ESTRO School

Teaching course on

BRACHYTHERAPY FOR PROSTATE CANCER

Course Director:
P. HOSKIN

Teaching staff:

B. AL-QAISIEH
J.-M. COSSET
S. MACHTENS
F.-A. SIEBERT

Contouring Administrator:
C. SALEMBIER

Local organiser:
G. GOLDNER

Project Manager:
G. AXELSSON

Brussels, Belgium
5-7 June 2016

ACKNOWLEDGEMENTS

ESTRO
the European Society for Radiotherapy and Oncology
wishes to thank:

Eckert & Ziegler BEBIG : www.bebig.com
Elekta : www.elekta.com
Varian Medical Systems: www.varian.com

For their support and collaboration in the promotion of the course

FALCON
Fellowship in Anatomic deLineation & CONtouring

This course includes delineation workshops performed in the framework of the Falcon platform

16th ESTRO Teaching Course on

BRACHYTHERAPY FOR PROSTATE CANCER

Introduction

Welcome to the beautiful city of Brussels for the 16th ESTRO Prostate Brachytherapy Course.

Over the last few years more and more younger men have been diagnosed with localised potentially curable prostate cancer. While radical prostatectomy remains the gold standard for treatment in many countries, there is an increasing interest in the role of brachytherapy which proves a much simpler alternative and achieves similar outcomes with less risk of severe side effects. Several thousand patients now have the treatment each year in Europe.

Prostate brachytherapy is not something that can be taken up by a solitary enthusiast. It requires a significant amount of team work and there needs to be careful attention to patient selection, techniques of implantation and quality assurance to ensure that optimum outcomes can be achieved. A very experienced teaching staff in all aspects of both HDR and LDR Brachytherapy will be present at the meeting and will be happy for you to ask questions both during or after the lectures. Please make use of their expertise.

We hope that the teaching course will provide a foundation to begin the steep learning curve towards the achievement of consistent high quality implants and that more patients will have the option to choose this form of treatment.

On behalf of the teaching staff,

Peter Hoskin,
Course Director

Teaching staff:

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siebert@onco.uni-kiel.de

Contouring Administrator:

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Europe Hospitals - Site St Elisabeth
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NOTE TO THE PARTICIPANTS OF THE ESTRO TEACHING COURSE ON

BRACHYTHERAPY FOR PROSTATE CANCER

The present texts and slides are provided to you as a basis for taking notes during the course. In as many instances as practically possible, we have tried to indicate from which author these slides have been borrowed to illustrate this course.

It should be realised that the present text can only be considered as notes for a teaching course and should not in any way be copied or circulated. They are only for personal use. Please be very strict in this as it is the only condition under which such services can be provided to the participants of the course.

Disclaimer

EUROPEAN ACCREDITATION COUNCIL FOR CONTINUING MEDICAL EDUCATION

Institution of the UEMS

This course has been accredited by ACOE/UEMS

The faculty of the teachers for this event has disclosed any potential conflict of interest that the teachers may have.

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ESTRO
TEACHING COURSE ON BRACHYTHERAPY FOR PROSTATE CANCER
Brussels, Belgium 5-7 June 2016

Teaching staff

B Al-Qaisieh	BA
JM Cosset	JMC
P Hoskin	PH
S Machtens	SM
C Salembier	CS
FA Siebert	FAS

Sunday June 5

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	JMC
10:00-10:30	Patient Selection for HDR seed brachytherapy	PH
10:30-11:00	BREAK	
11:00-11:30	QA for brachytherapy	BA
11:30-12:30	LDR seed techniques and video demonstrations	CS/JMC SM/BA
12:30-13:30	LUNCH	
13:30-14:30	HDR techniques and video demonstrations	PH/FAS
14:30-15:30	CTV definition	CS
15:30-16:00	BREAK	
16:00-16:30	Imaging for prostate brachytherapy	SM
16:30-17:00	Image registration and planning principles:	FAS/BA
17:00-17:30	Review and interactive session	

Monday June 6

09:00-09:40	Clinical results of LDR	CS
09:40-10:30	Clinical results of HDR	PH
10:30-11:00	BREAK	
11:00-1200	Interactive session: planning HDR & LDR	ALL
12:00-13:00	Post plan imaging, dosimetry and implications	FAS/CS
13:00-14:00	LUNCH	
14:00-14:40	Complications of prostate brachytherapy	SM
14:40-15:30	Management of toxicity and complications	SM

15:30-16:00	BREAK	
16:00-17:00	Radiation protection	JMC
1700-1730	Review and interactive session:	

Tuesday June 7

09:00-10:30	Focal therapy: concepts and LDR Focal therapy: HDR	JMC/SM PH
10:30-11:00	BREAK	
11:00-11:30	Brachytherapy for salvage	JMC
11:30-12:00	Prostate brachytherapy: LDR, HDR, surgery or IMRT	PH
12:00-12:30	Final discussion session	All

A NEW AND IMPROVED MEMBERSHIP PROGRAMME
Bringing you more benefits & online services

BECOME AN ESTRO MEMBER
TODAY AND JOIN THE RADIATION
ONCOLOGY COMMUNITY

ESTRO members

ESTRO has renewed its membership categories for 2013 in order to bring you more benefits that are better suited to your needs. ESTRO's mission is to guide your day-to-day professional development and to disseminate all the latest findings and knowledge that are crucial to our rapidly evolving field.
Join ESTRO, become an integral part of the Radiation Oncology Community.

The European SocieTy for Radiotherapy & Oncology (ESTRO), with its active community of over 5000 members, has supported the role of Radiation Oncology within the multidisciplinary treatment of cancer for more than 30 years.

ESTRO is the ideal platform for the sharing of cutting-edge knowledge and ground-breaking know-how within the radiation oncology community. ESTRO provides numerous high-level educational opportunities through teaching courses, organises conferences and congresses that are at the forefront of our specialisation, and is responsible for several top-notch publications.

The Society has the mission to represent all the Radiotherapy professionals: Radiation Oncologists, Medical Physicists in the field of Radiotherapy, Radiobiologists and RTT (Radiotherapy Technologists). Membership is also open to other oncology specialists such as Medical Oncologists, Surgeons, Nuclear Medicine Physicians...

By joining ESTRO, you will receive numerous benefits that have been carefully designed to support and advance your career. We invite you to peruse the many Membership categories on offer and to sign-up for the one that is best tailored to meet your professional requirements.

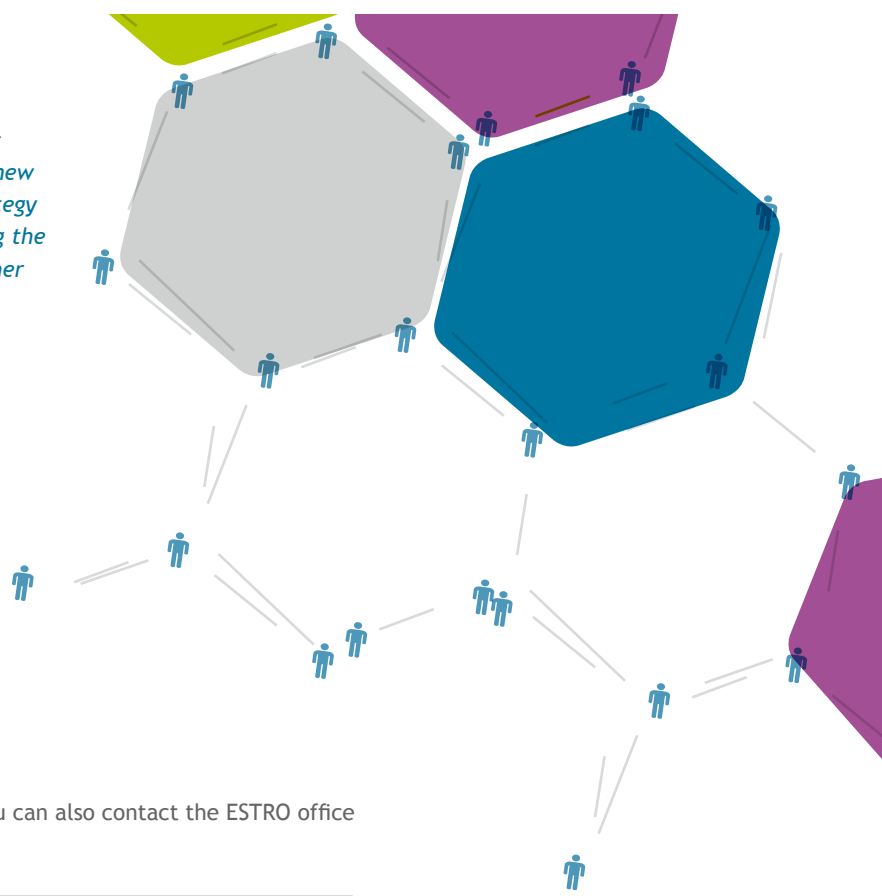
NEW FOR 2013!

ESTRO is developing additional new online services which will be functional as of January 2013: through our new search engine you will be able to access a comprehensive e-library containing documents such as the Green Journal and conference abstracts, webcasts, posters, free access to FALCON (our delineation tool), our newsletter, etc.

Don't forget that you can register for the 2013 ESTRO conferences and teaching courses at a discounted rate as soon as you have signed up for your 2013 membership!

"The new communication tools and on-line services create a personalised platform to help ESTRO members connect and network. Moreover, ESTRO members will find an environment that will stimulate education and development. As such the new membership categories will be an important part of the strategy of realising the central vision statement of ESTRO by offering the necessary tools for the individual member to develop his or her professional skills in the interests of our patients."

Dirk Verellen, ESTRO Membership Officer



How can you become an ESTRO member?

Please apply online via the ESTRO website www.estro.org. You can also contact the ESTRO office by email or by phone for any assistance you may require.

ESTRO
Rue Martin V, 40
1200 Brussels
Belgium

Tel.: +32 2 775 93 40
Fax: +32 2 779 54 94
Email: membership@estro.org
Website: www.estro.org

ESTRO
EUROPEAN SOCIETY FOR
RADIOTHERAPY & ONCOLOGY

INDIVIDUAL MEMBERSHIP | FULL

Full Membership is open to all healthcare providers who are active in the field of cancer care and/or cancer research, as well as related areas in a non-commercial setting.

ACTIVE MEMBER

Active Membership is open to all Radiation Oncology professionals. This category entitles you to the most complete range of benefits that the Society has on offer.

SUPPORTING AMBASSADOR MEMBERSHIP

This category is reserved for individuals who are strongly committed to the Society and who want to take an extra step to help ESTRO develop further by paying a higher membership fee. The additional income generated by these big-hearted members will be used to create a solidarity fund. The fund will be available to sponsor the membership fee of less fortunate individuals, finance support grants for ESTRO events, and help to ensure that Radiation Oncology professionals from economically challenged countries are also able to participate in our scientific arena.

INDIVIDUAL MEMBERSHIP | ASSOCIATE

IN TRAINING MEMBER

This category is open to all European healthcare providers who are active in the field of Radiation Oncology, as well as related areas in a non-commercial setting. In training members must be under the age of **35**, have relevant professional experience or a university diploma granted less than 5 years ago, and currently be in training.

AFFILIATE MEMBER

This category is available for Radiation Oncology professionals and/or individuals interested in the field of Radiation Oncology who do not require full involvement in the society but who still wish to enjoy some of the more basic benefits on offer.

CORPORATE REPRESENTATIVE

This category is reserved for individual members working for a company.

ESTRO membership runs from the 1st of January to the 31st of December.
N.B.: Please note these important changes: RTTs will now belong to all membership categories without distinction of disciplines. When registering for courses or conferences, whatever the membership category they belong to, RTTs will benefit from the 'In Training' rate.

PACKAGES OF BENEFITS FOR INDIVIDUAL MEMBERS

FULL MEMBERSHIP

SUPPORTING AMBASSADOR | 250€	will benefit from A + B + C + D + E
ACTIVE MEMBER | 95€	will benefit from A + B + C + D

ASSOCIATE MEMBERSHIP

IN TRAINING MEMBER | 75€	will benefit from A + B + C
AFFILIATE MEMBER | 55€	will benefit from A + B
CORPORATE REPRESENTATIVE | 55€	will benefit from A

A

- Subscription to the Green Journal
- Discounted price for ESTRO Publications and Handbooks
- Online access to ESTRO Handbooks
- Subscription to the ESTRO Newsletter
- Access to Conference Abstract Books
- Access to ESTRO Guidelines
- Access to the ESTRO Annual Reports

A

All the benefits listed above + Reduced registration fee for one ESTRO Conference or teaching course of choice per year (incl. joint conferences and courses)

B

- Eligibility for Awards
- Access to the "Members area" on the ESTRO website (read only)
- Access to Job advertisements
- Access to the ESTRO Annual Reports
- Reduced subscription rate to the European Journal of Cancer

B

All the benefits listed above + the possibility to get either a reduced registration fee for one ESTRO Conference or teaching course of choice (incl. joint conferences and courses) or a Grant once per year

C

- Reduced fee for attending ESTRO and Joint Conferences
- Reduced fee for attending ESTRO and Joint Courses
- Eligibility for Grants and Awards
- Eligibility to participate in ESTRO's Governance Activities
- Access to FALCON Cases (basic)
- Access to the Webcast library (after 6 months)

C

All the benefits listed above + Access to Membership Directory (young corner)

D

- Eligibility for Grants, Awards and Fellowships
- Eligibility for Working Groups, Task Force Groups, and Faculties
- Eligibility to hold formal positions such as President, being on the Board of Directors, Councils, Standing Committees, and participation in ESTRO's Governance Activities
- Access to the Membership Directory
- Access to the "Members area" on the ESTRO website enabling you to read and/or upload your presentations and research, etc.
- Voting rights in the General Assembly

E

- Online access to educational materials
- Contribution to the ESTRO Ambassador Solidarity fund (acknowledgement in the ESTRO webpage)
- Access to FALCON Cases (basic and endorsed cases)
- Access to the Webcast library (immediate access)

OTHER CATEGORIES

ESTRO can choose to bestow the following membership categories upon specially selected individuals. Neither of these memberships can be signed-up for.

HONORARY MEMBERSHIP

Honorary Members are professionals who have made a noteworthy contribution towards ESTRO's mission. They are selected by the Nominating Council of ESTRO.

DUAL MEMBERSHIP

This category can be granted to individual members who benefit from a JOINT membership agreement. The agreements are signed on a case-by-case basis between ESTRO and a National Society; the membership fee is covered by the annual fee paid by the partnering Society. The member is entitled to the same benefits as an Affiliate Member (with the exception that the discounted rate for attending courses and conferences is not limited to just one a year).

INSTITUTIONAL MEMBERSHIP

Institutional Membership is available for institutes who are willing to purchase several individual memberships in batch for their members. Your institute can buy several individual memberships (all benefits included) and enjoy additional benefits such as registration packages for online workshops, a dedicated corner in the Newsletter, the opportunity to disseminate standards/guidelines within the organisation and much more. Read the full details of all package deals available for institutes and the related list of benefits on www.estro.org or contact the ESTRO office by e-mail: institutional-membership@estro.org.

ESTRO

European SocieTy for
RADIOTHERAPY
& ONCOLOGY

www.estro.org

ESTRO VISION 2020

Every cancer patient in Europe will have access to state of the art radiation therapy, as part of a multidisciplinary approach where treatment is individualized for the specific patient's cancer, taking into account the patient's personal circumstances

Radiotherapy & Oncology 103(2012) 99-101

ESTRO SCHOOL

Improve your knowledge with the ESTRO School

The ESTRO School develops a wide array of educational activities that cover:

- Annual live teaching courses
- Pre-meeting teaching courses
- Workshops and teaching lectures during congresses
- E-learning courses and tools
- Hands-on experience through a mobility grants programme

ESTRO School

ESTRO SCHOOL OF RADIOTHERAPY AND ONCOLOGY

2016

ESTRO School

WWW.ESTRO.ORG

POSTGRADUATE COURSES IN EUROPE

BASIC CLINICAL RADIOBIOLOGY
27 February - 2 March 2016 | Budapest, Hungary

DOSE MODELLLING AND VERIFICATION FOR EXTERNAL BEAM RADIOTHERAPY
6 - 10 March 2016 | Utrecht, The Netherlands

MODERN BRACHYTHERAPY TECHNIQUES
13 - 16 March 2016 | Florence, Italy

PARTICLE THERAPY
14 - 18 March 2016 | Krakow, Poland

IMRT AND OTHER CONFORMAL TECHNIQUES IN PRACTICE
3 - 7 April 2016 | London, UK

TARGET VOLUME DETERMINATION - FROM IMAGING TO MARGINS
10 - 13 April 2016 | Barcelona, Spain

ESTRO 35 PRE-MEETING COURSES
29 April 2016 | Turin, Italy

ESNM/ESTRO COURSE ON MOLECULAR IMAGING AND RADIATION ONCOLOGY
19 - 22 May 2016 | Lisbon, Portugal

MULTIDISCIPLINARY MANAGEMENT OF PROSTATE CANCER
22 - 26 May 2016 | Istanbul, Turkey

LOWER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS NEW
25 - 27 May 2016 | Brussels, Belgium

UPPER GI: TECHNICAL AND CLINICAL CHALLENGES FOR RADIATION ONCOLOGISTS NEW
28 - 31 May 2016 | Brussels, Belgium

ADVANCED BRACHYTHERAPY PHYSICS
29 May - 1 June 2016 | Vienna, Austria

BRACHYTHERAPY FOR PROSTATE CANCER
5 - 7 June 2016 | Brussels, Belgium

CLINICAL PRACTICE AND IMPLEMENTATION OF IMAGE-GUIDED STEREOTACTIC BODY RADIOTHERAPY
5 - 9 June 2016 | Athens, Greece

EVIDENCE BASED RADIATION ONCOLOGY
How to evaluate the scientific evidence and apply it to daily practice
12 - 17 June 2016 | Porto, Portugal

ADVANCED SKILLS IN MODERN RADIOTHERAPY
19 - 23 June 2016 | Dublin, Ireland

MULTIDISCIPLINARY MANAGEMENT OF HEAD AND NECK ONCOLOGY
26 - 29 June 2016 | Florence, Italy

HAEMATOLOGICAL MALIGNANCIES
In collaboration with ILROG
1 - 3 September 2016 | Vienna, Austria

PALLIATIVE CARE AND RADIOTHERAPY NEW
A course on prognosis, symptom control, re-irradiation, oligometastases
8 - 10 September 2016 | Brussels, Belgium

PHYSICS FOR MODERN RADIOTHERAPY
A joint course for clinicians and physicists
11 - 15 September 2016 | Athens, Greece

BASIC TREATMENT PLANNING
9 - 13 September 2016 | Cambridge, UK

ADVANCED TREATMENT PLANNING
14 - 18 September 2016 | Cambridge, UK

IMAGING FOR PHYSICISTS
18 - 22 September 2016 | Florence, Italy

COMPREHENSIVE QUALITY MANAGEMENT IN RADIOTHERAPY - RISK MANAGEMENT AND PATIENT SAFETY
1 - 4 October 2016 | Avignon, France

BIOLOGICAL BASIS OF PERSONALISED RADIATION ONCOLOGY
17 - 20 October 2016 | Montpellier, France

IMAGE-GUIDED AND ADAPTIVE RADIOTHERAPY IN CLINICAL PRACTICE
23 - 27 October 2016 | Madrid, Spain

BEST PRACTICE IN RADIATION ONCOLOGY – A WORKSHOP TO TRAIN RTT TRAINERS
In collaboration with the IAEA
Part I - Train the RTT (Radiation Therapists) trainers
24 - 28 October 2016 | Vienna, Austria

ESOR/ESTRO MULTIDISCIPLINARY APPROACH OF CANCER IMAGING
10 - 12 November 2016 | Amsterdam, The Netherlands

ACCELERATED PARTIAL BREAST IRRADIATION
13 - 16 November 2016 | Paris, France

4TH ESO-ESTRO MASTERCLASS IN RADIATION ONCOLOGY
19 - 23 November 2016 | Prague, Czech Republic

POSTGRADUATE COURSES OUTSIDE EUROPE

IMAGE-GUIDED CERVIX CANCER RADIOTHERAPY - WITH A SPECIAL FOCUS ON ADAPTIVE BRACHYTHERAPY
4 - 6 April 2016 | Toronto, Canada

MULTIDISCIPLINARY MANAGEMENT OF BREAST CANCER
20 - 22 May 2016 | Tokyo, Japan

MULTIDISCIPLINARY MANAGEMENT OF LUNG CANCER
26 - 28 June 2016 | Moscow, Russia

BASIC CLINICAL RADIOBIOLOGY
3 - 7 July 2016 | Chengdu, China

EVIDENCE BASED RADIATION ONCOLOGY
How to evaluate the scientific evidence and apply it to daily practice
20 - 25 November 2016 | Sydney, Australia

PAEDIATRIC RADIATION ONCOLOGY
3 - 5 December 2016 | Bangkok, Thailand

ADVANCED TECHNOLOGIES
6 - 10 December 2016 | Pune, India

UNDERGRADUATE COURSES

MEDICAL SCIENCE SUMMER SCHOOL ONCOLOGY FOR MEDICAL STUDENTS NEW
4 - 15 July 2016 | Groningen, The Netherlands

ESO-ESSO-ESTRO MULTIDISCIPLINARY COURSE IN ONCOLOGY FOR MEDICAL STUDENTS NEW
29 August - 9 September 2016 | Poznan, Poland

MULTIMODAL CANCER TREATMENT | RADIOTHERAPY TREATMENT PLANNING AND DELIVERY | BIOLOGY | IMAGING | BEST PRACTICE

IMPROVE YOUR DELINEATION SKILLS WITH FALCON

FALCON
Fellowship in Anatomic deLineation & CONtouring

FALCON* is ESTRO's contouring platform that offers you the opportunity to practise your delineation skills online and to compare them with those made by experts and with the ESTRO/international guidelines.

3 FALCON cases for ESTRO members

Direclty accessible on DOVE, ESTRO's platform:

- Head and neck cancer
- Lymphoma
- Gynaecological cancer

* Fellowship in Anatomic delineation and CONtouring

ESTRO School

NEXT FALCON WORKSHOP

Lymphoma

- 14 June 2016
- 21 June 2016
- 5 July 2016

Each workshop includes 3 sessions

ESTRO School

E-LEARNING

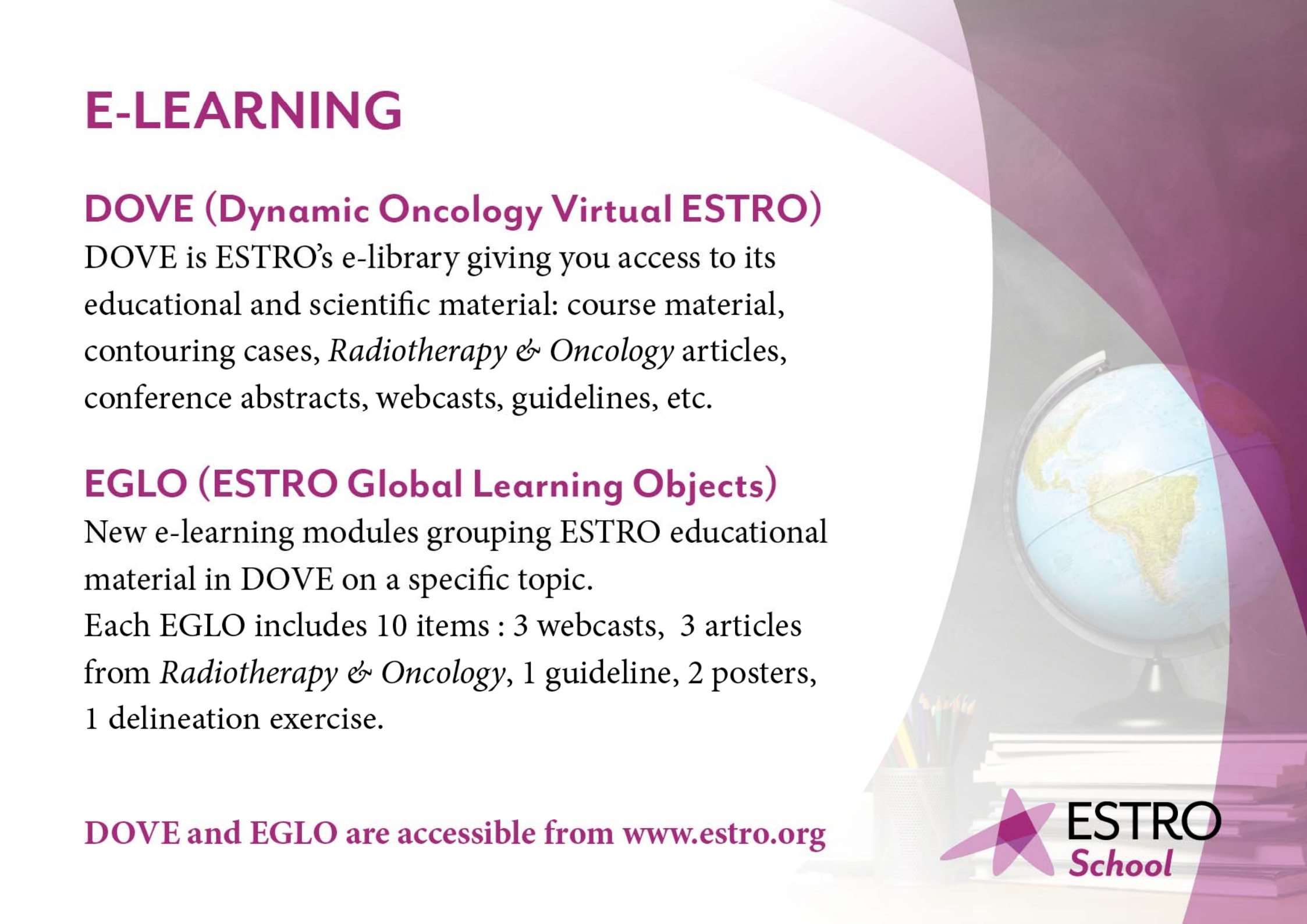
DOVE (Dynamic Oncology Virtual ESTRO)

DOVE is ESTRO's e-library giving you access to its educational and scientific material: course material, contouring cases, *Radiotherapy & Oncology* articles, conference abstracts, webcasts, guidelines, etc.

EGLO (ESTRO Global Learning Objects)

New e-learning modules grouping ESTRO educational material in DOVE on a specific topic.
Each EGLO includes 10 items : 3 webcasts, 3 articles from *Radiotherapy & Oncology*, 1 guideline, 2 posters, 1 delineation exercise.

DOVE and EGLO are accessible from www.estro.org



ESTRO School

ESTRO FELLOW

The ESTRO Fellow is a mark of distinction for competencies in radiation oncology.

The ESTRO Fellow process includes 3 steps and requires that candidates:

1. Meet the criteria

- Be an ESTRO member
- Be a board certified specialist in radiation or clinical oncology
- Have completed at least two years of working experience
- Have at least 50 ESTRO credits (attendance at ESTRO conferences and courses, online workshops, and publications in the *Green Journal*).

2. Send the application form

Deadline to submit the application form is on 5 April 2017.

3. Take the exam

The multiple choice exam will take place on 5 May 2017 in Vienna during ESTRO 36.

More information and application form are available on the ESTRO website on:
www.estro.org/careers-grants/estro-fellow/index

ESTRO School

ESTRO MOBILITY GRANTS (TTG)

Visit another institute

In order to learn about or gain experience with a technique, equipment or its application that is not easily available in your institute and which would be useful to you and your department, you can visit another institute for one to three weeks, in Europe or outside.

Just apply for an ESTRO Mobility Grant, the so-called "Technology Transfer Grants" (TTG).

Next deadline: 31 October 2016

Check the selection criteria on www.estro.org

REDUCED FEES FOR 2016 COURSES

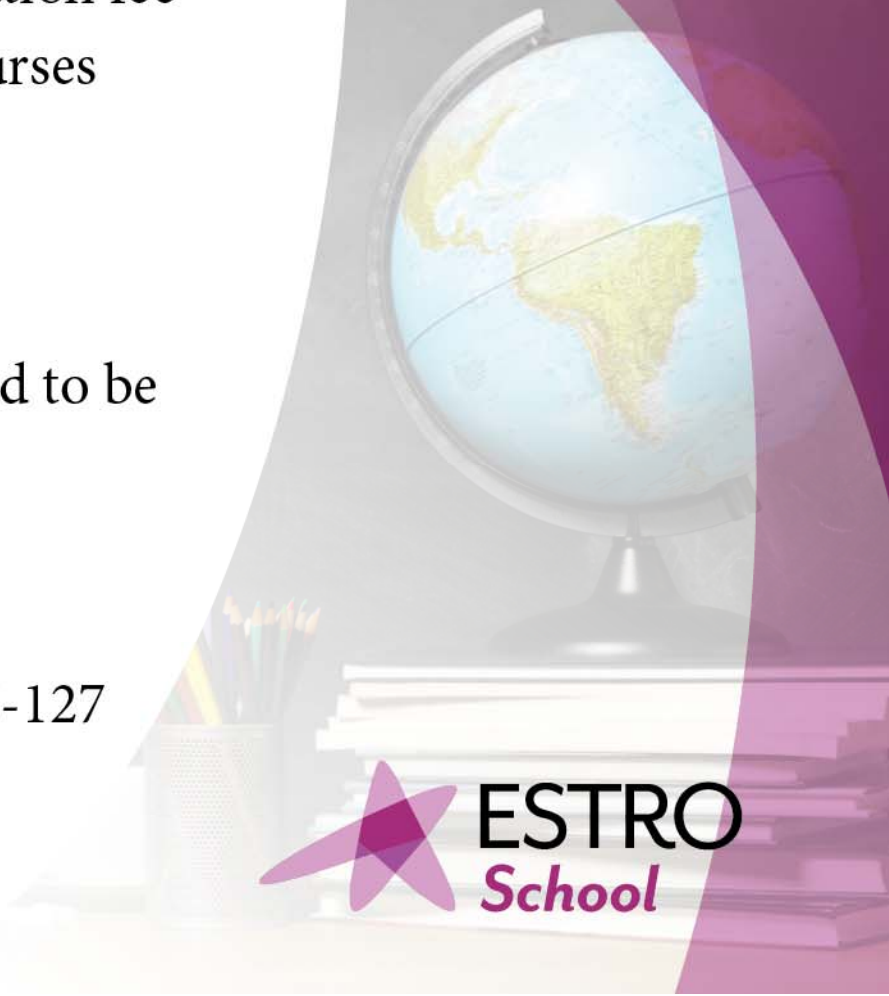
ESTRO members working in countries with a less competitive economic background can obtain a reduced registration fee and only pay 350€ to participate in live teaching courses organised in Europe.

How to apply

Applications forms and CV for the reduced fees need to be submitted to education@estro.org.

Eligible countries

Check the list of eligible countries and courses p126-127 of the 2016 ESTRO Guide or on www.estro.org



ESTRO School

ESTRO 36

5 - 9 May 2017

Vienna, Austria

WWW.ESTRO.ORG

ESTRO 36

5 - 9 May 2017 | Vienna, Austria

ESTRO 36 will draw attention on the multidisciplinarity and interdisciplinary components of radiation oncology, with emphasis on the new opportunities that they represent for all professionals of oncology, not only in research but also in the daily care of patients.

ESTRO 36

5 - 9 May 2017 | Vienna, Austria

Deadlines

- Abstract submission: 24 October 2016
- Early registration: 18 January 2017
- Late registration: 4 April 2017
- Desk registration as of 5 April 2017

6TH ICHNO

International Conference
on innovative approaches in

HEAD & NECK ONCOLOGY

16-18 March 2017
Barcelona, Spain

WWW.ESTRO.ORG

6TH ICHNO

16 - 18 March 2017 | Barcelona, Spain

Deadlines

- Early registration deadline: 26 October 2016
- Late registration deadline: 15 February 2017
- Desk registration as of 16 February 2017

4 GEC ESTRO workshop

FOURTH GEC-ESTRO WORKSHOP

"Techniques, Trials and Technologies for Brachytherapy Patients"

2-3 November 2016 | Poznan, Poland

ESTRO PUBLICATIONS

- ***Radiotherapy & Oncology***

- Publishes original research articles and review articles on all aspects of radiation oncology
- Is the leading publication in radiation oncology with an impact factor of 4.363
- Is a monthly publication available online and in hard-copy format to ESTRO members.

ESTRO NEWS APP

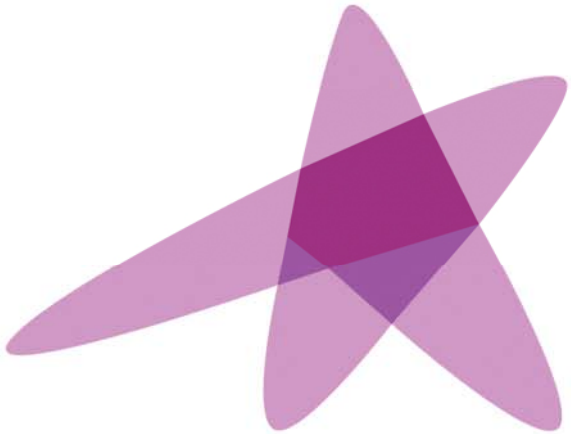
Keep pace with the activities of the Society and with the latest developments in radiation oncology

- The ESTRO newsletter is delivered in electronic format under the 'ESTRO News' app.
- The 'ESTRO News' app is available for:
  - tablets (Ipads and androids)
  - smartphones (android only)

The newsletter published every two months and covers a wide range of topics, and highlights – typically per discipline – latest advances, interviews with key opinion leaders, conference findings, research information, editor's picks, "Read it before your patients" columns, etc.

Each issue is also available on the ESTRO website.

App Store Google play



ESTRO School

WWW.ESTRO.ORG/SCHOOL

WELCOME TO ESTRO PROSTATE BRACHYTHERAPY IN BRUSSELS

ESTRO, Brussels
Gabriella Axelsson

ESTRO School

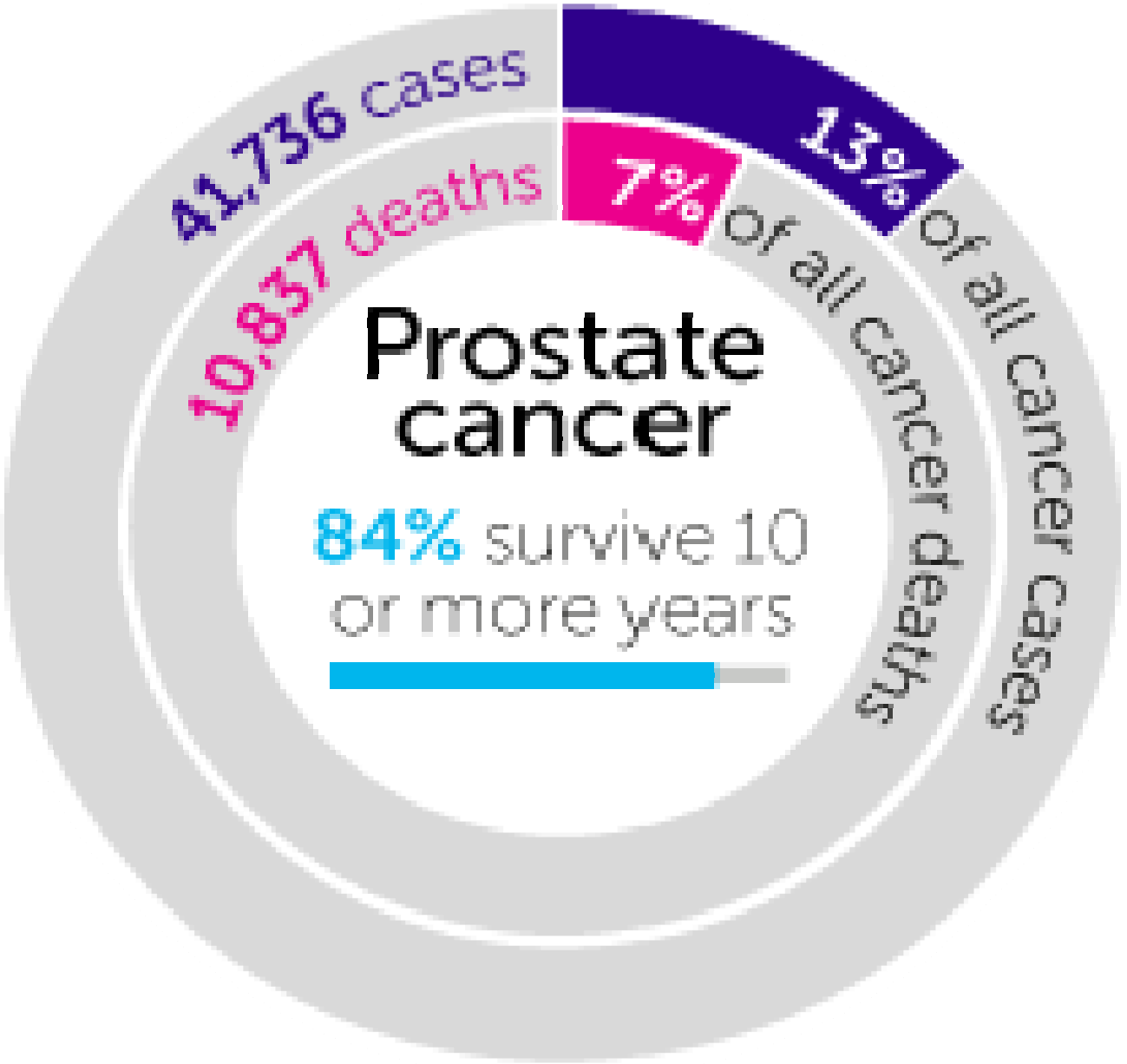
Your teachers ……..

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

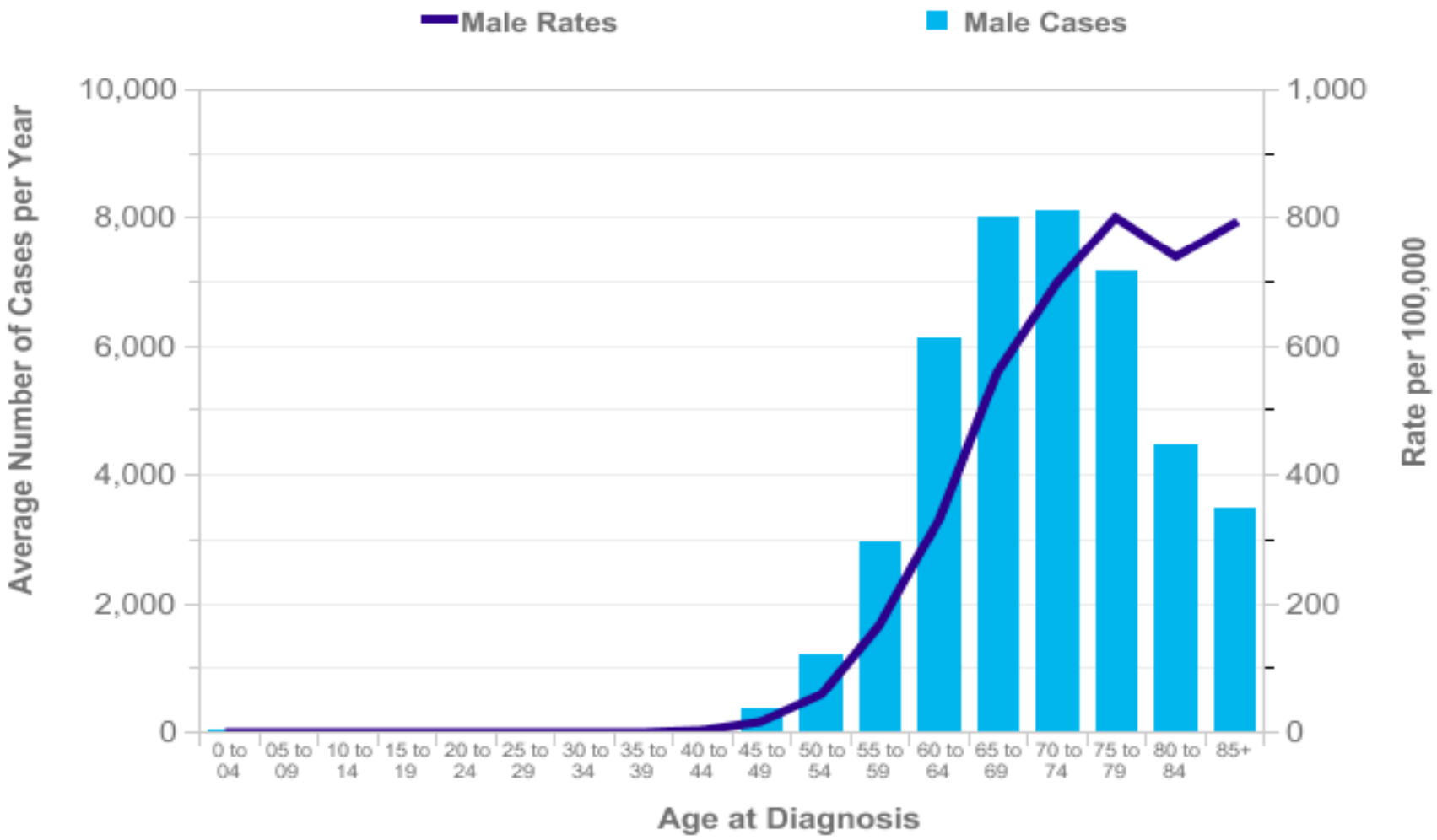
ESTRO School

Our exhibitors

- BSM
- Nucletron
- Varian


41,736 cases
10,837 deaths
13%
of all cancer cases
7%
of all cancer deaths
Prostate cancer
84% survive 10 or more years

Age specific incidence rates UK 2009/11



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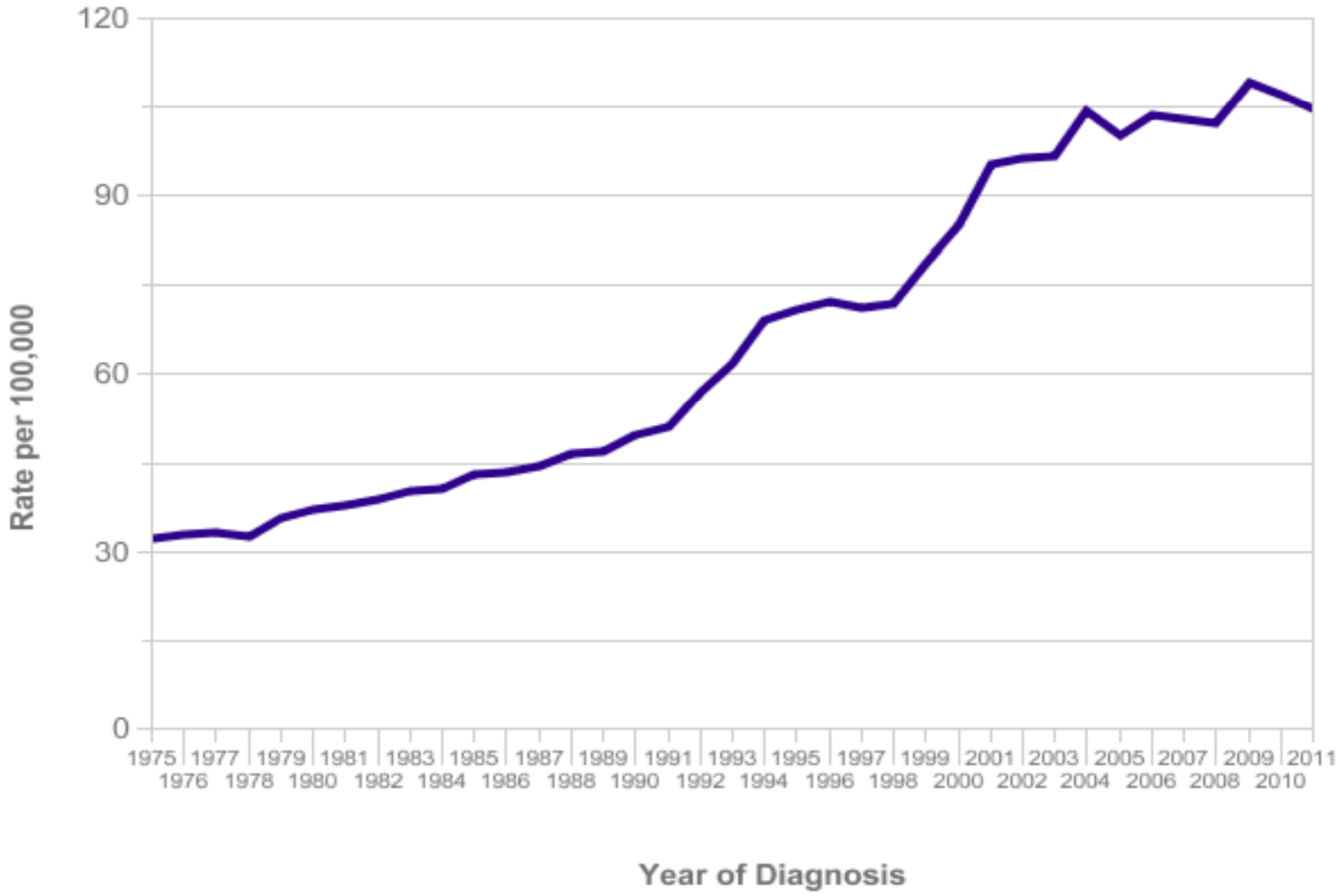
Age-Standardised Incidence Rates, , UK, 1993-2011



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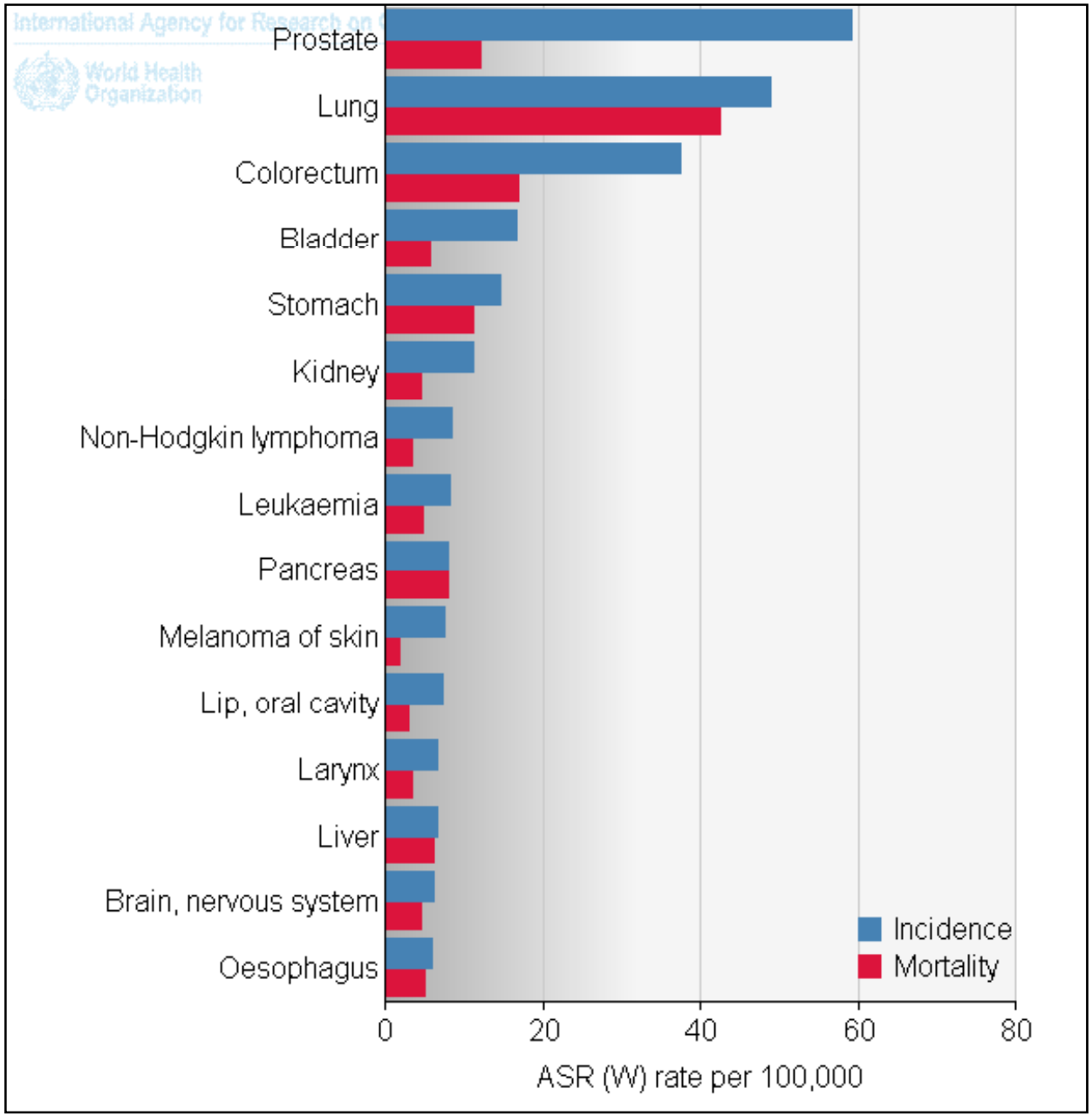
Cancer incidence and mortality, males, Europe: 2010



IARC

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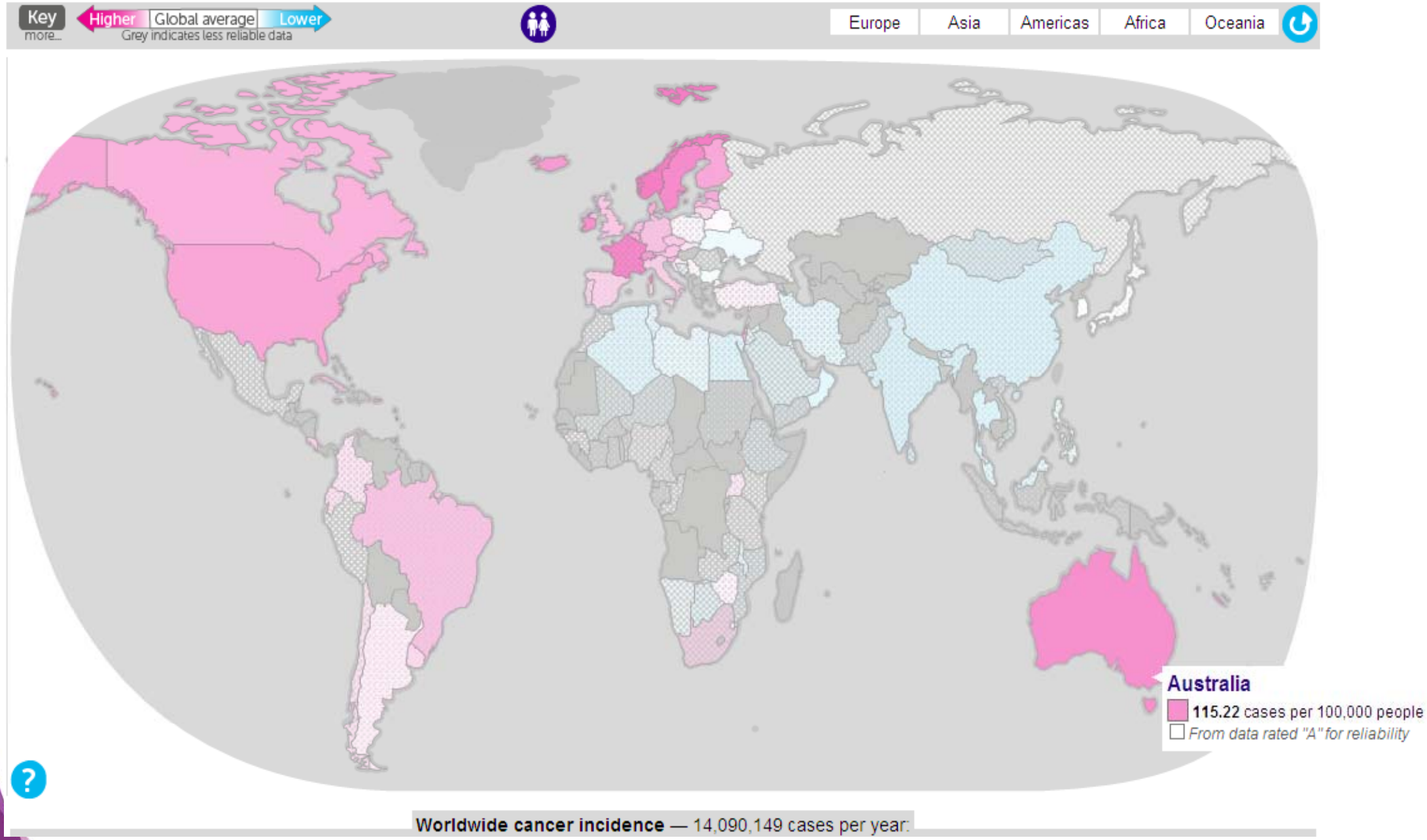
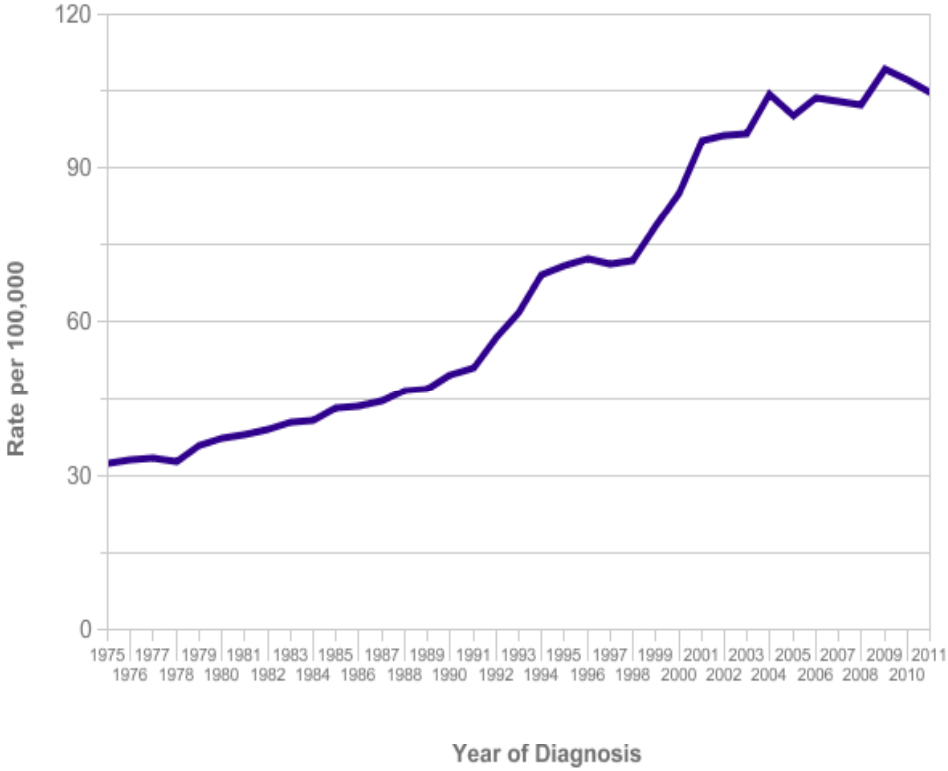
Prostate cancer incidence — Worldwide



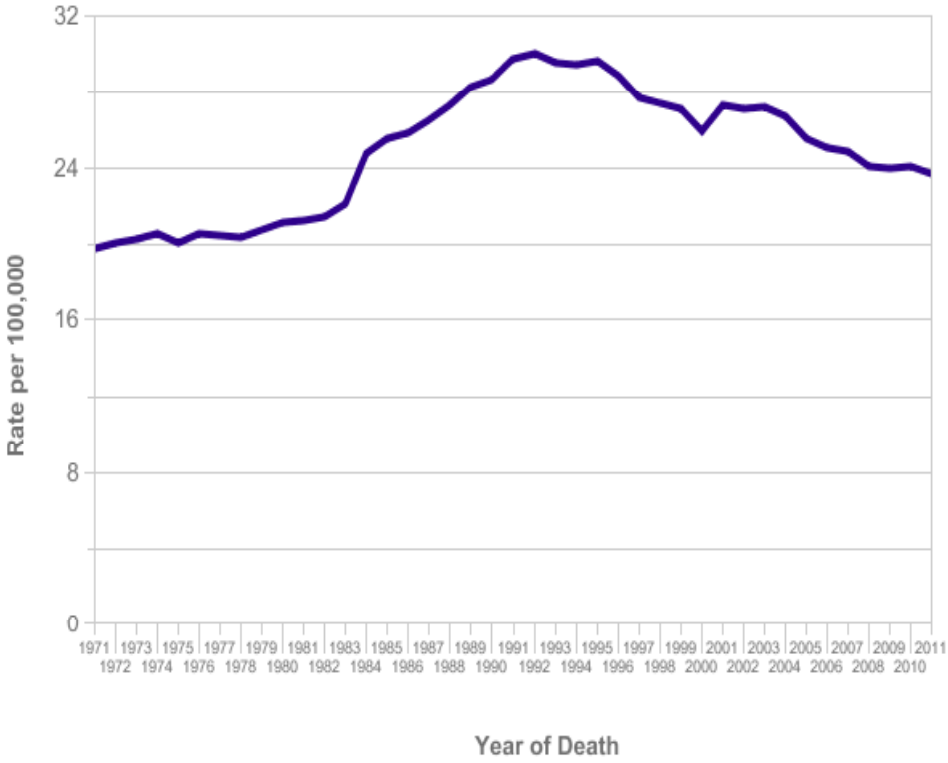
http://www.cancerresearchuk.org/cancer-info/cancerstats/world/incidence/#By

