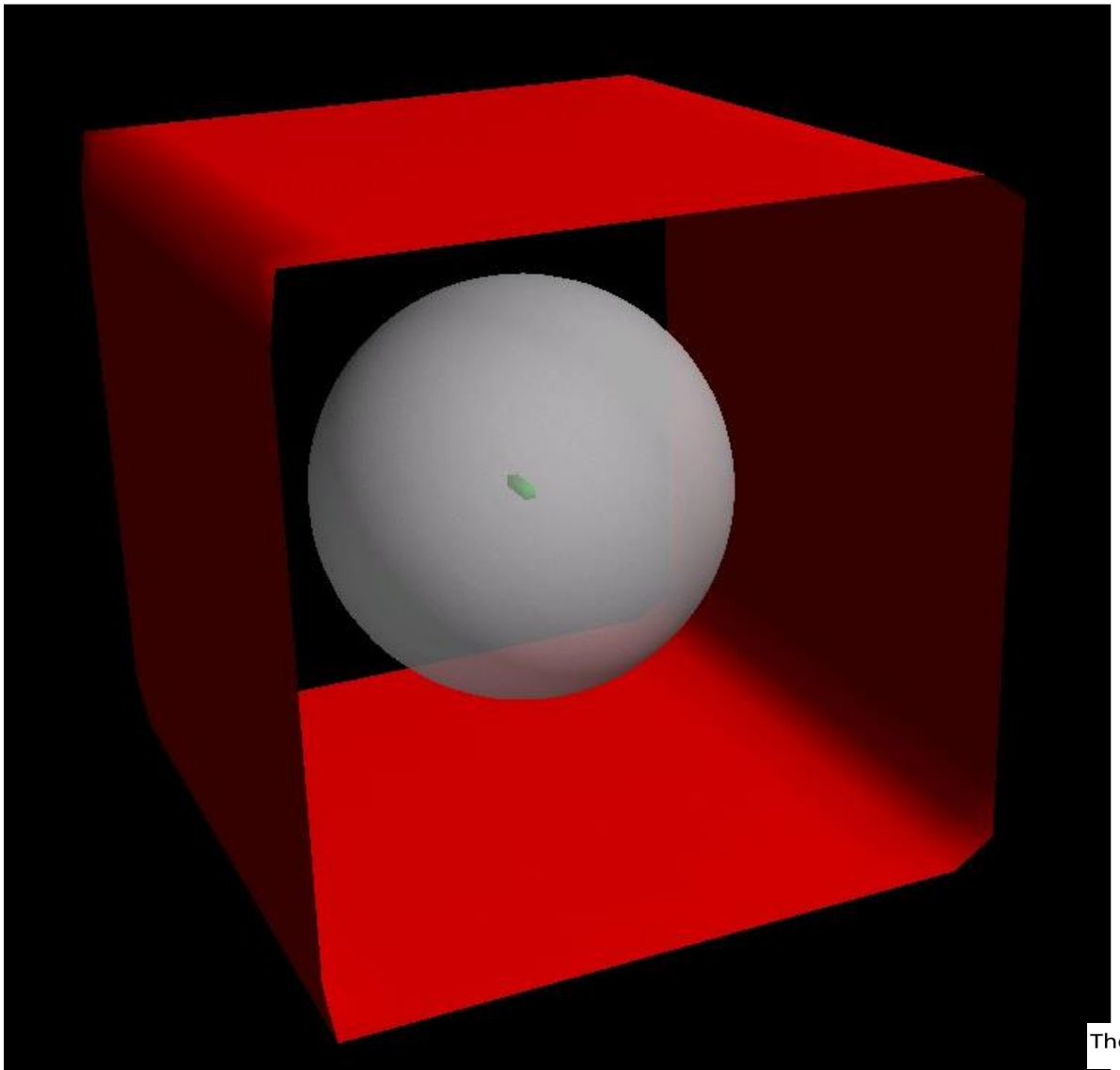
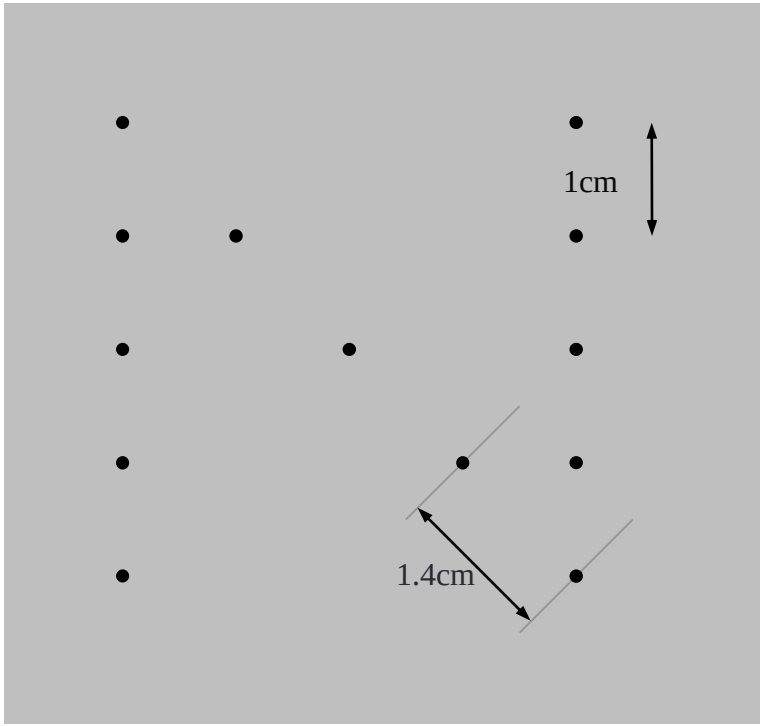
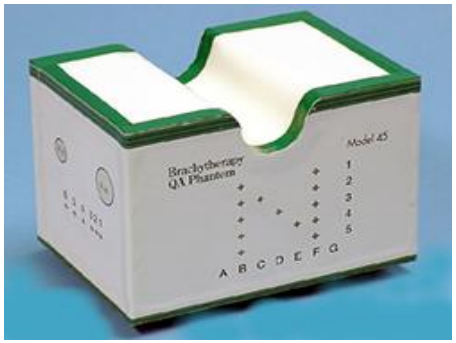


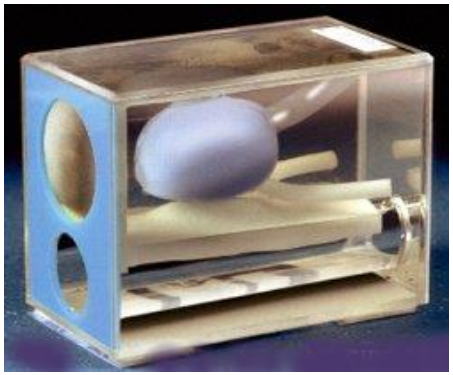
Image transfer check (Ultrasound phantom)

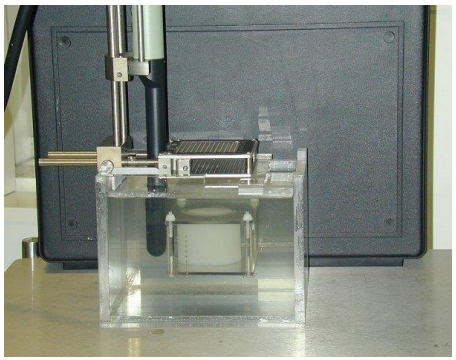


Volume Test

- Check volume captured from US is similar to the volume contoured on planning system.
- Discrepancy should be within ± 1cc.







Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 1, pp. 304–307, 2006

0360-3016/06/$–see front matter

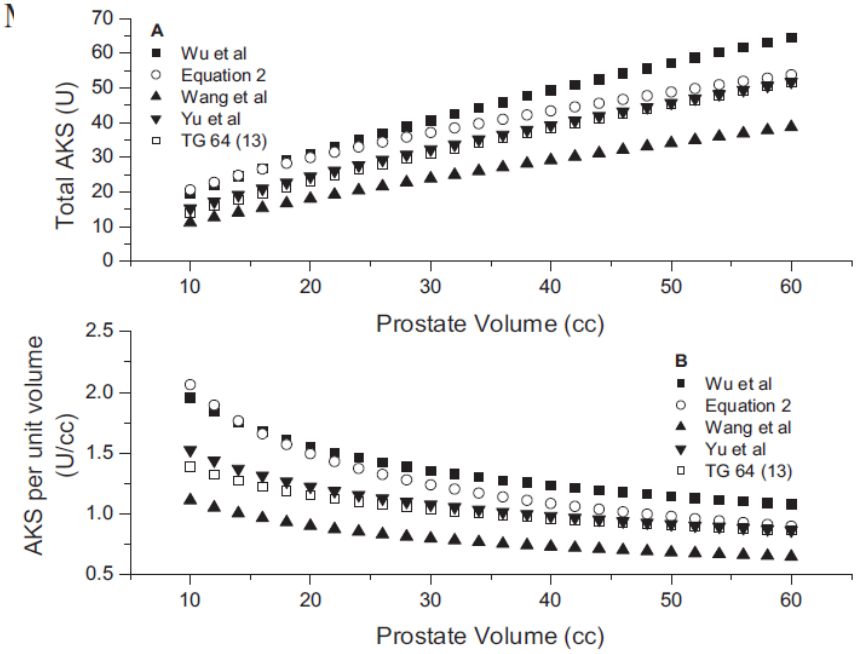
ELSEVIER

doi:10.1016/j.ijrobp.2005.12.030

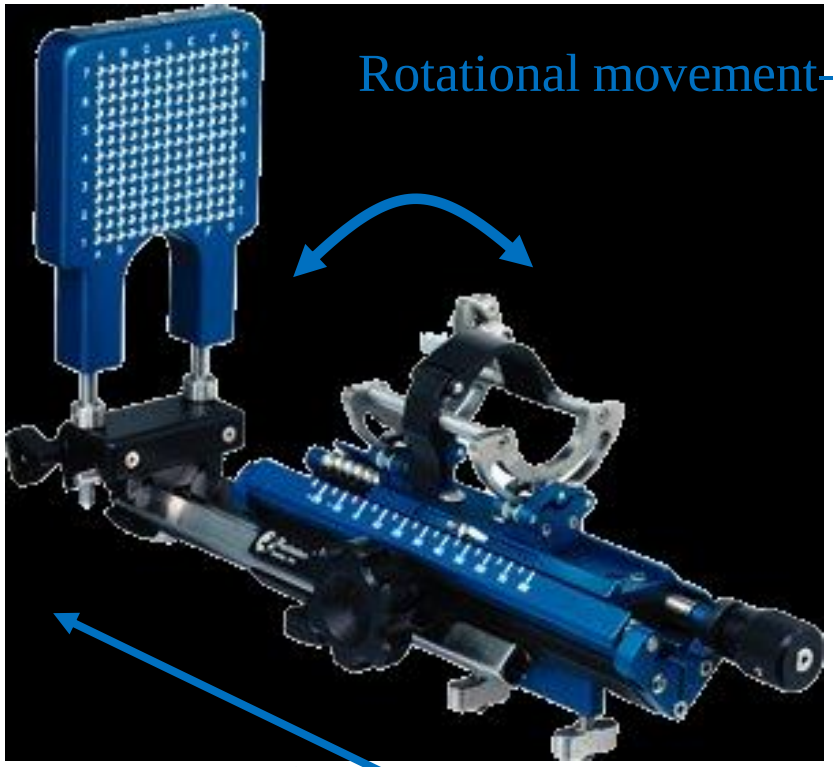
PHYSICS CONTRIBUTION

A STUDY OF A PRETREATMENT METHOD TO PREDICT THE NUMBER OF I-125 SEEDS REQUIRED FOR PROSTATE BRACHYTHERAPY

BASHAR AL-QAISIEH, PH.D., ELIZABETH BREARLEY, B.SC., SHAUN ST CLAIR, B.SC., AND ANTHONY FLYNN, M.SC.



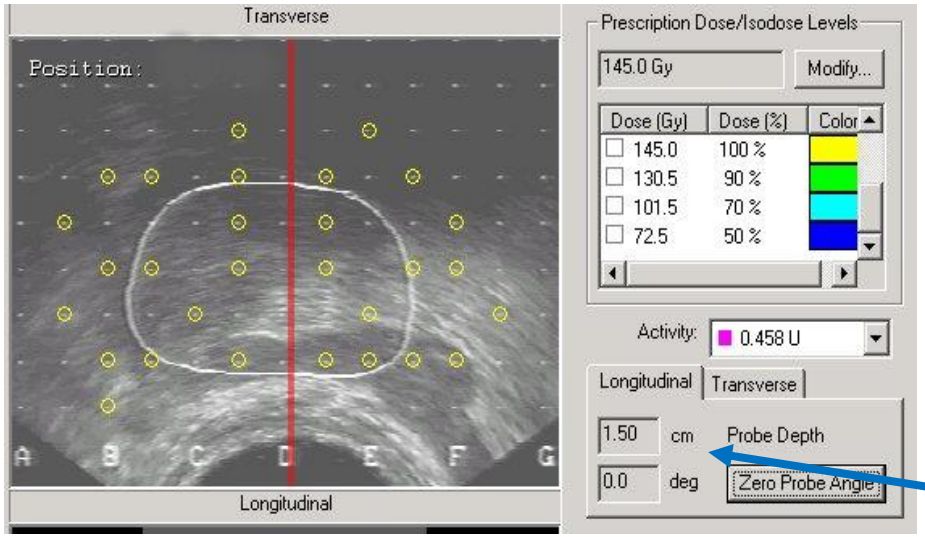
Stepper Depth and Angle Tracking Tests

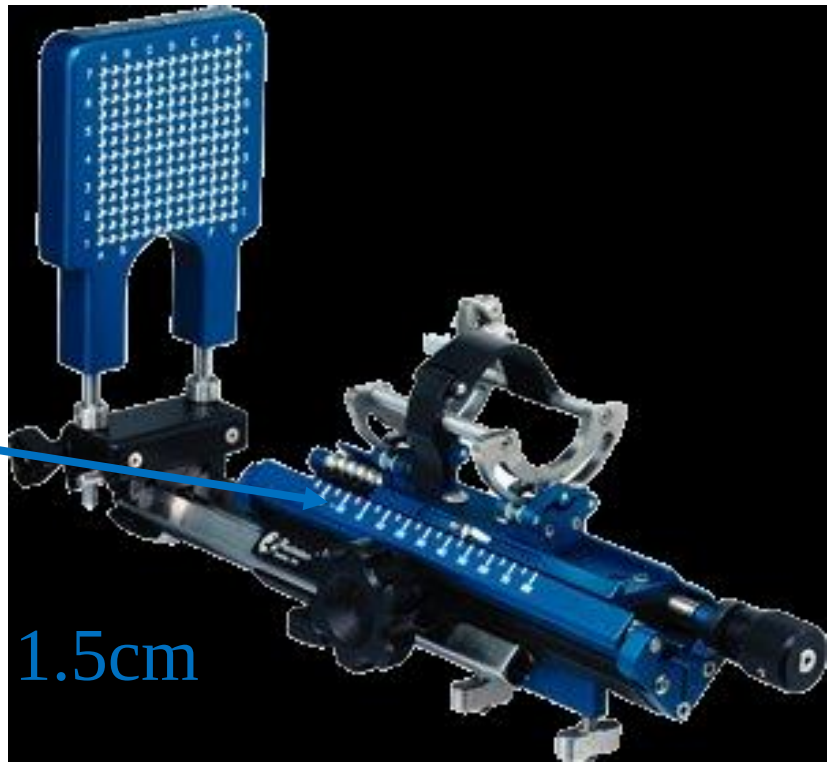


Stepper Depth and Angle Tracking Tests

- Longitudinal Position Tracking. Accuracy should be within 0.5mm.
- Rotational Tracking Test. Accuracy should be within 0.5 degrees.

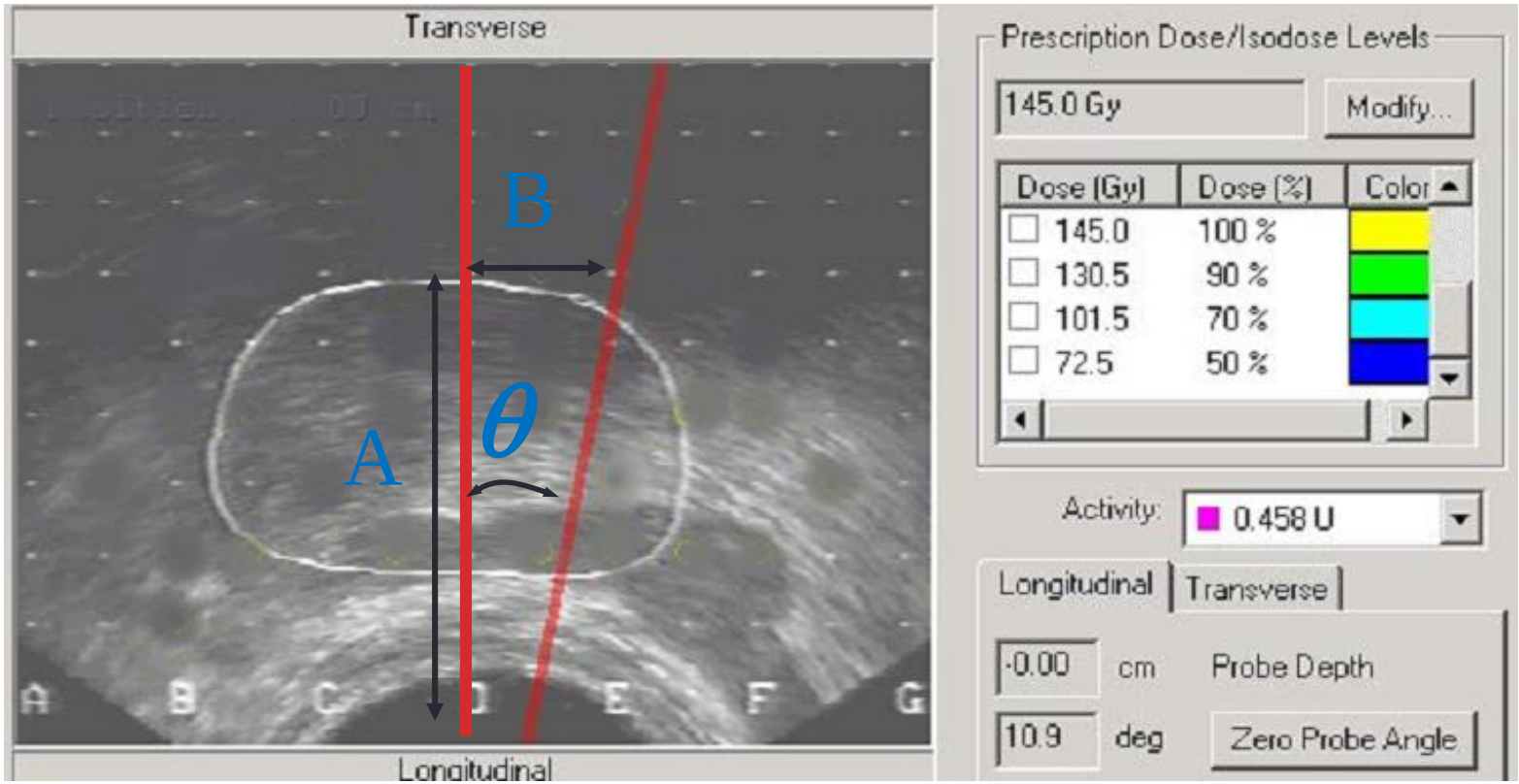
Stepper Depth Tracking Test





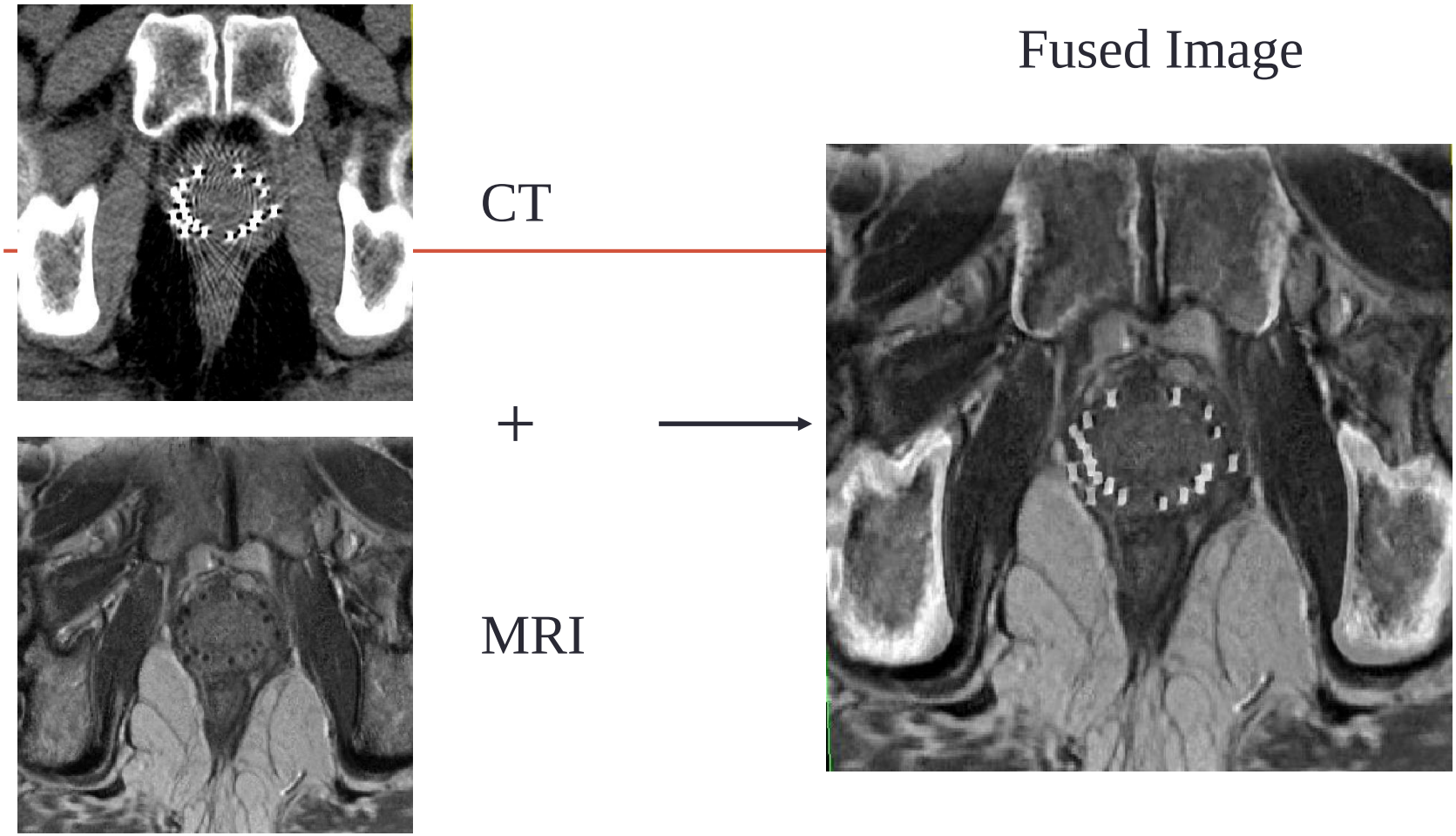
e.g: 3 clicks back = 1.5cm

Stepper Angle Tracking Test

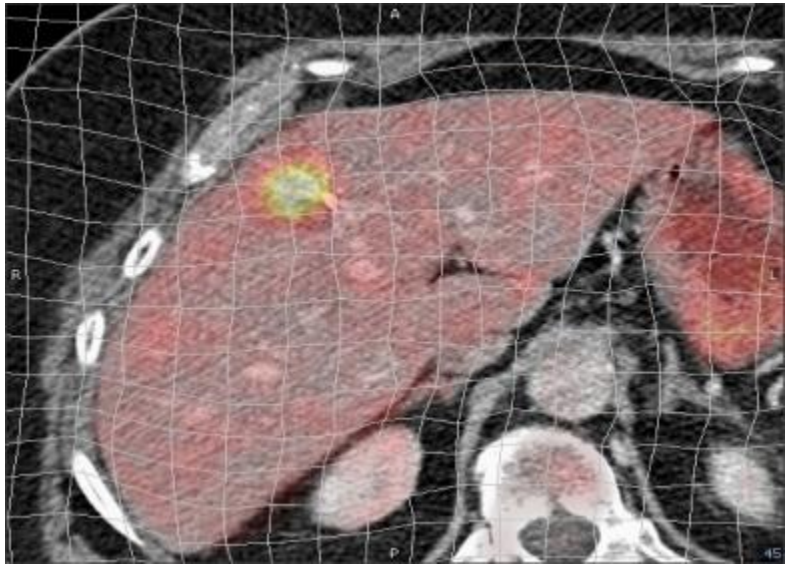


$$\theta = arc\ \tan(\frac{B}{A}) =$$

Post implant CT-MR Image Fusion QA



TG132:USE OF IMAGE REGISTRATION AND FUSION ALGORITHMS AND TECHNIQUES IN RADIOTHERAPY



CLINICAL ISSUES AND APPLICATIONS OF IMAGE REGISTRATION IN RADIOTHERAPY

- Sources of Error due to Data Acquisition
- Sources of Error in Registration
- Image Registration for Segmentation
- Image Registration for Multi-Modality or Adaptive Treatment Planning
- Image Registration for Image-Guided Radiotherapy
- Image Registration for Response Assessment

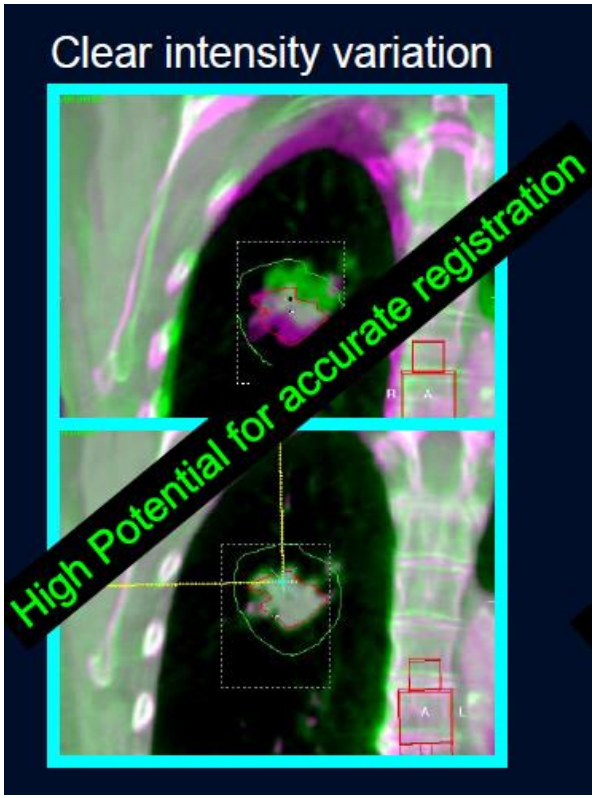
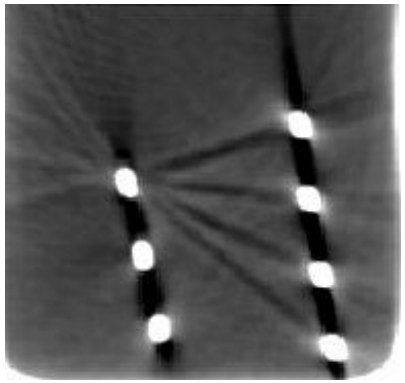


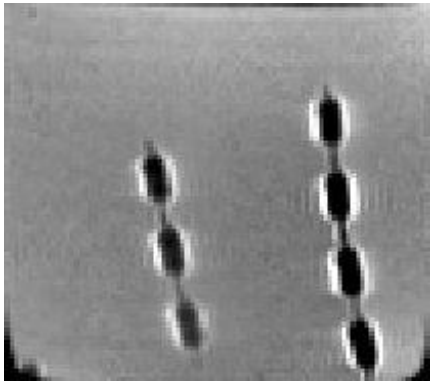
Image Fusion Protocol Phantom Study

CT



+

MRI



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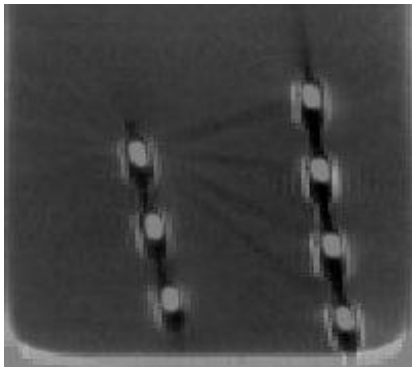
Fused Image



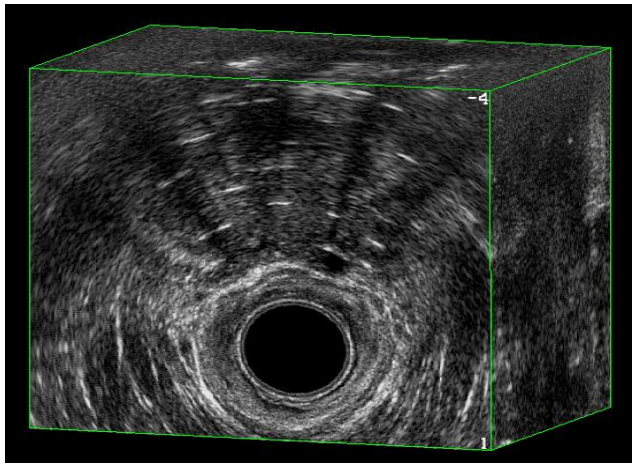
RMS Error < 1.0mm

QA for HDR Brachytherapy

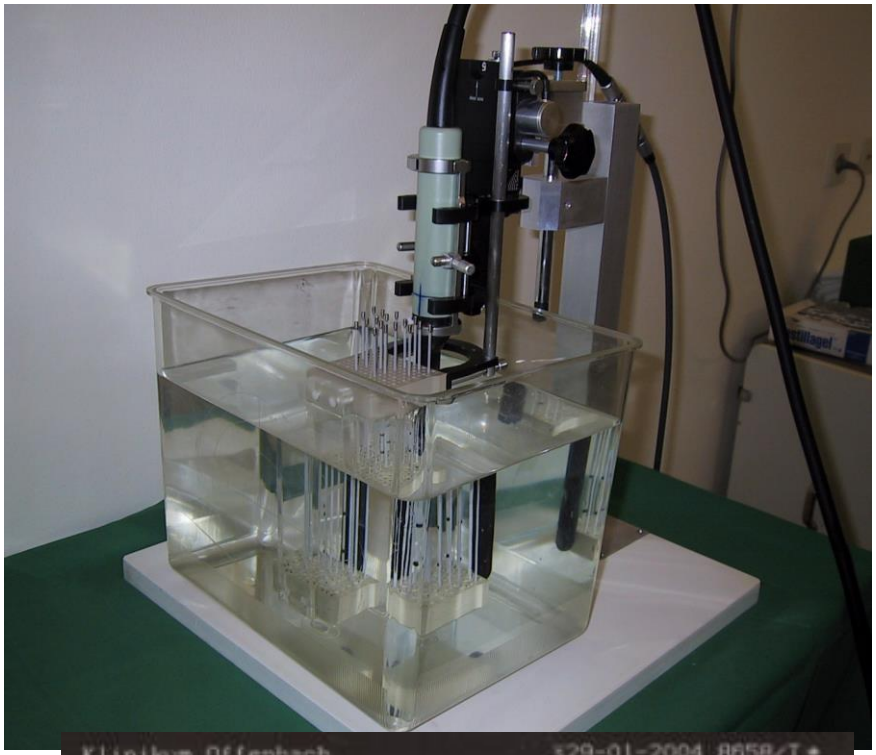
Besides the typical QA procedures established for common HDR Treatments, we need to implement additional ones

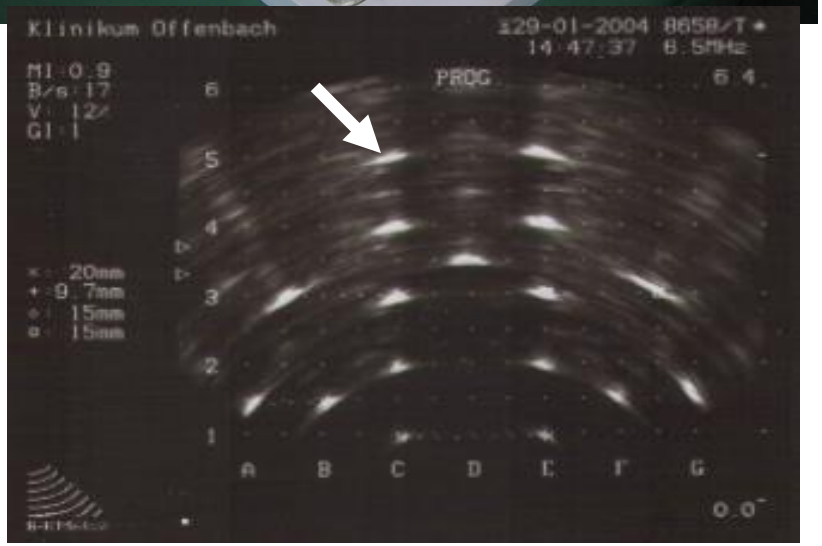
3D ultrasound

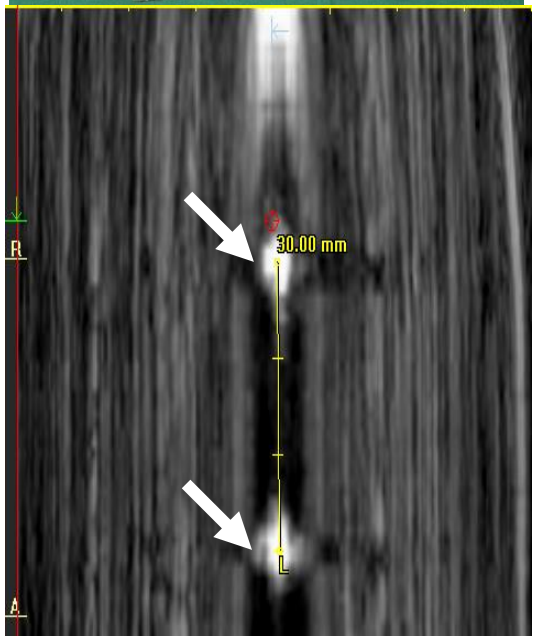
- Better visibility
- Improved treatment planning
- Reproducibility



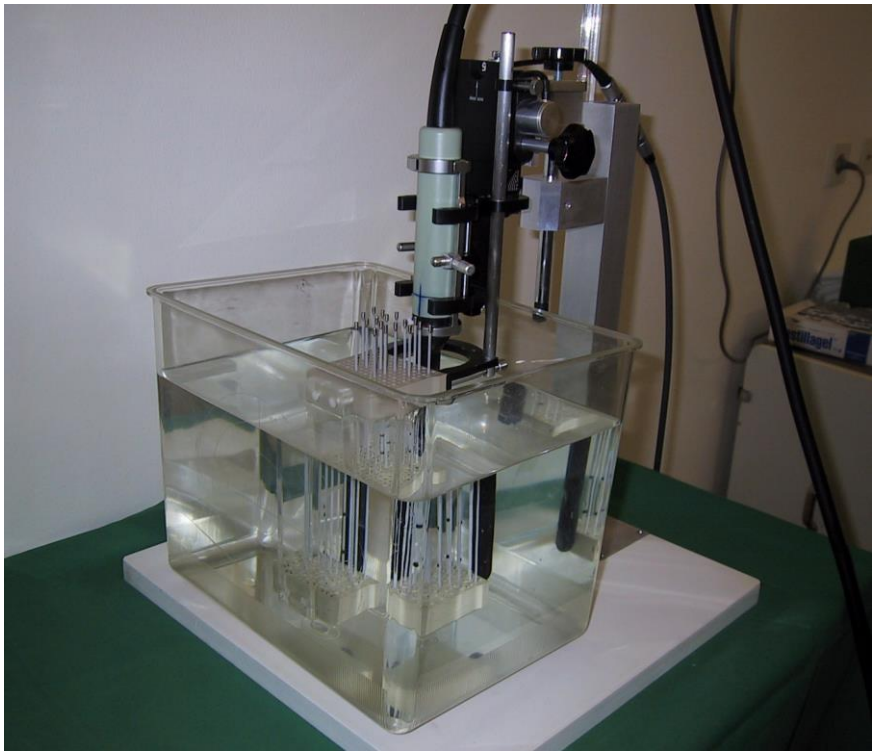
Mechanical & US Image Geometry

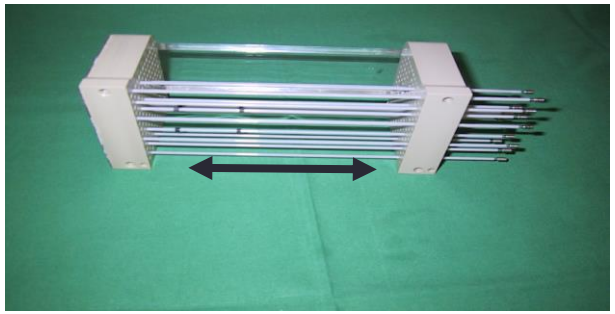


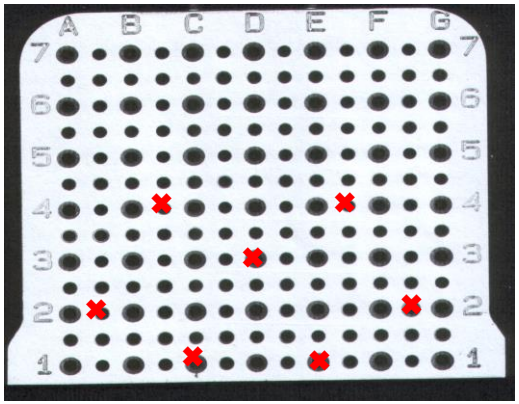




Catheter Reconstruction

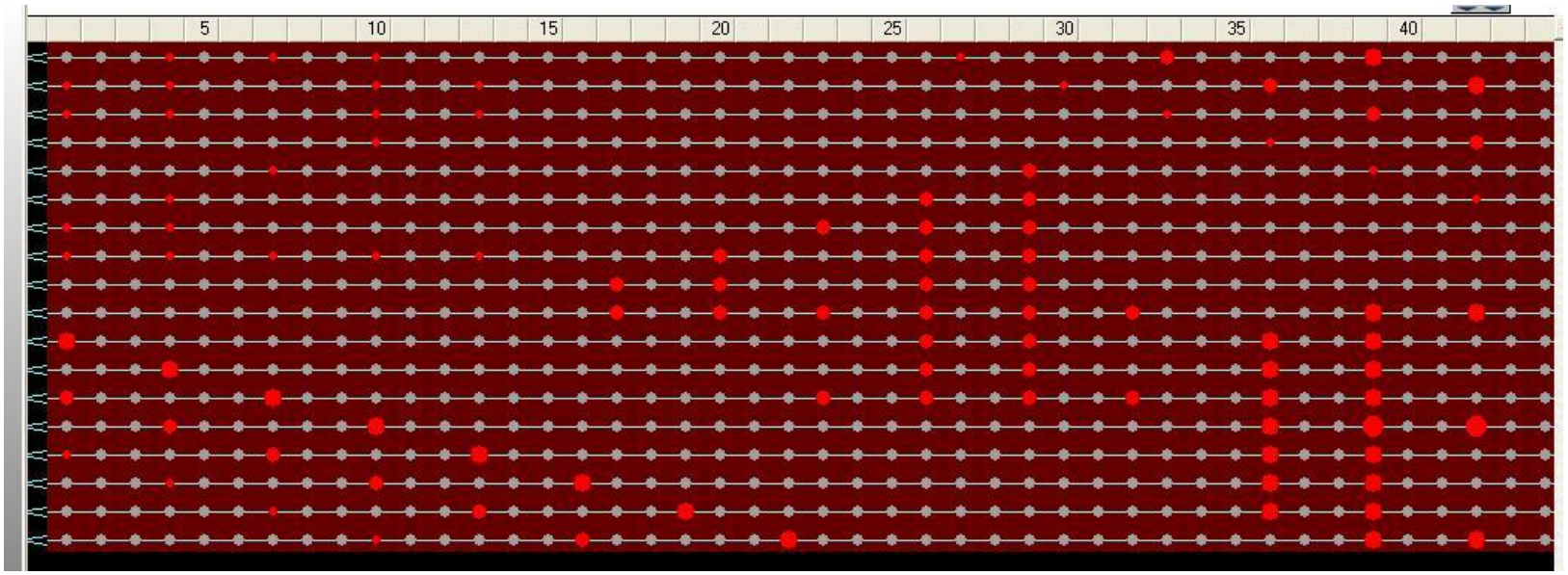






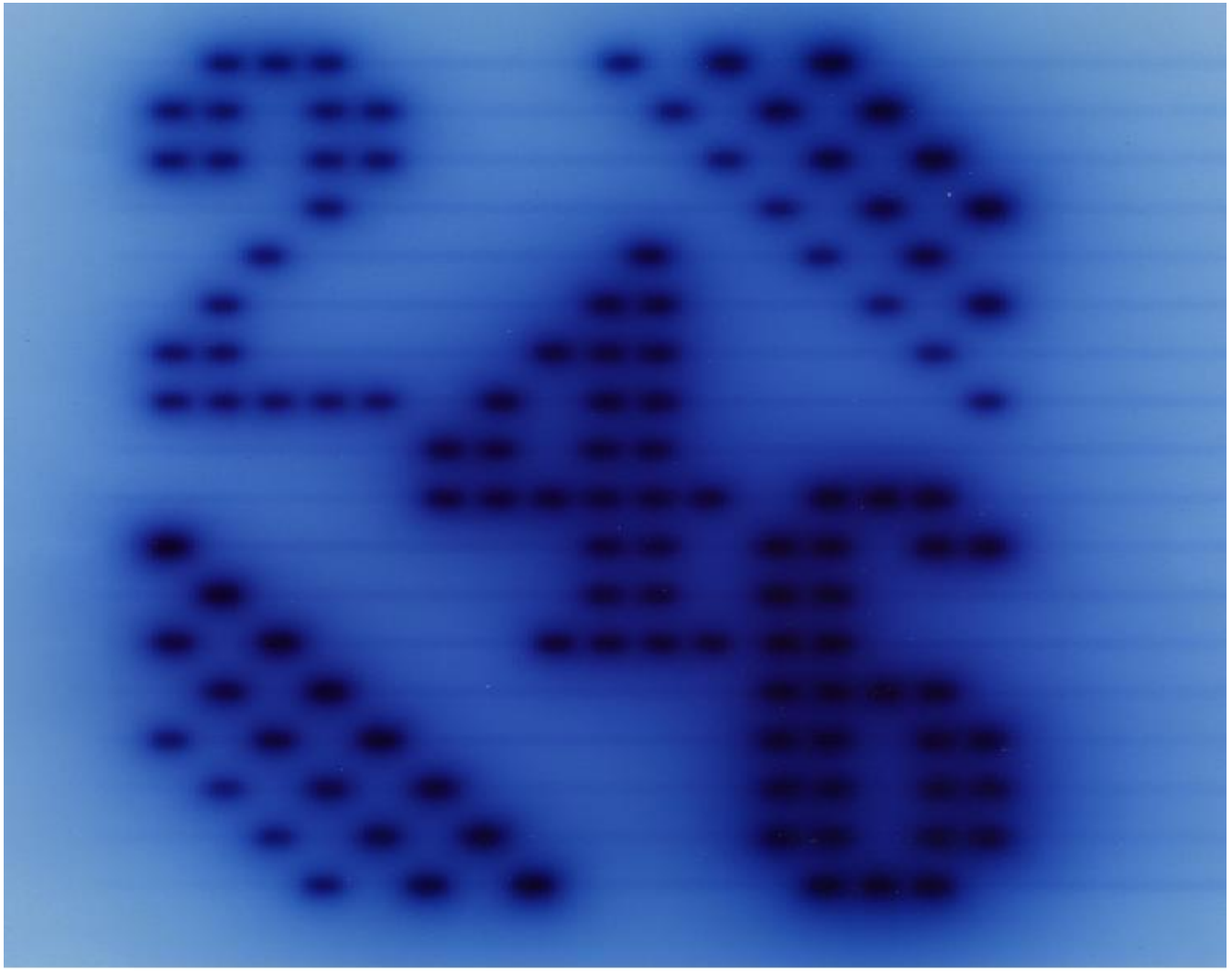
Data transfer check

e.g.



Data transfer check

e.g.



External Catheter Length QA Measurements

P.J. Hoskin et al. / Radiotherapy and Oncology 286 68 (2003) 285–288

Independent Calculation Check-TRAK

Radiotherapy and Oncology 103 (2012) 261–265

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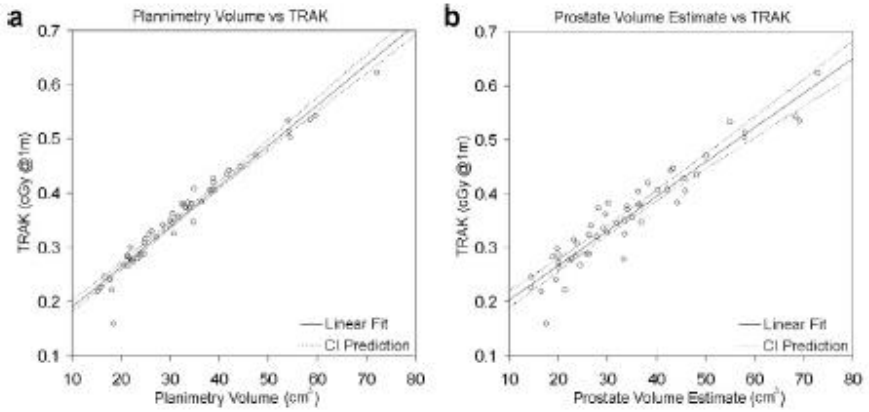
IGRT in prostate cancer

Methods of verifying the output of the treatment planning system used for high dose rate (HDR) prostate brachytherapy

Aaron Huckle *, Bashar Al-Qaisieh, Peter Bownes

St. James's Institute of Oncology, St. James's Hospital, Leeds, UK



Example

Treatment Plan Parameters					
AKR:	25133.67	cGy/h @1m			
Dwell Time:	513.69	s		Height	2.600
Fraction Dose:	15	Gy		Width	3.800
Actual TRAK:	0.3586	cGy/h @1m		Length	2.700
Corrected TRAK' :	0.2482	cGy/h @1m			
TRAK Verification					
Estimate PTV:	16.15	cm^3			
			Error:	-0.85cc	-5.02%
Actual PTV:	17.00	cm^3	WITHIN +/- 10%		
Predicted TRAK:	0.2429	cGy/h @1m	Error:	-2.14%	
(Using Estimate PTV)			WITHIN +/- 10%		
Predicted TRAK:	0.2427	cGy/h @1m	Error:	-2.23%	
(Using Actual PTV)			WITHIN +/- 10%		
Treatment plan verification:			PASSED		

with methods independent of the TPS

Summary

- Seed Calibration (Constancy check)
- Template Calibration
- Ultrasound Machine Check
- Commissioning Planning System
  - Test 1: Dose Point Calculation Test
  - Test 2: Isodose Level Test
  - Test 3: Volume and Dose Volume Test
  - Test 4: Anisotropy Function/Line Source Calculation
  - Test 5: Data transfer
  - Test 6: Stepper Depth and Angle Tracking Tests
- Treatment Plan Check
  - Check list
- Post Implant QA

Prostate Brachytherapy Course

“CTV”

C. Salembier

Prostate Brachytherapy Course

"CTV"

C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

Planning : the delineation and definition of GTV, CTV and PTV

-Delineation of the prostate gland

-Delineation of the urethra prostatica

-Delineation of the anterior rectal wall

-Definition of Gross Tumour Volume - GTV

-Definition of Clinical Target Volume - CTV

-Definition of Planning Target Volume - PTV

Gross tumour volume

GTV

The gross palpable,visible or clinically demonstrable location and extent of the malignant growth.

Prostate brachytherapy:

Delineation of the GTV is possible in T2a or T2b (or higher stage)

Eventually important for location for boost dose

Clinical Target Volume

CTV

Is a tissue volume that contains the GTV and/or subclinical malignant disease at a certain probability level.

The CTV is a clinical-anatomical concept. Delineation of the CTV is based on the probability of presence of subclinical malignant cells outside the GTV and thus requires the interpretation of data and some judgment of the radiation oncologist.

Planning Target Volume

PTV

The PTV surrounds the CTV with a margin to compensate for the different types of variations and uncertainties of treatment delivery to the CTV.

The PTV is a geometrical concept, introduced for treatment planning.

A margin must be added to the CTV

- ***to compensate for expected physiological movements and variations in size, shape and position of the CTV during therapy (internal margin)***
- ***for uncertainties (inaccuracies and lack of reproducibility) in patient irradiation.***

Questionnaire (49 European brachytherapy centers – 2007):

Prostate brachytherapy

CTV =

Prostate contour: 100 %

PTV = CTV + margin

Prostate + 0 mm = 18/49

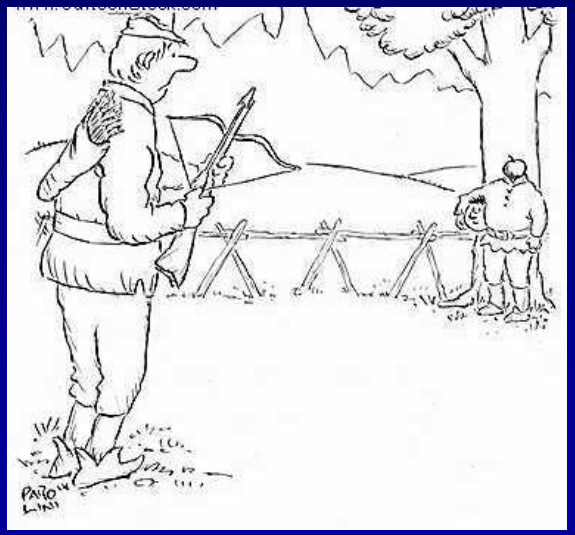
Prostate + margin = 31/49

base :	**0 mm = 13**
	3 – 5 mm = 25
	> 5mm = 5
midgland:	**0 mm= 13**
	3 – 5 mm = 28
	> 5 mm = 0
apex :	**0 mm = 13**
	3 – 5 mm = 27
	> 5 mm = 1

peri-prostatic extension ?

CTV = ?

subclinical disease ?

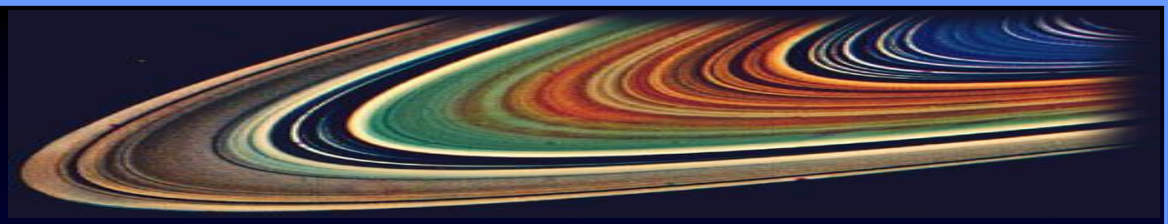


uncertainties in placement ?

PTV = ?

change of position ?

Margins ? ! ?



As shown, most centers consider a margin around the drawn prostatic contour for treatment planning.

But margins for ……

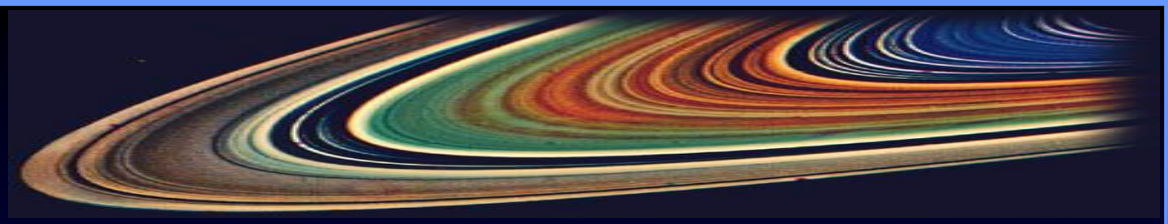
- ***microscopic spread ?***
- ***peri-prostatic extension ?***
- ***subclinical disease ?***

Δ CTV definition

- ***uncertainties in seed placement ?***
- ***change of volume ?***
- ***change of position ?***

Δ PTV definition

Margins ? ! ?



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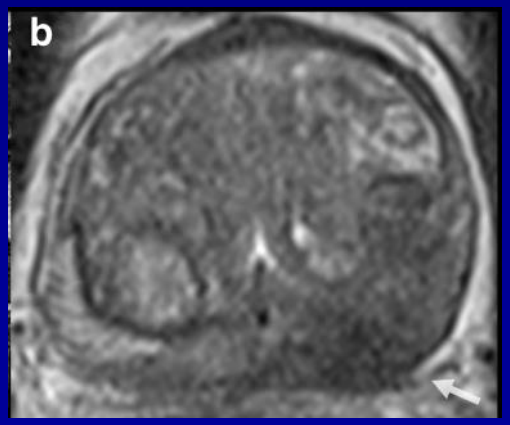
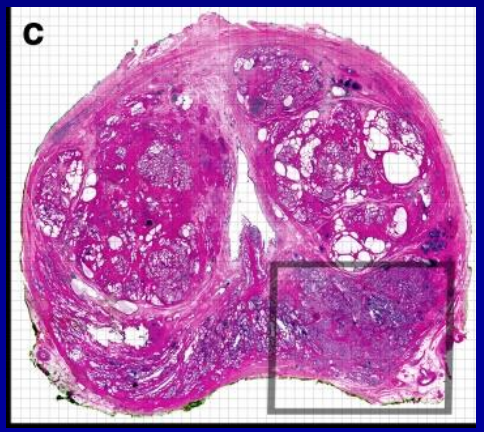
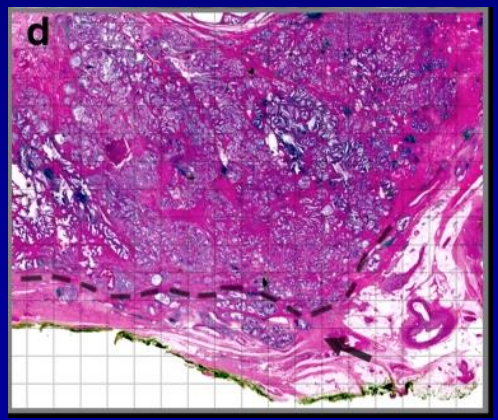
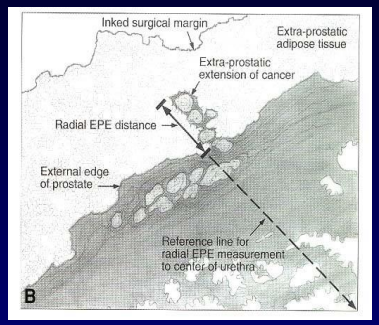
Δ CTV definition





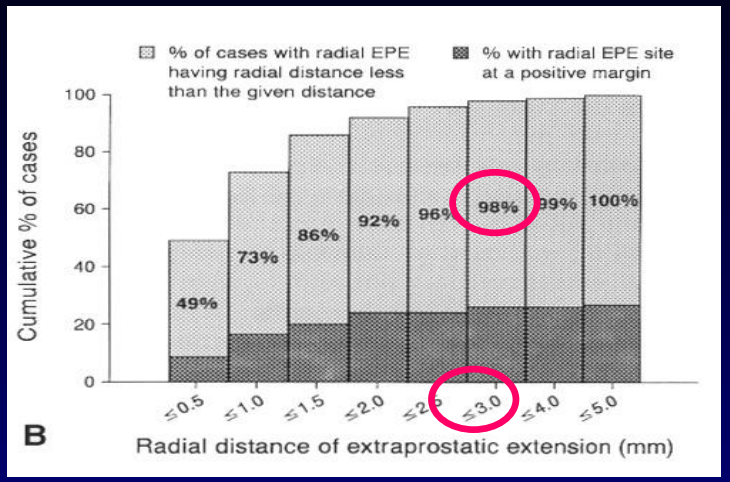


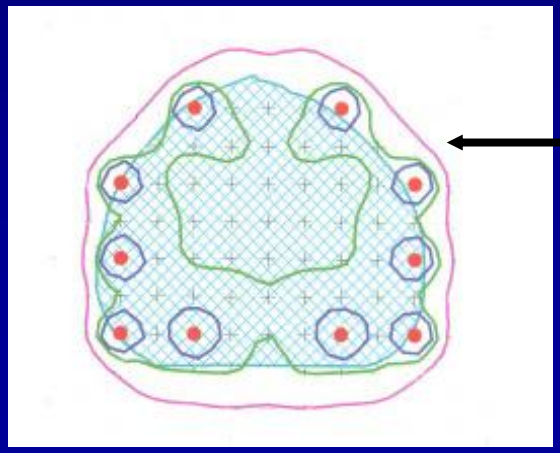
Extra-prostatic disease:



-105 prostatectomies
-Gleason 6.3 (range 3-9)
-PSA 8.6 (range 0.3-98)

Davis et al. Cancer 85(12) 1999



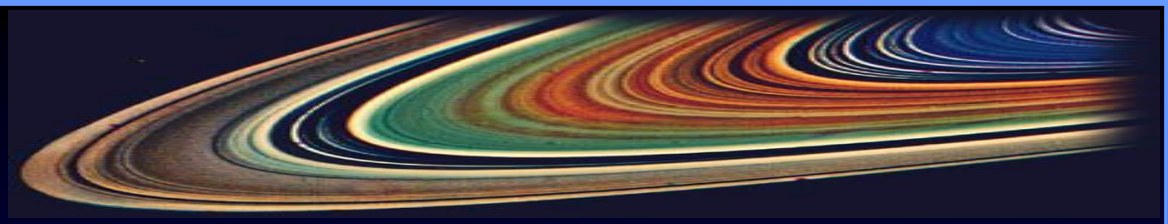


Extraprostatic disease

3 mm margins :

critical to success

Margins ? ! ?



So margins for ……

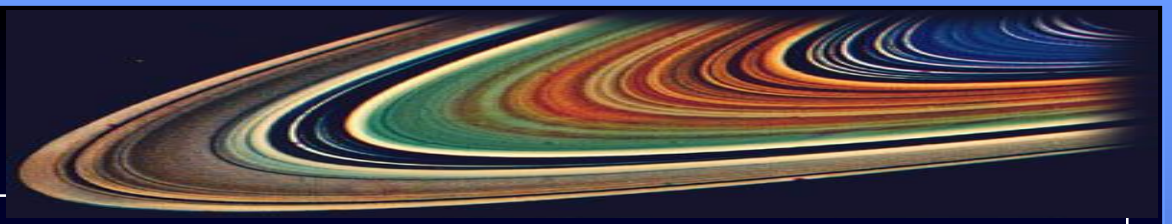
- ***microscopic spread ?***
- ***peri-prostatic extension ?***
- ***subclinical disease ?***

Δ CTV definition

ONE DEFINITION:

For prostate brachytherapy the **CTV corresponds to the visible contour of the prostate expanded with a three-dimensional volume expansion of 3 mm**.
This three-dimensional expansion can be constrained to the anterior rectal wall (posterior direction) and the bladder neck (cranial direction).
In case of >T2 disease, the macroscopic extracapsular extension in taken into account when contouring the prostate volume.

Margins ? ! ?



But margins for ……

- *uncertainties in seed placement ?*
  - *x/y direction – no problems*
  - *z direction – corrections during implantation*
- *change of volume ?*
  - *only temporary problem*
  - *edema resolves within the first ½ life of seeds*
- *change of position ?*
  - **eventual use of stabilization needles**
  - **continuous on-line verification of position**

So: *forget about margins for PTV definition ⟶ PTV = CTV*

Radiotherapy and Oncology 83 (2007) 3–10
www.thegreenjournal.com

Guidelines prostate brachytherapy

Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy

Carl Salembier[a], Pablo Lavagnini[b], Philippe Nickers[c], Paola Mangili[d], Alex Rijnders[a], Alfredo Polo[e], Jack Venselaar[f], Peter Hoskin[g,*], on behalf of the PROBATE group of GEC ESTRO

[a]*Department of Radiation Oncology, Europe Hospitals, Brussels, Belgium,* [b]*Department of Radiation Oncology, MultiMedica Institute, Milan, Italy,* [c]*Department of Radiation Oncology, Domaine Universitaire du Sart Tilman, Liège, Belgium,* [d]*Department of Medical Physics, IRCCS, S-Raffaele, Milan, Italy,* [e]*Department of Radiation Oncology, Catalan Institute of Oncology, Barcelona, Spain,* [f]*Department of Radiotherapy, Dr B. Verbeeten Institute, Tilburg, The Netherlands,* [g]*Mount Vernon Cancer Centre, Northwood, UK*

The aim of this paper is to supplement the GEC/ESTRO/EAU recommendations for permanent seed implantations in prostate cancer to develop consistency in target and volume definition for permanent seed prostate brachytherapy.

Recommendations on target and organ at risk (OAR) definitions and dosimetry parameters to be reported on post implant planning are given.

Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy

Carl Salembier[a], Pablo Lavagnini[b], Philippe Nickers[c], Paola Mangili[d], Alex Rijnders[a], Alfredo Polo[e], Jack Venselaar[f], Peter Hoskin[g,*], on behalf of the PROBATE group of GEC ESTRO

In addition:

Description of :

- Organs at risk contouring
- Recommended prescription doses
- Dosimetric parameters related to ICRU definitions for dose prescription
- Physical parameters for dose reporting
- Post-planning – definitions and parameters
-Target definition in relation to the post-plan dosimetry
- Dose parameters in the post-implant setting

The aim of this paper is to supplement the GEC/ESTRO/EAU recommendations for permanent seed implantations in prostate cancer to develop consistency in target and volume definition for permanent seed prostate brachytherapy.

Recommendations on target and organ at risk (OAR) definitions and dosimetry parameters to be reported on post implant planning are given.

AAPM recommendations on dose prescription and reporting methods for permanent interstitial brachytherapy for prostate cancer: Report of Task Group 137

sist in understanding differences in outcomes and morbidity as well as differences in postoperative dosimetry. Users are encouraged to use the following definitions and procedures for planning and postimplant evaluations, which were proposed by the PROBATE group of GEC ESTRO.[19] A brief summary of these PROBATE recommendations is presented below, and the reader is referred to the original document by Salembier *et al.* for details.[19] We acknowledge that parts of the following recommendations in this section were based on this protocol.

The aim of this paper is to supplement the GEC/ESTRO/EAU recommendations for permanent seed implantations in prostate cancer to develop consistency in target and volume definition for permanent seed prostate brachytherapy.

Recommendations on target and organ at risk (OAR) definitions and dosimetry parameters to be reported on post implant planning are given.

ELSEVIER

BRACHYTHERAPY

Brachytherapy 11 (2012) 6–19

American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy

Brian J. Davis[1,*], Eric M. Horwitz[2], W. Robert Lee[3], Juanita M. Crook[4], Richard G. Stock[5], Gregory S. Merrick[6], Wayne M. Butler[6], Peter D. Grimm[7], Nelson N. Stone[8], Louis Potters[9], Anthony L. Zietman[10], Michael J. Zelefsky[11]

Table 5
Prescription doses to the planning target volume

^{125}I	
Monotherapy	140–160 Gy

lymph node involvement. Consequently, the recommended margin of 5 mm around the prostate to form the planning target volume in all directions except posteriorly should readily encompass the vast majority of occult EPE in intermediate-risk disease. Furthermore, the radiation dose

The Corner Stone =

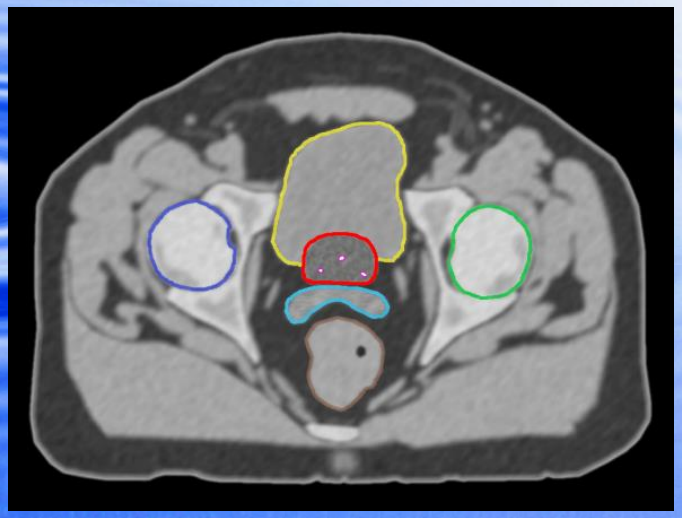
DELINEATION

Increasing importance of an accurate target definition because of highly conformal therapies

- *Underestimation* of prostate volume: possible under dosage and treatment failure

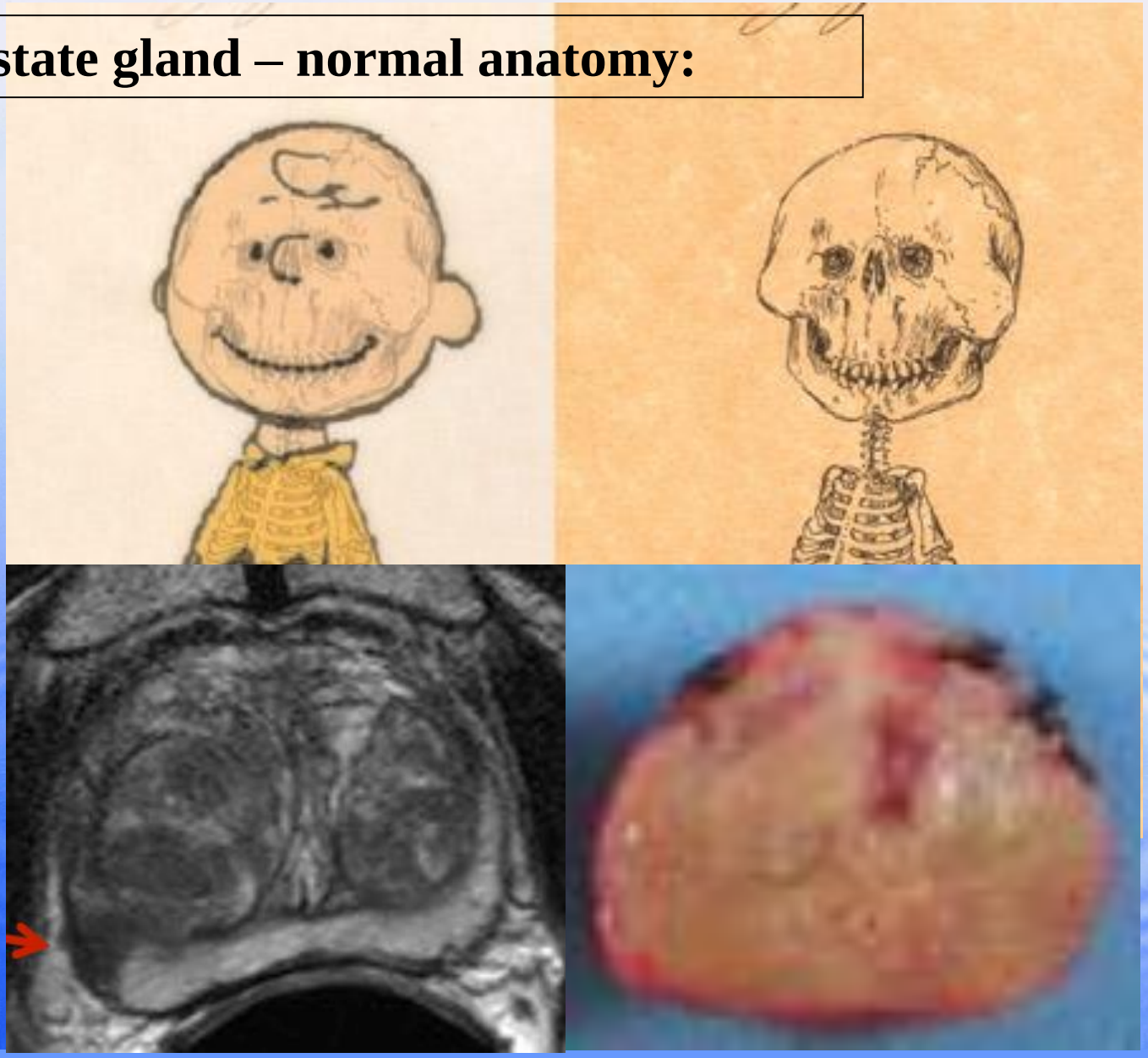
- *Overestimation* of prostate volume: risk of increased acute and late toxicity.

Optimal result of a prostate contouring exercise




Reality ?

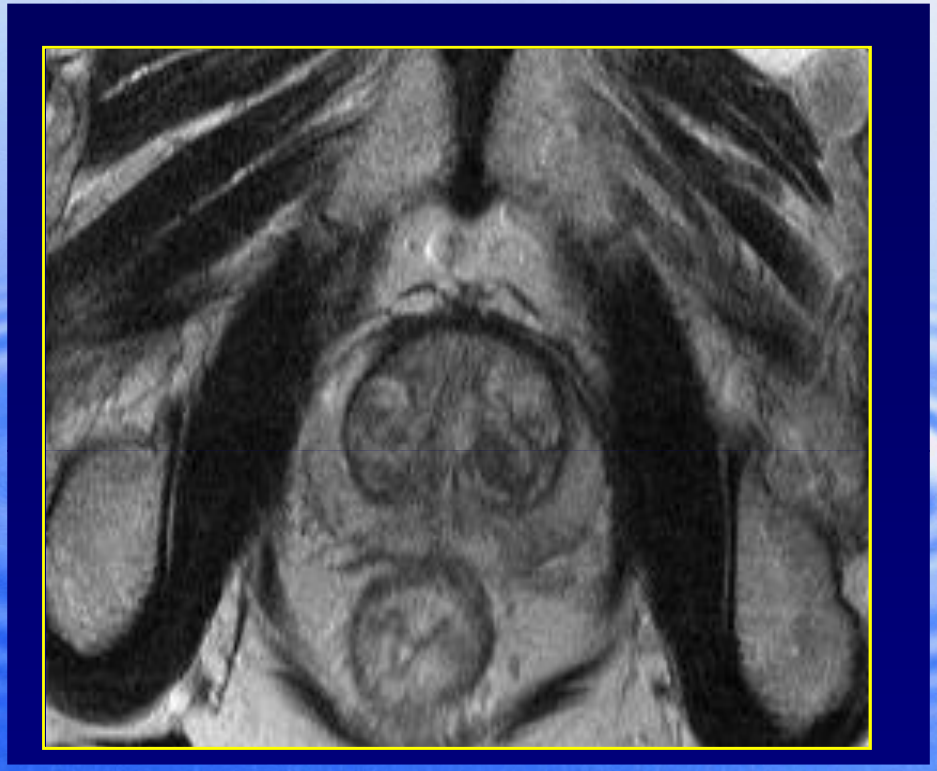
Prostate gland – normal anatomy:

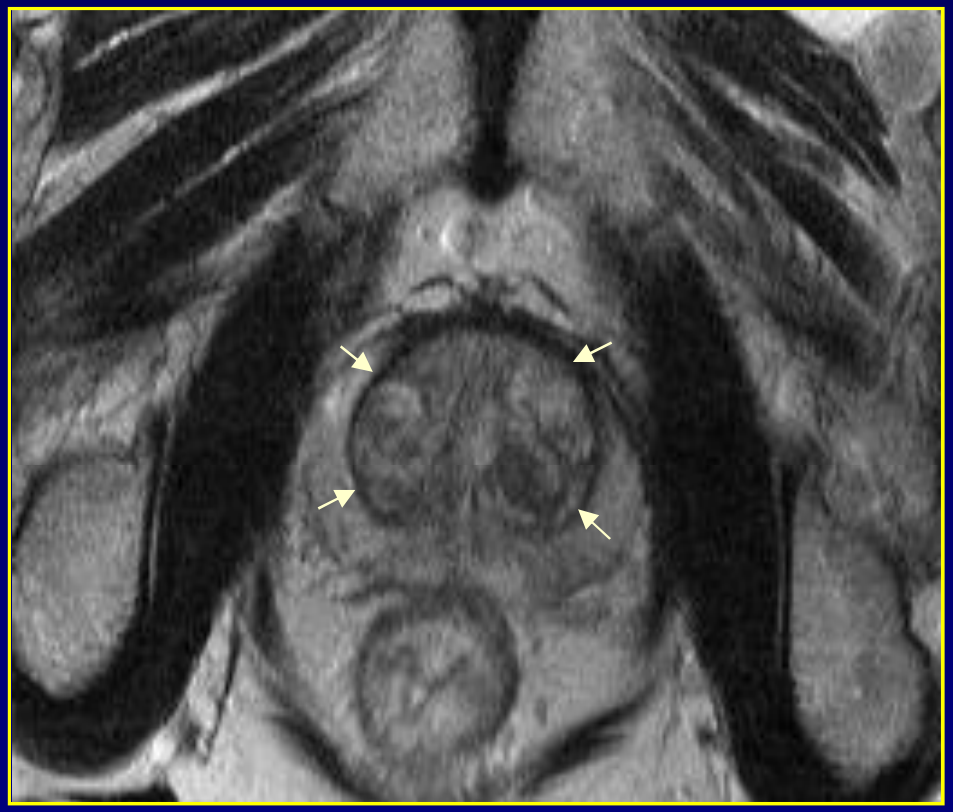


MRI:

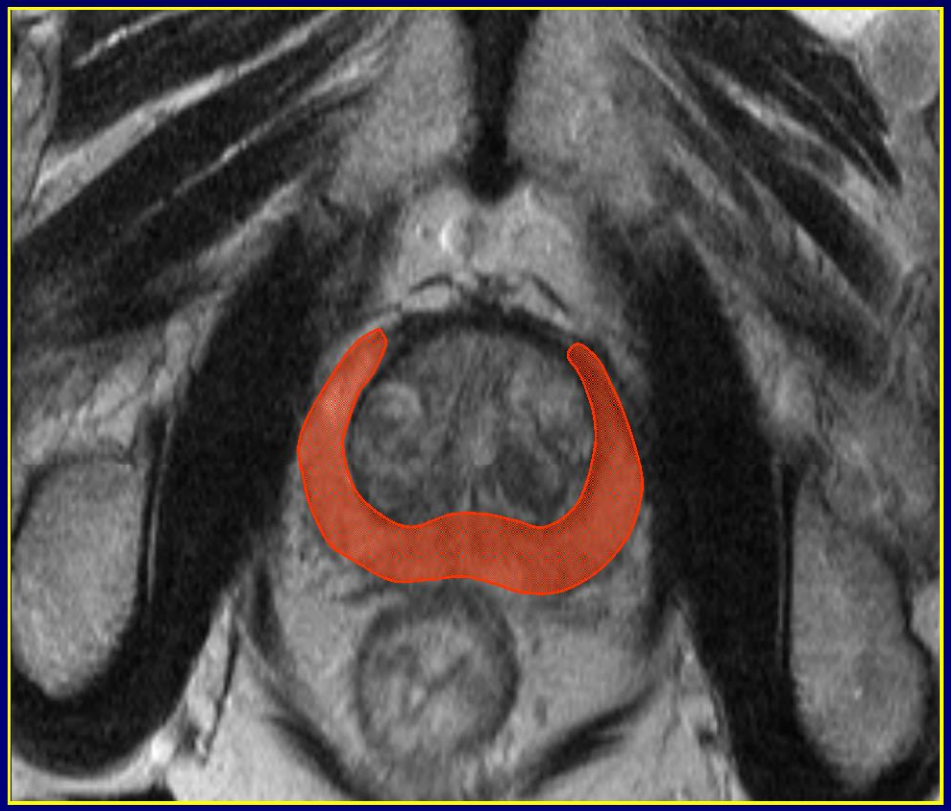
- superb soft tissue contrast (T2w)
- direct multi-planar image acquisition

→ more detailed than CT

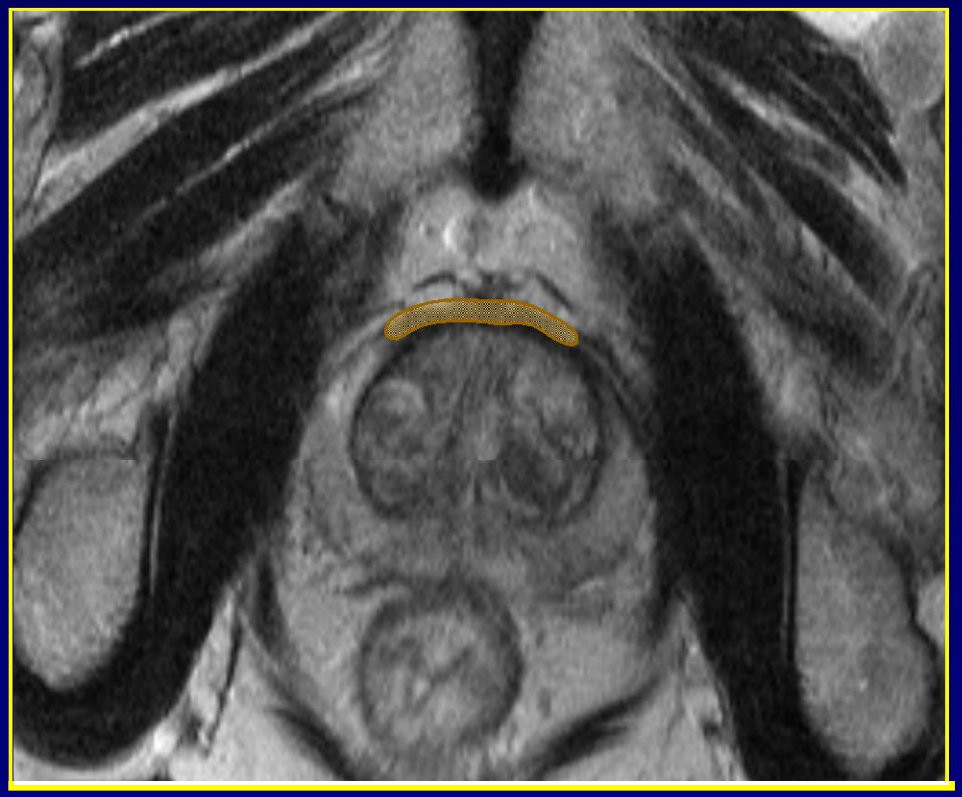




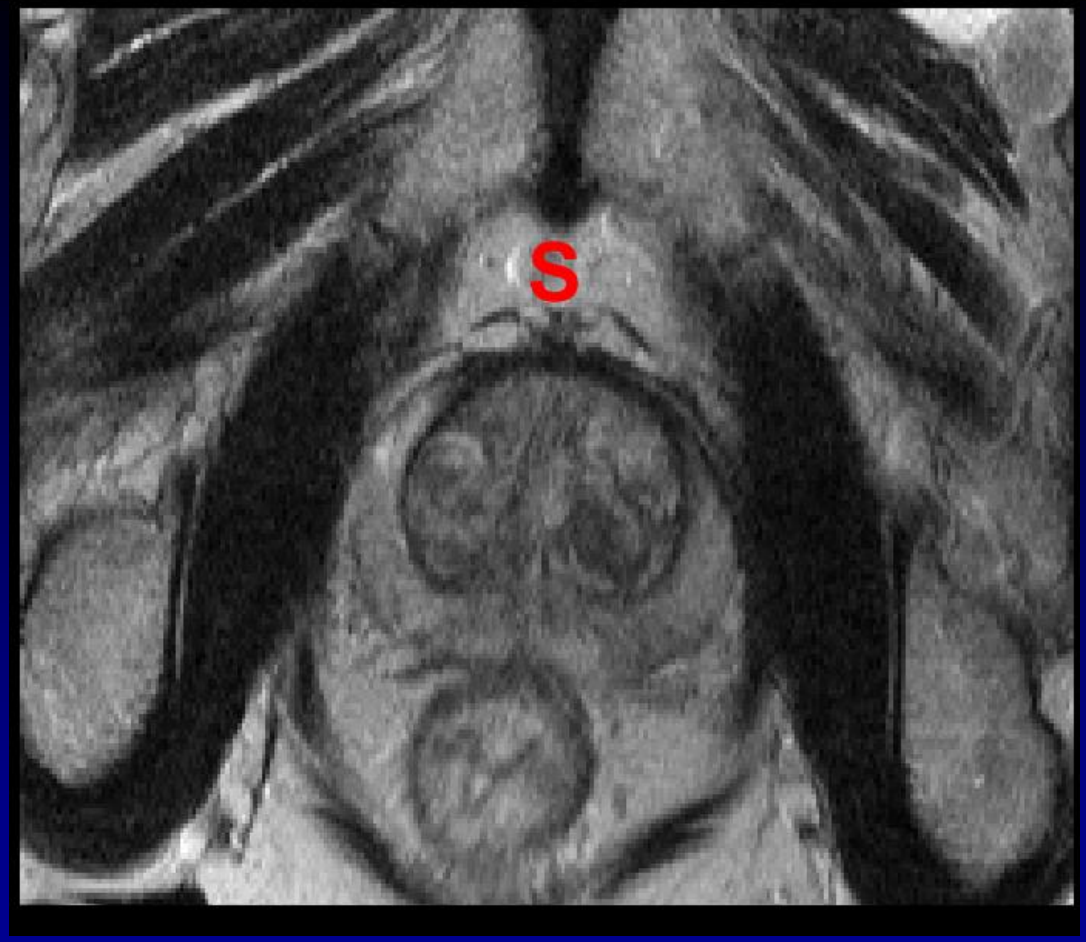
Central Zone =
Surgical Pseudocapsule



Peripheral Zone



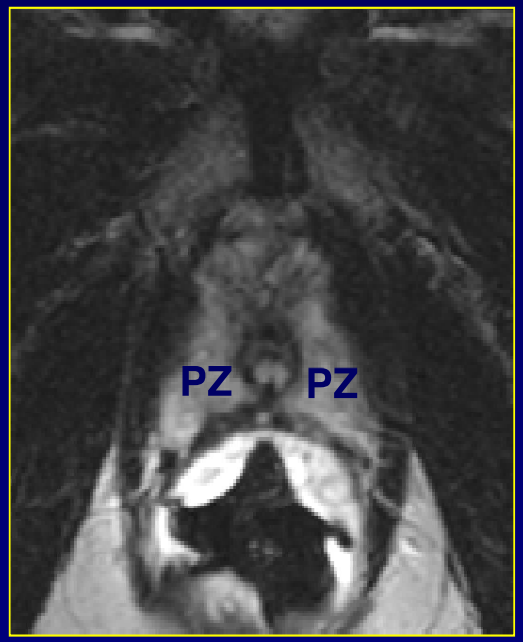
Anterior
Fibromuscular
Stroma



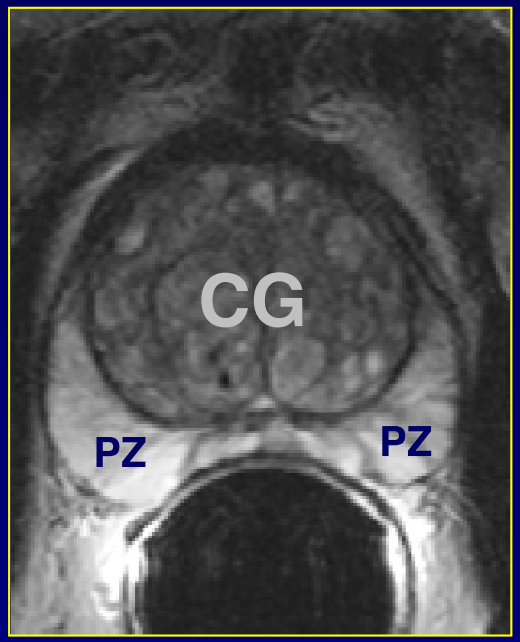
Santorini Plexus

Anatomy

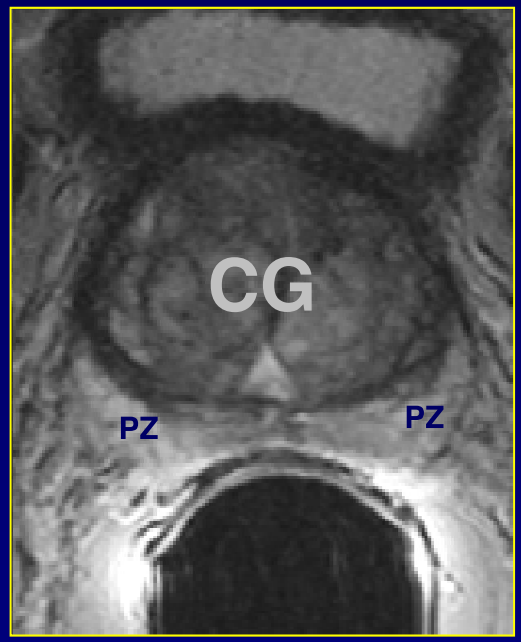
Prostate



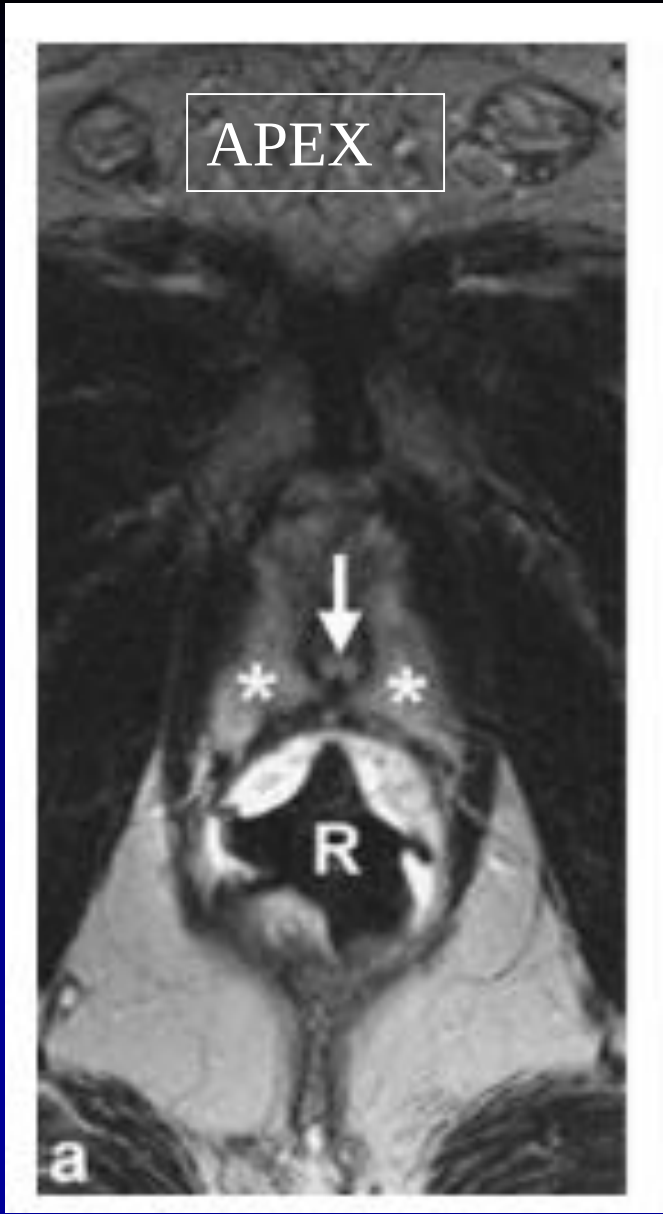
Prostatic Apex



Midprostate

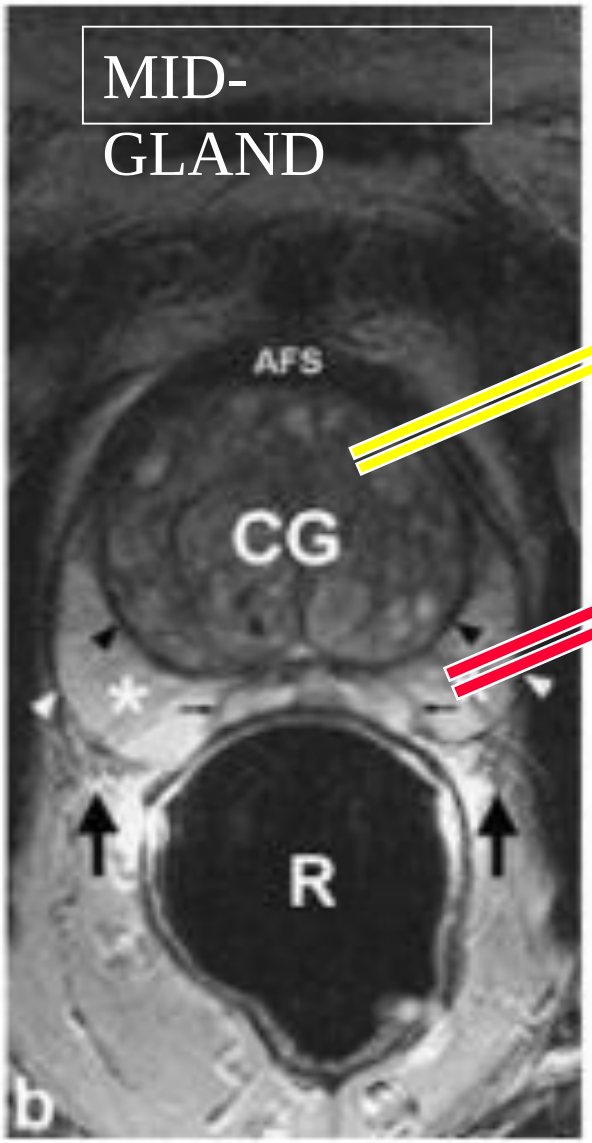


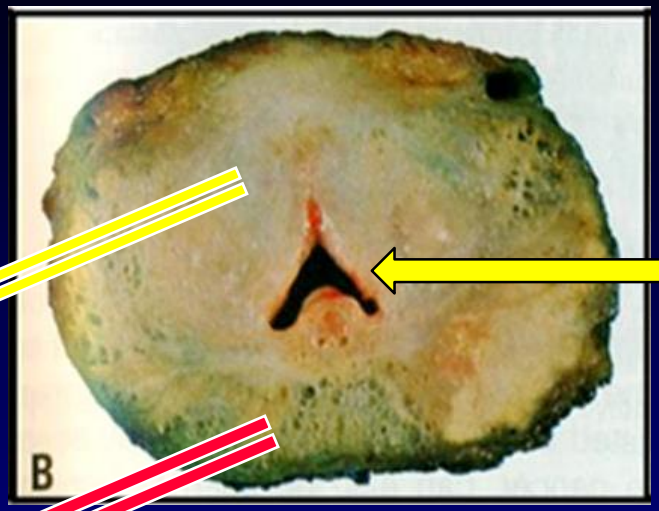
Prostatic Base

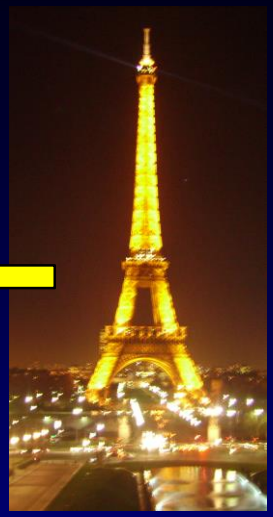


- Distal part of the prostatic urethra
- High signal-intensity peripheral zone tissue

MID-
GLAND



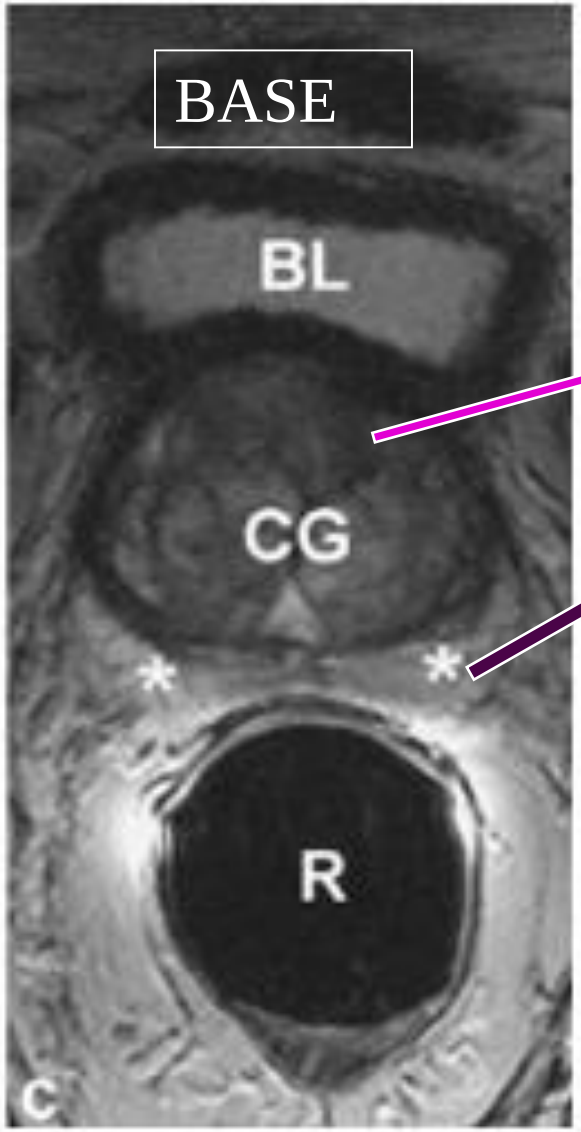


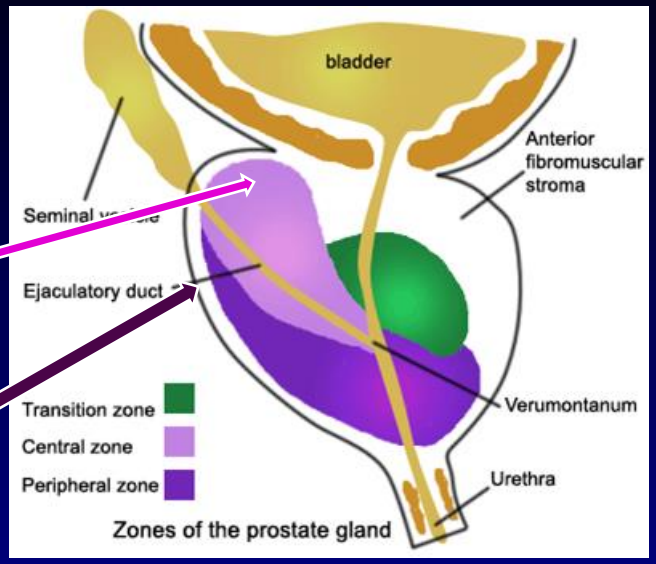


- Mixed signal-intensity central gland

- High signal-intensity peripheral zone tissue
- Dark fibromuscular rim (prostatic capsula)

- (anterior fibromuscular stroma)
- (neurovascular bundles)

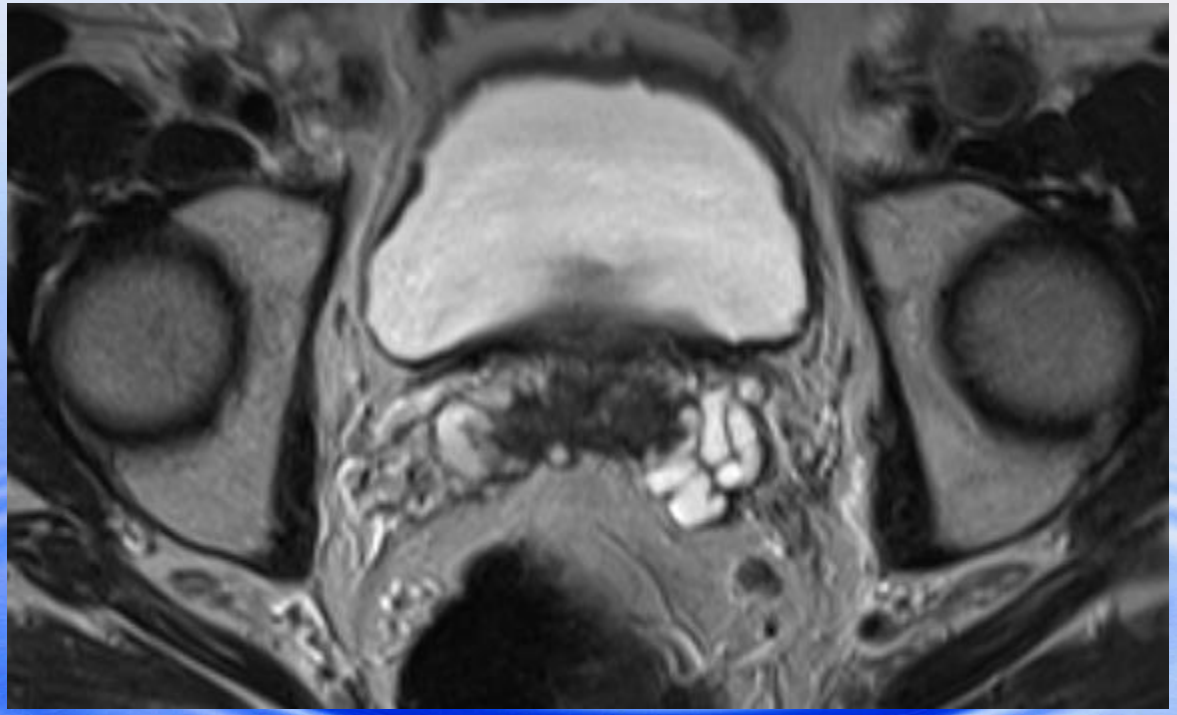


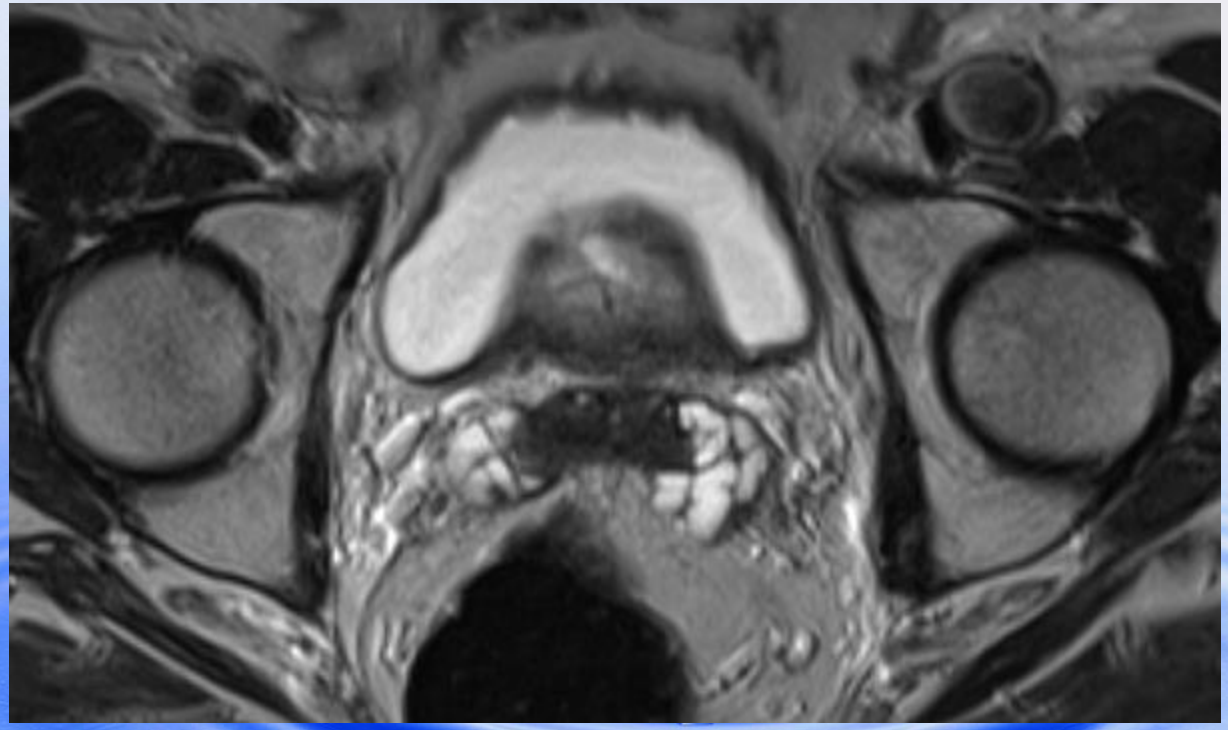


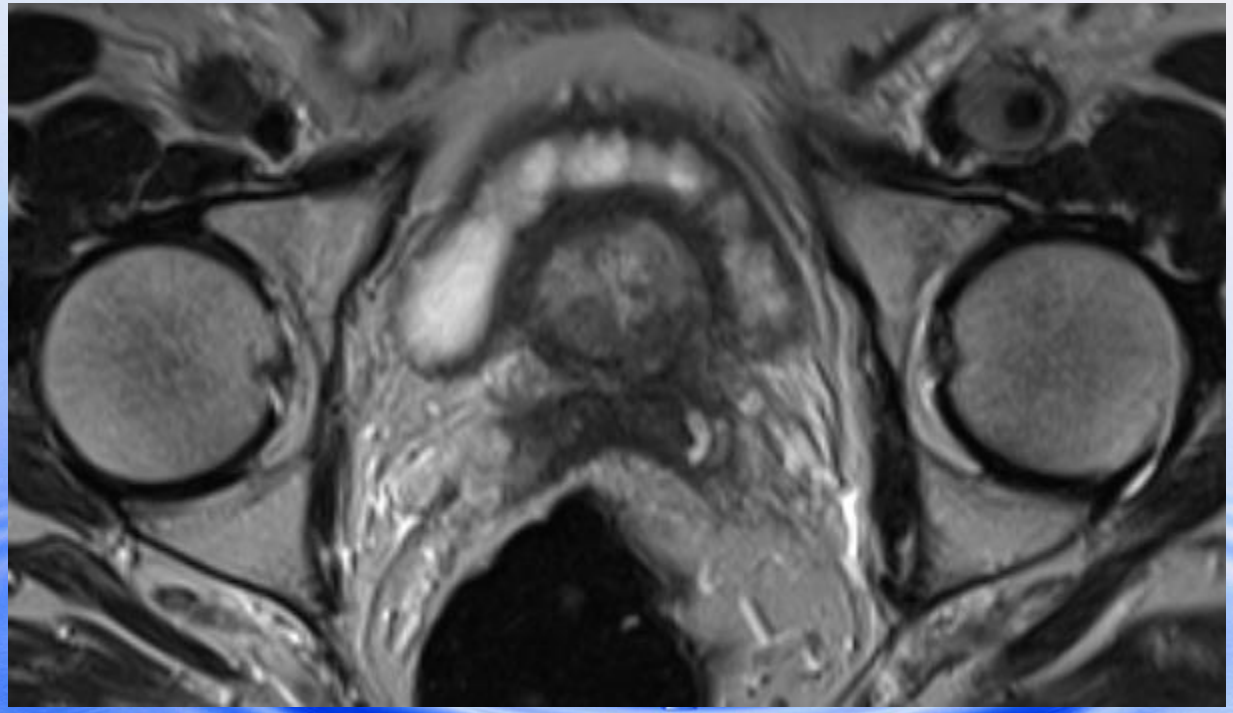
- Almost entirely composed of mixed signal-intensity central gland
- Narrow posterior band of high signal-intensity peripheral zone tissue

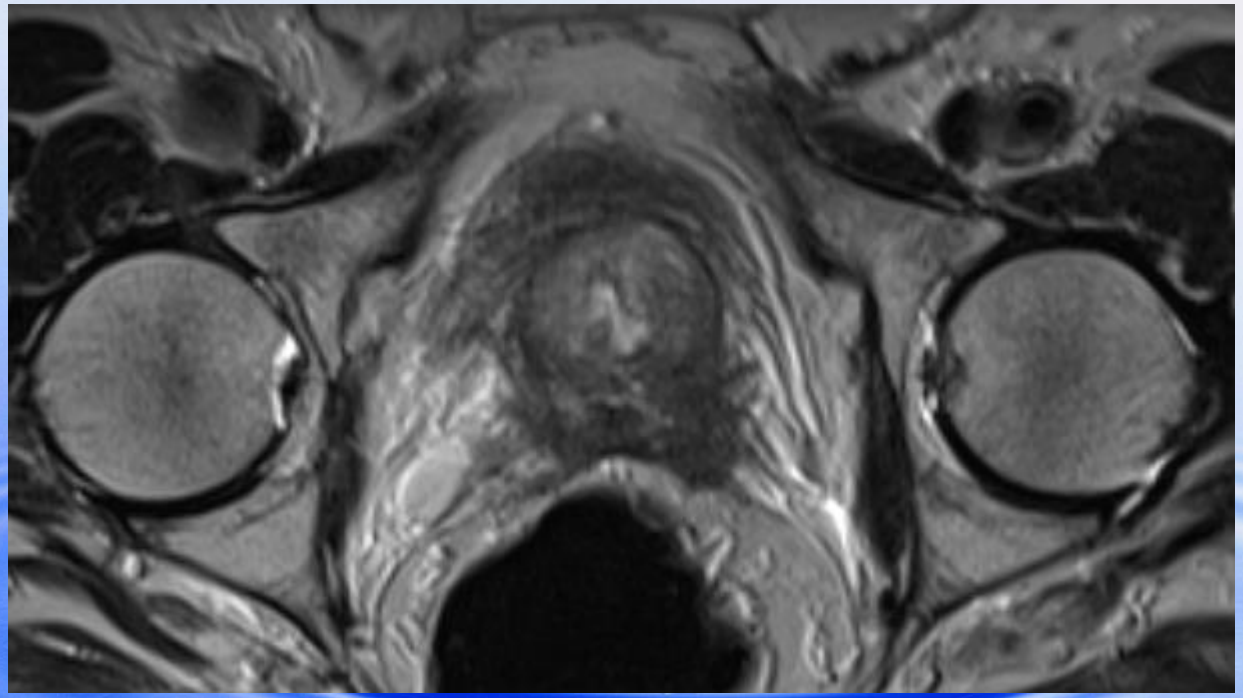
T3-

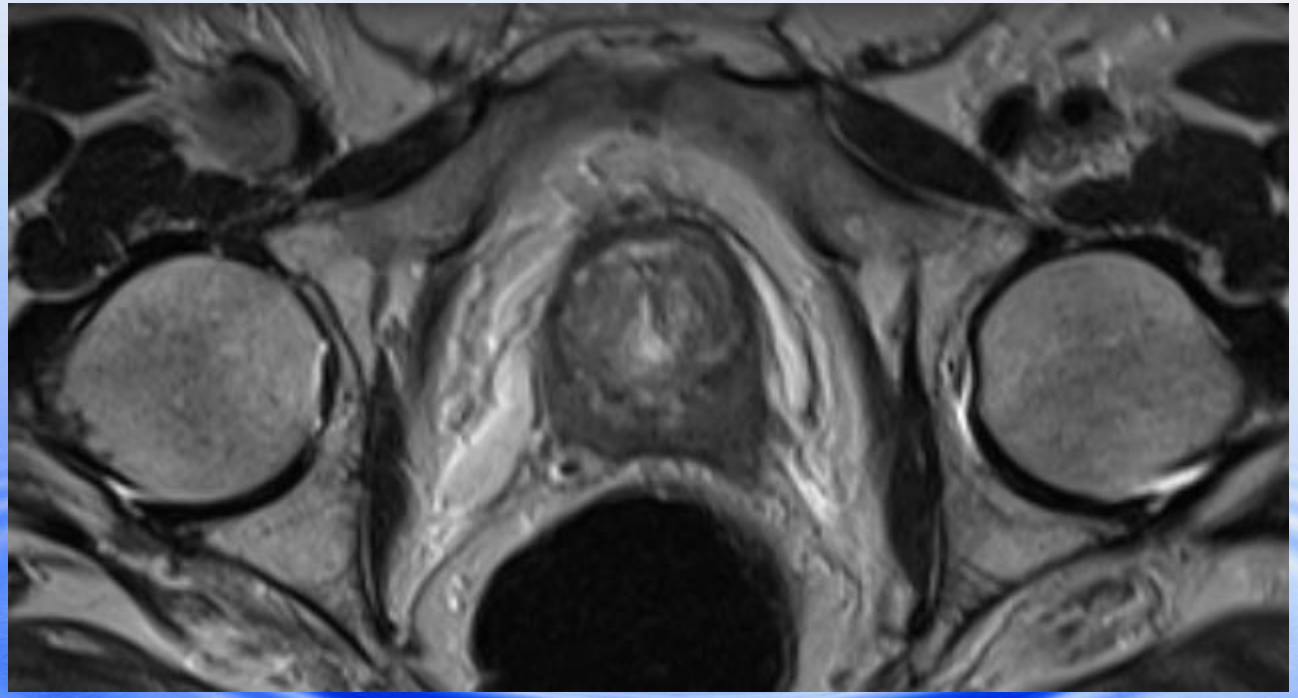
disease:

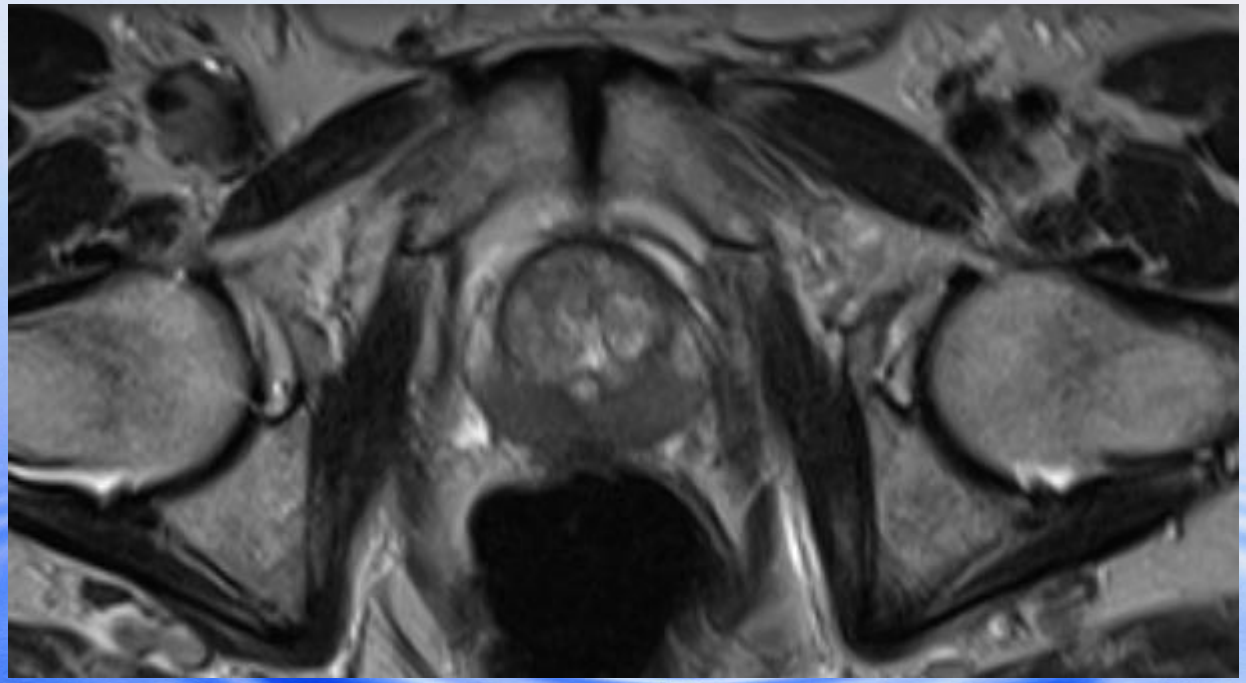


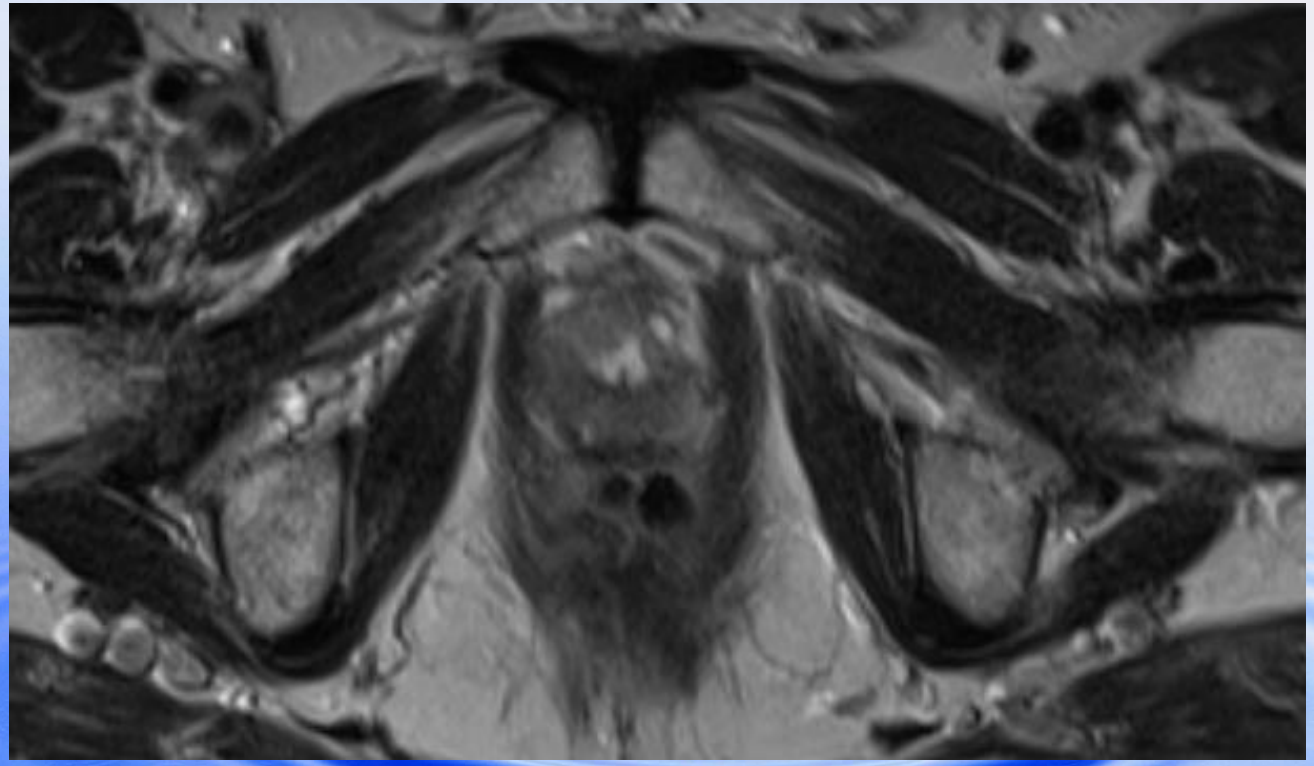




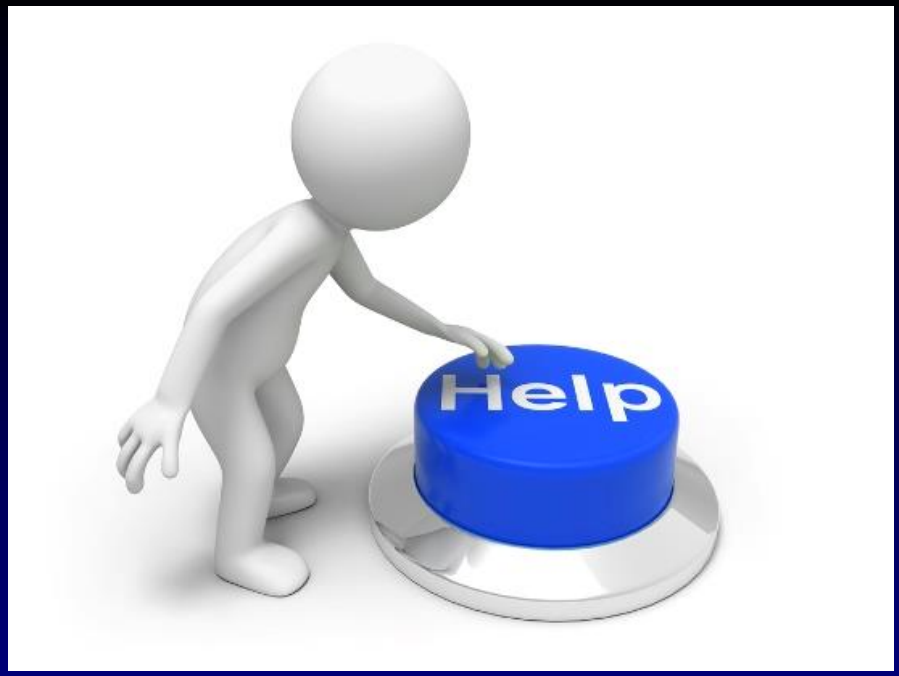








I have no MRI !!!

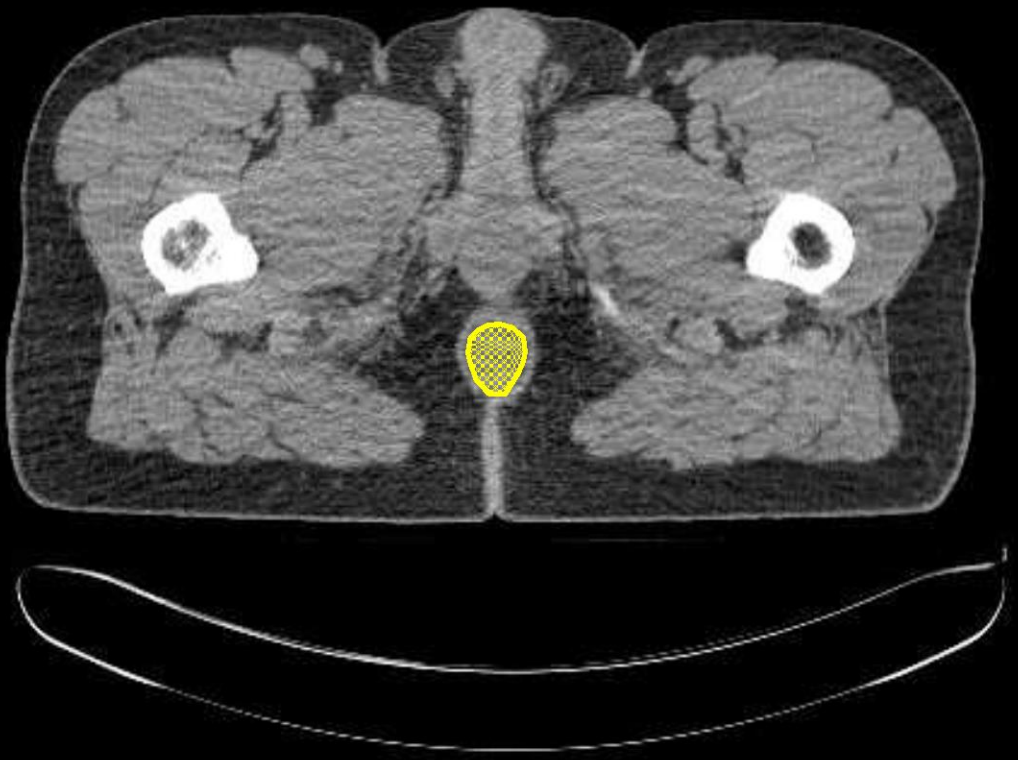


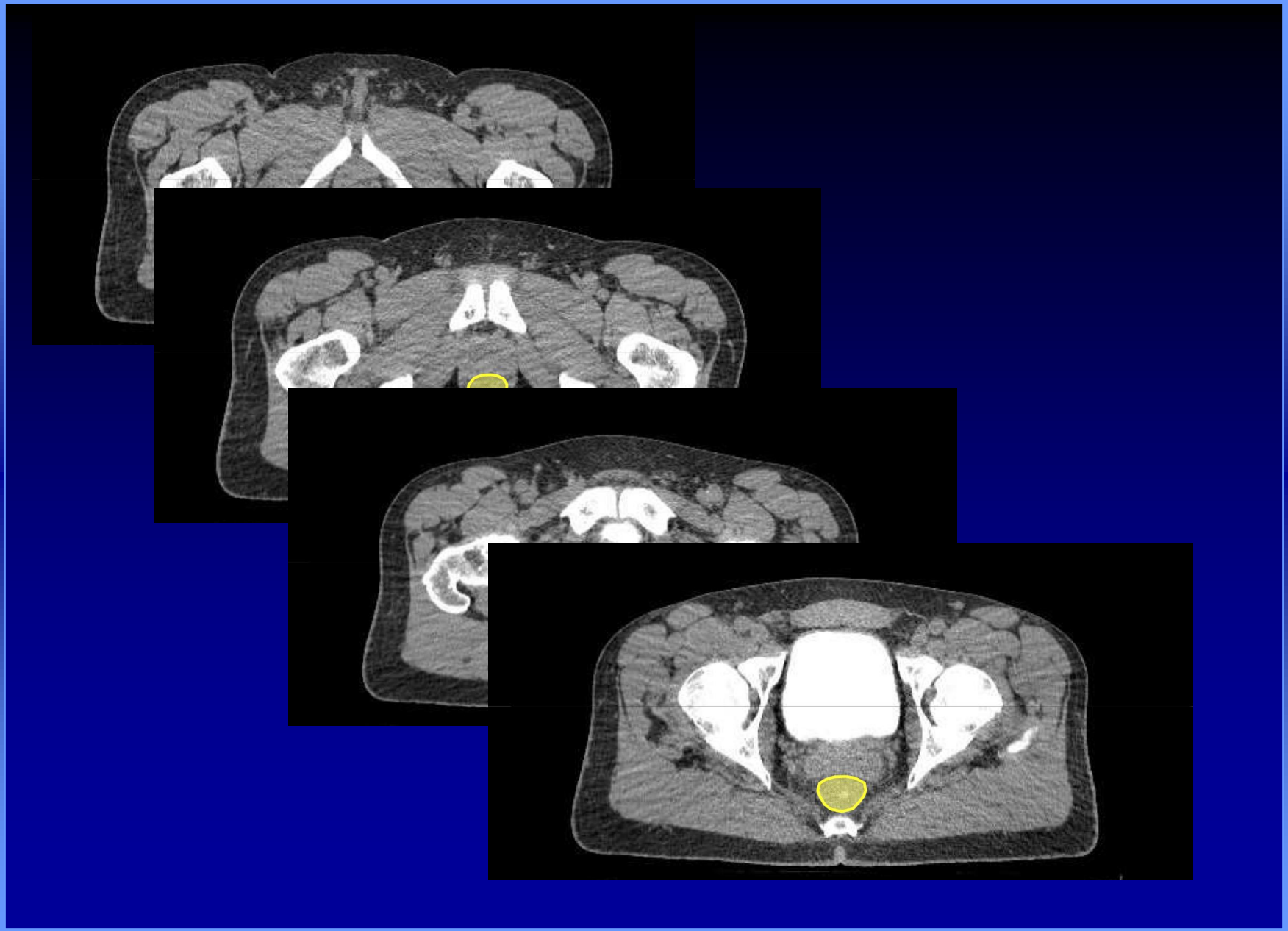
Delineation on CT-scan

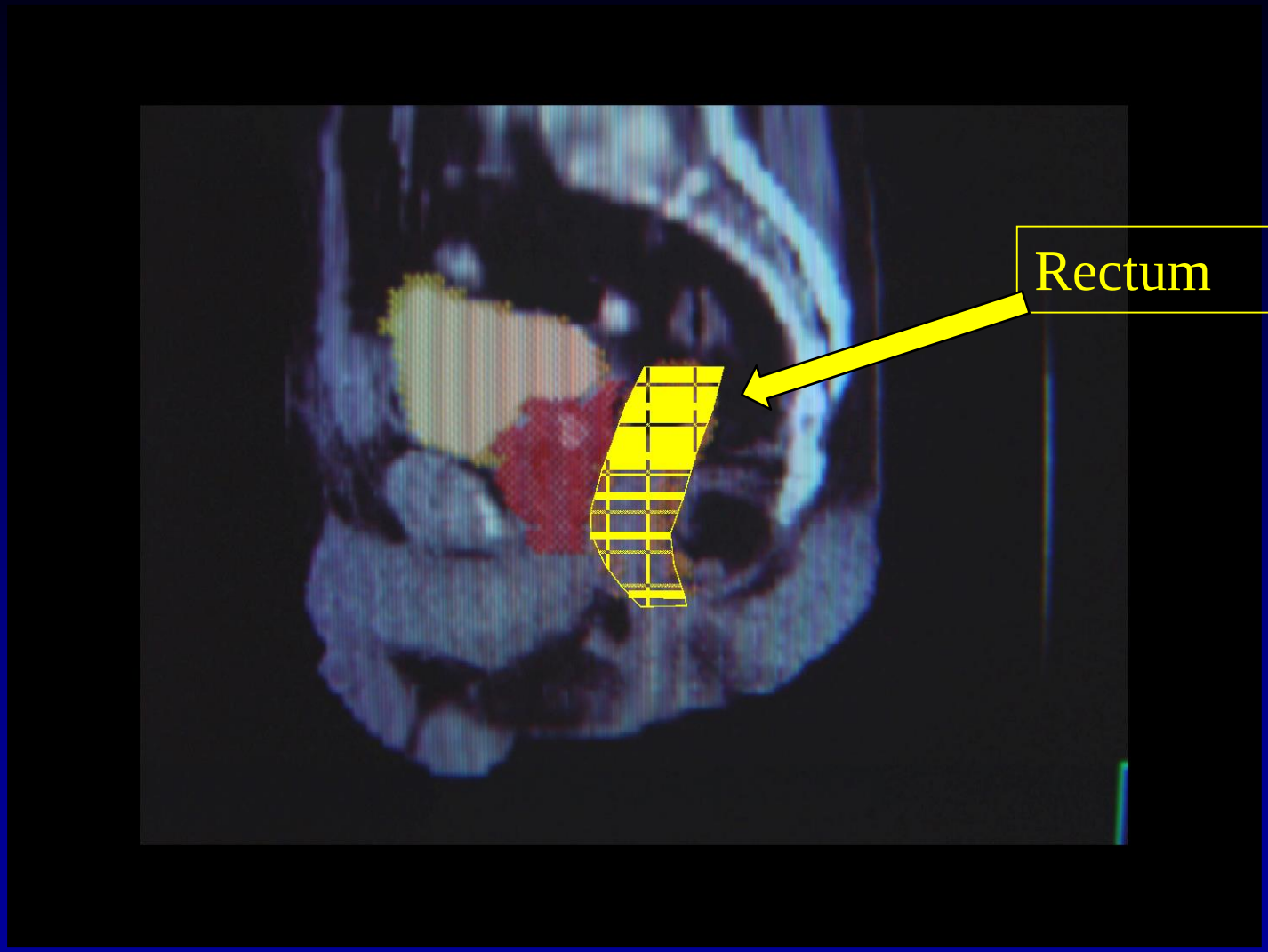
Delineation on CT-scan:

where to start ?

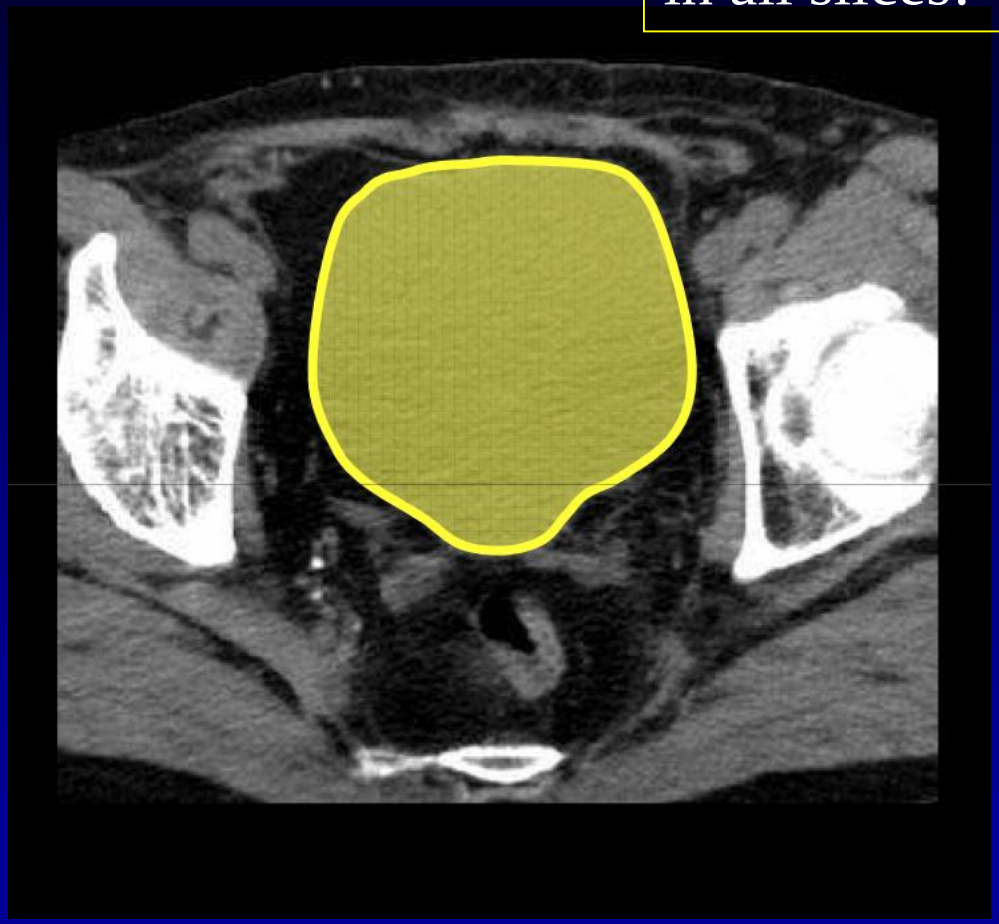
Start with the delineation of the rectum in all slices!






Rectum

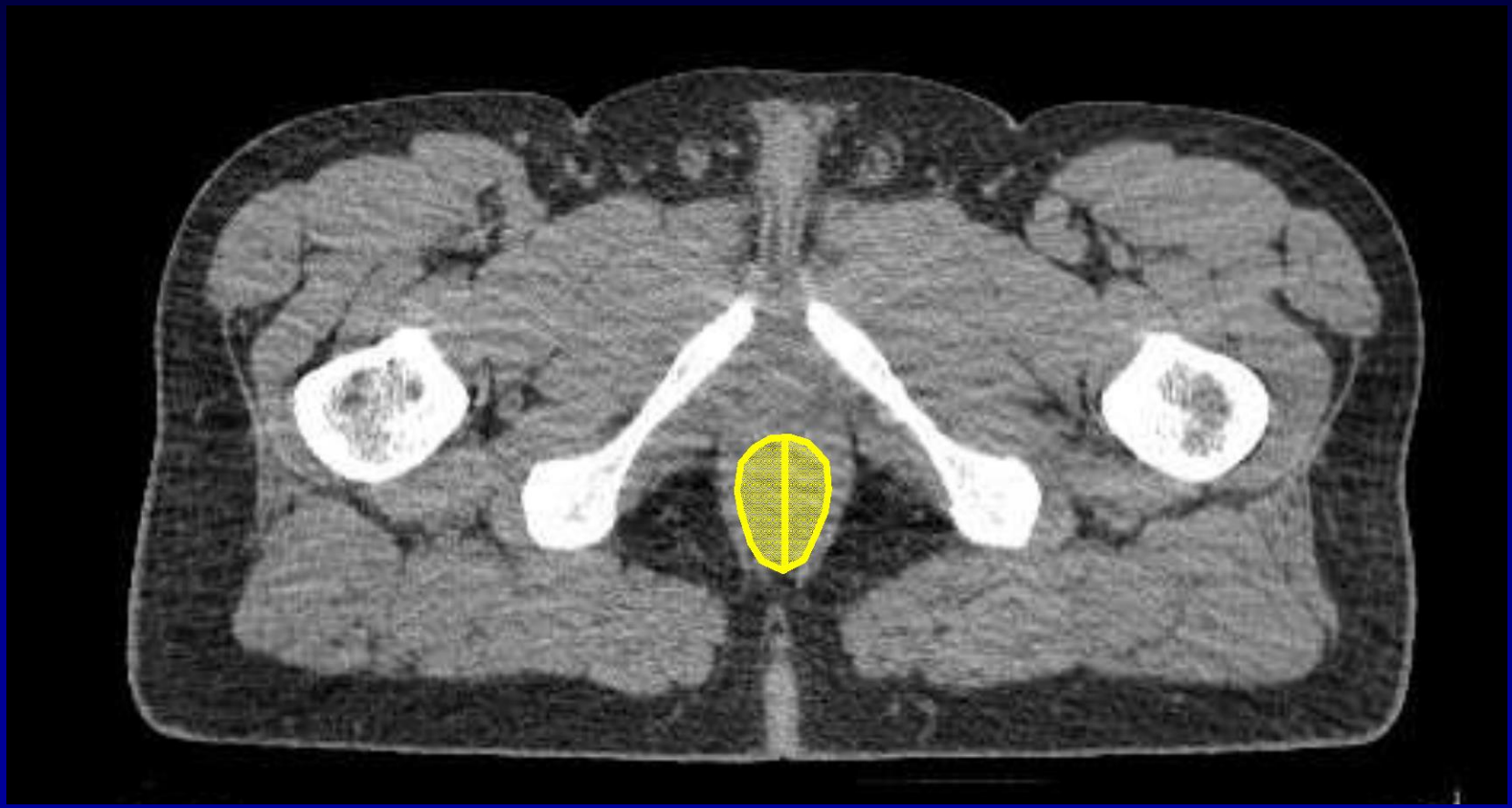
Continue with the delineation of the bladder in all slices!

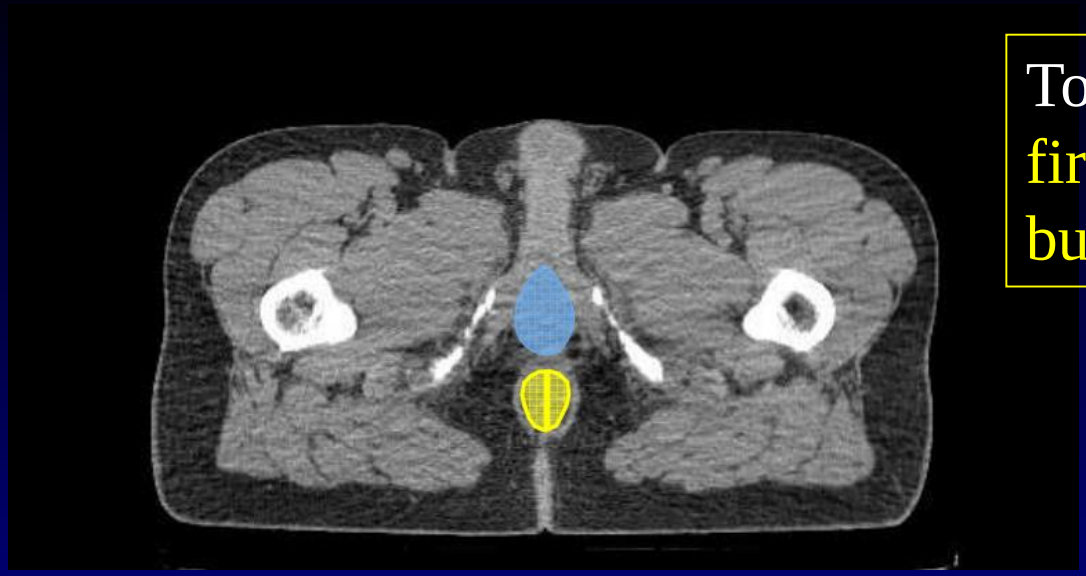


Now we attack the prostate ……

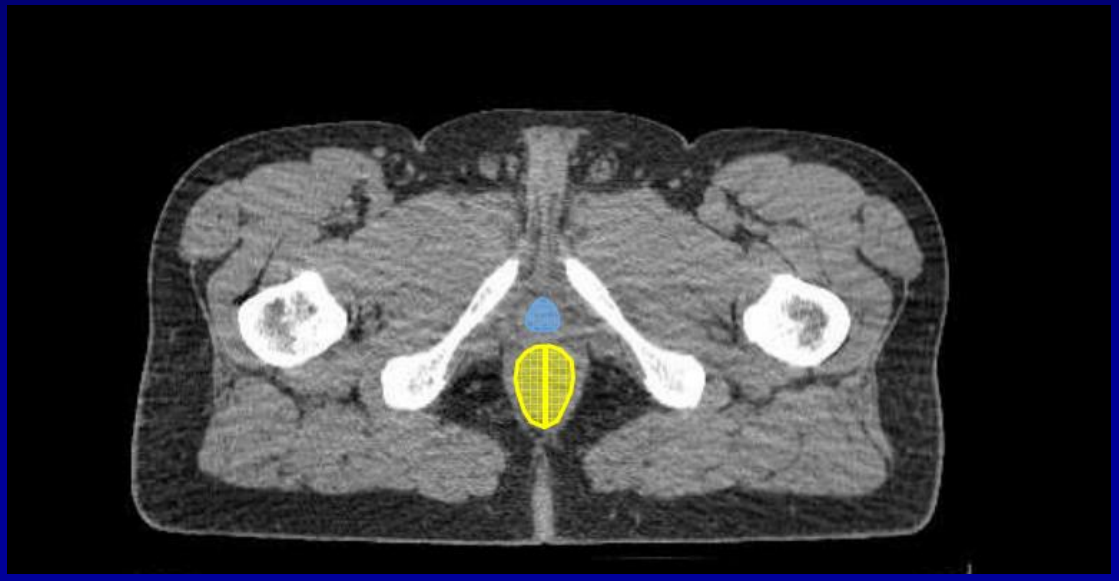
Hey ……

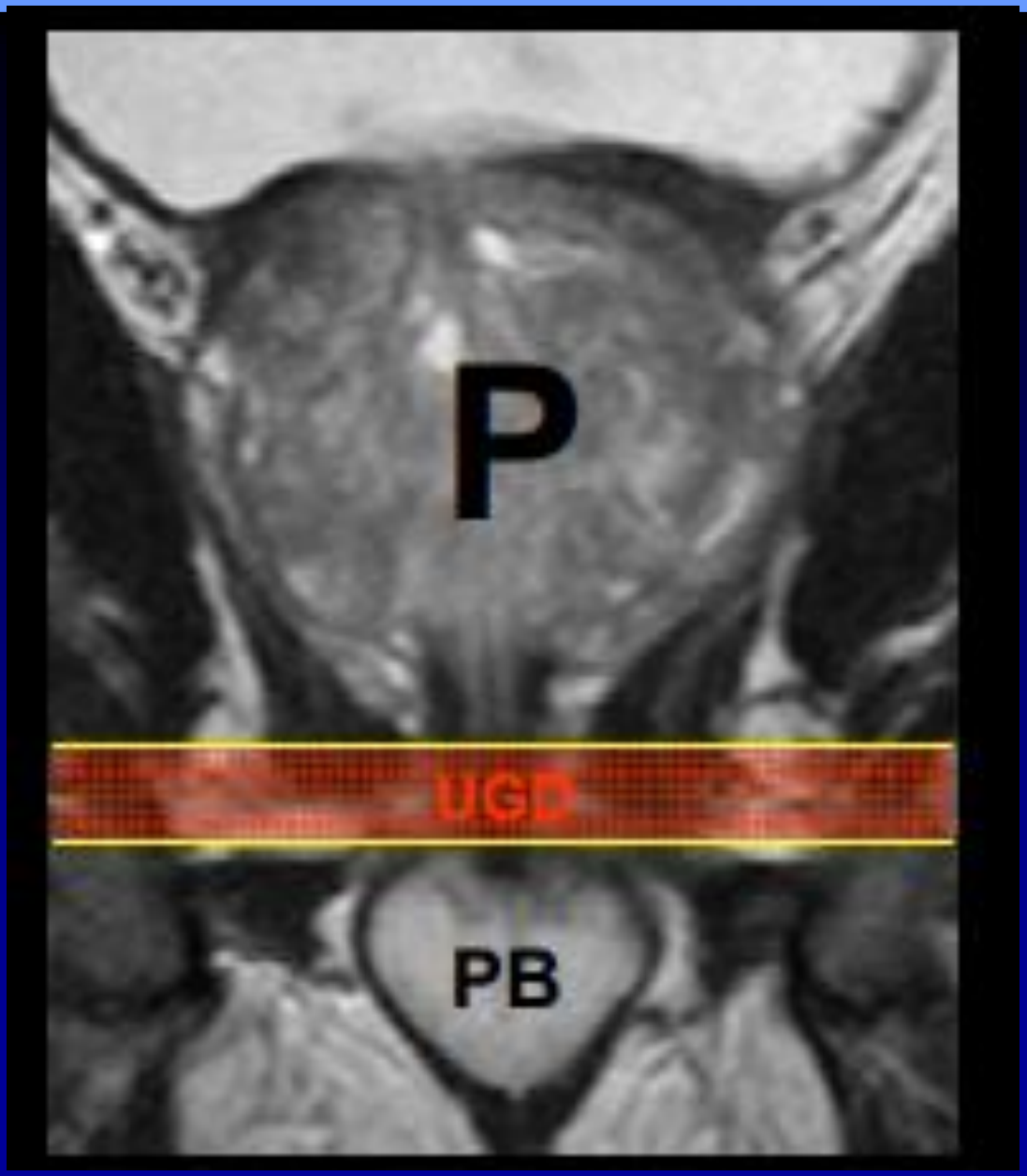
Where is the apex of the prostate ???





To find the apex:
first delineate the penile bulbus !

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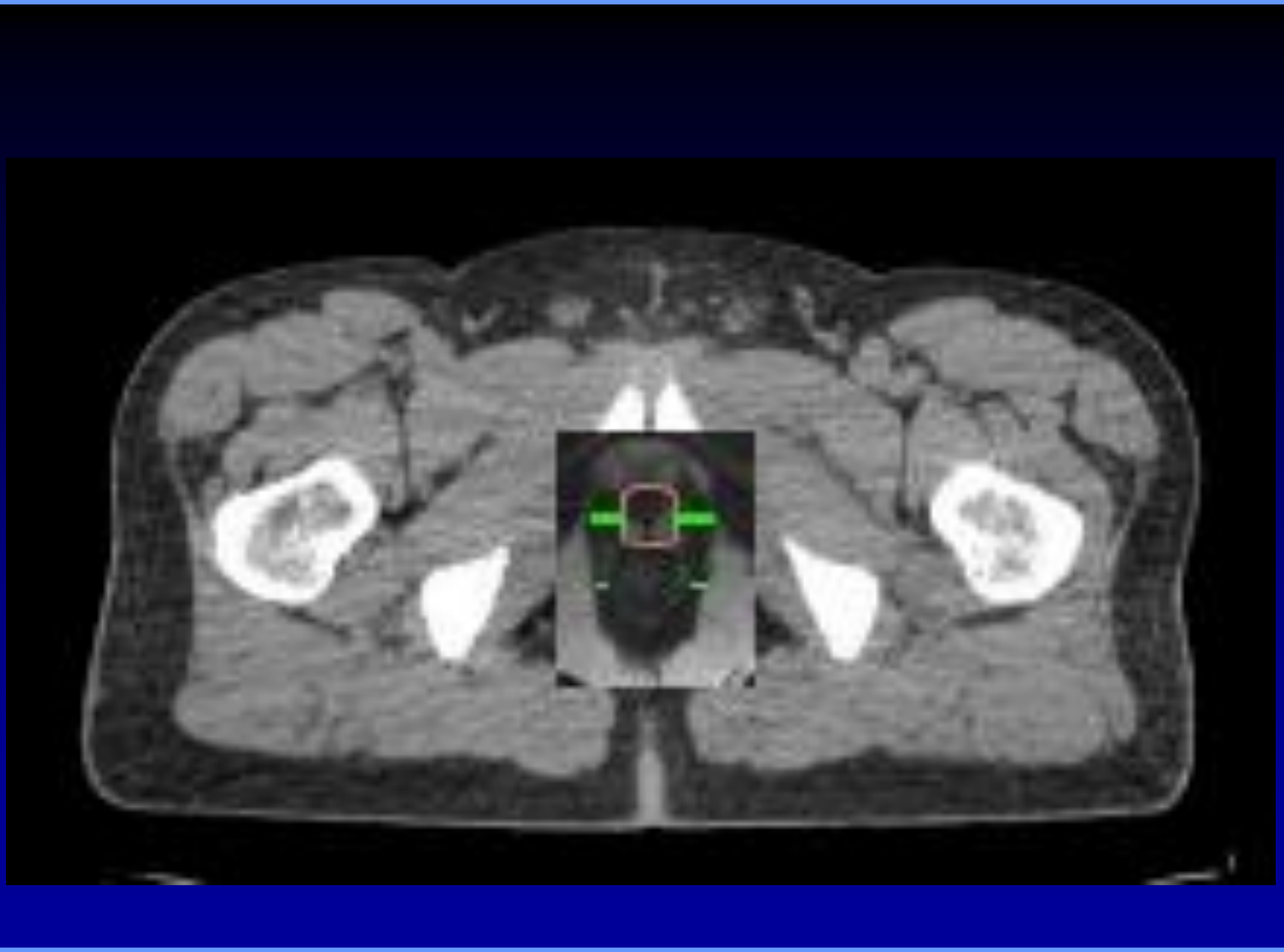
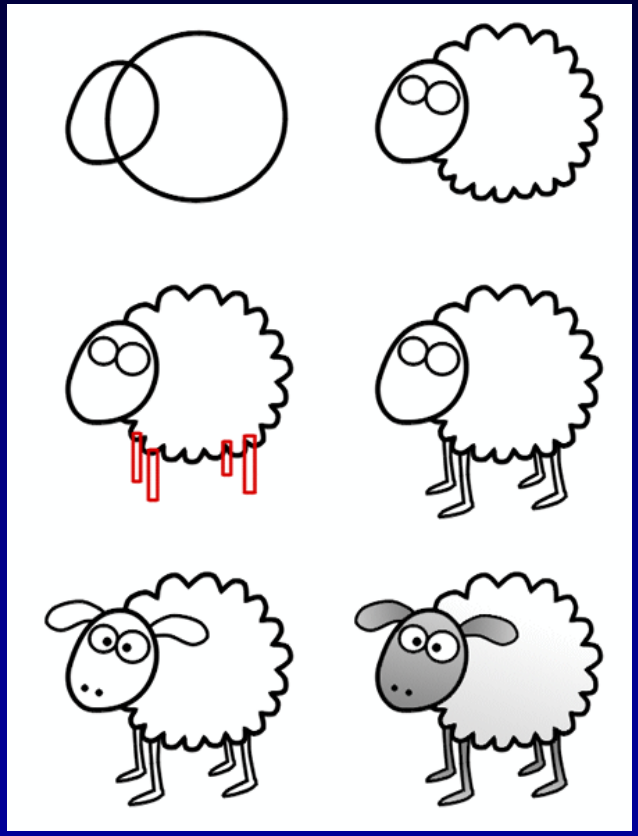
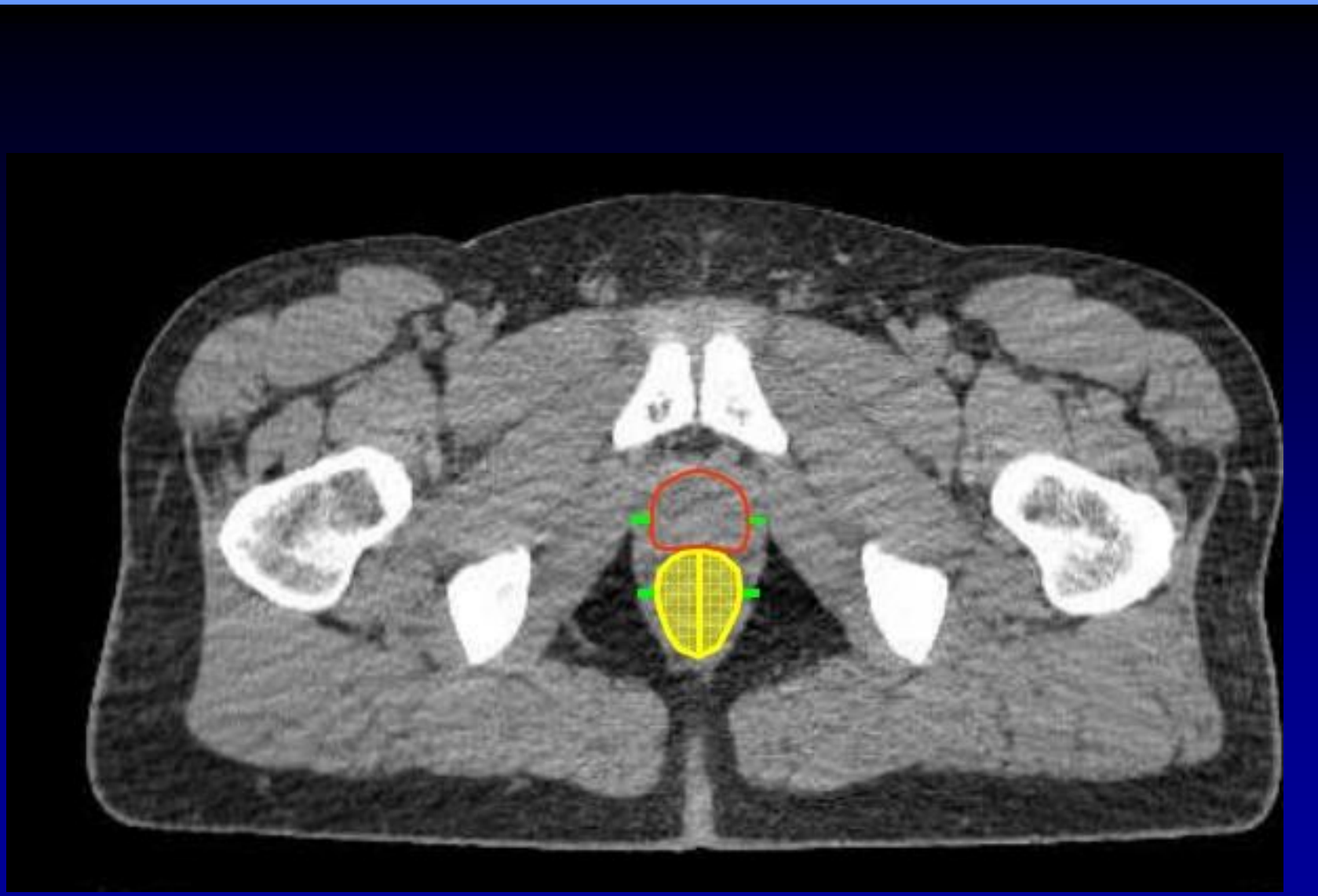
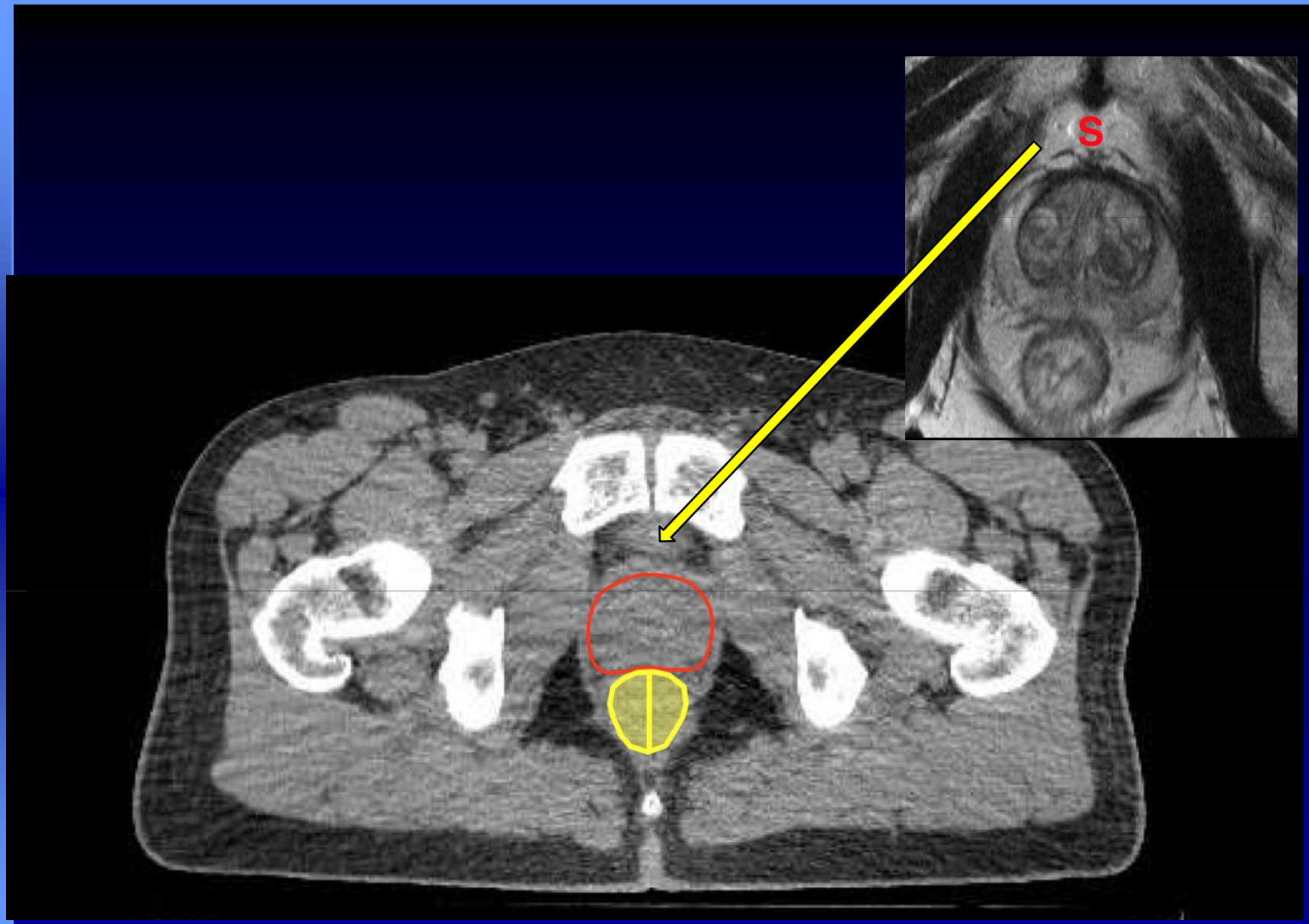
UGD
PB



…… And now ???



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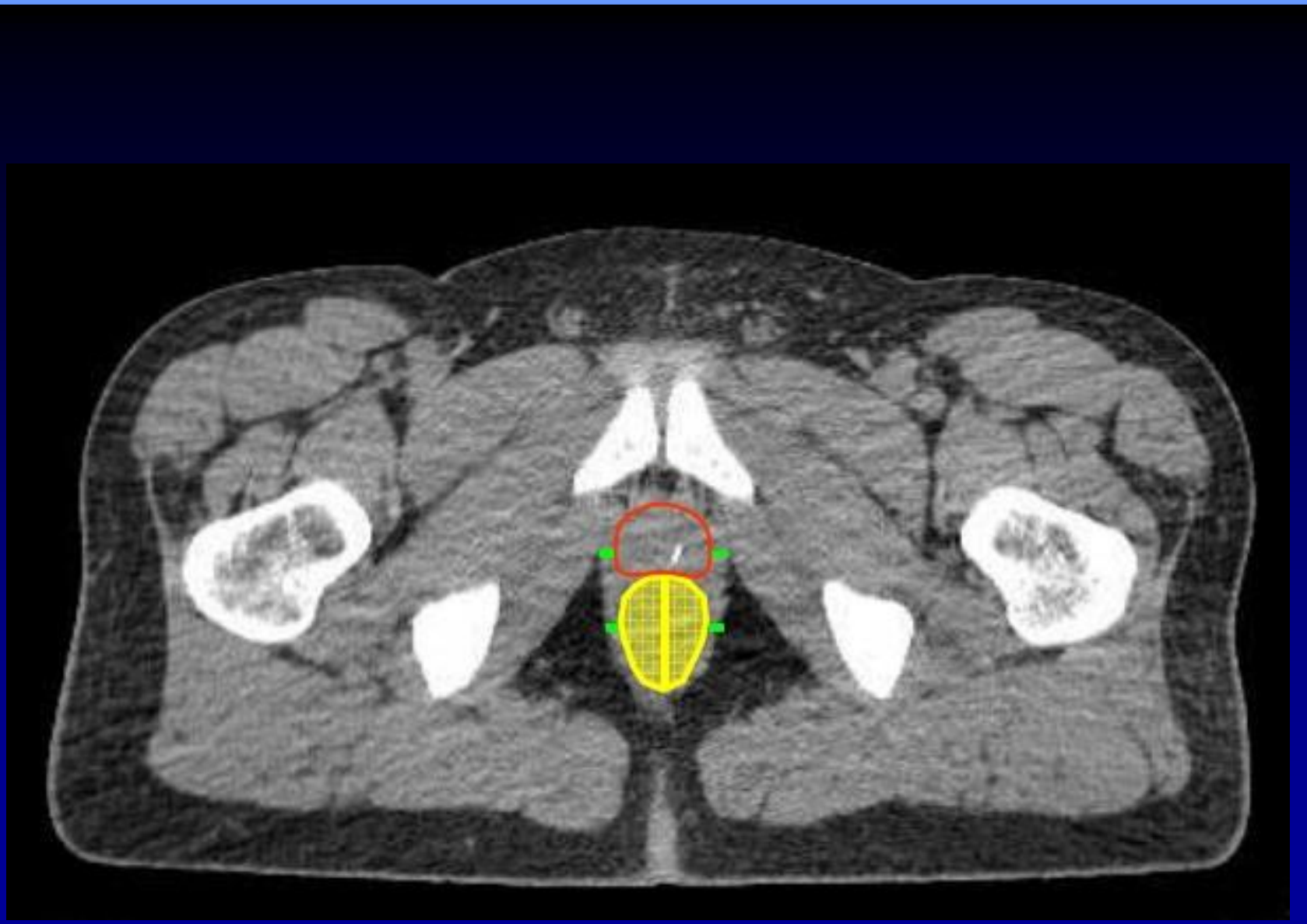
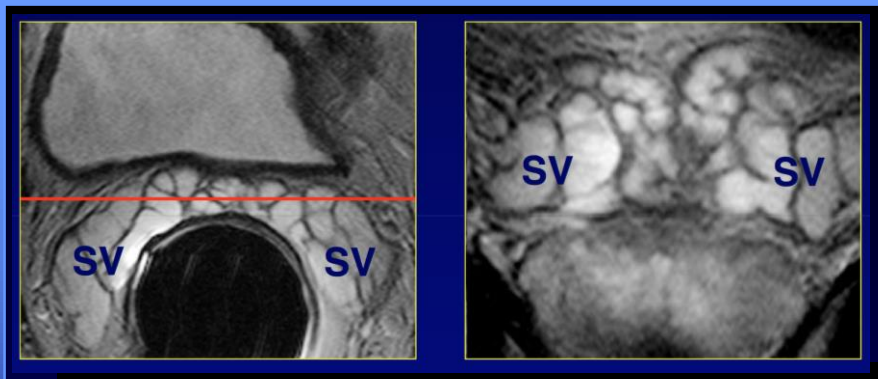
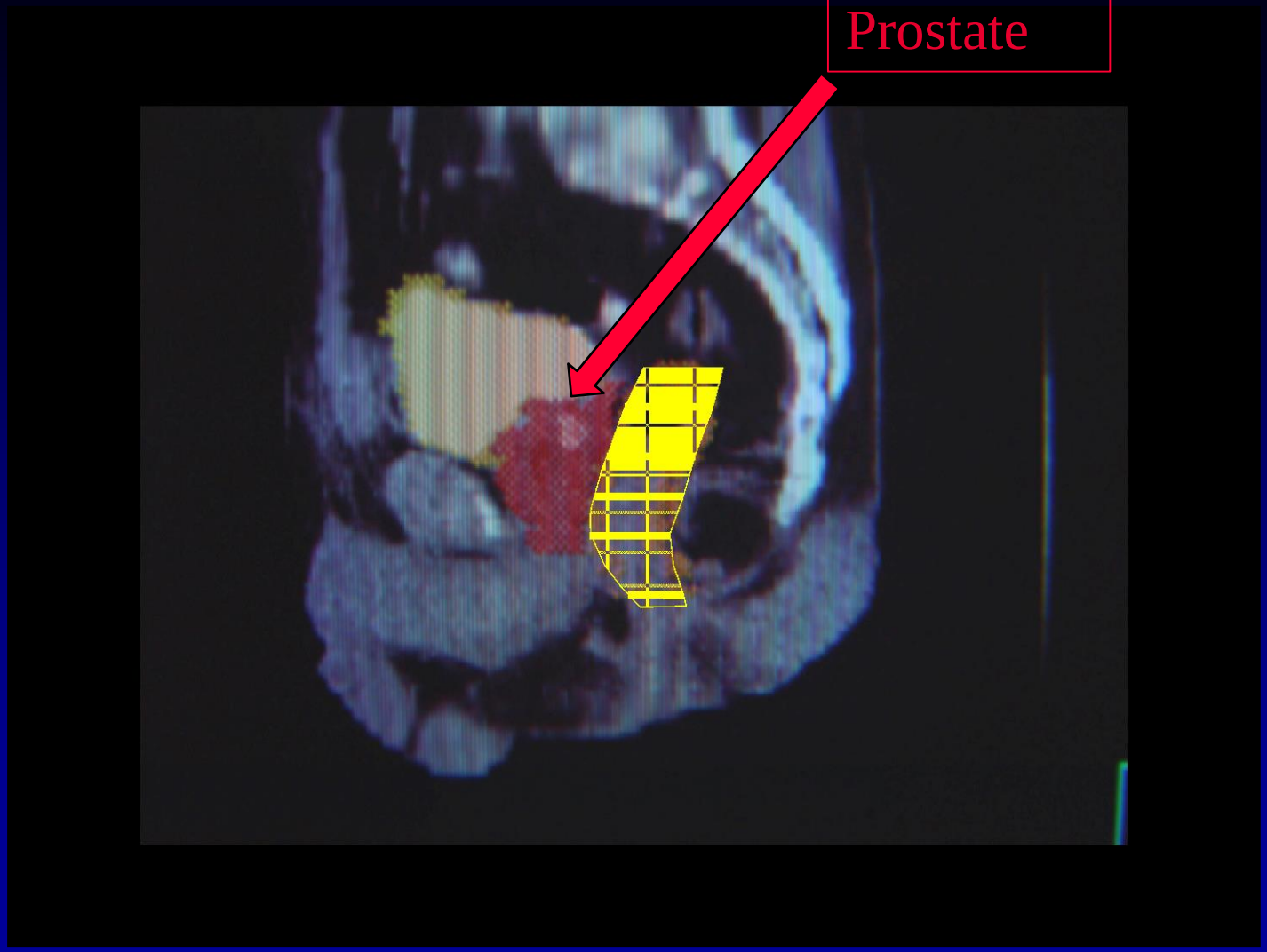




SEMINAL VESICLES


Prostate

Radiotherapy and Oncology xxx (2018) xxx–xxx

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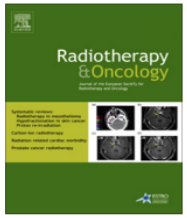

Original article

ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer

Carl Salembier [a], Geert Villeirs [b], Berardino De Bari [c], Peter Hoskin [d], Bradley R. Pieters [e], Marco Van Vulpen [f], Vincent Khoo [g], Ann Henry [h], Alberto Bossi [i], Gert De Meerleer [j], Valérie Fonteyne [k,*]

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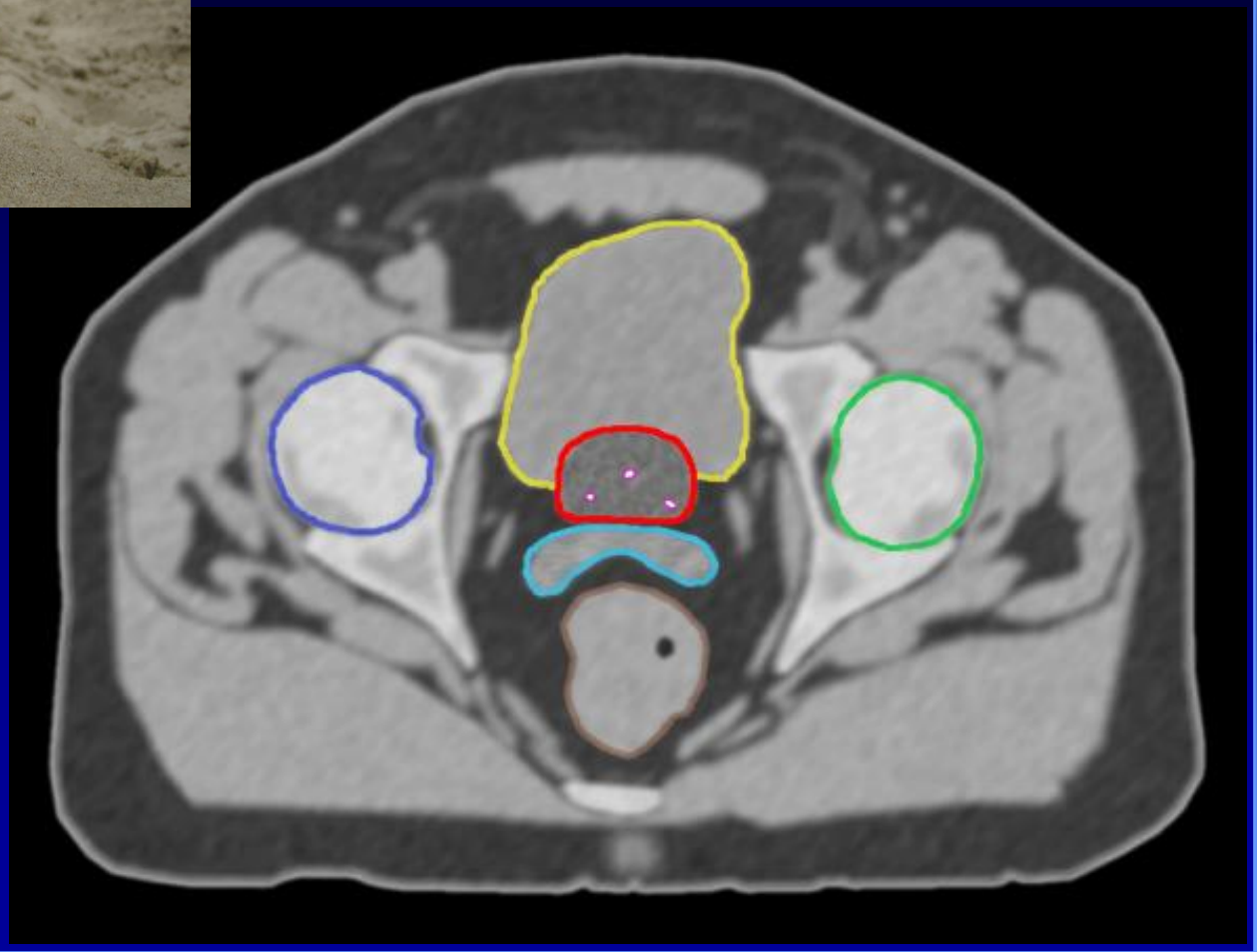


During delineation:

- Apply continuously ‘look ahead and back approach’

- Verify definitive results on delineation inconsistencies

- Check your delineation on sagittal and coronal views

One step back doesn't mean you're defeated, it only means you're going to take the same step forward again, but this time, WISER...


Ceci n’est pas une prostate
Rock Strangers - Arne Quinze

The Sequence - Arne Quinze


I hear and I forget
I see and I remember
I do and I understand

ESTRO Course 2018

RADIATION PROTECTION

Bashar Al-Qaisieh

Orignal material prepared by Jean-Marc Cosset

ESTRO School

NEW ENERGY FOR WEAK, SAGGING MEN

Front View—Showing full, comfortable bag that entirely encloses and supports the scrotum. Note wide, adjustable, comfortable tapes that hold suspensory in position with no chance for discomfort.

Rear View—Shows radium pad, containing 20 micrograms of refined, measured radium. Size of pad, 2 in. wide, 3 in. deep. Size of suspensory, 8 in. deep, 5 in. wide. Very comfortable. Can't bind.

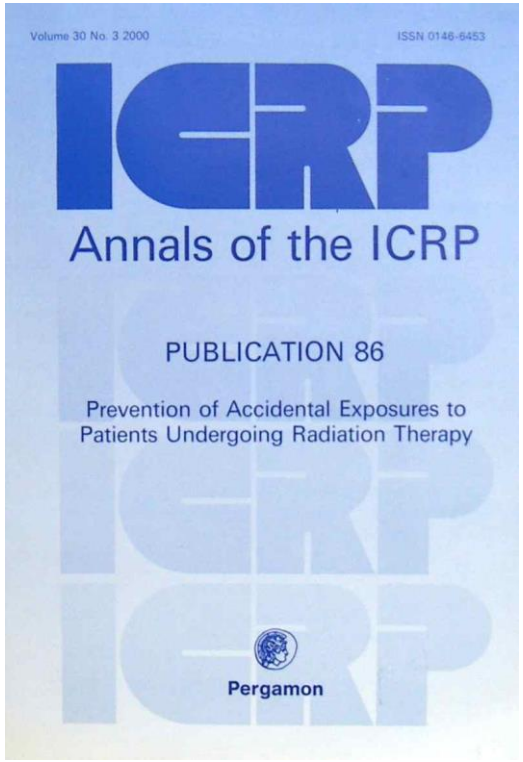
Testone Radium Energizer and Suspensory

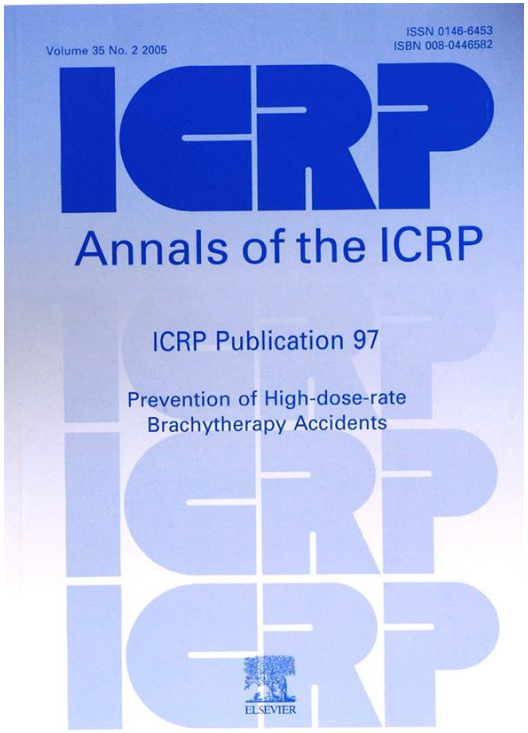
Contains 20 Micrograms Refined, Measured Radium

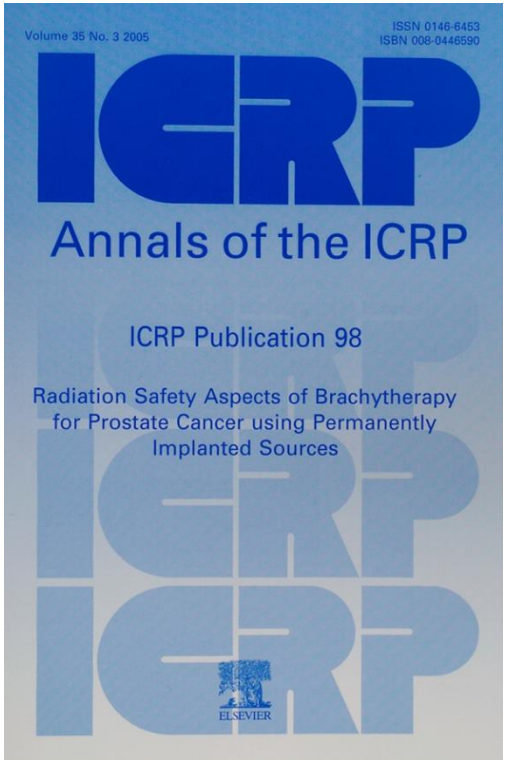
For that sagging, dragging weight that pulls you down and saps your energy—and for storing up and husbanding strength in that seat of all male activity—the testicles—this marvelous appliance has no equal!

We GUARANTEE that the Testone Radium Appliance contains only purified, highly refined radium salts, free from all injurious metallic substances. Actually contains 20 micrograms of this precious sub-

ICRP Publications







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ICRP 86 , released in 2000, was dealing with all types of accidents in radiotherapy, *with specific chapters for LDR and HDR brachytherapy*

- After an analysis of the accidents reported at that moment (2000),
- ICRP tried to identify the causes and the factors contributing to accidental exposures in brachytherapy

ICRP 86 : Generic lessons learned :

- In most of the accidents, a combination of contributing factors allowed an initial mistake to escalate into an accidental exposure …
- Often , the lack of concern of management was the underlying root cause…

Among the main contributing factors ;

- Lack of appropriate staff ressources
- Insufficiently qualified or untrained staff
- Lack of effective, systematic quality assurance programme/procedures
- Lack of effective communication procedures….

Not to be forgotten:

- Hospital management, source suppliers, and importers, can cause catastrophic accidents involving the public and severely affecting the environment (Examples ; the Mexico,Brazilian -Goïana- and Istanbul accidents ...)
- *(Although those accidents were linked to the loss of external radiotherapy sources).*

In 2005 ; the more specific ICRP 97 publication on « Prevention of High-dose-rate Brachytherapy accidents »

- Again, the reported accidents were analyzed …

The ICRP 97 Main points

- High-dose-rate (HDR) brachytherapy is a rapidly growing technique that has been replacing low-dose-rate (LDR) procedures over the last few years in both industrialised and developing countries. It is estimated that about 500,000 procedures (administrations of treatment) are performed by HDR units annually.

- LDR equipment has been discontinued by many manufacturers over the last few years, leaving HDR brachytherapy as the major alternative.

- HDR techniques deliver a very high dose, of the order of 1.6-5.0 Gy/min, so mistakes can lead to under- or overdosage with the potential for clinical adverse effects.

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The ICRP 97 main points

- More than 500 HDR accidents (including one death) have been reported along the entire chain of procedures from source packing to delivery of dose. Human error has been the prime cause of radiation events.
- Many accidents could have been prevented if staff had had functional monitoring equipment and paid attention to the results.
- Since iridium has a relatively short half-life, the HDR sources need to be replaced approximately every 4 months. Over 10,000 HDR sources are transported annually, with the resultant potential for accidents.

The ICRP 97 main points

- A team of trained personnel following quality assurance (QA) procedures is necessary to prevent accidents. QA should include peer review of cases.

- Accidents and incidents should be reported and the lessons learned should be shared with other users to prevent similar mistakes.

The most severe case …

- Occurred in 1992 ;
- The source (HDR Iridium) became detached from the drive mechanism during an anorectal cancer treatment
- Conflicting signals; the area monitor actually detected the radiation, while the equipment indicated « source shielded »
- Unfortunately, previous radiation monitor malfunctions encouraged misinterpretation and induced the staff not to trust it …

- Therefore the wrong indication of the equipment was accepted …
- And the patient, clothes and room were not checked with another radiation monitor
- The patient kept the HDR source 4 days , for a total dose of about 16,000 Gy ! (18 Gy prescribed …..)
- … and was disposed in a waste container, without identification of the source …

- The waste container was picked up by a commercial medical waste disposal company 5 days later ,
- It was then taken to an incinerator where (at last…) the source radiation was detected.
- The patient died on day 4
- During the days the source remained in the patient or in the waste container, it irradiated at various levels 94 persons …

ICRP 98 :
Radiation safety aspects of brachytherapy for prostate cancer using permanently implanted sources

published in 2005

- **At the time of publication**
- **No « real » accident reported with this technique :**
- ***« No adverse effects to medical staff and/or the patient family have been reported to date »***

However ; since that time: the reports on the Philadelphia Veteran hospital « accident »

- A succession of « malpractices » leading to ***97 medical errors out of 116 prostate cancer implantations***
- ***During 6 years,*** from 2002 to 2008 !! ....

- February 2002 : the Philadelphia Veterans Affairs Medical Center (PVAMC) initiated its prostate brachytherapy program

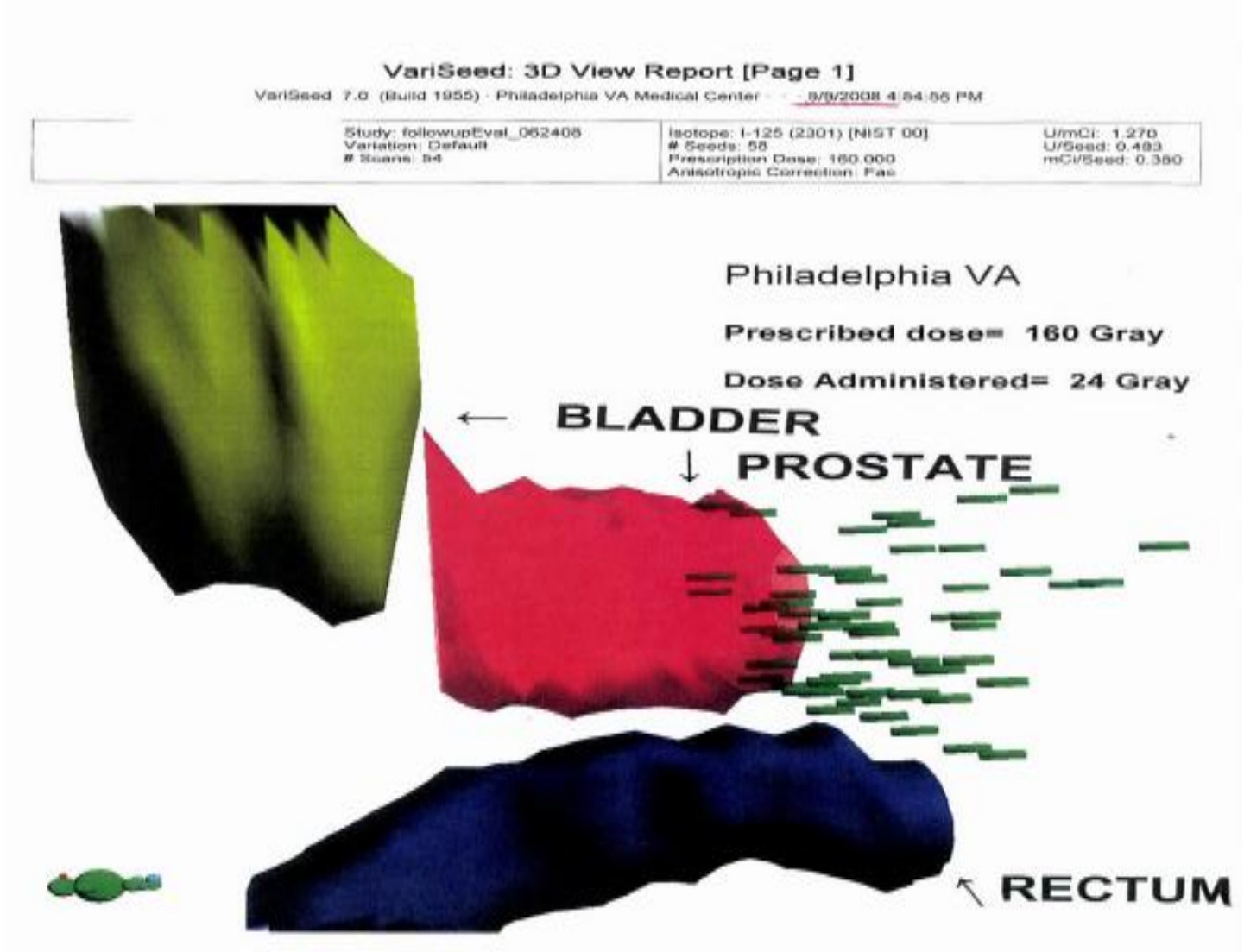
- February 2003 ; during a seed prostate implant**, 40 out of 74 seeds were « implanted » in the patient's bladder**; they were subsequently expelled and recovered …

- October 2005 ; 45 out of 90 seeds were again mistakenly implanted into the patient's bladder and recovered…

- May 2008 ; the National Health Physics Program (NHPP) notified the U.S. NRC (Nuclear Regulatory Commission) of a possible medical event involving a patient that received a dose less than 80 % of the prescribed dose….

- This triggered (at last …) an on site inspection
- With the first results available, the PVAMC prostate brachytherapy program was suspended in June 2008
- In October 2008, prostate cancer brachytherapy was suspended in three other VA hospitals ; Cincinatti, Jackson, and Washington …

- The first survey identified 92 medical events:
- 57 were due to a dose less than 80% of the prescribed dose (underdose),
- 35 were due to a dose to an organ or tissue out of the treatment site that exceeded the accepted limit. (Overdoses of rectum, bladder wall or prostate surrounding tissues)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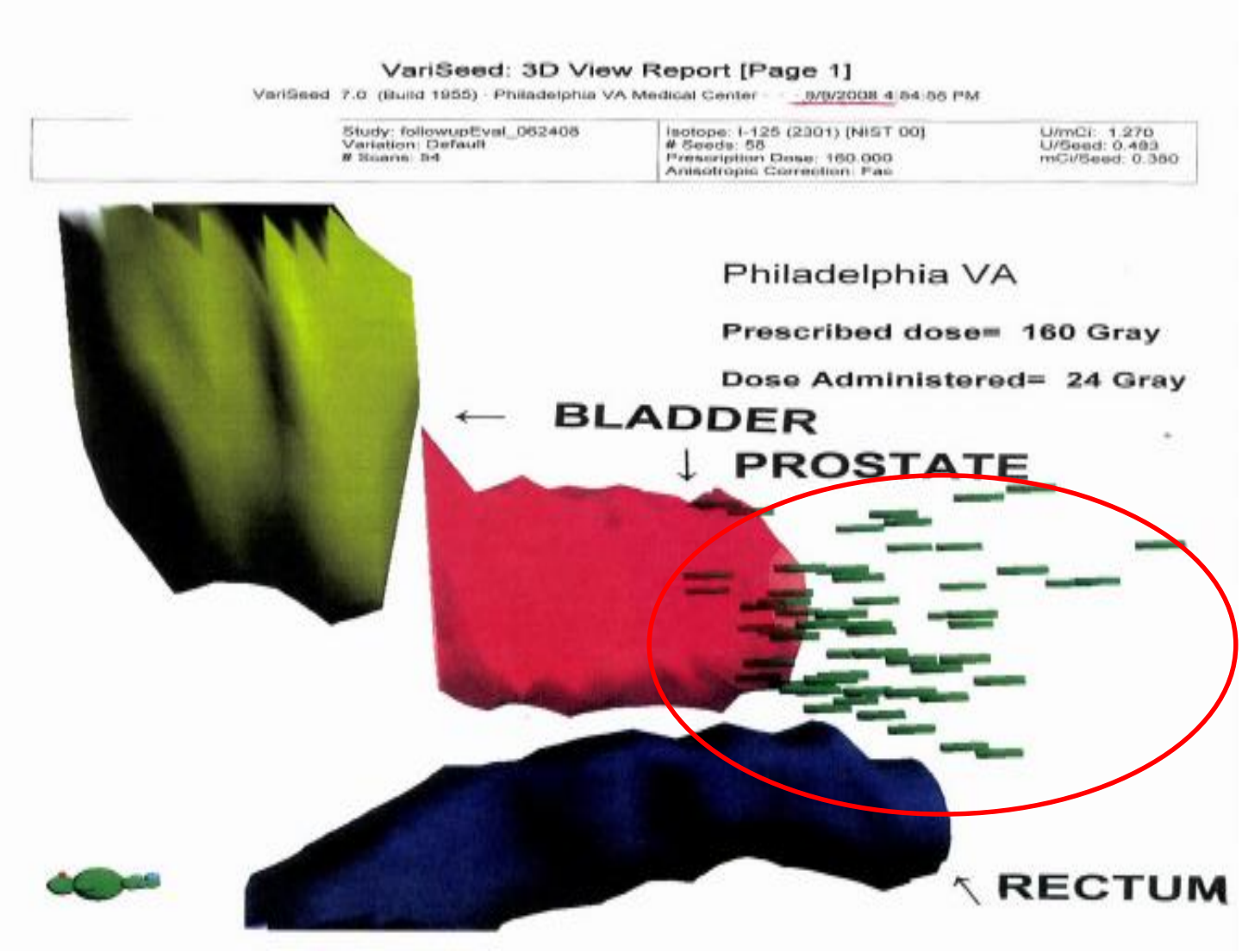
Anisotropic Correction: Fas
U/mCi: 1.270
U/Seed: 0.483
mCi/Seed: 0.380
Philadelphia VA
Prescribed dose= 160 Gray
Dose Administered= 24 Gray
BLADDER
PROSTATE
RECTUM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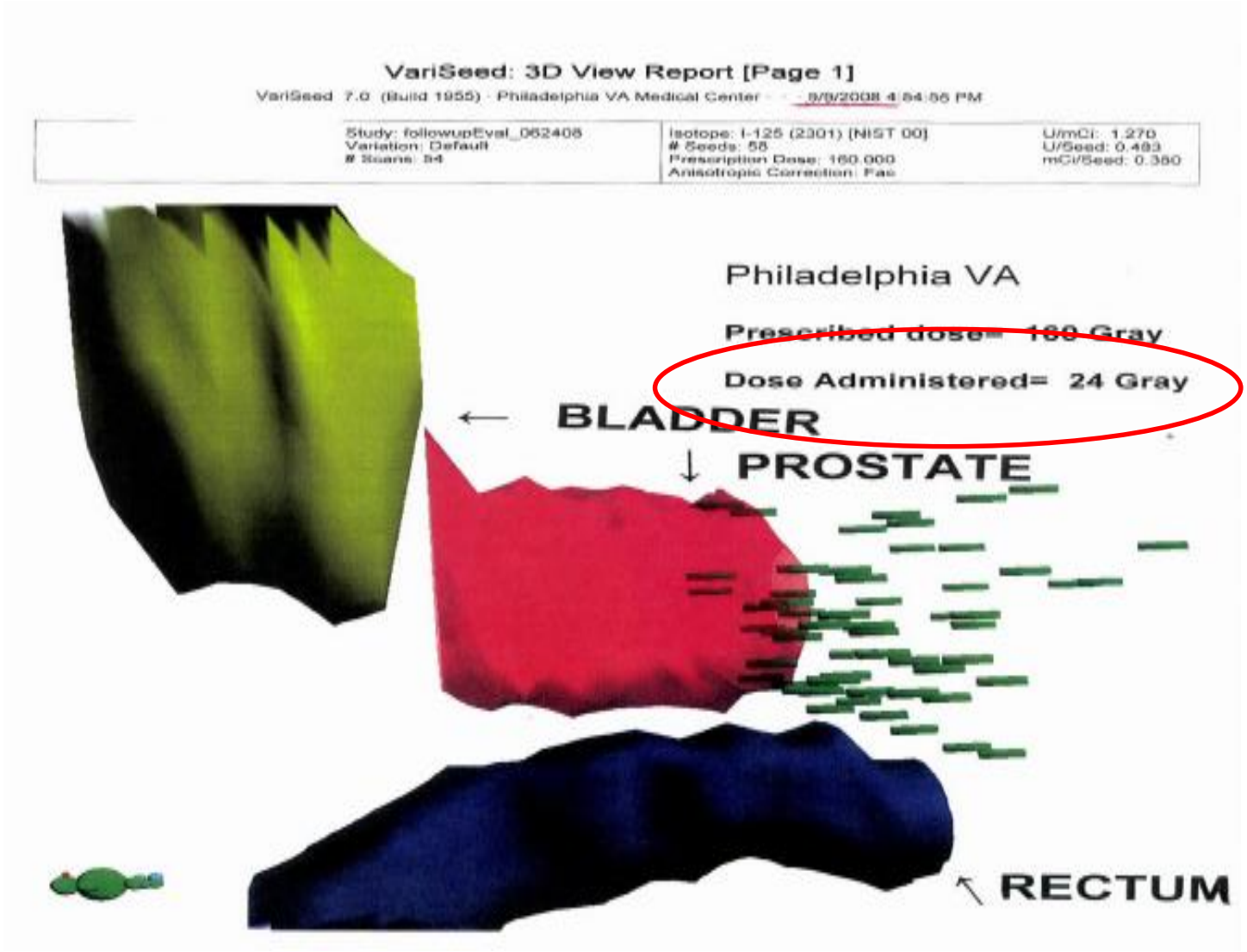
Anisotropic Correction: Pac
U/mCi: 1.270
U/Seed: 0.483
mCi/Seed: 0.380
Philadelphia VA
Prescribed dose= 160 Gray
Dose Administered= 24 Gray
BLADDER
PROSTATE
RECTUM


VariSeed: 3D View Report [Page 1]
VariSeed 7.0 (Build 1955) - Philadelphia VA Medical Center - 9/9/2008 4:54:55 PM
Study: followupEval_062408
Variation: Default
Scans: 84
Isotope: I-125 (2301) [NIST 00]
Seeds: 55
Prescription Dose: 160.000
Anisotropic Correction: Fac
U/mCi: 1.270
U/Seed: 0.483
mCi/Seed: 0.380
Philadelphia VA
Prescribed dose= 160 Gray
Dose Administered= 24 Gray
BLADDER
PROSTATE
RECTUM

- Identified causes :
- Incorrect placement of seeds
- Inadequate procedures
- Poor management oversight of contractors
- Inadequate training of licensee staff
- Poor management oversight of brachytherapy program
- No peer review
- Observed poor placement of seeds and no correction actions taken (!)
- Lack of safety culture

Rare accidents with implanted seeds

- Iodin contamination from seeds accidentally ruptured ; 4 cases reported ;
- Broga DW, Gilbert MA ; Health Physics 1983, 45(3):593-7
- Caldwell C et al. Health Physics 2007, 92 (2suppl.) :S8-S12
- Patients demonstrated significant thyroid uptake and were administered potassium iodide as a blocking agent

- Contamination from Iodin seeds ;
- May be due to the accidental rupture of a seed during the implantation (very rare)
- May be also due to a *poor design of the seeds,* with iodin leakage …

Contents

ESTRO School

Findings;

- ***Very low*** doses to family and household members
- Usually well below the 1 mSv limit for the public
- Not even reaching the « constraint level » of 5 mSv set for comforters and carers of such patients by the IAEA (1996)…

- **Recommendations**
- Doses to family or others will be below 1mSv therefore no routine precautions necessary
- Children not to sit on lap of patient for 2 months
- Avoid prolonged close contact with pregnant women

- NB: If partner is pregnant consider individual risk assessment with dose rate measurement.

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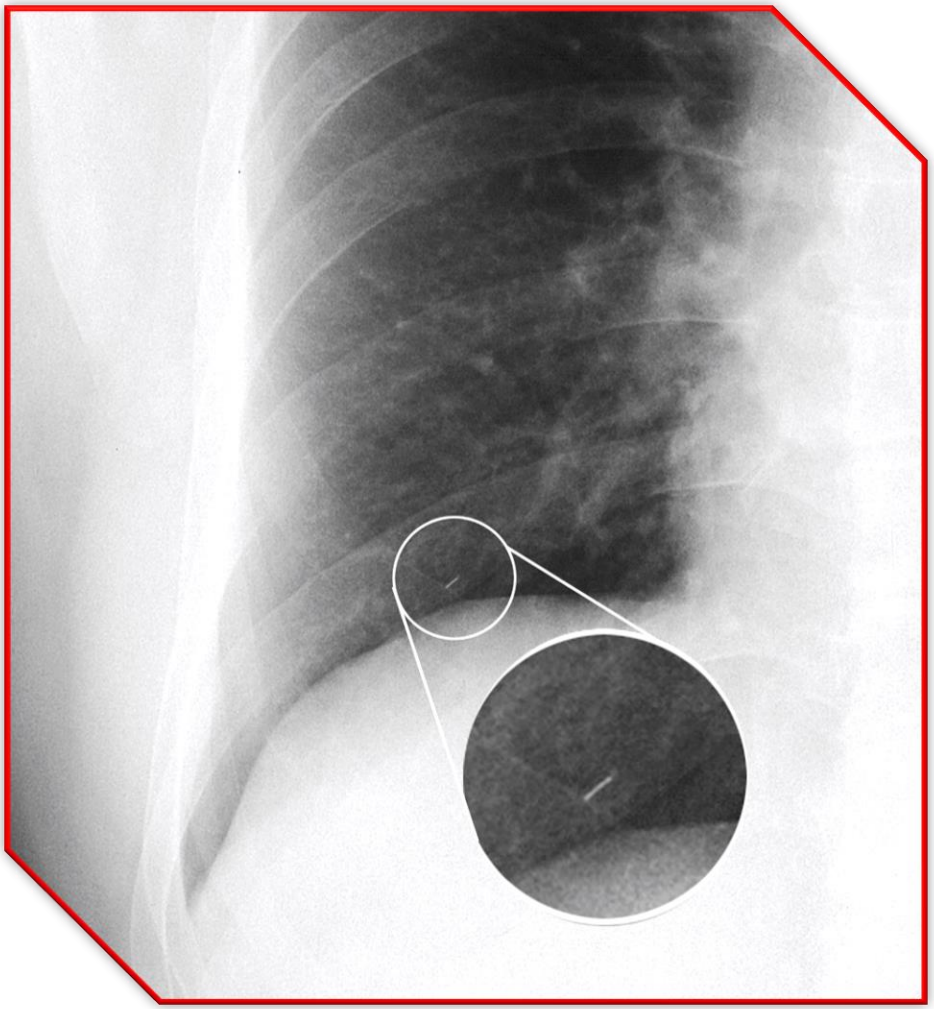
Seeds may migrate to the lungs (no radioprotection problem …)



- **Recommendations**

- (1) sieve the urine while in hospital and for 3 days after implant
- (2) wear condom for first five ejaculations
- (3) if seed "found" do not touch. Put in protective container with spoon or tweezers and return to department.
- (4) if seed in lavatory bowl - flush away

Cremation

- Uncommon in a number of countries
- Frequent in some others (China, India ...)
- The rule in Japan !

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Current national recommandations

- Delay before allowing cremation : Large variations from country to country …
- Briefly;
- From 1 year or less (Japan, US NCRP -with precautions -)
- To 2 years (Canada)
- And even 3 years (UK , France)

After considering and calculating the activity remaining in the patient's ashes and the potential airborne release,

- The ICRP considered that :
- *« Cremation can be allowed… if 12 months have elapsed since an implantation performed with ^{125}I (3 months for ^{103}Pd)… »*
- *However, it must be kept in mind that some national authorities (UK , France) selecting worse-case scenarios and using different types of calculations are recommending much longer times … (up to 3 years for ^{125}I) »*

5. SUBSEQUENT PELVIC OR ABDOMINAL SURGERY 31

- In rare cases, limited and careful transurethral resection may be necessary after brachytherapy ;
- Must be done by an ***experienced surgeon***, aware of the brachytherapy technique,
- And no sooner than 6 months after an ^{125} I implantation.
- Moreover , in case of subsequent abdominal or pelvic surgery ; warn the surgeon ! (« wallet card » ; see below)

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- Due to the drastic reduction in the volume of the ejaculate, patients may think they are definitively infertile ….
- Actually, the dose from the implant may not reach the threshold for castration, and a few cases of fatherhood have been reported after permanent implants !

7. TRIGGERING OF RADIATION DETECTION MONITORS..... 35

- Some radiation detection monitors are set at a very low alarm level (1.5-2 times the natural background level in given places ...)
- Entry/exit of nuclear plants and nuclear research centers, waste areas, scrap metal factories/yards, and, more and more;
- Airports and crossing borders (« nuclear terrorism »)
- Should be explained to the patient !
- Wallet card +++

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- **Almost no case of second cancers reported after prostate brachytherapy**

Legislation- UK

The Police, Health & Safety Executive and the Environment Agency can all prosecute us

IRR99, The Environmental Permitting (Regulations 2010 (EPR2010) and the Radioactive Substance Act 1993 [RSA93], Ionising Radiation (Medical Exposure) Regulations, [IR(ME)R 2000], Medicines (Administration of Radioactive Substances) Regulations 1978 [MARS1978], Health and Safety at work Act 1974.

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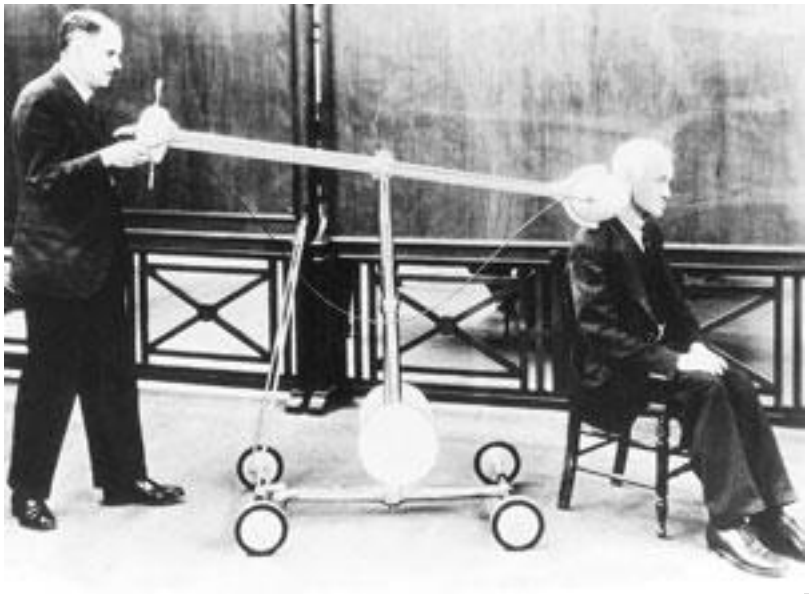

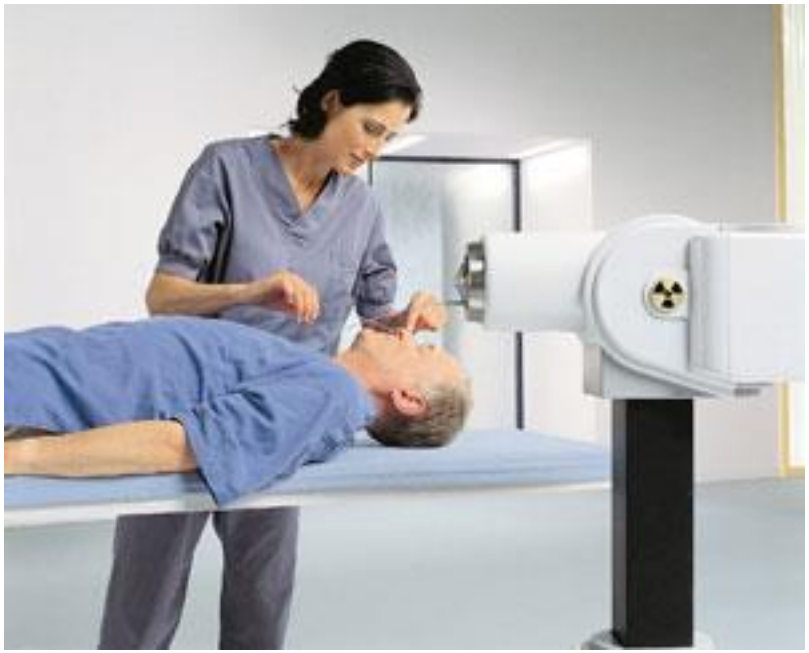

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Thank You !

ESTRO School

ADT and prostate brachytherapy

C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

Localized prostate cancer: heterogeneous group of tumours

Prognostic 'risk' groups: Low – Intermediate - High

Depending on:

- Extension of the tumour
- Initial PSA
- Gleason Score

Low Risk

Stage: T1 or T2a,b
Gleason Sum ≤ 6
PSA ≤ 10 ng/ml

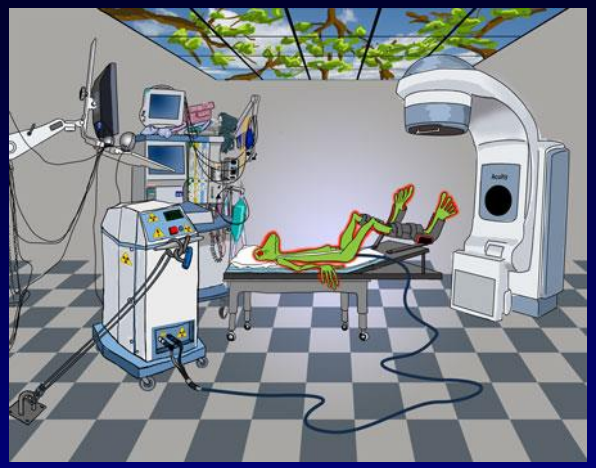
Intermediate Risk

Stage T1 or T1-2 Stage T1-2
Gleason Score 7 or Gleason 6
PSA < 10 PSA 10-20

High Risk

Stage T2c or T3
Gleason score ≥ 8
PSA > 20 ng/mL

Treatment options - localized prostate cancer



External beam radiotherapy

Hormonal treatment

Interstitial: low or high dose rate

(robotic) surgery

WHAT DO YOU WANT?

QUALITY OF LIFE

1. BRACHYTHERAPY

WE ARE THE BEST DEAL WITH IT

RATIONALE for BRACHYTHERAPY

- Brachytherapy is the most conformal treatment modality
- Brachytherapy increases LC by delivering a higher radiation dose
  - Metabolic activity studies by MRI and MRI-spectroscopic imaging shows higher complete prostate metabolic atrophy and lower nadir PSA at 48 mths after PB vs EBRT
  - This higher intraprostatic tumor control is indicative of a positive therapeutic effect of the higher biological dose given with PB vs EBRT
- This observation is supported by clinical results from 3 RCTs of dose escalation using EBRT + PB vs EBRT

Morris et al, J Clin Oncol 2015;33-3
Hoskin et al, Radioth Oncol 2012; 103:217-222
Sathya et al, J Clin Oncol 2005; 23:1192-1199

- BT is considered as the ultimate dose escalation modality

- RCTs in PCA comparing EBRT with EBRT+PB in HR and high-tier IR PCA indicate further improvement of PSA recurrence free survival (20-30% at 7-10 years) with no documented CSS or OS benefit.

- However, recent publications using large databases indicate an increase in CSS and OS in PCA patients treated with any form of BT

- BT results in
  - Superior disease outcomes (mainly bPFS)
  - Higher complete prostate metabolic atrophy
  - Lower nadir PSA

Morris et al, J Clin Oncol 2015;33-3
Hoskin et al, Radioth Oncol 2012; 103:217-222
Sathya et al, J Clin Oncol 2005; 23:1192-1199
Shen et al, Int J Radiat Oncol Biol Phys 2012; 83:1154-1159
Amini et al, J Urol 2015;195:1453-1458
Picket et al, Int J Radiat Oncol Biol Phys 2006;65:65-72

Results

Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

Peter Grimm[1], Ignace Billiet[2], David Bostwick[3], Adam P. Dicker[4], Steven Frank[5], Jos Immerzeel[6], Mira Keyes[7], Patrick Kupelian[8], W. Robert Lee[9], Stefan Machtens[10], Jyoti Mayadev[11], Brian J. Moran[12], Gregory Merrick[13], Jeremy Millar[14], Mack Roach[15], Richard Stock[16], Katsuto Shinohara[15], Mark Scholz[17], Ed Weber[18], Anthony Zietman[19], Michael Zelefsky[20], Jason Wong[21], Stacy Wentworth[22], Robyn Vera[23] and Stephen Langley[24]

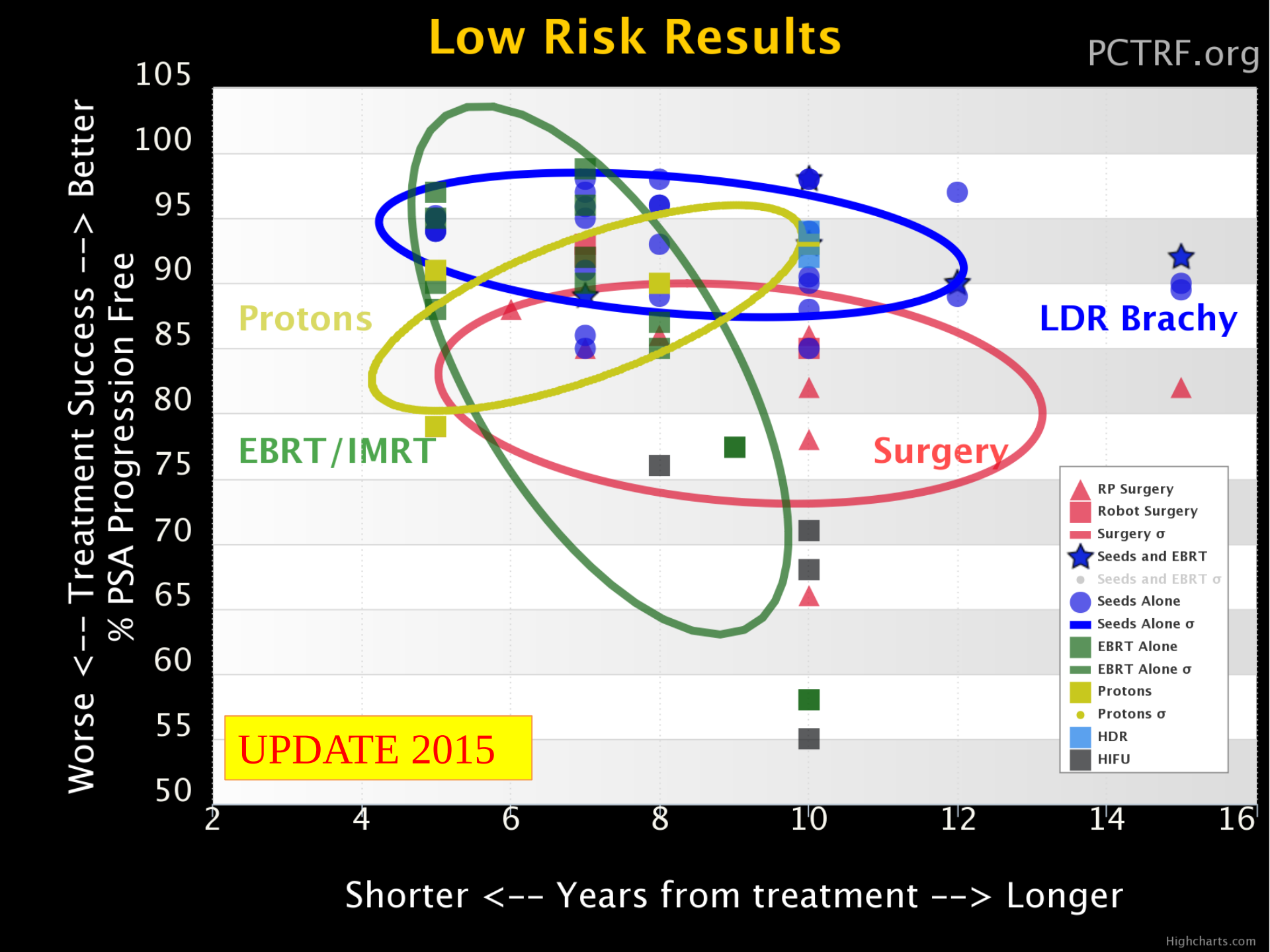
BJUI SUPPLEMENTS

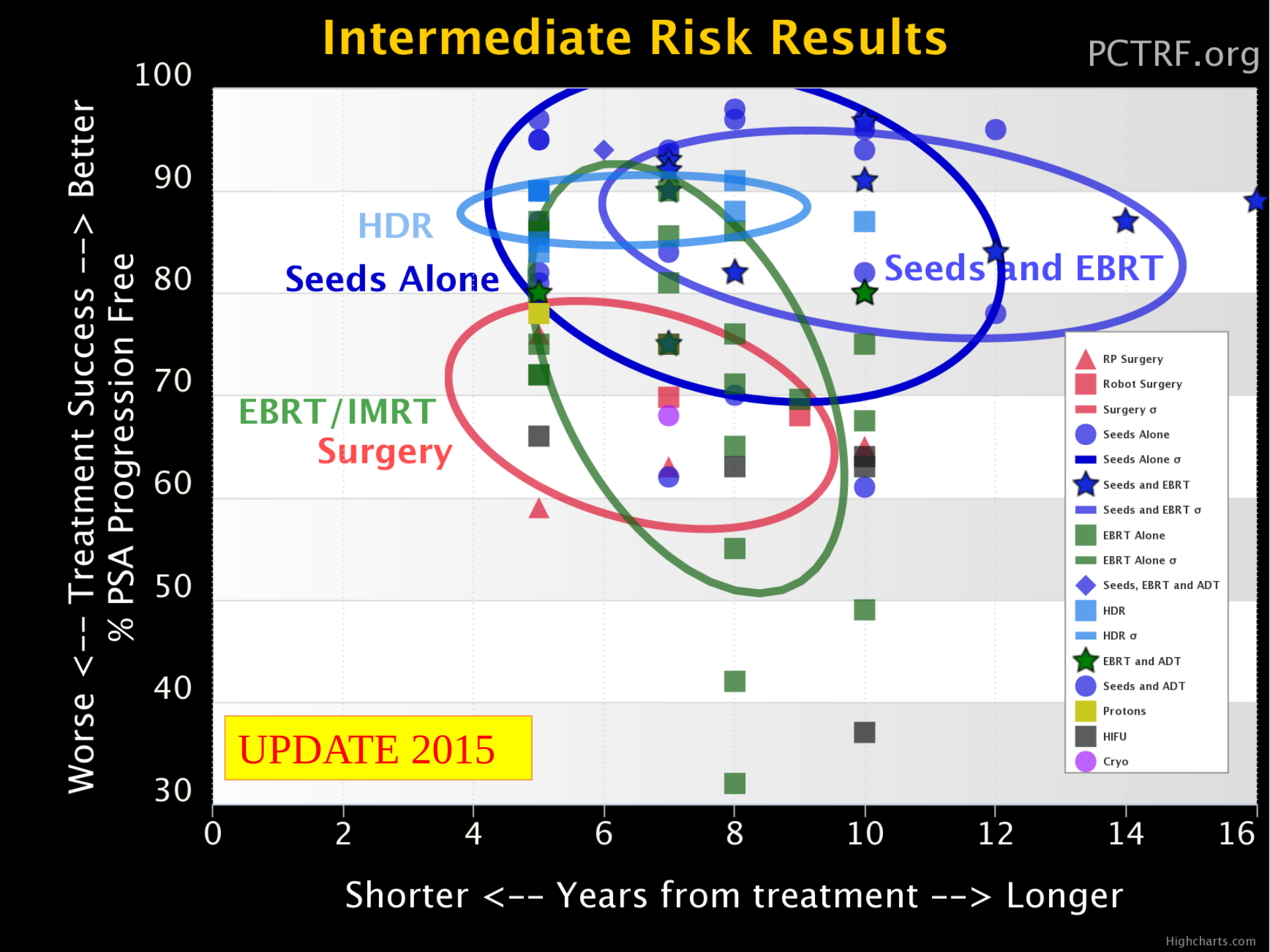
BJU INTERNATIONAL © 2012 BJU INTERNATIONAL | 109, SUPPLEMENT 1, 22–29

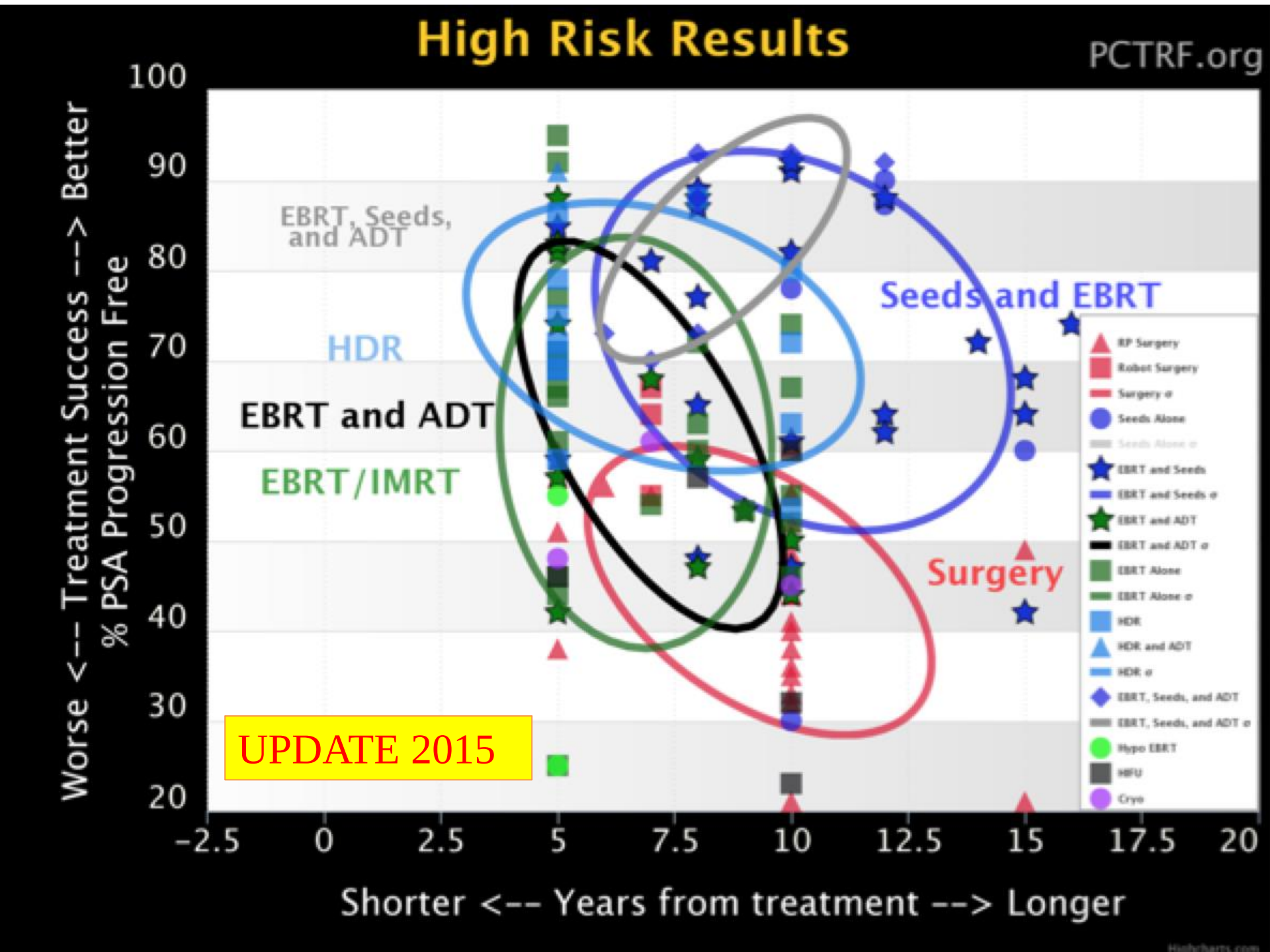
Literature review of all prostate cancer related papers published between 2000 and 2010

-5 strict criteria: - minimum/median follow-up of 5 years
- stratification into low, intermediate and high risk groups
- clinical (and pathological) stage
- accepted definition for prostatic specific antigen failure
- more than 100 patients in each risk group (high risk > 50)

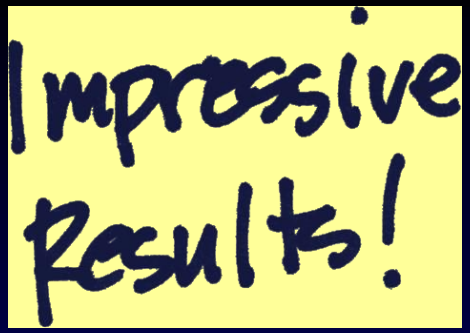
18000 papers - 848 treatment related – 140 papers encountering these criteria


Low Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
105
100
95
90
85
80
75
70
65
60
55
50
2
4
6
8
10
12
14
16
Shorter <-- Years from treatment --> Longer
Protons
LDR Brachy
EBRT/IMRT
Surgery
UPDATE 2015
RP Surgery
Robot Surgery
Surgery σ
Seeds and EBRT
Seeds and EBRT σ
Seeds Alone
Seeds Alone σ
EBRT Alone
EBRT Alone σ
Protons
Protons σ
HDR
HIFU
Highcharts.com


Intermediate Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
Shorter <-- Years from treatment --> Longer
HDR
Seeds Alone
Seeds and EBRT
EBRT/IMRT
Surgery
UPDATE 2015
RP Surgery
Robot Surgery
Surgery σ
Seeds Alone
Seeds Alone σ
Seeds and EBRT
Seeds and EBRT σ
EBRT Alone
EBRT Alone σ
Seeds, EBRT and ADT
HDR
HDR σ
EBRT and ADT
Seeds and ADT
Protons
HIFU
Cryo
Highcharts.com


High Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
100
90
80
70
60
50
40
30
20
EBRT, Seeds, and ADT
HDR
EBRT and ADT
EBRT/IMRT
Seeds and EBRT
Surgery
UPDATE 2015
-2.5
0
2.5
5
7.5
10
12.5
15
17.5
20
Shorter <-- Years from treatment --> Longer
RP Surgery
Robot Surgery
Surgery σ
Seeds Alone
EBRT and Seeds
EBRT and Seeds σ
EBRT and ADT
EBRT and ADT σ
EBRT Alone
EBRT Alone σ
HDR
HDR and ADT
HDR σ
EBRT, Seeds, and ADT
EBRT, Seeds, and ADT σ
Hypo EBRT
HIFU
Cryo

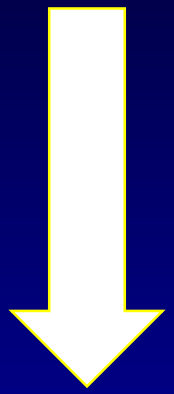
Overall, patients treated with PB have exceptionally good long-term disease outcomes and compare favorably with other treatment modalities.



- For LR and fIR: bPFS, CSS and OS are 77-95%, 93-99% and 81-99%
- For IR, bPFS, CSS and OS are 88-95%, 98-77% and 77%
- For IR and HR , bPFS, CSS and OS are 68-95%, 95-98% and 57-79%
- for HR, bPFS, CSS and OS are 80-92%, 86-98% and 68-97%

Results given in terms of biochemical control ….

However, this biochemical control depends on “local” control but also on “distant” control



What about the “local cure rates” after PB?

Patterns of Recurrence After Low-Dose-Rate Prostate Brachytherapy: A Population-Based Study of 2223 Consecutive Low- and Intermediate-Risk Patients

Andrea C. Lo, MD, W. James Morris, MD, FRCPC,
Tom Pickles, MD, FRCPC, Mira Keyes, MD, FRCPC,
Michael McKenzie, MD, FRCPC, and Scott Tyldesley, MD, FRCPC

"we estimate that the local recurrence rate of LDR-PB in our study cohort likely lies in the range of 1.8% to 2.7%."

10-YEAR EXPERIENCE WITH I-125 PROSTATE BRACHYTHERAPY AT THE PRINCESS MARGARET HOSPITAL: RESULTS FOR 1,100 PATIENTS

JUANITA CROOK, M.D.,* JETTE BORG, PH.D.,† ANDREW EVANS, M.D.,‡ ANTS TOI, M.D.,¶
E. P. SAIBISHKUMAR, M.D.,* SHARON FUNG, M.SC.,§ AND CLEMENT MA, M.SC.§

Thus, *the local relapse rate should range from 1.0% to 2.2%*, but it is likely to be closer to the biopsy-proven 1.0% of patients, because all other men with biochemical failure in this cohort had negative biopsy results

Distant and local recurrence in patients with biochemical failure after prostate brachytherapy

Richard G. Stock, Jamie A. Cesaretti, Pamela Unger, Nelson N. Stone

"Hence, at a median follow-up of 6.8 years, the local recurrence rate of the Mt. Sinai cohort treated with LDR-PB should fall between 1.3% and 4.5%"

Brachytherapy, 7 (2008), pp. 217–222

Patterns of failure after iodine-125 seed implantation for prostate cancer ☆

David S. Lamb [a,b,*], Lynne Greig [c], Grant L. Russell [d], John N. Nacey [a,d], Kim Broome [e], Rod Studd [d], Brett Delahunt [a], Douglas Iupati [b], Mohua Jain [f], Colin Rooney [c], Judy Murray [a], Peter J. Lamb [a], Peter B. Bethwaite [a]

"by combining the 0.2% who had local failure with the 2.2% whose site of failure was unknown, the local relapse rate should range from 0.2% to 2.4%"

Radiotherapy and Oncology 112 (2014) 68–71

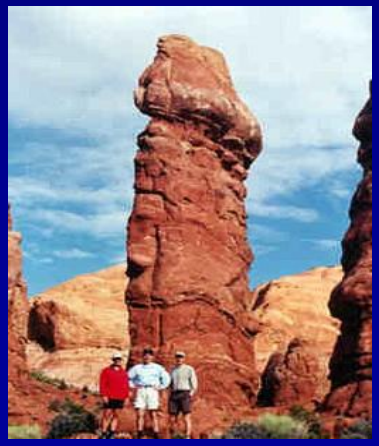
Cure

Prostate brachytherapy

Is highly effective

Local control is extremely high

Quality of Life – Side Effects



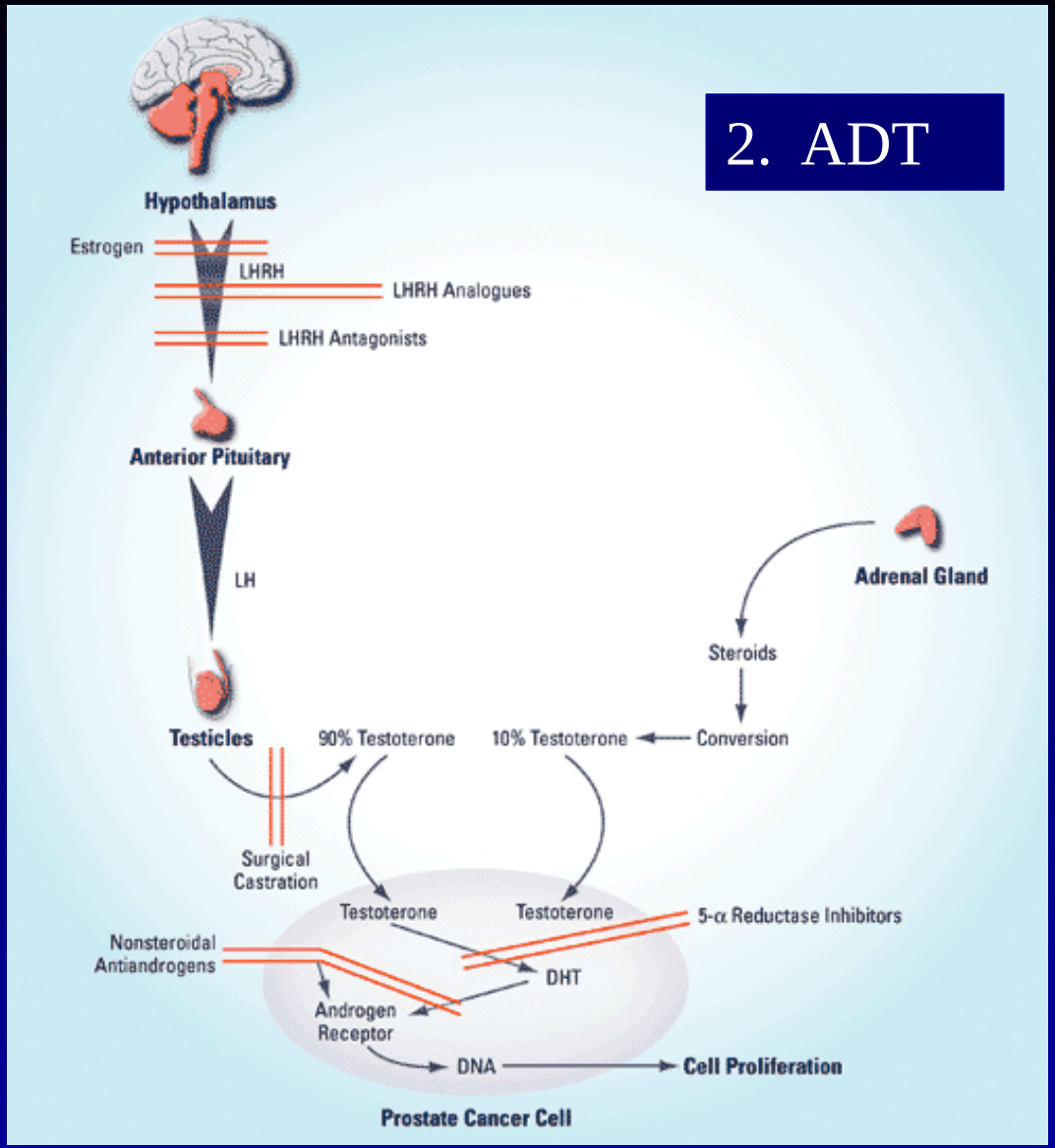
Quality of Life – Side Effects

Prostate brachytherapy

Toxicity is low and acceptable

No decrease in long term QoL

2. ADT

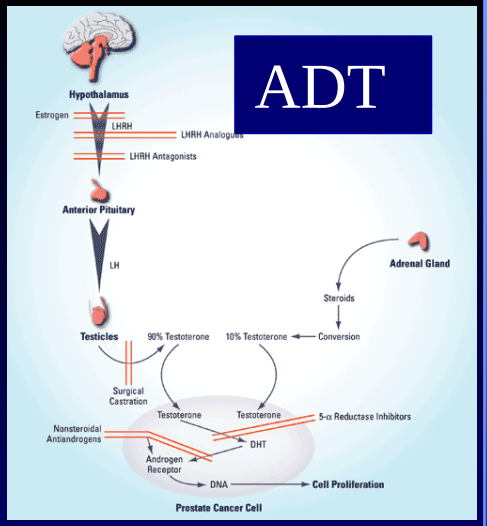

Hypothalamus
Estrogen
LHRH
LHRH Analogues
LHRH Antagonists
Anterior Pituitary
LH
Testicles
Adrenal Gland
Steroids
90% Testoterone
10% Testoterone
Conversion
Surgical Castration
Testoterone
Testoterone
5-α Reductase Inhibitors
Nonsteroidal Antiandrogens
DHT
Androgen Receptor
DNA
Cell Proliferation
Prostate Cancer Cell

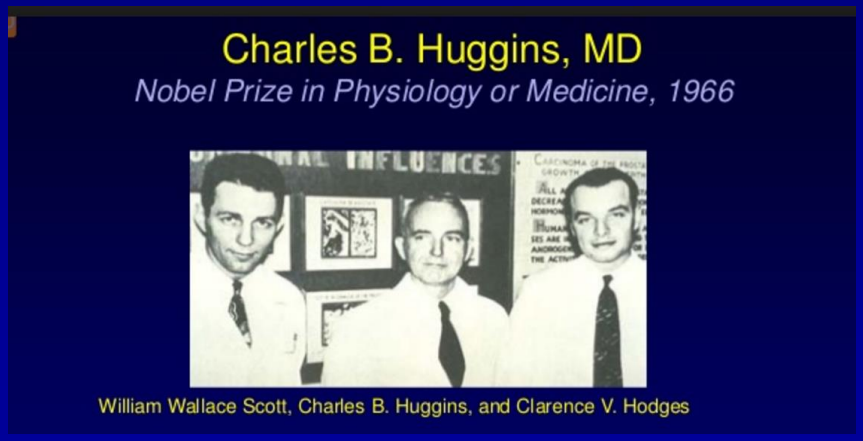
1940: Canadian born Charles Huggins recognized the androgen dependence of PCA

1966: nobel price for medecine: discoveries concerning hormonal treatment of PCA

1997: Zietman: the combination of radiation with orchiectomy for Shionogi tumors treated in vitro resulted in significant increase in control

Now, several large national and international RCT's confirmed and quantified the therapeutic benefit of ADT in combination with EBRT





Wolff FR et al: Eur J Cancer, 2015;51:2345-2367

The Seven Dwarves of ~~Menopause~~ ADT

Itchy, Bitchy, Sweaty, Sleepy, Bloated, Forgetful & Psycho

….. and they still have many other friends …

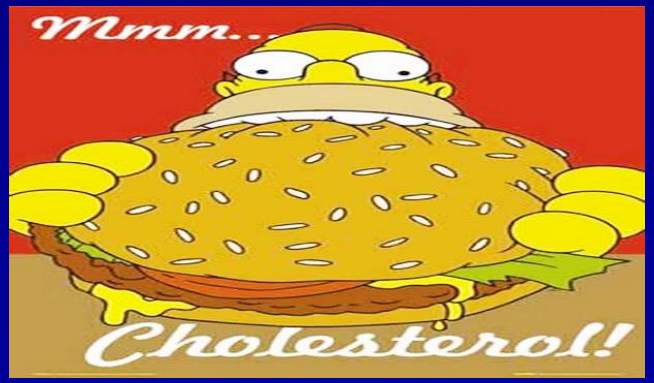
Well-documented side effets of ADT are:

- Sexual dysfunction
- Loss of libido
- Hot flashes
- Fatigue
- Decreased muscle mass
- Cognitive dysfunction
- Depression – where as up to 27% of patients on ADT may suffer psychiatric illness during their treatment

Well-documented side effets are:

- Increased risk of osteoporosis (23% increase in incidence of fractures)
- Increased incidence of metabolic syndrome (50% in ADT patients vs 20% in normal population - even with 1 year ADT)
- Central and peripheral obesity (9 – 11% increase in fat mass after 1 yr of ADT)
- Increase of total cholesterol (by 9%), Triglycerides (by 27%) and decreased HDL-cholesterol (by 11%) after only 3 mths of ADT
- Elevated blood pressure
- Elevate fasting glucose and fasting insulin
- Decrease insulin sensitivity and increase of diabetes

➔ All increasing the risk of a cardiovascular event and/or sudden cardiac death 12-60 mths after starting ADT



Even short time ADT can:

- negatively impact QOL
- increase morbidity
- increase mortality

Evidence shown in observational studies

This is however NOT confirmed in RCTs

(? inclusion of older, more frail patients – reports on non-fatal events?)

Voog et al Eur Urolo 2016;69:204-210
Sanda et al N Eng J Med 2008; 358:1250-1261
Beyer D et al Int J Radiat Oncol Biol Phys 2005; 61:1299-1305

PRIMARY CAUSES OF DEATH AFTER PERMANENT PROSTATE BRACHYTHERAPY

NATHAN BITTNER, M.D., M.S.,[†] GREGORY S. MERRICK, M.D.,[*] ROBERT W. GALBREATH, PH.D.,[*]
WAYNE M. BUTLER, PH.D.,[*] KENT E. WALLNER, M.D.,[†‡] ZACHARIAH A. ALLEN, M.S.,[*]
SARAH G. BRAMMER, B.S.,[*] AND MARK MOYAD, M.D., M.P.H.[§]

1354 patients – 5,4 years median FU – 51% ADT use

Primary causes of death in patients treated with PB (+EBRT) (+ADT)

- cardiovascular disease 42 %
- 30% other cancer 30 %
- Prostate cancer: 8,7 %

Patients with HR-disease had double the risk of dying from CVD compared with IR and LR

- HR: 19,8% vs IR 9,3% vs LR 8,7%

Excess morbidity and mortality is seen predominantly in patients with pre-existing cardiovascular co-morbidity

Bittner et al, Int J Radiat Oncol Biol Phys 2008;72:433-440

Nanda et al, JAMA 2009;302:866-873
Nguyen et al, Int J Radiat Oncol Biol Phys 2012;82:1411-1416

Even short term ADT gives an absolute increase 5,3% at 10 years ! (Kobutek et al)

Re-analysis of 6 RCTs (Albertsen et al)

- the increase in cardio-vascular mortality and morbidity might be an LHRH agonist class effect
- significantly less CVD events in men treated with LHRH antagonists vs LHRH agonists (HR: 0,44 - 95% CI 0,26-0,74 - p=0,002)

Pronounce NCT02663908: RCT comparing major CV events with LHRH agonists vs antagonists in patients with pre-existing CV morbidity

Kobutek et al, Int J Radiat Oncol Biol Phys 2014;90:S15
Albertsen et al, Eur Urol 2014;65:565-573

3. EBRT + ADT

RATIONALE for combining EBRT and ADT:

-(neo-adjuvant ADT) improves the geometry of the prostate target by decreasing the volume juxtaposed to adjacent OAR

-If given before EBRT (in experimental setting), the anti-angiogenesis effect of ADT may

- 'normalize' the vasculature and lead to better perfusion
- increase the oxygenation
- increase the radiation tumor sensistivity
- increase the LC. Reducing local failure may reduce second-wave metastatic spread and thus improve OS

-The synergistic relationship in concurrent administration might produce a biologic advantage

-Several RCTs show an improvement in bPFS and LC but also in DSS and 0S … so … ADT might have an influence on local and systemic disease

-Clinical evidence supports the hypothesis that ADT can eliminate subclinical micro-metastases.

- Addition of ADT to EBRT, RCTs have shown benefit in improving OS, CSS and bPFS in HR
  - RTOG 85-31 - RTOG 92-02 - TROG 96-01
  - RTOG 86-10 - RTOG 94-08 - EORTC 22961
  - EORTC 22863 - Harvard/DFCI - TROG 96-01
- Addition of ADT to EBRT, RCTs have shown benefit in improving OS, CSS and bPFS in IR
  - RTOG 94-08
  - Harvard/DFCI 95-096

- A Spanish RCT showed even in a dose escalation to 78 Gy, 24 vs 4 months of ADT improves bPFS, metastatic-free survival and OS in patients with IR and HR disease.

- It is clear that ADT has an additive effect on improving disease outcomes with EBRT even at high doses of 78 or 81 Gy

  Optimal duration with EBRT for each risk category has not been established

Zapatero et al, Lancet Oncol; 2015;16:320-327
Zelefsky et al, Eur Urol: 2011; 60; 60:1133-1139

REFLECTIONS:

- The benefit of ADT in combination with EBRT (even with dose-escalated EBRT) may be because of compensation for suboptimal radiation dose and less effective therapy.

- Because of the very high intraprostatic dose and excellent disease control, ADT is likely to have less biologic effect with PB, except perhaps in cases with very high-volume diesease or through spatial cooperation for suppression of micrometastic disease

- Addition of ADT to PB in IR and HR patients has been shown to decrease 2-yr post PB positive biopsy rate from 14% to 3,5%

Lo et al, Int J Radiat Biol Phys, 2015;91:745-751
Stone et al, Int J Radiat Biol Phys, 2010; 76:355-360
Stone et al: Mol Urol 2000; 4(3): 163-168

REFLECTIONS:

If we disregard normal tissue tolerance, one can speculate that any truly localized PCA can be cured with radiation alone, given suffisiently high dose and ensuring complete coverage of the tumortarget.

4. Do we need ADT in addition to PB ?

Cytoreduction

- The aim is to downsize the prostate
- Most common used is a LHRH agonist
- Alternative: dutasteride and bicalutamide
  - RCT shows a non-inferiority of this regimen in comparaison with LHRH
  - So because of the potential impairment of QoL associated with ADT, one may consider the less toxic combination fo 5-&-reductase inhibitor + oral anti-testosterone for cytoreduction.
- No improved oncologic outcome

Gaudet et al; Brachytherapy 2015;14:S33-34
Ciezki et al; Int J Radiat Oncol Biol Phys 2004;60:1347-1350
Potters et al; J Urol 2005;173:1562-66
Ohashi et al; Radioth Oncol 2013;109:241-245
Morris et al; Cancer 2013; 119:1537-1546
Martin et al; Int J Radiat Oncol Biol Phys 2007:67:334-341

American Brachytherapy Society Task Group Report: Use of androgen deprivation therapy with prostate brachytherapy—A systematic literature review

M. Keyes[1,*], G. Merrick[2], S.J. Frank[3], P. Grimm[4], M.J. Zelefsky[5]

In this review: studies grouped based on risk stratification

Low Risk and favourable Intermediate Risk

5 studies

- 4 studies describing outcome in patients treated with LDR +/- ADT
- 1 study describing outcome in patients treated with LDR +/- EBRT +/- ADT

ADT used in 27-65% of patients
ADT duration 3-6 mths

Most often: downside prostate volume before BT and in one study for IR features

- None of the studies showed any benefit from ADT to bPFS.
- Effect on CSS not reported
- Not associated with improved or detrimental OS

Ciezki *et al.* (70)	Multi-institutional, USA	1996—2001	1668
Potters *et al.* (71)	New York Institutions, USA	1992—2000	1449
Ohashi *et al.* (72)	Multi-institutional Japan	2003—2009	663
Morris *et al.* (73)	British Columbia, Canada	1998—2003	1006
Martin *et al.* (74)	Quebec City Canada	1994—2001	396

Intermediate Risk

6 studies describing outcome in patients treated with LDR +/- ADT or LDR +/- EBRT +/- ADT (5854 patients)

ADT used in 17-81% of patients
ADT duration 4 months

Results:

- bPFS:
  - 4 studies: no overall benefit with ADT
  - 2 studies: no report on bPFS
- CSS:
  - 1 study shows an absolute 2% benefit on CSS with ADT
  - 1 study shows a benefit in unfavourable IR patients
  - 1 study shows a benefit if BED < 150 Gy
- OS:
  - 4 studies did not report on the association between ADT and OS
  - 1 study showed no benefit

Rosenberg *et al.* (75)	Chicago	1997–2007	807
Tran *et al.* (76)	Multi-institutional, UK	2003–2007	615
Ho *et al.* (77)	Mount Sinai, NY	1990–2004	558
Keane *et al.* (78)	Harvard, Boston, MA	1997–2013	2510
Bittner *et al.* (79)	Multi-institutional, USA	1995–2001	932
Stock *et al.* (80)	Mount Sinai, NY	1994–2006	432

Intermediate and High Risk

8 studies describing outcome in patients treated with mono(brachy-)therapy or combination therapy

- 6 LDR – 1 HDR and 1 HDR or LDR
- ADT used in 32-66% of patients
- ADT median duration 6 months (4-28 months)

LDR			
Lee (81)	Mount Sinai, NY	1990–1998	201
Strom (82)	Tampa, FL	2001–2011	120
Merrick *et al.* (83)	Multi-institutional, USA	1995–2003	530
Merrick *et al.* (84)	Multi-institutional, USA RCT—20 vs. 44 Gy EBRT + PB	1999–2004	247
Dattoli *et al.* (85)	Multi-institutional, USA	1992–1997	321
Merrick *et al.* (86)	Multi-institutional, USA RCT—0 vs. 20 vs. 44 Gy EBRT + PB	1999–2013	630
HDR/LDR			
Kraus *et al.* (87)	William Beaumont	1991–2004	1044 Patients
HDR			
Schiffmann *et al.* (88)	Hamburg Germany	1999–2009	392

Results:

•bPFS:

- 6 (out of the 8) studies: no benefit with ADT except in patients with low D90
- 1 (HDR) study showed 12% (in IR disease) and 20% (in HR disease) benefit to adding ADT

•CSS:

- None of the studies showed overall benefit

•OS:

- None of the studies showed overall benefit

High Risk

11 studies describing outcome in patients treated with combination therapy

- 10 LDR + EBRT and 1 HDR + EBRT
- 1 included also patients treated by LDR PB alone
- ADT used in 40-91% of patients
- ADT median duration 3-12 months

LDR			
Ohashi *et al.* (89)	Japan	2003–2009	206
Bittner *et al.* (56)	Multi-institutional, USA (very high risk)	1995–2007	131
Bittner *et al.* (90)	Multi-institutional, USA	1995–2005	186
Wattson *et al.* (91)	Multi-institutional, USA	1991–2007	2234
D'Amico *et al.* (92)	Multi-institutional, USA	1991–2005	1342
Merrick *et al.* (93)	Multi-institutional, USA	1995–2002	204
Shilkurt *et al.*(94)	Multi-institutional, USA	1995–2010	448
Merrick *et al.* (55)	Multi-institutional, USA	1995–2005	284
Liss (95)	Multi-institutional, USA	1998–2008	141
Fang *et al.* (96)	Multi-institutional, USA	1995–2005	174
HDR			
Prada *et al.* (97)	Oviedo, Spain	1998–2006	252

Results:

- bPFS: 9 studies showed an association between ADT and bPFS
  - 6 showed a benefit with ADT (2 studies showed a 13% benefit with longer ADT duration)
  - 3 showed no benefit with ADT
- CSS: 9 studies showed an association between ADT and CSS
  - 3 showed a benefit with ADT
  - 6 showed no benefit with ADT
- OS: 5 studies reported on an association between ADT and OS
  - None of the studies showed an overall benefit

LR – IR - HR

A lot of studies describe outcomes in all risk categories
In the ABS review: 22 studies – 23.180 patients
16 using LDR (20991 patients) – 5 using HDR (2189 patients)
Median FU: 3,8 – 10 years
ADT use: 18 – 83 % - median duration: 3 – 9 months

Results:

- bPFS: 16 studies showed an association between ADT and bPFS
    - 4 showed a benefit with ADT
        - 1 study reported a 15% benefit only with longer ADT duration
        - 1 study reported a 24% benefit only if BED was < 150 Gy
        - 1 study reported a 9-15% benefit only in HR disease
    - 12 showed no benefit with ADT (including all HDR studies)
    - Remark: one study showed a detriment to bPFS with the addition of ADT in IR disease

LR – IR - HR

Results:

- CSS: 7 studies showed an association between ADT and CSS
    - All 7 showed no benefit with ADT

- OS: 6 studies reported on an association between ADT and OS
    - 3 studies showed no impact on OS
    - 3 showed a statistically detriment to OS using ADT
    - One showed a trend to worse OS

- 6 ongoing RCTs evaluation the role of ADT with PB in IR and HR patients
- Only one completed RCT adressed (at least indirectly) the role of ADT in PB

Australian multicenter TROG 03.04 RADAR 2 x 2 factorial RCT in men with locally advanced PCA

–1071 men

–randomization to receive ADT for 6 to 18 months with dose-escalated EBRT (66-70-74 or 46 Gy + HDR 19,5 Gy in 3 fractions) and also randomized between 0 and 18 months of Zoledronic Acid

–Primary endpoint bPFS subsequently changed to a PCSM. Median follow-up: 7,4 years

–No significant difference in PCSM or OS

–However: 18 months of ADT had a positive effect on the PSA and LC outcome on all EBRT dose levels with greater benefit in lower doses and had almost NO effect for patients treated with HDR boost (absolute difference 3%)

–This data suggest minimal (if any) benefit to longer ADT using PB – however, it does not answer the question if ADT is needed with PB at all

Denham et al; Radiother Oncol 2015;15:1076-1089

Literature shows significant heterogeneity

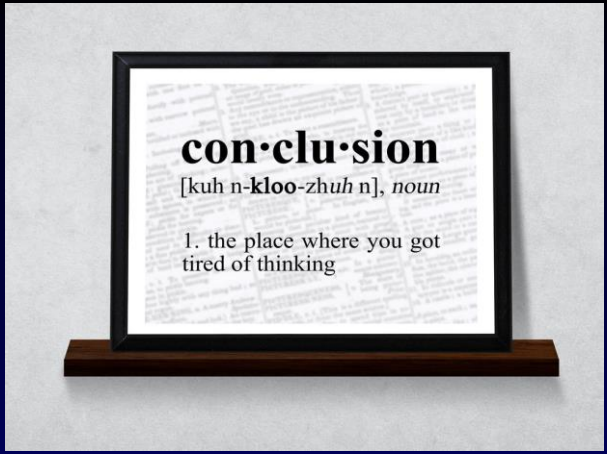
- of the patient populations
- in the risk categories
- in the definition of risk factors
- in the follow-up time
- in ADT administration
- in the duration for ADT administration

The retrospective analyses induces unavoidable patient selection and treatment selection bias !

	bPFS	CSS	OS
Total studies 52	Reported in 42 studies (80%)	Reported in 24 studies (46%)	Reported in 19 studies (36%)
Benefit to ADT	12 (28%)	4 (16%)	0
No benefit	30 (71%)	19 (79%)	16 (84%)
Detriment with ADT	1 (2%)	—	3 (15%)

- No clinical or biochemical benefits from the addition of ADT in LR en fIR

- Beneficial in bPFS
  - in most patients with HR disease using LDR
  - some patients with uIR
  - In patients with low D90 or low BED



- Not beneficial in CSS
  - A very small absolute benefit (2%) to CSS was found in only a few studies and was predominantly with 3-modality treatment vs PB monotherapie

- No OS survival benefit was found in any study

- However: three studies reported on a detriment to OS using ADT (cave: older patients, existing CV disease)

- With high-quality brachytherapy, the dose is sufficient so that any synergistic local effect of ADT with radiation is likely to be of little benefit (unless high volume disease *perhaps …*)
- uIR and HR: ADT is likely to play a role through spatial cooperation for suppression of micro-metastatic disease
- Duration in addition to BT: none or short(er) than with EBRT


THANK
YOU!

Prostate Brachytherapy Course

“Outcome of LDR prostate brachytherapy”

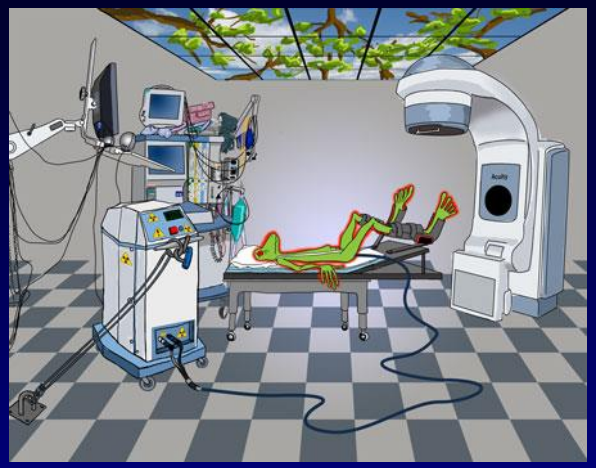
C. Salembier

Outcome of LDR prostate brachytherapy

C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

Treatment options - localized prostate cancer



External beam radiotherapy

Hormonal treatment

Interstitial: low or high dose rate

(robotic) surgery

Localized prostate cancer: heterogeneous group of tumours

Prognostic groups: Good – Intermediate - Poor

Depending on:

- Extension of the tumour
- Initial PSA
- Gleason Score

Low Risk

Stage: T1 or T2a,b
Gleason Sum ≤ 6
PSA ≤ 10 ng/ml

Intermediate Risk

Stage T1 or T1-2 Stage T1-2
Gleason Score 7 or Gleason 6
PSA < 10 PSA 10-20

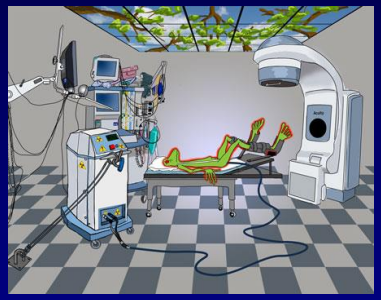
High Risk

Stage T2c or T3
Gleason score ≥ 8
PSA > 20 ng/mL

Which treatment should be given?

No randomized trials

Comparing RP, EBRT, seeds:



Outcome:

Up to high risk patients:

- No difference in outcome
- Total BED dose matters

Toxicity

- Type of toxicity differs
- No difference severe toxicity rate

Quality of life

- No difference baseline – 6 months

CLINICAL INVESTIGATION Prostate

RADICAL PROSTATECTOMY, EXTERNAL BEAM RADIOTHERAPY <72 Gy, EXTERNAL BEAM RADIOTHERAPY ≥72 Gy, PERMANENT SEED IMPLANTATION, OR COMBINED SEEDS/EXTERNAL BEAM RADIOTHERAPY FOR STAGE T1–T2 PROSTATE CANCER

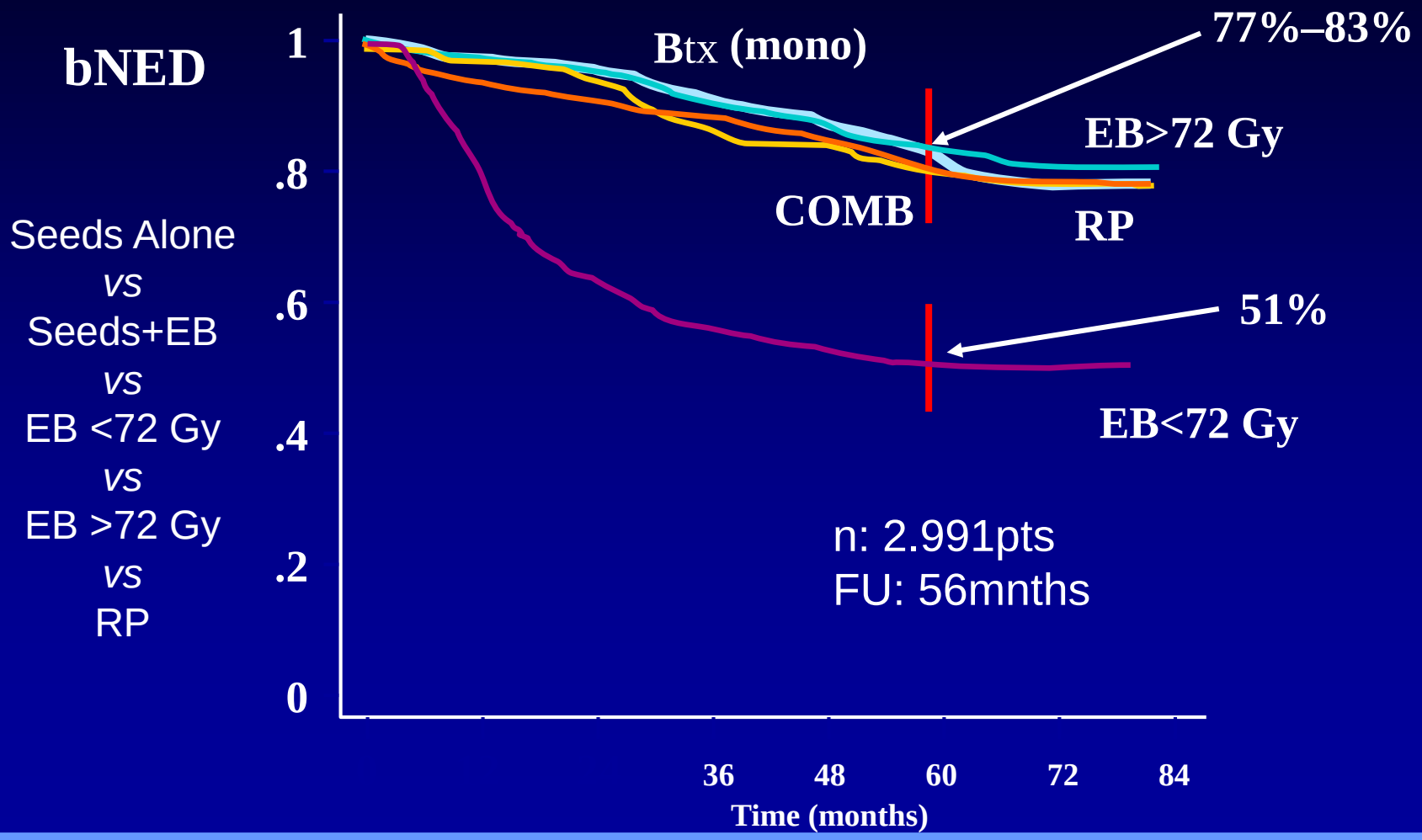
PATRICK A. KUPELIAN, M.D.,* LOUIS POTTERS, M.D.,† DEEPAK KHUNTIA, M.D.,‡ JAY P. CIEZKI, M.D.,‡ CHANDANA A. REDDY, M.S.,‡ ALWYN M. REUTHER, M.P.H.,‡ THOMAS P. CARLSON, M.D.,‡ AND ERIC A. KLEIN, M.D.‡

*Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, FL; †Department of Radiation Oncology, Memorial Sloan-Kettering at Mercy Medical Center, Rockville Centre, NY; ‡Department of Radiation Oncology and the Urological Institute, Cleveland Clinic Foundation, Cleveland, OH

- **Comparative Cohort Study**
  - Total 1866 consecutive cases, Treated 1992 to 1998
  - Clinical Stage T1-T2
- **Facility:**
  - Cleveland Clinic Foundation:
    - *1225 cases (94 PI, 348 EBRT, 783 RP)*
  - Memorial Sloan Kettering @ Mercy Medical Center:
    - *641 cases (641 PI)*
- **All patients treated with monotherapy**
  - Radical prostatectomy
  - External beam radiation (min dose 70 Gy)
  - Permanent Implant

Treatment comparison - Cleveland Clinic/MSKCC

Kupelian PA et al. IJROBP 58: 25-33: 2004



Brachy bNED in literature

Many studies published

No real comparison possible because of differences in:

- patient selection
- treatment differences
- follow-up differences
- …

Study	n=	Study period	bNED	low	int	high	total
D'Amico et al 1998	66	1989-1997	x	85	35	x	x
Beyer et al 2000	695	1988-1995	5 y	83	67	x	x
Beyer et al 1997	499	1988-1993	5 y	94	70	34	x
Beyer et al 2003	1266/1141	1988-1998	5/10y	x	x	x	76/65
Blank et al 2000	102	1985-1996	5/7 y	x	x	x	39/44
Brachman et al 2000	695/633	1988-1995	5 y	x	x	x	71
Cosset et al 2008	809	1999-2004	5 y	x	x	x	97/94
Guedea et al 2006	1175	1998-2003	3 y	93	88	80	91
Khaksar et al 2006	300	1999-2003	5 y	96	89	93	93
Kwok et al 2002	102	1991-1994	5 y	85	62	24	x
Lawton et al 2007	101	1998-2000	5 y	x	x	x	94
McMullen et al 2004	63	1997-1998	5 y	x	x	x	95-70
Merrick et al 2005	202	1995-2001	8 y	x	x	x	93,3
Papagikos et al 2007	132	1997-2001	5 y	x	x	x	88
Polascik et al 1998	76	1988-1990	7 y	x	x	x	79
Potters et al 2004	733	1992-1998	7 y	x	x	x	74
Potter et al 2005	1449/1148	1992-2000	12 y	88	76	62	77
Ragde et al 2001	769/542	1987-1997	5/10/13y	79/76/76	x	x	x
Stone et al 2007	3928/2293	x	10 y	63,6	64	58	70
Stone et al 2005	279	1990-1998	10 y	91,3	x	X	78
Grimm et al 2001	125	1988-1990	10 y	87	x	x	x
Zelefsky et al 2007	367	1998-2002	5 y	96	88	x	x
Zelefsky et al 2007	2693/1831	1988-1998	8 y	74	61	39	x
Zelefsky et al 2000	248	1989-1996	5 y	88	77	38	71
Sylvester et al 2007	223	1987-1993	15 y	85,8	80	68	74
Kupelian et al 2004	950/264	1990-1998	5/7 y	x	x	x	83/76
Block et al 2006	118	1999-2002	5 y	94,7	x	x	x
Kao et al 2008	435	1995-2005	5 y	X	x	x	96,5
Peschel et al 2006	330	1992-2004	5 y	93/84	x	x	x
Stokes et al 2000	186	1988-1994	5 y	75	65	35	70
Storey et al 1999	206	1988-1993	5 y	x	x	x	63
Wallner et al 2003	57	2000-?	3 y	x	x	x	89

Brachy bNED in literature

Study	n=	Study period	bNED	low	int	high	total
Beyer et al 2003	1141	1988-1998	10 yr	x	x	x	65
Stone et al 2007	2293		10 yr	63.6	64.4	58.2	70
Stone et al 2005	279	1990-1998	10 yr	91.3	x	x	78
Zelefsky et al 2007	1831	1988-1998	8 yr	74	61	39	x
Potters et al 2005	1148	1992-2000	12 yr	88	76	62	77
UMCutrecht	921	1989-2004	10 yr	88.2	60.6	29.9	57.0

Comparing studies with approximately the same:

- patient selection and treatment characteristics
- $\geq$ 8 years of follow-up

Results

Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group

Peter Grimm[1], Ignace Billiet[2], David Bostwick[3], Adam P. Dicker[4], Steven Frank[5], Jos Immerzeel[6], Mira Keyes[7], Patrick Kupelian[8], W. Robert Lee[9], Stefan Machtens[10], Jyoti Mayadev[11], Brian J. Moran[12], Gregory Merrick[13], Jeremy Millar[14], Mack Roach[15], Richard Stock[16], Katsuto Shinohara[15], Mark Scholz[17], Ed Weber[18], Anthony Zietman[19], Michael Zelefsky[20], Jason Wong[21], Stacy Wentworth[22], Robyn Vera[23] and Stephen Langley[24]

BJUI SUPPLEMENTS

BJU INTERNATIONAL © 2012 BJU INTERNATIONAL | 109, SUPPLEMENT 1, 22–29

Literature review of all prostate cancer related papers published between 2000 and 2010

-5 strict criteria: - minimum/median follow-up of 5 years
- stratification into low, intermediate and high risk groups
- clinical (and pathological) stage
- accepted definition for prostatic specific antigen failure
- more than 100 patients in each risk group (high risk > 50)

18000 papers - 848 treatment related – 140 papers encountering these criteria

Comparing Treatment Results Of PROSTATE CANCER

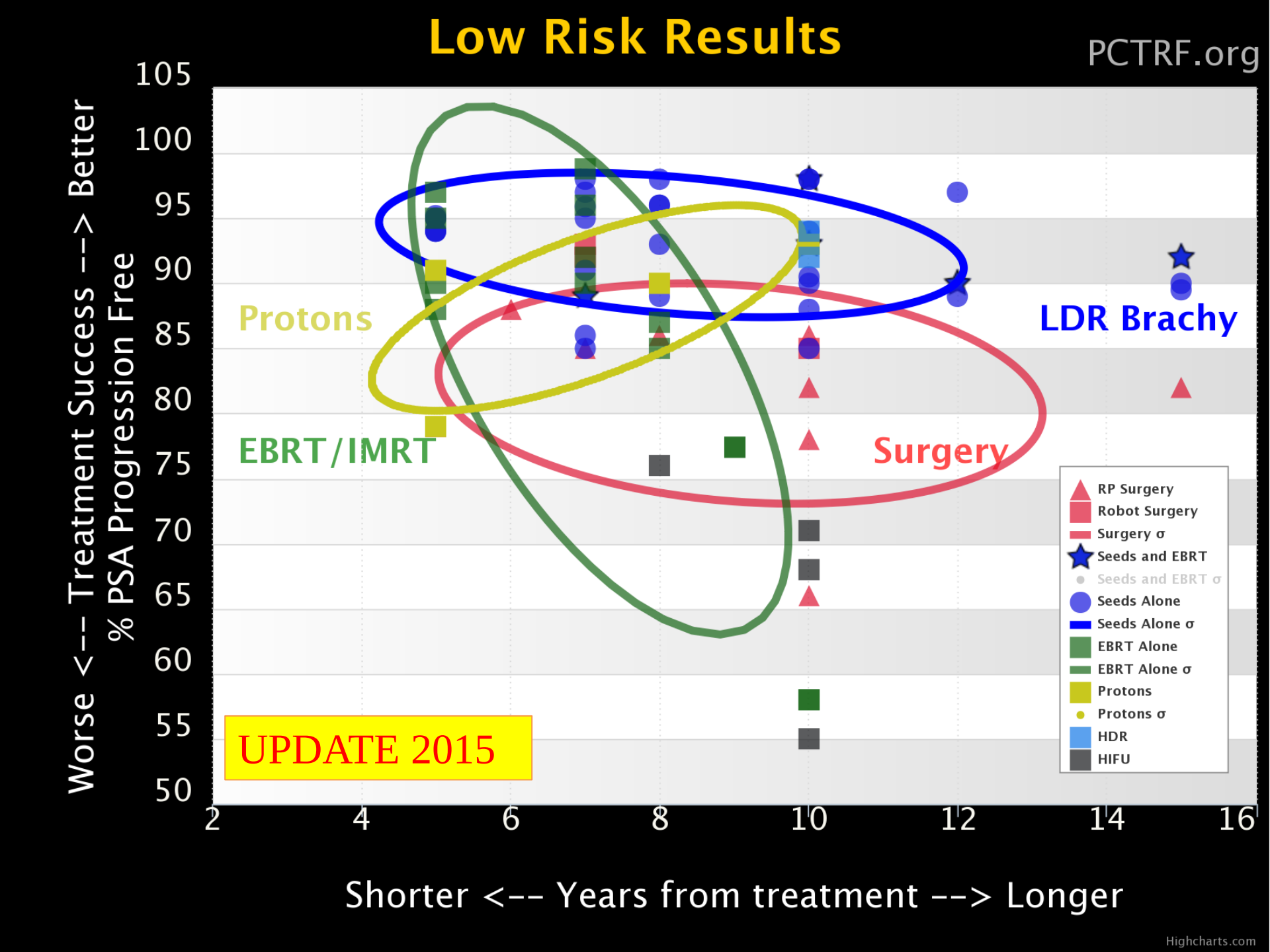
Prostate Cancer Results Study Group
Updated June 2015

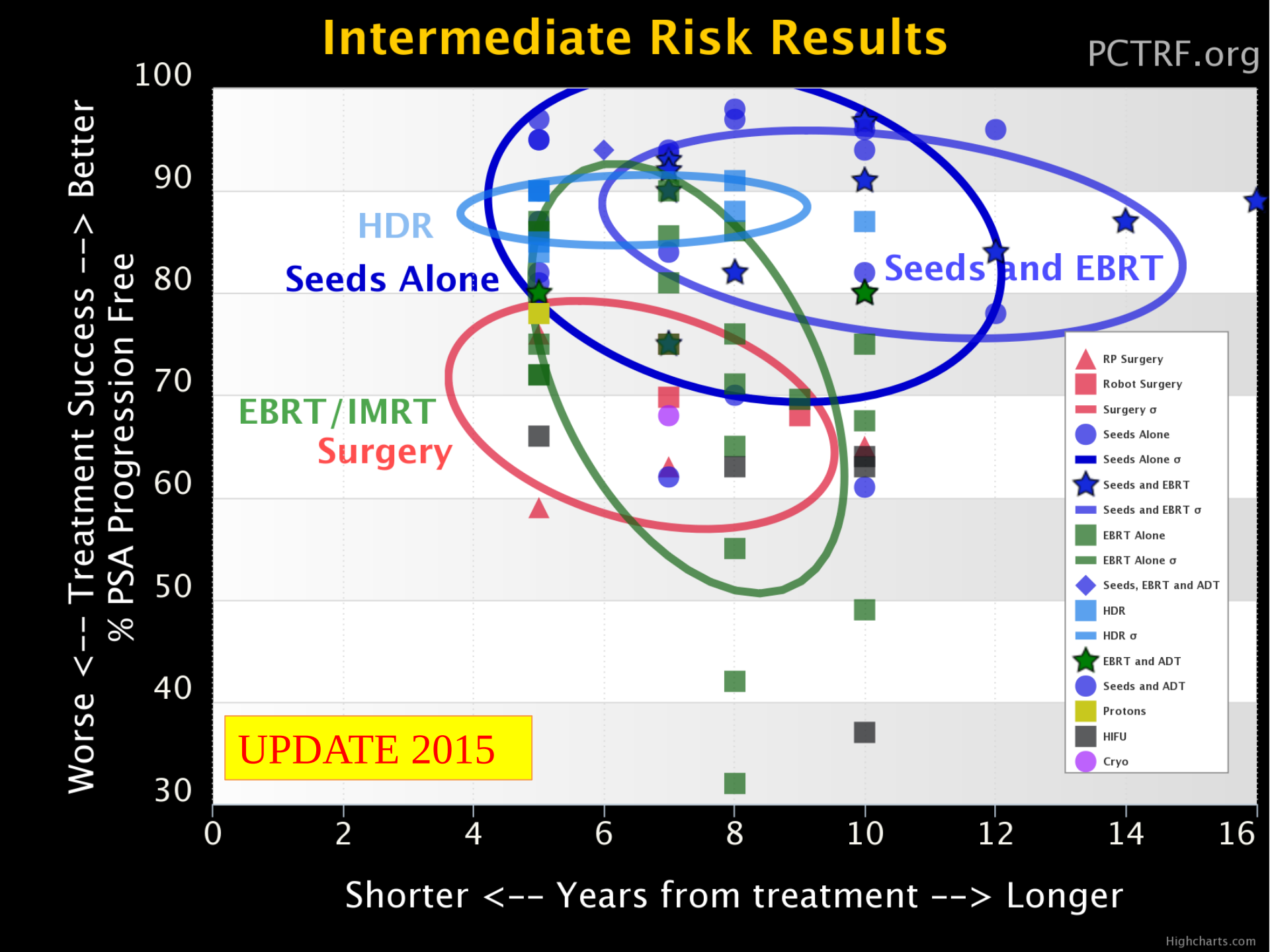
Peter Grimm, DO
Prostate Cancer Center of Seattle

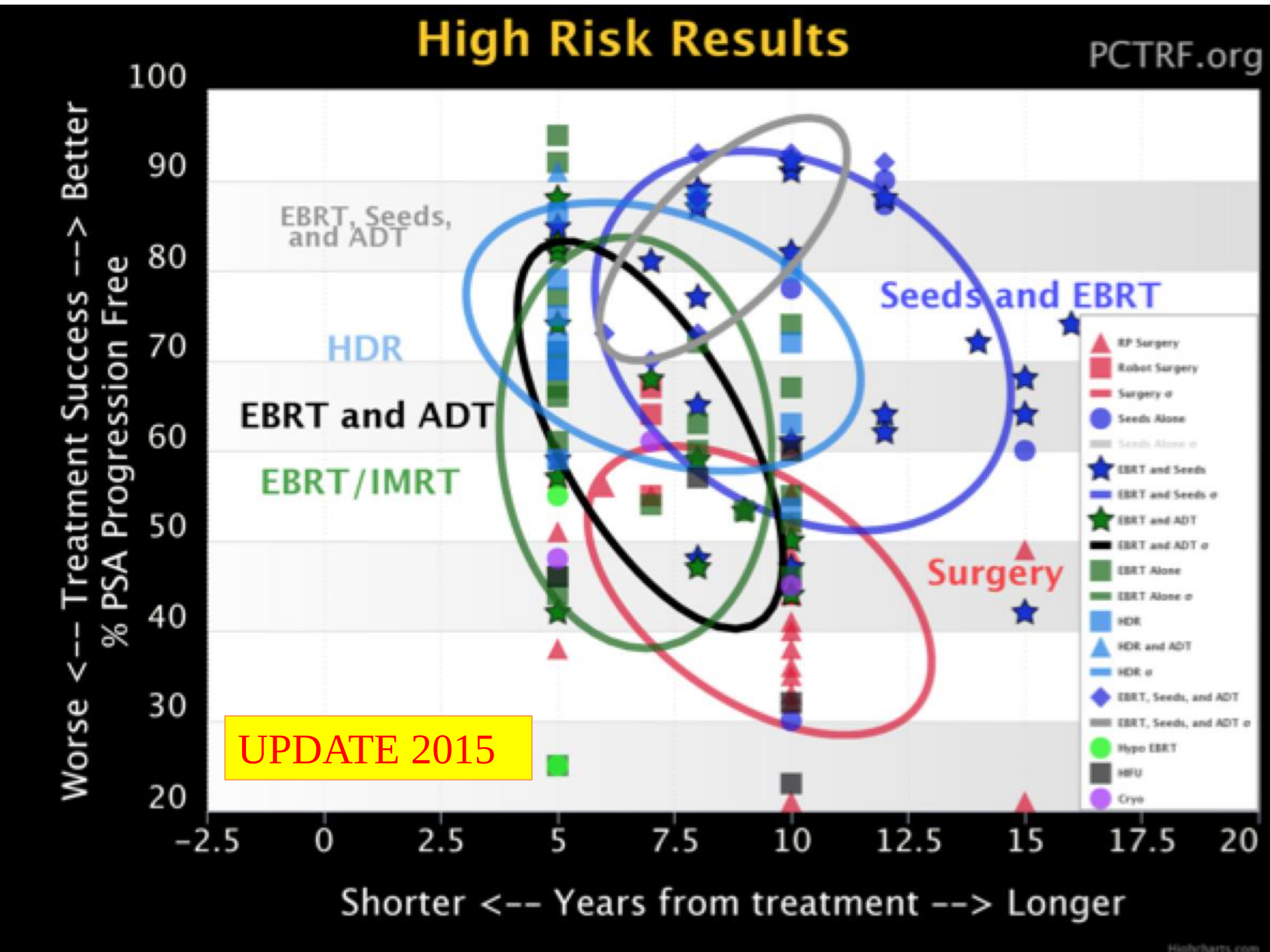
% Articles Meeting Criteria

RP	EBRT/ IMRT	Cryo	Brachy/ HDR	Robot RP	Proton	HIFU
8.7%	14.6%	6.5%	23%	3.5%	22%	13.6%
32/366	50/343	3/46	80/351	3/86	4/18	6/44

UPDATE 2015


Low Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
105
100
95
90
85
80
75
70
65
60
55
50
2
4
6
8
10
12
14
16
Shorter <-- Years from treatment --> Longer
Protons
LDR Brachy
EBRT/IMRT
Surgery
UPDATE 2015
RP Surgery
Robot Surgery
Surgery σ
Seeds and EBRT
Seeds and EBRT σ
Seeds Alone
Seeds Alone σ
EBRT Alone
EBRT Alone σ
Protons
Protons σ
HDR
HIFU
Highcharts.com

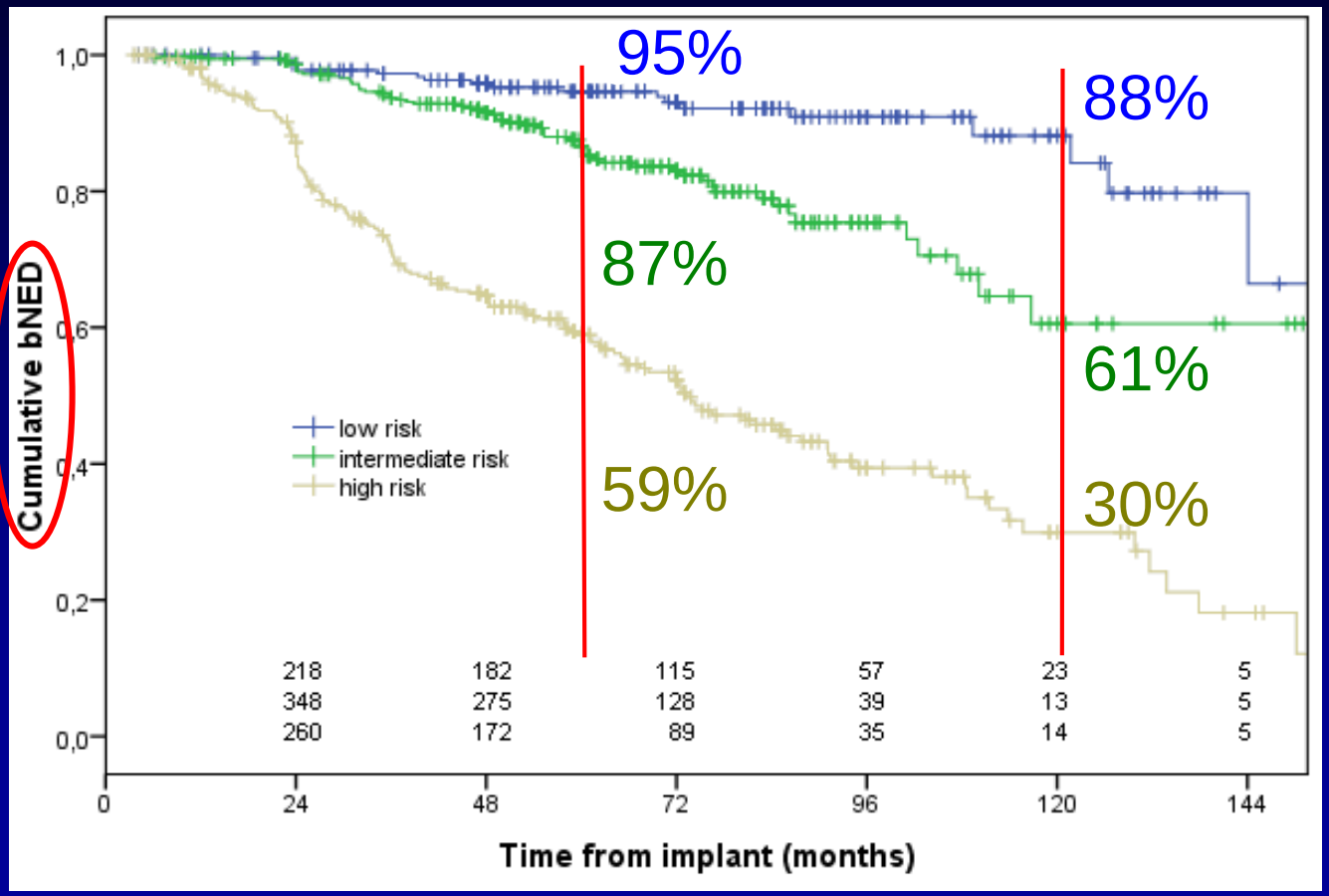

Intermediate Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
Shorter <-- Years from treatment --> Longer
HDR
Seeds Alone
Seeds and EBRT
EBRT/IMRT
Surgery
UPDATE 2015
RP Surgery
Robot Surgery
Surgery σ
Seeds Alone
Seeds Alone σ
Seeds and EBRT
Seeds and EBRT σ
EBRT Alone
EBRT Alone σ
Seeds, EBRT and ADT
HDR
HDR σ
EBRT and ADT
Seeds and ADT
Protons
HIFU
Cryo
Highcharts.com


High Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
100
90
80
70
60
50
40
30
20
EBRT, Seeds, and ADT
HDR
EBRT and ADT
EBRT/IMRT
Seeds and EBRT
Surgery
UPDATE 2015
-2.5
0
2.5
5
7.5
10
12.5
15
17.5
20
Shorter <-- Years from treatment --> Longer
RP Surgery
Robot Surgery
Surgery σ
Seeds Alone
EBRT and Seeds
EBRT and Seeds σ
EBRT and ADT
EBRT and ADT σ
EBRT Alone
EBRT Alone σ
HDR
HDR and ADT
HDR σ
EBRT, Seeds, and ADT
EBRT, Seeds, and ADT σ
Hypo EBRT
HIFU
Cryo

Long-term biochemical and survival outcome of 921 patients treated with I-125 permanent prostate brachytherapy

IJROBP 2010;76(5):1433-8.

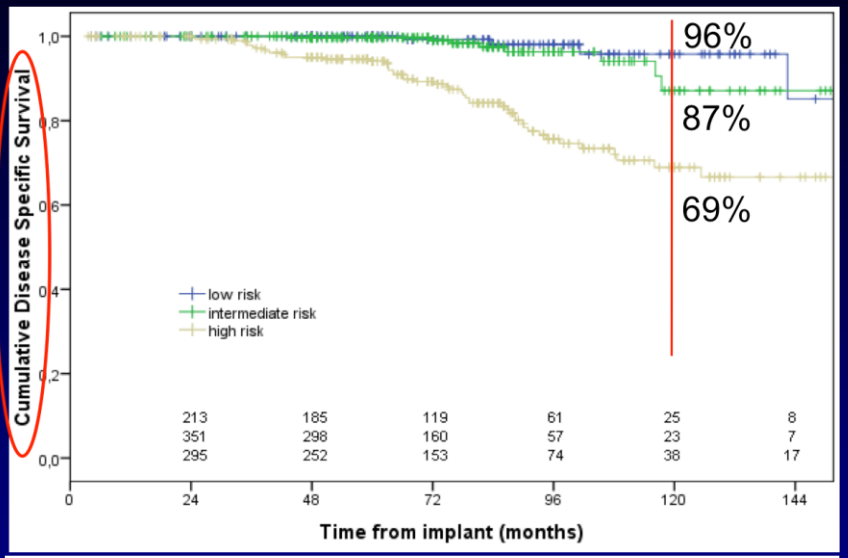
Hinnen et al.



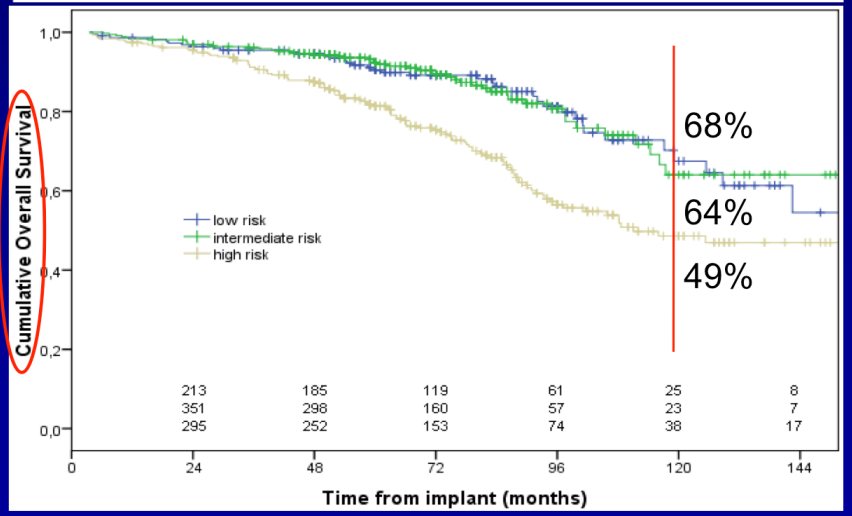
bNED

Long-term biochemical and survival outcome of 921 patients treated with I-125 permanent prostate brachytherapy

Hinnen et al.



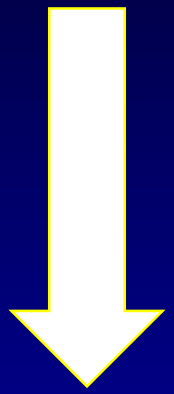
Disease specific survival



Overal survival

Results given in terms of biochemical control ….

However, this biochemical control depends on “local” control but also on “distant” control



What about the “local cure rates” after PB?

Patterns of Recurrence After Low-Dose-Rate Prostate Brachytherapy: A Population-Based Study of 2223 Consecutive Low- and Intermediate-Risk Patients

Andrea C. Lo, MD, W. James Morris, MD, FRCPC, Tom Pickles, MD, FRCPC, Mira Keyes, MD, FRCPC, Michael McKenzie, MD, FRCPC, and Scott Tyldesley, MD, FRCPC

"we estimate that the local recurrence rate of LDR-PB in our study cohort likely lies in the range of 1.8% to 2.7%."

"In the context of the limitations of our study design, this population-based analysis indicates that the local recurrence rate after LDR-PB appears to be as low or lower than that following RP in our jurisdiction."

IJROBP, Vol 91, Issue 4, 15 March 2015, Pages 745–751

Distant and local recurrence in patients with biochemical failure after prostate brachytherapy

Richard G. Stock, Jamie A. Cesaretti, Pamela Unger, Nelson N. Stone

"Hence, at a median follow-up of 6.8 years, the local recurrence rate of the Mt. Sinai cohort treated with LDR-PB should fall between 1.3% and 4.5%"

Brachytherapy, 7 (2008), pp. 217–222

Patterns of failure after iodine-125 seed implantation for prostate cancer ☆

David S. Lamb [a,b,*], Lynne Greig [c], Grant L. Russell [d], John N. Nacey [a,d], Kim Broome [e], Rod Studd [d], Brett Delahunt [a], Douglas Iupati [b], Mohua Jain [f], Colin Rooney [c], Judy Murray [a], Peter J. Lamb [a], Peter B. Bethwaite [a]

"by combining the 0.2% who had local failure with the 2.2% whose site of failure was unknown, the local relapse rate should range from 0.2% to 2.4%"

Radiotherapy and Oncology 112 (2014) 68–71

10-YEAR EXPERIENCE WITH I-125 PROSTATE BRACHYTHERAPY AT THE PRINCESS MARGARET HOSPITAL: RESULTS FOR 1,100 PATIENTS

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E. P. SAIBISHKUMAR, M.D.,* SHARON FUNG, M.SC.,§ AND CLEMENT MA, M.SC.§

In the Toronto study of 776 patients, all patients with a PSA rising beyond 30 months were investigated by prostate biopsy examination,
and, if the biopsy was negative, systemic staging was initiated as PSA approached 10 ng/ml and there were:

- 8 local failures (1.0%)
- 8 distant failures (1.0%)
- 9 failures of unknown site (1.2%)

Thus, *the local relapse rate should range from 1.0% to 2.2%*, but it is likely to be closer to the biopsy-proven 1.0% of patients, because all other men with biochemical failure in this cohort had negative biopsy results

So……..monotherapy gives:

- excellent results for low risk disease
- very good results for intermediate risk disease
- not optimal results for high risk disease

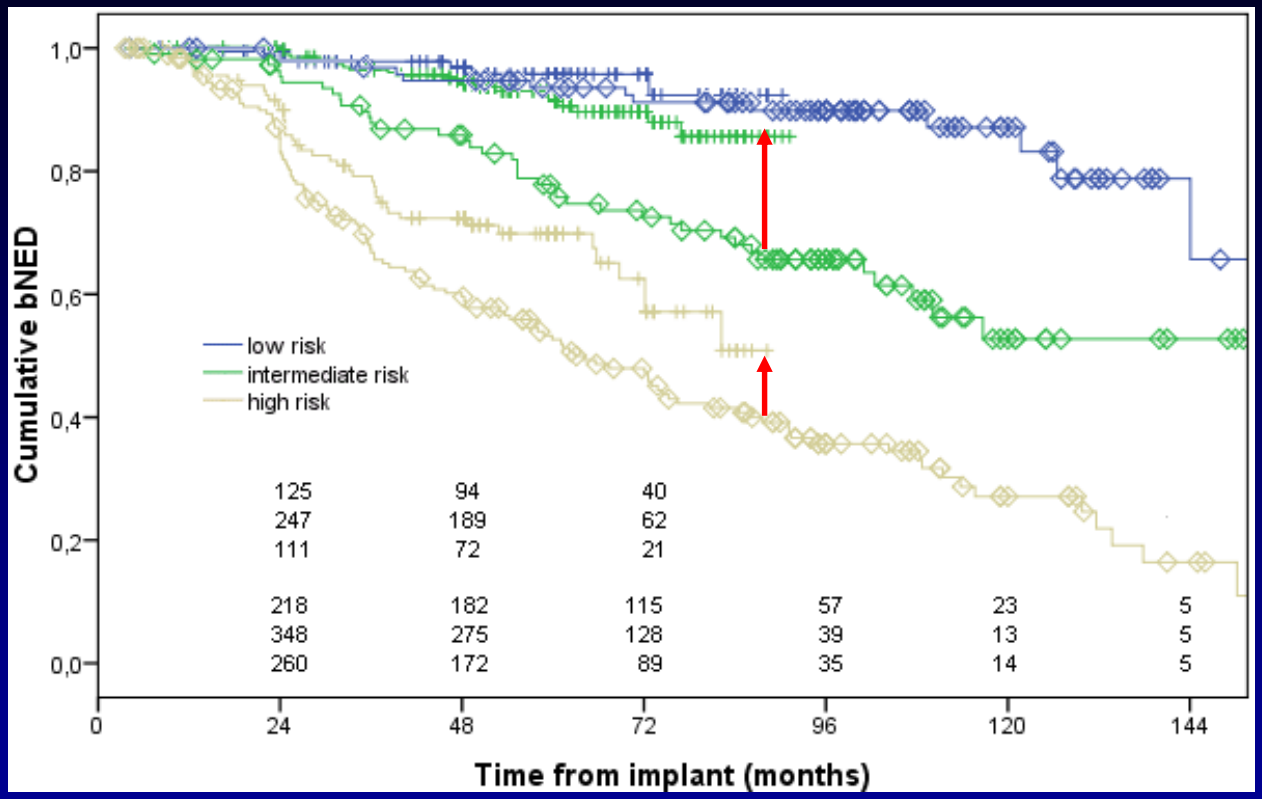
Seeds: factors that might or might not influence outcome

Factors:

1. Implant related -technique:
   - Margins
   - D90
   - Total BED
   - …
2. Risk groups - individual tumor characteristics – staging uncertainties
3. Age

1. Hormonal therapy
2. PSA bouncing
3. Obesity
4. …

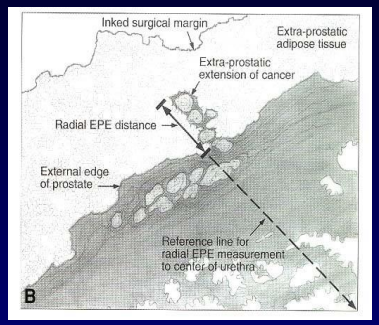
UMC database: bNED before and after 2000



n=921 - 1989-2004

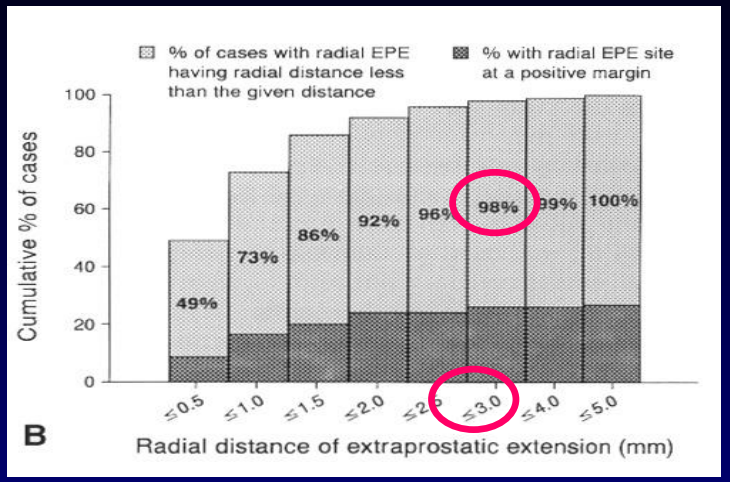
- There seems to be a trend for improved outcome in time
- Raison: technique? patient selection? learning curve? other factors?

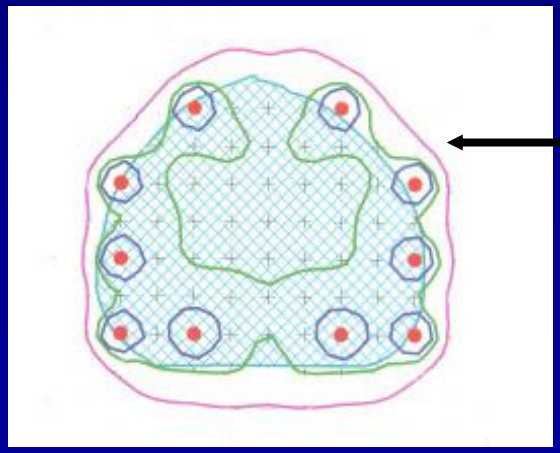
Implant related: Margins:



-105 prostatectomies
-Gleason 6.3 (range 3-9)
-PSA 8.6 (range 0.3-98)

Davis et al. Cancer 85(12) 1999



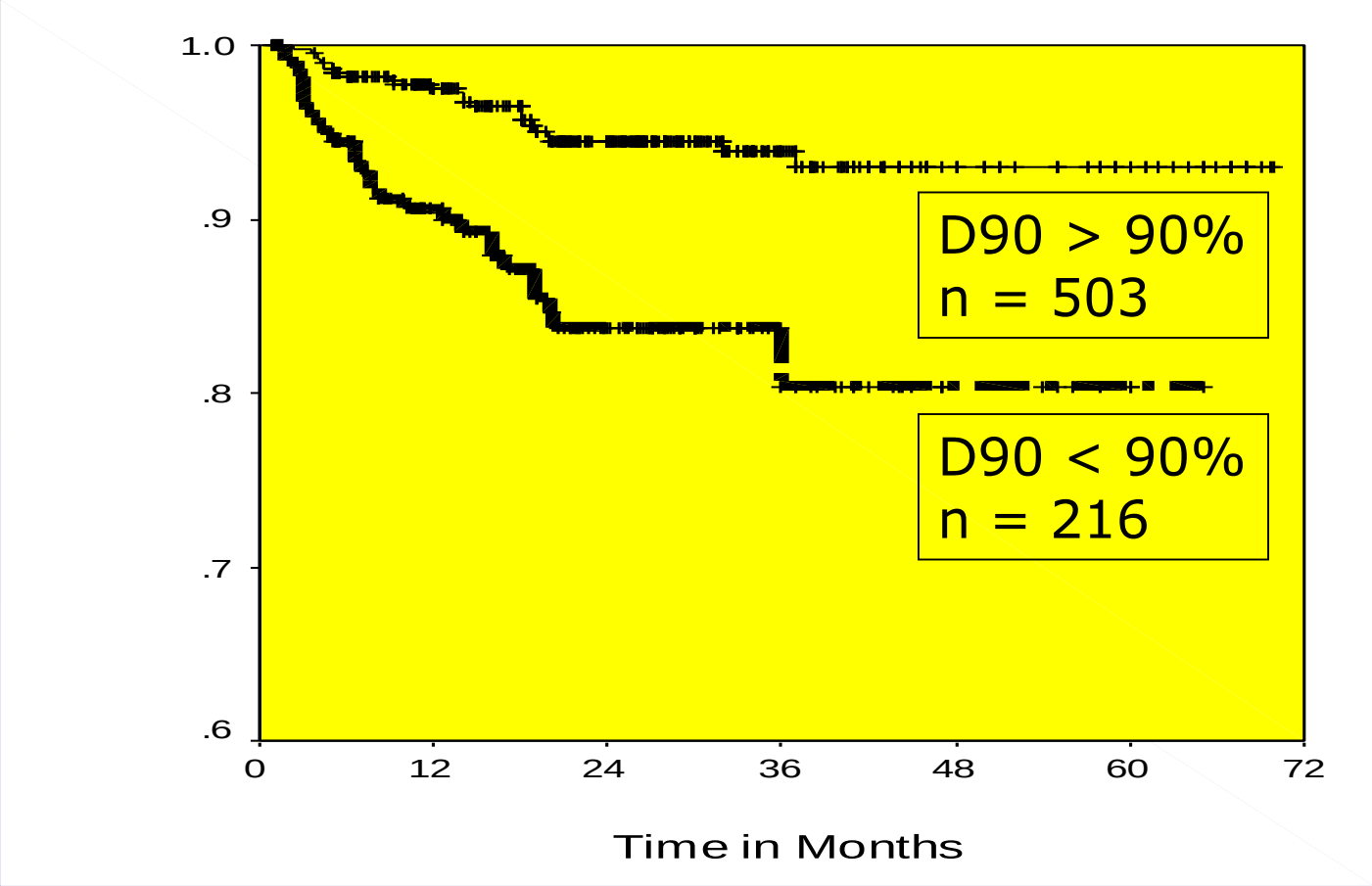


Extraprostatic disease

3 mm margins :

critical to success

Implant quality: Post-implant D90:



Potters et al Urology 62 (6) 2003

Risk groups - Staging:

- Finding capsula infiltration large consequences with regard to outcome
  - Choice of treatment (outcome, hormonal therapy)

- Differentiate between stage 2 and 3: specificity
  - Ultrasound 40 – 50%
  - MRI 80 – 90%

Still, current clinical practice Ultrasound….

Conclusion: many brachy studies in literature contain T3 patients

Risk groups – Individual tumor characteristics:

Biopsies: at random - systematic

- Chance of hitting tumor per biopsy=15-20%

Gleason score: poorly reproducible

- Biopsy agreement with prostatectomy: (n=1670)
  - Gleason 5-6 undergrading: 35%
  - Gleason 8-10 overgrading: 35%

PSA

  - Suspected linear relation with amount of tumor cells
  - Irreliable due to leakage, often false positive

Conclusion: Literature contains probably higher Gleason scores too

Age:

Treatment outcomes in men aged ≤55 yrs (1)

- 1,204 pts treated (Surgery *vs* External Beam RT *vs* Brachytherapy) between 1996-2008. (ASTRO#2283)
- median FU: 4.25 yrs

	Low-risk				
%	RP (N=412)	LRP (N=166)	Brachy (N=188)	EBRT (N=127)	*P*-value
3-yr bRFS	96.5	97.5	100	92.2	0.61
OS	99.7	100	100	100	0.15
	Intermediate risk				
	RP (N=179)	LRP (N=81)	Brachy (N=32)	EBRT (N= 92)	*P*-value
3-yr bRFS	93.6	89.3	96.8	95.1	0.50
OS**	100	98.6	100	95.8	0.12
	High risk				
	RP (N=109)	LRP (N=24)		EBRT (N=95)	*P*-value
3-yr bRFS	64.6	61.6		66.2	0.41
OS	96	95		95	0.31

RP: radical prostatectomy; LRP: laparoscopic RP; bRFS: biochemical relapse-free survival; OS: overall survival

L. J. Sheplan Olsen et al.
ASTRO 2008
Abstract #2283

Men aged ≤55 yrs have excellent outcomes after treatment with Permanent Implant Brachytherapy

Age:

Figure 1. Kaplan–Meier curve for freedom from biochemical failure in patients aged ≤60 years versus >60 years. Log-rank test p=0.1

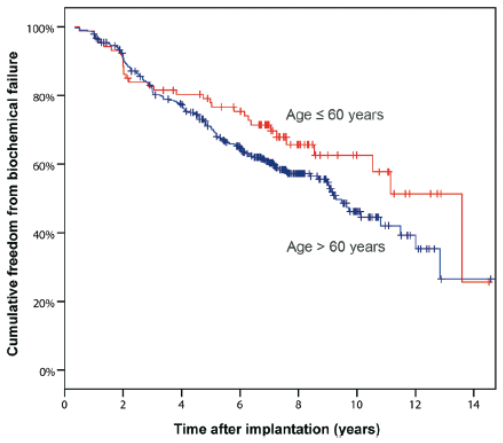


Figure 2. Kaplan–Meier curve for disease-specific survival in patients with aged ≤60 years versus > 60 years. Log-rank test p=0.1

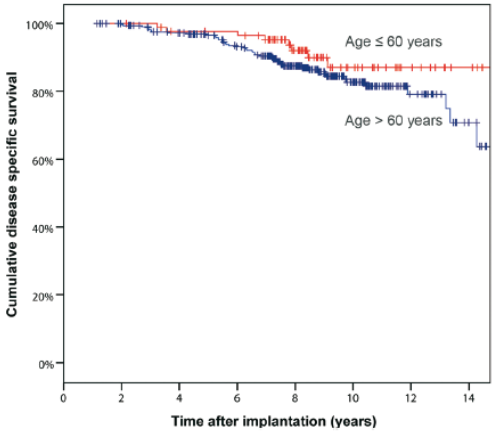
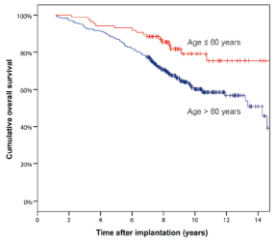
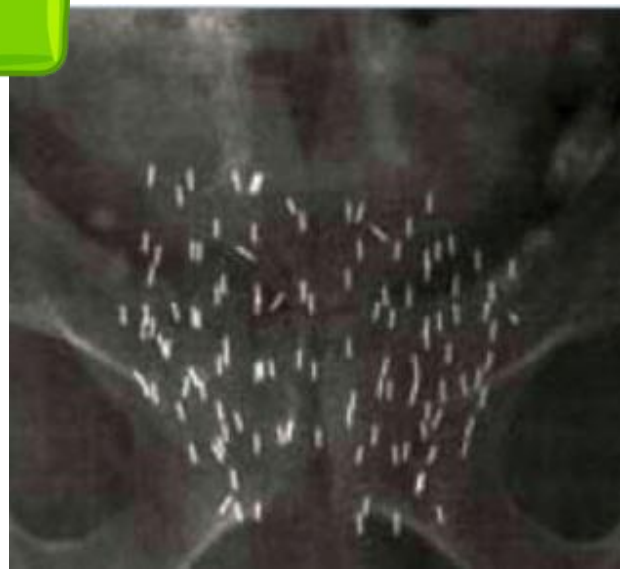


Figure 3. Kaplan–Meier curve for overall survival in patients aged ≤60 years versus >60 years. Log-rank test p<0.01



Karel A. Hinnen et al.
BJU International 05/2011
107(12):1906 - 1911.

Younger patients have excellent outcomes after treatment with Permanent Implant Brachytherapy



EBRT + seeds versus prostatectomy

Biochemical Relapse–Free Survival in Prostate Cancer Patients With Gleason Score ≥ 8 Treated With Radical Prostatectomy or Interstitial Brachytherapy Implant With Supplemental Beam Radiation

Treatment Modality	Institution	Sample Size	Follow-up	Failure Definition	BRFS Rate
Radical prostatectomy	Johns Hopkins University[76]	220	10 yr	PSA > 0.2 ng/mL	27%
	Mayo Clinic[77]	584	7 yr	PSA > 0.4 ng/mL	37%-47%
	Memorial Sloan-Kettering[78]	274	10 yr	PSA > 0.4 ng/mL	47%
	Northwestern University[79]	237	10 yr	PSA > 0.2 ng/mL	32%
Brachytherapy + EBRT (± ADT)	Dattoli Cancer Center[15]	26	14 yr	ASTRO consensus; PSA > 0.2 ng/mL; and nadir + 2 ng/mL	80% (Gleason 8) 56% (Gleason 9)
	Seattle Prostate Institute[3]	23	15 yr	2 consecutive PSA rises	61%
	Mount Sinai[11]	124	7 yr	ASTRO consensus	77.5%
	Schiffler Cancer Center[14]	120	10 yr	PSA > 0.4 ng/mL	89% (+ADT) 80% (–ADT)
	Puget Sound VA Hospital[80]	47	5 yr	PSA > 0.5 ng/mL	56% (Gleason 8) 60% (Gleason 9)

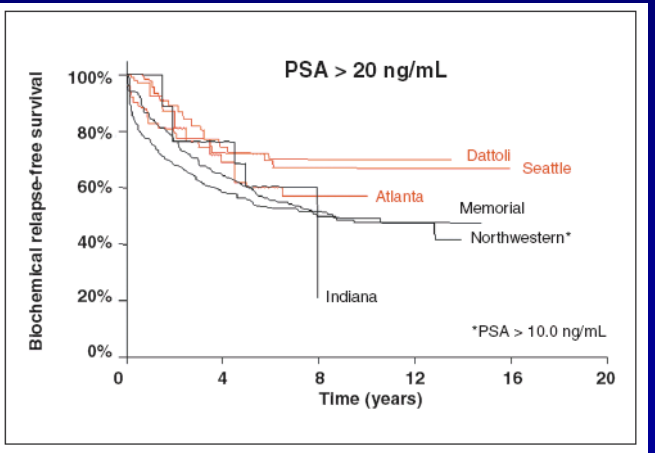


Figure 5: Survival After Brachytherapy vs Prostatectomy, by PSA Level—Biochemical relapse-free survival among patients with prostate-specific antigen (PSA) > 20 ng/mL treated definitively with brachytherapy and supplemental external-beam radiation (red) or radical prostatectomy (black).

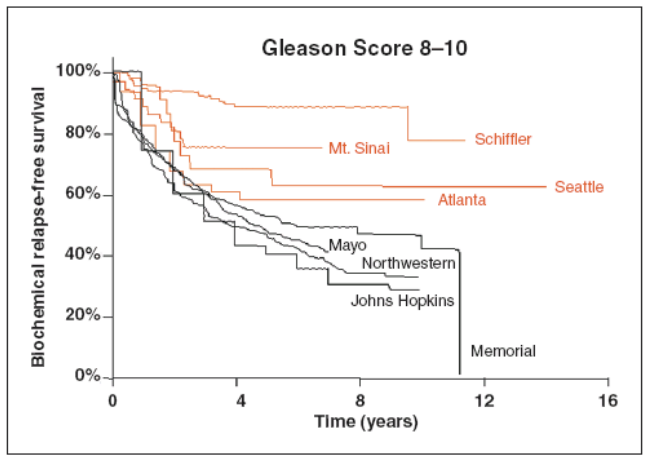
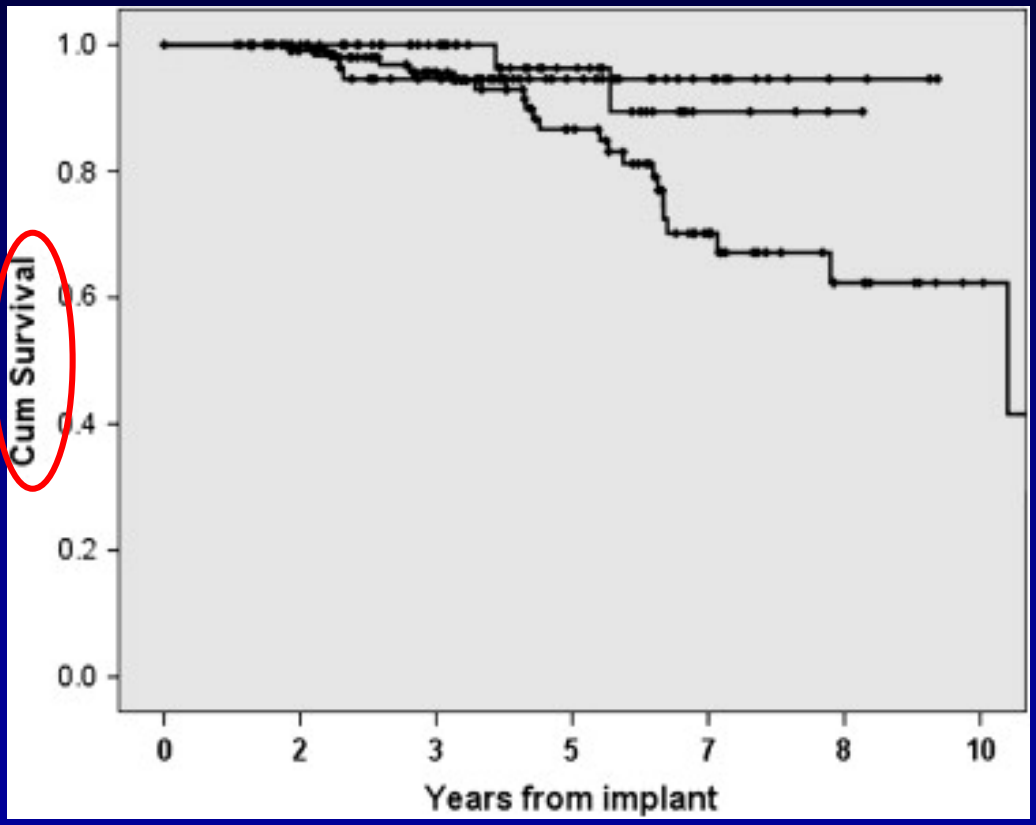


Figure 4: Survival After Brachytherapy vs Prostatectomy, by Gleason Score—Biochemical relapse-free survival among patients with Gleason score 8–10 treated definitively with brachytherapy and supplemental external-beam radiation (red) or radical prostatectomy (black).

High risk patients: EBRT + seeds (+ADT)

Survival by dose group for Gleason 8–10
Treatment: EBRT + seed implant + ADT



Overall survival

- < 200 Gy 86.6%
- 200–220 Gy 89.4%
- > 220 Gy 94.6%

($p < 0.05$)

(Stone 2009)

The Addition of Low-Dose-Rate Brachytherapy and Androgen-Deprivation Therapy Decreases Biochemical Failure and Prostate Cancer Death Compared With Dose-Escalated External-Beam Radiation Therapy for High-Risk Prostate Cancer

Mark Shilkrut, PhD, MD[1]; Gregory S. Merrick, MD[2]; P. William McLaughlin, MD[1]; Matthew H. Stenmark, MD[1]; Eyad Abu-Isa, MD[1]; Sean M. Vance, MD[1]; Howard M. Sandler, MD[3]; Felix Y. Feng, MD[1]; and Daniel A. Hamstra, MD, PhD[1]

In conclusion, the results from this multi-institutional, retrospective study suggest that, for patients with HiRPCa, the receipt of an LDR brachytherapy boost decreased the risk of BF and PCSM compared with dose-escalated EBRT. Furthermore, even with dose-escalated EBRT or combination therapy, ADT decreased BF and PCSM in a duration-dependent fashion, and the greatest benefit was observed for long-term ADT. Validation of these findings in the University of British Columbia Androgen Suppression Combined with Elective Nodal and Dose-Escalated RT trial, which is comparing dose-escalated EBRT (78 Gy) versus CMRT plus ^{125}I LDR boost (both with 12 months of ADT), may significantly change the treatment standard for patients with HiRPCa.[31]

RTE + Seeds (+ ADT) > (Dose escalated) RTE (+ ADT)

Cancer 2013;119:681-90.

Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer

Daniel E. Spratt, Zachary S. Zumsteg, Pirus Ghadjar, Marisa A. Kollmeier, Xin Pei, Gilad Cohen*, William Polkinghorn, Yoshiya Yamada and Michael J. Zelefsky

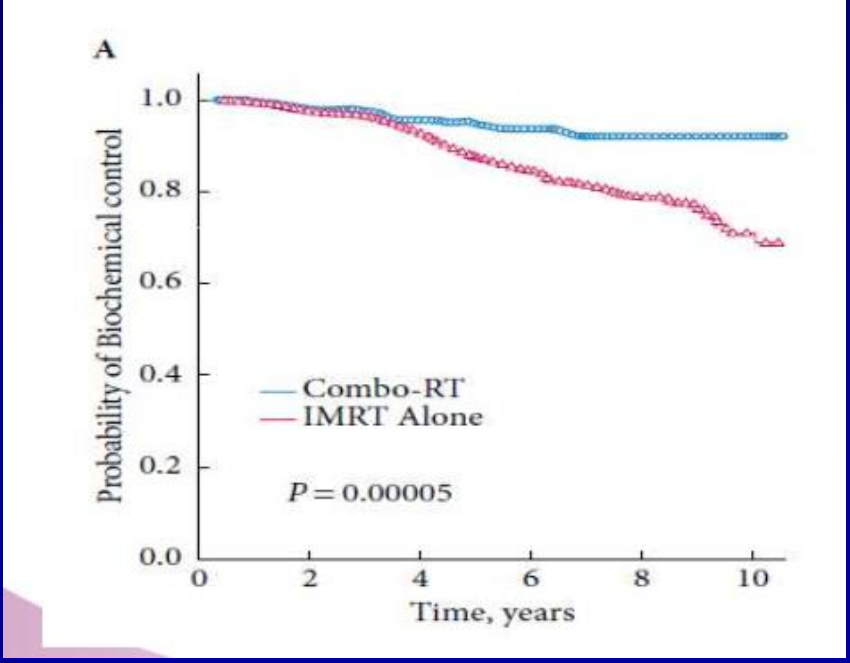
*Departments of Radiation Oncology and *Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY,*

BJU Int 2014; **114:** 360–367

IMRT 86.4Gy: 470

vs

IMRT 45-50.4+ BT : 400 (LDR 100-110Gy - 260, HDR 16.5-22.5 in 3f - 140)



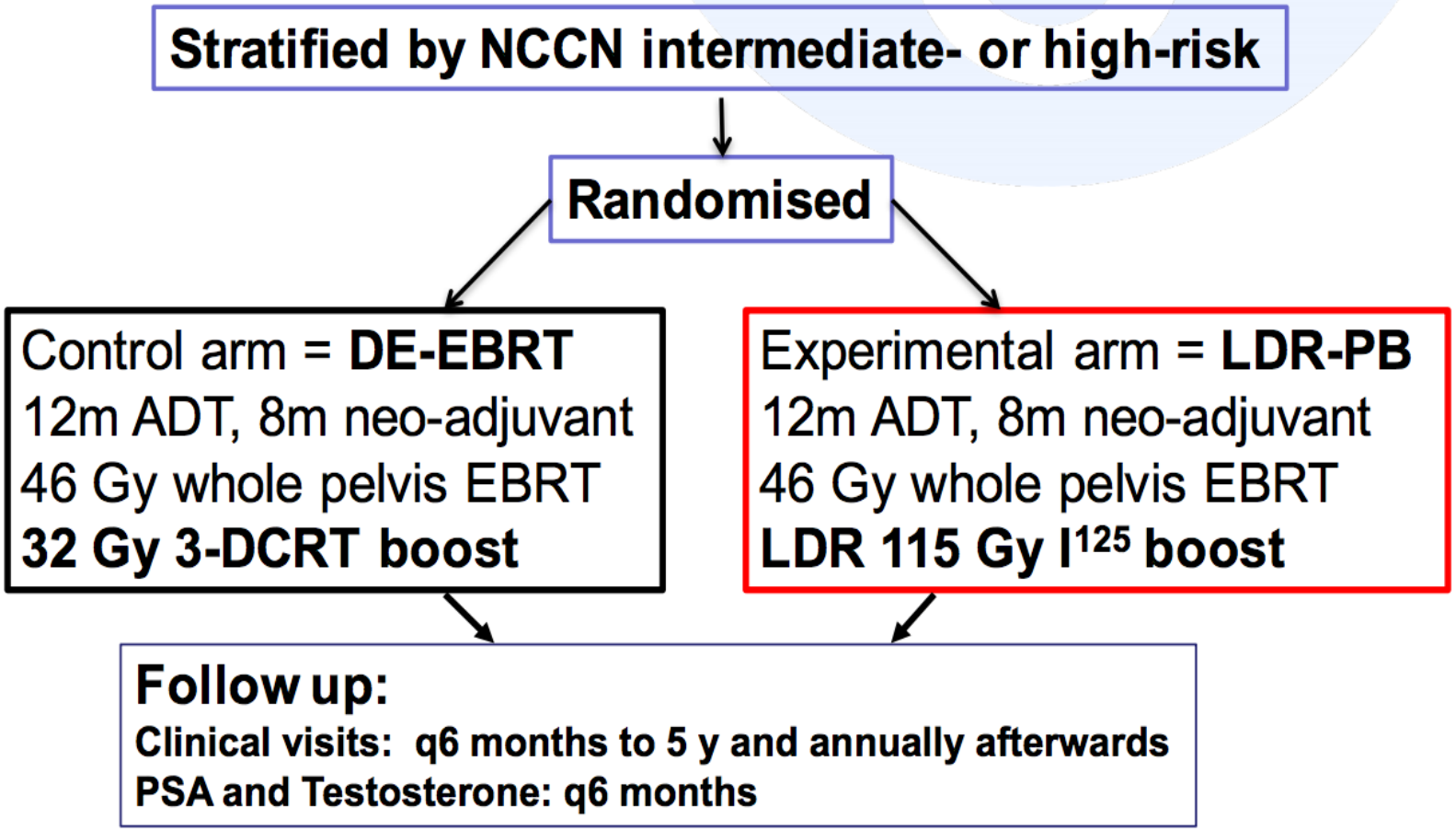
RTE + HDR or Seeds

>

Escalated dose RTE

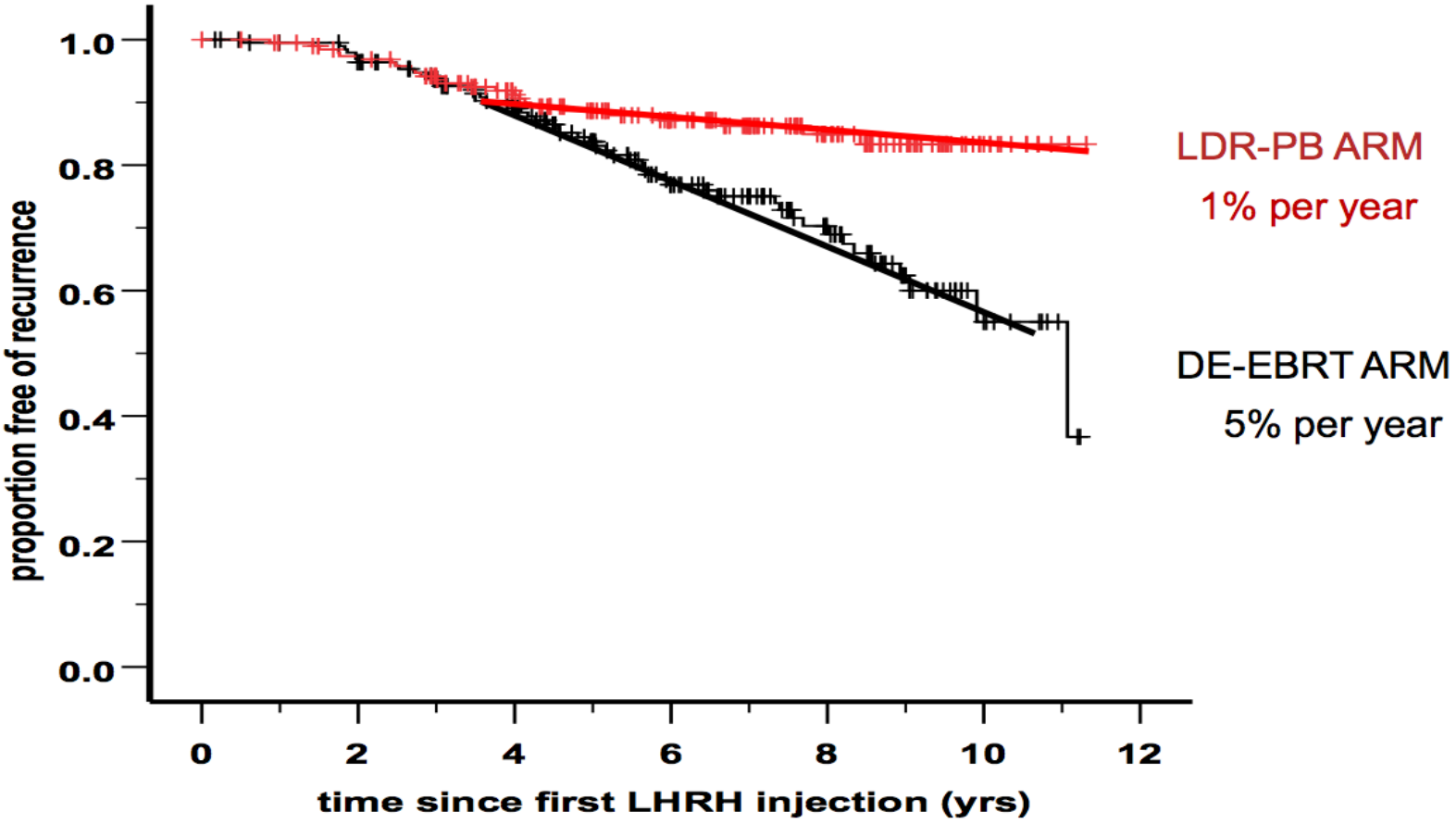
BJU Int. 2014 Sep;114(3):360-7.

ASCENDE-RT simplified schema



Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint



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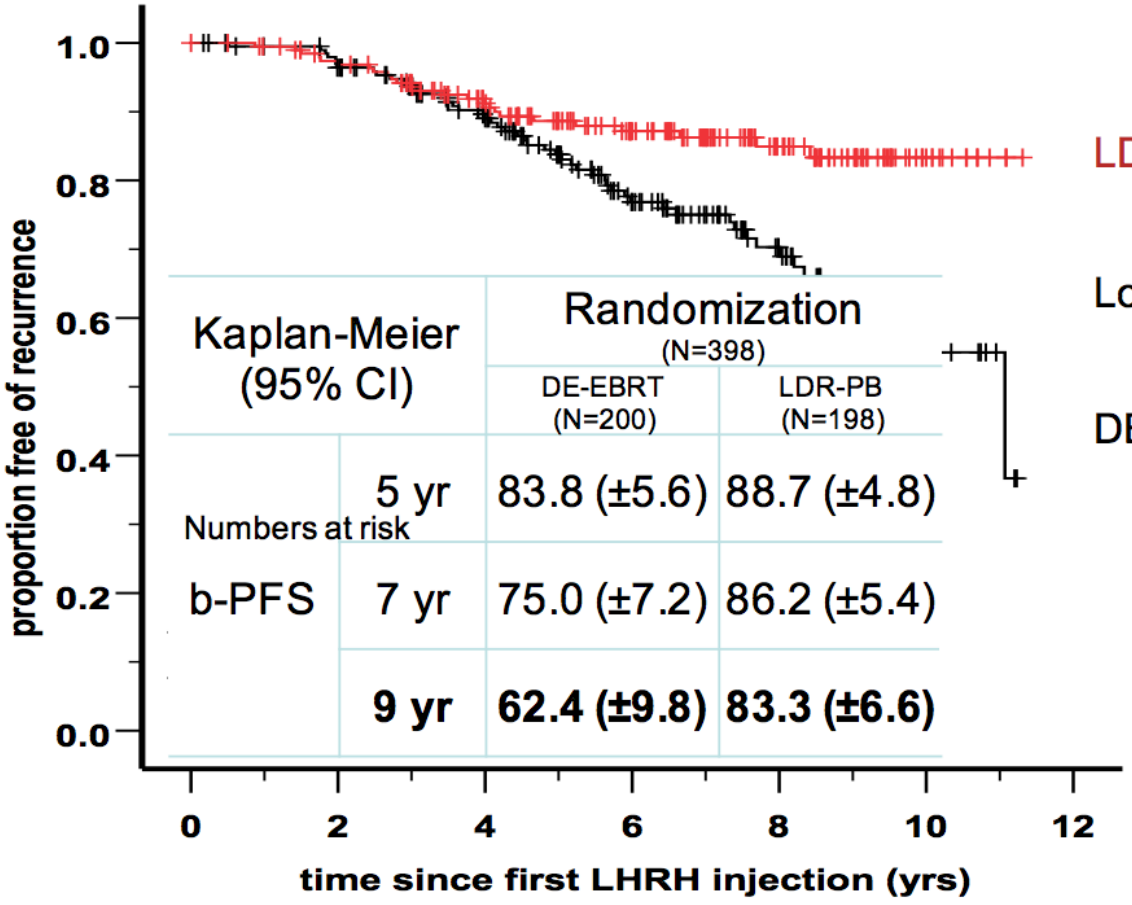


Kaplan-Meier (95% CI)		Randomization (N=398) DE-EBRT (N=200)	LDR-PB (N=198)
Numbers at risk b-PFS	5 yr	83.8 (±5.6)	88.7 (±4.8)
	7 yr	75.0 (±7.2)	86.2 (±5.4)
	9 yr	**62.4 (±9.8)**	**83.3 (±6.6)**

LDR-PB ARM

Log rank P =0.001

DE-EBRT ARM

VOLUME 35 · NUMBER 17 · JUNE 10, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

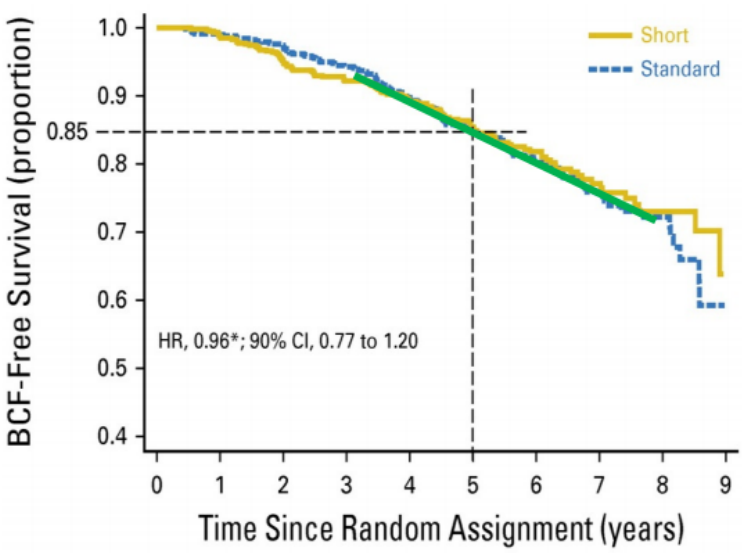
Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer

Charles N. Catton, Himu Lukka, Chu-Shu Gu, Jarad M. Martin, Stéphane Supiot, Peter W.M. Chung, Glenn S. Bauman, Jean-Paul Bahary, Shahida Ahmed, Patrick Cheung, Keen Hun Tai, Jackson S. Wu, Matthew B. Parliament, Theodoros Tsakiridis, Tom B. Corbett, Colin Tang, Ian S. Dayes, Padraig Warde, Tim K. Craig, Jim A. Julian, and Mark N. Levine

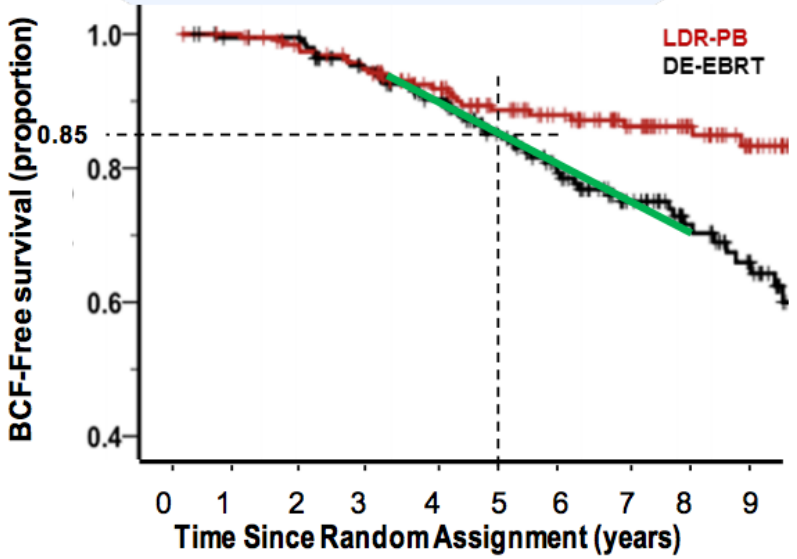
Conclusion

The hypofractionated RT regimen used in this trial was not inferior to conventional RT and was not associated with increased late toxicity. Hypofractionated RT is more convenient for patients and should be considered for intermediate-risk prostate cancer.

Catton *et al.* Hypofractionation Trial vs ASCENDE-RT

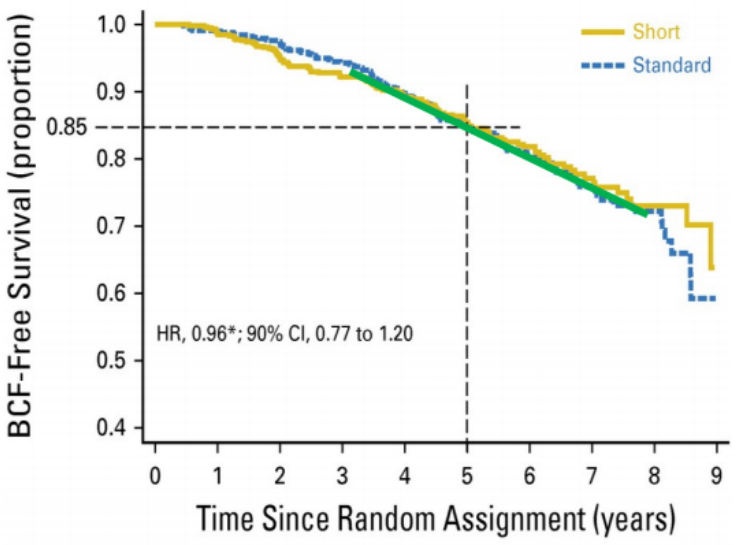


78 Gy/39#s or 60/20#s IMRT
All low and intermediate risk PCa
Only 6% had ADT
Median FU = 6 years



78 Gy/39#s (black line)
69% high risk PCa, no low risk
100% got ADT
Median FU =6.5 years

Catton *et al.* Hypofractionation Trial vs ASCENDE-RT



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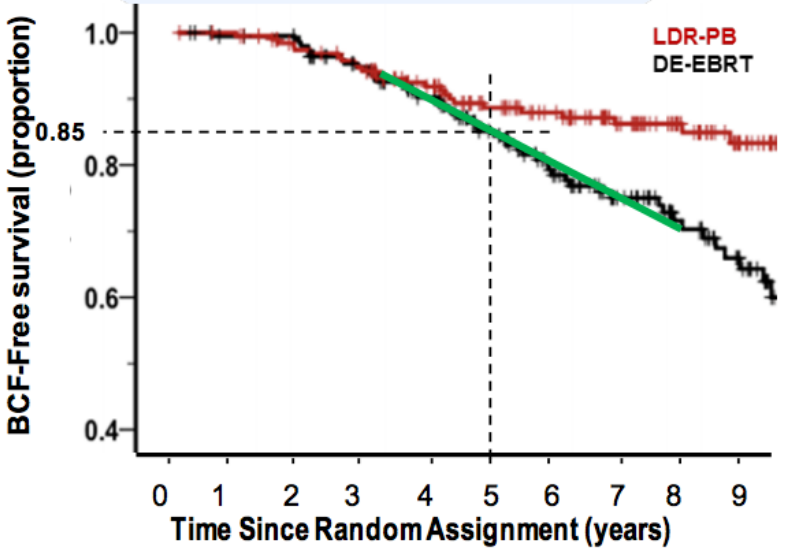

78 Gy/39#s (black line)
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JAMA | Original Investigation

Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

Amar U. Kishan, MD; Ryan R. Cook, MSPH; Jay P. Ciezki, MD; Ashley E. Ross, MD, PhD; Mark M. Pomerantz, MD; Paul L. Nguyen, MD; Talha Shaikh, MD; Phuoc T. Tran, MD, PhD; Kiri A. Sandler, MD; Richard G. Stock, MD; Gregory S. Merrick, MD; D. Jeffrey Demanes, MD; Daniel E. Spratt, MD; Eyad I. Abu-Isa, MD; Trude B. Wedde, MD; Wolfgang Lilleby, MD, PhD; Daniel J. Krauss, MD; Grace K. Shaw, BA; Ridwan Alam, MPH; Chandana A. Reddy, MS; Andrew J. Stephenson, MD; Eric A. Klein, MD; Daniel Y. Song, MD; Jeffrey J. Tosoian, MD; John V. Hegde, MD; Sun Mi Yoo, MD, MPH; Ryan Fiano, MPH; Anthony V. D'Amico, MD, PhD; Nicholas G. Nickols, MD, PhD; William J. Aronson, MD; Ahmad Sadeghi, MD; Stephen Greco, MD; Curtiland Deville, MD; Todd McNutt, PhD; Theodore L. DeWeese, MD; Robert E. Reiter, MD; Johnathan W. Said, MD; Michael L. Steinberg, MD; Eric M. Horwitz, MD; Patrick A. Kupelian, MD; Christopher R. King, MD, PhD

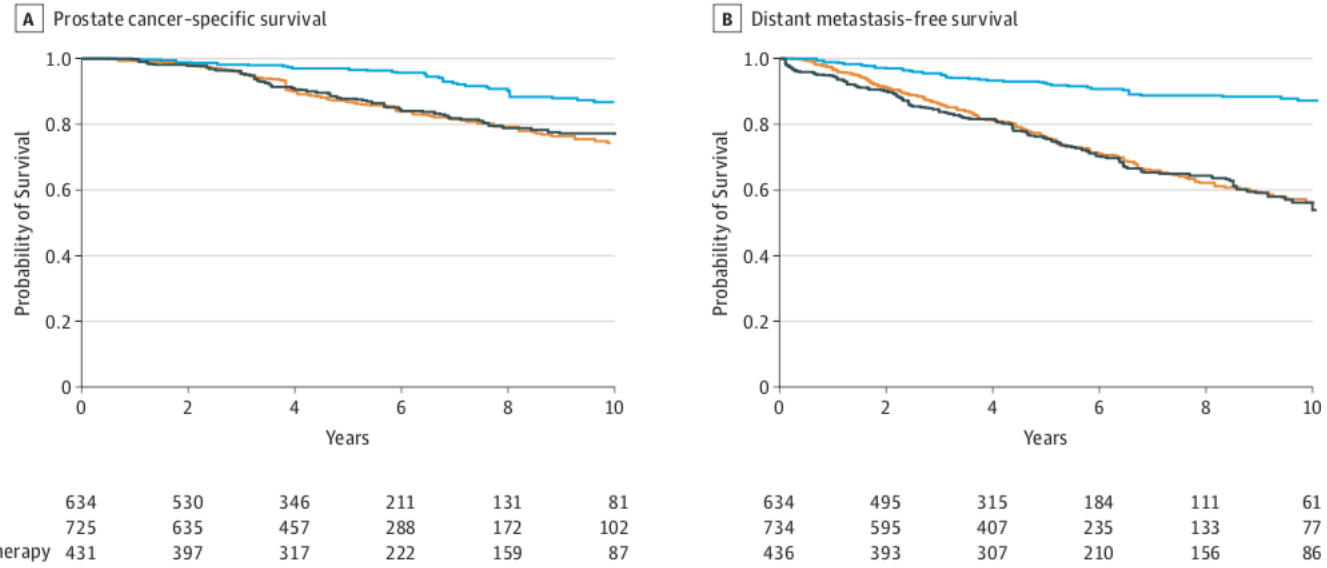
OBJECTIVE To compare clinical outcomes of patients with Gleason score 9-10 prostate cancer after definitive treatment.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study in 12 tertiary centers (11 in the United States, 1 in Norway), with 1809 patients treated between 2000 and 2013.

EXPOSURES Radical prostatectomy (RP), external beam radiotherapy (EBRT) with androgen deprivation therapy, or EBRT plus brachytherapy boost (EBRT+BT) with androgen deprivation therapy.

Brachytherapy type	
Low-dose rate	262 (62.0)
High-dose rate	174 (38.0)

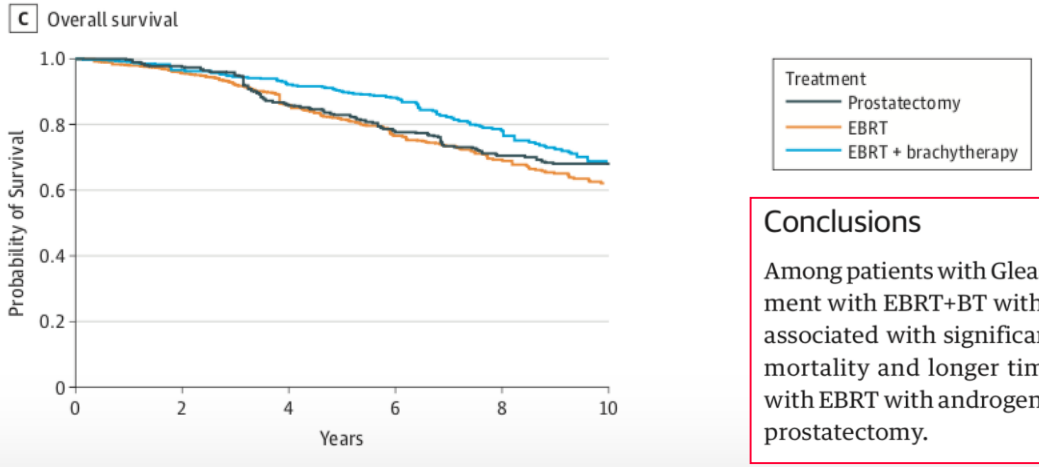
Figure. Adjusted Survival Curves for Prostate Cancer-Specific Survival, Distant Metastasis-Free Survival, and Overall Survival by Treatment Group, Weighted by the Inverse Probability of Treatment



No. at risk

Prostatectomy	634	530	346	211	131	81
EBRT	725	635	457	288	172	102
EBRT + brachytherapy	431	397	317	222	159	87

634	495	315	184	111	61
734	595	407	235	133	77
436	393	307	210	156	86



Conclusions

Among patients with Gleason score 9-10 prostate cancer, treatment with EBRT+BT with androgen deprivation therapy was associated with significantly better prostate cancer-specific mortality and longer time to distant metastasis compared with EBRT with androgen deprivation therapy or with radical prostatectomy.

Conclusions

- Low Risk: Brachy alone

- (F) Intermediate Risk: Brachy + EBRT = Brachy alone

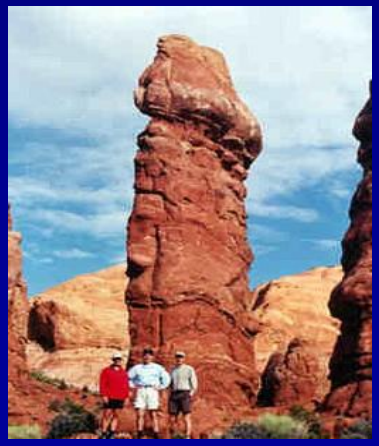
- UF Intermediate Risk: Brachy + EBRT >>> EBRT
- High Risk: Brachy + EBRT >>> EBRT

So: in all cases: Brachy (+/- EBRT)

The question becomes:

"When do we need to do 'a EBRT boost' to Brachy ?"

Quality of Life – Side Effects



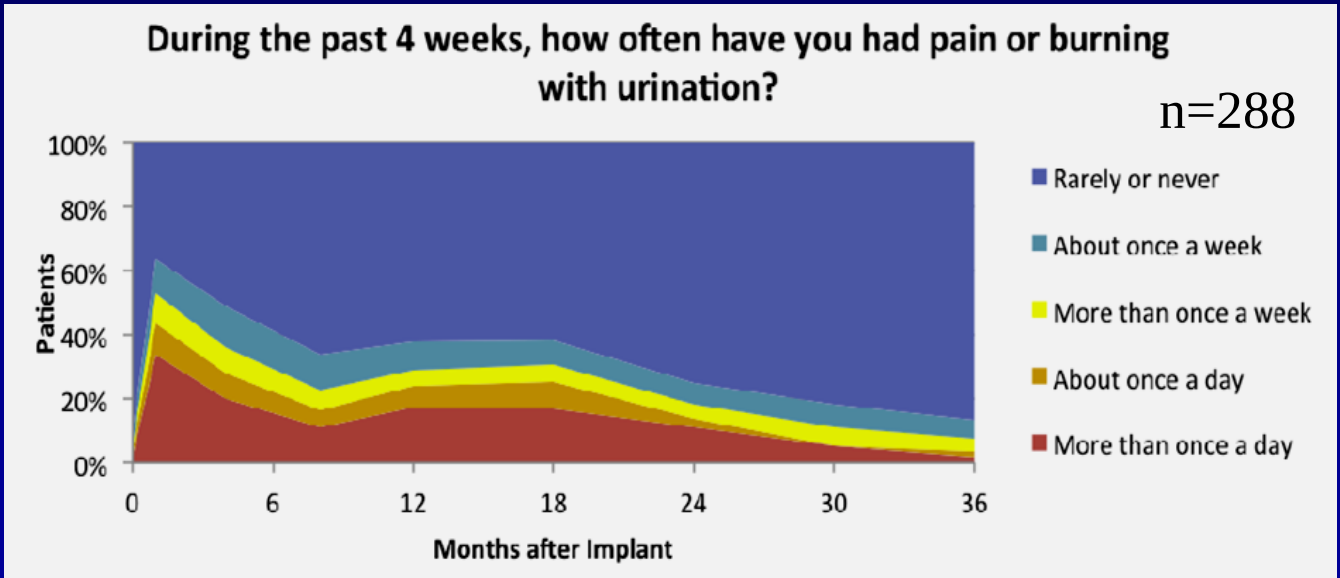
Toxicity grading:

- Severe toxicity (grade ≥ 3) most important
- Urinary Grade ≥ 3 toxicity rates:
  - Acute urinary retention: ± 10% (5-34%) = highest incidence
  - Urinary incontinence: ±1.5% (0-17%)
  - Urinary bother: ± 1-3%
  - Hemorr. cystitis <<<1%
  - Infection <<<1%
  - Fistula <<<1%
- Rectal Grade ≥ 3 toxicity rates: <1%
- Erectile dysfunction: complicated, baseline function matters

Anderson et al. Urol 2009;74:601-5
Gore et al. JNCI 2009;101:888-92
Bottomley et al. RO 2007;82-46-9
Chen et al. JCO 2009;27:3916-22

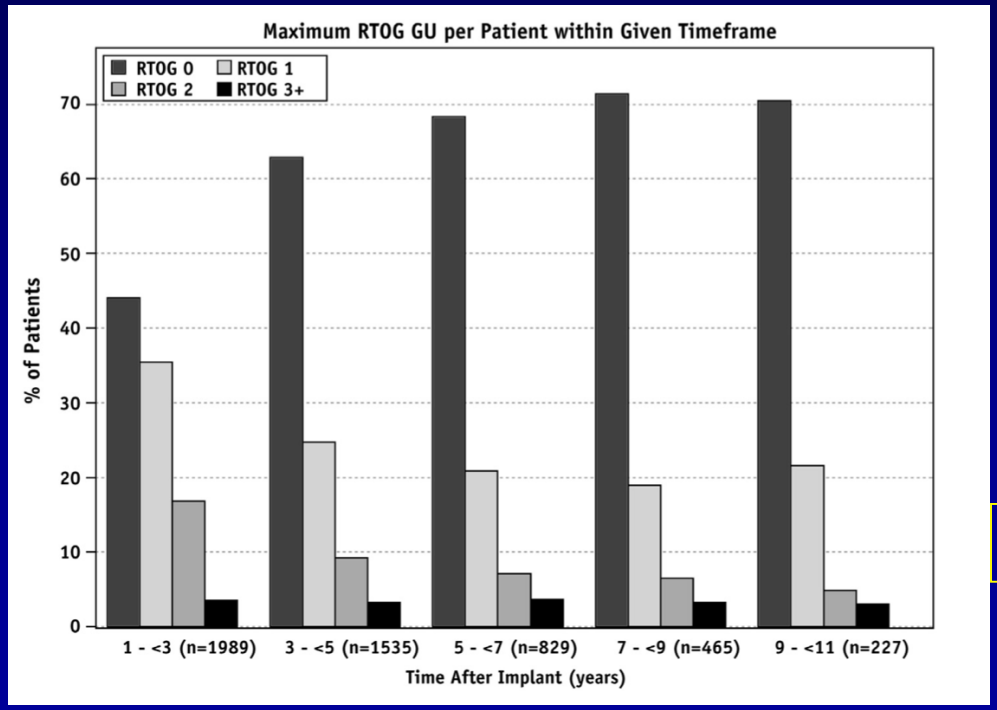
Urinary Bother

- Is pain or burning with urination
- Cause: detrusor overactivity
- Grade 3 urinary bother: 1-3%
- Even grade I and 2 urinary bother may severely disturb quality of life



Late Urinary Side Effects 10 Years After Low-Dose-Rate Prostate Brachytherapy: Population-Based Results From a Multiphysician Practice Treating With a Standardized Protocol and Uniform Dosimetric Goals

Mira Keyes, MD, Stacy Miller, MD, Tom Pickles, MD, Ross Halperin, MD, Winkle Kwan, MD, Vincent Lapointe, BSc, Michael McKenzie, MD, Ingrid Spadinger, PhD, Howard Pai, MD, Elisa K. Chan, MD, and W. James Morris, MD



"At 5-13 years' follow-up, 90% of patients have no (RTOG 0) or minimal (RTOG 1) urinairy morbidity"

"Long-term urinary toxicity is low"

Dose to the Bladder Neck Is the Most Important Predictor for Acute and Late Toxicity After Low-Dose-Rate Prostate Brachytherapy: Implications for Establishing New Dose Constraints for Treatment Planning

Lara Hathout, MD,* Michael R. Folkert, MD,* Marisa A. Kollmeier, MD,* Yoshiya Yamada, MD,* Gil'ad N. Cohen, MS,† and Michael J. Zelefsky, MD*

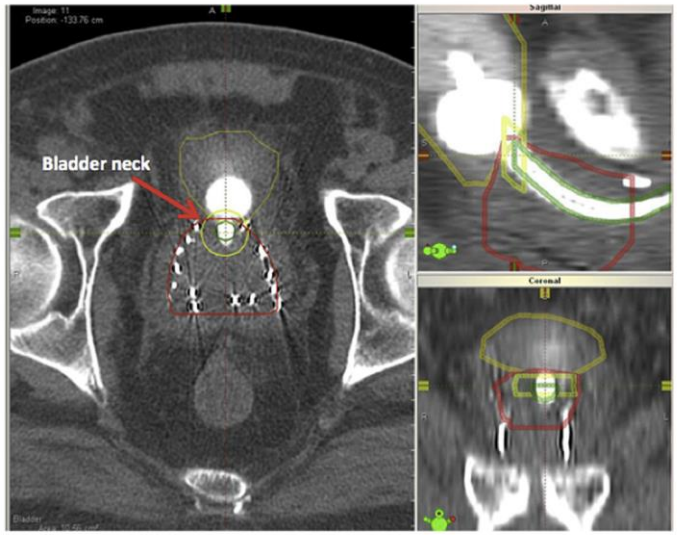


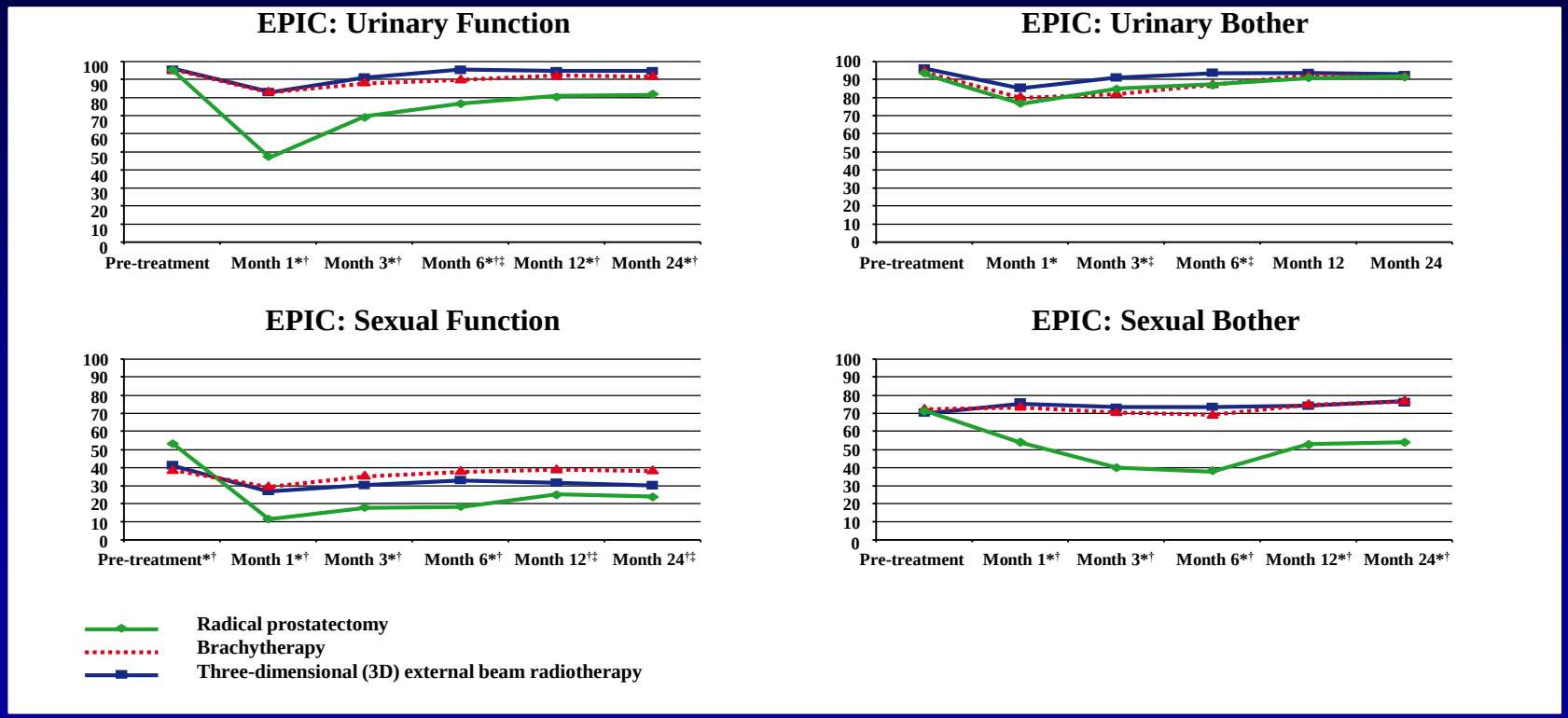
Fig. 1. Contour of bladder neck on computed tomographic scan on day 0 after implantation.

Bladder neck D2cc >50% was identified as a strong predictor of acute and late urinary toxicity in patients treated with LDR brachytherapy with and without supplemental EBRT. These data support the potential benefit for inclusion of bladder neck constraints into brachytherapy treatment planning, because constraining the dose to this region may decrease urinary-related symptoms after treatment. Our findings will require further studies to validate. A prospective study is presently under way at our institution to assess the validity of the proposed bladder neck dose constraint.

Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 312-319, 2014

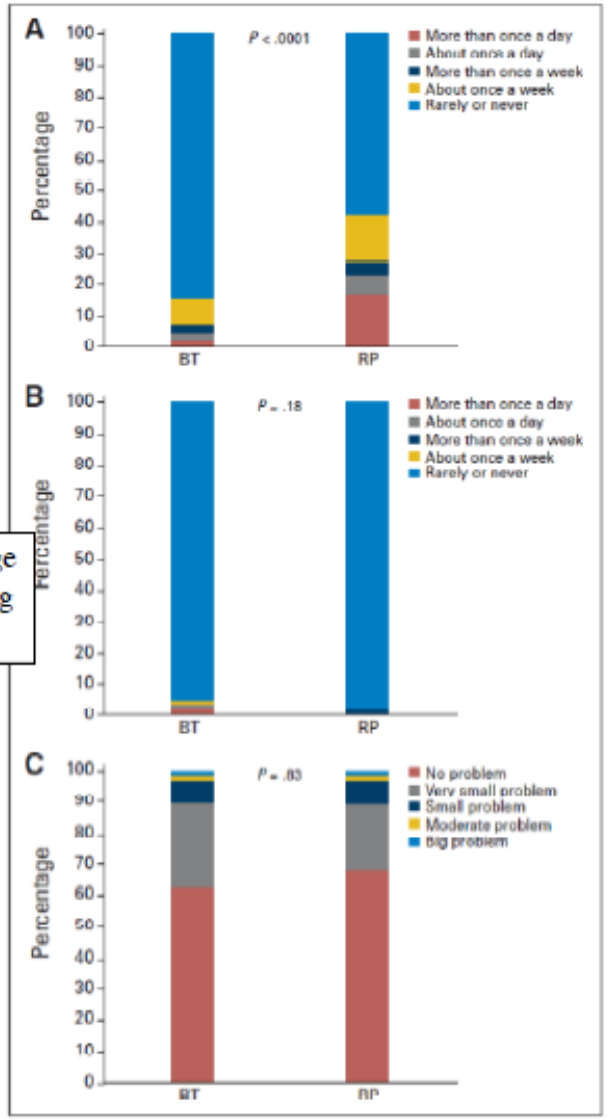
Quality of life following prostate cancer treatment

Prostate brachytherapy, prostatectomy and EBRT have different effects on patients' quality of life

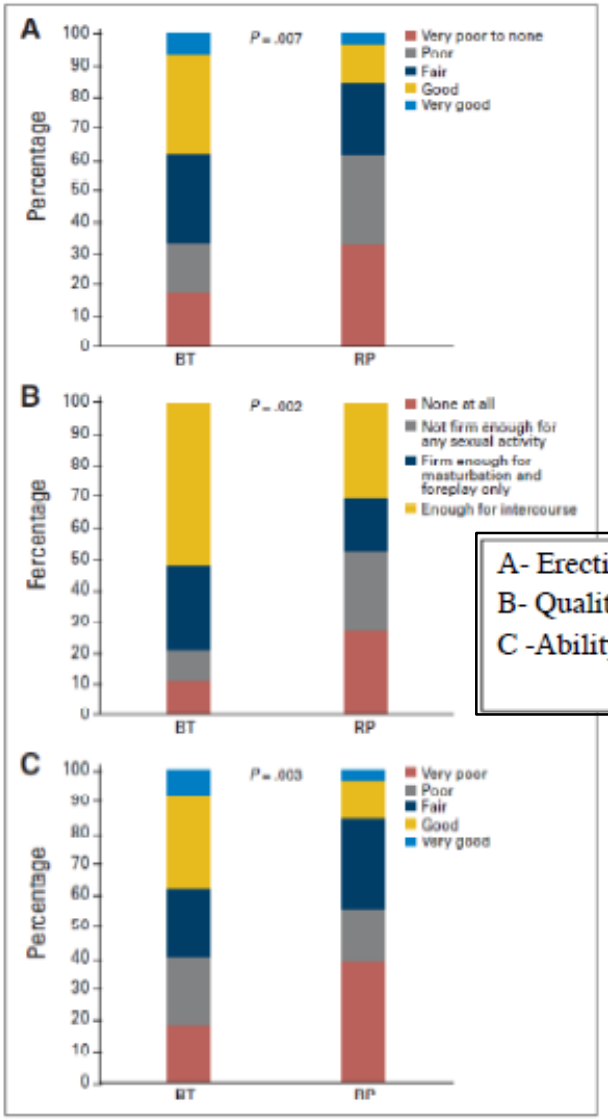


Ferrer M et al. *Int J Radiat Oncol Biol Phys* 2008; 72: 421–32.

- Crook J. et al : JCO 2010 29 362-368



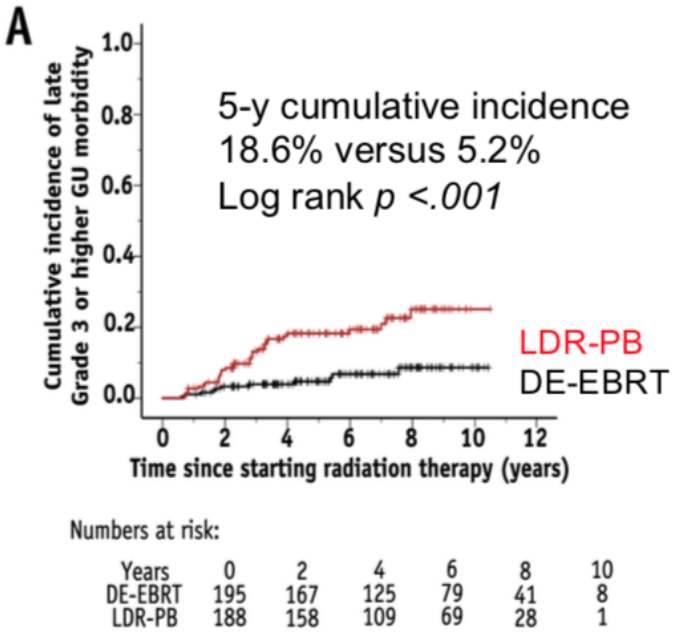
A- urinary leakage
B -pain & burning
C -weak stream

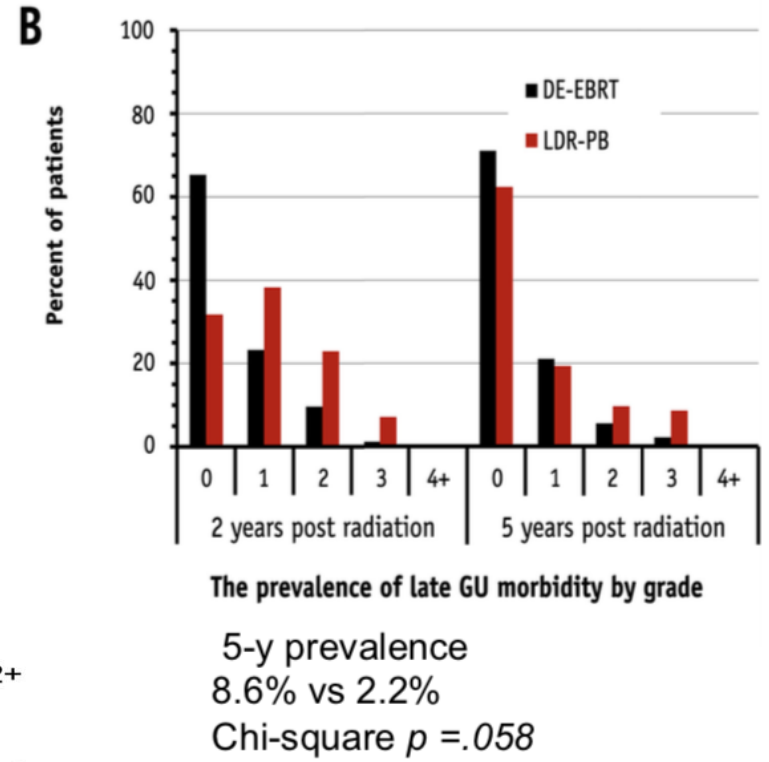


A- Erection
B- Quality of E
C -Ability to sex

The addition of Brachy to EBRT increases the toxicity
The addition of EBRT to Brachy increases the toxicity

ASCENDE-RT: Late GU Adverse Events





- LDR-PB ARM - twice as likely to have **acute** Grade 2+ GU toxicity (32.5% vs 16.3%, Chi square p <.001)
- LDR-PB ARM ~3 times higher cumulative incidence of **late** grade 3 GU adverse event (18.6% versus 5.2%, Log rank p <.001)

Brachytherapy	External Beam	Surgery
Less time of work	8 weeks of treatment + recuperation	6 -12 weeks recovery
Continence unaffected Mild LUTS in 70% Moderate LUTS in 30%	Continence unaffected Mild LUTS in majority Moderate LUTS in 50%	50% immediate continence 75% by 3 months 90-95% by 6 months
Very low gastro-intestinal toxicity	Moderate GI toxicity in majority Severe GI toxicity low, but dose related	Extremely low GI toxicity
Preservation of potency Preservation of ejaculation but may be reduced Fertility is preserved	Relative preservation of potency Preservation of ejaculation but may be reduced Potential impact on fertility	Potency never the same True ejaculation does not occur Infertile (need IVF)

Cave: - adjunction of adjuvant external beam after surgery
- adjunction of hormonal treatment

Conclusions

- Excellent long term results of permanent seed implants for low-risk and (F) IR-patients
- UF- IR and HR patients may benefit from combined EBRT and seed treatment (+ ADT)
- Toxicity is low and acceptable
- No decrease in long term QoL
- Quality assurance very important


THANK
YOU!

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High dose rate brachytherapy for prostate cancer: RESULTS

Peter Hoskin
Mount Vernon Cancer Centre
Northwood, UK
University of Manchester

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HDR prostate brachytherapy

- HDR Boost
- HDR Monotherapy

EQD2 for common fractionation schedules

	α/β 1.5	α/β 3.5	α/β 10
Ext beam			
78Gy/39f	78	78	78
HDR Boost schedules after 45Gy/25f			
16Gy/4f	67.5	65.1	62.8
16Gy/2f	85.8	76.8	68.4
23Gy/2f	127.8	106.1	85.4
HDR Boost after 35.7Gy/13f			
17Gy/2f	91.8	77.6	64.1

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Prostate HDR brachytherapy doses -BOOST after 45-50Gy ext beam

Centre	Total dose	Fractions
Michigan Oakland,CA	18Gy	3
Seattle	16.5Gy	3
Goteborg	20Gy	2
Kiel	30Gy	2
Berlin	18Gy	2
Offenbach	28Gy	4
Melbourne	20Gy	4
MVH	17Gy	2
Toronto	15Gy	1

HDR brachytherapy doses: BED and 2Gy equivalents for different α/β ratios

Centre	α/β =1.5		α/β =3		α/β =10	
	BED	2Gy eq	BED	2Gy eq	BED	2Gy eq
Michigan	90.0	38.6	48.0	28.8	28.8	24.0
Oakland,CA						
Seattle	77.0	33.0	46.7	28.0	25.6	21.3
Goteborg	153.3	65.7	86.7	52.0	40.0	33.3
Kiel	330	141.4	180	108	75.0	62.5
Berlin	126	54.0	72.0	43.2	34.2	28.5
Offenbach	158.7	68.0	93.3	56.0	47.6	39.7
Melbourne	86.7	37.2	53.3	32.0	30.0	25.0
MVH	113.3	48.6	65.2	39.1	31.5	26.3
Toronto	165	70.7	90	33.7	37.5	31.25

LONG-TERM OUTCOME BY RISK FACTORS USING CONFORMAL HIGH-DOSE-RATE BRACHYTHERAPY (HDR-BT) BOOST WITH OR WITHOUT NEOADJUVANT ANDROGEN SUPPRESSION FOR LOCALIZED PROSTATE CANCER

RAZVAN M. GALALAE, M.D.,* ALVARO MARTINEZ, M.D.,† TIM MATE, M.D.,‡ CHRISTINA MITCHELL, R.N.,† GREGORY EDMUNDSON, M.S.,† NILS NUERNBERG, M.D.,* STEPHEN EULAU, M.D.,‡ GARY GUSTAFSON, M.D.,† MICHAEL GRIBBLE, M.S.,‡ AND GYOERGY KOVÁCS, M.D.*

*Clinics for Radiation Therapy and Urology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; †Radiation Oncology and Urology Departments, William Beaumont Hospital, Royal Oak, MI; ‡Clinic for Radiation Therapy, Seattle Prostate Institute, Seattle, WA

IJROB 2004

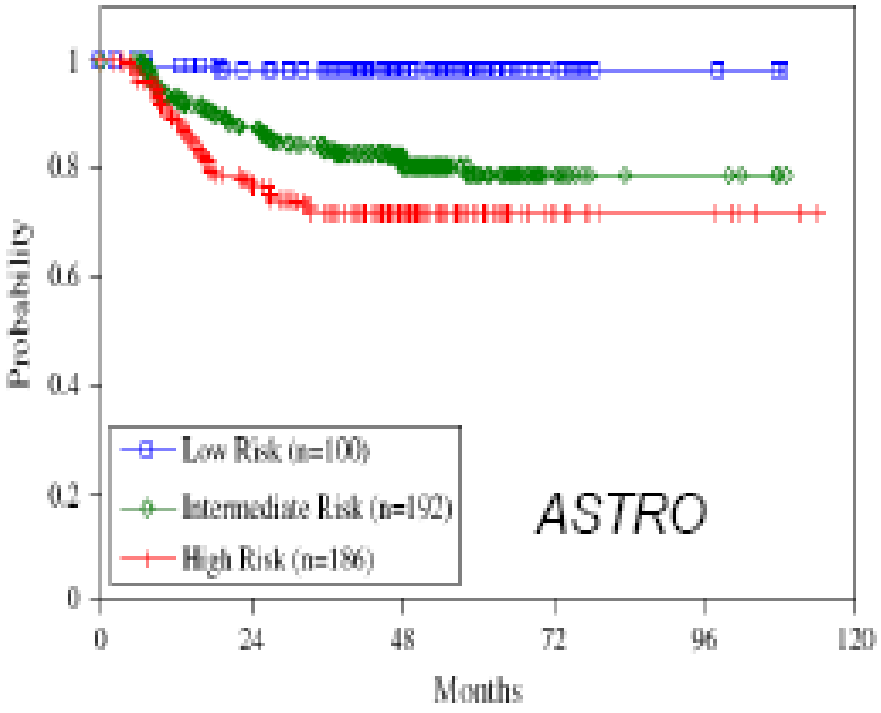
611 patients:
Seattle:
Kiel:
WBM:

Ext Beam: 45-50Gy in 5 - 5.5 wks

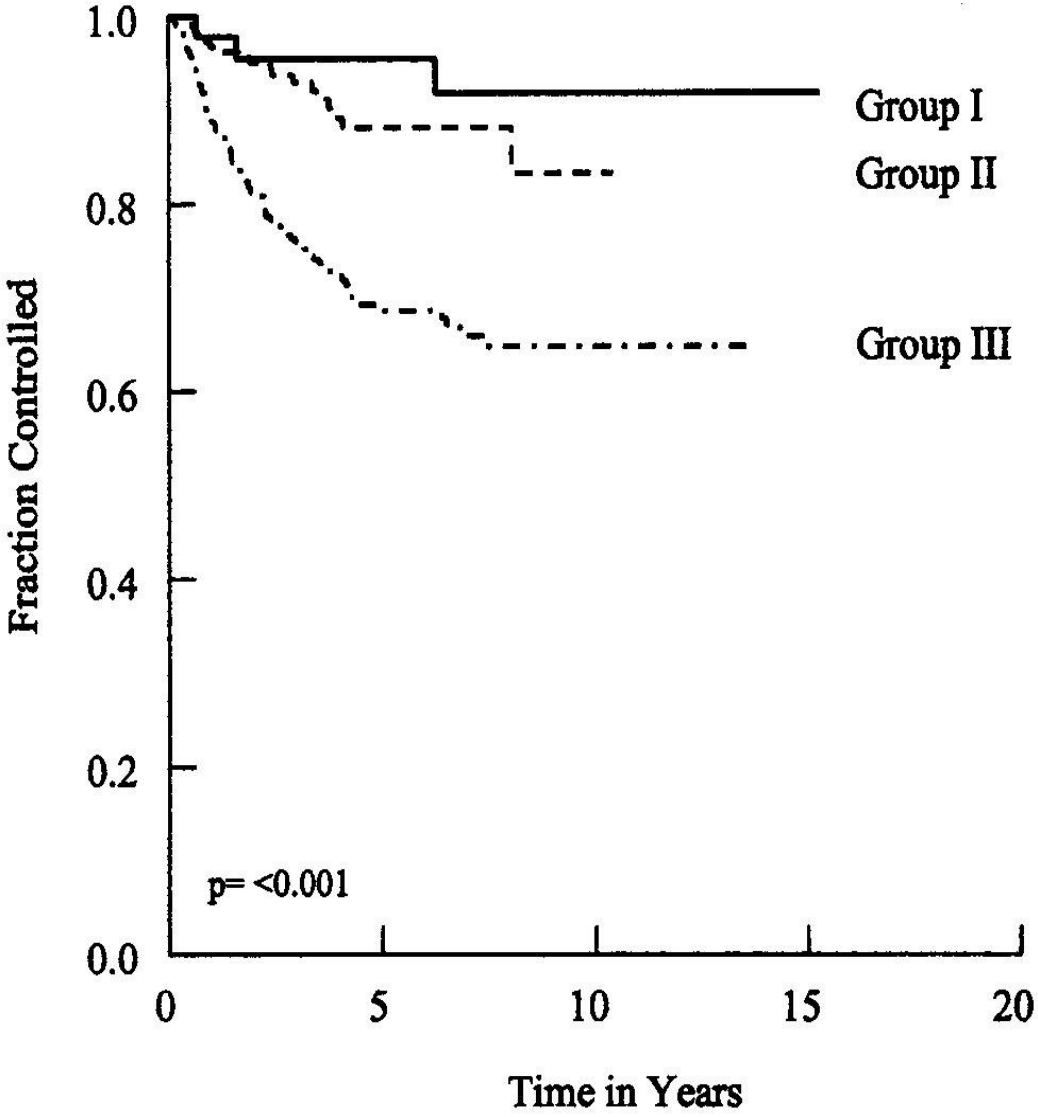
CTV= Prostate + pelvic LN

HDR
Seattle: 3Gy-4Gy per # ? X4
Kiel: 15Gy to PTV1 x 2
(= 8-9Gy to PTV2)
WBM: 5.5Gy-11.5Gy x2

Long term outcome of prostate HDR boost brachytherapy
Kiel: Michigan: Seattle [Galalae et al 2004] n=611



n=359

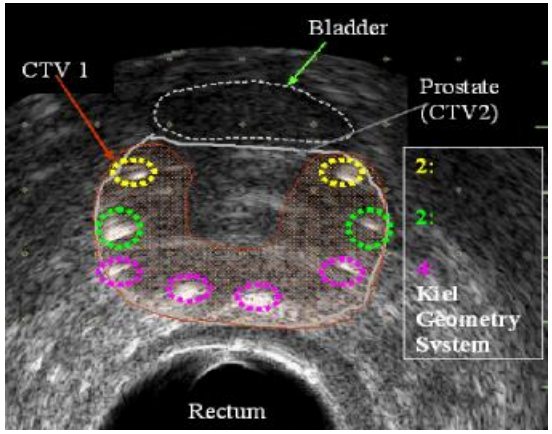


The 15-year outcomes of high-dose-rate brachytherapy for radical dose escalation in patients with prostate cancer—A benchmark for high-tech external beam radiotherapy alone?

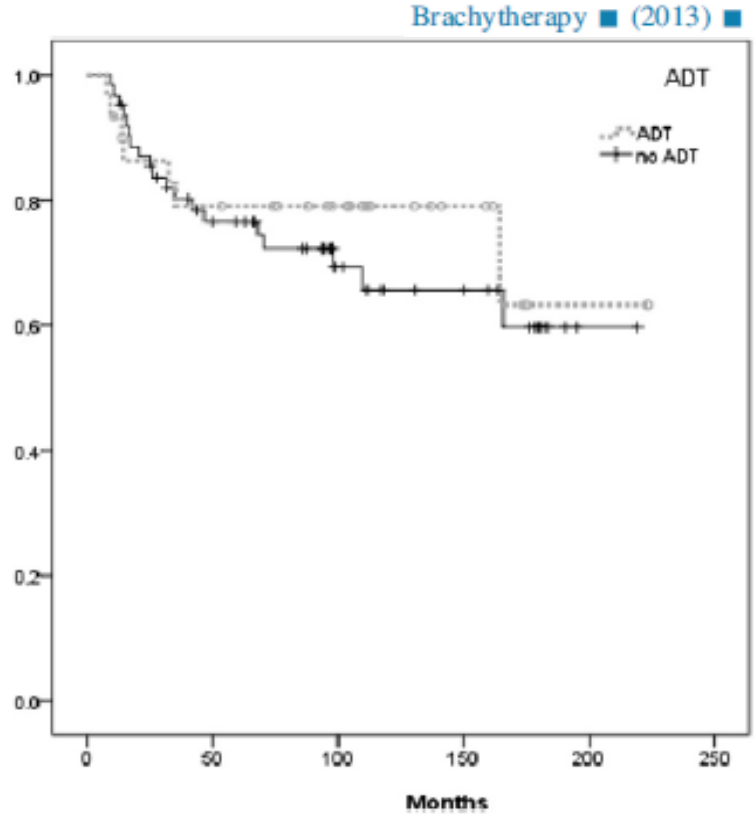
Razvan M. Galalae[1,*], Nuria Helena Zakikhany[1], Friedemann Geiger[2], Frank-Andre Siebert[3], Gunnar Bockelmann[3], Jürgen Schultze[3], Bernhard Kimmig[1,3]

[1]*Medical Faculty, Christian-Albrechts-University Kiel, Kiel, Germany*
[2]*Department of Pediatrics, Christian-Albrechts-University Kiel, Kiel, Germany*
[3]*Clinic for Radiotherapy, Christian-Albrechts-University Kiel, Kiel, Germany*

N=122 (45% HR;30% IR)
45Gy + 9Gy x2
(HDR 15Gy x2 peripheral dose)



End point	At 5 yr, %[a]	At 10 yr, %[a]	At 15 yr, %[a]
Overall survival	81	62.1	45
Cancer-specific survival	92.1	83.1	75.3
Local recurrence—free survival	92.5	91.4	83.9
Distant metastasis—free survival	83.8	81.2	69.2



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Low Risk

			#	bRFS
EBRT + HDR-BT				
Eulau *et al.* (37)	T1-T2b, Gleason score ≤6, PSA <10 ng/mL	EBRT 50 HDR-BT 12–16	6	96
Galalae *et al.* (27)	T1-T2a, Gleason score ≤6, PSA ≤10 ng/mL	EBRT 46–50 HDR-BT 16–30	5	96
Present study	T1-T2a, Gleason score ≤6, PSA ≤10 ng/mL	EBRT 36 HDR-BT 22–24	7.25	90

Intermediate /High risk

			#	bRFS
EBRT + HDR-BT				
Eulau *et al.* (37)	T2c-T3, Gleason score 7–10, PSA >15 ng/mL	EBRT 50	6	
	Intermediate: one or two factors	HDR-BT 12–16		72
	High: three factors			49
Martinez *et al.* (42)	T2b-T3, Gleason score 7–10, PSA ≥10 ng/mL	EBRT 46	4	87
	High-dose group	HDR-BT 23		
Galalae *et al.* (27)	≥T2b, Gleason score ≥7, PSA ≥10 ng/mL	EBRT 46–50	5	
	Intermediate: any one factor	HDR-BT 16–30		88
	High: any two factors			69
Present study	Intermediate: T2bc, PSA >10, ≤20 ng/mL, Gleason score 7	EBRT 36 HDR-BT 22–24	7.25	87
	High: T3, PSA >20 ng/mL, Gleason score 8–10—1 or more factors			69

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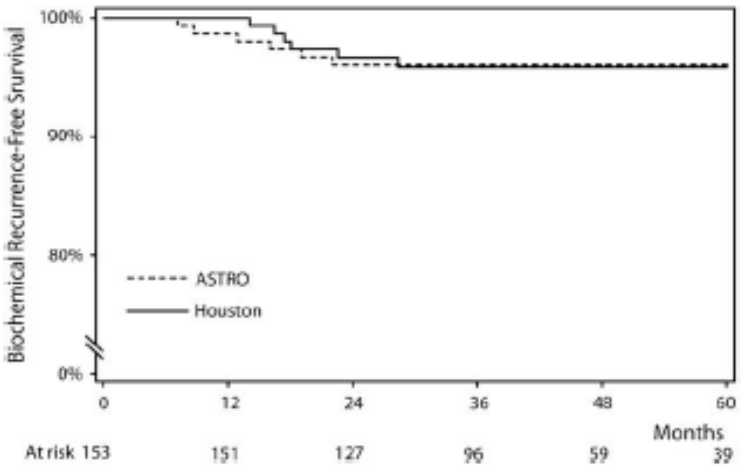
AN EIGHT-YEAR EXPERIENCE OF HDR BRACHYTHERAPY BOOST FOR LOCALIZED PROSTATE CANCER: BIOPSY AND PSA OUTCOME

FRANÇOIS BACHAND, M.D.,* ANDRÉ-GUY MARTIN, M.D., M.SC.,* LUC BEAULIEU, PH.D.,*†
FRANÇOIS HAREL, M.SC.,† AND ÉRIC VIGNEAULT, M.D., M.SC.*

*Département de Radio-oncologie, and †Centre de Recherche de L'Hôtel-Dieu de Québec, L'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec (CHUQ), Centre de Recherche en Cancérologie de l'Université Laval, Québec, Canada

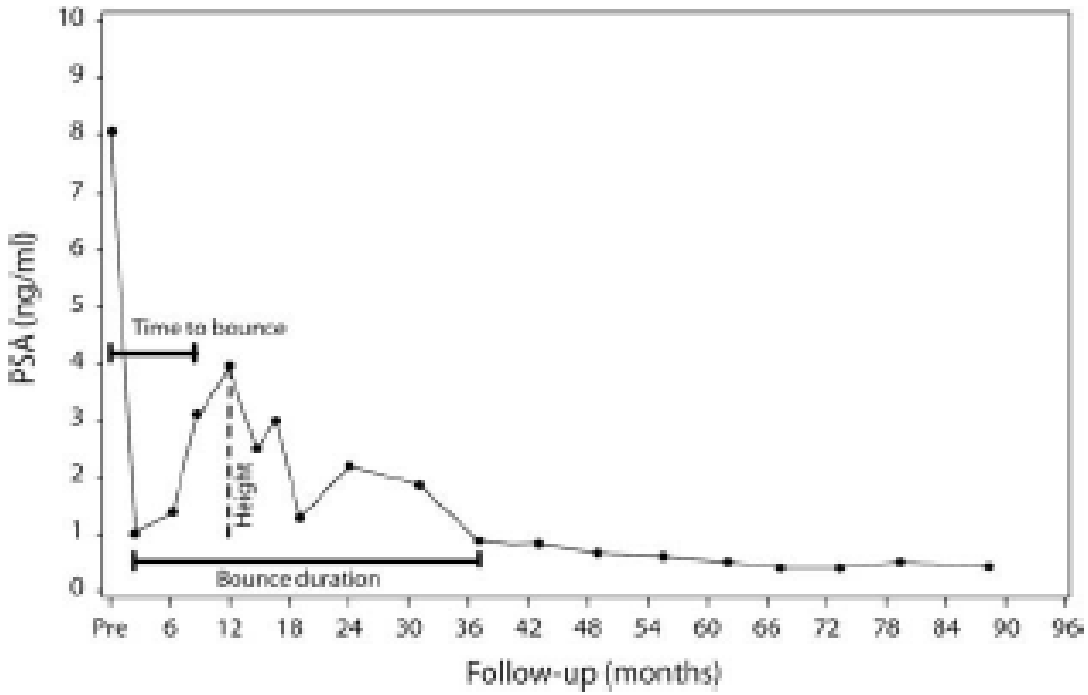
IJROB 2009

1996-2001: 40-44Gy + 18-20Gy/2f HDR
antiandrogens in 51%



n=153

Bounce (≥2 ng/ml above nadir) in 9.8%
Median time 15.2mo (IQR 11.1-17.7)
Median duration 18.7 (IQR 12.1-29)
Median height 3.24ng/ml (IQR 2.51-3.98)



DOSE ESCALATION IMPROVES CANCER-RELATED EVENTS AT 10 YEARS FOR INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER PATIENTS TREATED WITH HYPOFRACTIONATED HIGH-DOSE-RATE BOOST AND EXTERNAL BEAM RADIOTHERAPY

ALVARO A. MARTINEZ, M.D., F.A.C.R.,* JOSE GONZALEZ, M.D.,* HONG YE, M.S.,* MIHAI GHILEZAN, M.D., PH.D.,* SUGANDH SHETTY, M.D.,* KENNETH KERNEN, M.D.,† GARY GUSTAFSON, M.D.,* DANIEL KRAUSS, M.D.,* FRANK VICINI, M.D.,* AND LARRY KESTIN, M.D.*

IJROB 2010

472 patients: 1992-2007: inter/high risk

Age	
Median (range)	68 yrs (42–85)
T stage	
T1c	25.0% (118)
T2	63.3% (298)
T3	11.7% (55)
Pre-RT PSA	
< 4 ng/ml	6.6% (31)
4 to <10 ng/ml	51.6% (242)
10 to <20 ng/ml	28.6 % (134)
≥ 20 ng/ml	13.2% (62)
Gleason score	
≤ 6	35.0% (165)
7	44.2% (209)
8–10	20.8% (98)
Follow-up	
median (range)	8.2 (0.4–17.0)

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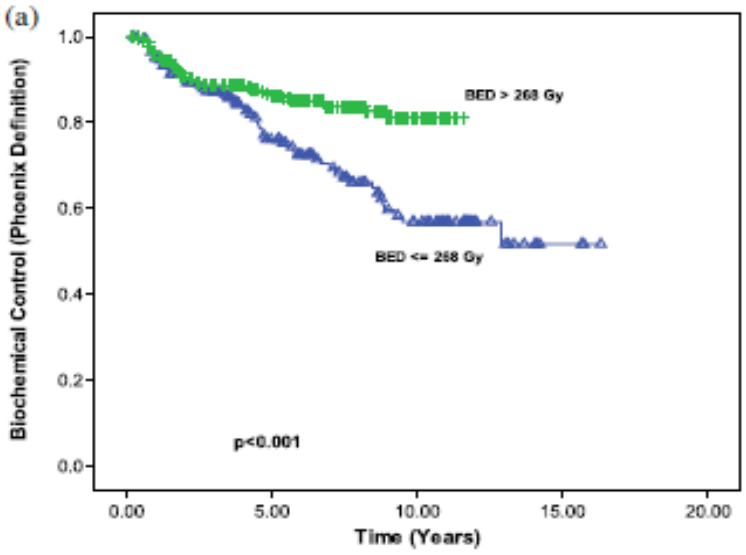
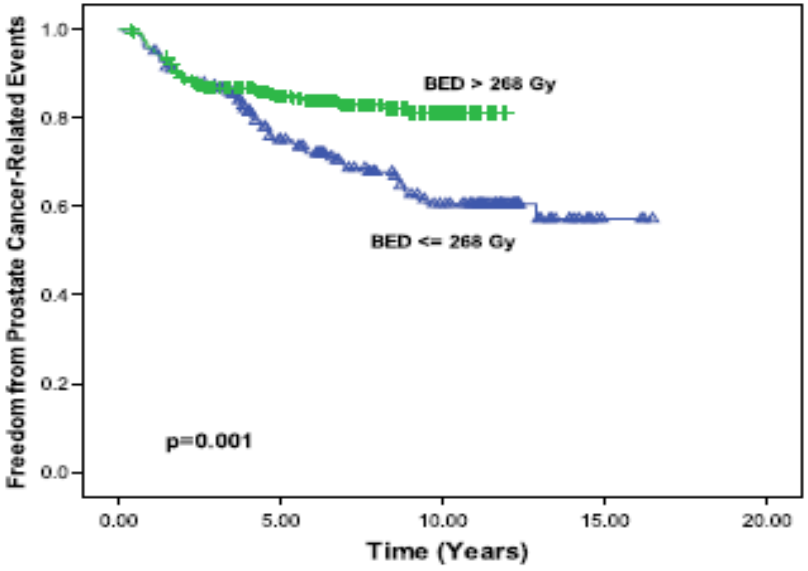
Dose group	Group	No. of cases (n = 472)	Mean follow-up (years)	Median follow-up (years)	Range (years)	BED (α/β of 1.2) P-EBRT plus HDR
Low dose	5.5 Gy x 3 fractions	26	11.2	11.2	2.1–17.0	215 Gy
	6.0 Gy x 3 fractions	21	10.3	10.9	1.1–16.1	231 Gy
	6.5 Gy x 3 fractions	32	10.5	10.9	2.0–15.0	248 Gy
	8.25 Gy x 2 fractions	44	8.2	8.9	1.5–13.3	253 Gy
	8.75 Gy x 2 fractions	44	8.7	9.3	3.4–12.3	268 Gy
High dose	9.50 Gy x 2 fractions	111	8.3	9.7	1.2–11.9	292 Gy
	10.5 Gy x 2 fractions	125	6.2	7.0	0.4–11.0	327 Gy
	11.5 Gy x 2 fractions	69	6.0	6.2	0.4–9.3	366 Gy
All cases		471	7.8	8.2	0.4–17.0	

Dose group	No. of cases (n = 472)	BF (nadir +2)	BF(nadir +5 in 24 month, then nadir +2)	Locoregional failure	Distant metastasis failure	Clinical failure	Clinical DFS	Prostate cancer-related events
Low dose	167	43.1%	41.2%	14.3%	12.4%	23.4%	55.2%	39.4%
High dose	305	18.9%	15.5%	2.8%	5.7%	7.7%	71.9%	18.9%
p value		<0.001	<0.001	0.001	0.028	<0.001	0.014	0.001
All cases	472	29.4%	26.6%	7.8%	8.3%	14.3%	64.8%	27.5%





268Gy = 100.5Gy (αβ=1.2)

Martinez et al 2010

Which boost dose?

Is single fraction 15 Gy the preferred high dose-rate brachytherapy boost dose for prostate cancer?

Gerard Morton [a,*], Andrew Loblaw [a], Patrick Cheung [a], Ewa Szumacher [a], Manraj Chahal [a], Cyril Danjoux [a], Hans T. Chung [a], Andrea Deabreu [a], Alexandre Mamedov [a], Liying Zhang [a], Raxa Sankreacha [a], Eric Vigneault [b], Colvin Springer [c]

Radiotherapy and Oncology 100 (2011) 463–467

High dose-rate brachytherapy boost for intermediate risk prostate cancer: Long-term outcomes of two different treatment schedules and early biochemical predictors of success

Joelle Helou [a,b], Laura D'Alimonte [a,b], Andrew Loblaw [a,b], Hans Chung [a,b], Patrick Cheung [a,b], Ewa Szumacher [a,b], Cyril Danjoux [a,b], Ananth Ravi [a,b], Andrea Deabreu [a], Liying Zhang [a], Gerard Morton [a,b,*]

[a] *Sunnybrook Odette Cancer Centre; and* [b] *University of Toronto, Canada*

Radiotherapy and Oncology xxx (2015)

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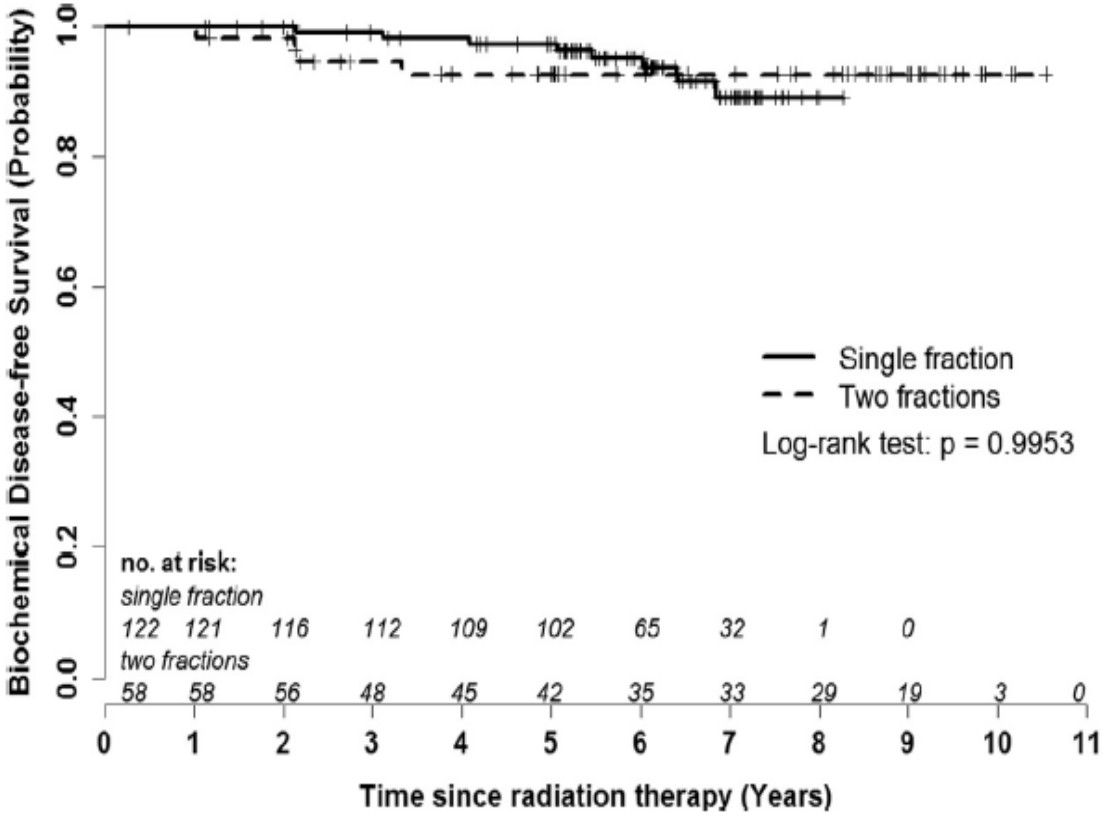
Toronto experience 15Gy single fraction HDR boost

Toxicity	Follow-up (mo) 6 (n = 121)	12 (n = 120)	18 (n = 97)	24 (n = 65)
GU frequency (%)				
Grade 1	32	39	47	54
Grade 2	4	7	5	3
GU retention (%)				
Grade 1	36	31	39	52
Grade 2	29	33	29	23
GI proctitis (%)				
Grade 1	8	5	4	6
Grade 2	0	2	3	3
Rectal bleeding (%)				
Grade 1	3	6	11	11
Grade 2	0	4	1	5
Erectile dysfunction (%)				
Grade 1	26	20	20	17
Grade 2	42	52	57	65
Grade 3	7	9	9	11



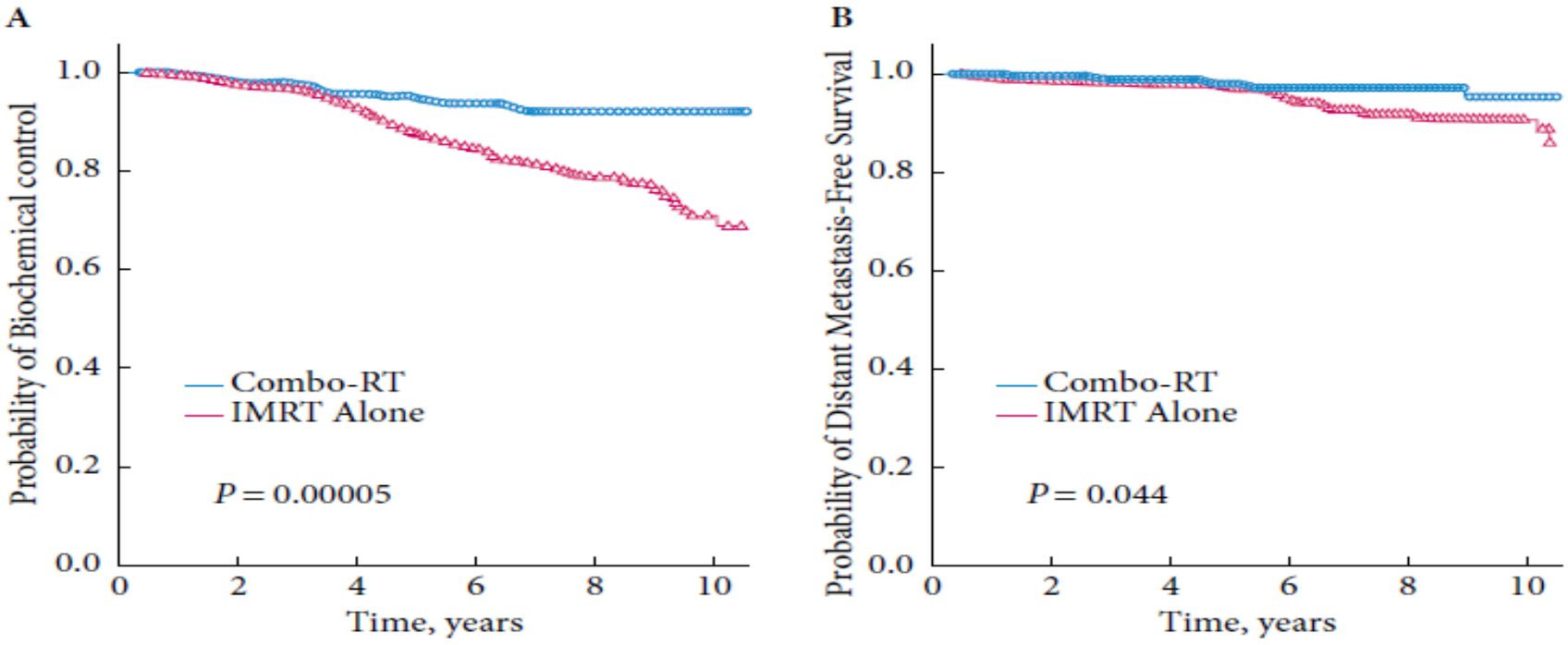
Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer

Daniel E. Spratt, Zachary S. Zumsteg, Pirus Ghadjar, Marisa A. Kollmeier, Xin Pei, Gilad Cohen*, William Polkinghorn, Yoshiya Yamada and Michael J. Zelefsky

*Departments of Radiation Oncology and *Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY,*

BJU Int 2014; **114**: 360–367

IMRT 86.4Gy: 470
vs
IMRT 45-50.4+ BT : 400 (LDR 100-110Gy - 260, HDR 16.5-22.5 in 3f - 140)



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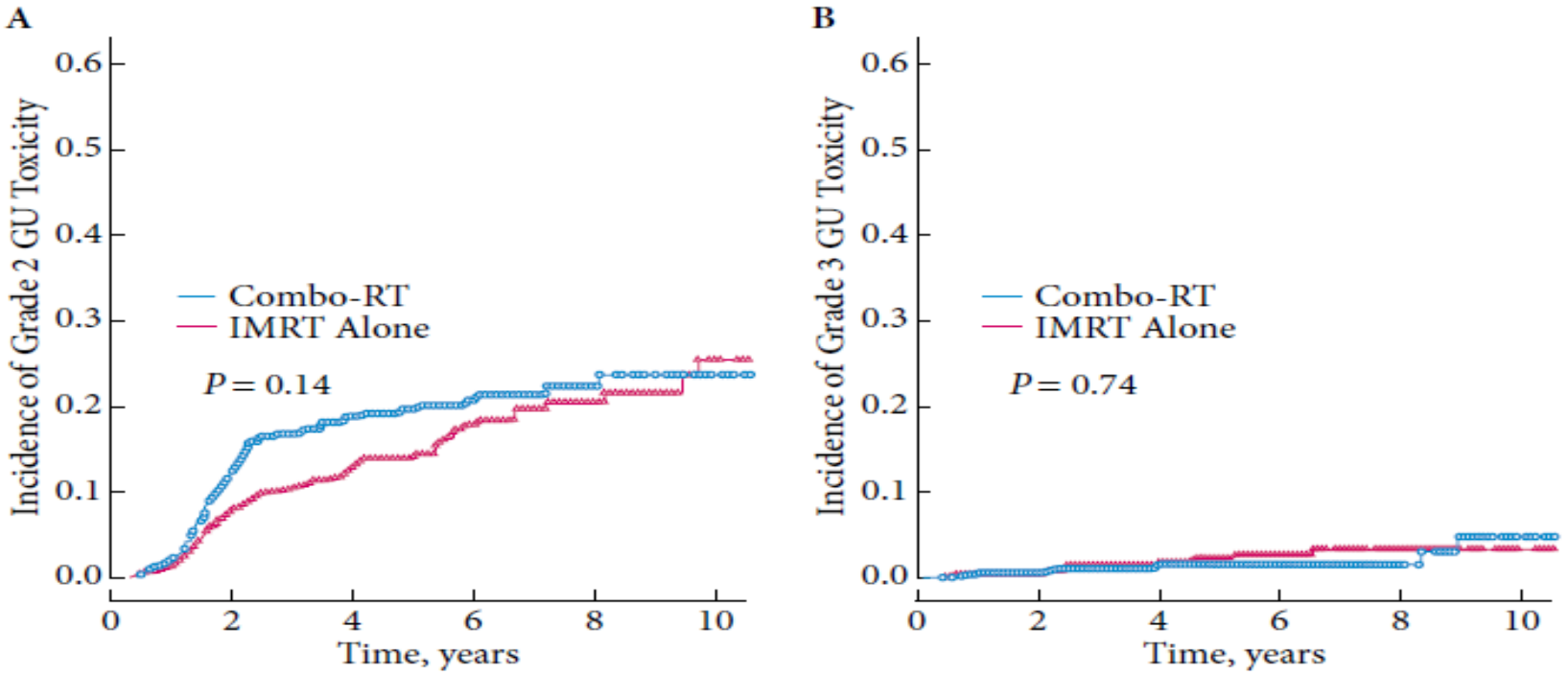

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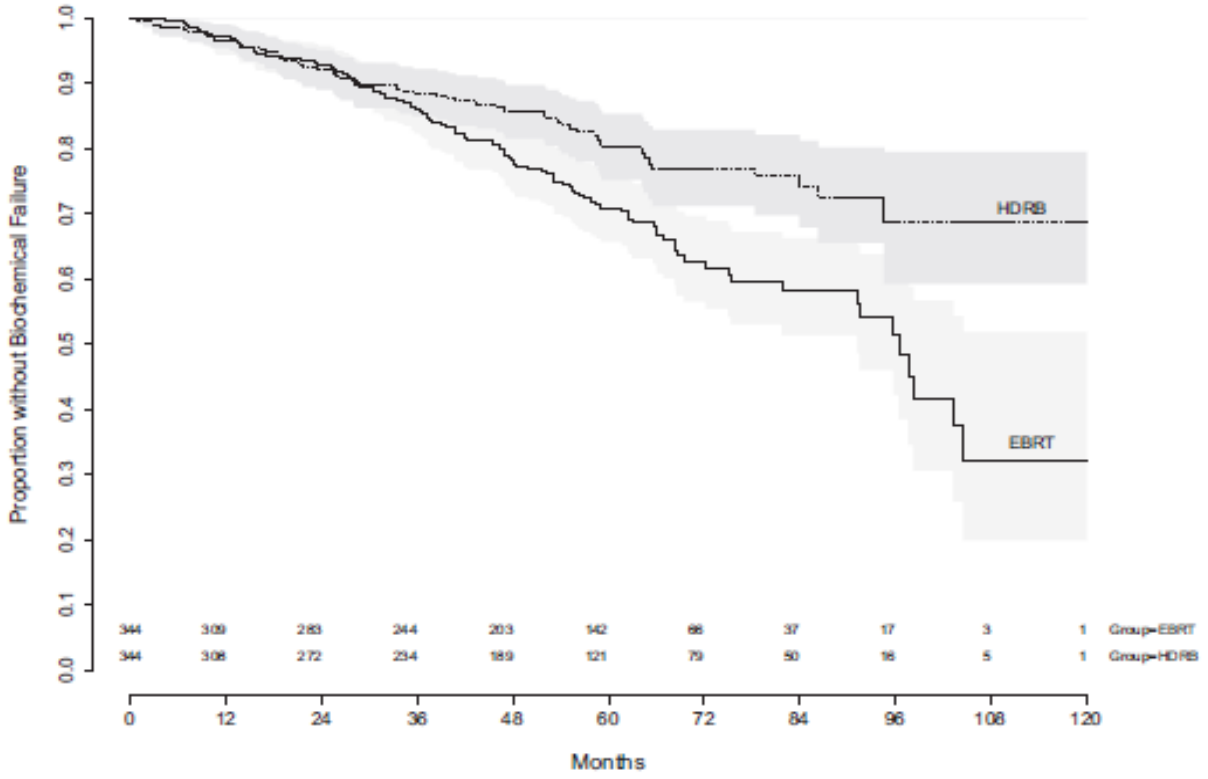
Direct 2-Arm Comparison Shows Benefit of High-Dose-Rate Brachytherapy Boost vs External Beam Radiation Therapy Alone for Prostate Cancer

Richard Khor, MBBS,* Gillian Duchesne, MD, FRANZCR,*,† Keen-Hun Tai, FRANZCR,* Farshad Foroudi, FRANZCR,* Sarat Chander, FRANZCR,* Sylvia Van Dyk, DipAppSc,* Margaret Garth, DipAppSc,* and Scott Williams, MD, FRANZCR*

**Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, and University of Melbourne, Melbourne, Australia; and †Monash University, Melbourne, Australia*

Int J Radiation Oncol Biol Phys, Vol. 85, No. 3, pp. 679–685, 2013

344 patients 46Gy/23f + 19.5GY/3f HDR vs
344 patients 3D CRT 74Gy/37f
Risk group: Intermediate 41%; High 59%



Actuarial FFbF plots of matched EBRT and HDRB treatment cohorts. Bands indicate 95% confidence intervals.

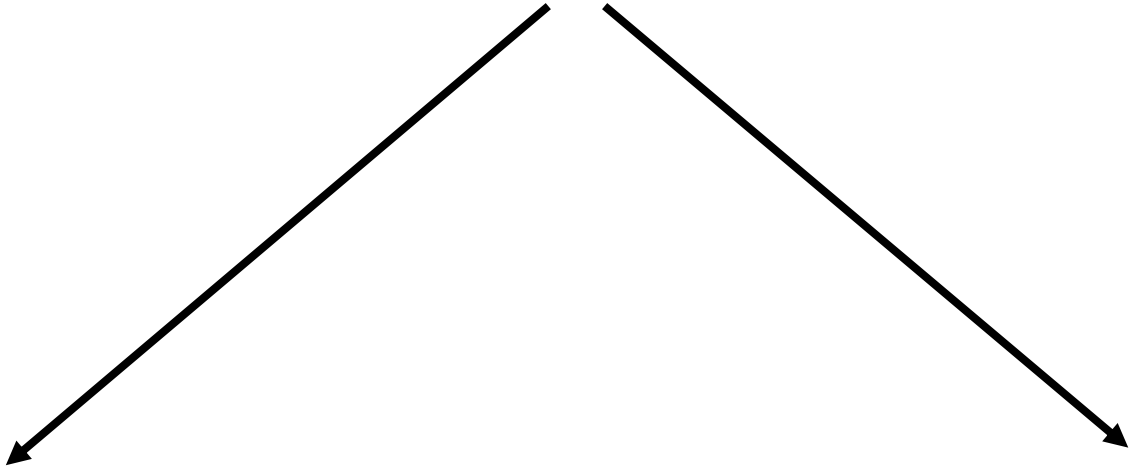
ESTRO School

Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer

Peter J. Hoskin [a], Ana M. Rojas [a,*], Peter J. Bownes [b], Gerry J. Lowe [a], Peter J. Ostler [a], Linda Bryant [a]

[a] Cancer Centre, Mount Vernon Hospital, Northwood, UK; [b] St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK

Radiotherapy and Oncology xxx (2012)



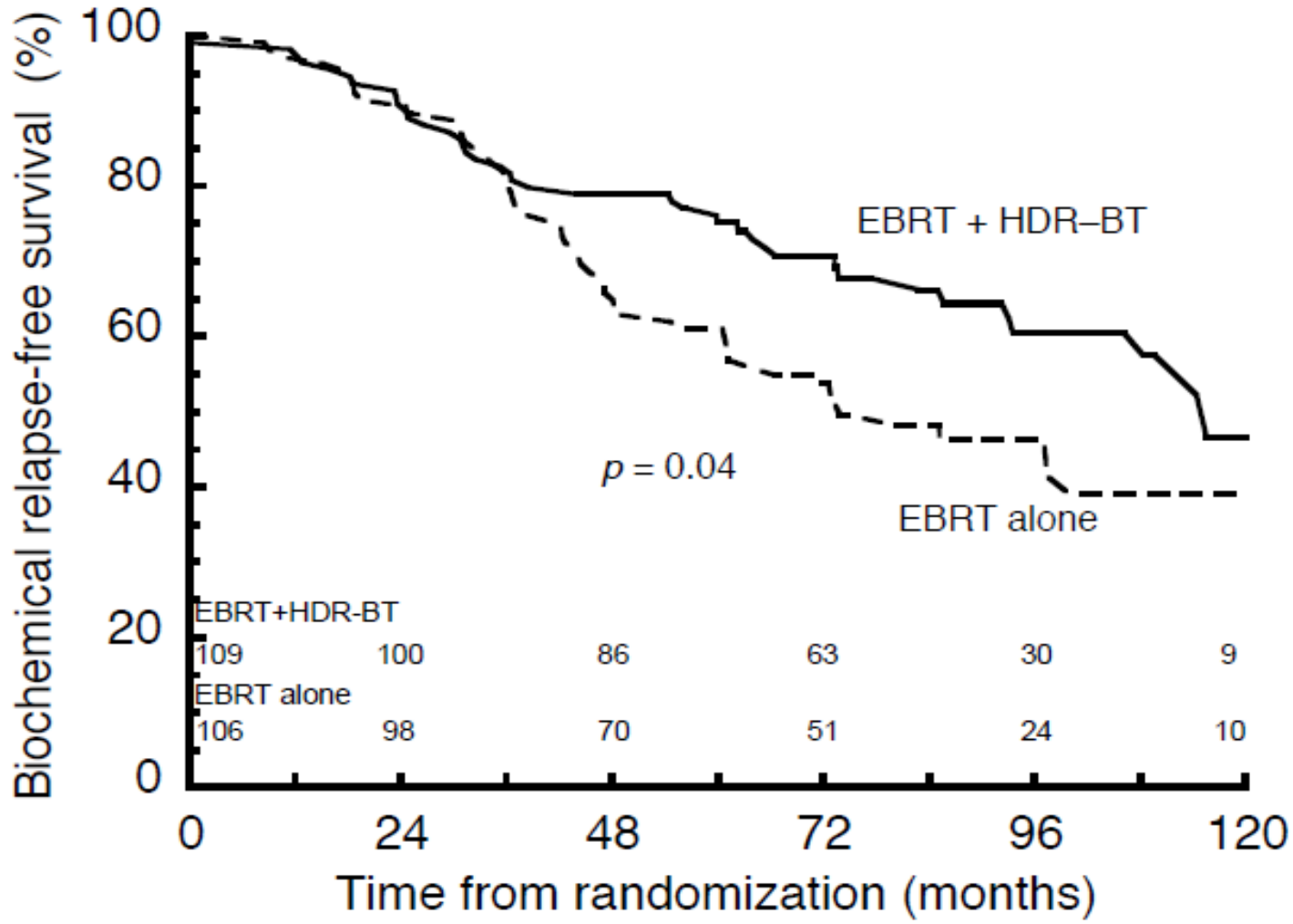
55Gy/20f
Ext beam

35.7Gy/13f
+
17Gy/2f HDR

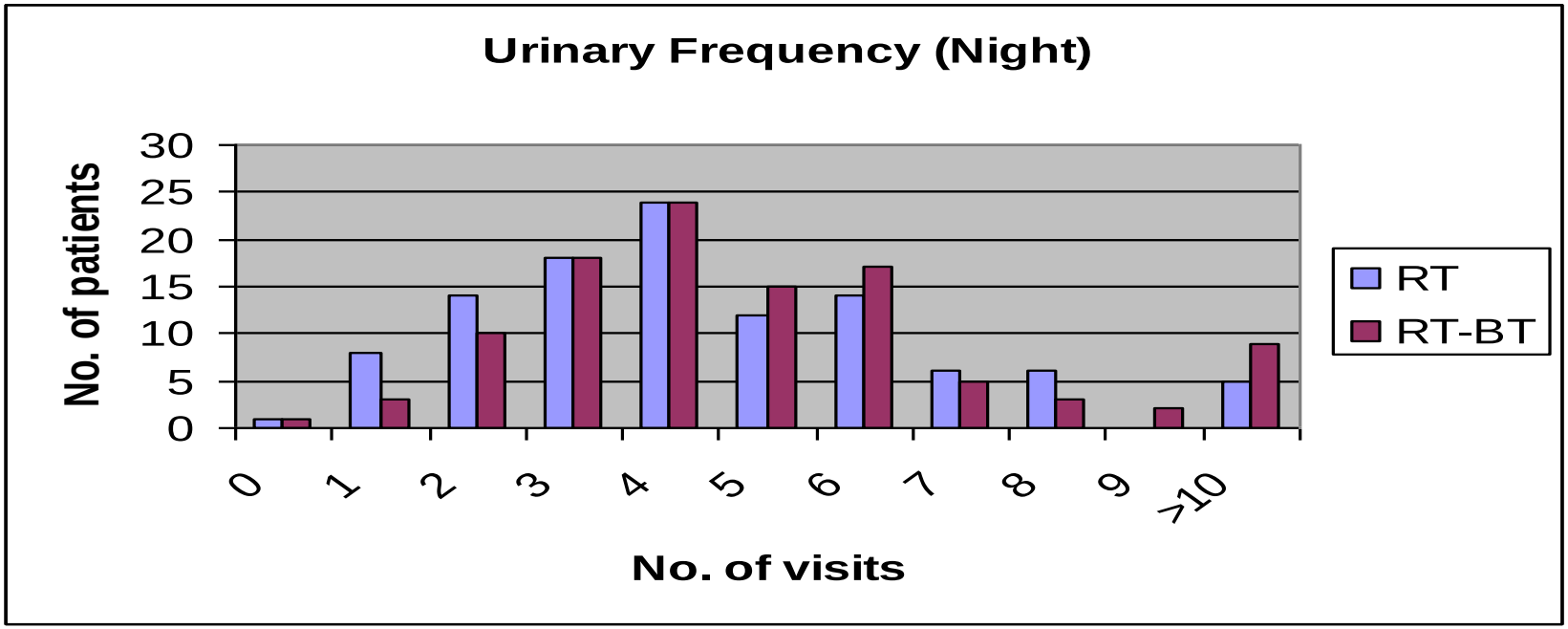
Closed 08/05: 220 patients randomised

ESTRO School

MV RCT HDR Boost



Acute toxicity:



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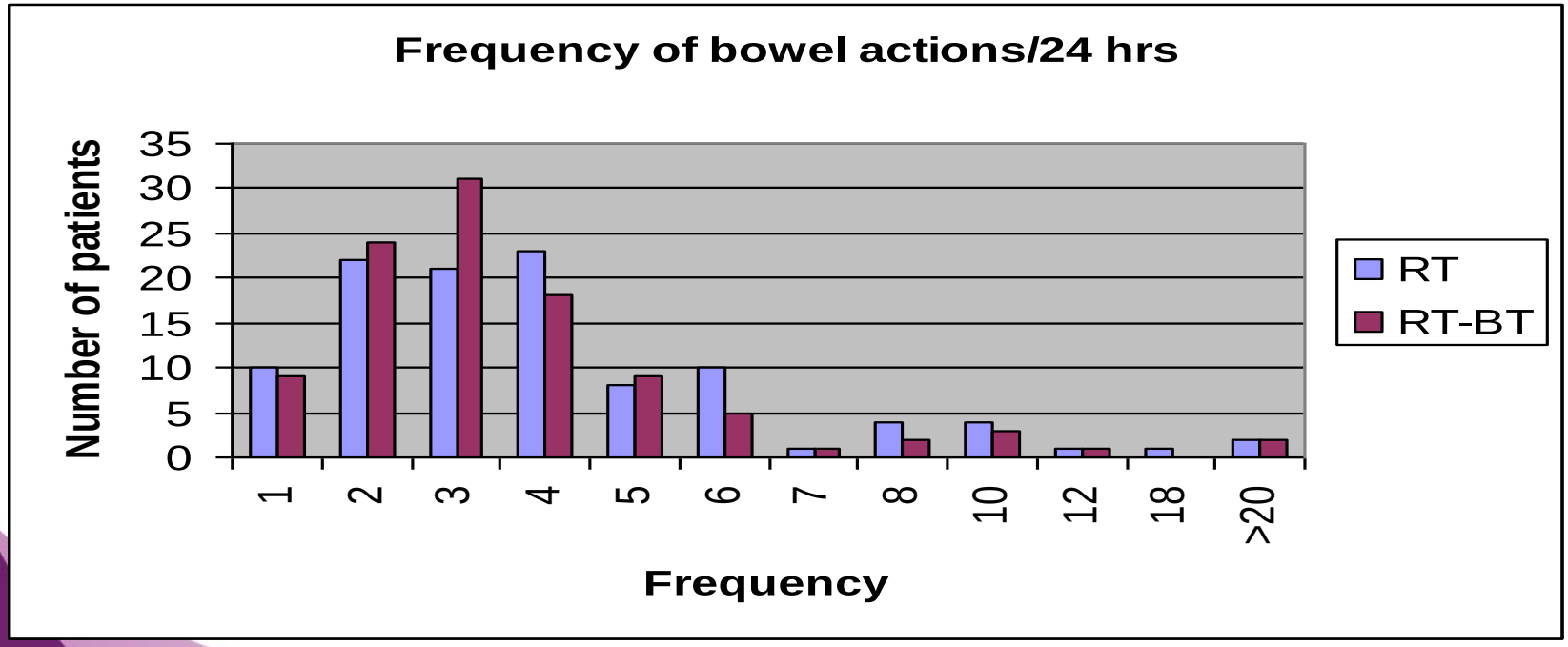
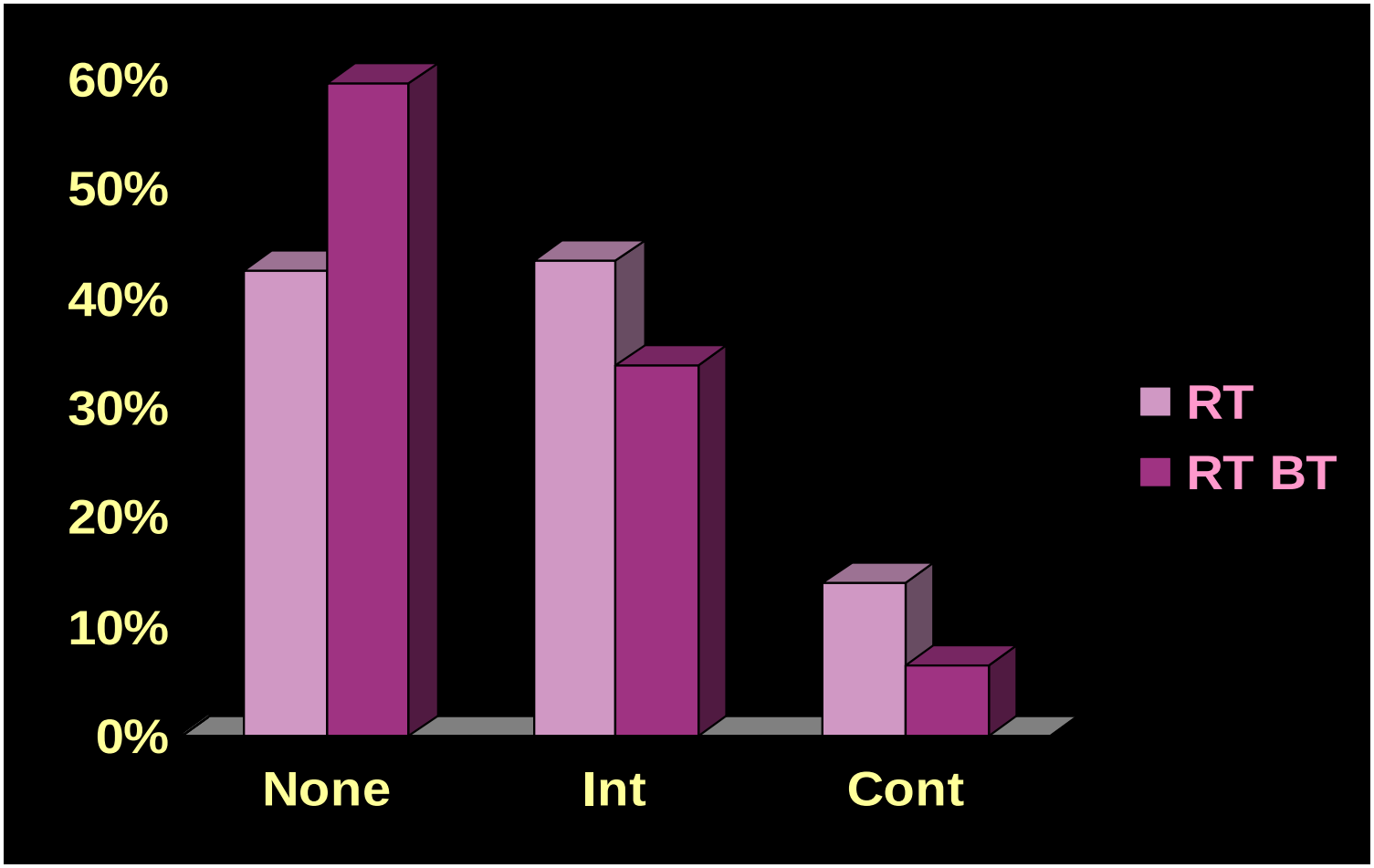


P=0.352

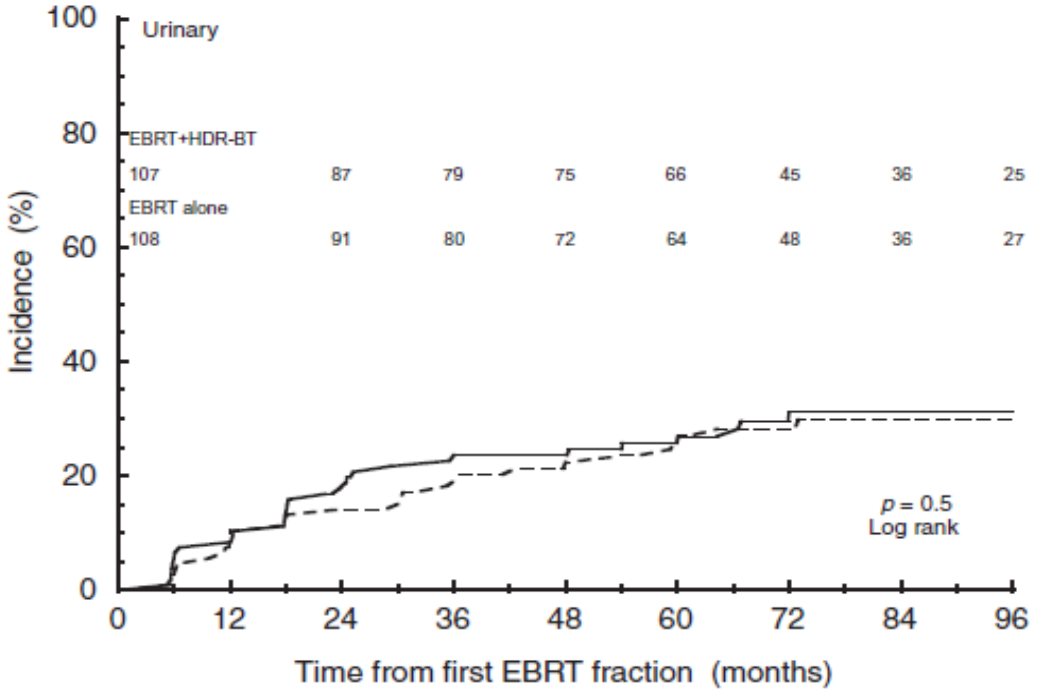
ESTRO School

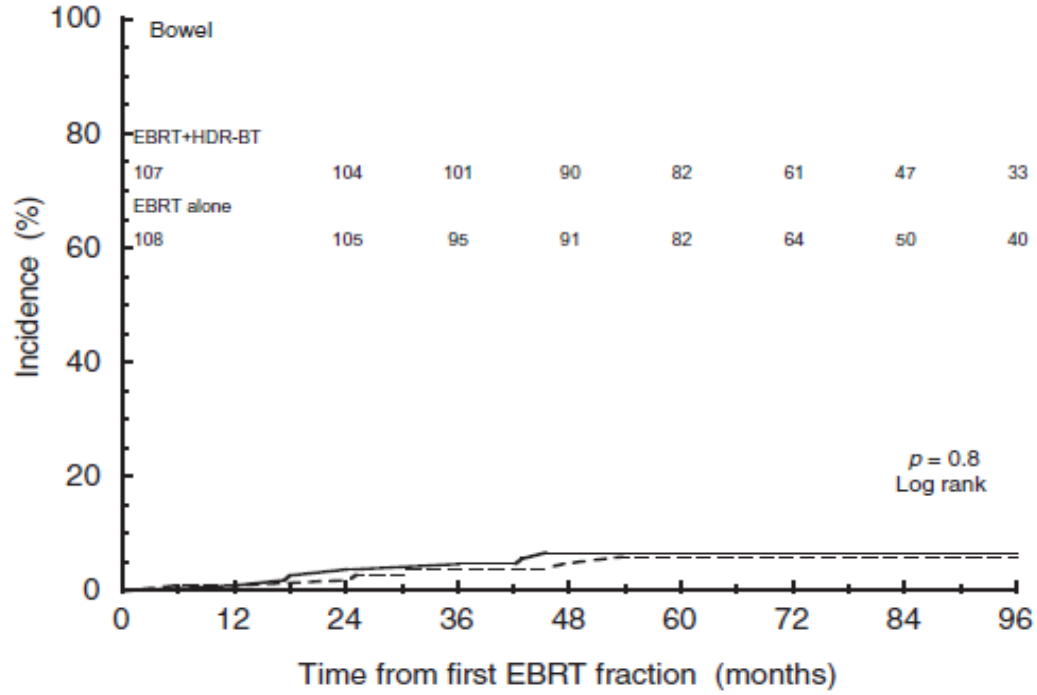
Acute toxicity: rectal discharge



P=0.025

MV RCT
Late toxicity





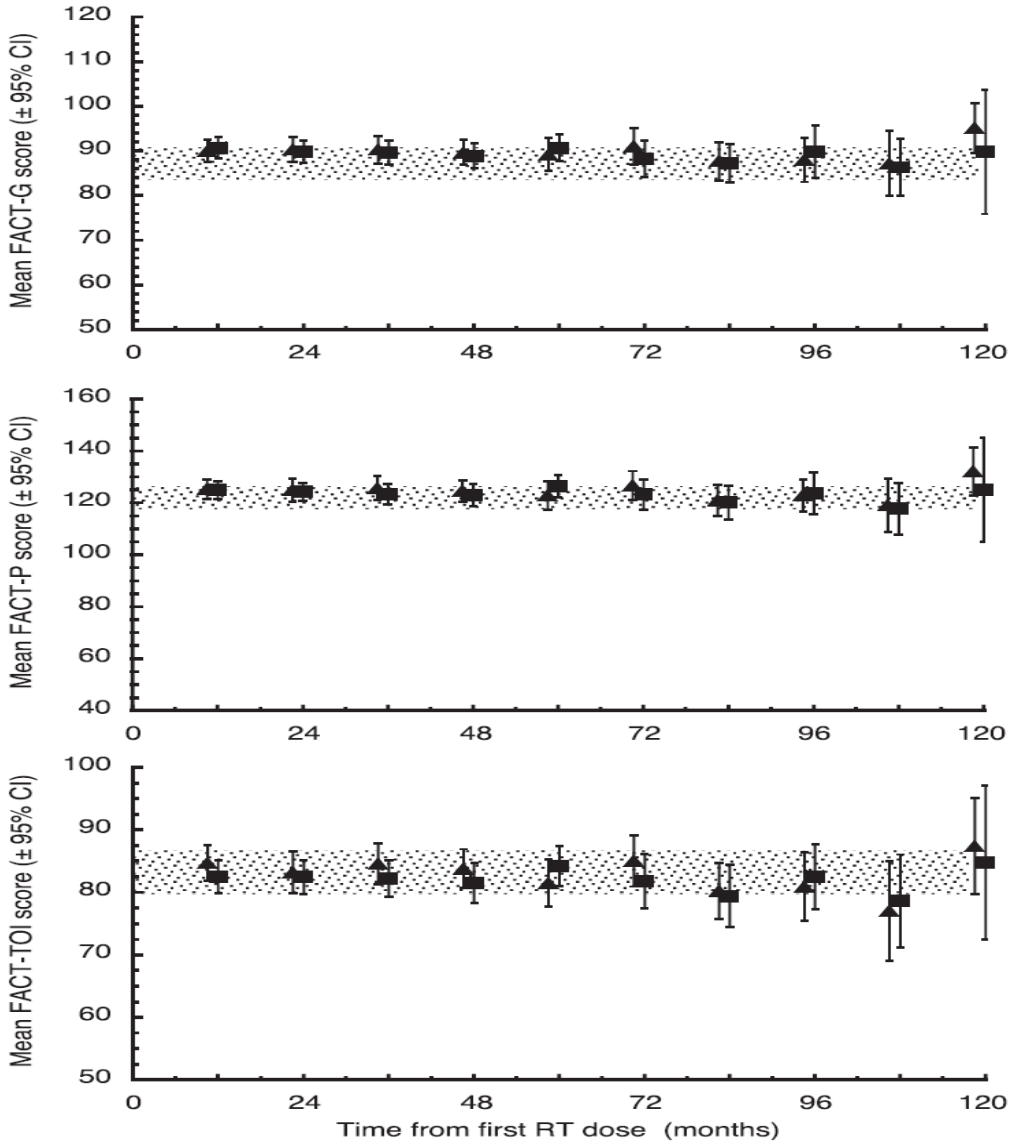
TRO School

Quality of Life after Radical Radiotherapy for Prostate Cancer: Longitudinal Study from a Randomised Trial of External Beam Radiotherapy Alone or in Combination with High Dose Rate Brachytherapy

P.J. Hoskin, A.M. Rojas, P.J. Ostler, R. Hughes, G.J. Lowe, L. Bryant

Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex, UK

Clinical Oncology 25 (2013) 321–327



ESTRO School

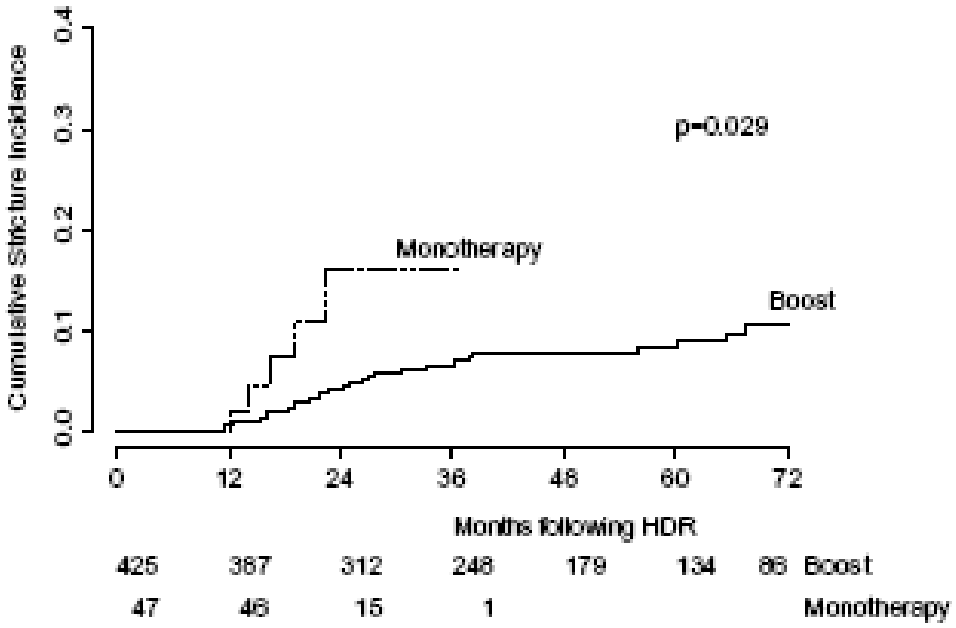
Prostate cancer brachytherapy

Urethral stricture following high dose rate brachytherapy for prostate cancer

Lisa Sullivan, Scott G. Williams *, Keen Hun Tai, Farshad Foroudi, L. Cleeve, Gillian M. Duchesne

Division of Radiation Oncology, Peter MacCallum Cancer Centre and University of Melbourne, Australia

RT&O 2009



30-33Gy/3f

46Gy/23f
+ 19.5Gy/3f

Prostate cancer brachytherapy

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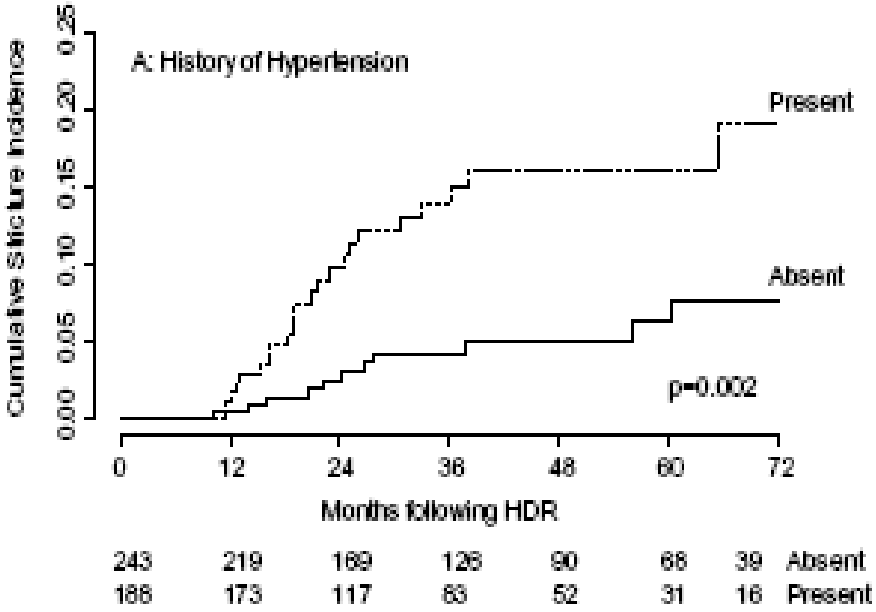
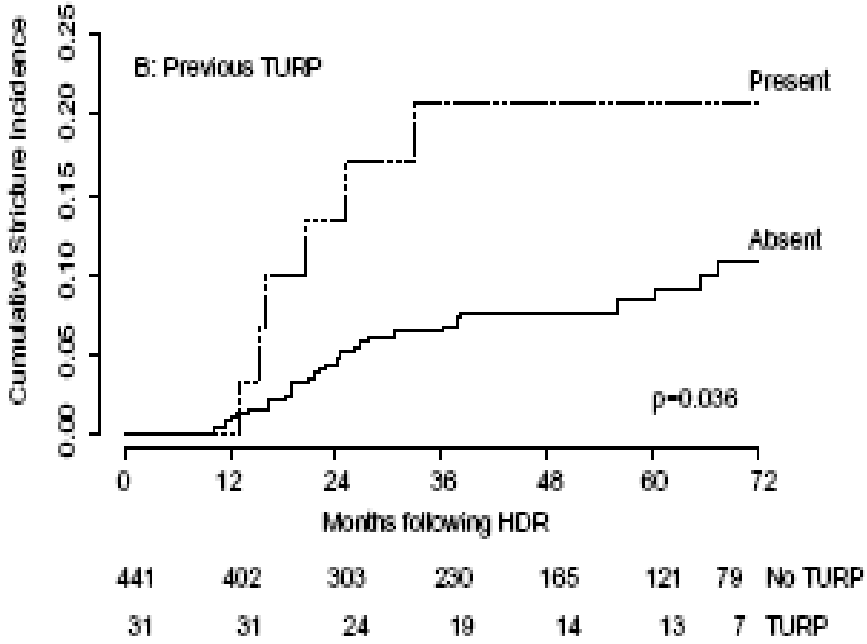




PHASE II TRIAL OF COMBINED HIGH-DOSE-RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY FOR ADENOCARCINOMA OF THE PROSTATE: PRELIMINARY RESULTS OF RTOG 0321

I-Chow Hsu, M.D.,* Kyounghwa Bae, Ph.D.,† Katsuto Shinohara, M.D.,* Jean Pouliot, Ph.D.,* James Purdy, Ph.D.,‡ Geoffrey Ibbott, Ph.D.,§ Joycelyn Speight, M.D., Ph.D.,* Eric Vigneault, M.D.,¶ Robert Ivker, M.D.,‖ and Howard Sandler, M.D.#

IJROB 2010

129 patients ; 14 institutions **median F/U 29.6 mo**

45Gy in 25# ext beam
HDR 19Gy in 2#: single implant

Table 3. Acute adverse events (≤9 months) by category ($n = 112$)

	Grade			
Adverse events	2	3	4	5
GU/GI *(n)*				
Frequency	0	2	0	0
Urinary retention	8	1	0	0
Non-GU/GI *(n)*				
Kidney infection	0	1	0	0
Erectile dysfunction	17	2	0	0

Table 4. Late adverse events (>9 months) by category ($n = 112$)

	Grade			
Adverse events	2	3	4	5
GU/GI				
Urinary retention	0	1	0	0
Cystitis	4	1	0	0
Urinary incontinence	1	1	0	0
Proctitis	2	1	0	0
Non-GU/GI				
Proctalgia	0	1	0	0
Urogenital hemorrhage	3	1	0	0
Rectal hemorrhage	0	1	0	0
Anemia	0	1	0	0
Kidney infection	0	1	0	0
Ejaculatory disorder	3			
Erectile dysfunction	26	5		

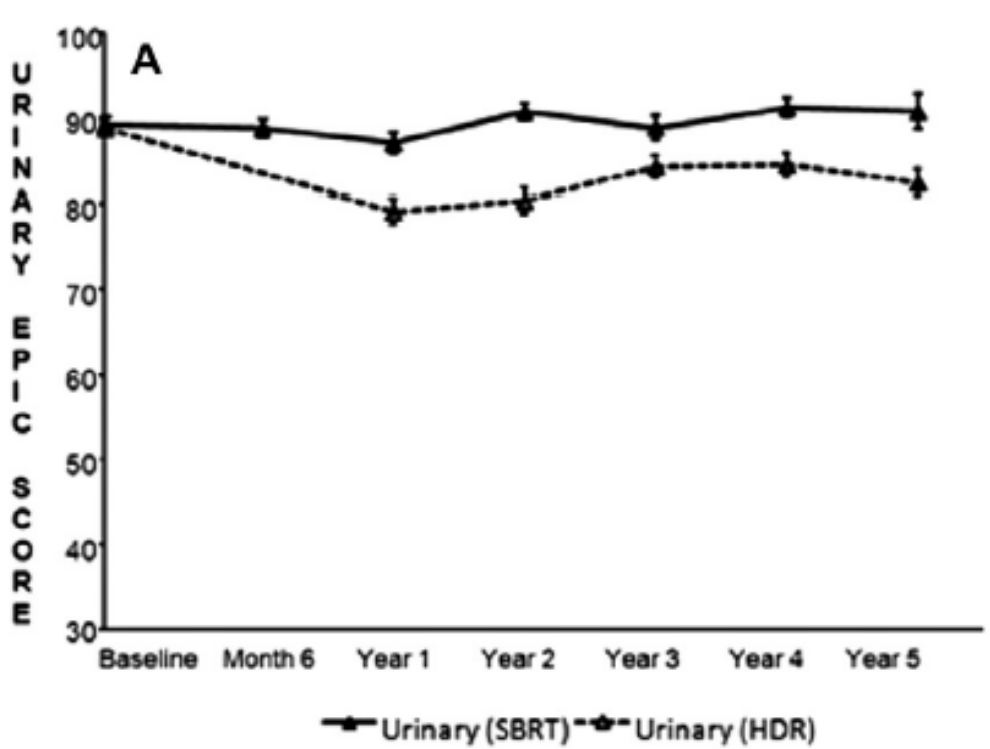
A comparative study of quality of life in patients with localized prostate cancer treated at a single institution: Stereotactic ablative radiotherapy or external beam + high dose rate brachytherapy boost

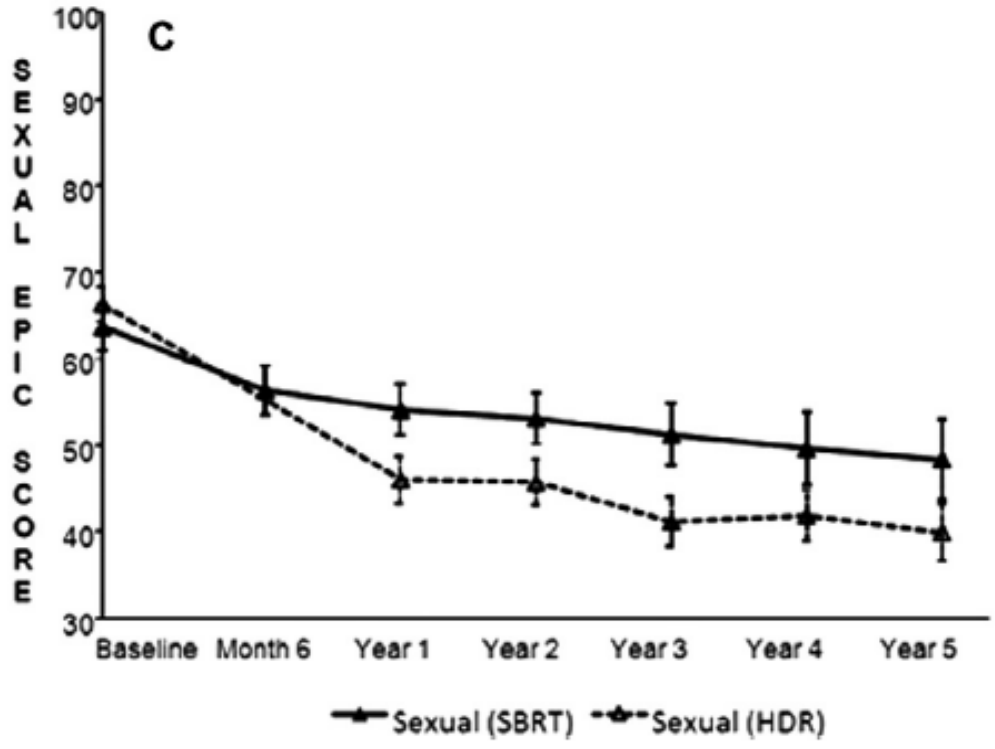
Joelle Helou [a,b], Gerard Morton [a,b], Liying Zhang [a], Andrea Deabreu [a], Laura D'Alimonte [a,b], Evelyn Elias [a], Hima Bindu Musunuru [a,b], Alexandre Mamedov [a], Ananth Ravi [a,b], Hans Chung [a,b], Patrick Cheung [a,b], Andrew Loblaw [a,b,c,*]

[a] Odette Cancer Centre, Sunnybrook Health Sciences Centre; [b] Department of Radiation Oncology; and [c] Institute for Health, Policy, Measurement and Evaluation, University of Toronto, Canada

Radiotherapy and Oncology 113 (2014) 404–409

35Gy/5f SABR vs 37.5Gy/15f EBRT + 15Gy HDR





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Radiotherapy and Oncology 113 (2014) 404–409

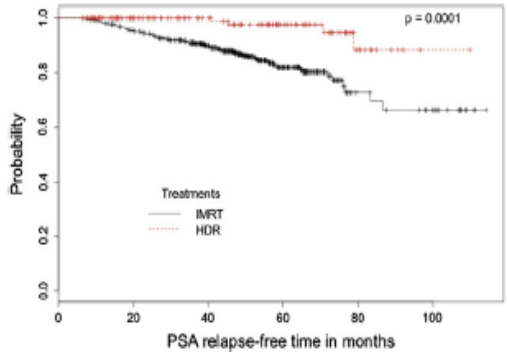
	Treatment groups		
	HDR boost *n* (%)	SABR *n* (%)	*p*-Value*
	N = 117	*N* = 84	
Urinary	68 (58)	15 (18)	**<0.0001**
Urinary function	63 (54)	16 (20)	**<0.0001**
Urinary bother	55 (47)	11 (13)	**<0.0001**
	N = 117	*N* = 84	
Bowel	51 (44)	27 (32)	0.2466
Bowel function	43 (37)	26 (31)	**0.0216**
Bowel bother	48 (39)	21 (25)	0.0760
	N = 110	*N* = 76	
Sexual	61 (55)	33 (43)	0.1903
Sexual function	58 (53)	26 (34)	0.0290
Sexual bother	57 (52)	27 (35)	**0.0419**

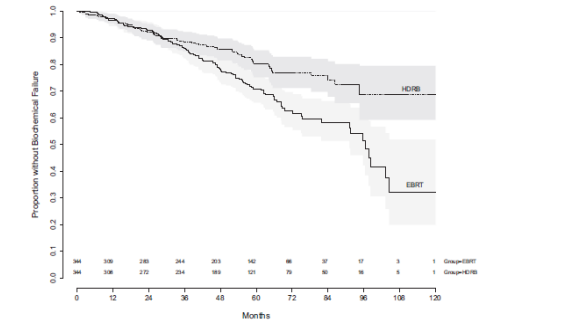
Evidence for HDR boost with external beam

Prospective series >1000 patients

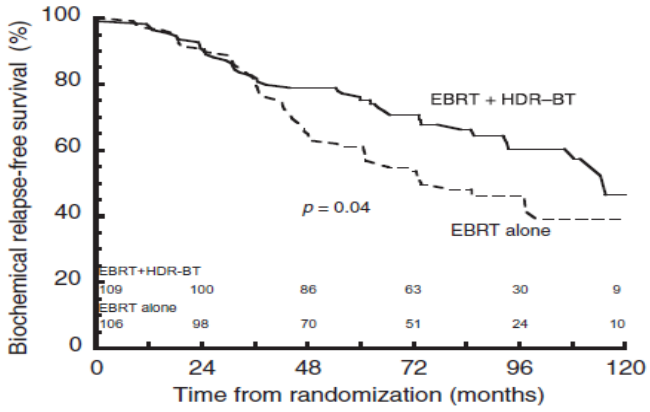
Case control studies

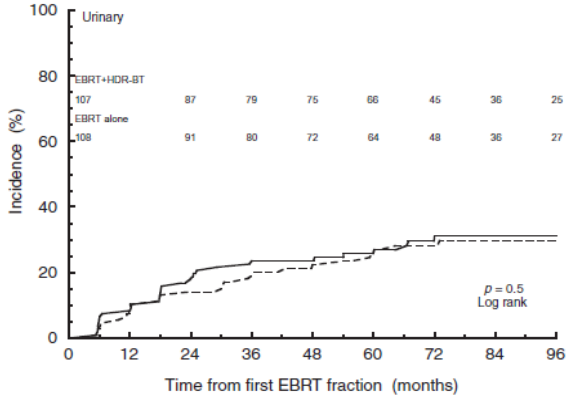
RCT





Actuarial FFbF plots of matched EBRT and HDRB treatment cohorts. Bands indicate 95% confidence intervals.





ESTRO School

Long-Term Results of a Randomized Trial Comparing Iridium Implant Plus External Beam Radiation Therapy With External Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate

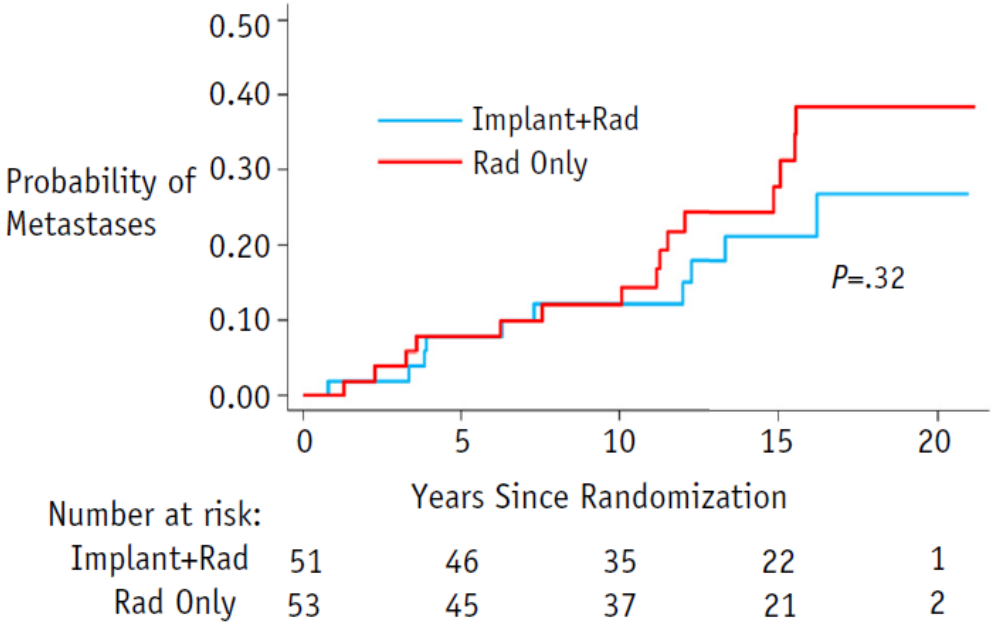
Ian S. Dayes, MD,* Sameer Parpia, PhD,† Jaclyn Gilbert, MD,‡ Jim A. Julian, MMath,† Ian R. Davis, MD,§ Mark N. Levine, MD,*,† and Jinka Sathya, MD‖

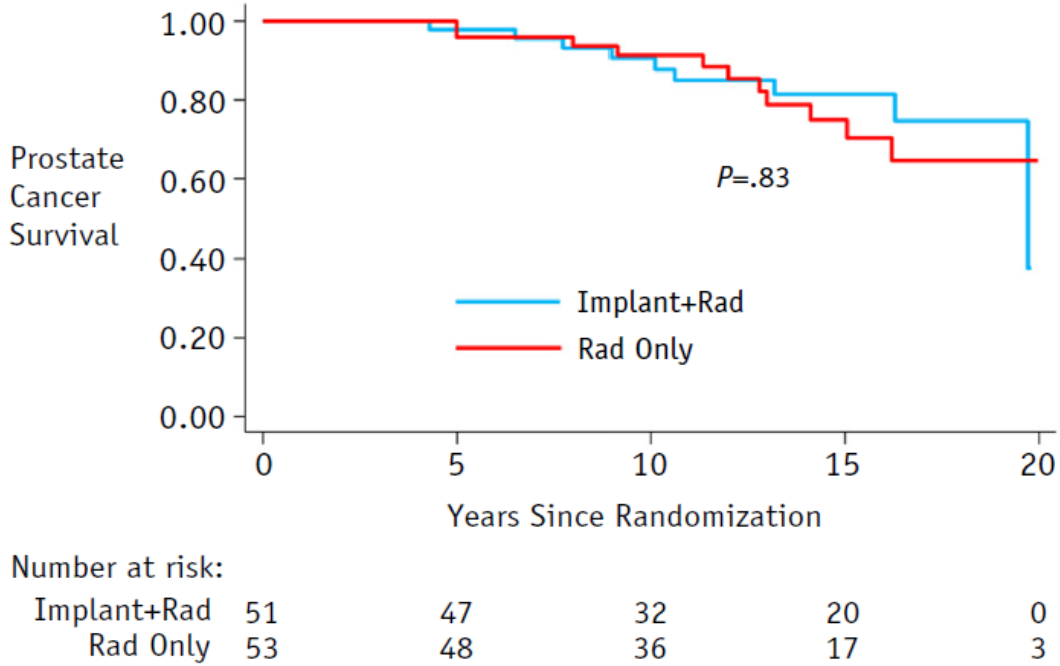
Int J Radiation Oncol Biol Phys, Vol. 99, No. 1, pp. 90–93, 2017

1992-1997: 105 men:
60% high risk……. No ADT

66Gy in 33 fractions
vs
40Gy in 29 fractions
+ Ir implant 35Gy in 48 hours

Median follow up 14yrs bRFS: 66Gy - 30%
40Gy + Ir - 53%





NICE National Institute for Health and Care Excellence

Prostate cancer: diagnosis and treatment

Issued: January 2014

Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. **[new 2014]**

ESTRO School

HDR prostate brachytherapy

- HDR Boost
- HDR Monotherapy

HDR implant: biological advantage 2Gy EQD

	α/β 10	α/β 1.5	α/β 3.5
Ext beam			
78Gy/37f	**78**	**78**	**78**
HDR mono			
34Gy/4f	**96.9**	**74.2**	**52.4**
36Gy/4f	**108**	**81.8**	**57.0**
31.5Gy/3f	**108**	**80.2**	**53.8**
26Gy/2f	**108**	**78.0**	**49.8**

ESTRO School

High-Dose-Rate Brachytherapy as Monotherapy for Intermediate- and High-Risk Prostate Cancer: Clinical Results for a Median 8-Year Follow-Up

Yasuo Yoshioka, MD,* Osamu Suzuki, MD,* Fumiaki Isohashi, MD,* et al

Int J Radiation Oncol Biol Phys, Vol. 94, No. 4, pp. 675–682, 2016

- 54Gy in 9 fractions
- 112 patients 1996-2005
  - 15 LOW RISK
  - 29 INTER RISK
  - 68 HIGH RISK

  - Neoadjuvant hormones in 94

ESTRO School

High-Dose-Rate Brachytherapy as Monotherapy for Intermediate- and High-Risk Prostate Cancer: Clinical Results for a Median 8-Year Follow-Up

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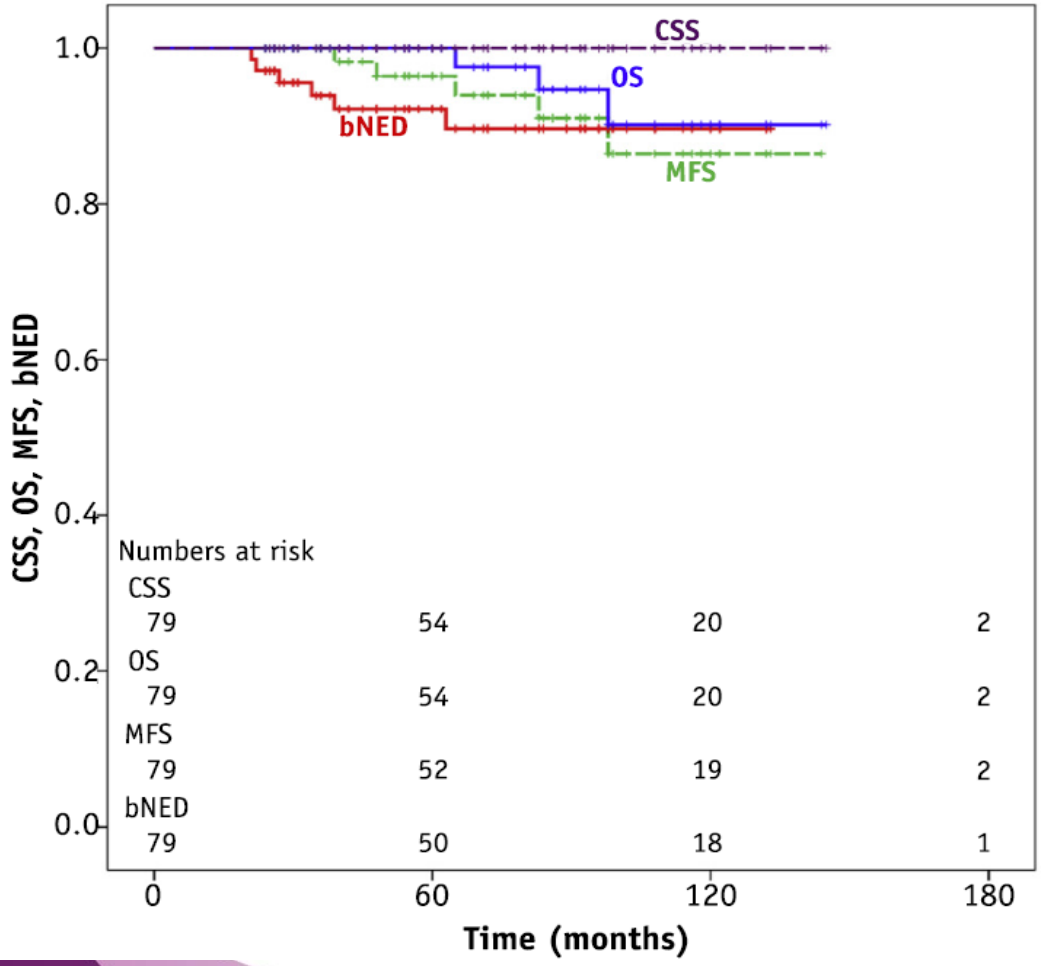
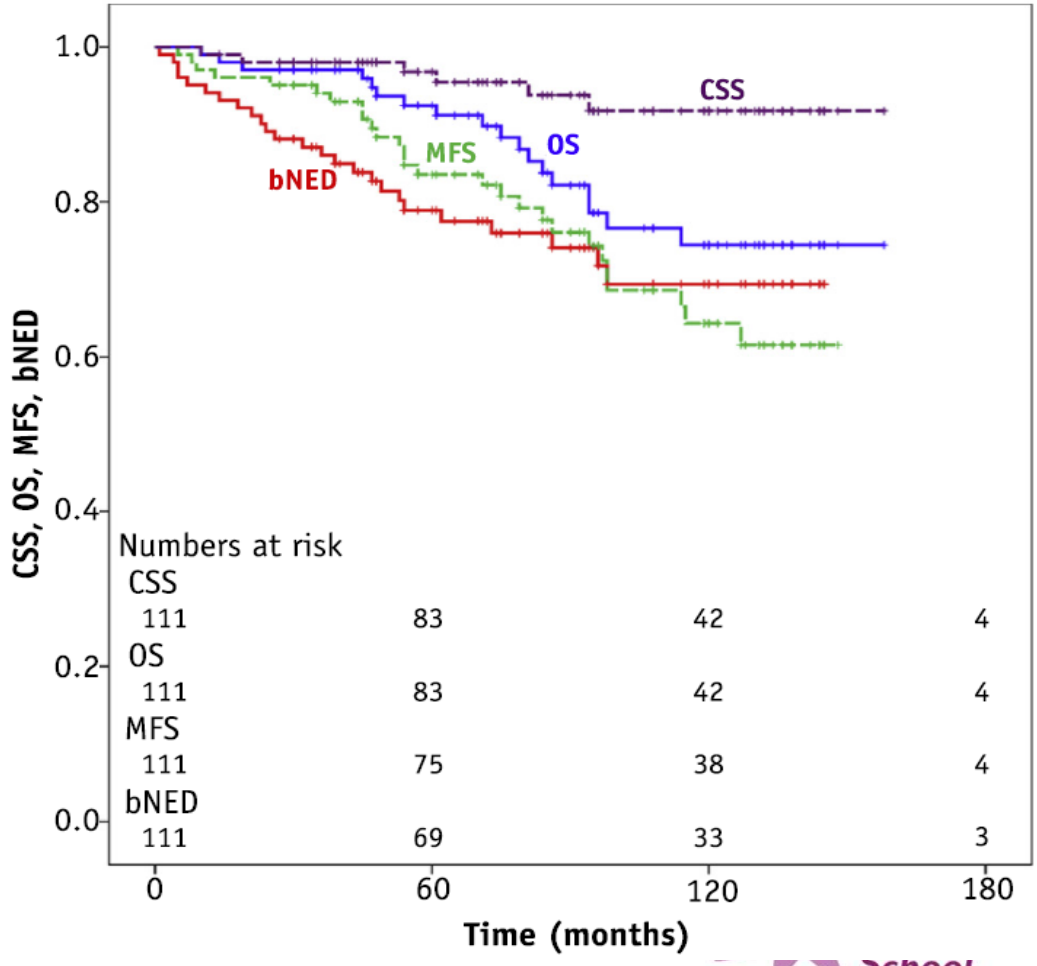
Intermediate risk



High risk



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	Acute toxicity grade			Late toxicity grade		
Toxicity	2	3	4	2	3	4
Genitourinary toxicity						
Hematuria	4 (2)	1 (1)	0	3 (2)	1 (1)	0
Urethral injury	0	1 (1)	0	—	—	—
Urinary incontinence	—	—	—	2 (1)	0	0
Urinary frequency /urgency	15 (8)	0	0	5 (3)	0	0
Urinary retention	8 (4)	0	0	3 (2)	0	0
Urinary tract obstruction	—	—	—	3 (2)	1 (1)	0
Urinary tract pain	1 (1)	0	0	2 (1)	0	0
Gastrointestinal toxicity						
Anal pain	3 (2)	0	0	—	—	—
Constipation	1 (1)	0	0	—	—	—
Rectal hemorrhage	—	—	—	7 (4)	0	0
Sigmoid colon perforation	—	—	—	0	1 (1)	0
Urethrorectal fistula	—	—	—	0	1 (1)	0
Other toxicity						
Thromboembolic event	0	1 (1)	0	—	—	—

ESTRO School

Published HDR monotherapy studies

High-dose-rate monotherapy disease control

First author	Year	*N*	Dose × fractions	Years median fu	Local control (%)	PSA-PFS low (%)	PSA-PFS interm. (%)	PSA-PFS high (%)
Barkati	2012	79	10–11.5 Gy × 3	3.3	99		88	n/a
Demanes	2010	157	7 Gy × 6	5.2	99		97	n/a
Ghadjar	2009	36	9.5 Gy × 4	3	n/a	100	100	n/a
Hoskins	2012	55	8.5–9 Gy × 4	4.5	n/a	n/a	95	87
		109	10.5 Gy × 3	3				
Komiya	2013	51	6.5 Gy × 7	1.5	n/a		96	
Mark	2010	317	7.5 Gy × 6	8	n/a		88	
Martinez	2010	141	9.5 Gy × 4	5.2	99	97		n/a
Prada	2012	40	19 Gy × 1	1.6	100	100	88	n/a
Rogers	2012	284	6 Gy × 6	3	100	n/a	94	n/a
Yoshioka	2011	111	6 Gy × 9	5.4	97	85	93	79
Zamboglou	2013	492	9.5 Gy × 4	4.4	n/a	95	93	93
		225	11.5 Gy × 3					

From Demanes and Ghilezan 2014

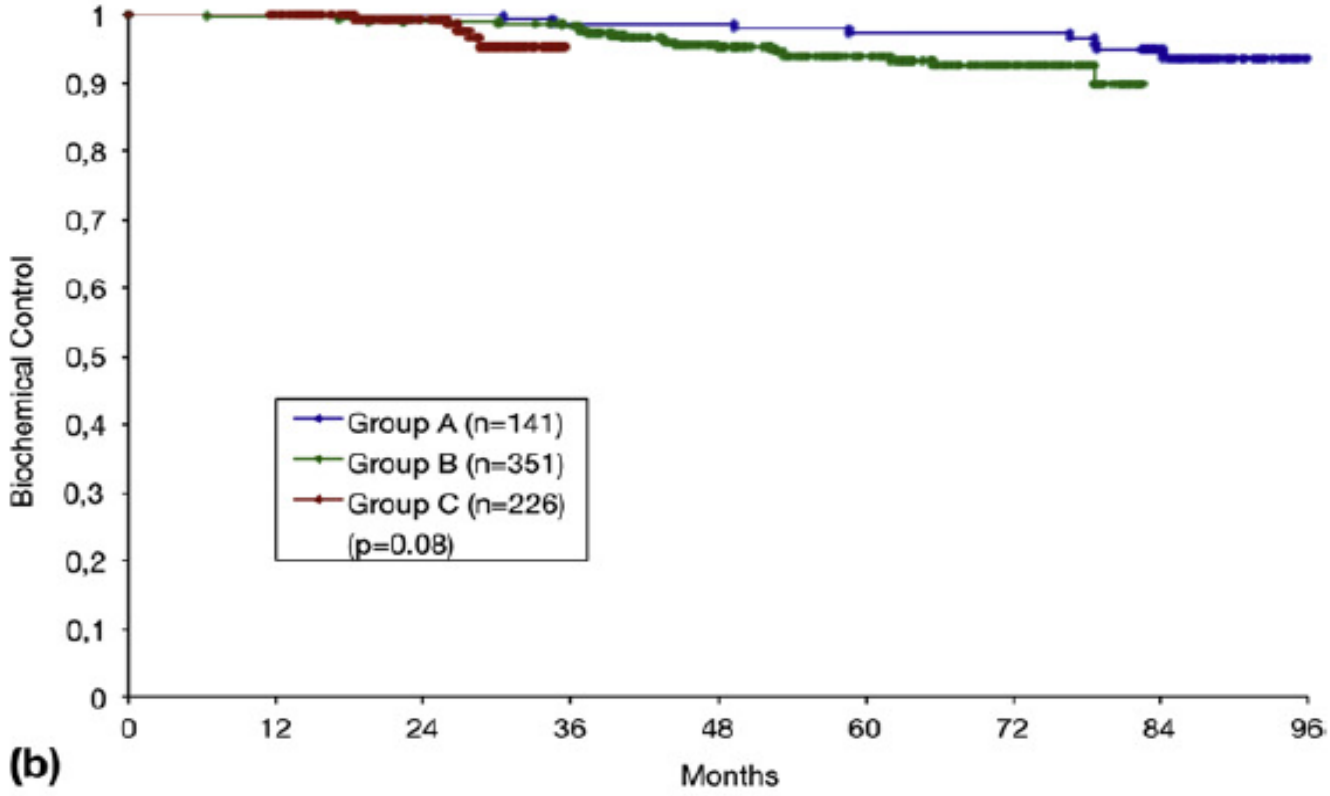
High-Dose-Rate Interstitial Brachytherapy as Monotherapy for Clinically Localized Prostate Cancer: Treatment Evolution and Mature Results

Nikolaos Zamboglou, MD, PhD,* Nikolaos Tselis, MD, PhD,* Dimos Baltas, PhD,† Thomas Buhleier, MD, PhD,* Thomas Martin, MD, PhD,‡ Natasa Milickovic, PhD,† Sokratis Papaioannou, MSc,† Hanns Ackermann, PhD,§ and Ulf W. Tunn, MD, PhD||

**Department of Radiation Oncology, Klinikum Offenbach, Offenbach, Germany; †Department of Medical Physics and Engineering, Klinikum Offenbach, Offenbach, Germany; ‡Department of Radiation Oncology, Klinikum Bremen-Mitte, Bremen, Germany; §Institute of Biostatistics, J.W. Goethe University of Frankfurt, Frankfurt, Germany; and ||Department of Urology, Klinikum Offenbach, Offenbach, Germany*

Int J Radiation Oncol Biol Phys, Vol. 85, No. 3, pp. 672–678, 2013

718 patients: 38Gy/4f/48hrs
38Gy/4f/15days
34.5Gy/3f/6weeks



ESTRO School

High Dose Rate Brachytherapy as Monotherapy for Localised Prostate Cancer: Review of the Current Status

N. Tselis *, P. Hoskin †, D. Baltas ‡, V. Strnad §, N. Zamboglou *, C. Rödel *, G. Chatzikonstantinou *

Clinical Oncology 29 (2017) 401–411

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
		6.0 Gy	9 (1 implant)	54.0 Gy				
		6.5 Gy	7 (1 implant)	45.5 Gy				
[8]	448	7.0–7.25 Gy	6 (2 implants)	42–43.5 Gy	6.5	98.9% LR, 95.2% IR at 10 years	238–253	102–108
[9]	494	9.5 Gy	4 (1 implant)	38.0 Gy	4.1	98% LR, 95% IR at 5 years	270–279	115–119
		12.0 Gy	2 (1–2 implants)	24.0 Gy		92% LR, 81% IR at 5 years		
		13.5 Gy	2 (1–2 implants)	27.0 Gy		100% LR,79% IR at 5 years		
[50]	60	19.0 Gy	1 (1 implant)	19.0 Gy	6.0	66% LR, 63% IR at 6 years	260	111
[32]	77	15.0 Gy	3 (3 implants)	45.0 Gy	4.7	96.7% all risk groups at 5 years	495	212
[34]	51	6.5 Gy	7 (1 implant)	45.5 Gy	1.4	94% all risk groups at 17 months	243	104
[5]	197	8.5–9.0 Gy	4 (1 implant)	34–36.0 Gy	3.1	95% IR, 87% HR at 4 years	227–252	97–108
		10.5 Gy	3 (1 implant)	31.5 Gy				
		13.0 Gy	2 (1 implant)	26.0 Gy				
[53]	284	6.5 Gy	6 (2 implants)	39.0 Gy	2.7	94% IR at 5 years	208	89
[33]	718	9.5 Gy	4 (1 implant)	38.0 Gy	4.4	95% LR, 93% IR, 93% HR at 5 years	279–299	119–128
		9.5 Gy	4 (2 implants)	38.0 Gy				
		11.5 Gy	3 (3 implants)	34.5 Gy				
[56]	79	10–11.5 Gy	3 (1 implant)	30–34.5 Gy	3.3	85.1% LR/IR at 5 years	230–299	99–128
[38]	298	7.0 Gy	6 (2 implants)	42.0 Gy	5.2	97% LR/IR at 5 years	238–279	102–119
		9.5 Gy	4 (1 implant)	38.0 Gy				
[55]	301	7.5 Gy	6 (2 implants)	45.0 Gy	8.0	88% all risk groups at 8 years	270	117
[57]	248	7.0 Gy	6 (2 implants)	42.0 Gy	4.8	87% LR/IR at 5 years	238–279	102–119
		9.5 Gy	4 (1 implant)	38.0 Gy		91% LR/IR at 5 years		
[58]	36	9.5 Gy	4 (1 implant)	38.0 Gy	3.0	100% LR/IR at 3 years	279	119
[54]	65	9.5 Gy	4 (1 implant)	38.0 Gy	2.9	98% LR/IR at 3 years	279	119

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
		6.0 Gy	9 (1 implant)	54.0 Gy				
		6.5 Gy	7 (1 implant)	45.5 Gy				
[8]	448	7.0–7.25 Gy	6 (2 implants)	42–43.5 Gy	6.5	98.9% LR, 95.2% IR at 10 years	238–253	102–108
[9]	494	9.5 Gy	4 (1 implant)	38.0 Gy	4.1	98% LR, 95% IR at 5 years	270–279	115–119
		12.0 Gy	2 (1–2 implants)	24.0 Gy		92% LR, 81% IR at 5 years		
		13.5 Gy	2 (1–2 implants)	27.0 Gy		100% LR,79% IR at 5 years		
[50]	60	19.0 Gy	1 (1 implant)	19.0 Gy	6.0	66% LR, 63% IR at 6 years	260	111
[32]	77	15.0 Gy	3 (3 implants)	45.0 Gy	4.7	96.7% all risk groups at 5 years	495	212
[34]	51	6.5 Gy	7 (1 implant)	45.5 Gy	1.4	94% all risk groups at 17 months	243	104
[5]	197	8.5–9.0 Gy	4 (1 implant)	34–36.0 Gy	3.1	95% IR, 87% HR at 4 years	227–252	97–108
		10.5 Gy	3 (1 implant)	31.5 Gy				
		13.0 Gy	2 (1 implant)	26.0 Gy				
[53]	284	6.5 Gy	6 (2 implants)	39.0 Gy	2.7	94% IR at 5 years	208	89
[33]	718	9.5 Gy	4 (1 implant)	38.0 Gy	4.4	95% LR, 93% IR, 93% HR at 5 years	279–299	119–128
		9.5 Gy	4 (2 implants)	38.0 Gy				
		11.5 Gy	3 (3 implants)	34.5 Gy				
[56]	79	10–11.5 Gy	3 (1 implant)	30–34.5 Gy	3.3	85.1% LR/IR at 5 years	230–299	99–128
[38]	298	7.0 Gy	6 (2 implants)	42.0 Gy	5.2	97% LR/IR at 5 years	238–279	102–119
		9.5 Gy	4 (1 implant)	38.0 Gy				
[55]	301	7.5 Gy	6 (2 implants)	45.0 Gy	8.0	88% all risk groups at 8 years	270	117
[57]	248	7.0 Gy	6 (2 implants)	42.0 Gy	4.8	87% LR/IR at 5 years	238–279	102–119
		9.5 Gy	4 (1 implant)	38.0 Gy		91% LR/IR at 5 years		
[58]	36	9.5 Gy	4 (1 implant)	38.0 Gy	3.0	100% LR/IR at 3 years	279	119
[54]	65	9.5 Gy	4 (1 implant)	38.0 Gy	2.9	98% LR/IR at 3 years	279	119

1#: 1
2#: 3
3#: 4
4#: 8
6#: 5
≥7: 4

15: 1 implant

4.5yr

LR: 95%
IR: 85%
HR: 80+%

100-120Gy EQD2

Late toxicity data of high dose rate monotherapy for localised prostate cancer

Reference	*n*	High dose rate protocol			Toxicity			
		Gy/fraction	Fractions (implants)	Total	Genitourinary grade 2 (%)	Genitourinary grade 3 (%)	Gastrointestinal grade 2 (%)	Gastrointestinal grade 3 (%)
[7]	190	6.0 Gy	8 (1 implant)	48.0 Gy	6	2	4	2
		6.0 Gy	9 (1 implant)	54.0 Gy				
		6.5 Gy	7 (1 implant)	45.5 Gy				
[8]	448	7.0–7.25 Gy	6 (2 implants)	42–43.5 Gy	–	4.7	–	0
[9]	494	9.5 Gy	4 (1 implant)	38.0 Gy	20	1	2	0
		12.0 Gy	2 (1–2 implants)	24.0 Gy				
		13.5 Gy	2 (1–2 implants)	27.0 Gy				
[50]	60	19.0 Gy	1 (1 implant)	19.0 Gy	0	0	0	0
[32]	77	15.0 Gy	3 (3 implants)	45.0 Gy	25	0	0	0
[34]	51	6.5 Gy	7 (1 implant)	45.5 Gy	QoL (IPSS, FACT–P & IIEF) at baseline after 12 weeks			
[5]	197	8.5–9.0 Gy	4 (1 implant)	34–36.0 Gy	33–40*	3–16*	4–13*	0–1*
		10.5 Gy	3 (1 implant)	31.5 Gy		3–6 strictures		
		13.0 Gy	2 (1 implant)	26.0 Gy				
[53]	284	6.5 Gy	6 (2 implants)	39.0 Gy	1.5	0.6	0	0
[33]	718	9.5 Gy	4 (1 implant)	38.0 Gy	15.6	9.2	0	0.7
		9.5 Gy	4 (2 implants)	38.0 Gy	16.5	4.8	1.7	0
		11.5 Gy	3 (3 implants)	34.5 Gy	17.6	3.9	3.5	0
[51]	50	12.0 Gy	2 (1 implant)	24.0 Gy	16	1	1	1
		13.5 Gy	2 (1 implant)	27.0 Gy				
[56]	79	10–11.5 Gy	3 (1 implant)	30–34.5 Gy	2–6	2–4	0–3	0
[38]	298	7.0 Gy	6 (2 implants)	42.0 Gy	10	3	1	0
		9.5 Gy	4 (1 implant)	38.0 Gy				
[55]	301	7.5 Gy	6 (2 implants)	45.0 Gy	3.2	0	1.3	1
[57]	248	7.0 Gy	6 (2 implants)	42.0 Gy	0.5–13	0.5–3	0–1	0–0.5
		9.5 Gy	4 (1 implant)	38.0 Gy	0.5 strictures	3 strictures		
[58]	36	9.5 Gy	4 (1 implant)	38.0 Gy	25	11	6	0
[54]	65	9.5 Gy	4 (1 implant)	38.0 Gy	3–15	0–3	0	0
[62]	170	19.0 Gy	1 (1 implant)	19.0 Gy	31	1.7	3	0
		13.5 Gy	2 (2 implant)	27.0 Gy				

GU: 14% G2
3-6% strictures
3.5% G3

GI: negligible

ESTRO School

HIGH-DOSE-RATE BRACHYTHERAPY AS A MONOTHERAPY FOR FAVORABLE-RISK PROSTATE CANCER: A PHASE II TRIAL

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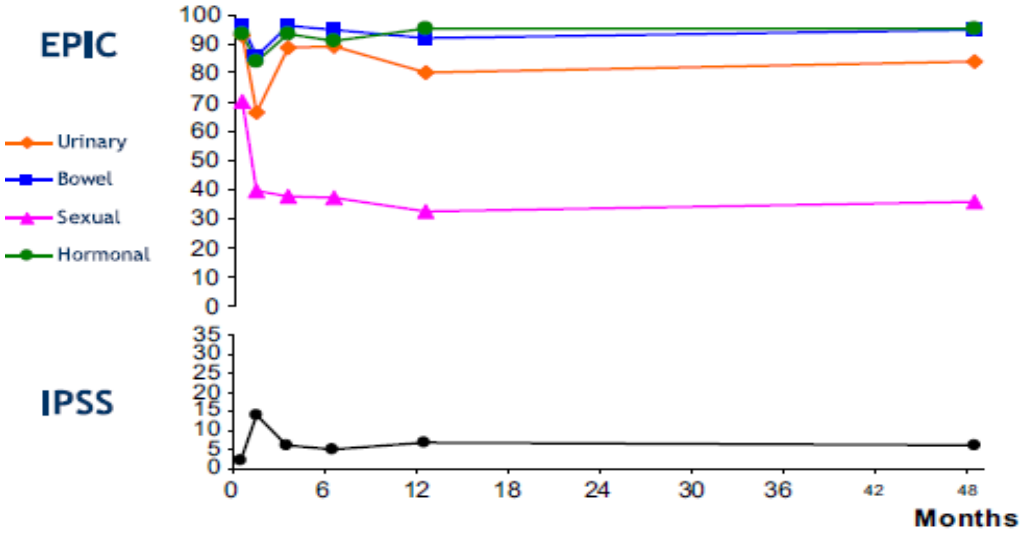
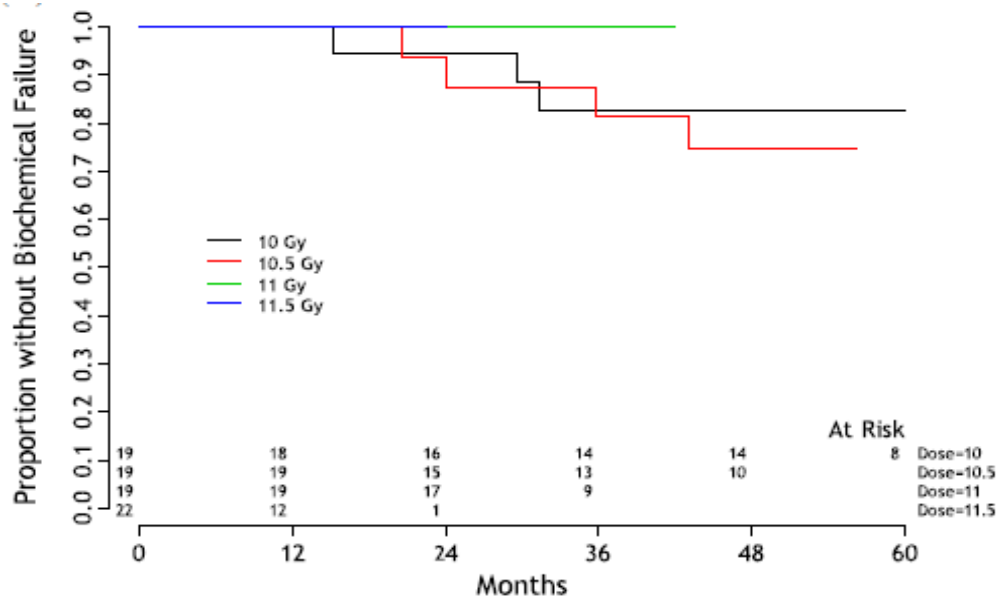
FARSHAD FOROUDI, F.R.A.N.Z.C.R.,*‡ KEEN HUN TAI, F.R.A.N.Z.C.R.,*‡
SARAT CHANDER, F.R.A.N.Z.C.R.,*‡ SYLVIA VAN DYK, D.APP.SC.,* ANDREW SEE, F.R.A.N.Z.C.R.,†
AND GILLIAN M. DUCHESNE, M.D., F.R.C.R., F.R.A.N.Z.C.R.*‡

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1889–1896, 2012

Characteristic	Grade or score	No. of patients or test value (range)
No. of patients		79
Median age (range)		66 (47–77)
T stage	1c	34
	2a	23
	2b	18
	2c	4
PSA at diagnosis (ng/ml)	Mean	6.8
	Median	6.8
	Range	2–10
Gleason score	5	1
	6	38
	7	40
Neoadjuvant hormone therapy	Yes	7
	No	72
Brachytherapy dose level	3 × 10 Gy	19
	3 × 10.5 Gy	19
	3 × 11Gy	19
	3 × 11.5 Gy	22





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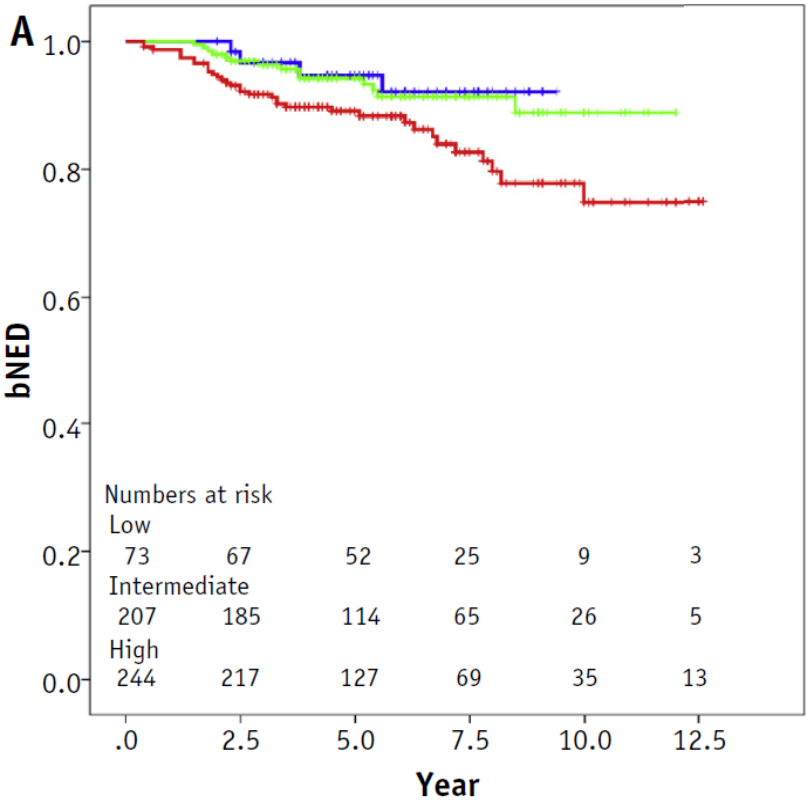
Nationwide, Multicenter, Retrospective Study on High-Dose-Rate Brachytherapy as Monotherapy for Prostate Cancer

Yasuo Yoshioka, MD,* Tadayuki Kotsuma, MD,† Akira Komiya, MD,‡,§ et al

Int J Radiation Oncol Biol Phys, Vol. 97, No. 5, pp. 952–961, 2017

1995-2013 5 institutions
524 patients
73 low, 207 inter, 244 high risk
Median follow up: 5.9 years

27Gy/2f: 13%
45.5Gy/7f: 32%
49Gy/7f: 28%
54Gy/9f: 25%



Toxicity	Acute toxicity grade 2	3	4	Late toxicity grade 2	3	4
Genitourinary toxicity						
Hematuria	18 (3)	1 (0.2)	0	18 (3)	3 (1)	0
Urinary frequency/ urgency	35 (7)	0	0	35 (7)	0	0
Urinary incontinence	2 (0.4)	0	0	11 (2)	0	0
Urethral injury	0	1 (0.2)	0	-	-	-
Urinary retention	14 (3)	0	0	5 (1)	0	0
Urinary tract obstruction	28 (5)	0	0	28 (5)	9 (2)	0
Urinary tract pain	8 (2)	1 (0.2)	0	8 (2)	0	0
Gastrointestinal toxicity						
Constipation	1 (0.2)	0	0	-	-	-
Proctitis	2 (0.4)	0	0	1 (0.2)	0	0
Rectal hemorrhage	1 (0.2)	0	0	11 (2)	0	0
Rectal obstruction	-	-	-	0	1 (0.2)	0
Rectal pain	1 (0.2)	0	0	-	-	-
Urethrorectal fistula	-	-	-	0	1 (0.2)	0
Other toxicity						
Thromboembolic event	0	1 (0.2)	0	-	-	-

ESTRO School

- HDR monotherapy:
  - how many fractions
  - can we give a single dose

HIGH-DOSE-RATE BRACHYTHERAPY AS MONOTHERAPY DELIVERED IN TWO FRACTIONS WITHIN ONE DAY FOR FAVORABLE/INTERMEDIATE-RISK PROSTATE CANCER: PRELIMINARY TOXICITY DATA

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Department of Radiation Oncology, William Beaumont Hospital and Rose Cancer Institute, Royal Oak, MI

doi:10.1016/j.ijrobp.2011.05.001

173 patients: low/intermeduiate risk

Median follow up 17 months

50: 12Gy x 2

49: 13.5Gy x 2

		Toxicity grade				
Toxicity	Total	0	1	2	3	4
Gastrointestinal						
Diarrhea	99	77 (91.7)	7 (8.3)	0	0	0
Rectal bleeding	99	84 (100)	0	0	0	0
Proctitis	99	83 (100)	0	0	0	0
Rectal pain/tenesmus	99	52 (100)	0	0	0	0
Rectal fistula	99	92 (100)	0	0	0	0
Anal fissure	99	84 (100)	0	0	0	0
Genitourinary						
Dysuria	99	67 (77.9)	15 (17.4)	4 (4.7)	0	0
Frequency/urgency	99	39 (45.9)	34 (40)	11 (12.9)	1 (1.2)	0
Retention	99	75 (88.2)	9 (10.6)	1 (1.2)	0	0
Incontinence	99	85 (100)	0	0	0	0
Hematuria	99	81 (96.4)	1 (1.2)	2 (2.4)	0	0
Urethral stricture	99	80 (96.4)	3 (3.6)	0	0	0

HIGH-DOSE-RATE BRACHYTHERAPY ALONE FOR LOCALIZED PROSTATE CANCER IN PATIENTS AT MODERATE OR HIGH RISK OF BIOCHEMICAL RECURRENCE

PETER HOSKIN, M.D., ANA ROJAS, PH.D., GERRY LOWE, MSC., LINDA BRYANT, D.C.R. (T.), PETER OSTLER, F.R.C.R., ROB HUGHES, F.R.C.R., JESSICA MILNER, B.SC., AND HELEN CLADD, B.SC.

Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex, United Kingdom

doi:10.1016/j.ijrobp.2011.04.031

Variable	Category	26 Gy $n = 33$	31.5 Gy $n = 109$	34 Gy $n = 30$	36 Gy $n = 25$	All $n = 197$
Age (y)	Median	73	69	68	67	69
	Range	61–80	55–81	60–77	57–77	55–81
Follow-up (months)	Median	6	34	54	60	37
	Range	2–13	16–50	42–58	37–72	2–72
T stage	T1–2a	10 (30)	24 (22)	17 (57)	10 (40)	61 (31)
	T2b–2c	15 (46)	66 (61)	6 (20)	7 (28)	94 (48)
	≥T3	8 (24)	19 (17)	7 (23)	8 (32)	42 (21)
Gleason	<7	5 (15)	30 (27)	11 (37)	6 (24)	52 (26)
	7	21 (64)	73 (67)	15 (50)	16 (64)	125 (64)
	≥8	7 (21)	6 (6)	4 (13)	3 (12)	20 (10)
PSA $\mu g/l$	<10	13 (39.4)	43 (39)	11 (37)	10 (40)	77 (39)
	10–20	13 (39.4)	38 (35)	12 (40)	8 (32)	71 (36)
	>20	7 (21.2)	28 (26)	7 (23)	7 (28)	49 (25)
Risk group	Low	0	2 (2)	5 (17)	1 (4)	8 (4)
	Intermediate	19 (58)	61 (56)	14 (47)	9 (36)	103 (52)
	High	14 (42)	46 (42)	11 (37)	15 (60)	86 (44)
ADT duration (months)	N	25	96	17	19	157
	Median	6	6	17.3	19	6.3
	Range	3–36	1–37	3–36	1–40	1–40
IPSS ($n = 177$)	Median	6	6.5	5	3	6
	Range	0–24	0–27	0–22	0–21	0–27

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HDR implant: biological advantage EQD2Gy

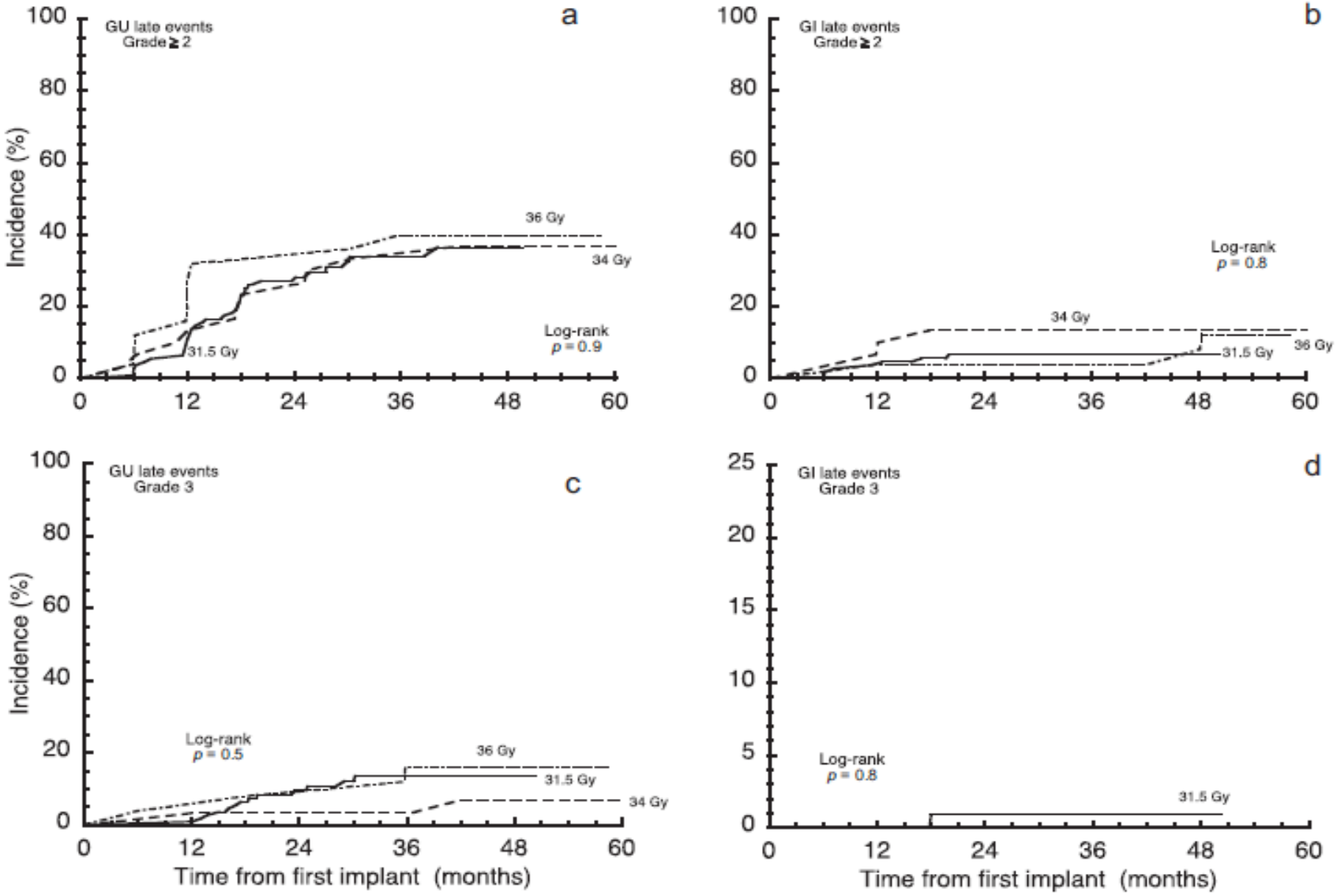
	α/β 10	α/β 1.5	α/β 3.5
Ext beam			
74Gy/37f	74	74	74
HDR mono			
34Gy/4f	96.9	74.2	52.4
36Gy/4f	108	81.8	57.0
31.5Gy/3f	108	80.2	53.8
26Gy/2f	108	78.0	49.8

ESTRO School

HIGH-DOSE-RATE BRACHYTHERAPY ALONE FOR LOCALIZED PROSTATE CANCER IN PATIENTS AT MODERATE OR HIGH RISK OF BIOCHEMICAL RECURRENCE

doi:10.1016/j.ijrobp.2011.04.031

Late toxicity (>6 months)

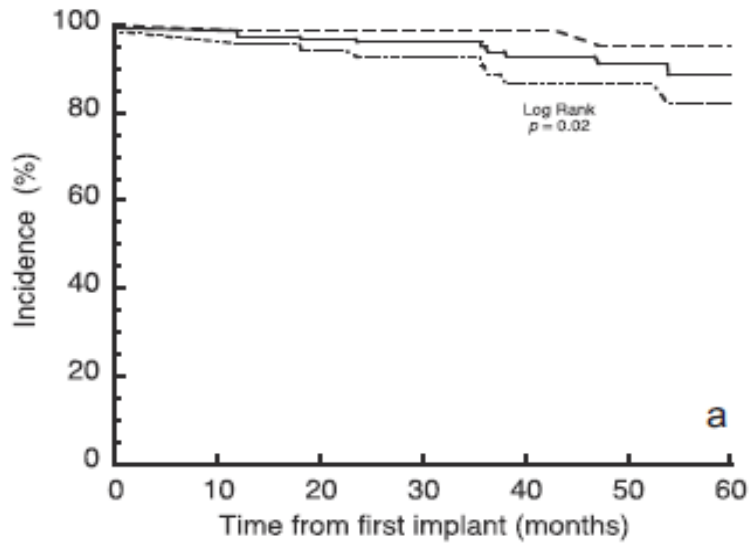


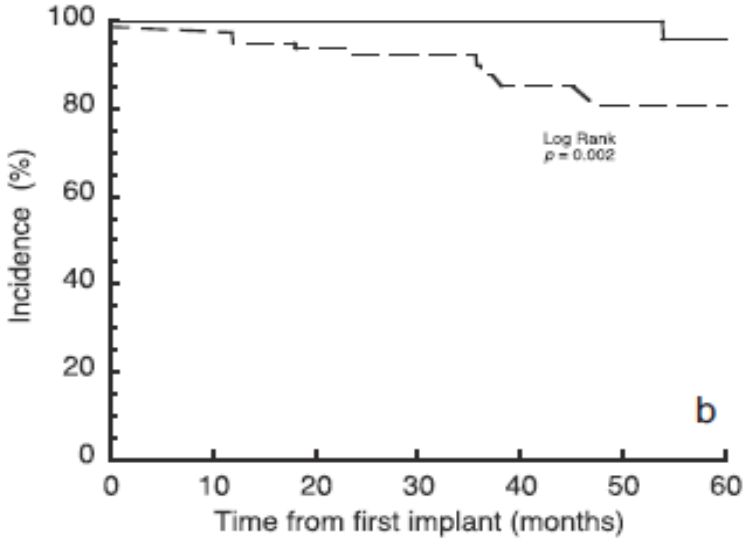
ESTRO School

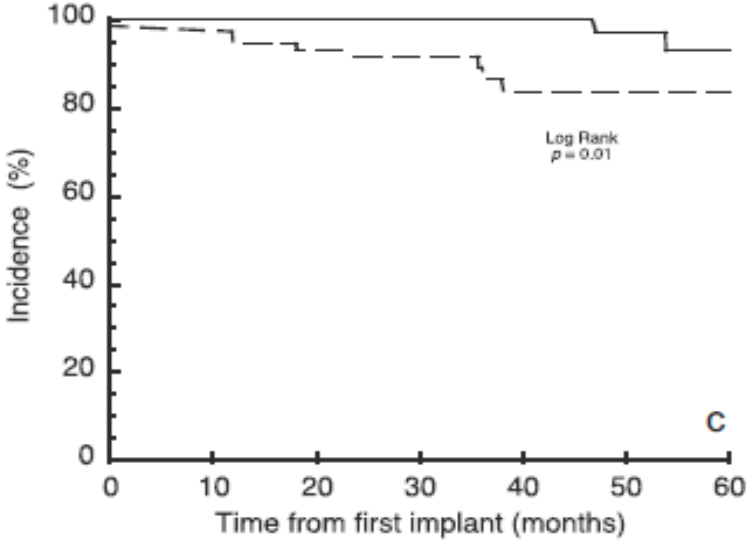
HIGH-DOSE-RATE BRACHYTHERAPY ALONE FOR LOCALIZED PROSTATE CANCER IN PATIENTS AT MODERATE OR HIGH RISK OF BIOCHEMICAL RECURRENCE

doi:10.1016/j.ijrobp.2011.04.031

Freedom from biochemical failure







d

Variable	Risk ratio	Lower CI	Upper CI	*p*
Dose	0.573	0.277	0.934	0.02
Risk group	0.182	0.026	0.848	0.03
TnPSA	0.855	0.722	0.944	0.0002
[nPSA]	4.971	2.123	12.856	< 0.0001

ESTRO School

Single dose HDR monotherapy

- **Biology**
  - Unknown!
    - ? Effect on vasculature as well as tumour cell
    - No reoxygenation, repair, reassortment,repopulation
- **Delivery**
  - High QA essential …..only one chance!
  - OAR tolerances more difficult to achieve

High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results

Radiotherapy and Oncology xxx (2016) xxx–xxx

Pedro J. Prada [a,*], Juan Cardenal [a], Ana García Blanco [a], Javier Anchuelo [a], María Ferri [a], Gema Fernández [c], Elisabeth Arrojo [c], Andrés Vázquez [b], Maite Pacheco [b], José Fernández [d]

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60 patients: inter 27%, low 73%
19Gy HDR single dose
Median follow up 72 months

Prospective follow up
CTCAE v4.0

Toxicity	Grade	Pretreatment *n* (%)	1 week* *n* (%)	3 months* *n* (%)	6 months* *n* (%)	Last toxicity+ *n* (%)
Urinary tract pain (Dysuria)	0	60 (100)	21 (35%)	56 (93)	57 (95)	60 (100)
	1	0 (0.0)	39 (65%)	4 (7)	3 (5)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract obstruction	0	15 (25)	13 (23)	44 (73)	44 (73)	44 (73)
	1	45 (75)	47 (77)	16 (27)	16 (27)	16 (27)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Incontinence	0	60 (100)	60 (100)	60 (100)	60 (100)	60 (100)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Frequency/urgency	0	42 (70)	41 (68)	44 (73)	51 (85)	56 (93)
	1	18 (30)	19 (32)	16 (27)	9 (15)	4 (7)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Retention	0	60 (100)	59 (98)	60 (100)	60 (100)	60 (100)
	1	0 (0.0)	1 (2)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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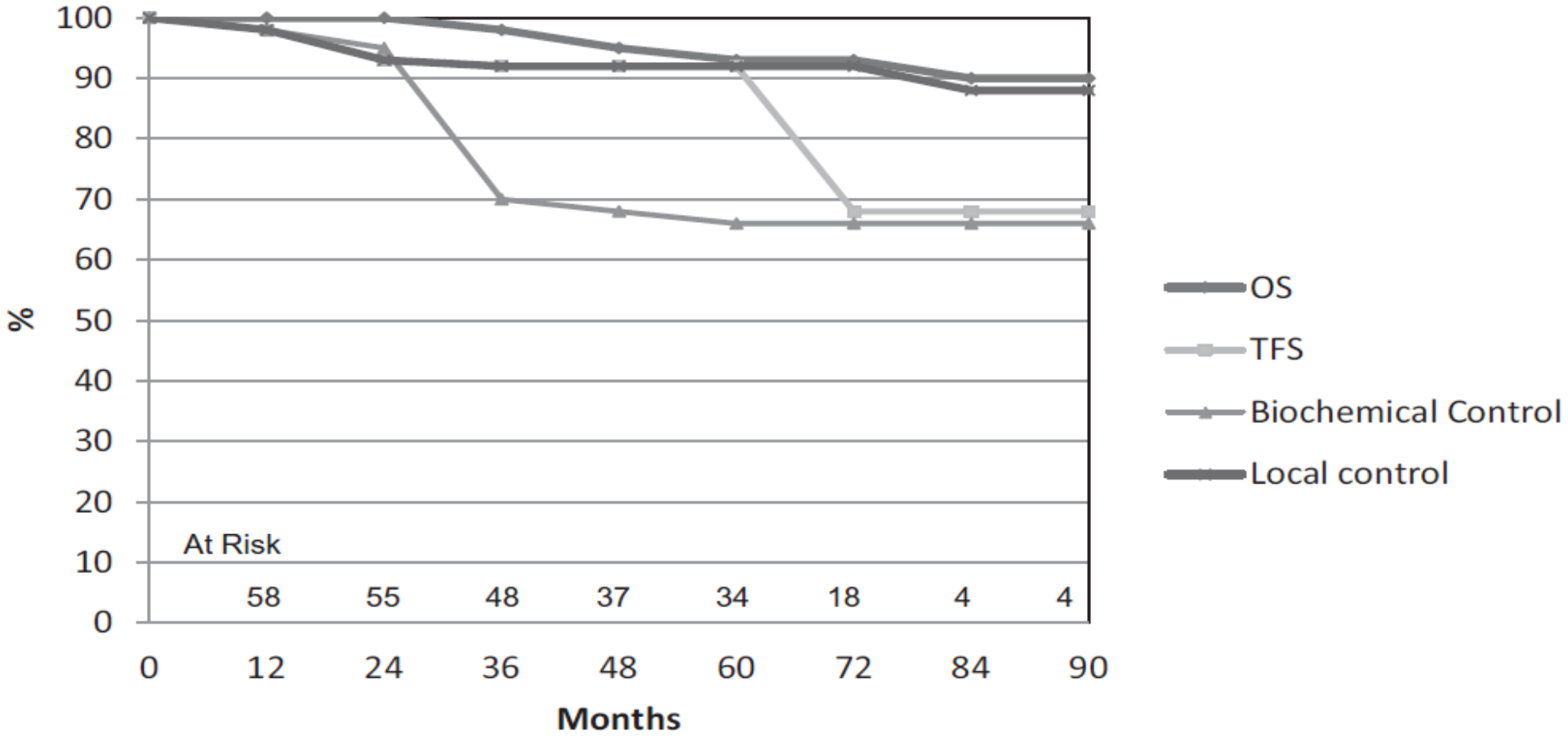
High-dose-rate interstitial brachytherapy as monotherapy in one fraction for the treatment of favorable stage prostate cancer: Toxicity and long-term biochemical results

Radiotherapy and Oncology xxx (2016) xxx–xxx

Pedro J. Prada [a,*], Juan Cardenal [a], Ana García Blanco [a], Javier Anchuelo [a], María Ferri [a], Gema Fernández [c], Elisabeth Arrojo [c], Andrés Vázquez [b], Maite Pacheco [b], José Fernández [d]

[a] *Department of Radiation Oncology;* [b] *Department of Radiation Physics, Hospital Universitario Marqués de Valdecilla, Santander;* [c] *Department of Radiation Oncology; and* [d] *Department of Radiation Physics, Hospital Universitario Central de Asturias, Oviedo, Spain*



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Favorable Preliminary Outcomes for Men With Low- and Intermediate-risk Prostate Cancer Treated With 19-Gy Single-fraction High-dose-rate Brachytherapy

Daniel J. Krauss, MD,* Hong Ye, MS,* Alvaro A. Martinez, MD,†
Beth Mitchell, RN,* Evelyn Sebastian, BS,* Amy Limbacher, BS RTT,*
and Gary S. Gustafson, MD*

Int J Radiation Oncol Biol Phys, Vol. 97, No. 1, pp. 98–106, 2017

Late ≤6 months

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Genitourinary (any)	26 (44.8)	7 (12.1)	0 (0)	0 (0)
Frequency/urgency	23 (39.7)	4 (6.9)	0 (0)	0 (0)
Dysuria	10 (17.2)	2 (3.4)	0 (0)	0 (0)
Retention	14 (24.1)	1 (1.7)	0 (0)	0 (0)
Incontinence	1 (1.7)	0 (0)	0 (0)	0 (0)
Hematuria	0 (0)	2 (3.4)	0 (0)	0 (0)
Gastrointestinal (any)	7 (12.1)	0 (0)	0 (0)	0 (0)
Diarrhea	3 (5.2)	0 (0)	0 (0)	0 (0)
Pain/tenesmus	1 (1.7)	0 (0)	0 (0)	0 (0)
Rectal bleeding	3 (5.2)	0 (0)	0 (0)	0 (0)
Proctitis	0 (0)	0 (0)	0 (0)	0 (0)

Favorable Preliminary Outcomes for Men With Low- and Intermediate-risk Prostate Cancer Treated With 19-Gy Single-fraction High-dose-rate Brachytherapy

Daniel J. Krauss, MD,* Hong Ye, MS,* Alvaro A. Martinez, MD,†
Beth Mitchell, RN,* Evelyn Sebastian, BS,* Amy Limbacher, BS RTT,*
and Gary S. Gustafson, MD*

Int J Radiation Oncol Biol Phys, Vol. 97, No. 1, pp. 98–106, 2017

Late ≥6 months

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Genitourinary (any)	26 (44.8)	6 (10.3)	0 (0)	0 (0)
Frequency/urgency	23 (39.7)	3 (5.2)	0 (0)	0 (0)
Dysuria	5 (8.6)	1 (1.7)	0 (0)	0 (0)
Retention	18 (31.0)	0 (0)	0 (0)	0 (0)
Incontinence	3 (5.2)	0 (0)	0 (0)	0 (0)
Hematuria	1 (1.7)	3 (5.2)	0 (0)	0 (0)
Gastrointestinal (any)	5 (12.1)	1 (1.7)	1 (1.7)	0 (0)
Diarrhea	4 (6.9)	0 (0)	1 (1.7)	0 (0)
Pain/tenesmus	0 (0)	0 (0)	0 (0)	0 (0)
Rectal bleeding	2 (3.4)	0 (0)	0 (0)	0 (0)
Proctitis	2 (3.4)	1 (1.7)	0 (0)	0 (0)

Favorable Preliminary Outcomes for Men With Low- and Intermediate-risk Prostate Cancer Treated With 19-Gy Single-fraction High-dose-rate Brachytherapy

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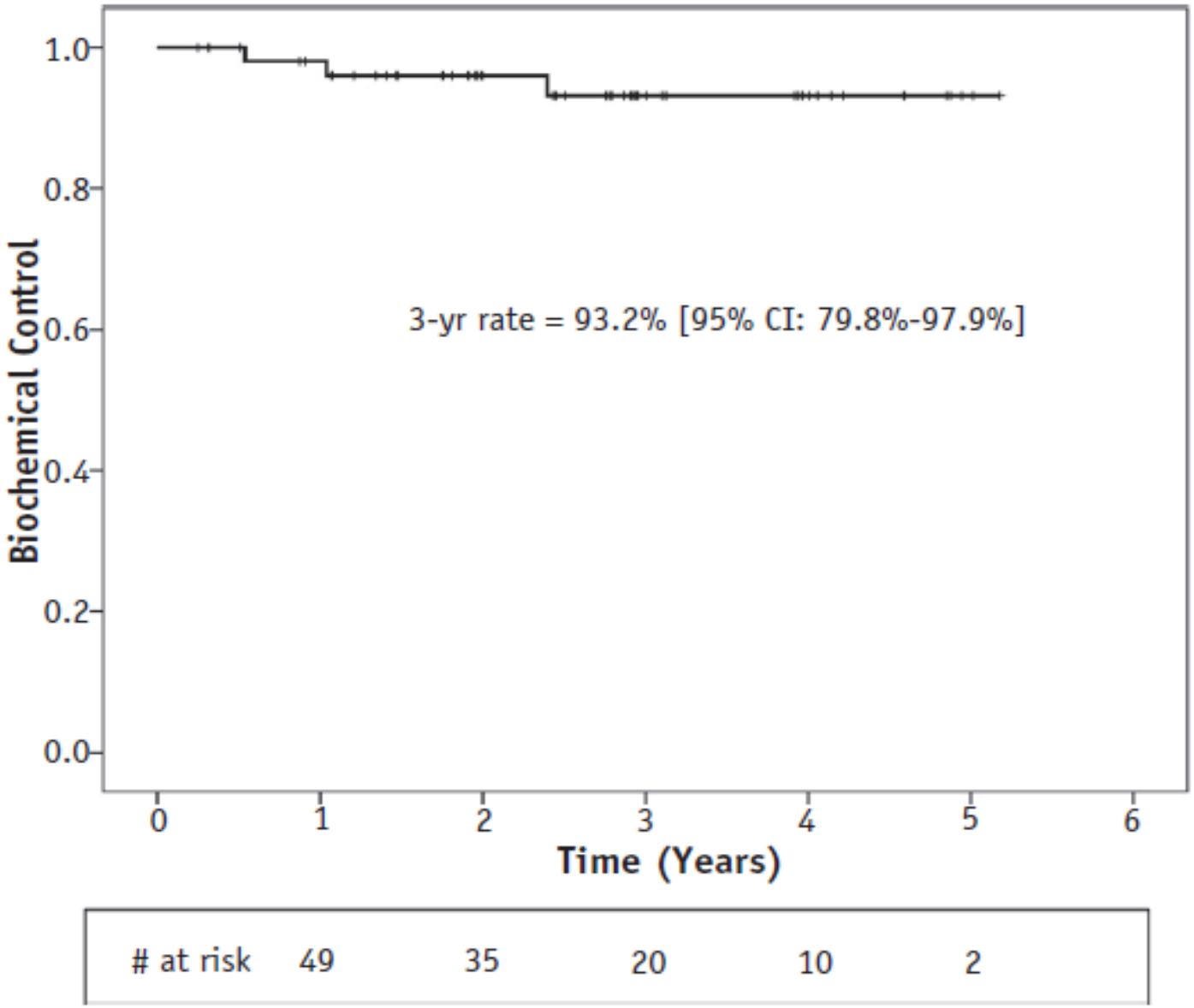


ESTRO School

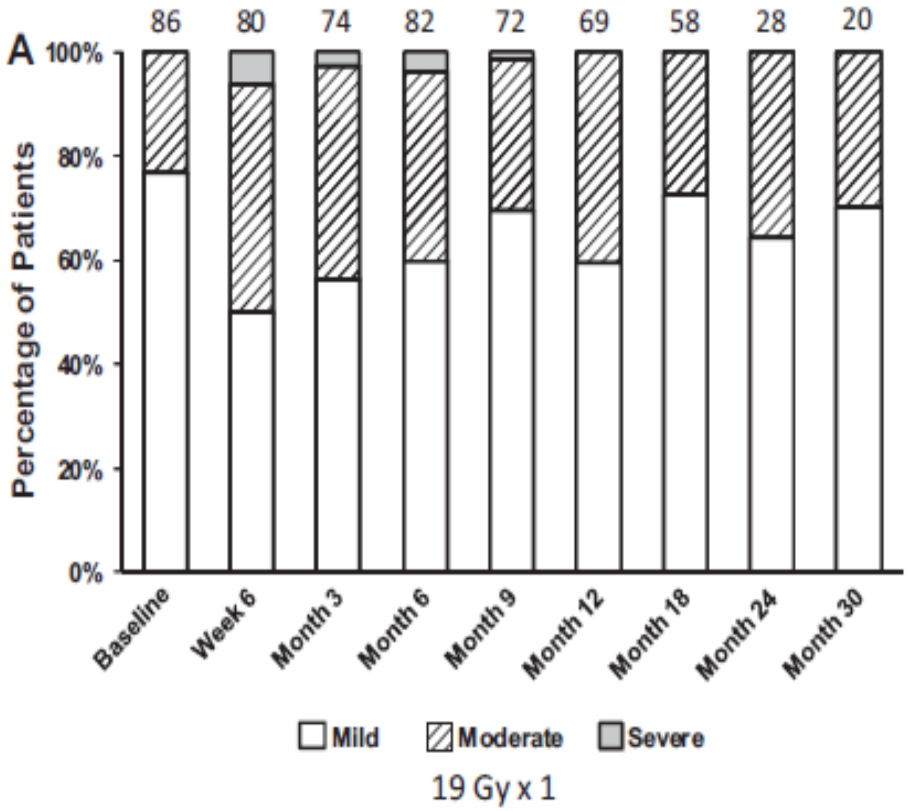
Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy

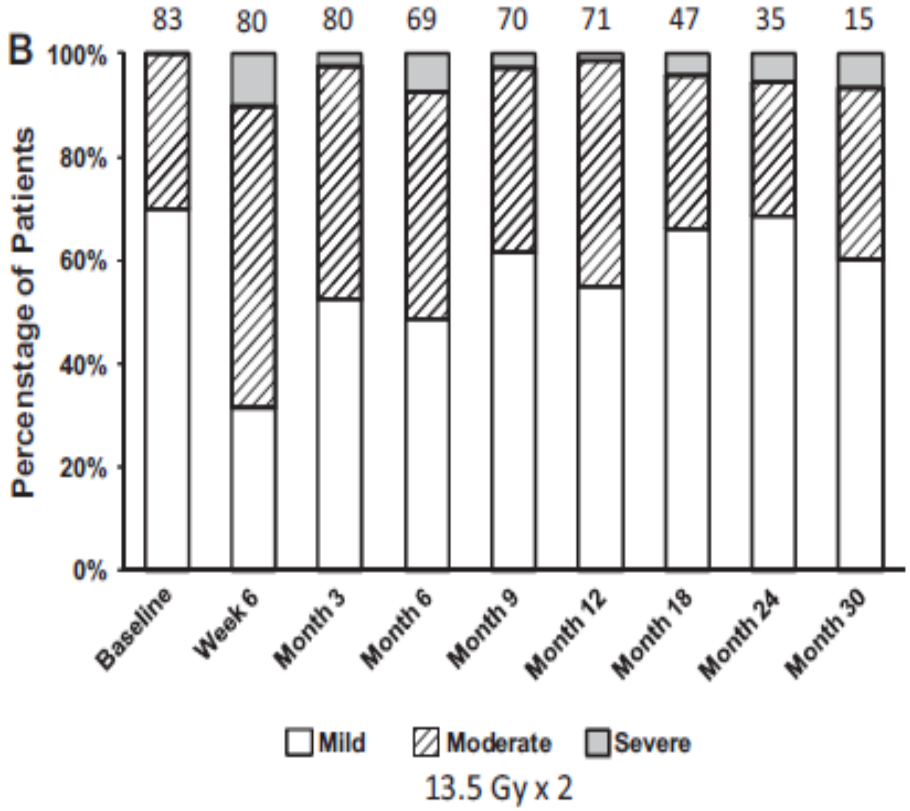
Radiotherapy and Oncology xxx (2016)

Gerard Morton *, Hans T. Chung, Merrylee McGuffin, Joelle Helou, Laura D'Alimonte, Ananth Ravi, Patrick Cheung, Ewa Szumacher, Stanley Liu, Motasem Al-Hanaqta, Liying Zhang, Alexandre Mamedov, Andrew Loblaw

170 patients; median follow up 20 months

IPSS





Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19 Gy or two fractions of 13.5 Gy

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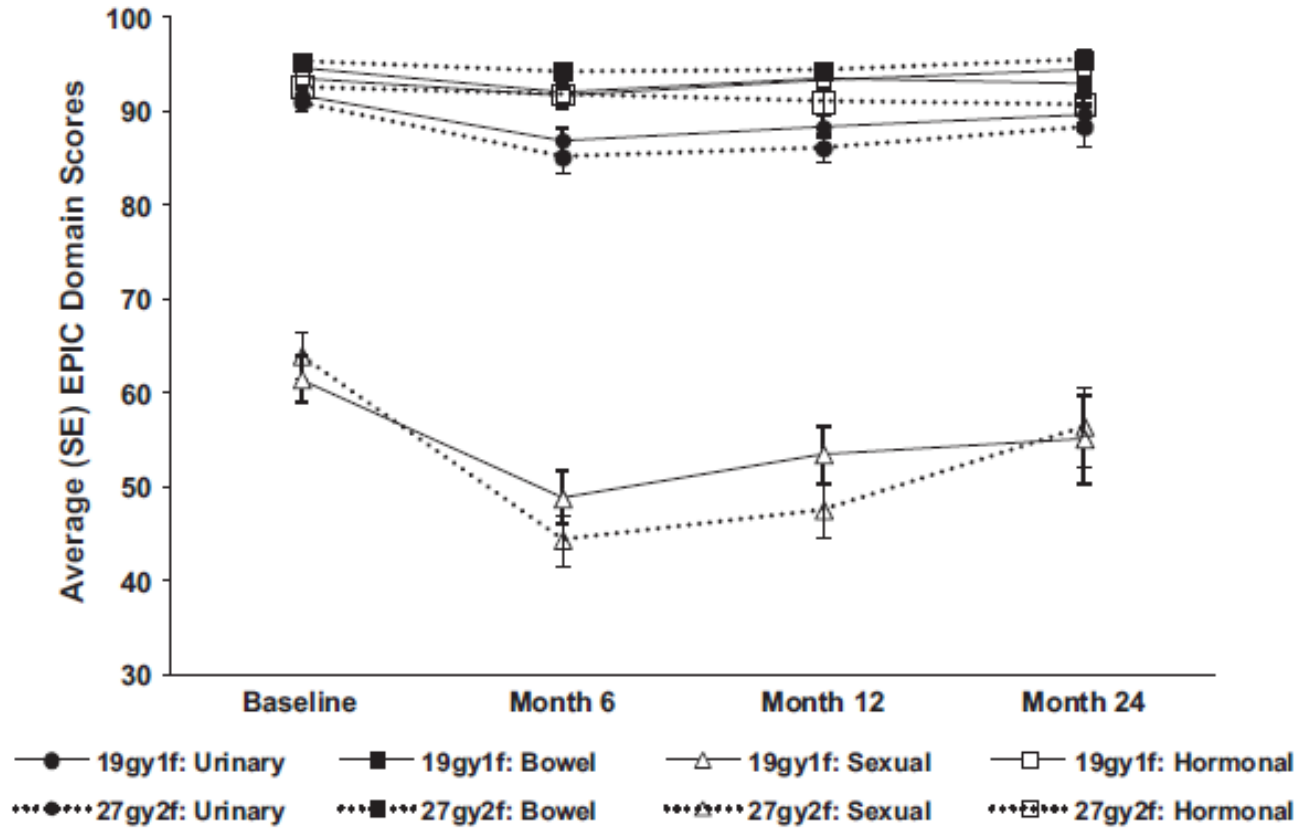

ESTRO School

Pattern of relapse and dose received by the recurrent intraprostatic nodule in low- to intermediate-risk prostate cancer treated with single fraction 19 Gy high-dose-rate brachytherapy

Lucas C. Mendez, Ananth Ravi, Hans Chung, Chia-Lin Tseng, Matt Wronski, Moti Paudel, Merrylee McGuffin, Patrick Cheung, Andrew Loblaw, Gerard Morton*

Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, Ontario, Canada

Brachytherapy 17 (2018) 291–297

N=87: median time to recurrence = 36 months

7/8 relapses in same sextant as original site of tumour

Pretreatment and posttreatment biopsy characteristics

Patients	Initial Gleason	Pattern 4 (%)	Post-BT Gleason	Pattern 4 (%)
1	3 + 3	0	4 + 3	95
2	3 + 3	0	3 + 4	15
3	3 + 4	NR	4 + 3	70
4	3 + 4	10	3 + 4	5
5	3 + 4	25	4 + 3	80
6	4 + 3	65	4 + 4	100
7	3 + 3	0	4 + 3	85
8	3 + 4	20	4 + 3	70

HDR-BT alone schedules

From 2005-2013, two hundred and ninety three patients enrolled:

- **19 Gy single dose: n = 23**
- **20 Gy single dose: n = 26**
- **26 Gy in 2 fractions: n = 138**
- **31.5 Gy in 3 fractions: n = 106**

Number of patients treated with single-doses is small,
Late morbidity and bRFI are similar……
……therefore the two groups were combined

***Group A** (19 Gy and 20 Gy), **Group B** (26 Gy) and **Group C** (31.5 Gy)*

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Late IPSS and catheter use

Dose	Follow-up (months)	n	IPSS ≥ 8 %	IPSS ≥ 20 %	n	Catheter use %
Group A SINGLE	24	42	43	10	40	5
	48	35	26	6	24	4
	60	5	60	20	2	0
Group B 13Gyx2	24	125	24	5	129	2
	48	98	24	3	93	1
	60	90	30	4	80	0
	72	57	35	9	48	0
Group C 10.5Gyx3	24	91	30	7	95	3
	48	88	22	6	91	1
	60	87	28	1	94	3
	72	94	29	4	95	2

Group A:1 x 19 and 1 x 20 Gy. Group B: 2 x 13 Gy. Group C:3 x 10.5 Gy

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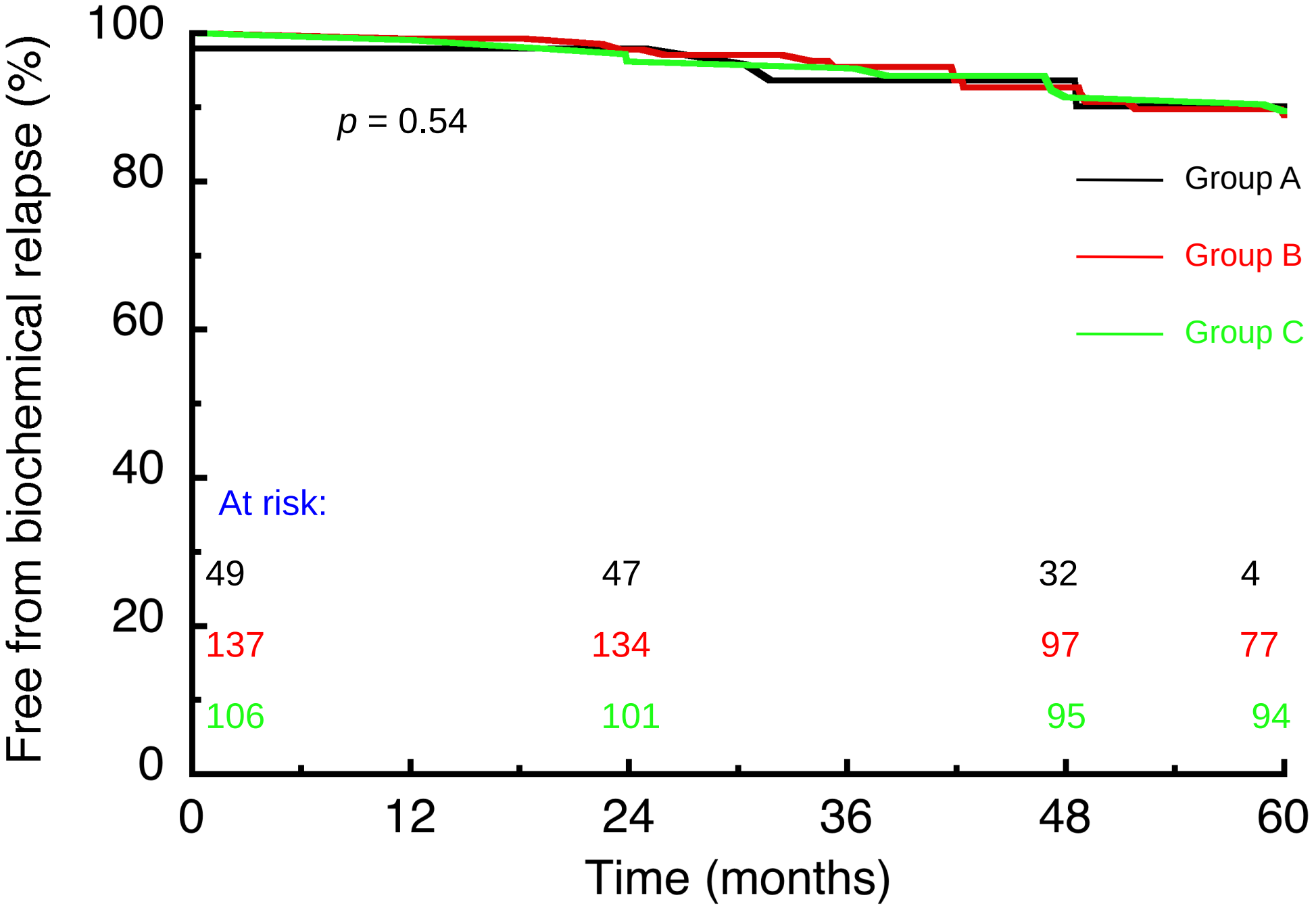
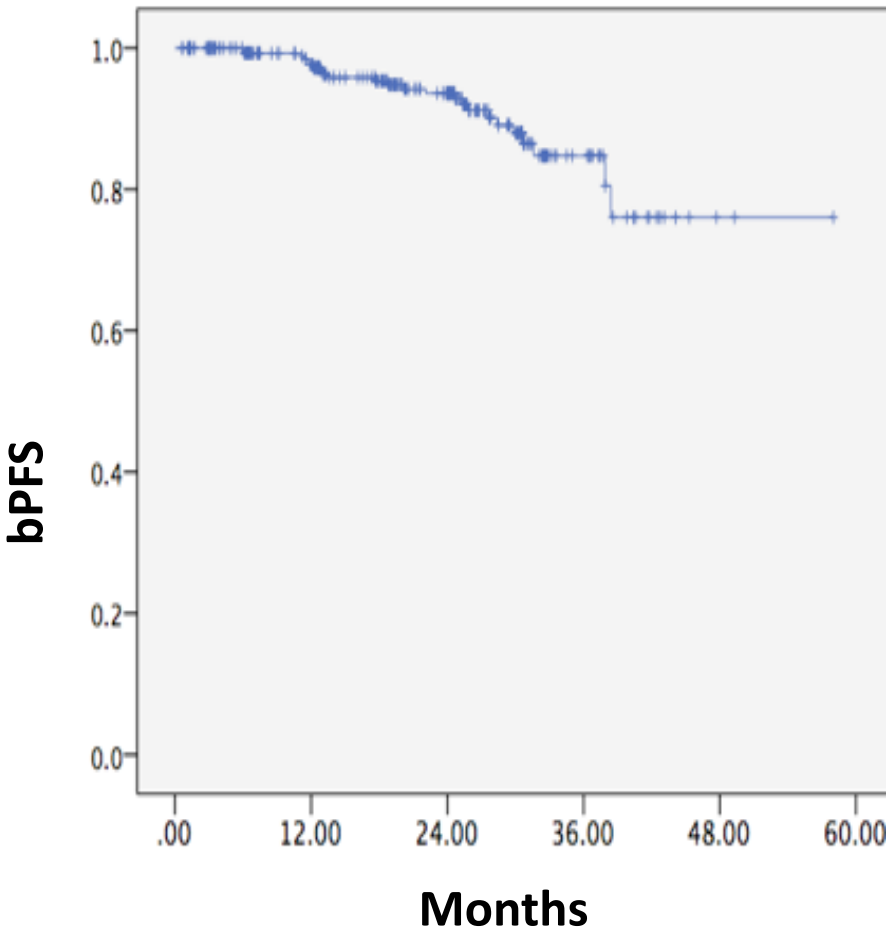
Biochemical relapse-free interval

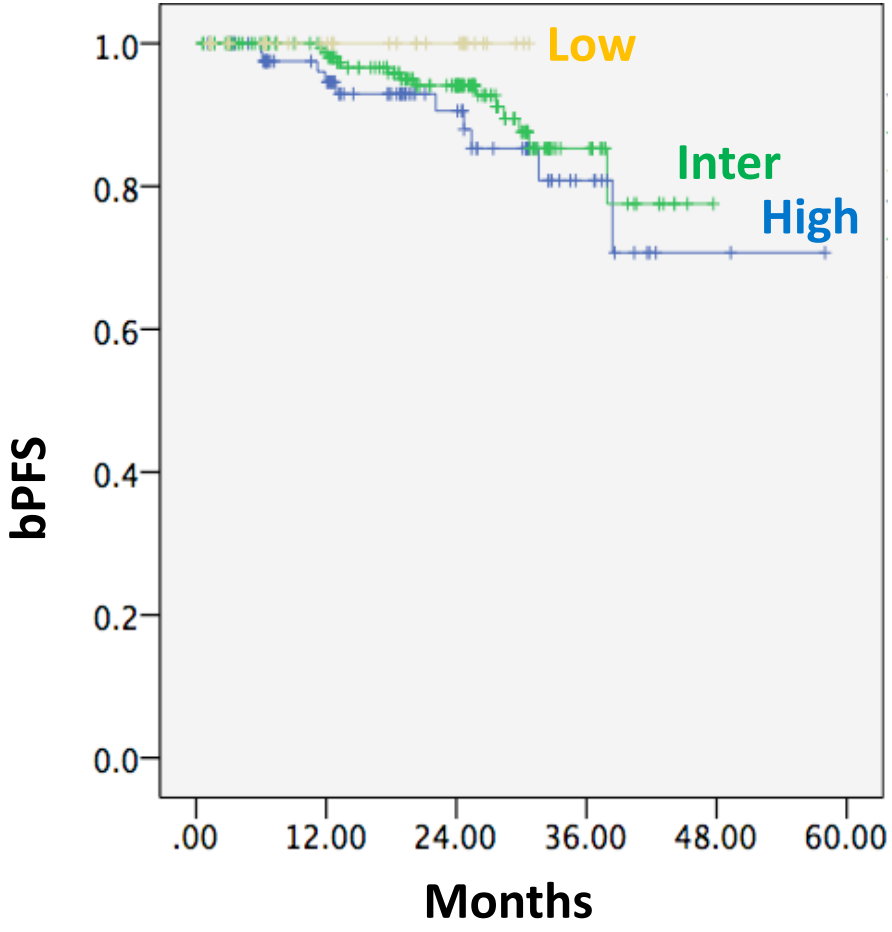


UK 19Gy database: bRFS: (n=310)

All patients



Risk groups



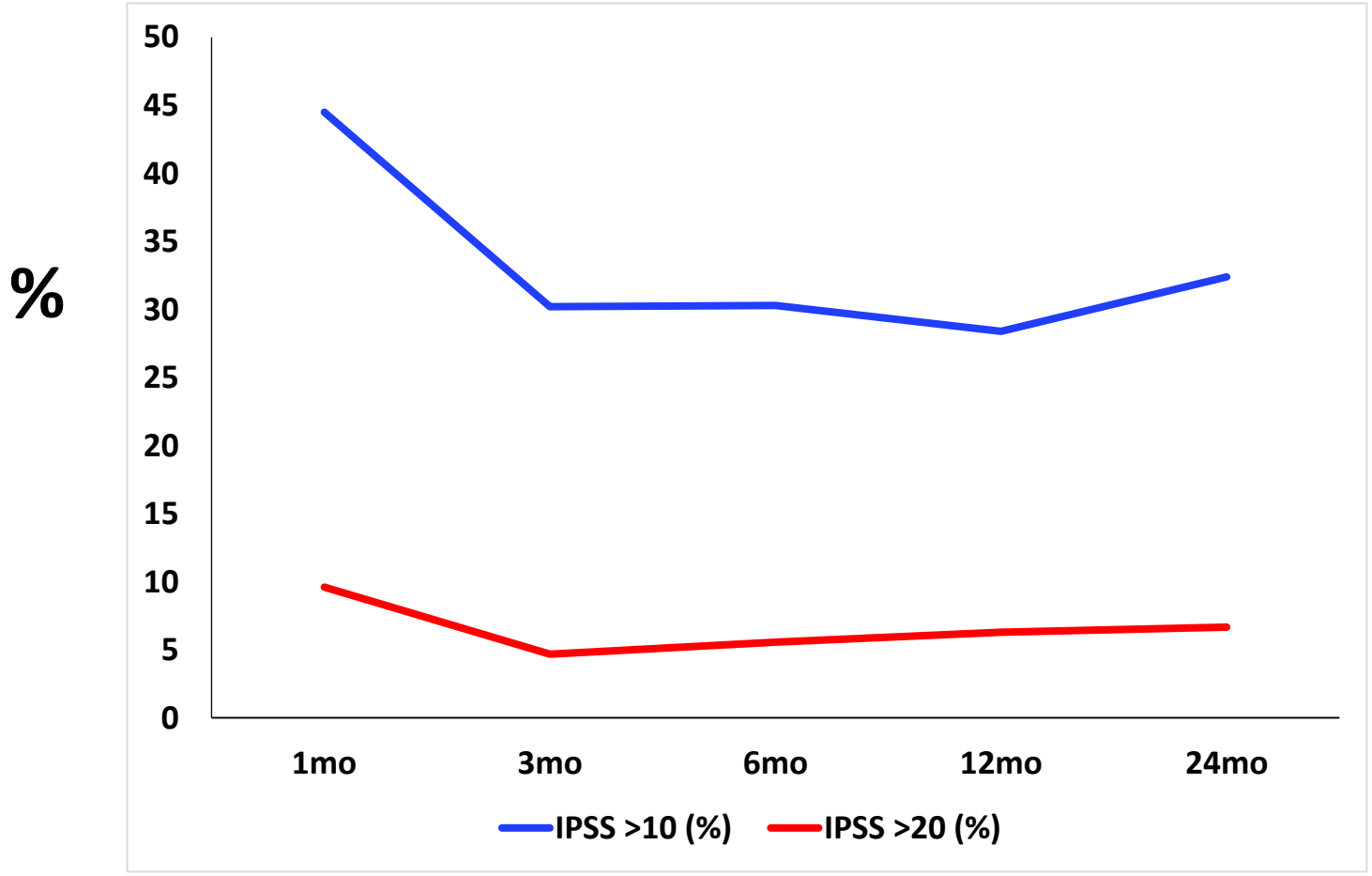
Overall 2-year bPFS: 94%

High-risk (88): **93%** **Inter-risk** (186): **94%** **Low-risk** (36): **100%**

(p = 0.26)

IPSS Post Monotherapy

	1mo	3mo	6mo	12mo	24mo
N	209	192	198	190	105
Median	9	7	6	6	6
Range	0-34	0-31	0-34	0-33	0-28



HDR BOOST

- **Optimal means of dose escalation for intermediate/high risk patients**
- **Dose escalation results in better PSA RFS**

- **Acute toxicity equivalent or less than external beam**
- **Late toxicity equivalent to external beam…but ?SABR**

HDR MONOTHERAPY

- **High rates of biochemical control in early years**
- **Optimal indication yet to be defined: ?intermediate/high risk…?low risk**

- **Acute toxicity short-lived cf LDR BT**
- **Late toxicity profile favourable with low rates of late urinary and erectile dysfunction**

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Functional MRI guided HDR prostate brachytherapy tumour boost

ELSEVIER

Brachytherapy - (2013) -

BRACHYTHERAPY

Multi-parametric MRI-guided focal tumor boost using HDR prostate brachytherapy: A feasibility study

Josh Mason[1,4,*], Bashar Al-Qaisieh[1], Peter Bownes[1], Dan Wilson[1], David L. Buckley[4], David Thwaites[4,5], Brendan Carey[2], Ann Henry[3]

- HDR prostate brachytherapy
- Trans-rectal ultrasound guided catheter insertion and treatment planning
- 15Gy to whole prostate in 1 fraction followed by 37.5 Gy/15 fraction external beam treatment

F-GTV delineation

F-GTV = union of suspicious areas in all 3 MRI datasets

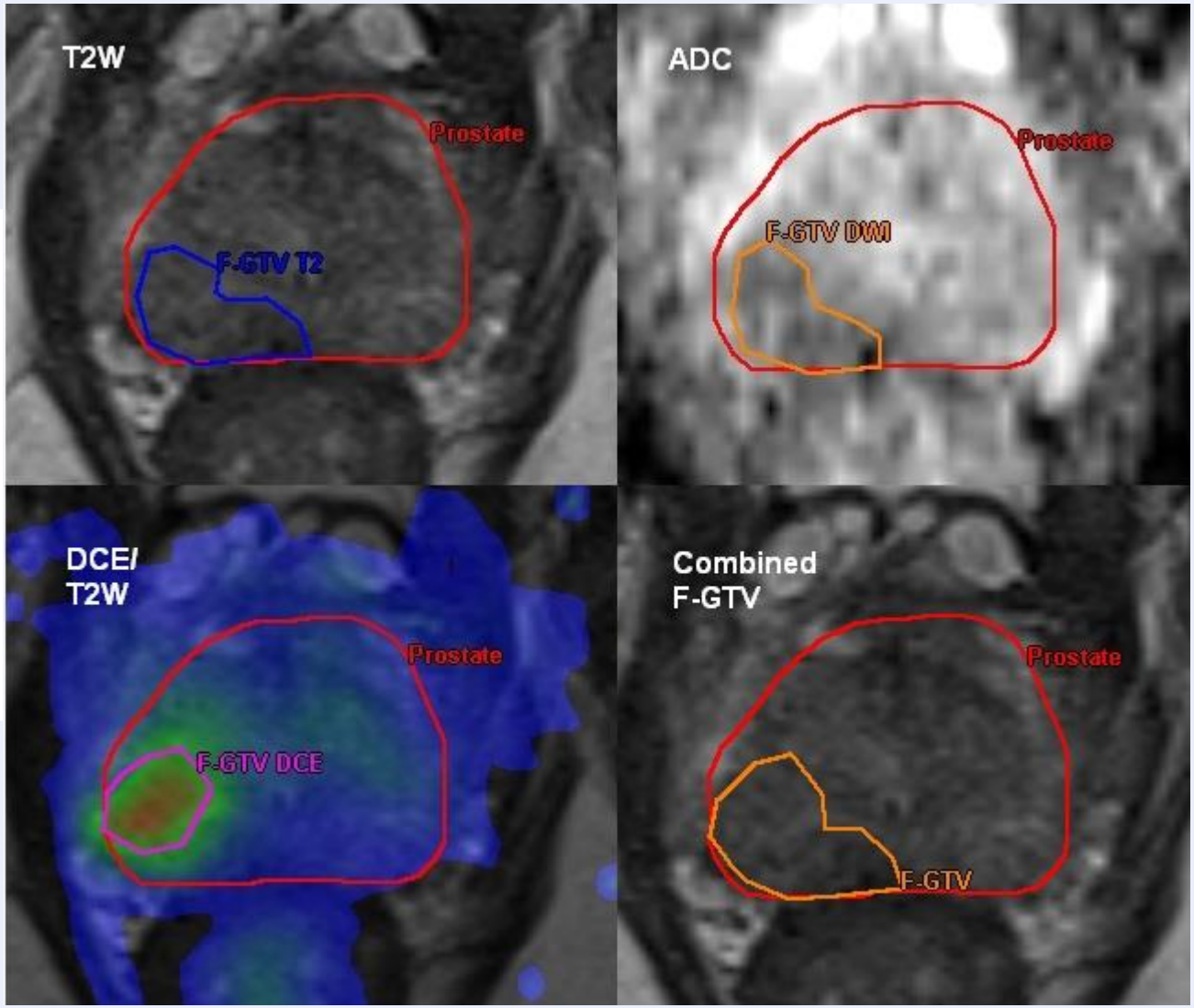
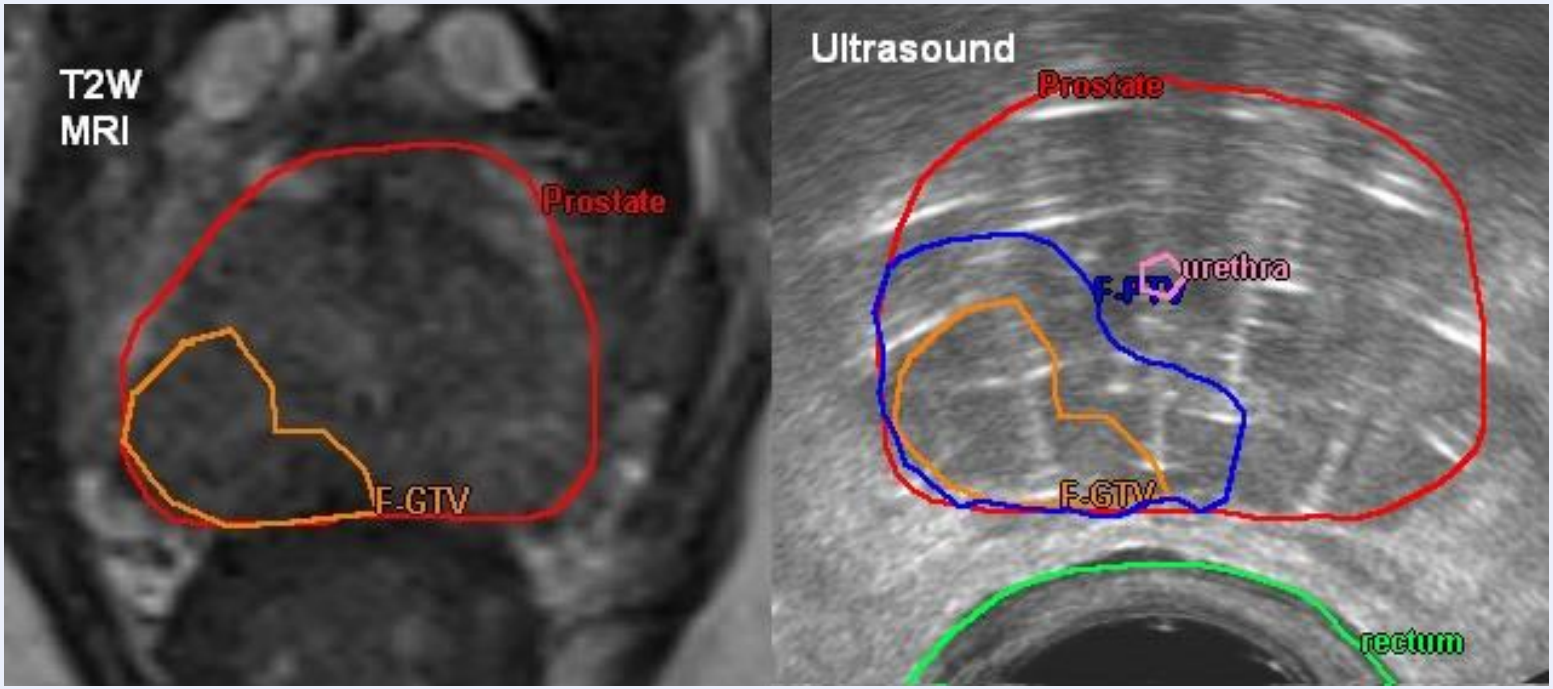


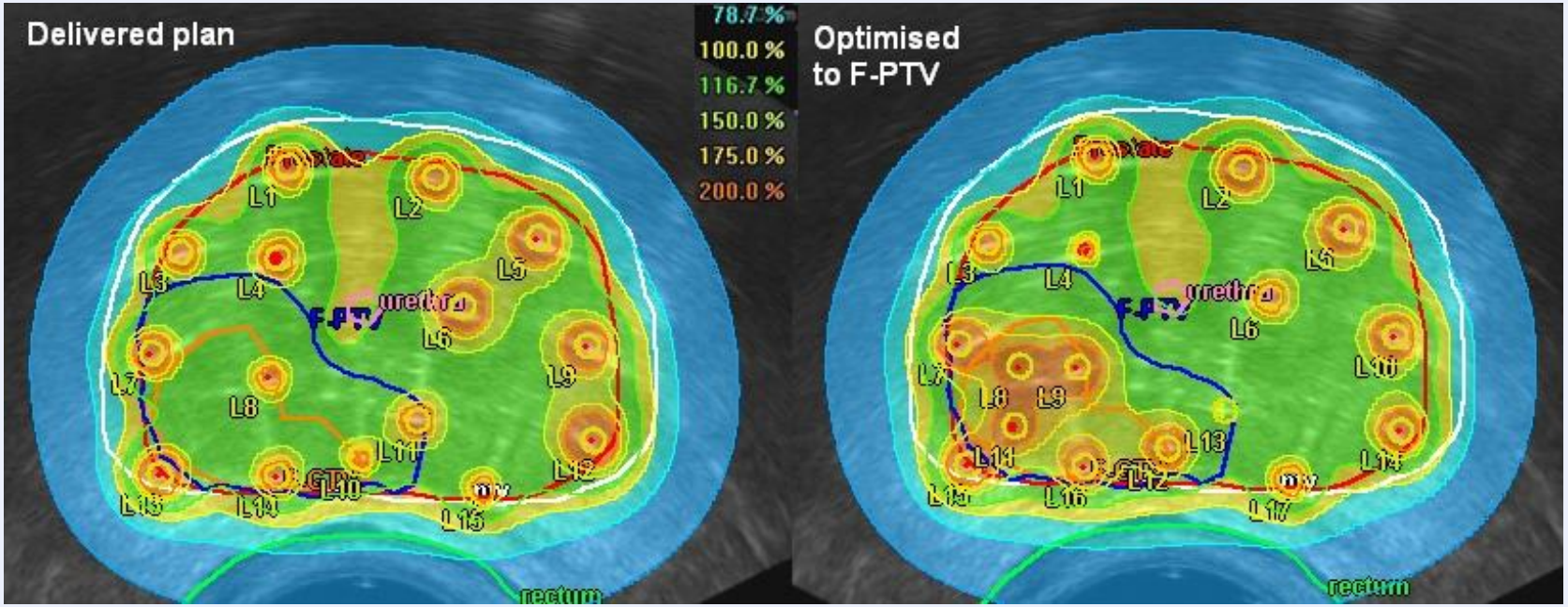
Image registration MRI-TRUS

- Manual rigid registration
- Margin added to F-GTV (constrained by prostate/OAR) to create F-PTV



Dose optimisation

- Compared delivered plan to plan optimised to boost dose to F-PTV
- Added up to 2 needles to target F-PTV if necessary
- Maintain dose objectives/constraints for prostate, PTV, urethra, rectum



Results – median values for 15 patients

	Volume (cc)	DVH parameter	Objective/ constraint	Delivered plan	Optimised to F-PTV
Prostate	29.7	V100 (%)	>95%	99.5	99.4
		D90 (Gy)	-	16.8	17.0
PTV	43.3	V100 (%)	>90%	90.7	93.7
Urethra	0.3	D10 (Gy)	<17.5Gy	17.2	17.4
Rectum	13.2	D2cc (Gy)	<11.8 Gy	8.0	9.1
F-GTV	1.9	D90 (Gy)	-	18.2	23.4
		V150 (%)	-	23.2	99.2
F-PTV	6.5	D90 (Gy)	-	17.6	20.9
		V150 (%)	-	27.3	75.9

Summary

- MRI guided tumour boost is feasible
- Main uncertainties are in tumour delineation and image registration
- F-PTV boost dose is achievable in HDR brachytherapy

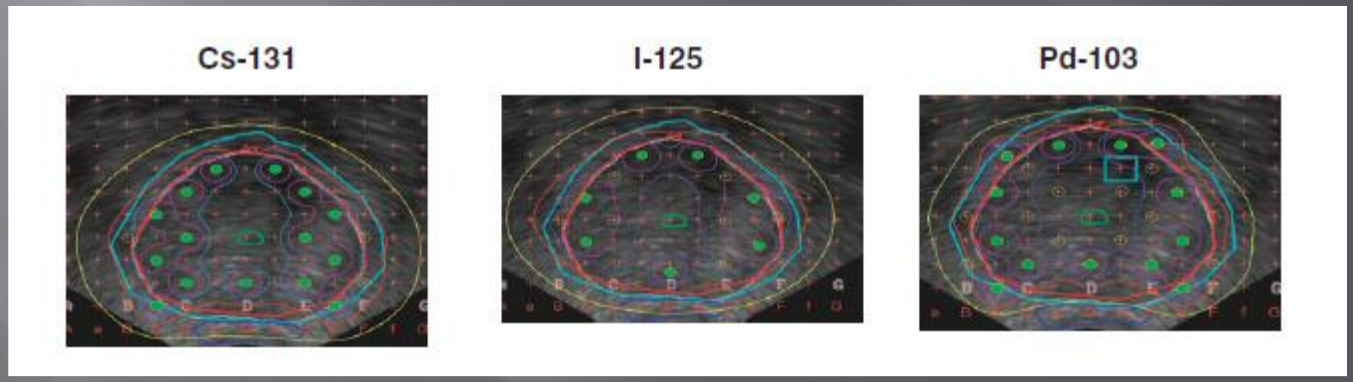
TREATMENT PLANNING FOR PERMANENT SEED IMPLANTATION

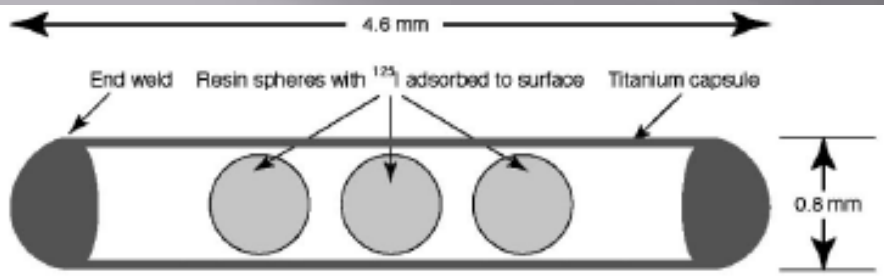
Bashar Al-Qaisieh

The Leeds Teaching Hospitals NHS
NHS Trust

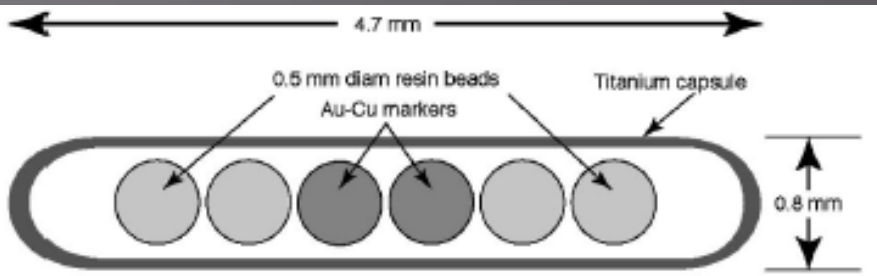
Seed Type

I-125	Pd-103	Cs-131
• 4.6mm long and 0.8mm diameter • I-125 adsorbed on silver rod, encased in titanium • Half-life of 59.4 days • Energy 27.4 & 31.4keV x-rays (electron capture) Also 35.5keV gamma photons	• 4.6mm long and 0.8mm diameter • Pd plated graphite pellets 0.9mm x 0.6mm • Titanium end cap • Half-life 17 days • Energy 20.8 KeV	• Short half-life (9.7 days) may provide radiobiological advantage for some prostate cancers • γ-ray emitter with highest peaks from 29 to 34 keV • Clinical protocol developed in Texas Cancer Center by Prestidge et al.

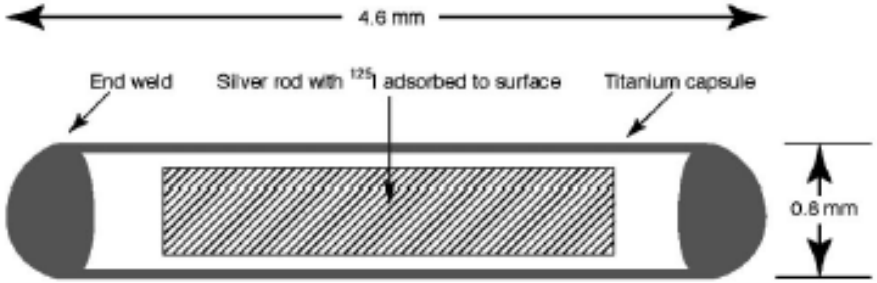




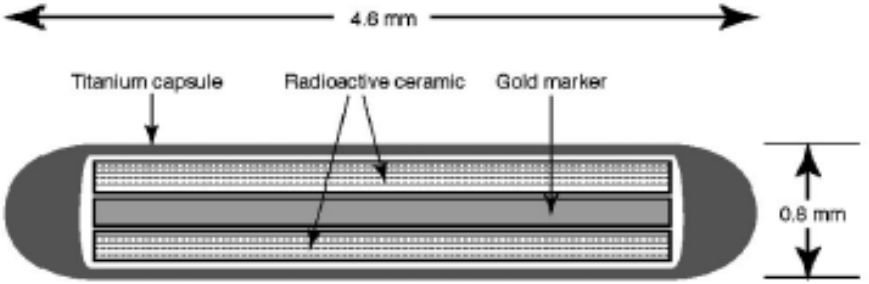
Amersham Health model 6702 source



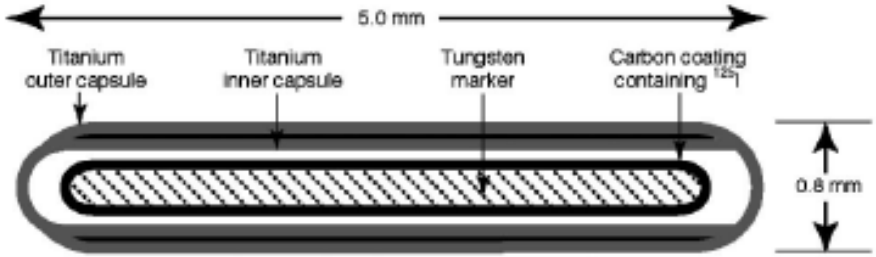
NASI model MED3631-A/M or MED3633 source



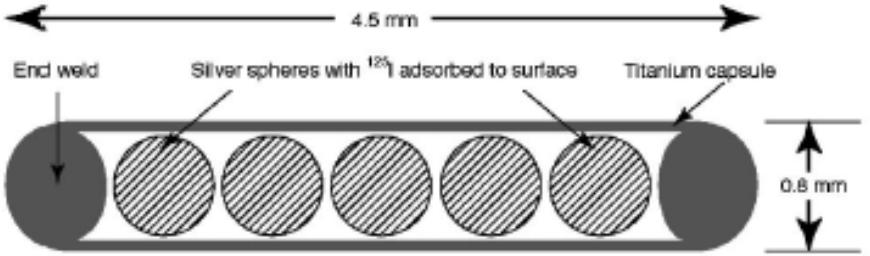
Amersham Health model 6711 source



Bebig model I25.S06 source

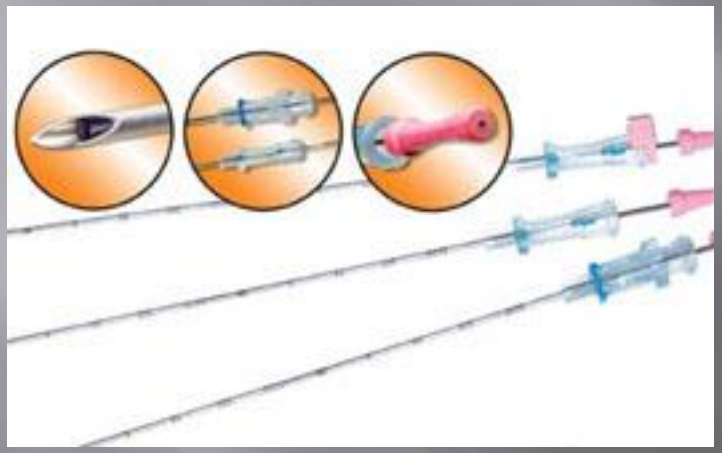


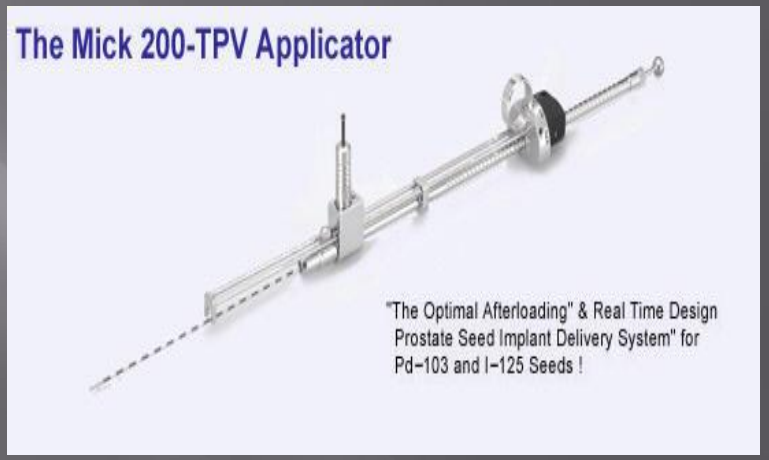
Best model 2301 source



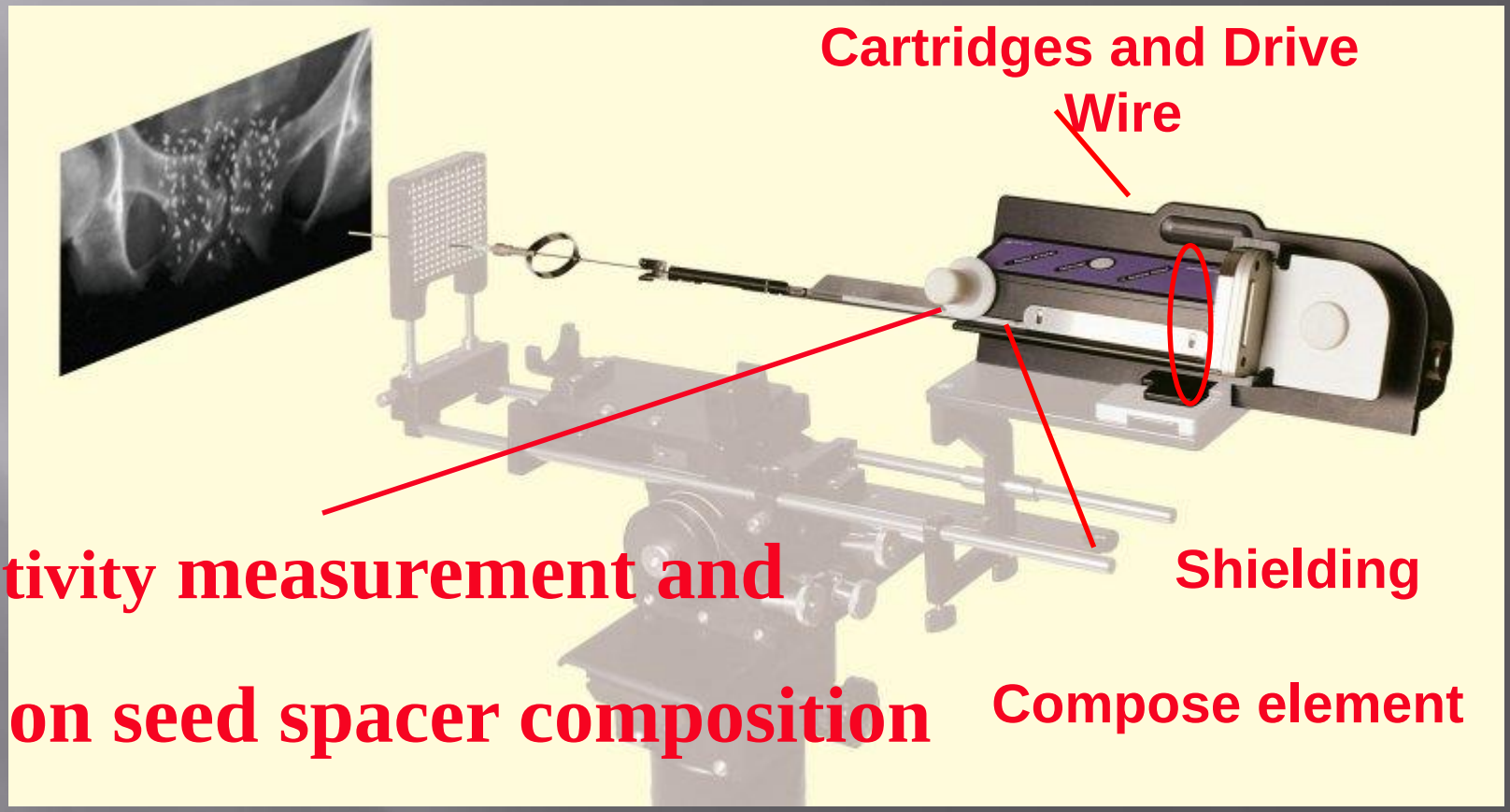
Imagyn model IS-I2501 source

Delivery Systems

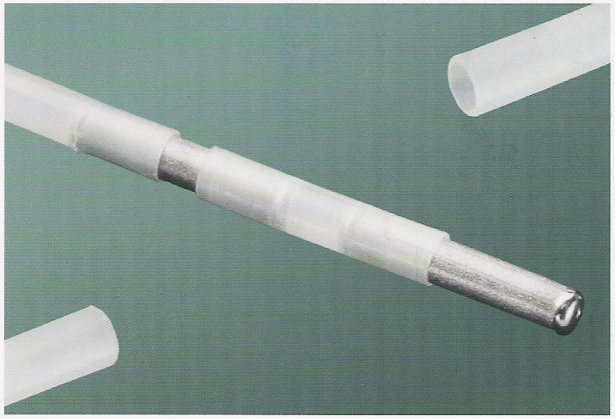




Developments in seed delivery

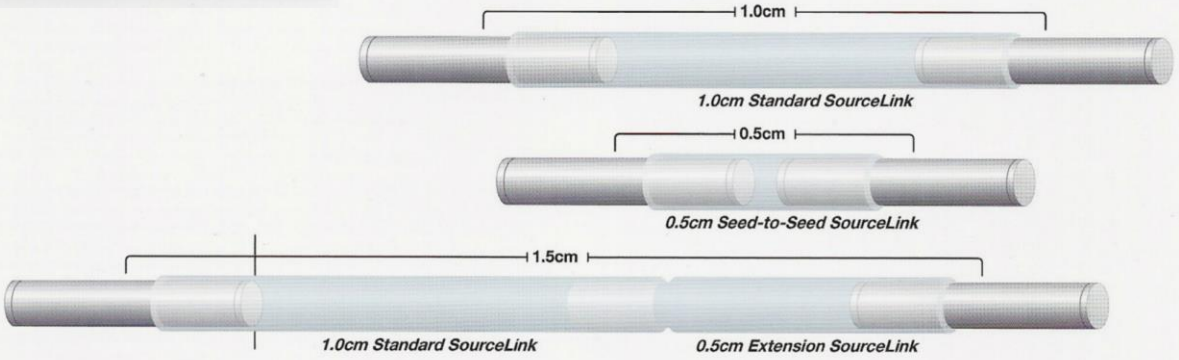


Developments in seed delivery

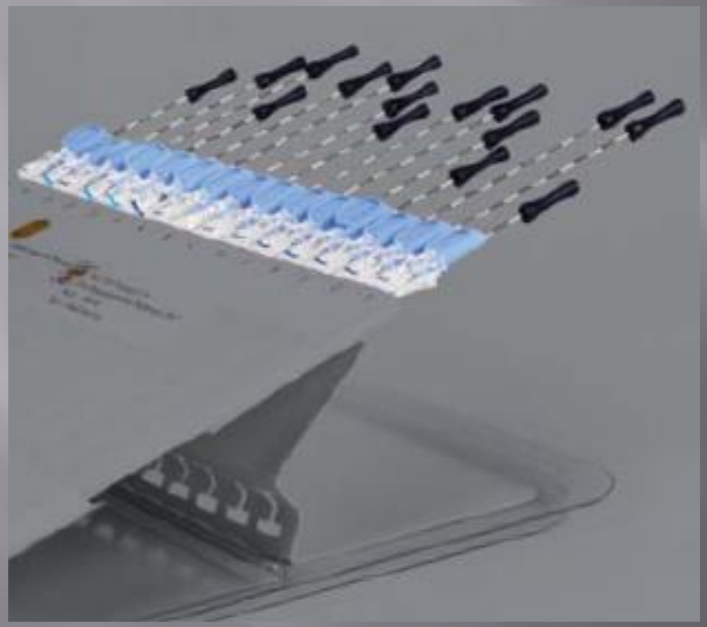


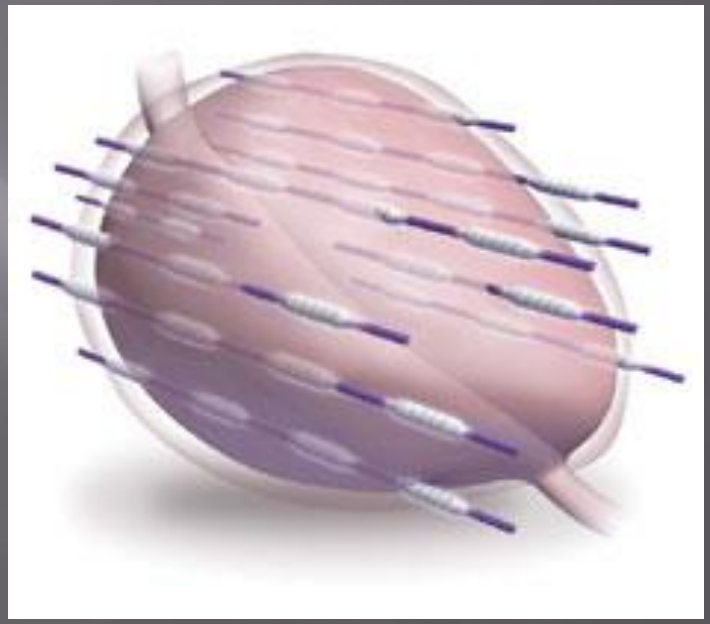
SourceLink™

CONNECTED. SPACED. SOURCES.



RSRx





TG 43 and TG 43-U1

Report of American Association of Physicists in Medicine Radiation Therapy Committee Task Group 43

Medical Physics, 22(2), 209-235, Feb 1995

Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations

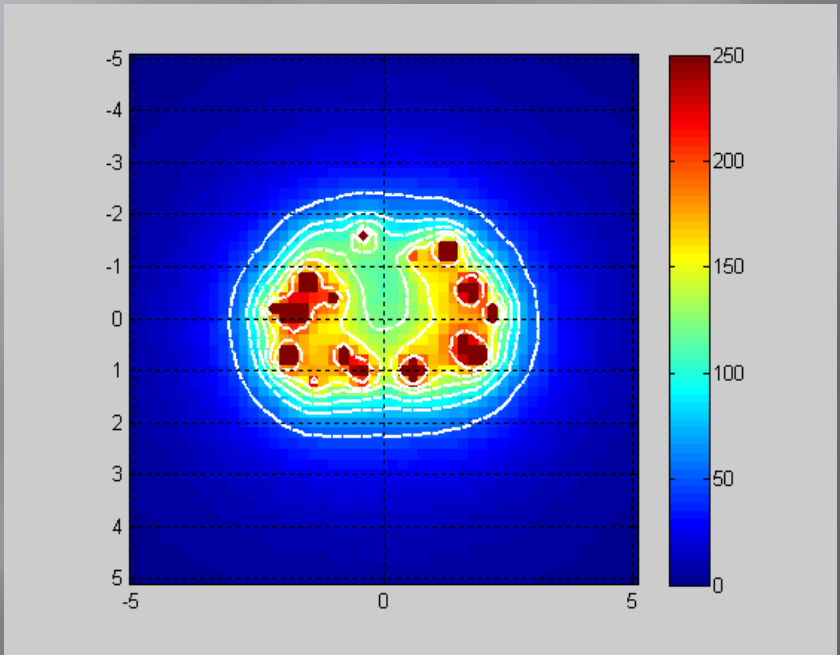
Medical Physics, 31 (3), 633-674 Mar 2004

Clinical dose calculations

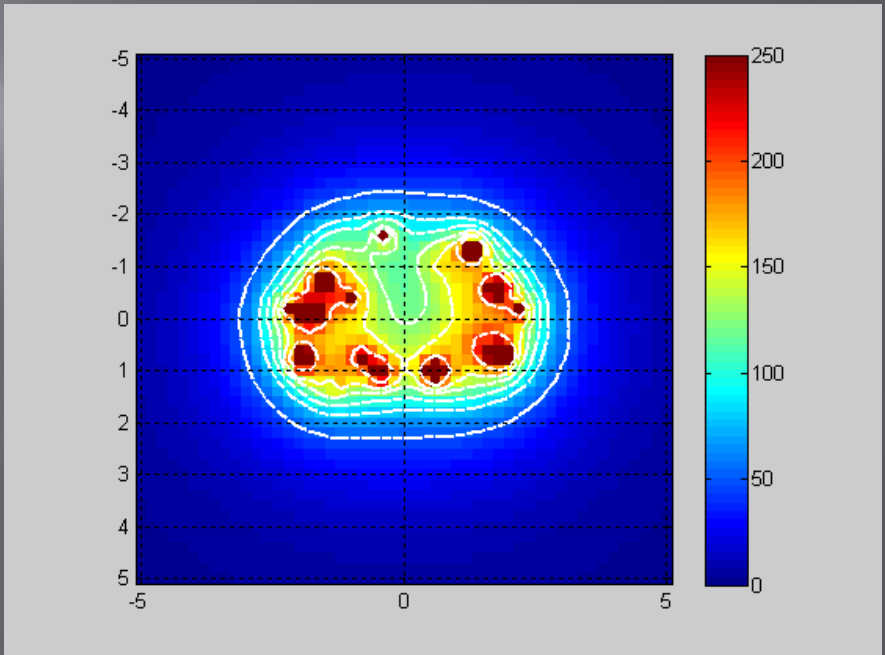
- Assumptions and possible errors in TG43
  - Dose to liquid water
    - Tissue variation/air/bone/calcification
  - Superposition of independent sources
    - Applicators/seeds attenuation
  - Fixed phantom dimensions
    - Patient boundaries

Initial results

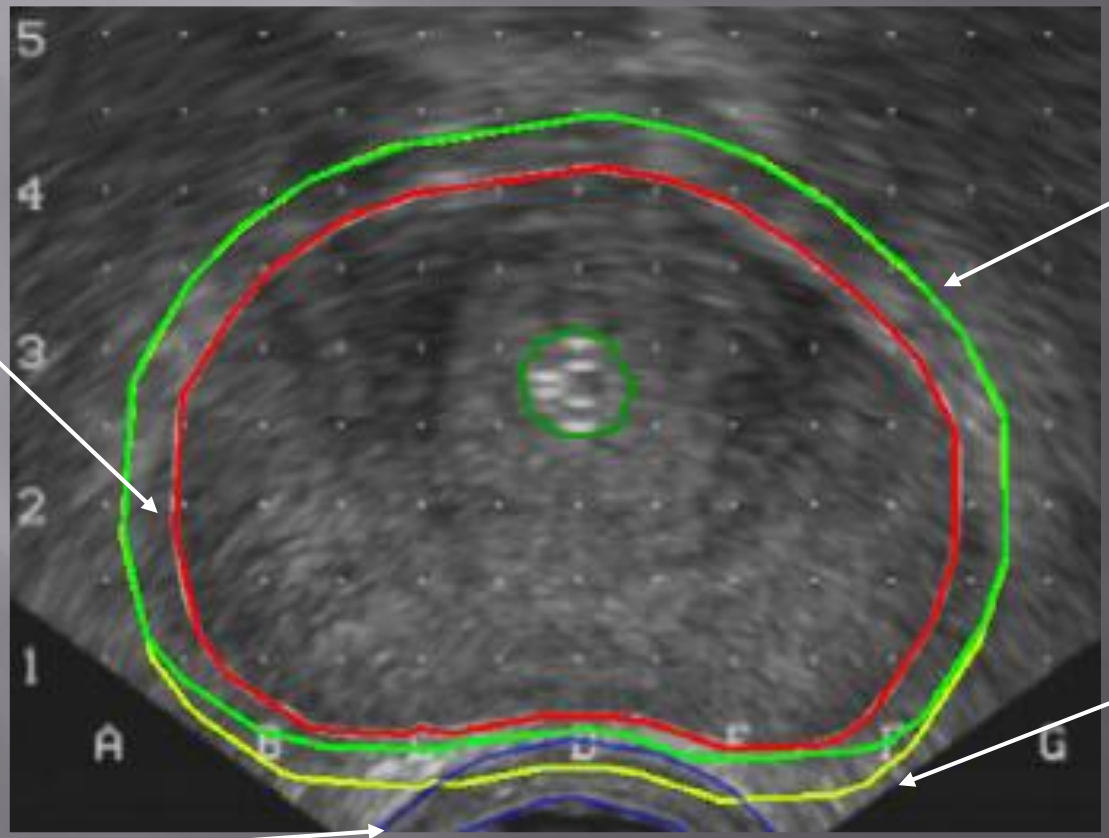
MC Simulation



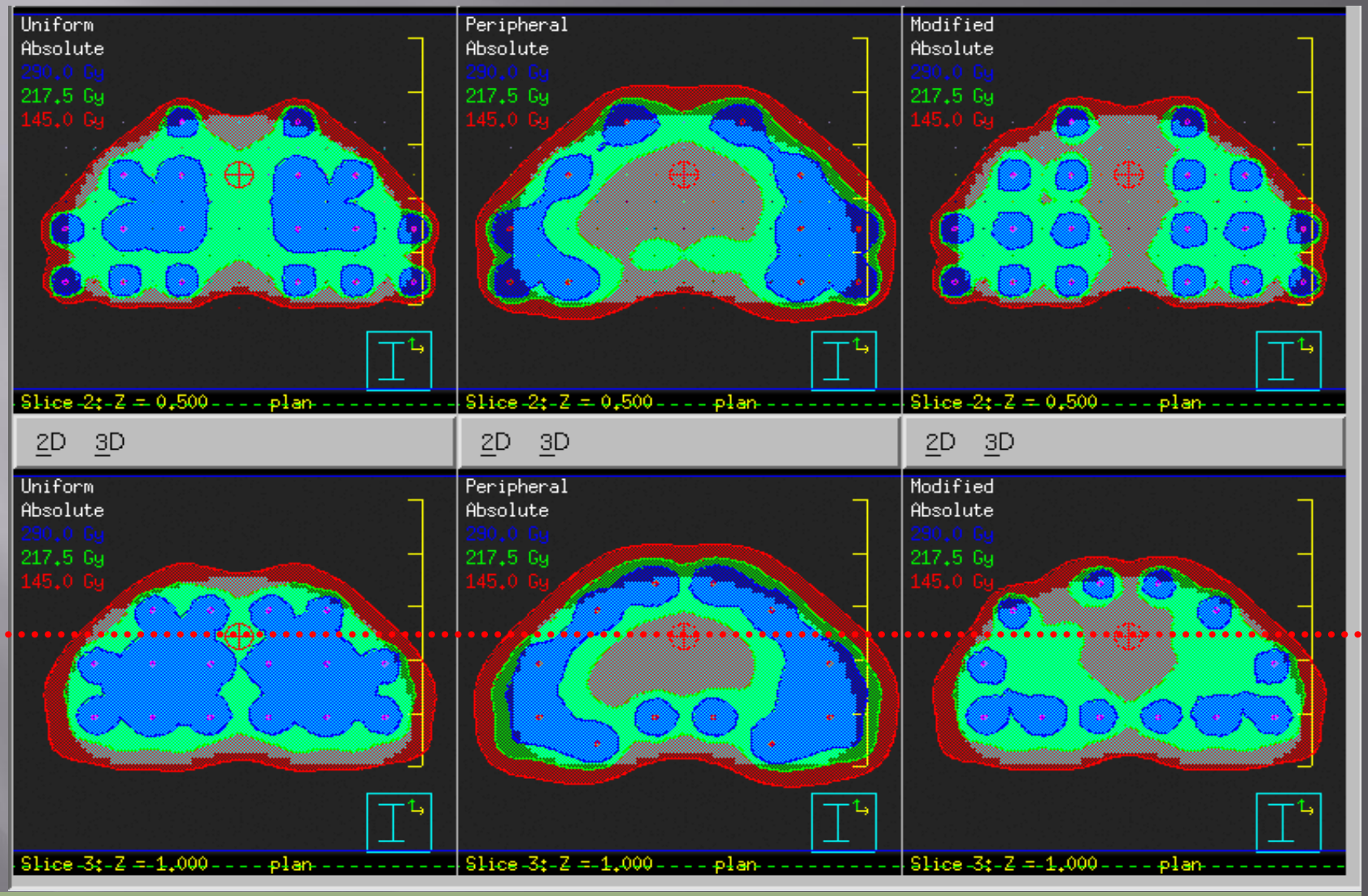
Superposition



PTV= CTV = Prostate Gland + "0-3mm" margin *(GEC/ESTRO Recommendations, Salembier et al 2007)*

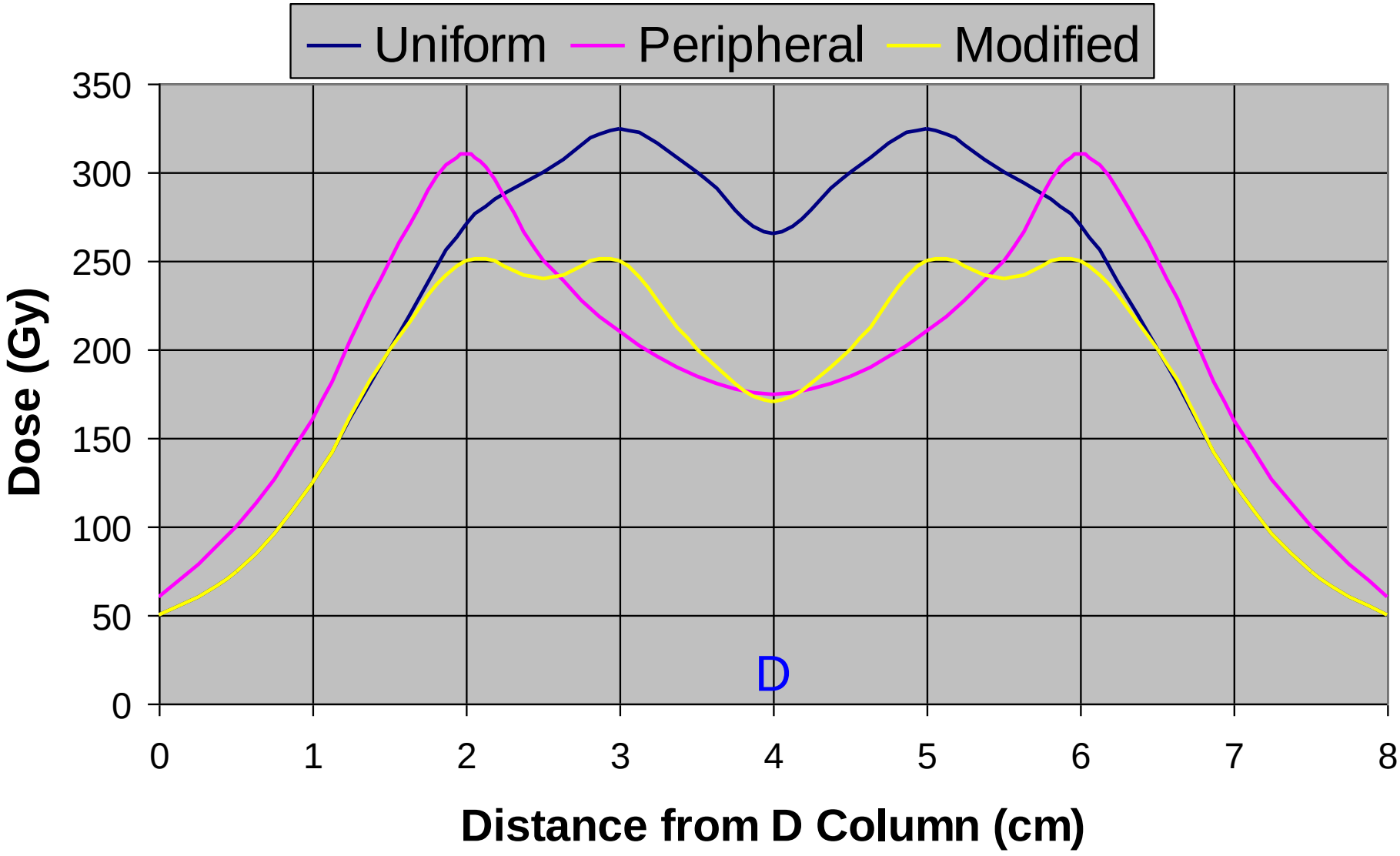


Seed Distribution



Uniform Loading	Peripheral Loading	Modified Peripheral
<0.3U	>0.8U	~0.4U

Dose Profile Through Urethra and Row 3 for Different Loading Techniques



Factors may affect accurate seeds positioning

- Patient set-up:

  - Prostate mis-match (day of volume study/day of implant).

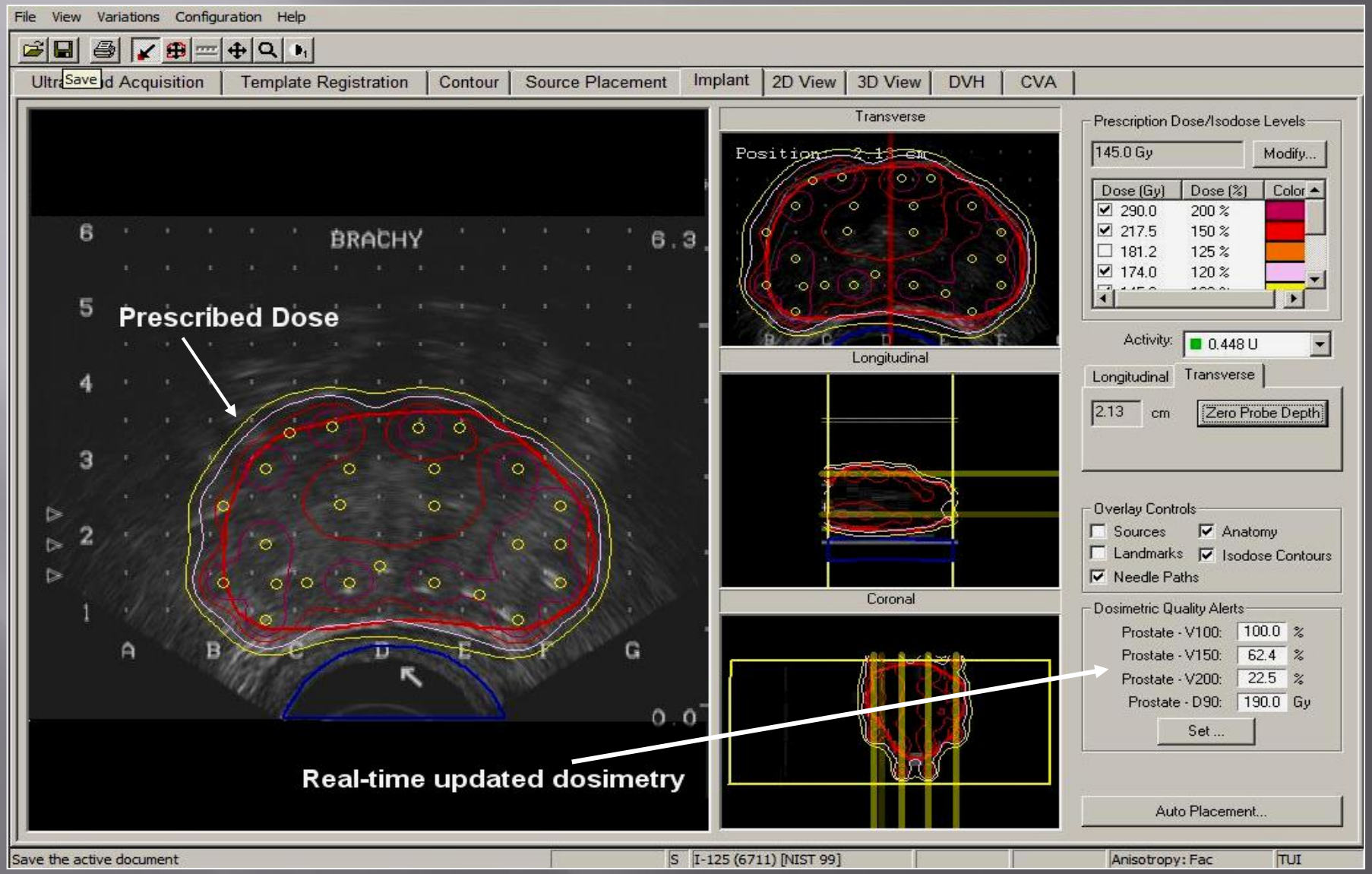
- Implant progression:

  - Pubic-arch interference.
  - Prostate movement (linear and rotational).
  - Bleeding affect seeds and needles visualisation on U/S.
  - Seeds jamming and operator error.

- Prostate oedema:

  - Change in prostate size during and after the implant (seeds migration).

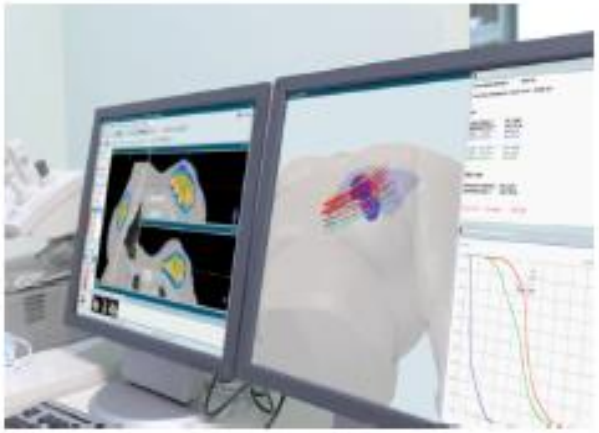
Theatre Dosimetry Planning



Bebig: Choices in HDR Brachytherapy

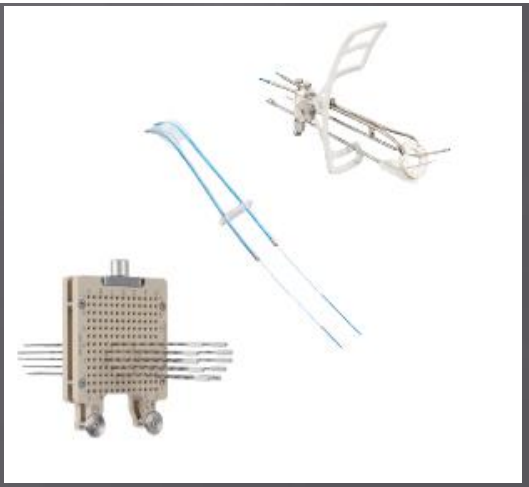
SagiNova® Afterloader

SagiPlan® Treatment Planning

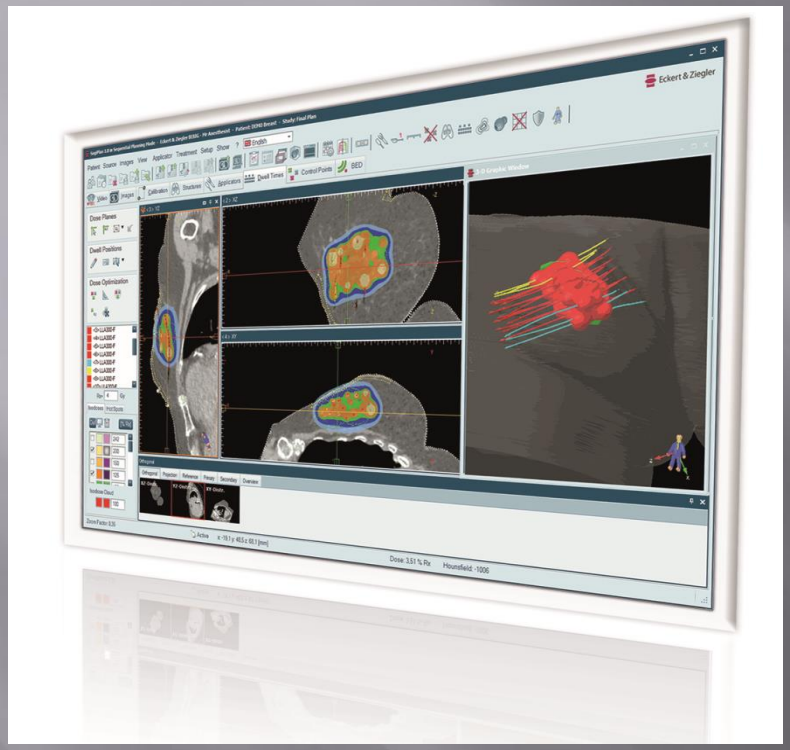


Round-the-Clock Service Excellence

Complete Range of HDR Applicators



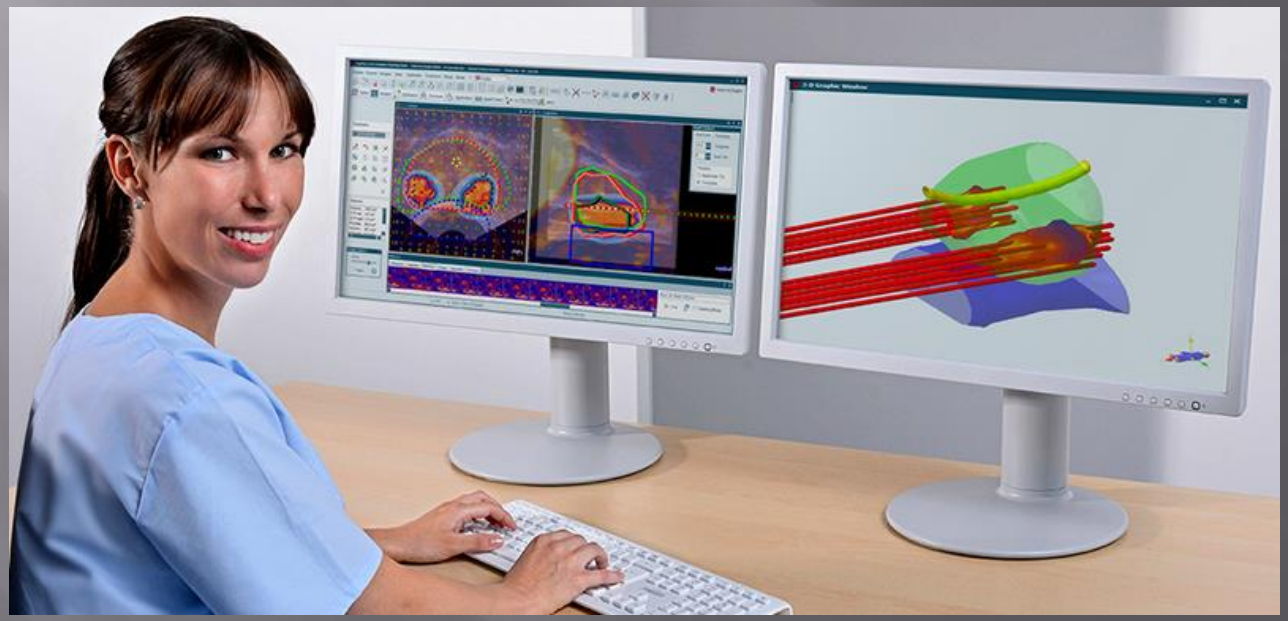
SagiPlan® Treatment Planning



- One platform for all HDR treatment planning needs, 2D nd 3D.
- User-friendly and intuitive interface
- Precise, targeted, and conformal
- Full and flexible connectivity
- Comprehensive plan evaluation features

One Platform for All HDR Planning Needs

- **Real-time prostate planning**
- Import of real-time ultrasound images with frame grabber and stepper
- Actual position of needles visible and therefore real-time adaption of treatment plans is done easy in operating theatre
- Live dose cursor and real-time update of DVH parameters



Prostate Brachytherapy Course

ESTRO School

“Post-Implant Dosimetry”

C. Salembier

Prostate Brachytherapy Course

"Post-Implant Dosimetry"

C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

Why evaluate after the procedure ?

- Individual implant assessment
- Programmatic improvements
- External incentives
- Standard of Care

Individual Implant Assessment: Inadequate Target Dose

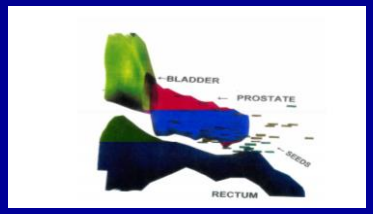
- Therapeutic intervention
  - Adjuvant therapies
    - Re-implantation
    - External beam radiation
    - Chemotherapy / hormonal manipulation
    - Surgical intervention
  - Salvage therapy: follows recurrence
- Increased vigilance
  - Follow up and diagnostics (imaging and biochemical evaluation)

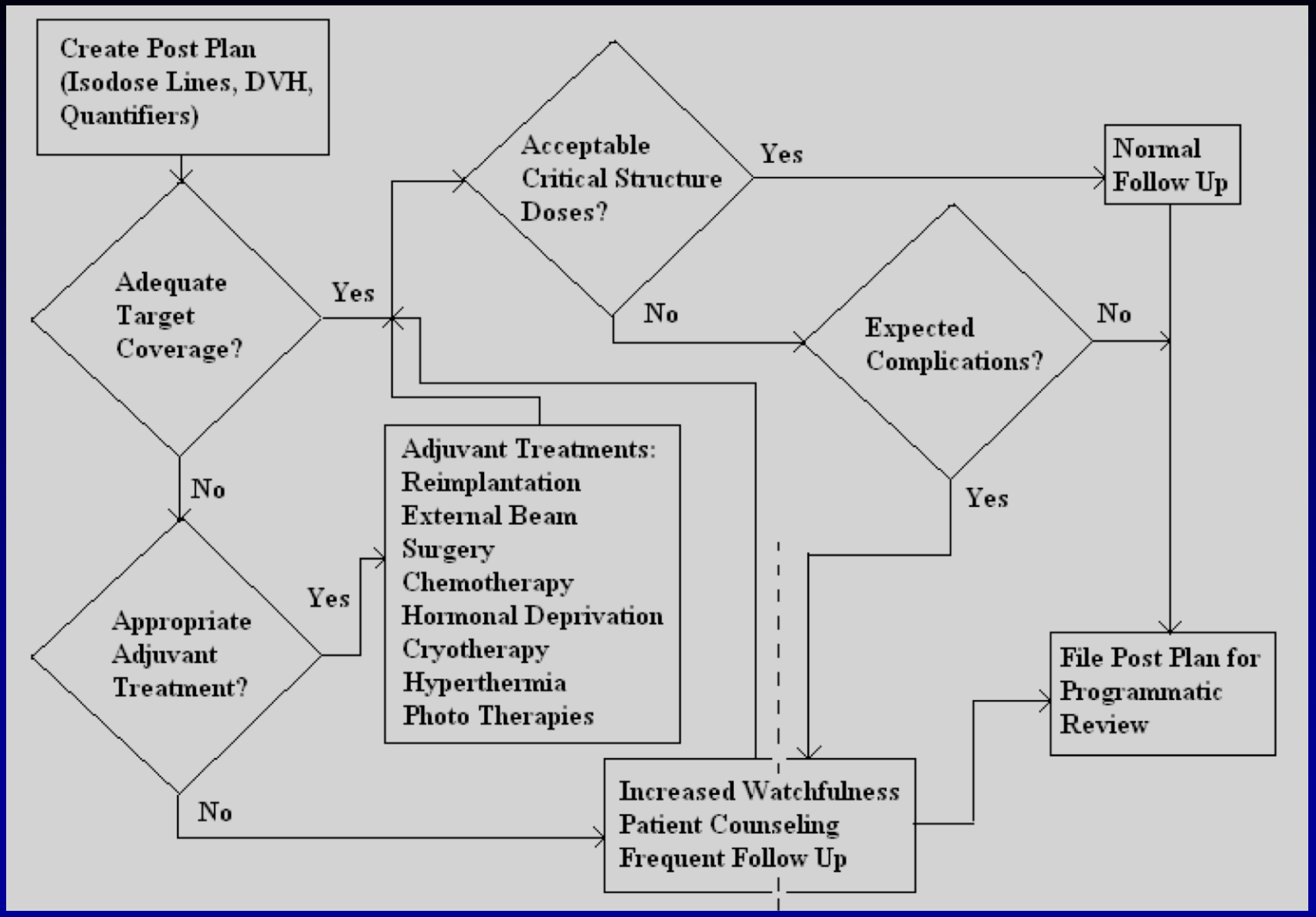
Individual Implant Assessment: Excessive dose to normal tissues

- Therapeutic intervention:
  - Almost always salvage rather than adjuvant (cross your fingers)
  - Hyperbaric oxygen to promote healing
  - Surgical intervention
- Increased vigilance
  - Patient awareness
  - Follow-up visits
  - Diagnostic procedures

Programmatic Improvement

- Technique evaluation
  - Planning
  - Delivery
    - OR methods (Example: patient alignment)
    - Brachytherapist
- Equipment evaluation
  - Delivery systems
    - Example: Loose seeds / Mick applicator
    - Example: Loose / stranded seeds
  - Broken on maladjusted equipment




Create Post Plan (Isodose Lines, DVH, Quantifiers)
Adequate Target Coverage?
Yes
No
Appropriate Adjuvant Treatment?
Yes
No
Adjuvant Treatments:
Reimplantation
External Beam
Surgery
Chemotherapy
Hormonal Deprivation
Cryotherapy
Hyperthermia
Photo Therapies
Acceptable Critical Structure Doses?
Yes
No
Normal Follow Up
Expected Complications?
No
Yes
Increased Watchfulness
Patient Counseling
Frequent Follow Up
File Post Plan for Programmatic Review

Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy

Carl Salembier[a], Pablo Lavagnini[b], Philippe Nickers[c], Paola Mangili[d], Alex Rijnders[a], Alfredo Polo[e], Jack Venselaar[f], Peter Hoskin[g,*], on behalf of the PROBATE group of GEC ESTRO

- CTV = prostate + 3mm margin

  (can be constrained to the anterior rectal wall and the bladder neck)

- Dose (AAPM TG 64): 100 % isodose = 145 Gy for I^{125}

Radiotherapy and Oncology 83 (2007) 3–10

Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy

Carl Salembier[a], Pablo Lavagnini[b], Philippe Nickers[c], Paola Mangili[d], Alex Rijnders[a], Alfredo Polo[e], Jack Venselaar[f], Peter Hoskin[g,*], on behalf of the PROBATE group of GEC ESTRO

- **V100 (percentage of CTV receiving the prescribed dose) is at least 95 %**
- **D90 (dose that covers 90 % volume of the CTV) will be larger than the prescription dose**
- V150 should be less than or equal to 50 %

Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy

Carl Salembier[a], Pablo Lavagnini[b], Philippe Nickers[c], Paola Mangili[d], Alex Rijnders[a], Alfredo Polo[e], Jack Venselaar[f], Peter Hoskin[g,*], on behalf of the PROBATE group of GEC ESTRO

- Rectum:
  - Primary parameter: D 2 cc < 145 Gy
  - Secondary parameter: D 0.1cc (about D Max)< 200 Gy
- Prostatic urethra:
  - D 10 < 150 % of the prescription dose
  - D 30 < 130 % of the prescription dose
- Penile bulb and NV bundles : investigational …

Change, like sunshine, can be a friend or a foe, a blessing or a curse, a dawn or a dusk.

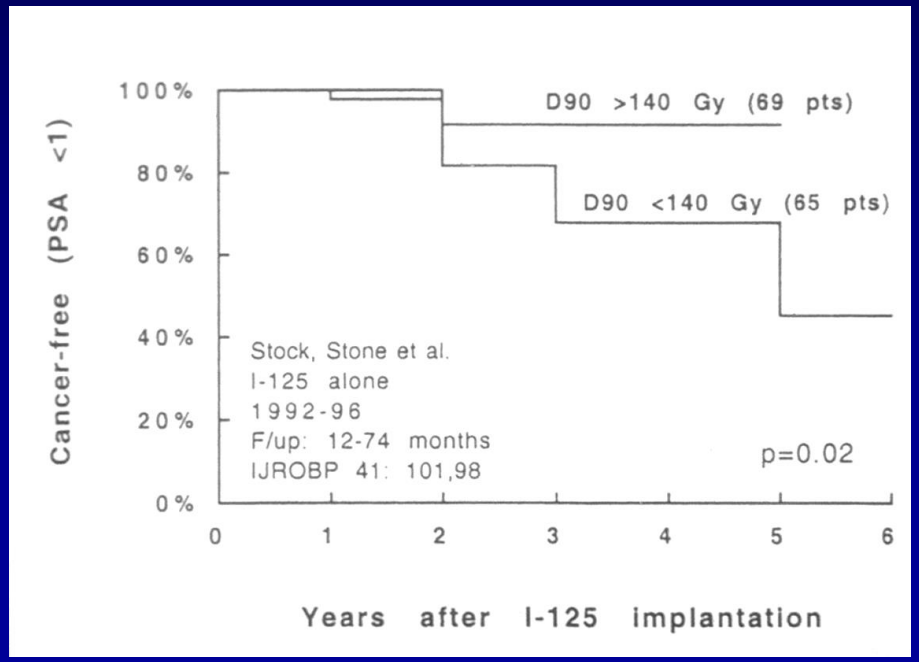
(William Arthur Ward)

D90 , like sunshine, can be a friend or a foe, a blessing or a curse, a dawn or a dusk.

(CS and JMC)

D90 as THE predictor of bNED ?

- For more than a decade, D90 appeared for a number of authors as the best dosimetric parameter able to « predict » bNED



Multivariate analysis of factors affecting biochemical failure

Factor	p-Value
Dose	0.001
PSA	0.02
Score	0.2
Stage	0.9

R. G. Stock *et al* 1998

Customized dose prescription for permanent prostate brachytherapy: insights from a multicenter analysis of dosimetry outcomes.

Stone NN, Potters L, Davis BJ, Ciezki JP, Zelefsky MJ, Roach M, Fearn PA, Kattan MW, Stock RG

- 6 centers – 3928 PB patients with post-implant dosimetry results
- Stratification in low- (2188), intermediate (n=1188) and high (n=522) risk groups

AND

- Into 3 BED groups:
  - < 140 Gy (n = 524)
  - 140-200 Gy (n = 2284)
  - >200 Gy (n = 1115)

Int J Radiat Oncol Biol Phys. 2007 Dec 1;69(5):1472-7

- The corresponding bFFF rate for the low-risk patients by dose group was **85.2%, and 88.1% and 88.3%** for the low-, intermediate, and high-dose group, respectively (p <0.0001).
- The corresponding bFFF rate for the intermediate-risk patients by dose group was 77.7%, and 94.3% and 88.8% for the low-, intermediate-, and high-dose group, respectively (p < 0.0001).
- The corresponding bFFF rate for high-risk patients by dose group was 53.2%, 90% and 69.6% for the low-, intermediate-, and high-dose group, respectively (p < 0.0001).

These data suggest that PB-dose prescriptions can be customized to risk status. In low-risk patients, achieving a BED of >or=140 Gy might be adequate for prostate-specific antigen control.

However, high-risk disease might require a BED dose of >or=200 Gy.

ASTRO 2009 , Abstract 2974:

The Mount Sinaï experience ; 1072 patients: 10 years RFS

- D90 < 120 Gy ; 42 %
- D90 120-140 Gy ; 74 %
- D90 140-160 Gy ; 82 %
- D90 160-180 Gy ; 87 %
- D90 > 180 Gy ; 89 %

RADIATION DOSE PREDICTS FOR BIOCHEMICAL CONTROL IN INTERMEDIATE-RISK PROSTATE CANCER PATIENTS TREATED WITH LOW-DOSE-RATE BRACHYTHERAPY

ALICE Y. HO, M.D.,[‡] RYAN J. BURRI, M.D.,* JAMIE A. CESARETTI, M.D.,* NELSON N. STONE, M.D.,[†] AND RICHARD G. STOCK, M.D.*

Departments of *Radiation Oncology and [†]Urology, Mount Sinai School of Medicine, New York, NY; and [‡]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

- Prospectively collected database
  - 2250 men treated with PBI
  - Period 1990 – 2004

- Overall: the actuarial FFbF at 10 years was 86 %

- Dose (BED <150 Gy vs >150 Gy) was the only significant predictor of FFbF (p<0,001) in intermediate risk patients

International Journal of Radiation Oncology, Biology, Physics, 2009, Vol.75(1), pp.16-22

LOCAL CONTROL FOLLOWING PERMANENT PROSTATE BRACHYTHERAPY: EFFECT OF HIGH BIOLOGICALLY EFFECTIVE DOSE ON BIOPSY RESULTS AND ONCOLOGIC OUTCOMES

NELSON N. STONE, M.D.,* RICHARD G. STOCK, M.D.,† JAMIE A. CESARETTI, M.D.,† AND PAM UNGER, M.D.‡

*Departments of Urology, †Radiation Oncology, and ‡Pathology, Mount Sinai School of Medicine, New York, New York

- Higher radiation doses are required to achieve local control following PPB.
- A BED of > 200 Gy with an alpha/beta ratio of 2 yields 96,9% local control rate.

International Journal of Radiation Oncology, Biology, Physics, 2010, Vol.76(2), pp.355-360

POSTOPERATIVE NOMOGRAM PREDICTING THE 9-YEAR PROBABILITY OF PROSTATE CANCER RECURRENCE AFTER PERMANENT PROSTATE BRACHYTHERAPY USING RADIATION DOSE AS A PROGNOSTIC VARIABLE

LOUIS POTTERS, M.D.,* MACK ROACH, III, M.D.,† BRIAN J. DAVIS, M.D., PH.D.,‡
RICHARD G. STOCK, M.D.,§ JAY P. CIEZKI, M.D.,‖ MICHAEL J. ZELEFSKY, M.D.,¶
NELSON N. STONE, M.D.,# PAUL A. FEARN, B.A.,** CHANGHONG YU, M.S.,††
KATSUTO SHINOHARA, M.D.,† AND MICHAEL W. KATTAN, PH.D.††

CONCLUSION: A predictive model for a postimplant nomogram for prostate cancer recurrence at 9-years after PPB has been developed and validated from a large multi-institutional database.

This study also demonstrates the significance of implant dosimetry for predicting outcome.

International Journal of Radiation Oncology, Biology, Physics, 2010, Vol.76(4), pp.1061-1065

NATURAL HISTORY OF CLINICALLY STAGED LOW- AND INTERMEDIATE-RISK PROSTATE CANCER TREATED WITH MONOTHERAPEUTIC PERMANENT INTERSTITIAL BRACHYTHERAPY

AL V. TAIRA, M.D.,* GREGORY S. MERRICK, M.D.,† ROBERT W. GALBREATH, PH.D.,† KENT E. WALLNER, M.D.,‡ AND WAYNE M. BUTLER, PH.D.†

*Department of Radiation Oncology, University of Washington, Seattle, WA; †Schiffler Cancer Center and Wheeling Jesuit University, Wheeling, WV; and ‡Puget Sound Healthcare Corporation, Group Health Cooperative, University of Washington, Seattle, WA

RESULTS: ….The bPFS rate was

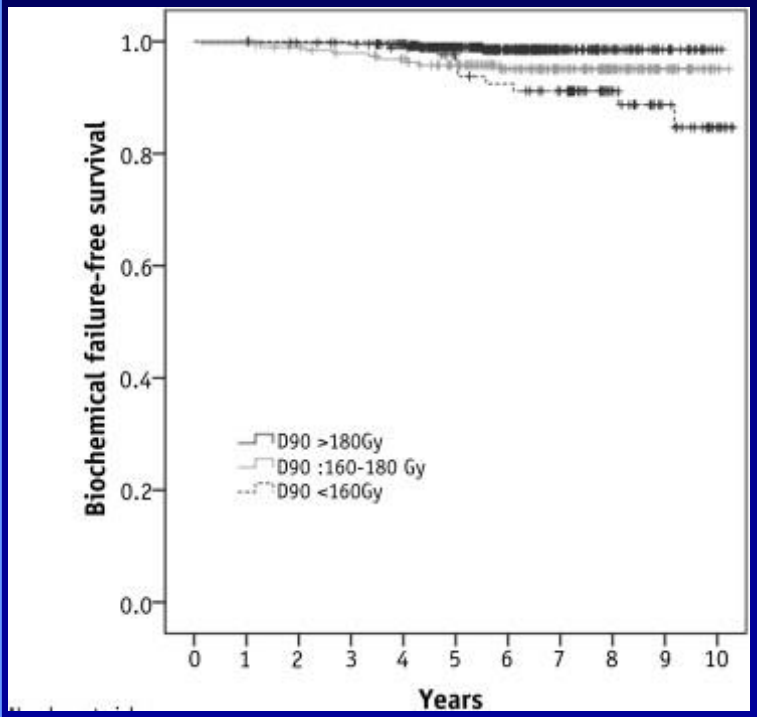
98.8% for low-risk patients with high-quality implants
versus
92.1% for those with less adequate implants ($p < 0.01$)

98.3% for intermediate-risk patients with high-quality implants
versus
86.4% for those with less adequate implants ($p < 0.01$).

International Journal of Radiation Oncology, Biology, Physics, 2010, Vol.76(2), pp.349-354

A Dose—Response Analysis of Biochemical Control Outcomes After ^{125}I Monotherapy for Patients With Favorable-Risk Prostate Cancer

Yutaka Shiraishi, MD, PhD,*,† Atsunori Yorozu, MD, PhD,† Toshio Ohashi, MD, PhD,* Kazuhito Toya, MD, PhD,† Shiro Saito, MD, PhD,‡ Toru Nishiyama, MD, PhD,‡ Yasuto Yagi, MD, PhD,‡ and Naoyuki Shigematsu, MD, PhD*



Improvements in BFFS rates were seen with increasing D90 levels. Day 30 D90 doses of 130 to 180 Gy were found to serve as cutoff levels.

For low-risk and low-tier intermediate-risk prostate cancer patients, high prostate D90s, even with doses exceeding 180 Gy, achieve better treatment results and are feasible.

International Journal of Radiation Oncology, Biology, Physics, 2014, Vol.90(5), pp.1069-1075

When I disagree with a rational man, I let reality be our final arbiter; if I am right, he will learn; if I am wrong, I will; one of us will win, but both will profit.

(Ayn Rand)

Other authors did not find this relationship …….

However;

- **Ash 2006 (for intermediate and high risk),**
- **Morris IJROBP 2009**
- **Bittner 2010**
- **Butler 2011**
- **Wakil 2011**
- **Wilcox 2011 …**

EVALUATION OF DOSIMETRIC PARAMETERS AND DISEASE RESPONSE AFTER ^{125}IODINE TRANSPERINEAL BRACHYTHERAPY FOR LOW- AND INTERMEDIATE-RISK PROSTATE CANCER

W. James Morris, M.D.,* Mira Keyes, M.D.,* David Palma, M.D.,* Michael McKenzie, M.D.,* Ingrid Spadinger, Ph.D.,* Alex Agranovich, M.D.,† Tom Pickles, M.D.,* Mitchell Liu, M.D.,† Winkle Kwan, M.D.,† Jonn Wu, M.D.,* Vince Lapointe, B.Sc.,* Eric Berthelet, M.D.,‡ Howard Pai, M.D.,‡ Robert Harrison, Ph.D.,* William Kwa, Ph.D.,* Joe Bucci, M.D.,§ Violet Racz, R.T.T.,* and Ryan Woods, Ph.D.‖

In contrast to some previous studies, dosimetric outcomes did not correlate with biochemical recurrence in the first 1,006 patients treated with 125I prostate brachytherapy at the British Columbia Cancer Agency.

International Journal of Radiation Oncology, Biology, Physics, 2009, Vol.73(5), pp.1432-1438

The correlation between annular treatment margins and biochemical failure in prostate brachytherapy patients with optimized intraprostatic dosimetry

Nathan Bittner, Gregory S. Merrick, Wayne M. Butler, Zachariah A. Allen, Brittany White, Ashley Adamovich, Kent E. Wallner

- …The D(90) and V(100) at the anterior, posterior, superior, inferior, right lateral, and left lateral aspects of the annulus were not statistically different between biochemically controlled and failed groups
- In this study, there was no relationship observed between annular dosimetry and biochemical control.

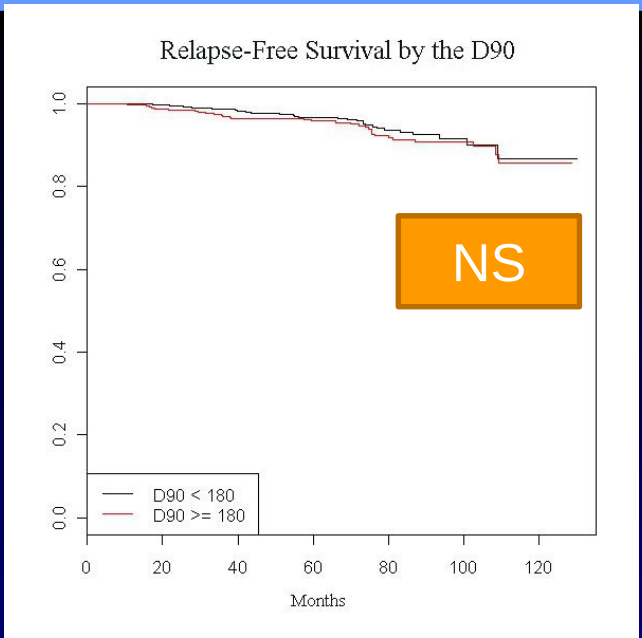
Evaluation of radiobiologic biochemical control in a large permanent prostate brachytherapy population from a single institution using AAPM TG-137 parameters.

Butler WM[1], Stewart RR, Merrick GS.

- There was no significant difference in BED between biochemical failures and nonfailures
- In a large prostate implant population, dosimetric and derived radiobiologic parameters did not predict for failure.
- Apparently, too few patients had total BEDs below the level necessary for optimum biochemical control.

Brachytherapy. 2011 Jan-Feb;10(1):16-28

ABS 2011: Wakil et al.
The Paris group experience



ABS 2011: Wilcox et al
The Dallas group experience

When tested for their association with PSA-RFS: D90,V100 and BED were not found to be statistically significant

HAL ROACH

Presents

and

In

The BATTLE OF THE CENTURY

A Metro-Goldwyn-Mayer PICTURE

PASSED BY THE NATIONAL BOARD OF REVIEW

The controversy !

Point: the relationship between postimplant dose metrics and biochemical no evidence of disease following low dose rate prostate brachytherapy: is there an elephant in the room?

Morris WJ, Halperin R, Spadinger I.

Counterpoint: there is a dose-response relationship in the low-dose rate brachytherapy management of prostate cancer.

Stock RG.

Brachytherapy. 2010 Oct-Dec;9(4):289-92; discussion 297-8.

2014 :The never-ending controversy between the Vancouver and New-York (Mount Sinaï) groups

ELSEVIER

BRACHYTHERAPY

Brachytherapy 13 (2014) 42–43

Editorial

Does dose matter? Editorial comments to Morris *et al.* Whole prostate D_{90} and V_{100}: A dose–response analysis of 2000 consecutive ^{125}I monotherapy cases

ELSEVIER

BRACHYTHERAPY

Brachytherapy 13 (2014) 44–45

Editorial

Rebuttal to Drs Stone and Stock

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

[1]*Department of Medical Physics, Vancouver Cancer Centre, British Columbia Cancer Agency, Vancouver, BC, Canada*
[2]*Department of Surgery, University of British Columbia, and Department of Radiation Oncology, Vancouver Cancer Centre, British Columbia Cancer Agency, Vancouver, BC, Canada*

A partial agreement ? (Morris 2014)

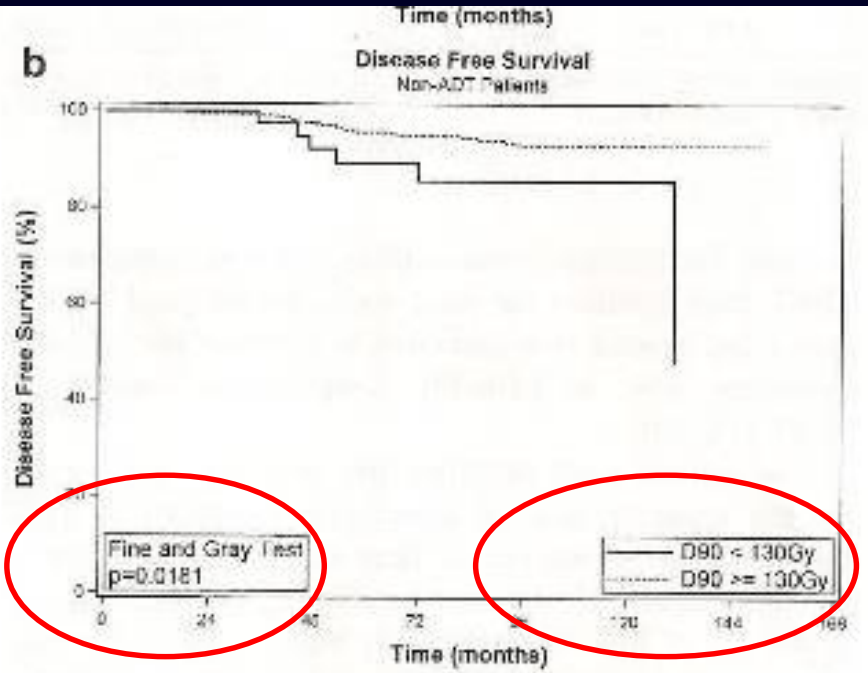


Fig. 3. The competing risks actuarial estimates of disease-free survival by Fine and Gray showing the interaction of D_{90} and receipt of androgen deprivation therapy (ADT). (a) Compares the ADT subset with D_{90} values <130 Gy with those ≥130 Gy (log rank, $p = 0.9427$). (b) Compares the non-ADT subset with D_{90} values <130 Gy with those ≥130 Gy (log rank, $p = 0.0181$).

For very low D90 (< 130 Gy), the difference in DFS *is* significant …

The Leeds Data …..

The correlation between D90 and outcome for I-125 seed implant monotherapy for localised prostate cancer

Dan Ash, Bashar Al-Qaisieh, David Bottomley, Brendan Carey, Joji Joseph

Received: August 16, 2005; Received in revised form: April 4, 2006; Accepted: April 19, 2006; Published Online: May 24, 2006

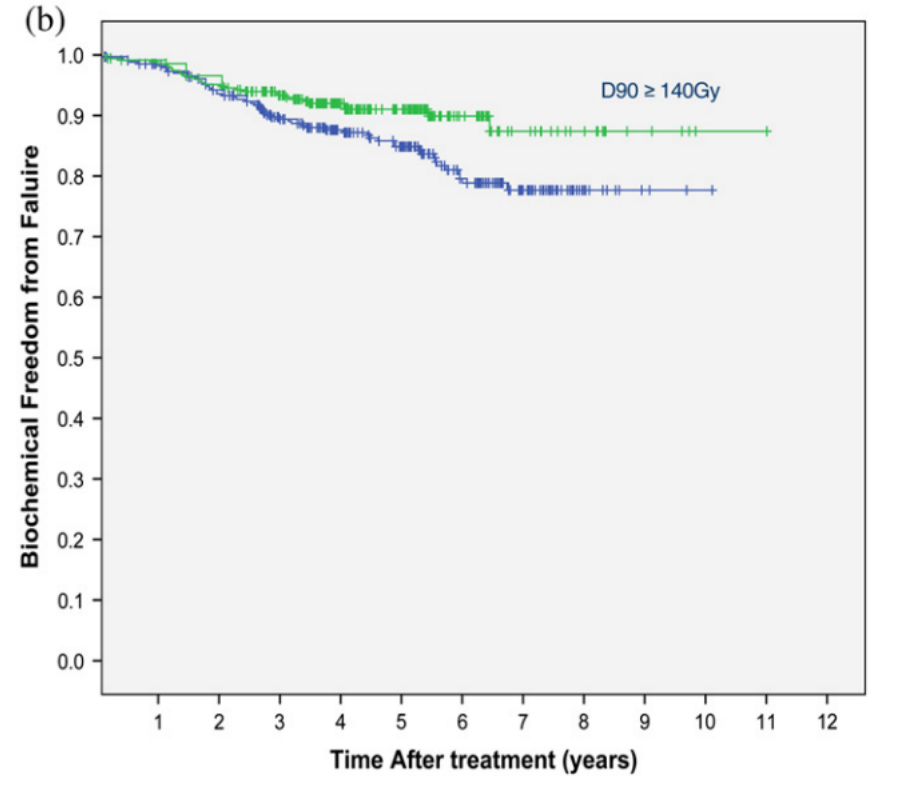
Only patients of low risk group have correlation with D90

Risk Group		P value D90
Low		0.006
Intermediate		0.489
High	.	0.852

Radiother Oncol 2006;79:185-189.

OUTCOMES FOLLOWING IODINE-125 MONOTHERAPY FOR LOCALIZED PROSTATE CANCER: THE RESULTS OF LEEDS 10-YEAR SINGLE-CENTER BRACHYTHERAPY EXPERIENCE

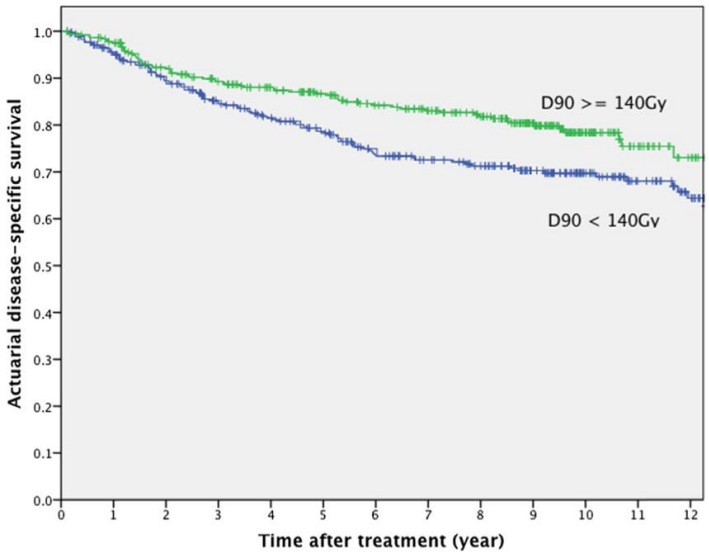
ANN M. HENRY, M.D.,* BASHAR AL-QAISIEH, PH.D.,† KATHY GOULD, R.G.N.,* PETER BOWNES, M.SC.,† JONATHAN SMITH, F.R.C.R.,‡ BRENDAN CAREY, F.R.C.R.,‡ DAVID BOTTOMLEY, F.R.C.R.,* AND DAN ASH, F.R.C.R.*



International Journal of Radiation Oncology, Biology, Physics, 2010, Vol.76(1), pp.50-56

The Effect of Dose and Quality Assurance in Early Prostate Cancer Treated with Low Dose Rate Brachytherapy as Monotherapy

A.M. Henry *†, S.L. Rodda *, M. Mason *, H. Musurunu *, B. Al-Qaisieh *, P. Bownes *, J. Smith *, K. Franks *, B. Carey *, D. Bottomley *



Numbers at risk at entry into each year

Year	0	1	2	3	4	5	6	7	8	9	10	11	12
>140Gy	365	348	313	290	269	247	227	212	191	144	81	45	27
<140Gy	346	317	284	255	235	218	189	174	162	132	94	68	48

Fig 2. Overall actuarial prostate-specific antigen (PSA) relapse-free survival (nadir+2) using a D90 threshold of 140 Gy as calculated from computed tomography post-implant dosimetry ($P < 0.01$) in cohort of 711 historic patients with post-implant dosimetry and a minimum follow-up of 5 years.