Age standardised incidence and mortality rates Europe 1975-2011

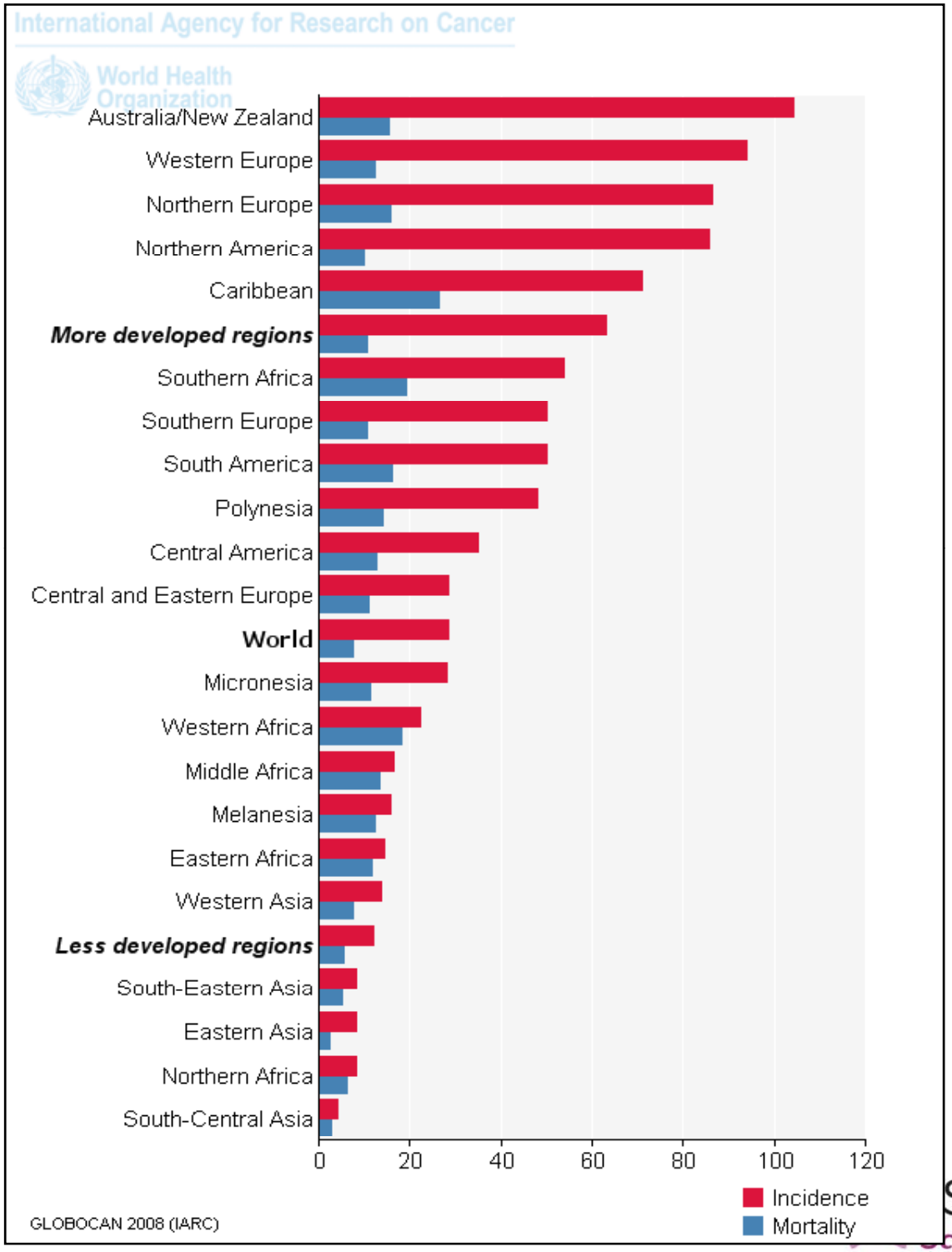
Incidence



Mortality



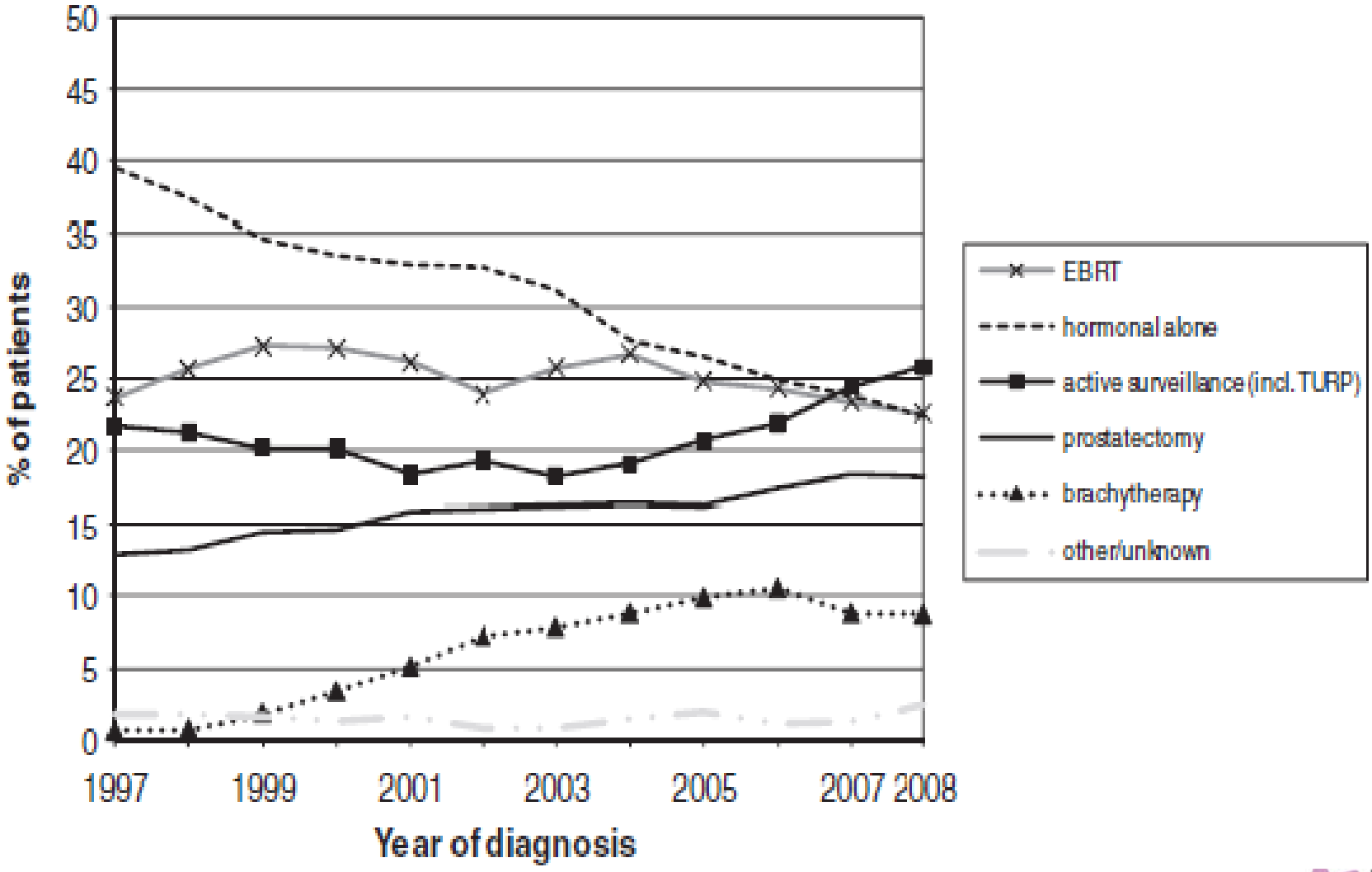
Worldwide
Age standardised incidence and mortality rates 2010



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



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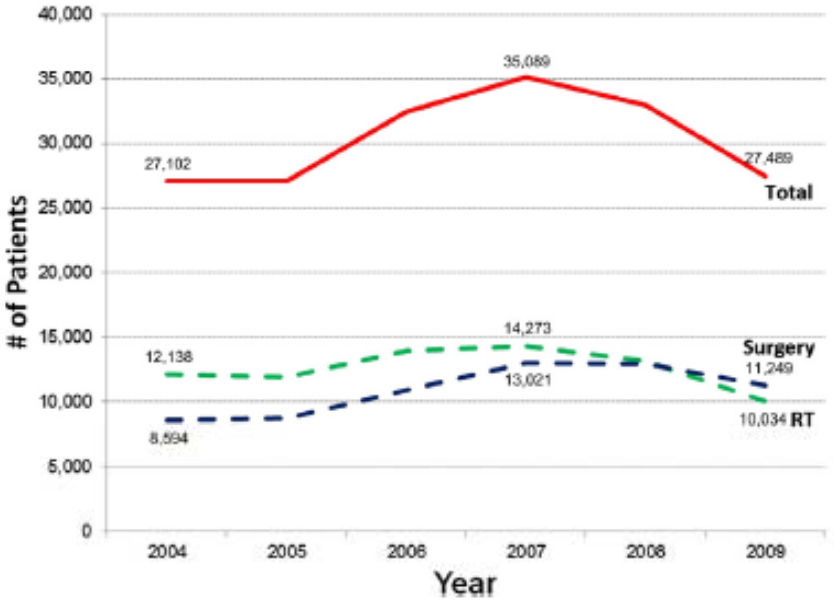
Declining use of brachytherapy for the treatment of prostate cancer

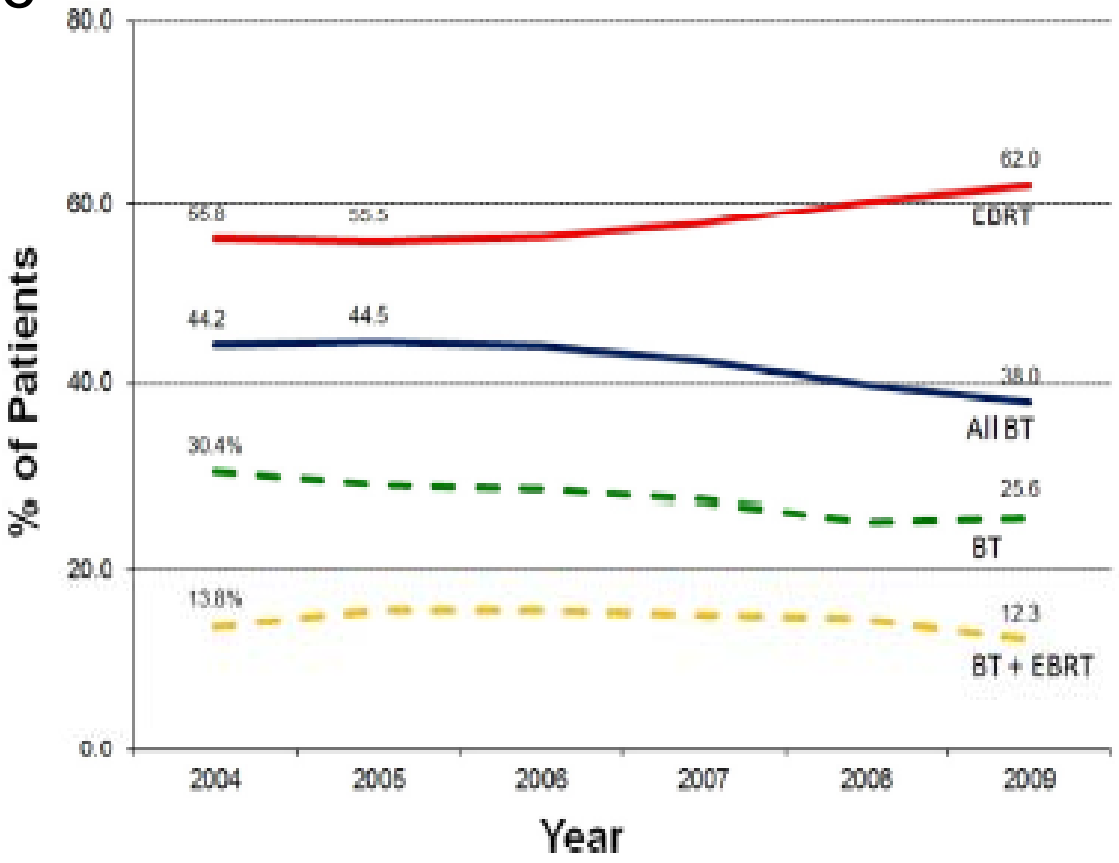
Usama Mahmood[1,*], Thomas Pugh[1], Steven Frank[1], Lawrence Levy[1], Gary Walker[1], Waqar Haque[1], Matthew Koshy[2], William Graber[3], David Swanson[3], Karen Hoffman[1], Deborah Kuban[1], Andrew Lee[1]

[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





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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:

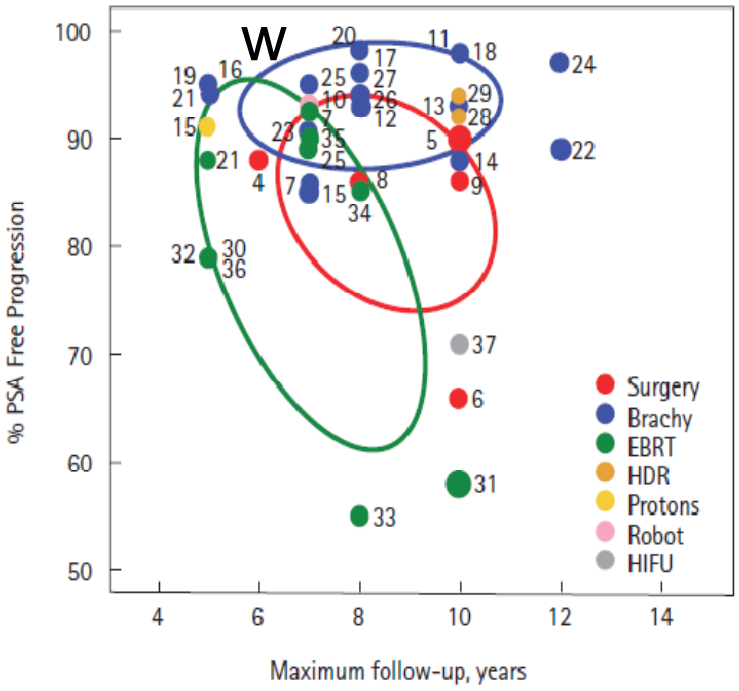
RP: 13-44%
EBRT: 43-56%
BT: 1.8-10.9%

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

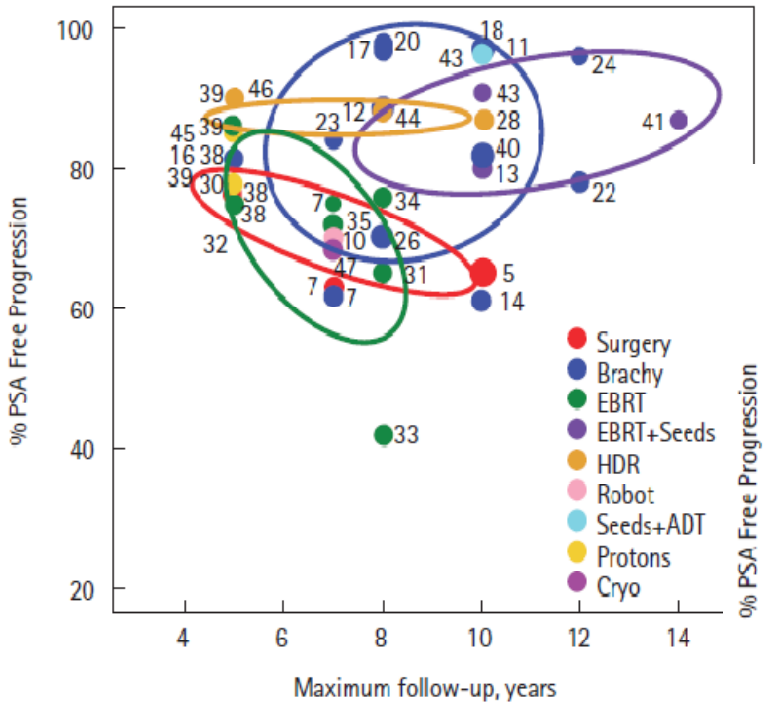
BJUI SUPPLEMENTS

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]

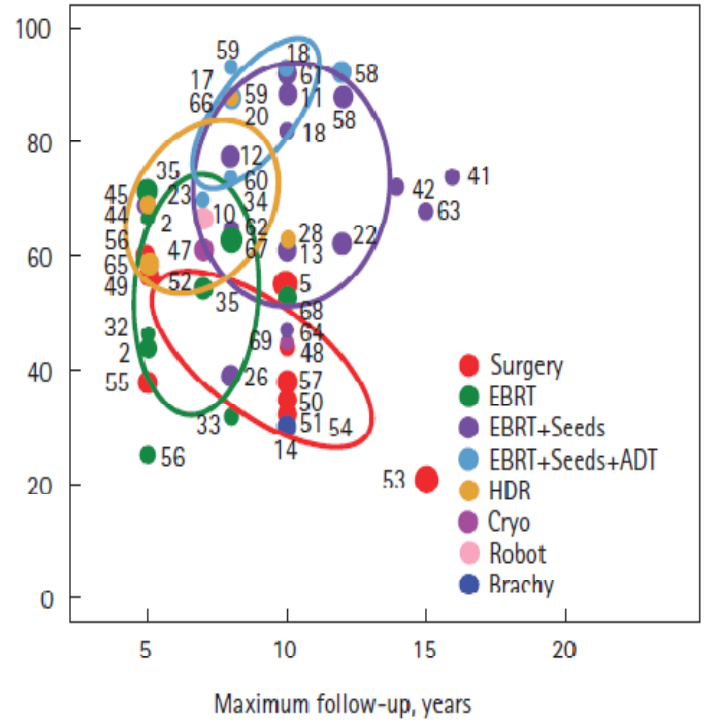
Low

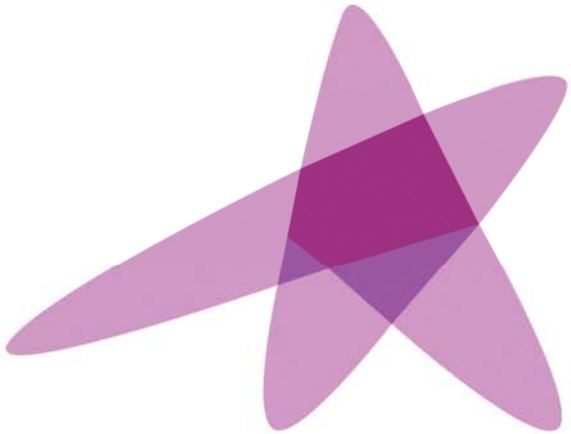


Intermediate



High





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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

With Courtesy from Geert Villeirs UZ Gent

ESTRO Teaching Course on Brachytherapy for Prostate Cancer
Brussels, June 05th-07th 2016

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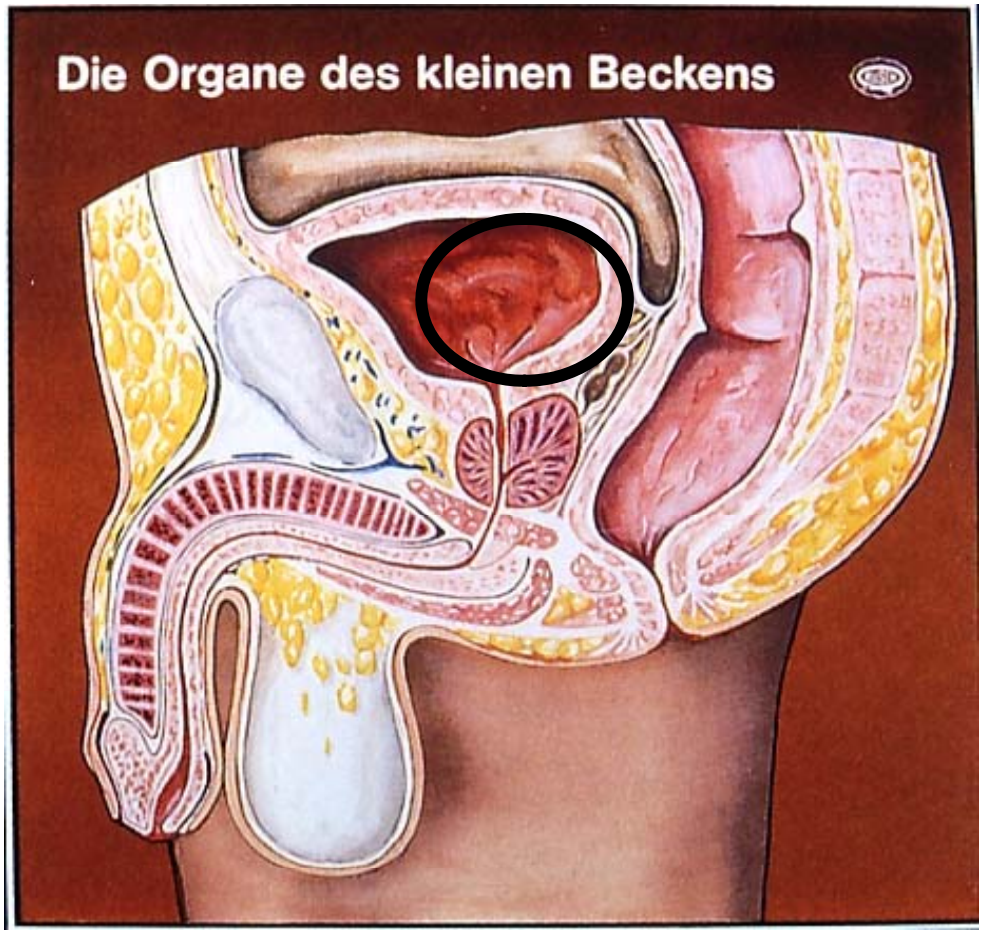
The prostate surrounds the urethra and is situated below the bladder.

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



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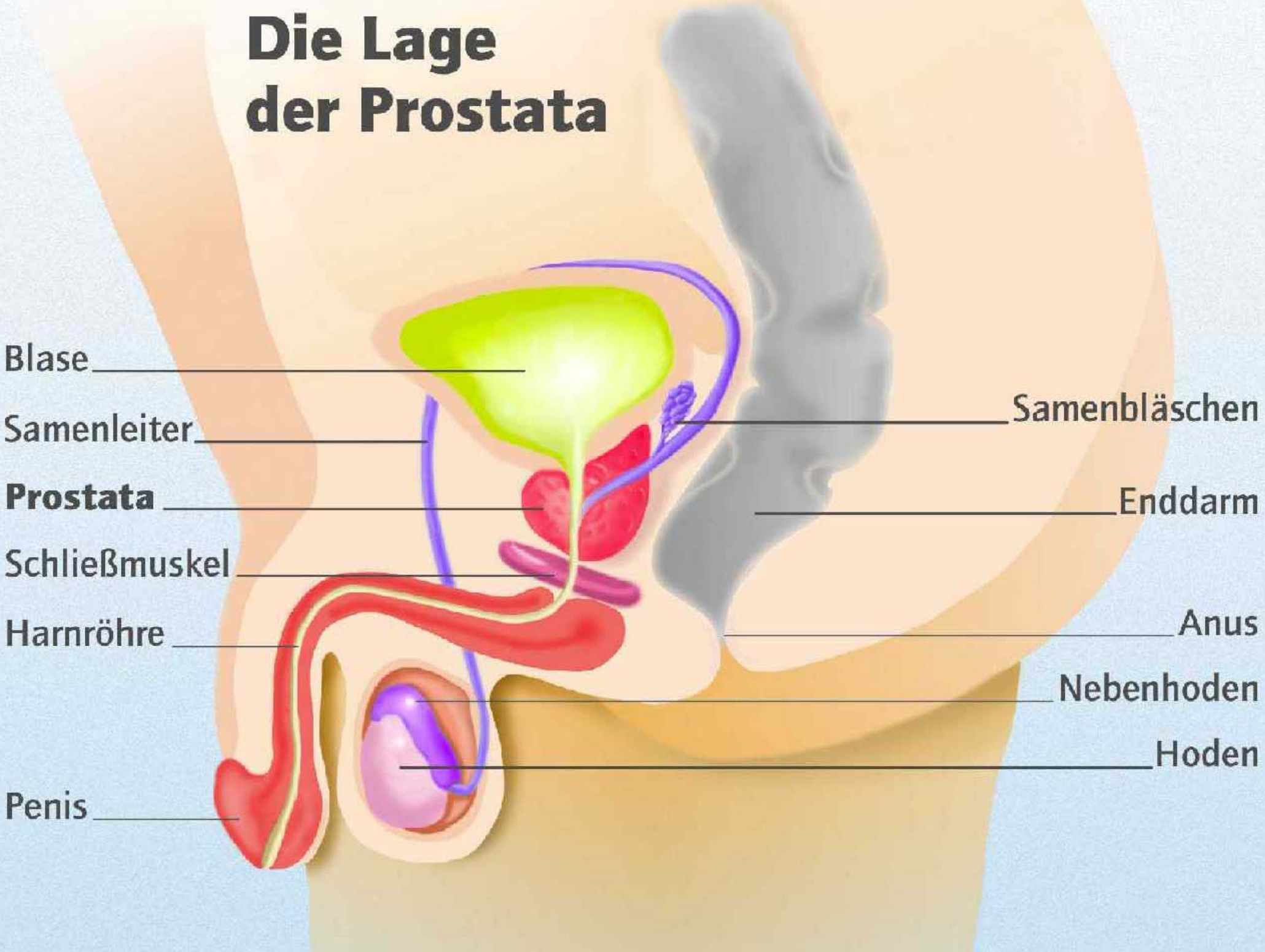
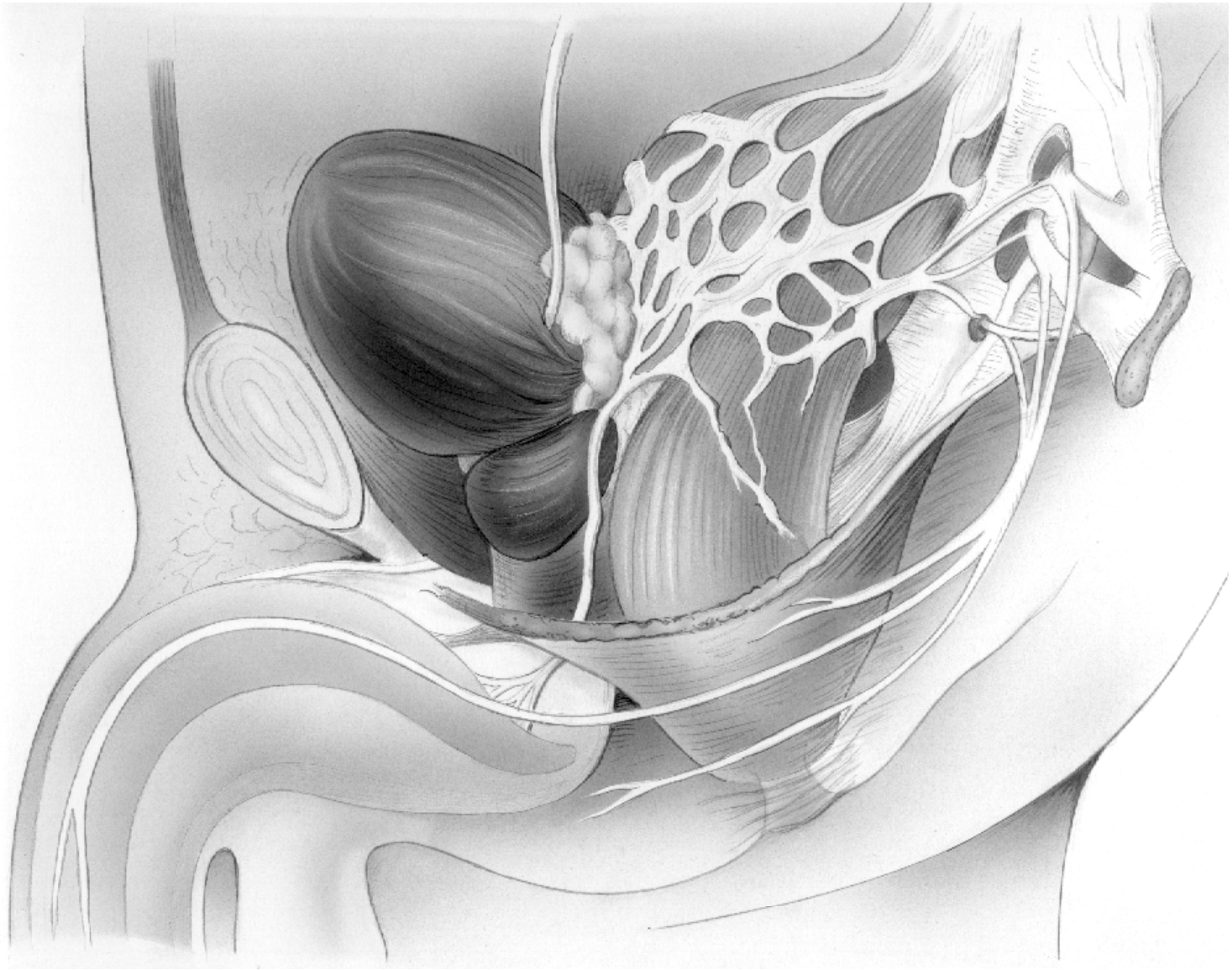
Die Lage der Prostata



Parasympathic nerves



Course of neurovascular bundle

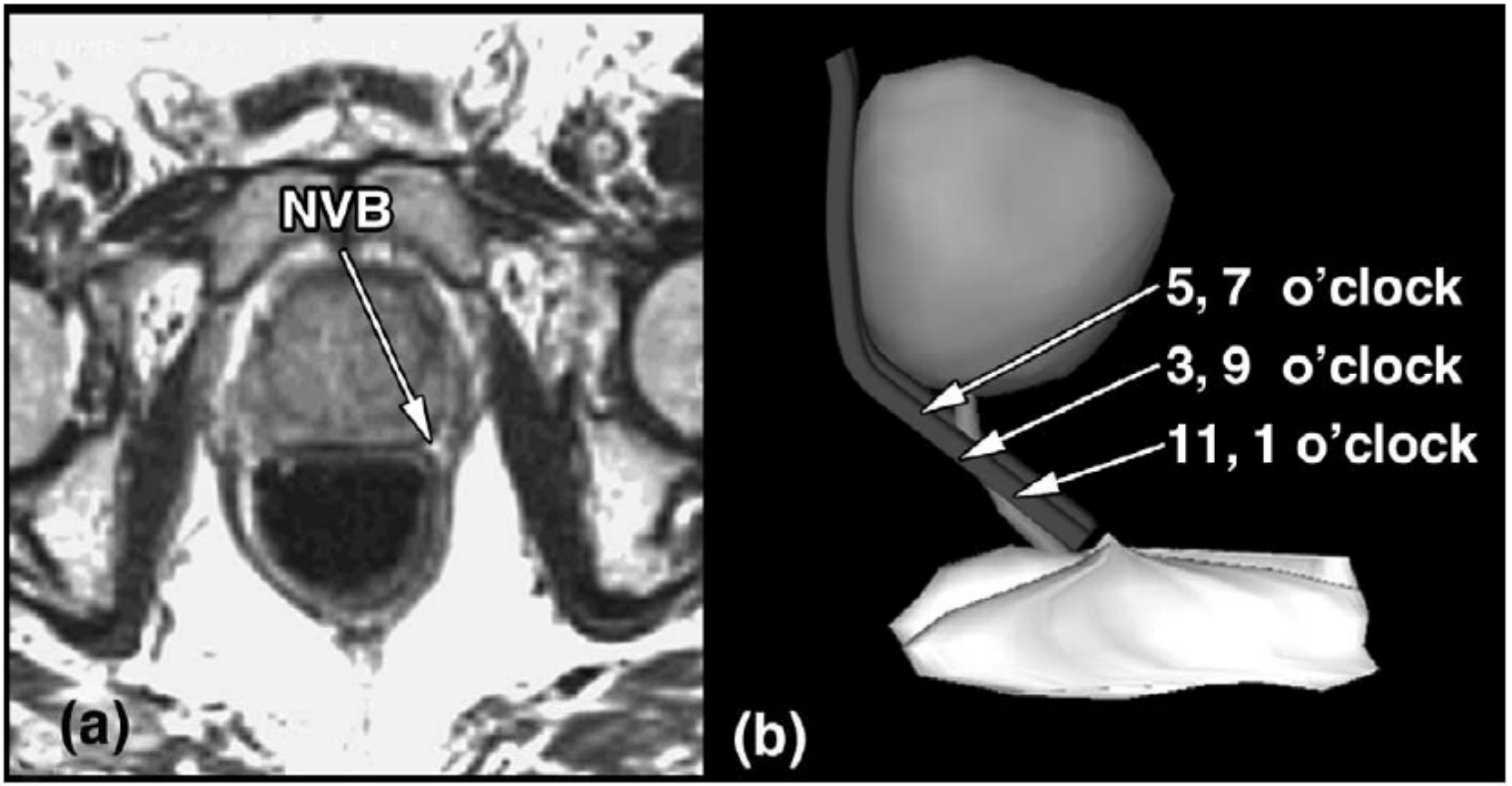


Fig. 7. Neurovascular bundle (NVB) and terminal branches. (a) Axial magnetic resonance imaging. (b) Three-dimensional reconstruction with cavernosal nerve defined by relationship to membranous urethra.

Nerve and vascular pathways

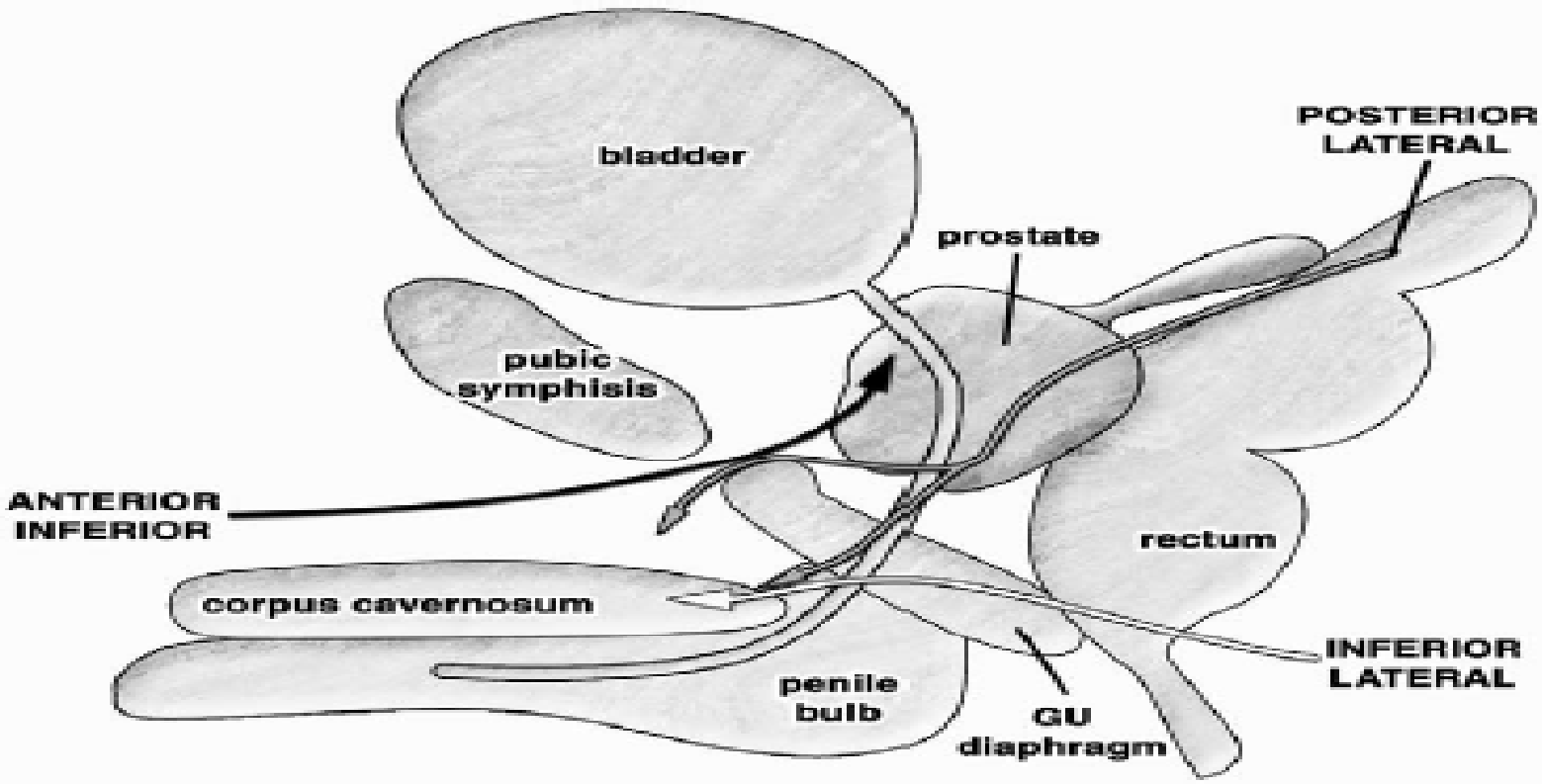
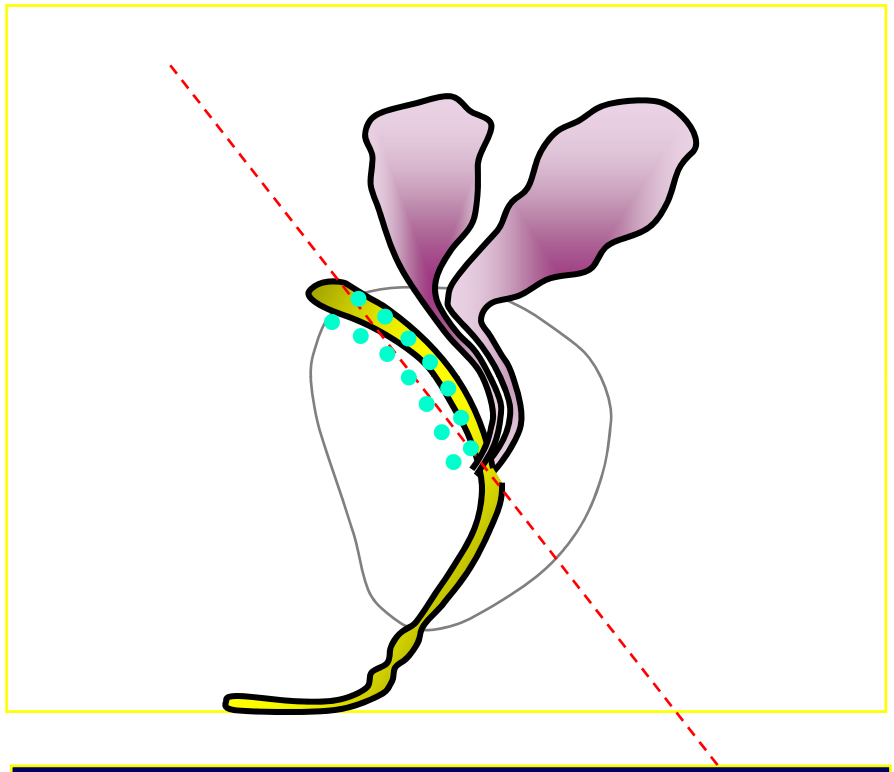
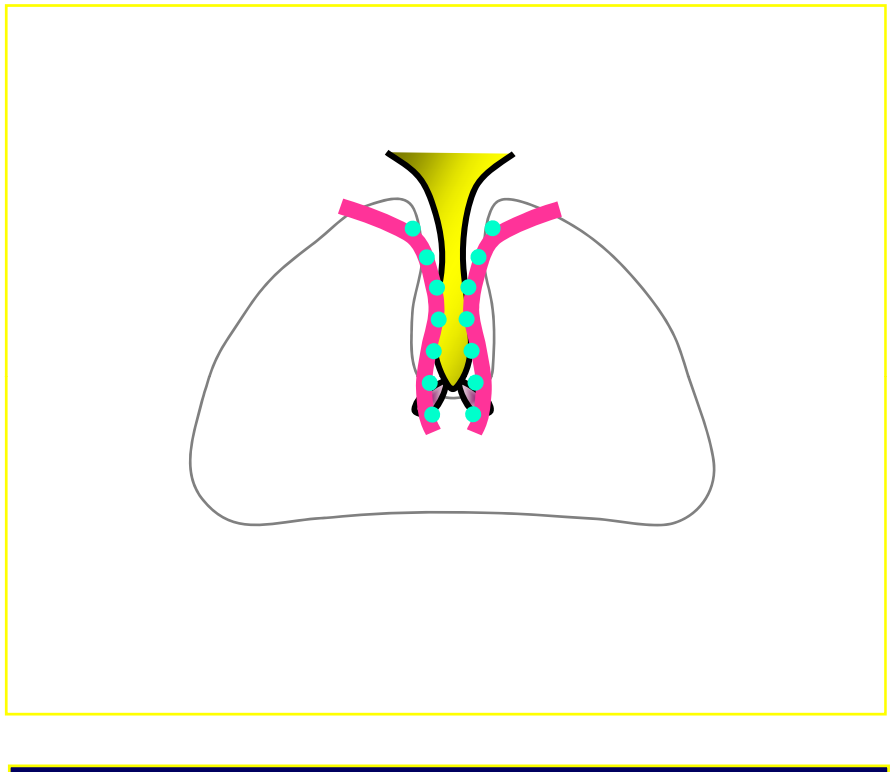


Fig. 3. Nerve and vascular pathways. The posterolateral (PL) pathway proceeds from superior (seminal vesicle) and along the posterior lateral prostate and pierces the genitourinary diaphragm (GUD) lateral to the urethra. The inferior lateral (IL) proceeds from posterior through the GUD and includes the internal pudendal artery and nerve. The anterior inferior (AI) proceeds under the pubic symphysis and over the anterior prostate surface and includes the dorsal venous complex.

Zonal Anatomy
Central Gland



Periurethral Glands



Periurethral Glands
(paracoronal view)

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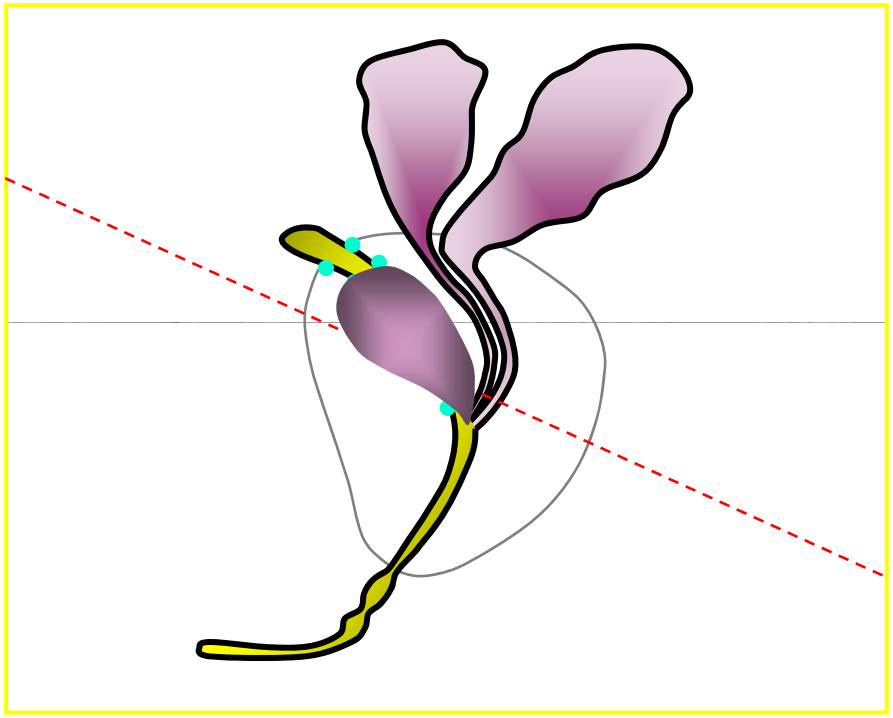
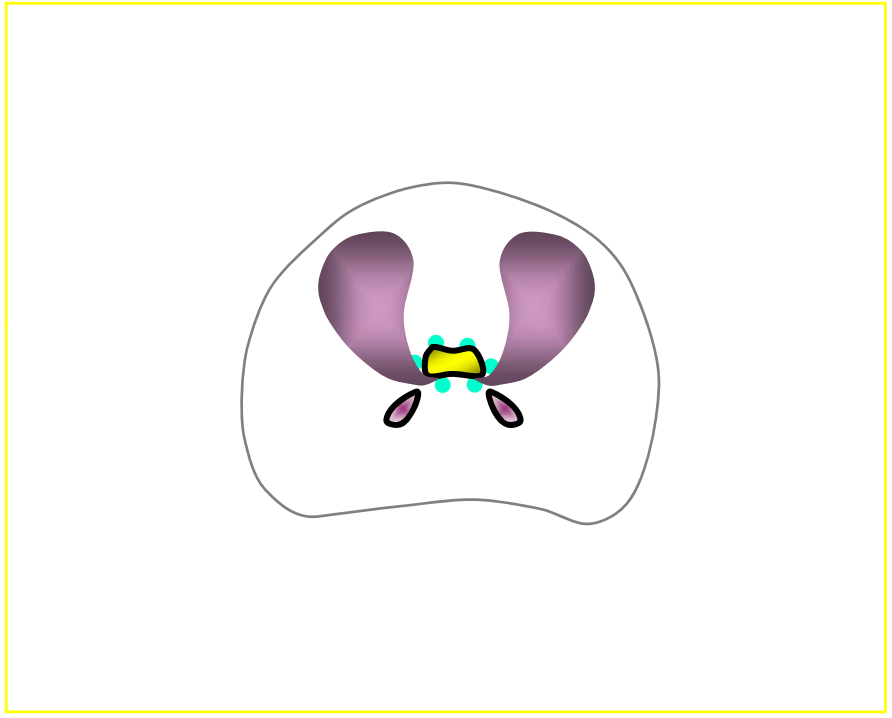
Zonal Anatomy
Central Gland



Transition Zone



Transition Zone
(transverse view)

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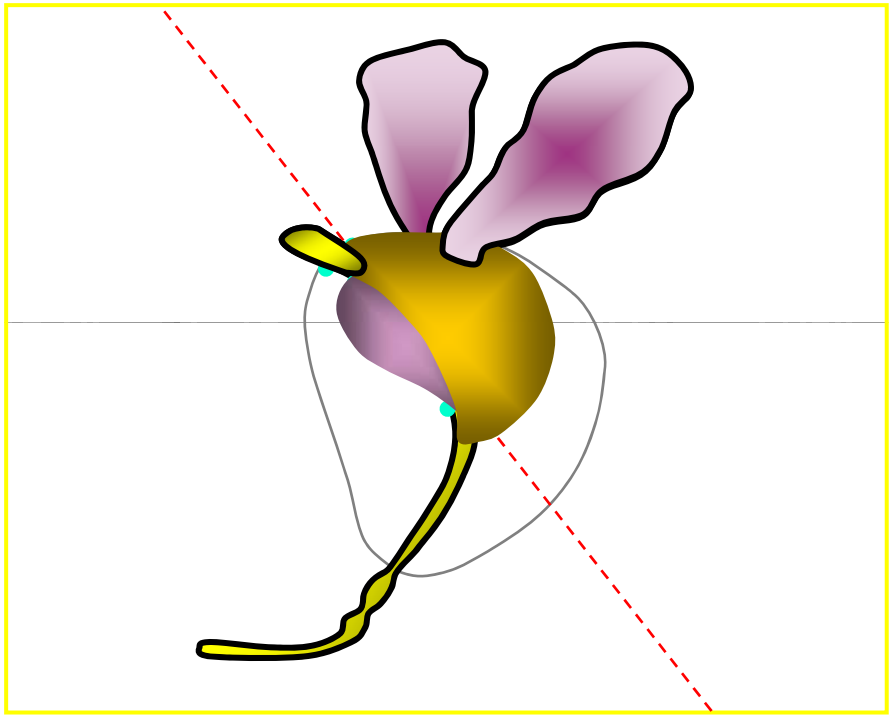
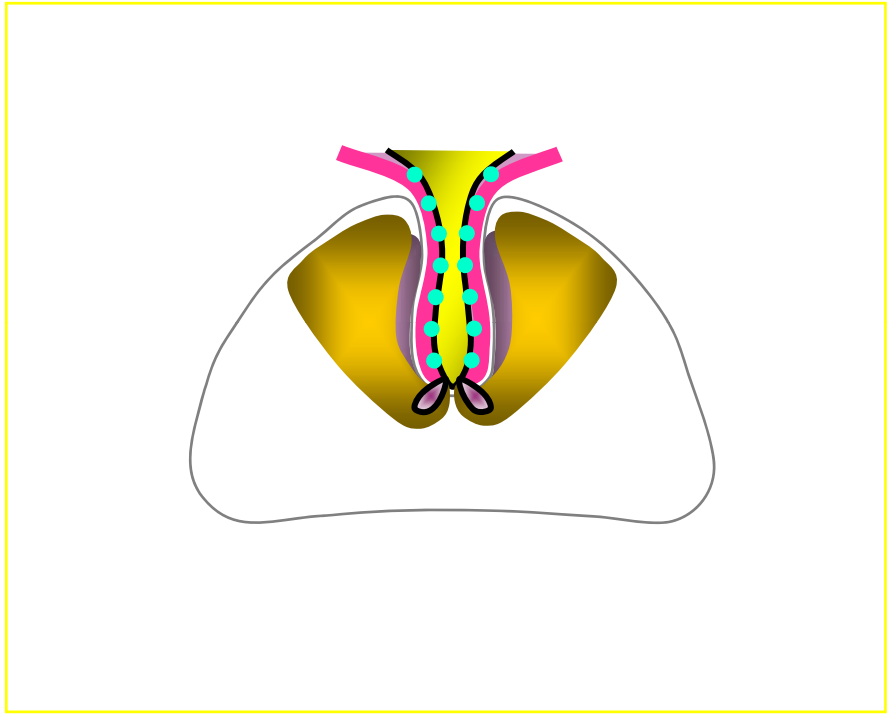
Zonal Anatomy
Central Gland

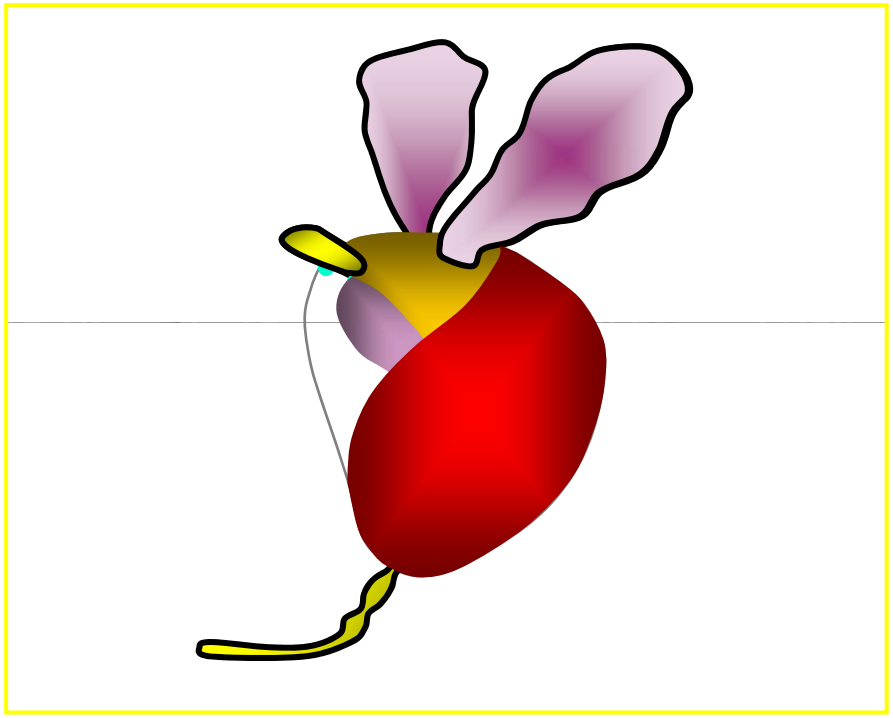


Central Zone

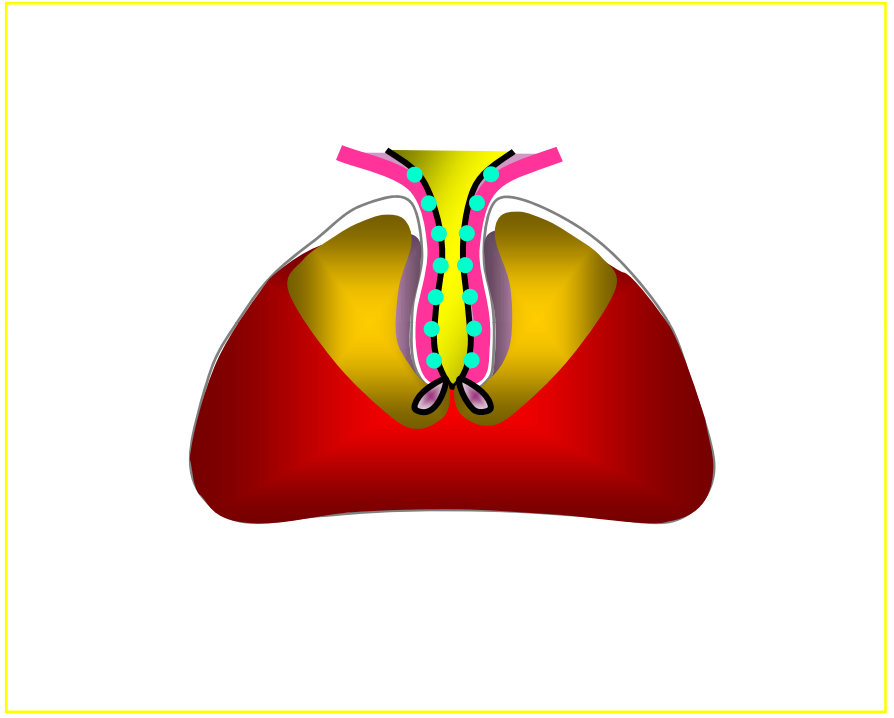


Central Zone
(paracoronal view)

Zonal Anatomy
Overview



Peripheral Zone



Peripheral Zone
(paracoronal view)