Clinical Oncology (2015)

Factors influencing the calculation of the D90

Post-implant dosimetry

Contouring

Seed reconstruction

- CT
- MRI

- CT

Fusion process

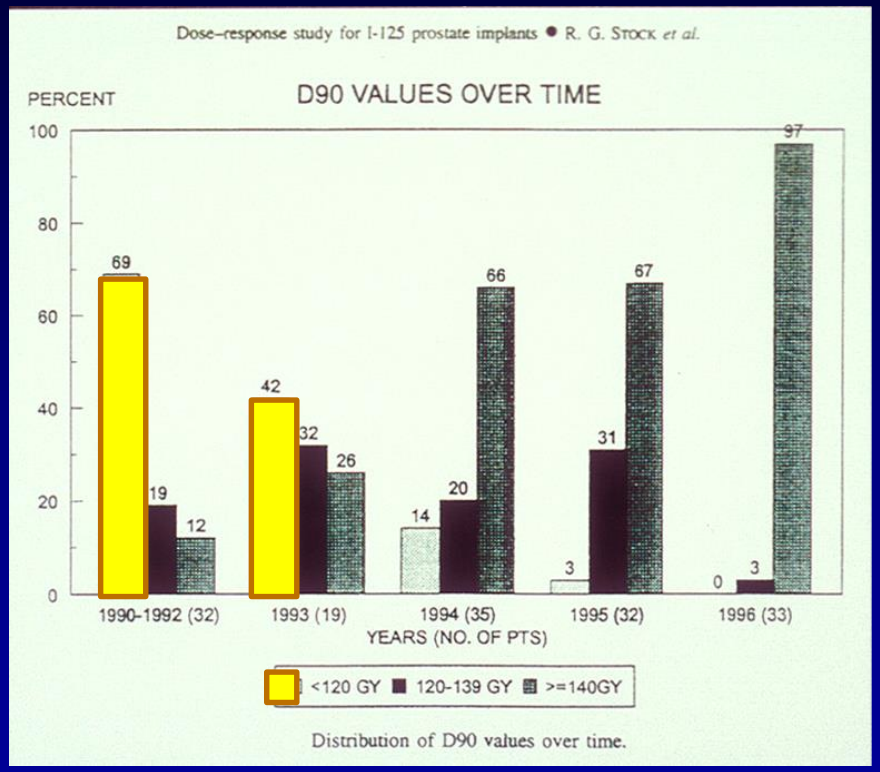
Prostate post-implant dosimetry: interobserver variability in seed localisation, contouring and fusion.
De Brabandere M, Hoskin P, Haustermans K, Van den Heuvel F, Siebert FA
Radiother Oncol. 2012 Aug;104(2):192-8.

Timing of post-implant evaluation is important

If too early: possible persistance of some oedema increasing the distance between seeds and thus leading to *decrease* the D90 !

Interpretation of the D90

To detect a role for D90 implies at least some variability of D90



Distribution of D90 values over time.

A number of D90 < 120 Gy before 1993 !!…

Series with a very homogeneous D90 can hardly detect a difference in DFS…

And actually, most « modern » published series presently show D90 with (often very) limited variations …

7.1. Post-implant dosimetry

Table 40: Completion of the post-implant dosimetry section

Post-implant dosimetry	N	%
Yes	3,188	78.4
No	761	18.7
Not yet done	119	2.9
Total	**4,068**	**100.0**

The section "Post-implant dosimetry" was completed for 3,188 of the 4,068 (78.4 %) registrations.

Belgian Cancer Registry: 2005-2012

7.2. Postop prostate D90

Table 41: Postop prostate D90 (Gy) by radiotherapy cent

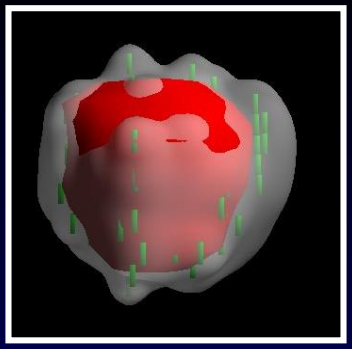
RT center	Average of postop prostate D90 (Gy)
RT 01	166.6
RT 02	132.5
RT 03	152.9
RT 04	171.8
RT 05	no data ava
RT 06	140.2
RT 07	111.3
RT 08	138.2
RT 09	168.8
RT 10	153.0
RT 11	155.6
RT 12	152.7
RT 12	no data ava
RT 13	no data ava
RT 14	157.5
RT 15	172.3
RT 16	167.3
RT 17	161.5
RT 18	164.1
RT 19	164.7
Total*	**157.5**

7.2. Postop prostate D90

Table 41: Postop prostate D90 (Gy) by radiotherapy center.

RT center	Average of postop prostate D90 (Gy)	SD	Min	Max	
RT 01	166.6	19.4	112.0	215.0	
RT 02	132.5	23.6	85.6	190.3	
RT 03	152.9	15.6	87.0	198.0	
RT 04	171.8	17.4	147.9	209.1	
RT 05	no data available				
RT 06	140.2	23.2	92.0	169.0	
RT 07	111.3	19.3	85.5	187.3	
RT 08	138.2	21.0	88.4	229.9	
RT 09	168.8	21.4	95.5	230.0	
RT 10	153.0	20.8	117.9	185.0	
RT 11	155.6	18.2	88.0	200.0	
RT 12	152.7	n.a.	152.7	152.7	
RT 12	no data available				
RT 13	no data available				
RT 14	157.5	13.3	128.0	186.0	
RT 15	172.3	16.9	91.2	233.3	
RT 16	167.3	7.1	152.0	188.6	
RT 17	161.5	18.0	98.3	204.6	
RT 18	164.1	12.1	102.0	210.0	
RT 19	164.7	16.5	118.5	209.0	
Total*	**157.5**	**22.0**	**85.5**	**233.3**	**N_{total}= 3,196**

Where is the underdosage?



”Significant underdosage of the ASQ relative to other regions of the prostate <u>was not</u> predictive of relapse”

Quadrant dosimetry as a predictor of relapse in I^{125} prostate brachytherapy
Spadinger et al. ABS 2009 ; OR47

In contrast, a significant underdose at the apex (f.ex.), in a patient with an histological apex involvement on biopsies, must be taken into account …

What to do about a low D_{90} ?

Ask a few questions (and act if necessary):

1. How “low” is it ?
   - If < 120 Gy , maybe something should be done …
   - If between 120 and 145 Gy, maybe ***nothing*** should be done
2. Was it measured accurately ? (image modalities, contouring, time frame, …)
3. Where is the underdose ?
4. Where is the tumour ?

Low D 90 ….

According to the answers to the previous questions :

- Watch and wait ?
- Add external beam RT ?
- Add complementary seeds ?

Conclusions

Available data strongly suggest that ***there might be*** a dose-response relationship for permanent implant brachytherapy of prostate cancers.

- However, one cannot expect this relationship to be a very close one
- a large number of reasons may bias, or even totally hide, the relationship between dose and clinical issues
- The main reasons which may be responsible for such a blurring of the results are the following:
  - Variations in the prostate contours
  - Timing of the post-implant CT
  - The underdose location

BUT ALSO:

-Results given in terms of biochemical control (almost the rule); this biochemical control depends on local control (expected to be related to dose), but also on “distant” control (this essentially for high-risk patients), with no (or much less) relation to local dose (?)

-The percentage of patients receiving Androgen deprivation therapy (ADT). Large variations from one series to another may introduce a bias in biochemical control in some instances.

-The follow-up, which may be inadequate in some series.

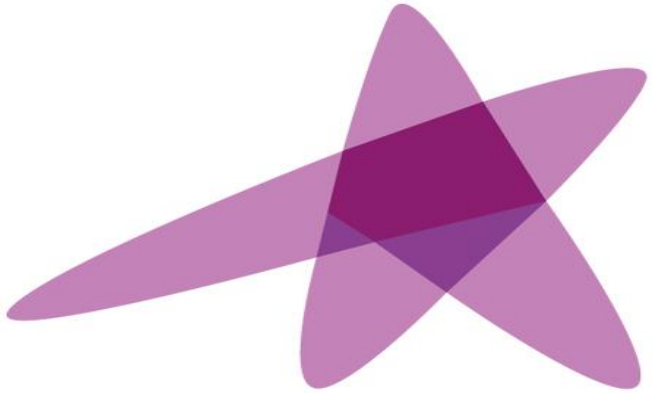
-The narrow range in D90 in most of the modern series

-……..

Post-implant dosimetry :

Do it but do not overestimate it


Thank you



ESTRO School

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Incidence of Complications of Prostate Brachytherapy

S. Machtens

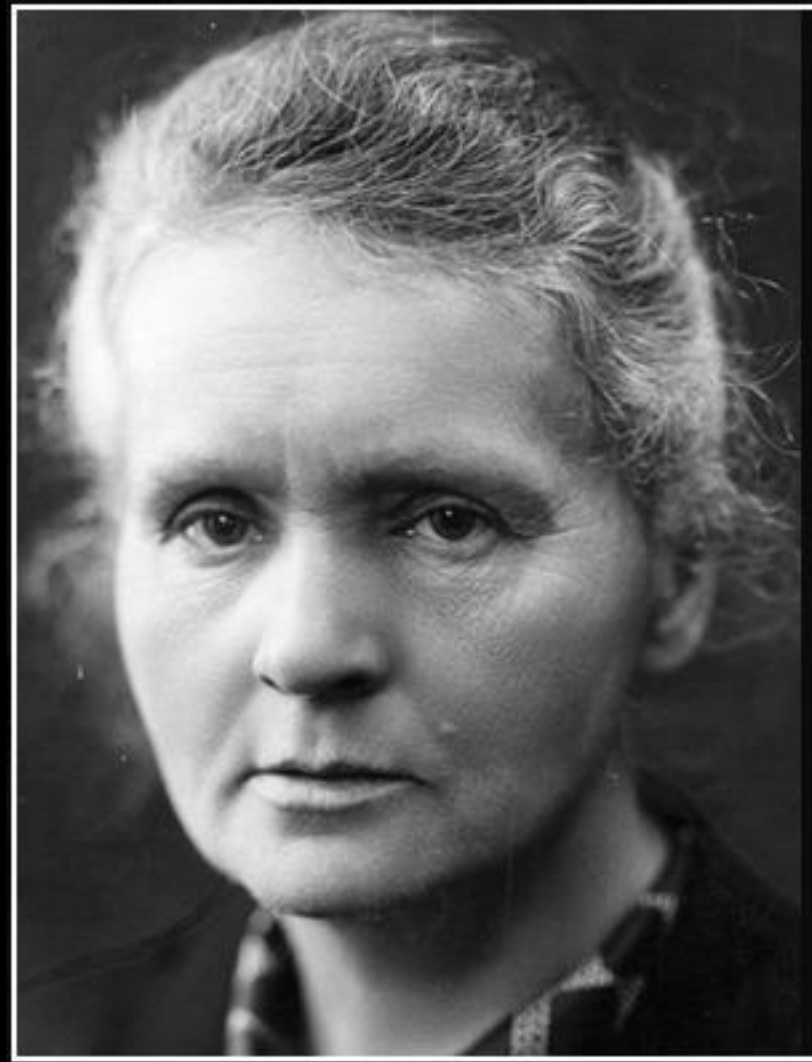
Director of the

Department of Urology and Paediatric Urology

Academic Teaching Hospital

Marien-Hospital Bergisch Gladbach

ESTRO Teaching Course
14th-16th June 2018



Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

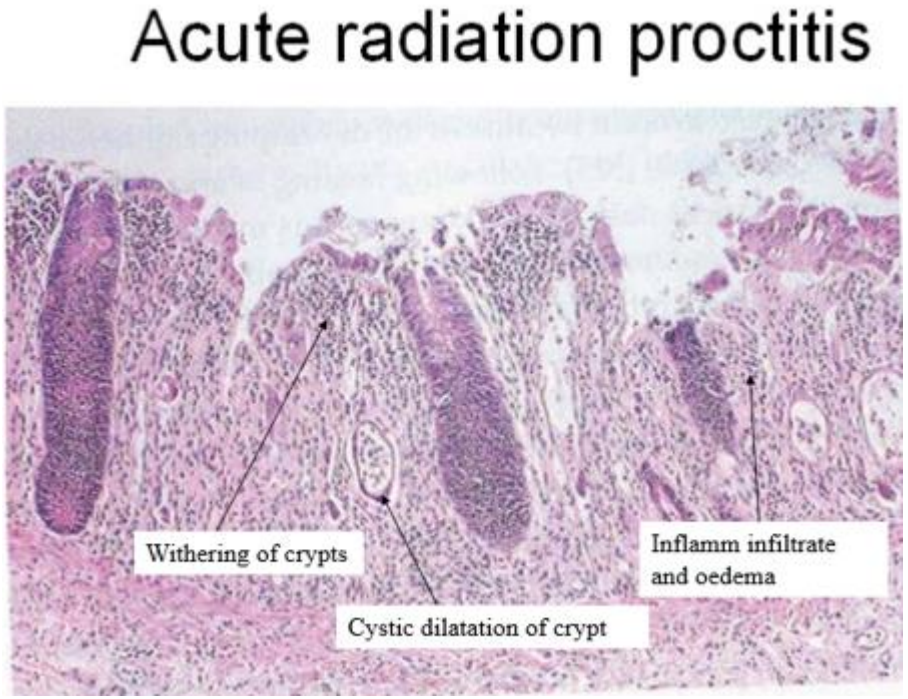
— Marie Curie —

Radiation proctitis - Acute

Pathophysiology

Histopathology findings

- Transient mucosal atrophy
- Submucosal oedema
- Inflammation and infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells
- In addition, mitotic arrest, karyorrhexis, and lysis of the crypt and deep epithelial cells



Radiation proctitis - **Acute**

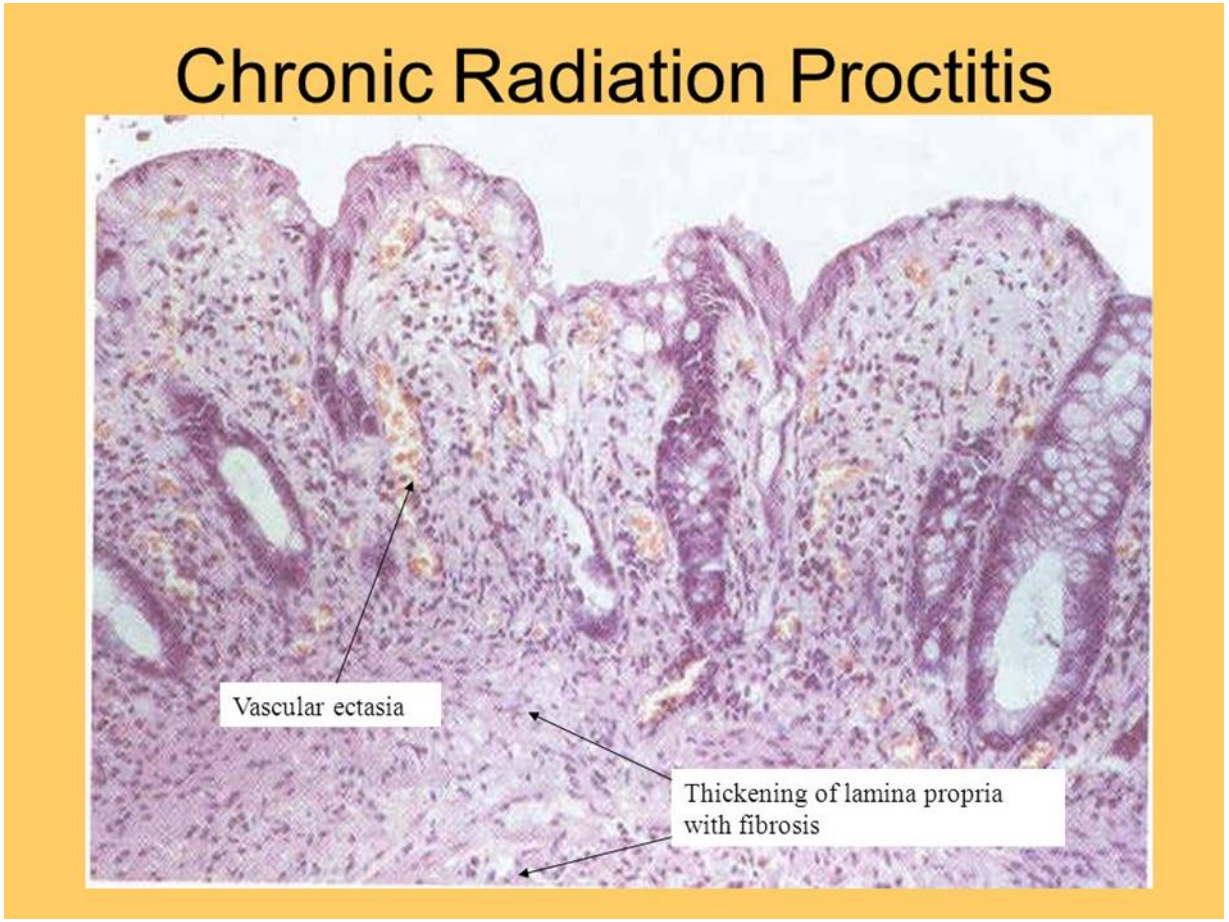
- If the submucosal damage is not prominent, the epithelial cells regenerate and the changes regress.
- Severe submucosal changes leads to progression of mucosal injury, ulcerations, and erosion of the villi.
- histologic findings in the acute phase correlate poorly with clinical symptoms.

Normal tissue effects and injury – **Acute effects** – LDR prostate brachytherapy – **rectal mucosa**

	Acute effects	symptoms	outcome	management
Rectal mucosa	Inflammation, oedema, hyperaemia, cellular loss with loss of epithelial integrity	• diarrhoea • tenesmus • mucoid discharge • haematochezia • anorectal pain • cramps	• Mostly self-limiting • Resolves spontaneously • Typically takes a few months • Does not generally convey risk of late complications	Reassurance Pharmacological • Antidiarrhoeals • Antispasmodics • laxatives • Dietary modification • Steroid enemas

Radiation proctitis - **Chronic**

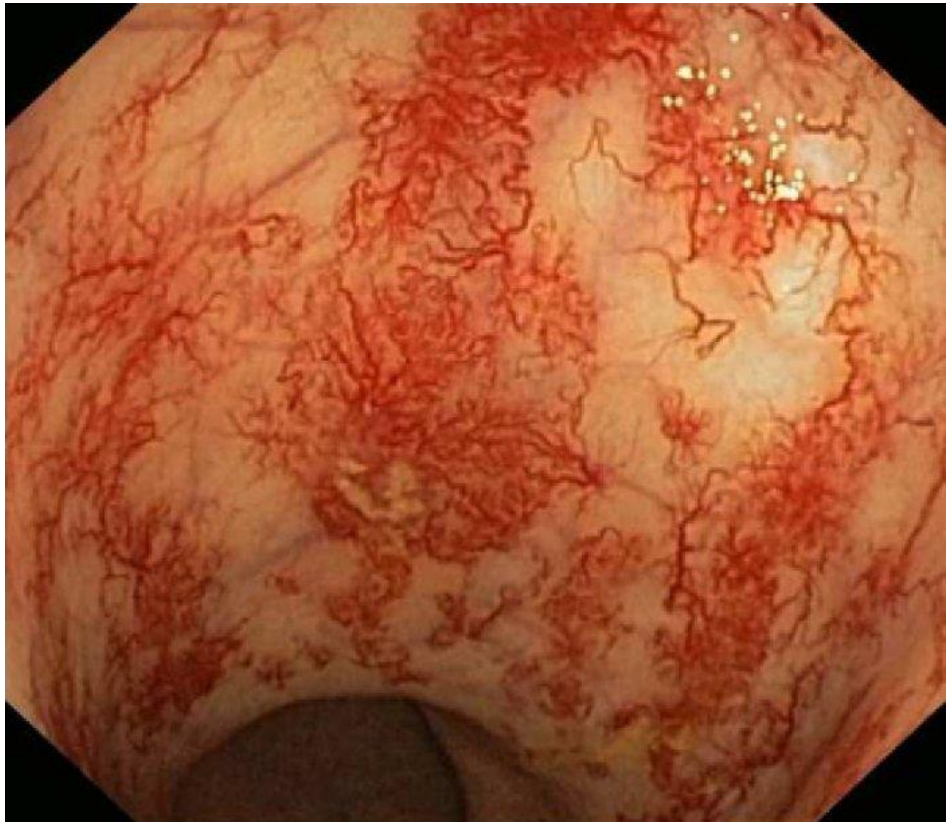
- Repopulation of the mucosal cells occurs in the later stage of the acute phase
- The severity of the damage to supportive connective tissue limits the degree of reepithelialization
- Fibrosis of the underlying connective tissue causes patchy ischemia of the mucosa, which may cause ulceration
- Local trauma or infection often precipitates these ulcers



Radiation proctitis - **Chronic**

Histological findings

- obliterative endarteritis of the small vessels in the intestinal wall characterizes chronic radiation intestinal injury
- Associated lymphoid atrophy, lymphatic dilation, and fibrosis of the submucosal tissue are observed
- The progressive vascular sclerosis leads to chronic ischemia of the overlying tissue, ultimately resulting in mucosal atrophy
- Scar tissue replaces the submucosal tissue, resulting in further decrease in vascularity and contracture of the intestinal wall
- Chronic mucosal ulceration may result in fistula formation and hemorrhage



Rectal Morbidity

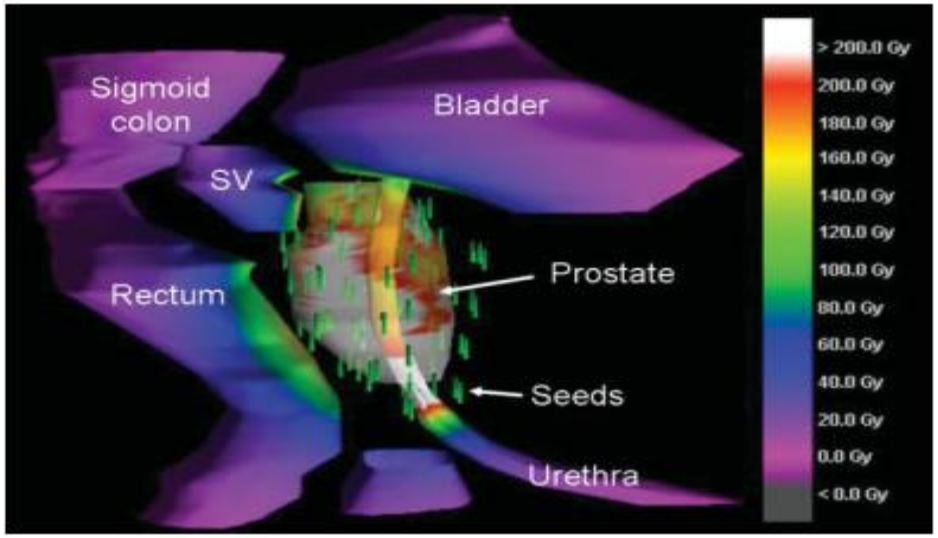
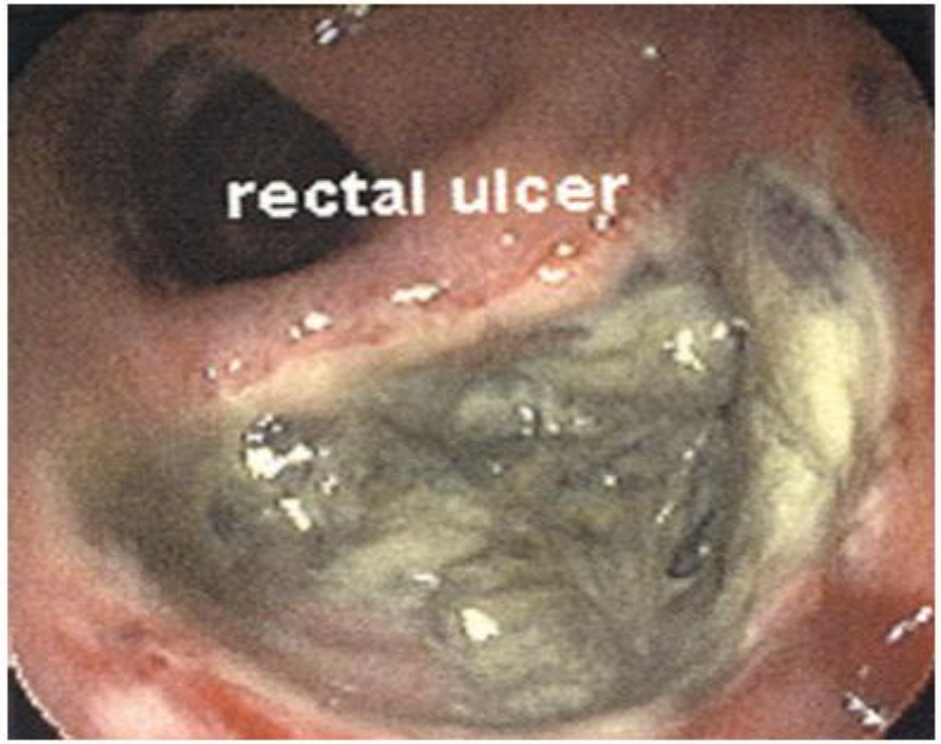


FIGURE 1. A typical 3-dimensional-rendered plan (lateral view) of a stranded seed implant. The close proximity of the anterior rectal makes it difficult to limit radiation dose to this area without compromising prostate dose coverage. Stranded seeds were used to maintain better seed spacing and alignment. SV indicates seminal vesicle; Gy, grays.



Classification of Rectal Morbidity

Table 1. Modified Radiation Therapy Oncology Group Rectal Toxicity Scale

Grade 1	Mild and self-limiting	Minimal, infrequent bleeding or clear mucous discharge, rectal discomfort not requiring analgesics, loose stools not requiring medications
Grade 2	Managed conservatively, lifestyle (performance status) not affected	Intermittent rectal bleeding not requiring regular use of pads, erythema of rectal lining on proctoscopy, diarrhea requiring medications
Grade 3	Severe, alters patient lifestyle	Rectal bleeding requiring regular use of pads and minor surgical intervention, rectal pain requiring narcotics, rectal ulceration
Grade 4	Life-threatening and disabling	Bowel obstruction, fistula formation, bleeding requiring hospitalization, surgical intervention required

RTOG indicates Radiation Therapy Oncology Group.

Cancer 2009;115:1827–39.

Overestimation of Contact between posterior prostate and rectum in CT

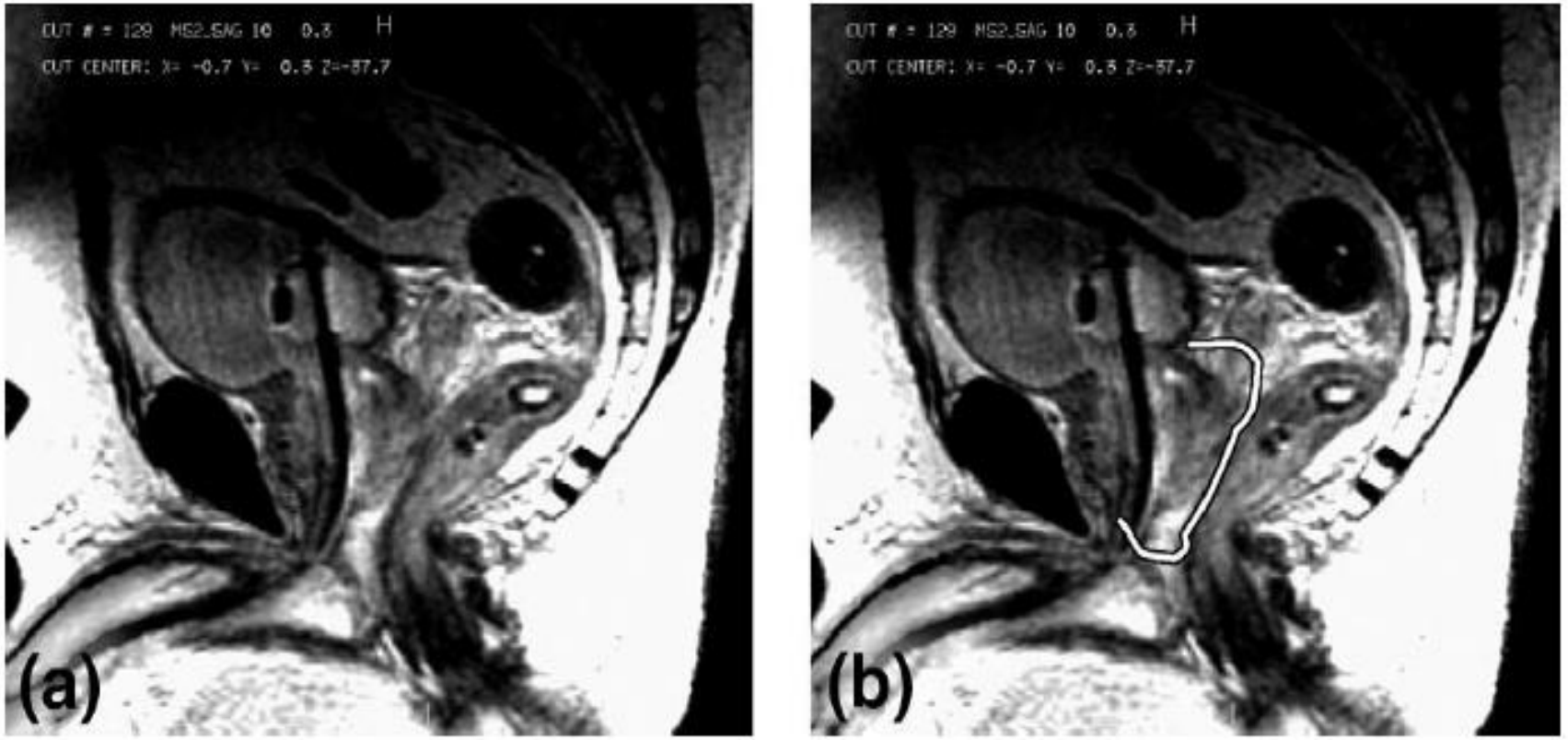


Fig. 8. Contact of prostate and rectum. (a) Minimal contact by magnetic resonance imaging. (b) White line demonstrates a typical computed tomography prostate contour drawn in reference to rectum.

RECTAL TOXICITY PROFILE AFTER TRANSPERINEAL INTERSTITIAL PERMANENT PROSTATE BRACHYTHERAPY: USE OF A COMPREHENSIVE TOXICITY SCORING SYSTEM AND IDENTIFICATION OF RECTAL DOSIMETRIC TOXICITY PREDICTORS

JINESH N. SHAH, M.D., AND RONALD D. ENNIS, M.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 3, pp. 817–824, 2006

0360-3016/06/$–see front matter

- **Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.**
- **n=135 patients; median follow-up:41months**
- **65% Iodine-125**
- **33% with HT**

Table 4. Rates of acute and late rectal toxicities by grade for each adverse rectal event item (expressed as percentages of total number of patients)

Adverse rectal event item	Acute toxicity (% of patients)			Late toxicity (% of patients)		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Diarrhea	82.6	16.7	0.8	92.7	7.3	0
Incontinence	94.7	5.3	0	96.7	3.3	0
Urgency	90.2	9.8	0	93.5	6.5	0
Proctitis	91.7	5.3	3.0	95.9	3.3	0.8
Pain	90.9	7.6	1.5	97.6	1.6	0.8
Spasms	99.2	0.8	0	99.2	0.8	0
Hemorrhage	91.7	8.3	0	92.7	7.3	0
Maximum	62.1	34.1	3.8	82.1	17.1	0.8

JINESH N. SHAH, M.D., AND RONALD D. ENNIS, M.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 3, pp. 817–824, 2006

0360-3016/06/$–see front matter

Study	No. of Patients	Year(s)	Median Follow-Up, mo	Hormones, %	EBRT, %	AE Criteria	5-Year Actuarial Incidence of Late Rectal Toxicity, %		
							Grade 2	Grade 3	Grade 4
Phan 2008[38]	263	1998-2006	68	55	0	Modified RTOG	3.7	0.4	0
Zelefsky 2007[37]	562	1998-2004	40	31	0	NCI CTCAE	6	1	NR
Zelefsky 2007[15]	367	1998-2002	63	35	0	NCI CTCAE	7	1	0.3
Martin 2007[39]	396	1994-2001	60	65	0	Modified RTOG	<1	0	0
Albert 2003[41]	201	1997-2002	34	NR	33	Modified RTOG	18	8	NR
Waterman & Dicker 2003[17]	98	1997-1999	32	0	0	Modified RTOG	9.8	<1	0
Zelefsky 2000[14]	248	1989-1996	48	NR	NR	Modified RTOG	9	0	0.4
Gelblum & Potters 2000[16]	825	1992-1998	48	NR	17	Modified RTOG	6.6	0.5	NR

Phan et al., Cancer 115:1827-1839, 2009

Rectal toxicity and rectal dosimetry in low-dose-rate iodine-125 permanent prostate implants: A long-term study in 1006 patients

Mira Keyes[1,*], Ingrid Spadinger[1], Mitchell Liu[1], Tom Pickles[1], Howard Pai[2], Amy Hayden[1], Veronika Moravan[1], Ross Halperin[3], Michael McKenzie[1], Winkle Kwan[4], Alexander Agranovic[4], Vince Lapointe[1], W. James Morris[1]

RESULTS: Rectal dosimetry in 93.5% and rectal toxicity in 96.2% have been recorded. Median VR_{100} = 1.05 cc. Late RTOG Grades 0, 1, 2, 3, and 4 were recorded in 68%, 23%, 7.3%, 0.9%, and 0.2% patients, respectively. On multivariate analysis, acute RTOG ≥2 rectal toxicity was associated with urinary retention ($p = 0.036$) and learning curve ($p = 0.015$); late RTOG ≥2 was associated with the presence of acute toxicity ($p = 0.0074$), higher VR_{100} ($p = 0.030$) and learning curve ($p = 0.027$).

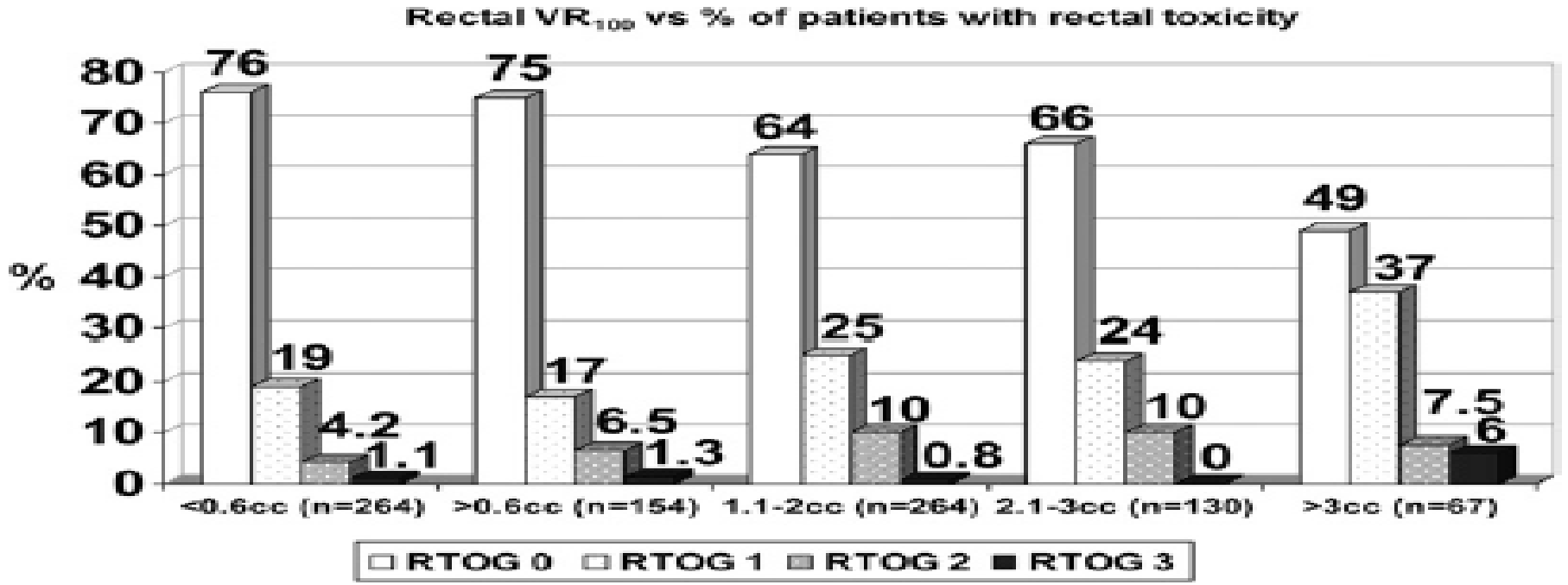


Fig. 1. Percentage of patients with late rectal toxicity by rectal V_{100cc}, patients with available toxicity data ($\geq$12 months followup) and available rectal dosimetry ($n = 879$). For each dose—volume histogram group, we gave number of patients and percentage of patients in the group with Radiation Therapy Oncology Group (RTOG) 0, 1, 2, and $\geq$3 toxicity. For patients with $VR_{100} \leq 3$ cc incidence of RTOG 3 is 0.8%. For those with $VR_{100} > 3$ cc, incidence of RTOG $\geq$3 is 6%.

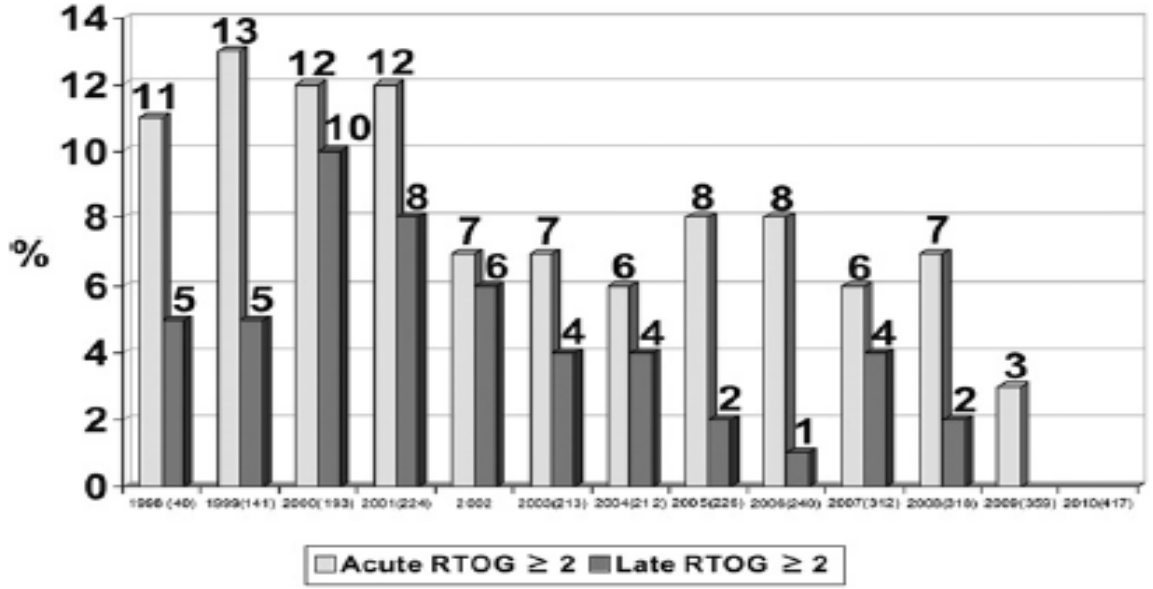


Fig. 3. Institutional crude Radiation Therapy Oncology Group ≥2 acute and late rectal toxicity, expressed as a percentage of patients wit toxicity recorded for each implant year 1998–2009.

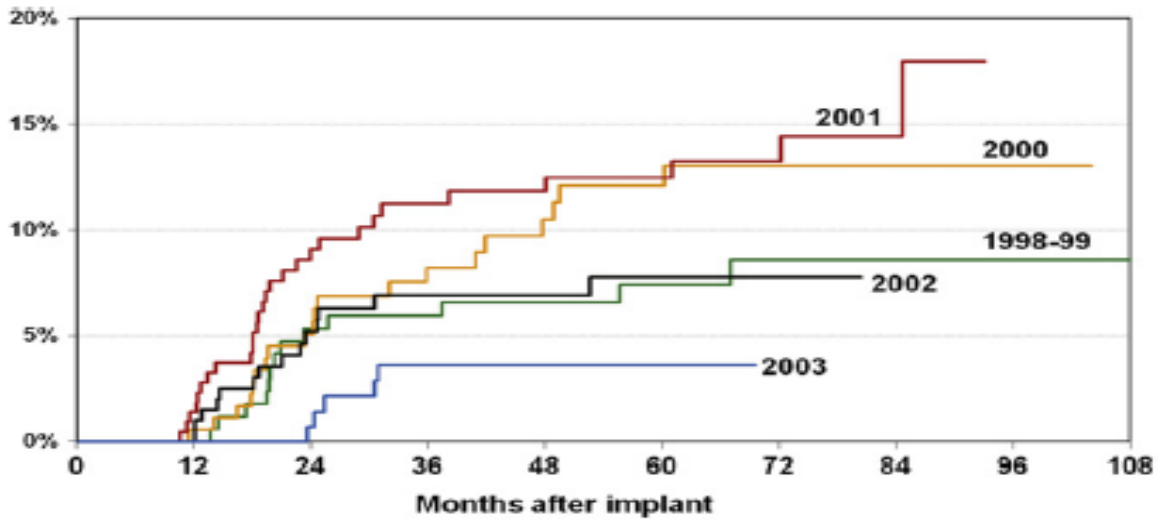
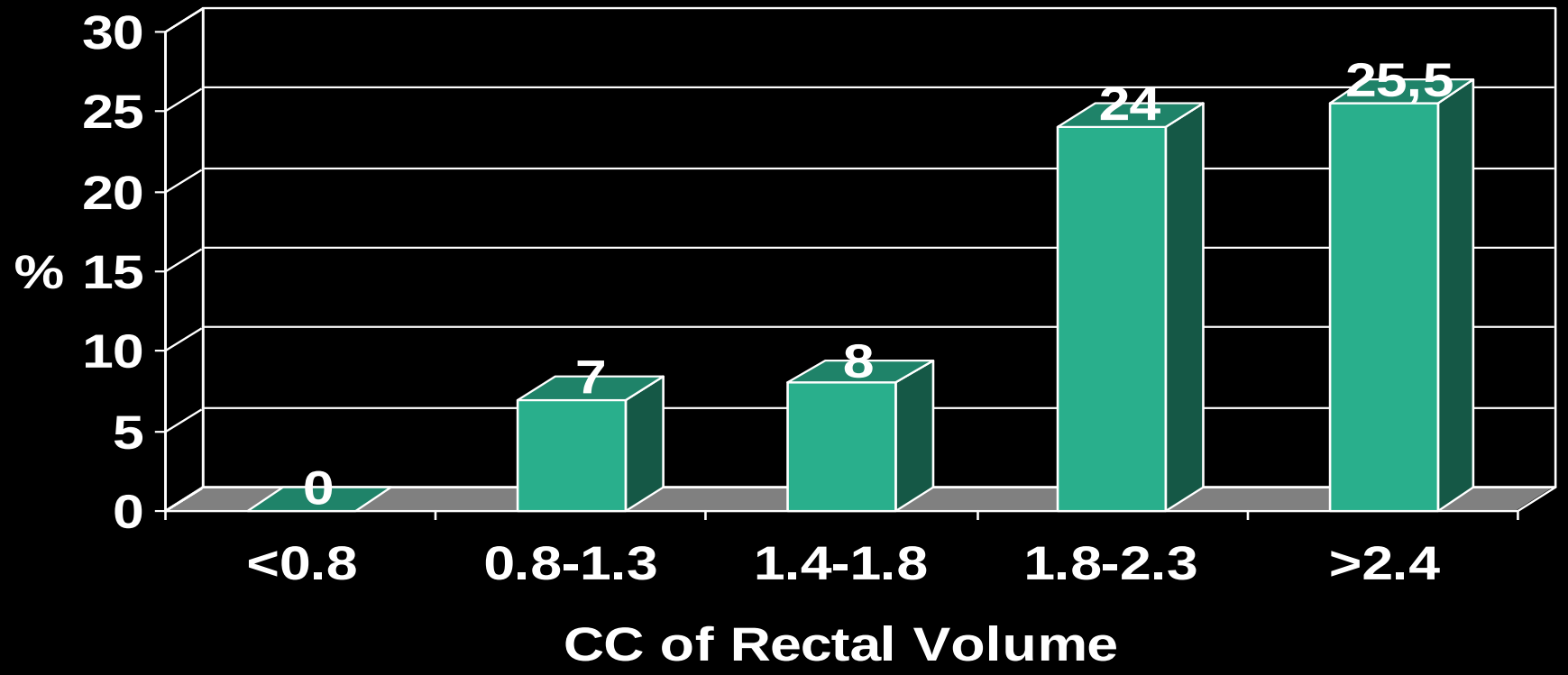


Fig. 2. Kaplan–Meier curves for late rectal Radiation Therapy Oncology Group ≥2, illustrating the institutional learning curve.

Proctitis rate for rectal volume irradiated with 160Gy



[Snyder et al., Int J Radiat Oncol Biol Phys, 2001]

dose constraints - Rectum

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J Radiat Res. 2012 Nov; 53(6): 923–929. PMCID: PMC3483856
Published online 2012 Aug 1. doi: 10.1093/jrr/rrs059

Risk factors for rectal bleeding associated with I-125 brachytherapy for prostate cancer

Kosaku Harada,[1,*] Hitoshi Ishikawa,[1] Yoshitaka Saito,[2] Soken Nakamoto,[1] Hidemasa Kawamura,[3] Masaru Wakatsuki,[3] Toru Etsunaga,[2] Yutaka Takezawa,[2] Mikio Kobayashi,[2] and Takashi Nakano[3]

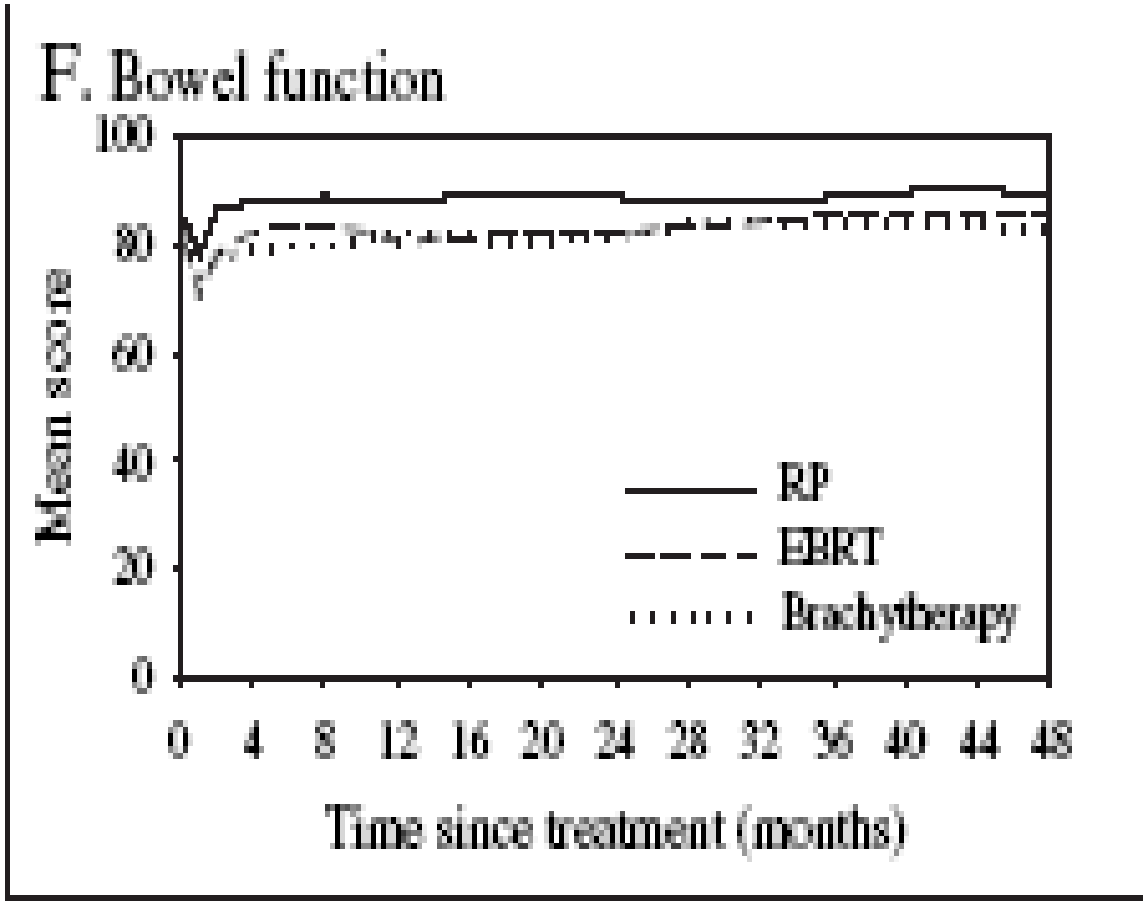
Rectum RV100 (145Gy)	Gr 1 bleed Median 20 months *p=0.02*	Grade 2 or higher
>1cm³	36%	0
<1cm³	14%	0

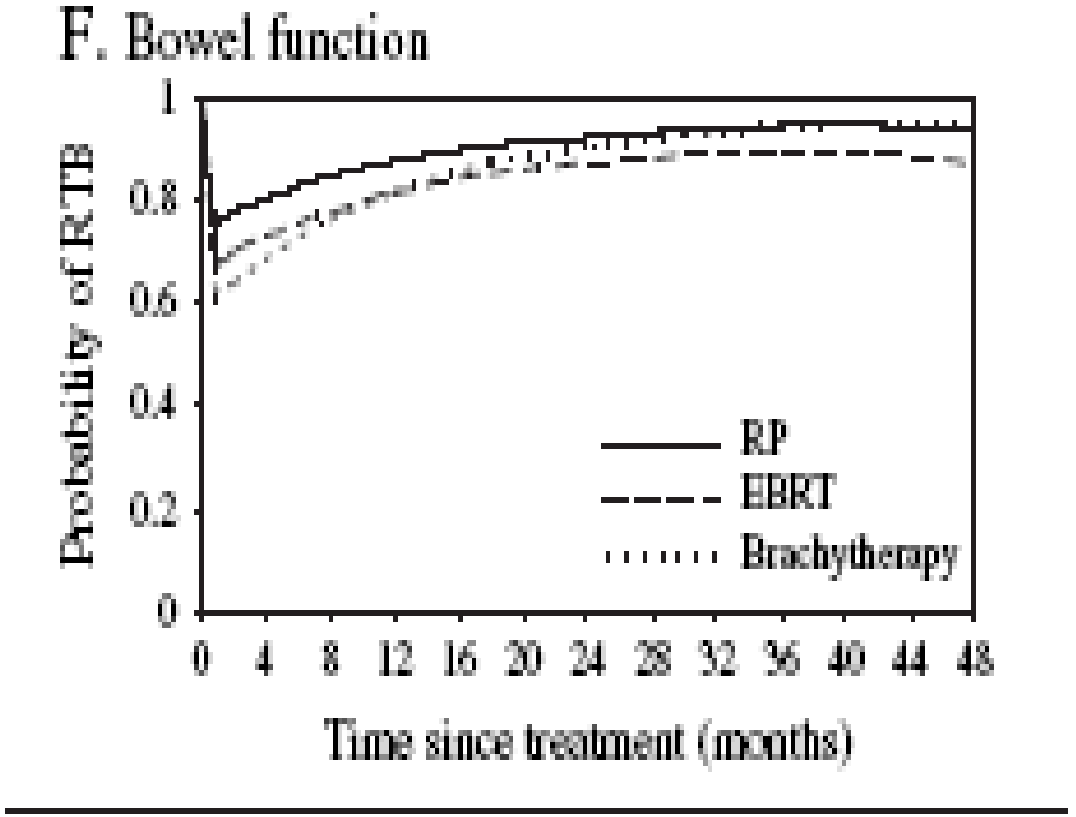
Caution! Dose constraint for 145Gy not 160Gy

Survivorship Beyond Convalescence: 48-Month Quality-of-Life Outcomes After Treatment for Localized Prostate Cancer

John L. Gore, Lorna Kwan, Steve P. Lee, Robert E. Reiter, Mark S. Litwin

J Natl Cancer Inst 2009;101:888–892





Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy

Carl Salembier[a], Pablo Lavagnini[b], Philippe Nickers[c], Paola Mangili[d], Alex Rijnders[a], Alfredo Polo[e], Jack Venselaar[f], Peter Hoskin[g,*], on behalf of the PROBATE group of GEC ESTRO

ELSEVIER

Brachytherapy 11 (2012) 6–19

BRACHYTHERAPY

American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy

Brian J. Davis[1,*], Eric M. Horwitz[2], W. Robert Lee[3], Juanita M. Crook[4], Richard G. Stock[5], Gregory S. Merrick[6], Wayne M. Butler[6], Peter D. Grimm[7], Nelson N. Stone[8], Louis Potters[9], Anthony L. Zietman[10], Michael J. Zelefsky[11]

- Dose to 2cm³ <145-150Gy
- Volume receiving 100% of the prescription on post-op CT should be <1cm³ for a D1 CT or <1.3cm³ for a D30 CT

Rectum	GEC-ESTRO	ABS
D2cc	<145Gy	<150%
D0.1cc (~Dmax)	<200Gy	
V100		<1cc on D1 CT <1.3cc on D30 CT

Genetic influence on rectal morbidity?

- **Genetic alterations in the ATM (Ataxia Teleangiectasia) gene are associated with rectal bleeding.**

- **4/13 (31%) vs 1/23 (4%) if MPD <0,7cm^3**
- **4/11 (36%) vs 1/21 (5%) if MPD 0,7-1,4cm^3**

Cesaretti et al; Int J Radiat Oncol Biol Phys, 2007]

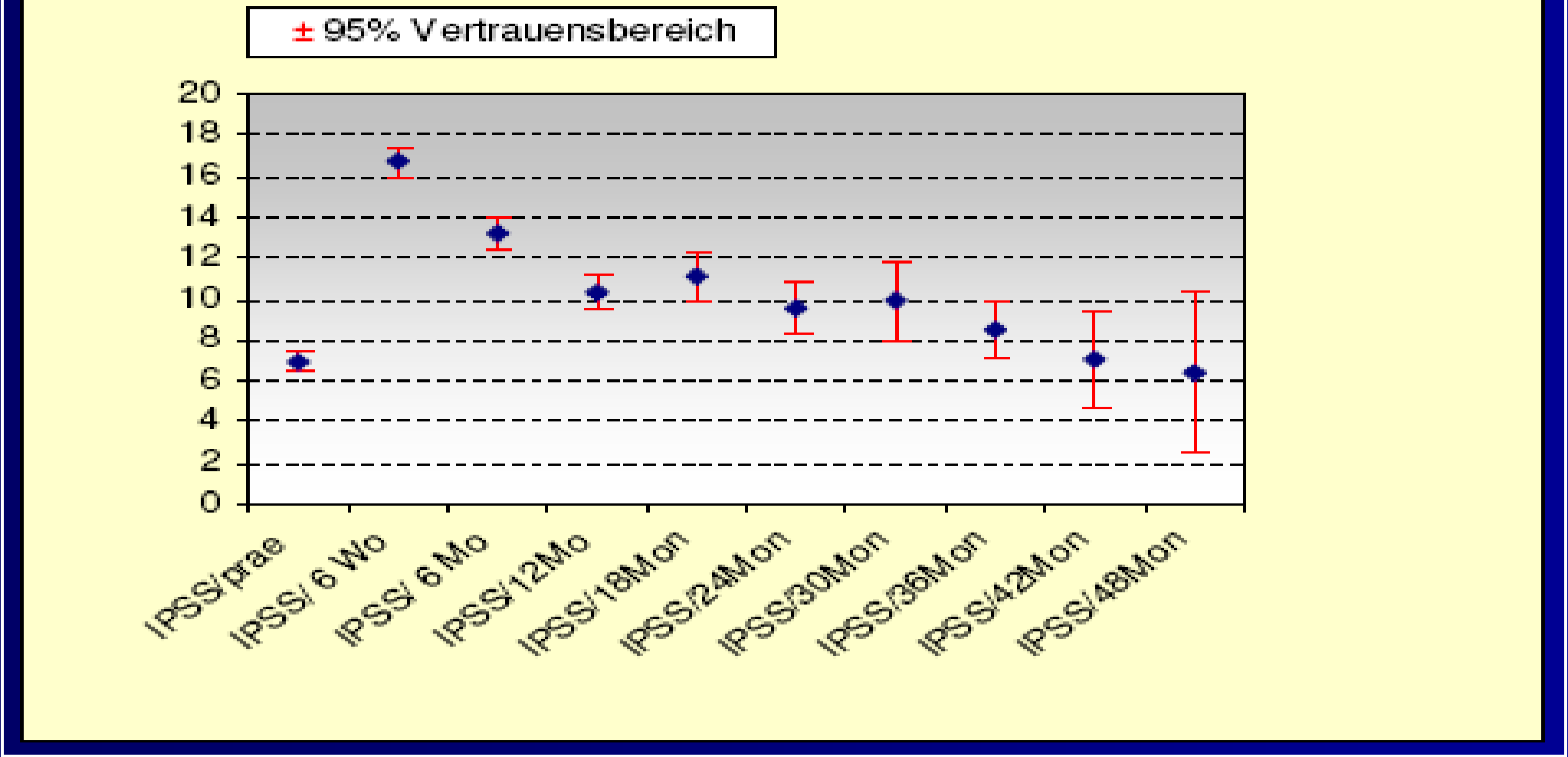
Normal tissue effects and injury – **Acute effects**
LDR prostate brachytherapy - **urothelium**

	Acute effects	symptoms	outcome	management
urothelium	Inflammation, oedema, hyperaemia, cellular loss with loss of epithelial integrity	irritative and obstructive – • Burning • urgency • frequency • nocturia • urge incontinence • urinary retention • haematuria • spasmodic pain	• Mostly self-limiting • Resolves spontaneously • Symptoms subside gradually as radiation diminishes. • Typically takes 6-12 months • Do not generally convey risk of late complications	Supportive Reassurance Pharmacological – • NSAID • Cortisone • cholinergic agonists • alpha-adrenergic blocking agents • anticholinergic agents • tricyclic antidepressants (TCAs) • sympathomimetic agents • Dr Stone's urethral instillation formula Catheterization for retention

Normal tissue effects and injury – **late effects**
LDR prostate brachytherapy - **urothelium**

	Chronic effects	symptoms	findings	management
urothelium	Chronic Inflammation +/- oedema, ulceration, telangiectasia, fibrosis, ischaemia	irritative and obstructive symptoms persisting for over 1 year • Burning • urgency • frequency • nocturia • urge incontinence • urinary retention • haematuria • spasmodic pain	Rigid, ischaemic tissue, ulceration, telangiectasia, haemorragic epithelium, fibrotic distortion, friable atrophic tissue, necrosis fistula, stricture, perforation, obstruction	Dr Jeff Glocer

IPSS (international prostatic symptom score) im Zeitverlauf



The pathophysiology of lower urinary tract symptoms after brachytherapy for prostate cancer

Jerry G. Blaivas, Jeffrey P. Weiss and Mark Jones
The Joan and Sanford I. Weill Medical College of Cornell University, New York, NY, USA

JOURNAL COMPILATION © 2006 BJU INTERNATIONAL | 98, 1233–1237 | doi:10.1111/j.1464-410X.2006.06491.x

- **Comparison of 47 men with LUTS after brachytherapy with 541 men with LUTS without prostate cancer.**
- **Significant more detrusor overactivity (47 vs.85%) after brachytherapy.**
- **Higher incidence of urethral and prostatic strictures.**

Urinary incontinence following Brachytherapy

Study	Patient number	Treatment	Incontinence(%)
Wallner	92	^{125}J	6
Storey	206	^{125}J	10
Machtens	452	^{125}J	1,8
Blasko	184	$^{125}J/^{103}Pd$	0
Talcott	105	$^{125}J/^{103}Pd$	15
Gelblum	693	$^{125}J/^{103}Pd$	0,7
Benoit	2124	$^{125}J/^{103}Pd$	6,6
Talcott	13	TUR-P + Implant	85
Ragde	48	TUR-P + Implant	12,5
Stone	43	TUR-P + Implant	0
Terk	6	Implant + TUR-P	0
Gelblum	28	Implant + TUR-P	17

Radiotherapy and Oncology 82 (2007) 46—49
www.thegreenjournal.com

Prostate brachytherapy

Side effects of permanent I125 prostate seed implants in 667 patients treated in Leeds

David Bottomley[a], Dan Ash[a], Bashar Al-Qaisieh[b,*], Brendan Carey[a], Joji Joseph[a], Shaun St Clair[b], Kathy Gould[a]

[a]*Regional Cancer Treatment Centre, and* [b]*Medical Physics Department, Cookridge Hospital, Leeds, UK*

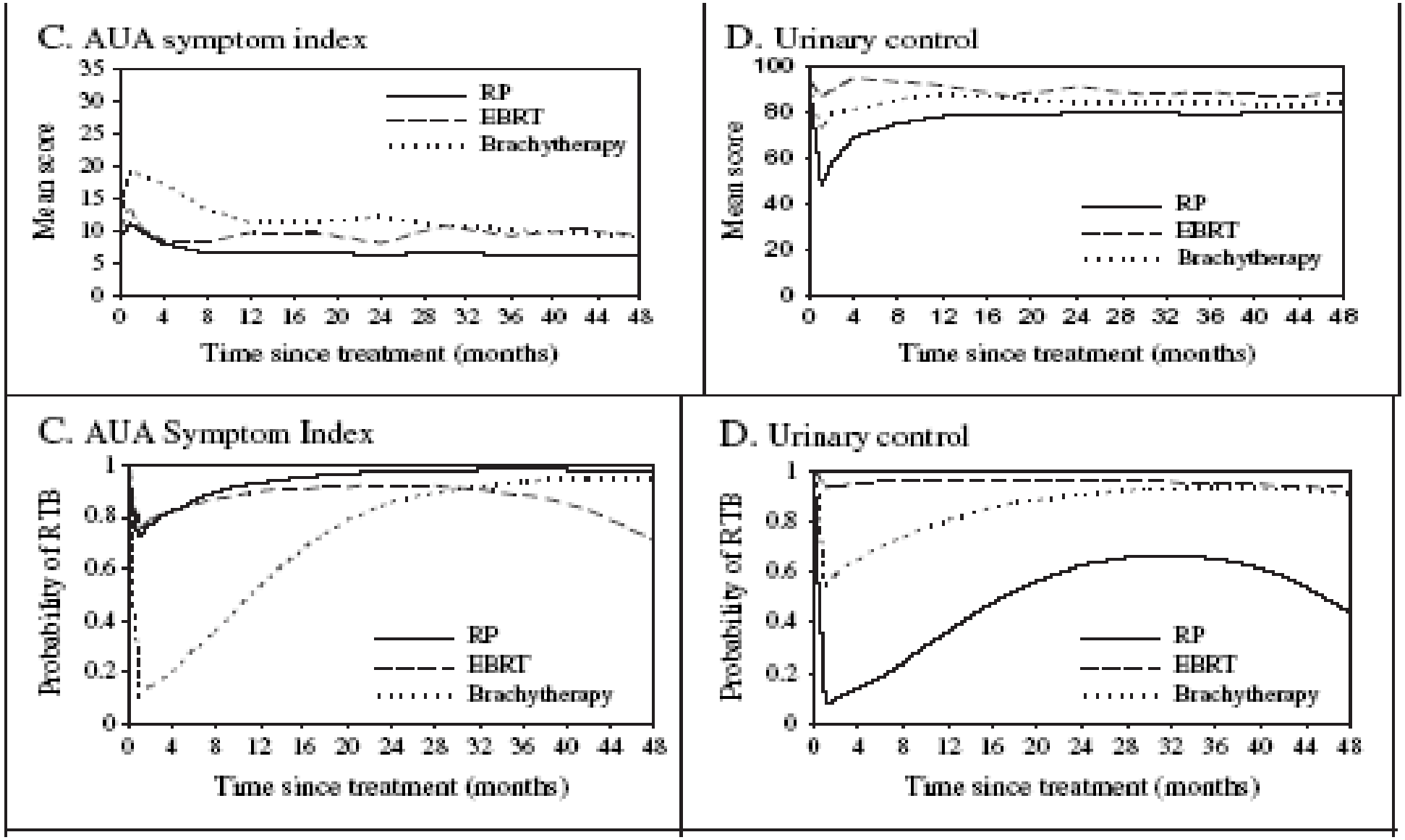
- **667 patients with a median follow-up of 31 months**

Table 2
Incontinence after treatment ($n = 667$)

Follow-up period	*n* (%)
Pre-treatment	9 (1.4%)
Post-treatment	
6 months	15 (2.3%)
12 months	12 (1.8%)
24 months	10 (1.5%)

Table 6
Logistic-regression analysis to determine factors contributing to patients being catheterised after treatment

Regressor	*P* value
Pre treatment prostate volume	<0.0001
Year of implant	0.015
Number of seeds implanted	0.005
Number of needles implanted	0.008
Hormone	0.020
Mean central dose ($n = 413$)	0.037
D_{90} ($n = 413$)	0.867



John L. Gore, Lorna Kwan, Steve P. Lee, Robert E. Reiter, Mark S. Litwin

J Natl Cancer Inst 2009;101:888–892

Urinary retention Rate

Study	Patient number	Treatment	Retention rate(%)
Blasko	196	^{125}J	7
Vijverberg	46	^{125}J	22
Wallner	92	^{125}J	14
Storey	206	^{125}J	11
Terk	251	$^{125}J/^{103}$ Pd	5
Kaye	76	EBRT/^{125}J	5
Dattoli	73	EBRT+^{103}Pd	7
Ragde	152	EBRT/$^{125}J/^{103}Pd$	10
Merrick	170	EBRT/$^{125}J/^{103}Pd$	6
Benoit	1409	EBRT/$^{125}J/^{103}Pd$	14,5
Machtens	452	^{125}J	4,5

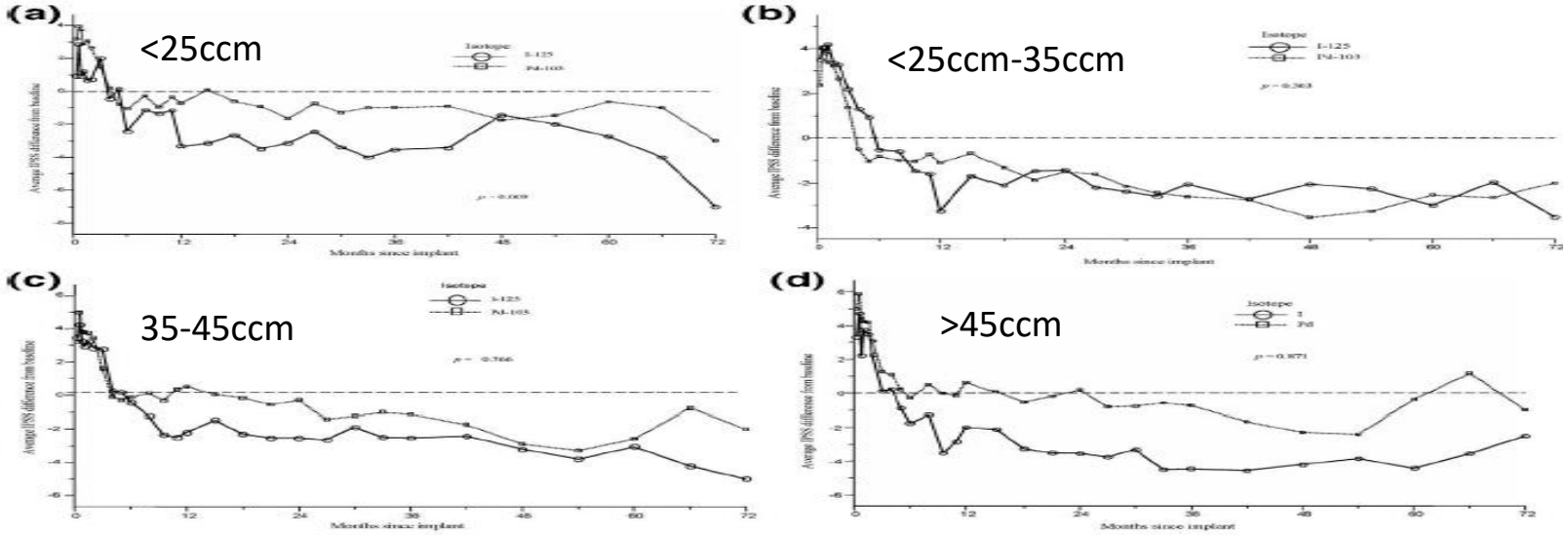
THE INFLUENCE OF ISOTOPE AND PROSTATE VOLUME ON URINARY MORBIDITY AFTER PROSTATE BRACHYTHERAPY

ANGELA NIEHAUS, B.S.,* GREGORY S. MERRICK, M.D.,* WAYNE M. BUTLER, PH.D.,* KENT E. WALLNER, M.D.,† ZACHARIAH A. ALLEN, M.S.,* ROBERT W. GALBREATH, PH.D.,*‡ AND EDWARD ADAMOVICH, M.D.§

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 1, pp. 136–143, 2006

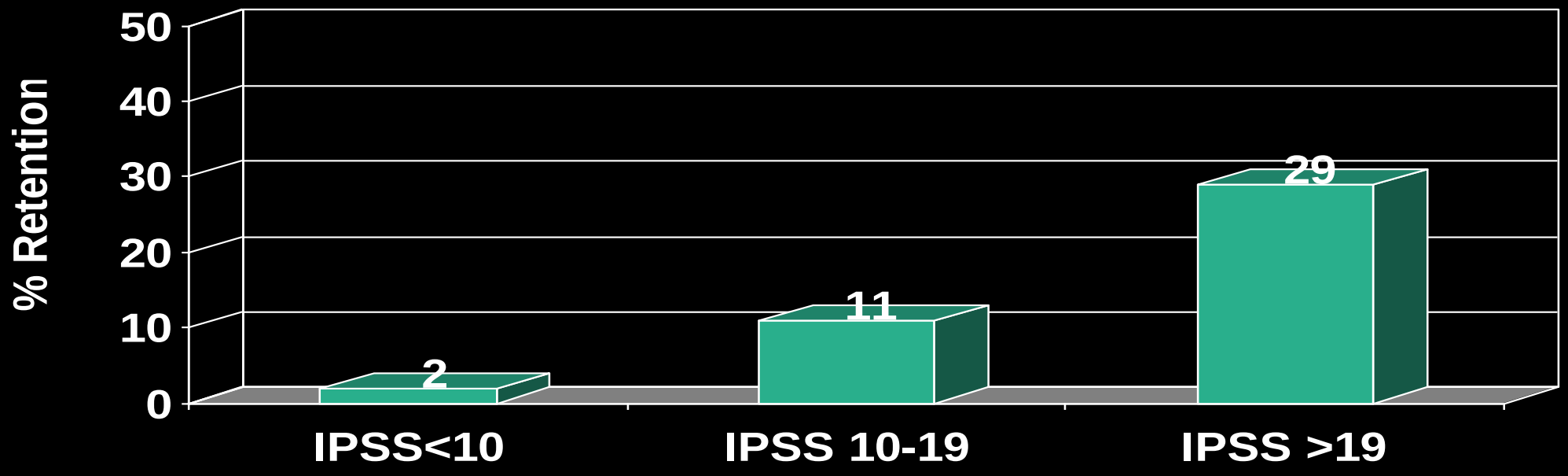
0360-3016/06/$–see front matter

N=976; median Follow-up: 41,2months



Conclusion: Higher acute retention (<5days), but equal resolution

Identification of patients with higher risk for urinary retention



Terk, Stock and Stone, J Urol, 160: 379, 1998

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1445–1449, 2010

0360-3016/10/$–see front matter

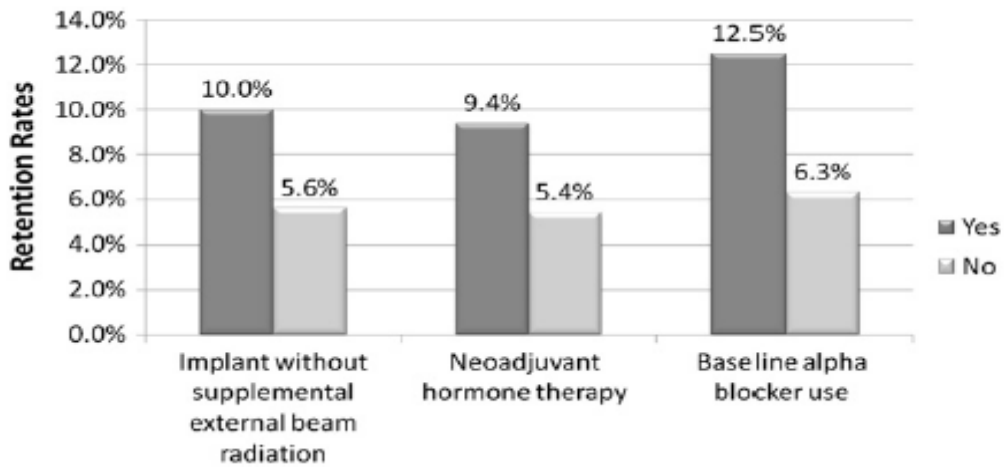
doi:10.1016/j.ijrobp.2009.04.008

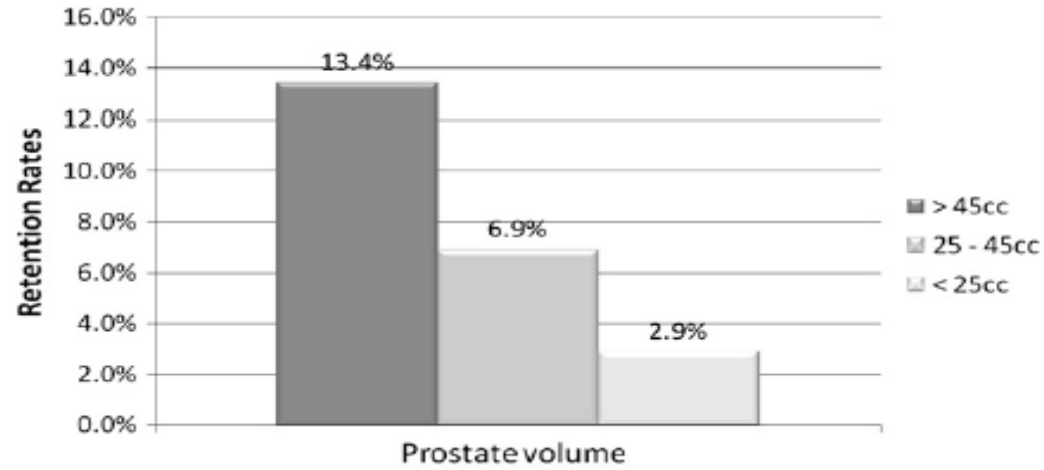
CLINICAL INVESTIGATION **Prostate**

SEED IMPLANT RETENTION SCORE PREDICTS THE RISK OF PROLONGED URINARY RETENTION AFTER PROSTATE BRACHYTHERAPY

Hoon K. Lee, M.D.,*‡ Marc T. Adams, M.D.,*‡ Qiuhu Shi, Ph.D.,† Jay Basillote, M.D.,§ Joanne LaMonica, M.D.,§ Luis Miranda, M.D.,§ and Joseph Motta, M.D.§

*Regional Radiation Oncology, Staten Island, NY; †Department of Biostatistics, School of Public Health, New York Medical School, Valhalla, NY; Departments of ‡Radiation Oncology and §Urology, Richmond University Medical Center, Staten Island, NY





Prostatic length predicts functional outcomes after iodine-125 prostate brachytherapy

Raj P. Pal[1,*], Jaimin R. Bhatt[1], Masood A. Khan[1], Stuart Duggleby[2], Philip Camilleri[3], C. Richard Bell[1], Christine Elwell[3], Roger B. Kunkler[1]

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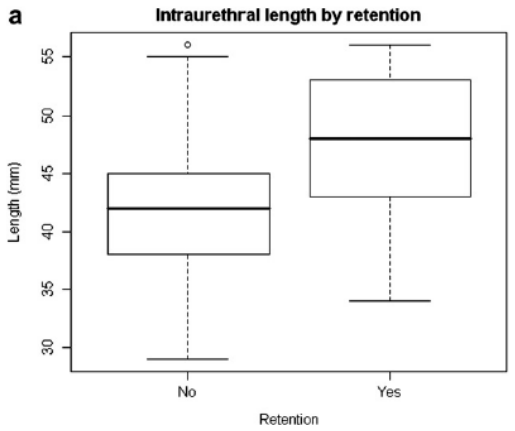
[3]*Department of Oncology, Northampton General Hospital, Cliftonville, Northampton, UK*

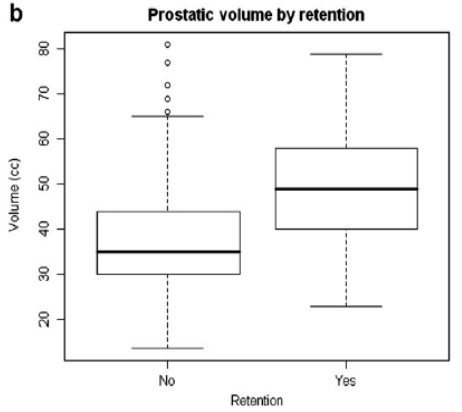
a



Prostatic urethral length

Mean difference in length = 5.77 mm
P-value < 0.001

b



Prostatic volume

Mean difference in volume = 11.24 cc
P-value < 0.001

Table 5
Multivariable logistic regression estimates for prediction of urinary retention (only statistically significant variables displayed)

Variable	Estimate	95% Confidence interval	*p*-Value
Prostatic volume (cc)	1.08	1.03, 1.09	<0.001
Intraurethral length (mm)	1.20	1.11, 1.31	<0.001
Volume:length ratio	6.55	1.23, 36.46	0.029

Clinical Investigation

Dose to the Bladder Neck Is the Most Important Predictor for Acute and Late Toxicity After Low-Dose-Rate Prostate Brachytherapy: Implications for Establishing New Dose Constraints for Treatment Planning

Lara Hathout, MD,* Michael R. Folkert, MD,* Marisa A. Kollmeier, MD,* Yoshiya Yamada, MD,* Gil'ad N. Cohen, MS,† and Michael J. Zelefsky, MD*

*Departments of *Radiation Oncology and †Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York*

Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 312–319, 2014

Methods and Materials: From July 2002 to January 2013, 927 patients with prostate cancer (median age, 66 years) underwent LDR brachytherapy with Iodine 125 (n=753) or Palladium 103 (n=174) as definitive treatment (n=478) and as a boost (n=449) followed by supplemental EBRT (median dose, 50.4 Gy). Structures contoured

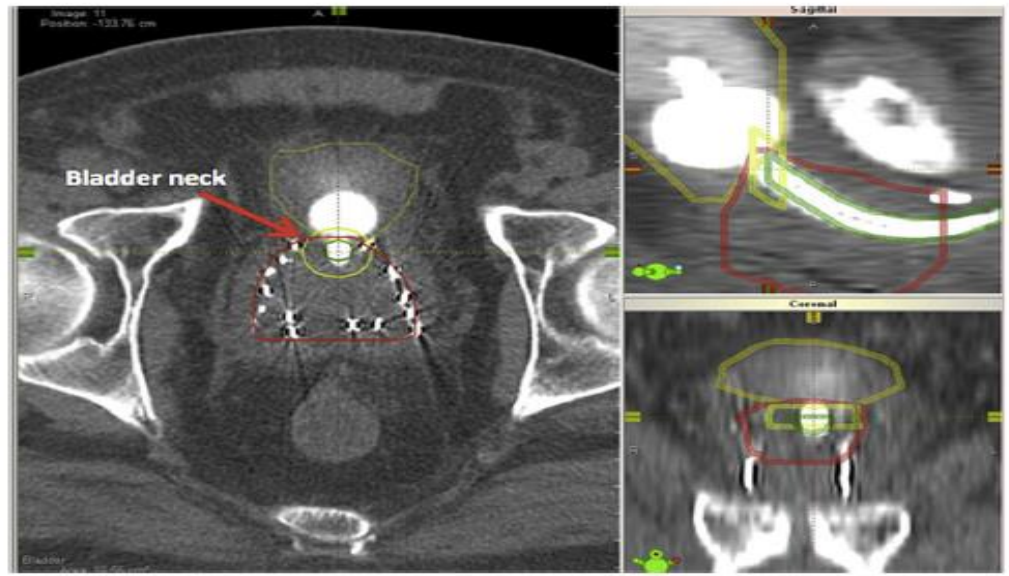


Fig. 1. Contour of bladder neck on computed tomographic scan on day 0 after implantation.

Clinical Investigation

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Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 312–319, 2014

Table 2 Univariate and multivariate analysis for acute urinary toxicity

Variable	Univariate		Multivariate	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Baseline IPSS (continuous)	.30	-	-	-
Age (continuous)	.88	-	-	-
Prostate volume on pretreatment MRI (cm^3)	<.0001	1.01 (1.01-1.02)	.43	-
Prostate V100 (continuous)	.13	-	-	-
Prostate D90 (continuous)	.02	1.013 (1.002-1.023)	.09	
Prostate V150 (continuous)	.05	-	-	-
Urethra D20 (continuous)	.41	-	-	-
Urethra D5 (continuous)	.41	-	-	-
Urethra D1 (continuous)	.93	-	-	-
Bladder V100	<.0001	1.12 (1.05-1.19)	.29	-
Bladder D2cc (continuous)	<.0001	1.01 (1.00-1.01)	.54	-
Bladder D1 (continuous)	<.0001	1.01 (1.00-1.01)	.34	-
Bladder neck V100 (continuous)	.1	-	-	-
Bladder neck D2cc	<.0001	1.04 (1.03-1.04)	<.0001	1.03 (1.03-1.04)
HI ([Prostate V100—V150]/V100)	.07	0.56 (0.30-1.06)	.2	-
Use of neoadjuvant ADT (yes vs no)	.42	-	-	-
Choice of isotope (^{103}Pd vs ^{125}I)	.94	-	-	-
Definitive treatment vs combined therapy with EBRT	<.0001	1.49 (1.25-1.78)	.008	1.32 (1.08-1.63)
Number of seeds (continuous)	<.0001	1.01 (1.01-1.02)	.24	-
Number of needles implanted (continuous)	<.0001	1.07 (1.04-1.10)	.12	-
Diabetes (yes vs no)	.35	-	-	-
Smoking habits (current vs former vs never vs unknown)	.64	-	-	-
Use of PDE-5I at diagnosis (yes vs no)	.66	-	-	-

Abbreviations: ^{103}Pd = Palladium 103; ^{125}I = Iodine 125; ADT = androgen-deprivation therapy; CI = confidence interval; HI = homogeneity index; HR = hazard ratio; EBRT = external beam modulated radiation therapy; IPSS = International Prostate Symptom Score; MRI = magnetic resonance imaging; PDE-5I = phosphodiesterase type 5 inhibitor.

Clinical Investigation

Dose to the Bladder Neck Is the Most Important Predictor for Acute and Late Toxicity After Low-Dose-Rate Prostate Brachytherapy: Implications for Establishing New Dose Constraints for Treatment Planning

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*Departments of *Radiation Oncology and †Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York*

Int J Radiation Oncol Biol Phys, Vol. 90, No. 2, pp. 312–319, 2014

Table 3 Receiver operator curve analysis for acute and late urinary toxicity

Variable	Area under the curve	*P* value	(95% CI)
Acute urinary toxicity			
Prostate V100 >90%	0.51	.63	-
Prostate D90 >100%	0.51	.58	-
Prostate V150 >60%	0.50	.94	-
Urethra D20 >130%	0.50	.81	-
Bladder neck D2cc >50%	0.697	<.0001	0.66-0.73
Late urinary toxicity			
Prostate V100 >90%	0.53	.22	-
Prostate D90 >100%	0.53	.19	-
Prostate V150 >60%	0.54	.06	-
Urethra D20 >130%	0.52	.40	-
Bladder neck D2cc >50%	0.620	<.0001	0.57-0.67

Abbreviation: CI = confidence interval.

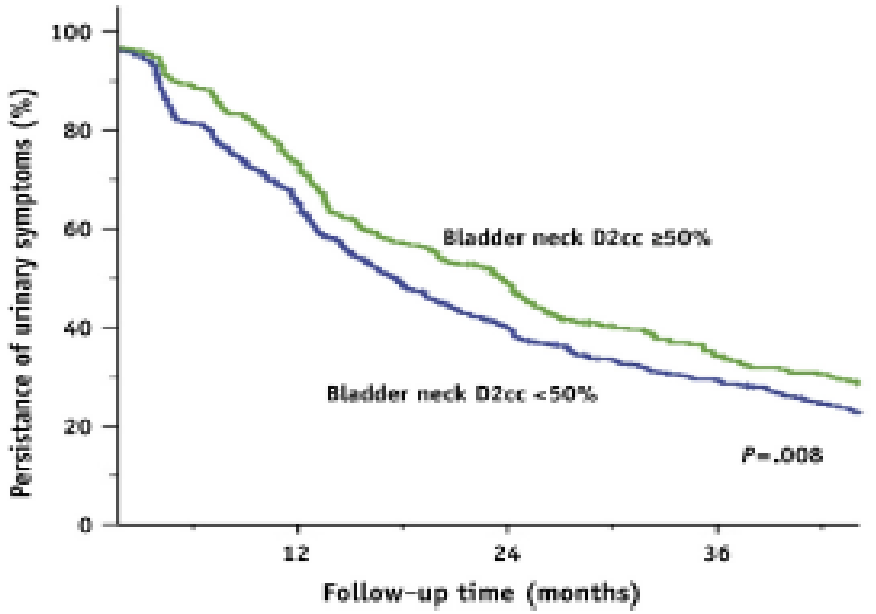

Fig. 2. Kaplan-Meier survival curves: time to International Prostate Symptom Scores resolution according to the bladder neck D2cc dose.

Focal brachytherapy for localized prostate cancer: Urinary toxicity depends on tumor location

Victor Srougi[1,2], Eric Barret[1], Igor Nunes-Silva[1], Mohammed Baghdadi[1], Silvia Garcia-Barreras[1], Noelle Pierrat[3], Francois Rozet[1], Marc Galiano[1], Rafael Sanchez-Salas[1], Xavier Cathelineau[1], Jean-Marc Cosset[1,3,4,*]

[1]*Department of Urology, Institut Montsouris, Université Paris-Descartes, Paris, France*
[2]*Division of Urology, University of Sao Paulo, Sao Paulo, Brazil*
[3]*Département d'oncologie-radiothérapie, Institut Curie, Paris, France*
[4]*Centre de radiothérapie Charlebourg-La Défense, groupe Amethyst, La Garenne-Colombes, France*

Brachytherapy 2017, in press

METHODS AND MATERIALS: The functional outcomes of patients treated with FBT at the base of the prostate were compared with those of patients treated with FBT at the apex. Urinary symptoms, continence, and erectile dysfunction were measured using the International Prostate Symptom Score (IPSS), International Continence Score (ICS), and International Index of Erectile Function (IIEF-5) questionnaires, respectively, at baseline and at 6, 12, and 24 months after treatment.

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[4]Centre de radiothérapie Charlebourg-La Défense, groupe Amethyst, La Garenne-Colombes, France

Brachytherapy 2017, in press

Table 2
Comparison of functional outcomes: apex versus base

	N		Mean score		
	Apex	Base	Apex	Base	*p*
IPSS					
Baseline	28	13	4.9 ± 5.1	6.3 ± 4.9	0.39
6 months	28	13	6.4 ± 4.7	10.6 ± 5.7	0.02
12 months	28	13	5.1 ± 4.3	7.6 ± 5.0	0.09
24 months	20	12	6.4 ± 5.2	6.2 ± 5.3	0.90
ICS					
Baseline	31	100	0.04 ± 0.2	0.08 ± 0.3	0.58
6 months	28	13	0.25 ± 0.7	0	0.21
12 months	27	13	0.59 ± 1.1	0.46 ± 0.9	0.71
24 months	20	12	0.55 ± 1.4	0.08 ± 0.3	0.26
IIEF5					
Baseline	18	12	19 ± 7.6	18 ± 6.9	0.71
6 months	26	13	14.7 ± 8.7	16.3 ± 5.6	0.56
12 months	28	13	16.5 ± 7.5	16.2 ± 6.3	0.92
24 months	20	13	17 ± 7.7	16.5 ± 7.4	0.84

IPSS = International Prostate Symptom Score; ICS = International Continence Score; IIEF-5 = International Index of Erectile Function.

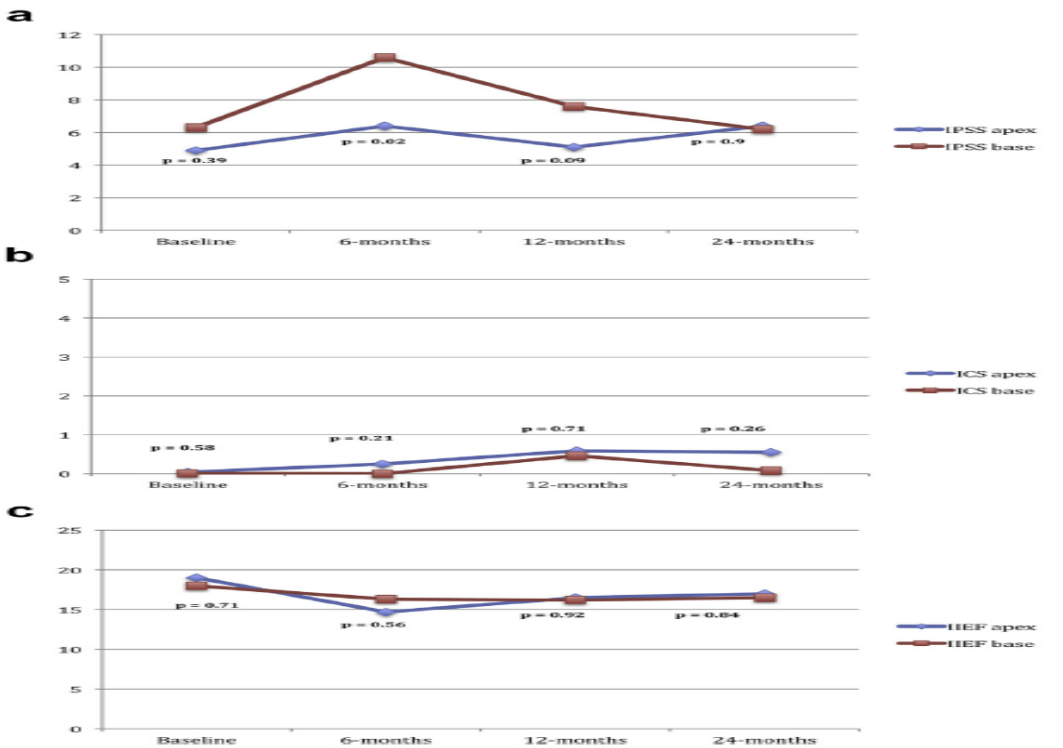

Fig. 2. (a) IPSS among treatment location in different time points: apex versus base. (b) ICS among treatment location in different time points: apex versus base. (c) IIEF among treatment location in different time points: apex versus base. IPSS = International Prostate Symptom Score; ICS = International Continence Score; IIEF = International Index of Erectile Function.

Focal brachytherapy for localized prostate cancer: Urinary toxicity depends on tumor location

Victor Srougi[1,2], Eric Barret[1], Igor Nunes-Silva[1], Mohammed Baghdadi[1], Silvia Garcia-Barreras[1], Noelle Pierrat[3], Francois Rozet[1], Marc Galiano[1], Rafael Sanchez-Salas[1], Xavier Cathelineau[1], Jean-Marc Cosset[1,3,4,*]

[1]*Department of Urology, Institut Mutualiste Montsouris, Université Paris-Descartes, Paris, France*
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[3]*Département d'oncologie-radiothérapie, Institut Curie, Paris, France*
[4]*Centre de radiothérapie Charlebourg-La Défense, groupe Amethyst, La Garenne-Colombes, France*

Brachytherapy 2017, in press

RESULTS: Twenty-eight and 13 patients were treated with FBT at the apex and the base, respectively, of the prostate. A significant difference between groups was found in the IPSS score at 6 months (mean IPSS: apex 6.4 ± 4.7, base 10.6 ± 5.7; $p = 0.02$), but not at baseline or at 12 and 24 months after treatment. On multivariate analysis, only FBT at the base of the prostate remained an independent predictor of worsening urinary symptoms (odds ratio, 5.8; $p = 0.04$).

CONCLUSIONS: At 6 months after FBT, significantly less urinary toxicity was found in patients who underwent FBT at the apex versus the base of the prostate. Continence and sexual side effects were minimal in all patients.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1445–1449, 2010

0360-3016/10/$–see front matter

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doi:10.1016/j.ijrobp.2009.04.008

CLINICAL INVESTIGATION **Prostate**

SEED IMPLANT RETENTION SCORE PREDICTS THE RISK OF PROLONGED URINARY RETENTION AFTER PROSTATE BRACHYTHERAPY

Hoon K. Lee, M.D.,*‡ Marc T. Adams, M.D.,*‡ Qiuhu Shi, Ph.D.,† Jay Basillote, M.D.,§ Joanne LaMonica, M.D.,§ Luis Miranda, M.D.,§ and Joseph Motta, M.D.§

*Regional Radiation Oncology, Staten Island, NY; †Department of Biostatistics, School of Public Health, New York Medical School, Valhalla, NY; Departments of ‡Radiation Oncology and §Urology, Richmond University Medical Center, Staten Island, NY

Table 3. Seed Implant Retention Score (SIRS) Model

No supplemental external beam radiation						1
Baseline alpha blocker use						1
Neoadjuvant hormone therapy						1
Prostate size 25–45 cc						1
Prostate size > 45cc						2
					Total	
SIRS	0	1	2	3	4	5
Retention Risk	0%	4%	5.6%	9%	20.9%	36.4%

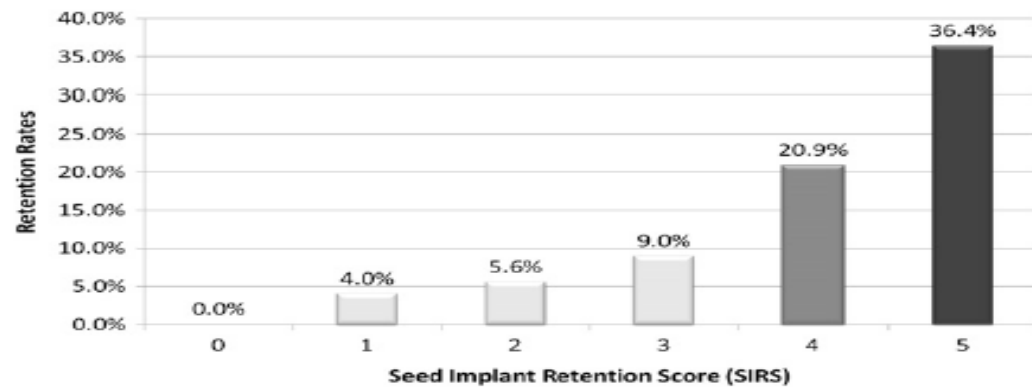


Fig. 3. Seed implant retention score and retention.

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 1, pp. 76–84, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2010.01.022

CLINICAL INVESTIGATION **Prostate**

ACUTE URINARY RETENTION AFTER I-125 PROSTATE BRACHYTHERAPY IN RELATION TO DOSE IN DIFFERENT REGIONS OF THE PROSTATE

Ellen M. A. Roeloffzen, M.D.,* Evelyn M. Monninkhof, Ph.D.,† Jan J. Battermann, M.D. Ph.D.,* Joep G. H. van Roermund, M.D.,‡ Marinus A. Moerland, Ph.D.,* and Marco van Vulpen, M.D., Ph.D.*

Table 3. Univariate and multivariate logistic regression analysis

	Mean (± SD)		UVA		MVA†	
Factor	AUR (n = 50)	No-AUR (n = 50)	OR (95% CI)	p	OR (95% CI)	p
Bladder neck D_{10} (Gy)	127.7 (50.8)	106.7 (33.8)	1.13 (1.02–1.26)‡	0.023*	1.11 (1.00–1.24)‡	0.080
Bladder overlap (mm)	8.0 (5.0)	5.4 (3.7)	1.16 (1.04–1.28)	0.005*	1.11 (0.98–1.26)	0.116
Prostate bulge (mm)	3.5 (3.0)	1.0 (1.1)	1.83 (1.37–2.45)	<0.001*	1.77 (1.28–2.44)	<0.001*

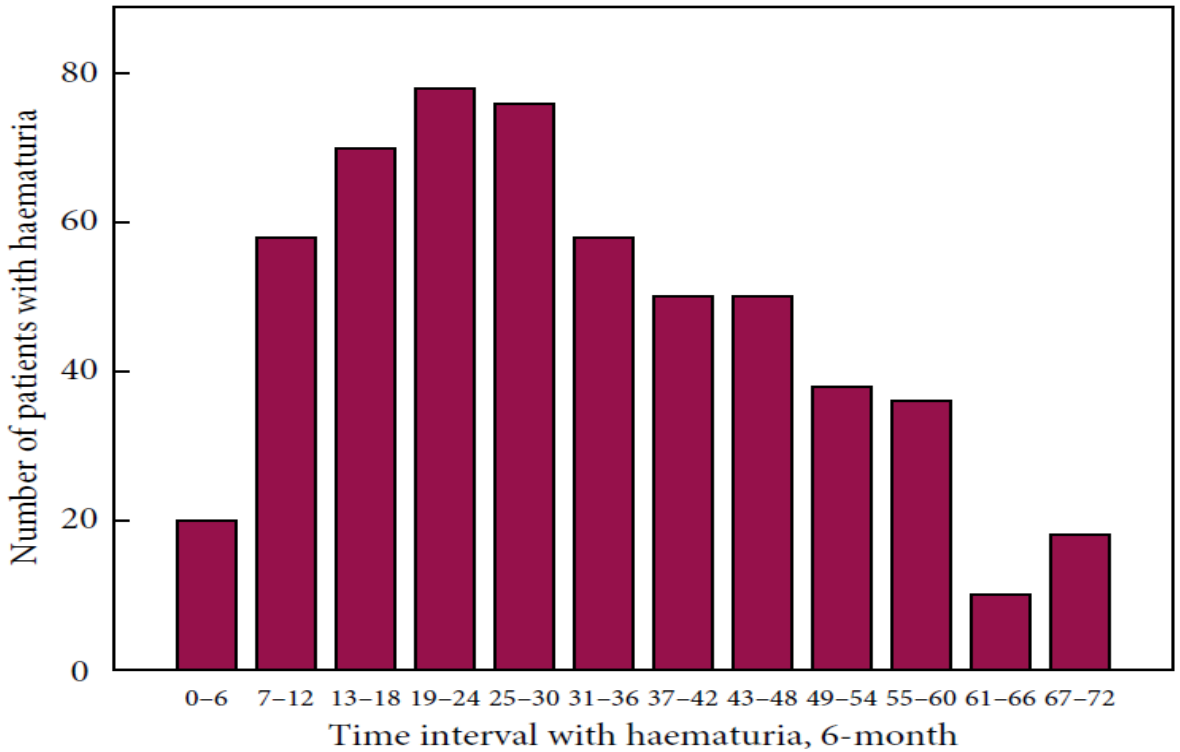
Haematuria after prostate brachytherapy

Michael S. Leapman*, Simon J. Hall*, Nelson N. Stone*† and Richard G. Stock†

*Departments of *Urology and †Radiation Oncology, Mount Sinai School of Medicine, New York, NY, USA*

© 2013 BJU International | 111, E319–E324 | doi:10.1111/j.1464-410X.2012.11697.x

Fig. 2 Number of patients with haematuria in each 6-month time interval post-implantation.



Patients and Methods

- We reviewed haematuria outcomes collected prospectively in 2454 patients treated with transperineal prostate brachytherapy over a 20-year period at a single institution.
- Patients were followed for a median of 5.9 years.

Results

- A total of 218 men (8.9%) reported gross haematuria at a median time of 772.2 days after implantation.

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© 2013 BJU International | 111, E319–E324 | doi:10.1111/j.1464-410X.2012.11697.x

Table 3 Binary logistic regression model for covariants associated with haematuria.

Variable	SE	Significance	95% CI	
			Lower	Upper
Race	0.085	0.854	0.859	1.201
Prostate cancer stage	0.073	0.052	0.753	1.002
Biochemical failure	0.355	0.035	1.052	4.222
ADT	0.173	0.478	0.631	1.241
Urinary retention	0.254	0.404	0.751	2.034
PSA >10 ng/mL	0.201	0.151	0.505	1.111
Gleason score >7	0.232	0.720	0.690	1.712
BED >200 Gy	0.157	0.268	0.875	1.621
Prostate volume >40 cm^3	0.152	0.002	1.193	2.166
External beam radiation	0.240	0.001	0.289	0.738

- Haematuria was associated with prostate volume >40 cm^3 ($P < 0.01$), use of external beam radiation ($P < 0.01$), Gleason score >7 ($P = 0.037$), Asian ethnicity ($P < 0.001$), BED >200 Gy ($P = 0.01$), and freedom from biochemical failure ($P = 0.004$).
- On multivariate analysis, prostate volume >40 cm^3 ($P = 0.002$), external beam radiation, ($P = 0.001$), and freedom from biochemical failure ($P = 0.035$) were predictors of haematuria.

TUR-P rates following Brachytherapy

Study	Patient number	Treatment	TUR-P-Rate(%)
Wallner	**92**	**^{125}J**	**8,7**
Storey	**206**	**^{125}J**	**0**
Nag	**32**	**^{103} Pd**	**6,2**
Terk	**251**	**^{125}J/ ^{103} Pd**	**2,4**
Dattoli	**73**	**EBRT+^{103}Pd**	**2,8**
Merrick	**170**	**EBRT/^{125}J/^{103}Pd**	**1,2**
Benoit	**1409**	**EBRT/^{125}J/^{103}Pd**	**8,3**
Machtens	**452**	**^{125} J**	**2,5**

One-step customized transurethral resection of the prostate and permanent implant brachytherapy for selected prostate cancer patients: Technically feasible but too toxic

Jean-Marc Cosset[1,2,*], Eric Barret[2], Pablo Castro-Pena[1], Xavier Cathelineau[2], Marc Galiano[2], François Rozet[2], Noëlle Pierrat[1], Michel Timbert[2], Guy Vallancien[2]

[1]*Department of Radiotherapy, Institut Curie, Paris, France*
[2]*Institut Mutualiste Montsouris, Paris, France*

ABSTRACT

INTRODUCTION: Patients with prominent median lobe hyperplasia and/or high International Prostate Symptom Score (IPSS) are often contraindicated for prostate brachytherapy, mainly because of the risk of post-implant urinary retention. We evaluated an approach combining in the same operative step a limited transurethral resection (TURP) of the median lobe, immediately followed by permanent implant-free seed brachytherapy.

METHODS AND MATERIALS: From January 2007 to November 2008, 22 patients underwent a customized limited TURP of their median lobe immediately before brachytherapy. All patient fulfilled our criteria for permanent implant brachytherapy, but presented with a more or less prominent median lobe and/or a high IPSS.

RESULTS: The procedure appeared to be technically feasible, with only 0.3% of migrating seeds, a mean post-implant D90 of 173.4 Gy and a mean post-implant V100 of 96.6%. However, 5 patients (23%) experienced a urinary retention, with two patients having to undergo a complementary post-implant TURP. Moreover, urinary toxicity was more pronounced than in our current experience, with high IPSS at 2 months (mean 19.2) and 6 months (mean 15.8).

CONCLUSION: Although technically feasible, with relatively few migrating seeds and satisfactory post-implant dosimetric parameters, one-step TURP and brachytherapy was found to be poorly tolerated, with higher than usual urinary retention and urinary toxicity rates. Considering those results, our group is presently evaluating a two-step procedure, with a customized TURP followed after 4–6 months by brachytherapy.

Keywords: Brachytherapy; Prostate cancer; Median lobe hyperplasia; TURP

Brachytherapy.2011 Jan;10:29-34

One-step customized transurethral resection of the prostate and permanent implant brachytherapy for selected prostate cancer patients: Technically feasible but too toxic

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Table 2
Technical results: resection data and dosimetric parameters

	TURP		Dosimetry parameters				
				Preimplant		Postimplant	
Patient number	Resected histology (g)		Number of seeds	D_{90} (Gy)	V_{100} (%)	D_{90} (Gy)	V_{100} (%)
1	2	—	78	184	99.9	202	96.4
2	1.7	—	75	178	99.8	192	98.1
3	2.8	—	74	184	99.5	180	96.4
4	0.2	—	77	177	99.8	184	95.7
5	0.5	—	65	179	100	176	97.2
6	1.5	—	71	177	99.7	175	95.9
7	0.5	—	83	171	100	191	98
8	1.2	—	63	179	99.8	167	94.8
9	2.2	—	65	178	99.4	147	93
10	0.6	—	55	174	99.9	169	99.9
11	0.5	—	86	175	99.6	179	96.1
12	0.5	—	58	182	99.9	148	91.8
13	0.5	—	54	178	99.9	180	98.4
14	1	—	92	177	99.9	185	97.6
15	1	—	61	179	99.1	158	97.9
16	3	—	90	180	99.7	185	98.8
17	1.1	—	72	176	100	157	95.3
18	0.2	—	63	180	100	161	97.6
19	5	—	53	183	100	145	89.9
20	1.7	—	67	182	99.5	159	97.6
21	1	—	75	179	99.9	175	99.5
22	1	—	77	179	99.9	199	99.1

TURP = transurethral resection of prostate.

Brachytherapy.2011 Jan;10:29-34

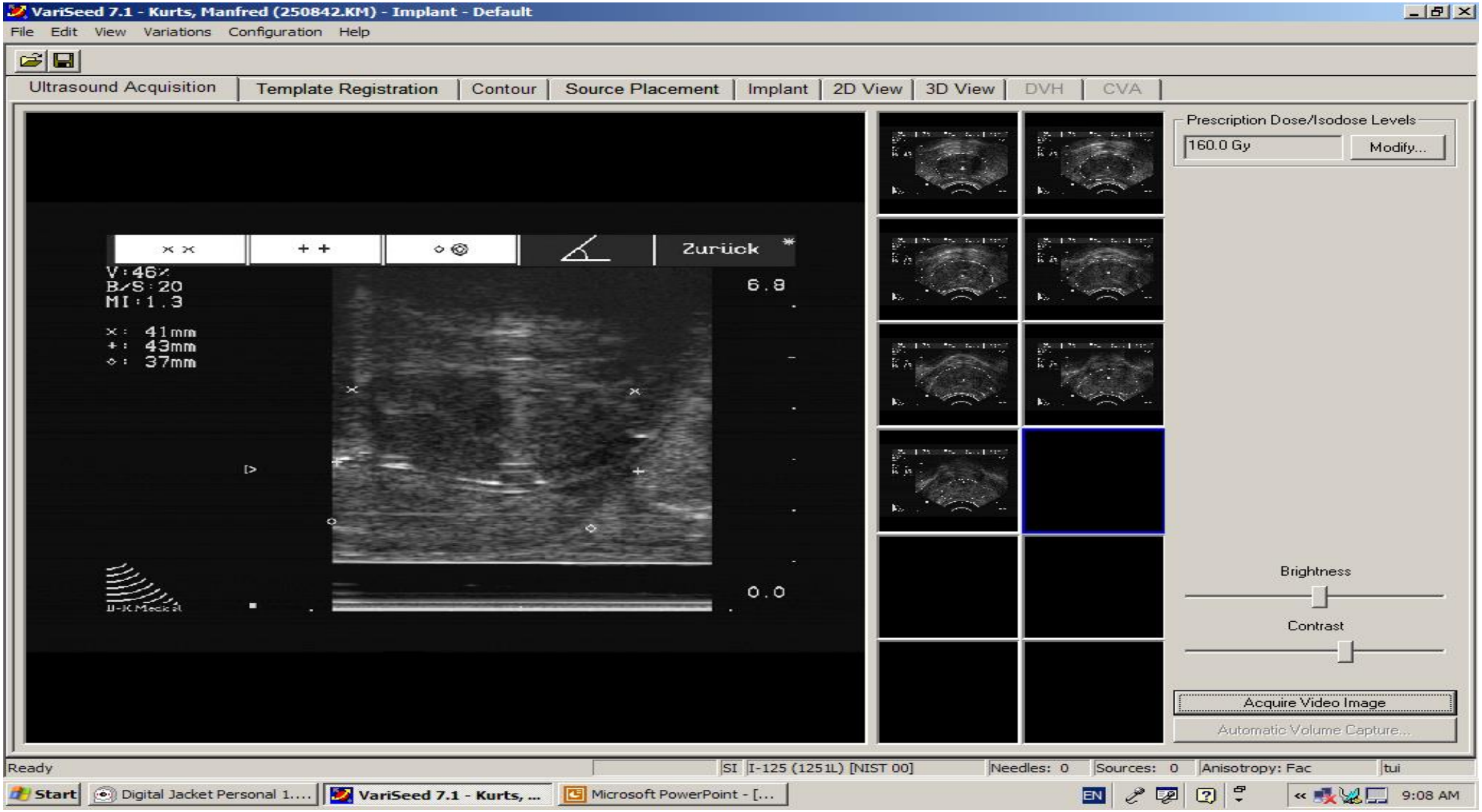
One-step customized transurethral resection of the prostate and permanent implant brachytherapy for selected prostate cancer patients: Technically feasible but too toxic

Jean-Marc Cosset[1,2,*], Eric Barret[2], Pablo Castro-Pena[1], Xavier Cathelineau[2], Marc Galiano[2], François Rozet[2], Noëlle Pierrat[1], Michel Timbert[2], Guy Vallancien[2]

RESULTS

- 0.3 % migrating seeds
- D90 : 173.4 GY
- V100 : 96.6 %
- 23 % Urinary Retention, 10 % redo – TURP
- High IPSS scores 2m & 6m

Brachytherapy.2011 Jan;10:29-34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V:46%
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MI:1.3
x: 41mm
+: 43mm
◇: 37mm
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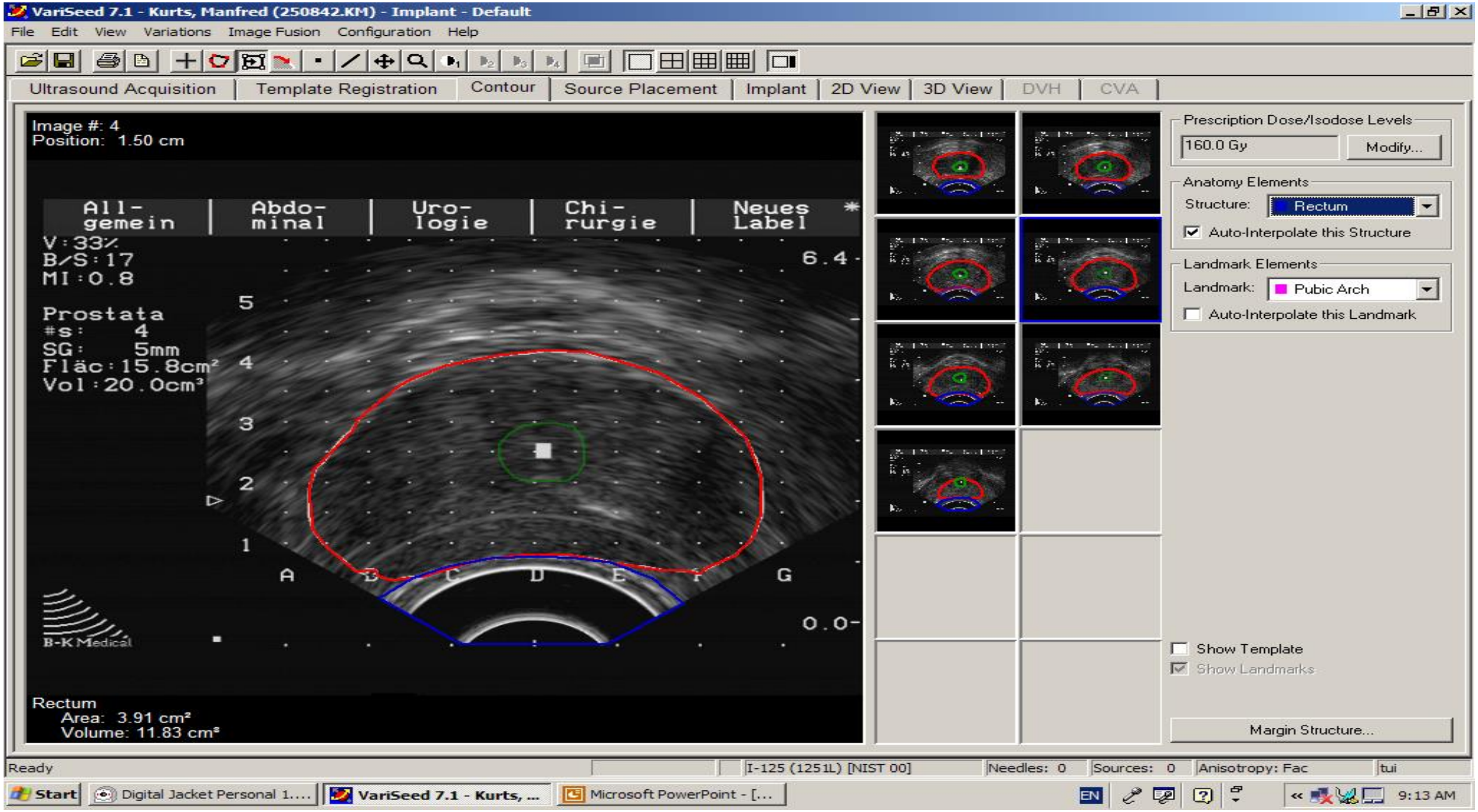
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All-gemein
Abdo-minal
Uro-logie
Chi-rurgie
Neues Label
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B/S:17
MI:0.8
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SG: 5mm
Fläc:15.8cm²
Vol:20.0cm³
6.4
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A
B
C
D
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B-K Medical
Rectum
Area: 3.91 cm²
Volume: 11.83 cm³
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160.0 Gy
Modify...
Anatomy Elements
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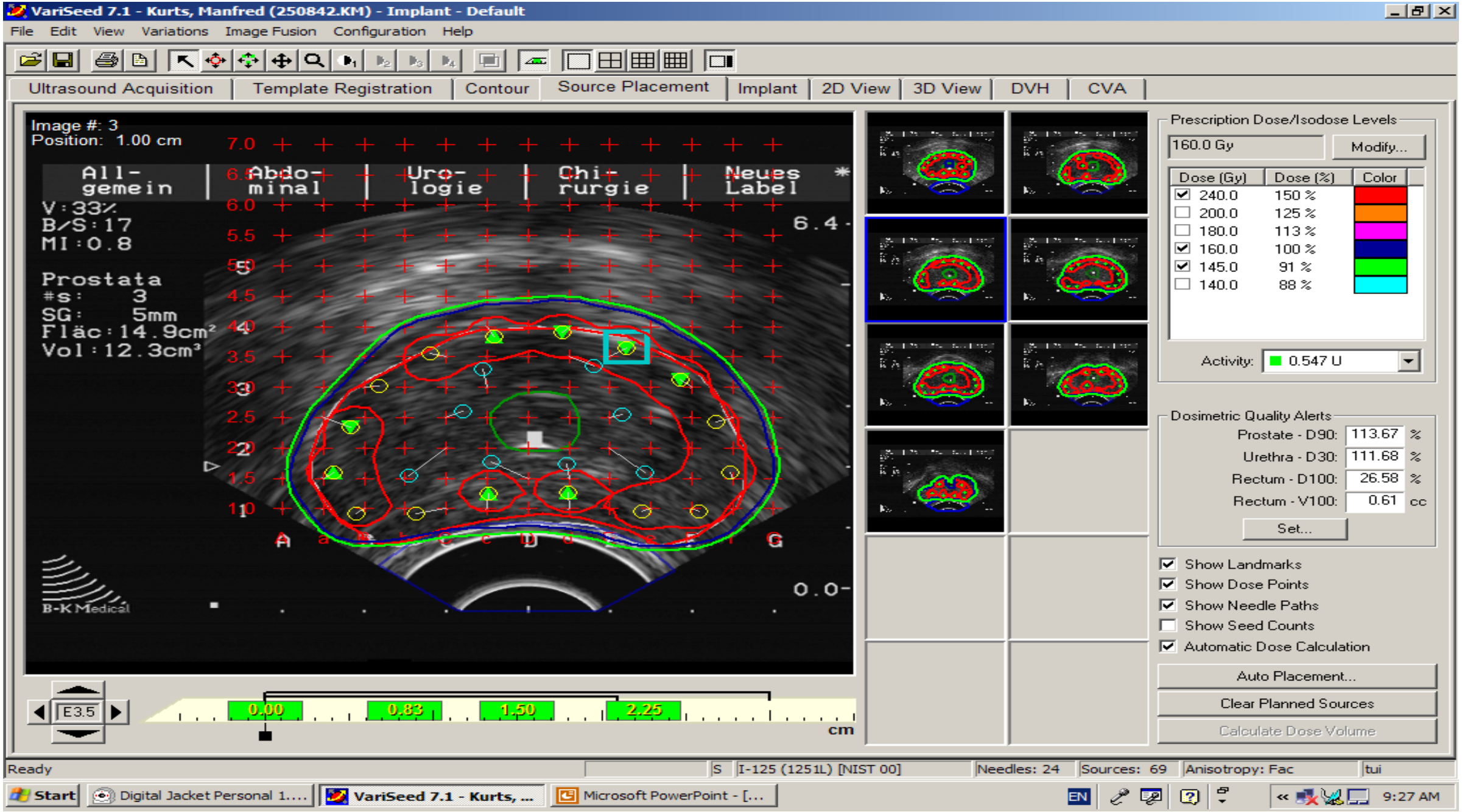
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Image #: 3
Position: 1.00 cm
All-gemein
Abdo-minal
Uro-logie
Chi-rurgie
Neues Label
V:33%
B/S:17
MI:0.8
Prostata
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Prescription Dose/Isodose Levels
160.0 Gy
Modify...
Dose (Gy)
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Color
240.0 150 %
200.0 125 %
180.0 113 %
160.0 100 %
145.0 91 %
140.0 88 %
Activity: 0.547 U
Dosimetric Quality Alerts
Prostate - D90: 113.67 %
Urethra - D30: 111.68 %
Rectum - D100: 26.58 %
Rectum - V100: 0.61 cc
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Show Landmarks
Show Dose Points
Show Needle Paths
Show Seed Counts
Automatic Dose Calculation
Auto Placement...
Clear Planned Sources
Calculate Dose Volume
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ESTRO and ABS dose constraints - Urethra

urethra	GEC-ESTRO	ABS
uV5		<150%
uV10	<150%	
uV30	<130%	<125%

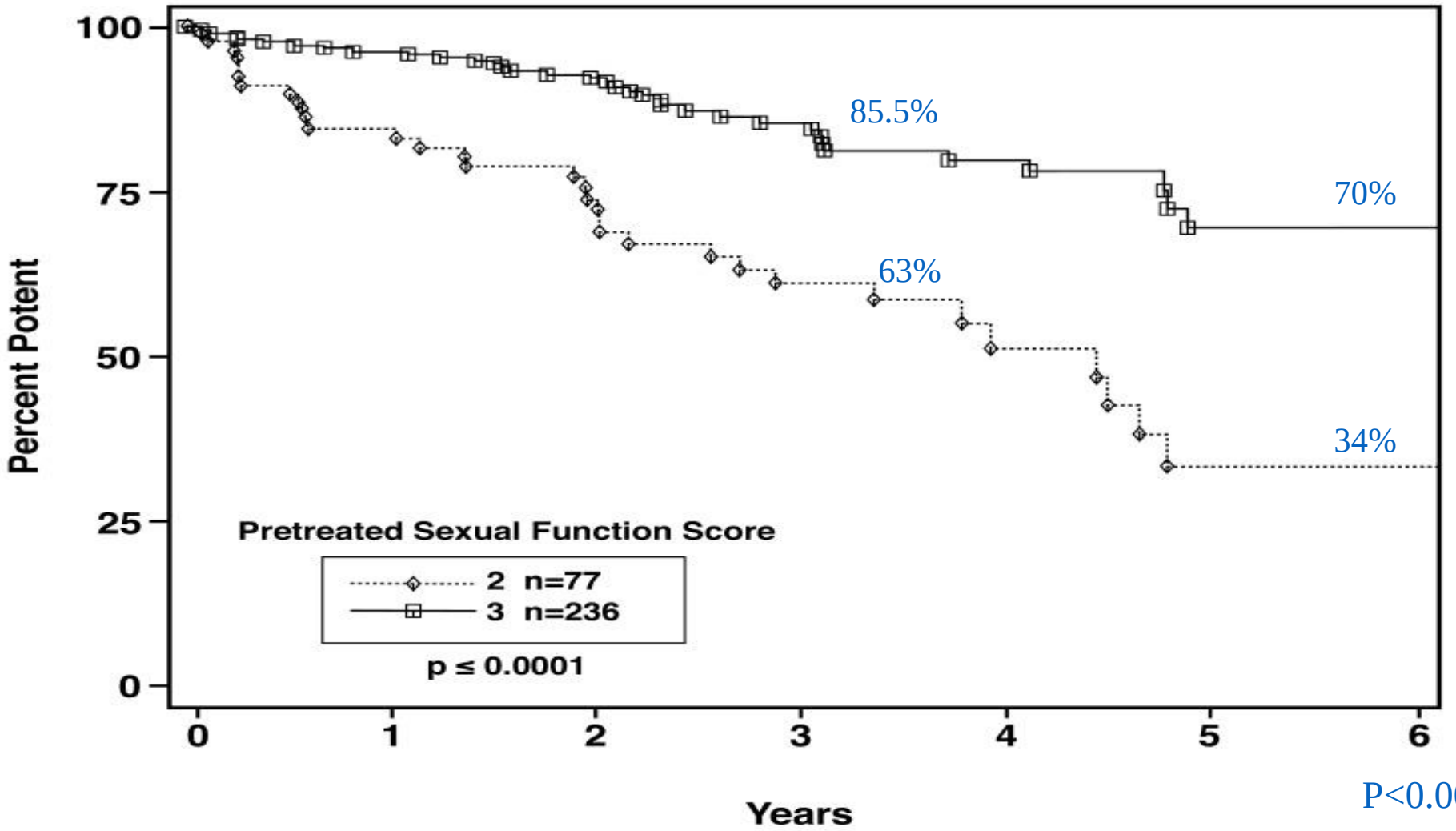
- Urethral volume getting 30% of the dose (uV30)<125-130% of prescription
- Urethral volume getting 10% of the dose (uV10) <150% of prescription

Avoid the 150% isodose cutting into the urethra

Potency Rates following prostate brachytherapy

Study	Treatment	Patients(n)	Potency Rate (%)	Follow-up (years)
Wallner	^{125}J	92	86	3
Kao	$^{125}J/^{103}Pd$	236	70	6
Kaye	EBRT/^{125}J	73	75	1
Dattoli	EBRT+^{103}Pd	73	77	3
Zeitlin	EBRT+$^{125}J/^{103}$ Pd	212	62	5
Critz	EBRT+^{125}J	239	76	5
Machtens	^{125} J	173	64	5

Effect of Pretreatment Sexual Function on Potency (Score ≥2)



P<0.0001

Radiotherapy and Oncology 82 (2007) 46—49
www.thegreenjournal.com

Prostate brachytherapy

Side effects of permanent I125 prostate seed implants in 667 patients treated in Leeds

David Bottomley[a], Dan Ash[a], Bashar Al-Qaisieh[b,*], Brendan Carey[a], Joji Joseph[a], Shaun St Clair[b], Kathy Gould[a]

[a]*Regional Cancer Treatment Centre, and* [b]*Medical Physics Department, Cookridge Hospital, Leeds, UK*

- **667 patients with a median follow-up of 31 months.**

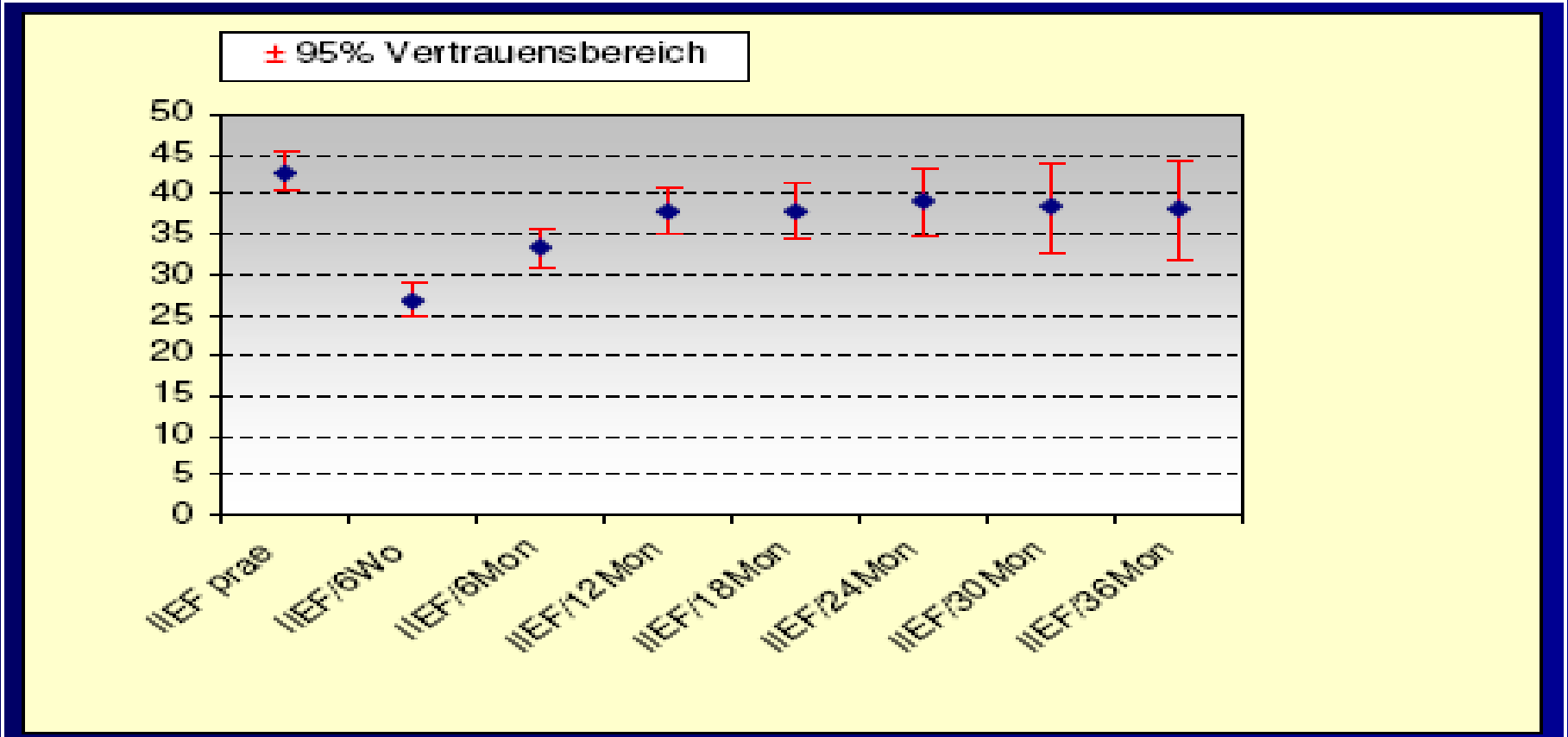
Table 4
Sexual function of 521 patients prior and after treatment

Score	Pre-treatment *n* (%)	Post-treatment *n* (%)
100	402 (77.2%)	169 (32.4%)
67	69 (13.2%)	159 (30.5%)
33	38 (7.3%)	117 (22.5%)
0	12 (2.3%)	76 (14.5%)

Table 5
Post implant sexual function for 402 patients who scored 100 on the pre-treatment quality of life questionnaire

Post-treatment score	*n* (%)
100	168 (41.8%)
67	120 (29.9%)
33	72 (17.9%)
0	42 (10.4%)

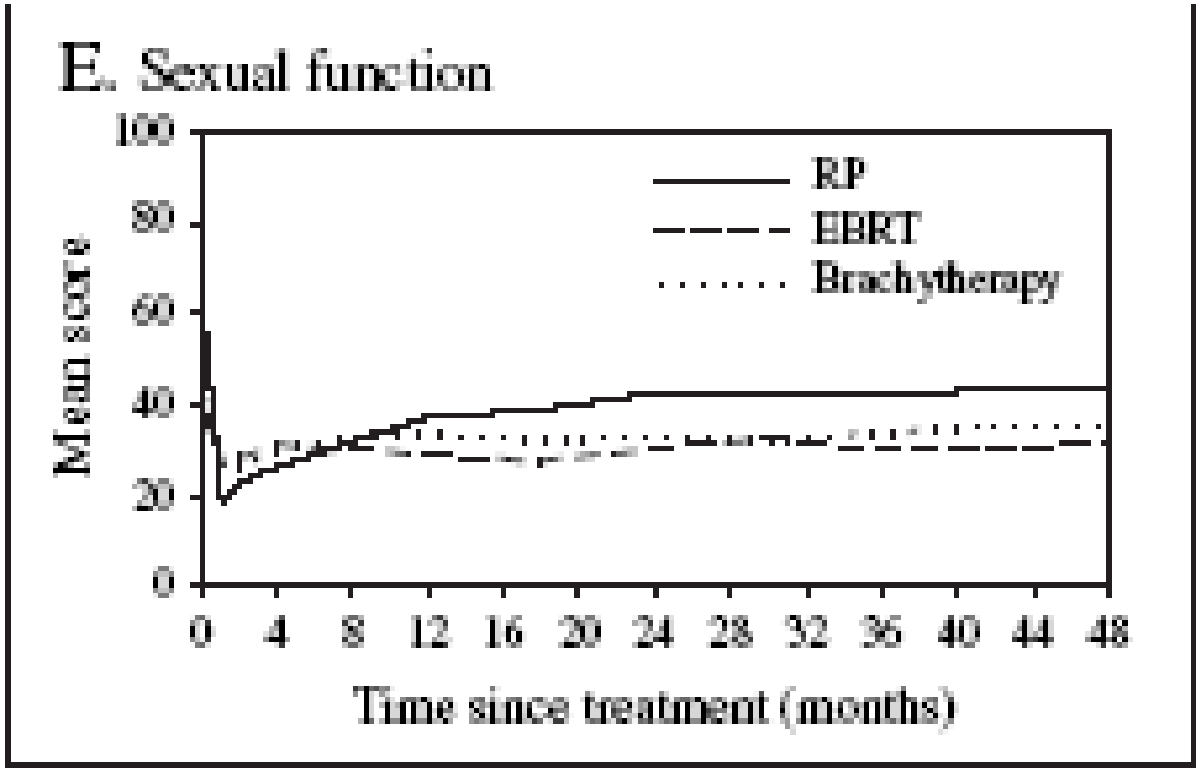
IIEF (International Index of Erectile Function) im Zeitverlauf

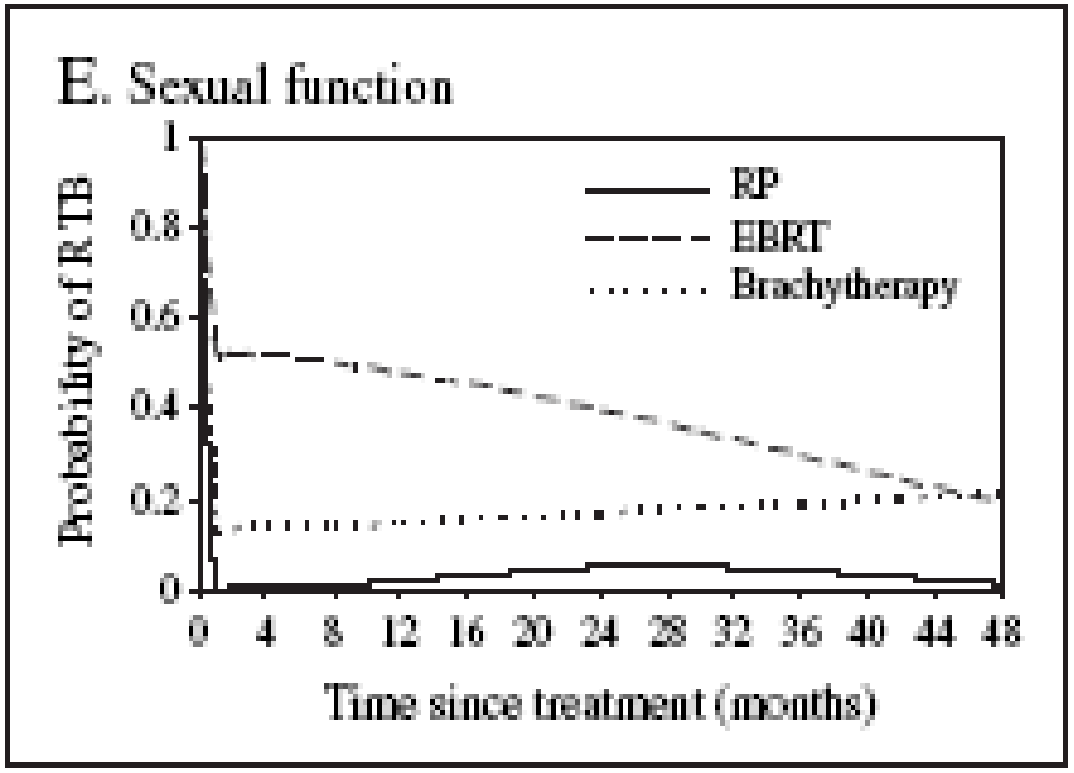


Survivorship Beyond Convalescence: 48-Month Quality-of-Life Outcomes After Treatment for Localized Prostate Cancer

J Natl Cancer Inst 2009;101:888–892

John L. Gore, Lorna Kwan, Steve P. Lee, Robert E. Reiter, Mark S. Litwin





Clinical Investigation

Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer

W. James Morris, MD, FRCPC,*,† Scott Tyldesley, MD, FRCPC,*,†
Sree Rodda, MBBS, MRCP, FRCR,* Ross Halperin, MD, FRCPC,*,‡
Howard Pai, MD, FRCPC,*,§ Michael McKenzie, MD, FRCPC,*,†
Graeme Duncan, MB, ChB, FRCPC,*,†
Gerard Morton, MB, MRCPI, FRCPC, FFRRCSI,‖ Jeremy Hamm, MSC,¶
and Nevin Murray, MD, FRCPC†,#

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–11, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2016.11.026

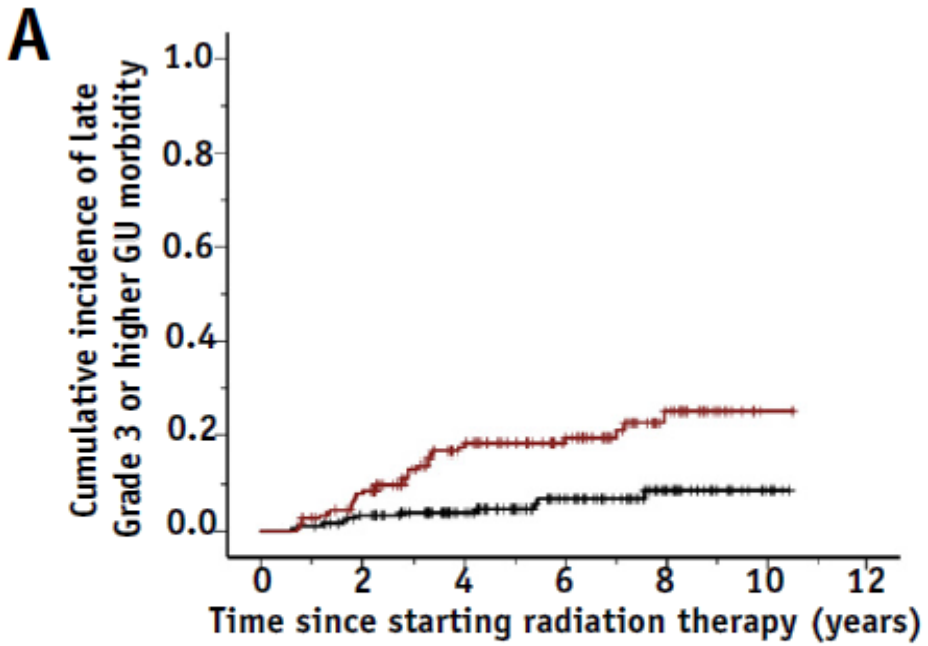
Table 2 Disease status at data lockdown (September 30, 2014) by randomization (intent-to-treat) and actual treatment arm received

		By randomization		By actual treatment received		
Analysis	All patients (n=398)	DE-EBRT (n=200)	LDR-PB (n=198)	DE-EBRT (n=195)	LDR-PB (n=188)	Neither (n=15)
Patients						
Relapsed*	76 (19.1)	51 (25.5)	25 (12.6)	48 (24.6)	21 (11.2)	7 (46.7)
Nonrelapsed	322 (80.9)	149 (74.5)	173 (87.4)	147 (75.4)	167 (88.8)	8 (53.3)
Metastatic disease	35 (8.8)	18 (9.0)	17 (8.6)	18 (9.2)	14 (7.4)	3 (20.0)

ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

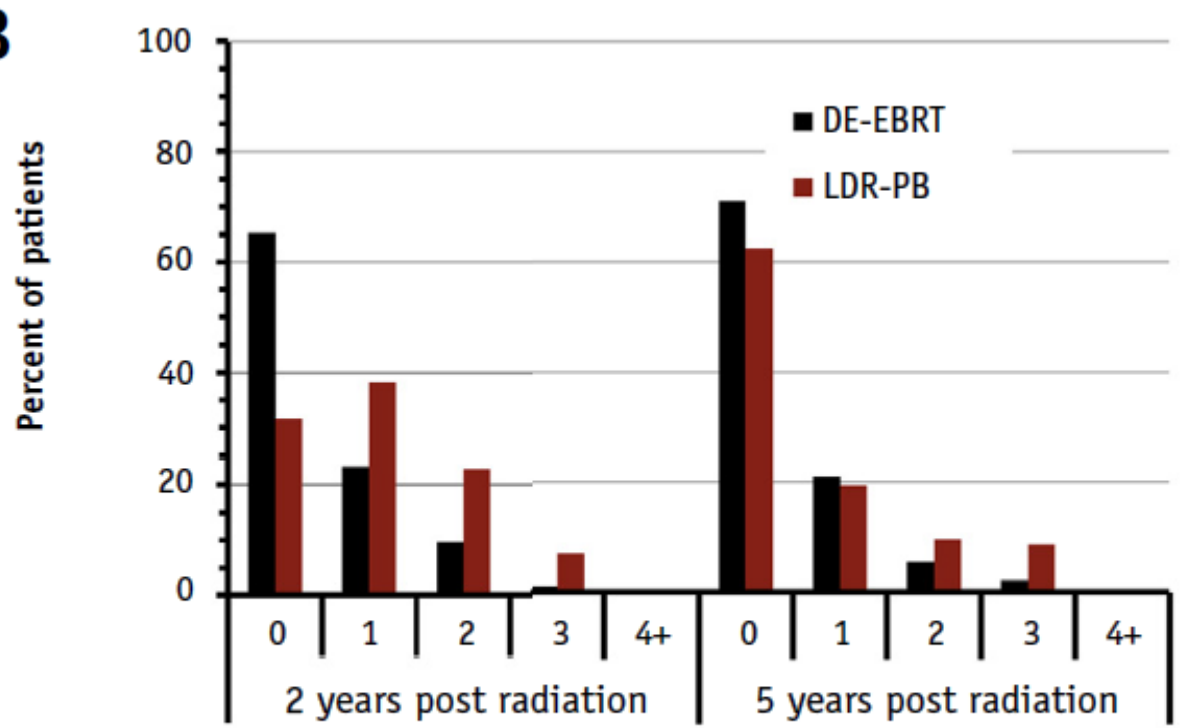
Sree Rodda, MBBS, MRCP, FRCR,* Scott Tyldesley, MD, FRCPC,*,† W. James Morris, MD, FRCPC,*,† Mira Keyes, MD, FRCPC,*,† Ross Halperin, MD, FRCPC,†,‡ Howard Pai, MD, FRCPC,†,§ Michael McKenzie, MD, FRCPC,*,† Graeme Duncan, MB, ChB, FRCPC,*,† Gerard Morton, MB, MRCPI, FRCPC, FFRRCSI,||,¶ Jeremy Hamm, MSC,# and Nevin Murray, MD, FRCPC*,**

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 286–295, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2017.01.008



Numbers at risk:

Years	0	2	4	6	8	10
DE-EBRT	195	167	125	79	41	8
LDR-PB	188	158	109	69	28	1



The prevalence of late GU morbidity by grade

ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

Sree Rodda, MBBS, MRCP, FRCR,* Scott Tyldesley, MD, FRCPC,*,† W. James Morris, MD, FRCPC,*,† Mira Keyes, MD, FRCPC,*,† Ross Halperin, MD, FRCPC,†,‡ Howard Pai, MD, FRCPC,†,§ Michael McKenzie, MD, FRCPC,*,† Graeme Duncan, MB, ChB, FRCPC,*,† Gerard Morton, MB, MRCPI, FRCPC, FFRRCSI,||,¶ Jeremy Hamm, MSC,# and Nevin Murray, MD, FRCPC*,**

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 286–295, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2017.01.008

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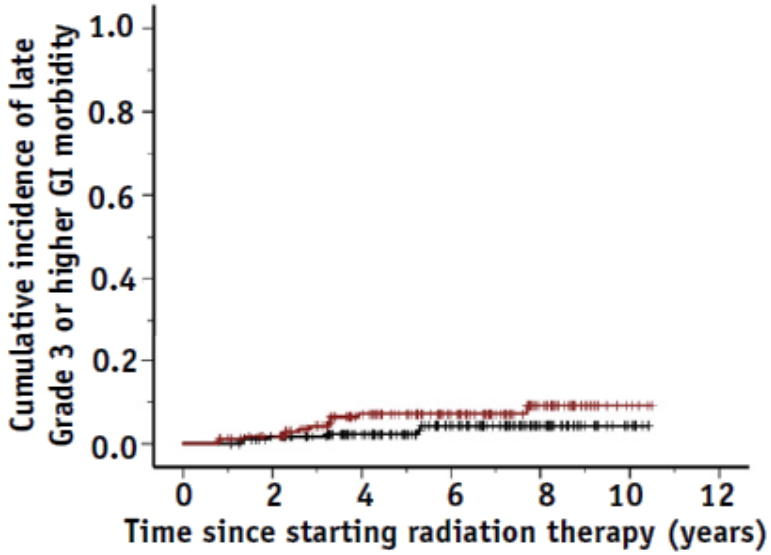

Numbers at risk:

Years	0	2	4	6	8	10
DE-EBRT	195	172	129	80	41	9
LDR-PB	188	168	119	80	36	4

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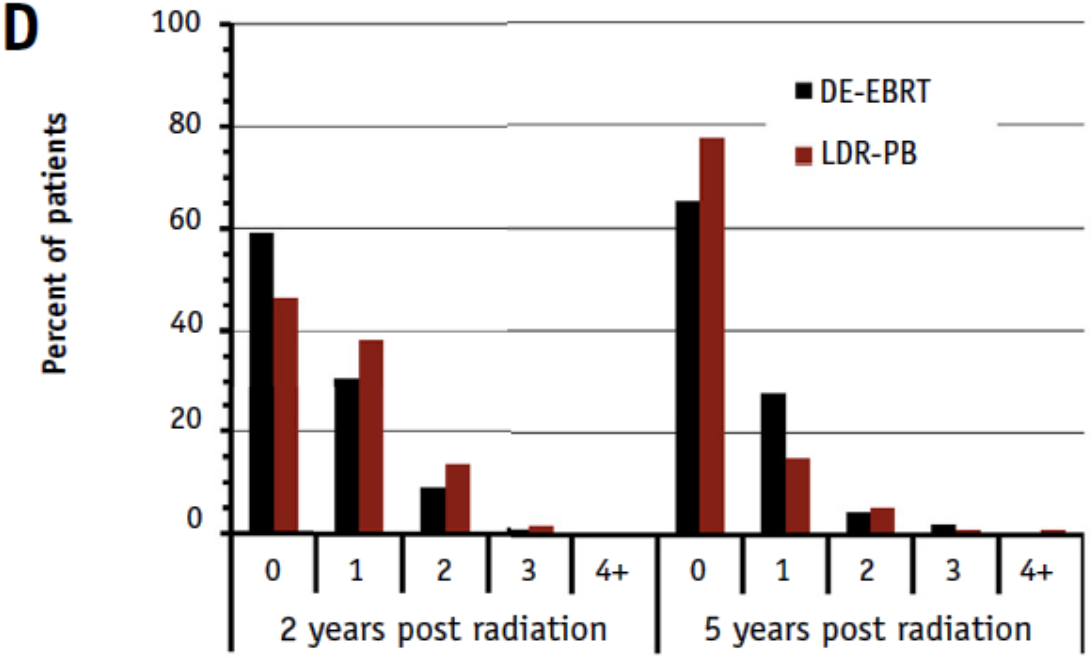


The prevalence of late GI morbidity by grade

ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

Sree Rodda, MBBS, MRCP, FRCR,* Scott Tyldesley, MD, FRCPC,*,† W. James Morris, MD, FRCPC,*,† Mira Keyes, MD, FRCPC,*,† Ross Halperin, MD, FRCPC,†,‡ Howard Pai, MD, FRCPC,†,§ Michael McKenzie, MD, FRCPC,*,† Graeme Duncan, MB, ChB, FRCPC,*,† Gerard Morton, MB, MRCPI, FRCPC, FFRRCSI,||,¶ Jeremy Hamm, MSC,# and Nevin Murray, MD, FRCPC*,**

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 286–295, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2017.01.008

Results: The LDR-PB boost increased the risk of needing temporary catheterization and/or requiring incontinence pads. At 5 years the cumulative incidence of grade 3 GU events was 18.4% for LDR-PB, versus 5.2% for DE-EBRT ($P<.001$). Compared with the cumulative incidence, the 5-year prevalence of grade 3 GU morbidity was substantially lower for both arms (8.6% vs 2.2%, $P=.058$). The 5-year cumulative incidence of grade 3 GI events was 8.1% for LDR-PB, versus 3.2% for DE-EBRT ($P=.124$). The 5-year prevalence of grade 3 GI toxicity was lower than the cumulative incidence for both arms (1.0% vs 2.2%, respectively). Among men reporting adequate baseline erections, 45% of LDR-PB patients reported similar erectile function at 5 years, versus 37% after DE-EBRT ($P=.30$).

Secondary malignancy after prostate radiation

Rectal cancer RR compared to RP (SEER database – *Nieder et al - 2008*)

- RP - 1.0
- EBXRT – 1.26
- BT – 1.08
- BT + EBXRT – 1.21

Bladder cancer – more common than rectal cancer - RR 1.5

Secondary malignancy after prostate radiation

Second malignancies after prostate brachytherapy: Incidence of bladder and colorectal cancers in patients with 15 years of potential follow-up

Stanley L. Liauw, M.D., John E. Sylvester, M.D., Christopher G. Morris, M.S., John C. Blasko, M.D., Peter D. Grimm, D.O.

- *Liauw et al* reported a 4.3% incidence in second cancers at 15 years after BT (n=125) or BT + EBXRT (n=223)
- **bladder 3.1%**
- **colorectal 0.8%**

Absolute excess risk 35 per 10 000 treated patients

Secondary malignancy after prostate radiation

Consistent direct causal correlation difficult to quantify

CaP conveys increased risk of developing second malignancy regardless of treatment

Guideline for the Management of Clinically Localized Prostate Cancer: 2007 Update

Ian Thompson (Chair),* James Brantley Thrasher (Co-Chair),† Gunnar Aus,‡ Arthur L. Burnett,§ Edith D. Canby-Hagino, Michael S. Cookson,¶ Anthony V. D'Amico, Roger R. Dmochowski,‖ David T. Eton, Jeffrey D. Forman, S. Larry Goldenberg, Javier Hernandez, Celestia S. Higano, Stephen R. Kraus,** Judd W. Moul†† and Catherine M. Tangen (Prostate Cancer Clinical Guideline Update Panel)

Standard. Patient preferences and health conditions related to urinary, sexual, and bowel function should be considered in decision making. Particular treatments have the potential to improve, to exacerbate or to have no effect on individual health conditions in these areas, making no one treatment modality preferable for all patients.

Standard. Patient preferences and functional status with a specific focus on functional outcomes including urinary, sexual, and bowel function should be considered in decision making.