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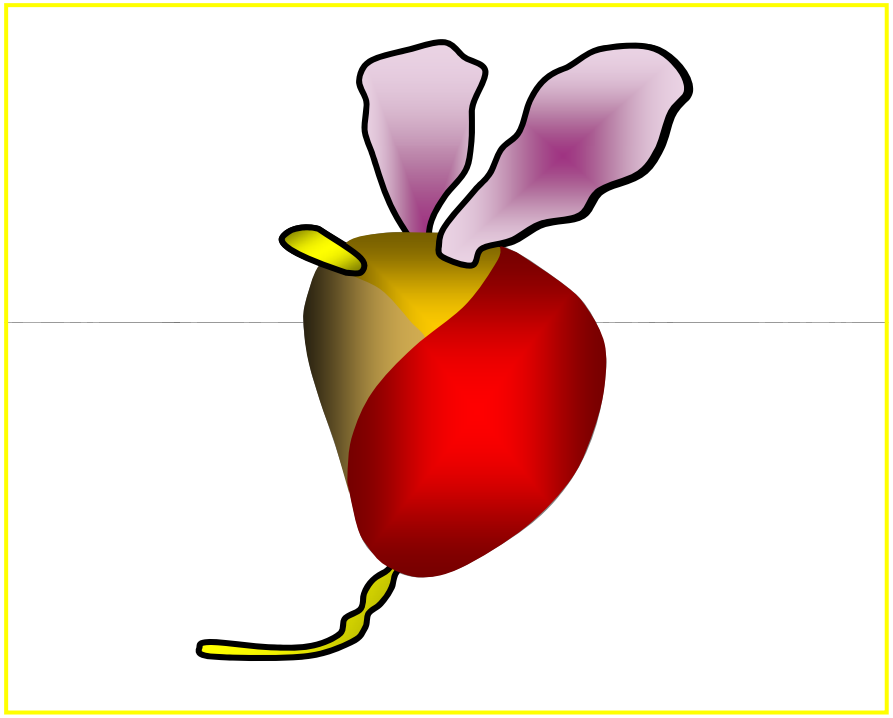
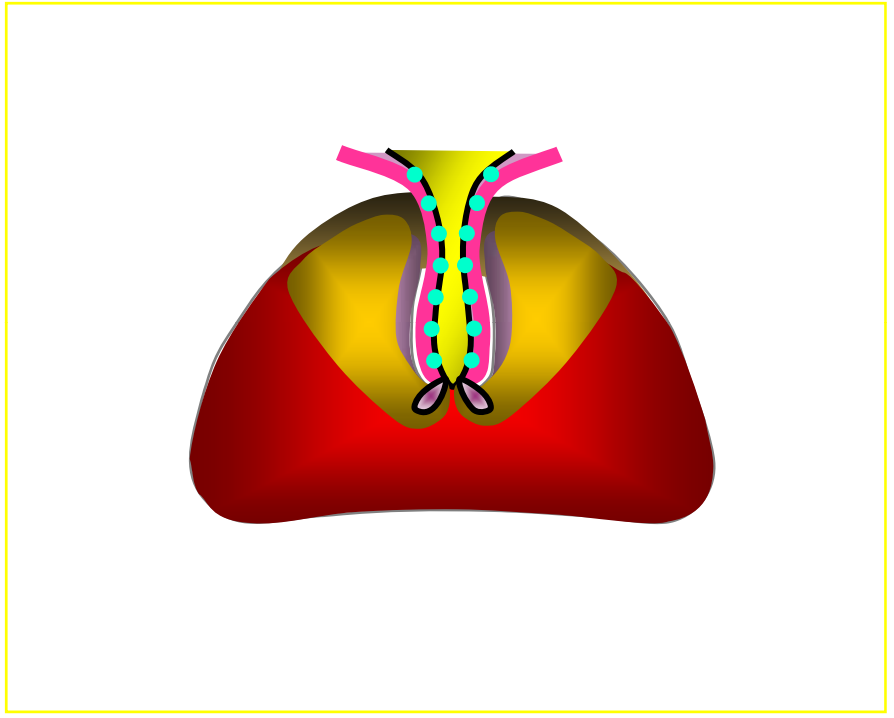
Zonal Anatomy
Overview



Anterior Fibromuscular Stroma



AFS (paracoronal view)

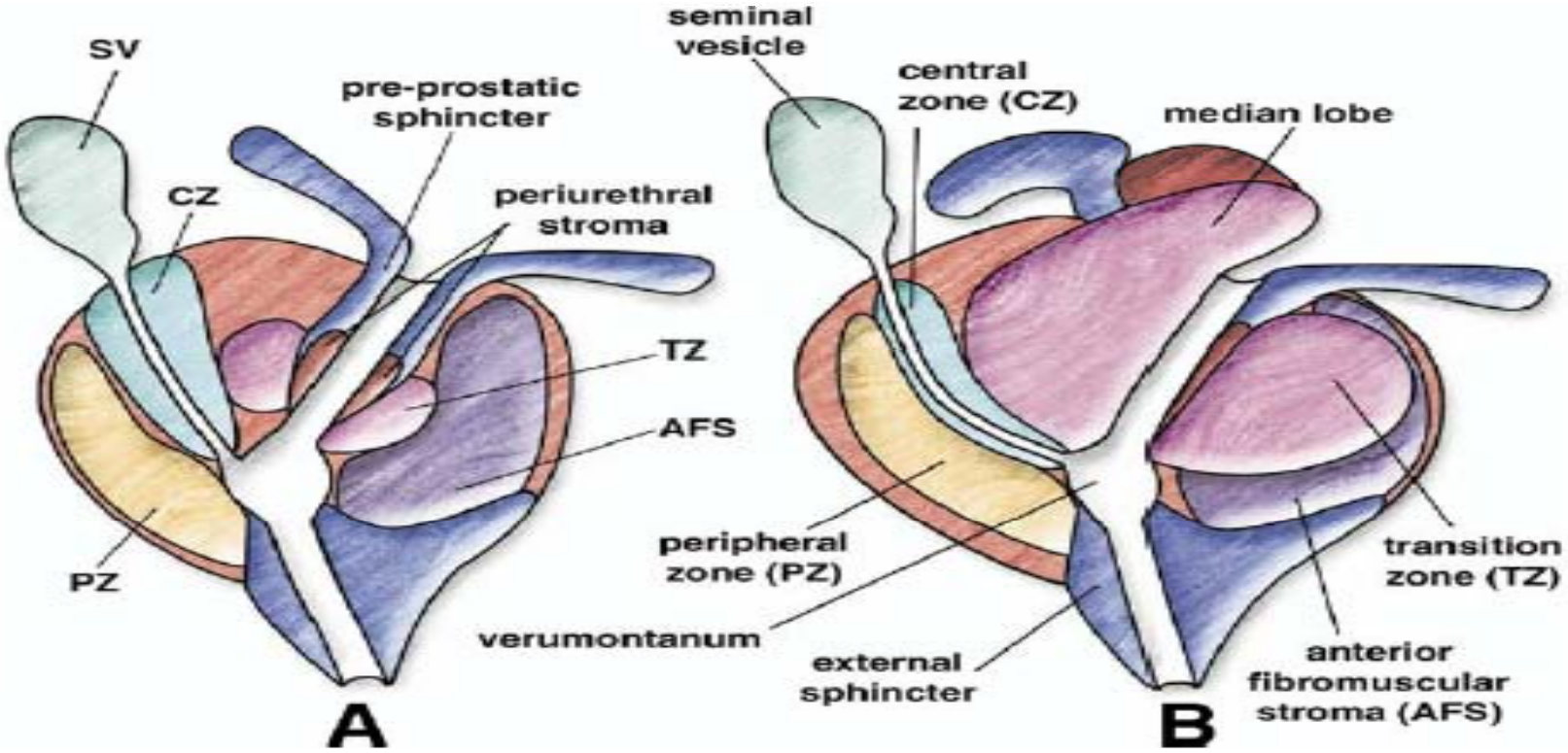
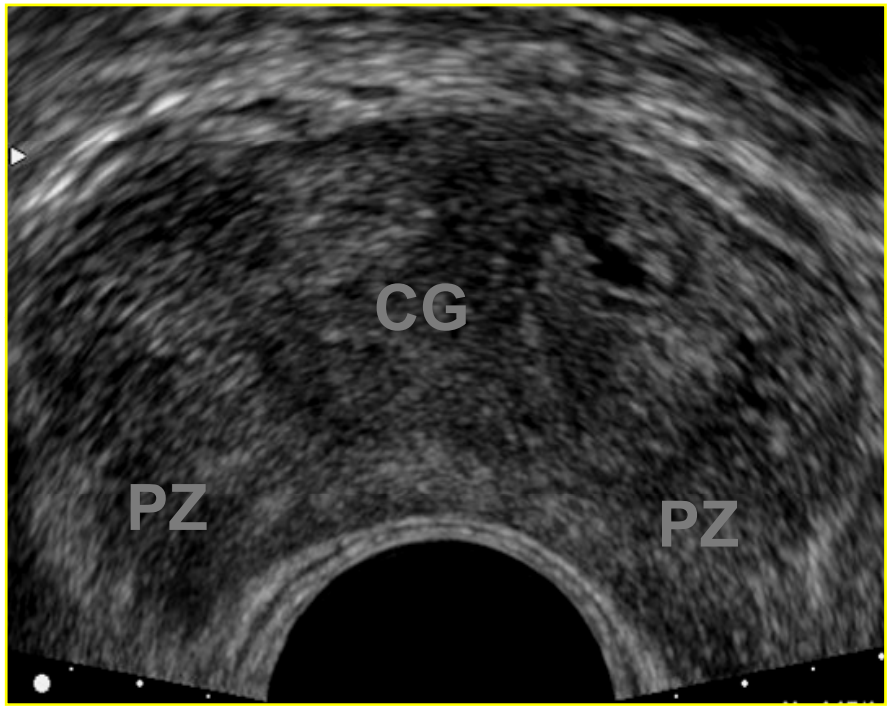
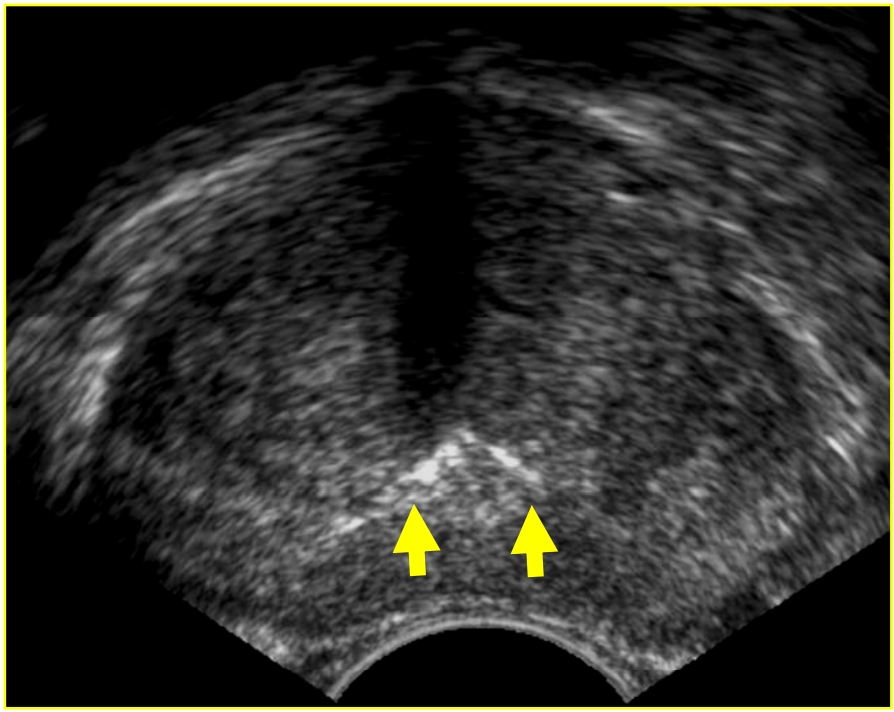


Fig. 1. Zonal anatomy of the prostate. (A) Young male with minimal transition zone hypertrophy. Note preprostatic sphincter and peri-ejaculatory duct zone (central zone of McLean) are clearly defined. (B) Older male with transition zone hypertrophy, which effaces the preprostatic sphincter and compresses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

Ultrasound
Normal Anatomy

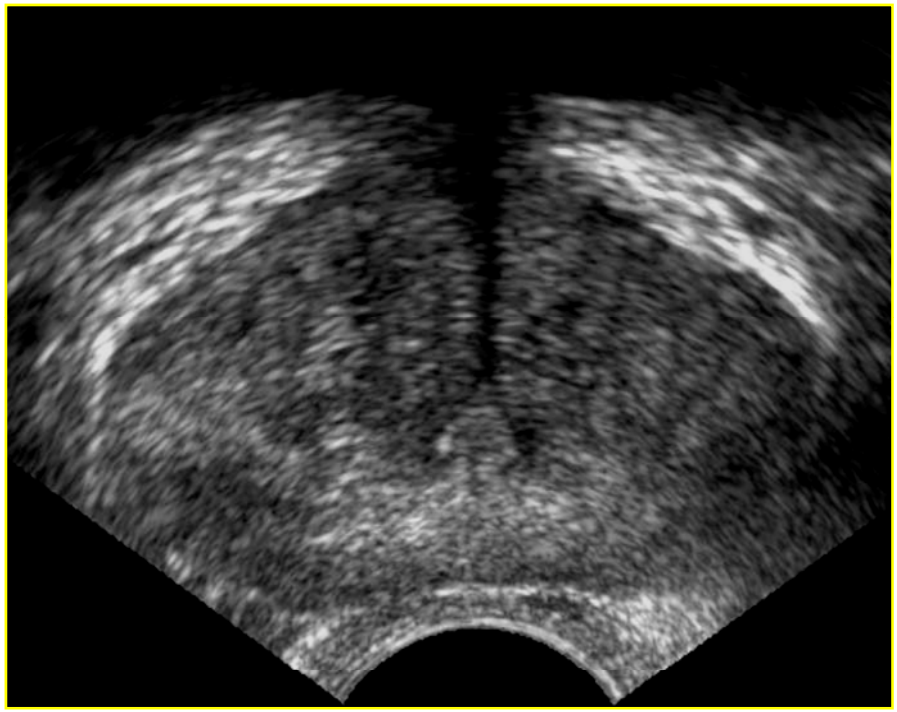


Isoechoic PZ
Hypo/hyperechoic CG

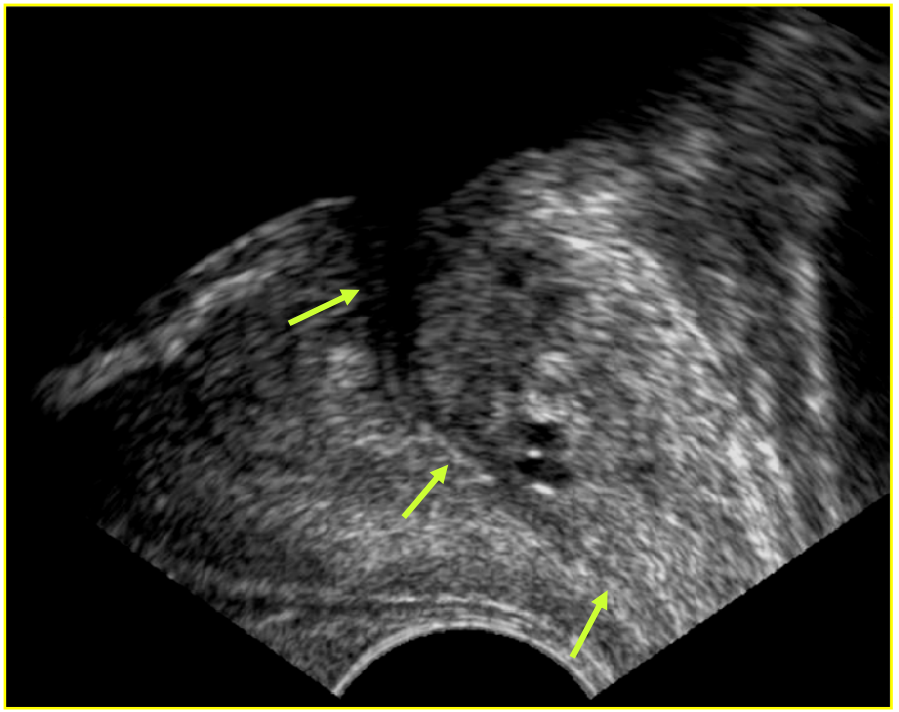


Corpora Amylacea

Ultrasound
Normal Anatomy



Urethra



Urethra
Sagittal

Zonal anatomy in MRI and Ultrasound

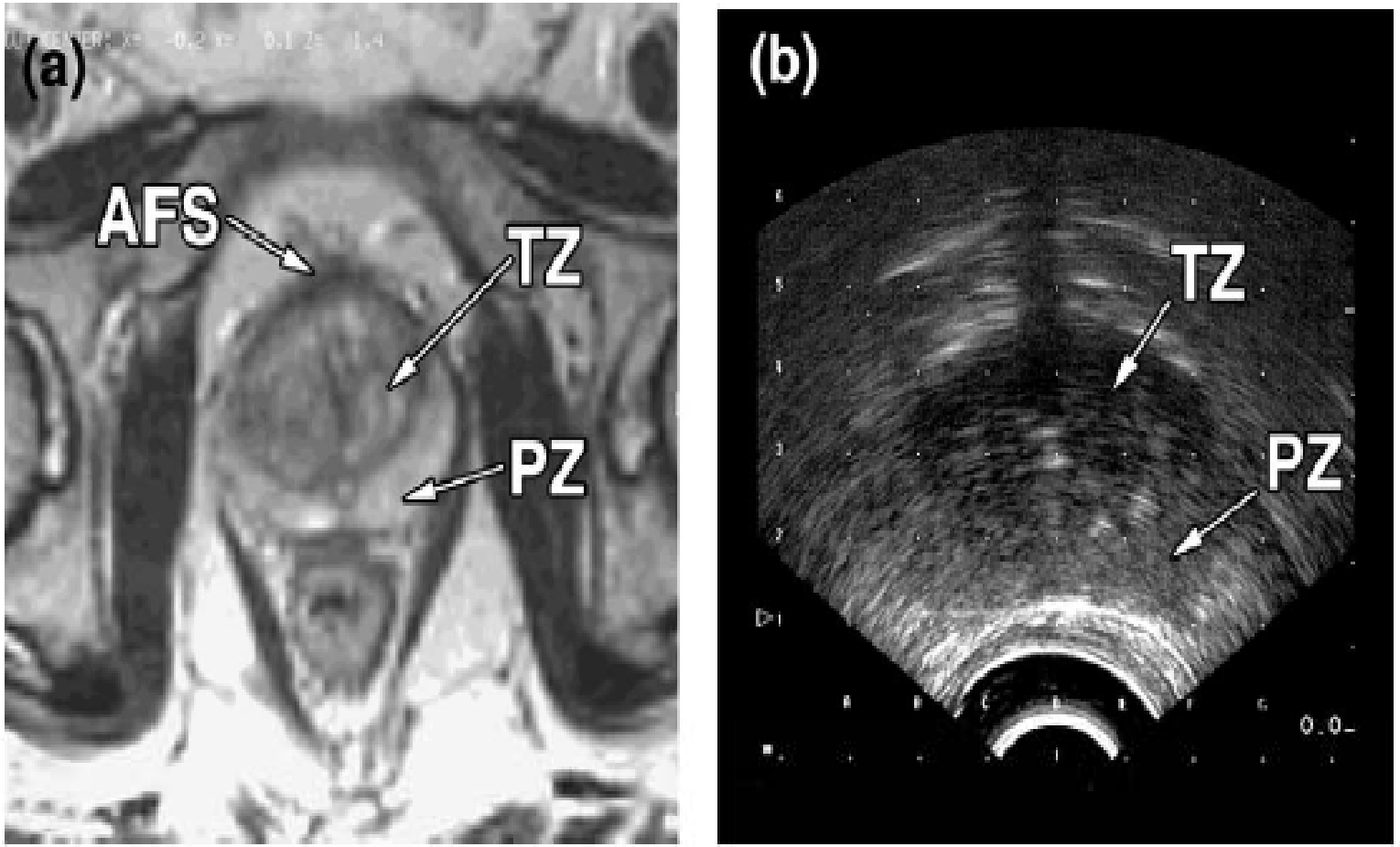


Fig. 2. Zonal anatomy of the prostate. Transition zone and peripheral zone on (a) T2 magnetic resonance imaging and (b) ultrasound. AFS = anterior fibromuscular stroma; PZ = peripheral zone; TZ = transition zone.

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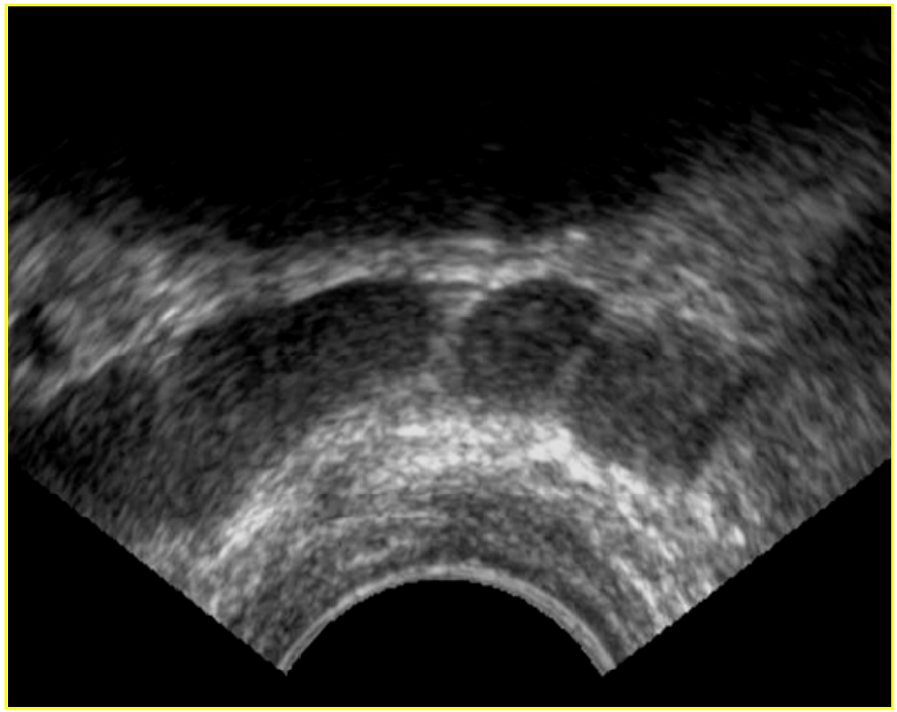
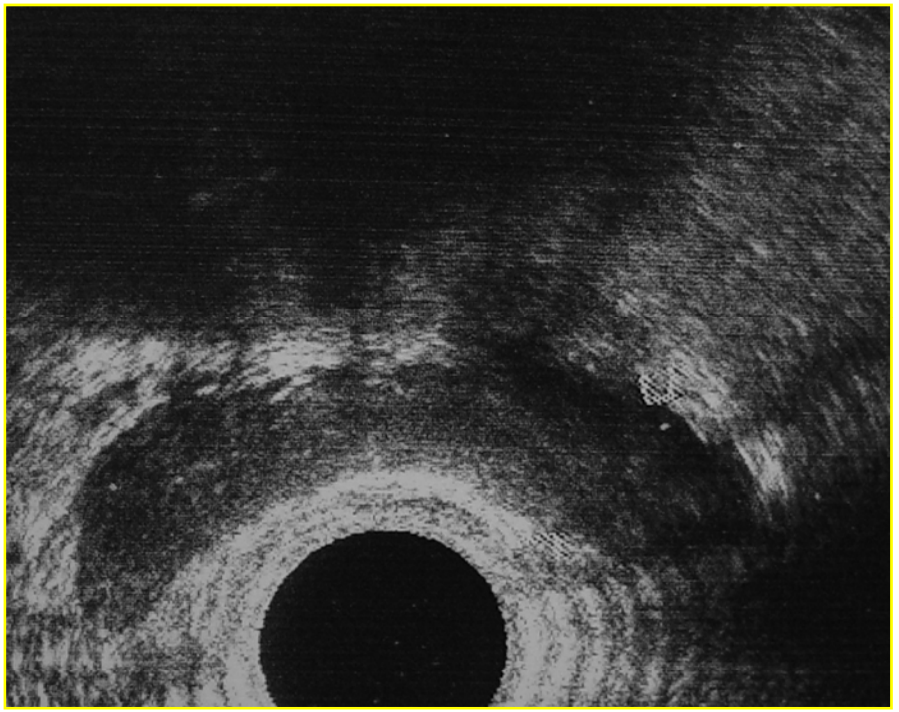
Ultrasound
Normal Anatomy





Seminal Vesicles
Convoluted Hypoechoic Cystic Structures

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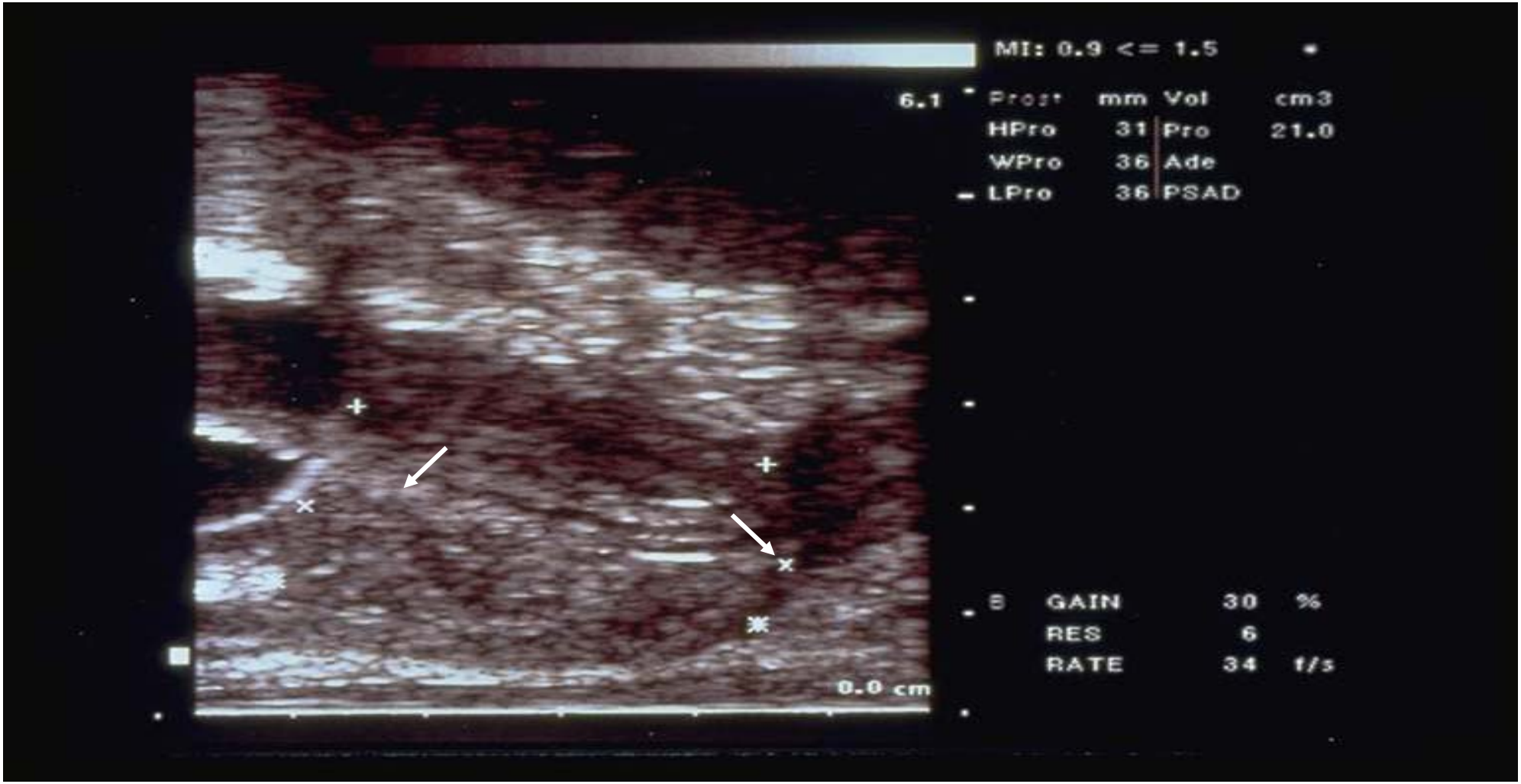
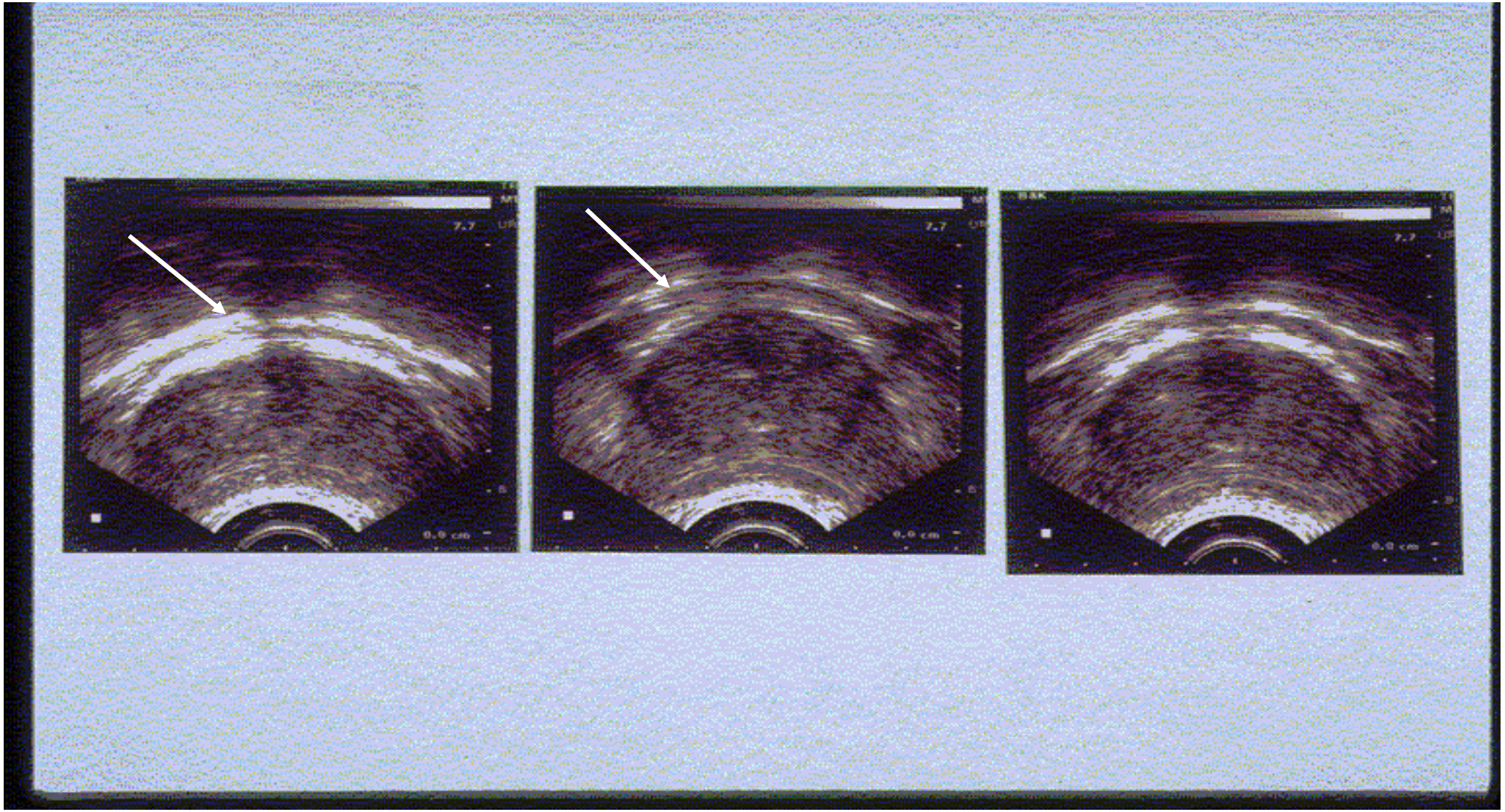
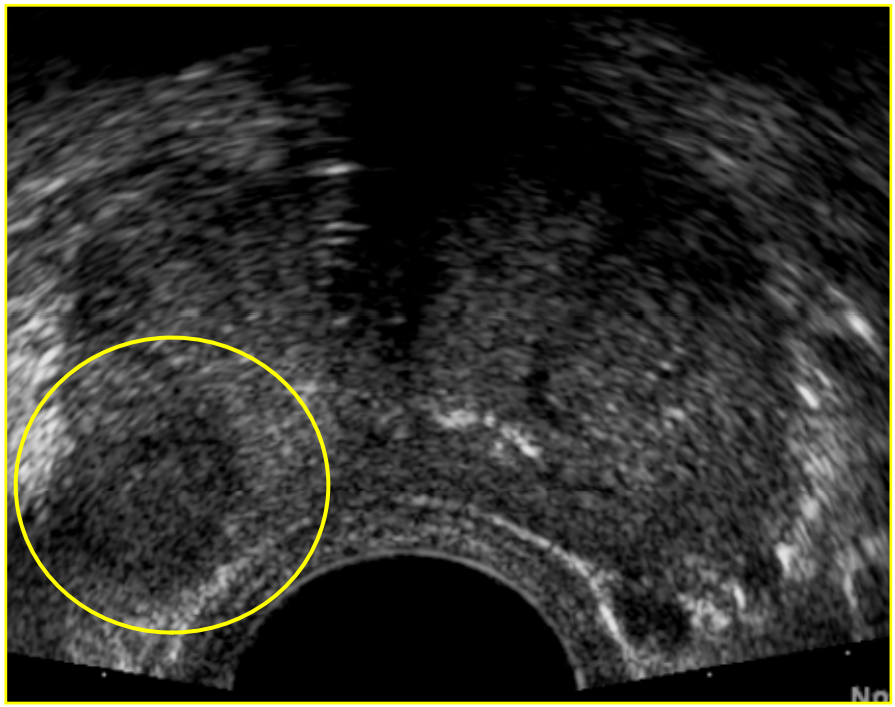
Ultrasound
Sagittal: urethral measurements

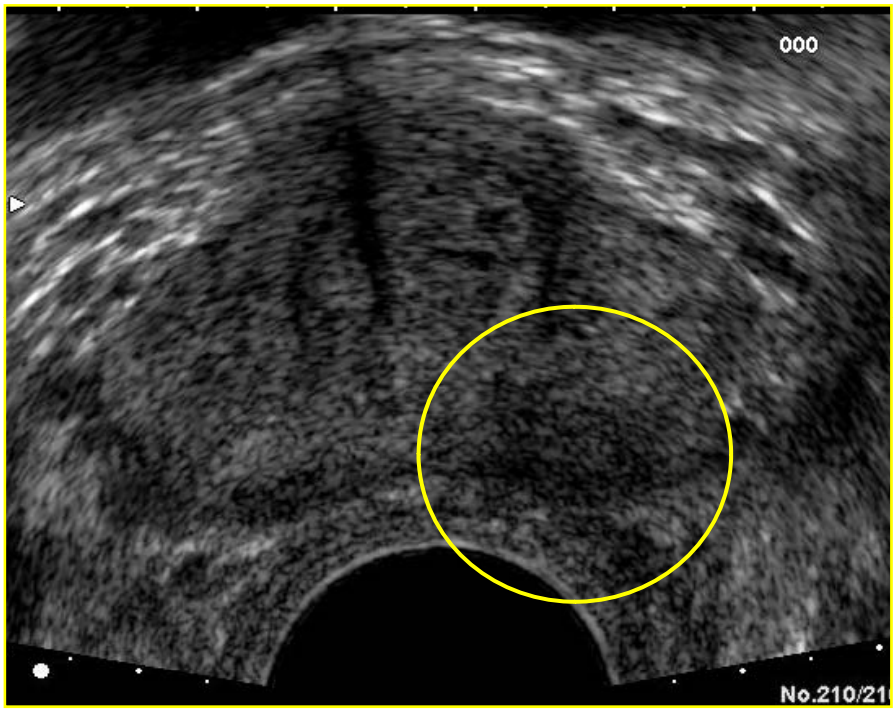


ULTRASOUND – Dorsal vein plexus



Ultrasound
Prostate Carcinoma





Hypoechoic nodule compared to normal PZ
Low specificity (atrophy, prostatitis, ...)

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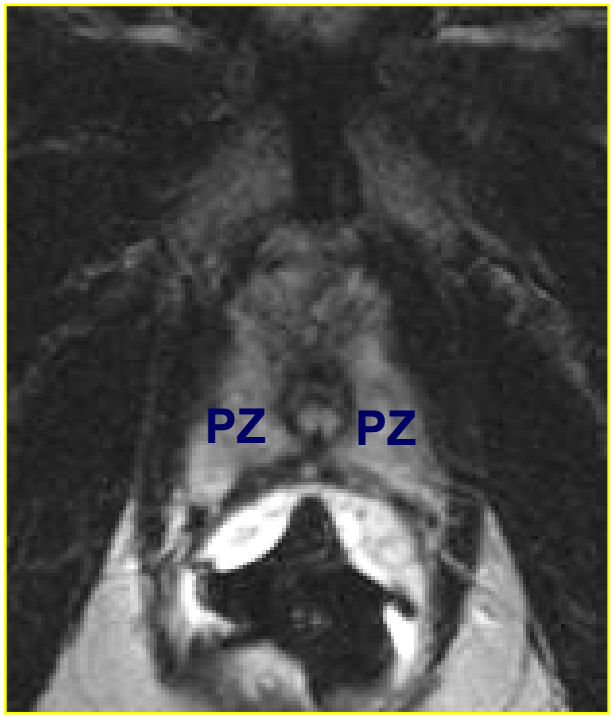
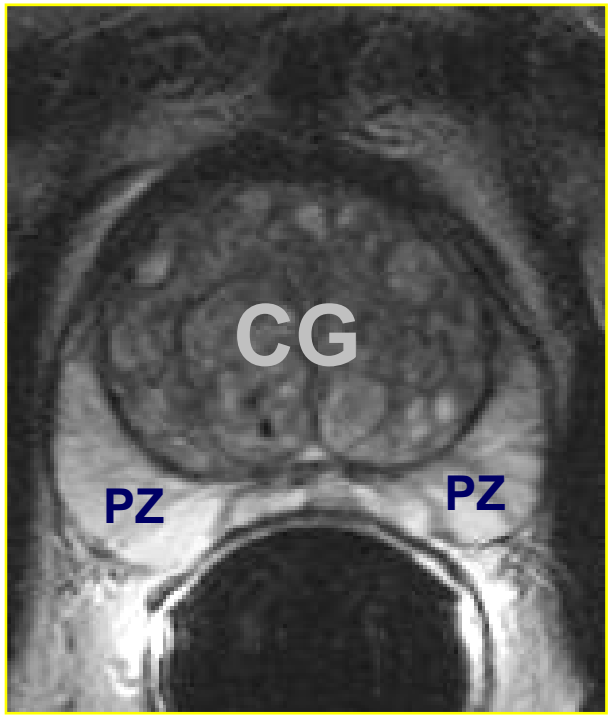
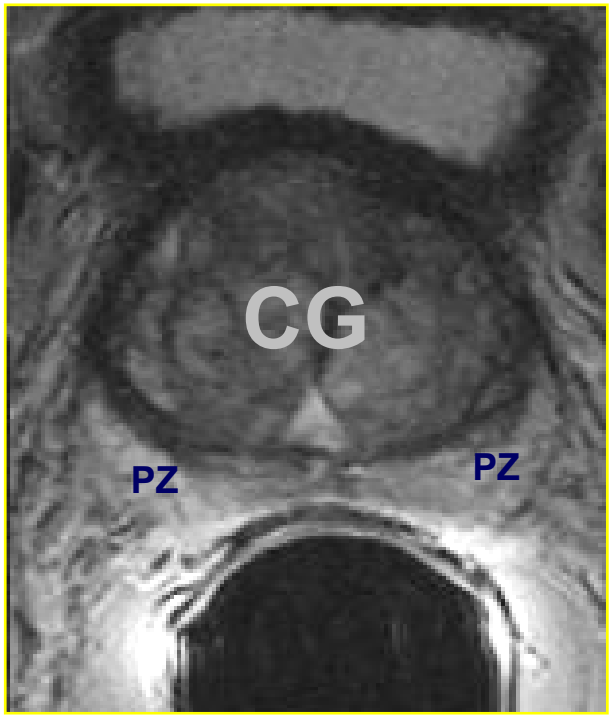
Anatomy
Prostate







Prostatic Apex | **Midprostate** | **Prostatic Base**

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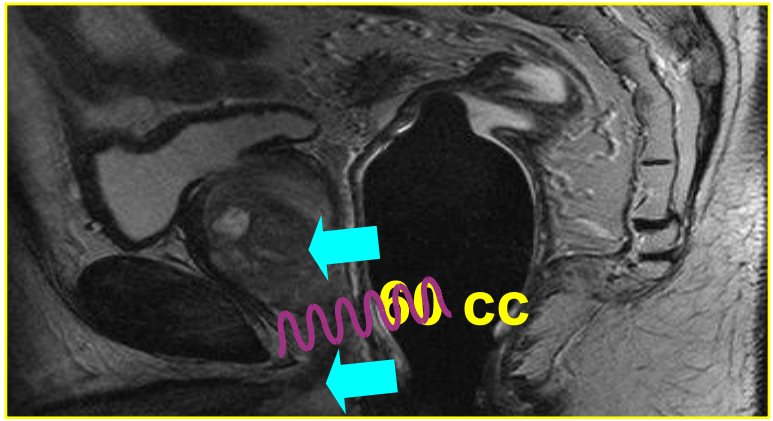
Imaging of Prostate Cancer
Endorectal Coil Imaging

Endorectal Coil



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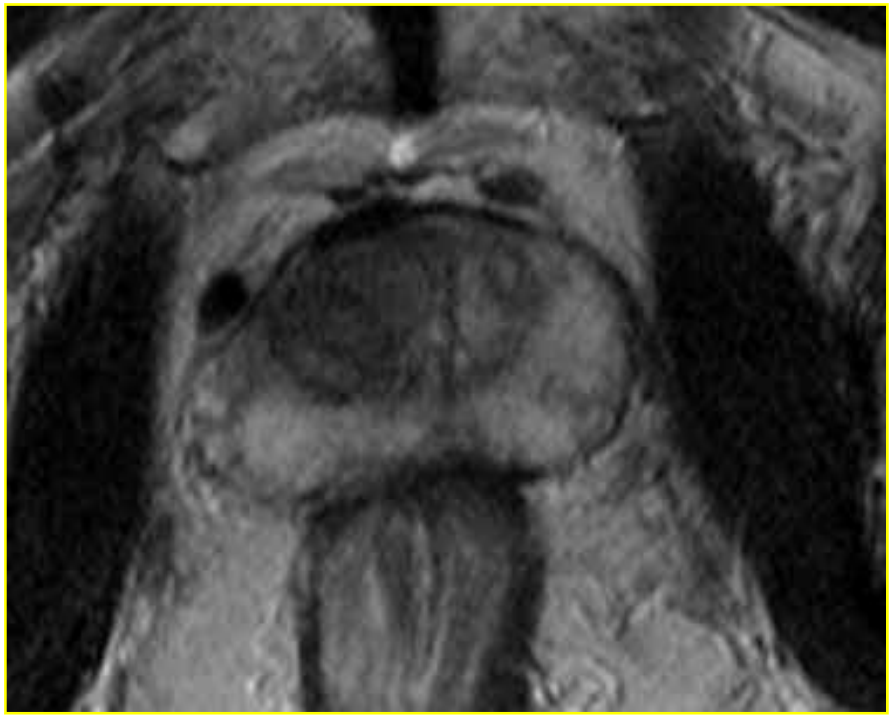
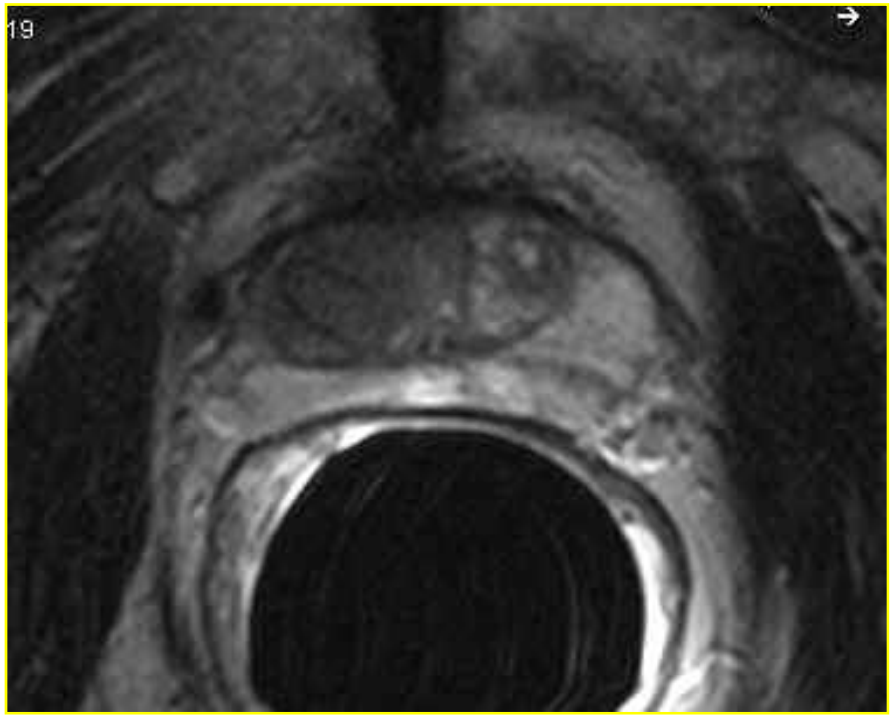
Imaging of Prostate Cancer
Body coil versus Endorectal coil



Normal Prostate with Body Coil



Normal Prostate with Endorectal Coil

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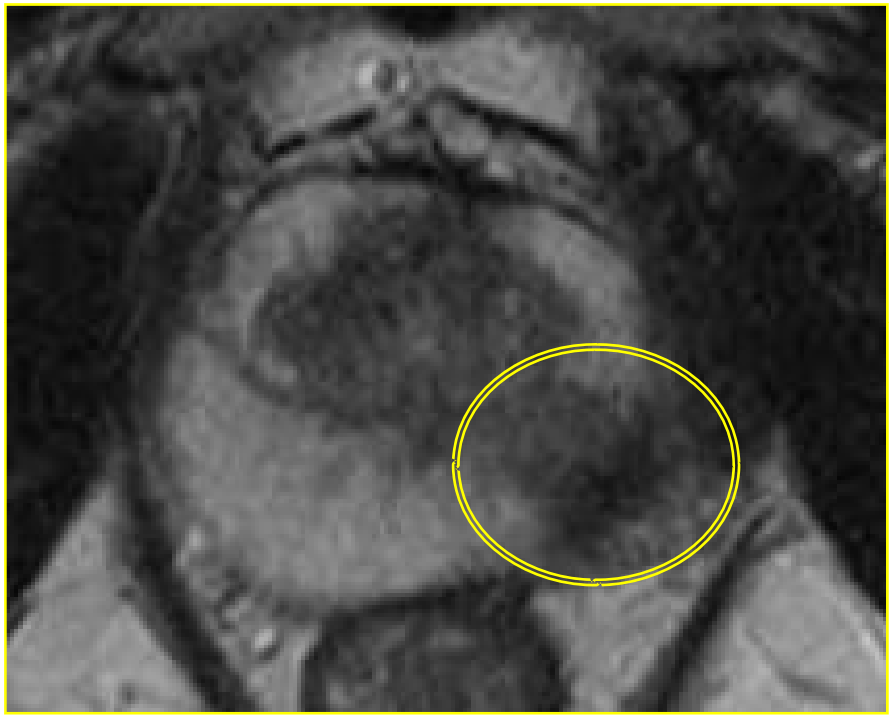
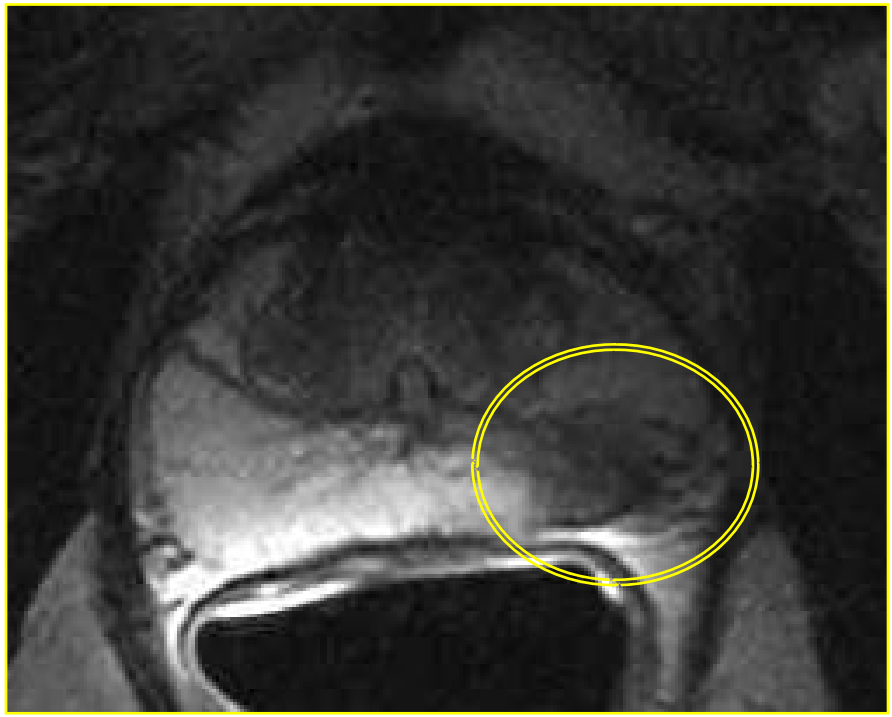
Imaging of Prostate Cancer
Tumour Presence (Endorectal Coil)

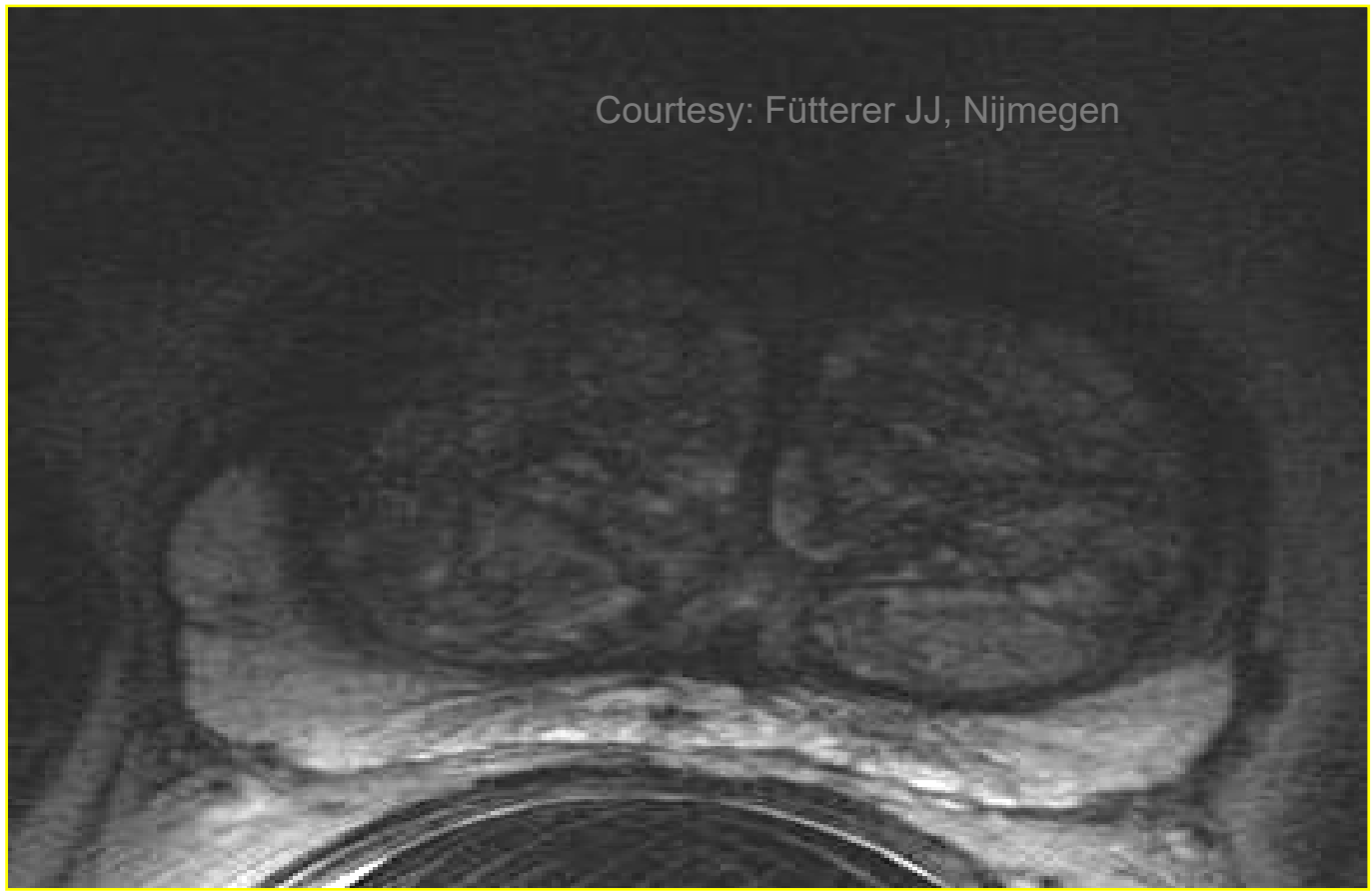


Peripheral Zone Tumour with Body Coil



Peripheral Zone Tumour with Endorectal Coil

Imaging of Prostate Cancer
Tumour detection @ 3 Tesla



Kim, J Comput Assist Tomogr 2006;30:7-11 (70%)
Heijmink, Radiology 2007;244:184

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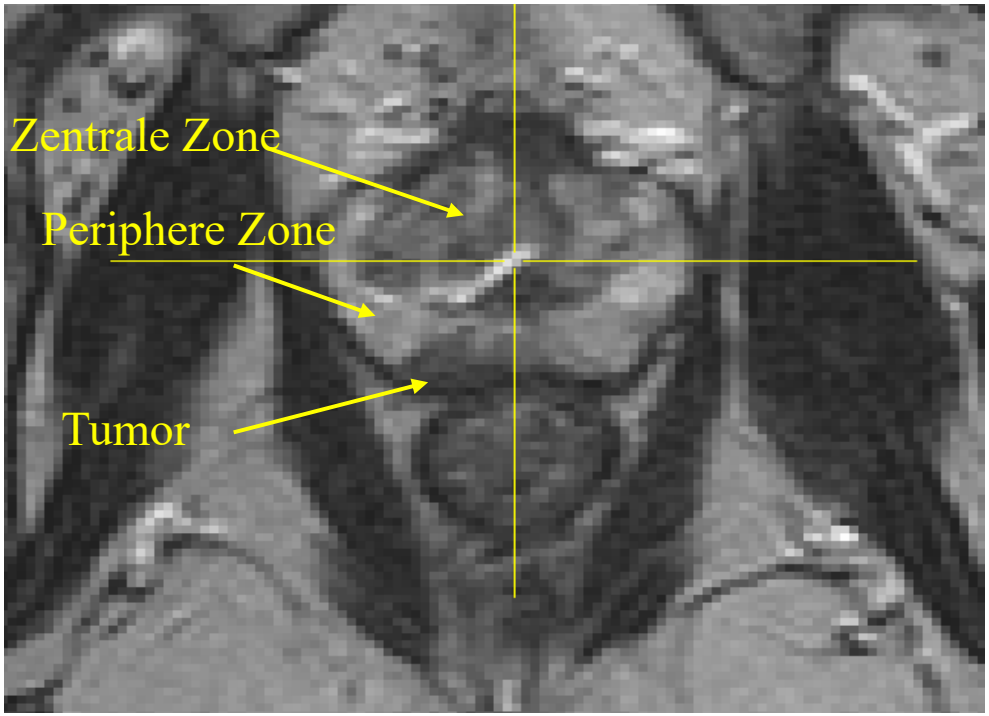
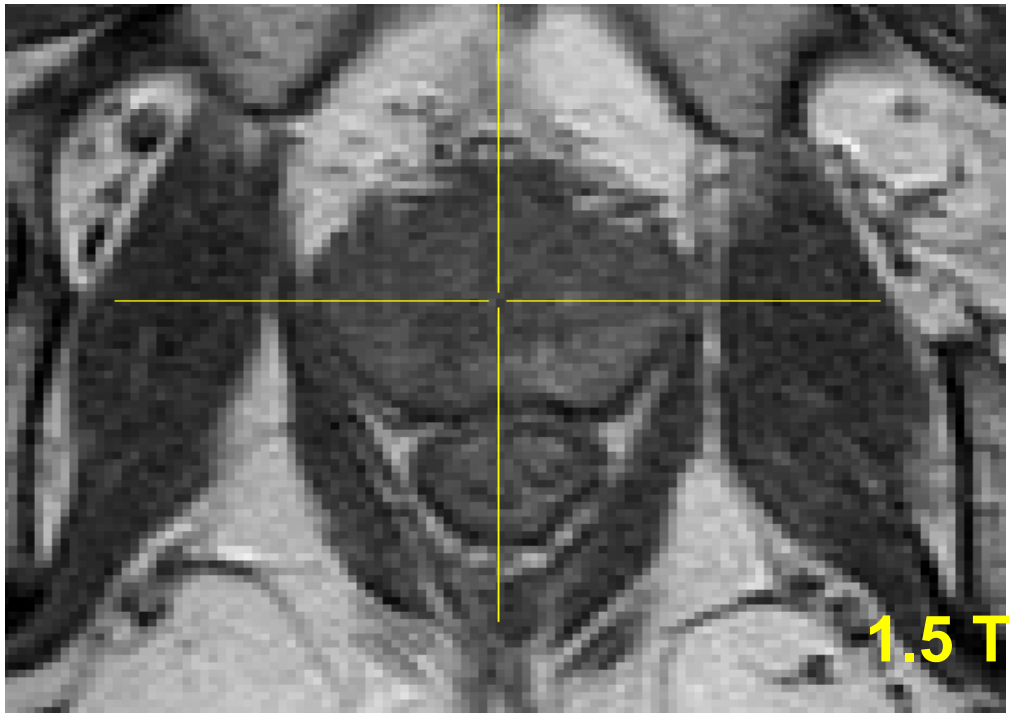
1.5 Tesla MRI