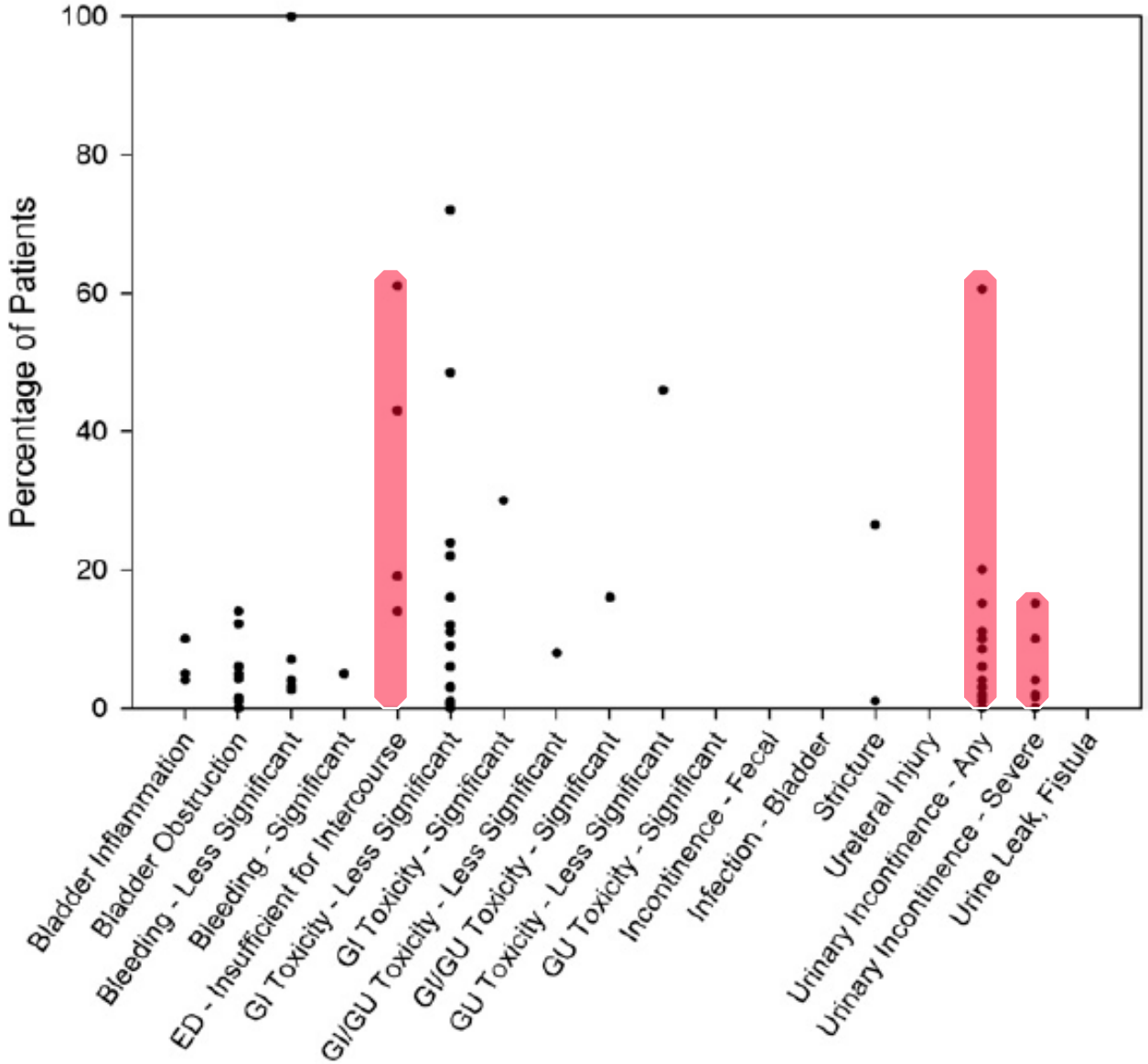


FIG. 3. Rate of complications reported with interstitial prostate brachytherapy.*

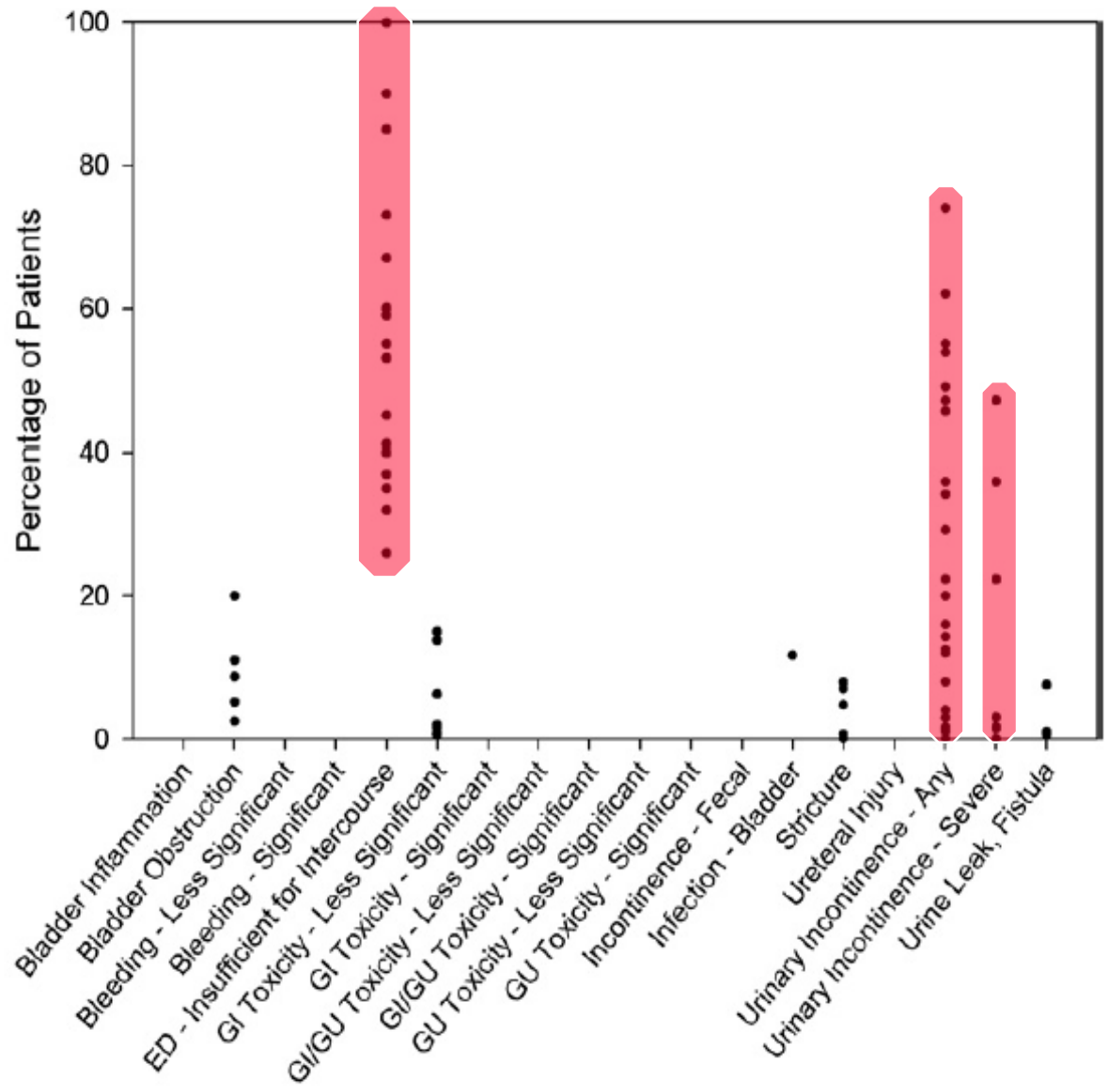


FIG. 5. Rate of complications reported with radical prostatectomy.*

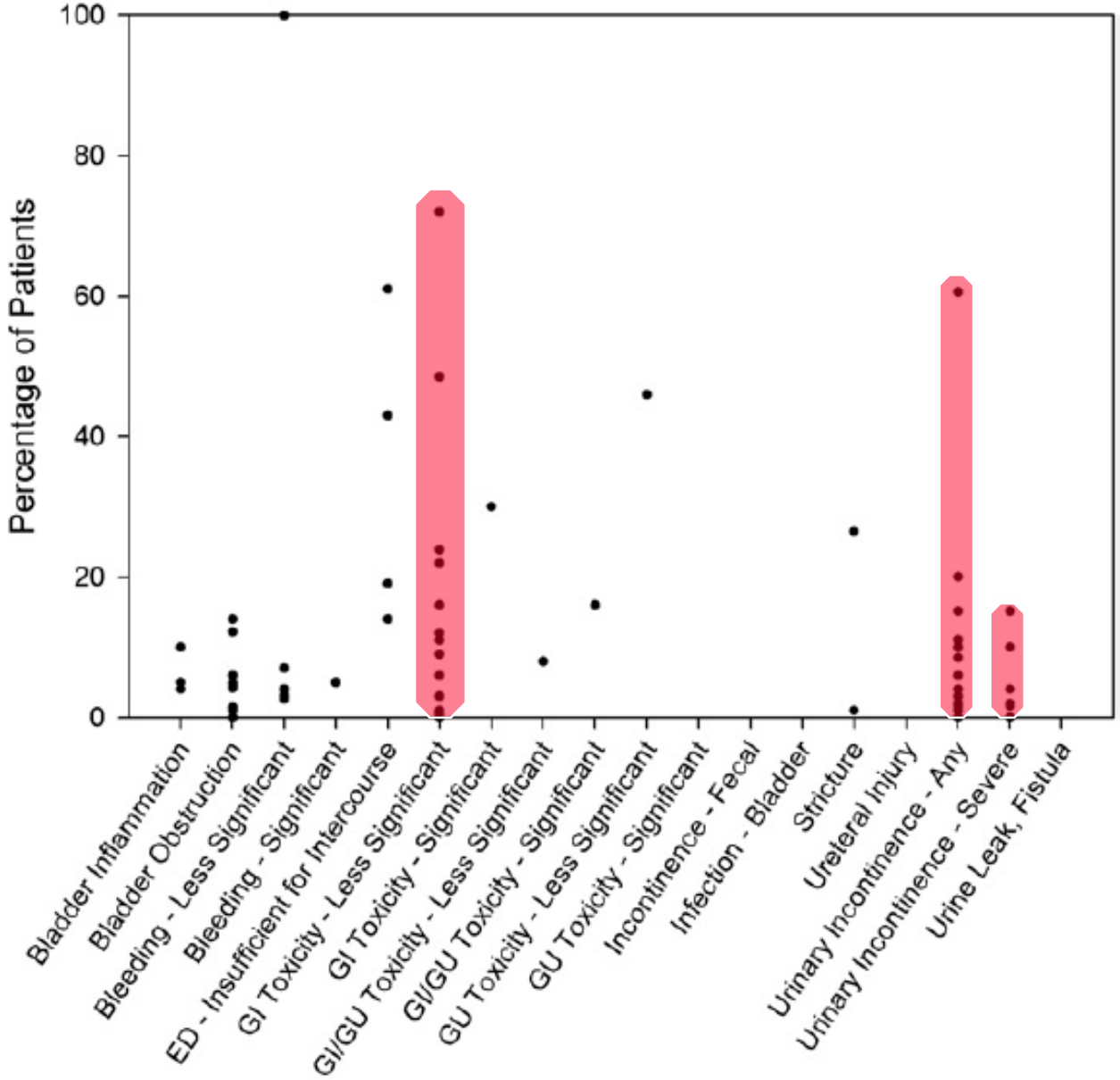


FIG. 3. Rate of complications reported with interstitial prostate brachytherapy.*

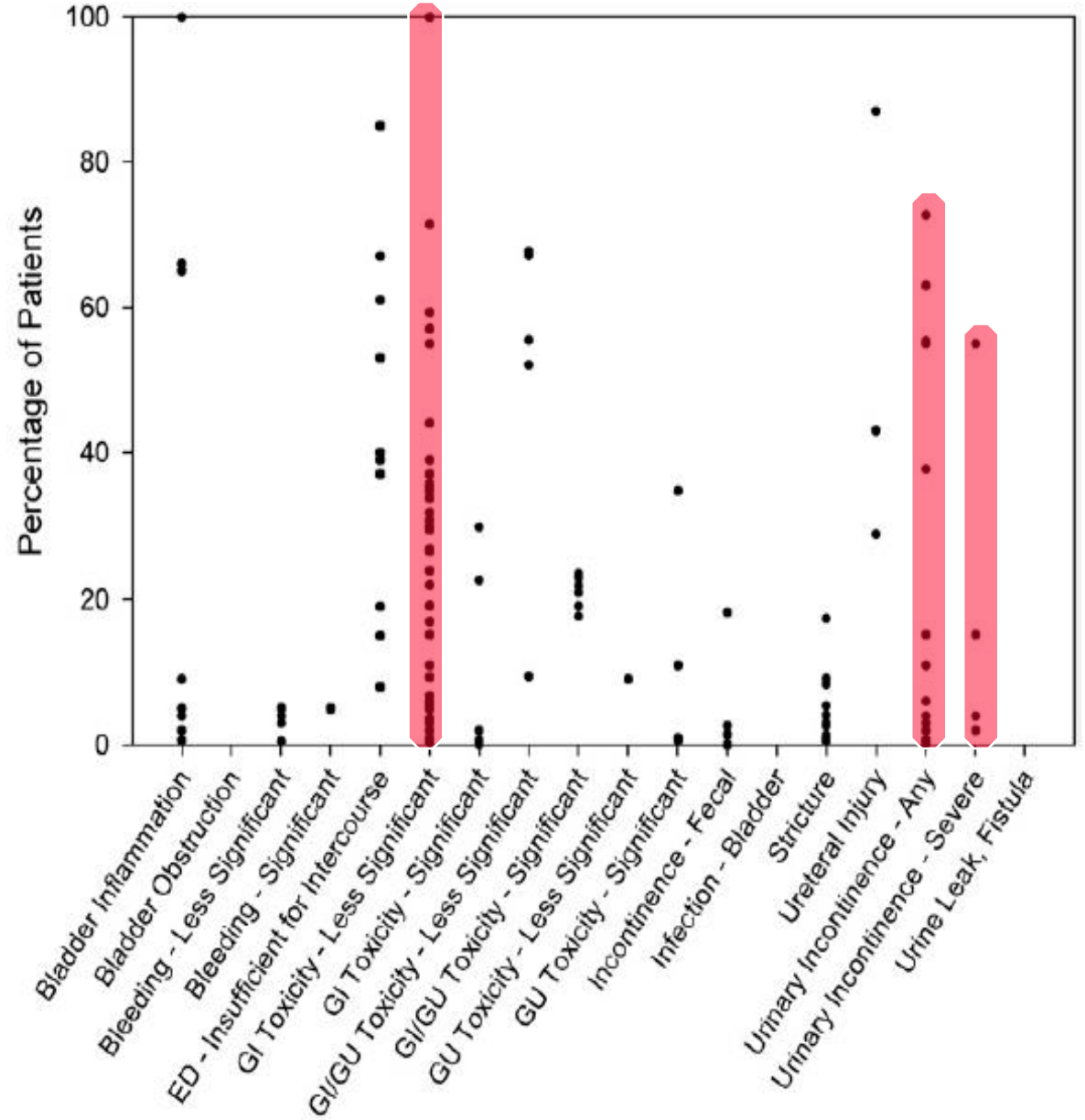


FIG. 4. Rate of complications reported with external beam radiotherapy.*

Survival and Complications Following Surgery and Radiation for Localized Prostate Cancer: An International Collaborative Review

Christopher J.D. Wallis[a,b], *Adam Glaser*[c], *Jim C. Hu*[d], *Hartwig Huland*[e], *Nathan Lawrentschuk*[f,g,h], *Daniel Moon*[h,i,j], *Declan G. Murphy*[h,j], *Paul L. Nguyen*[k], *Matthew J. Resnick*[l,m], *Robert K. Nam*[a,b,*]

[a] *Division of Urology, Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada;* [b] *Institute of Health Policy, Management, & Evaluation, University of Toronto, Toronto, ON, Canada;* [c] *Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK;* [d] *Department of Urology, Weill Cornell Medicine, New York, NY, USA;* [e] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [f] *Department of Surgery, University of Melbourne, Austin Health, Melbourne, Australia;* [g] *Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Australia;* [h] *Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia;* [i] *Central Clinical School, Monash University, Clayton, Australia;* [j] *The Epworth Prostate Centre, Epworth Hospital, Richmond, Australia;* [k] *Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA;* [l] *Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA;* [m] *Geriatric Research, Education, and Clinical Center, Tennessee Valley VA Health Care System, Nashville, TN, USA*

Eur Urol in press, 2017

Background: Evaluation of treatment options for localized prostate cancer (PCa) remains among the highest priorities for comparative effectiveness research. Surgery and radiotherapy (RT) are the two interventions most commonly used.
Objective: To provide a critical narrative review of evidence of the comparative effectiveness and harms of surgery and RT in the treatment of localized PCa.
Evidence acquisition: A collaborative critical narrative review of the literature was conducted.

Table 2 – Key studies examining functional outcomes for treatment of localized prostate cancer with radiotherapy and radical prostatectomy

	Study			
	Hamdy [17]	Lennernas [21]	Gilberti [37]	Resnick [42]
Study design	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial	Observational cohort study
Exposures	RP vs EBRT + ADT	RP vs EBRT + BT boost + ADT	RP vs BT	RP vs EBRT
Sample size	1098	89	174	1655
Findings				
Global HRQoL	Equivalent	Equivalent	Equivalent	-
Incontinence	Greater in RP	Equivalent	Equivalent	Greater in RP at 2/5 yr Equivalent at 15 yr
Erectile dysfunction	Greater in RP	Equivalent	Greater in RP (short term) Equivalent (long term)	Greater in RP at 2/5 yr Equivalent at 15 yr
Bowel symptoms	Greater in RT	Equivalent	Greater in RT (short term) Equivalent (long term)	Greater in RT at 2/5 yr Equivalent at 15 yr
Obstructive urinary symptoms	Greater in RT	Equivalent	Greater in RT (short term) Equivalent (long term)	

EBRT = external beam radiotherapy; BT = brachytherapy; ADT = androgen deprivation therapy; RP = radical prostatectomy; RT = radiotherapy; HRQoL = health-related quality of life.

Table 3 – Comparison of key outcomes following radical prostatectomy and radiotherapy in the treatment of locali stratified by evidentiary study design

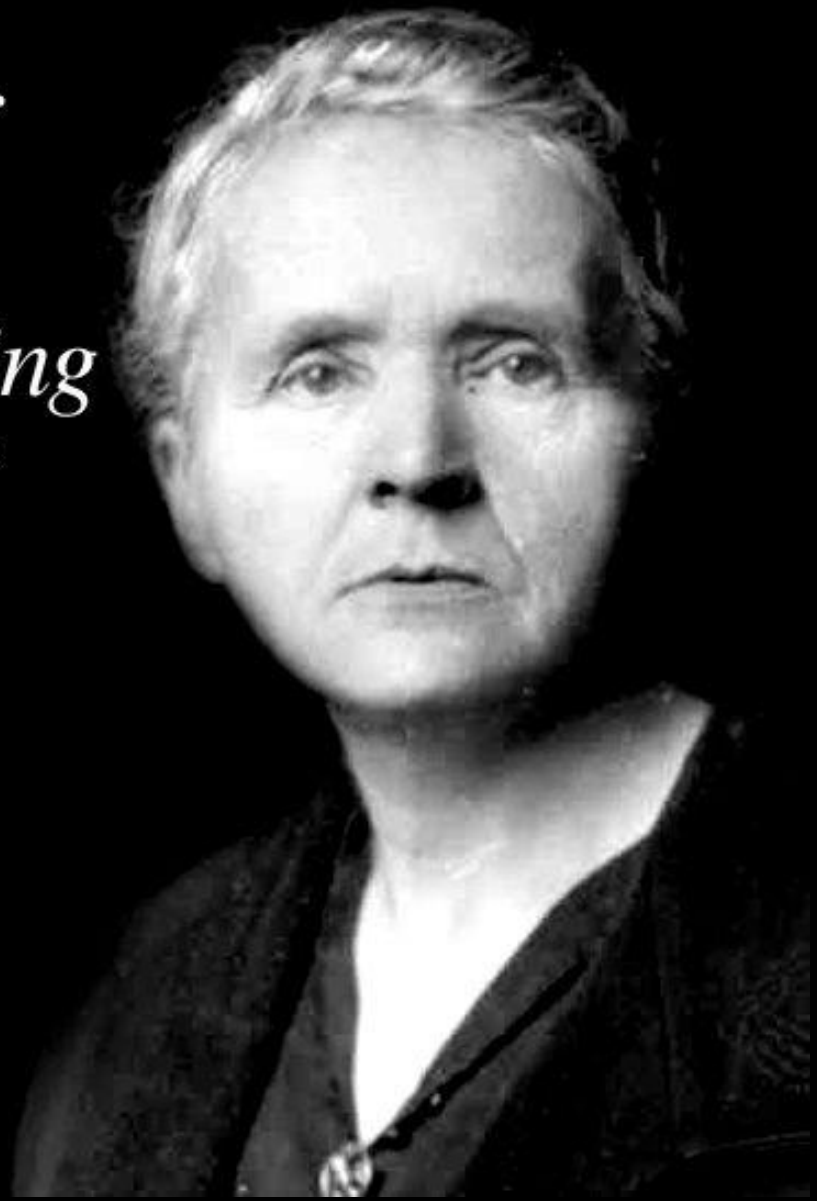
Outcome	Randomized controlled trials		Observational cohort studies	
	Evidence	Caveats	Evidence	
Survival	No difference	Underpowered and over-representation of low-risk patients	Significantly better overall and prostate cancer–specific survival for patients treated with surgery	Residual c design un baseline d
Global HRQoL	No difference	–	No difference	Residual c
Urinary function	Conflicting evidence: probably no long-term differences	–	Greater incontinence early after surgery and greater urinary bother after RT; no differences long term	Residual c
Erectile function	Conflicting evidence: probably no long-term differences	–	Worse erectile function early after surgery; no difference long term	Residual c
Bowel function	Worse after RT	–	Worse bowel function early after RT; no difference long term	Residual c
Other complications	No data		Higher risk of urologic and rectal-anal procedures, major surgeries, and hospitalization to manage treatment-related effects after RT	Residual c
Secondary malignancies	No data		Higher risk of bladder, rectal, and colorectal cancer after RT	Despite si small abs confoundi

Summary

- Long-term morbidity rate is low. (LoE: III)
- Technical advances improve tumor control and lower toxicity.
- Careful patient selection is important to avoid unacceptable morbidity
- Urgent need for prospective trials to investigate on medical approaches to the treatment of morbidity.

“You must never be fearful about what you are doing when it is right.”

-Marie Curie



Thank You

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Management of toxicity and complications

S. Machtens

Director of the

Department of Urology and Paediatric Urology

Academic Teaching Hospital

Marien-Hospital Bergisch Gladbach

Teaching Course Avignon 14th-16th June 2018

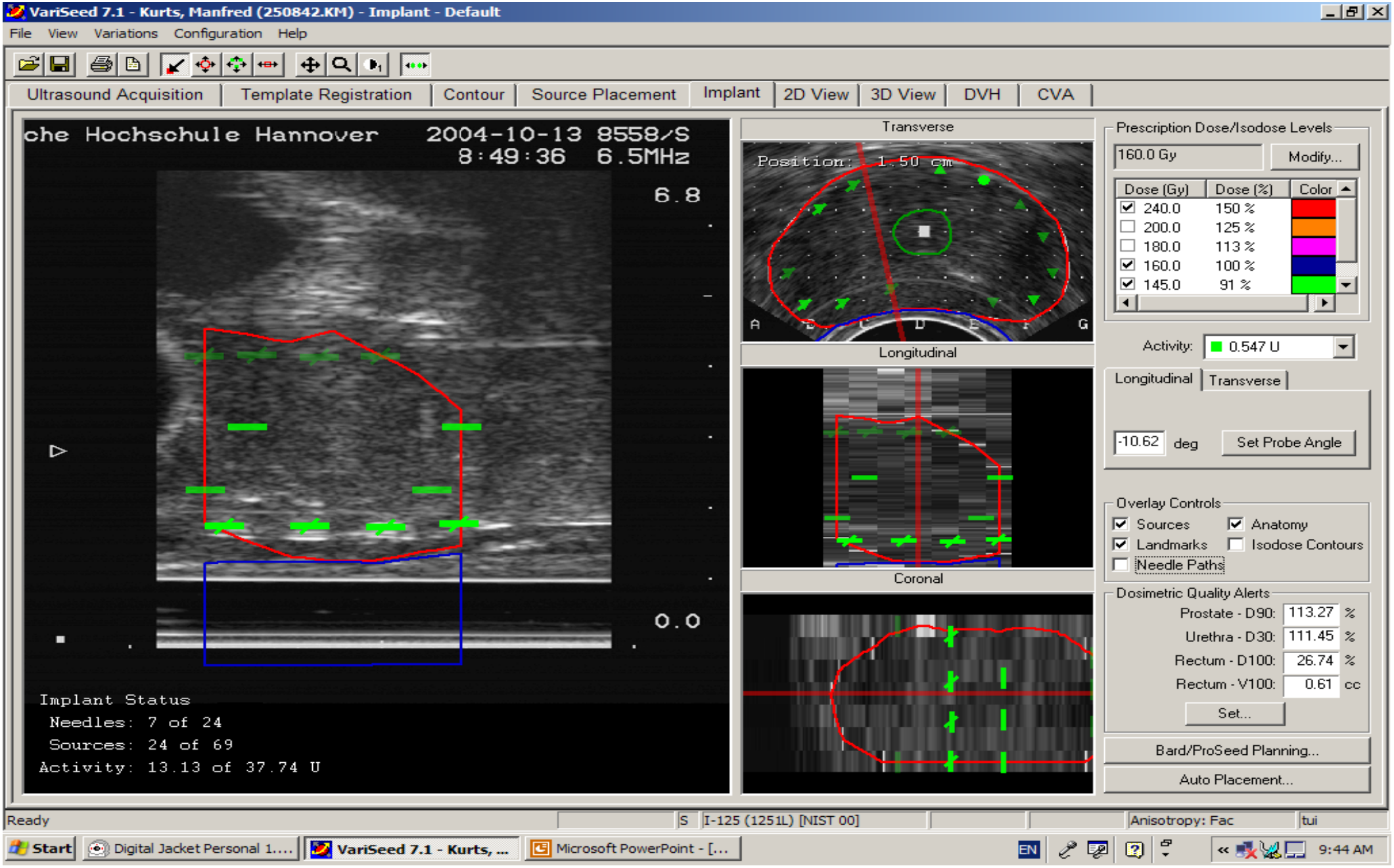
ESTRO School

Summary of first presentation

- **Long-term morbidity rate is low. (LoE: III)**
- **Technical advances improve tumor control and lower toxicity.**
- **Careful patient selection is important to avoid unacceptable morbidity.**
- **Urgent need for prospective trials to investigate on medical approaches to the treatment of morbidity.**

Reduction of rectal morbidity

- **Limiting the anterior maximal mucosal dose to 120% mPD.**
- **Limiting the length of the rectal mucosa receiving 100-120% mPD to 10 and 5mm.**
- **Avoid constipation.**



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- **Moving seeds from 5mm to 3mm from the edge increases maximum rectal dose by 17%.**

- **Posterior seeds 3mm from edge:**

  - 1mm margin: 187±6Gy; ≤ 1% (max. rectal dose; % late rectal toxicity)

  - 2mm margin: 222±8Gy; ≤ 2%

  - 3mm margin: 257±11Gy; ≤ 3%

  -4 mm margin: 292±14Gy; ≤ 5%

  -5mm margin: 327 ±17Gy; ≤ 7%

[Waterman et al.; Int J Radiat Oncol Biol Phys, 2003]

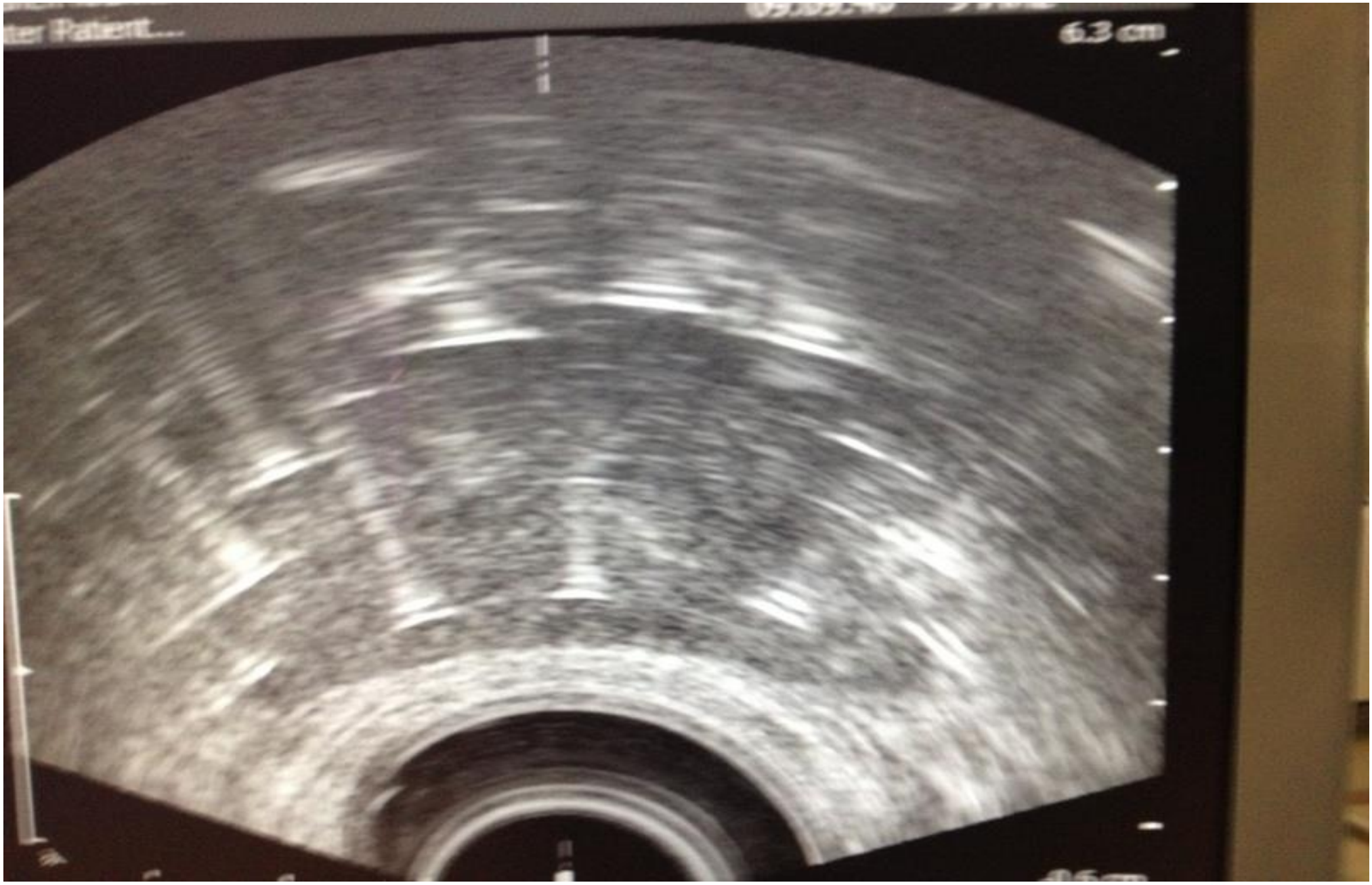
Reduction of rectal morbidity

- **3/3 (1455) patients with recto-urethral fistulas had undergone endoscopy and low rectal biopsy.**

[Shakespeare et al., May 9(4):328-331, 2007

Reduction of rectal morbidity

- **Biopsies of the anterior rectal wall should be avoided !!!**
- **Injection of hyaluronic acid into the anterior rectal wall in the end of procedure.**



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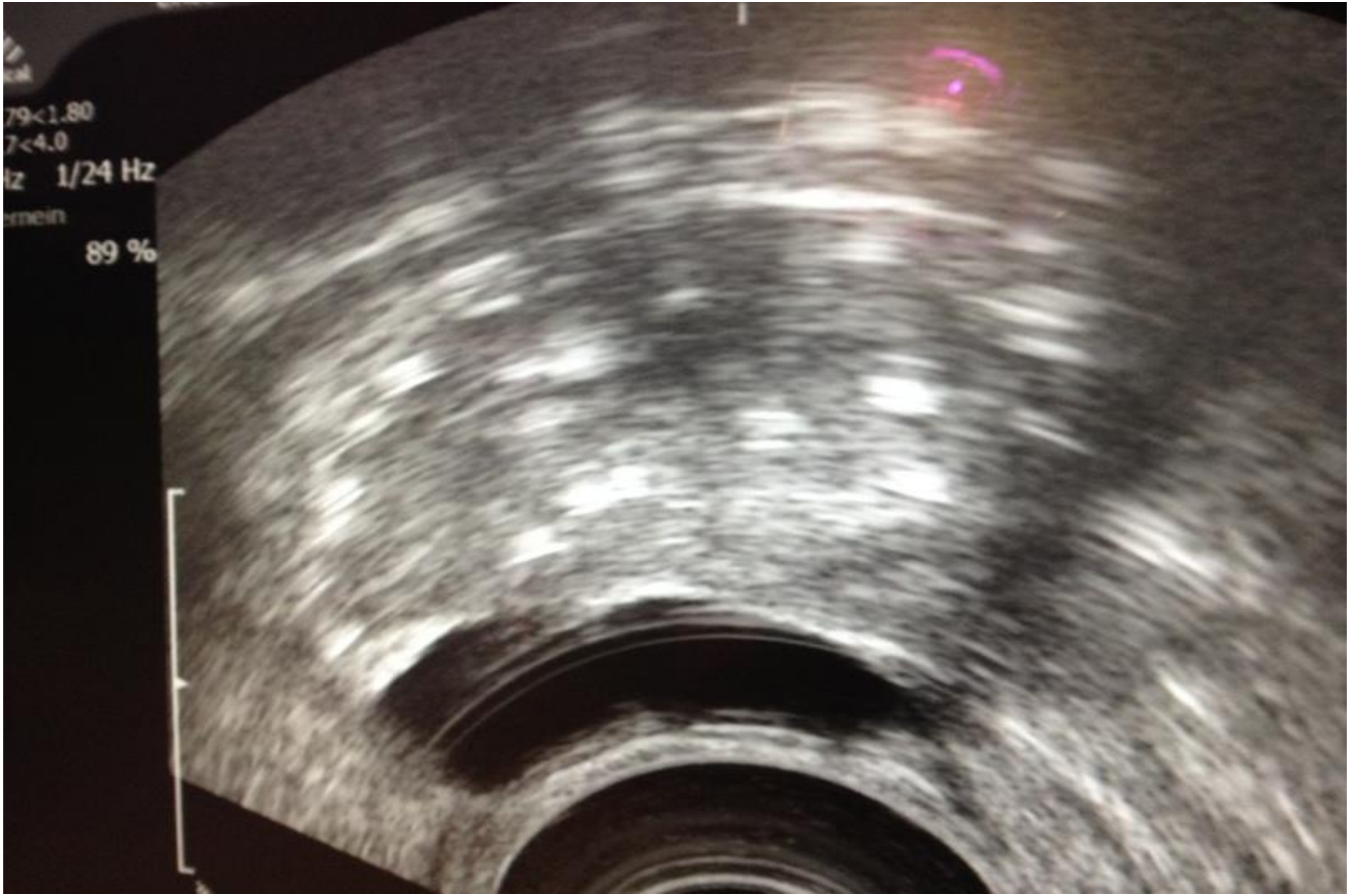
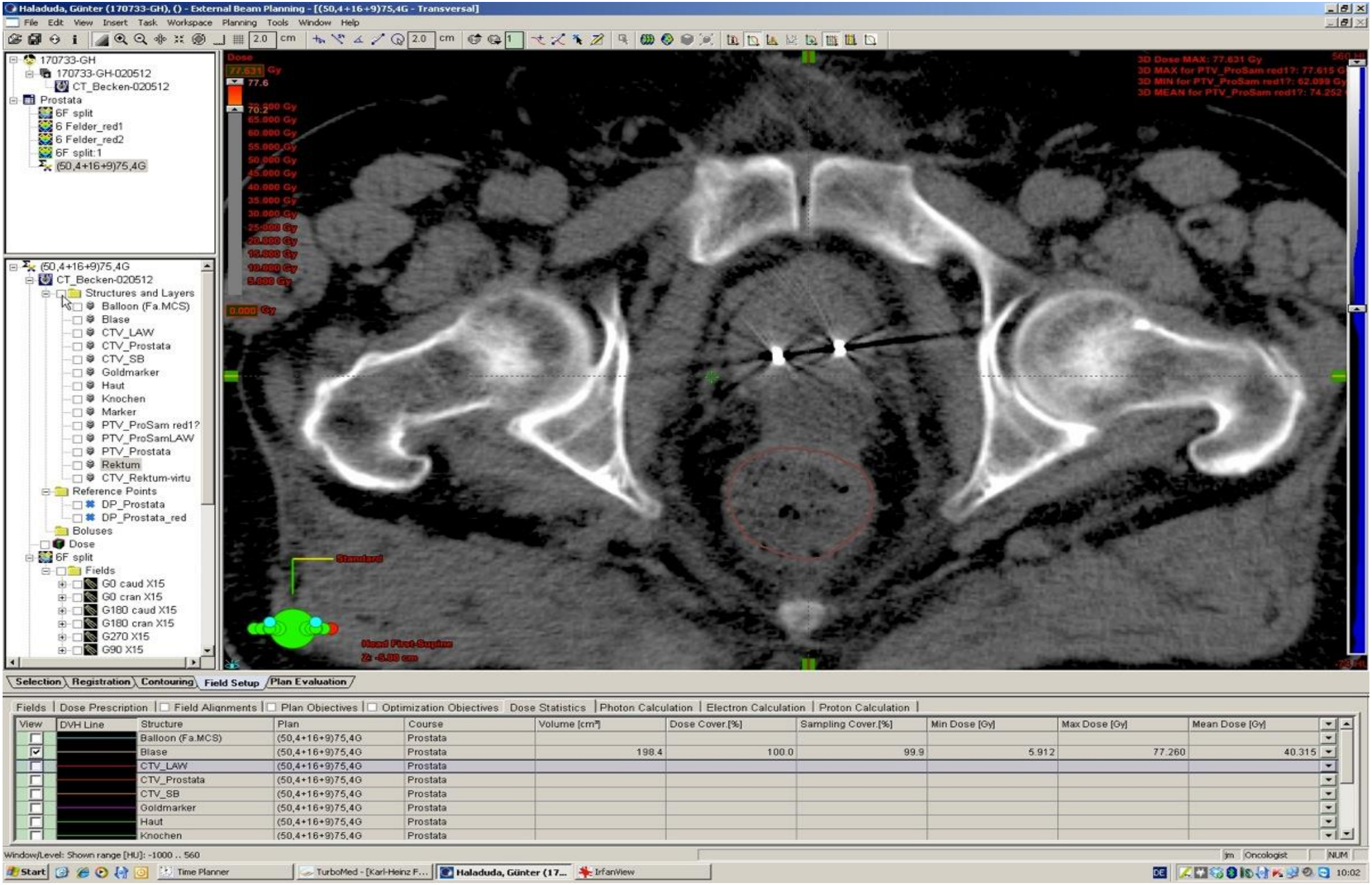

79<1.80
7<4.0
1/24 Hz
89 %



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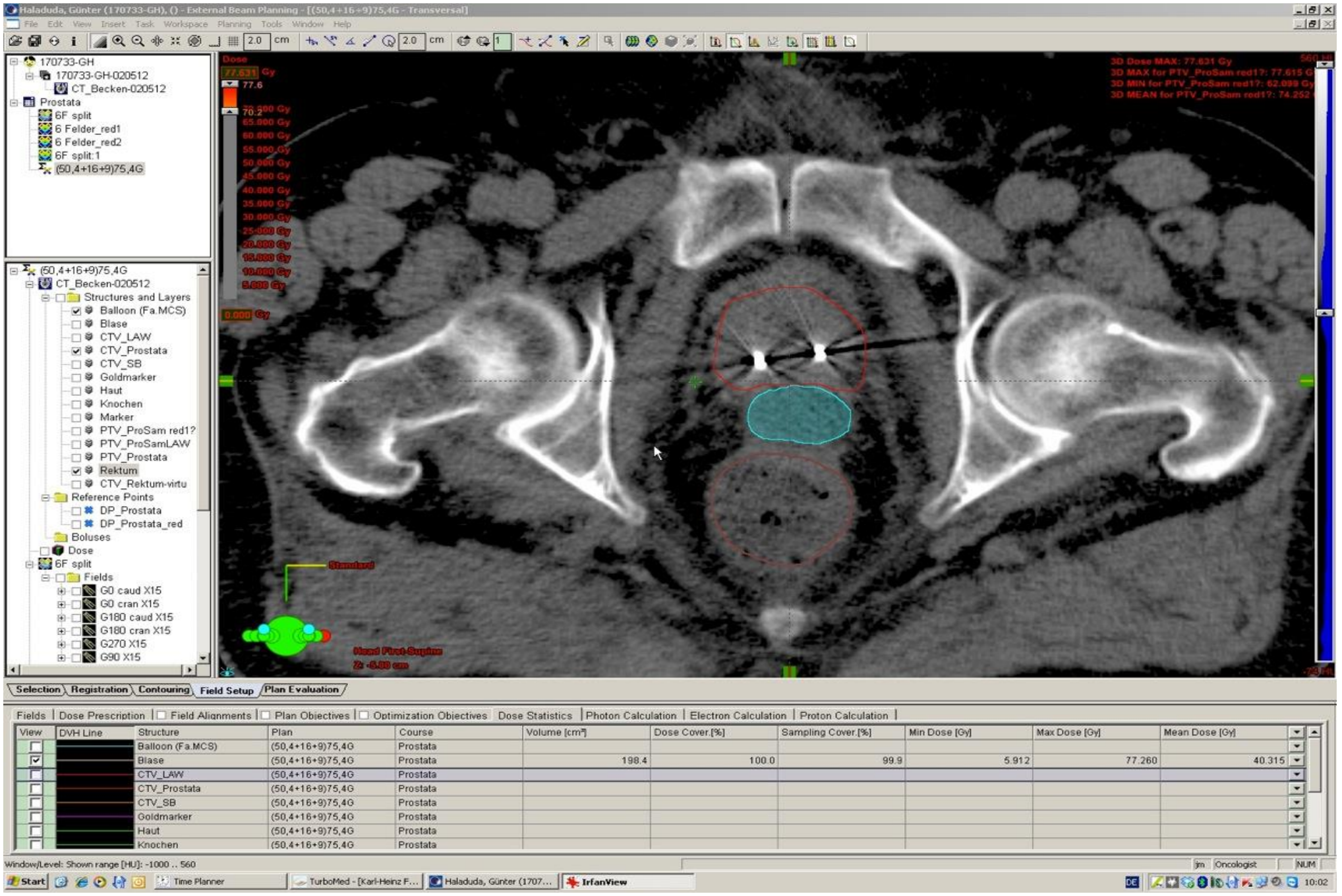
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170733-GH
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CT_Becken-020512
Prostata
6F split
6 Felder_red1
6 Felder_red2
6F split:1
(50,4+16+9)75,4G
Dose
77.631 Gy
77.6
70.2
3D Dose MAX: 77.631 Gy
3D MAX for PTV_ProSam red1?: 77.615 G
3D MIN for PTV_ProSam red1?: 62.099 Gy
3D MEAN for PTV_ProSam red1?: 74.252
(50,4+16+9)75,4G
CT_Becken-020512
Structures and Layers
Balloon (Fa.MCS)
Blase
CTV_LAW
CTV_Prostata
CTV_SB
Goldmarker
Haut
Knochen
Marker
PTV_ProSam red1?
PTV_ProSamLAW
PTV_Prostata
Rektum
CTV_Rektum-virtu
Reference Points
DP_Prostata
DP_Prostata_red
Boluses
Dose
6F split
Fields
G0 caud X15
G0 cran X15
G180 caud X15
G180 cran X15
G270 X15
G90 X15
Standard
Head First-Supine
Selection Registration Contouring Field Setup Plan Evaluation
Fields Dose Prescription Field Alignments Plan Objectives Optimization Objectives Dose Statistics Photon Calculation Electron Calculation Proton Calculation
View DVH Line Structure Plan Course Volume [cm³] Dose Cover.[%] Sampling Cover.[%] Min Dose [Gy] Max Dose [Gy] Mean Dose [Gy]
Balloon (Fa.MCS) (50,4+16+9)75,4G Prostata
Blase (50,4+16+9)75,4G Prostata 198.4 100.0 99.9 5.912 77.260 40.315
CTV_LAW (50,4+16+9)75,4G Prostata
CTV_Prostata (50,4+16+9)75,4G Prostata
CTV_SB (50,4+16+9)75,4G Prostata
Goldmarker (50,4+16+9)75,4G Prostata
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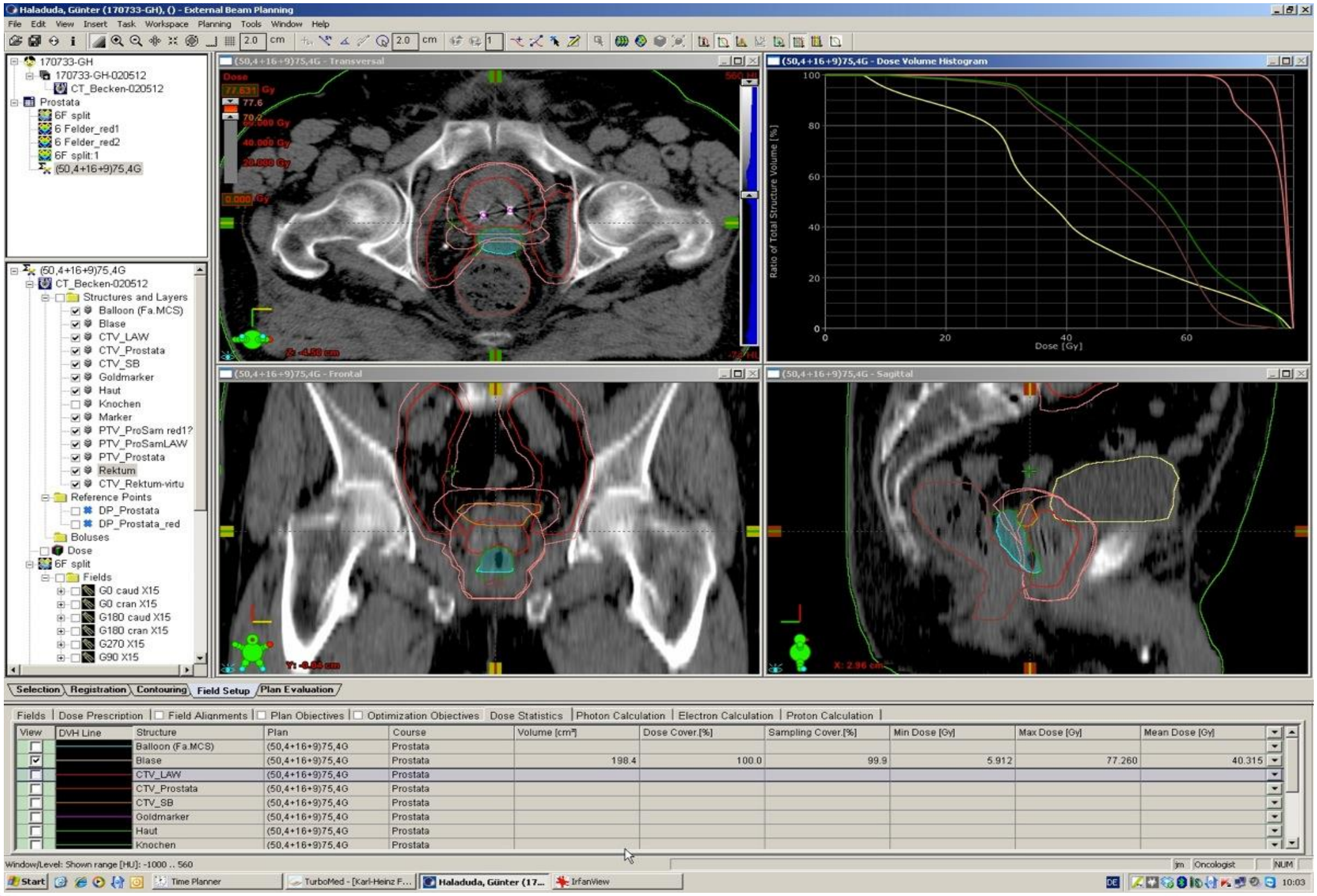

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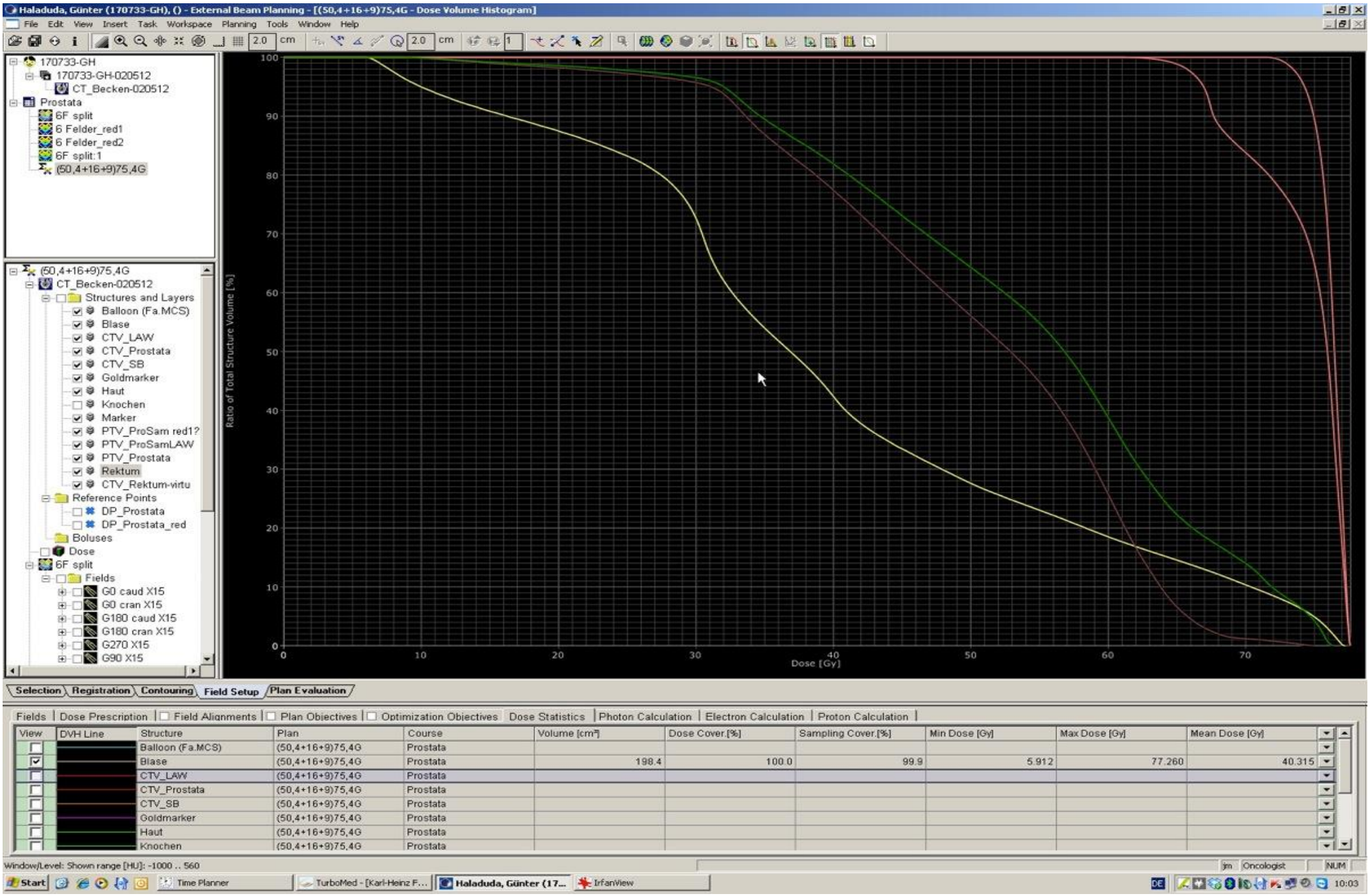

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Treatment of rectal complications

- **Calm the patient! Expectative management as long as possible.**
- **Local application of corticosteroides.**
- **Protective AP in case of fistulas.**

Type of Therapy	Proposed Mechanism	Summary
Medical therapies		Historically used as first-line therapy with mixed results; few randomized trials available; HBOT appears to be effective
5-Aminosalicylic acid	Anti-inflammatory	
Sucralfate	Anti-inflammatory	
Steroid enemas	Anti-inflammatory	
Short-chain fatty acid enemas	Promote healing	
HBOT	Promote healing	
Endoscopic therapies		More effective than medical therapies but associated with higher rectal complication rate; APC is preferred over laser coagulation
Topical formalin	Chemical cauterization	
Heater and bipolar cautery	Thermoelectric cauterization	
Nd:YAG and KTP laser	Noncontact electrocoagulation	
Argon plasma coagulation	Noncontact electrocoagulation	
Surgical therapies		High risk of postoperative morbidity, reserved for severe rectal strictures and rectal fistulas
Proctectomy		
Diverting colostomy		

Phan et al., Cancer 115:1827-1839, 2009

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Table 4. Literature Review of Endoscopic Therapies

Therapy	No. of Studies	Results	No. of Sessions Needed	Complications	Study(s)
Topical formalin	5	Initial response rate, 59%-100%; PR rate at 1 y, 19%-38%	1-3	Rectal strictures, <1%; perianal ulcers fissures, 5%	Wilson & Rex 2006,[65] Mathai & Seow-Chen 1995,[67] Seow-Chen 1993,[68] Saclarides 1996,[69] Biswal 1995,[70] Counter 1999,[71] Roche 1996,[72] Yegappan 1998[73]
Heater and bipolar probe	2	Response rate, 100%	1-4	None	Fuentes 1993,[75] Davila 1996[76]
Nd:YAG and KTP laser	5	Response rate at 1-3 y, 75%-90%	2-5	Ileus, pain, 1%-5%; rectal fistula, <1%	Taylor 1993,[78] Buchi 1991,[80] Buchi & Dixon 1987,[82] Chapuis 1996,[83] Taylor 2000[84]
Argon plasma coagulation	5	Response rate at 1-2 y, 90%-100%	2-3	Rectal strictures, 2%	Tam 2000,[88] Silva 1999,[89] Fantin 1999,[90] Sebastian 2004,[91] Rotondano 2003[93]

Phan et al., Cancer 115:1827-1839, 2009

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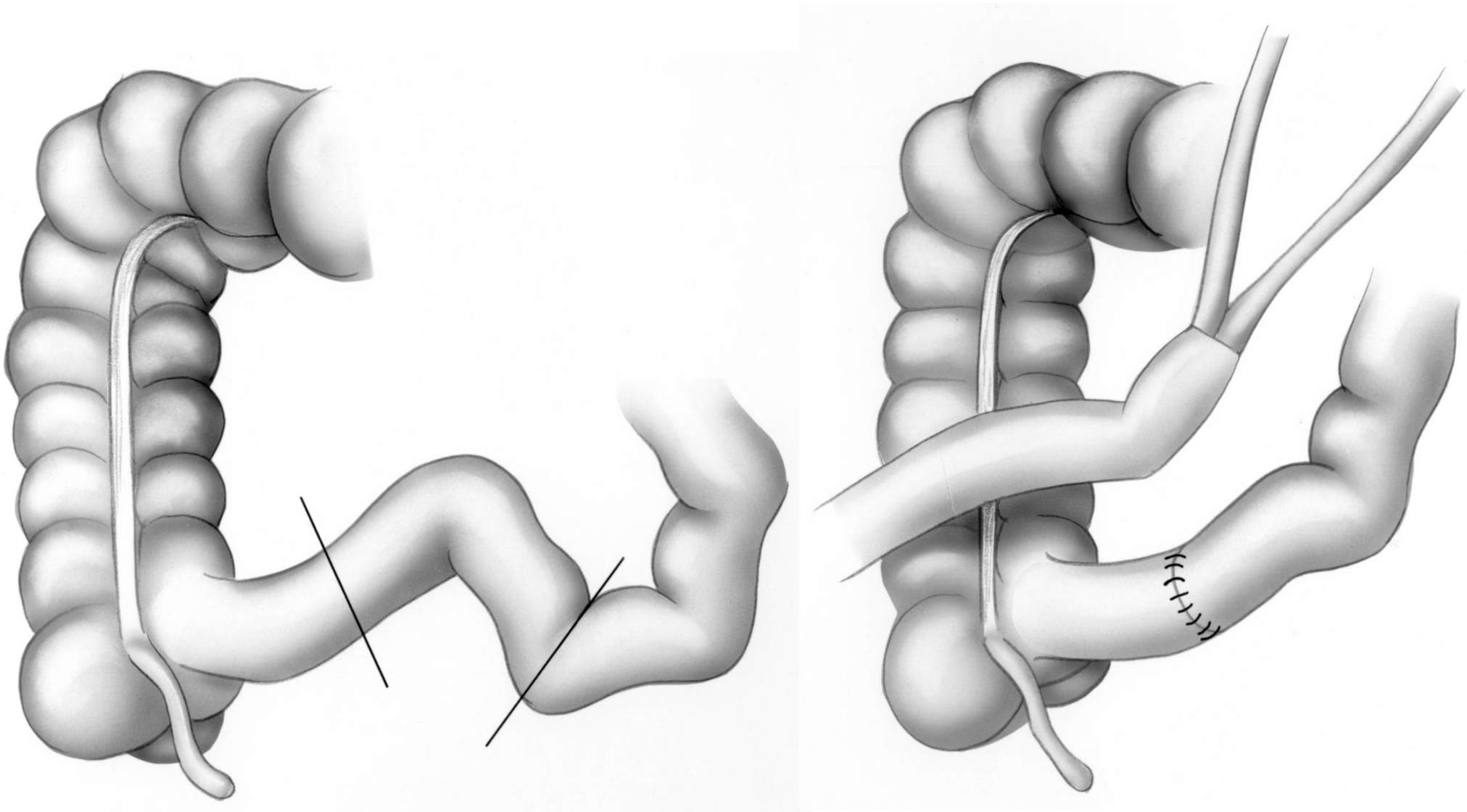
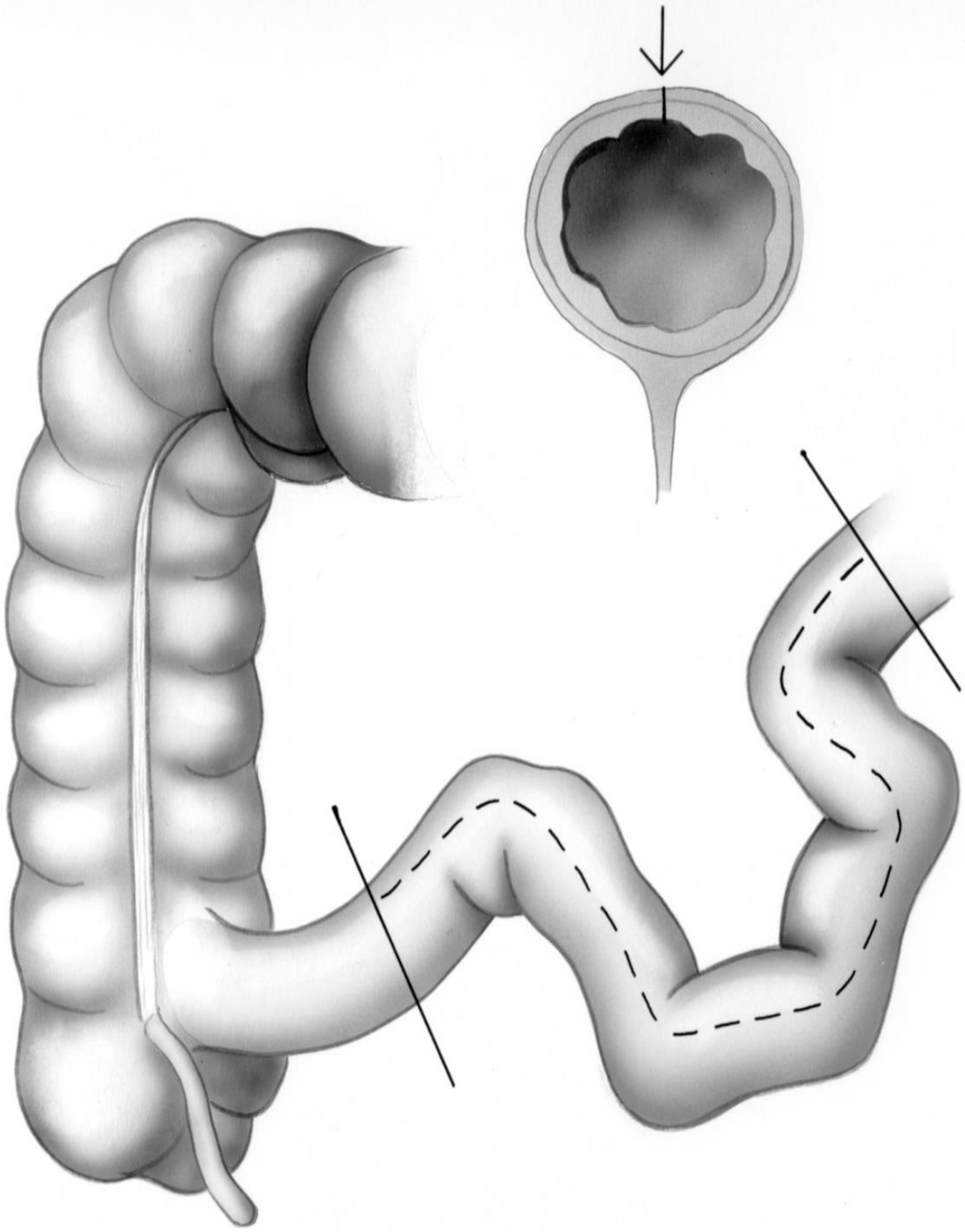
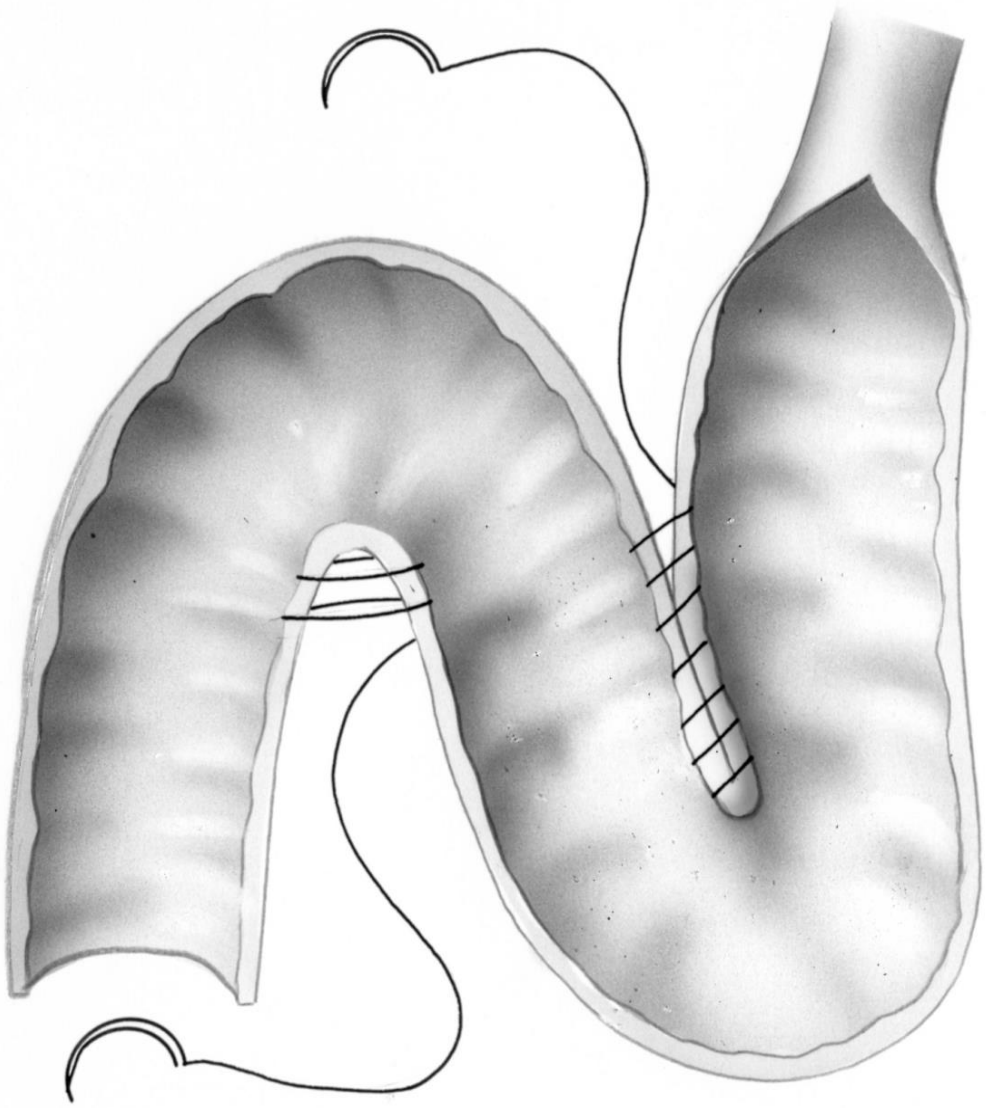
Treatment of rectal complications

- **Plastic reconstruction of the rectal wall with gracilis muscle.**
- **Radical operation with construction of neobladder.**







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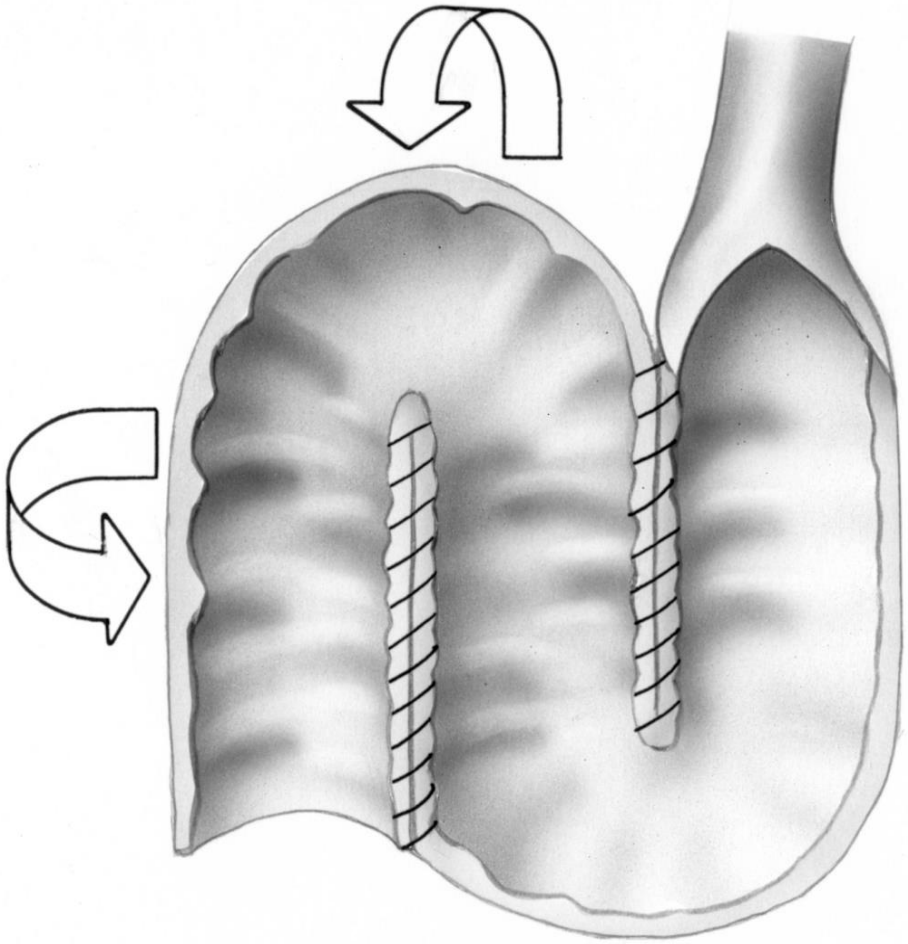
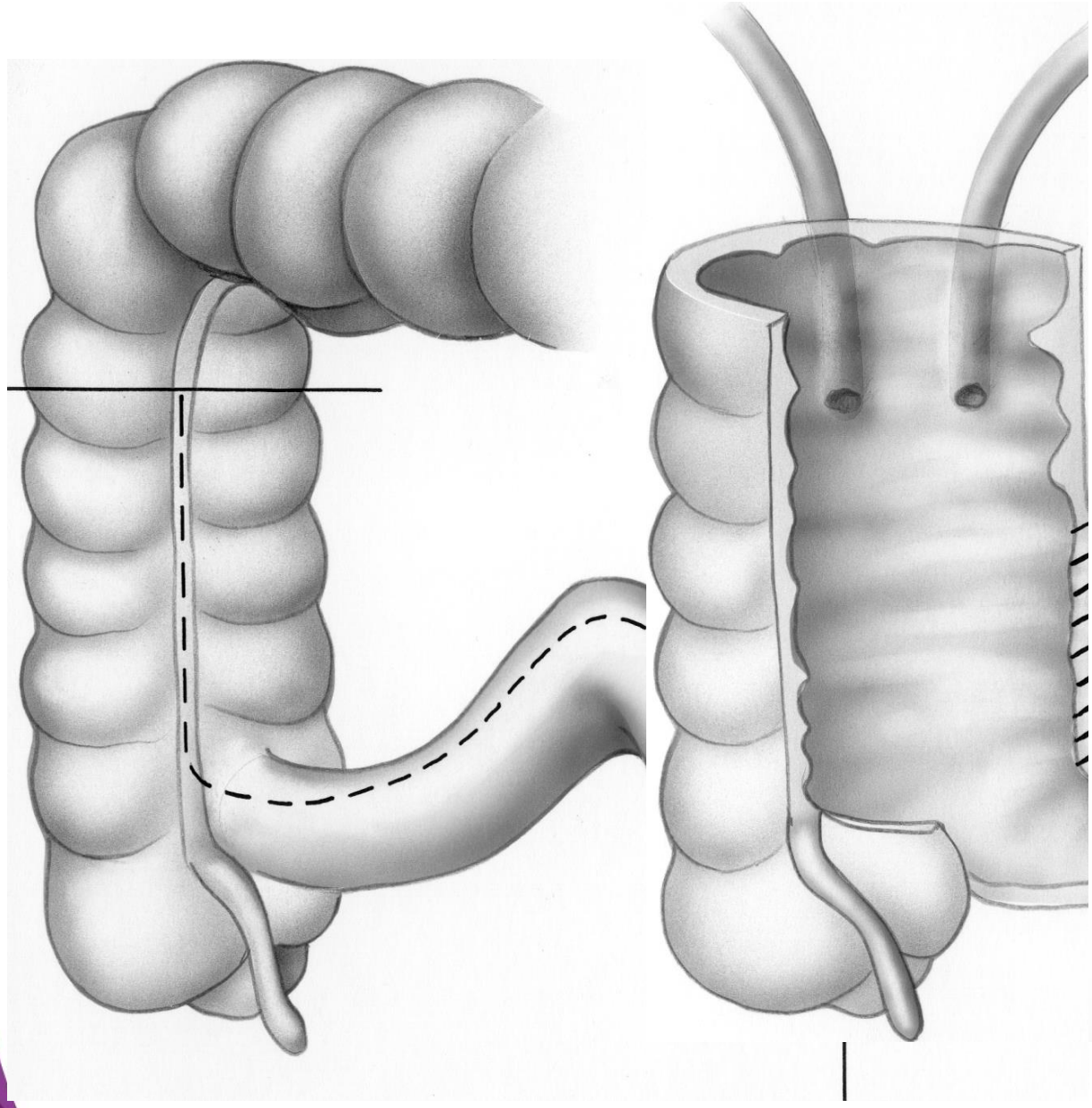
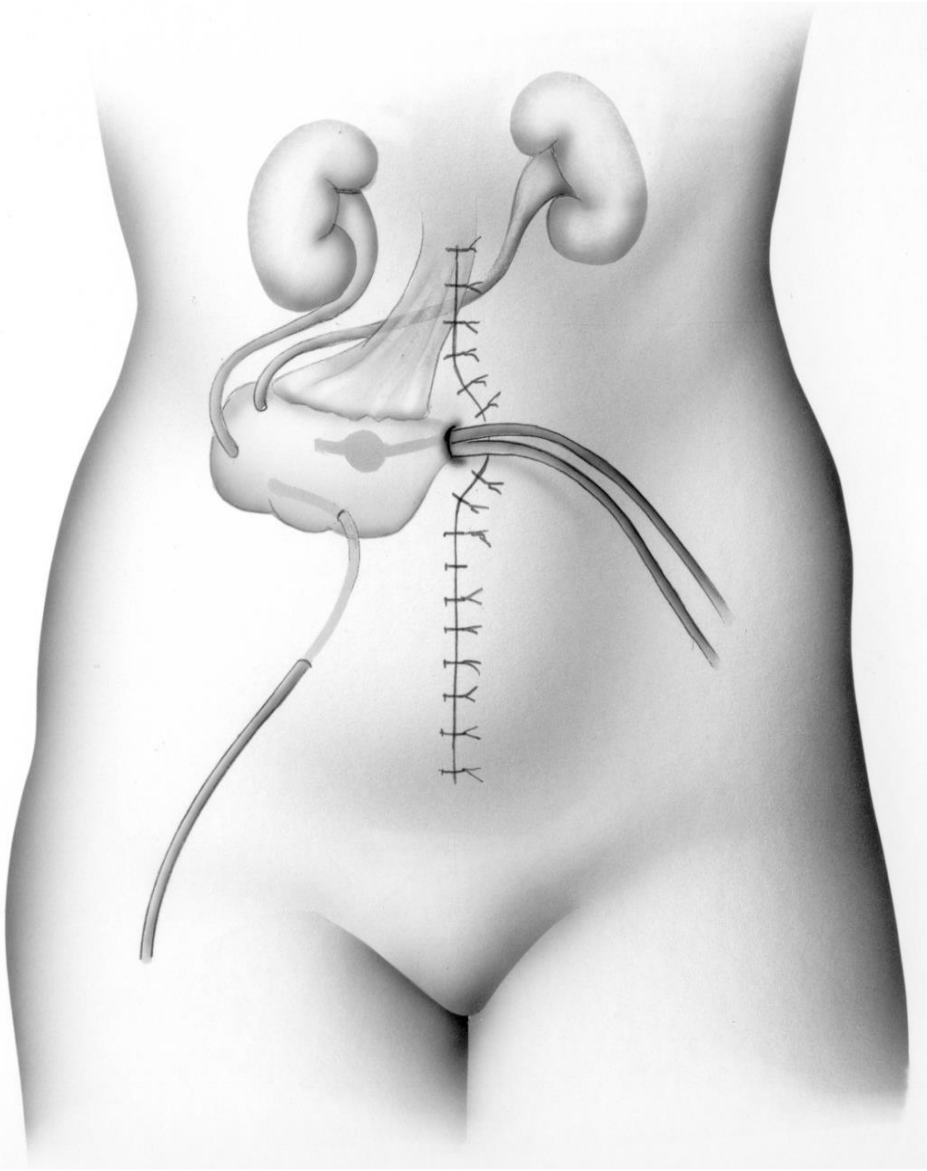






Reduction of urinary morbidity

- **Careful selection of patients by IPSS.**
- **Technical considerations in planning.**
- **Careful resection of large medium lobes preinterventionally.**
- **Expectative management in the first 12 months after implant.**

Treatment of urinary morbidity

- α-Blockers in obstructive patients.
- Suprapubic catheter in case of complete urinary retention for 12 months.
- Anticholinergics in irritative patients
- Increase in urinary pH by medication. Avoidance of acidic diet.

The pathophysiology of lower urinary tract symptoms after brachytherapy for prostate cancer

Jerry G. Blaivas, Jeffrey P. Weiss and Mark Jones
The Joan and Sanford I. Weill Medical College of Cornell University, New York, NY, USA

JOURNAL COMPILATION © 2006 BJU INTERNATIONAL | 98, 1233–1237 | doi:10.1111/j.1464-410X.2006.06491.x

- **Comparison of 47 men with LUTS after brachytherapy with 541 men with LUTS without prostate cancer.**
- **Significant more detrusor overactivity (47 vs.85%) after brachytherapy.**
- **Higher incidence of urethral and prostatic strictures.**

Treatment of urinary morbidity

- **Hyaluronic acid intravesically after failure of anticholinergics.**
- **Botox injection to the bladder neck in patients with prolonged irritation.**
- **Careful TUR-P after 12 months in patients with complete urinary retention without irritation.**

TUR-P after implantation

- **As late as possible.**
- **Best timíng between 12-24months after implantation to avoid incontinence .**
- **Safe 5‘ and 7‘ o clock position at the baldder neck.**

Technical considerations in TUR-P

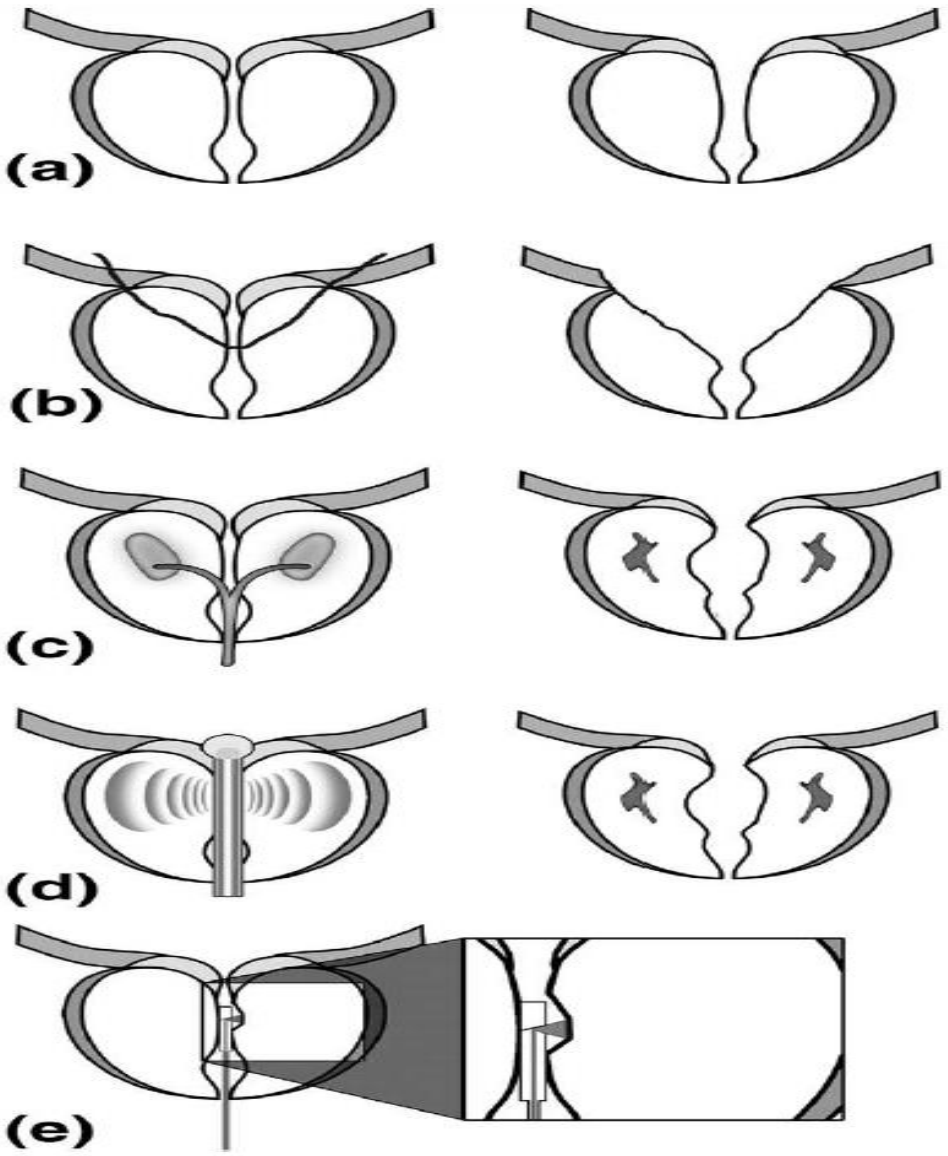


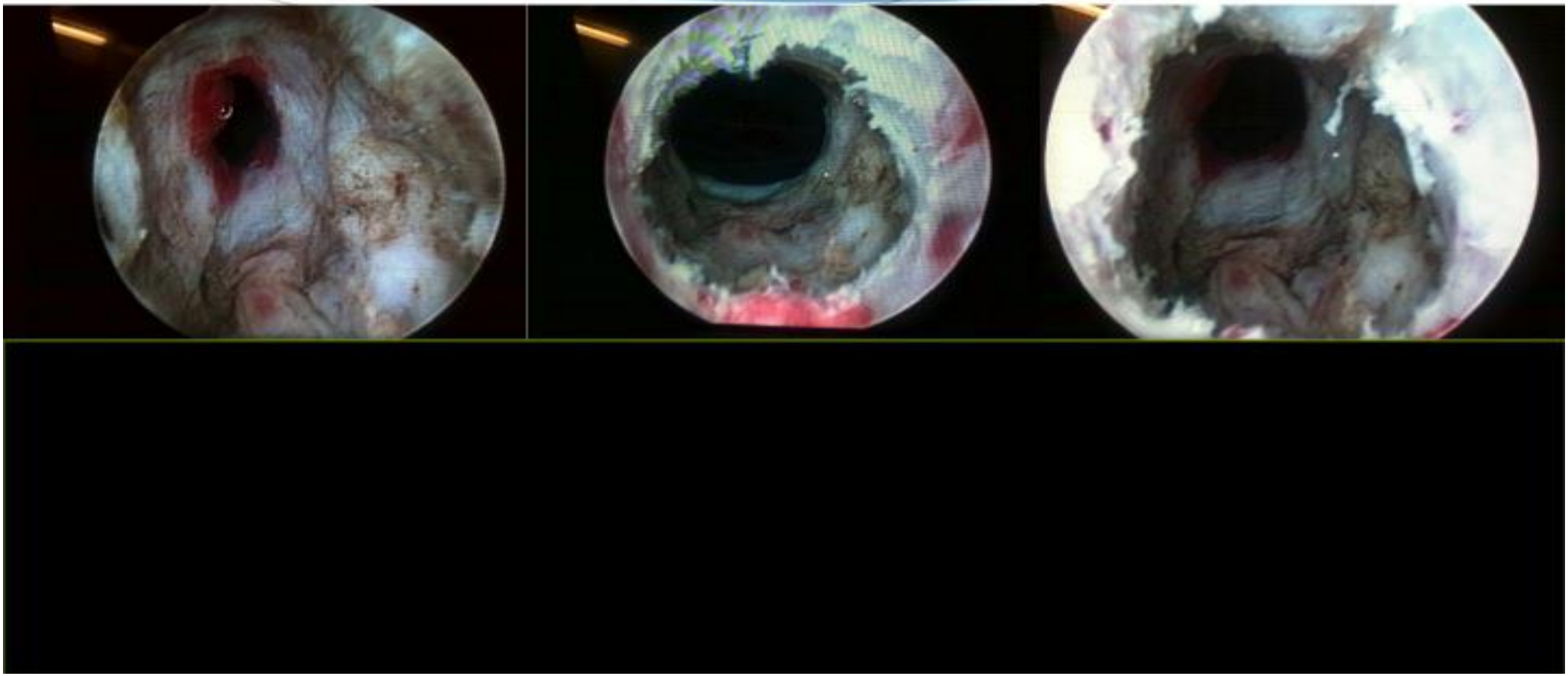
Fig. 9. Surgical procedures to relieve obstruction. (a) Transurethral incision. (b) transurethral prostatectomy. (c) Interstitial (laser or ultrasound). (d) Microwave. (e) Superficial (holmium) laser.

FUNCTIONAL ANATOMY OF THE PROSTATE: IMPLICATIONS FOR TREATMENT PLANNING

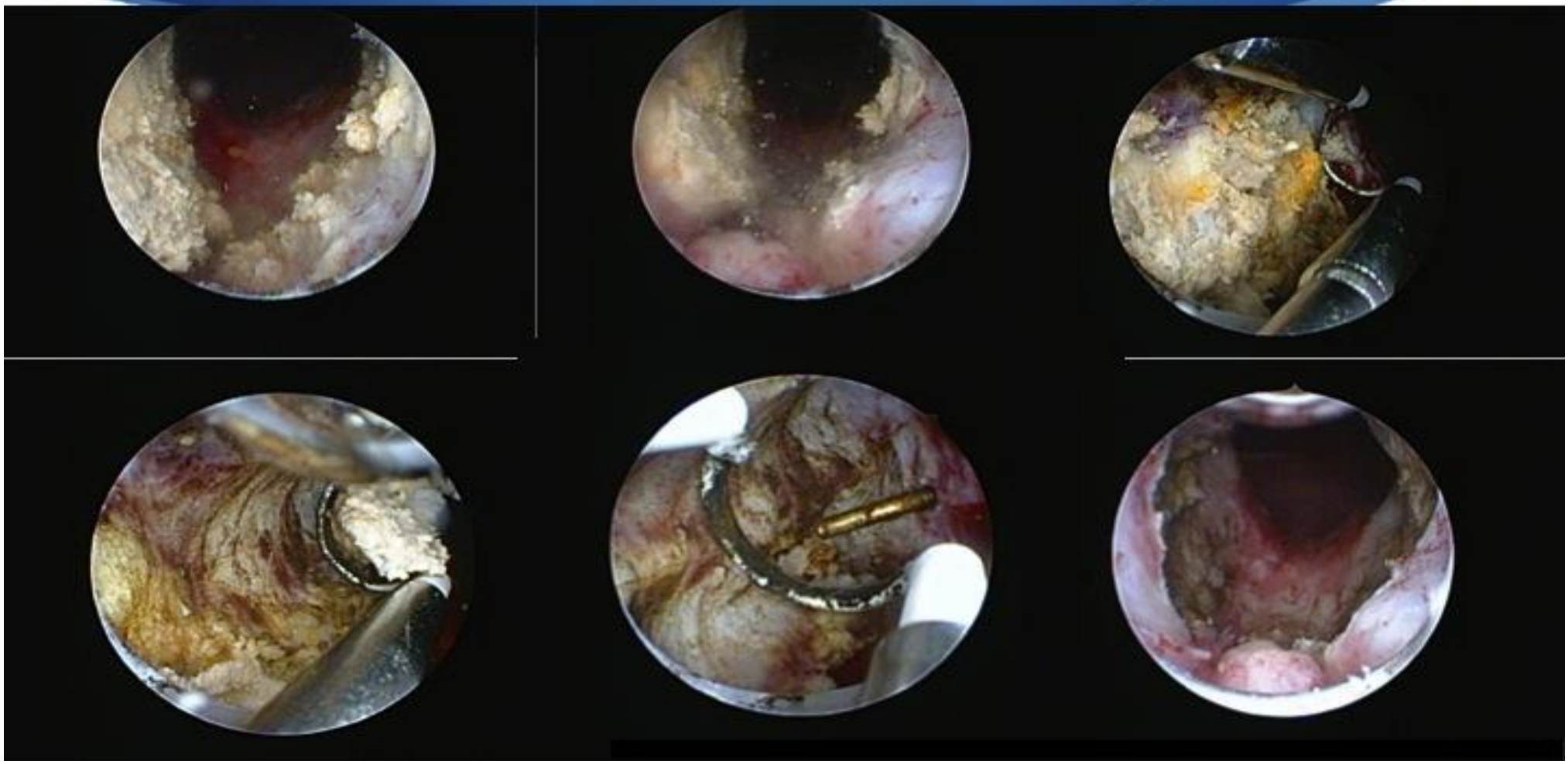
PATRICK W. MCLAUGHLIN, M.D.,*† SARA TROYER, B.S.,† SALLY BERRI, M.D.,† VRINDA NARAYANA, PH.D.,*† AMICHAY MEIROWITZ, M.D.,† PETER L. ROBERSON, PH.D.,† AND JAMES MONTIE, M.D.‡

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, pp. 479–491, 2005

TURP 6 M after IPB



TURP 12 M after IPB



0022-5347/05/1733-0808/0
THE JOURNAL OF UROLOGY®

Vol. 173, 808–812, March 2005
Printed in U.S.A.
DOI: 10.1097/01.ju.0000152698.20487.0e

URINARY MORBIDITY AND INCONTINENCE FOLLOWING TRANSURETHRAL RESECTION OF THE PROSTATE AFTER BRACHYTHERAPY

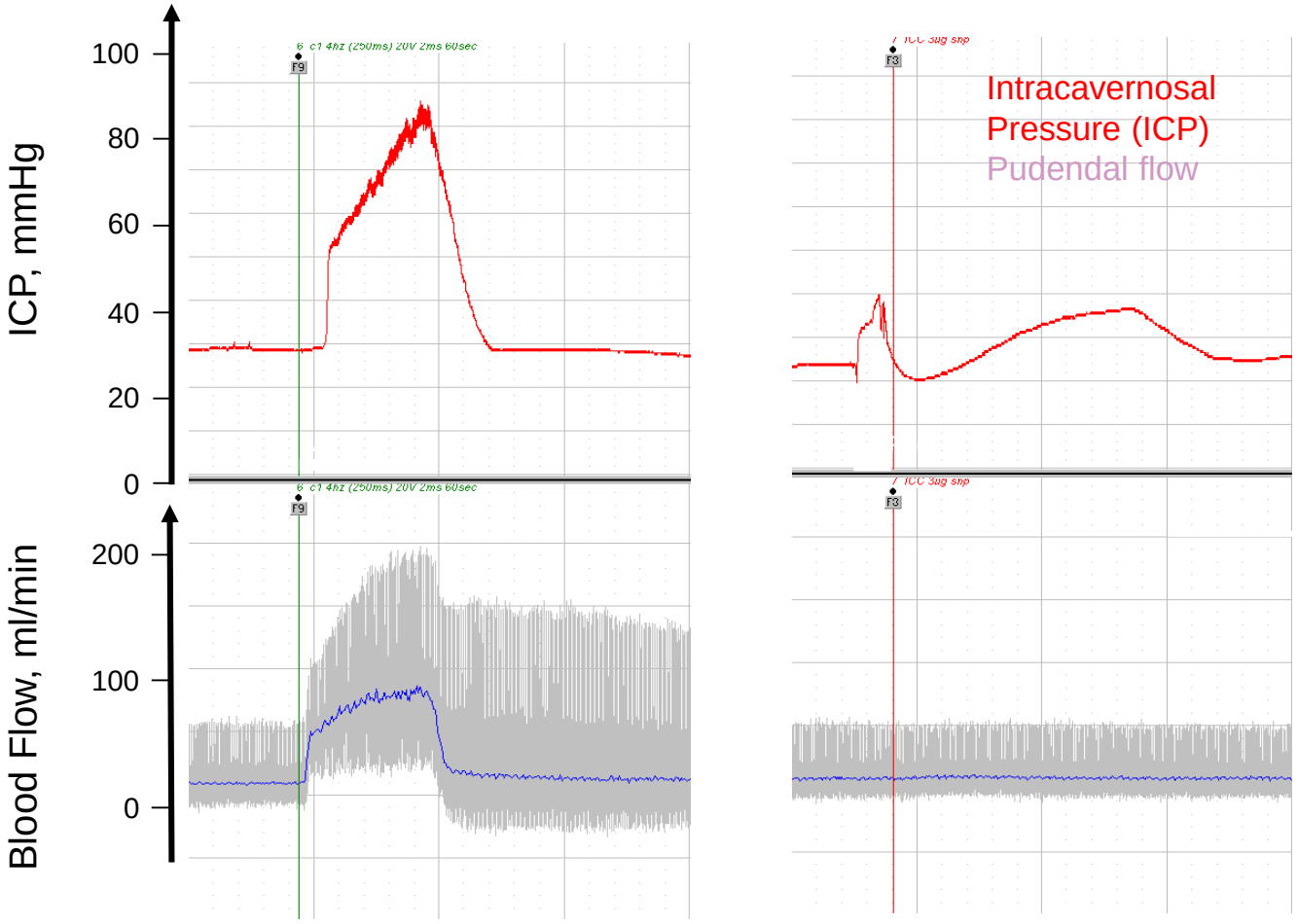
M. A. KOLLMEIER,* R. G. STOCK, J. CESARETTI AND N. N. STONE
From the Departments of Radiation Oncology and Urology (NNS), Mount Sinai School of Medicine, New York, New York

- **38/2050 (2%) patients underwent minimal TUR-P.**
- **7/38 (18%) with incontinence.**
- **2/24 (8%) against 5/14 (36%) with incontinence in case TUR-P was performed <1 or > 2years after implant.**
- **No correlation of incontinence with D90 prostate or D30 urethra or dose to 5cm² urethra.**

Reduction of erectile dysfunction

- **50% of the bulb of the penis should not receive more than 40% mPD.**
- **Judicious use of EBRT and hormonal therapy.**
- **Early use of PDE Inhibitors.**

Rate of Erection Hardness (ICP) Increases With Increased Pudendal Flow to the Penis



- Electrical cavernous nerve stimulation increases pudendal blood flow and provides rapid increases in intracavernosal pressure (ICP)
- Intracavernosal injection of a nitric oxide donor, sodium nitroprusside, produces slow increases in ICP but has no effect on pudendal flow

Illustrates importance of flow-mediated vasodilation in the initiation and maintenance of penile erection in preclinical model

Wayman C et al. ESSM. 4-7 December2005. Poster M-05-141.

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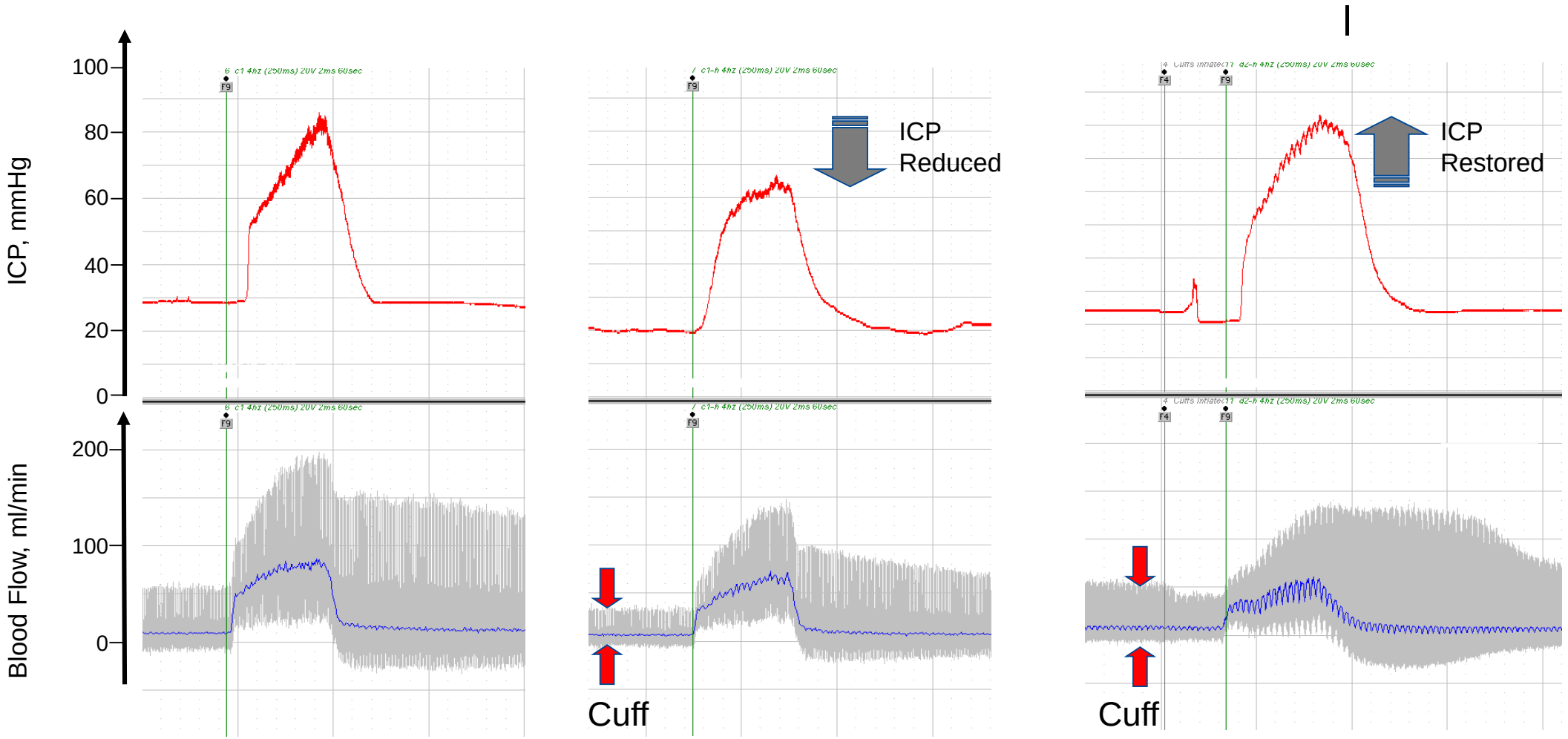
Sildenafil Restores Erection Hardness (ICP)



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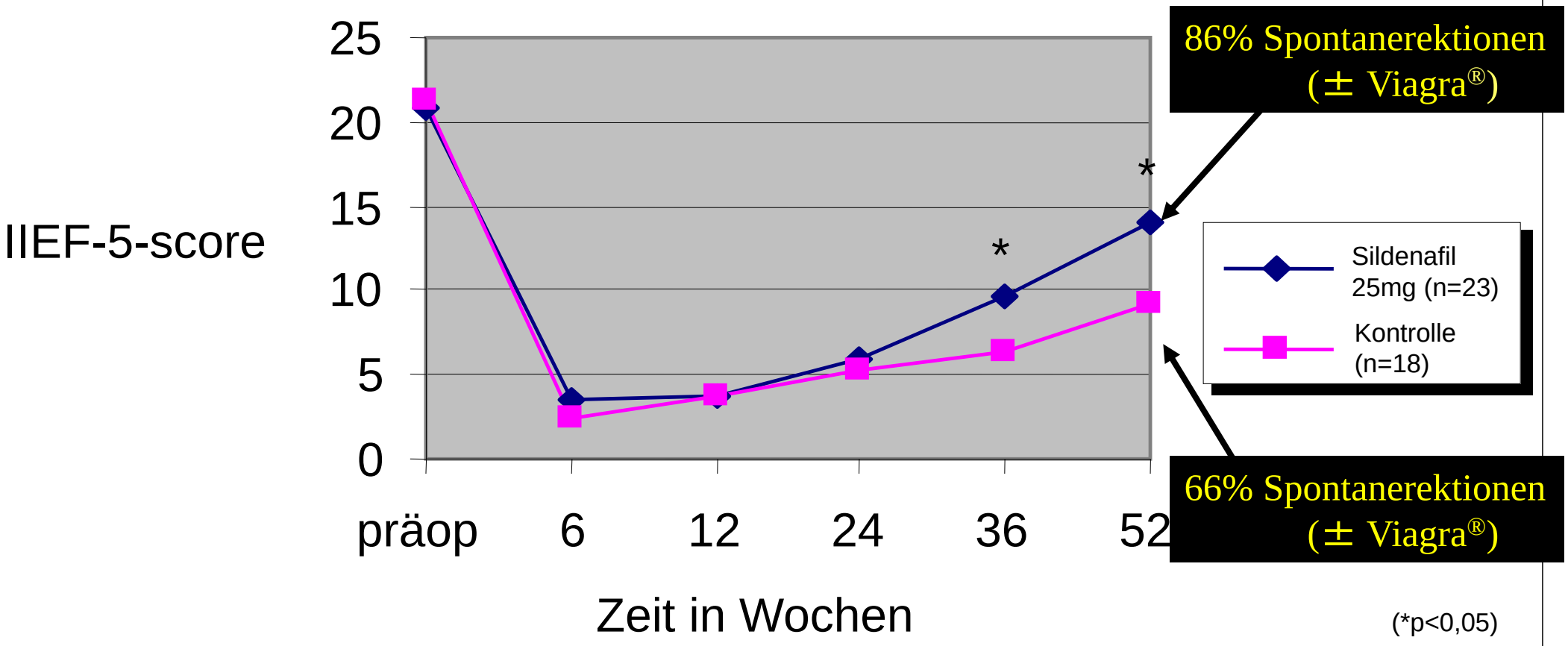
Erholung der erektilen Funktion "Kieler Konzept" nach nsRRP (n=41)



(*p<0,05)

Early use of a phosphodiesterase inhibitor after brachytherapy restores and preserves erectile function

Jonathan D. Schiff, Natan Bar-Chama, Jaime Cesaretti and Richard Stock

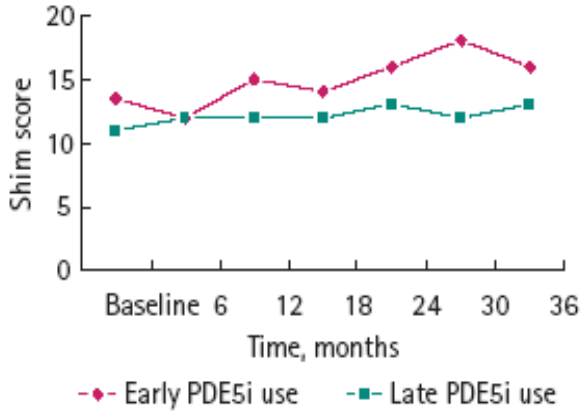
JOURNAL COMPILATION © 2006 BJU INTERNATIONAL | 98, 1255–1258 | doi:10.1111/j.1464-410X.2006.06441.x

Variable	Early group	Late group	P
N	85	125	
Median age, years	62	63	0.020
Median stage (n at stage)	T1C (54)	T1C (79)	
Median Gleason score	6	6	
N with Gleason >7	23	31	
Median PSA level, ng/mL	6.5	5.6	0.053
D90	15800	17460	0.150
n with EBRT	35	40	
Median dose EBRT, Gy	45	45	
n (%) with HST	41 (48)	63 (50)	
PSA level at last follow-up	0.3	0.11	<0.001

TABLE 1
The baseline and demographic data

EBRT, external beam radiotherapy.

FIG. 1. Differences in SHIM scores at 18, 24, 30 and 36 months were significant, with P = 0.04, 0.03, 0.04 and 0.03, respectively.



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Principles of the management of complications

- **Avoidance is better than treatment.**
- **Management as minimal invasive as possible.**
- **Overtreatment can cause series of serious further complications.**

Measures to improve outcome and minimize risk of complications

- Work patients up thoroughly
- Identify and alleviate obstructive prostates beforehand
- Tailor the seed activity according to the volume
  – NB volume measurement of the prostate should always be done at initial assessment prior to referral
- Optimal procedure setup, good u/s visualization
- Accurate contouring of structures of interest
- Critically observe dose constraints

Measures to improve outcome and minimize risk of complications

- Apply meticulous technique
- Don’t drag seeds back into the rectal hump
- Keep implant needles closest to the rectum at the prostato-rectal interface at least 5mm higher than the posterior prostatic boundry (c1 and d1 – use the 1.5 row rather) particularly in thin patients and prostates with longer sagittal measurements (long prostates – more than 8 slices)
- Keep the urethra and TURP defect cooler than the periphery
- Avoid implanting seeds into the urethra or TURP defect
- If the seeds are too hot for the volume, use some cooler seeds even if they are just used for the rows closest to the rectum or urethra

Measures to improve outcome and minimize risk of complications

- Understand the biology and pathophysiology of the type of radiation being delivered and timing of side effects and complications
- Patients must be well informed regarding anticipated irritative and obstructive symptoms and duration, risks of rectal procedures after BT and informed to seek guidance from their Radonc or Urologist first before undergoing any investigation or intervention
- Avoid biopsy the rectum or prostate transrectally after BT
- Manage side effects and complications with efficiency
- Many side effects and complications resolve spontaneously
  – don’t be in a rush to intervene!

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Salvage options

1. Salvage radical prostatectomy (RPE) after radiation therapy
2. Salvage EBRT after RPE
3. Salvage HDR or LDR brachytherapy after EBRT or after seeds
4. Salvage EBRT after EBRT
5. (Cryotherapy, HIFU)

There are these two dogmas…

- 1. RPE after radiation therapy is not possible
- 2. If performed, significant complications will occur

Salvage RPE (SRP)

- In the past major morbidity after SRP
- New datas show acceptable morbidity because of better radiotherapeutic and surgical techniques

best candidate

- histologically verified recurrent prostate cancer
- neg. CT scan and skeletal scintigraphy
- PSADT> 12 months
- PSA $\leq$ 15ng/ml
- bladder capacity $\geq$ 300ml, competent sphincter, no bladder neck invasion

4 larger studies complications and outcome

Heidenreich et al 2010 / ESTRO 2012

	Ward et al	Stephenson	Gheiler et al	Heidenreich
Year of SRP	1990-2000	1993-2003	1992-1997	2004-2008
Year of RT	1985-1997	1980-2000	1980-1996	2000-2006
No patients	89	60	40	188
Median time to SRP(months)	40	50	58	28
PSA> 10ng/ml	29%	41%	48%	18.4%
≤ pT2c	39%	35%	43%	71.4%
complications	27%	13%	17%	9%
Rectal injury	3%	2%	3%	1.7%
Urinary continence	56%	68%	50%	81%
Transfusion rates	-	29%	-	4.1%

Perioperative risk dependent on type of RT

No 188	LDR	EBRT	HDR	Total
OP time(min)	115(95-130)	128(112-137)	145(105-165)	120(95-165)
Blood loss(ml)	300(150-450)	375(150-550)	420(200-1450	360(150-1450)
Rectal injury	1/66(1,5%)	1/30(3%)	1/22 (4,5%)	3/118(1.7%)
Perioperativ complications	4/66(6%)	1/30(3%)	2/22 (9%)	7/118(5.9%)
Catheterization(days)	7.5(7-10)	8(7-15)	8.5(7-28)	8(7-28)
Hospitalisation	8.5(8-11)	9.5(8-12)	10(8-14)	9.2(8-14)

Heidenreich et al 2010 / ESTRO 2012

Pathohistology after SRP correlates to type of RT ?!

	EBRT	Temporary BT	Permanent BT	p
n	30	22	66	0.02
pT2a-c	20(66.7%)	11(50%)	54(81.8%)	0.001*
pT3a-b	10(33.3%)	11(50%)	12(18.2%)	0.001*
pN1	5(16.6%)	7(32%)	4(6.1%)	0.001*
SM+	4(13.3%)	4(18.2%)	4(6.1%)	0.001*

*p for comparison permanent BT vs EBRT/temporary BT

Heidenreich et al ESTRO 2012

ESTRO School

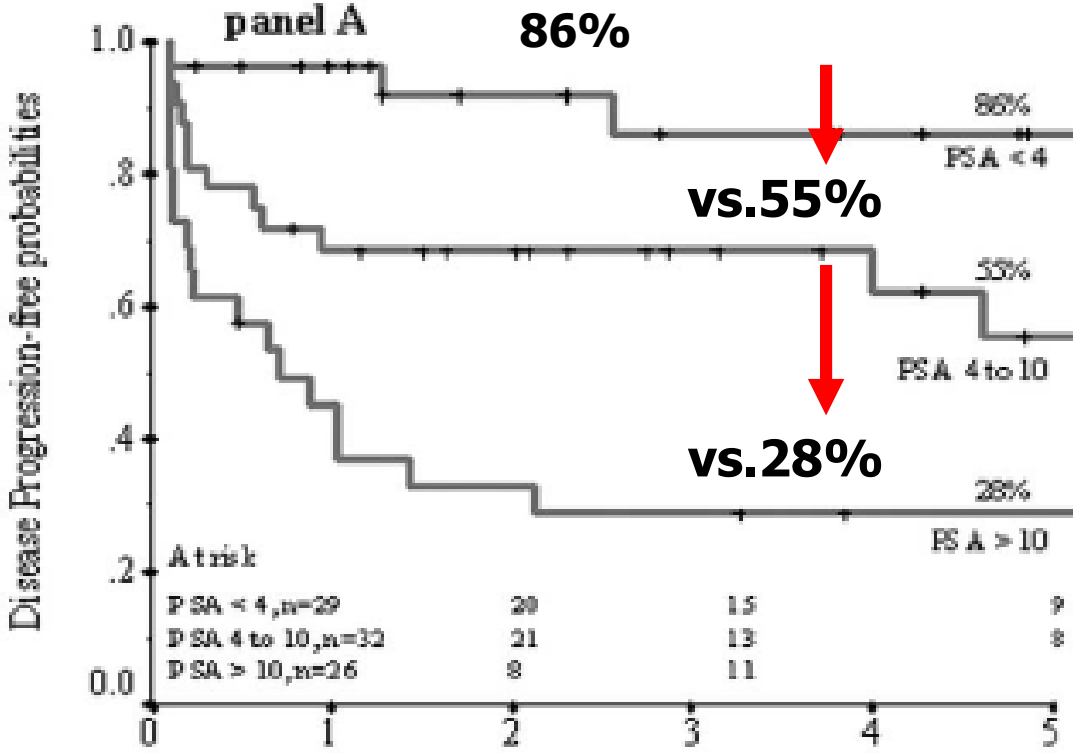
Significant prognostic risk factors for organ-confined disease at salvage therapy

	UVA	MVA
Biopsy Gleason Score $\leq$ 7 (RPE)	0.001	0.02
< 50% positive cores	0.0001	0.001
LDR – Brachytherapy	0.0001	0.001
PSA-DT > 12 months	0.0002	0.002

Heidenreich A et al Eur Urol 2009

Disease progression free survival dependent on PSA level, preoperativ parameter

< 4ng/ml → 5 years progression free probabiity



Cancer survival < 10ng/ml vs >10ng/ml → 10 years

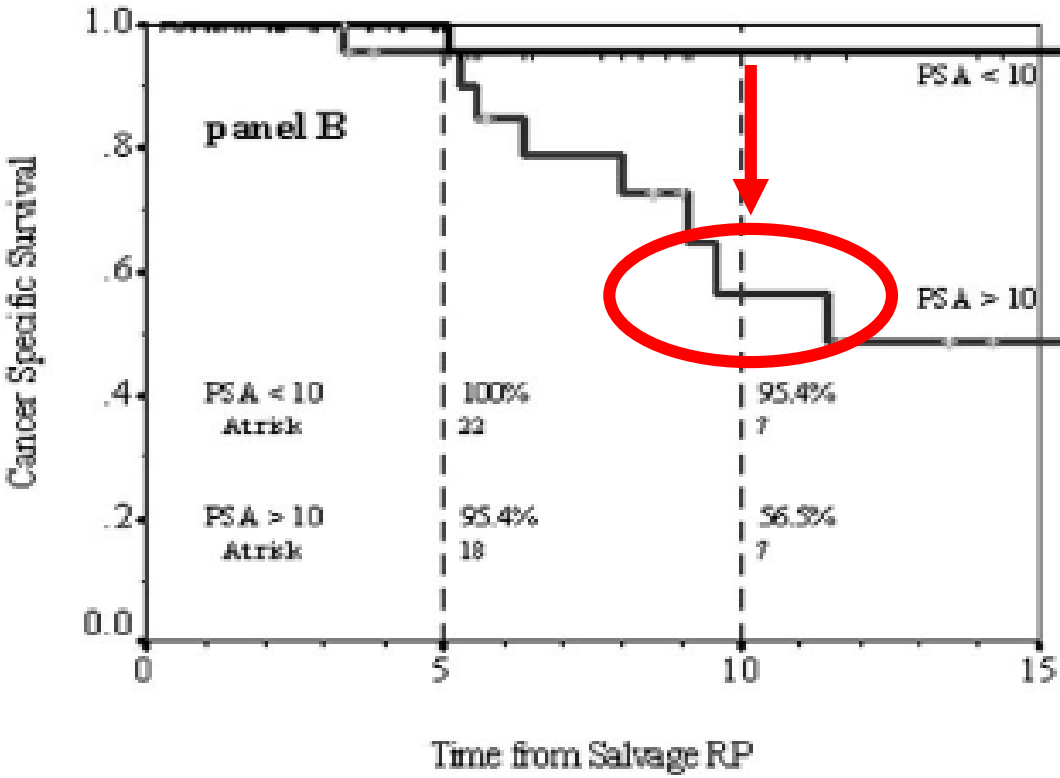


Fig. 3. (A) Disease progression-free probabilities by preoperativ serum PSA strata. (B) Cancer survival categorized by preoperativ serum PSA level (<10 vs. ≥10 ng/mL). PSA = prostate-specifi antigen.

Bianco FJ IJROBP 2005

ESTRO School

Long term cancer control: Standard versus salvage RP

	Standard RRP*		Salvage RRP**	
PFP:	**5-year**	**10-year**	**5-year**	**10-year**
Organ Confined	94.9%	92.2%	86.0%	86.0%
ECE	76.3%	71.4%	61.6%	41.0%
SVI	37.4%	37.4%	47.6%	32.6%
LN +	18.5%	7.4%	60.0%	-
	N=1,000		N=100	

Bianco FJ IJROBP 2005

*Hull et al. J. Urol, 167: 528, 2002

ESTRO School

Predicting disease progression free

→Salvage radical prostatectomy offers 5-year biochemical relapse-free rates between

→55 and 69%

→good option in the patient with a life expectancy of at least 10 years, preradiation and preoperative prostate specific antigen less than 10 ng/ml,

Touma NJ J Urol. 2005

PFP:	5-year	10-year
	86.0%	86.0%

´Bianco FJ IJROBP 2005

Continence after SRP

- EBRT 78%
- HDR 76%
- LDR 92%

} Mean : 7.9±4.5months

EF after SRP

Preservation of EF in 25%

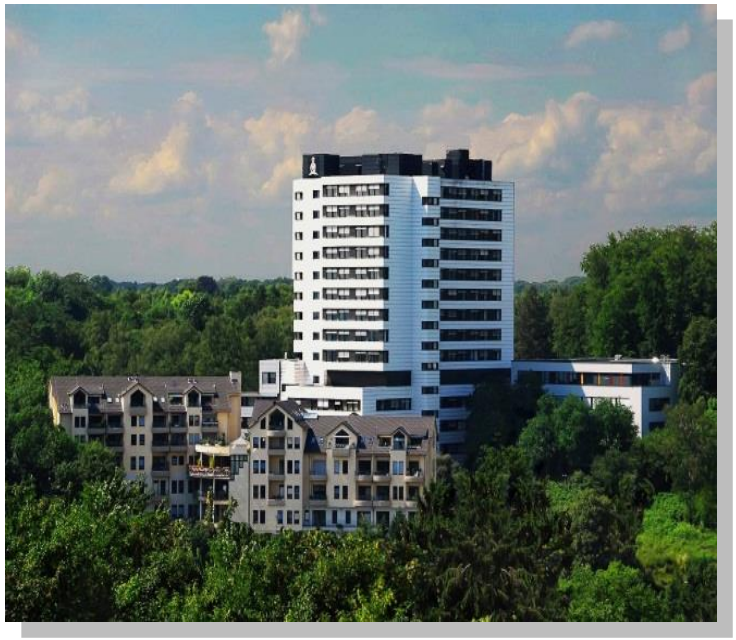
Heidenreich A et al Eur Urol 2010

ESTRO School

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Focal Therapy: concepts and LDR Brachytherapy



Stefan Machtens

Abteilung Urologie und Kinderurologie

Marienkrankenhaus Bergisch Gladbach
Akademisches Lehrkrankenhaus Uni Köln

ESTRO Teaching Course on Brachytherapy for Prostate Cancer

Avignon, 14th-16th June 2018

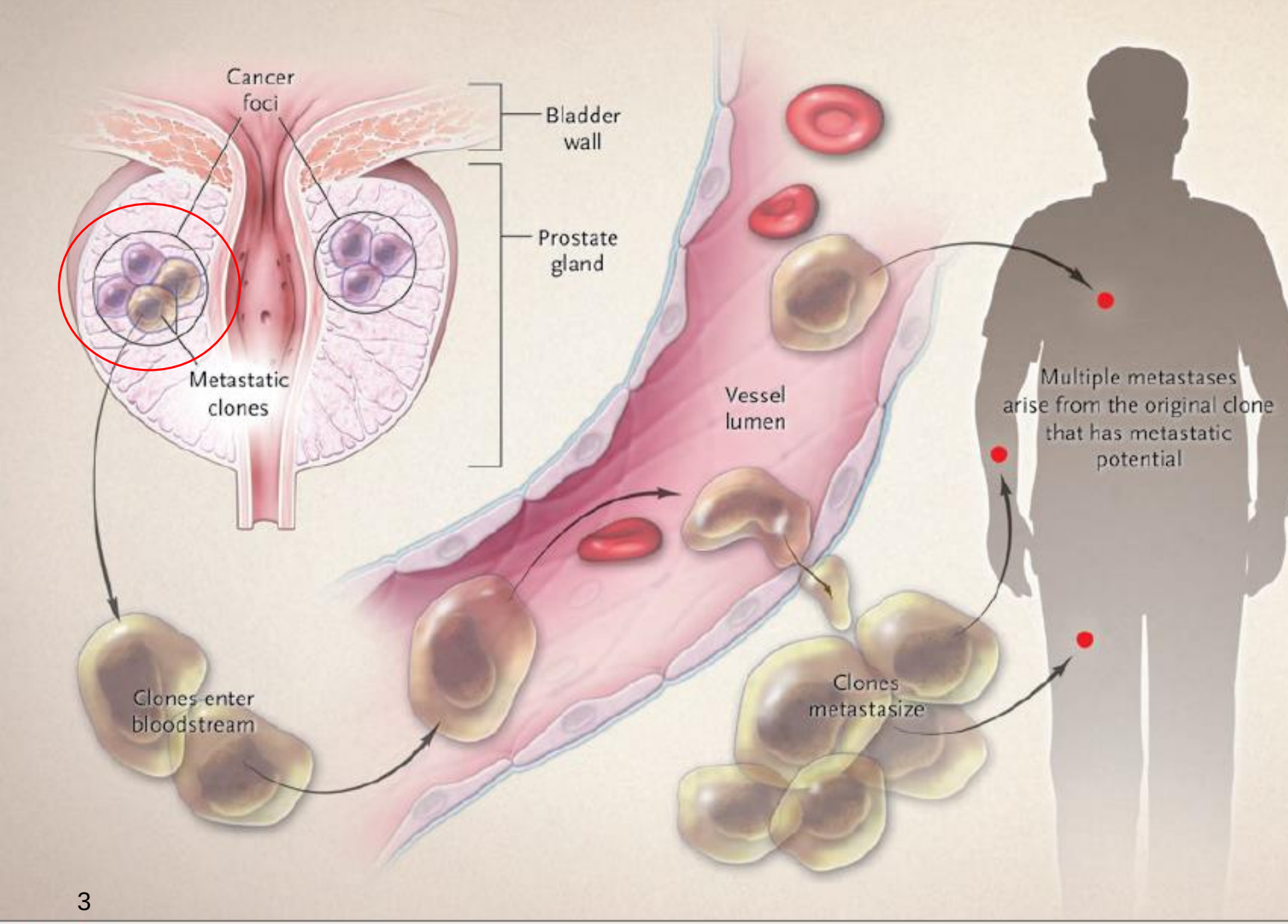
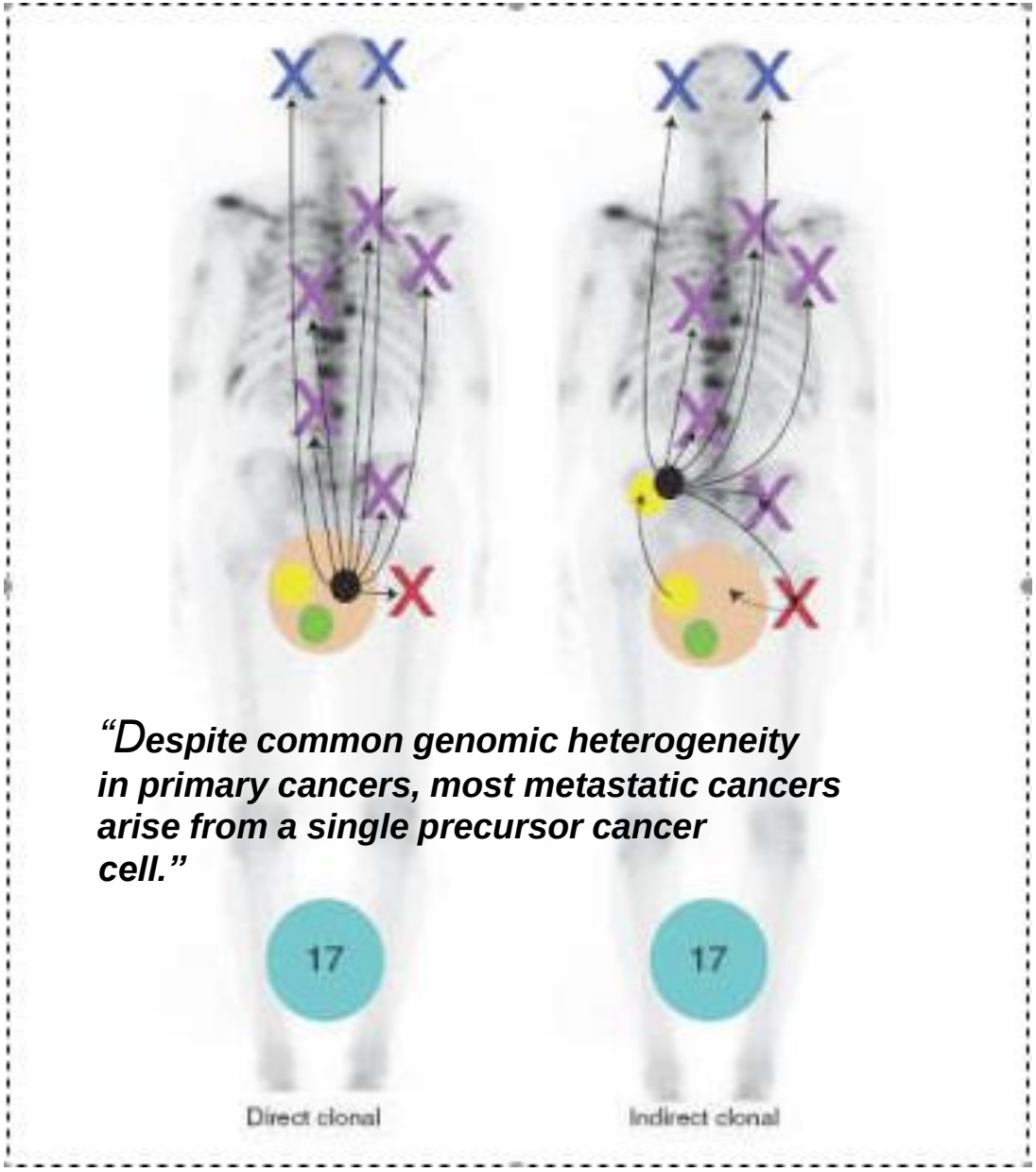


Figure 1. Monoclonal Origin of Prostate Cancer Metastases.

Ahmed HU, NEJM, 2009

High-resolution genome-wide single nucleotide polymorphism and copy number survey



"Despite common genomic heterogeneity in primary cancers, most metastatic cancers arise from a single precursor cancer cell."

Non metastatic

Metastatic / non lethal

Metastatic / lethal

Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, Chen L, Ewing CM, Eisenberger MA, Carducci MA, Nelson WG, Yegnasubramanian S, Luo J, Wang Y, Xu J, Isaacs WB, Visakorpi T, Bova GS. Nat Med. 2009 Apr 12. [Epub ahead of print]

BJUI SUPPLEMENTS

Report of a consensus meeting on focal low dose rate brachytherapy for prostate cancer

Stephen Langley[1], Hashim U. Ahmed[2], Bashar Al-Qaisieh[3], David Bostwick[4], Louise Dickinson[2], Francisco Gomez Veiga[5], Peter Grimm[6], Stefan Machtens[7], Ferran Guedea[8] and Mark Emberton[2]

BJU INTERNATIONAL © 2012 BJU INTERNATIONAL | 109, SUPPLEMENT 1, 7–16

TABLE 3 Consensus findings on patient selection for focal therapy

1. Life expectancy >10 years
2. PSA ≤15 ng/mL
3. Multi-parametric (T1W/T2W, diffusion-weighting, dynamic contrast enhancement ± spectroscopy) MRI prior to biopsy
4. Bilateral template-guided prostate mapping biopsy with 5-mm sampling frame
5. Unilateral disease; lesion size ≤0.5 mL (approximately equates to maximum cancer length of 10 mm) with or without clinically insignificant disease on the contralateral side (cancer core length ≤3 mm)
6. Gleason score of index lesion 6–7 (3 + 4)
7. Tumour stage ≤T2b
8. Prostate size ≤60 mL

Focal Therapy: Patients, Interventions, and Outcomes—A Report from a Consensus Meeting

Ian A. Donaldson [a,b,], Roberto Alonzi [c], Dean Barratt [d], Eric Barret [e], Viktor Berge [f], Simon Bott [g], David Bottomley [h], Scott Eggener [i], Behfar Ehdaie [j], Mark Emberton [a,b], Richard Hindley [k], Tom Leslie [l], Alec Miners [m], Neil McCartan [a], Caroline M. Moore [a,b], Peter Pinto [n], Thomas J. Polascik [o], Lucy Simmons [a,b], Jan van der Meulen [m], Arnauld Villers [p], Sarah Willis [m], Hashim U. Ahmed [a,b]*

Design, setting, and participants: Fifteen experts in focal therapy followed a modified two-stage RAND/University of California, Los Angeles (UCLA) Appropriateness Methodology process. All participants independently scored 246 statements prior to rescoring at a face-to-face meeting. The meeting occurred in June 2013 at the Royal Society of Medicine, London, supported by the Wellcome Trust and the UK Department of Health.

There was agreement, with a high level of consensus, that based on current National Comprehensive Cancer Network classifications [7], focal therapy should be recommended for intermediate-risk patients. There was also agreement, with a lower level of consensus, for treating men with low-risk disease.

The shift in the attitude of the group over time from providing focal treatment to low-risk patients to now treating intermediate-risk patients was discussed. The shift was thought to be in part because of growing confidence in the technique and promising medium-term follow-up results [8,9]. The group recognized concerns about overdiagnosis and overtreatment [10–12] and agreed that providing focal therapy to men with well-characterized low-risk disease would represent overtreatment and that these men may be best served with active surveillance.

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It was agreed that focal therapy can be performed in patients who have undergone an MRI-targeted prostate biopsy and in patients who have had a standard transrectal ultrasound (TRUS) biopsy in which the positive cores reflect, and are concordant with, a high-quality mp-MRI reported by an expert radiologist. When using an MRI-targeted strategy, the Standards of Reporting for MRI-targeted Biopsy Studies guidelines [14] should be followed.

For patients who have not had an mp-MRI because of lack of availability or physician preference, it was agreed that only a full transperineal template–mapping biopsy was sufficient to perform focal therapy [15]. The panel did not agree that the delivery of focal therapy can be based on only the information from a standard or extended TRUS biopsy without further imaging or template-mapping biopsies.

Utilization of multiparametric prostate magnetic resonance imaging in clinical practice and focal therapy: report from a Delphi consensus project

M. J. Scheltema[1] · K. J. Tay[3] · A. W. Postema[1] · D. M. de Bruin[1,2] · J. Feller[5] · J. J. Futterer[6] · A. K. George[7] · R. T. Gupta[4] · F. Kahmann[8] · C. Kastner[9] · M. P. Laguna[1] · S. Natarajan[10] · S. Rais-Bahrami[11] · A. R. Rastinehad[12,13] · T. M. de Reijke[1] · G. Salomon[15] · N. Stone[12,14] · R. van Velthoven[16] · R. Villani[17] · A. Villers[18] · J. Walz[19] · T. J. Polascik[3] · J. J. M. C. H. de la Rosette[1]

Received: 1 August 2016 / Accepted: 6 September 2016

Results mpMRI should be performed in patients with prior negative biopsies if clinical suspicion remains, but not instead of the PSA test, nor as a stand-alone diagnostic tool or mpMRI-targeted biopsies only. It is not recommended to use a 1.5 Tesla MRI scanner without an endorectal or pelvic phased-array coil. mpMRI should be performed following standard biopsy-based PCa diagnosis in both the planning and follow-up of FT. If a lesion is seen, MRI-TRUS fusion biopsies should be performed for FT planning. Systematic biopsies are still required for FT planning in biopsy-naïve patients and for patients with residual PCa after FT.

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Standard repeat biopsies should be taken during the follow-up of FT. The final decision to perform FT should be based on histopathology. However, these consensus statements may differ for expert centers versus non-expert centers.

Conclusions The mpMRI is an important tool for characterizing and targeting PCa in clinical practice and FT. Standardization of acquisition and reading should be the main priority to guarantee consistent mpMRI quality throughout the urological community.

Urologe 2013 · 52:549–556 DOI 10.1007/s00120-012-3002-7

D. Baumunk · A. Blana · R. Ganzer · T. Henkel · J. Köllermann · A. Roosen
S. Machtens · G. Salomon · L. Sentker · U. Witzsch · K.U. Köhrmann · M. Schostak
Arbeitsgruppe für Fokale und Mikrotherapie

Fokale Therapie des Prostatakarzinoms. Möglichkeiten, Limitierungen und Ausblick

Intensiver fokussierter Ultraschall (HIFU)

Kryotherapie

Fokale Laserablation

Photodynamische Therapie

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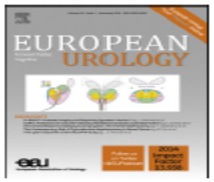


Platinum Priority – Collaborative Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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]*

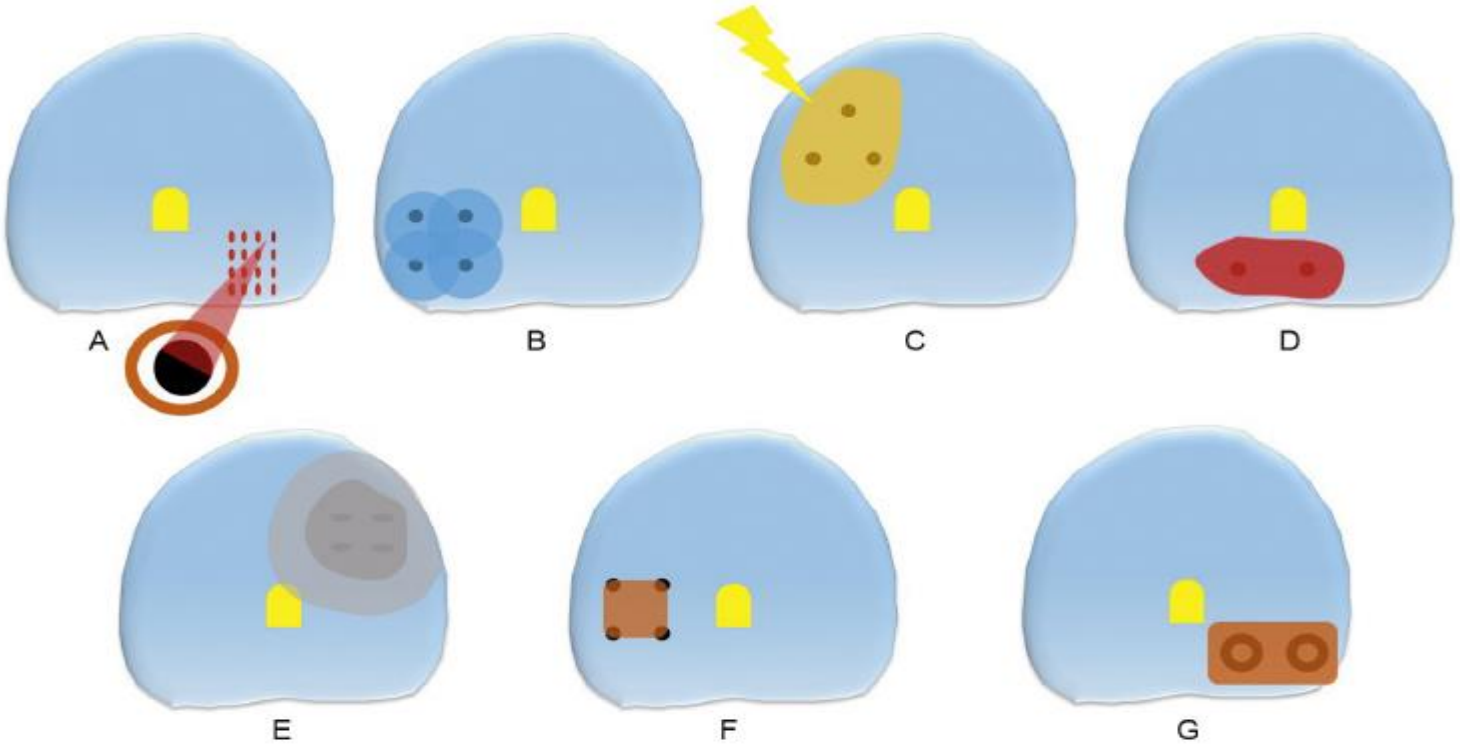
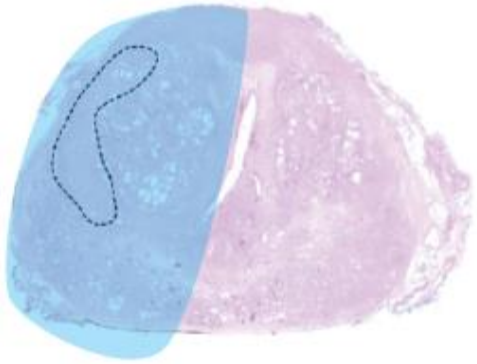


Fig. 2 – Schematic representation of the sources of energy used in actual series: (A) high-intensity focused ultrasound, (B) cryotherapy, (C) photodynamic therapy, (D) laser-induced interstitial thermotherapy, (E) brachytherapy, (F) irreversible electroporation, and (G) radiofrequency ablation.

Ultra-Focal Therapy



Focal Therapy

Focused Therapy

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Evidence synthesis: Thirty-seven articles reporting on 3230 patients undergoing focal therapy were selected. Thirteen reported on high-intensity focused ultrasound, 11 on cryotherapy, three on photodynamic therapy, four on laser interstitial thermotherapy, two on brachytherapy, three on irreversible electroporation, and one on radiofrequency. High-intensity focused ultrasound, cryotherapy, photodynamic therapy, and brachytherapy have been assessed in up to Stage 2b studies. Laser interstitial thermotherapy and irreversible electroporation have been evaluated in up to Stage 2a studies. Radiofrequency has been evaluated in one Stage 1 study. Median follow-up varied between 4 mo and 61 mo, and the median rate of serious adverse events ranged between 0% and 10.6%. Pad-free leak-free continence and potency were obtained in 83.3–100% and 81.5–100%, respectively. In series with intention to treat, the median rate of significant and insignificant disease at control biopsy varied between 0% and 13.4% and 5.1% and 45.9%, respectively. The main limitations were the length of follow-up, the absence of a comparator arm, and study heterogeneity.

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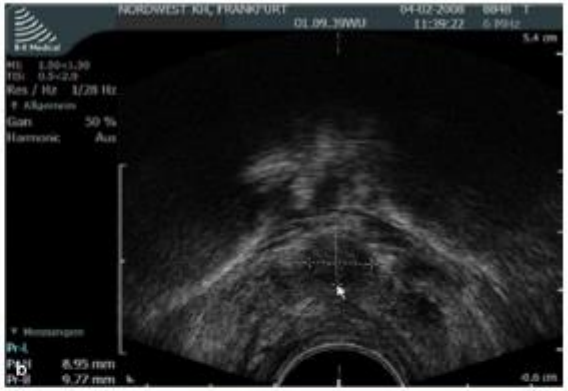
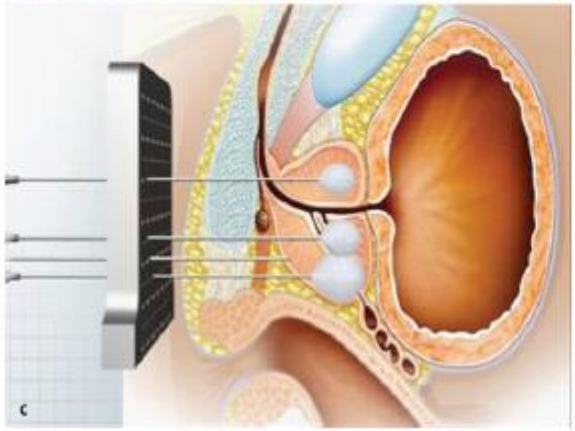
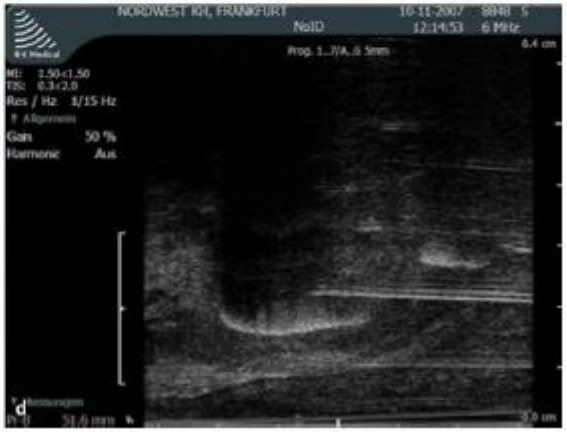
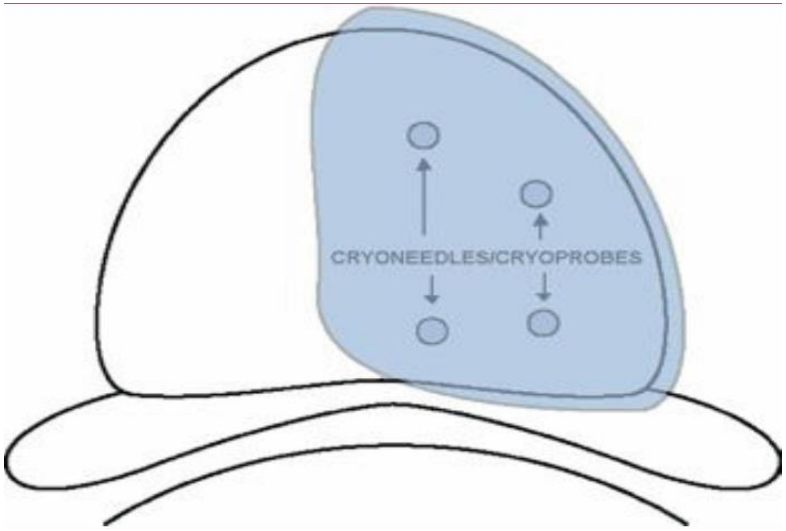
Conclusions: Focal therapy has been evaluated using seven sources of energy in single-arm retrospective and prospective development studies up to Stage 2b. Focal therapy seems to have a minor impact on quality of life and genito-urinary function. Oncological effectiveness is yet to be defined against standard of care.








CRYONEEDLES/CRYOPROBES

Cryotherapy Focal Therapy Series Reported

	Onik et al (2009) (Endocare)	Ellis et al (2007) (Endocare)	Lambert et al (2007) (Oncura)	Bahn et al (2006) (Endocare)	Crawford/ Barqawi (2009) (Endocare)	COLD Registry (2009) (Endocare)
No.	112	60	25	31	100	795
Therapy	Hemi	Hemi	Hemi	Hemi	Focal	'Focal/Partial'
Biopsy	Template	TRUS	TRUS	TRUS +Doppler	Template	TRUS
Mean PSA (ng/ml)	8.3	7.2 +/- 4.7	6 (range 1-13)	4.95	5.2 +/- 4.1	
Gleason Score	≤6	</=8	</=7	</=7	</=7	</=8
Potency	85%	70.6%	70.8%	89%	83%	65%
Incontinence	0%	3.6%	0%	0%	-	2.8%
F/U (mean, months)	43.2	15.2	28	70	-	12
Disease control	93% NED	76.7% (biopsy)	88% (>50% nadir reduction)	96% (biopsy) 92% (ASTRO)	97% (biopsy at 12/12)	4.5% (36/235) 25% (36/199) 83% (ASTRO)

Table 1 (*Continued*)

Ref.	Source of energy	IDEAL stage	Design	Biopsy	Imaging	Location	Type of ablation	No.	Age (yr)	PSA (ng/ml)	Gleason score	Risk stratification
Ellis 2007	Cryotherapy	2a	Retrospective case series	NR	NR	Unilateral	Dog-leg ablation	60	69 ± 7.8 (mean ± SD)	7.2 ± 4.7 (mean ± SD)	Gleason 6: 78.3%; Gleason 7: 20%; Gleason 8–10 1.7%	Low: 66.7%; intermediate: 23.3%; high: 10%
Onik 2007	Cryotherapy	2a	Retrospective case series	TRUS standard or template mapping	NR	Unilateral	Focal ablation	55	NR	8.3 (mean; IQR NR)	NR	Low: 47.3% (*n* = 26); intermediate: 36.4% (*n* = 20); high: 16.4% (*n* = 9)
Truesdale 2010	Cryotherapy	2b	Retrospective case series	TRUS standard	NR	Unilateral	Hemi-ablation	77	69.5 ± 6.7 (mean ± SD)	6.5 ± 4.9 (mean ± SD)	Gleason 6: 64.9% (*n* = 50); Gleason 7: 32.5% (*n* = 25); Gleason 8: 2.6% (*n* = 2)	Low: 57.1% (*n* = 44); intermediate: 40.3% (*n* = 31); high: 2.6% (*n* = 2)
Bahn 2012[a]	Cryotherapy	2b	Retrospective case series	TRUS standard + targeted	Color-Doppler	Unilateral	Hemi-ablation	73	64; 47–79 (median; range)	5.4; 0.01–20 (median; range)	3+3: 41% (*n* = 30); 3+4: 34% (*n* = 25); 4+3: 25% (*n* = 18)	Low: 33% (*n* = 24); intermediate: 67% (*n* = 49)
Ward 2012	Cryotherapy	2b	Retrospective case series	NR	NR	Organ-confined	NR	1160	67.8 ± 7.8 (mean ± SD)	NR	Gleason 6: 73.6%; Gleason 7: 20.9%; Gleason ≥8: 5.6%	Low: 46.8%; intermediate: 40.9%; high: 12.4%
Hale 2013	Cryotherapy	2a	Retrospective case series	Template mapping	NR	Organ-confined	Hemi-ablation or subtotal	26	65; 55–74 (median; range)	NR	3+3: 96.2% (*n* = 25); 3+4: 3.8% (*n* = 1)	Low: 88.5% (*n* = 23); intermediate: 11.5% (*n* = 3)
Al Barqawi 2014	Cryotherapy	2b	Prospective development study	Template mapping	NR	Organ-confined	Focal ablation	62	60.5 ± 6.8 (mean ± SD)	5.1 ± 2.2 (mean ± SD)	Gleason 3+3 or Gleason 3+4	Low to intermediate risk
Durand 2014	Cryotherapy	2b	Prospective case series	TRUS standard	MRI	Unilateral	Hemi-ablation	48	67; 50–77 (median; IQR)	6.1; 3.1–9.7 (mean; range)	Gleason 3+3: 100%	Low: 100%
Lian 2015	Cryotherapy	2b	Retrospective case series	NR	NR	Unilateral	Hemi-ablation	41	67; 56–76 (median; IQR)	7.1; 2.6–14.1 (median; range)	3+3: 58.5% (*n* = 24); 3+4: 24.4% (*n* = 10); 4+3: 17.1% (*n* = 7)	Low: 56.1% (*n* = 23); intermediate: 43.9% (*n* = 18)
Mendez 2015	Cryotherapy	2b	Retrospective case series	NR	NR	NR	NR	317	66.5 ± 6.6 (mean ± SD)	NR	Gleason 3+3: 100%	Low: 100%
Total	Cryotherapy	2a–2b	Retrospective case series to prospective development study	Combination (see above)	MRI or color-Doppler	Unilateral or organ-confined	Combination (see above)	1950	66.8 (IQR 63.8–68.1)	6.3 (IQR 5.2–7.2)	3+3 to ≥8	Low, intermediate or high

Hemi-HIFU - Functional and Cancer Control

UCL

Parameter	Follow-up (months					
	Baseline	1	3	6	9	12
Erections sufficient for penetration (>/2 Q2 on IIEF-15)	100% (20/20)	86.7% (13/15)	80% (12/15)	83.3% (15/18)	94.4% (17/18)	95% (19/20)
Continence (pad-free)	100% (20/20)	85% (17/20)	95% (19/20)	95% (19/20)	95% (19/20)	95% (19/20)
Continence (leak-free, pad-free)	100% (20/20)	85% (17/20)	75% (15/20)	90% (18/20)	90% (18/20)	90% (18/20)
Mean PSA (ng/ml)	7.3	2.1	1.5	1.4	1.6	1.7
Absence of clinically significant cancer in treated side on TRUS biopsy (</=3mm & Gleason pattern </=3)				95% (18/19) (One Refused)		
Absence of any cancer in treated side on biopsy				89% (17/19)		

Focal HIFU publications

Two strategies

- Hemiablation treatments
- Multi-focal treatments

THE JOURNAL of UROLOGY

American Urological Association

International Braz J Urol

THE LANCET Oncology

Focal Therapy for Localized Prostate Cancer: A Phase I/II Trial

Clinical Urology

Focal Therapy with High-Intensity Focused Ultrasound for Prostate Cancer in the Elderly. A Feasibility Study with 10 Years Follow-Up

Articles

Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study

Focal HIFU publications

THE LANCET Oncology

Articles

Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study

Hashim U. Ahmed, Richard G. Pendsé, Louise Dickinson, Ahmed Sarwar, Alex Freeman, Mahua Dutta, Rebecca Lyon, Clare Hilton, Jan Van der Meulen, Mark Emberton

Summary

Background Radical whole-gland therapy can lead to significant genitourinary and sexual side-effects for men with localised prostate cancer. We report on whether selective focal ablation of unifocal and multifocal cancer lesions can reduce this treatment burden.

Methods Men aged 45–80 years were eligible for this prospective development study if they had low-risk or high-risk localised prostate cancer (prostate specific antigen [PSA] ≤15 ng/mL, Gleason score ≤4+3, stage ≤T2c) with no previous androgen deprivation or treatment for prostate cancer, and who could safely undergo multiparametric MRI and have a general anaesthetic. Patients received focal therapy using high-intensity focused ultrasound, delivered to all known cancer lesions, with a margin of normal tissue, identified on multiparametric MRI, template prostate-mapping biopsies, or both. Primary endpoints were adverse events (serious and otherwise) and urinary symptoms and erectile function assessed using patient questionnaires. Analyses were done on a per-protocol basis. This study is registered with ClinicalTrials.gov, number NCT00651314.

Findings 41 men were included between June 27, 2007, and June 30, 2008; one man died from an unrelated cause (post-enrolment) 3 months after treatment and was excluded from analyses. After treatment, one man was admitted to hospital for acute urinary retention, and another had urethral instrumentation requiring hospital admission. Nine men (22%, 95% CI 11–37) had mild-resolving, mild to moderate, intermittent dysuria (median duration 5·0 days [IQR 2·5–18·5]). Urinary sepsis occurred in six men (15%, 95% CI 6–30), with a median duration of 11·5 days (IQR 6·8–16·5). Urinary tract infection was noted in seven men (17%, 95% CI 7–32). Median overall International Index of Erectile Function-15 (IIEF-15) scores were similar at baseline and at 12 months (p=0·868), as were median IIEF-15 scores for intercourse satisfaction (p=0·414), sexual desire (p=0·444), and overall satisfaction (p=0·357). Significant deteriorations between baseline and 12 months were noted for IIEF-15 erectile (p=0·047) and orgasmic functions (p=0·005). Of 35 men with good baseline function, 31 (89%, 95% CI 75–97) had erections sufficient for penetration 12 months after focal therapy. Median UCLA Expanded Prostate Cancer Index Composite (EPIC) urinary incontinence scores were similar at baseline and 12 months (p=0·969). There was an improvement in lower urinary tract symptoms, assessed by International Prospective Symptom Score (IPSS), between baseline and 12 months (p=0·026), but the IPSS-quality of life score showed no difference between baseline and 12 months (p=0·078). All 18 men with no baseline urinary incontinence were leak-free and pad-free by 3 months. All 40 men pad-free at baseline were pad-free by 3 months and maintained pad-free continence at 12 months. No significant difference was reported in median Trial Outcomes Index scores between baseline and 12 months (p=0·115) but significant improvements were shown in median Functional Assessment of Cancer Therapy (FACT)-Prostate (p=0·042) and median FACT-General scores (p=0·048). No histological evidence of cancer was identified in 68 of 98 cases biopsied at 6 months (77%, 95% CI 63–87); 36 (88%, 75–95) were free of clinically significant cancer. After retreatment for four men, 39 of 41 (95%, 95% CI 83–99) had no evidence of disease on multiparametric MRI at 12 months.

Interpretation Focal therapy of individual prostate cancer lesions, whether unifocal or multifocal, leads to a low rate of genitourinary side-effects and an encouraging rate of early absence of clinically significant prostate cancer.

Funding Medical Research Council (UK), Wellcome Trust Cancer Foundation, and St Peter's Trust

Introduction

The management of localised prostate cancer remains controversial because the systematic over-diagnosis that accompanies the current diagnostic pathway results in over-treatment.[1] At present, radical whole-gland surgery or radiotherapy can result in substantial side effects that are a consequence of damage to surrounding structures. These include urinary incontinence (5–20%), erectile dysfunction (10–70%), and bowel toxicity (5–10%).[2,3] Technological refinements do not seem to have reduced the burden of harm.[4]

Apart from active surveillance for low risk disease, few strategies are available to address the burden of treatment-related side-effects in older risk categories. One strategy that has shown promise relates to managing prostate cancer in the same manner as most other solid organ malignancies—by focusing the therapy to the cancer lesion, sparing as the

- **41 patients** treated by focal HIFU
- 92% free from clinically significant PCa
- **100% continence preservation**
- QOL preservation
- **89% erection sufficient for penetration**

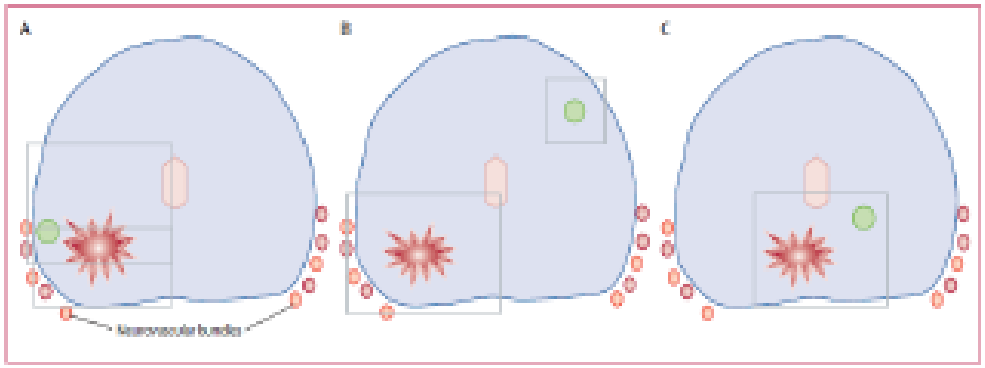
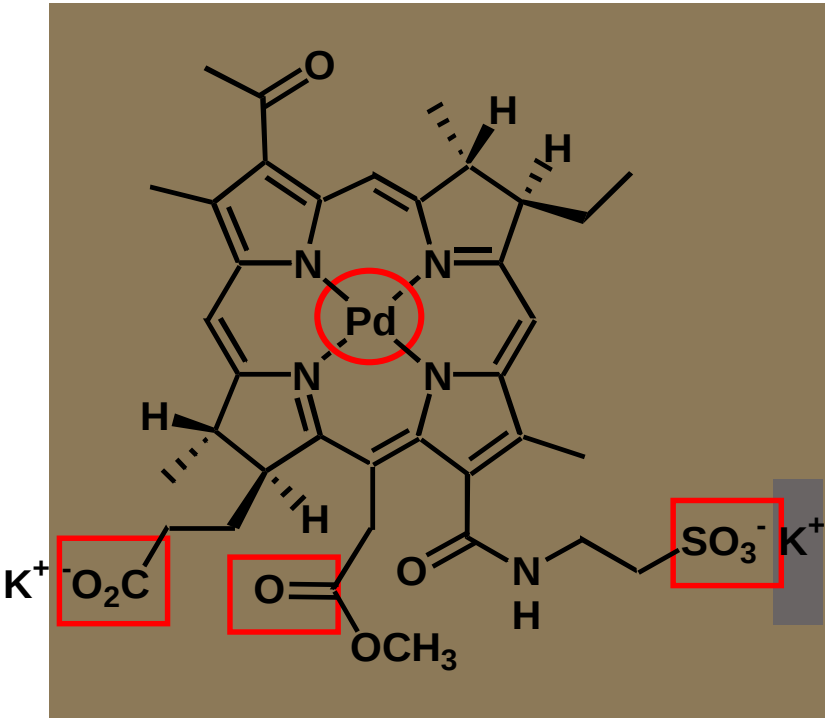


Table 1 – Design, focal therapy strategy, and study population of the 37 series included

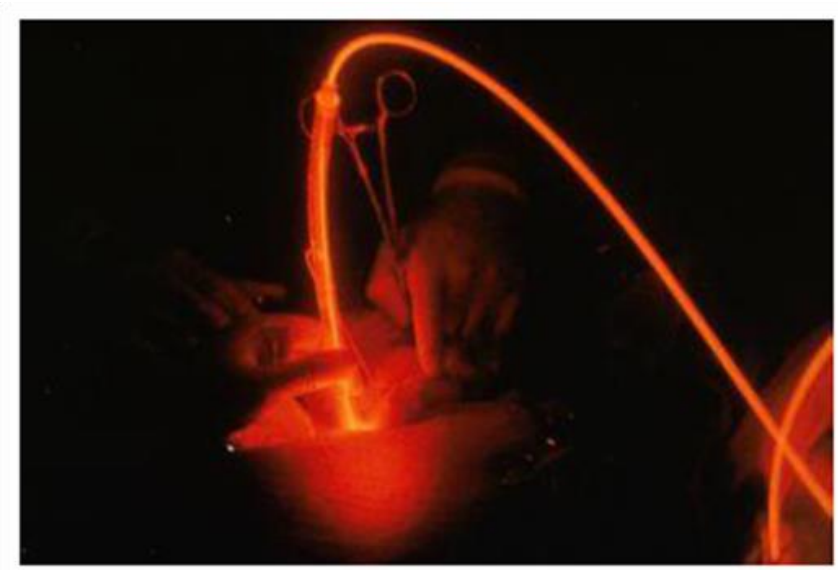
Ref.	Source of energy	IDEAL stage	Design	Biopsy	Imaging	Location	Type of ablation	No.	Age (yr)	PSA (ng/ml)	Gleason score	Risk stratification
Madersbacher 1995	HIFU	1	Prospective development study	NR	NR	Unifocal or organ-confined	Hemi-ablation or focal ablation with no intention to treat	29	64; 7.2 (mean; SD)	24.5; 18.8 (mean; SD)	NR	NR
Beerlage 1999	HIFU	1	Retrospective case series	TRUS standard	MRI	NR	Hemi-ablation with no intention to treat	14	62; 55–69 (mean; range)	10.8; 3.5–20 (mean; range)	NR	NR
Muto 2008	HIFU	2a	Prospective case series	TRUS extended	MRI	Unilateral	Dog-leg ablation	29	72; 62–80 (median; range)	5.4; 1.8–25.1 (median; range)	6: 55.2% (n = 16); 7: 20.7% (n = 6); 8+: 17.2% (n = 5); unknown: 6.9% (n = 2)	NR
Ahmed 2011	HIFU	2a	Prospective development study	Template mapping	MRI	Unilateral	Hemi-ablation	20	60.4; 5.4 (mean; SD)	7.3; 2.8 (mean; SD)	NR	Low: 25% (5/20); intermediate: 75% (15/20)
El Fegoun 2011	HIFU	2a	Retrospective case series	NR	NR	Unilateral	Hemi-ablation	12	70; 4.8 (mean; SD)	7.3; 2.6–10 (mean; range)	3+3: 83.3% (n = 10); 3+4: 16.7% (n = 2)	NR
Ahmed 2012	HIFU	2b	Prospective development study	Template mapping	MRI	Unifocal or multifocal	Focal ablation	41	63; 58–66 (median; IQR)	6.6; 5.4–7.7 (median; IQR)	3+3: 31.7% (n = 13); 3+4: 58.6% (n = 24); 4+3: 9.8% (n = 4)	Low: 26.8% (n = 11); intermediate: 63.4% (n = 26); high: 9.8% (n = 4)
Chopra 2012	HIFU	1	Proof of concept	NR	MRI	NR	Focal ablation with no intention to treat	8	60; 49–70 (mean; range)	6.2; 2.7–13.1 (median; range)	3+3: 25% (n = 2); 3+4: 50% (n = 4); 4+3: 25% (n = 2)	NR
Dickinson 2013	HIFU	1	Proof of concept	Template mapping	MRI	Unilateral, unifocal, or multifocal	Index lesion ablation or hemi-ablation	26	61; 40–79 (mean; range)	7.7; 1.5–14.2 (mean; range)	3+3: 34.6% (n = 9); 3+4: 65.4% (n = 17)	Low: 11.5% (n = 3); intermediate: 42.3% (n = 11); high: 46.2% (n = 12)
Napoli 2013	MR-HIFU	1	Prospective development study	NR	MRI	Unifocal	Index lesion ablation	5	65.4; 50–75 (median; range)	8.8 (median; IQR and range NR)	3+3: 60% (n = 3); 3+4: 40% (n = 2)	NR
Van Velthoven 2013	HIFU	2a	Prospective development study	NR	MRI	Unifocal	Hemi-ablation	31	71; 55–83 (median; range)	5.3; 0.3–11.0 (median; range)	≤6: 61.3% (n = 19); 7: 32.2% (n = 10); ≥8: 6.5% (n = 2)	Low: 54.8% (n = 17); intermediate: 38.7% (n = 12); high: 6.5% (n = 2)
Ahmed 2015	HIFU	2b	Prospective development study	TRUS standard and/or template mapping	MRI	Unifocal	Index lesion ablation	56	63.9; 5.8 (mean, SD)	7.4; 5.6–9.5 (median, IQR)	NR	Low: 12.5% (n = 7); intermediate: 83.9% (n = 47); high: 3.6% (n = 2)
Feijoo 2015	HIFU	2b	Prospective case series	TRUS extended or template mapping	MRI	Unilateral	Hemi-ablation	71	70.2; 6.8 (mean; SD)	6.1; 1.6–15.5 (median; IQR)	3+3: 86.6% (n = 58); 3+4: 13.4% (n = 9); NR: 4 lost to follow-up	NR
Ghai 2015	MR-HIFU	1	Prospective development study	TRUS extended + targeted	MRI	Unifocal or multifocal	Index lesion ablation	4	63; 56–68 (median; range)	4.7; 0.9–6.7 (median, IQR)	3+3 (100%)	Low: 100% (4/4)
Total	HIFU or MR-HIFU	1–2b	Proof of concept to prospective development studies	Combination (see above)	MRI	Unilateral, unifocal, or multifocal	Combination (see above)	346	63 (IQR 62–70)	7.3 (IQR 5.8–8.3)	3+3 to ≥8	Low, intermediate or high

Focal therapy: VTP – a combination

TOOKAD Soluble®

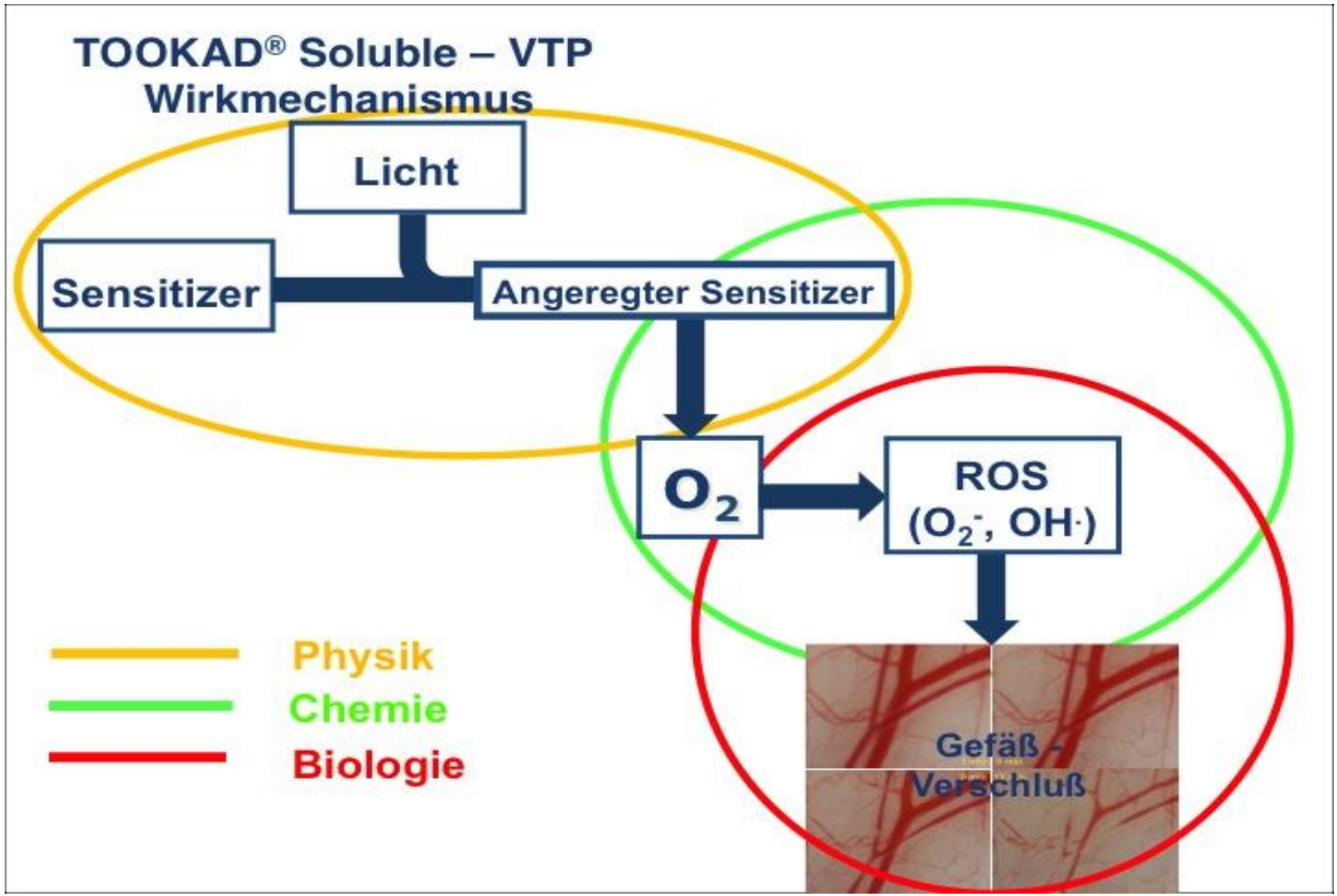


Laser Aktivierung

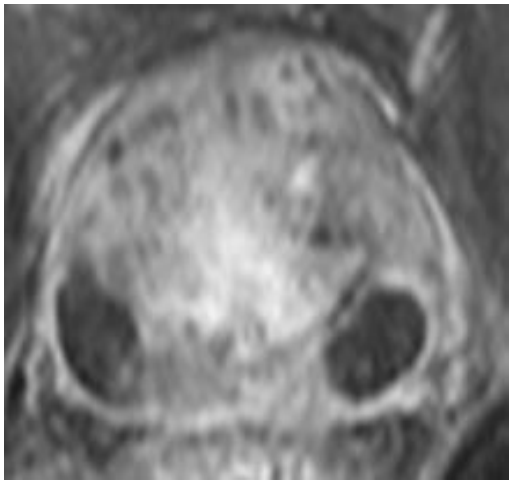


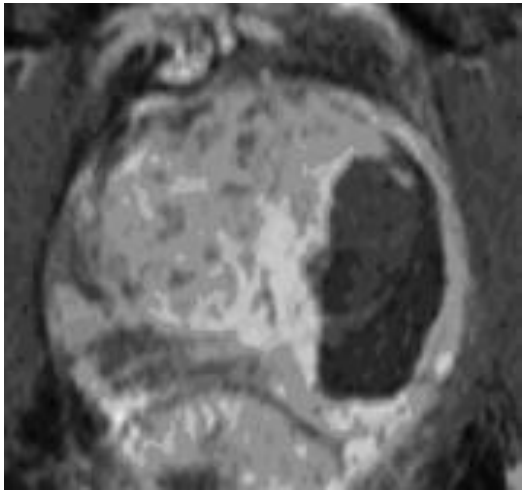
Padeliporfin
(*Pd Bacteriopheophorbide monolysotaurine)*

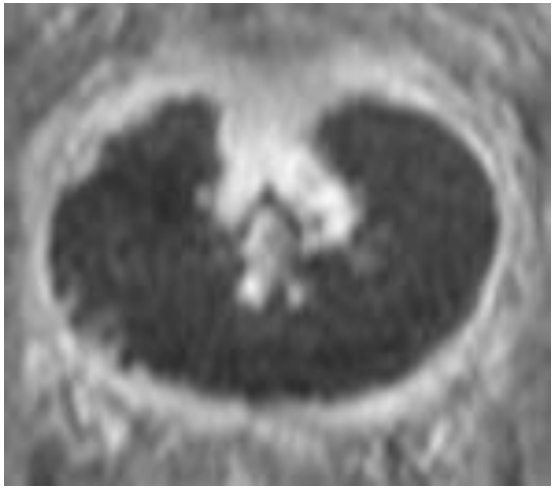
Fokaltherapie : VTP – mechanism of action



Focaltherapy : VTP







Lokale / Fokale Behandlung…

Regionale (hemi-ablation …)

oder Sub-totale …

MRT one week after therapy

A european randomised phase III study to evaluate the effect and safety of **TOOKAD® Soluble**
In localized prostate cancer in comparison with active surveillance.

Study CLIN1001 PCM301

EAU16 | MUNICH
11-15 March 2016

TOOKAD® (Padeliporfin) Vascular-Targeted Photodynamic therapy versus Active Surveillance in men with low risk prostate cancer

A randomized phase 3 clinical trial

Azzouzi AR, Vincendeau S, Barret E, Cicco A, Kleinclauss F, Van Der Poel H, Stief C, Rassweiler J, Salomon G, Solsona E, Alcaraz A, Tammela T, Ahlgren G, Gratzke C, Debruyne F, Gaillac B, Benzaghou F and **Emberton M** on behalf of the PCM301 study group

European Association of Urology

Steba biotech Innovation

Study Group

- **BELGIUM** **Leuven** (Joniau)
- **FINLAND** **Tampere** (Tammela)
- **FRANCE** **Angers** (Azzouzi) /**Besançon** (Kleinclauss) / **Grenoble**(Descotes) / **Lille** (Villers) / **Lyon** (Ruffion) / **Marseille** (Karsenty) / **Nantes** (Potiron) / **Paris (**Barret, Botto, Cussenot, Delongchamps, Galiano, Guetta,Zerbib) / **Perpignan** (Cicco) / **Reims** (Staerman) / **Rennes** (Vincendeau, Coeurdacier) / **Toulouse** (Malavaud)
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- **ITALY** **Roma (**Tubaro) / **Turin** (Gontero)/ **Lucca** (Pinzi) / **Savona** (Giberti)
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- **SPAIN** **Barcelona** (Alcaraz, Palou, Suarez, Morote) / **La Coruna** (G.Veiga)/ **Sevilla (**Medina) / **Valencia** (Solsona, Casanova)
- **SWEDEN** **Malmö** (Ahlgren)
- **SWITZERLAND** **Bern** (Thalmann)
- **UK** **London** (Emberton, Muir) / **Oxford** (Hamdy) / **Sheffield** (Rosario)

- **DSMB** Debruyne, Hammerer, Bown, Kay
- **ORP** Gratzke, Fromont-Ankart, Michiels
- **CTGC (MRI)** Allen, Renard-Pena, Toledano, Sufana, Younes, Nicolau, Salvador

- **LASER Analytica** Amzal and team
- **ICON CRO** team , **IXICO** Ltd(MRI), **HISTOLOGIX** Ltd (biopsies)

Steba biotech Innovation

Inclusion criteria

- 1 positive core of 3-5mm CCL*
- 2-3 positive cores and ≤5mm CCL per core
- Absence of Gleason pattern 4 or 5
- PSA ≤ 10 ng/ml
- Clinical stage up to cT2a
- Prostate volume ≥ 25 cc and ≤ 70 cc

*Cancer Core length

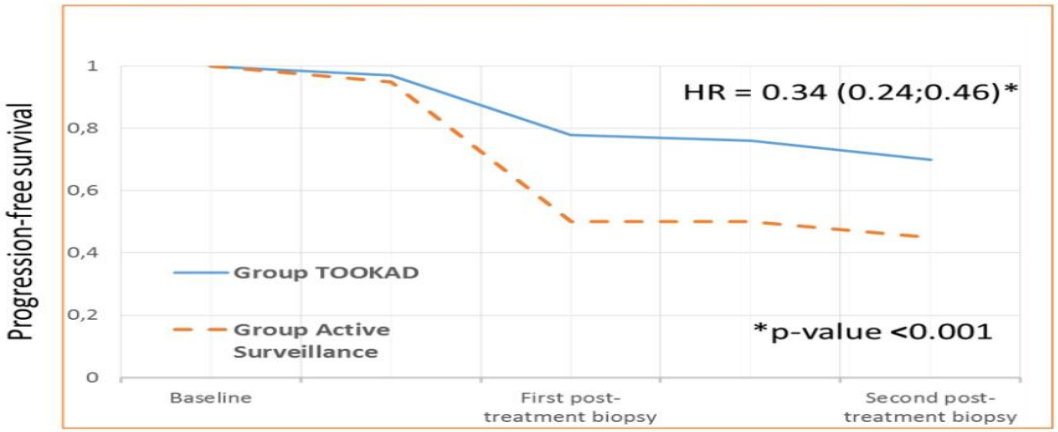
Primary End points (24 months)

- **Cancer progression**
  - from histological low risk to a higher risk
- **Absence of cancer**

Secondary End points (24 months)

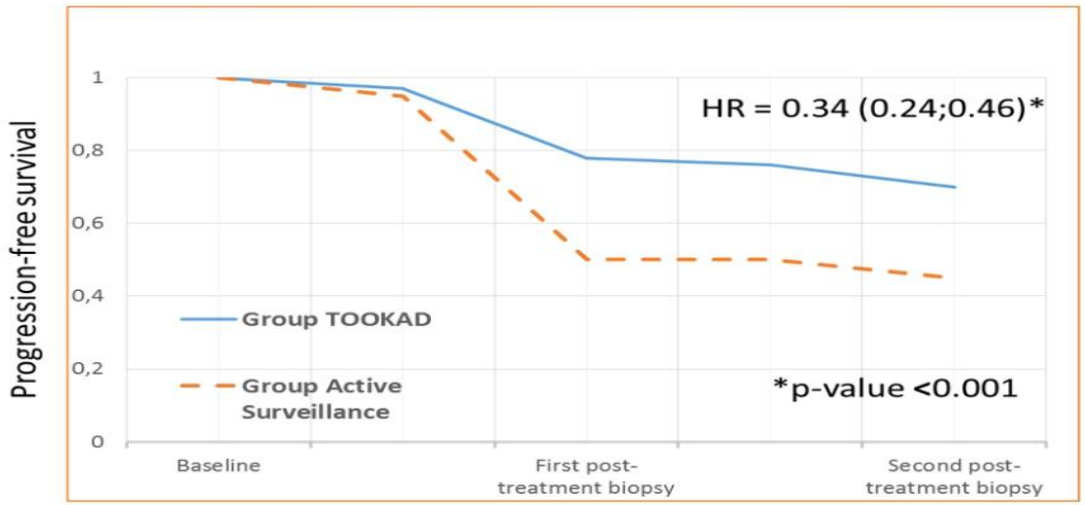
- **Cross-over to radical therapy**
- **Safety**
- **Functional status / Quality of life**

Results - Progression



	TOOKAD® [N=206]	Active surveillance [N=207]
Subjects who progressed – n (%)	58 (28%)	120 (58%)

Results - Progression



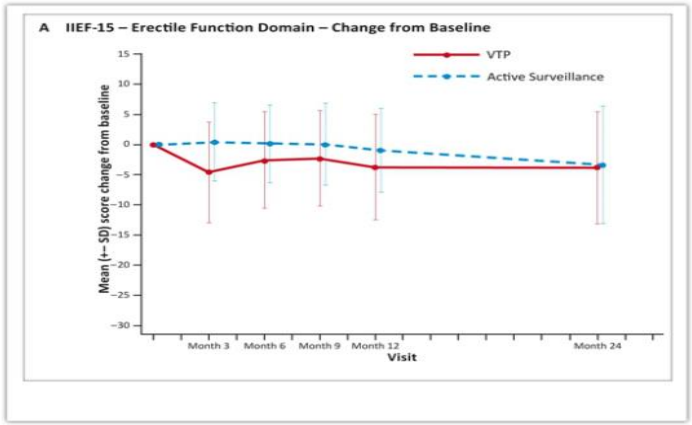
Fewer TOOKAD® treated men underwent radical therapy within 24-months: 6% vs. 29%, RR=0.20 [0.11-0.36]

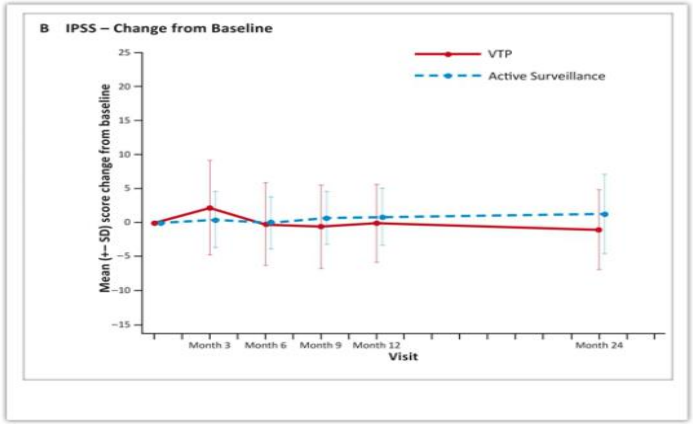
Results – Negative Biopsy

	TOOKAD® [N=206]	Active surveillance [N=207]
Number(%) of subjects with negative biopsies at 24 Months	101 (49%)	28 (14%)

TOOKAD® increased the probability (RR) of a negative prostate biopsy at 24 months after treatment by 3.62 times compared to active surveillance ($p<0.001$)

Results – Functional status





Results – Adverse events

	TOOKAD® VTP Drug, device or procedure related events [N=197]	Active Surveillance [N=207]
Grade 1 (Mild)	54 (27.4%)	42 (20.3%)
Grade 2 (Moderate)	81 (41.1%)	52 (25.1%)
Grade 3 (Severe)	19 (9.6%)	19 (9.2%)
Grade 4 (Life-threatening)	1* (0.5%)	1 (0.5%)
Grade 5 (Death)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)

*One Anaphylactic shock following general anesthesia before injection of TOOKAD®

One case of incontinence (previous TURP)
Two urethral strictures requiring dilatation
No recto-urethral fistulae

Summary

In a multi-centre, phase 3 pivotal randomized study, TOOKAD® VTP appears:

- ☐ **Desirable to European men**
- ☐ **Safe**
- ☐ **Well tolerated**
- ☐ **Amenable to quality control**
- ☐ **Effective at:**

  - **Reducing rates of progression**
  - **Conferring a negative biopsy status**
  - **Diminishing the need for radical therapy**

These are very low-risk patients

Inclusion criteria	Final cohort	PRIAS*
PSA <10 ng/mL	PSA 5.9-6.2ng/mL	5.6ng/mL
cT1c-cT2a	86% T1c	85.1% T1c
Gleason 3+3=6 • One core 3-5mm • Two-three cores <3mm length	Gleason 3+3=6 • No of cores =2.1 • Mean total core length = 3-8-4.3mm	Gleason 3+3=6 • One core 68.8% • Two cores 31.2%

100% disease-specific survival

Offer active surveillance to patients with the lowest risk of cancer progression: > 10 years life expectancy, cT1/2, PSA ≤ 10 ng/mL, biopsy Gleason score ≤ 6, ≤ 2 positive biopsies, minimal biopsy core involvement (≤ 50% cancer per biopsy).	2a	A

** Bul et al Eur Urol 2013;63(4):597-603; Mottet et al EAU Guidelines 2016*

Results at 24 months: summary

Parameter	TOOKAD arm (n=206)	Control arm (n=207)	PRIAS* (n=1480)
Histological progression	58 (28%)	120 (58%)	203 (13.7%)
Negative biopsy	101 (49%)	28 (14%)	687 (37%)
Radical intervention	12 (6%)	60 (29%)	336 (22.7%)

Why does the control arm seem to differ from other AS experience?

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

* Bul et al Eur Urol 2013;63(4):597-603

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BJU International

THE UNIVERSITY OF MELBOURNE

Feasibility, safety, and efficacy of salvage radical prostatectomy after Tookad® Soluble focal treatment for localized prostate cancer

Souhil Lebdai · Arnaud Villers · Eric Barret · Cosmina Nedelcu · Pierre Bigot · Abdel-Rahmène Azzouzi

- N=19 salvage radical prostatectomies; previous focal TOOKAD VTP
  - Biopsy progression in all cases
- No nerve-sparing surgery
  - *"not feasible due to lateral fibrosis"*

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Lebdai et al. World J Urol 2015;33(7):965-71

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European Association of Urology

Platinum Priority – Collaborative Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

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]

Nguyen 2012	Brachytherapy	2b	Retrospective case series	NR	MRI	Organ-confined	Peripheral zone ablation	318	NR	5; 3.8–6.9 (median; IQR)	3+3: 88% (*n* = 280); 3+4: 12% (*n* = 38)	Low: 83% (*n* = 265); intermediate: 17% (*n* = 53)
Cosset 2013	Brachytherapy	2a	Retrospective case series	TRUS extended	MRI	Unilateral	Focal ablation	21	62.3; 56–75 (mean; range)	6.9; 3.6–13.9 (mean; range)	3+3: 9.5% (*n* = 2); 3+4: 90.5% (*n* = 19)	NR
Total	Brachytherapy	2a–2b	Retrospective case series	TRUS extended	MRI	Unilateral or organ-confined	Focal or peripheral zone ablation	339	62.3 (IQR NA)	6 (IQR NA)	3+3 or 3+4	Low to intermediate risk

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European Association of Urology

Platinum Priority – Collaborative Review – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

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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]

Valerio 2014	IRE	2a	Retrospective case series	Template mapping and/or targeted	MRI	Organ-confined	Index lesion ablation	34	65 ± 6 (mean ± SD)	6.1; 4.3–7.7 (median; IQR)	3+3: 26% (*n* = 9); 3+4: 56% (*n* = 19); 4+3: 15% (*n* = 5); 4+4: 3% (*n* = 1)	Low: 26% (*n* = 9); intermediate: 71% (*n* = 24); high: 3% (*n* = 1)
Ting 2015[c]	IRE	2a	Retrospective case series	Template mapping or targeted	MRI	Organ-confined	Index lesion ablation	25	67; 60–71 (median; IQR)	6; 4.3–8.6 (median; IQR)	3+3: 8% (*n* = 2); 3+4: 60% (*n* = 15); 4+3: 32% (*n* = 8)	Low: 8% (*n* = 2); intermediate: 92% (*n* = 23)
Van den bos 2015	IRE	1	Proof of concept	TRUS standard	NR	Organ-confined	Focal ablation with no intention to treat	16	60; 44–75 (median; range)	9; 3.6–25 (median; range)	3+3: 50% (*n* = 8); 3+4: 18.8% (*n* = 3); 4+3: 18.8% (*n* = 3); 4+4: 12.5% (*n* = 2)	NR
Total	IRE	1–2a	Proof of concept to retrospective case series	Combination (see above)	MRI	Organ-confined	Index lesion or focal ablation with no intention to treat	66	65 (IQR NA)	6.1 (IQR NA)	3+3 to 4+4	Low to intermediate risk

Is the used technique safe oncologically?

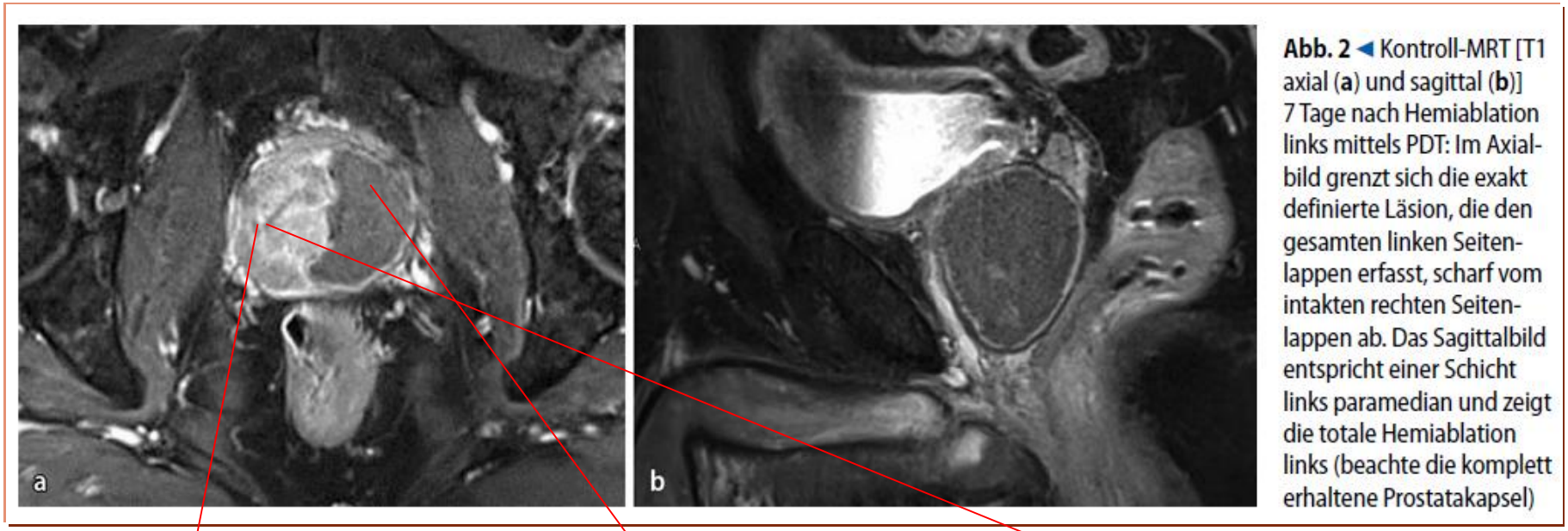


Abb. 2 ◀ Kontroll-MRT [T1 axial (**a**) und sagittal (**b**)] 7 Tage nach Hemiablation links mittels PDT: Im Axialbild grenzt sich die exakt definierte Läsion, die den gesamten linken Seitenlappen erfasst, scharf vom intakten rechten Seitenlappen ab. Das Sagittalbild entspricht einer Schicht links paramedian und zeigt die totale Hemiablation links (beachte die komplett erhaltene Prostatakapsel)

PSA> 0 ng/ml

Criteria for active surveillance (Rebiopsy???)

ASTRO/Phoenix criteria not applicable

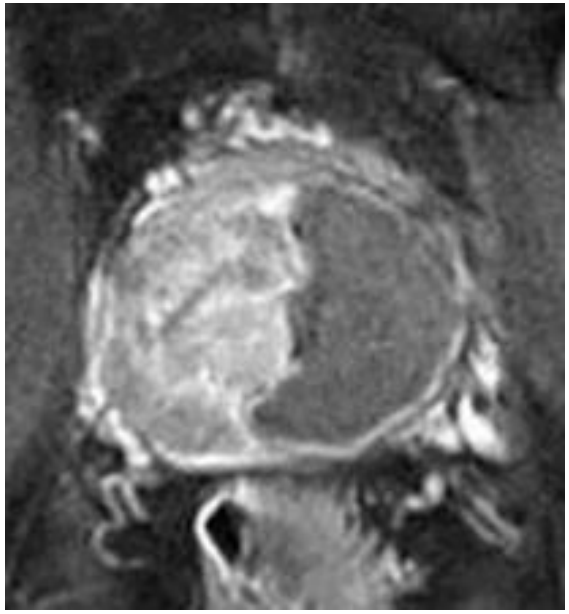
Platinum Priority – Prostate Cancer

Editorial by XXX on pp. x–y of this issue

Focal Therapy in Prostate Cancer: International Multidisciplinary Consensus on Trial Design

Willemien van den Bos [a,], Berrend G. Muller [a], Hashim Ahmed [b], Chris H. Bangma [c], Eric Barret [d], Sebastien Crouzet [e], Scott E. Eggener [f], Inderbir S. Gill [g], Steven Joniau [h], Gyoergy Kovacs [i], Sascha Pahernik [j], Jean J. de la Rosette [a], Olivier Rouvière [k], Georg Salomon [l], John F. Ward [m], Peter T. Scardino [n]*

- First Endpoint: Ablation of clinically significant carcinoma (>0,5 cc) with negative biopsy at 12 months



***Van den Bos et al. Eur Urol 2014**

Utilization of multiparametric prostate magnetic resonance imaging in clinical practice and focal therapy: report from a Delphi consensus project

M. J. Scheltema[1] · K. J. Tay[3] · A. W. Postema[1] · D. M. de Bruin[1,2] · J. Feller[5] · J. J. Futterer[6] · A. K. George[7] · R. T. Gupta[4] · F. Kahmann[8] · C. Kastner[9] · M. P. Laguna[1] · S. Natarajan[10] · S. Rais-Bahrami[11] · A. R. Rastinehad[12,13] · T. M. de Reijke[1] · G. Salomon[15] · N. Stone[12,14] · R. van Velthoven[16] · R. Villani[17] · A. Villers[18] · J. Walz[19] · T. J. Polascik[3] · J. J. M. C. H. de la Rosette[1]

Received: 1 August 2016 / Accepted: 6 September 2016

Standard repeat biopsies should be taken during the follow-up of FT. The final decision to perform FT should be based on histopathology. However, these consensus statements may differ for expert centers versus non-expert centers.

Conclusions The mpMRI is an important tool for characterizing and targeting PCa in clinical practice and FT. Standardization of acquisition and reading should be the main priority to guarantee consistent mpMRI quality throughout the urological community.

Focal radiotherapy as focal therapy of prostate cancer

György Kovács[a], Jean-Marc Cosset[b,c], and Brendan Carey[d]

Table 1. Comparison of advanced radiation therapy technologies regarding the potential of delivering high focal dose

	CK	IMRT	IGRT	IABT
Target definition	Worse[a]	Worse[a]	Worse[a]	Better
Interfraction movements	Better	Worse	Better	Better
Intrafraction movements	Better	Better 4D	Better 4D	Better
Target dose painting	Better	Better 4D	Better 4D	Better
Low-dose volumes	Worse	Worse	Worse	Better
Dose on OARs	Better	Worse	Worse	Better
Invasivity	better	Better	Better	Worse
Smallest reasonable CTV	~0.5 cm^3	>2 cm^3	>2 cm^3	~0.5 cm^3

CK, Cyber Knife (robotic radiotherapy); CTV, clinical target volume; IABT, image-adapted brachytherapy; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; OAR, organs at risk.
[a]Better if image fusion was used.

Dosimetry Modeling for Focal Low-Dose-Rate Prostate Brachytherapy

International Journal of Radiation Oncology biology • physics

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Bashar Al-Qaisieh, PhD,* Josh Mason, PhD,* Peter Bownes, MSc,* Ann Henry, MD,* Louise Dickinson, MD,[†,‡] Hashim U. Ahmed, MD,[†,§] Mark Emberton, MD,[§] and Stephen Langley, MD[||]

*Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; [†]Division of Surgery and Interventional Science, University College London, London, United Kingdom; [‡]Department of Radiology, Northwick Park Hospital, London North West NHS Trust, London, United Kingdom; [§]University College London Hospital, London, United Kingdom; and [||]St Luke's Cancer Centre, Guildford, United Kingdom

Received Dec 2, 2014, and in revised form Feb 2, 2015. Accepted for publication Feb 23, 2015.

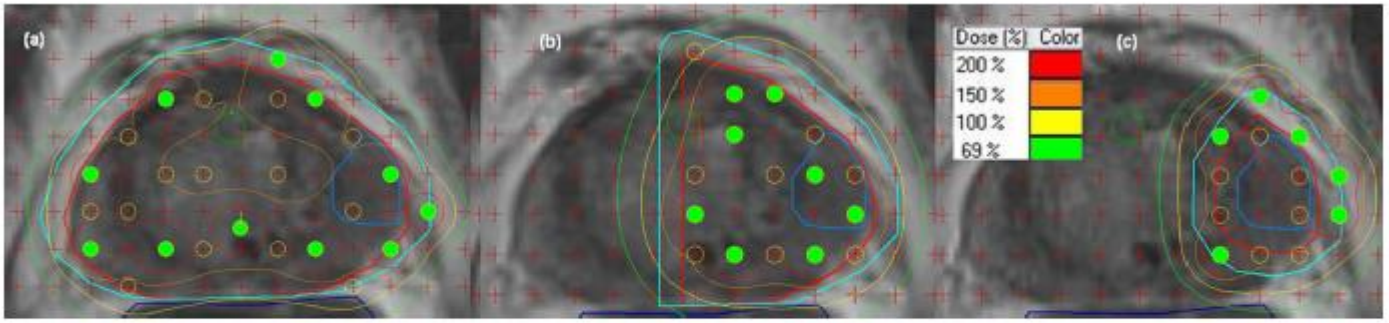

Fig. 2. Isodose comparison showing (a) whole-gland treatment plan, (b) hemi-gland treatment plan, and (c) ultra-focal treatment plan for the prostate, patient supine. The 100% isodose corresponds to 145 Gy. Prostate and hemi-prostate are shown in red, focal-gross tumor volume (F-GTV) is shown in blue; and planning target volume (PTV), hemi-PTV (H-PTV), and focal-PTV (F-PTV) are shown in light blue; the urethra is shown in green and the rectum is shown in dark blue. A color version of this figure is available at www.redjournal.org

Dosimetry Modeling for Focal Low-Dose-Rate Prostate Brachytherapy

Bashar Al-Qaisieh, PhD,* Josh Mason, PhD,* Peter Bownes, MSc,* Ann Henry, MD,* Louise Dickinson, MD,†,‡ Hashim U. Ahmed, MD,†,§ Mark Emberton, MD,§ and Stephen Langley, MD||

**Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; †Division of Surgery and Interventional Science, University College London, London, United Kingdom; ‡Department of Radiology, Northwick Park Hospital, London North West NHS Trust, London, United Kingdom; §University College London Hospital, London, United Kingdom; and ||St Luke's Cancer Centre, Guildford, United Kingdom*

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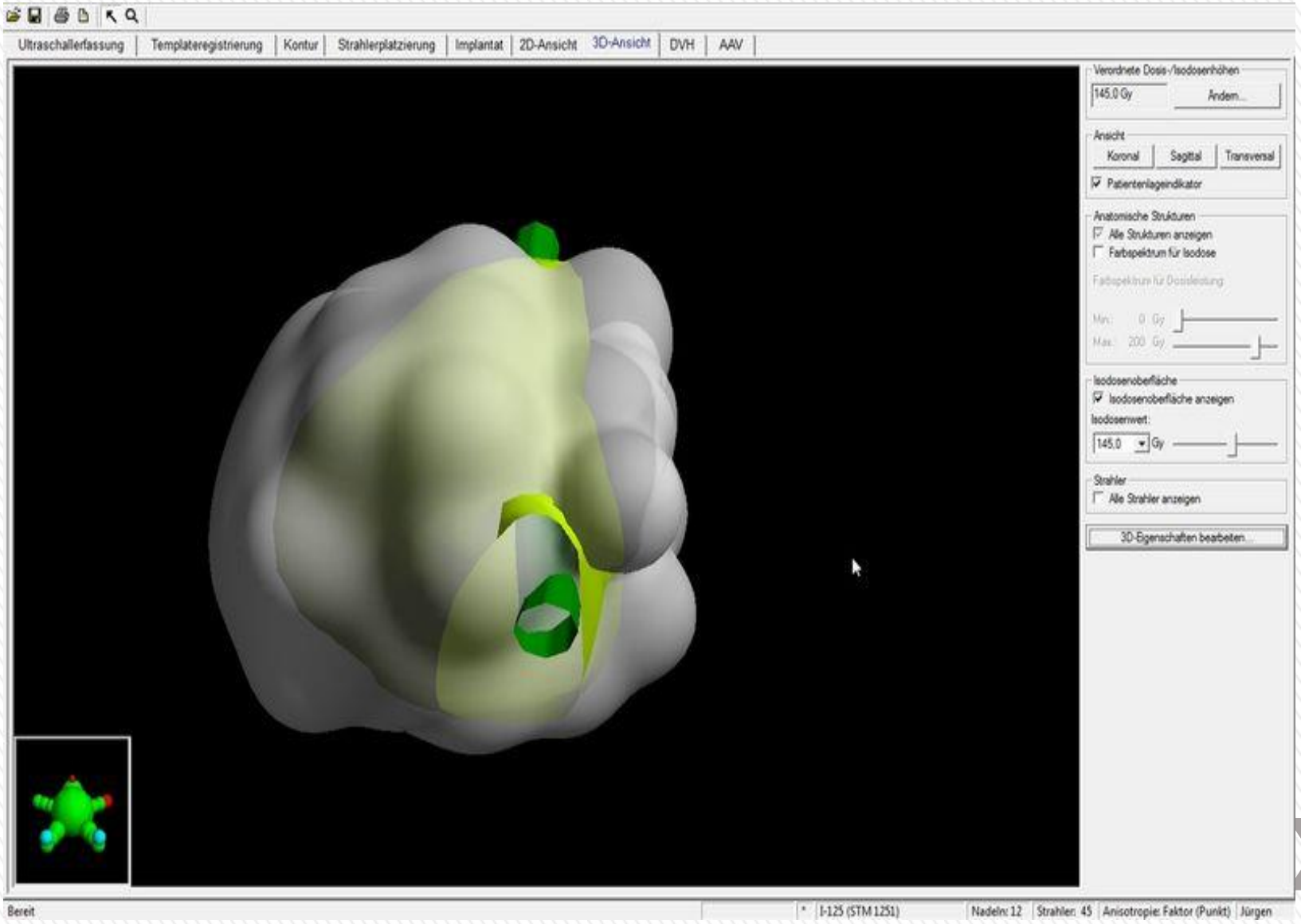
Table 1 Comparison of plans and DVH parameters for focal therapy treatments

Plan	Mean (range) for whole gland	Mean (range) for hemi-gland	Mean (range) for ultra-focal
No. of needles	20-37	12-21	10-15
No. of seeds	61-106	37-72	20-31
Seed density, seeds/cm^3 (range)	2.2 (1.8-2.7)	3.1 (2.5-4.0)	5.5 (3.8-7.2)
Prostate, cm^3		Volume 37.8 (22.7-58.6)	
D90%	181.3 (177.9-188.6)	42.9 (33.2-54.7)	14.1 (10.7-17.9)
V100%	99.8 (99.1-100)	54.7 (41.2-62.8)	19.9 (15.4-24.9)
V150%	59.6 (57.3-61.0)	41.5 (28.7-49.0)	13.6 (8.7-18.0)
V200%	21.5 (18.9-26.6)	22.1 (13.0-31.0)	7.5 (2.3-9.9)
Urethra			
D10%	205.9 (183.8-236.8)	191.4 (161.6-215.6)	92.4 (47.9-194.4)
V100 cm^3	0.40 (0.23-0.52)	0.27 (0.11-0.42)	0.02 (0.0-0.19)
Rectum			
D2cm^3 (Gy)	107.5 (85.0-131.6)	77.0 (39.2-105.1)	42.7 (13.7-86.7)
D0.1cm^3 (Gy)	163.2 (141.4-195.4)	136.8 (69.6-188.5)	94.1 (26.5-185.6)
Bladder			
D2cm^3 (Gy)	80.5 (18.5-116.3)	54.7 (13.2-87.2)	17.6 (2.5-69.5)
Penile bulb			
D0.1cm^3 (Gy)	50.2 (27.1-98.6)	34.9 (17.8-72.2)	13.9 (4.4-30.7)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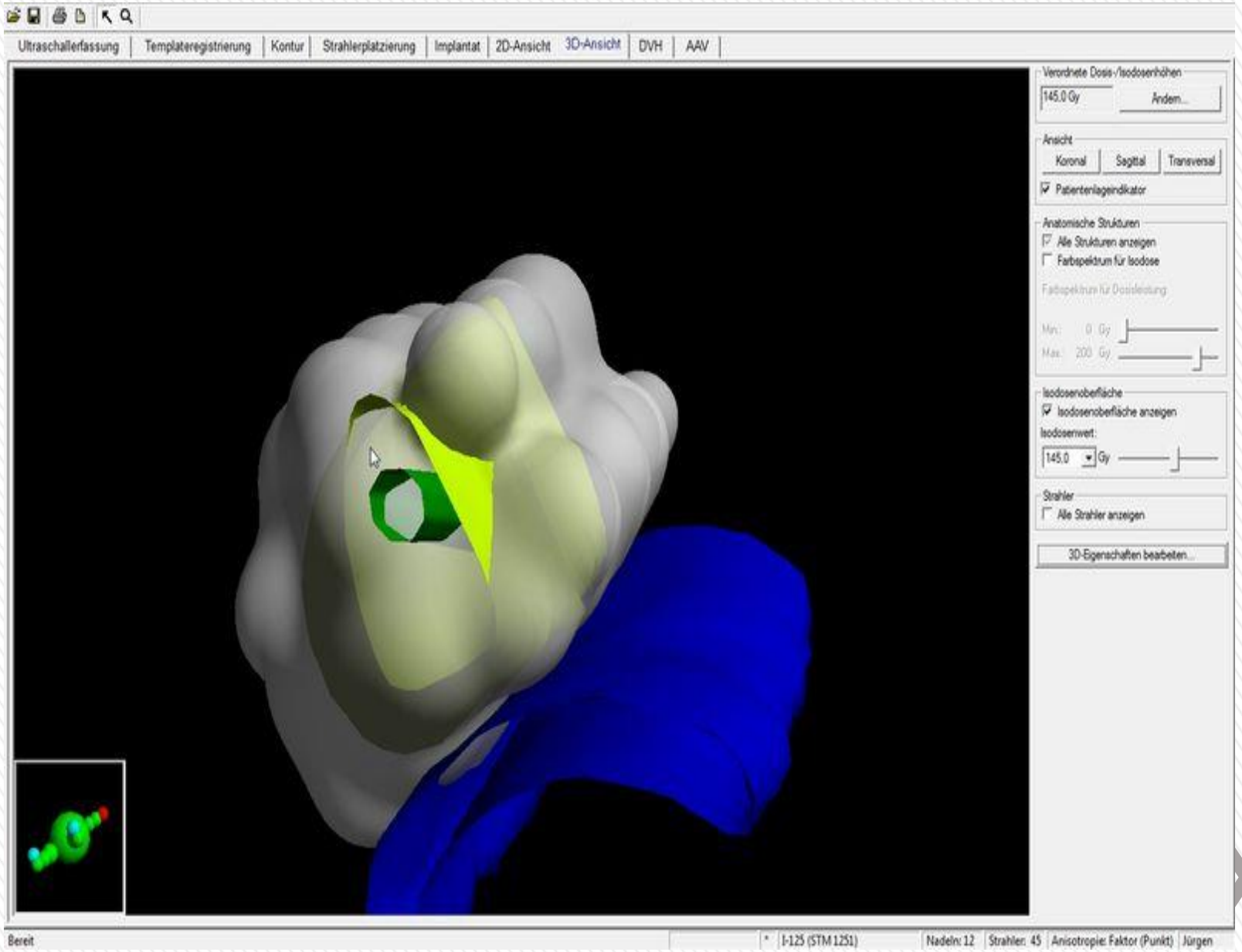
Templateregistrierung
Kontur
Strahlerplatzierung
Implantat
2D-Ansicht
3D-Ansicht
DVH
AAV
Verordnete Dosis-/Isodosenhöhen
145.0 Gy
Ändern...
Ansicht
Koronal
Sagittal
Transversal
Patientenlageindikator
Anatomische Strukturen
Alle Strukturen anzeigen
Farbspektrum für Isodose
Farbspektrum für Dosisleistung
Min: 0 Gy
Max: 200 Gy
Isodosenoberfläche
Isodosenoberfläche anzeigen
Isodosenwert:
145.0 Gy
Strahler
Alle Strahler anzeigen
3D-Eigenschaften bearbeiten...
Bereit
I-125 (STM 1251)
Nadeln: 12
Strahler: 45
Anisotropie: Faktor (Punkt)
Jürgen


Ultraschallerfassung
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2D-Ansicht
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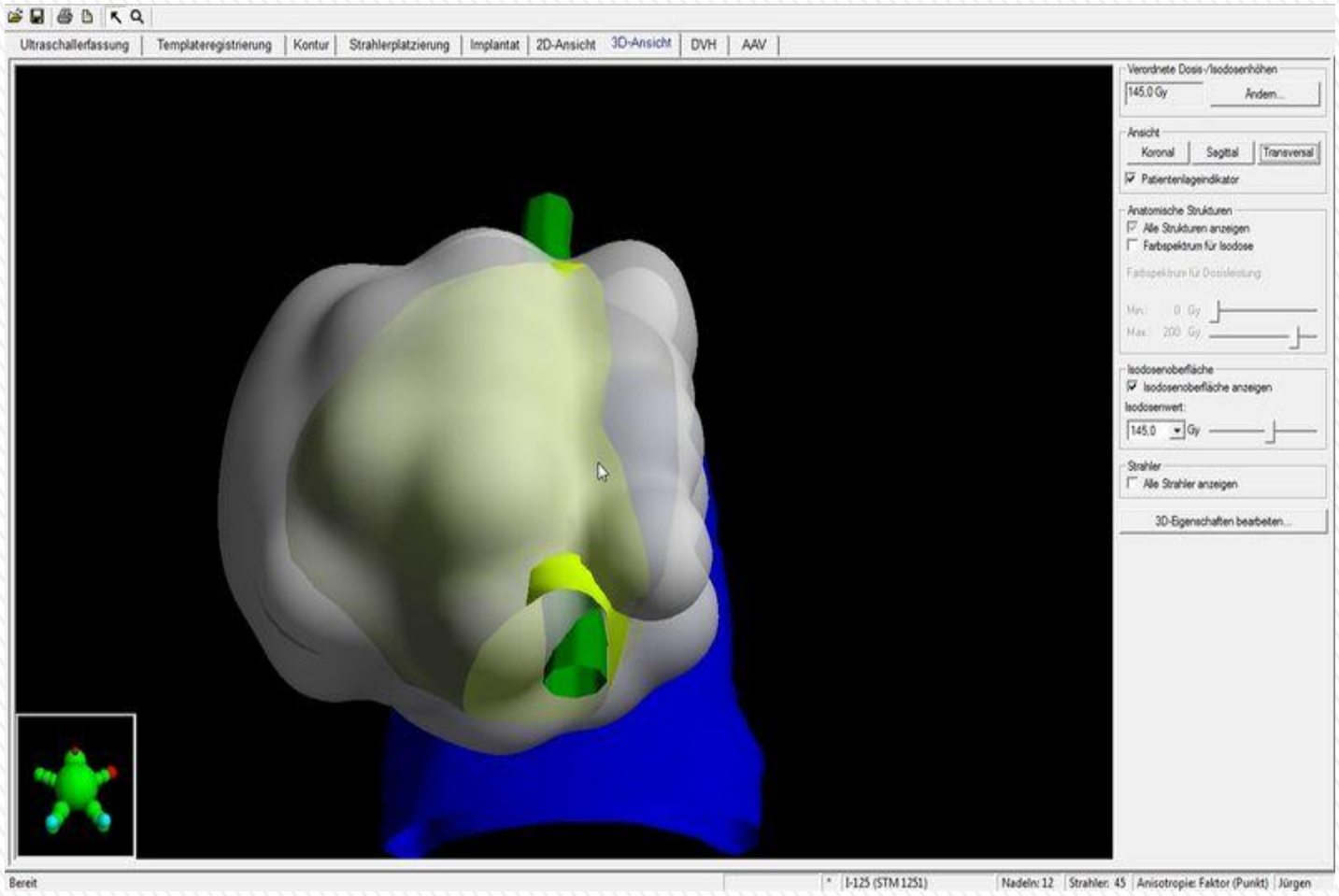
Ultraschallerfassung
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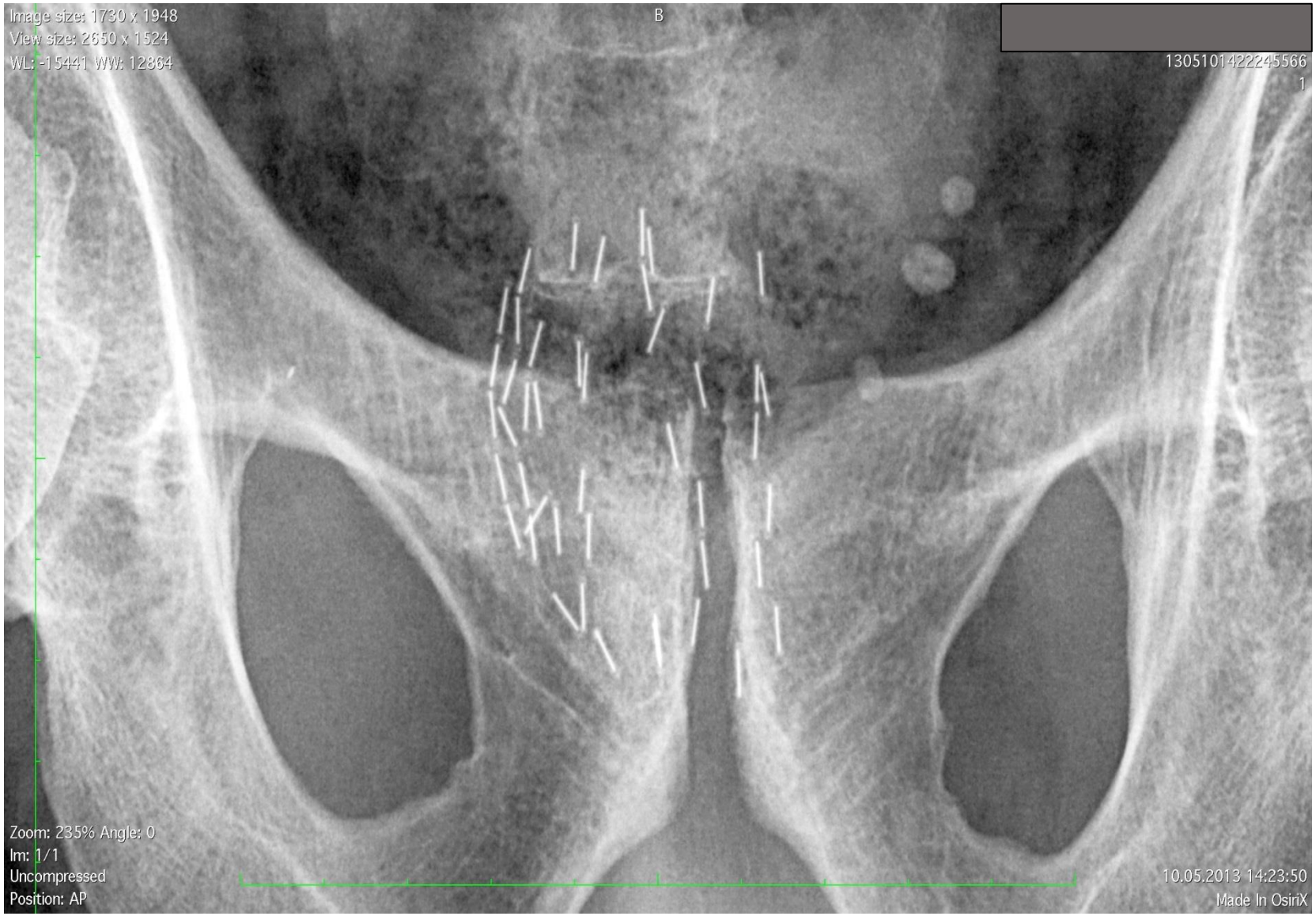
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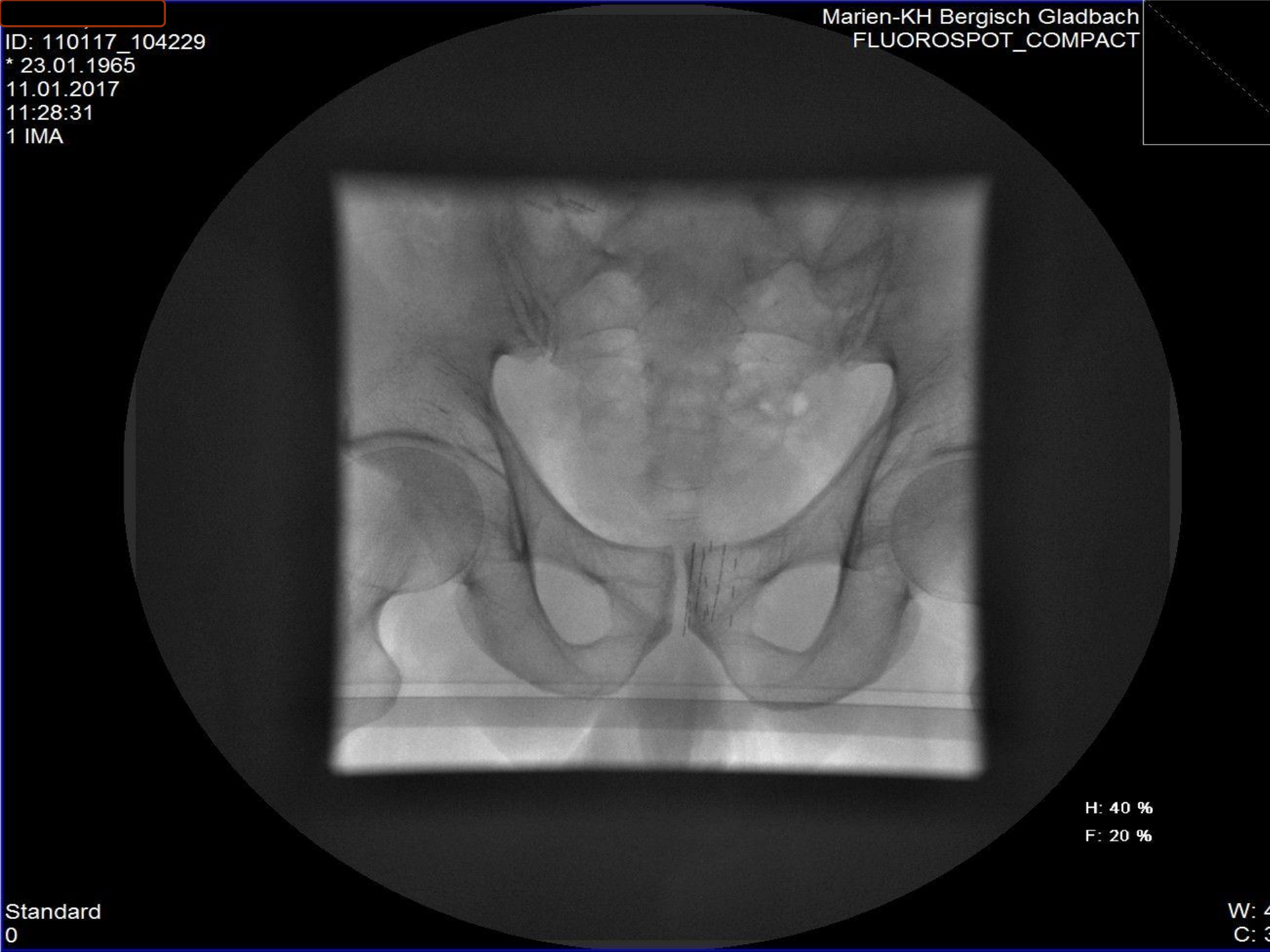
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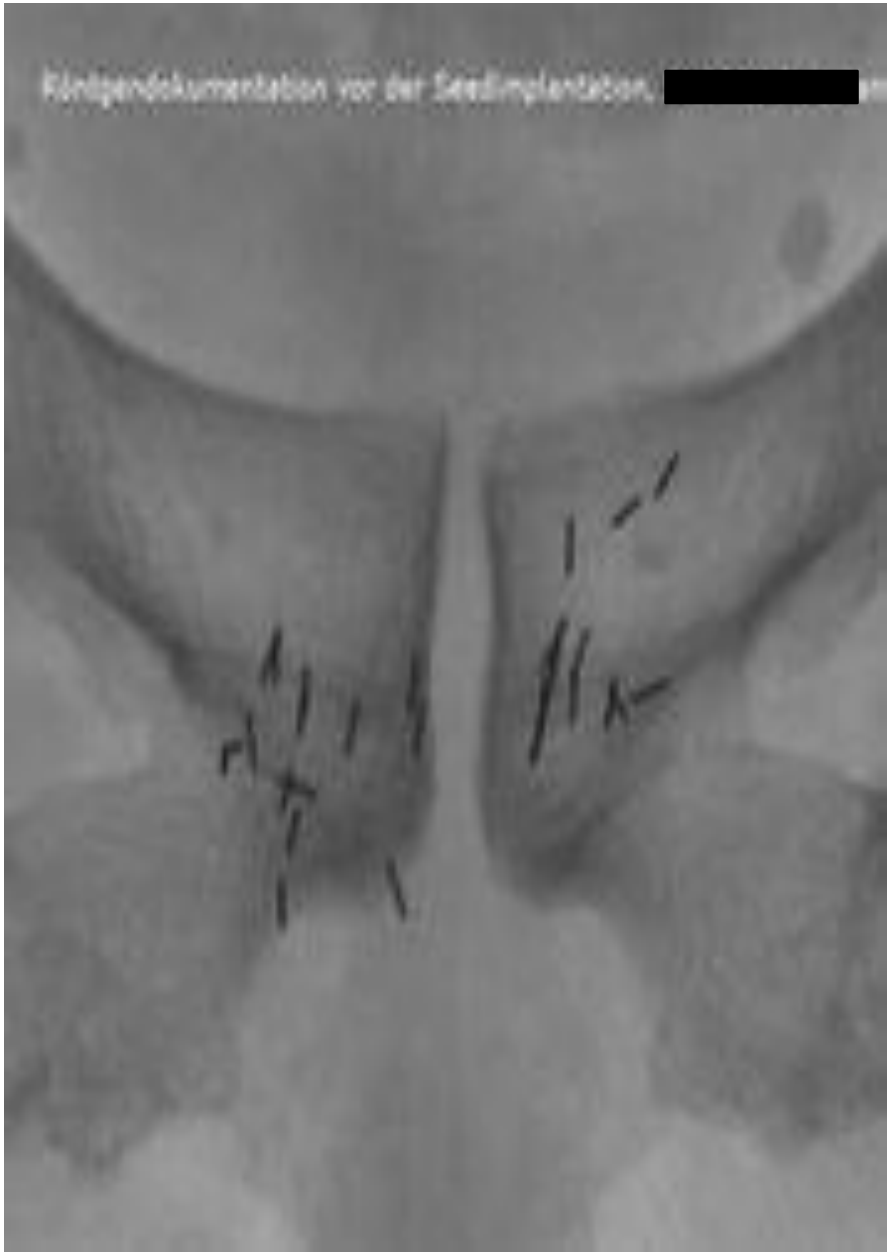
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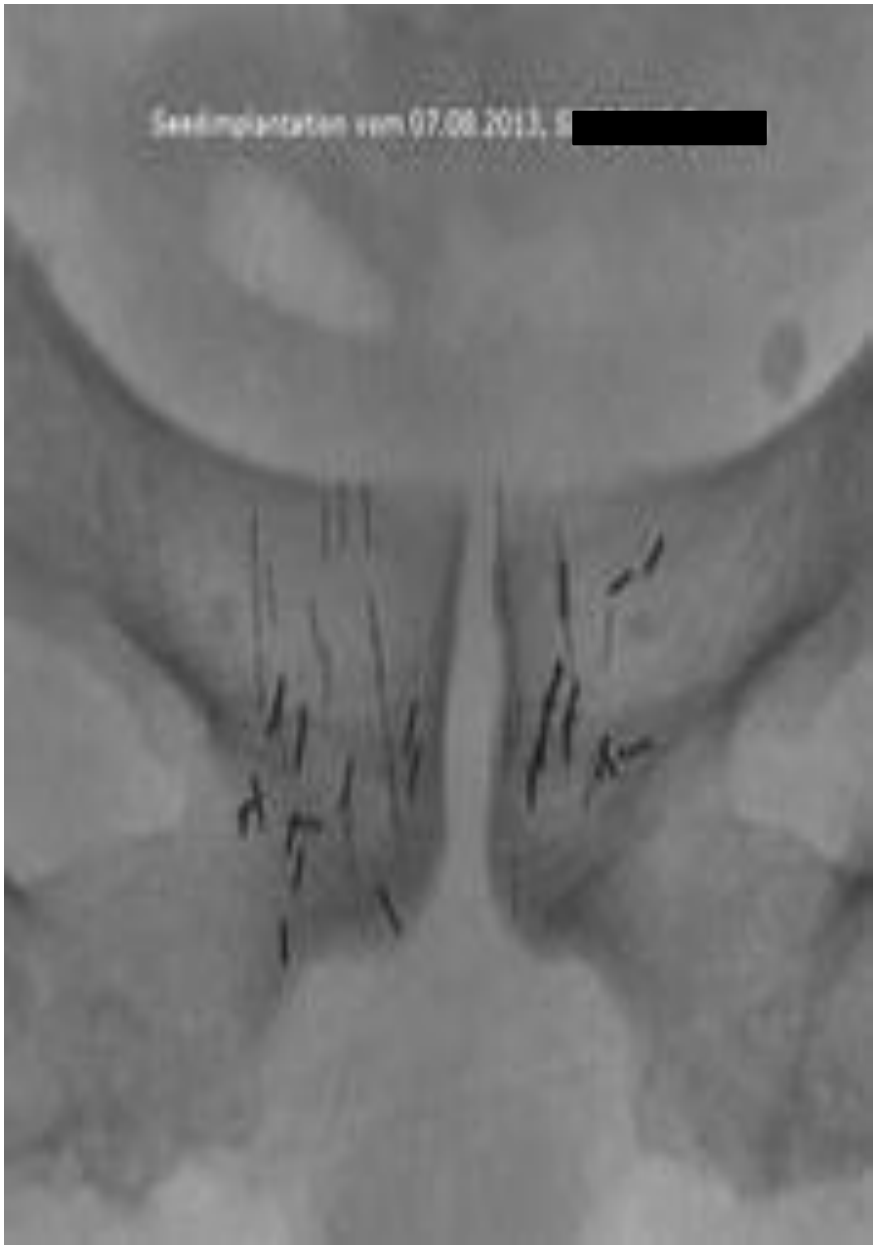
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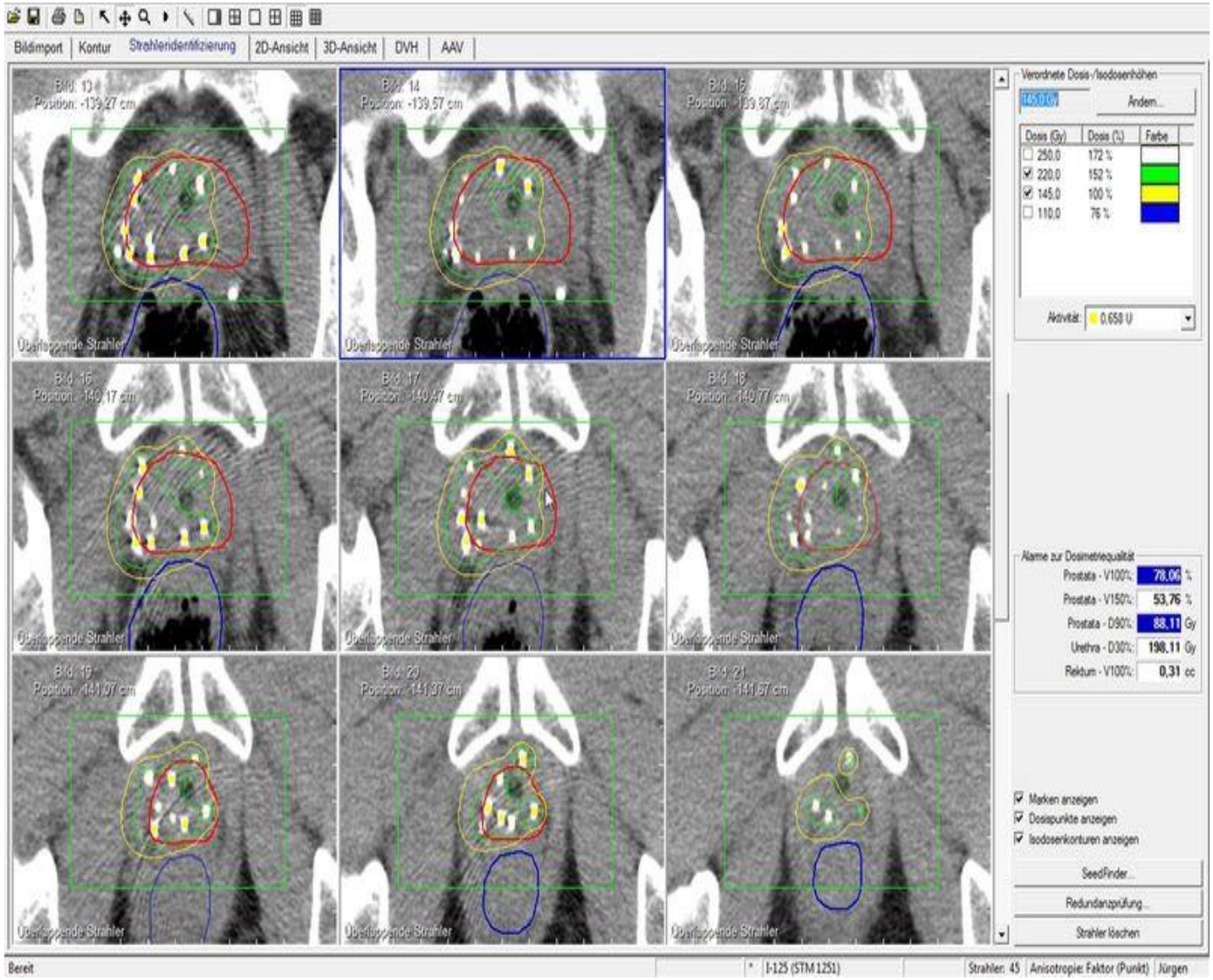
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Strahlenidentifizierung
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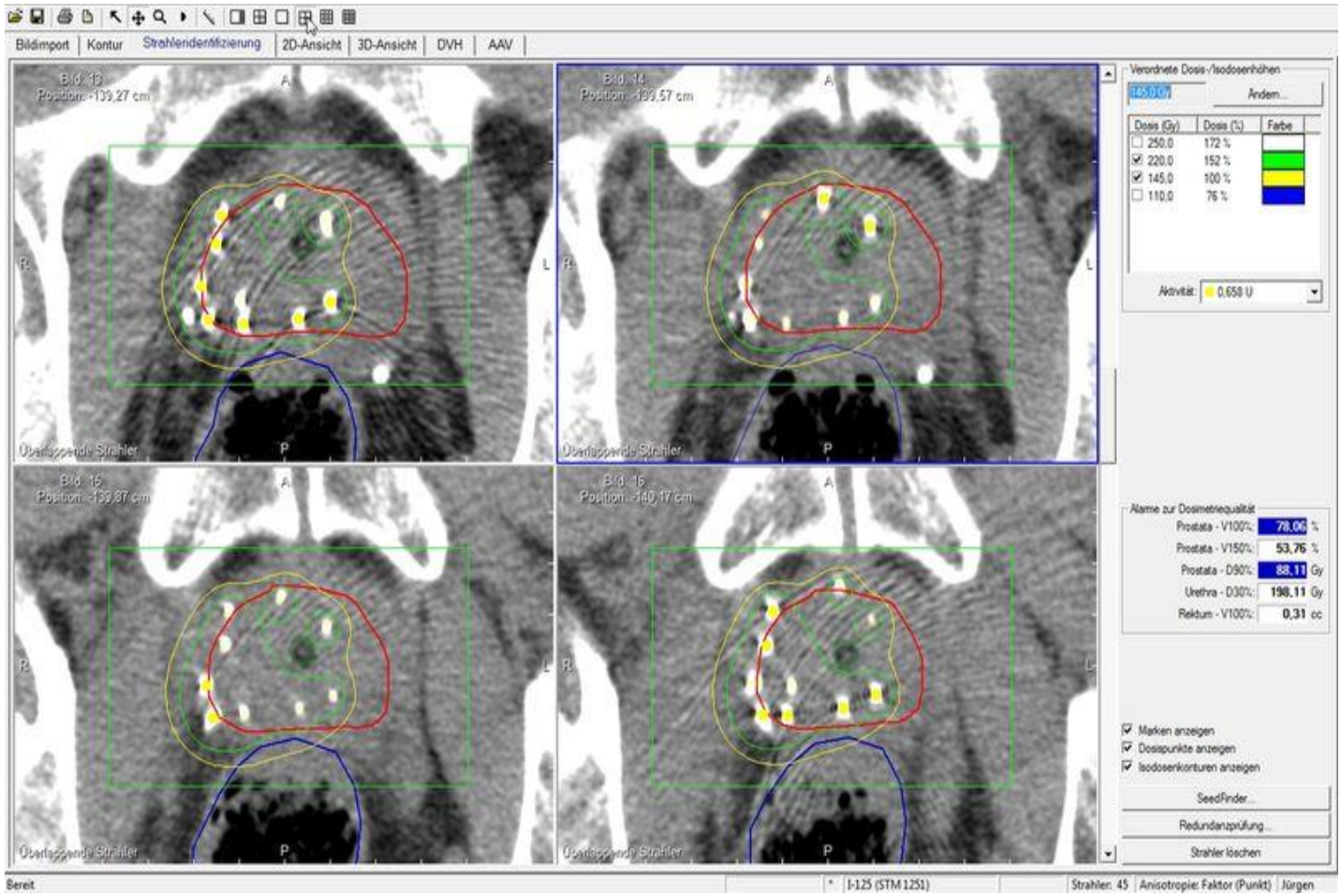
AAV
Verordnete Dosis-/Isodosenhöhen
145,0 Gy
Ändern...
Dosis (Gy)
Dosis (%)
Farbe
250,0 172 %
220,0 152 %
145,0 100 %
110,0 76 %
Aktivität: 0,658 U
Alarme zur Dosimetriequalität
Prostata - V100%: 78,06 %
Prostata - V150%: 53,76 %
Prostata - D90%: 88,11 Gy
Urethra - D30%: 198,11 Gy
Rektum - V100%: 0,31 cc
Marken anzeigen
Dosispunkte anzeigen
Isodosenkonturen anzeigen
SeedFinder...
Redundanzprüfung...
Strahler löschen
Bereit
I-125 (STM 1251)
Strahler: 45
Anisotropie: Faktor (Punkt)
Jürgen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3D-Ansicht
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Position: -139,27 cm
Bild 14
Position: -139,57 cm
Bild 15
Position: -139,87 cm
Bild 16
Position: -140,17 cm
Überlappende Strahler
Verordnete Dosis-/Isodosenhöhen
145,0 Gy
Ändern...
Dosis (Gy)
Dosis (%)
Farbe
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220,0 152 %
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Aktivität: 0,658 U
Alarme zur Dosimetriequalität
Prostata - V100%: 78,06 %
Prostata - V150%: 53,76 %
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Rektum - V100%: 0,31 cc
Marken anzeigen
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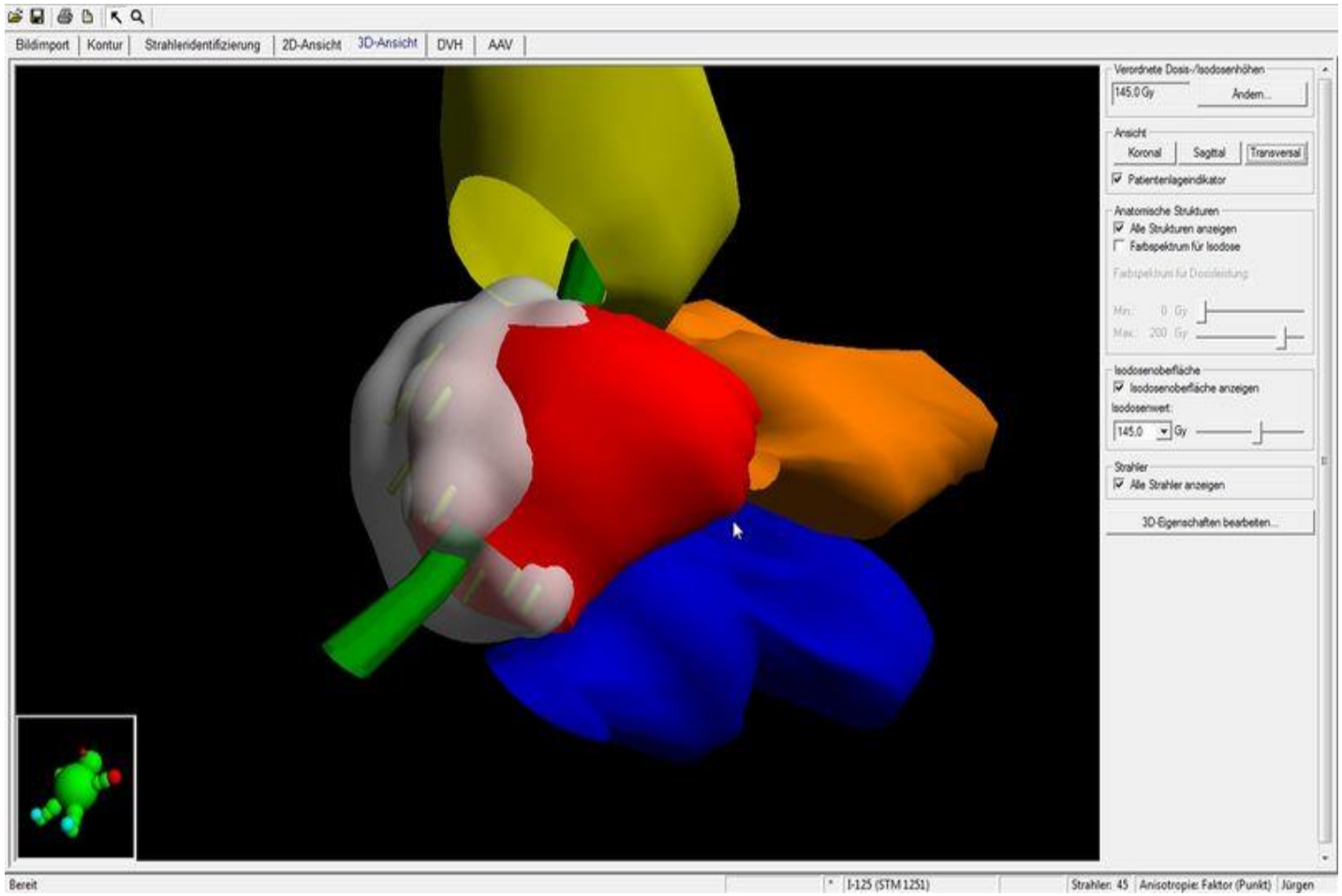
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Anisotropie: Faktor (Punkt)
Jürgen

Morbidity of Focal Therapy in the Treatment of Localized Prostate Cancer

Eric Barret[a,*], *Youness Ahallal*[a], *Rafael Sanchez-Salas*[a], *Marc Galiano*[a], *Jean-Marc Cosset*[a], *Pierre Validire*[b], *Petr Macek*[a], *Matthieu Durand*[a], *Dominique Prapotnich*[a], *François Rozet*[a], *Xavier Cathelineau*[a]

EUROPEAN UROLOGY 63 (2013) 618–622

Table 1 – Patient characteristics

Characteristic	Patients, *n* = 106
Age at first biopsy, yr (IQR)	66.5 (61–73)
PSA, ng/ml (IQR)	6.1 (5–8.1)
D'Amico low risk, %	100
Gleason score 3 + 3, %	100
Positive biopsies, no. (IQR)	1 (1–2)
Prostate weight g (IQR)	43 (33–55)
Energy modality for FT, no. (%)	
Cryotherapy	50 (47)
VTP	23 (22)
HIFU	21 (20)
Brachytherapy	12 (11)

IQR = interquartile range; PSA = prostate-specific antigen; FT = focal therapy; VTP = vascular-targeted photodynamic therapy; HIFU = high-intensity focused ultrasonography.

This pilot study showed that there is a reasonably low level of complications due to FT. This finding is very encouraging. There is more and more evidence accumulating that FT may represent a viable option for low-risk PCa, and because of our results, we think that this kind of treatment could potentially be extended to intermediate-risk patients. However, clinical trials and long-term follow-up data for assessing oncologic, functional, and quality-of-life outcomes are still needed before solid conclusions can be drawn.

Fazit: FT ist eine Therapiemodalität, die bei niedrig-Risiko Patienten berücksichtigt werden kann.Evtl. auch intermediäre-Risiko Patienten als Kandidaten.

Table 2 – Preliminary oncologic and functional results

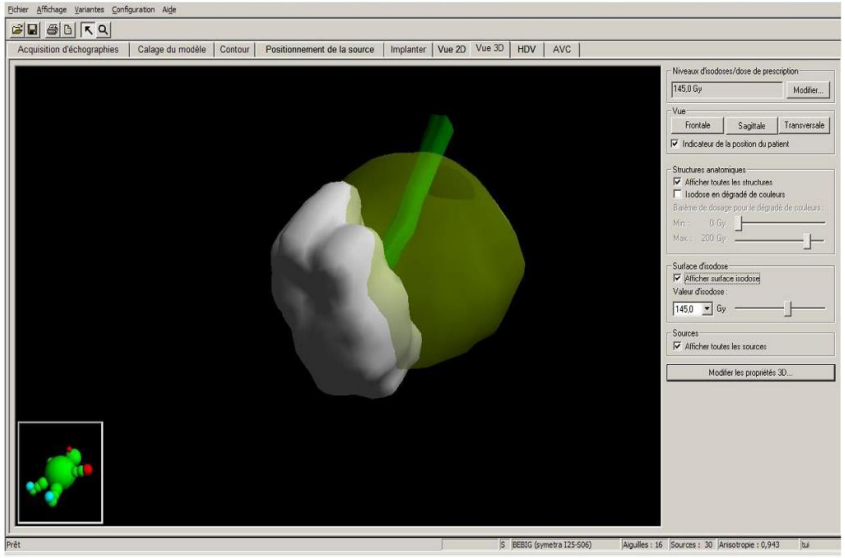
Energy modality	PSA, ng/ml, median (IQR)				IPSS, median (IQR)		IIEF-5, median (IQR)	
	Baseline	3 mo	6 mo	12 mo	Baseline	12 mo	Baseline	12 mo
Cryotherapy	6.2 (5.0–7.9)	2.9 (2.0–5.0)	2.8 (1.2–4.6)	2.5 (0.9–4.4)	9 (3–10)	5 (1–11)	19 (9–25)	14 (8–25)
Brachytherapy	6.2 (5.4–7.5)	3.3 (2.5–5.7)	3.2 (2.0–5.1)	2.8 (1.2–4.7)	3 (1–7)	7 (2–12)	21 (10–25)	14 (8–24)
VTP	5.7 (4.8–6.7)	3.0 (2.2–4.9)	2.8 (1.1–4.4)	3.2 (2.1–4.7)	6 (2–9)	6 (3–10)	23 (17–25)	13 (7–25)
HIFU	6.0 (5.1–8.1)	2.7 (1.8–4.7)	3.1 (2.1–5.3)	3.1 (2.4–4.3)	3 (1–7)	6 (2–11)	20 (15–25)	14 (8–25)

PSA = prostate-specific antigen; IQR = interquartile range; IPSS = International Prostate Symptom Score; IIEF-5 = International Index of Erectile Function; VTP = vascular-targeted photodynamic therapy; HIFU = high-intensity focused ultrasonography.

Focal brachytherapy for selected low-risk prostate cancers: A pilot study

Jean-Marc Cosset[1,2,*], Xavier Cathelineau[2], Georges Wakil[1,3], Noelle Pierrat[1], Olivier Quenzer[4], Dominique Prapotnich[2], Eric Barret[2], François Rozet[2], Marc Galiano[2], Guy Vallancien[2]

[1]*Department of Oncology/Radiotherapy, Institut Curie, Paris, France*
[2]*Department of Urology, Institut Mutualiste Montsouris, Paris, France*
[3]*Department of Radio-Oncology, Hospital Charles LeMoyne, Montréal, Canada*
[4]*Department of Statistics, Institut Curie, Paris, France*



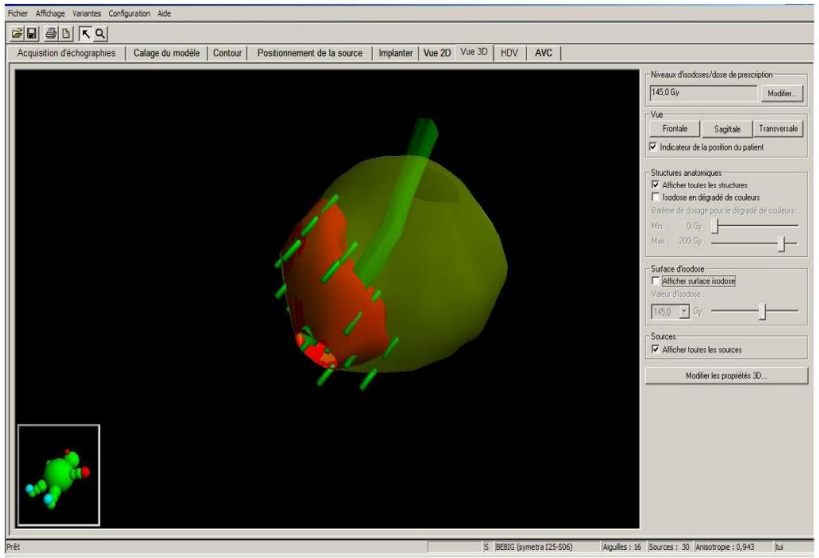


Table 1
Urinary toxicity (IPSS) and sexual toxicity (IIEF5) for focal prostate brachytherapy

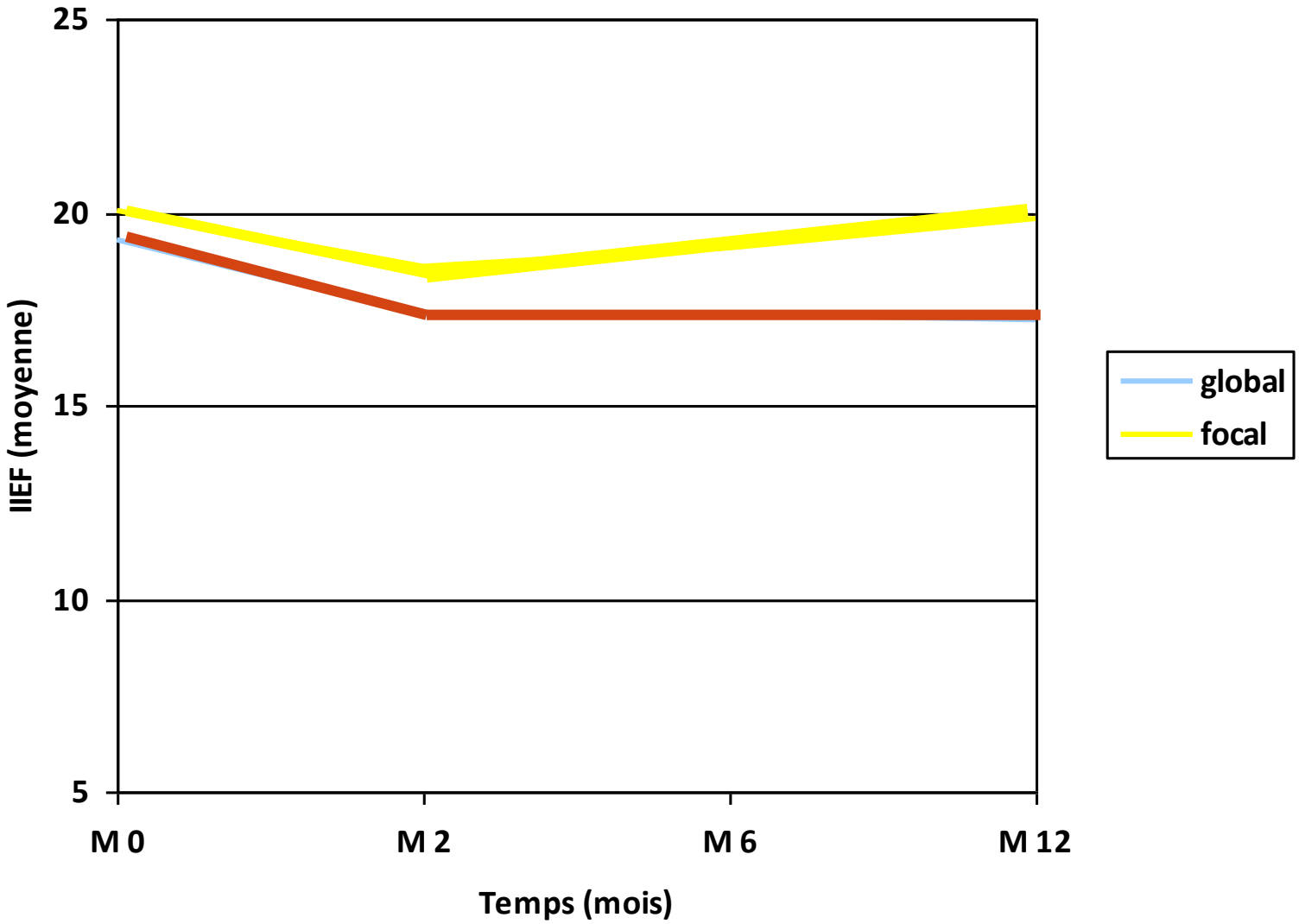
	Mean (range)
Initial IPSS	5.4 (0–15)
IPSS at 2 mo	11.8 (1–28)
IPSS at 6 mo	6.6 (2–17)
IPSS at 12 mo	6.1 (2–9)
Initial IIEF5	20.1 (5–25)
IIEF5 at 2 mo	18.6 (5–25)
IIEF5 at 6 mo	19.1 (5–25)
IIEF5 at 12 mo	19.8 (5–25)

RESULTS: The treated volume corresponded to a mean value of 34% of the total prostatic volume (range, 20–48%). For the focal volume, the mean D_{90} and V_{100} was 183.2 Gy (range, 176–188 Gy) and 99.3% (range, 98.8–100%), respectively. The technique was performed in an hour and a half. When compared with a previous cohort treated by whole-prostate brachytherapy, urinary toxicity (International Prostate Symptom Score) was borderline reduced ($p = 0.04$) at 6 months only, whereas the recovery of the International Index of Erectile Function 5 was better ($p = 0.014$). The International Continence Score was nil in almost all cases as well as rectal toxicity.

- **we did compare the toxicities observed in this series of focal brachytherapy with the ones that were registered in a series of 100 patients treated by a “whole prostate” brachytherapy by our group in the same institution (Institut Mutualiste Montsouris) , and analyzed with the same questionnaires.**

» **For IPSS,** the mean scores and variations were comparable at 2 and 12 months in both groups, focal and total***, but there was a borderline difference favoring the "focal"group at 6 months****, both in terms of direct comparison of the mean scores (p=0.04) and in terms of variation compared with the initial values (p=0.05).*

» **For erectile toxicity (IIEF)**, we did not observe any significant difference between the mean scores in the “focal” and “total” groups at 2, 6 and 12 months (p=0.43 ; p=0.46 ; p=0.17 respectively), *but* ***the re-increase of the score was significantly better in the focal group*** *at 6 and 12 months (p=0.014 et p=0.012, respectively).*


25
20
15
10
5
IIEF (moyenne)
M 0
M 2
M 6
M 12
Temps (mois)
global
focal

Focal brachytherapy for localized prostate cancer: Urinary toxicity depends on tumor location

Victor Srougi[1,2], Eric Barret[1], Igor Nunes-Silva[1], Mohammed Baghdadi[1], Silvia Garcia-Barreras[1], Noelle Pierrat[3], Francois Rozet[1], Marc Galiano[1], Rafael Sanchez-Salas[1], Xavier Cathelineau[1], Jean-Marc Cosset[1,3,4,*]

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[4]*Centre de radiothérapie Charlebourg-La Défense, groupe Amethyst, La Garenne-Colombes, France*

METHODS AND MATERIALS: The functional outcomes of patients treated with FBT at the base of the prostate were compared with those of patients treated with FBT at the apex. Urinary symptoms, continence, and erectile dysfunction were measured using the International Prostate Symptom Score (IPSS), International Continence Score (ICS), and International Index of Erectile Function (IIEF-5) questionnaires, respectively, at baseline and at 6, 12, and 24 months after treatment.

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Table 2
Comparison of functional outcomes: apex versus base

	N		Mean score		
	Apex	Base	Apex	Base	*p*
IPSS					
Baseline	28	13	4.9 ± 5.1	6.3 ± 4.9	0.39
6 months	28	13	6.4 ± 4.7	10.6 ± 5.7	0.02
12 months	28	13	5.1 ± 4.3	7.6 ± 5.0	0.09
24 months	20	12	6.4 ± 5.2	6.2 ± 5.3	0.90
ICS					
Baseline	31	100	0.04 ± 0.2	0.08 ± 0.3	0.58
6 months	28	13	0.25 ± 0.7	0	0.21
12 months	27	13	0.59 ± 1.1	0.46 ± 0.9	0.71
24 months	20	12	0.55 ± 1.4	0.08 ± 0.3	0.26
IIEF5					
Baseline	18	12	19 ± 7.6	18 ± 6.9	0.71
6 months	26	13	14.7 ± 8.7	16.3 ± 5.6	0.56
12 months	28	13	16.5 ± 7.5	16.2 ± 6.3	0.92
24 months	20	13	17 ± 7.7	16.5 ± 7.4	0.84

IPSS = International Prostate Symptom Score; ICS = International Continence Score; IIEF-5 = International Index of Erectile Function.

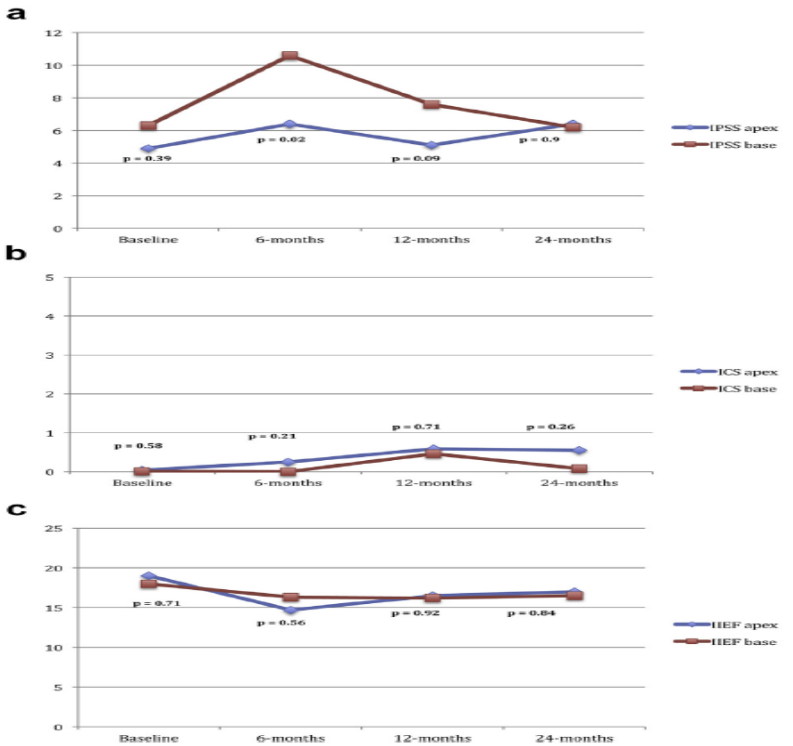

Fig. 2. (a) IPSS among treatment location in different time points: apex versus base. (b) ICS among treatment location in different time points: apex versus base. (c) IIEF among treatment location in different time points: apex versus base. IPSS = International Prostate Symptom Score; ICS = International Continence Score; IIEF = International Index of Erectile Function.

Focal brachytherapy for localized prostate cancer: Urinary toxicity depends on tumor location

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RESULTS: Twenty-eight and 13 patients were treated with FBT at the apex and the base, respectively, of the prostate. A significant difference between groups was found in the IPSS score at 6 months (mean IPSS: apex 6.4 ± 4.7, base 10.6 ± 5.7; $p = 0.02$), but not at baseline or at 12 and 24 months after treatment. On multivariate analysis, only FBT at the base of the prostate remained an independent predictor of worsening urinary symptoms (odds ratio, 5.8; $p = 0.04$).

CONCLUSIONS: At 6 months after FBT, significantly less urinary toxicity was found in patients who underwent FBT at the apex versus the base of the prostate. Continence and sexual side effects were minimal in all patients.

EAU Guideline 2016

Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials.	A

Conclusion

- **mpMRI and transperineal biopsies remain the most reliable tools to identify candidates for a focal therapy.**
- **Focal therapy should only be performed under controled conditions..**
- **So far focal therapy is not a guideline recommended therapy.**

"You must never be fearful about what you are doing when it is right."

-Marie Curie

Thank You

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How can we achieve focal therapy

- Radiation therapy
- Cryotherapy
- HIFU
- Electroporation
- Phototherapy
- Photothermal ablation
- .....

Non-radiation based thermal therapies

	Stage of assessment	Positive biopsy rate (treated area)	Potency preservation	Continence preservation	Recto-urethral fistula rate
Cryotherapy	IIb	3-26.3%	58.1–100%	96–100%	0–2%
HIFU	IIb	0–28%	54–95%	95–100%	0–1%
PDT	IIb	17.4–38.1%	NR	100%	0%
LITT	IIa	22–33%	96–100%	100%	0%
Irreversible electroporation	IIa	27%	89–100%	100%	0%

HIFU: High-intensity focused ultrasound; LITT: Laser interstitial thermotherapy; NR: Not reported; PDT: Photodynamic therapy.

Focal high-dose-rate brachytherapy: A dosimetric comparison of hemigland vs. conventional whole-gland treatment

Mitchell Kamrava[1,2], Melody P. Chung[1,*], Oluwatosin Kayode[1], Jason Wang[1], Leonard Marks[3], Patrick Kupelian[1], Michael Steinberg[1,2], Sang-June Park[1], D. Jeffrey Demanes[1,2]

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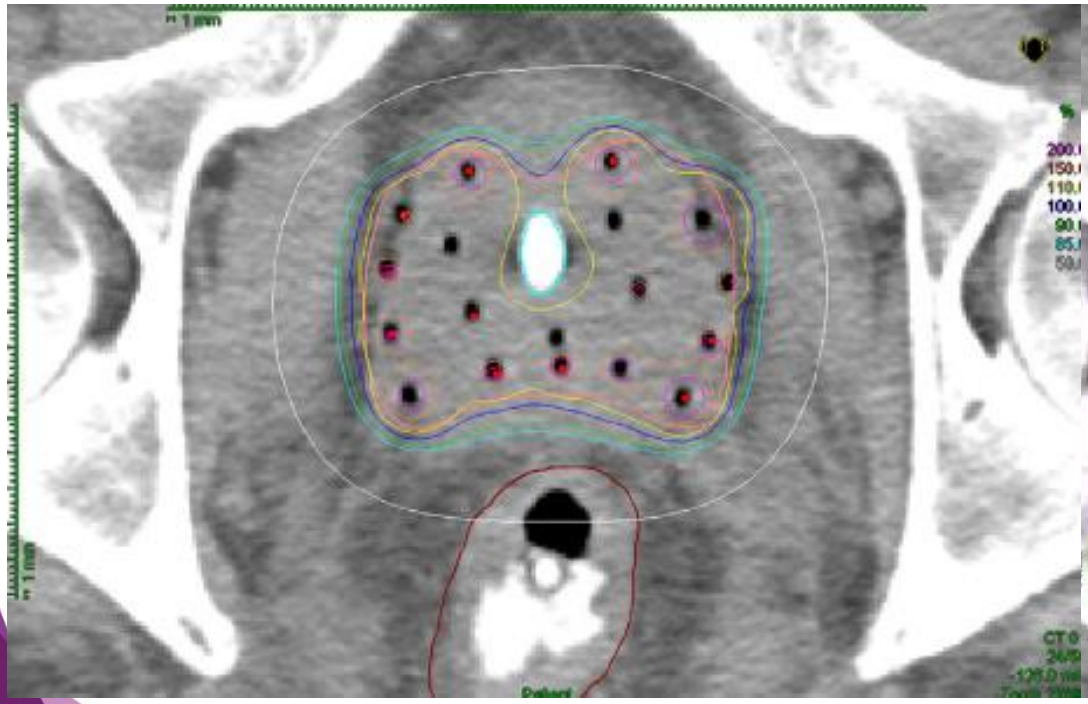
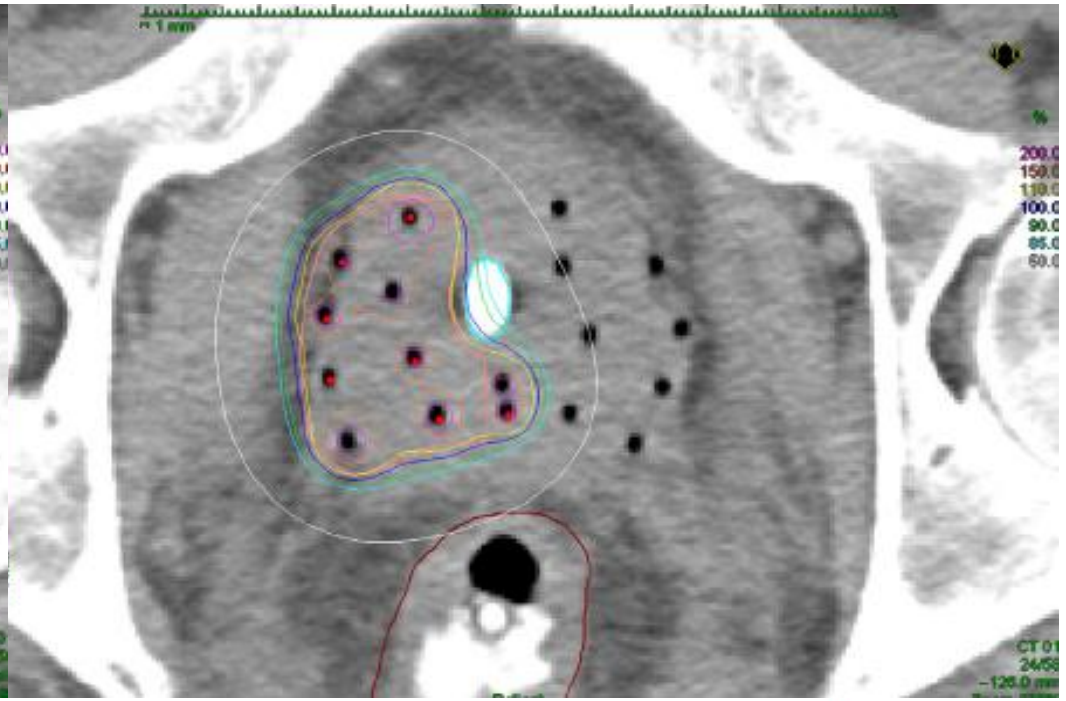
Brachytherapy 12 (2013) 434–441





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Brachytherapy 12 (2013) 434–441

Whole gland (WG) vs. hemigland (HG) radiation doses to organs at risk

Radiation	Rectum			Bladder			Urethra		
doses	WG	HG	*p*-value	WG	HG	*p*-value	WG	HG	*p*-value
$D_{0.1\ cc}$ (%)	76.0	71.2	0.0027	83.8	82.2	0.0925	106.5	97.7	<0.0001
$D_{1\ cc}$ (%)	68.4	59.0	<0.0001	73.4	64.0	<0.0001	103.1	82.9	<0.0001
$D_{2\ cc}$ (%)	64.1	53.1	<0.0001	67.5	55.9	<0.0001	95.2	69.3	<0.0001

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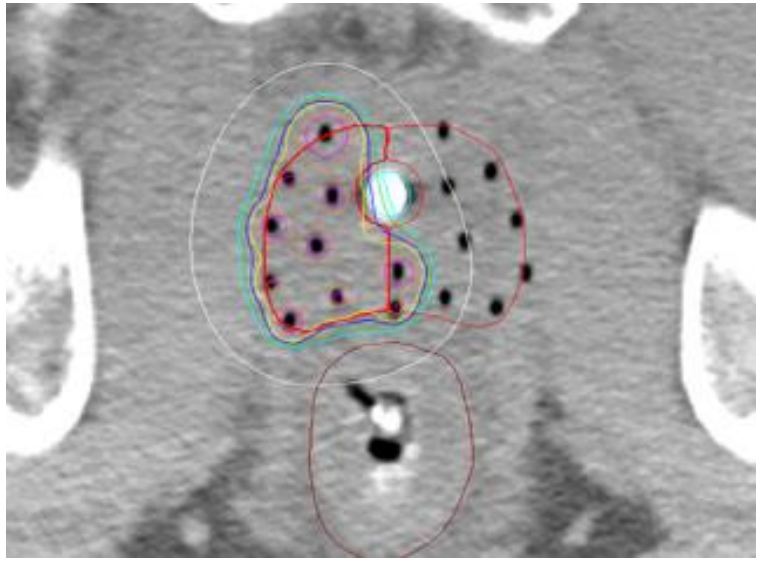
Brachytherapy 12 (2013) 434–441

Evaluation of "spill" dose from hemigland treatment to contralateral hemigland

Dosimetric variables	Dose to left side of the prostate gland for right hemigland treatment	Dose to right side of the prostate gland for left hemigland treatment
V_{100} (%)	12.5	7.1
V_{80} (%)	19.9	14.1
V_{60} (%)	33.8	27.9
V_{50} (%)	47.3	41.9
V_{20} (%)	100.0	100.0
D_{90} (%)	31.0	30.3
D_{70} (%)	38.8	37.4
D_{50} (%)	48.4	45.7
D_{30} (%)	63.9	58.2



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Dosimetry modeling for focal high-dose-rate prostate brachytherapy

Josh Mason[1,2,*], Bashar Al-Qaisieh[1], Peter Bownes[1], David Thwaites[2,3], Ann Henry[4]

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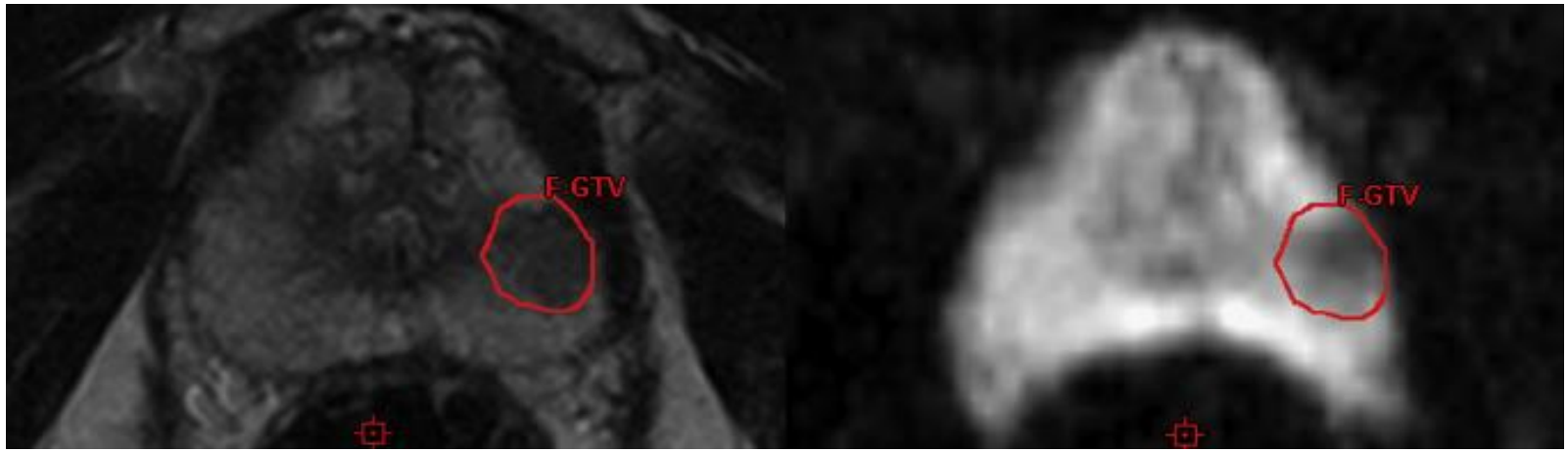

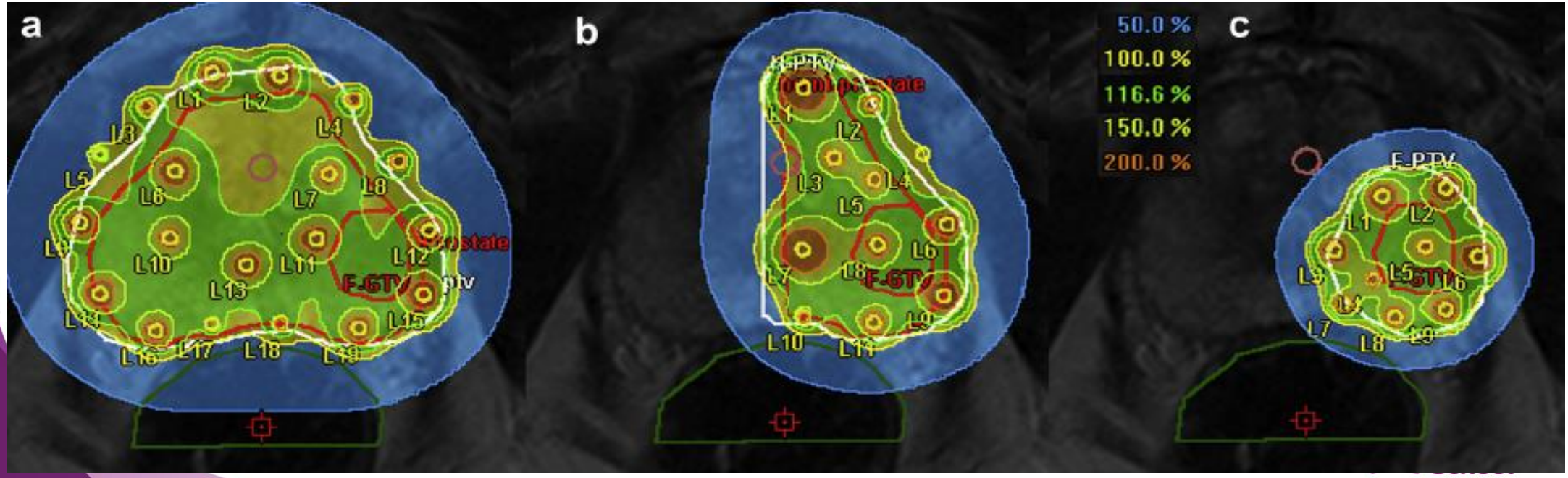

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Brachytherapy 13 (2014) 611–617

Impact of systematic shifts in dwell position

		Target D_{90} (Gy)			Target V_{100} (%)		
Shift	Direction	WG	HEMI	UF	WG	HEMI	UF
0 mm		20.5	22.3	23.2	97.9	98.2	98.3
1 mm	mean for all	20.4	22.1	22.7	97.7	97.8	97.5
2 mm	inf	20.3	22.0	21.6	97.0	97.6	96.3
	sup	20.3	21.8	22.4	96.9	97.1	97.4
	post	20.4	22.2	21.4	96.7	97.3	94.7
	ant	20.1	21.2	20.7	95.2	95.5	93.4
	left	20.4	21.5	21.0	97.7	95.6	94.0
	right	20.4	21.6	20.5	97.7	96.7	93.0
3 mm	mean for all	20.1	21.0	19.3	95.6	94.7	90.5
4 mm	inf	19.9	21.0	18.2	94.0	95.0	87.0
	sup	19.7	20.3	19.6	93.2	93.3	91.1
	post	19.8	21.0	16.7	93.3	94.2	84.7
	ant	18.7	18.8	16.0	89.6	89.6	82.2
	left	20.2	19.2	16.5	96.5	89.3	83.2
	right	20.2	19.5	15.5	96.4	91.0	81.2

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From whole gland to hemigland to ultra-focal high-dose-rate prostate brachytherapy: A dosimetric analysis

Robyn Banerjee[1], Sang-June Park[2], Erik Anderson[2], D. Jeffrey Demanes[2], Jason Wang[2], Mitchell Kamrava[2,*]

[1]*Department of Oncology, University of Calgary, Calgary, Alberta T2N 4N2, Canada*
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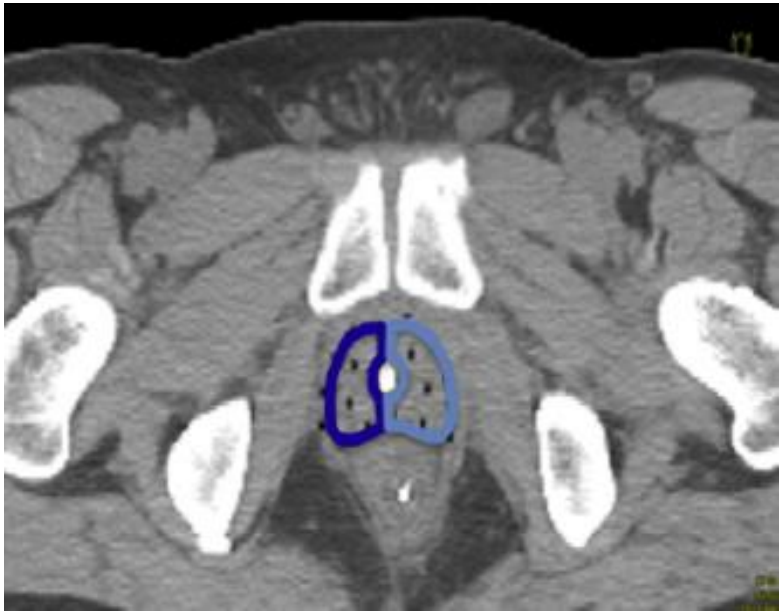
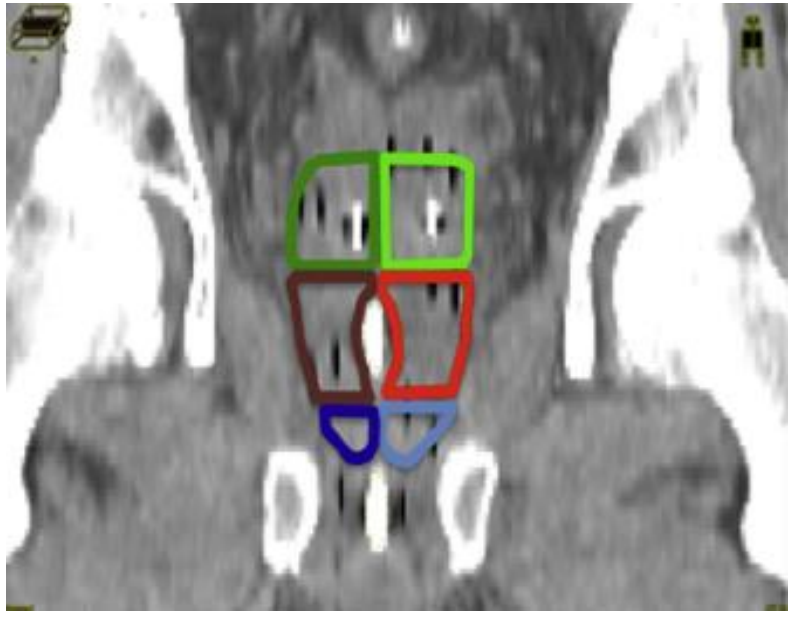
Whole gland vs hemigland vs focal





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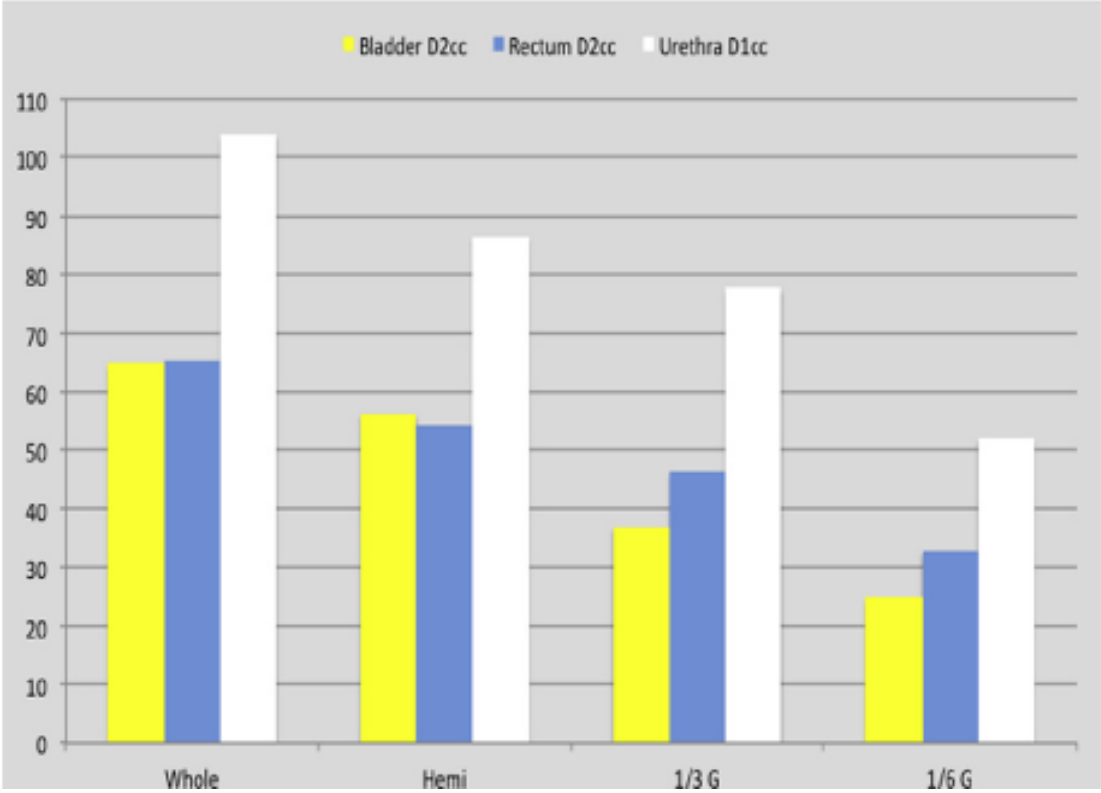
OAR Doses for WG vs. HG, 1/3G and 1/6G



Target dose coverage (%)

Target	D90%	V100%	V150%
WG	109.3	98.7	23.5
HG	112.7	97.8	32.9
1/3 G	112.6	97.4	34.2
1/6 G	114.7	97.3	44.9
Whole + 1/3 G	112.5	98.6	34.1
Whole + 1/6 G	111.1	98.7	28.3

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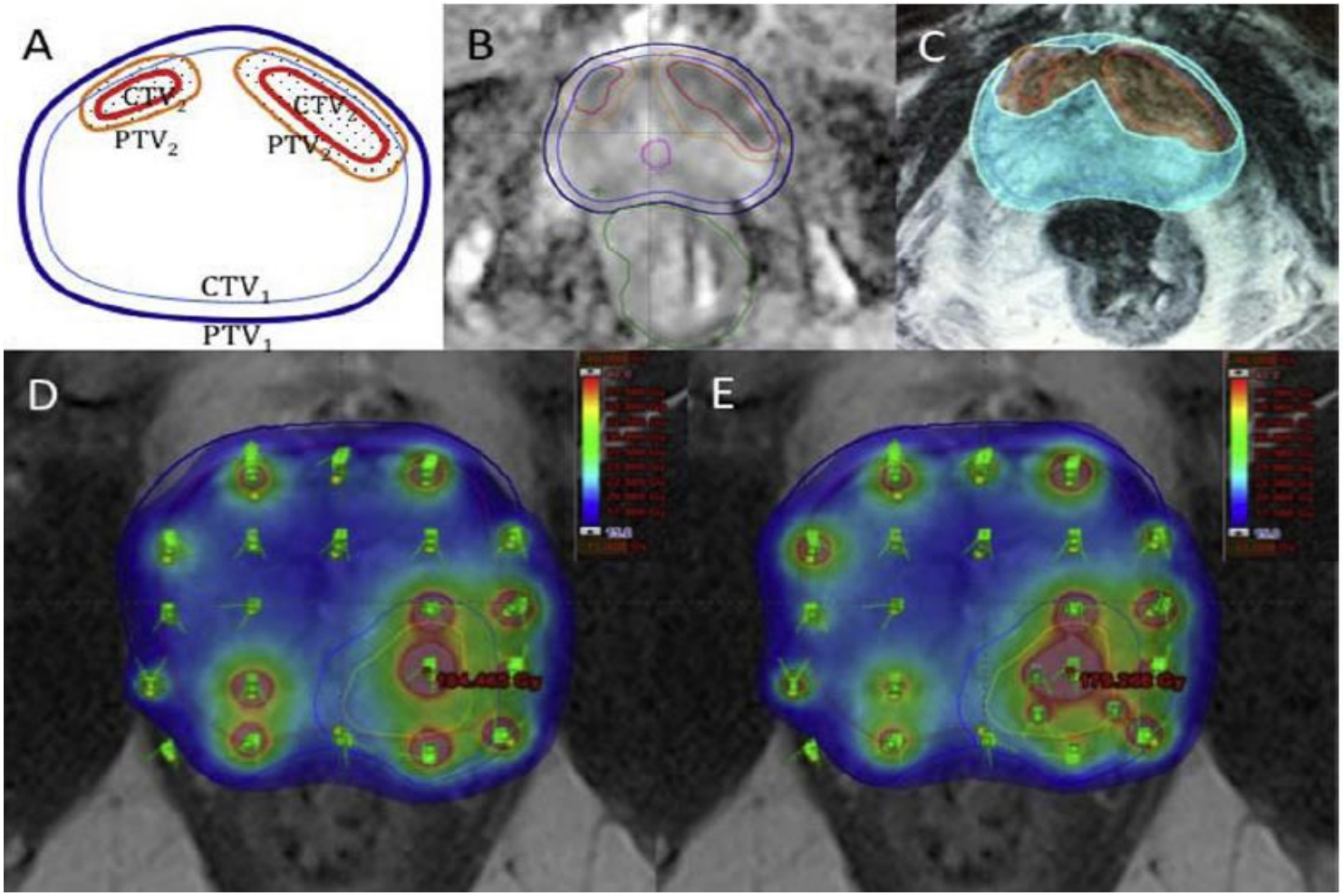
Optimal source distribution for focal boosts using high dose rate (HDR) brachytherapy alone in prostate cancer

Pittaya Dankulchai [a,b,*], Roberto Alonzi [a], Gerry J. Lowe [a], James Burnley [a], Anwar R. Padhani [c], Peter J. Hoskin [a]

Radiotherapy and Oncology xxx (2014)



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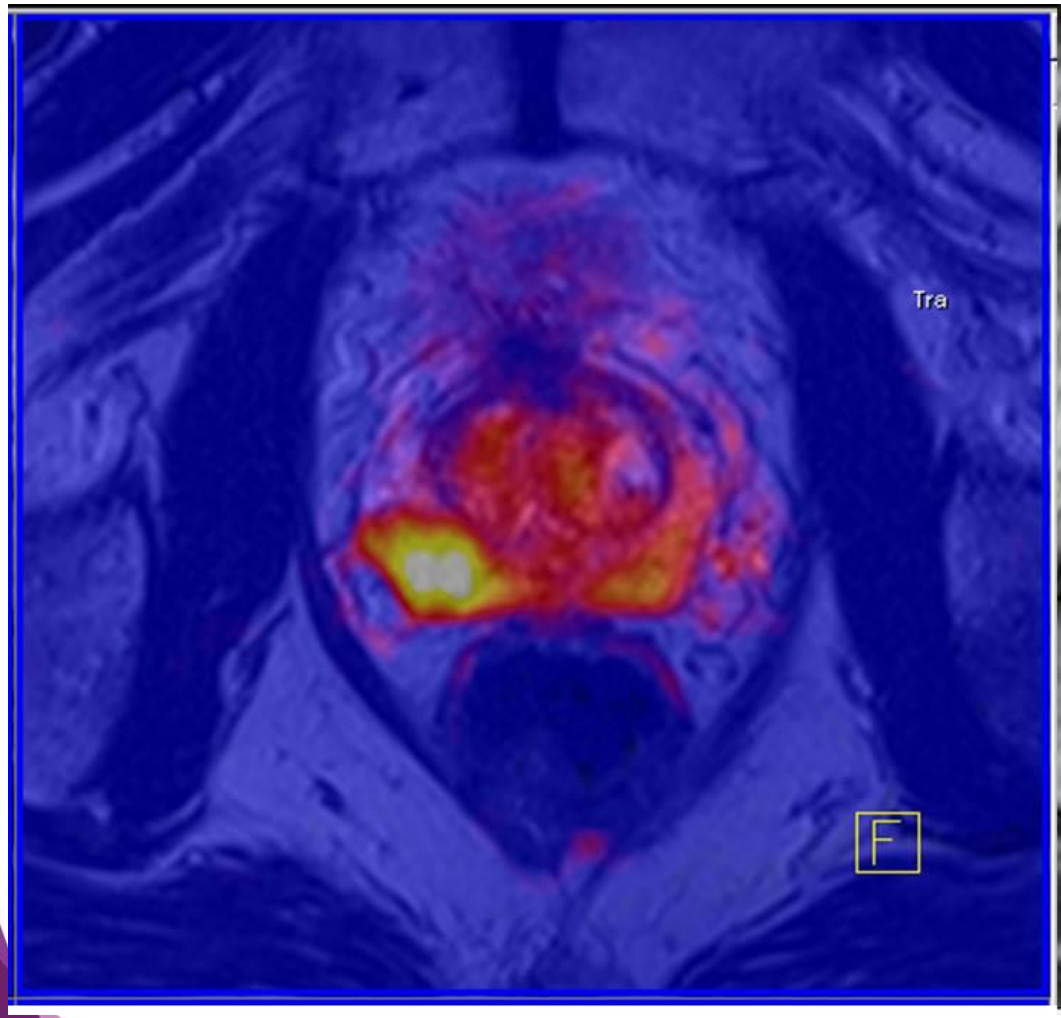
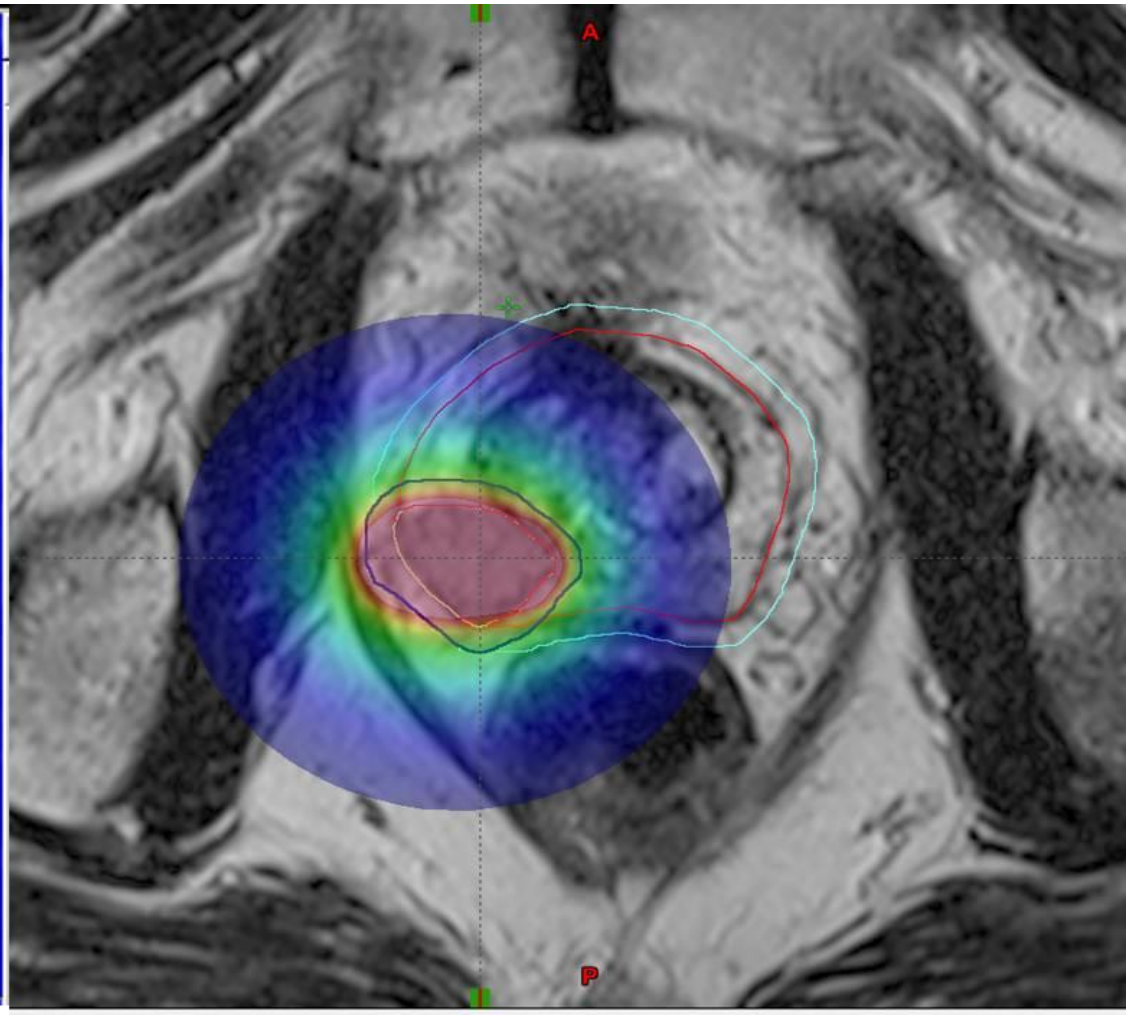
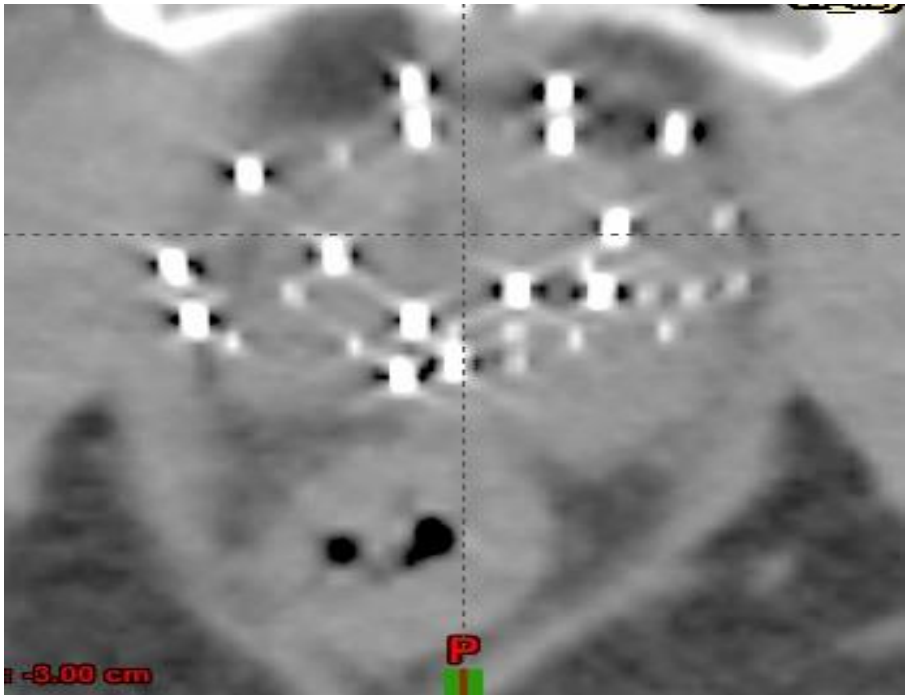
Focal Therapy



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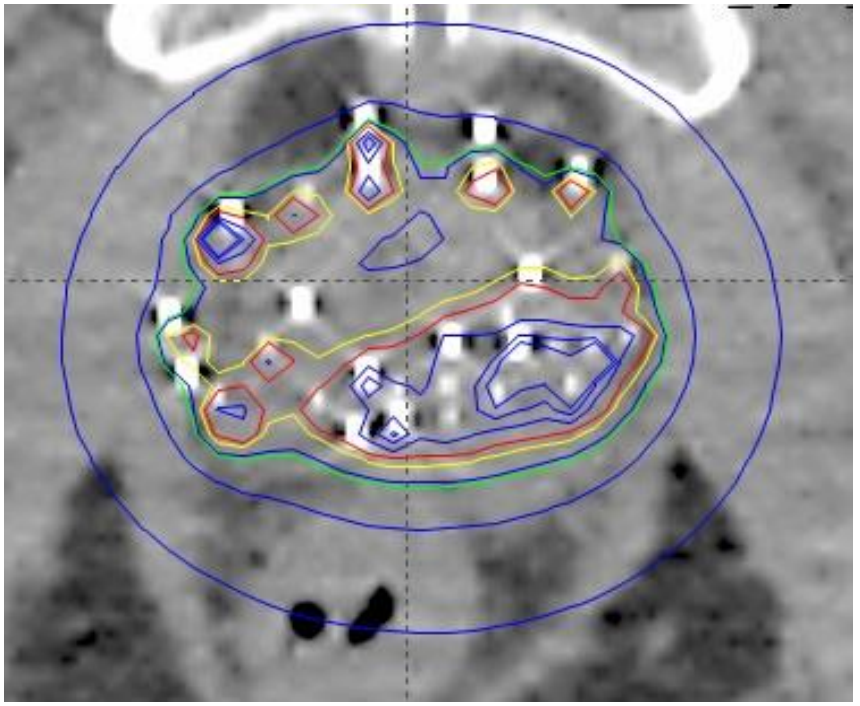
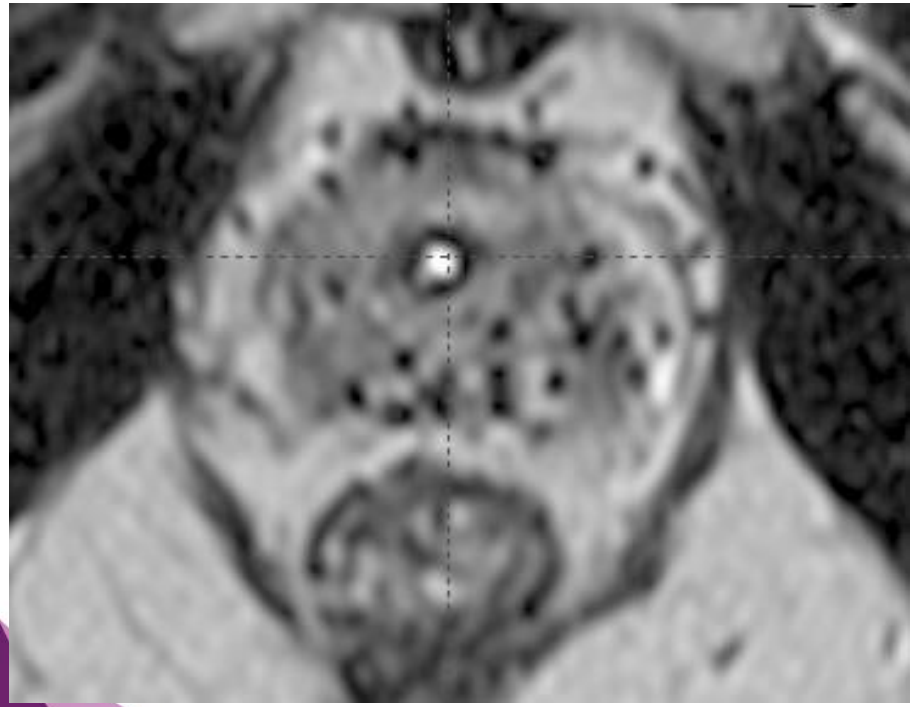
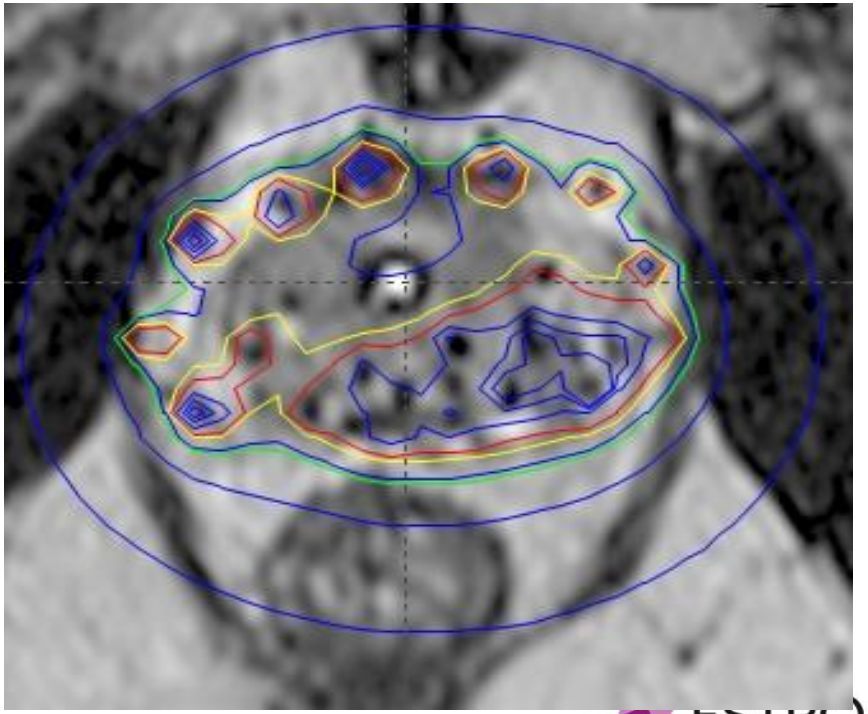




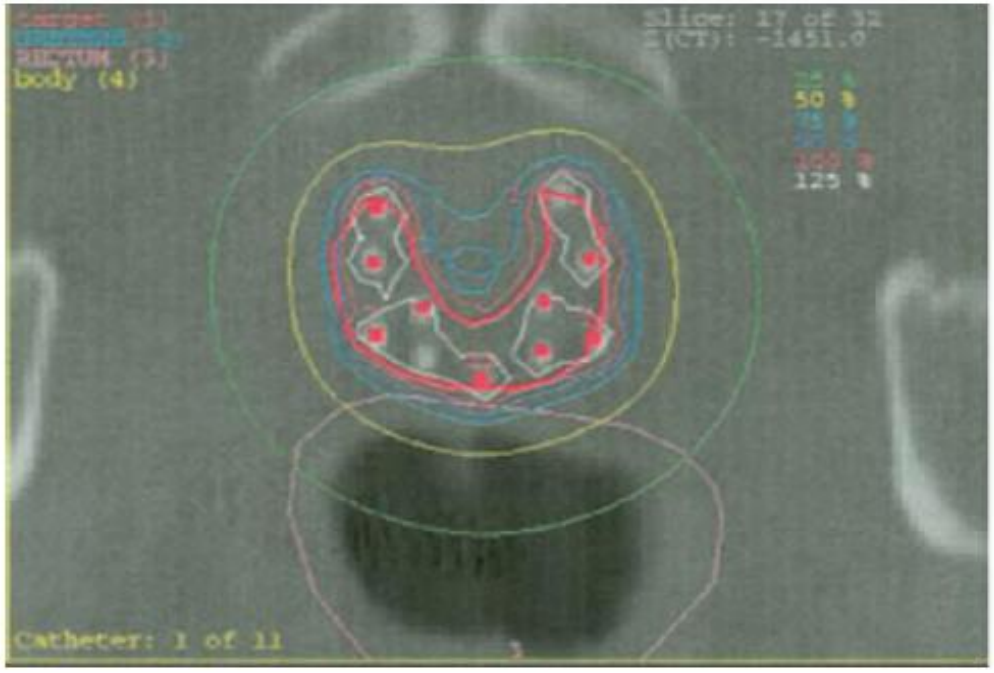


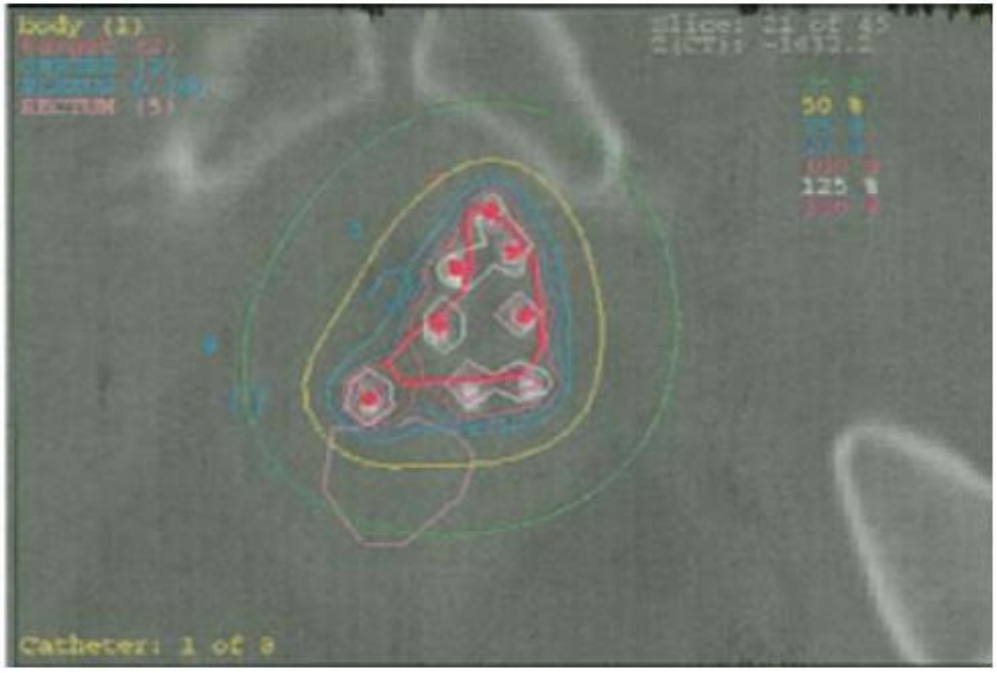
High-Dose-Rate Brachytherapy Boost to the Dominant Intra-ProstaticTumor Region: Hemi-Irradiation of Prostate Cancer

Ulrike Schick,[1] Youri Popowski,[1] Philippe Nouet,[1] Sabine Bieri,[2] Michel Rouzaud,[1] Haleem Khan,[3] Damien Charles Weber,[1] and Raymond Miralbell[1]*

77 high risk patients: 20 with unliateral tumours on biopsy mapping and MR

64Gy in 32 fractions + 12/14/18Gy in 2 fractions; whole gland or hemigland





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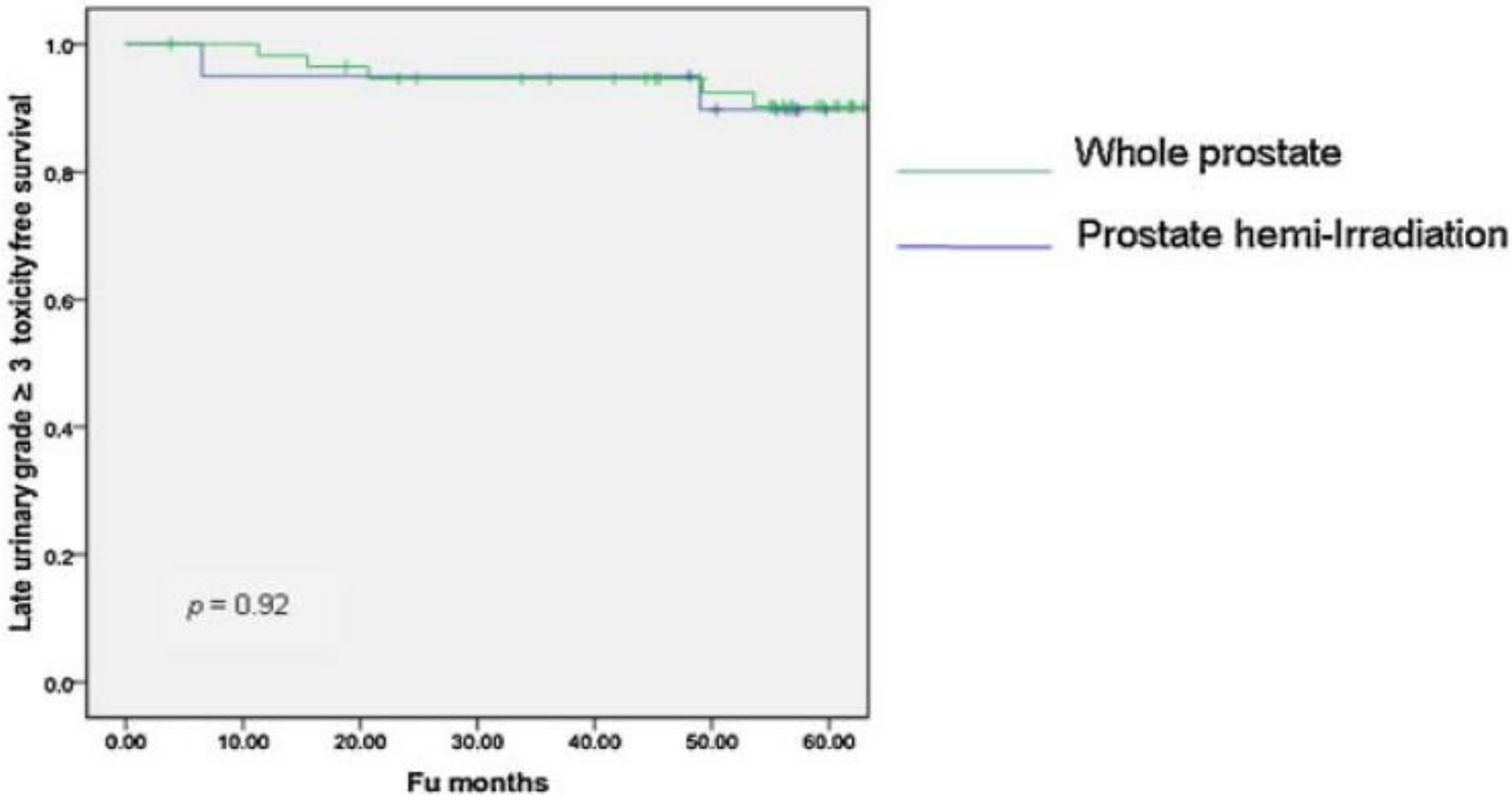
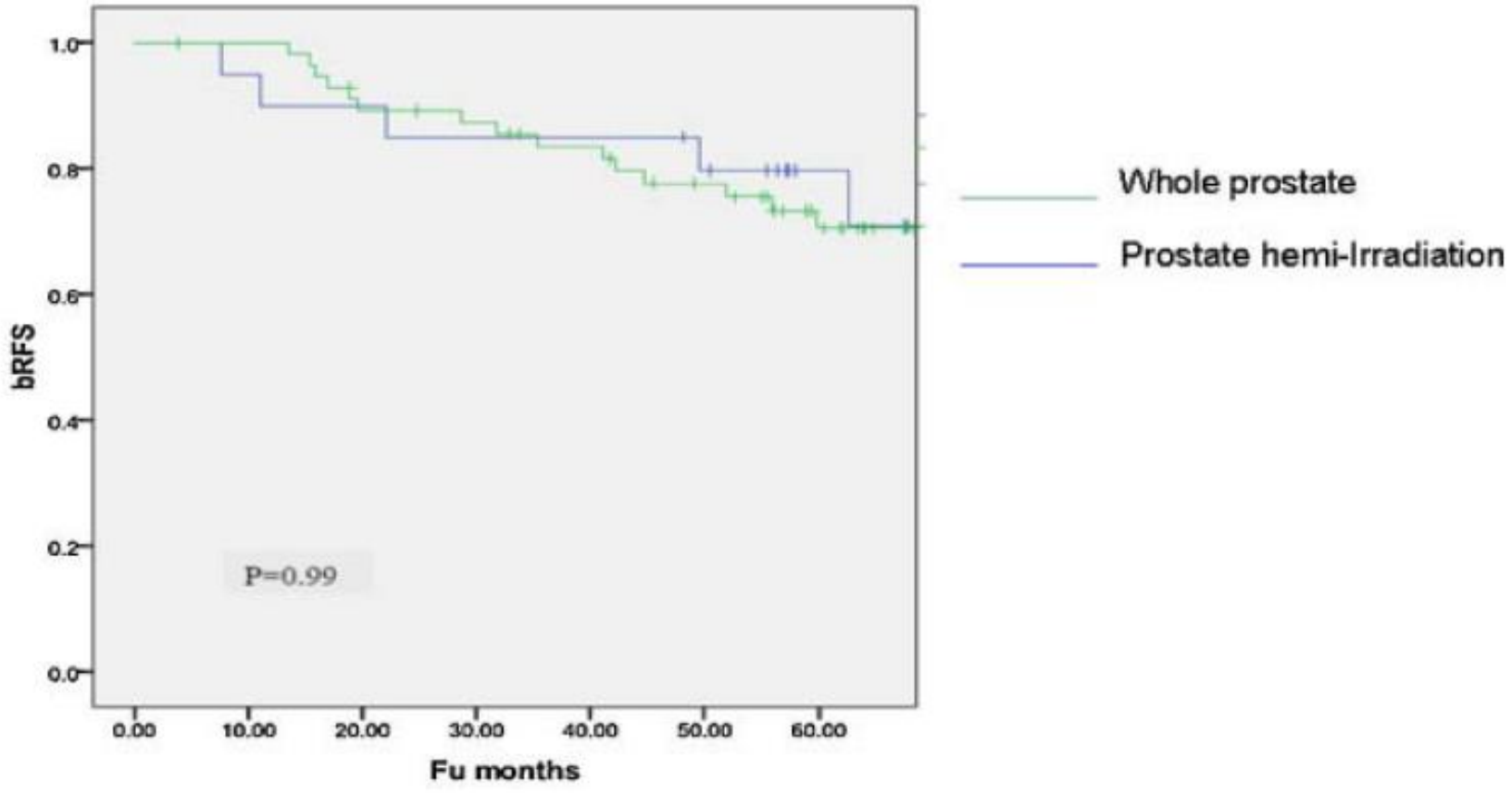


High-Dose-Rate Brachytherapy Boost to the Dominant Intra-ProstaticTumor Region: Hemi-Irradiation of Prostate Cancer

Ulrike Schick,[1] Youri Popowski,[1] Philippe Nouet,[1] Sabine Bieri,[2] Michel Rouzaud,[1] Haleem Khan,[3] Damien Charles Weber,[1] and Raymond Miralbell[1]*



Dose escalation to dominant intraprostatic lesions with MRI-transrectal ultrasound fusion High-Dose-Rate prostate brachytherapy. Prospective phase II trial

Radiotherapy and Oncology 119 (2016) 91–96

Alfonso Gomez-Iturriaga [a,*], Francisco Casquero [a], Arantza Urresola [b], Ana Ezquerro [b], Jose I. Lopez [c], Jose M. Espinosa [d], Pablo Minguez [d], Roberto Llarena [e], Ana Irasarri [f], Pedro Bilbao [a], Juanita Crook [g]

[a] *Hospital Universitario Cruces/Biocruces Health Research Institute, Radiation Oncology;* [b] *Hospital Universitario Cruces, Radiology;* [c] *Hospital Universitario Cruces/Biocruces Health Research Institute;* [d] *Hospital Universitario Cruces, Physics;* [e] *Hospital Universitario Cruces, Urology;* [f] *Hospital Universitario Cruces/Biocruces Health Research Institute, Clinical Epidemiology Unit, Barakaldo, Spain; and* [g] *Cancer Center for the Southern Interior, Radiation Oncology, British Columbia Cancer Agency, Kelowna, Canada*

15 patients: 37.5Gy in 15f + HDR 15Gy
BOOST to DIL volume to 18.75Gy (median volume 1.4ml)

Dosimetric parameters.