MRI:

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



T2-weigthed



T1-weighted

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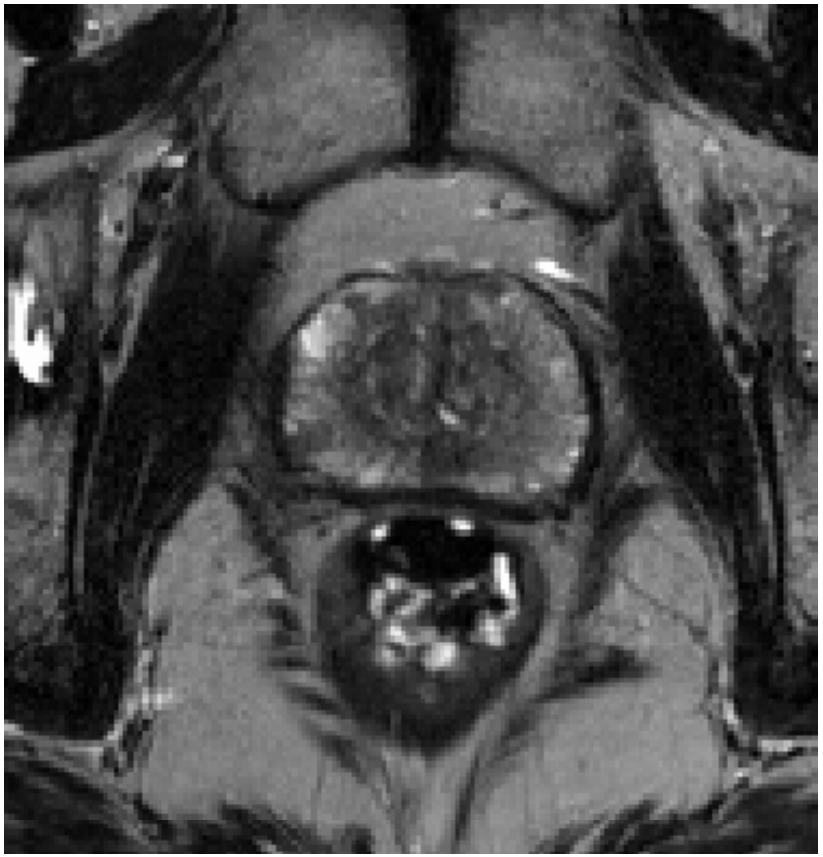
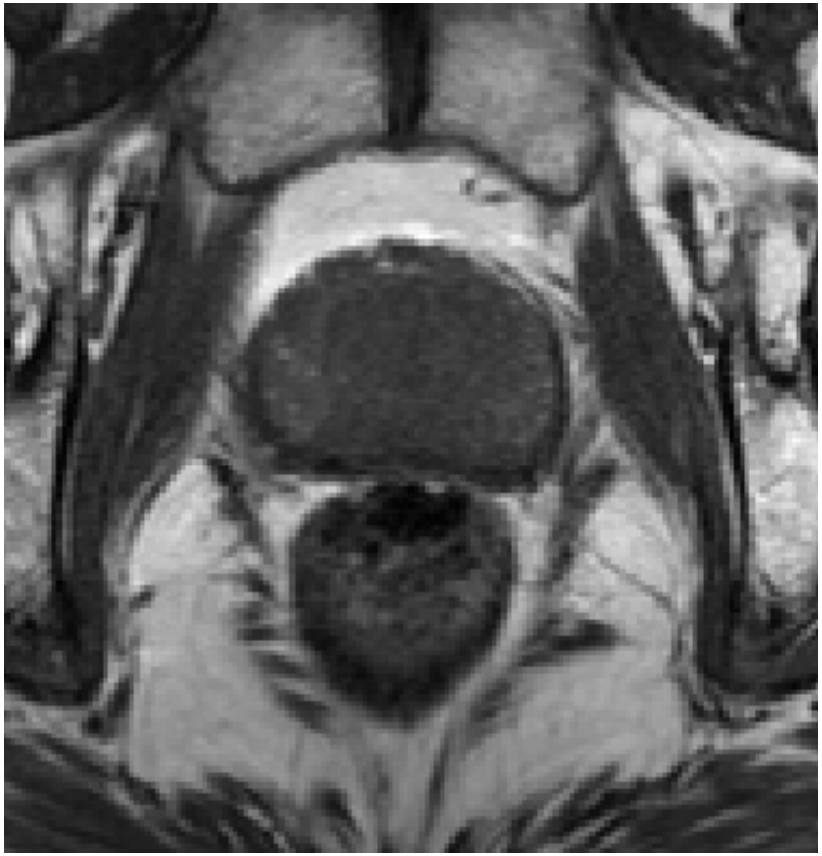
3.0 Tesla MRI

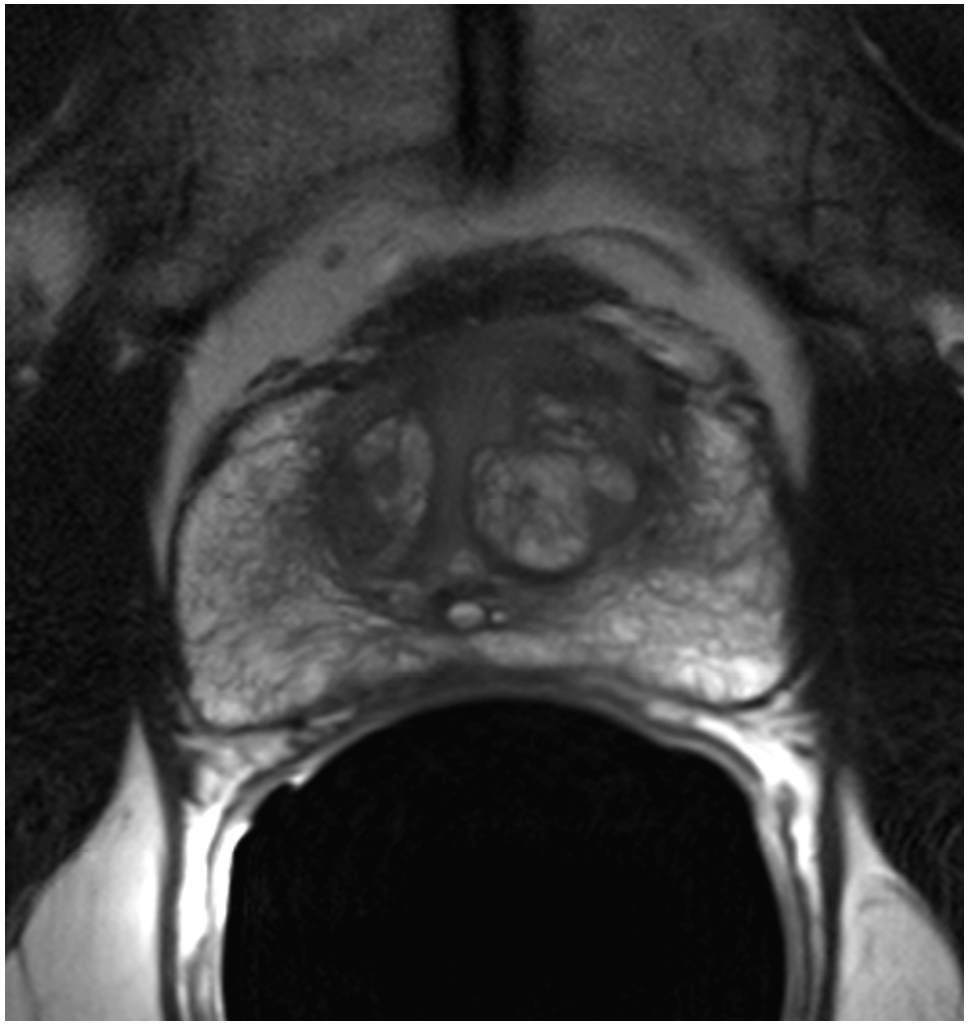


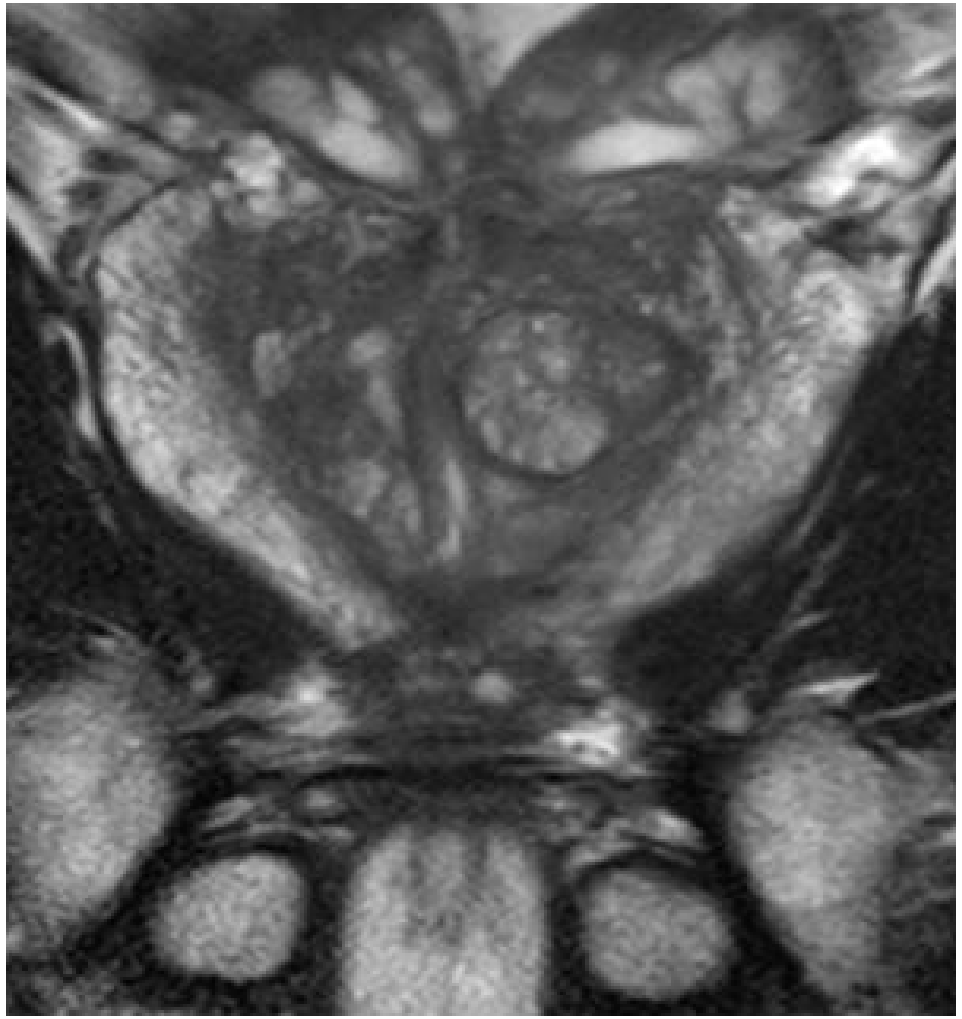
T2 -weighted



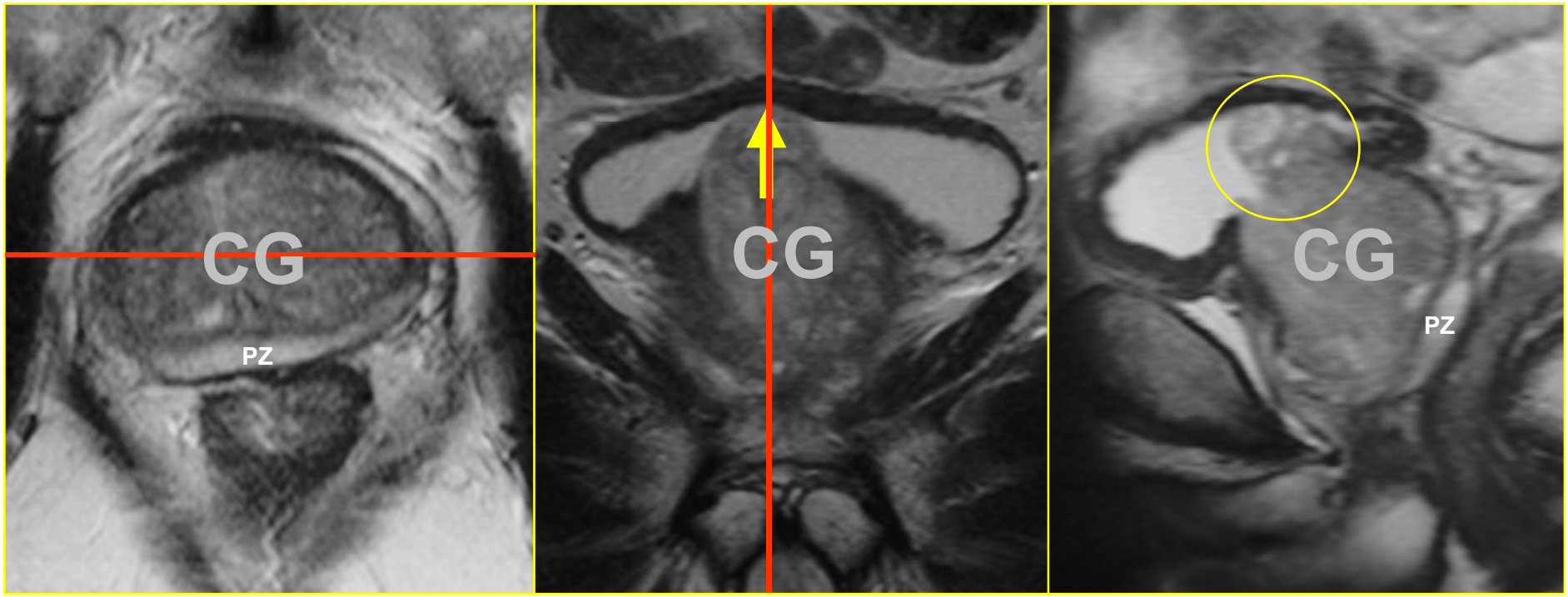
T1 weighted

3.0 Tesla MRI + Endorectal coil





Anatomy
Hyperplasia



Benign Prostatic Hyperplasia

Variation of bladder neck according to BPH

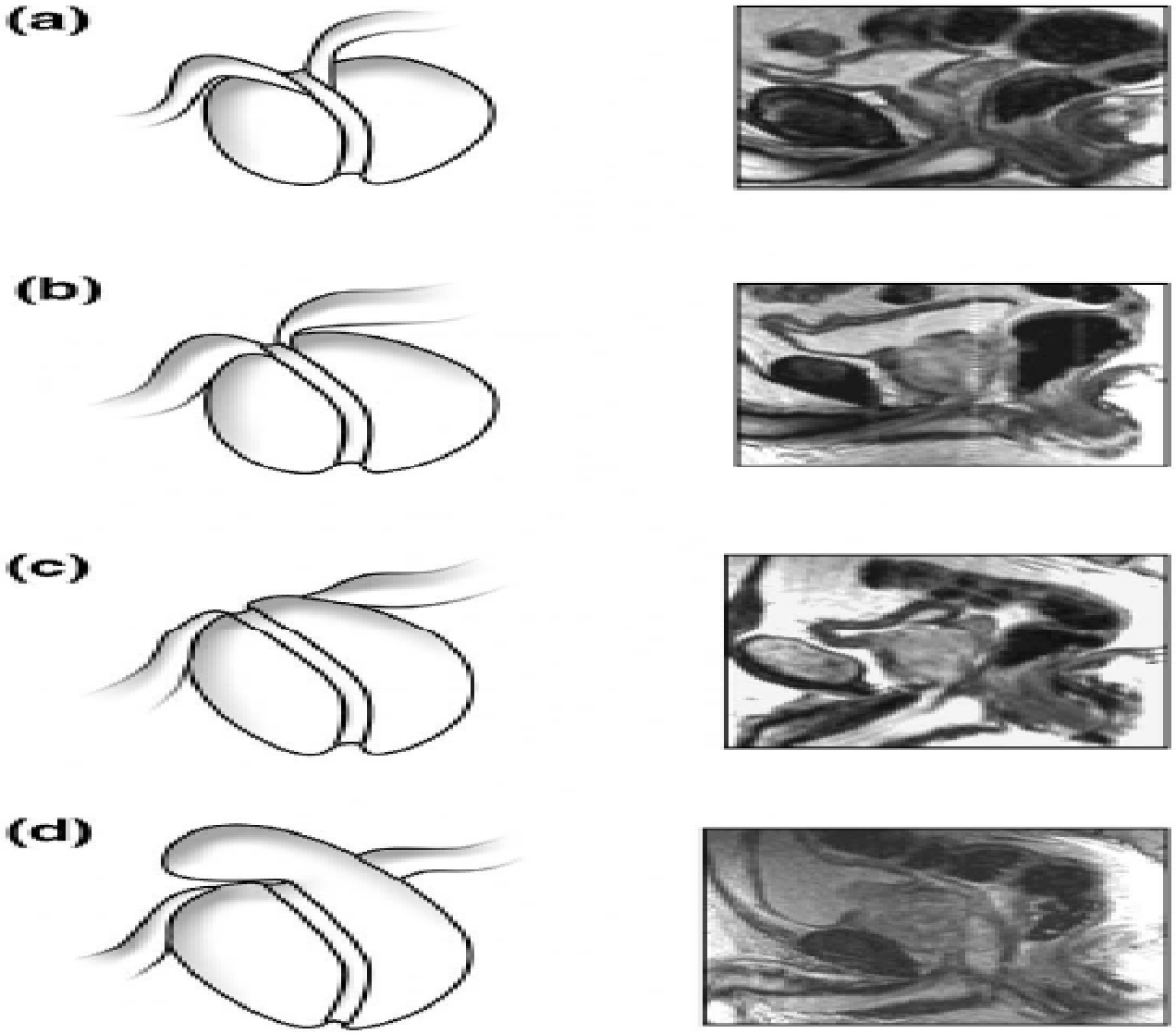


Fig. 4. Change in base anatomy with transition zone (TZ) enlargement. (a) A distinct bladder neck is apparent. With progressive TZ enlargement, the bladder neck is effaced by TZ enlargement (b, c). The most extreme change is median lobe enlargement (d) with associated ball valve obstruction.

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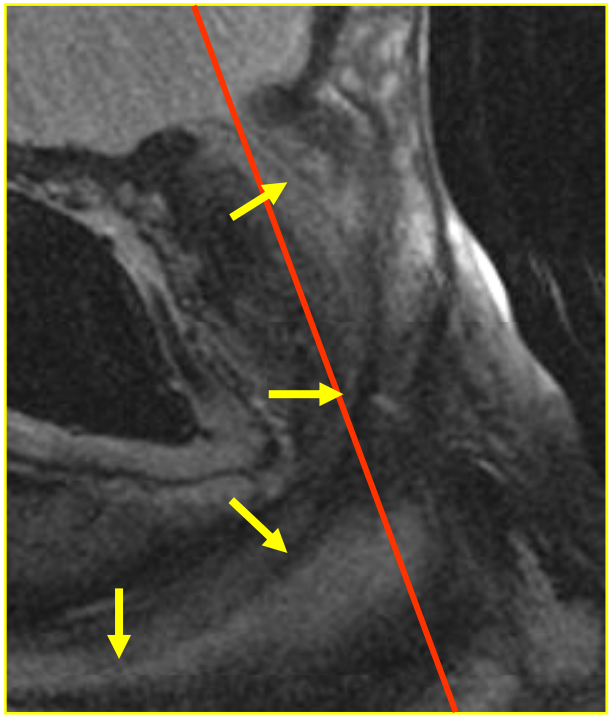
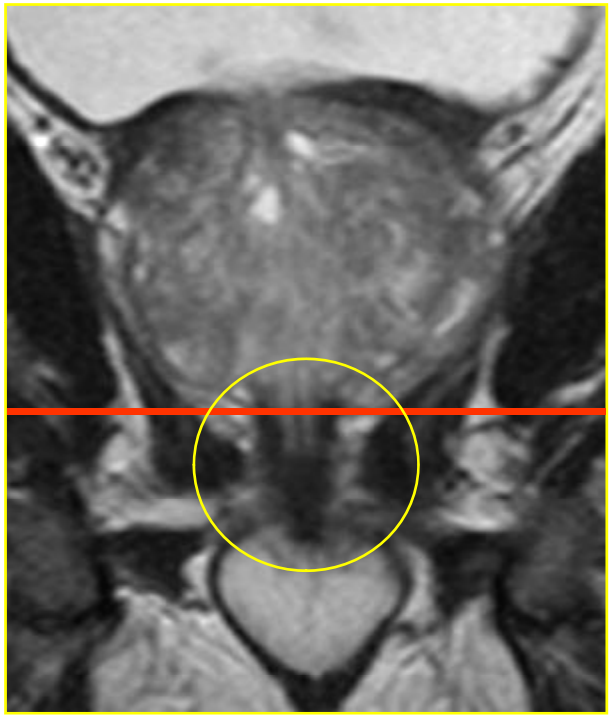
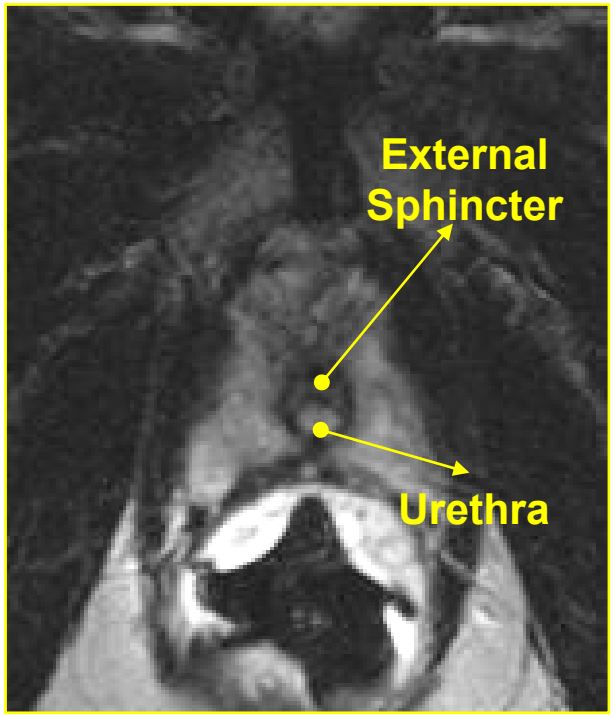
Anatomy
Urethra



Sagittal



Coronal



Transverse

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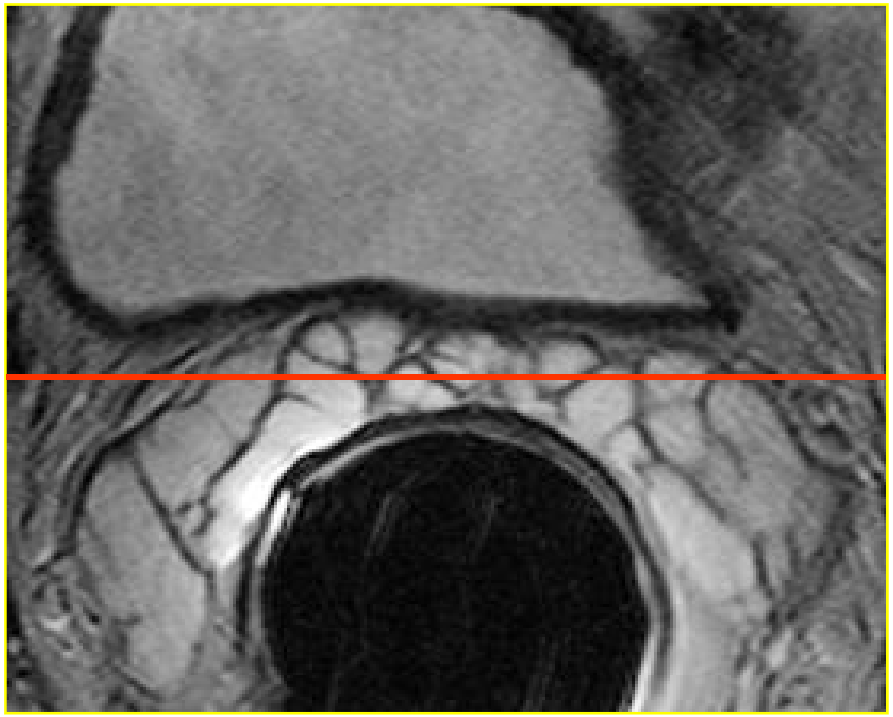
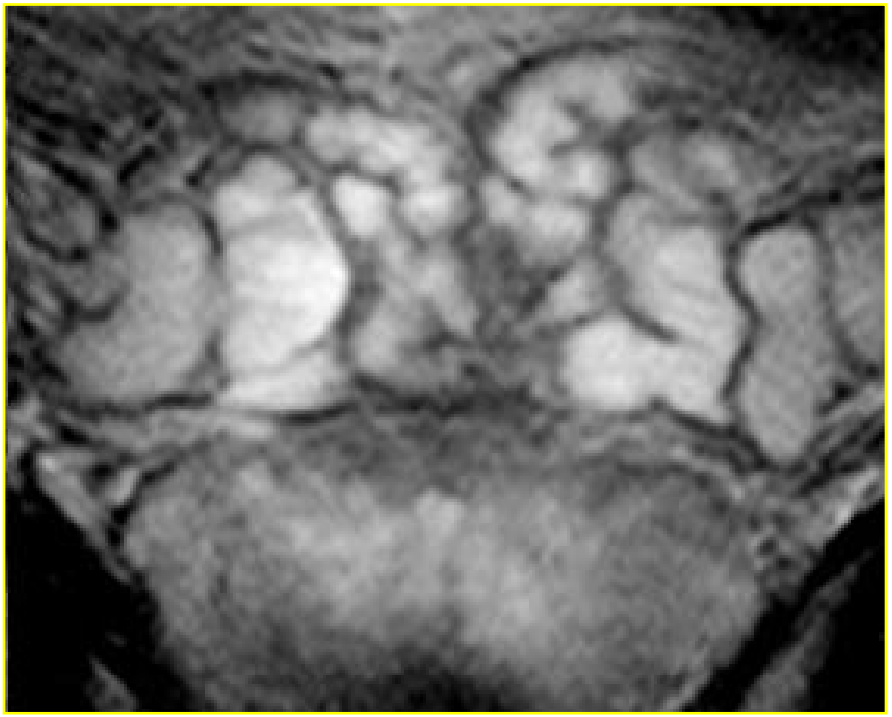
Anatomy
Seminal Vesicles

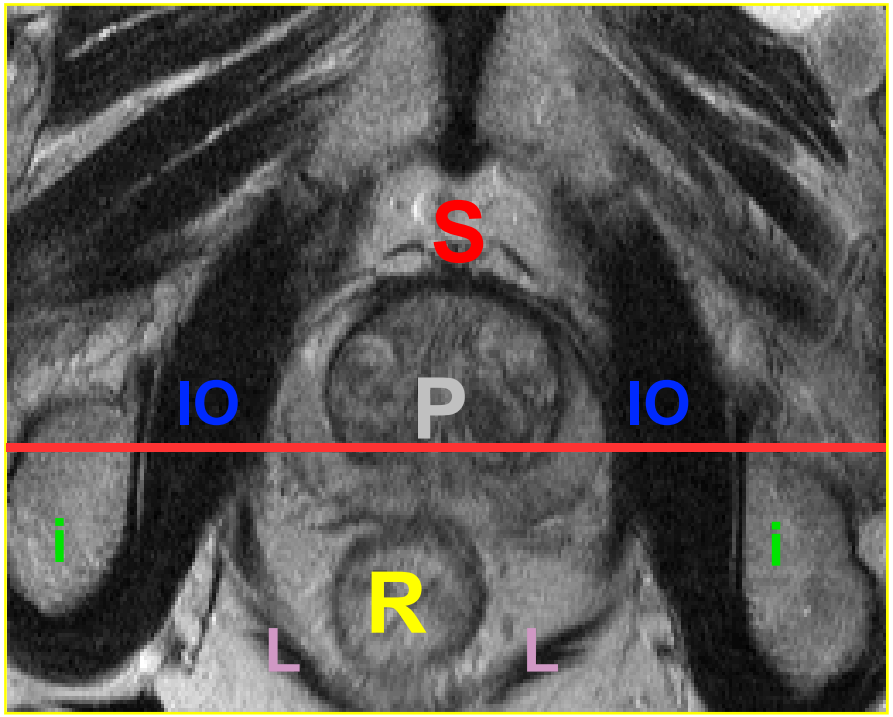


Transverse

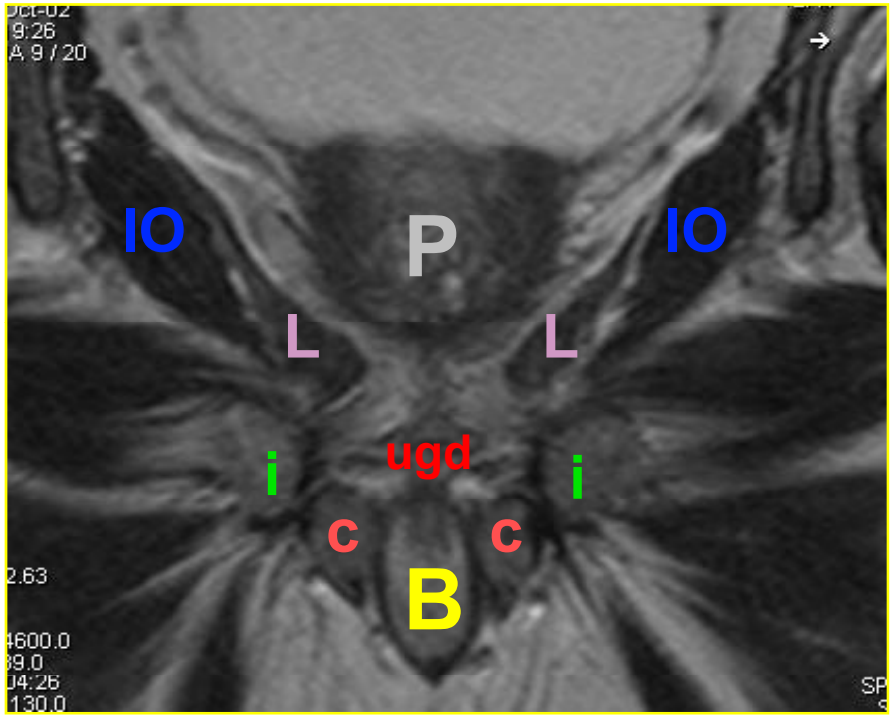


Coronal

Anatomy
Periprostatic Structures



Transverse



Coronal

Variation in Genitourinary diaphragm

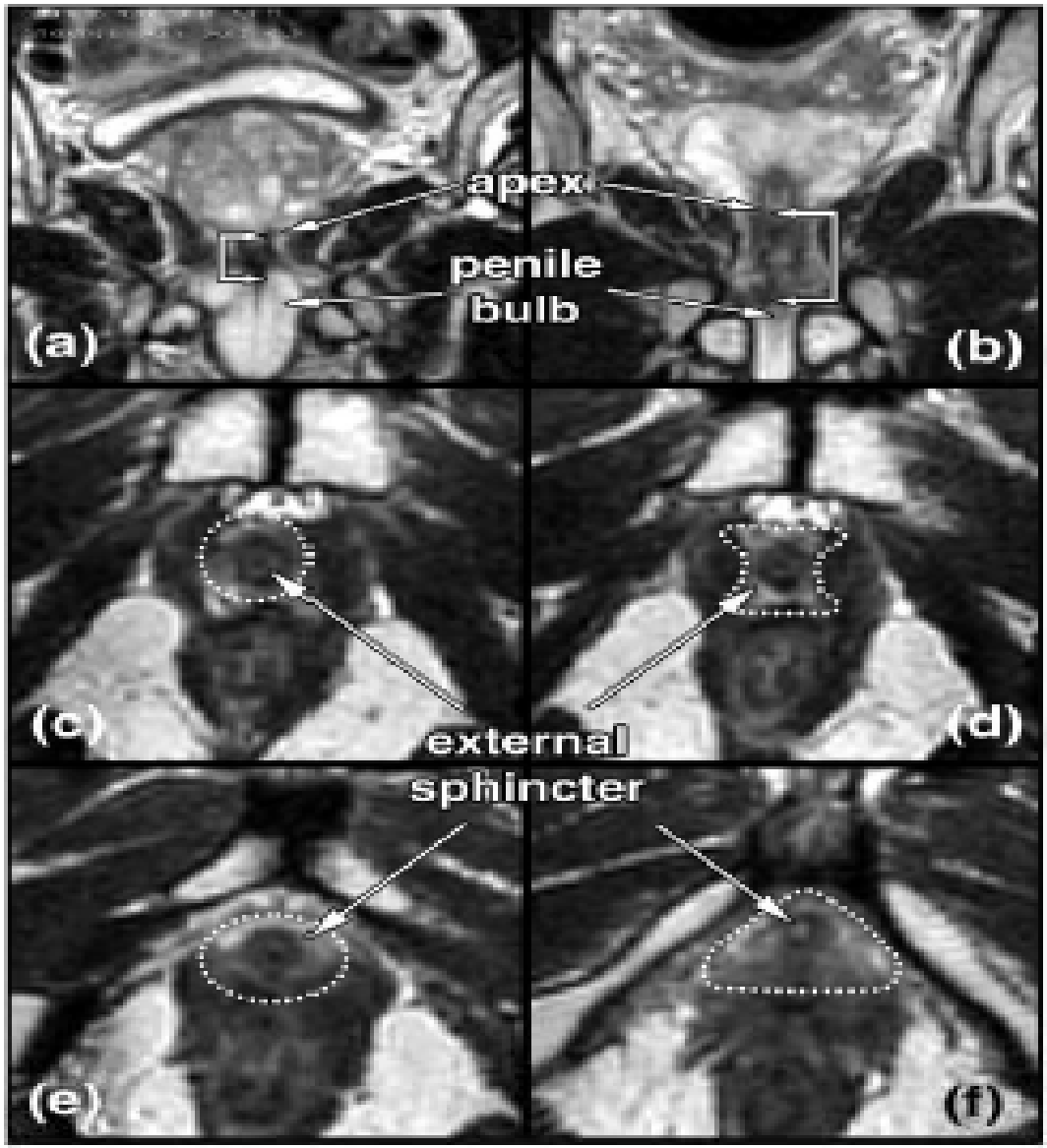


Fig. 5. Genitourinary diaphragm. Variation in thickness of the genitourinary diaphragm (GUD) (a, b). Levels of GUD from apex to penile bulb (c–f).

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ESTRO Course
Brussels 2016

Selection of patients for prostate cancer permanent implant brachytherapy

Jean-Marc Cosset, Institut Curie, Paris, France

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- **A brief history;**
- **The initial ABS recommendations (1999)**
- **The ESTRO recommendations (2000)**
- **The progressive evolution**
- **The 2012 ABS recommendations**

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- 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)*

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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

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- **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

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- **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

- Table 2. ABS prescription dose guidelines*

- Brachytherapy dose for monotherapy (Gy)
- 125I (pre TG-43) 160
- **125I (TG-43) 144**
- 103Pd 115–120
- **It should be recognized that the prescription dose is different from the dose actually delivered to the entire prostate.*

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- **Brachytherapy (including Boosting EBRT) in Conjunction with Androgen Deprivation:**

- Patients with initially large prostate (> 60 cc) that have downsized sufficiently

The ESTRO recommendations

- **The 2000 Dan Ash paper :**
- Radiother Oncol. 2000 Dec;57(3):315-21.
- **ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer.**
- *Ash D, Flynn A, Battermann J, de Reijke T, Lavagnini P, Blank L; ESTRO/EAU Urological Brachytherapy Group; EORTC Radiotherapy Group.*

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- **Actually only minor differences with the ABS paper …**

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**

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Relative contra-indications :

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

1999-2016 ; the evolution !

- **Ideas progressively changed …**
- **Risk groups ; should brachytherapy as monotherapy be reserved to low-risk patients ?**
- **What about age ?**
- **What about the biopsies ?(Percentage of involved samples, microfoci, bilaterality …)**
- **What about median lobes and obstructive syndroms ?**
- **Which role for MRI ?**

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- **Risk groups ; should brachytherapy as monotherapy be reserved to low-risk patients ?**

- Problems with the risk groups :
- Several definitions !

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Risk Group Definitions

	Author	T stage	PSA	Gleason	Indicator Rules
Low	ALL	T1c-T2a or T2	≤10	≤ 6	All required
Interm.	D'Amico	T2b	>10-20	7	One or more
	Blasko	T1T2	>10	7-10	One PSA or Gleason
	Zelefsky	T3	≥ 10	7-10	One
	Kuban	T1-T2a or T2bc	>10-20 or ≤20	≤7	All three
	Stock	T2b	>10	7	One
	Demanes	T2bc	>10-20	7	One or more
High	D'Amico	T2c	>20	8-10	One or more
	Blasko	T1T2	>10	7-10	Two or more PSA or Gleason
	Zelefsky	T3	≥ 10	7-10	Two or more
	Kuban	T3	>20	8-10	One
	Stock	T2c or T3	>20	8-10	One (or 2 Intermediate)
	Demanes	T3	>20	8-10	One or more

The main question :

- **<u>The intermediate risk group</u> :**
- **suitable for brachytherapy as monotherapy ?**

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- Brachytherapy. 2007 Jan-Mar;6(1):2-8.
  - Interstitial implant alone or in combination with external beam radiation therapy for intermediate-risk prostate cancer: a survey of practice patterns in the United States.

  Frank SJ, Grimm PD, Sylvester JE, Merrick GS, et al .

  PURPOSE: This study is aimed at understanding and defining the current patterns of care with respect to prostate brachytherapy for patients **with intermediate-risk localized disease** in the combined academic and community setting.

- RESULTS: *In the absence of PNI, all of those surveyed would perform monotherapy for intermediate-risk patients, GS 7 (3+4) or PSA 10-20, with cT1c and <30% cores +…*

- CONCLUSIONS: This Patterns of Care (POC) study reveals that certain subsets of intermediate-risk localized prostate cancer patients are considered appropriate candidates for an interstitial implant.

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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.*

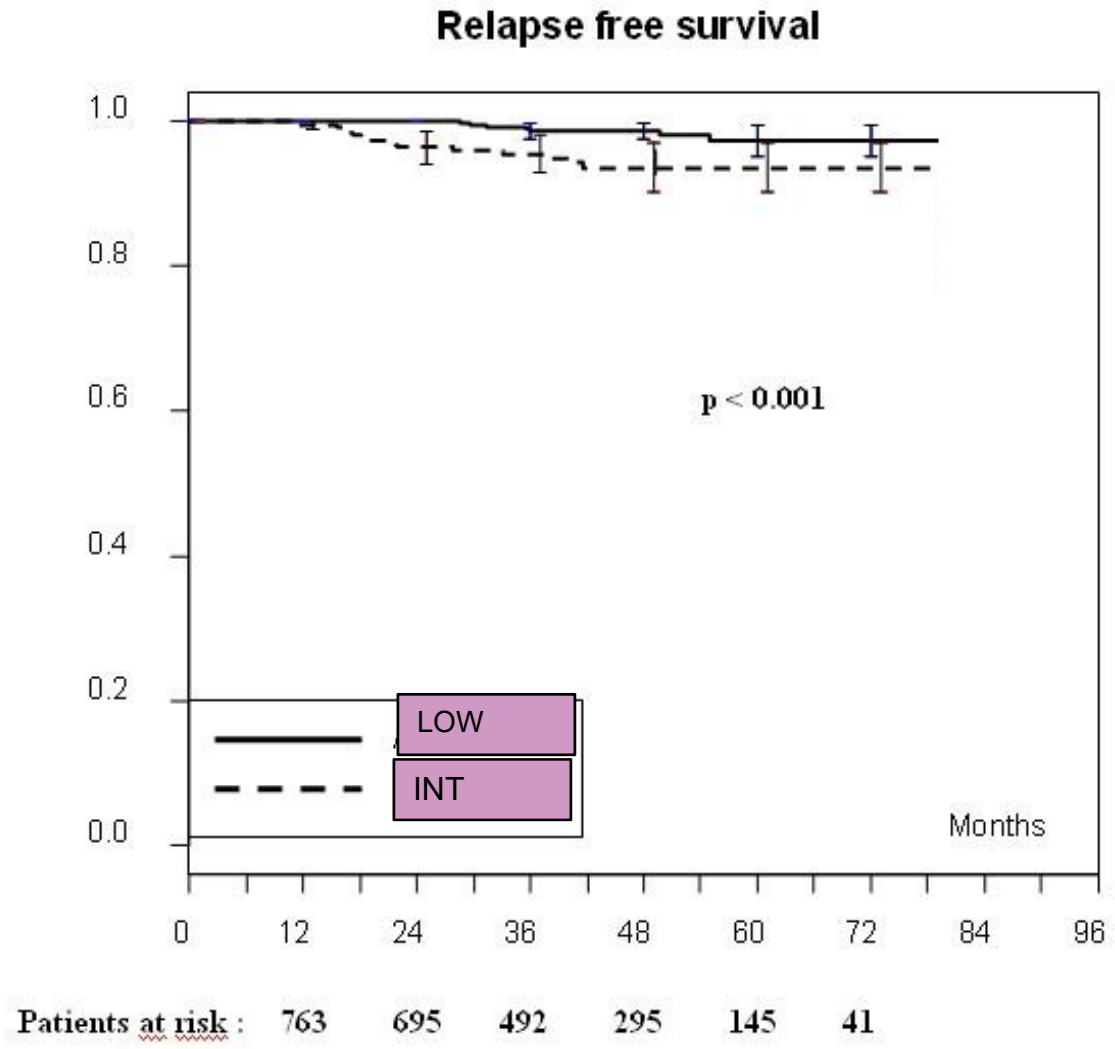
*Institut Curie, Paris, France; †Cochin Hospital, Paris, France; and ‡Necker Hospital, Paris, France

*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.

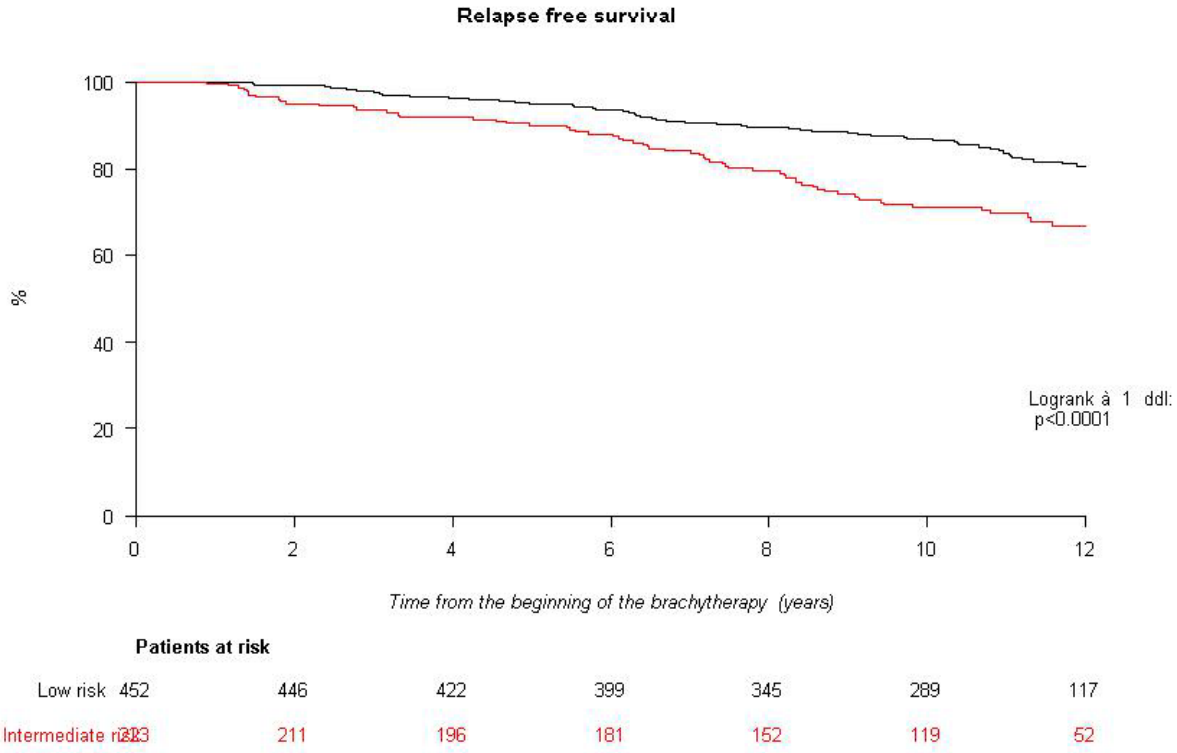
- For this Institut Curie series ;
- Low-risk patients
- and
- « Favorable intermediate » patients ;
- PSA between 10, and 15 and all other low-risk criteria
- Or ;
- Gleason 7, and all other low-risk criteria

2008 Paper


Relapse free survival
1.0
0.8
0.6
0.4
0.2
0.0
p < 0.001
LOW
INT
Months
0
12
24
36
48
60
72
84
96
Patients at risk : 763 695 492 295 145 41

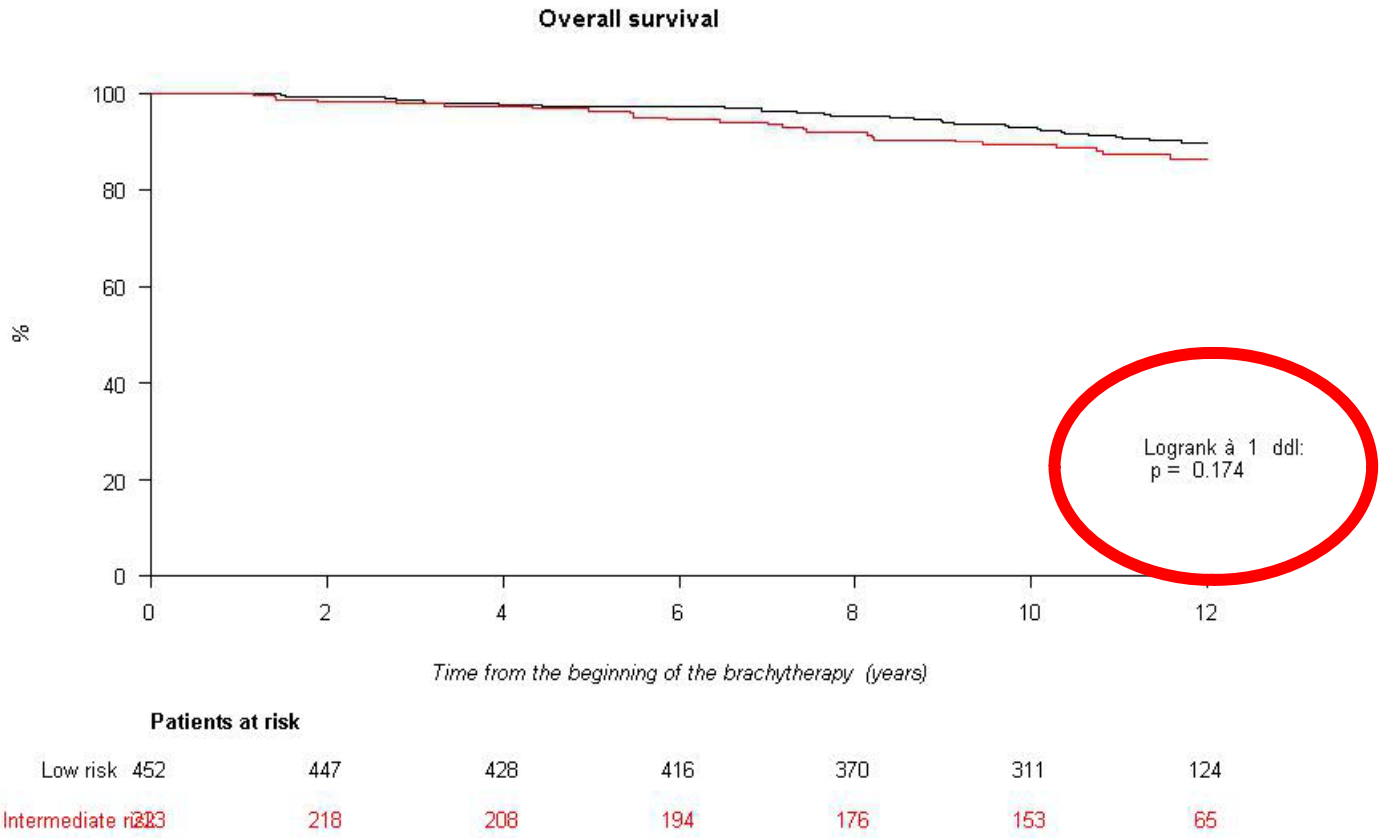
The 2016 Institut Curie experience (in Press)

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



No difference in long-term overall survival

...



- Conclusions (2008, confirmed in 2016)
- Our results suggest that at least selected patients in the intermediate-risk group of localized prostate cancers can be safely proposed permanent implant brachytherapy as monotherapy.

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 … »*

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- **ABS Meeting , 2009**
- **PO 65 : the PMH experience**
- **PO 101 : the Seattle experience**
- **Both favor Brachytherapy as**
- **monotherapy for intermediate-**
- **risk patients**
- **Seattle ; 9-year BRFS of 91.9 % …**

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- Finally, to make a long story short ;
- **The Prostate Cancer Results Study Group**
- Peter Grimm et al., 2011-2012 (BJU)
- With upgrade received every year !

Comparing Treatment Results Of PROSTATE CANCER

Prostate Cancer Results Study Group 2016

Peter Grimm, DO

Prostate Cancer Center of Seattle

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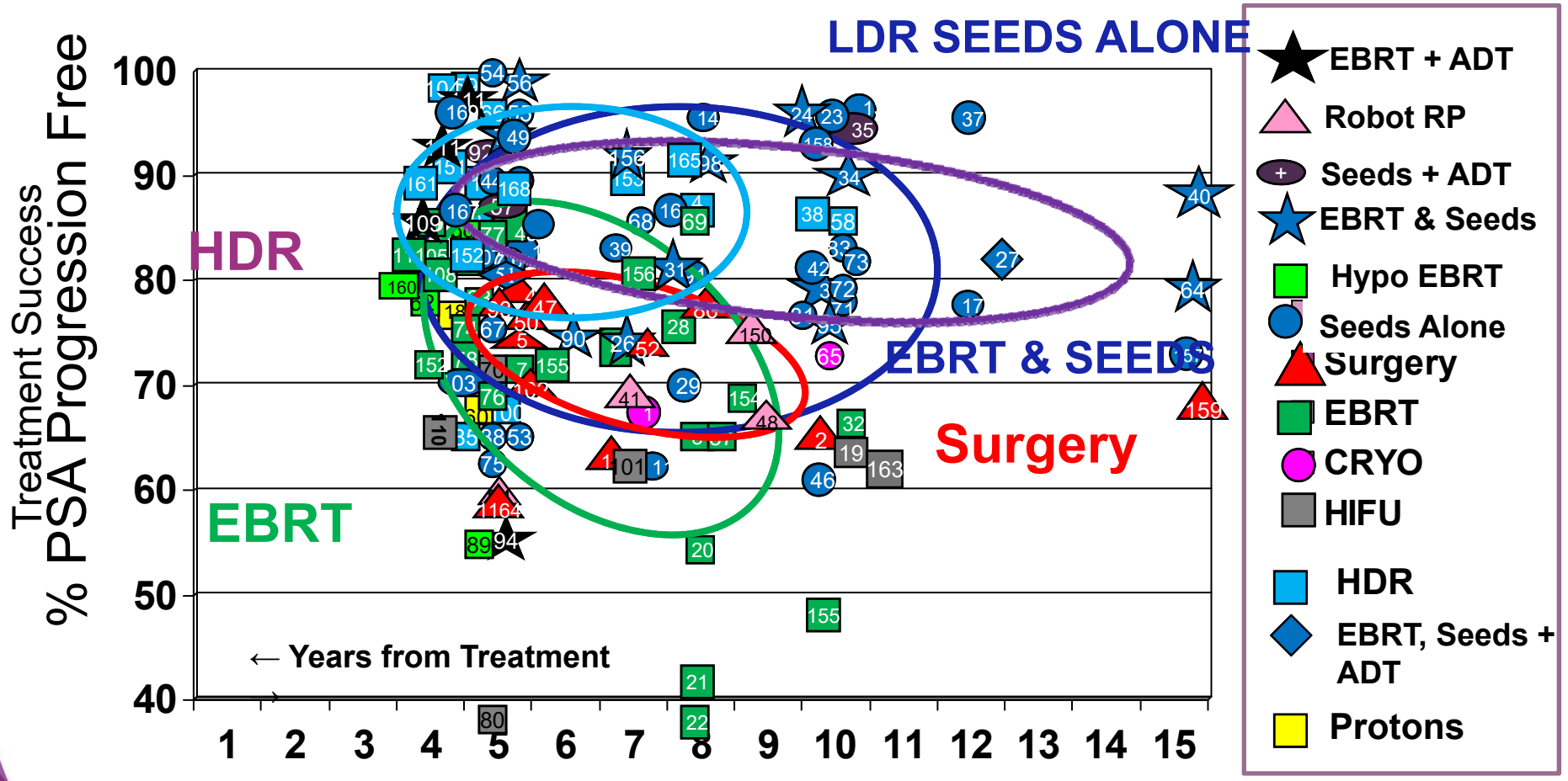
INTERMEDIATE RISK RESULTS weighted

>40 months follow-up or less than 100 patients



- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

Update of

6/11/2016

- **Most available data thus strongly suggest that at least a subset of selected patients in the intermediate-risk group may benefit from Brachytherapy as monotherapy …**

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- Eur Urol. 2013 Dec;64(6):895-902.
- **A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy.**
- Zumsteg ZS[1], Spratt DE, Pei I, Zhang Z, Yamada Y, Kollmeier M, Zelefsky MJ.
- **CONCLUSIONS:**
- **Intermediate-risk PCa is a heterogeneous collection of diseases that can be separated into favorable and unfavorable subsets. These groups likely will benefit from divergent therapeutic paradigms.**

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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.

- **New classification systems have been proposed that modify the existing National Comprehensive Cancer Network guidelines and that subdivide men with intermediate-risk prostate cancer into favorable and unfavorable subgroups**

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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.

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• 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 …

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- **However, since that time …**

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- 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.

ESTRO School

- 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.

ESTRO School

- 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.

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

- **What about the biopsies ?(Percentage of involved samples, microfoci, bilaterality …)**

- What about the impact of the percentage of positive biopsies ?
- Nil for some authors ;
- **Pe et al., Urology 2009**
- **No impact of the percentage of positive biopsies on Freedom From Biochemical Failure …**

ESTRO School

Int J Radiat Oncol Biol Phys. 2002 Mar 1;52(3):664-73.

Relationship between percent positive biopsies and biochemical outcome after permanent interstitial brachytherapy for clinically organ-confined carcinoma of the prostate gland.

Merrick GS[1], Butler WM, Galbreath RW, Lief JH, Adamovich E.

- ***CONCLUSION:***
- …. **Our results suggest that the percentage of positive biopsies is not statistically significant in predicting the 5-year biochemical disease-free outcome for patients with low, intermediate, and high-risk disease undergoing permanent prostate brachytherapy.**

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- **But to be taken into account for others :**
- Heidenreich A et al. EAU guidelines on prostate cancer. April 2010:
- **Criteria :**
- Stage cT1b-T2a, N0, M0
- Gleason score ≤6 7 (?) = “grey area”
- Initial PSA (ng/mL)<10
- **Amount of biopsy cores involved with cancer (%) ≤50**
- Prostate volume <50 cm^3
- IPSS ≤12

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What about microfoci ?

- **The « index lesion » concept !**
- **Treat the index (main) lesion and ignore the microfoci ?**
- **See presentation on focal brachytherapy …**

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- **Already quoted ;**
- Brachytherapy. 2007 Jan-Mar;6(1):2-8.
  - Interstitial implant alone or in combination with external beam radiation therapy for intermediate-risk prostate cancer: a survey of practice patterns in the United States.

  Frank SJ, Grimm PD, Sylvester JE, Merrick GS, et al .

« In the absence of PNI, all of those surveyed would perform monotherapy for intermediate-risk patients, GS 7 (3+4) or PSA 10-20, with cT1c ***and <30% cores +...*** *»*

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What about bilaterality ?