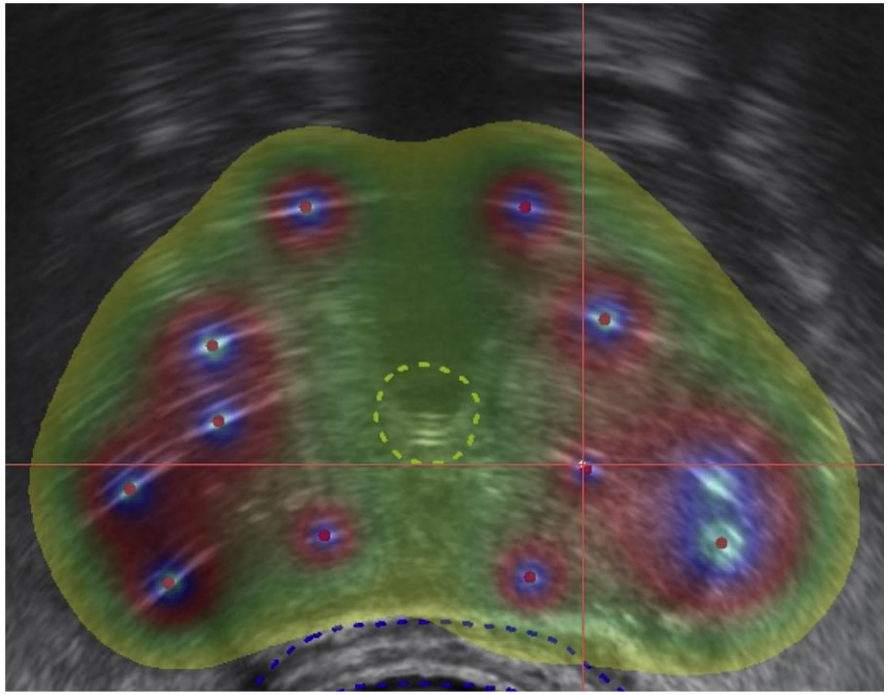
	D90 (%) Median (range)	V100 (%) Median (range)	V150 (%) Median (range)	V200 (%) Median (range)
CTV (prostate)	110.7 (107.9–113.6)	98.1 (97.8–99.1)	30.4 (20.9–34.5)	7.3 (5–8.7)
DIL	142.7 (131.4–151.7)	100 (100)	78.8 (48.3–90.6)	23.5 (10.9–60.3)
	Dmax (%)	D10 (%)		
Urethra	113.9 (111.4–115)	109.5 (108.4–113.2)		
	D1 cc (%)	D2 cc (%)		
Rectum	63.2 (49.9–69.6)	55.7 (44.2–61.2)		

ESTRO School

Results of multiparametric transrectal ultrasound–based focal high-dose-rate dose escalation combined with supplementary external beam irradiation in intermediate- and high-risk localized prostate cancer patients

Brachytherapy 16 (2017) 277–281

György Kovács[1,*], Klaudia Müller[1], Tamer Soror[1,2], Corinna Melchert[1], Xiyuan Guo[3], Dieter Jocham[3], Axel Merseburger[3]



Mean D_{90} (Gy)	6.58 (2.8–9.49; ±1.31)
Mean V_{100} (%)	30.31 (2.03–62.96; ±9.81)
Mean V_{150} (%)	10.03 (1.11–25.88; ±4.72)
Mean V_{200} (%)	3.1 (0.13–12.38; ±2.18)

N=130
70% low risk
50Gy + 2x15Gy peripheral HDR
Targetted focal boost to 60Gy

2 relapses

GU tox: G2: 11/130 G3: 2/130
GI tox: G2: 2/130

ESTRO School

Morbidity of Focal Therapy in the Treatment of Localized Prostate Cancer

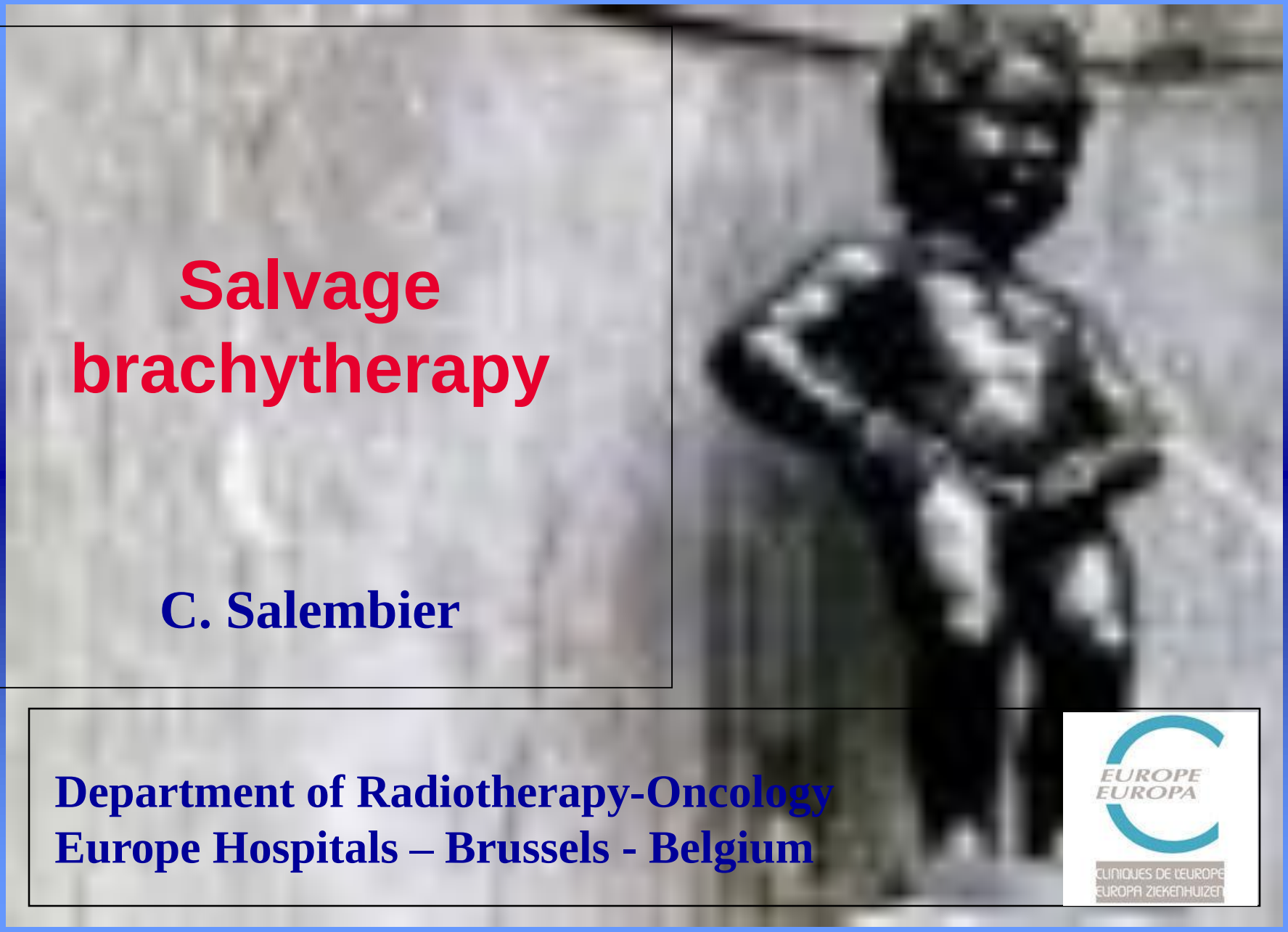
Eric Barret[a,*], *Youness Ahallal*[a], *Rafael Sanchez-Salas*[a], *Marc Galiano*[a], *Jean-Marc Cosset*[a], *Pierre Validire*[b], *Petr Macek*[a], *Matthieu Durand*[a], *Dominique Prapotnich*[a], *François Rozet*[a], *Xavier Cathelineau*[a]

EUROPEAN UROLOGY 63 (2013) 618–622

Energy modality	PSA, ng/ml, median (IQR)				IPSS, median (IQR)		IIEF-5, median (IQR)	
	Baseline	3 mo	6 mo	12 mo	Baseline	12 mo	Baseline	12 mo
Cryotherapy	6.2 (5.0–7.9)	2.9 (2.0–5.0)	2.8 (1.2–4.6)	2.5 (0.9–4.4)	9 (3–10)	5 (1–11)	19 (9–25)	14 (8–25)
Brachytherapy	6.2 (5.4–7.5)	3.3 (2.5–5.7)	3.2 (2.0–5.1)	2.8 (1.2–4.7)	3 (1–7)	7 (2–12)	21 (10–25)	14 (8–24)
VTP	5.7 (4.8–6.7)	3.0 (2.2–4.9)	2.8 (1.1–4.4)	3.2 (2.1–4.7)	6 (2–9)	6 (3–10)	23 (17–25)	13 (7–25)
HIFU	6.0 (5.1–8.1)	2.7 (1.8–4.7)	3.1 (2.1–5.3)	3.1 (2.4–4.3)	3 (1–7)	6 (2–11)	20 (15–25)	14 (8–25)

Cryotherapy: 50
Brachytherapy:12
Vascular Targeted Photodynamic therapy: 23
High Intensity Focussed Ultrasound: 21

Salvage brachytherapy



C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

For patients with locally or locally advanced prostate cancer, external beam radiation therapy is a commonly used primary treatment modality

Although conventional-dose EBRT may result in good clinical disease control, post-EBRT PSA determinations might suggest that locally persistent tumour may exist in a certain proportion of patients

Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: A review

Filippo Alongi [a], Berardino De Bari [b,*], Franco Campostrini [c], Stefano Arcangeli [d], Deliu Victor Matei [e], Egesta Lopci [f], Giuseppe Petralia [g], Massimo Bellomi [g], Arturo Chiti [f], Stefano Maria Magrini [b], Marta Scorsetti [a], Roberto Orecchia [h], Barbara Alicja Jereczek-Fossa [h]

The rate of intraprostatic relapses after primary EBRT is still not negligible:

- 20-40% (20-25.000 failure/year)
- 60% - 72% of patients with negative metastatic workup and rising PSA after RT will have positive prostatic biopsies

Zelefsky et al. Int. J. Radiat. Biol. Phys. 1998
Zagars et al. Int. J. Radiat. Biol. Phys. 1995
Pollack et al. Int. J. Radiat. Biol. Phys. 2002
Crook et al. Cancer. 1997
Alongi et al. CROH. 2013

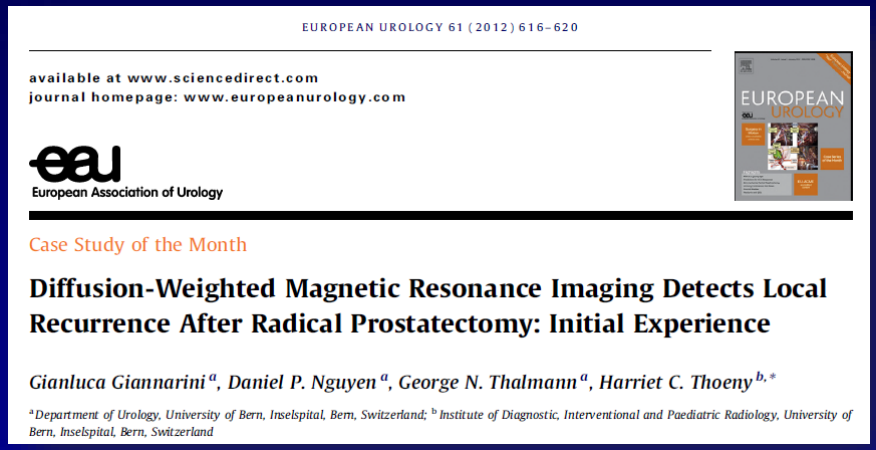
The prognosis of local relapses is POOR …

- . Fuks Z, Leibel SA, Wallner KE et al. **The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation.** Int J Radiat Oncol Biol Phys 1991; 21: 537-547.
- . Kuban DA, el-Mahdi AM, Schellhammer PF. **Effect of local tumor control on distant metastasis and survival in prostatic adenocarcinoma.** Urology 1987; 30: 420-426.

LOCAL RELAPSES

MORPHOLOGIC AND METABOLIC **IMAGING?**

2013



EUROPEAN UROLOGY 61 (2012) 616–620

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Case Study of the Month

Diffusion-Weighted Magnetic Resonance Imaging Detects Local Recurrence After Radical Prostatectomy: Initial Experience

Gianluca Giannarini [a], Daniel P. Nguyen [a], George N. Thalmann [a], Harriet C. Thoeny [b,]*

[a] Department of Urology, University of Bern, Inselspital, Bern, Switzerland; [b] Institute of Diagnostic, Interventional and Paediatric Radiology, University of Bern, Inselspital, Bern, Switzerland

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Critical Reviews in Oncology/Hematology 91 (2014) 234–247

CRITICAL REVIEWS IN *Oncology Hematology* Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

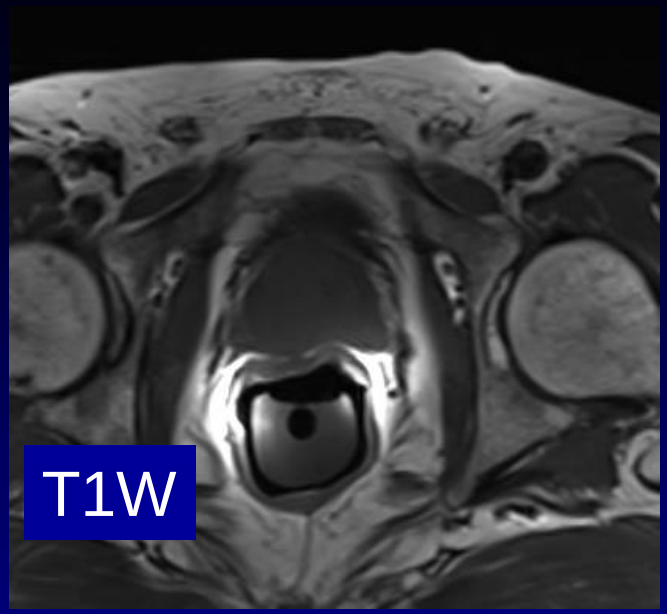
Choline-PET in prostate cancer management: The point of view of the radiation oncologist

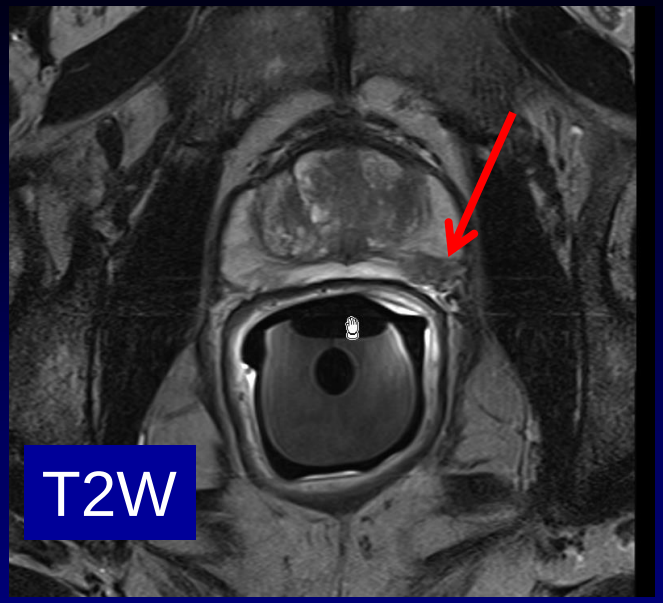
Berardino De Bari [a,*], Filippo Alongi [b], Laëtitia Lestrade [c], Francesco Giammarile [d]

➢**MRI** is often used for primary tumor and extra-capsular extent. However, contrast between recurrent carcinoma and benign tissue is not always evident after radiotherapy.

➢**PET** (Choline, PSMA..).could be of interest for target definition in salvage EBRT, but it should still be considered as an experimental procedure.

Giannarini et al, European Urology 2012





The first sequence to be used for a correct identification of the anatomy of the prostate is the T2W

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CrossMark

UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 34 (2016) 303–310

Seminar article

Magnetic resonance imaging for localization of prostate cancer in the setting of biochemical recurrence

Valeria Panebianco, M.D.[a,*], Flavio Barchetti, M.D.[a], Marcello Domenico Grompone, M.D.[a], Anna Colarieti, M.D.[a], Vincenzo Salvo, M.D.[a], Gianpiero Cardone, M.D.[b], Carlo Catalano, M.D.[a]

[a] *Departement of Radiological Sciences, Oncology and Pathology, Sapienza University of Rome, Rome, Italy*
[b] *Radiology Department, IRCCS San Raffaele Turro, Milan, Italy*

Abstract

The clinical suspicion of local recurrence of prostate cancer after radical treatment is based on the onset of biochemical failure. The use of multiparametric magnetic resonance imaging (MRI) for prostate cancer has increased over recent years, mainly for detection, staging, and active surveillance. However, suspicion of recurrence in the set of biochemical failure is becoming a significant reason for clinicians to request multiparametric MRI. Radiologists should be able to recognize the normal posttreatment MRI findings. Fibrosis and atrophic remnant seminal vesicles (SV) after radical prostatectomy are often found and must be differentiated from local relapse. Moreover, brachytherapy, external beam radiotherapy, and focal therapies tend to diffusely decrease the signal intensity of the peripheral zone on T2-weighted images due to the loss of water content, consequently mimicking tumor and hemorrhage. The combination of T2-weighted images and functional studies like diffusion-weighted imaging and dynamic contrast-enhanced imaging improves the identification of local relapse. Tumor recurrence tends to restrict on diffusion images and avidly enhances after contrast administration. The authors provide a review of the normal findings and the signs of local tumor relapse after radical prostatectomy, external beam radiotherapy, brachytherapy and focal therapies.

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UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 34 (2016) 303–310

Seminar article

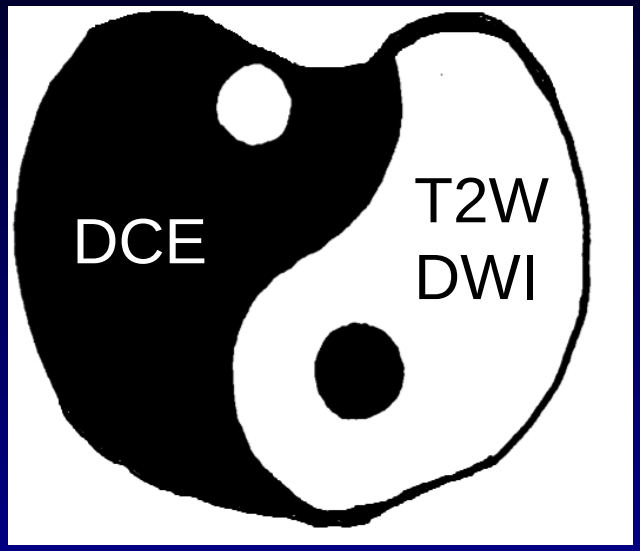
Magnetic resonance imaging for localization of prostate cancer in the setting of biochemical recurrence

Valeria Panebianco, M.D.[a,*], Flavio Barchetti, M.D.[a], Marcello Domenico Grompone, M.D.[a], Anna Colarieti, M.D.[a], Vincenzo Salvo, M.D.[a], Gianpiero Cardone, M.D.[b], Carlo Catalano, M.D.[a]

[a] *Departement of Radiological Sciences, Oncology and Pathology, Sapienza University of Rome, Rome, Italy*
[b] *Radiology Department, IRCCS San Raffaele Turro, Milan, Italy*

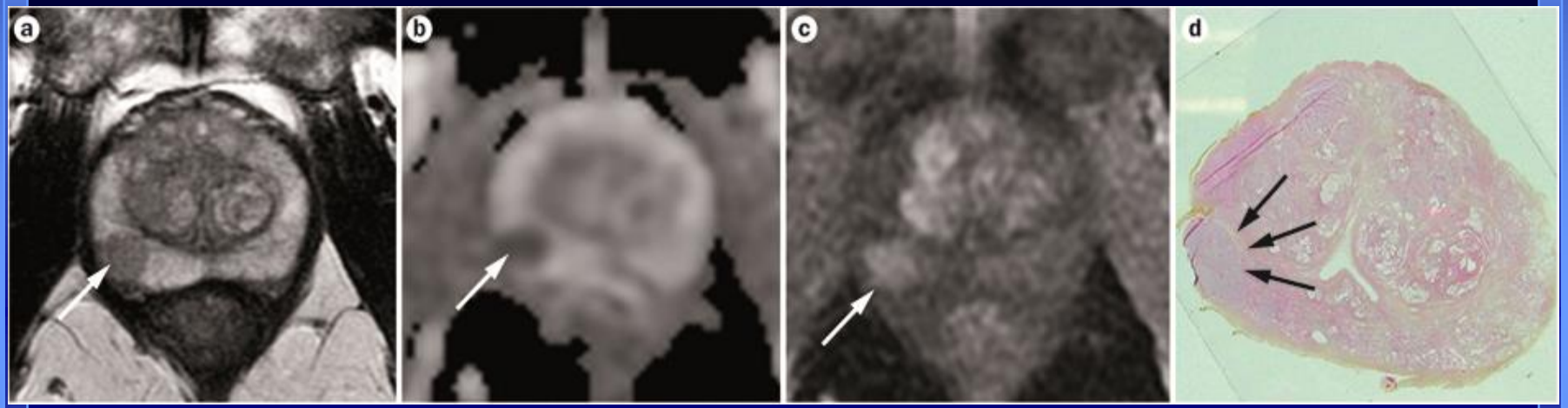
mp-MRI findings after prostate cancer primary treatment.

	T2WI	DWI	DCEI
Recurrent PCa after prostatectomy	Slightly high signal intensity	Restricted diffusion	Rapid wash in and wash out
Recurrent PCa after radiotherapy	Low signal intensity	Restricted diffusion	Rapid wash in and wash out
Recurrent PCa after focal therapies	Low signal intensity	Restricted diffusion	Rapid wash in and wash out
Fibrotic tissue	Low signal intensity	No restricted diffusion	Slightly delayed enhancement
Granulation tissue	High signal intensity	No restricted diffusion	Mild or no enhancement
Retained seminal vesicles	High signal intensity	No restricted diffusion	Delayed wash in and wash out
Residual glandular healthy tissue after prostatectmy	High signal intensity	No restricted diffusion	Mild or no enhancement



We look for something DARKER in T2W and in DWI….

….and for something BRIGHTER in late DCE!



We look for something DARKER in T2W and in DWI….

….and for something BRIGHTER in late DCE!

Rouvière, O. *et al*. (2012) *Nat. Rev. Clin. Oncol* 2012.136

Volumetry of the dominant intraprostatic tumour lesion: intersequence and interobserver differences on multiparametric MRI

[1]HUGH HARVEY, FRCR, [1]MATTHEW R ORTON, PhD, [1]VERONICA A MORGAN, MSc, [2]CHRIS PARKER, FRCR, [2]DAVID DEARNALEY, FRCR, [3]CYRIL FISHER and [1]NANDITA M DESOUZA, FRCR

[1]Cancer Research UK Imaging Centre, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, London, UK
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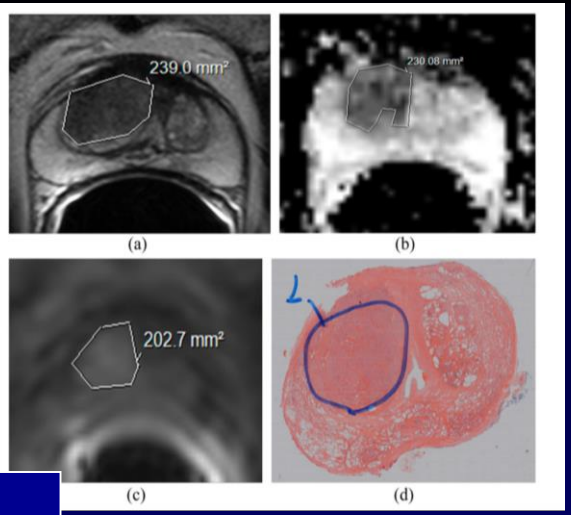


mpMRI-derived GTV measurements of DIPLs derived from T2W, DW-MRI and DCE sequences are reproducible

- GTV is largest on T2W images

- GTV is smallest on DCE-MRI images

- T2W GTVs best approximate to in vivo tumour volume.

Therefore, GTV should be delineated on T2W images when defining the DIPL

Harvey H, Orton MR, Morgan VA, Parker C, Dearnaley D, Fisher C, et al. Volumetry of the dominant intraprostatic tumour lesion: intersequence and interobserver differences on multiparametric MRI. *Br J Radiol* 2017; **90**: 20160416.

Prostate MR Imaging for Posttreatment Evaluation and Recurrence

Sonia Gaur, BS, Baris Turkbey, MD*

Radiol Clin N Am 56 (2018) 263–275

mpMR imaging after EBRT

- EBRT causes overall changes in signal intensity and structure of the prostate

- The irradiated prostate appears smaller as a result of gland atrophy and differentiation of the zones is made difficult by effacement of the prostatic tissue

- The entire prostate appears more hypointense on T2w imaging inducing difficulties in the:
  - differentiation between central and peripheral zone
  - distinction between benign and tumour tissues

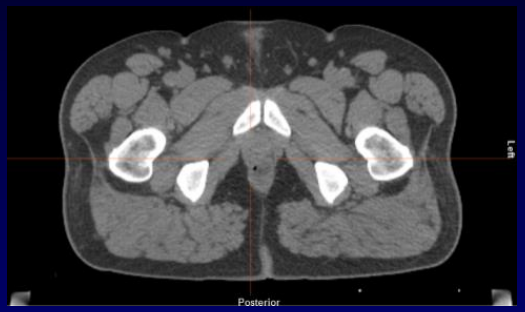
- Sensitivity for T2w alone is varies between 36% and 75% and specificity ranged fro m65% to 81% (Sala et al.)

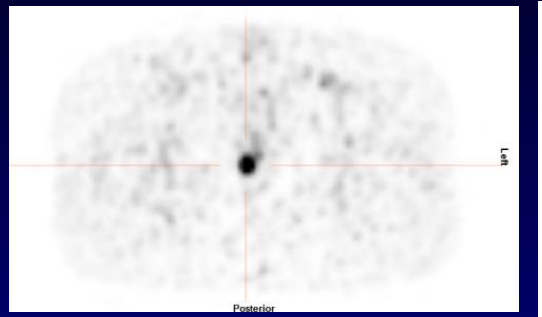
So: limited value of T2w in this setting.

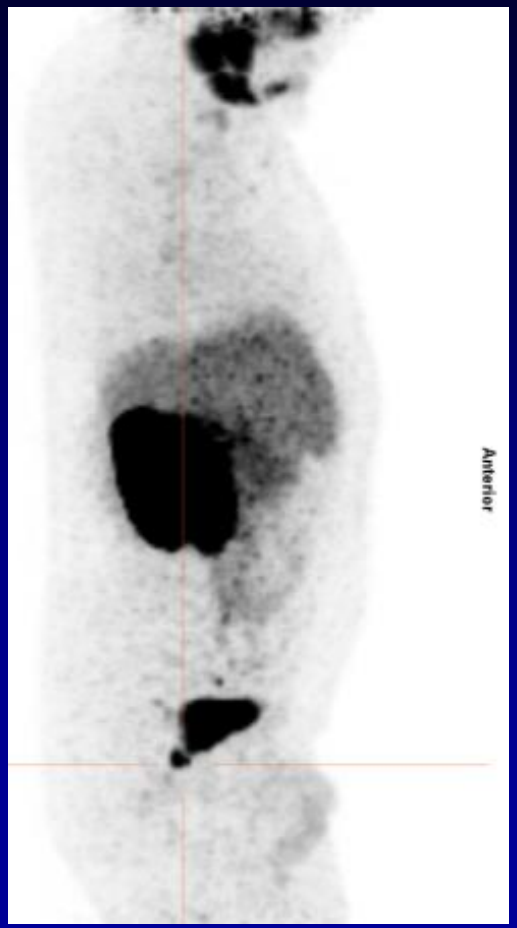
mpMR imaging after EBRT

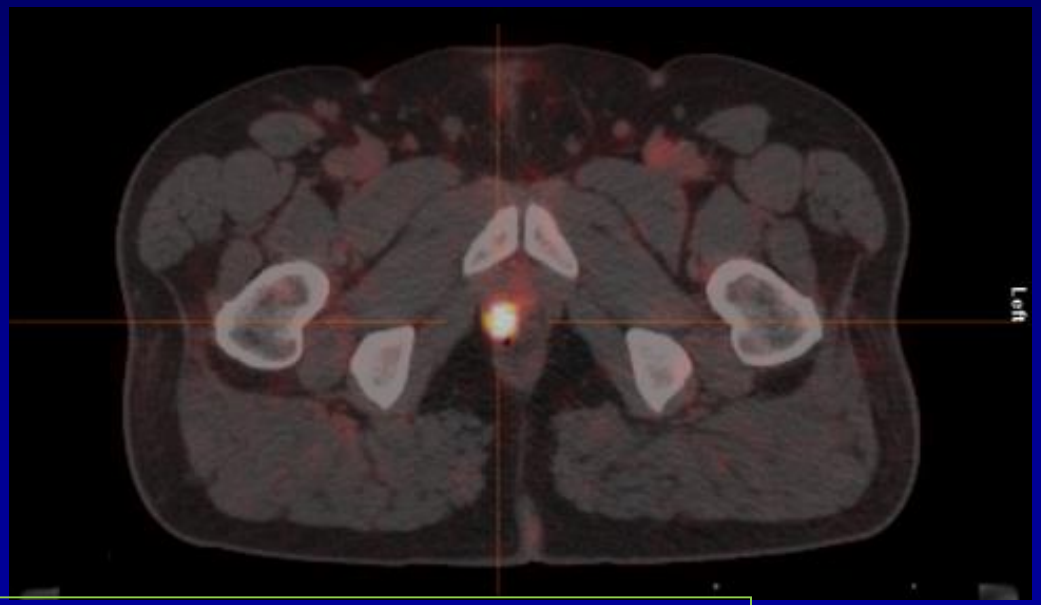
- Dominant role of the functional sequences of mpMRI
  - on DWI: signal characteristics are similar to normal setting with a focal hypointensity on the ADC map and hyperintensity on high-b value imaging
  - on DCE: although the vascularity of the overall irradiated prostate decreases with gland atrophy, the recurrences :
    - retain their highly vascular network
    - Show the early hyper-enhancement on DCE relative to the treated prostate.

CHOLINE - PSMA sensitivity









Afshar-Oromieh A. Eur J Nucl Med Mol Imaging. 2014

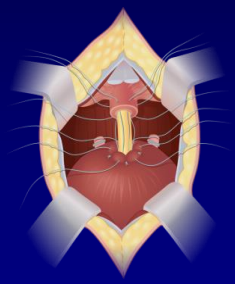
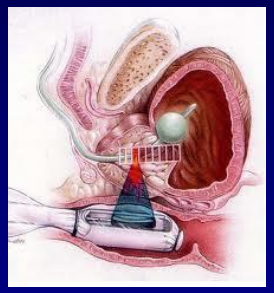
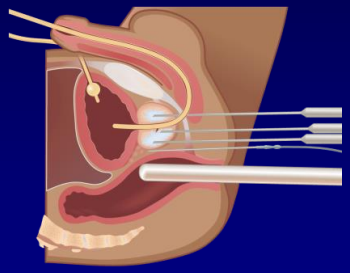
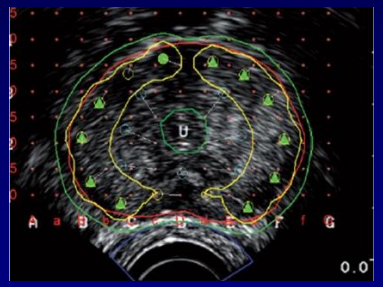
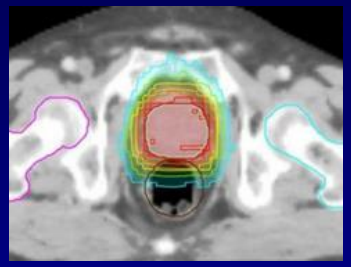
At present, many patients with locally recurrent prostate cancer after EBRT are often managed with palliative intent, such as watchful waiting or androgen suppression

What about local treatment for isolated local relapses?

Lacking of high level evidence supporting salvage therapies after EBRT.

Potential treatment options after intraprostatic failure alone are:

2013

Surgery HIFU Cryotherapy Brachytherapy EBRT

INTRAPROSTATIC FAILURE:

SURGERY AS AN OPTION

When curative therapy is considered, radical prostatectomy might be performed

However, EBRT induced fibrosis tends to obliterate the usual tissue planes for surgical resection. This increases the degree of technical difficulties as well as the morbidity of the procedure, resulting in a general reluctance amongst surgeons to perform salvage surgery.

Underutilization of Salvage Surgery after primary RT

Less than 800 of salvage RP in the literature

Metastasis After Radical Prostatectomy or External Beam Radiotherapy for Patients With Clinically Localized Prostate Cancer: A Comparison of Clinical Cohorts Adjusted for Case Mix

Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Zvi Fuks, Zhigang Zhang, Yoshiya Yamada, Andrew Vickers, and Peter T. Scardino

	Tx failure	Salvage therapy	Salvage RP	Salvage EBRT	Median time to secondary Tx (months)
EBRT	207	92 (44%)	4 (2%)	-	69
RP	141	107 (76%)	-	59 (42%)	13

Zelefsky, JCO, 2011

INTRAPROSTATIC FAILURE:

EBRT AS AN OPTION

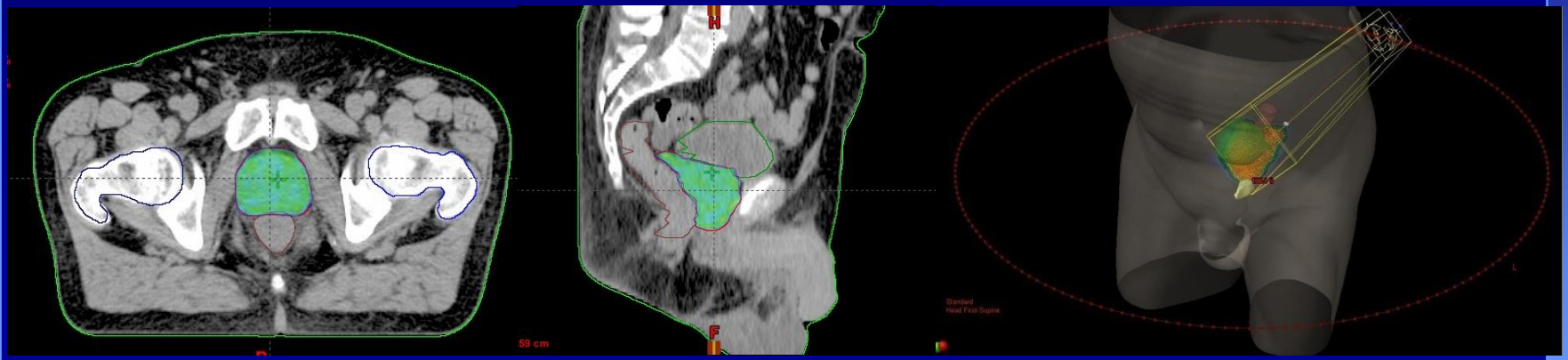
✓**EBRT** is the only NON INVASIVE approach for intra-prostatic relapse .

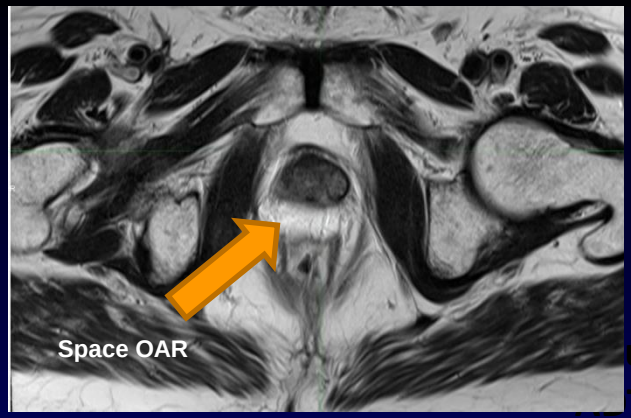
✓However, EBRT has been documented in a very limited group of patients.

SBRT in prostate re-irradiation:

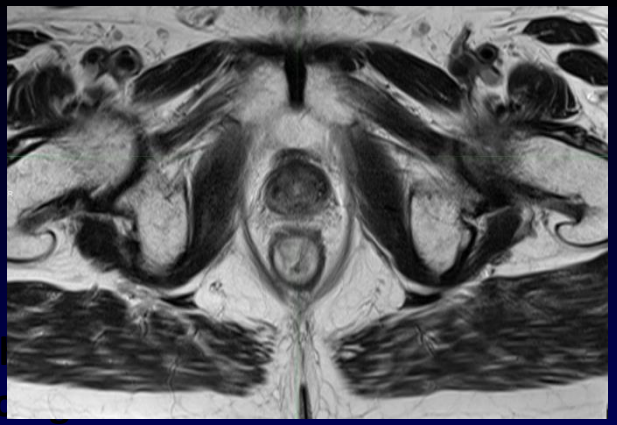
✓it allows the *reduction of the safety margins* around the target (thus minimizing the exposure of the previously irradiated surrounding normal tissues)

✓It can be delivered by *hypofractionation* that could be of particular value for PC considering its low alpha/beta ratio

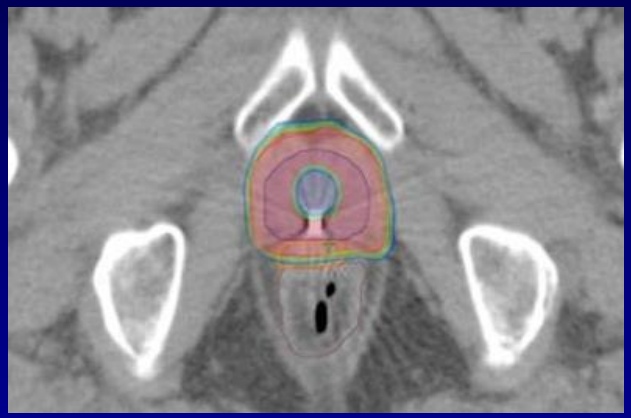




Pre treatment MRI



Post treatment MRI



Re-SBRT : 30Gy in 5 fractions
With VMAT FFF

Courtesy of Alongi F et al. Minerva Urologica 2016

Salvage EBRT or SBRT

Laws of Small Numbers: Extremes and Rare Events

Author	Nr. pts	Technique	Schedule	Results
Arcangeli (2015)	1	SBRT	30 Gy/5 fr	NED at 6 m
Kalapurakal (2001)	3	EBRT + hyperthermia	30-50 Gy /2 Gy/fr)	3/3 NED at 1 y
Vavassori/ Jereczek-Fossa (2010 e 2012)	15/4 prostate bed	CyberKnife	30 Gy/5 fr	30 m PFS: 23%
Zerini/Jereczek-Fossa (BJR 2015)	22 prostate/ 10 prostate bed	IMRT, SBRT	25-30 Gy/5 fr	**24 m BRFS: 50%**
Janoray (2016)	11 prostate/10 prostate bed	Cyberknife	36.25 Gy/5 fr	**83% at 1 y NED**

INTRAPROSTATIC FAILURE:

HIFU …. CRYOTHERAPY ….

Table 1 – Complications of salvage local procedures for radio-recurrent prostate cancer after ≥24 months of follow up.

Type of treatment	Total no. of pts	Median FU	Late toxicities					
		Months (range)	Incontinence		Stricture		Recto-urethral fistula	
			%	Range %	%	Range %	%	Range %
Surgery[26–38]	762	49 (24–120)	41	(0–79)	19.3	(0–40)	NR	
Brachytherapy[45–52]	236	66 (30–86)	10.4	(0–31)	NR		7	(2–12)
Cryotherapy[39–44]	1126	61.5 (22–120)	8.5	(4.4–13)	NR		1.8	(1–3.4)
HIFU[53–56]	211	39 (24–50)	33.7	(18–49.5)	NR		3	(1–5)

HIFU: high intensity focused ultrasound; NR: not reported; FU: follow up.

Arcangeli et et al, RPROR 2015

INTRAPROSTATIC FAILURE:

BRACHYTHERAPY AS AN OPTION

Prostate brachytherapy is increasingly common modality for the primary treatment in prostate cancer

Compared with EBRT, it is possible to administer a high radiation dose to a tightly confined volume

Thus, it may be possible to use this modality to provide a second opportunity for tumour control in the patient with locally recurrent prostate cancer after EBRT

INTRAPROSTATIC FAILURE:

QUESTIONS DURING THE PATIENT SELECTION FOR SALVAGE APPROACH

1. Is the cancer potentially curable?

- Initial cancer (before radiation) curable: T1-3a N0 M0
- Current cancer T1-3a, PSA < 10 - 15, no evidence of metastases, positive re-biopsy

2. Is the patient appropriate?

Good health, life expectancy >10 years

Highly motivated, willing to accept risks of salvage therapy

3. Would the treatment be safe?

No evidence of severe radiation cystitis or proctitis

Radiotherapy and Oncology 118 (2016) 122–130

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Prostate cancer

A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study

Emmie Kaljouw [a,*], Bradley R. Pieters [a], György Kovács [b], Peter J. Hoskin [c]

[a] Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands; [b] Interdisciplinary Brachytherapy Unit, University of Lübeck, Germany; and [c] Mount Vernon Cancer Centre, UK

A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study

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B. Diagnostic investigation before salvage prostate brachytherapy		
Image modality guiding biopsies	Ultrasound and MRI	Majority agreement
Number of biopsies at time of recurrence for whole gland treatment	12–24	Consensus
Number of biopsies at time of recurrence for partial gland treatment	<12 to >24	Divided opinion
Information from ultrasound	Prostate volume, capsule invasion, periprostatic extension and invasion in the seminal vesicles	Consensus
Evaluation metastatic disease	Choline PET or MRI	Majority agreement
Evaluation local disease	Ultrasound and MR pelvis	Majority agreement

A. Patient characteristics of patient eligible for salvage prostate brachytherapy		
Age	<80 years	Majority agreement
Life expectancy	>5 years	Majority agreement
Maximum ECOG/WHO performance score	1, symptomatic but completely ambulatory	Consensus
Previous ADT	No contraindication	Consensus
T-classification	⩽T3b	Consensus
Gleason score at primary treatment	<8	Consensus
Gleason score at relapse	Not a criterion	Consensus
PSA level at relapse	Maximum level	Divided opinion
PSA DT	>6 months	Majority agreement
Prostate site	Any part of the prostate can be re-irradiated	Consensus
Prostate volume	No maximal prostate volume	Majority agreement
Tumor lesion diameter	No maximum	Consensus
IPSS	8–15	Consensus
Qmax and PVRV	Should be known	Consensus
Qmax and PVRV level	Maximum or minimum values	Divided opinion

A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study

Emmie Kaljouw [a,*], Bradley R. Pieters [a], György Kovács [b], Peter J. Hoskin [c]

[a] Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands; [b] Interdisciplinary Brachytherapy Unit, University of Lübeck, Germany; and [c] Mount Vernon Cancer Centre, UK

C. Salvage brachytherapy treatment		
Minimum time interval between primary and salvage treatment	2 years	Majority agreement
Treatment modality	HDR	Consensus Majority agreement
	LDR	
Treatment volume	Whole gland, hemi gland or focal	Divided opinion
Planned dose	EQD2 (1.5 Gy): 70–150 Gy	Divided opinion
Dose constraints to OAR	Standard or adjusted	Divided opinion
Hormonal therapy	Should not be given	Consensus
Follow up examination	PSA test, record of urinary and bowel side effects and record of potency	Consensus

Consensus is defined as a ⩾80% agreement between participants.
Majority agreement is defined as a 65–80% agreement between participants.
Divided opinion is defined as a <65% agreement between participants.

Outcome rates of salvage BRT series

Low Dose Rate

Table 1: Outcome rates of salvage BRT series

Author	*No patients*	*Adjuvant ADT %*	*Median follow-up*	*BRFS (time point) %*	*Definition of failure*	*Whole gland or focal*	*Dose BRT*
Wallner *et al.*[6]	13	NR	36 months	51 (5 years)	Metastasis-free	Whole gland	^{125}I: 170 Gy
Grado *et al.*[2]	49	NR	64 months	34 (5 years)	Two rises above nadir	Whole gland	^{125}I: 160 Gy ^{103}Pd: 170 Gy
Beyer[7]	17	47	62 months	53 (5 years)	ASTRO criteria	Whole gland	^{125}I: 120 Gy ^{103}Pd: 90 Gy
Wong *et al.*[8]	17	71	44 months	75 (4 years)	ASTRO criteria	Whole gland	^{125}I: 120–126 Gy ^{103}Pd: 103–112 Gy
Nguyen *et al.*[3]	25	0	47 months	70 (4 years)	Phoenix criteria	Whole gland	^{125}I: 137 Gy
Burri *et al.*[10]	37	84	86 months	54 (10 years)	Phoenix criteria	Whole gland	^{125}I: 128.8 Gy or ^{103}Pd
Aaronson *et al.*[11]	37	17	30 months	88 (3 years)	Phoenix criteria	Whole gland	^{125}I: 108–122 Gy
Moman *et al.*[12]	31	NR	108 months	20 (5 years)	Phoenix criteria	Whole gland	^{125}I: 145 Gy
Peters *et al.*[4]	20	40	36 months	60 (3 years)	Phoenix criteria	Focal	^{125}I: 144 Gy

BRFS: biochemical recurrence-free survival; NR: not reported; ADT: androgen-deprivation therapy; BRT: brachytherapy; HDR: high dose rate

Complications of salvage BRT series

Low Dose Rate

Table 2: Complications of salvage BRT series

	Urinary incontinence (%)	*GU toxicity (%)*		*GI toxicity (%)*		*ED (%)*
		Grades 1–2	*Grades 3–4*	*Grades 1–2*	*Grades 3–4*	
Wallner *et al.*[6]	31	36	NR	36	4	NR
Grado *et al.*[2]	6	12	14	4	2	2
Beyer[7]	24	24	NR	NR	0	NR
Wong *et al.*[8]	6	53	47	65	6	NR
Nguyen *et al.*[3]	0	NR	20	NR	20	NR
Burri *et al.*[10]	NR	43	11	NR	NR	85
Aaronson *et al.*[11]	2.7	2.7	0	5.4	2.7	NR
Moman *et al.*[12]	NR	87	3	55	0	NR
Peters *et al.*[4]	20	30	5	15	0	65

GU: genitourinary; GI: gastrointestinal; ED: erectile dysfunction; NR: not reported; BRT: brachytherapy

Strahlenther Onkol
DOI 10.1007/s00066-017-1157-2

REVIEW ARTICLE

High-dose-rate brachytherapy as salvage modality for locally recurrent prostate cancer after definitive radiotherapy

A systematic review

Georgios Chatzikonstantinou[1] · Nikolaos Zamboglou[1] · Claus Rödel[1] · Eleni Zoga[2] · Iosif Strouthos[3] · Saeed Ahmed Butt[4] · Nikolaos Tselis[1]

Table 1 Overview of patient characteristics in salvage HDR studies for locally recurrent prostate cancer

Study	*n*	Pretreatment (%)/ median dose	iT stage	iGS (%)	iPSA (%)	pADT (%)	pGS (%)	pPSA (%)
Lyszek et al., [6]	115	RP (9.5) EBRT (62)/52 Gy HDR (22.5)/30 Gy EBRT+HDR (6)	cT1 (6) cT2 (52) cT3 (33) cTx (7)	≤6 (44) 7 (18) ≥8 (12) GSx (16)	≤10 (35) 10.1–19.9 (24) ≥20 (29) PSAx (12)	N. R.	N. R.	N. R.
Jo et al., [7]	11	EBRT (9)/72 Gy EBRT+HDR (55)/36.8 + 24 Gy HDR (36)/37.5 Gy	cT1 (27) cT2 (27) cT3 (46)	≤6 (36) 7 (46) ≥8 (18)	≤10 (55) 10.1–19.9 (9) ≥20 (36)	No	≤6 (27) 7 (46) ≥8 (27)	≤10 (73) 10.1–19.9 (27)
Tharp et al., [8]	7	EBRT (43)/68.4 Gy LDR (43) EBRT+LDR (14)	N. R.	≤6 (86) GSx (14)	≤10 (43) 10.1–19.9 (43) PSAx (14)	7 (100)	≤6 (28) 7 (44) ≥8 (28)	≤10 (86) 10.1–19.9 (14)
Yamada et al., [9]	45	EBRT (100)/81 Gy	N. R.	N.R	N.R.	18 (43)	≤6 (7) 7 (60) ≥8 (33)	<4 (55) 4.0–10 (33) >10 (12)
Chen et al., [10]	52	EBRT (77) EBRT+LDR (4) LDR (15) EBRT+protons (4)	cT1c (33) cT2 (47) cT3 (20)	≤6 (54) 7 (33) ≥8 (13)	<4 (6) 4–10.0 (50) 10.1–20.0 (36) >20 (8)	24 (52)	≤6 (4) 7 (44) ≥8 (52)	<4 (38) 4–10.0 (52) 10.1–20.0 (8) >20 (2)
Kukieka et al., [11]	25	EBRT (100)/73.9 Gy	cT1 (36) cT2 (44) cT3 (20)	≤6 (60) 7 (28) ≥8 (4) GSx (8)	Median 16.3	9 (36)	≤6 (20) 7 (40) ≥8 (20) GSx (20)	Median 2.8
Wojcieszek et al., [12]	83	EBRT (62)/74 Gy EBRT+HDR (38)/54 + 10 Gy	cT1 (40) cT2 (53) cT3 (6) cTx (1)	≤6 (60) 7 (20) ≥8 (4) GSx (16)	<10 (29) 10.0–20 (39) >20 (25) PSAx (7)	44 (53)	≤6 (19) 7 (27) ≥8 (7) GSx (47)	Median peak 3.1
Henriquez et al., [16]	56	EBRT (82)/72 Gy LDR (18)	cT1c (41) cT2 (46) cT3 (13)	≤6 (66) 7 (29) ≥8 (5)	<10 (46) 10.0–20 (32) >20 (22)	9 (60)	≤6 (16) 7 (25) ≥8 (14) GSx (45)	<10 (91) 10.0–20 (7) >20 (2)

HDR high-dose-rate brachytherapy, *iT* initial T stage, *iGS* initial Gleason score, *iPSA* initial prostate-specific antigen, *pADT* presalvage androgen deprivation therapy, *pPSA* presalvage prostatic specific antigen, *pGS* presalvage Gleason score, *RP* radical prostatectomy, *EBRT* external beam radiotherapy, *cTx* clinical T stage unknown, *GSx* Gleason score unknown, *PSAx* prostate-specific antigen unknown, *LDR* low-dose-rate brachytherapy, *N.R.* not reported

Table 3 Oncological outcomes and late toxicity rates of salvage HDR protocols

Study	*n*	HDR protocol Gy/fraction	Fractions (implants)	Total dose (Gy)	Med. f/u (m)	BC	Toxicity
Lyszek et al., 2009 [6]	115	10.0	1 (3)	30.0	60	46% for GS ≤ 6, 18% for GS ≥ 6	1.7% urethral fistulas 1.7% urinary incontinence 3.4% bladder outlet obstruction
Jo et al., 2011 [7]	11	11.0	2 (1)	22.0	29	63%	no grade 3 GI/GU low grade 2 GU
Tharp et al., 2008 [8]	7	7.0 6.0 7.0 9.0	3 (1) 2 (2) 3 (2) 1 (2)	21.0 24.0 42.0 18.0	58	71.5%	28% grade 3 GU no ≥ grade 3 GI
Yamada et al., 2014 [9]	45	8.0	4 (1)	32.0	36	68.5% at 5 years	48% late grade 2 GU 8.8% late grade 3 GU 14% late grade 2 GI
Chen et al., 2013 [10]	52	6.0	3 (2)	36.0	59.6	51.0% at 5 years	54% late grade 2 GU 2% late grade 3 GU 4% late grade 2 GI 6% late grade 3 sexual dysfunction
Kukieka et al., 2014 [11]	25	10.0	1 (3)	30.0	13	74% at 2 years	9% late grade 2 nocturia 4.5% late grade 2 obstruction 4.5% late grade 2 frequency no grade 3 GU
Wojcieszek et al., 2016 [12]	83	10.0	1 (3)	30.0	41	76% at 3 years 67% at 5 years	39% late grade 2 GU 13% late grade 3 GU 6% late grade 1 GI
Hanna et al., 2015 [13]	28	Med. 6.0	Med. 6	Med. 36.0	83	DMFS 11% at 15 years	N. R.
Oliai et al., 2013 [14]	22	6.0	3 (2)	36	45	95.5% at 2 years	18% hematuria 32% urethral strictures
Pellizzon et al., 2009 [15]	17	8.5–9.0	4 (1)	34–36	47	70.5%	5.9% late grade 4 urethral strictures 5.9% late grade 3 GI
Henriquez et al., [16]	19	Med. 5.25	1–4 (1–3)	17–39	48	77% at 5 years	21% late grade 3 GU no late grade 4 GU 2% late grade 3 GI

HDR high-dose-rate brachytherapy, *f/u* follow-up, *m* months, *med* median, *BC* biochemical control, *GS* Gleason Score, *GU* genitourinary, *GI* gastrointestinal, *DMFS* distant metastases-free survival, *N.R.* not reported

Whole-gland salvage

1. Prostatectomy n=404
2. Cryotherapy n=328
3. HIFU n=162
4. (Brachytherapy) n≈50

5. Plus maybe more reviews than original studies

- ≈50% bDFS 3-5 years
- 20-30% late severe GU+GI toxicity
- Often universal ED

Chade DC Eur. Urol. 2011
Wenske S, Eur. Urol 2013
Murat FJ, Eur. Urol. 2009
And a whole list of small studies and reviews

Salvage HDR Brachytherapy: Multiple Hypothesis Testing Versus Machine Learning Analysis

Gilmer Valdes, PhD,* Albert J. Chang, MD, PhD,*
Yannet Interian, PhD,† Kenton Owen, MS,* Shane T. Jensen, PhD,‡
Lyle H. Ungar, PhD,§ Adam Cunha, PhD,* Timothy D. Solberg, PhD,*
and I-Chow Hsu, MD*

*Radiation Oncology Department, University of California San Francisco, San Francisco, California; †Data Analytic Program, University of San Francisco, San Francisco, California; ‡Department of Statistics, The Wharton School, and §Department of Computer and Information Science, University of Pennsylvania, Philadelphia, Pennsylvania

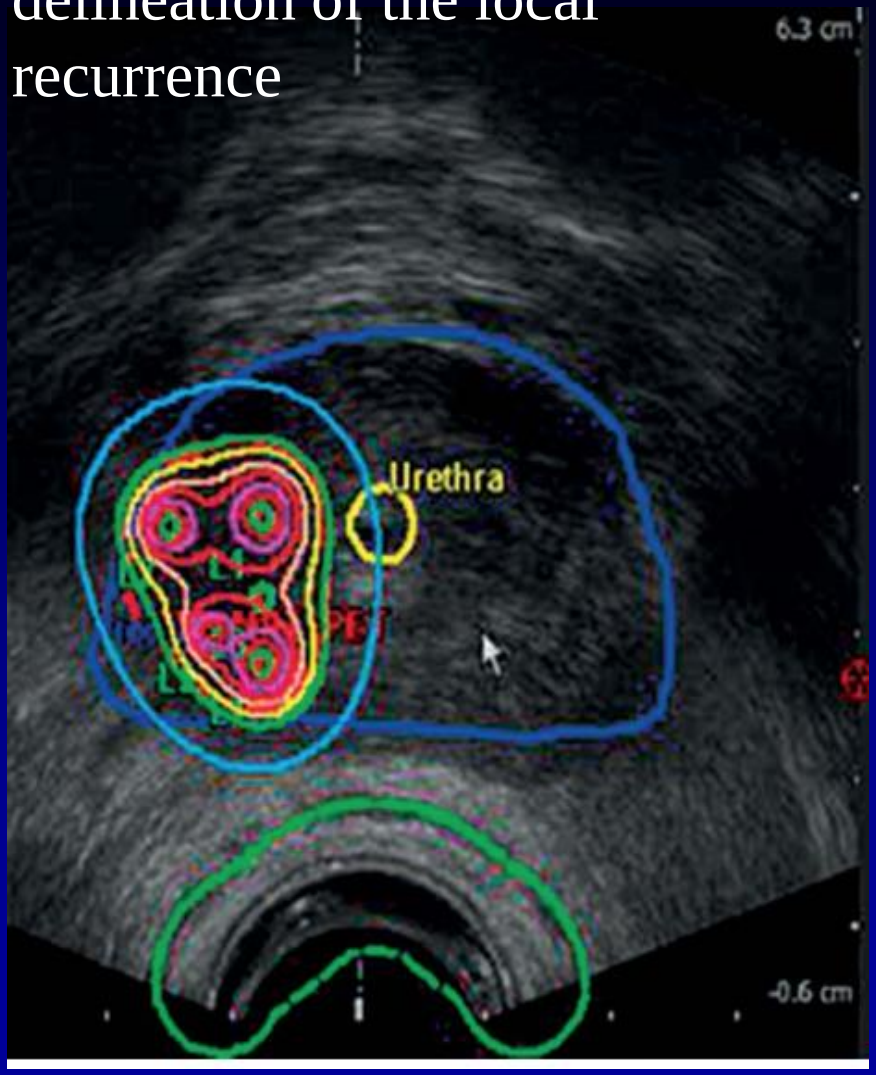
Received Jul 20, 2017, and in revised form Jan 7, 2018. Accepted for publication Mar 6, 2018.

- The most important features analyzed are percentage of positive cores after biopsy and disease-free interval after the first definitive treatment.
- Patients with HisPercentPositive $\geq$0.35 and a disease-free interval <4.1 years benefit the least from sHDRB (p[BF = yes] = 0.75).
- Patients with HisPercentPositive <0.354 or disease-free interval $\geq$4.1 years (p[BF = yes] = 0.38) benefit the most from sHDRB.
- There is a 70% probability that these findings are not due to chance.
- The accuracy is limited by the number of patients in the study and will be improved if additional data become available.
- It will take 20 years to collect data at 1 institution to statistically prove or disprove the hypothesis generated.

Focal salvage BRT

Focal salvage brachytherapy might reduce the frequency of adverse events while achieving acceptable cancer control.

Advances in imaging and delineation of the local recurrence



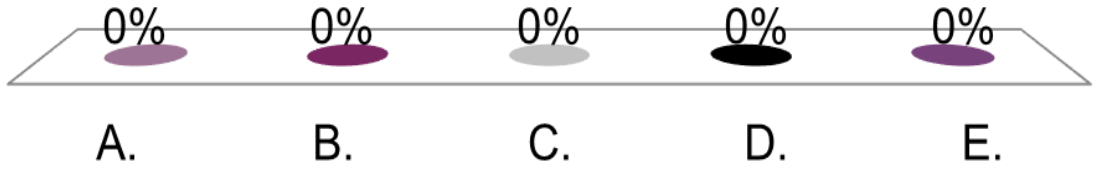

To be continued.
To be continued.
To be continued.

ESTRO School

WWW.ESTRO.ORG/SCHOOL

What is your preferred management for a patient aged 66 years presenting with a PSA of 13.6, Gleason score 4+3 prostate cancer which is stage T2B on MR staging? He has no significant co-morbidities

A. Radical prostatectomy
B. Active surveillance
C. External beam IMRT to 78Gy
D. LDR seed brachytherapy
E. External beam IMRT + HDR boost



Which is best?

- Surgery vs IMRT
- Surgery vs BT
- BT vs IMRT
- Surgery vs IMRT vs BT
- LDR BT vs HDR BT

Radical prostatectomy

ADVANTAGES

- Pathological diagnosis
- No bowel toxicity
- Relief of LUTS
- Established salvage with external beam RT
- No additional second malignancies

DISADVANTAGES

- Erectile dysfunction 50%+
- Urinary control
- Anaesthetic procedure

IMRT

ADVANTAGES

- Outpatient process
- No anaesthetic
- Low urinary toxicity
- Lymphatic treatment possible

DISADVANTAGES

- No pathological diagnosis
- Lengthy treatment course
- Bowel toxicity
- Erectile dysfunction
- Adjuvant ADT
- Second malignancies
- Limited salvage options

ESTRO School

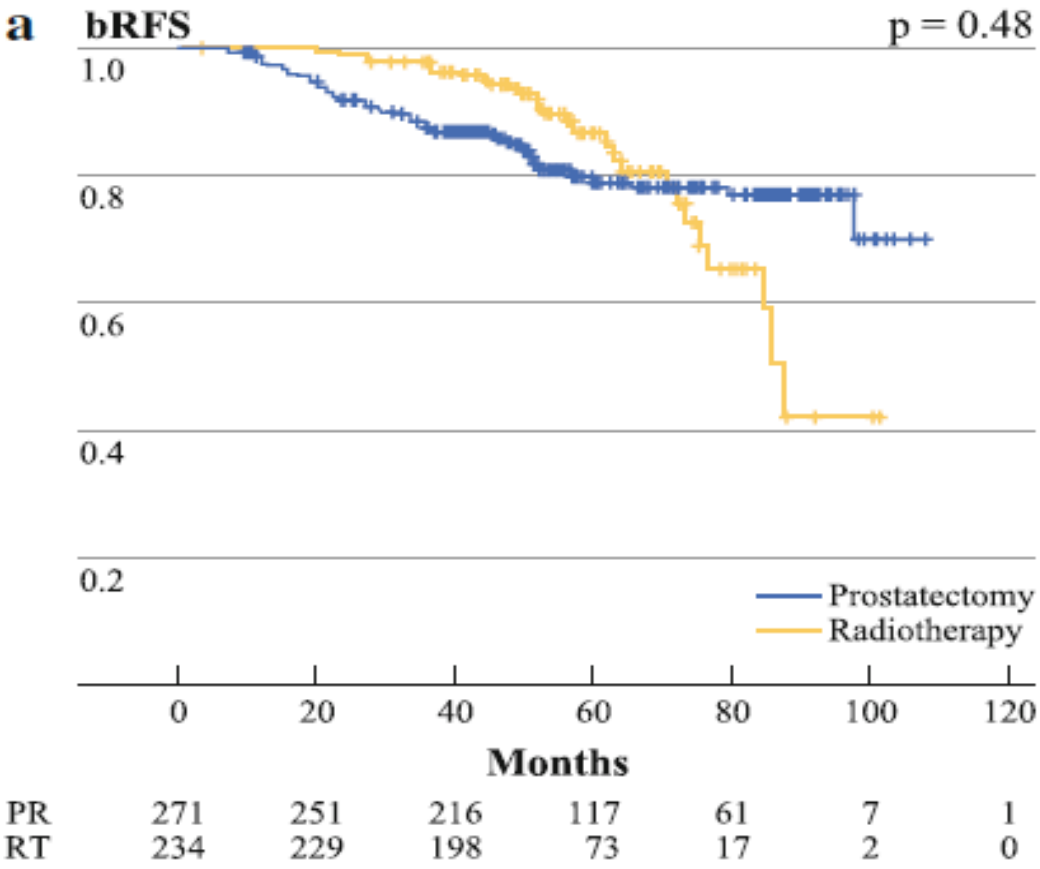
Which is best?

- Surgery vs IMRT
- Surgery vs BT
- BT vs IMRT
- Surgery vs IMRT vs BT
- LDR BT vs HDR BT

Radical Prostatectomy Versus External-Beam Radiotherapy for Localized Prostate Cancer: Long-Term Effect on Biochemical Control—In Search of the Optimal Treatment

Carmen González-San Segundo, MD, PhD[1], Felipe Herranz-Amo, MD, PhD[2], Ana Álvarez-González, MD[1], Pedro Cuesta-Álvaro, PhD[3], Marina Gómez-Espi, MD[1], Eva Paños-Fagundo, MD[2], and Juan A. Santos-Miranda, MD, PhD[1]

Ann Surg Oncol (2011) 18:2980–2987



Toxicity

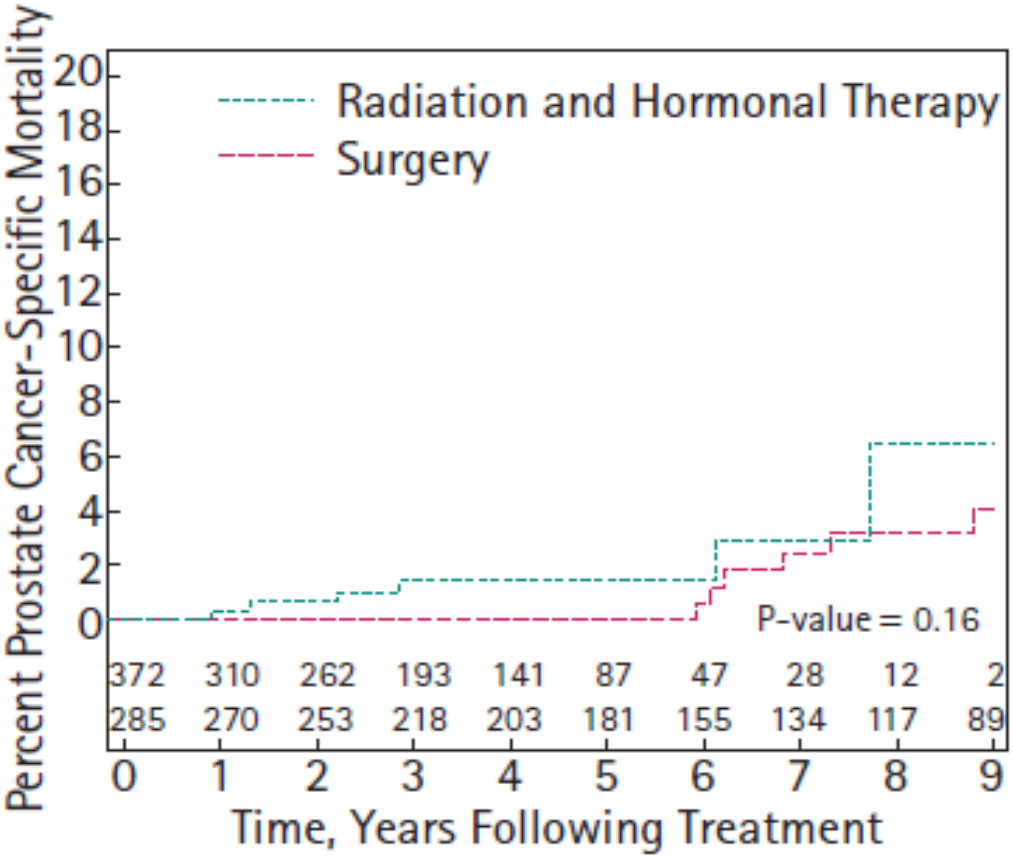
Radiation-induced toxicity greater than grade 2 in the rectum (acute 3%, late 0.5%) and bladder (acute 7.5%, late 3%) was low. The risk of incontinence in the surgical group was 25% (international prostate symptom score and/or expanded prostate cancer index composite scores). No sexual toxicity was analyzed because reliable data were only available for 211 cases.

Radical prostatectomy vs radiation therapy and androgen-suppression therapy in high-risk prostate cancer

Kenneth Westover, Ming-Hui Chen*, Judd Moul†, Cary Robertson†, Thomas Polascik†, Daniel Dosoretz‡, Michael Katin‡, Sharon Salenius‡ and Anthony V. D'Amico

2012 BJU INTERNATIONAL | 110, 1116–1121

High risk: Gleason 8-10



Adjuvant RT in only 17/285 RP patients

No toxicity data

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Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: A Swedish multicenter randomized trial with patient-reported outcomes

BO LENNERNÄS[2], KHAIRUL MAJUMDER[1], JAN-ERIK DAMBER[3],

Acta Oncologica, 2015; 54: 875–881

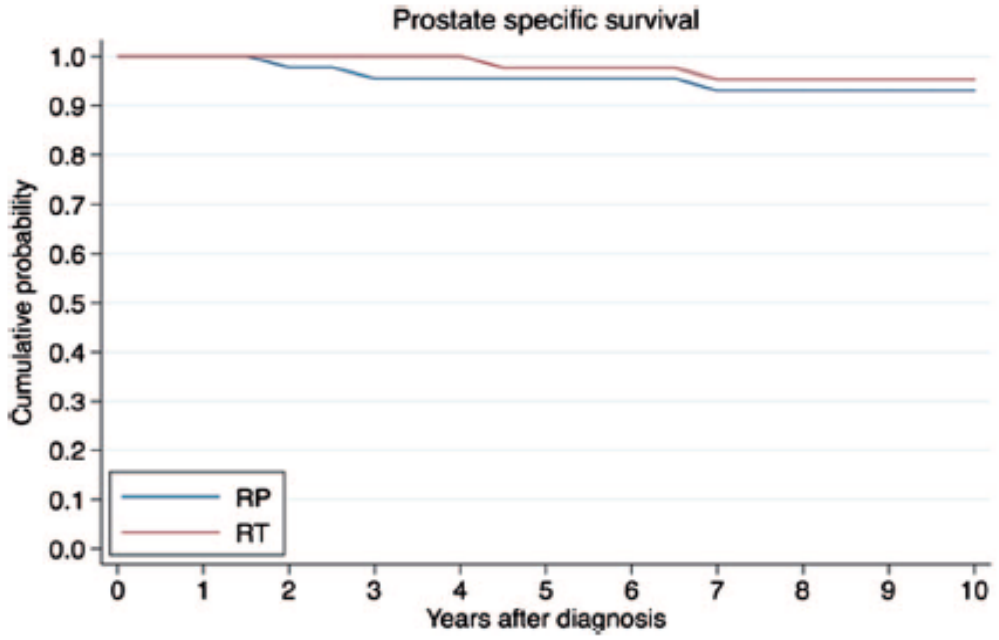
	Randomized to prostatectomy	Randomized to irradiation
T-stadium	n = 45	n = 44
	n (%)	n (%)
T1	18 (40)	17 (39)
T2	17 (38)	16 (36)
T3	4 (9)	3 (7)
Unknown	6 (13)	8 (18)

EBRT 50Gy in 25f + HDR 10Gy x 2

HRQOL: no difference

Toxicity: Grade 3/4 at 2 years

	RP	RT
Urinary	16%	10%
Faecal	8%	24%
ED	90%	86%



Which is best?

- Surgery vs IMRT
- Surgery vs BT
- BT vs IMRT
- Surgery vs IMRT vs BT
- LDR BT vs HDR BT

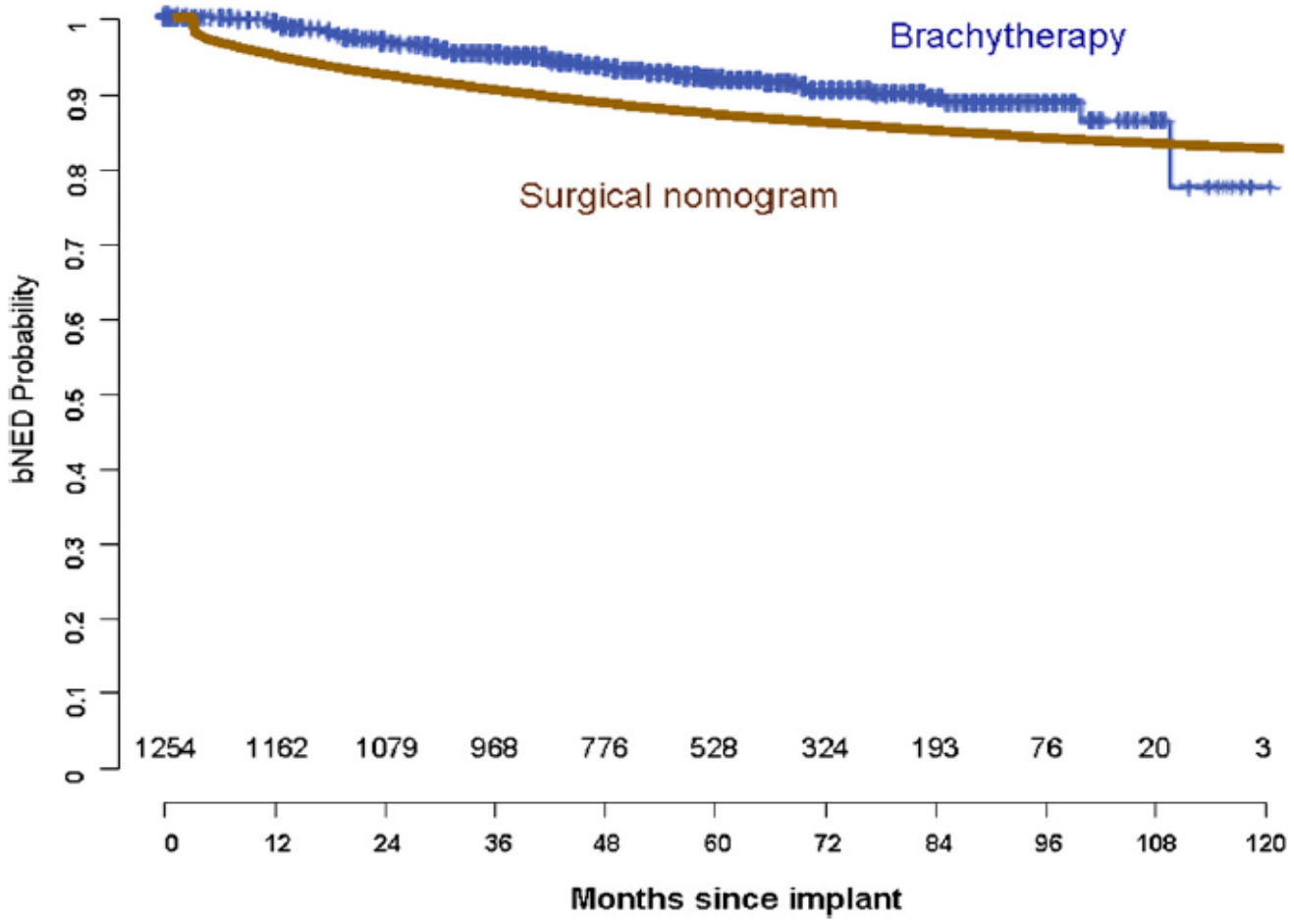
Comparative 5-year outcomes of brachytherapy and surgery for prostate cancer

Tom Pickles[1,*], W. James Morris[1], Michael W. Kattan[2], Changhong Yu[2], Mira Keyes[1]

[1]*BCCA PB Program, Vancouver Clinic, British Columbia Cancer Agency, Canada*
[2]*Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH*

Brachytherapy 10 (2011) 9–14

1254 patients having BT; median follow up 56 months
bRFS compared with predicted outcome after RP from Kattan nomogram



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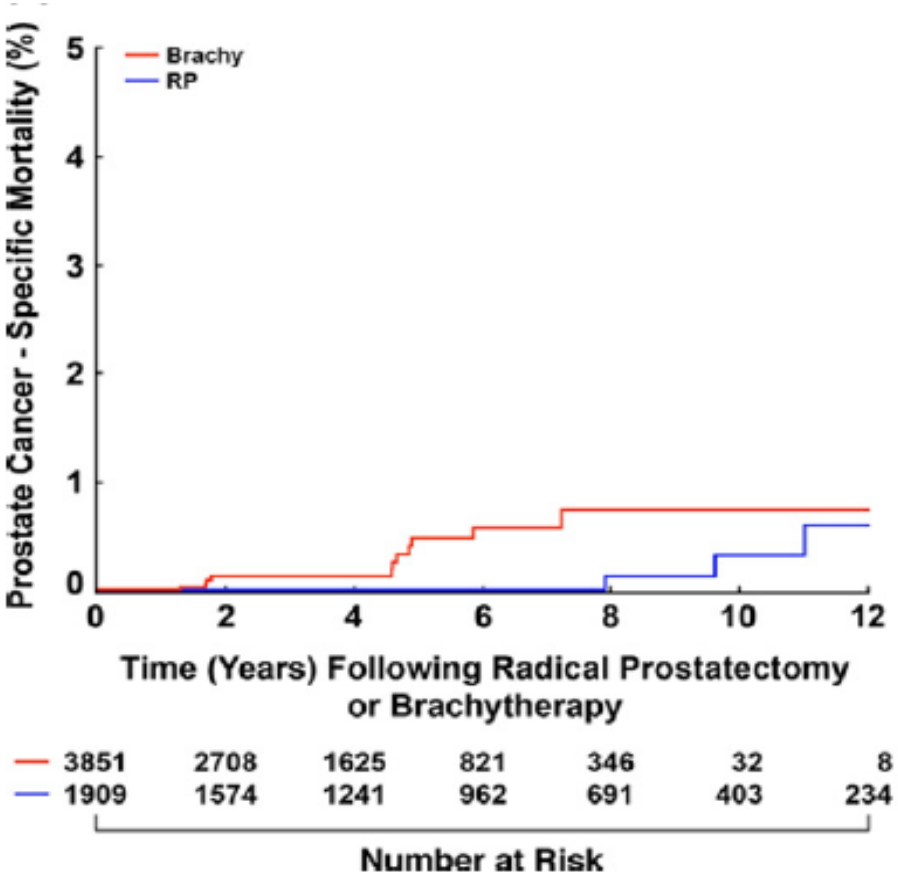
Risk of Death From Prostate Cancer After Radical Prostatectomy or Brachytherapy in Men With Low or Intermediate Risk Disease

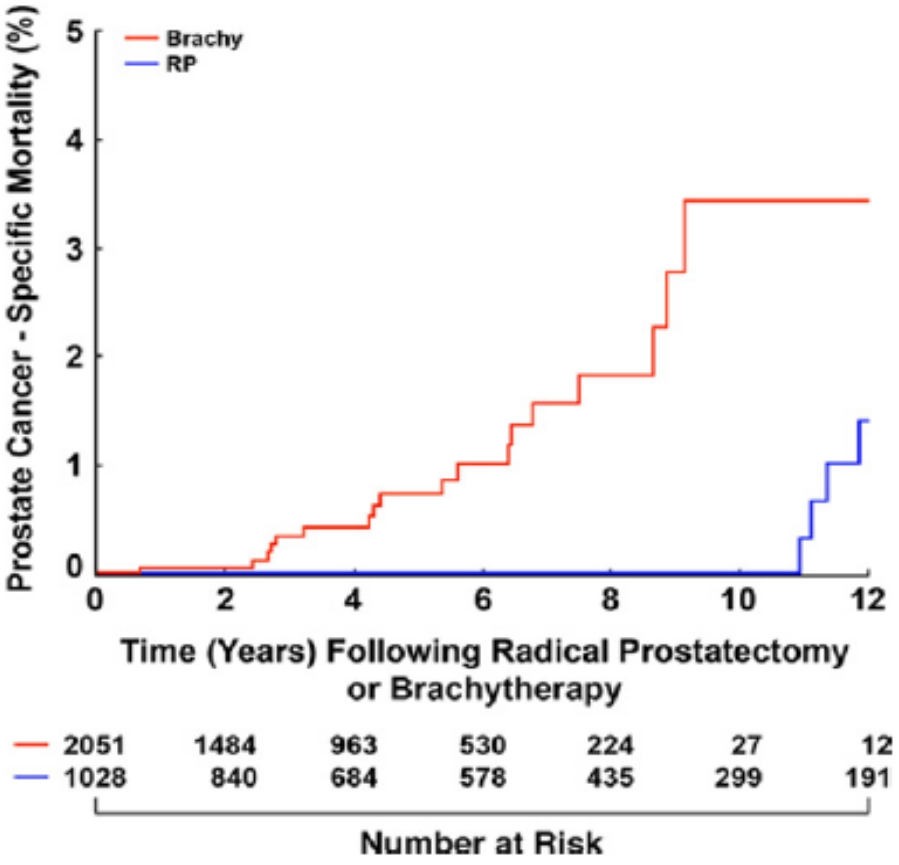
Nils D. Arvold,*,† Ming-Hui Chen,† Judd W. Moul,‡ Brian J. Moran,†
Daniel E. Dosoretz,† Lionel L. Bañez,† Michael J. Katin,† Michelle H. Bracciofortet
and Anthony V. D'Amico†

JOURNAL OF UROLOGY® Vol. 186, 91-96, July 2011

LOW RISK



INTERMEDIATE RISK



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SABRE 1 (Surgery Against Brachytherapy – a Randomised Evaluation): feasibility randomised controlled trial (RCT) of brachytherapy vs radical prostatectomy in low–intermediate risk clinically localised prostate cancer

Bryony K. Eccles[1], William Cross[2], Derek J. Rosario[4], Andrew Doble[5], Chris Parker[6], John Logue[7], Louisa Little[1], Louise Stanton[1] and David Bottomley[3]

Ann Intern Med. 2008;148:435-448.

- Feasibility study for phase III trial RP vs BT
- 2-step randomisation:
  - To receive decision aid or not
  - To receive RP or BT
- May 2009 - May 2011: 30 patients recruited.

Reasons for declining trial as detailed in screening logbooks	Number of patients
Wants active monitoring	34
Wants radiotherapy/brachytherapy	14
Wants surgery	11
Decided on treatment type (not specified)	1
Significant urinary tract problems	2
'Refused'	13
Not fit for one treatment type	9
Private patient	1

Which is best?

- Surgery vs IMRT
- Surgery vs BT
- BT vs IMRT
- Surgery vs IMRT vs BT
- LDR BT vs HDR BT

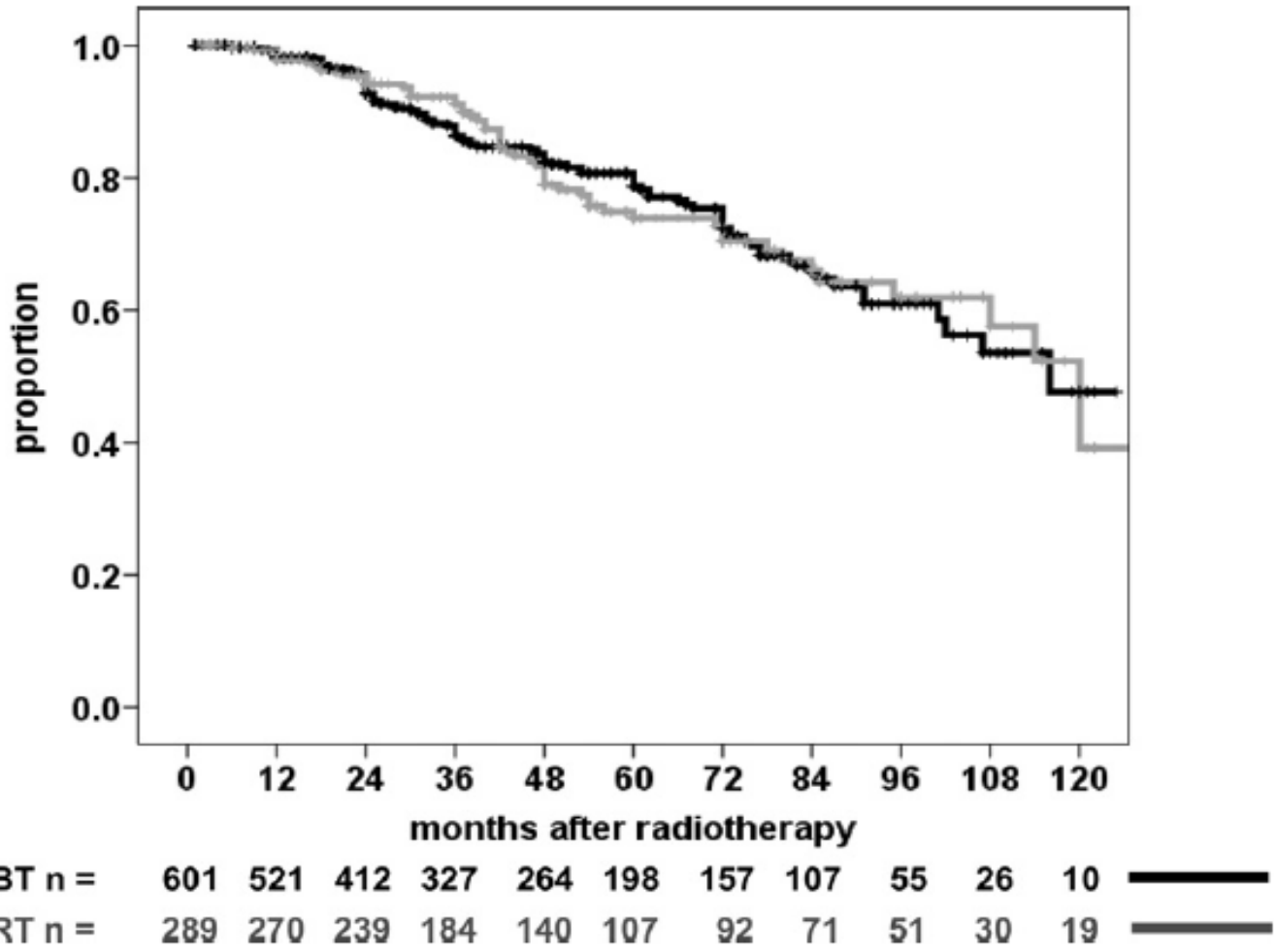
ESTRO School

Comparison between external beam radiotherapy (70 Gy/74 Gy) and permanent interstitial brachytherapy in 890 intermediate risk prostate cancer patients

Gregor Goldner [a,*], Richard Pötter [a], Jan J. Battermann [b], Christian Kirisits [a], Maximilian P. Schmid [a], Samir Sljivic [a], Marco van Vulpen [b]

[a] *Department of Radiation Oncology, Medical University of Vienna, Austria;* [b] *Department of Radiation Oncology, University Medical Center Utrecht, The Netherlands*

Radiotherapy and Oncology 103 (2012) 223–227



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Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT

Israel Deutsch[1], Michael J. Zelefsky[1], Zhigang Zhang[2], Qianxing Mo[2], Marco Zaider[3], Gil'ad Cohen[3], Oren Cahlon[1], Yoshiya Yamada[1,*]

[1]*Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center New York, New York, NY*
[2]*Department of Biostatistics, Memorial Sloan-Kettering Cancer Center New York, New York, NY*
[3]*Department of Medical Physics, Memorial Sloan-Kettering Cancer Center New York, New York, NY*

Brachytherapy 2010

160 patients: HDR 3 x 5.5-7Gy + 50.4Gy XRT
470 patients: IMRT 86.4Gy

	IMRT	HDR
Low risk	21%	14%
Inter risk	40%	71%
High risk	39%	15%

Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT

Israel Deutsch[1], Michael J. Zelefsky[1], Zhigang Zhang[2], Qianxing Mo[2], Marco Zaider[3], Gil'ad Cohen[3], Oren Cahlon[1], Yoshiya Yamada[1,*]

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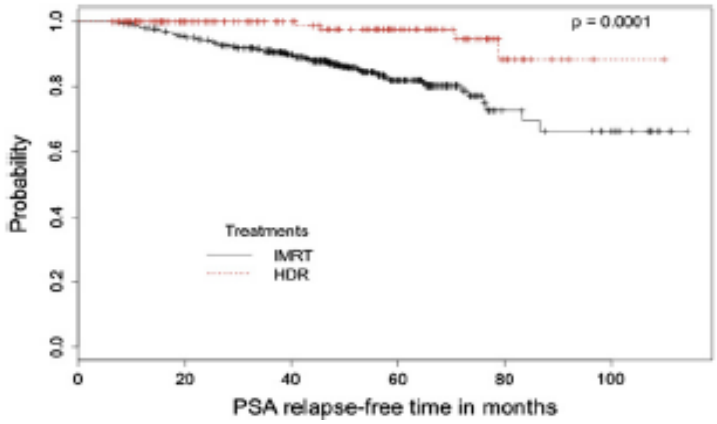
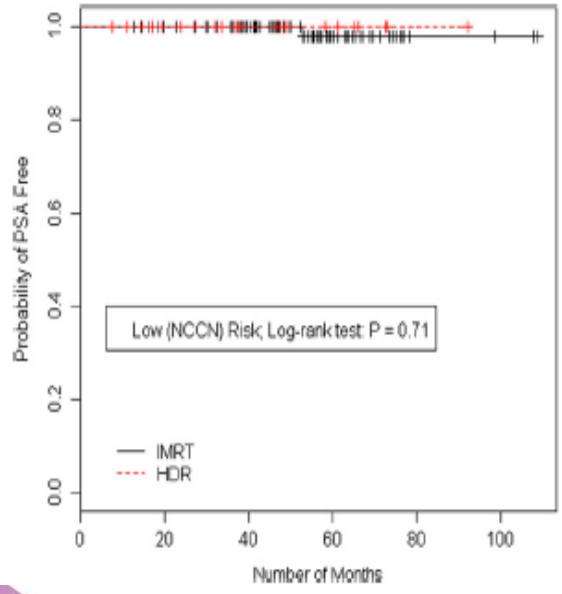
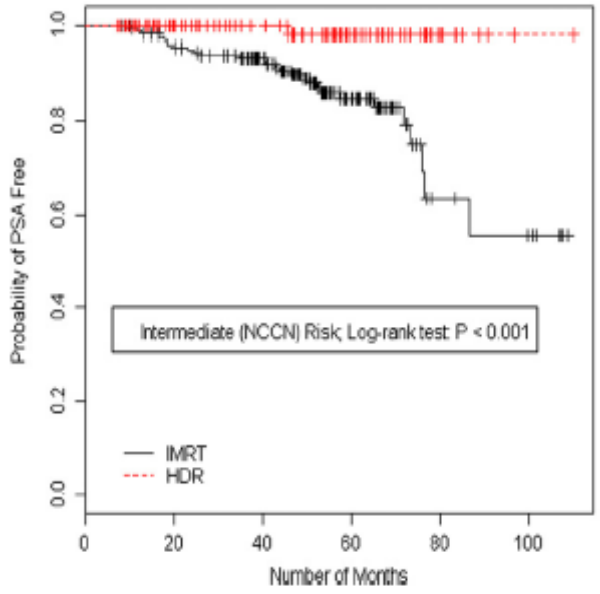
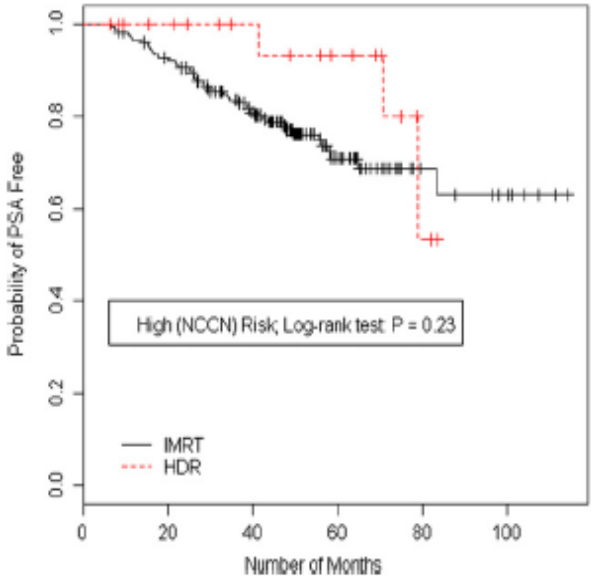
[3]Department of Medical Physics, Memorial Sloan-Kettering Cancer Center New York, New York, NY

Brachytherapy 2010









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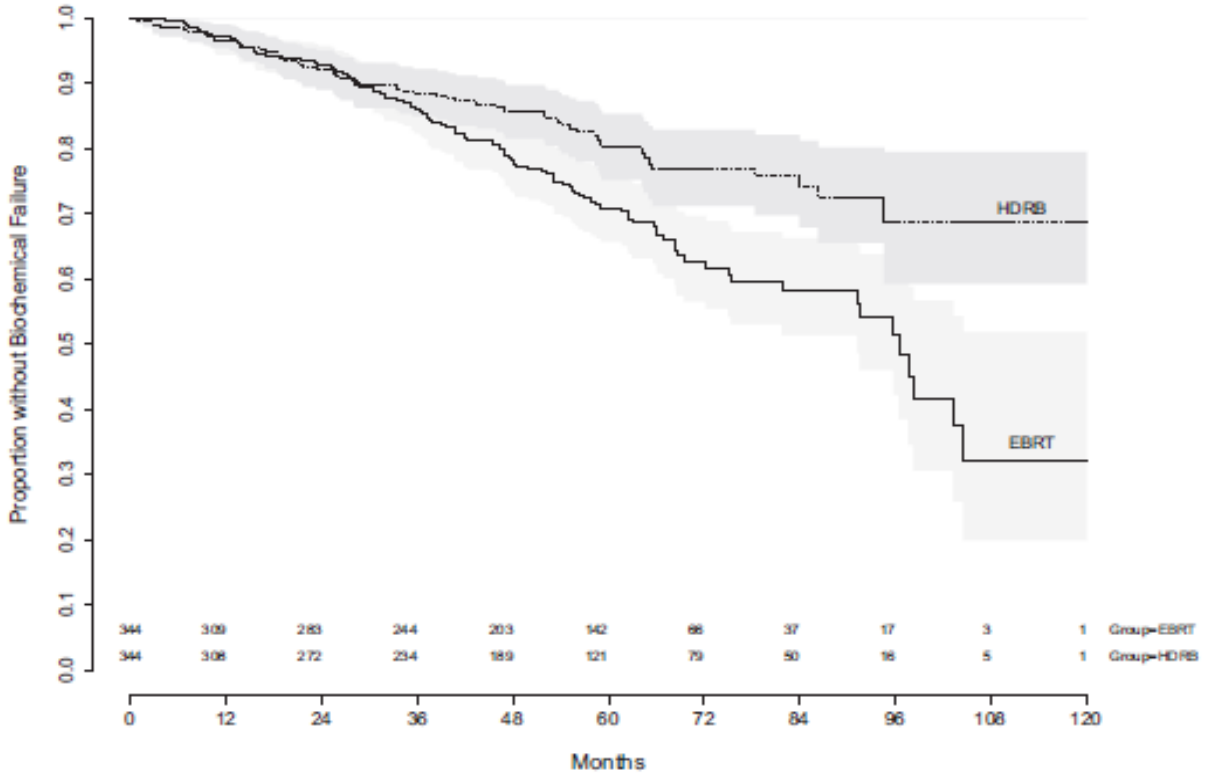
Direct 2-Arm Comparison Shows Benefit of High-Dose-Rate Brachytherapy Boost vs External Beam Radiation Therapy Alone for Prostate Cancer

Richard Khor, MBBS,* Gillian Duchesne, MD, FRANZCR,*,† Keen-Hun Tai, FRANZCR,* Farshad Foroudi, FRANZCR,* Sarat Chander, FRANZCR,* Sylvia Van Dyk, DipAppSc,* Margaret Garth, DipAppSc,* and Scott Williams, MD, FRANZCR*

*Division of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, and University of Melbourne, Melbourne, Australia; and †Monash University, Melbourne, Australia

Int J Radiation Oncol Biol Phys, Vol. 85, No. 3, pp. 679–685, 2013

344 patients 46Gy/23f + 19.5GY/3f HDR vs 344 patients 3D CRT 74Gy/37f
Risk group: Intermediate 41%; High 59%



Actuarial FFbF plots of matched EBRT and HDRB treatment cohorts. Bands indicate 95% confidence intervals.

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Efficacy: cost

HDR	
Afterloader:	£0.3m
TPS	
Physics	6h
RTT	1h
Clinician	1.5h
Anaesthetic	
Patient	3days

IMRT	
Linac:	£3m
TPS	
Physics	8h
RTT	6h
Clinician	0.75h
Patient	43days

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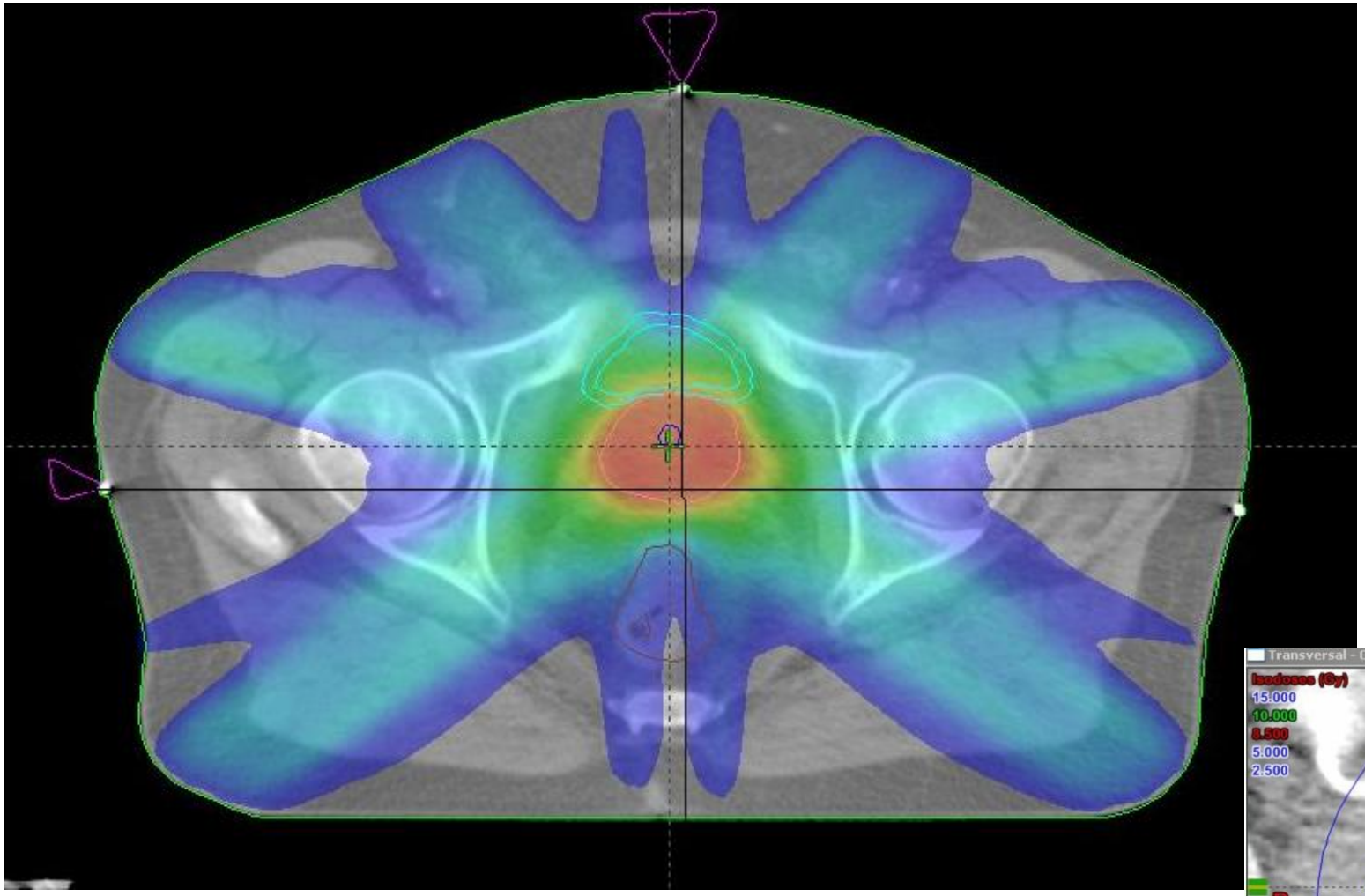
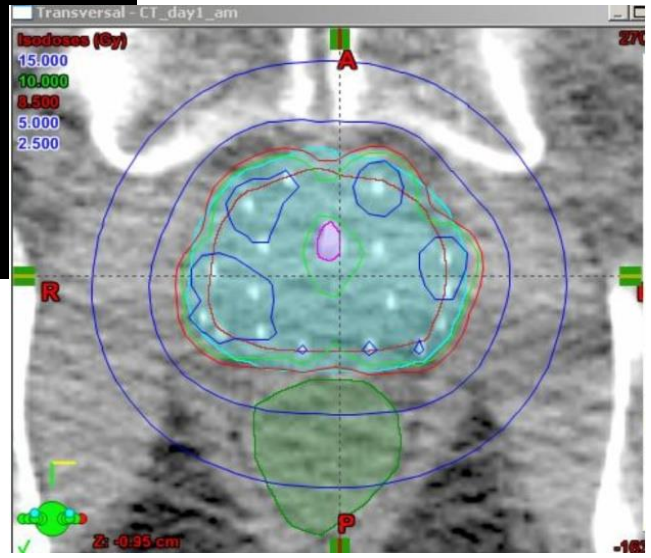




ESTRO School

THE CALCULATED RISKS OF SECOND MALIGNANCIES FROM INTENSITY-MODULATED RADIATION THERAPY

Kry et al 2005

% risk of fatal second malignancy

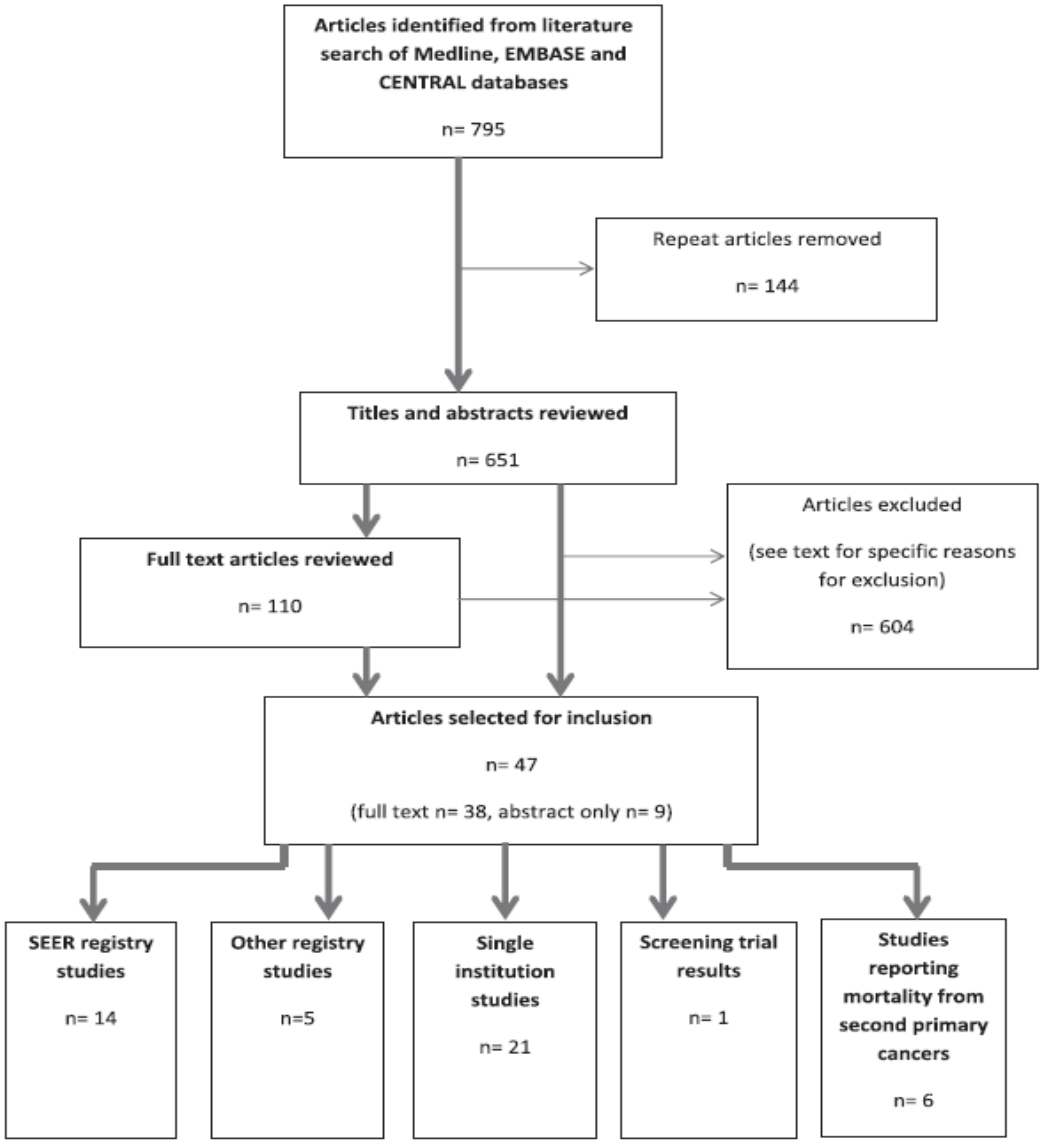
Conventional	IMRT					
18MV	6MV		10MV	15MV		18MV
	V	S	V	V	S	V
1.7%	**2.9%**	**3.7%**	**2.1%**	**3.4%**	**4.0%**	**5.1%**

ESTRO School

Second primary cancers after radiation for prostate cancer: A systematic review of the clinical data and impact of treatment technique

Louise Murray [a], Ann Henry [a,*], Peter Hoskin [b], Frank-Andre Siebert [c], Jack Venselaar [d], on behalf of the PROBATE group of the GEC ESTRO

Radiotherapy and Oncology 110 (2014) 213–228



Using ‘old’ ext beam techniques risk 1 in 220
Increasing to 1 in 70 after 10 years follow up

In 5 studies comparing BT to general population no increase

Which is best?

- Surgery vs IMRT
- Surgery vs BT
- BT vs IMRT
- Surgery vs IMRT vs BT
- LDR BT vs HDR BT

ESTRO School

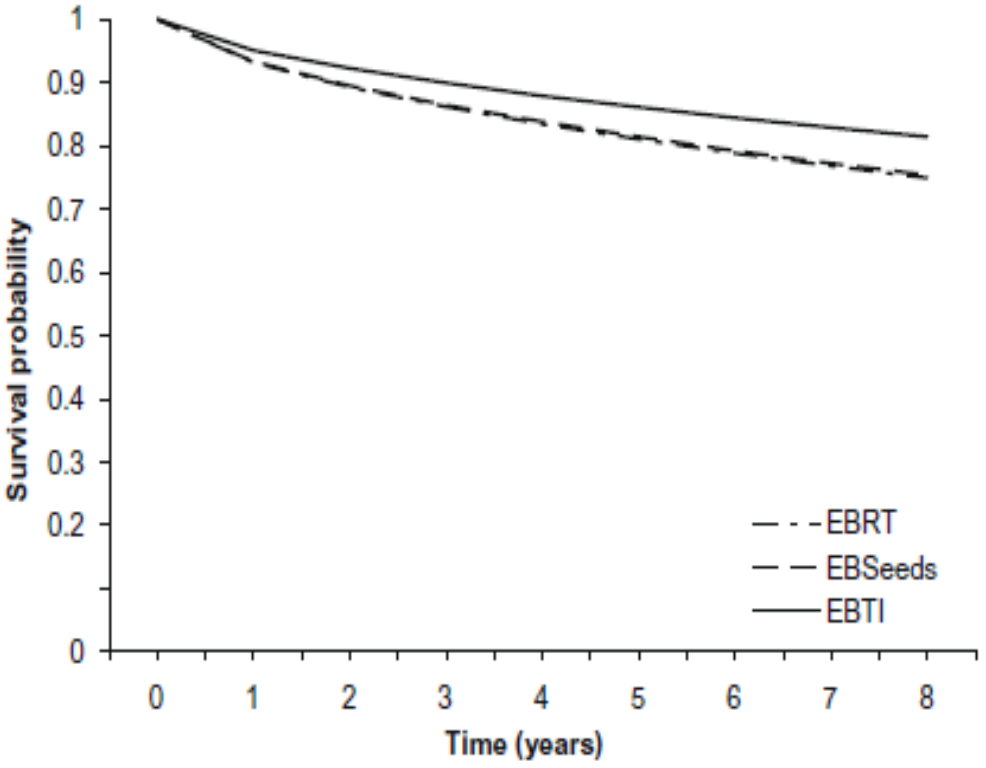
Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: A systematic review

Bradley R. Pieters [a,*], Djuna Z. de Back [a], Caro C.E. Koning [a], Aeilko H. Zwinderman [b]

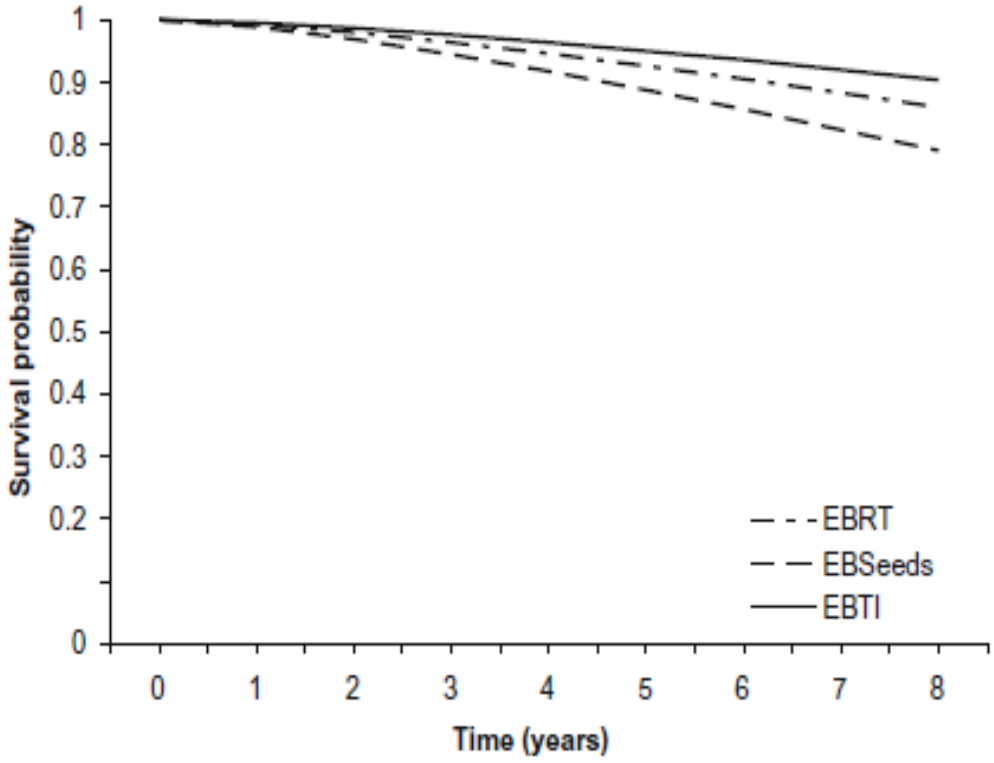
Radiotherapy and Oncology 93 (2009) 168–173

40 papers with 3,5 and 8 year data

bRFS



Overall survival



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JAMA | Original Investigation

Association Between Choice of Radical Prostatectomy, External Beam Radiotherapy, Brachytherapy, or Active Surveillance and Patient-Reported Quality of Life Among Men With Localized Prostate Cancer

JAMA. 2017;317(11):1141-1150.

Ronald C. Chen, MD, MPH; Ramsankar Basak, PhD; Anne-Marie Meyer, PhD; Tzy-Mey Kuo, PhD; William R. Carpenter, PhD; Robert P. Agans, PhD; James R. Broughman, BS; Bryce B. Reeve, PhD; Matthew E. Nielsen, MD, MS; Deborah S. Usinger, BA; Kiayni C. Spearman, BS; Sarah Walden, BA; Dianne Kaleel, BA; Mary Anderson, MPH; Til Stürmer, MD, PhD; Paul A. Godley, MD, PhD

Table 3. Propensity-Weighted Sexual, Urinary, and Bowel Function at 24 Months by Treatment Type Among Men With Newly Diagnosed Prostate Cancer, Stratified by Baseline Function Level[a] (continued)

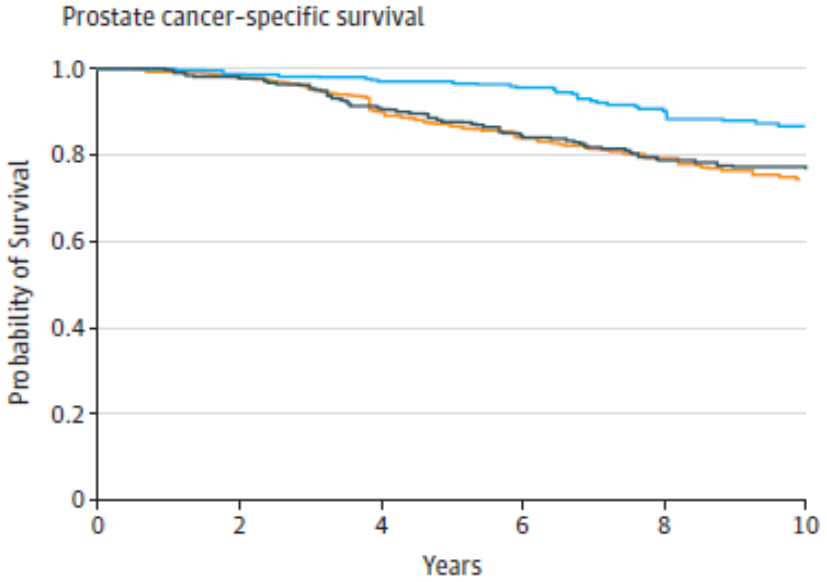
	No. of Patients[b]	Function Level at 24 Months, % (95% CI)		
		Normal[c]	Intermediate[d]	Poor[e]
Intermediate baseline level				
Active surveillance[f]	102	28.9 (28.1-29.5)	54.8 (54.1-55.6)	16.3 (15.5-17.1)
Brachytherapy	36	27.0 (26.1-27.8)	56.9 (56.1-57.7)	16.2 (15.7-16.7)
Radical prostatectomy	161	34.8 (34.4-35.2)	50.5 (50.1-50.9)	14.7 (14.3-15.1)
External beam RT	80	19.9 (19.0-21.1)	60.3 (59.1-61.5)	19.8 (19.1-20.4)

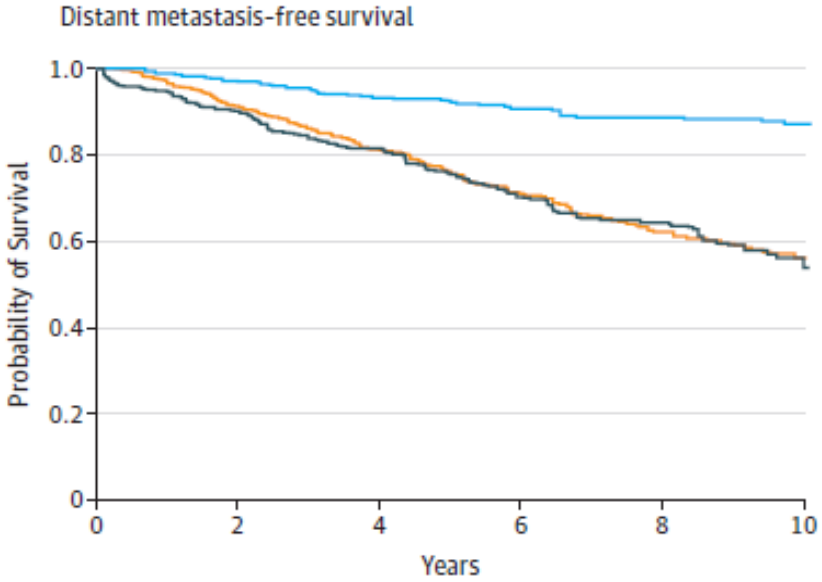
JAMA | Original Investigation

Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

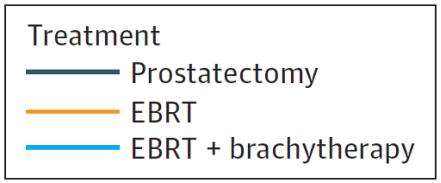
JAMA. 2018;319(9):896-905

Retrospective cohort study; 12 centres: 1809 men





No. at risk												
Prostatectomy	634	530	346	211	131	81	634	495	315	184	111	61
EBRT	725	635	457	288	172	102	734	595	407	235	133	77
EBRT + brachytherapy	431	397	317	222	159	87	436	393	307	210	156	86

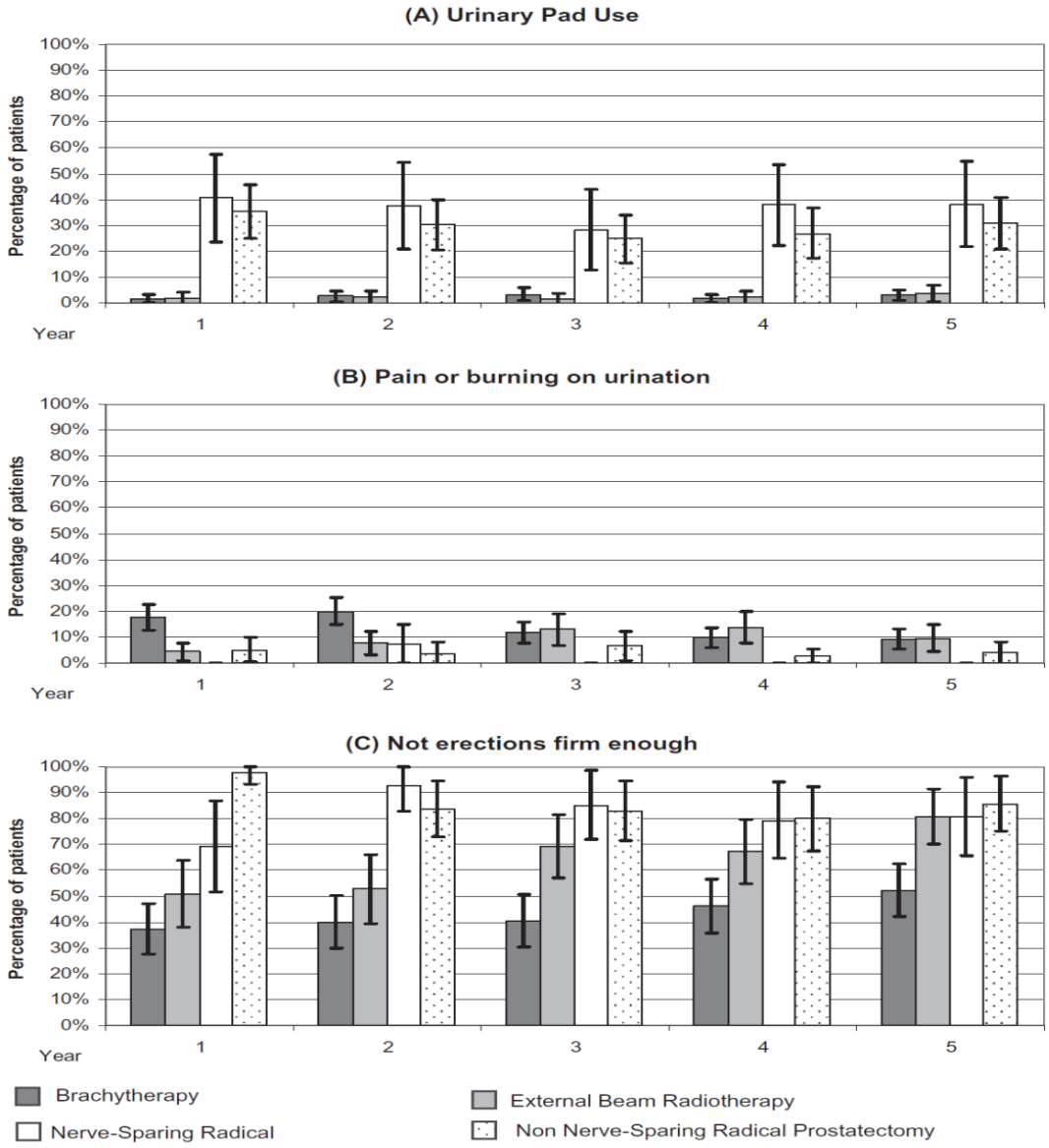


ESTRO School

Quality of life impact of treatments for localized prostate cancer: Cohort study with a 5 year follow-up

Montse Ferrer [a,b,c,*], Ferran Guedea [d], José Francisco Suárez [e], Belén de Paula [f], Víctor Macías [g,h], et al

Radiotherapy and Oncology 108 (2013) 306–313



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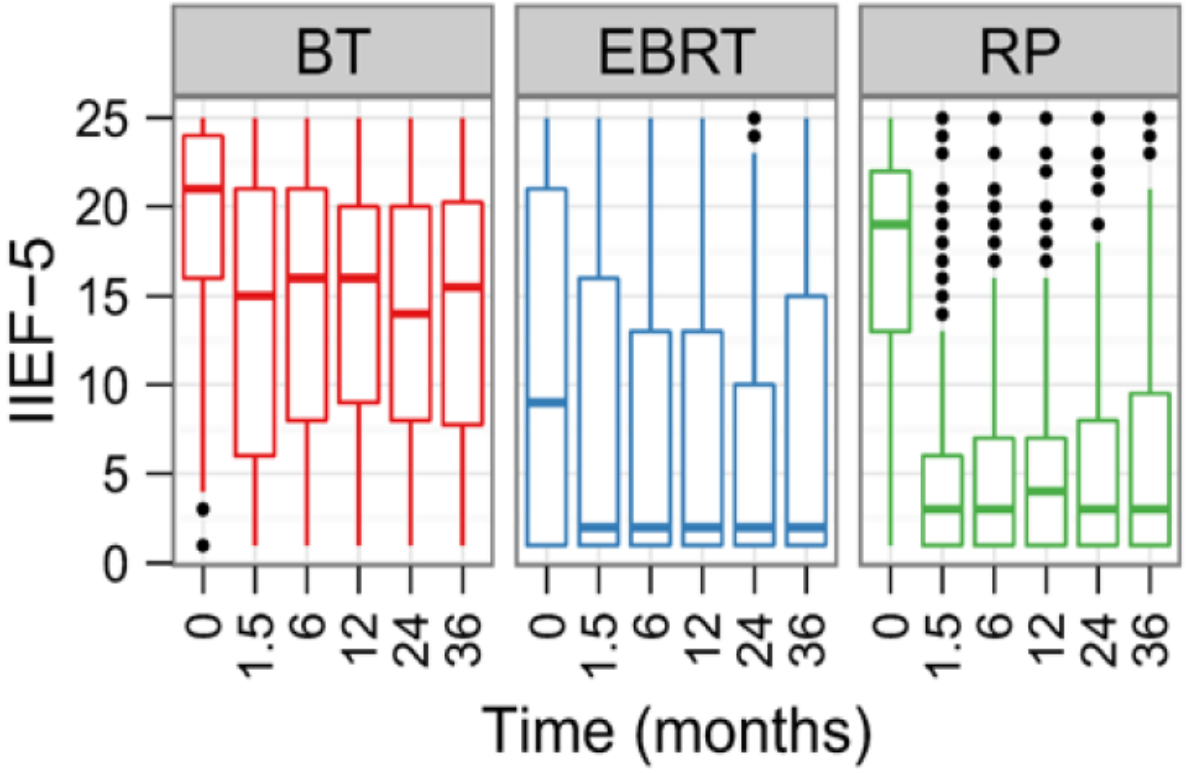
Erectile function following brachytherapy, external beam radiotherapy, or radical prostatectomy in prostate cancer patients

P. M. Putora · D. Engeler · S. R. Haile · N. Graf · K. Buchauer · H. P. Schmid · L. Plasswilm

Strahlenther Onkol (2016) 192:182–189

RP: 252
LDR BT: 135
EBRT 74Gy: 91



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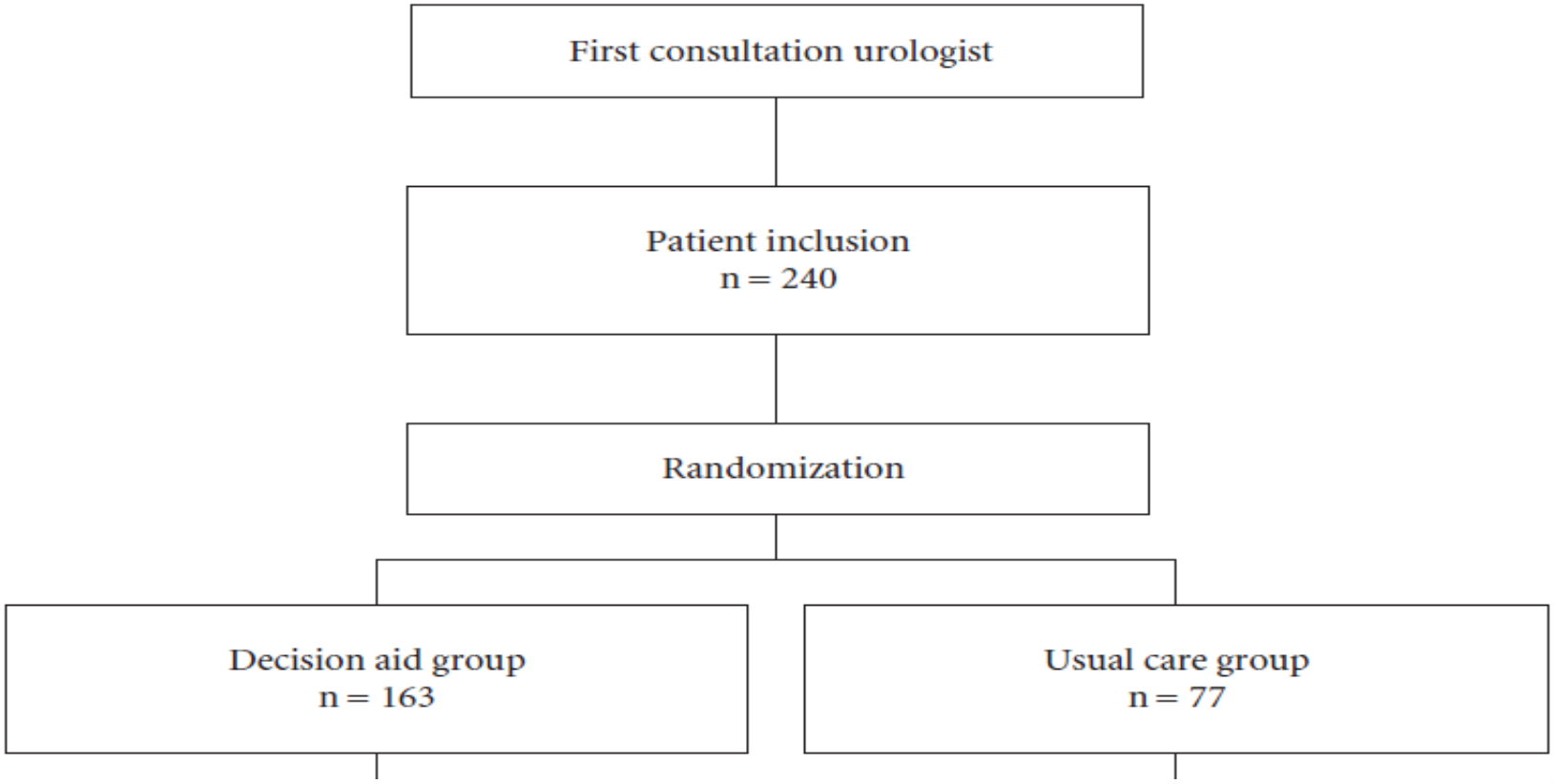
	Brachytherapy	RP	CK/IMRT
DAY 1:	Implant and home	Operate	Planning
DAY 2:	That's it!	ITU/HDU	Physics think!
DAY 5:		Home	Physics still thinking!
DAY 10:		Catheter out	Start RT
DAY 15:		Pelvic floor exercises	Finish CK
DAY 28:		Back to work (with a pad)	Finish RT (with diarrhoea)
DAY 52:		try the Vacupump)	

ESTRO School

Choice between prostatectomy and radiotherapy when men are eligible for both: a randomized controlled trial of usual care vs decision aid

Julia J. van Tol-Geerdink*, Jan Willem Leer*, Philip C. Weijerman†, Inge M. van Oort‡, Henk Vergunst§, Emile N. van Lin*, J. Alfred Witjes‡ and Peep F. Stalmeier*¶

2012 BJU International | 111, 564–573



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	Radical Prostatectomy	Brachy-therapy	Extern. beam radiotherapy
Tumour control No tumour detectable, PSA remains low (after 5 years)	yes 81 out of 100 no 19 out of 100	yes 80 out of 100 no 20 out of 100	yes 76 out of 100 no 24 out of 100
			
Died of prostate cancer (after 10 years)	yes 3 out of 100 no 97 out of 100	yes 5 out of 100 no 95 out of 100	yes 6 out of 100 no 94 out of 100
			
Loss of erections Few to no erections (after 2 years)	70 out of 100	35 out of 100	40 out of 100
			
Severe urinary problems viz. urine incontinence (after 2 years)	9 out of 100	6 out of 100	2 out of 100
			
Severe bowel problems viz. diarrhoea (after 2 years)	2 out of 100	9 out of 100	9 out of 100
			

2012 BJU International | 111, 564–573

ESTRO School

Choice between prostatectomy and radiotherapy when men are eligible for both: a randomized controlled trial of usual care vs decision aid

2012 BJU International | 111, 564–573

Table 2 Patients' final treatment preferences and treatments received in the usual care group ($n = 77$) and the decision aid group ($n = 163$).

	RP (%)	BT (%)	EBRT (%)	Undecided (%)
Treatment preference	67	17	13	4
Treatment received	71	12	18	–

RP, radical prostatectomy; BT, brachytherapy; EBRT, external beam radiotherapy.

Table 3 Effect of the decision aid on final treatment preferences and treatments received in the usual care group ($n = 77$) and the decision aid group ($n = 163$).

	RP (%)	BT (%)	EBRT (%)	Undecided (%)	P
Treatment preference					0.03
Usual care group	73	8	12	8	
Decision aid group	65	20	13	2	
Treatment received					0.04
Usual care group	78	4	18	–	
Decision aid group	68	15	17	–	

RP, radical prostatectomy; BT, brachytherapy; EBRT, external beam radiotherapy.

Which is best?

- Surgery vs IMRT
- Surgery vs BT
- BT vs IMRT
- Surgery vs IMRT vs BT
- LDR BT vs HDR BT

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Relative advantages and disadvantages: LDR vs HDR

LDR

- Single step procedure
- Low radioprotection

- Volume limited
- Limited cover of ECE/SV
- Dose determined by implant accuracy
- QA post implant

HDR

- (Fractionation)
- Requires HDR facility

- Can implant large glands
- Can implant ECE and SV
- Accurate dose delivery
- Biologically higher dose
- QA pre delivery

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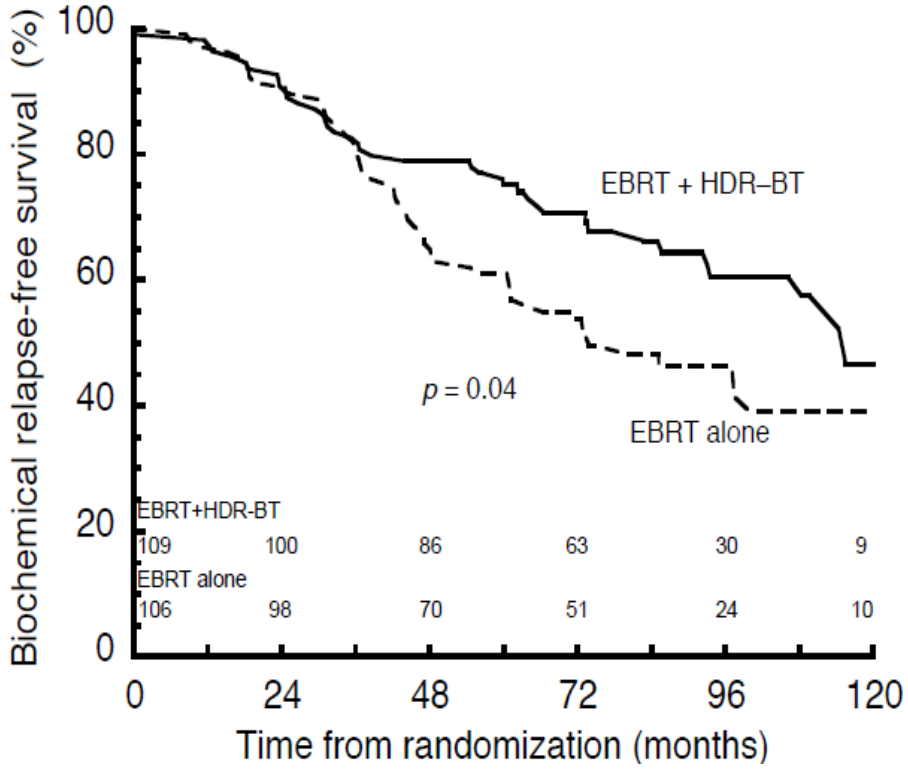
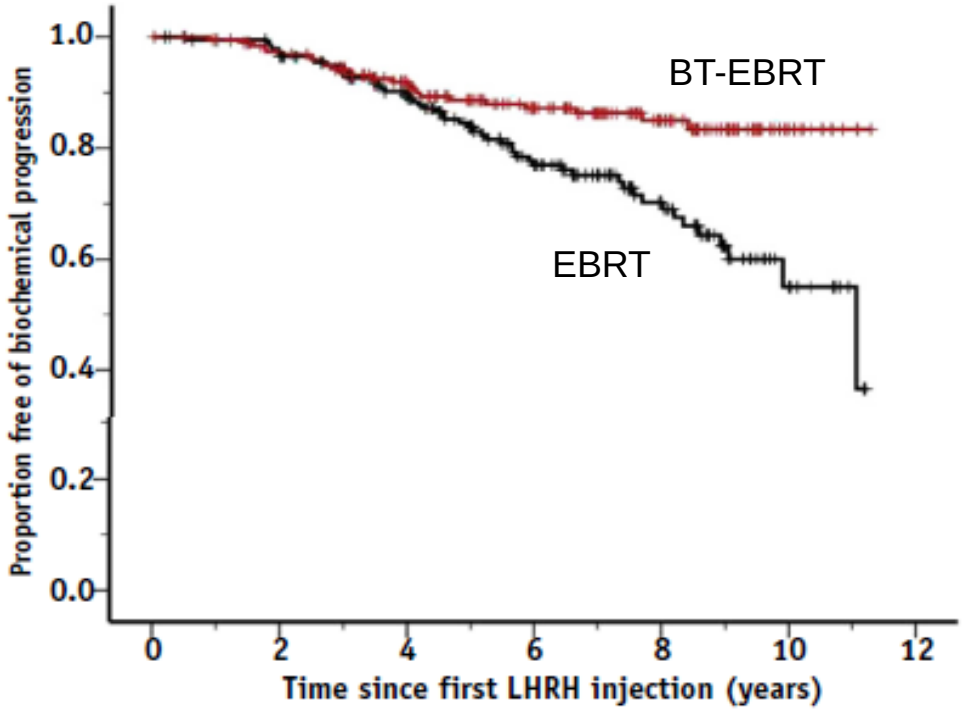
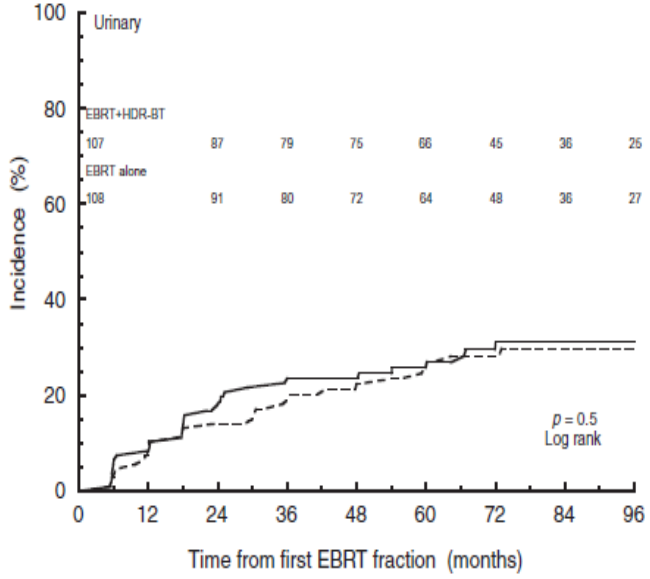
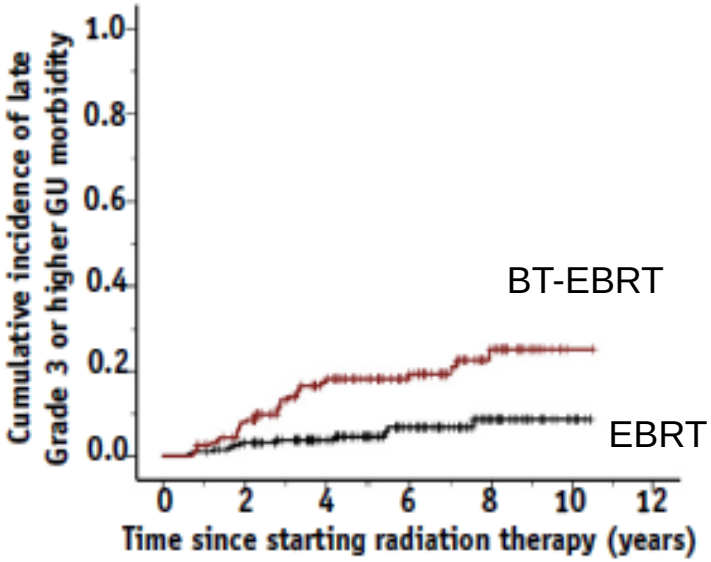
HDR Best Boost ? LDR









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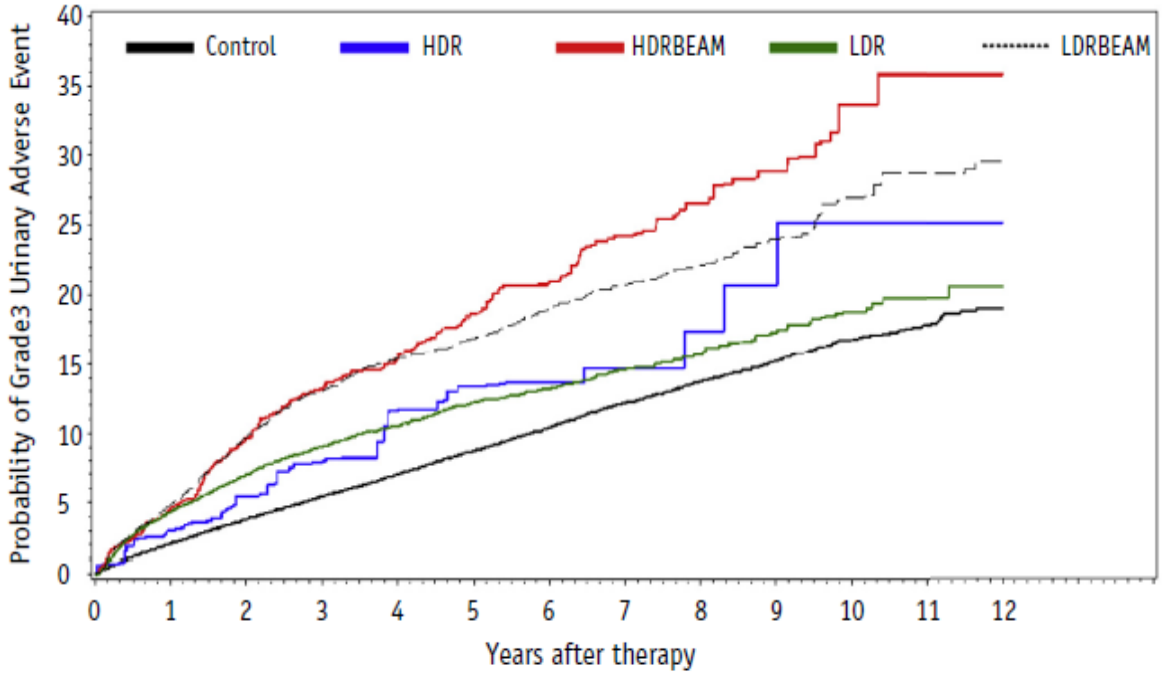
Time Course and Accumulated Risk of Severe Urinary Adverse Events After High- Versus Low-Dose-Rate Prostate Brachytherapy With or Without External Beam Radiation Therapy

Jonathan D. Tward, MD, PhD,* Stephanie Jarosek, RN,†
Haitao Chu, MD, PhD,† Cameron Thorpe, BS,*
Dennis C. Shrieve, MD, PhD,* and Sean Elliott, MD, MS†



	Number at Risk Years After Therapy										
	0	1	2	3	4	5	6	7	8	9	10
Control	93748	66008	48863	36338	26615	19075	13121	8662	5695	3275	1522
HDR	493	381	298	235	193	164	132	84	51	24	13
HDRBEAM	1842	1434	1091	829	645	477	339	240	162	93	46
LDR	11765	9239	7123	5576	4263	3211	2303	1597	1017	574	273
LDRBEAM	6971	5413	4275	3378	2644	2040	1456	991	628	363	173

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Dosimetric comparison between treatment plans of patients treated with low-dose-rate vs. high-dose-rate interstitial prostate brachytherapy as monotherapy: Initial findings of a randomized clinical trial

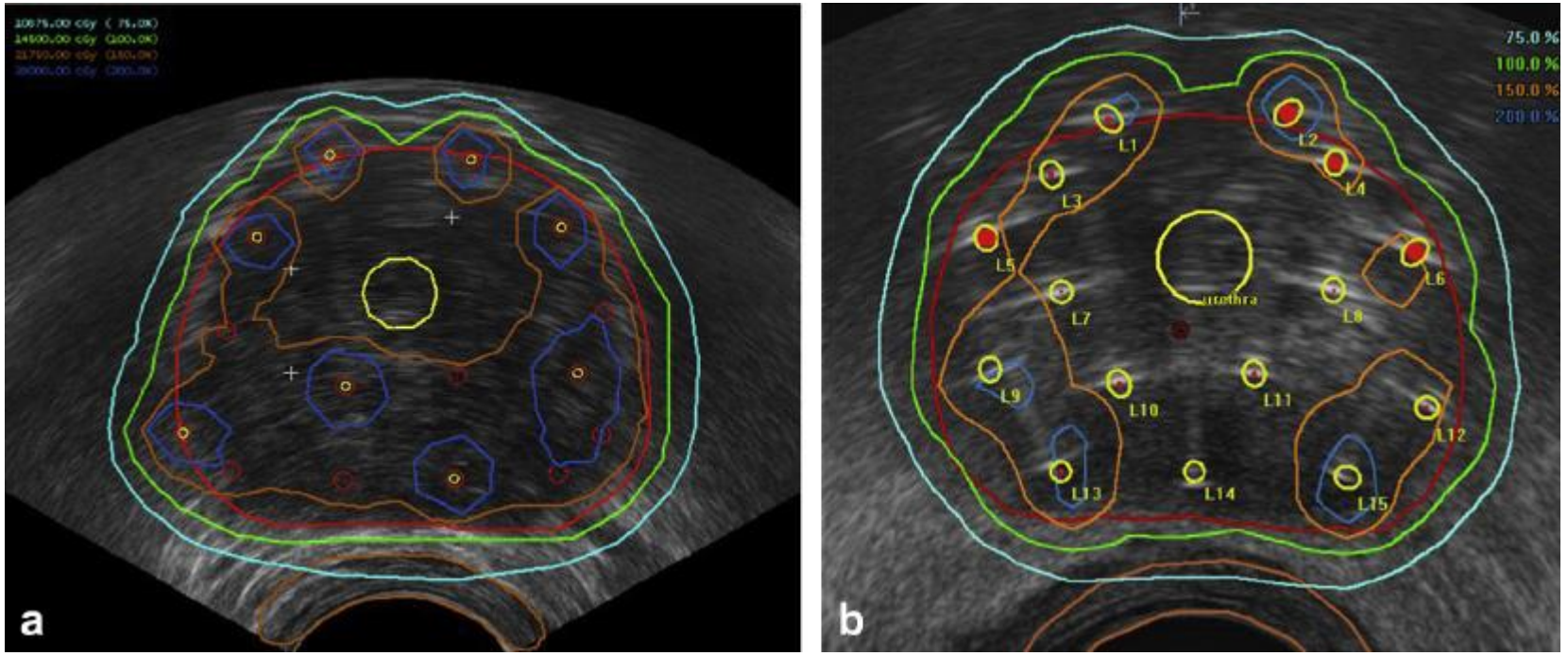
Brachytherapy 16 (2017) 608–615

T. Major*, C. Polgár, K. Jorgo, G. Stelczer, P. Ágoston

RCT → HDR 19Gy

RCT → LDR 145Gy

n=87



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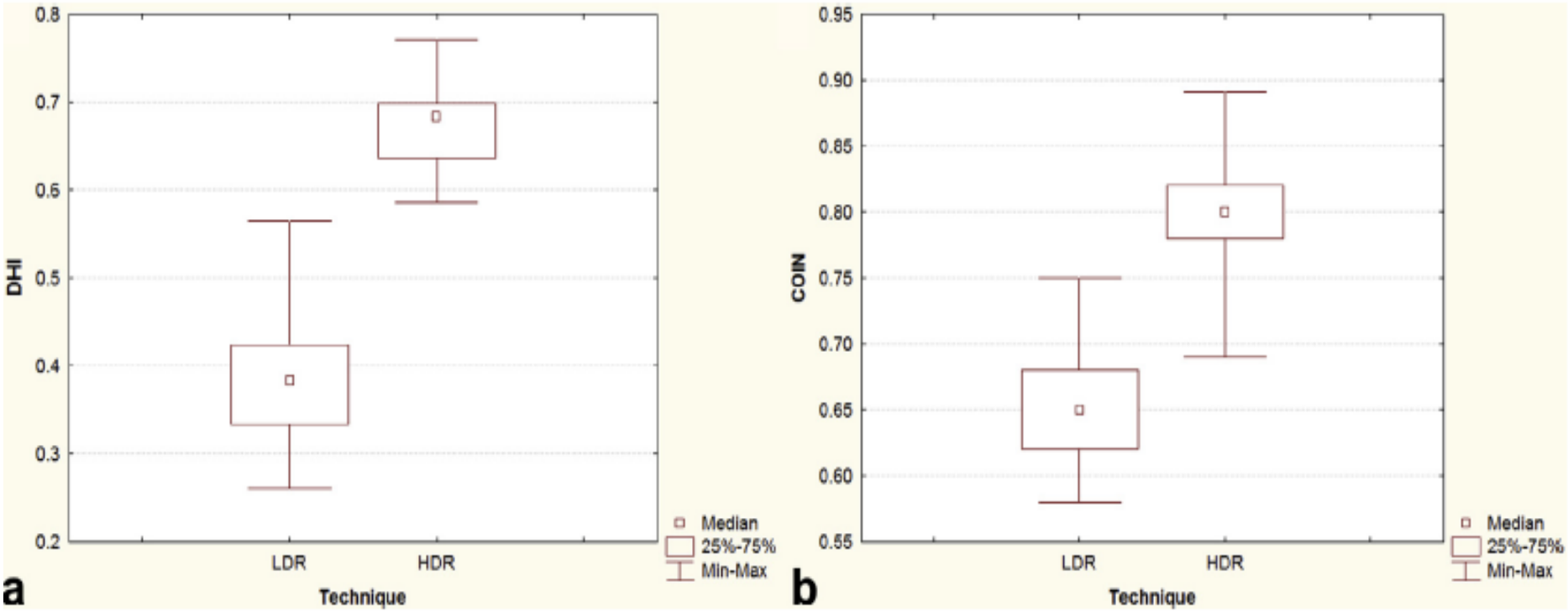

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RCT → HDR 19Gy

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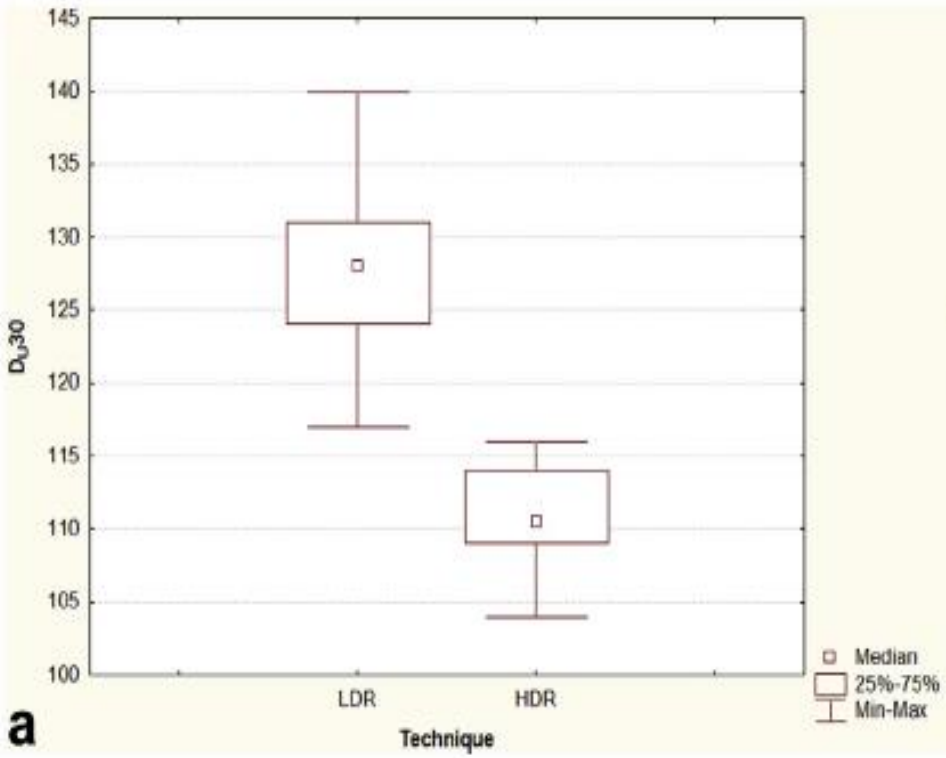
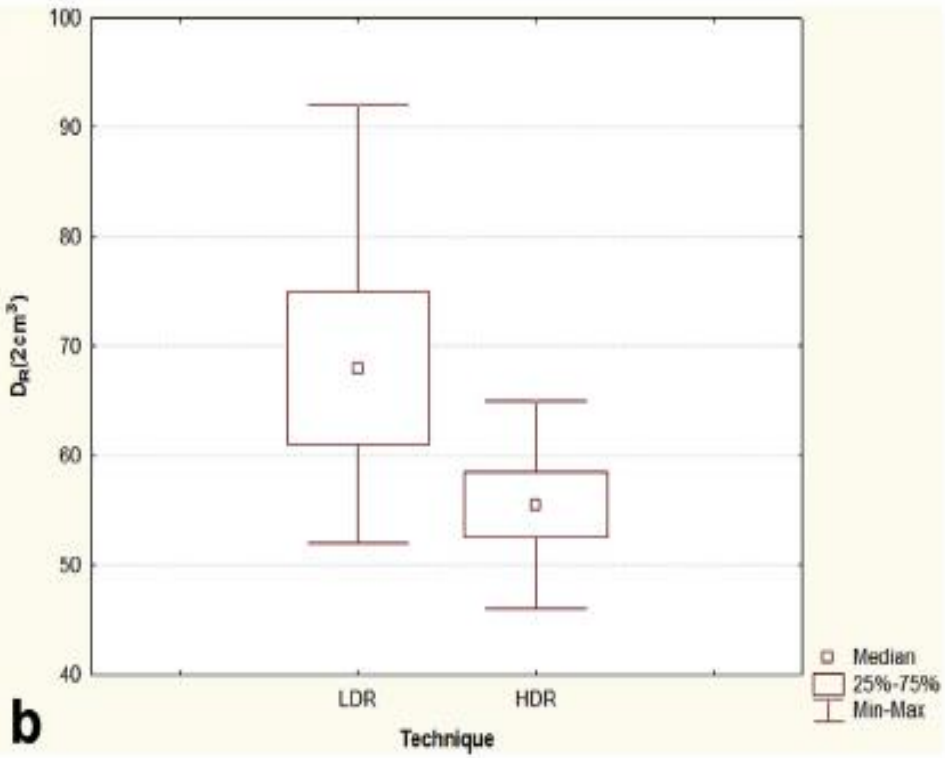
n=87

Urethra



Rectum



Treatment costs

- Implant equipment similar for PPB and HDR:
  - Fixation device with stepping unit
  - US apparatus
  - Planning system
  - Disposables: catheters, needles etc
  - OR facilities and support
  - Anaesthesia
  - Hospitalisation
  - Supportive medication

Treatment costs

HDR

Use of afterloader

Capital cost

- Assume 30% use for prostate and 50/year
- 400 Euro/patient

Source cost

- Assume as above
- 40 Euro/patient

TOTAL:

440 Euro/patient

LDR SEEDS

Cost of seeds

- Assume average 100 seeds per patient

TOTAL:

3500 Euro/patient

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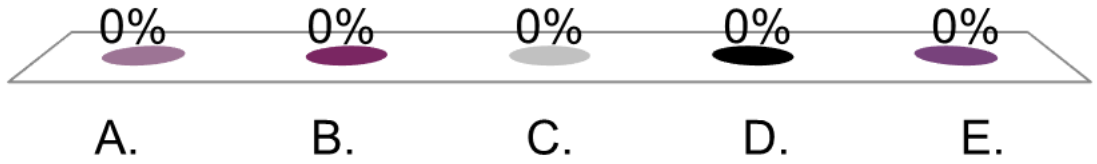
What is your preferred management for a patient aged 66 years presenting with a PSA of 13.6, Gleason score 4+3 prostate cancer which is stage T2B on MR staging? He has no significant co-morbidities

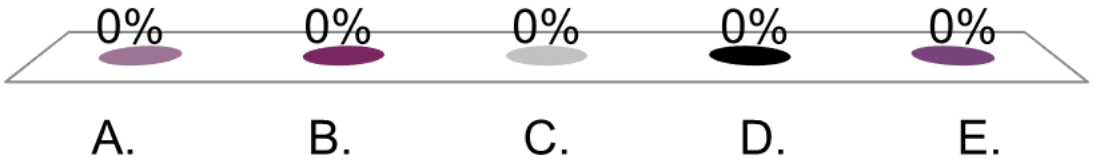
A. Radical prostatectomy
B. Active surveillance
C. External beam IMRT to 78Gy with ADT
D. LDR seed brachytherapy with ADT
E. External beam IMRT + HDR boost



ESTRO School

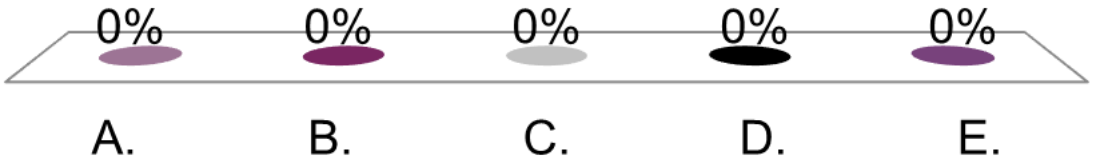
What is your preferred management for a patient aged 66 years presenting with a PSA of 13.6, Gleason score 4+3 prostate cancer which is stage T3a on MR staging? He has no significant co-morbidities

A. Radical prostatectomy
B. Active surveillance
C. External beam IMRT to 78Gy with ADT
D. LDR seed brachytherapy with ADT
E. External beam IMRT + HDR boost



What is your preferred management for a patient aged 66 years presenting with an IPSS of 19, PSA of 13.6, Gleason score 4+4 prostate cancer which is stage T3a on MR staging? He has no significant co-morbidities

A. Radical prostatectomy
B. Active surveillance
C. External beam IMRT to 78Gy with ADT
D. LDR seed brachytherapy
E. External beam IMRT + HDR boost



Does the technique matter?