- **Depends …**
- **Massive bilateral involvement ,**
- ***or***
- **Unilateral « index » lesion and controlateral microfoci ?**
- **Different impact on decision !**

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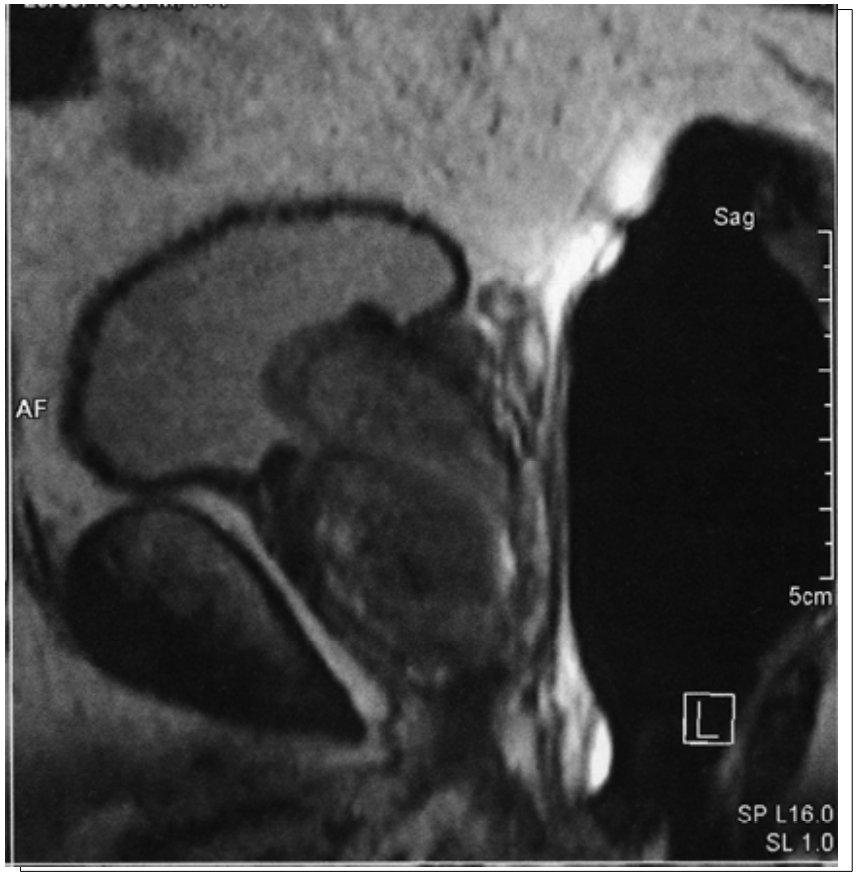
- **What about median lobes and obstructive syndroms ?**



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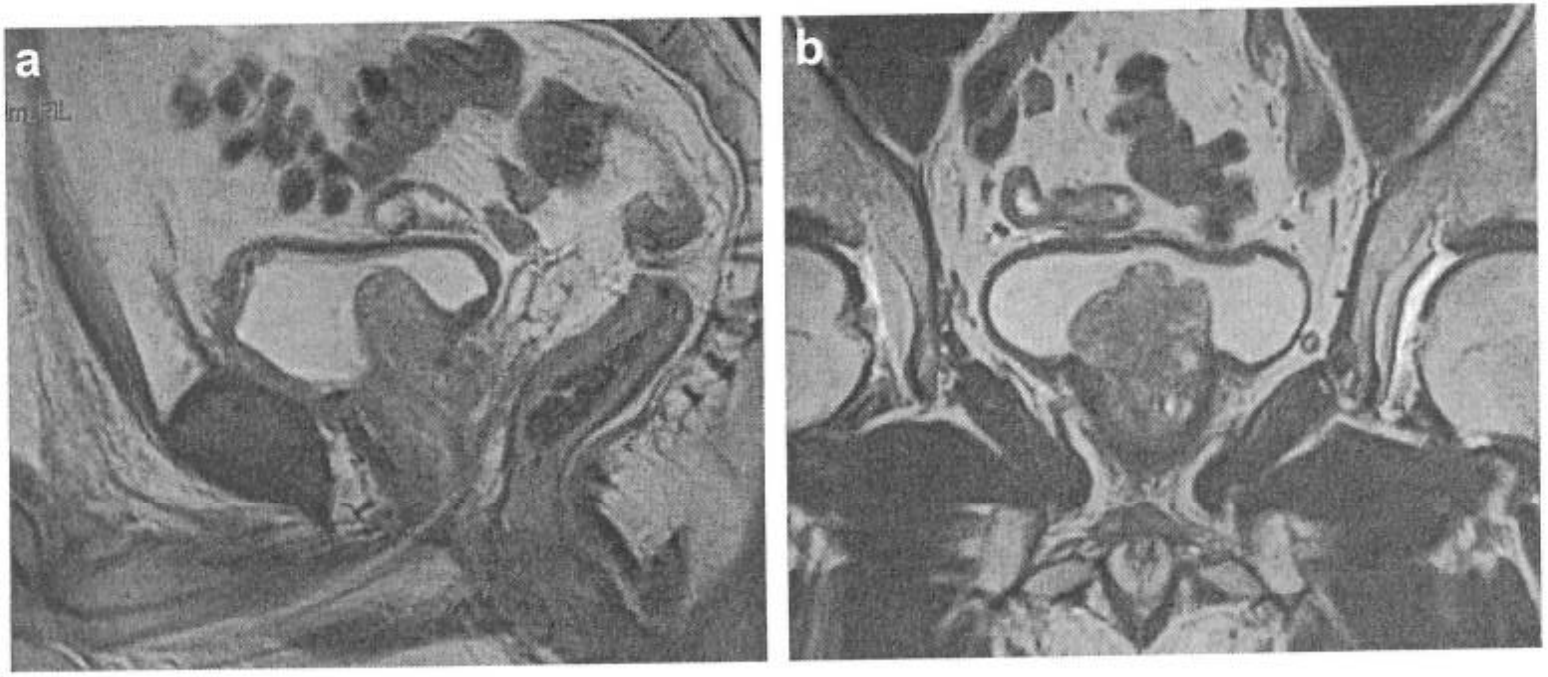
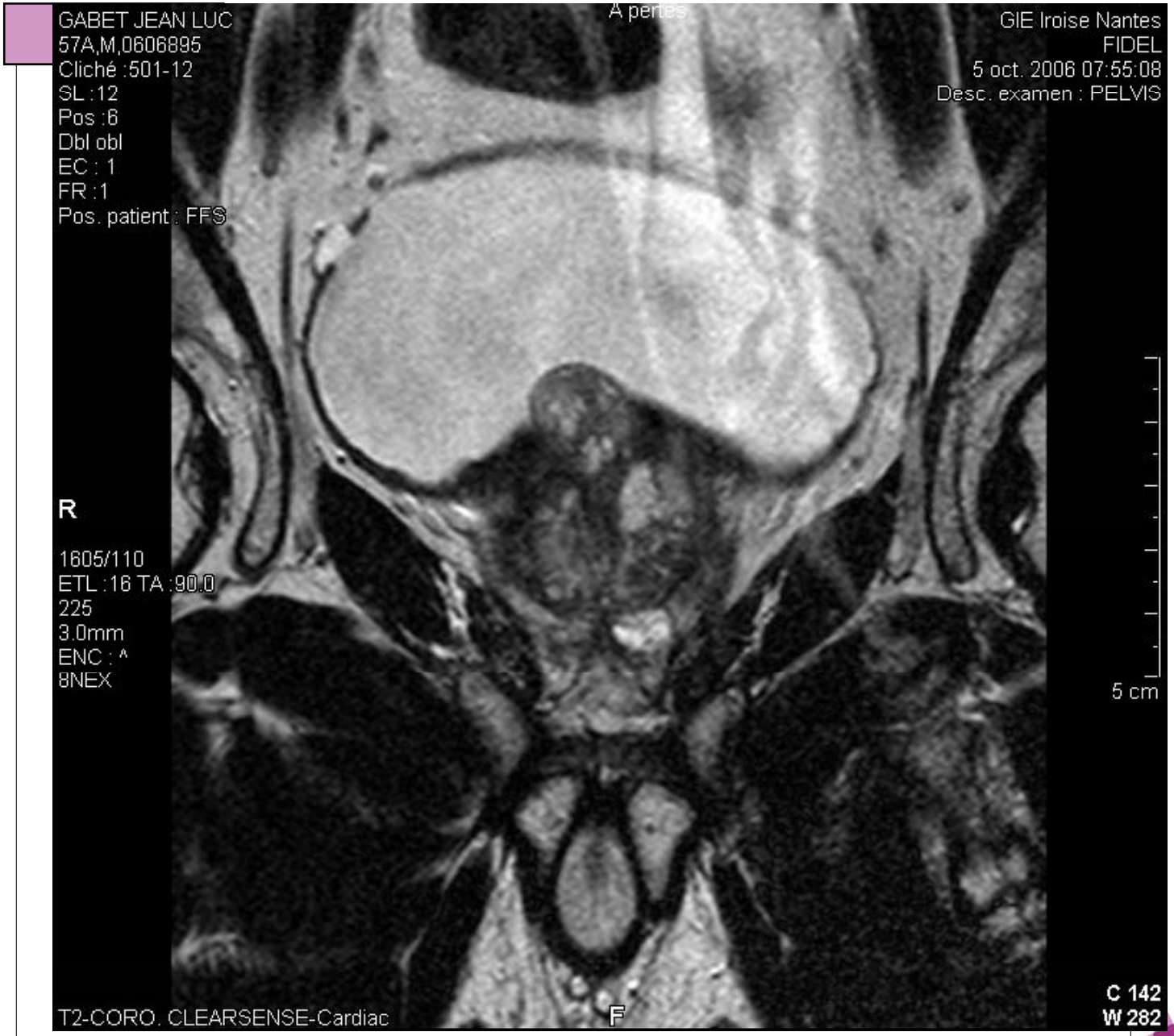


Fig. 1. (a and b) Example of a "very prominent" (+++) median lobe (Case $N = 19$).



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- 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'Ulm, Paris, France.

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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.

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- METHODS AND MATERIALS:

- From January 2007 to November 2008, 22 patients underwent a customized limited TURP of their median lobe immediately before brachytherapy.

- **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.

- ***(Encouraging preliminary results ...)***

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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**

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Which role for MRI ?

- With better and better MRIs in 2015:
- 3 Tesla, multiparametric, endorectal probe …
- **A prominent role for MRI ;**
- Most authors now take (more and more) the MRI images into account :
- Large MRI tumors, with extensive bilateral involvement and/or large « contact » with the capsule …
- … might be poor candidates for brachytherapy as monotherapy …

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This being said ….

- **The 2012 ABS recommendations**

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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*

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Risk groups

[redacted]. The ABS recommends the use of the National Comprehensive Cancer Network guidelines (2):

Low risk: Gleason score ≤6, and PSA <10 ng/mL, and clinical tumor classification, T1, T2a.

Intermediate risk: Gleason score 7, or, PSA >10 ng/mL < 20 ng/mL, or clinical tumor classification of T2b, T2c.

High risk: Gleason score 8–10, or, PSA >20 ng/mL, or clinical tumor classification of T3a.

Patients with seminal vesicle invasion (SVI), clinical tumor classification T3b, are considered to be high risk in terms of treatment and evaluation. Consideration may be given to performing seminal vesicle biopsies when evaluating intermediate- and high-risk patients (70).

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.

- **“Patients with high probability of organ-confined disease or limited extraprostatic extension are considered appropriate candidates for PPB monotherapy.**
- **Low-risk patients may be treated with PPB alone without the need for supplemental external beam radiotherapy.**
- **High-risk patients should receive supplemental external beam radiotherapy if PPB is used.”**

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- **Intermediate-risk patients** should be considered on **an individual case basis**.
- **Intermediate-risk patients with favorable features may appropriately be treated with PPB monotherapy but results from confirmatory clinical trials are pending.**

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Table 5
Prescription doses to the planning target volume

^{125}I	
Monotherapy	140–160 Gy
Combination	
EBRT	41.4–50.4 Gy (1.8 Gy/d[a])
PPB dose	108–110 Gy
^{103}Pd	
Monotherapy	110–125 Gy
Combination	
EBRT	41.4–50.4 Gy (1.8 Gy/d[a])
PPB dose	90–100 Gy

PPB = permanent prostate brachytherapy; EBRT = external beam radiation therapy.

[a] 2 Gy/d also acceptable.

Table 6
Radionuclides for permanent prostate brachytherapy

Radionuclide	Half-life (d)	Average energy (keV)	Year introduced	Typical monotherapy seed strength (mCi)	(U)
^{125}I	59.4	28.4	1965	0.3–0.6	0.4–0.8
^{103}Pd	17.0	20.7	1986	1.1–2.2	1.4–2.8
^{131}Cs	9.7	30.4	2004	2.5–3.9	1.6–2.5

The ABS recommends the following postoperative dosimetric parameters be determined:

Prostate: D_{90} (in Gy and percent)

V_{100} and V_{150} (in percent)

Urethra: UV_{150} (in volume)

UV_5, UV_{30} (percent)

Rectum: RV_{100} (in volume)

In 2016, the indications of permanent implant prostate cancer brachytherapy are expanding :

- **Towards …**

- **At least selected patients in the intermediate risk group**
- **Younger patients**
- **Bilateral lesions if only controlateral microfoci**
- **Larger prostates (after volumetric reduction or not)**
- **Obstructive prostate (after customized RTUP)**
- **Moreover …**

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New indications ;

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

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- With a recent additional competitor ;
- Active surveillance ….

Med Care. 2014 Jul;52(7):579-85..

Perceptions of Active Surveillance and Treatment Recommendations for Low-risk Prostate Cancer: Results from a National Survey of Radiation Oncologists and Urologists.

Kim SP[1], Gross CP, Nguyen PL, Smaldone MC, Shah ND, Karnes RJ, Thompson RH, Han LC, Yu JB, Trinh QD, Ziegenfuss JY, Sun M, Tilburt JC.

- ***CONCLUSIONS***
- Most prostate cancer specialists in the United States believe Active Surveillance effective and underused for low-risk prostate cancer …

… yet continue to recommend the primary treatments their specialties deliver (!)

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- **Considering the pending and unsolved questions about Active Surveillance, they could be right (?) …**

Thank you !

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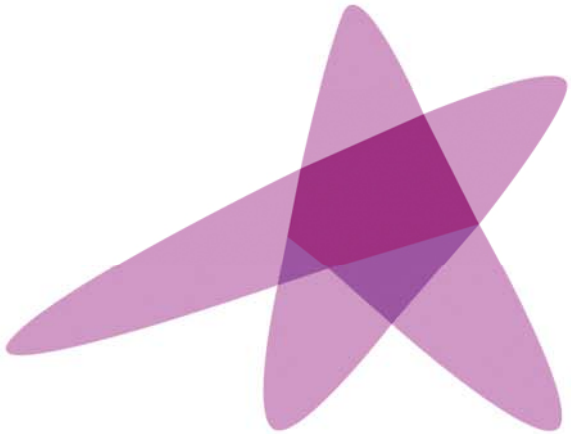

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WWW.ESTRO.ORG/SCHOOL

High dose rate brachytherapy for prostate cancer: PATIENT SELECTION

Peter Hoskin
Mount Vernon Cancer Centre
Northwood
UK

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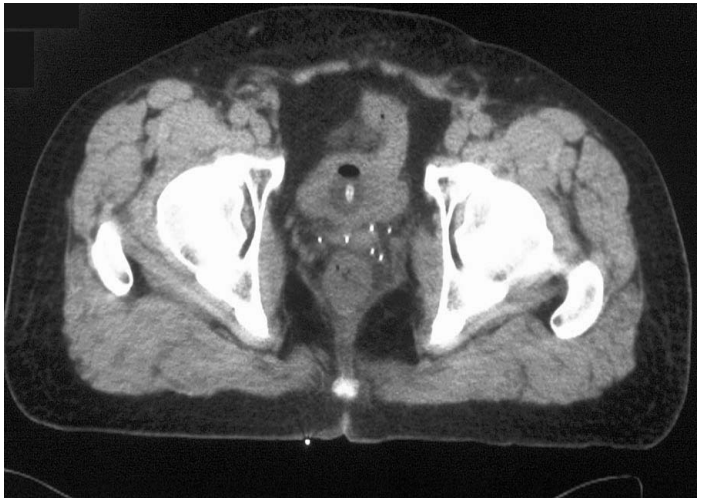
HDR prostate brachytherapy

- 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

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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)

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

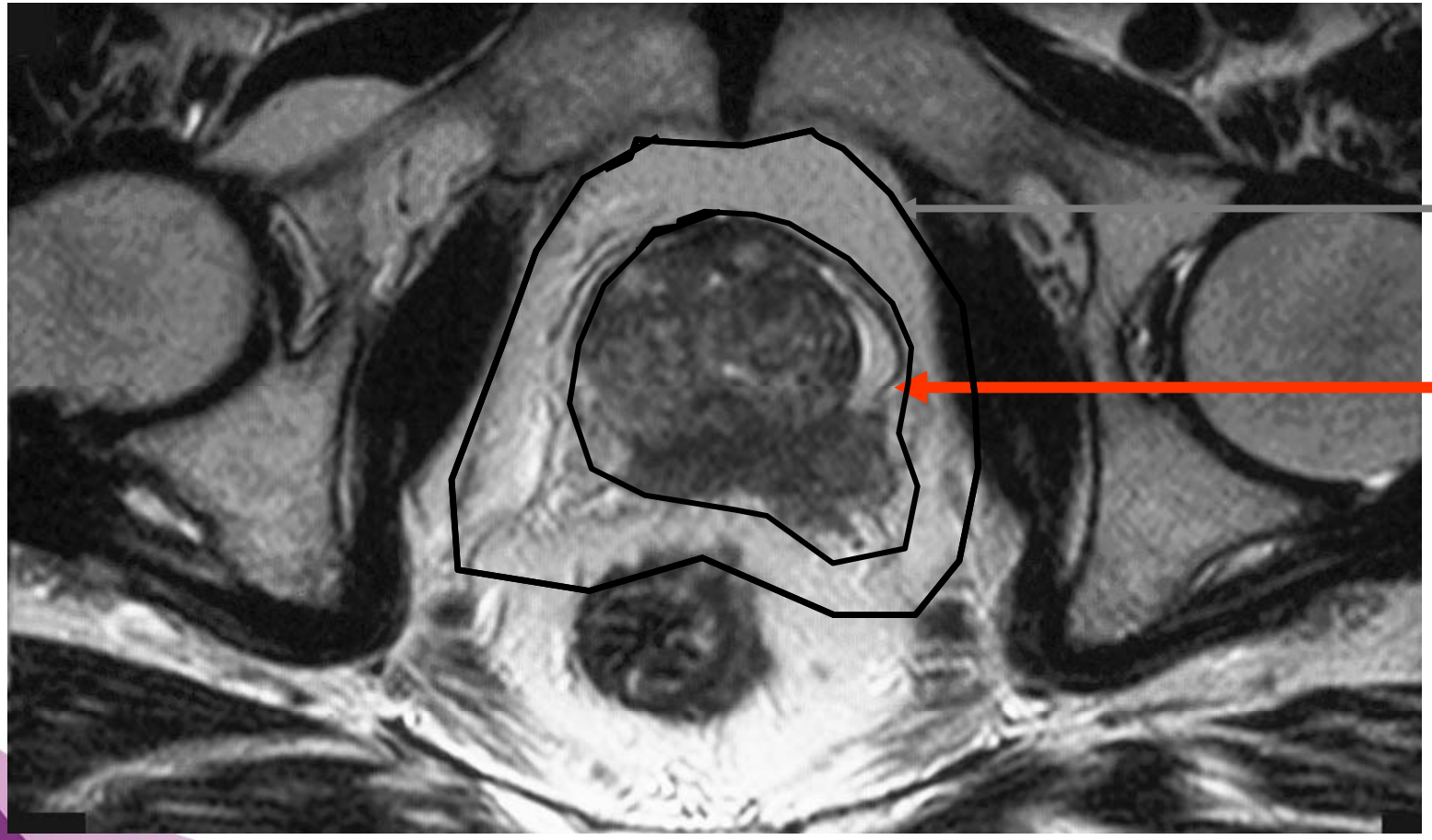
- Stages T1b–T3b
- Any Gleason score
- Any PSA level

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

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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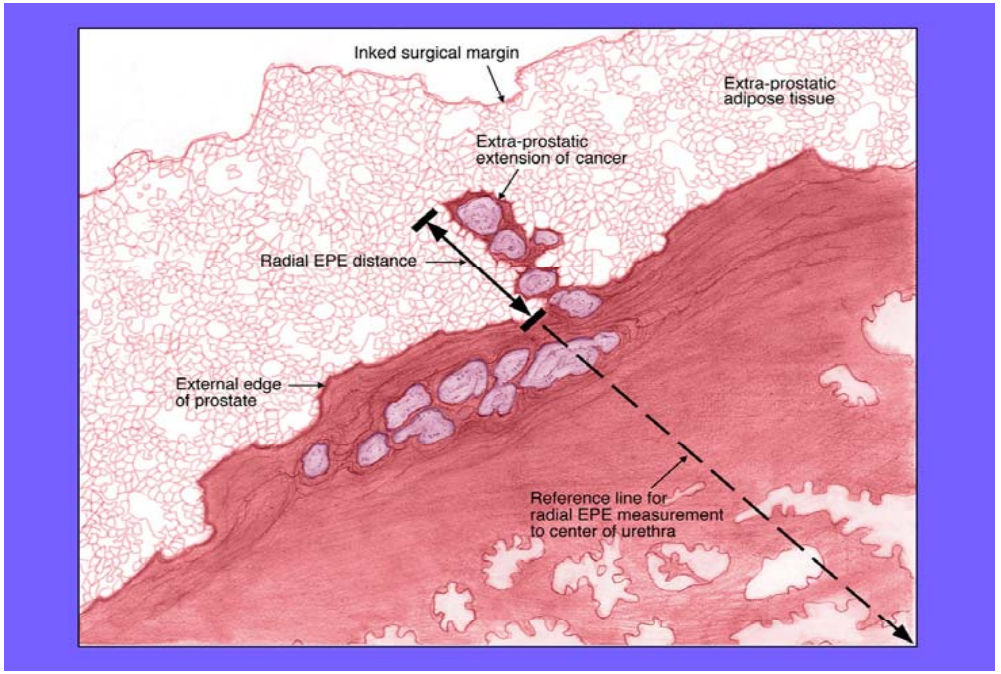
Ext beam/HDR boost for prostate

?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]

[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

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- IPSS > 20
- Pubic arch interference
- Lithotomy position or anaesthesia not possible
- Rectal fistula

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

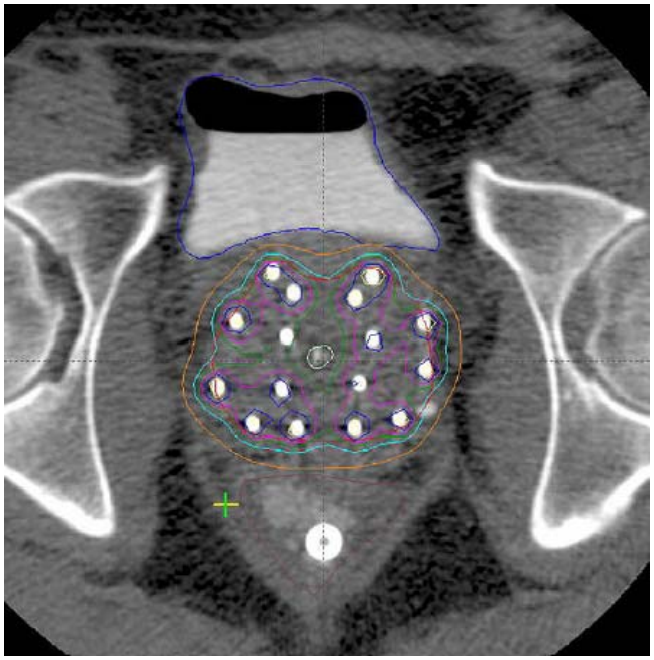
Alan T. Monroe*, Patrick O. Faricy, Scott B. Jennings, Robert D. Biggers, Gregory L. Gibbs, Anuj V. Peddada

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

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

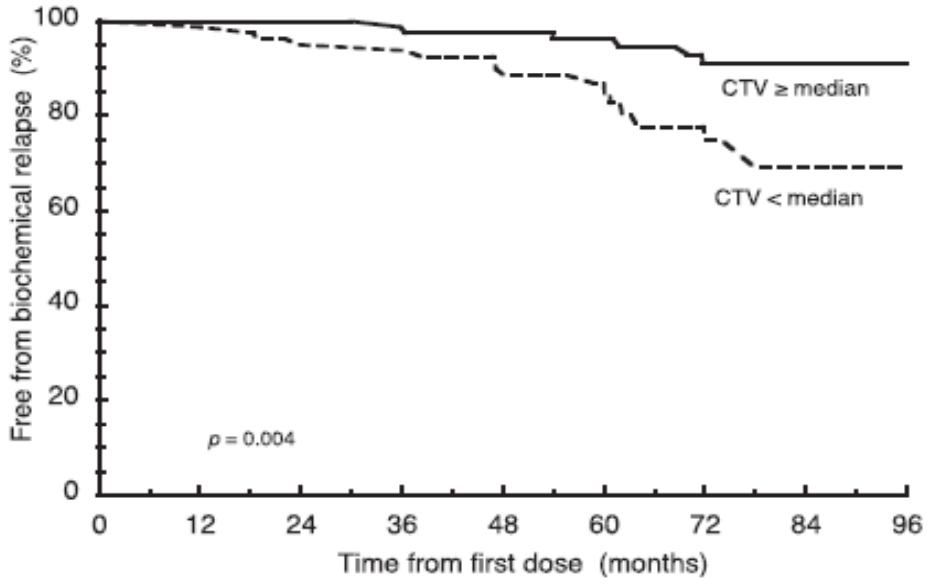
Mount Vernon Cancer Centre, Middlesex, UK

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

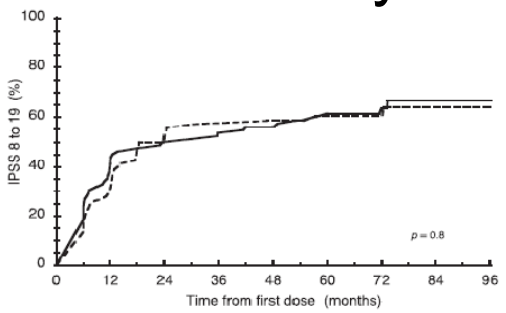
164 patients HDR monotherapy; median CTV volume 60mls (range 14-2

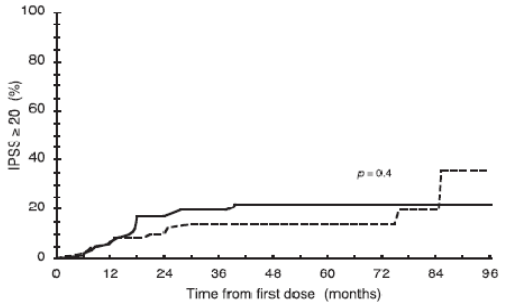
Volumes	V100 mean	*P* value	D90 mean	*P* value	V150 mean	*P* value	Urethral D30 mean	*P* value
≤Median	93	.24	103.7	.14	29.0	.97	11.2	<.0001
>Median	94	-	104.7	-	28.9	-	10.6	-

bRFS



Toxicity



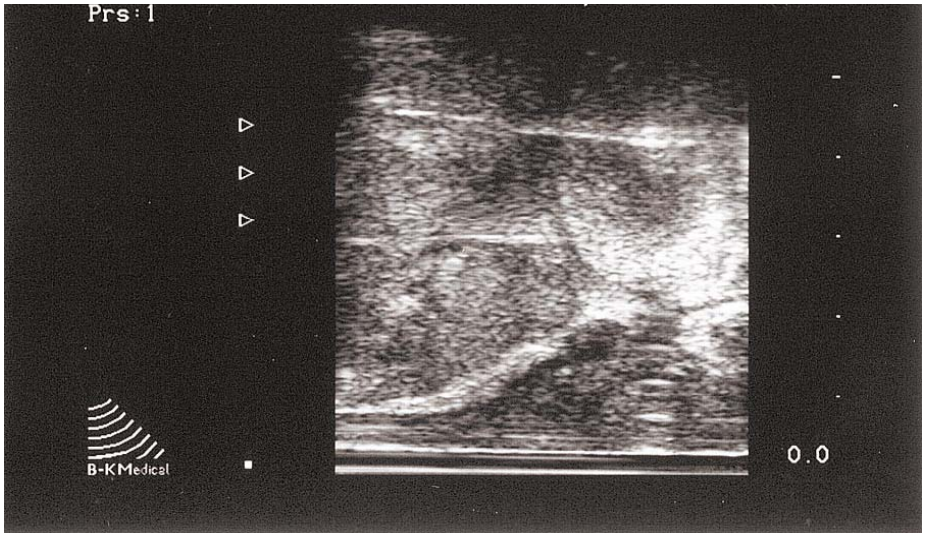


ESTRO School

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

ESTRO School

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.

ESTRO School

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
- Focal lesion identified by:
  - mpMRI ‘dominant’ lesion
  - Template biopsy mapping

QUALITY ASSURANCE (QA) FOR PROSTATE BRACHYTHERAPY

Bashar Al-Qaisieh

The Leeds Teaching Hospitals NHS
NHS Trust

Overview

- TG 43 and TG43-U1
- Seed & Needle Check
- Template Calibration
- Ultrasound Machine Check
- Commissioning Planning System
- Treatment Plan Check
- Post Implant QA

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

TG43-U1

- Clear definitions of physical quantities, and all the equations required for the calculation of dose.
- Treatment planning systems.
- Source calibration.
- Planning systems commissioning.
- Universal standards.
- Theoretical and experimental recommendations.
- And more…….

$$D(r,\theta)=S_k \Lambda [G(r,\theta)/G(r_0,\theta_0)]g(r)F(r,\theta)$$

S_k= air kerma strength of the source

Λ= dose rate constant

$G(r,\theta)$=geometry factor

$g(r)$=radial dose function

$F(r,\theta)$=anisotropy function

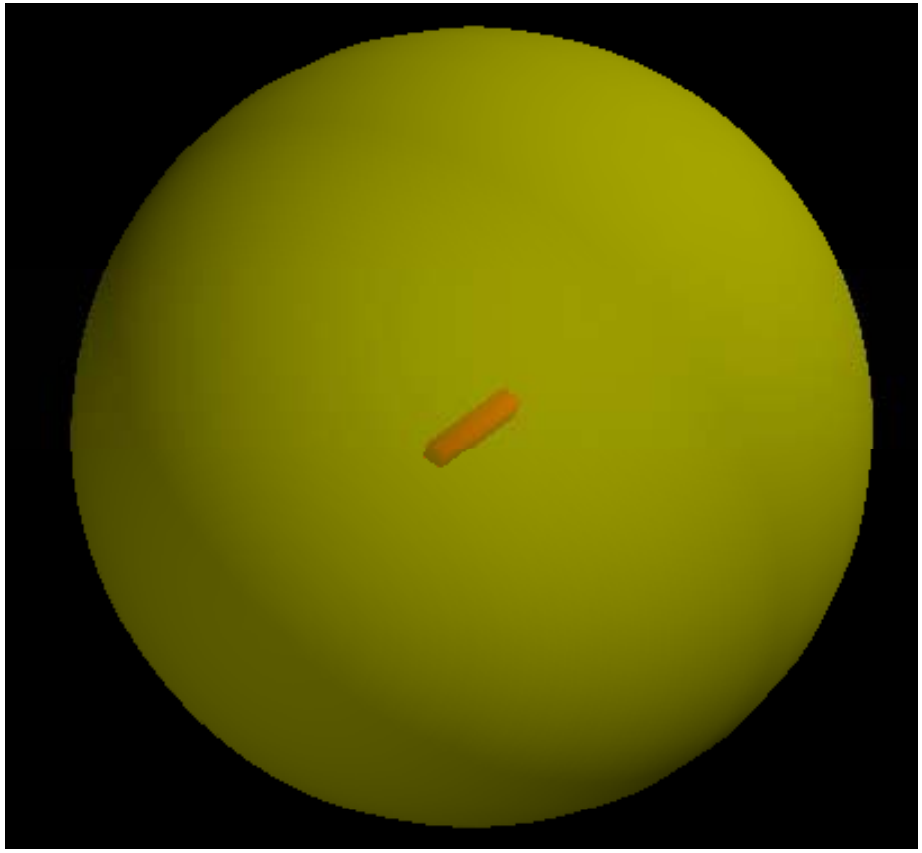
TG 43-U1, QA Table

r (cm)	Amersham model 6702	Amersham model 6711	Best model 2301	NASI model MED3631-A/M	Bebig model I25.S06	Imagyn model IS-12501	Theragenics model 200	NASI model MED3633
0.5	4.119	3.937	3.813	4.112	3.922	3.426	3.014	3.184
1.0	0.995	0.911	0.962	0.986	0.950	0.815	0.587	0.626
1.5	0.413	0.368	0.413	0.420	0.398	0.334	0.199	0.215
2.0	0.213	0.186	0.220	0.207	0.205	0.169	0.0837	0.0914
3.0	0.0768	0.0643	0.0783	0.0746	0.0733	0.0582	0.0206	0.0227
4.0	0.0344	0.0284	0.0347	0.0325	0.0323	0.0246	0.00634	0.00697
5.0	0.0169	0.0134	0.0171	0.0157	0.0157	0.0118	0.00221	0.00247
6.0	0.00890	0.00688	0.00908	0.00811	0.00840	0.00592	0.000846	0.000933
7.0	0.00490	0.00373	0.00506	0.00429	0.00459	0.00328	0.000342	0.000364

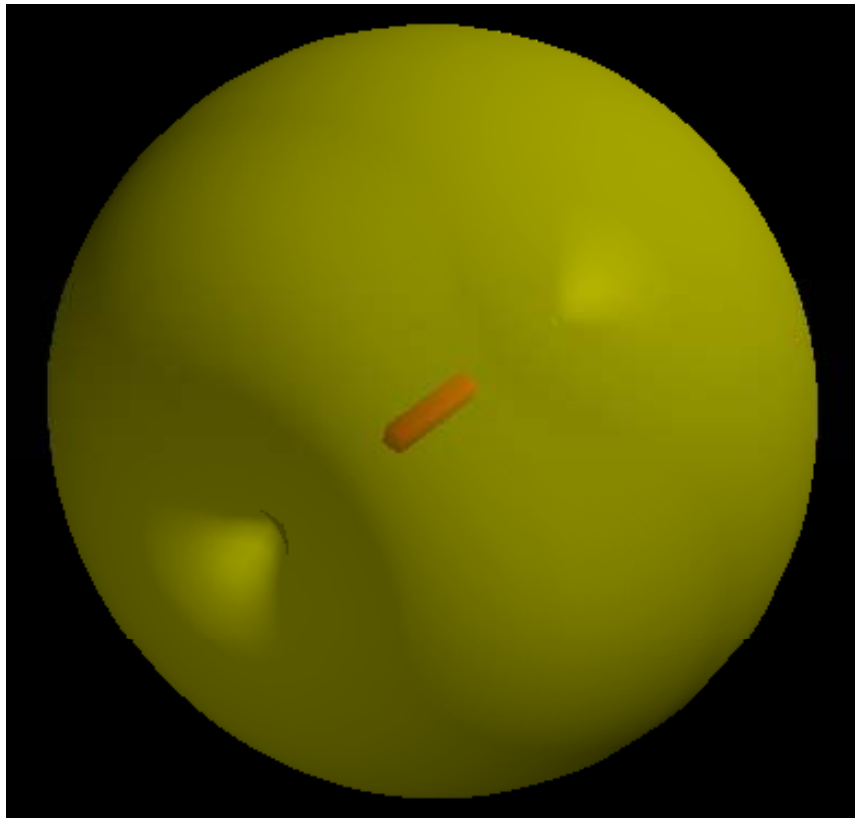
$$D(r) = D^{\cdot}(r,\theta) \times AL$$

$$AL = 1.44 \times 24 \times HL$$

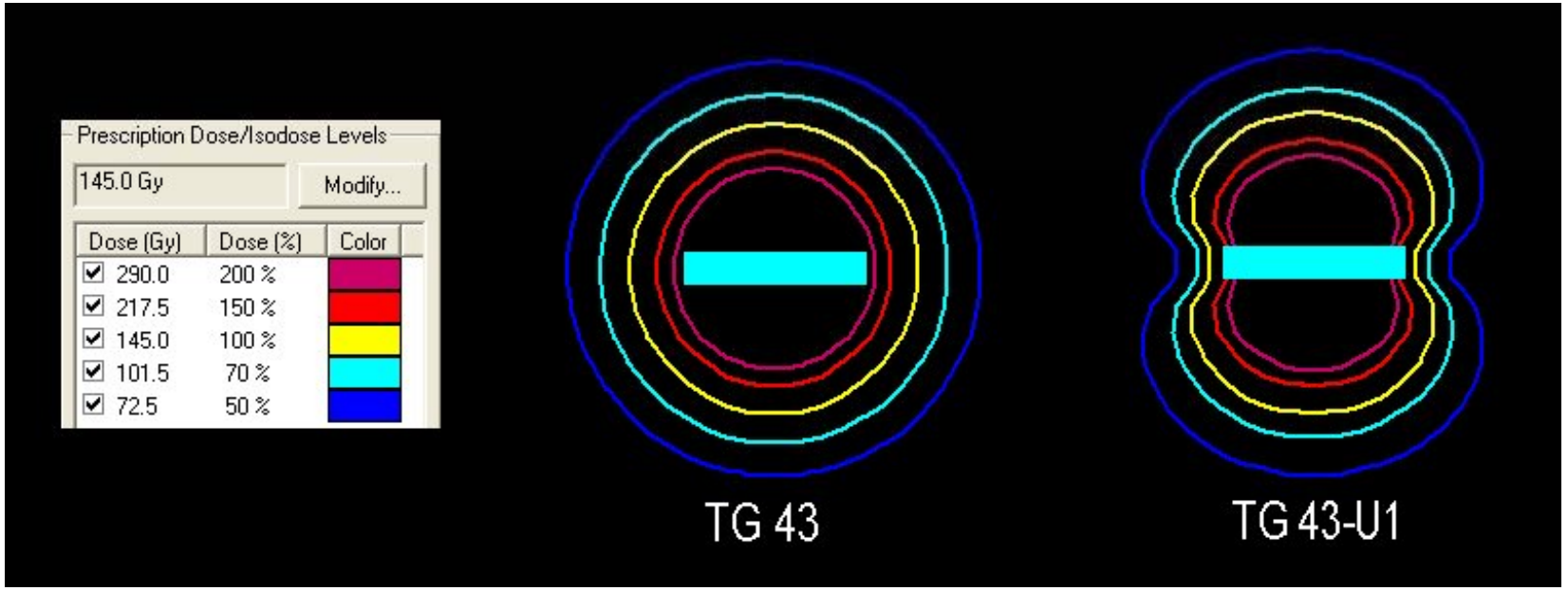
TG43



TG43-U1



TG43-U1


Prescription Dose/Isodose Levels
145.0 Gy
Modify...
Dose (Gy)
Dose (%)
Color
290.0 200 %
217.5 150 %
145.0 100 %
101.5 70 %
72.5 50 %
TG 43
TG 43-U1

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

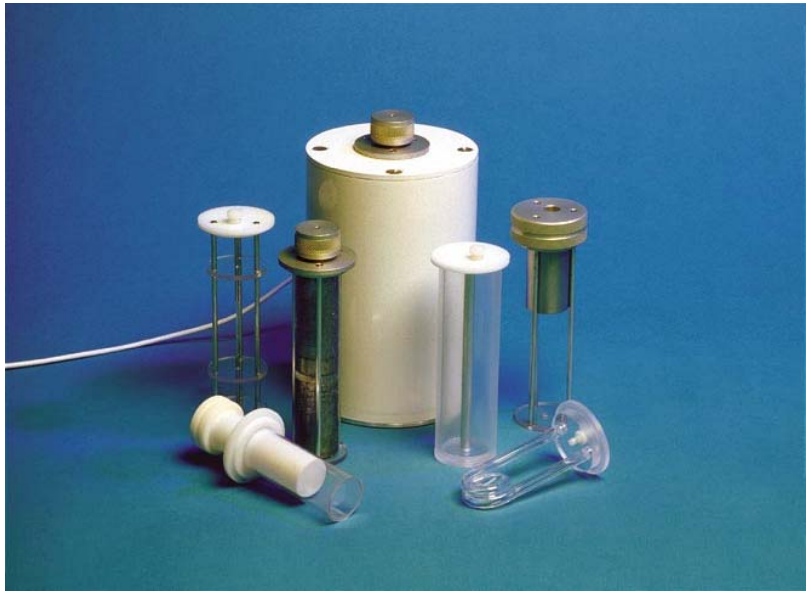
- a minimum of 10% of the total or two magazine cartridges of 15 seeds, whichever is greater.

• 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.



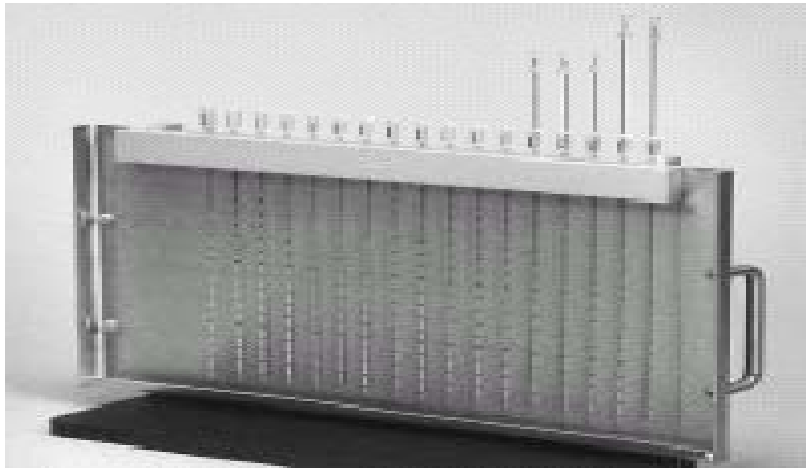
Action level if seeds are out of tolerance

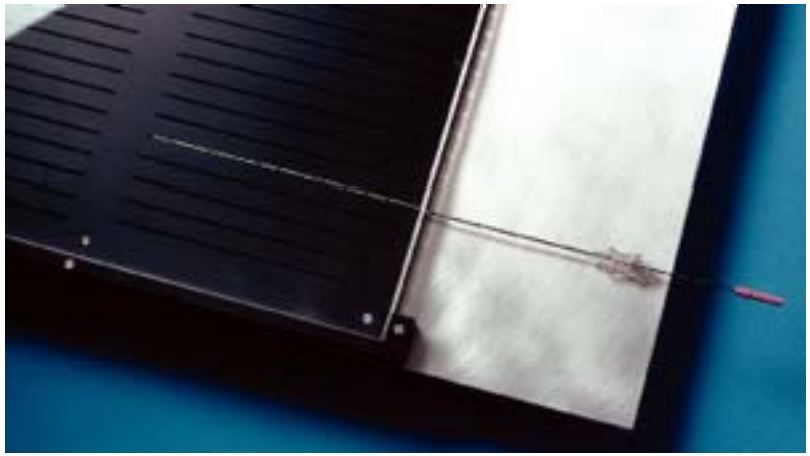
- If the mean source strength of the measured sources agrees within 3% of the manufacturer's stated source strength and the absolute difference of all the individual source/strand measurements are within the quoted calibration uncertainty on the manufacturer's certificate, the sources can be used clinically.
- 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

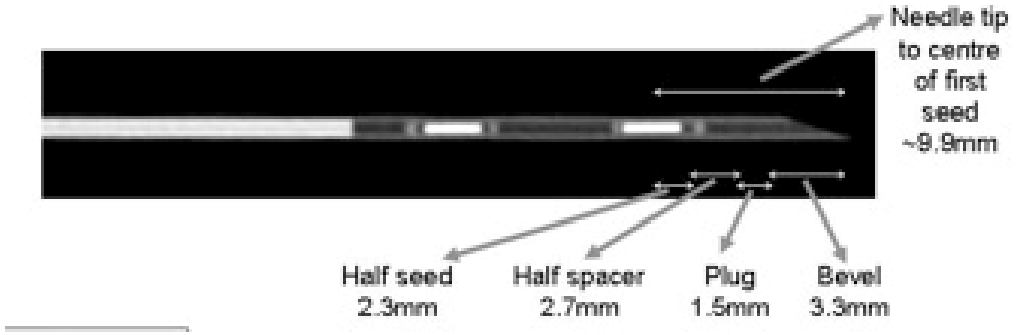
Needles Check

- 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.

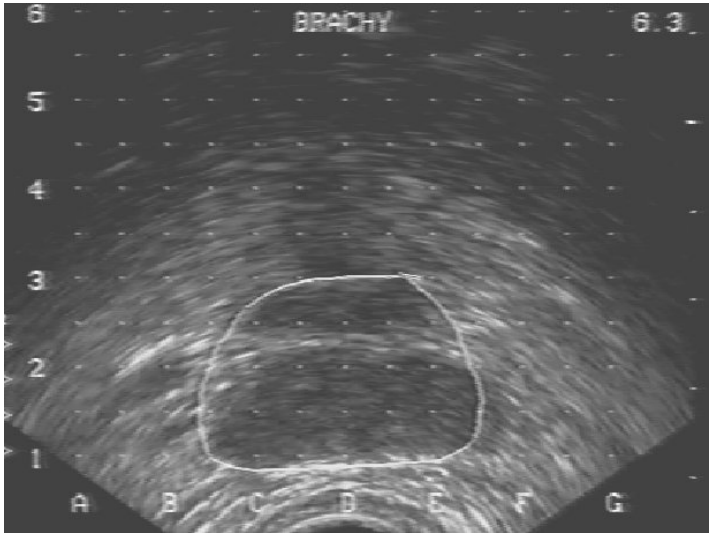




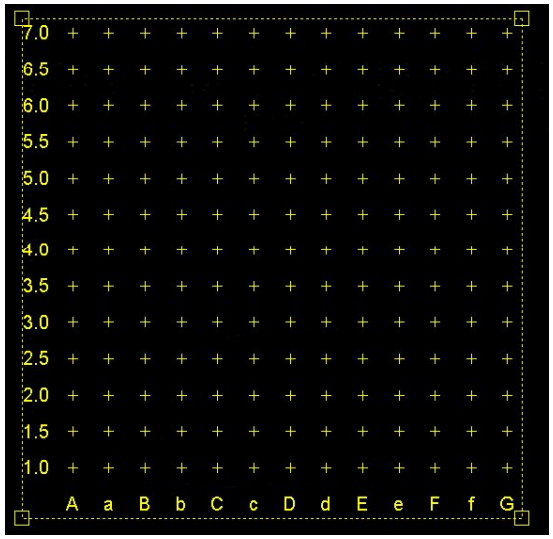
Needles Check



Template Calibration



Ultrasound Template

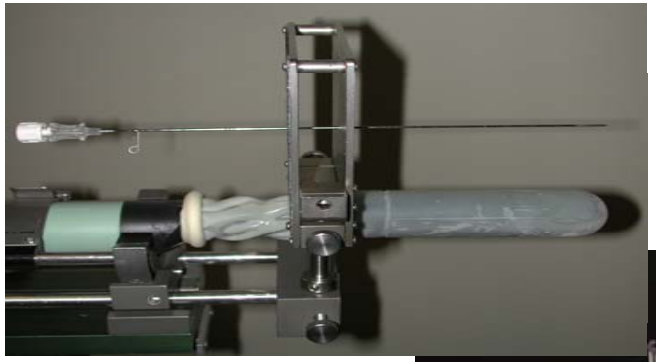


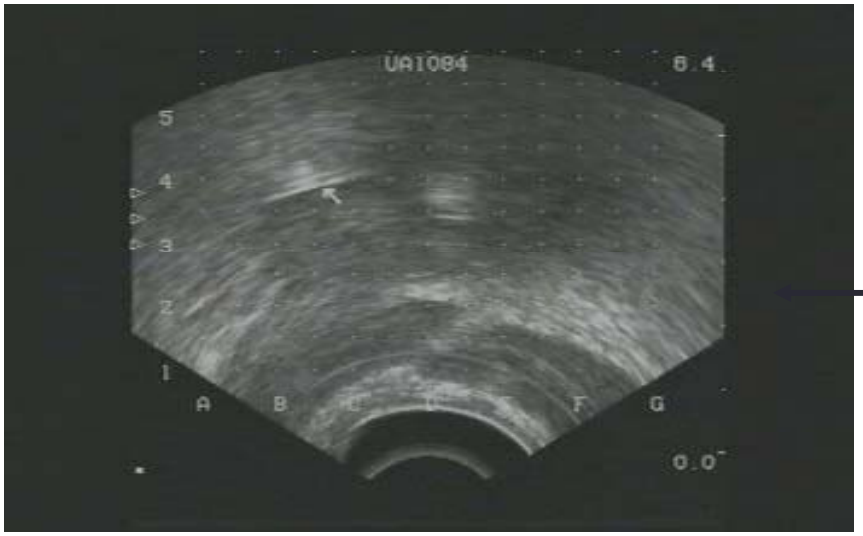
Guidance Template

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

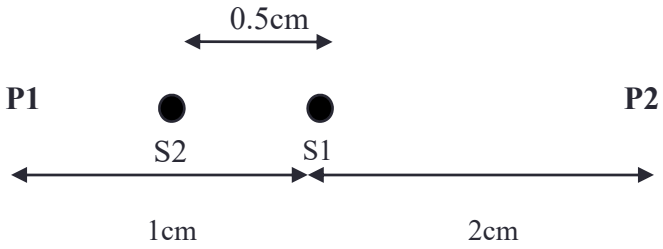
-TG –1: Goodsitt et al. Med Physics 25(8) 1998.

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%.

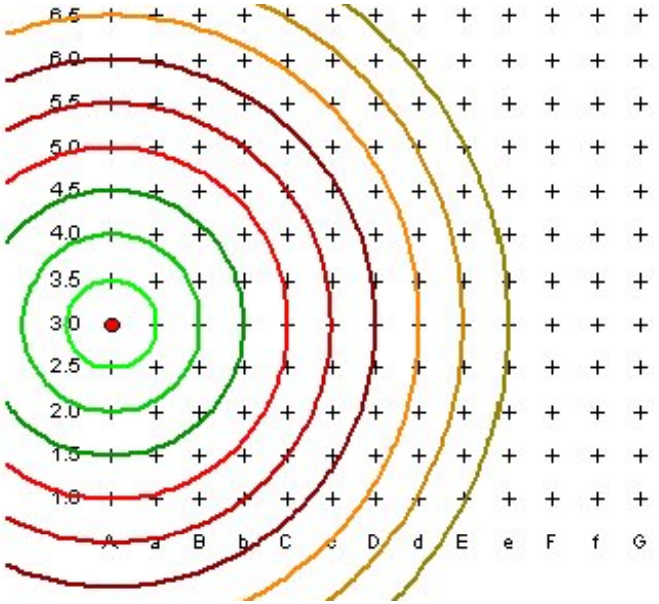


Dose rates (cGy h^{-1} U^{-1}) as a function of distance

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

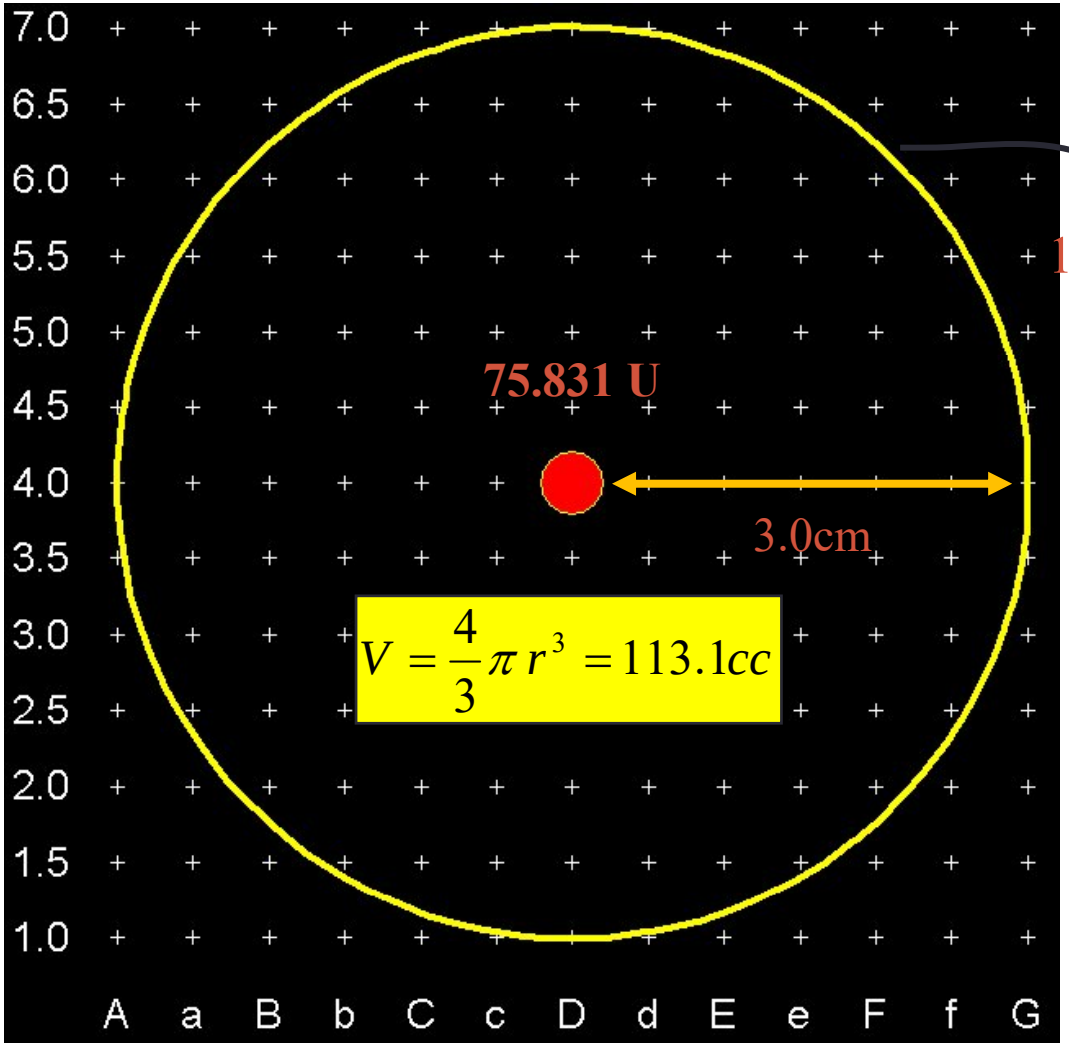
- This test is to verify the display of isodose levels
- The distance discrepancy of contours and template should be within ± 2 mm



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

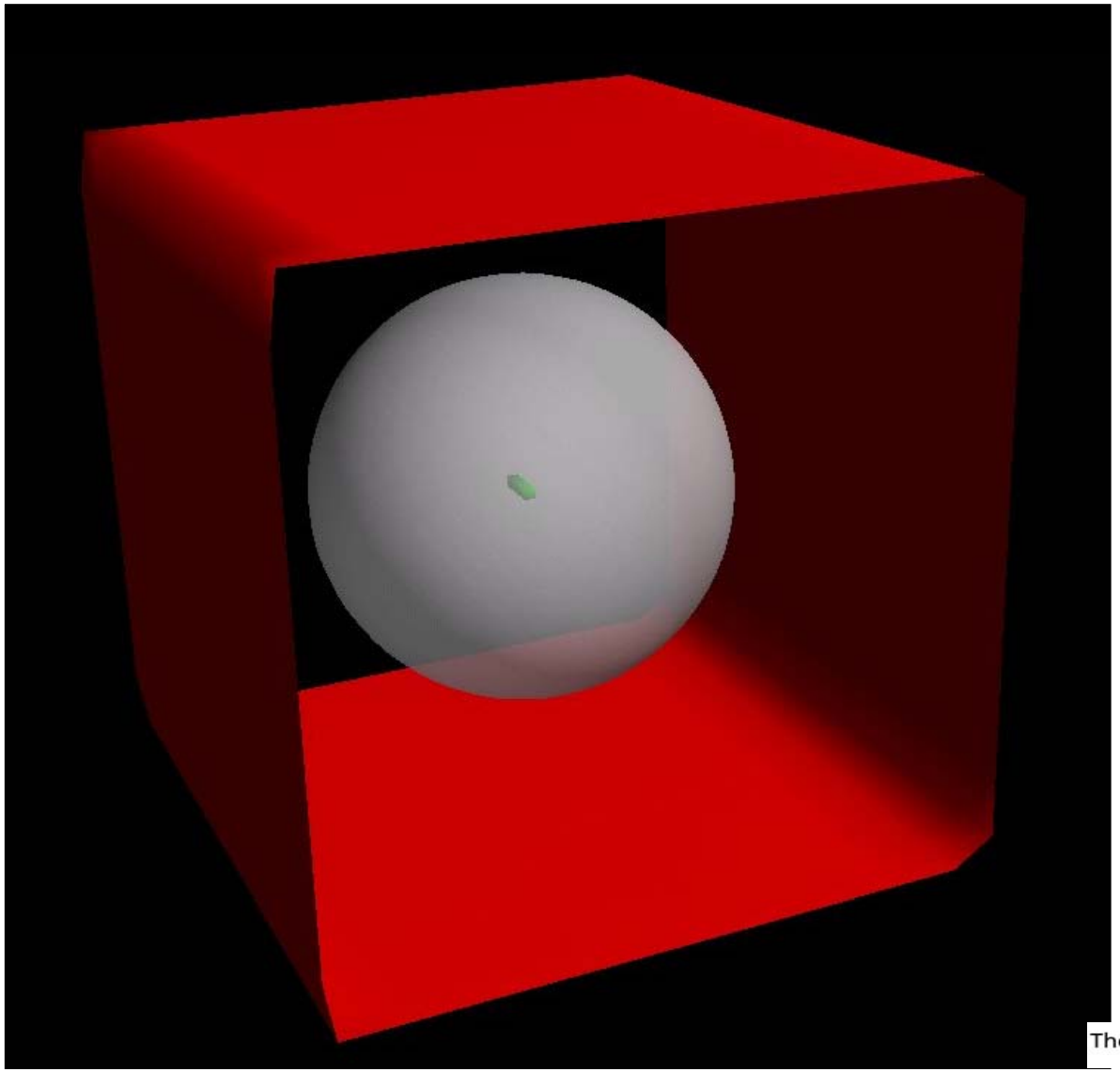
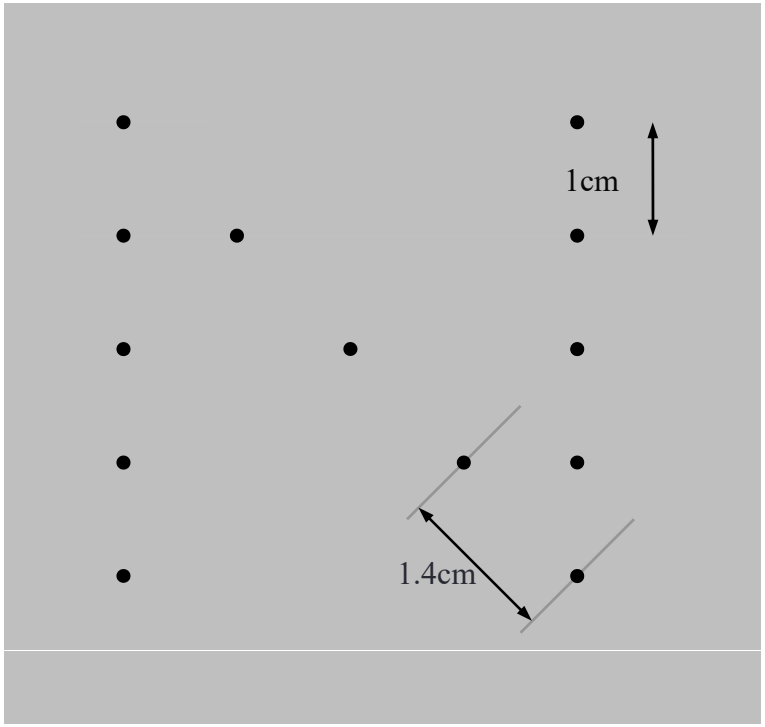
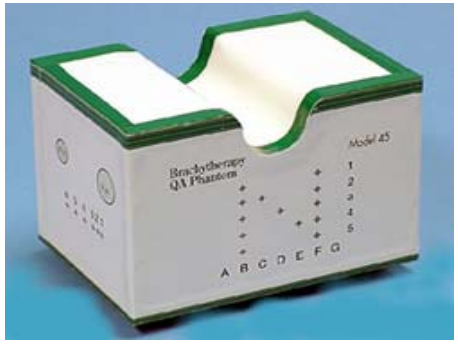


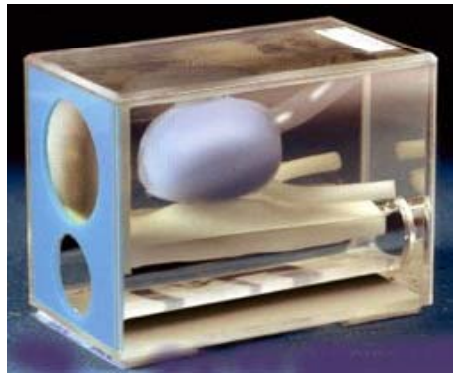
Image transfer check (Ultrasound phantom)

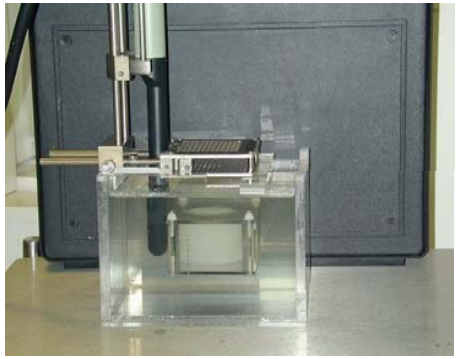


Volume Test

- 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

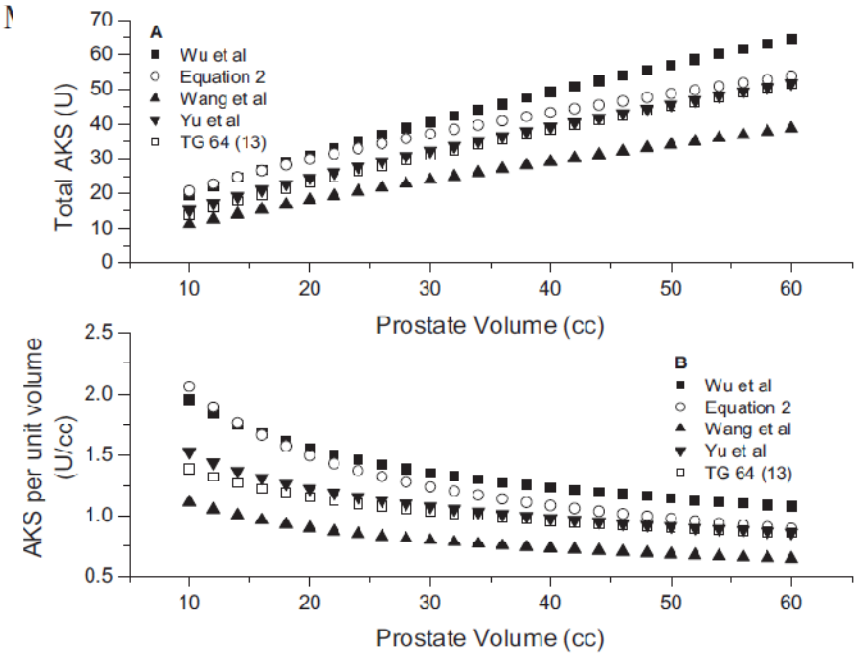
0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2005.12.030

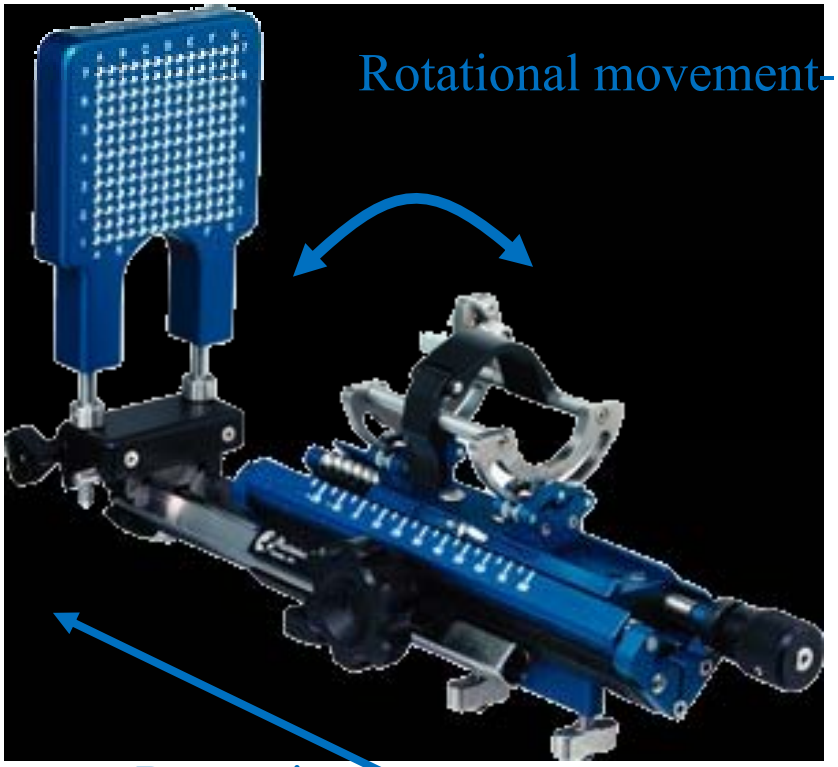
PHYSICS CONTRIBUTION

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.



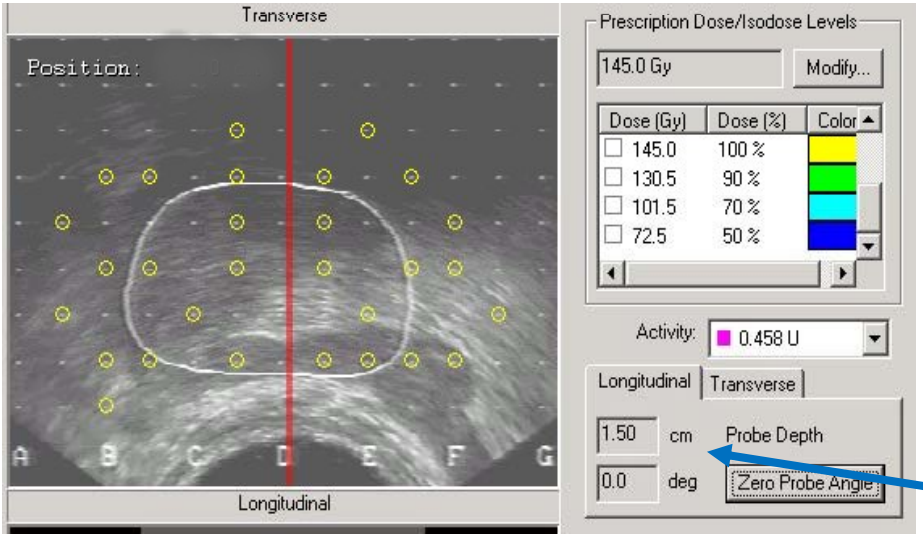
Stepper Depth and Angle Tracking Tests



Stepper Depth and Angle Tracking Tests

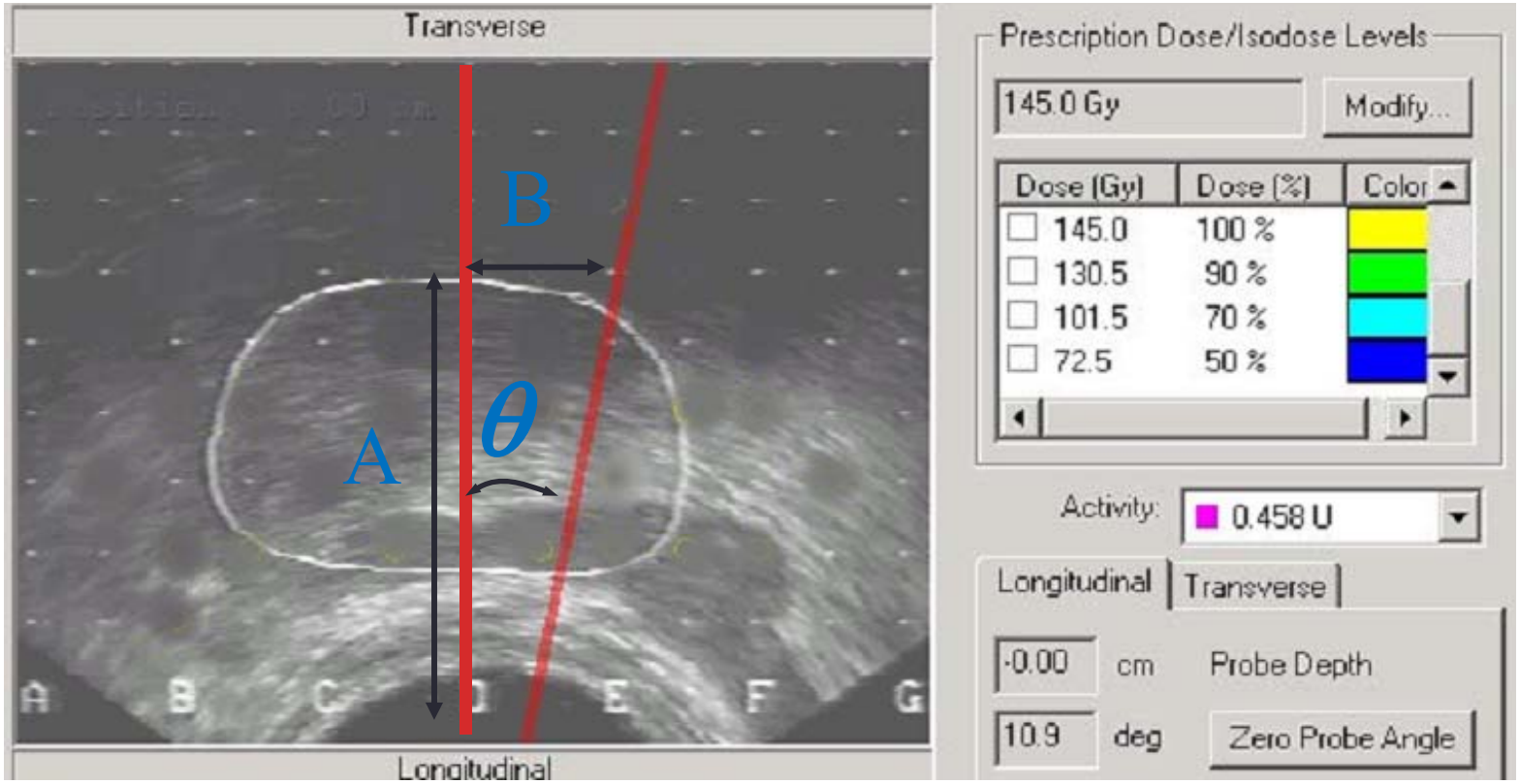
- Longitudinal Position Tracking. Accuracy should be within 0.5mm.
- Rotational Tracking Test. Accuracy should be within 0.5 degrees.

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

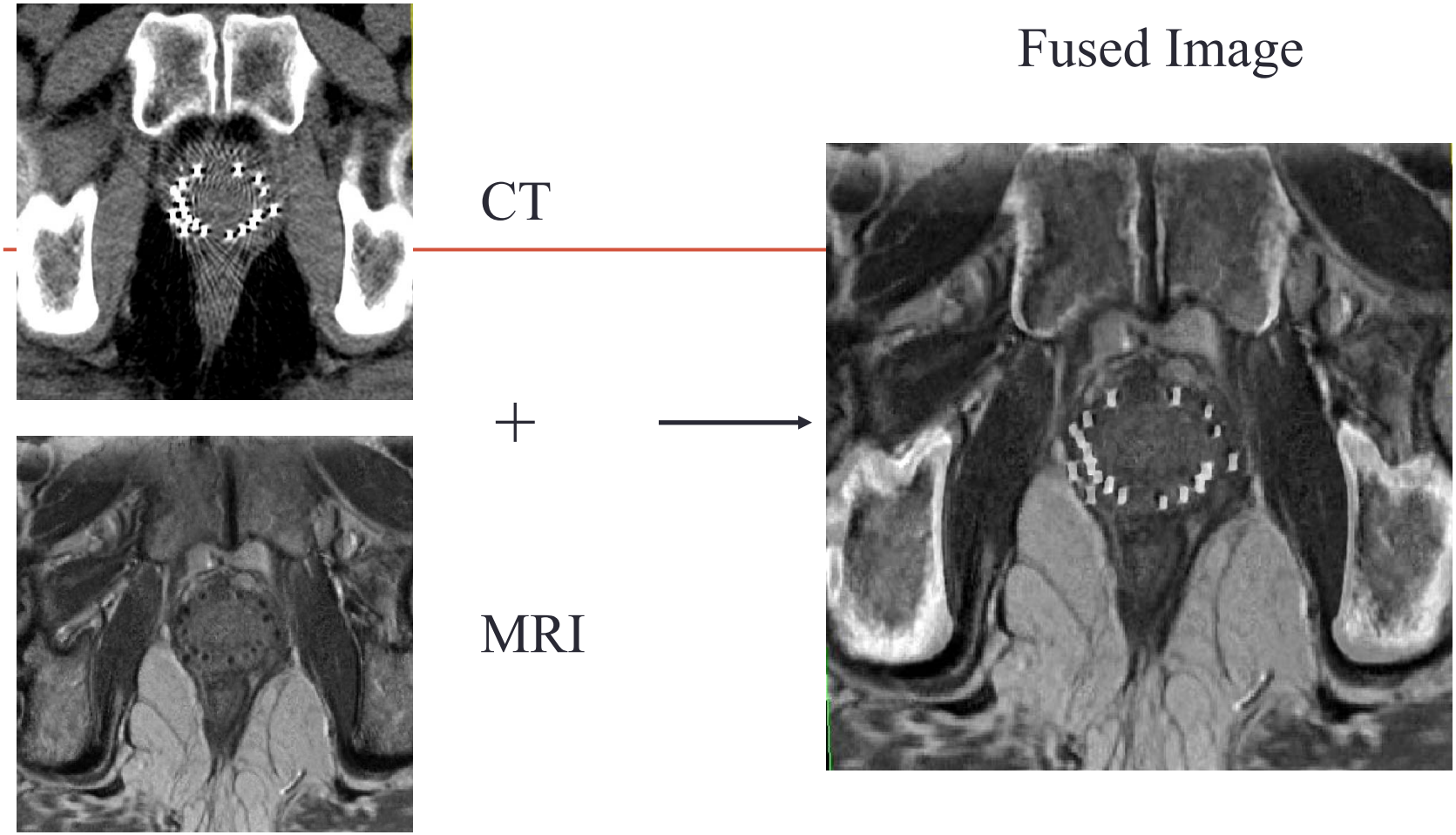
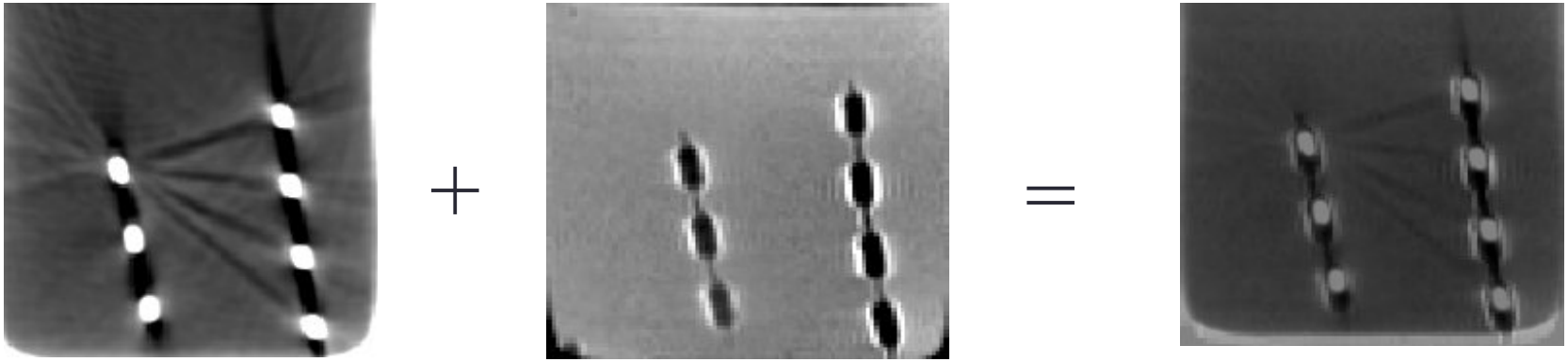


Image Fusion Protocol Phantom Study

CT + MRI = Fused Image



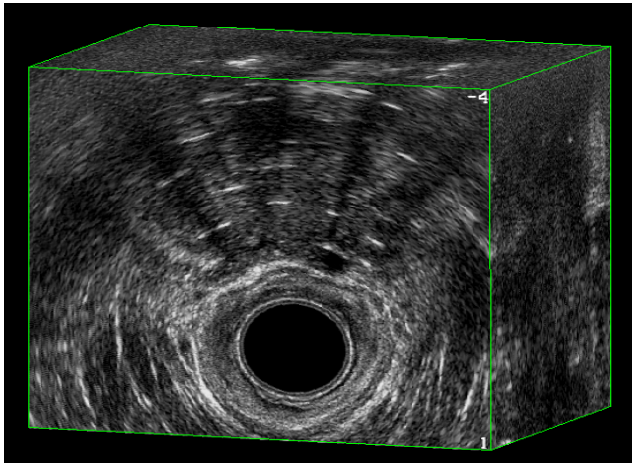
RMS Error < 1.0mm

QA for HDR Brachytherapy

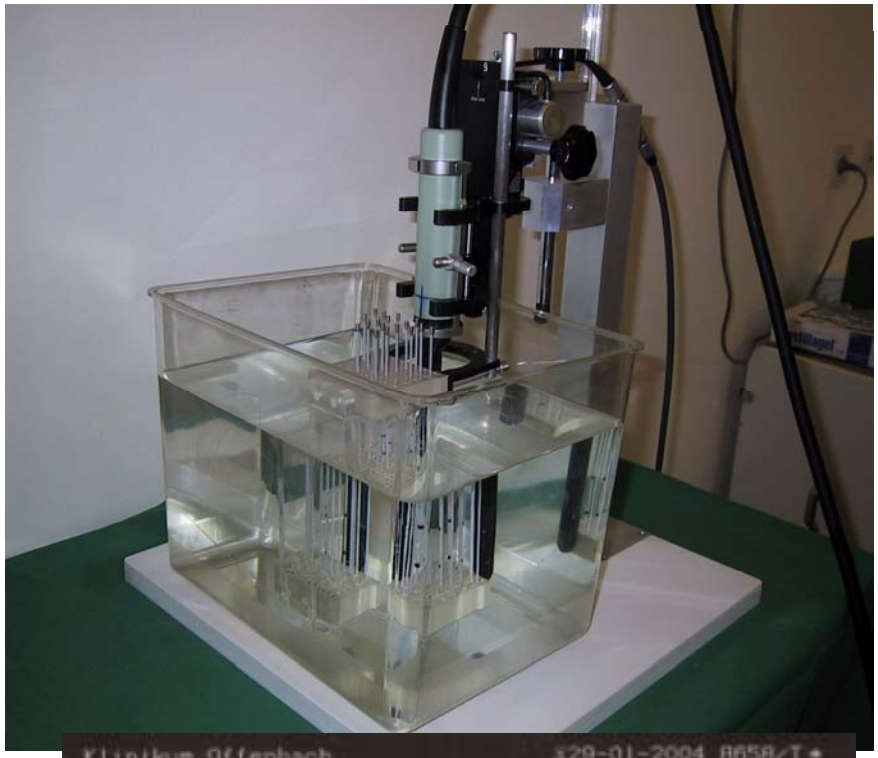
Besides the typical QA procedures established for common HDR Treatments, we need to implement additional ones

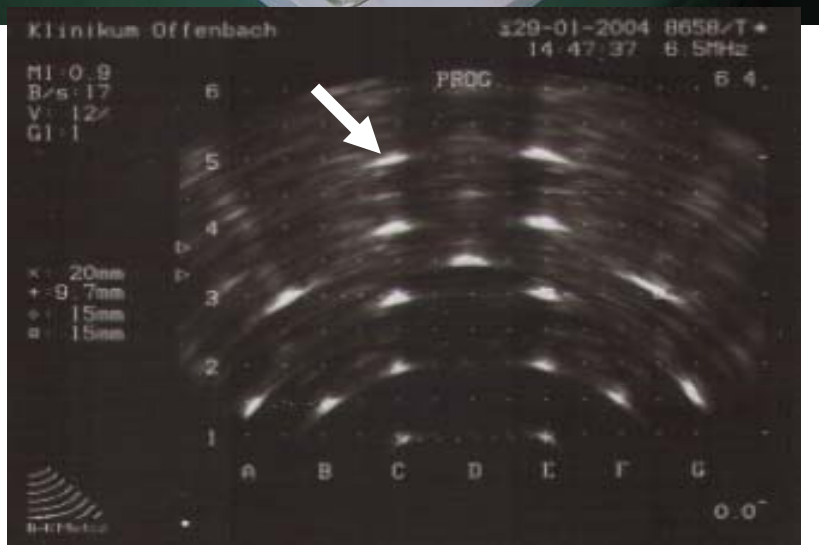
3D ultrasound

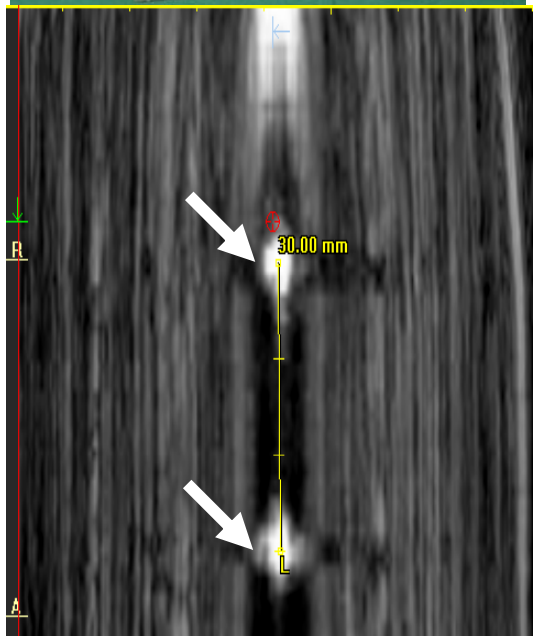
- Better visibility
- Improved treatment planning
- Reproducibility



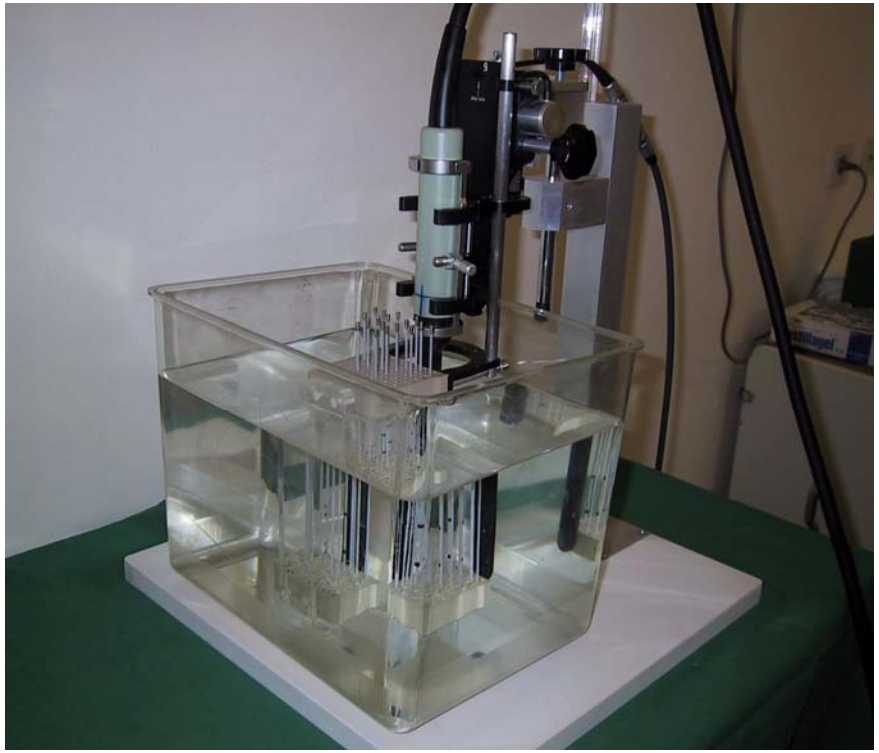
Mechanical & US Image Geometry

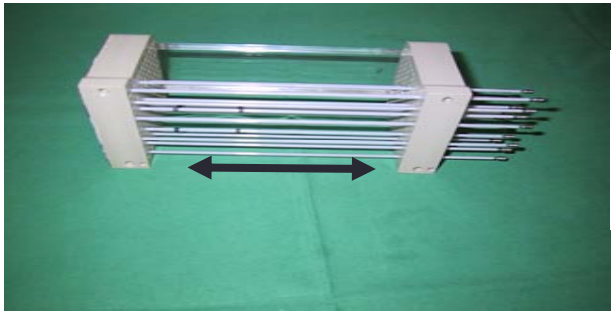


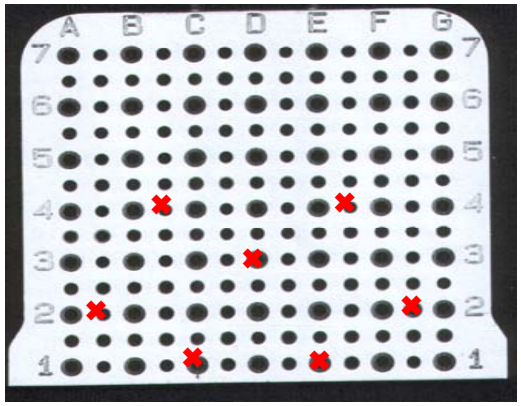




Catheter Reconstruction

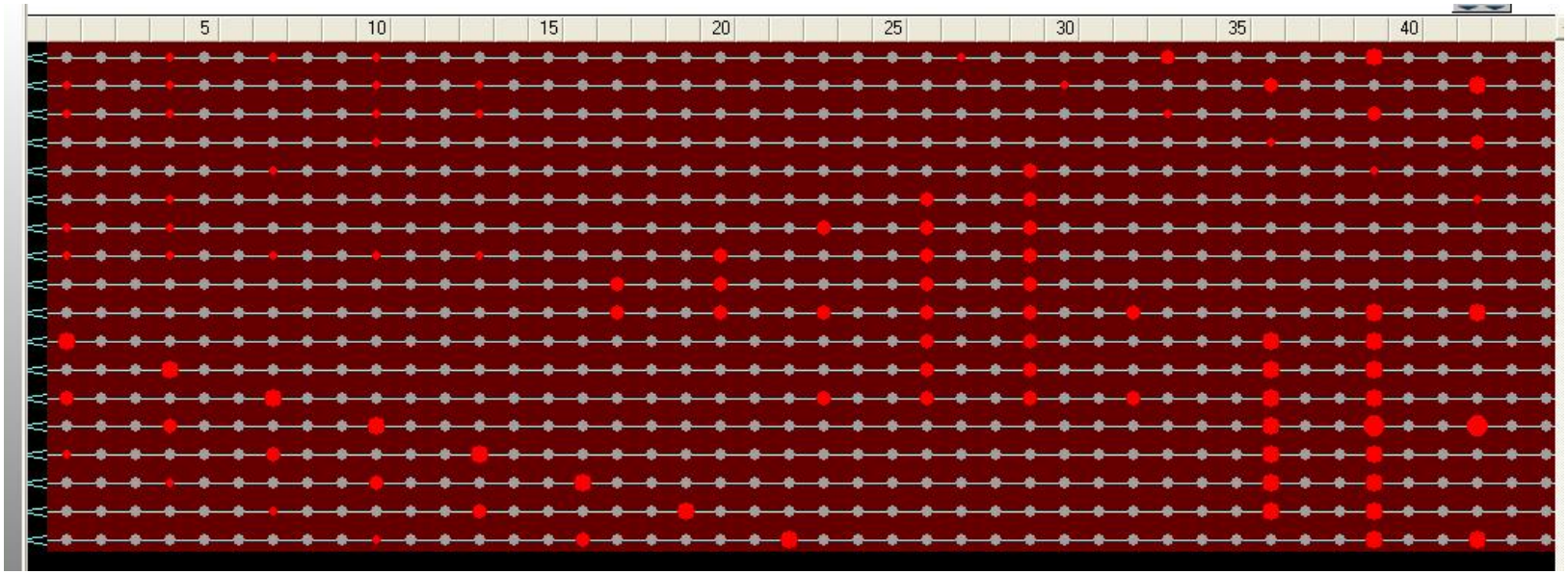






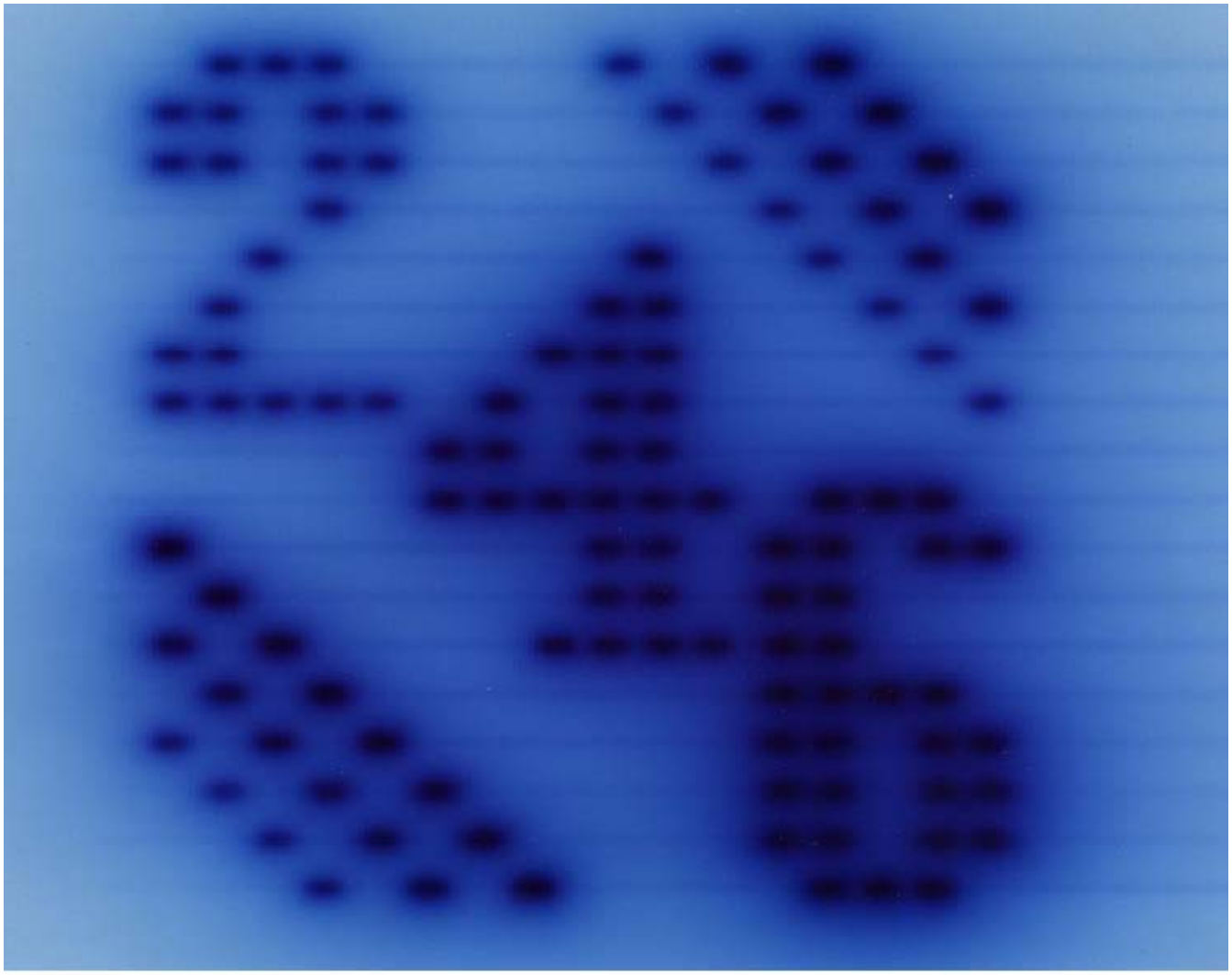
Data transfer check

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

Radiotherapy and Oncology 103 (2012) 261–265

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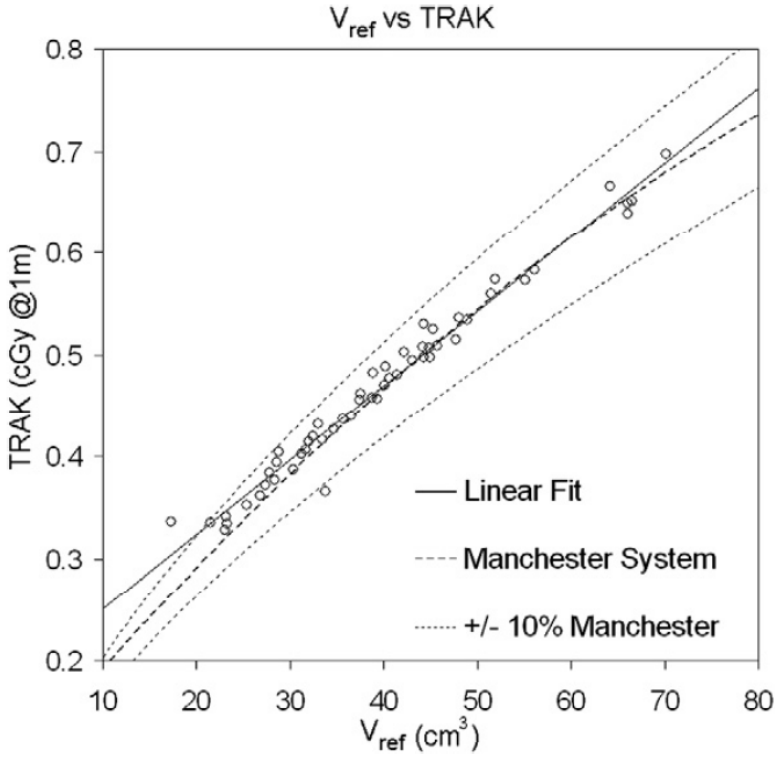
IGRT in prostate cancer

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



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

TREATMENT PLANNING FOR PERMANENT SEED IMPLANTATION

Bashar Al-Qaisieh

The Leeds Teaching Hospitals NHS
NHS Trust

Prostate Brachytherapy

The procedure involves implanting radioactive seeds directly into the prostate gland where they continuously give off low level radiation. Since only a small area is irradiated by each seed, relatively little radiation reaches the adjacent normal organs.

The evolution of Prostate Brachytherapy
ABS convention (2002)

- Pre –Plan: 2 step procedure (delayed execution of a pre-plan)
- Intra-operative: Pre-plan (immediate execution of a pre-plan)
- Interactive planning: incremental refinement of a plan based on needle tracking
- Dynamic dose calculation: incremental refinement of a plan based on seed deposition

Intra-operative planning: Terminology

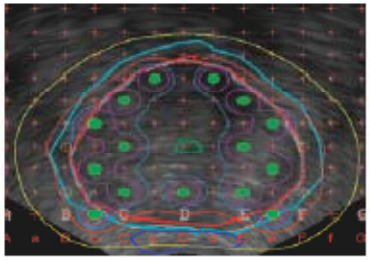
Planning modality	Description
Intra-operative planning	Creation of a plan on the OR just before the implant procedure, with immediate execution of the plan
Interactive planning	Stepwise refinement of the treatment plan using computerised dose calculations derived from image-based needle position feedback
Dynamic dose distribution	Constant updating of calculations of dose distribution, using continuous deposited seed position feedback

From Polo et al. Review of intraoperative imaging and planning techniques in permanent seed prostate brachytherapy. RO 94(2010) 12-23.

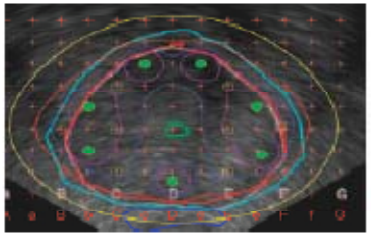
Seed Type

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.

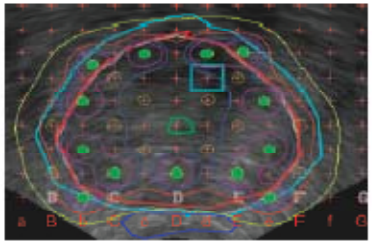
Cs-131

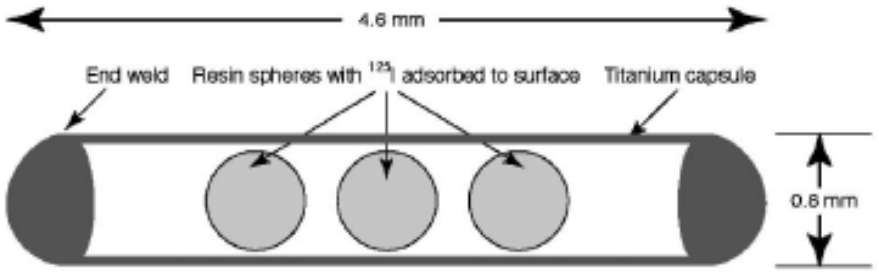


I-125

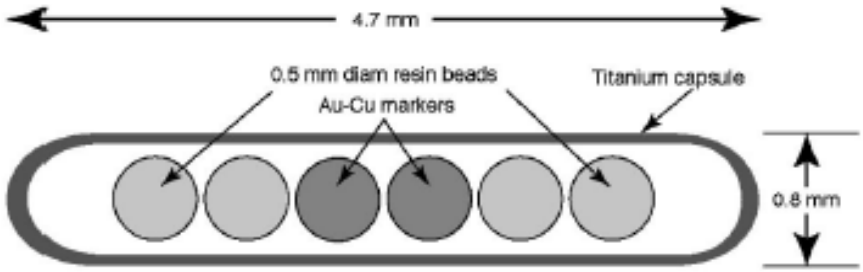


Pd-103

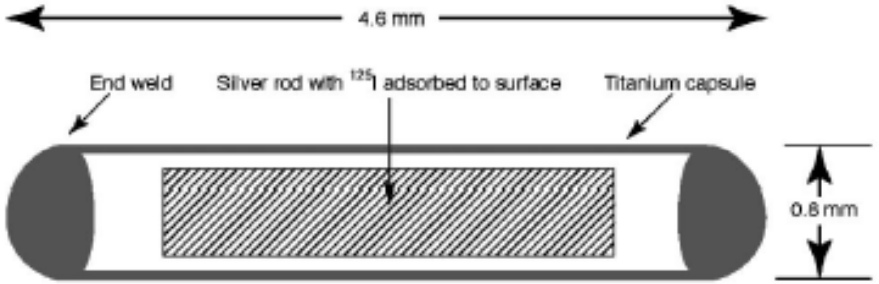




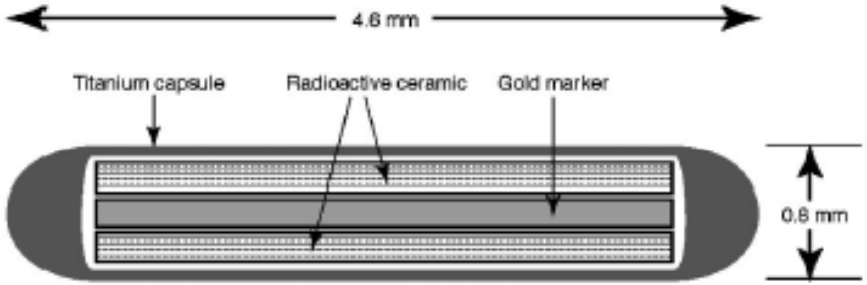
Amersham Health model 6702 source



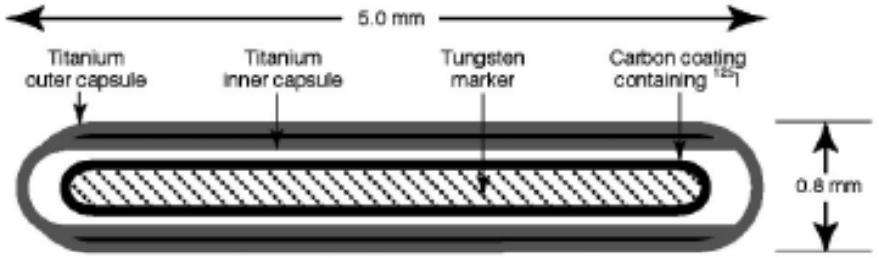
NASI model MED3631-A/M or MED3633 source



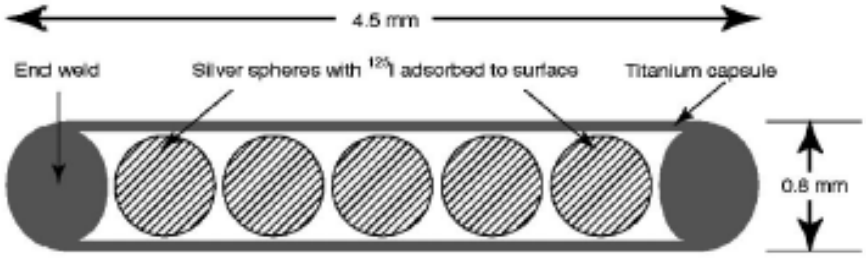
Amersham Health model 6711 source



Bebig model I25.S06 source

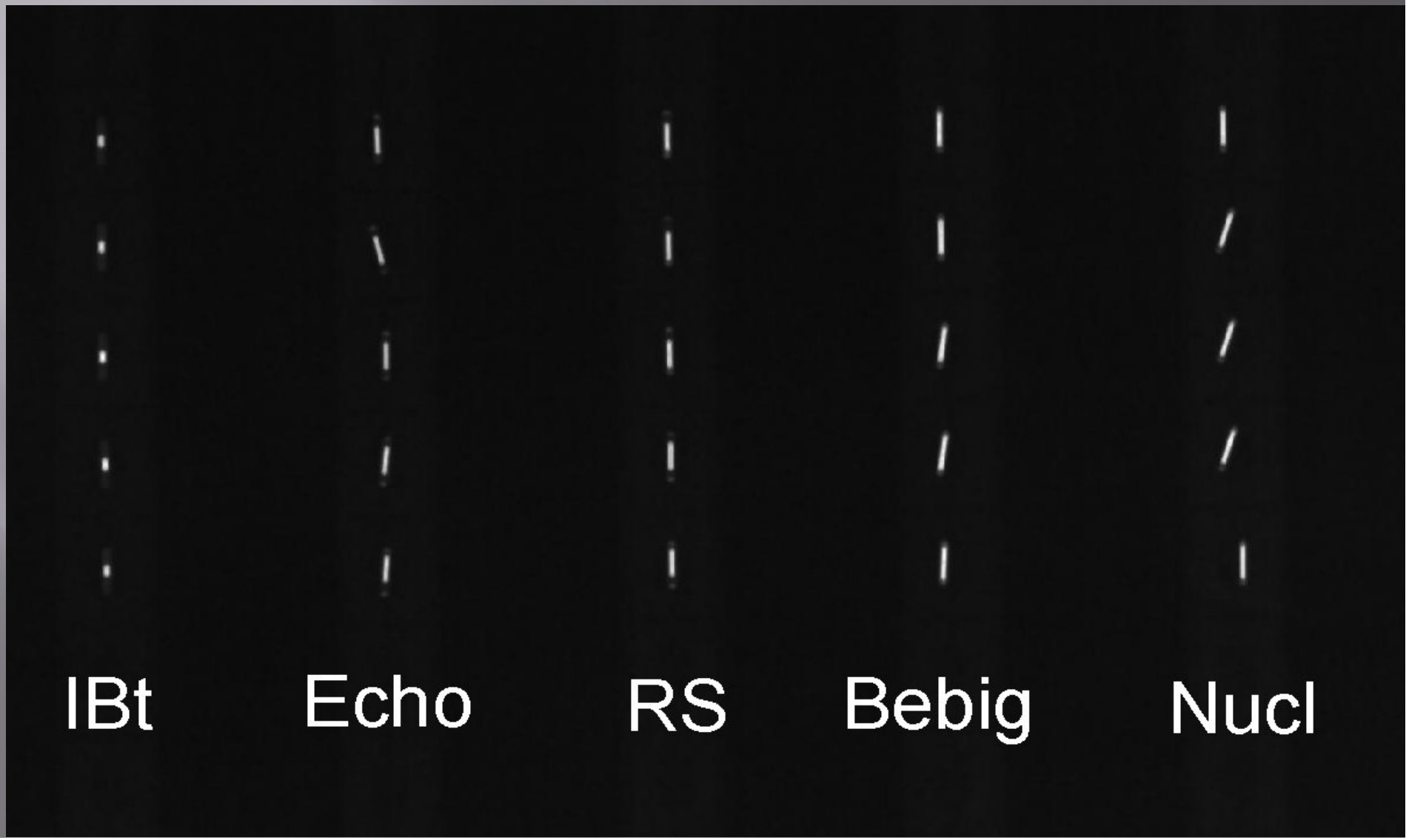


Best model 2301 source

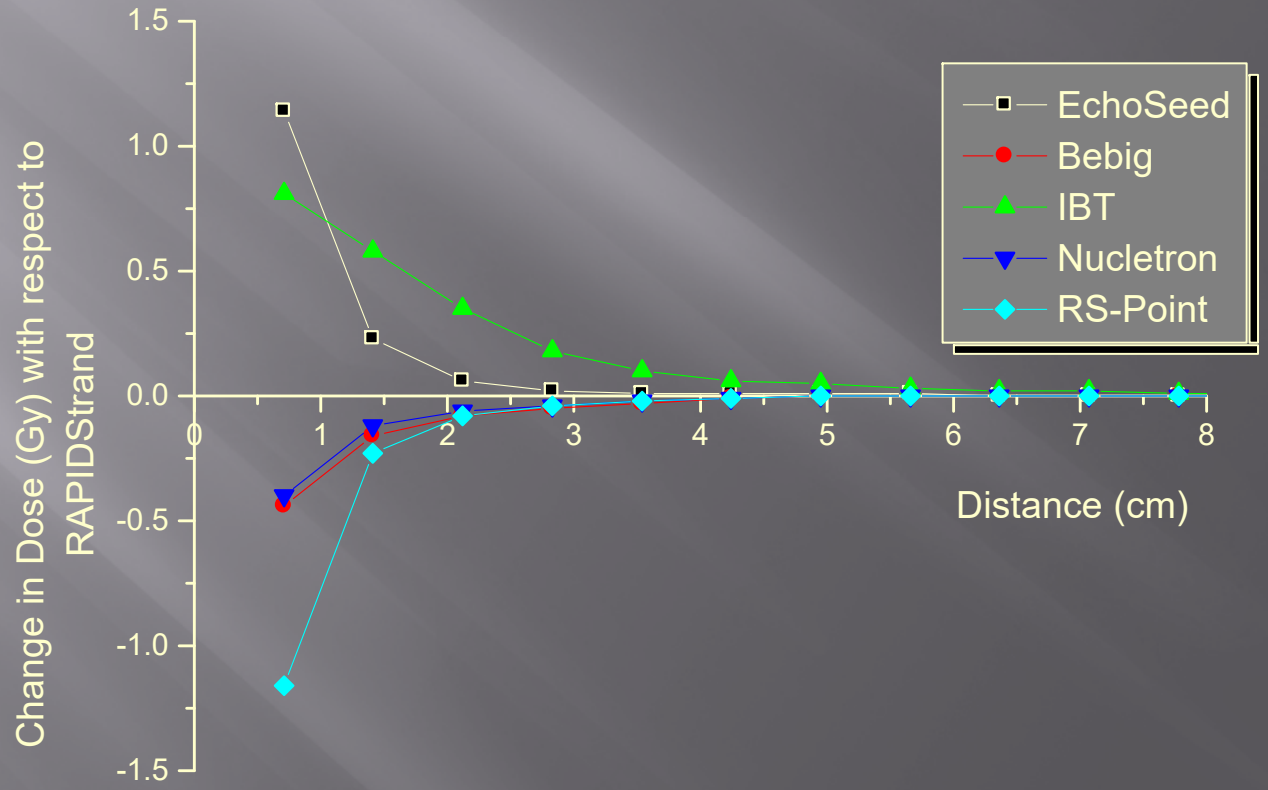


Imagyn model IS-I2501 source

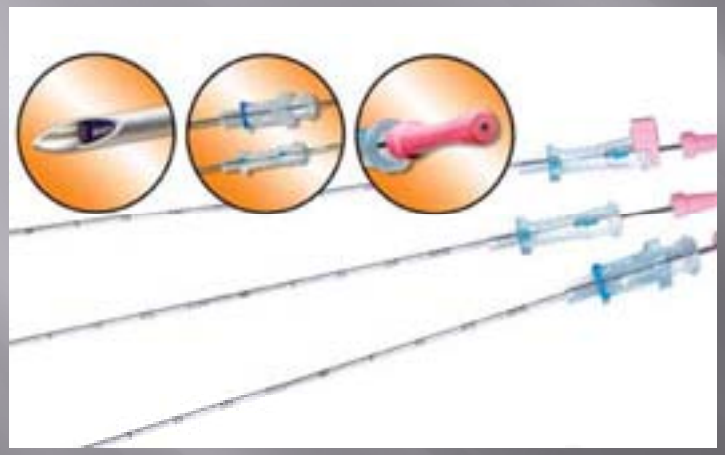
Visibility on X-Ray



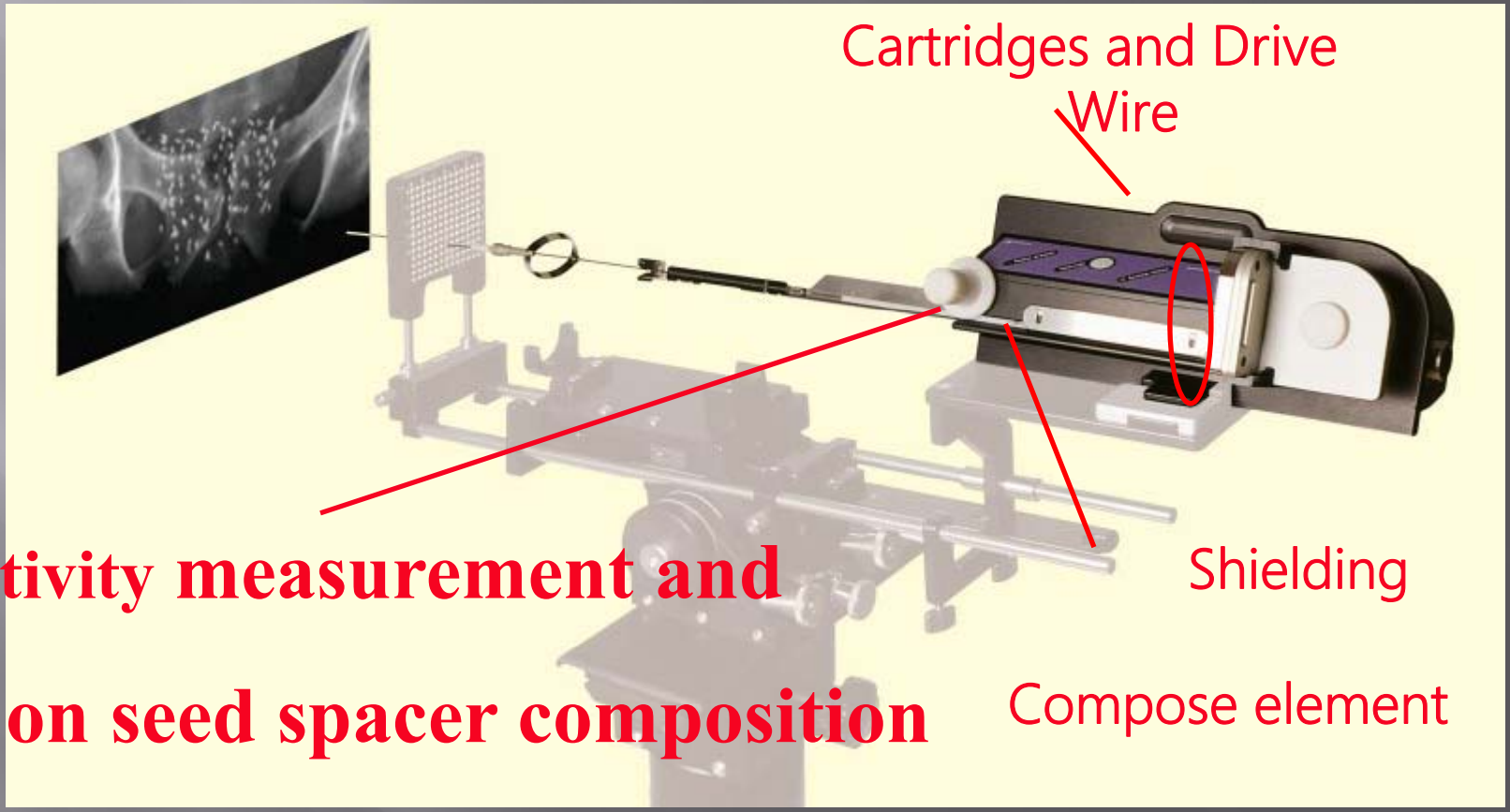
Point Dose Calculation @ θ=45⁰ normalised to 6711 line source



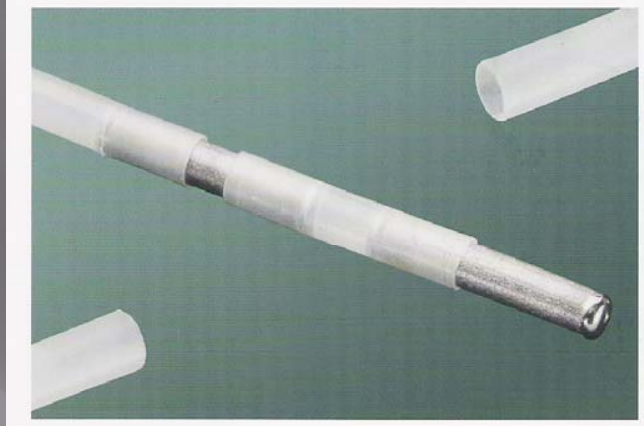
Delivery Systems



Developments in seed delivery

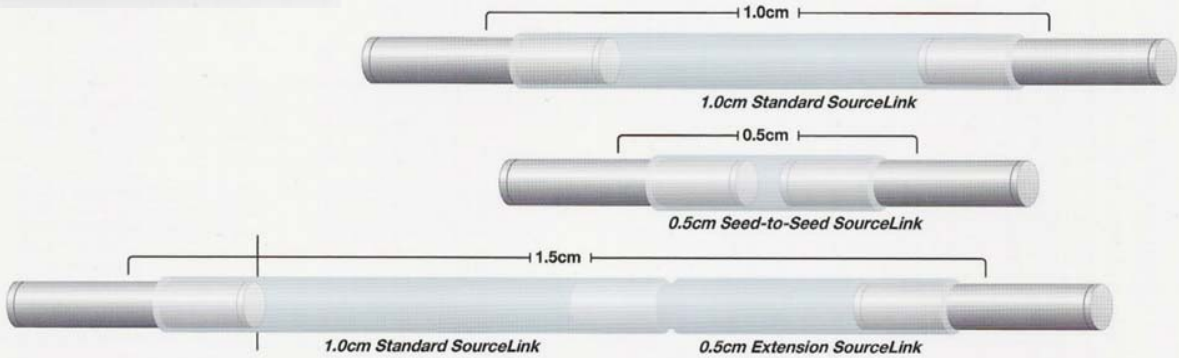


Developments in seed delivery

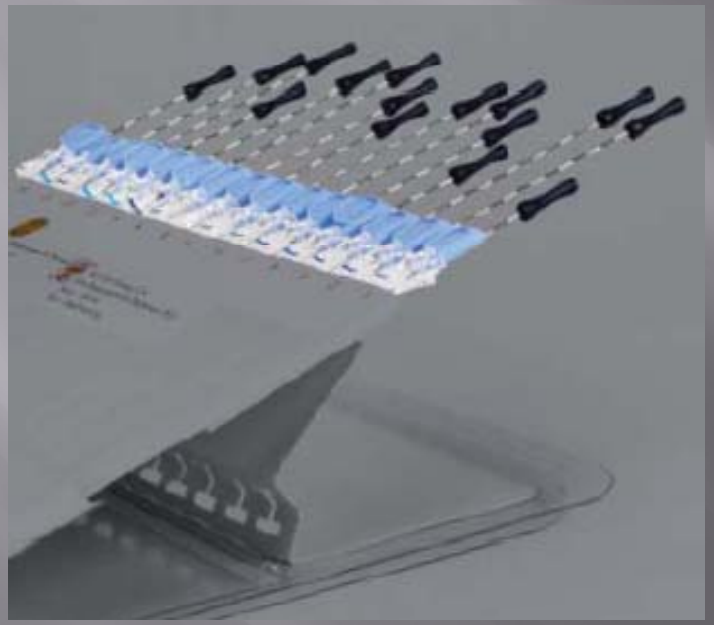


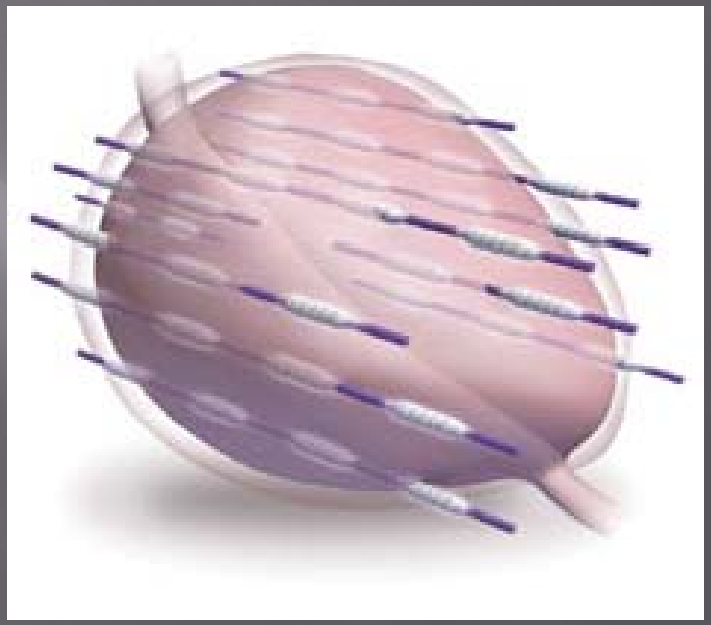
SourceLink™

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

What difference does it make?

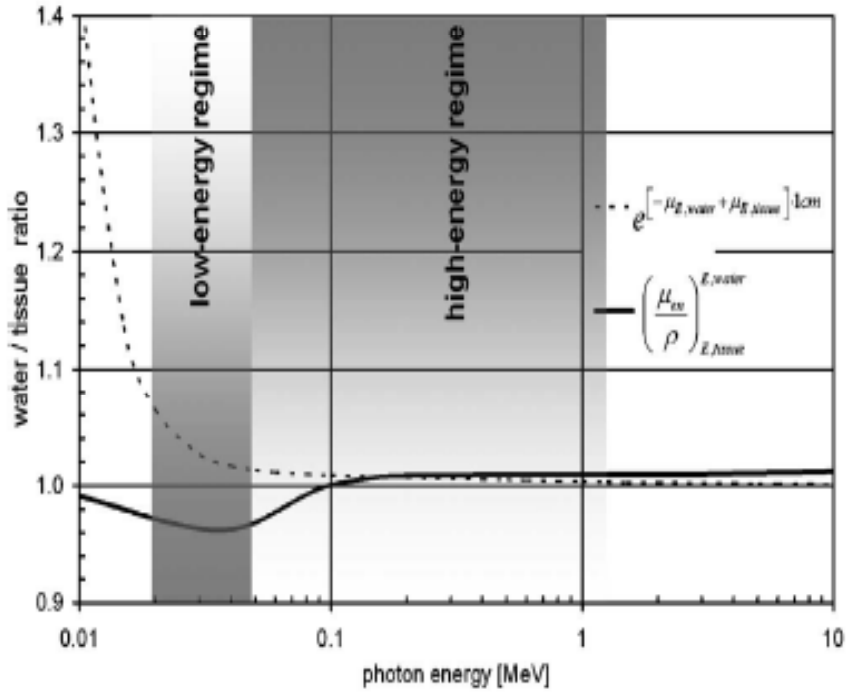


FIG. 3. Effect of phantom medium on absorbed dose and attenuation at $r=1$ cm as a function of photon energy.

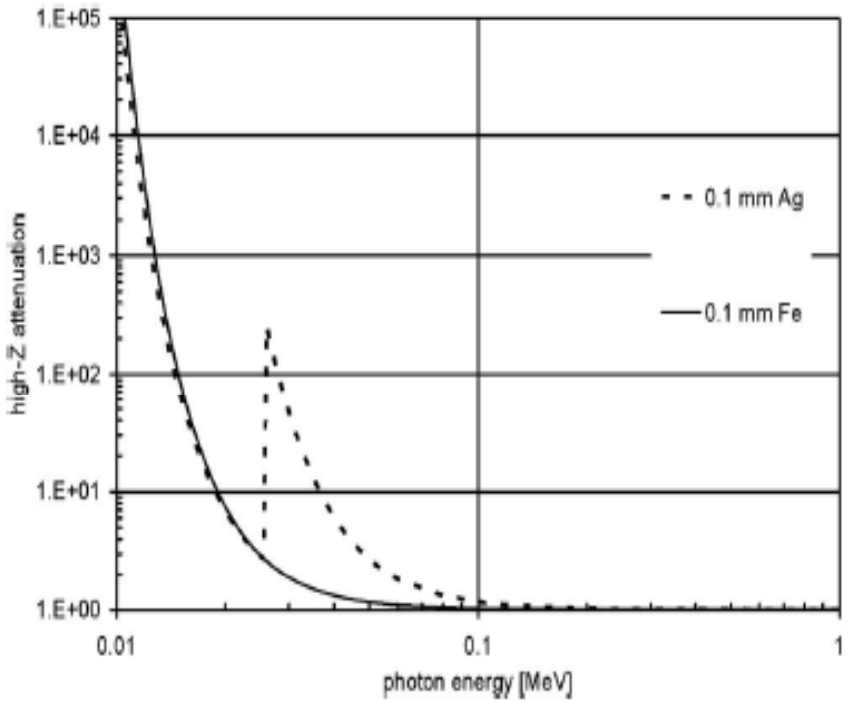
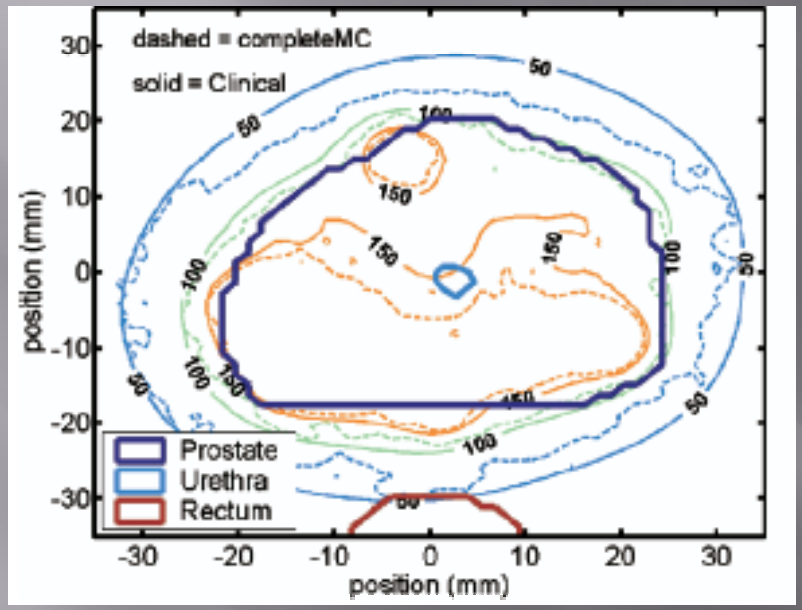


FIG. 4. Photon transmission ratios through water or high-Z attenuators as a function of photon energy. The Ag K edge (0.02 551 MeV) is indicated in the dashed curve.

(From: The evolution of brachytherapy treatment planning, Rivard et al., Med.Phys. 36 (6), 2009: 2136-2153.)

Prostate I-125 studies in literature

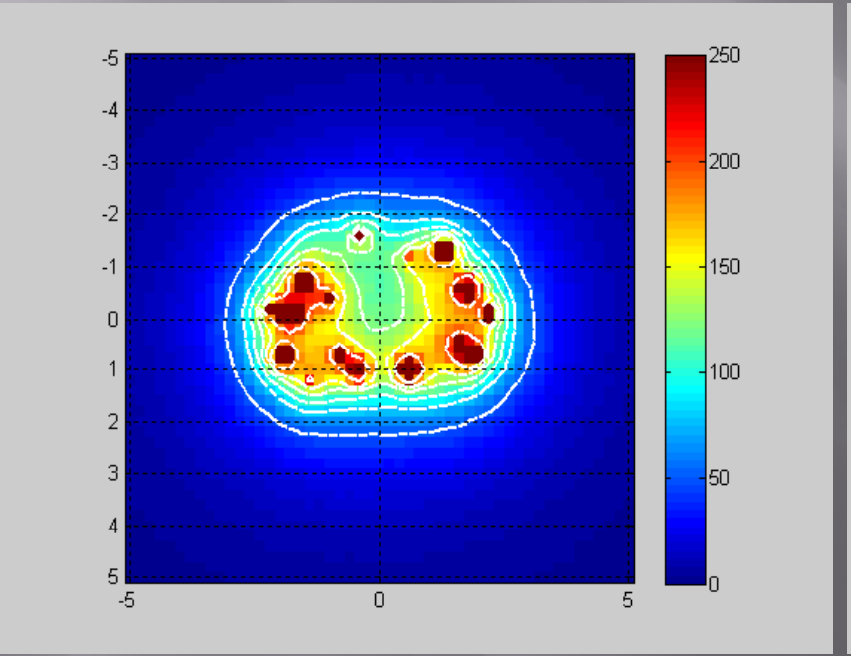


(From: Carrier, J.F., et al., Postimplant dosimetry using a Monte Carlo dose calculation engine: A new clinical standard. International Journal of Radiation Oncology* Biology* Physics, 2007. 68(4): p. 1190-1198.)

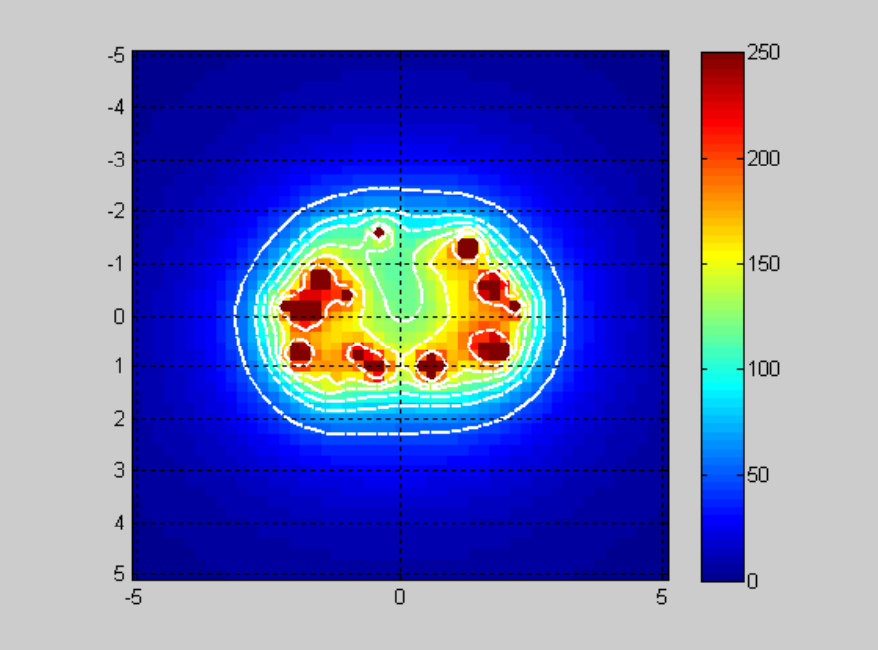
- Interseed attenuation reduces D90 by 4-6 %
  - *reduces urethral dose by few %*
  - *size of effect depends on seed activity*
- Water/prostate tissue difference reduces D90 by 3-5%

Initial results

MC Simulation



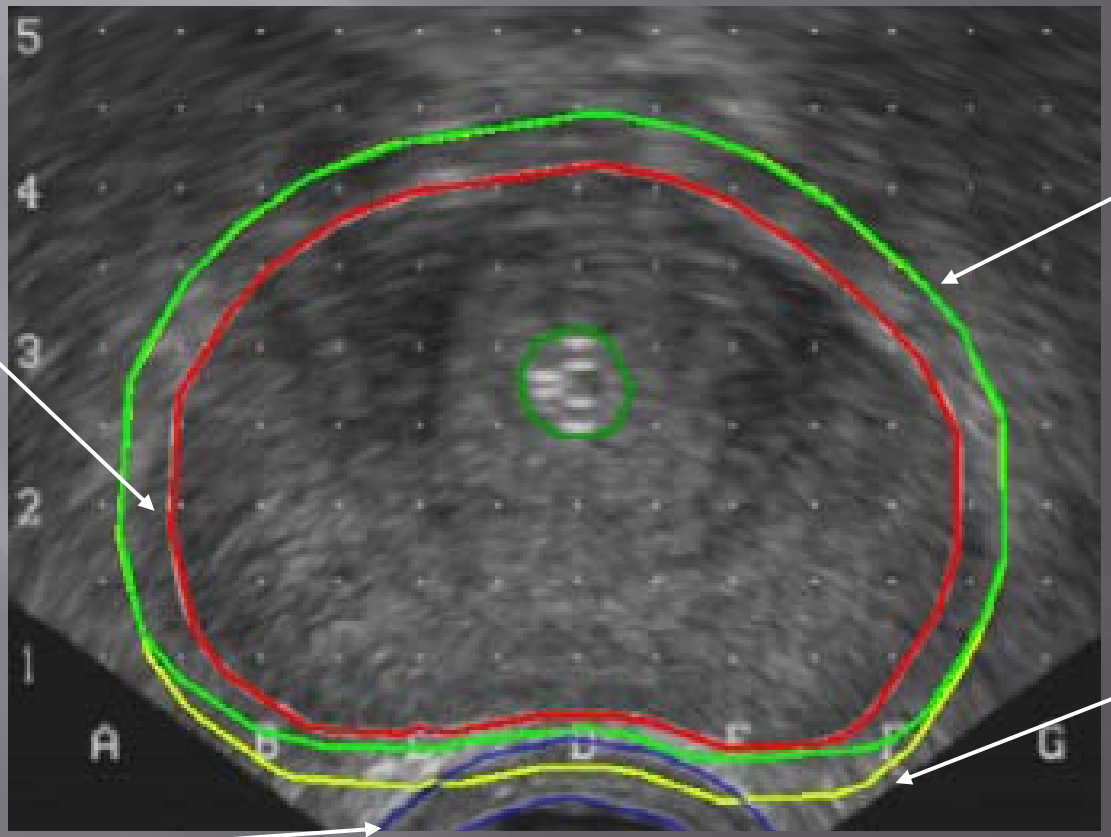
Superposition



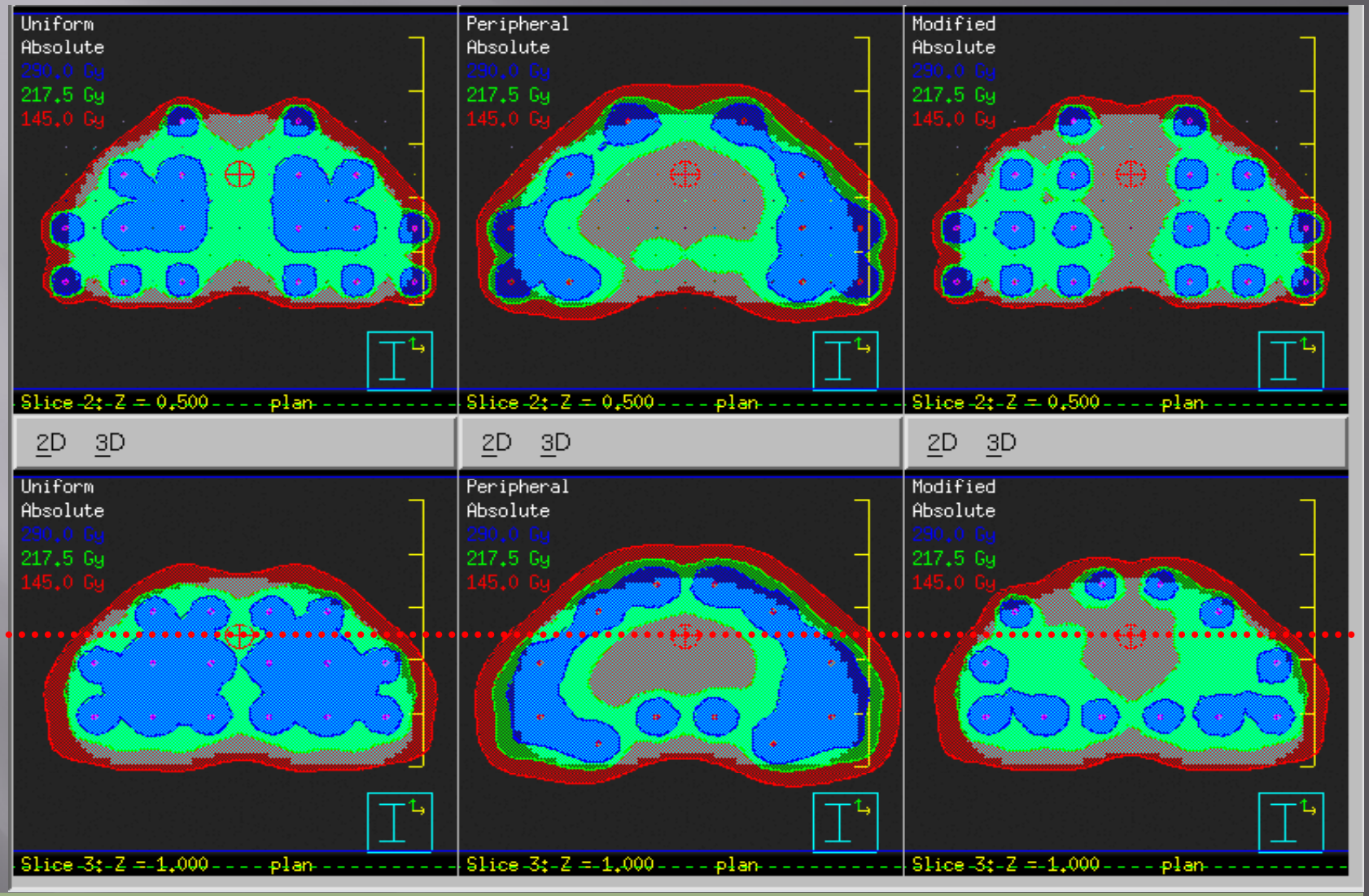
Treatment planning

- aim to deliver a minimum of 145Gy to periphery of prostate (TG43 calculation)
- to deliver an even dose where possible, minimising the dose to the urethra and rectum
- minimising dose to normal tissue eg. neurovascular bundles
- TP manual/forward or inverse

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

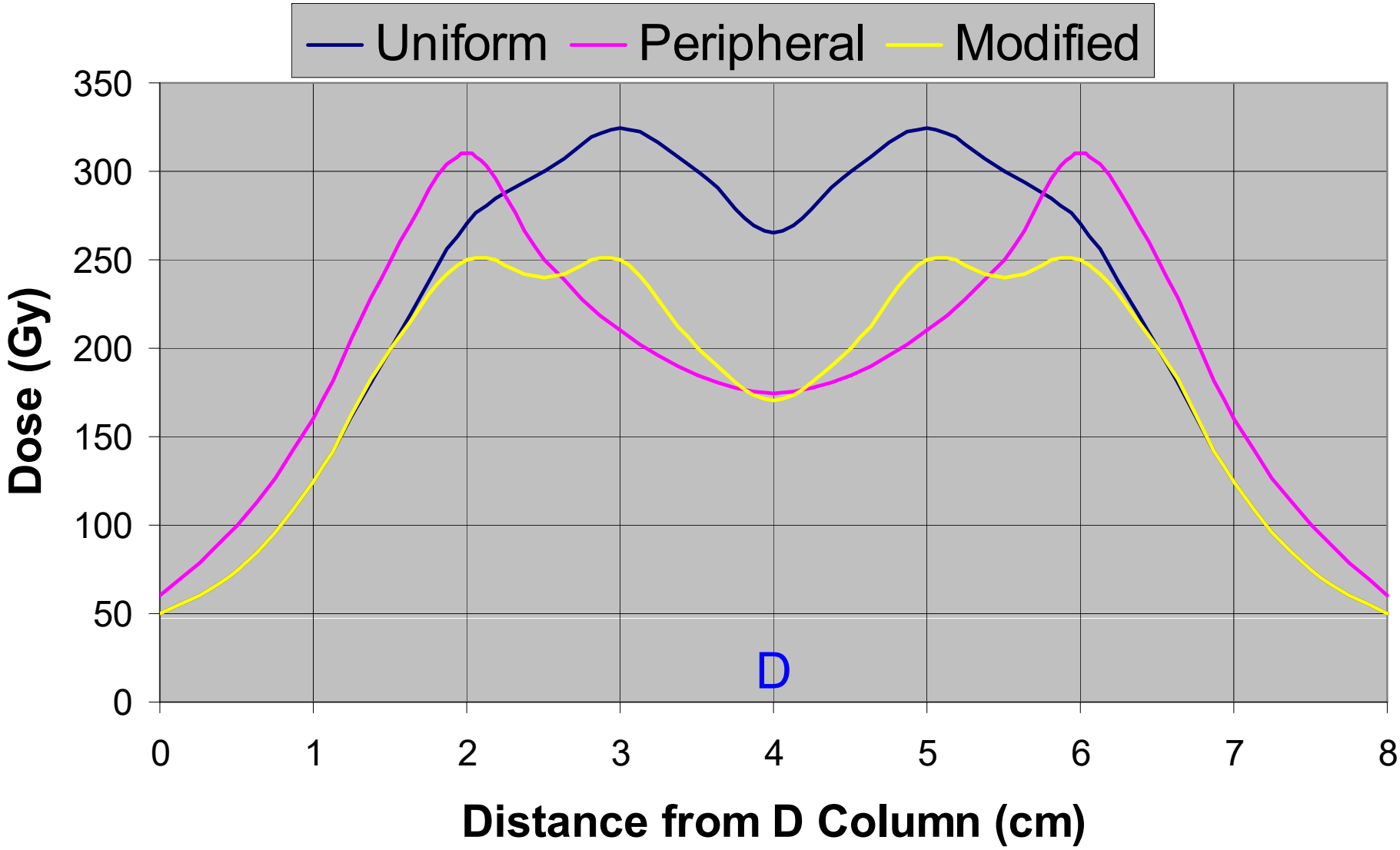


Seed Distribution

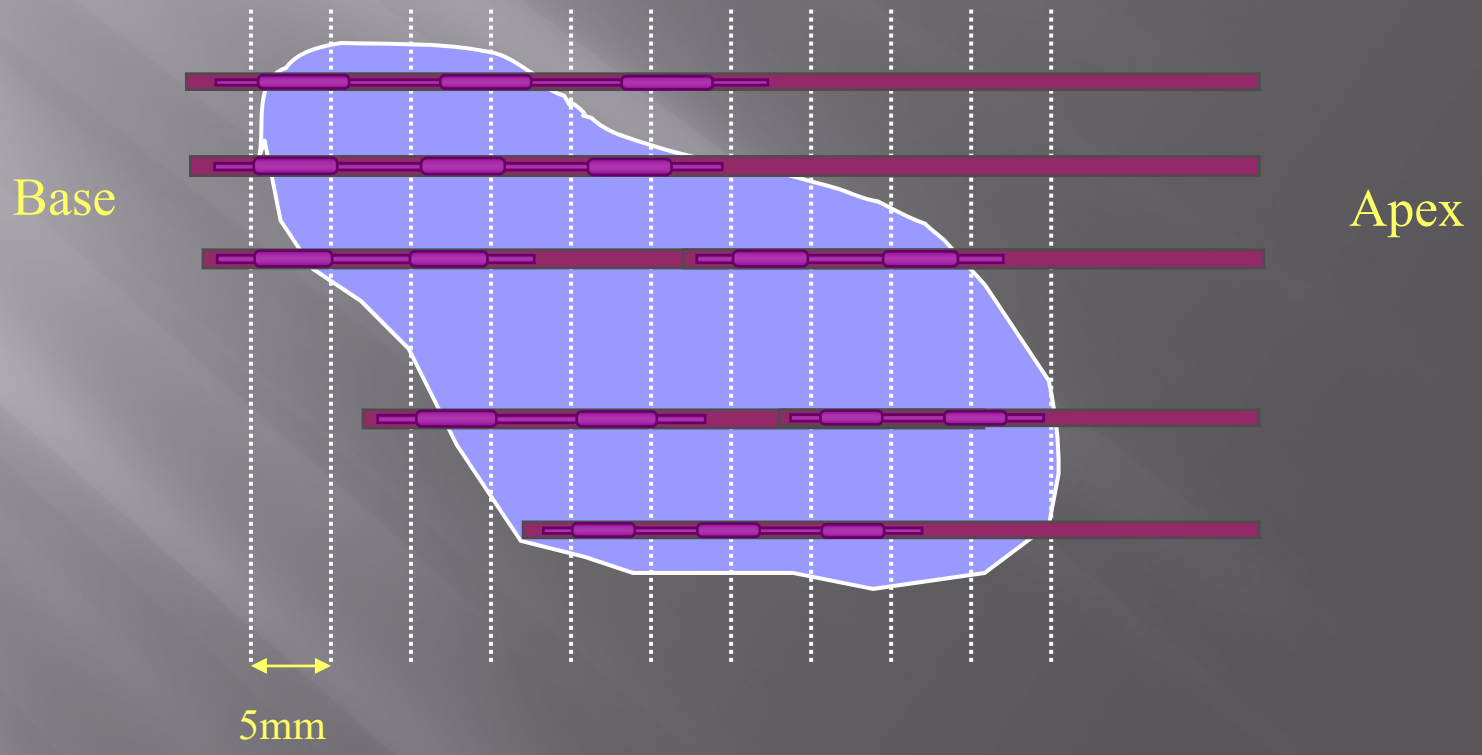


Uniform Loading	Peripheral Loading	Modified Peripheral
<0.3U	>0.8U	~0.4U

Dose Profile Through Urethra and Row 3 for Different Loading Techniques



Planning the Seed Locations



DVH Constrains

(GEC/ESTRO Recommendations, Salembier et al 2007)

Prostate:

- The V100 (the percentage of the CTV that receives the prescribed dose) must be at least 95% (V100 ≥ 95% of CTV).
- The D90 (the dose that covers 90% volume of the CTV) will be larger than the prescription dose D90 > 100% of prescription dose).
- The V150 (the percentage of the CTV that receives 150% of the prescription dose), should be equal to or less than 50% (V150 ≤ 50% of CTV).

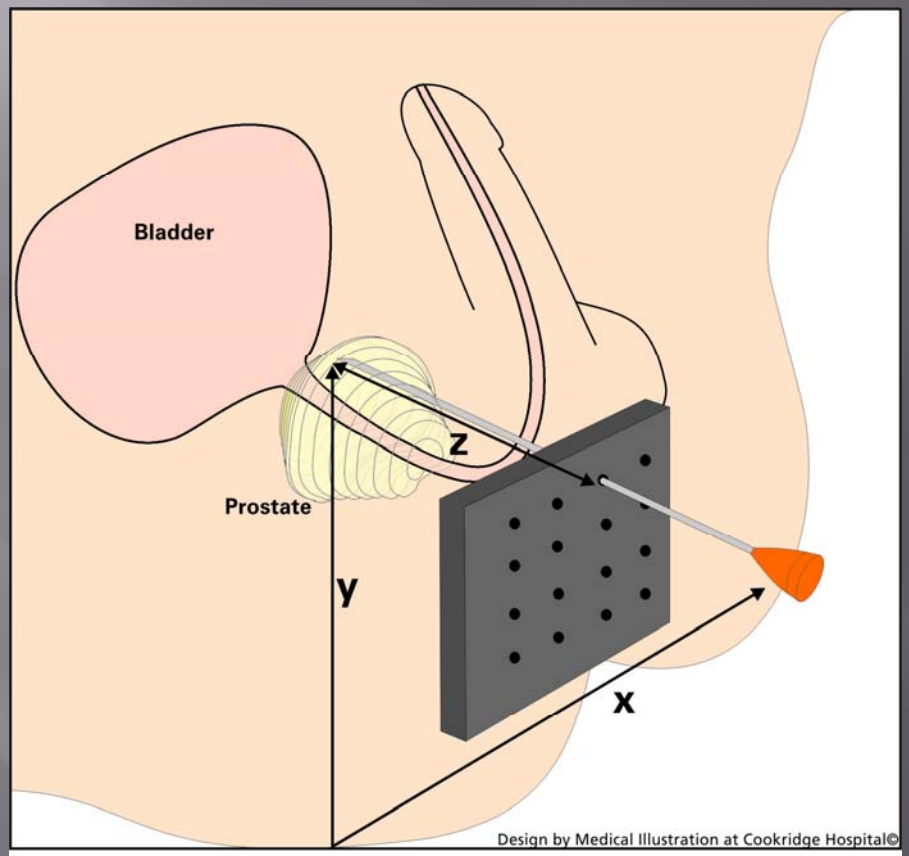
Rectum:

- Primary parameter: D_{2cc} ≤ reference prescription dose of 145 Gy.
- Secondary parameter: $D_{0.1cc}$ (~Dmax) < 200 Gy.

Urethra:

- Primary parameter: D_{10} < 150% of the prescription dose.
- Secondary parameter: D_{30} < 130% of the prescription dose.

Planning the Seed Locations

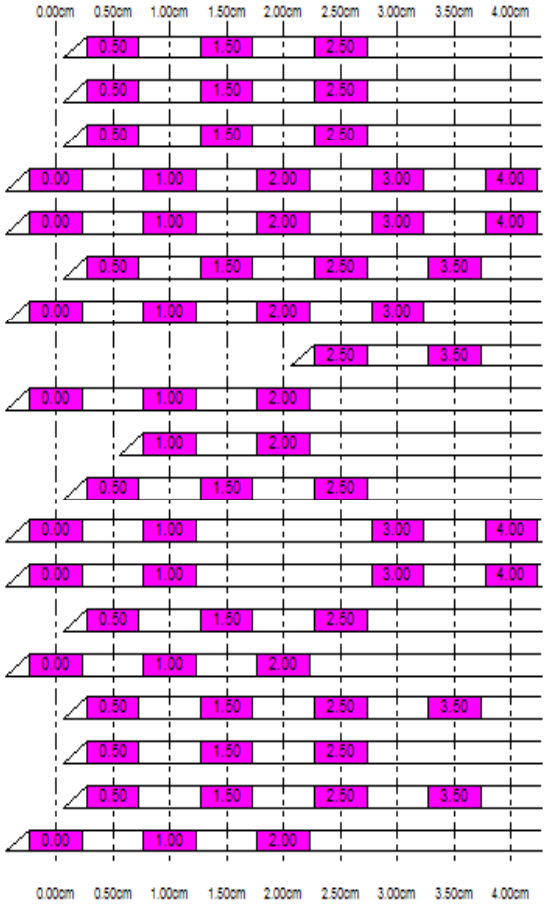


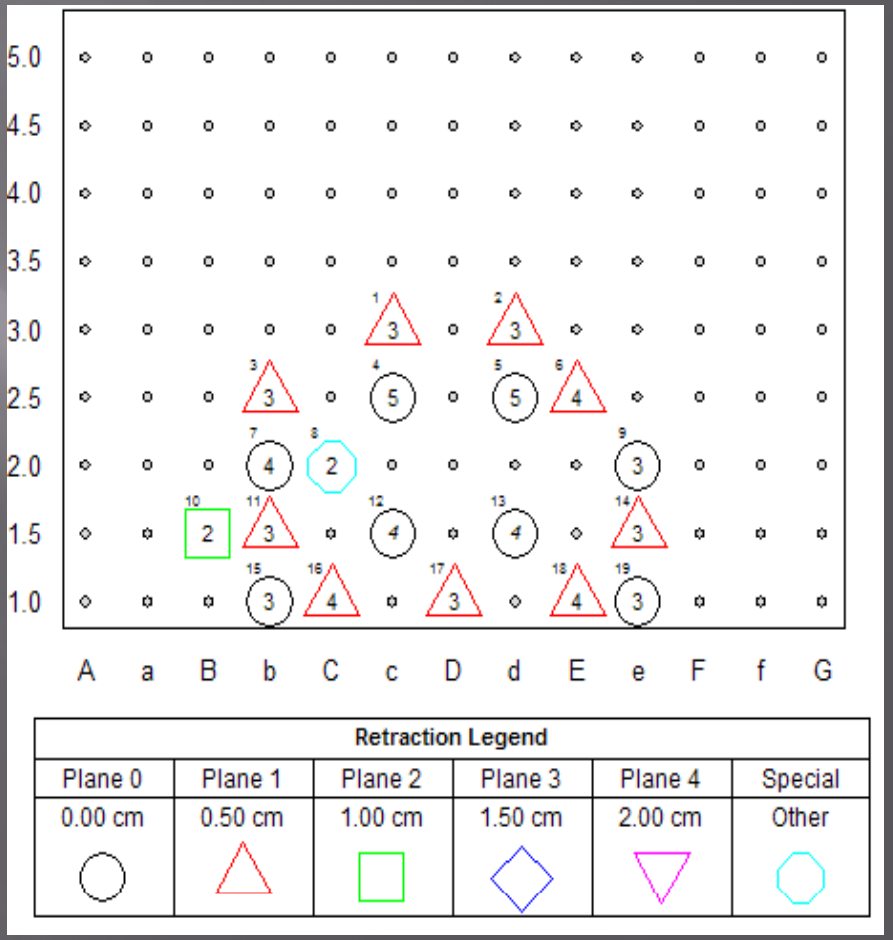
Schematic Representation of Prostate Implant

Planning the Seed Locations

Needle Number	Retraction (cm)	Hole Location	Number Seeds
1	0.50	c3.0	3
2	0.50	d3.0	3
3	0.50	b2.5	3
4	0.00	c2.5	5
5	0.00	d2.5	5
6	0.50	E2.5	4
7	0.00	b2.0	4
8	2.50	C2.0	2
9	0.00	e2.0	3
10	1.00	B1.5	2
11	0.50	b1.5	3
12	0.00	c1.5	4
13	0.00	d1.5	4
14	0.50	e1.5	3
15	0.00	b1.0	3
16	0.50	C1.0	4
17	0.50	D1.0	3
18	0.50	E1.0	4
19	0.00	e1.0	3

= *Special loading*





Retraction Legend					
Plane 0	Plane 1	Plane 2	Plane 3	Plane 4	Special
0.00 cm	0.50 cm	1.00 cm	1.50 cm	2.00 cm	Other

The Leeds Teaching Hospitals NHS
NHS Trust

Evaluating the plan

- Viewing the isodoses
- Looking at individual points
- Looking at DVHs of prostate, urethra etc.

Planning errors

- Systematic/random
  - template grid not calibrated correctly
  - planning grid not aligned with template grid correctly
  - wrong activity seed used (beware boosts!)
  - wrong dosimetry data in computer
  - incorrect manual transfer of information

Factors may affect accurate seeds positioning

- Patient set-up:

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

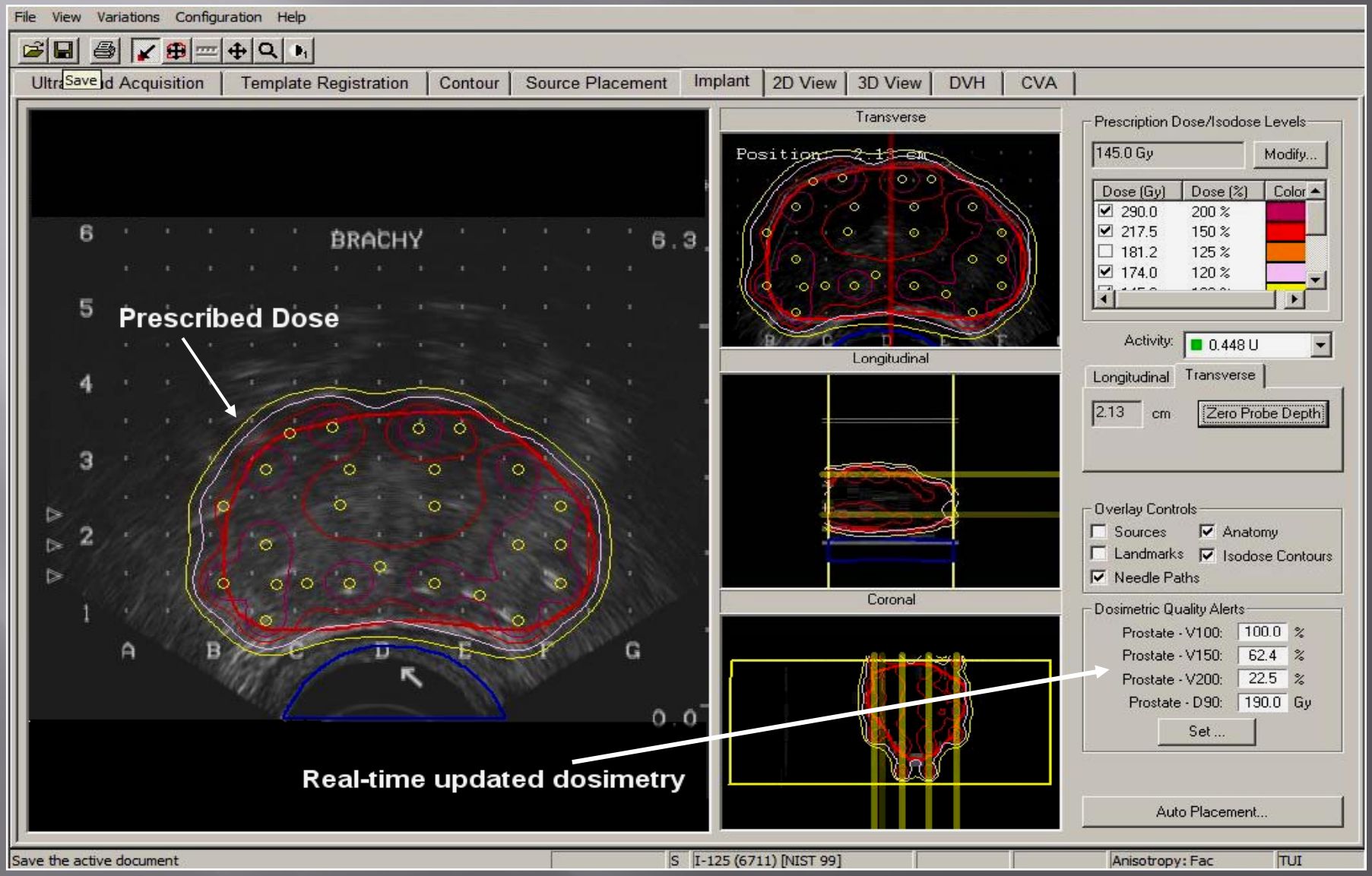
- Implant progression:

  - 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).

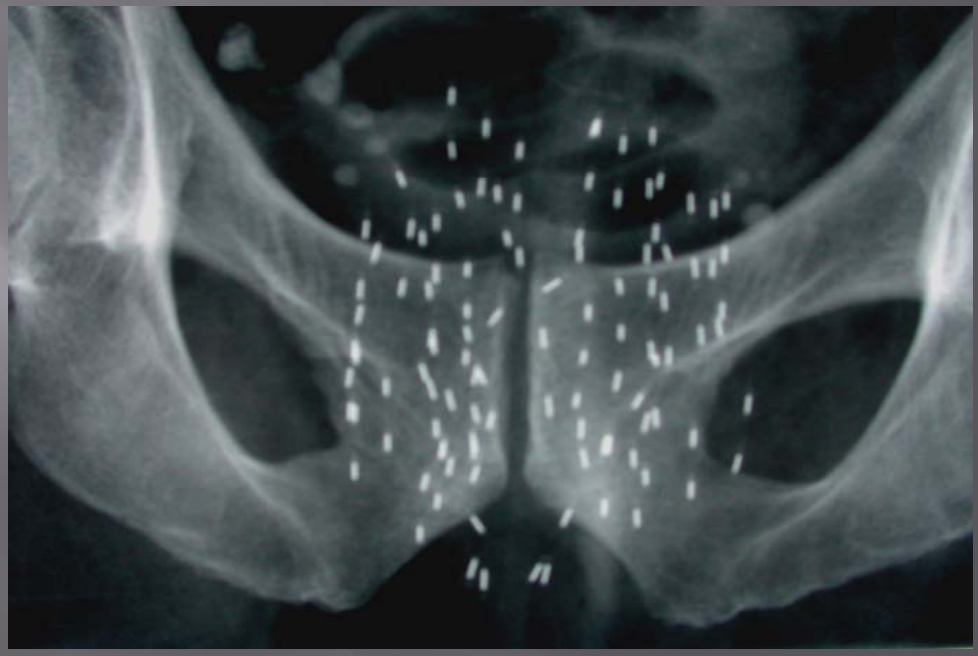
Theatre Dosimetry Planning

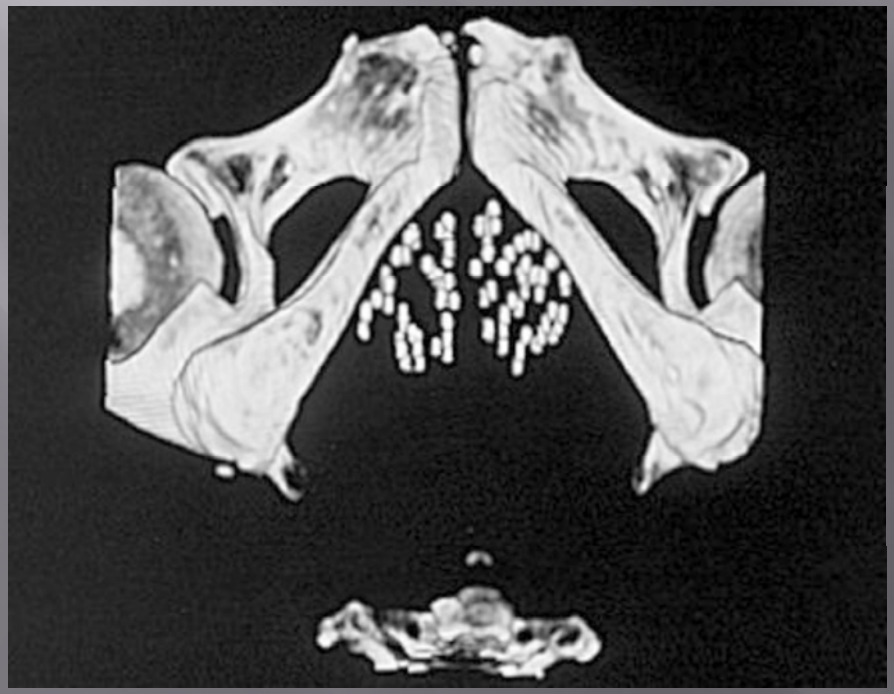


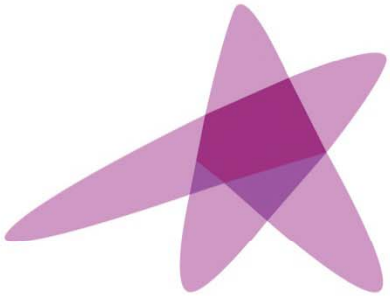
Planning and implant techniques

	Pre-plan	Intra-operative	Interactive planning
Pros	-Less complex -Requires less technology, equipment and physics input -No seed wastage -No significant difference in clinical outcome -Long term outcome	-Reduces risk of introducing systematic error between pre-plan and implant -More convenient for patient -Overall time in OR less	Interactive may result in improved dosimetry but ? Clinical impact -In multi-operator teams interactive may produce more consistent dosimetry
Cons	-Patient setup -Long overall time in OR -Less convenient for patient	-Risk of seed wastage/over-ordering -Risk of being unable to implant if gland larger than expected -Plans need to be produced quickly -Resources: multiple physics staff need to be available	-Interactive planning based on needle position may not replicate actual seed position -Changes in prostate volume are not accounted for by TPS -Loose seeds may move and strands may retract after deposition and over time -For new operators there is still a learning curve

Implant Result







ESTRO

School

WWW.ESTRO.ORG/SCHOOL

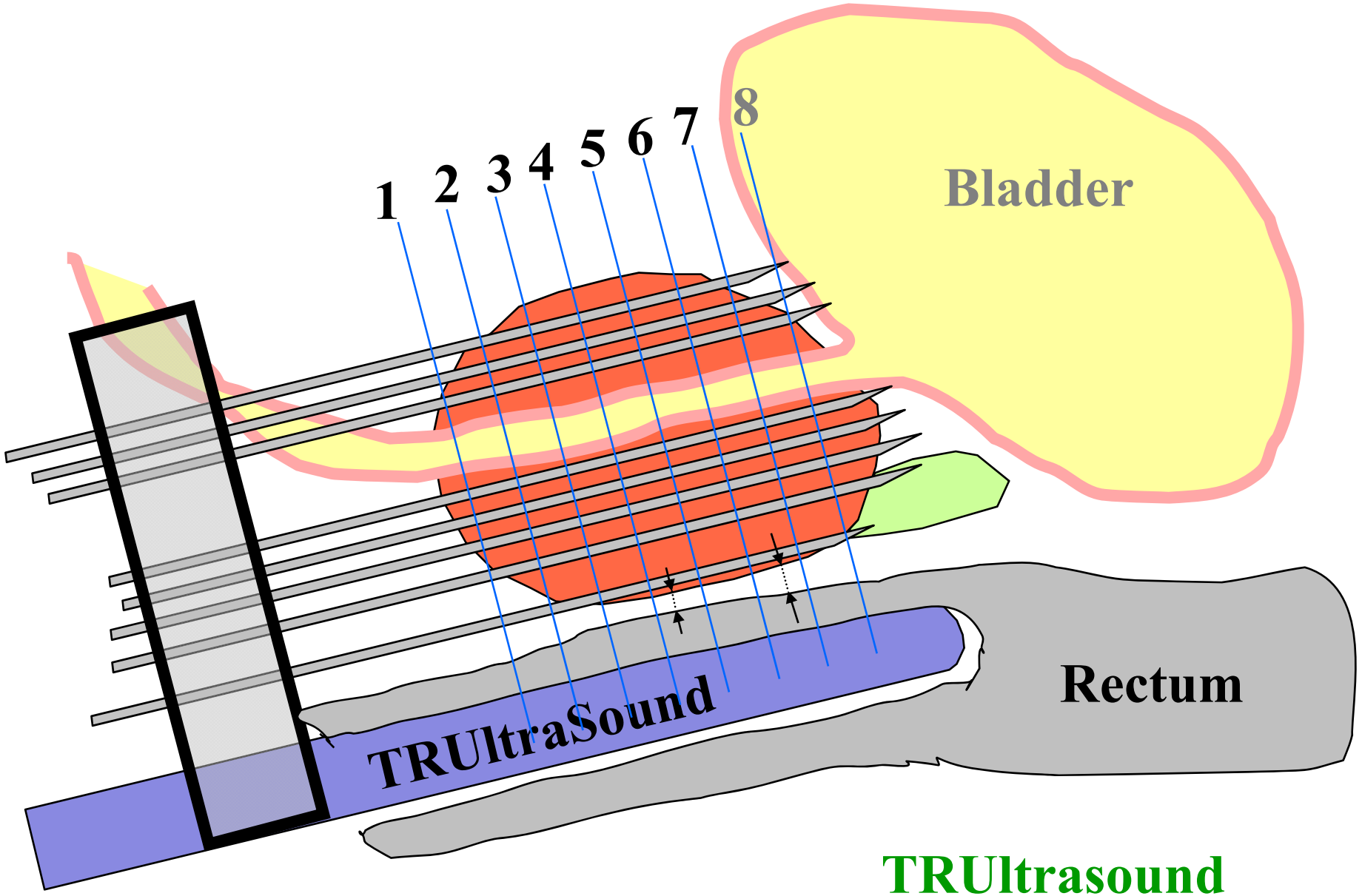
High dose rate brachytherapy for prostate cancer
TIPS and TRICKS

Peter Hoskin

Mount Vernon Cancer Centre

Northwood

UK

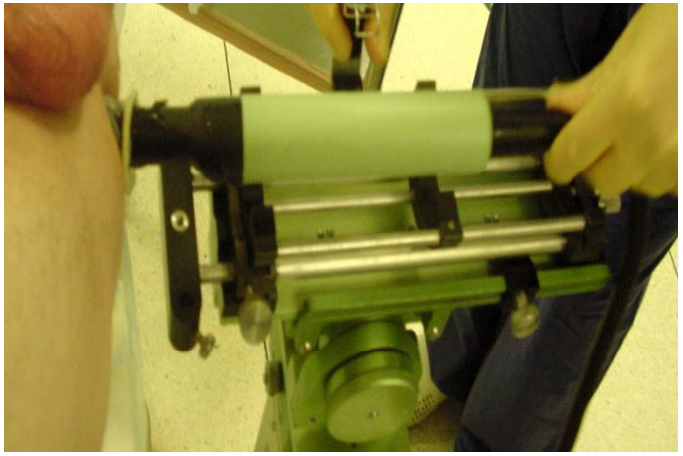


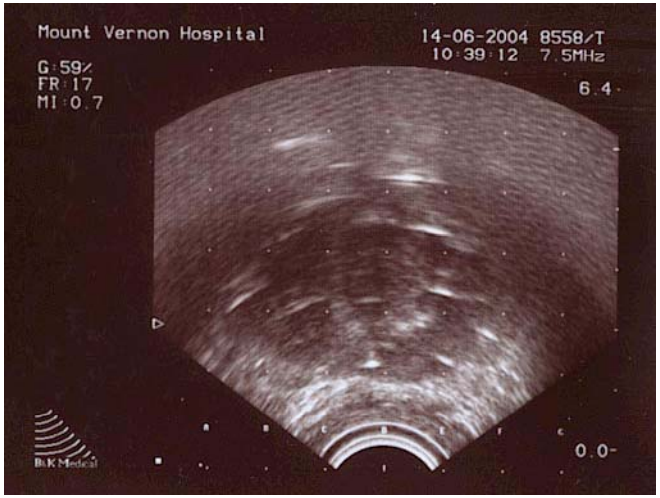
TRUltrasound
5 mm planes

Steps in HDR prostate brachytherapy

- Implantation
- Volume definition
- Dosimetry planning
- QA
- Treatment delivery

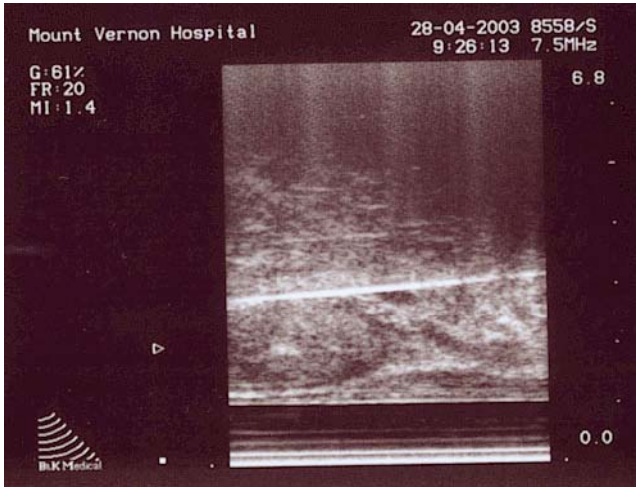
Implant technique





- TRUS guided
  - Transaxial and sagittal

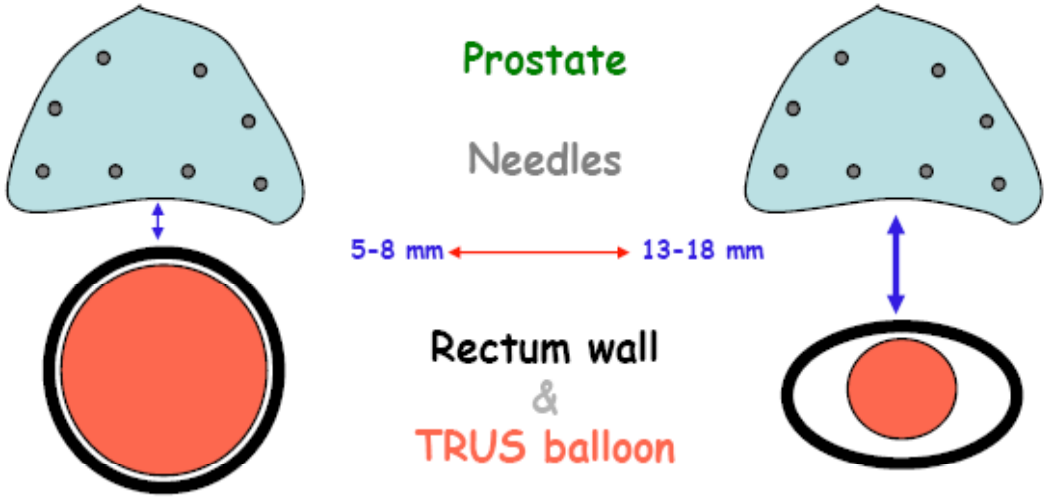
- SET UP:
  - Baseline to include posterior capsule and seminal vesicles
  - Urethra along Row D
  - Minimise probe pressure



-

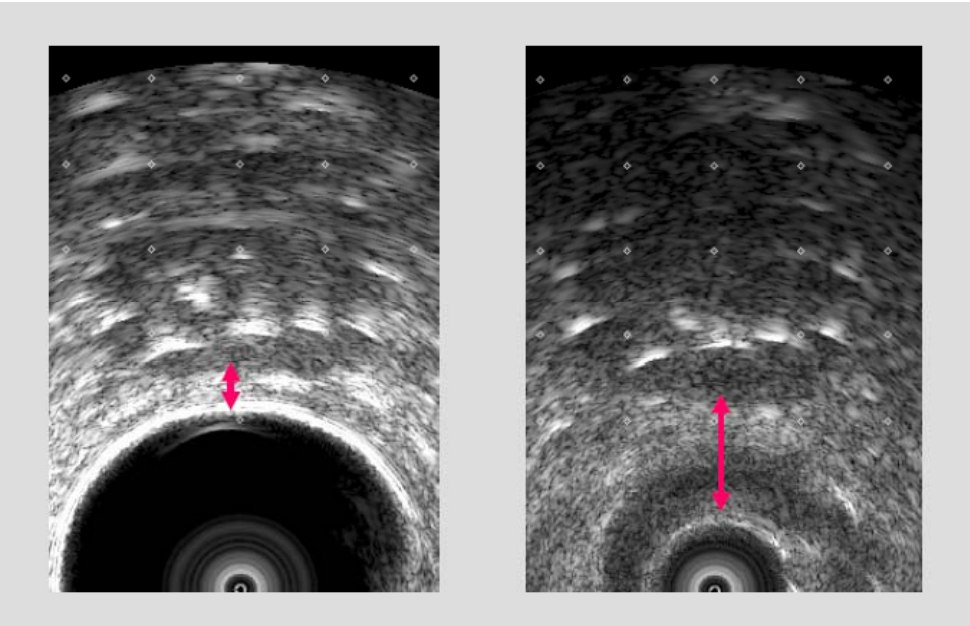
Tips for a good implant

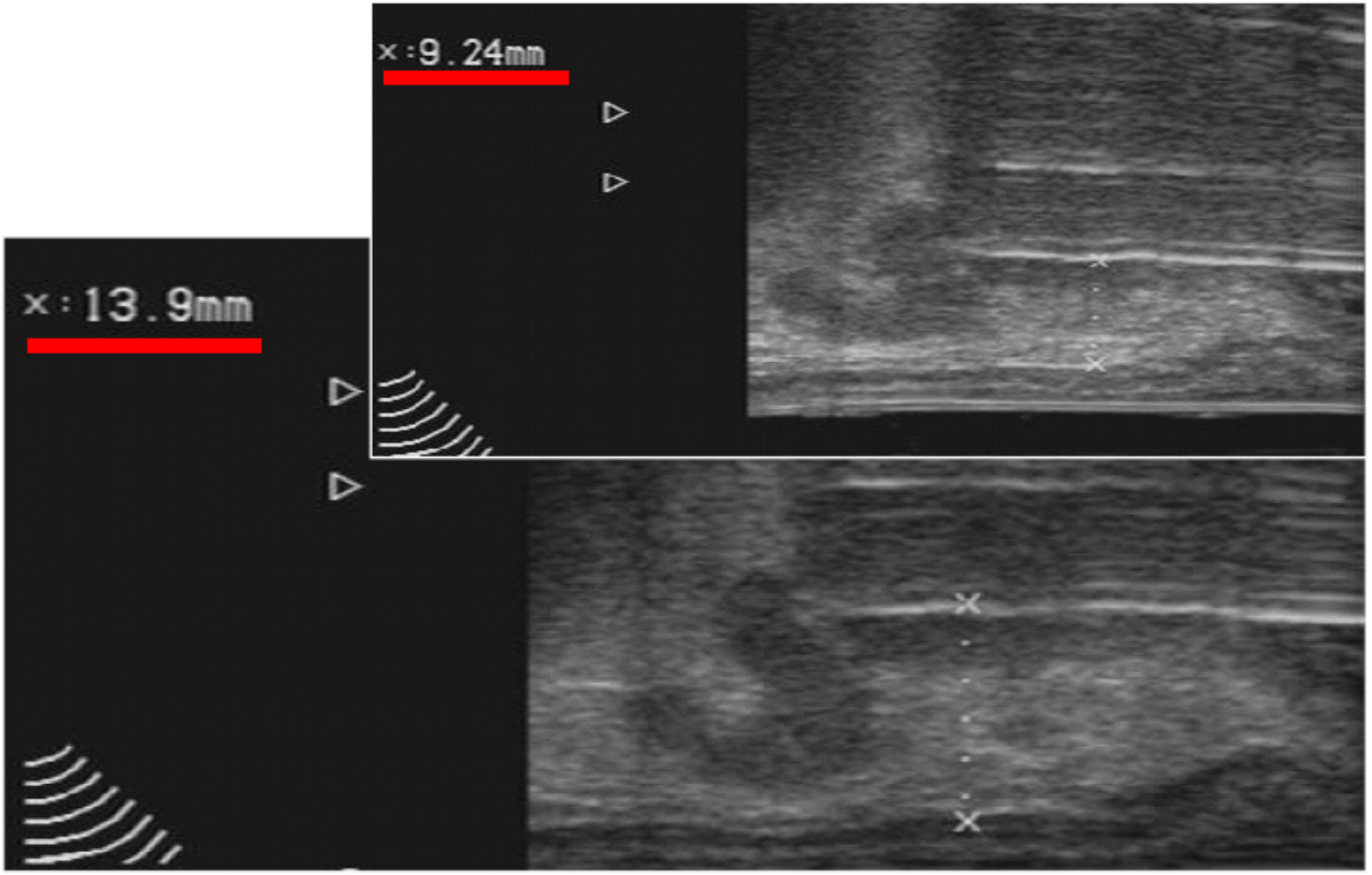
- Good peripheral coverage is essential
- Pay particular attention to superior catheters and baseline
- Monitor both transaxial and sagittal images; scroll through prostate length regularly



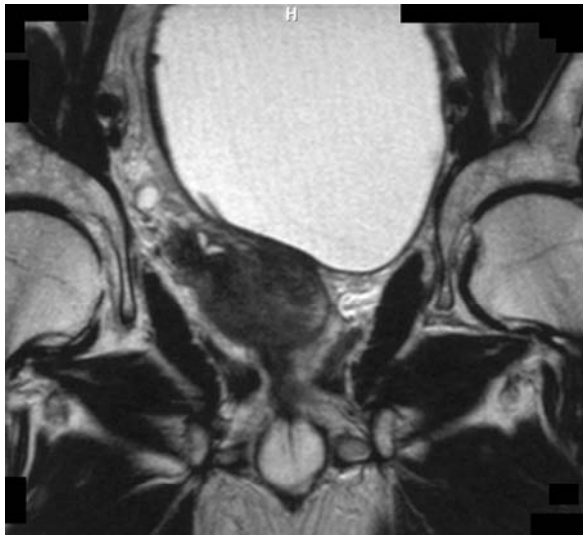
Positioning of posterior template row is crucial

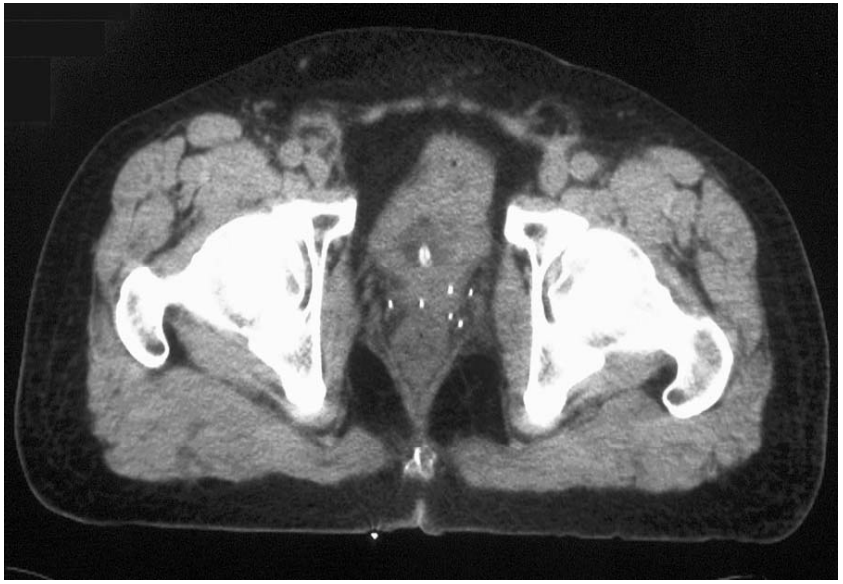
Adjustment through probe position and build up cap

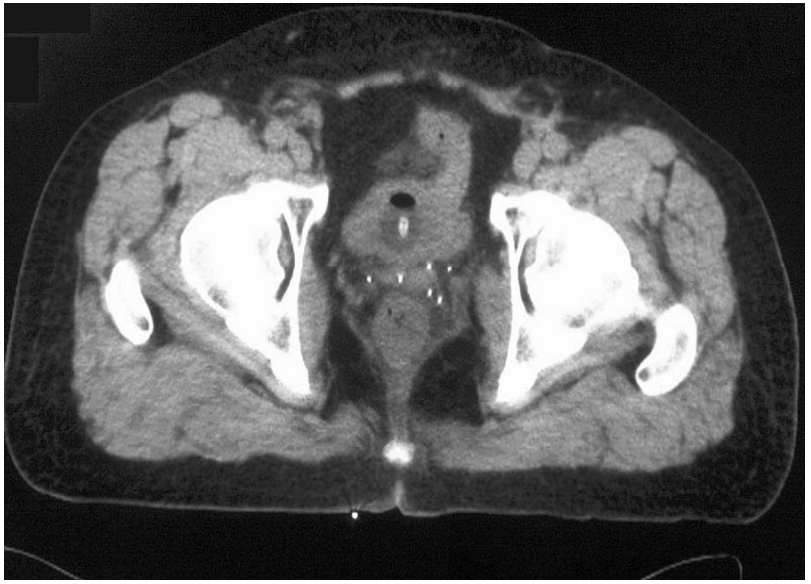


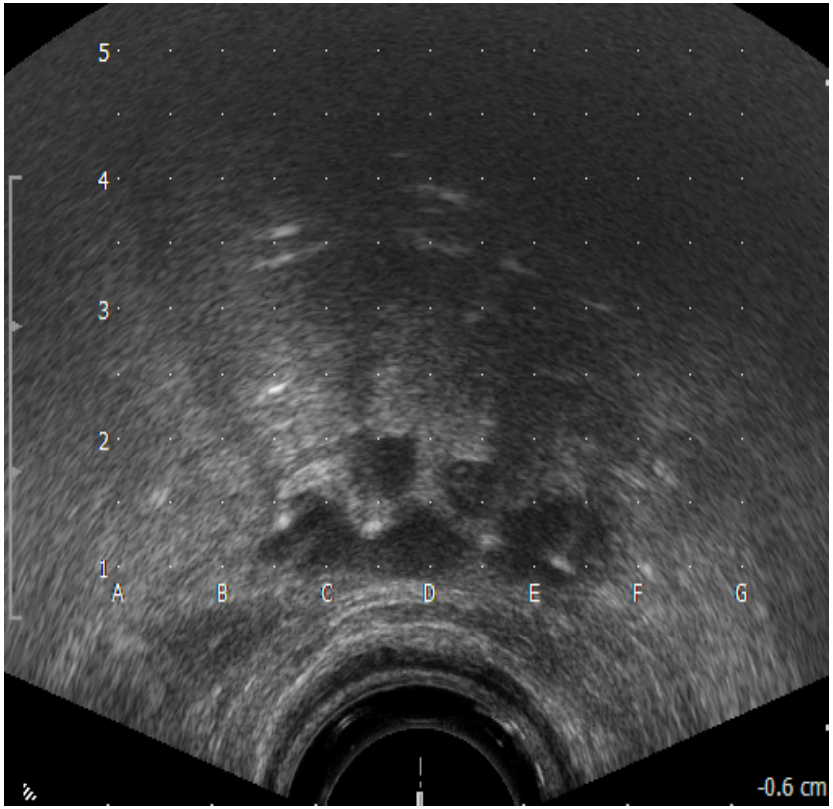

x:9.24mm
x:13.9mm

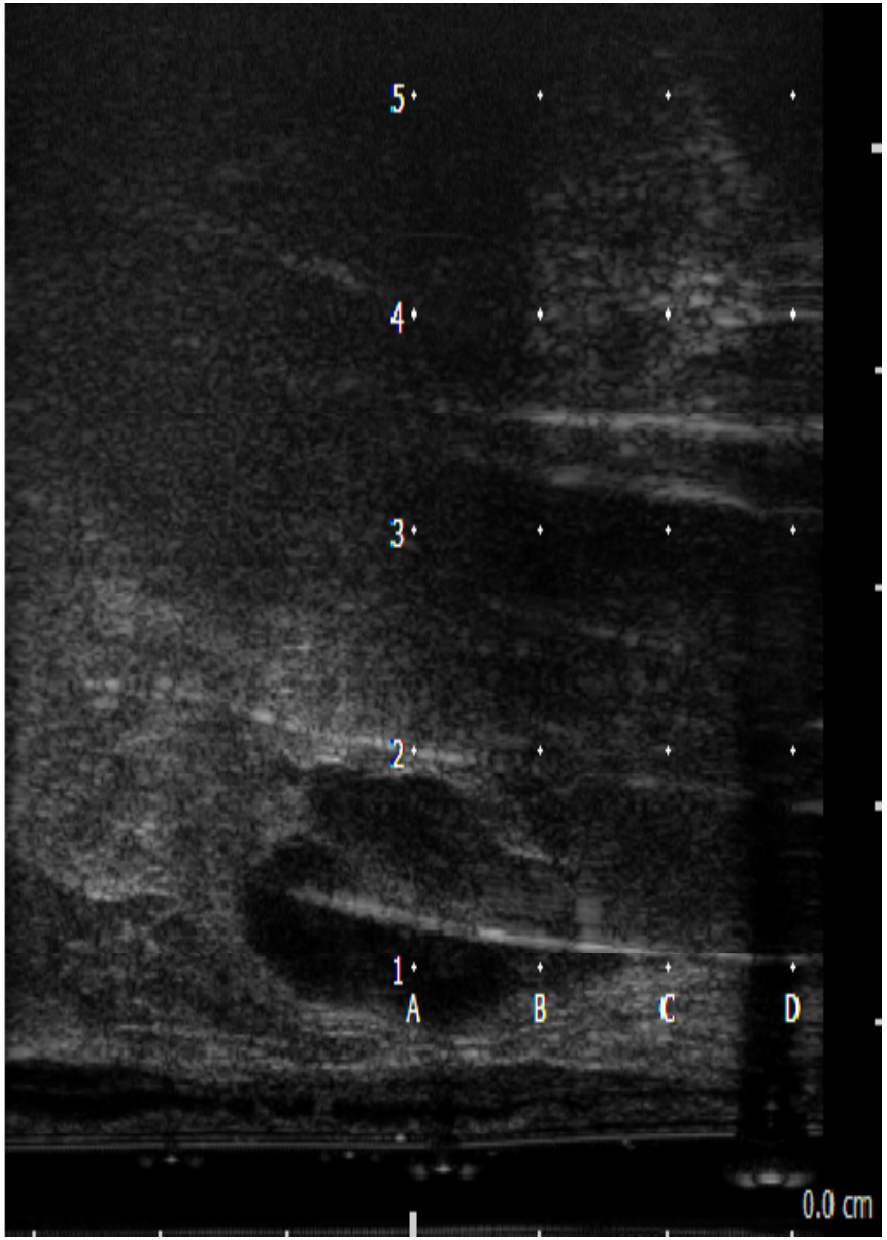
HDR implant: seminal vesicles

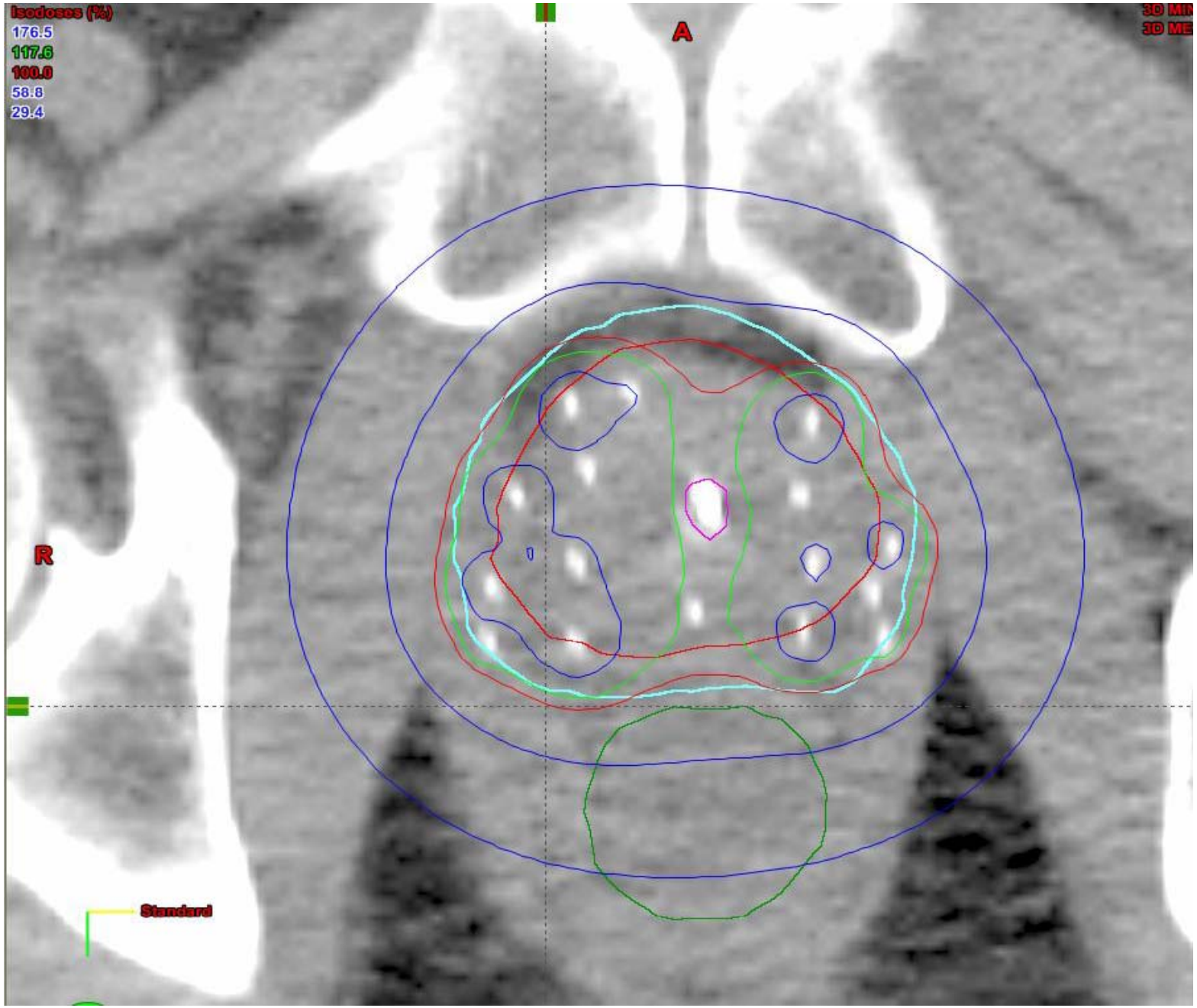




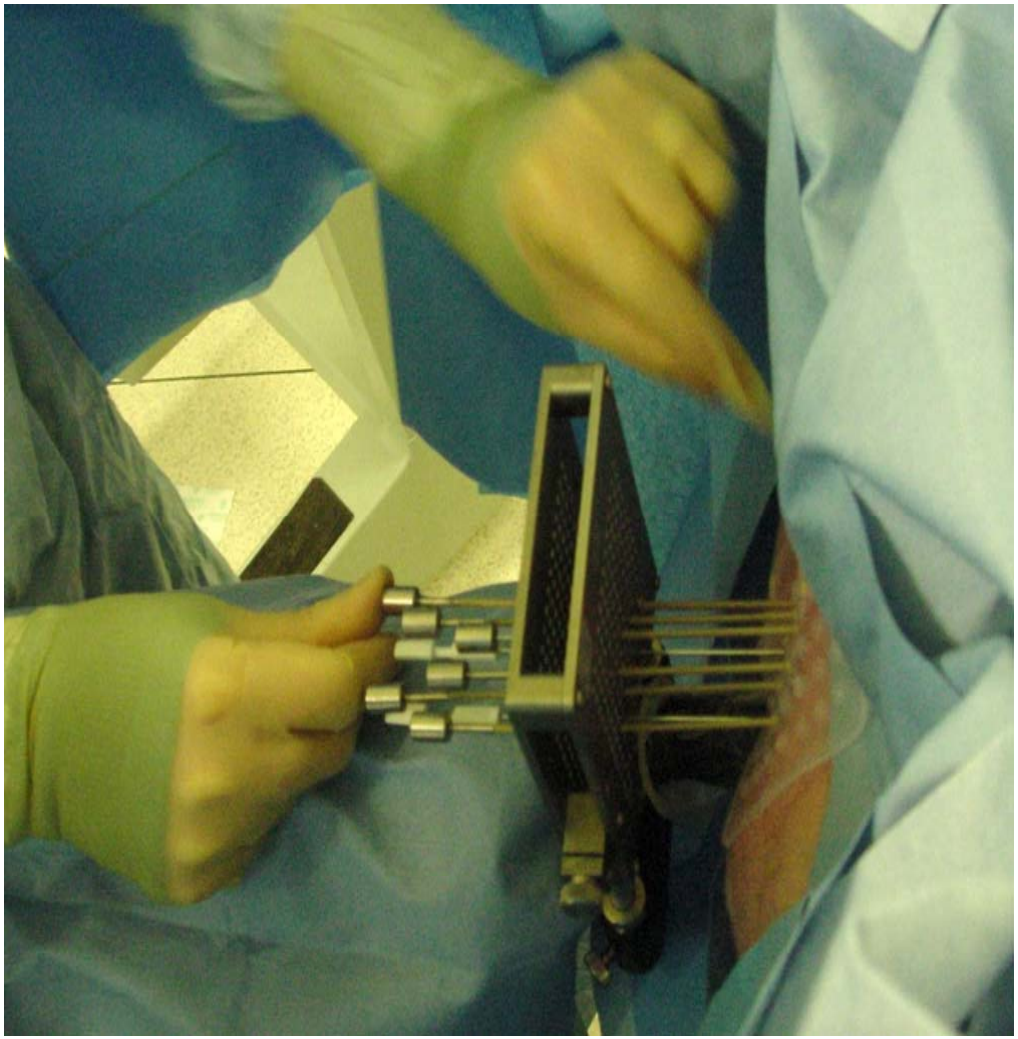


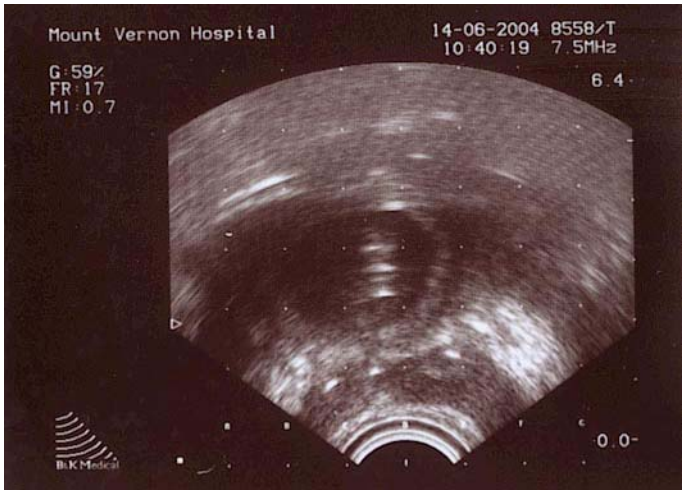

5
4
3
2
1
A
B
C
D
E
F
G
-0.6 cm

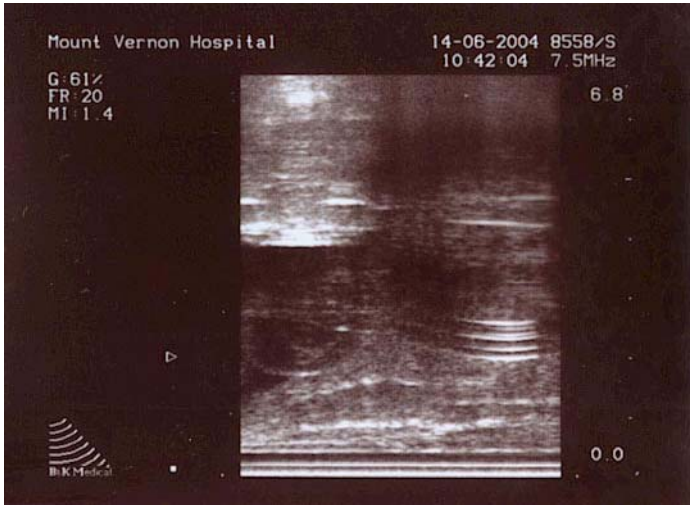

5
4
3
2
1
A
B
C
D
0.0 cm

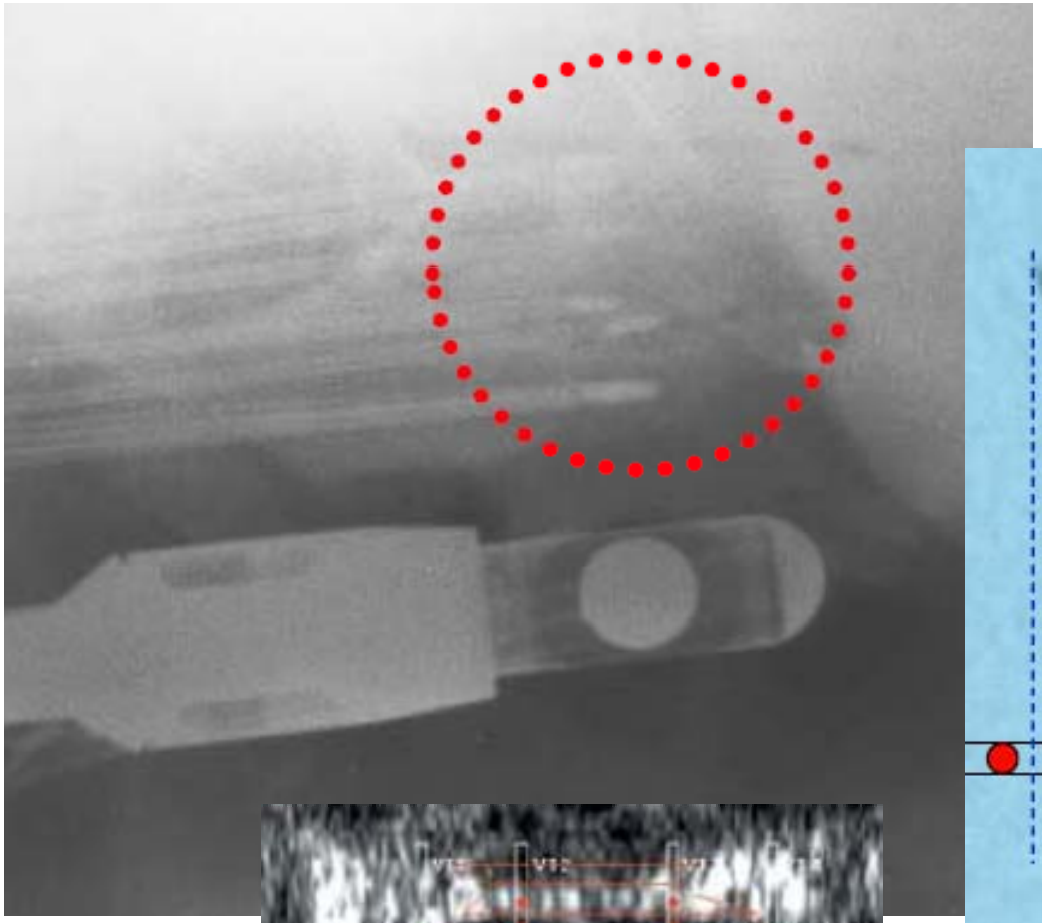

Isodoses (%)
176.5
117.6
100.0
58.8
29.4
A
R
Standard

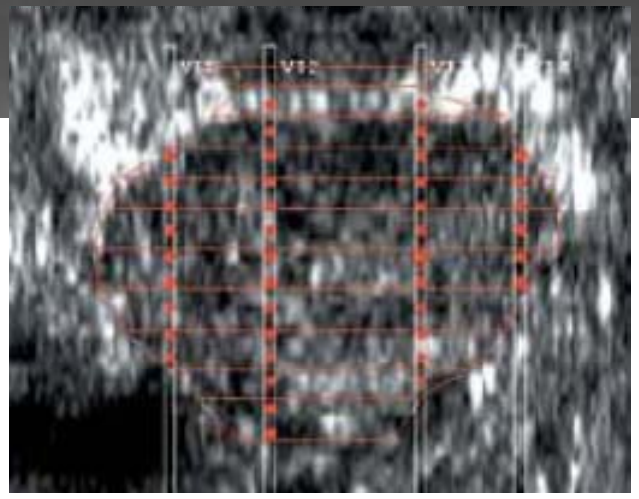
‘Overinsertion’

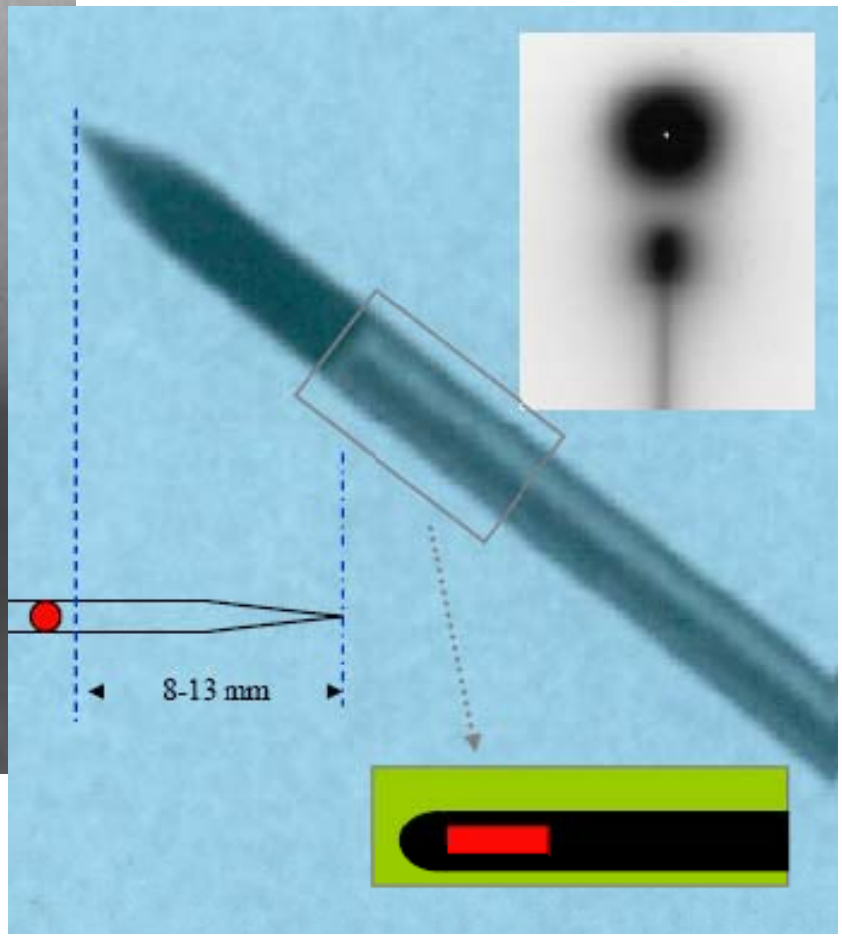











8-13 mm

Steps in HDR prostate brachytherapy

- Implantation
- Volume definition
- Dosimetry planning
- QA
- Treatment delivery

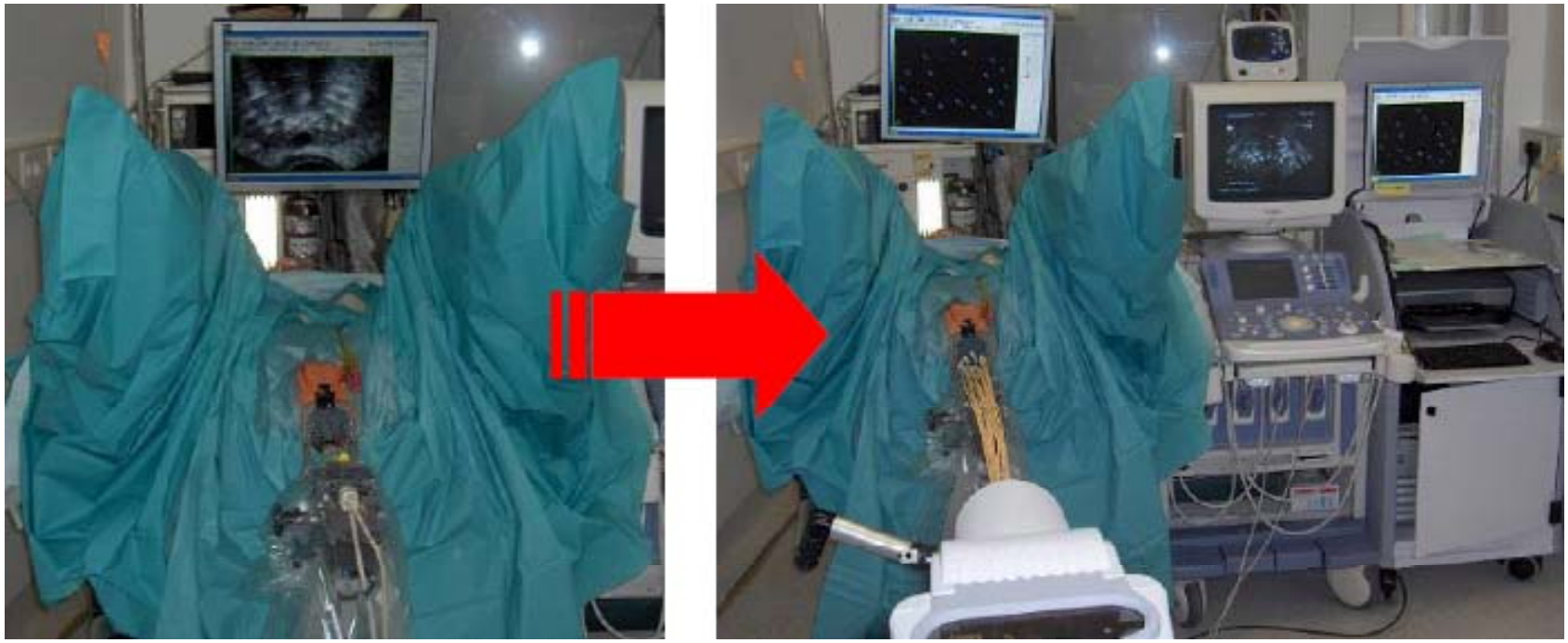
CTV definition

- Ultrasound
- CT
- MR

Ultrasound

- Intraoperative HDR planning
- Eliminates the CT scanner step
- Plan is created with patient remaining in lithotomy position in operating room

Offenbach

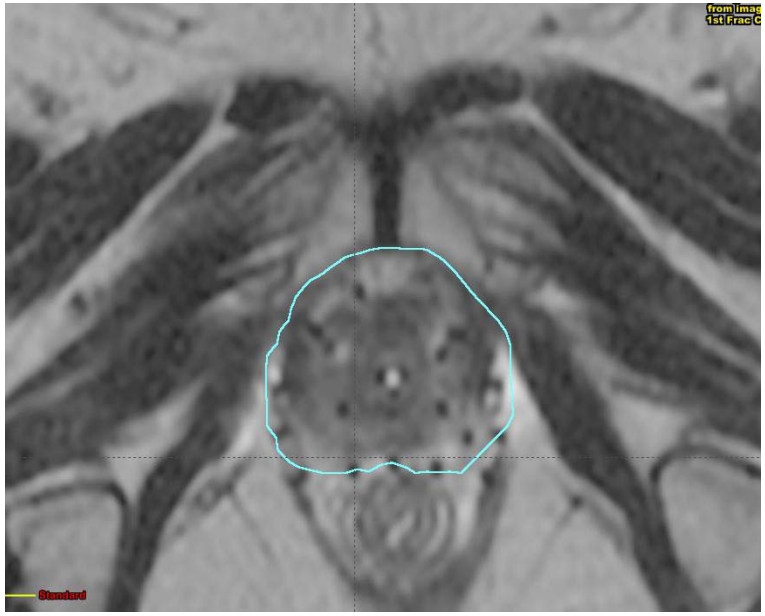


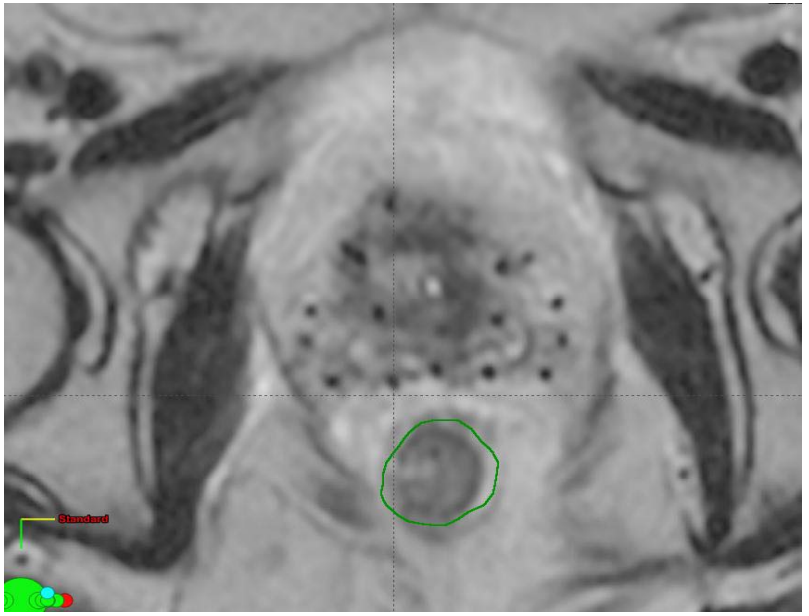
CT / MR based planning

- After recovery from implant
- Requires movement of patient
- Prolongs overall time
- May give additional information over US

MR vs CT outlining

- CT: better needle tracking
- MR: better soft tissue definition
- Image registration:
  - NB potential matching errors





CTV criteria
GEC ESTRO guidelines
2013

- Clinical target volume (CTV) is defined by:
  - the prostate capsule
  - plus any macroscopic extracapsular disease or seminal vesicle involvement identified on diagnostic images expanded by 3 mm to encompass potential microscopic disease. This is usually constrained posteriorly to the anterior rectal wall and superiorly to the bladder base.

OAR criteria
GEC ESTRO guidelines
2013

- Organs at risk (OAR) which should include as a minimum:
  - Rectum: outlining of the outer wall alone is considered adequate for brachytherapy dosimetry as defined for LDR seed techniques.
  - Urethra using the urethral catheter as the landmark on imaging for the urethral contour which should extend from bladder base to 5–10 mm below the prostatic apex. Contrast such as aerated gel within the catheter will aid visualisation on ultrasound.

- Other OARs of interest may include
  - Penile bulb.
  - Bladder neck.
  - Neurovascular bundle.

HDR brachytherapy: dose prescription

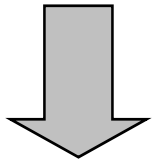
- Planning aim
  - Dose prescribed prior to planning
- Prescription dose
  - Finally accepted dose after planning to account for any compromise between PTV and OAR doses
- Reported dose
  - Dose as delivered using recommended reporting parameters

HDR brachytherapy boost: Planning aim

after

External beam

- 45 Gy in 25 fractions over 5 weeks.
- 46 Gy in 23 fractions over 4.5 weeks.
- 35.7 Gy in 13 fractions over 2.5 weeks.
- 37.5.Gy in 15 fractions over 3 weeks.



- 15 Gy in 3 fractions.
- 11–22 Gy in 2 fractions.
- 12–15 Gy in 1 fraction.

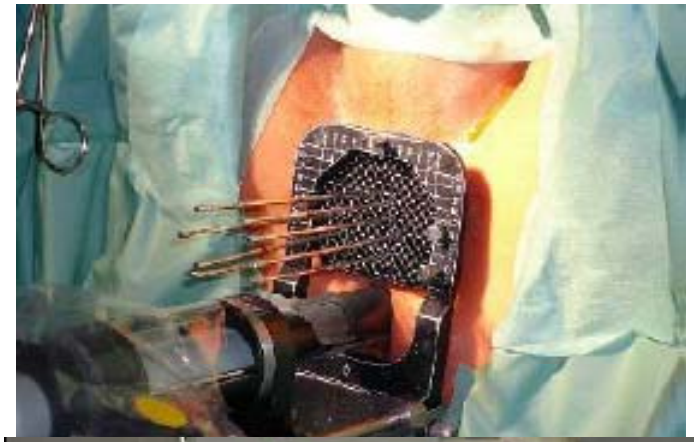
HDR brachytherapy monotherapy: Planning aim

34 Gy in 4 fractions.
36–38 Gy in 4 fractions.
31.5 Gy in 3 fractions.
26 Gy in 2 fractions.

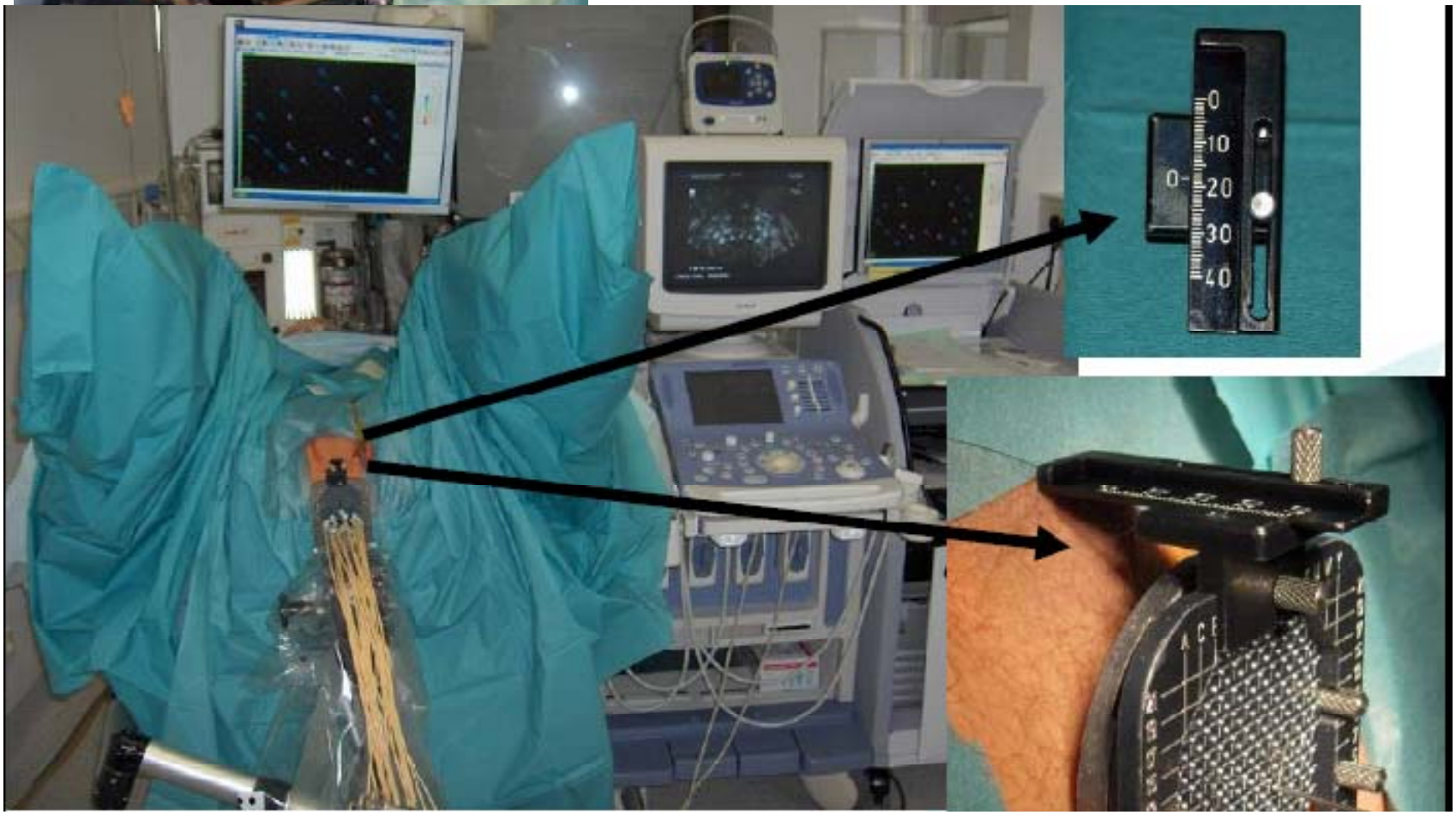
Steps in HDR prostate brachytherapy

- Implantation
- Volume definition
- Dosimetry planning
- QA
- Treatment delivery

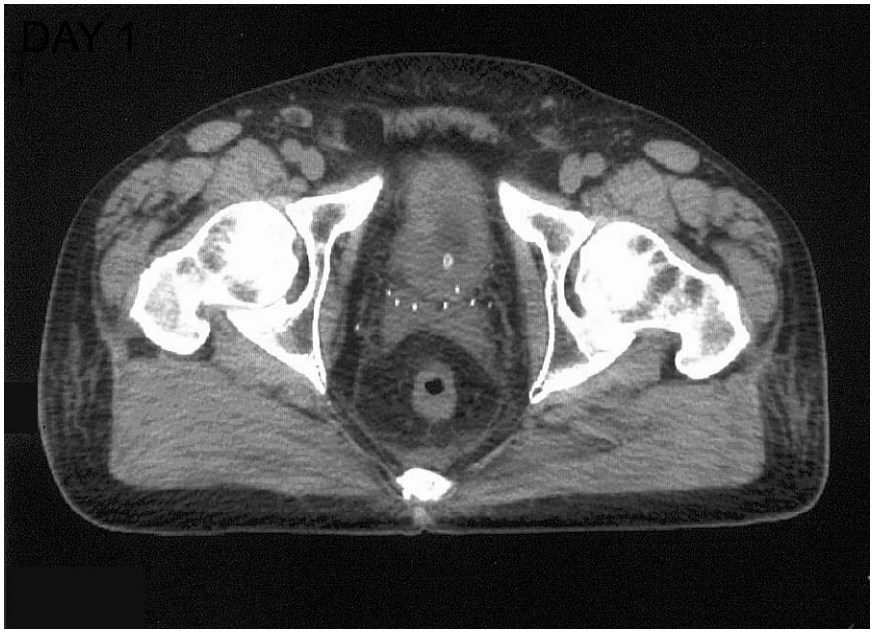
Quality control

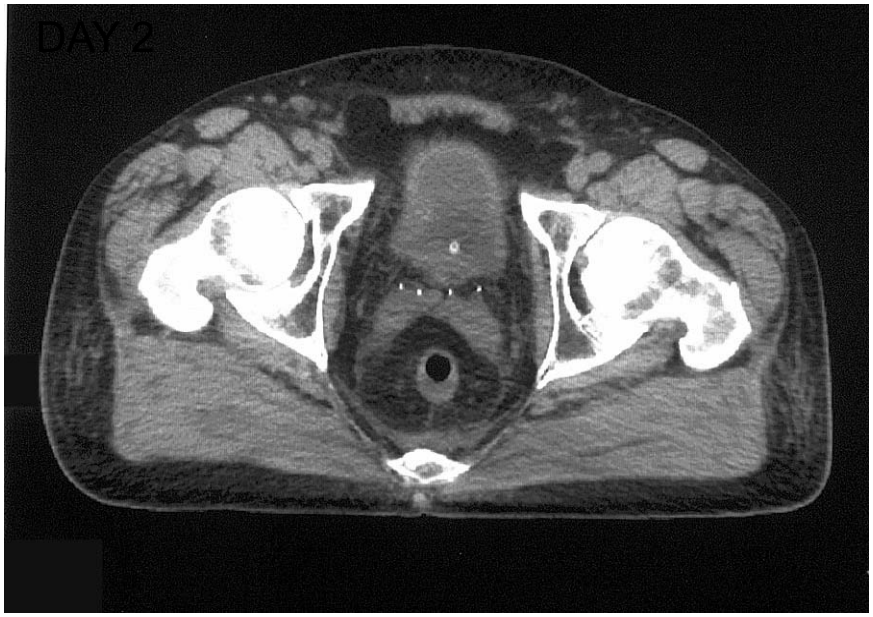


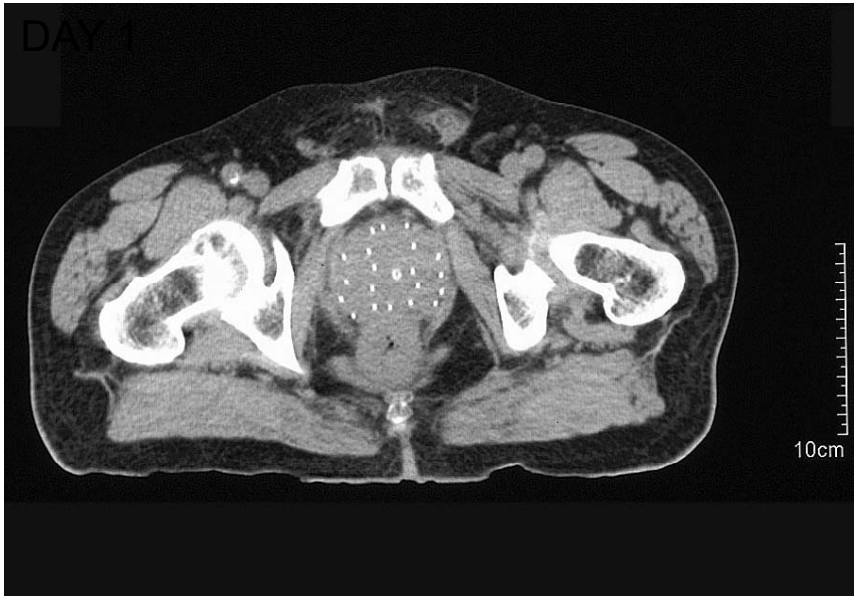
Single step technique:
Movement of template
with catheters

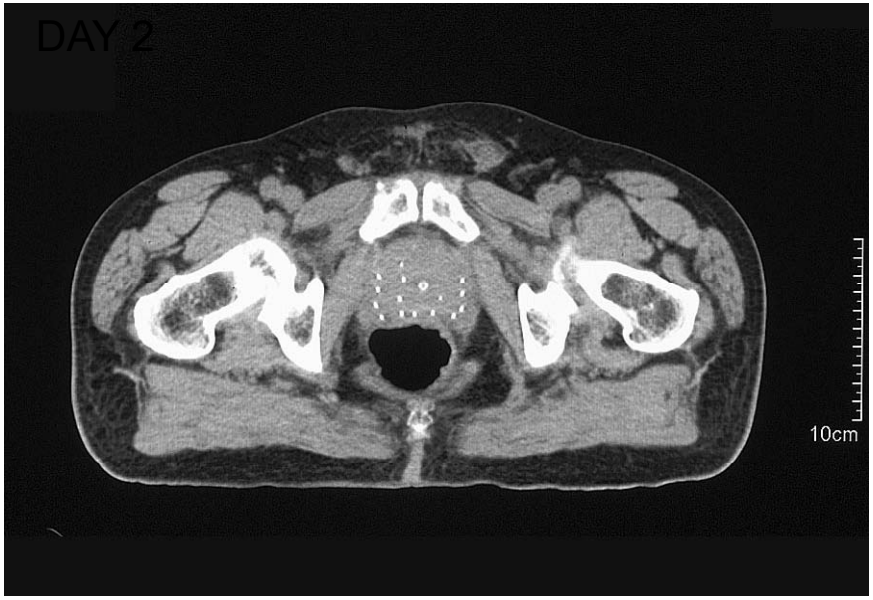


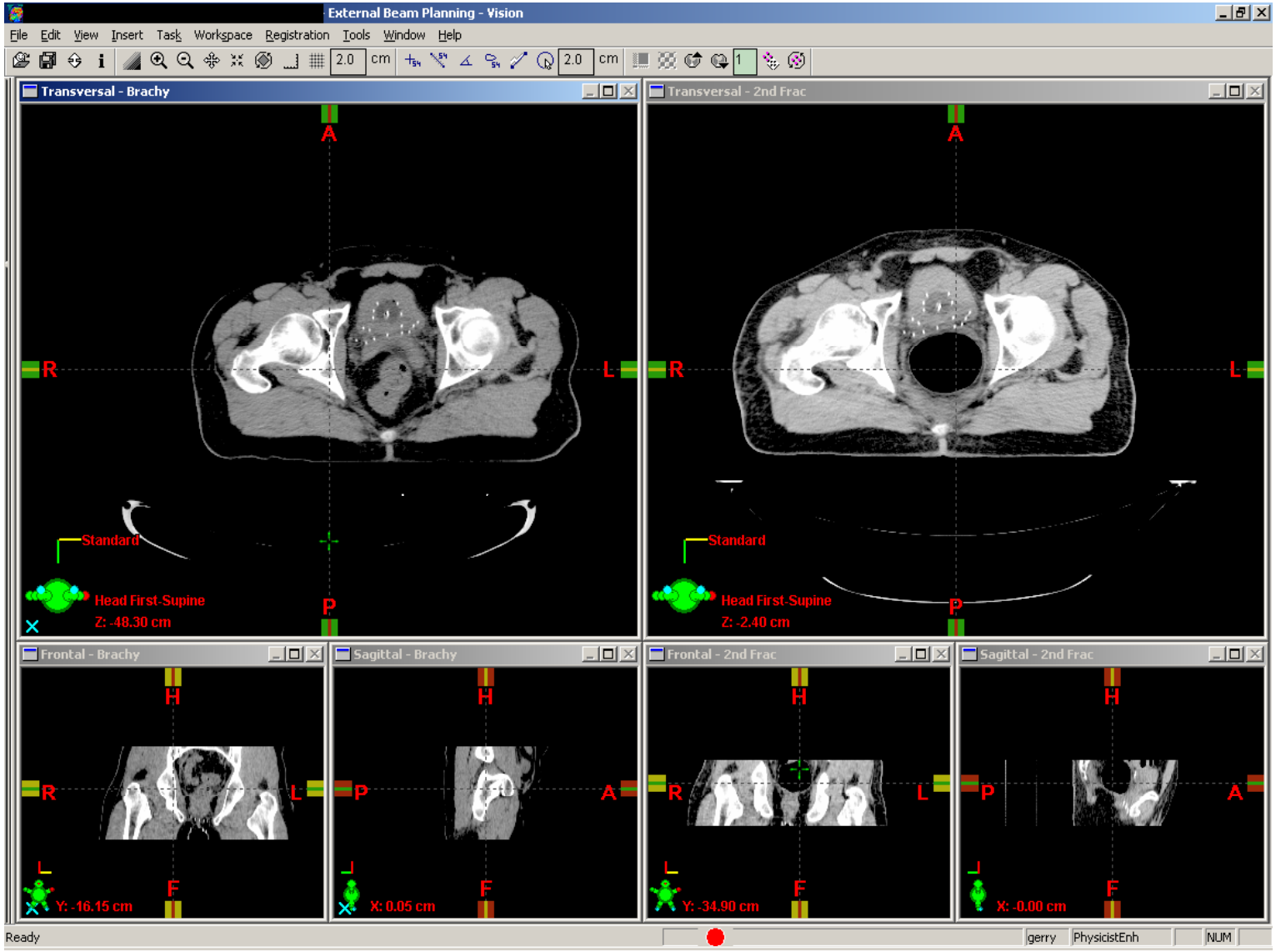
Baltas 2009


DAY 1


DAY 2


DAY 1
10cm


DAY 2
10cm


External Beam Planning - Vision
File Edit View Insert Task Workspace Registration Tools Window Help
Transversal - Brachy
Transversal - 2nd Frac
Standard
Head First-Supine
Z: -48.30 cm
Z: -2.40 cm
Frontal - Brachy
Sagittal - Brachy
Frontal - 2nd Frac
Sagittal - 2nd Frac
Y: -16.15 cm
X: 0.05 cm
Y: -34.90 cm
X: -0.00 cm
Ready
gerry
PhysicistEnh
NUM

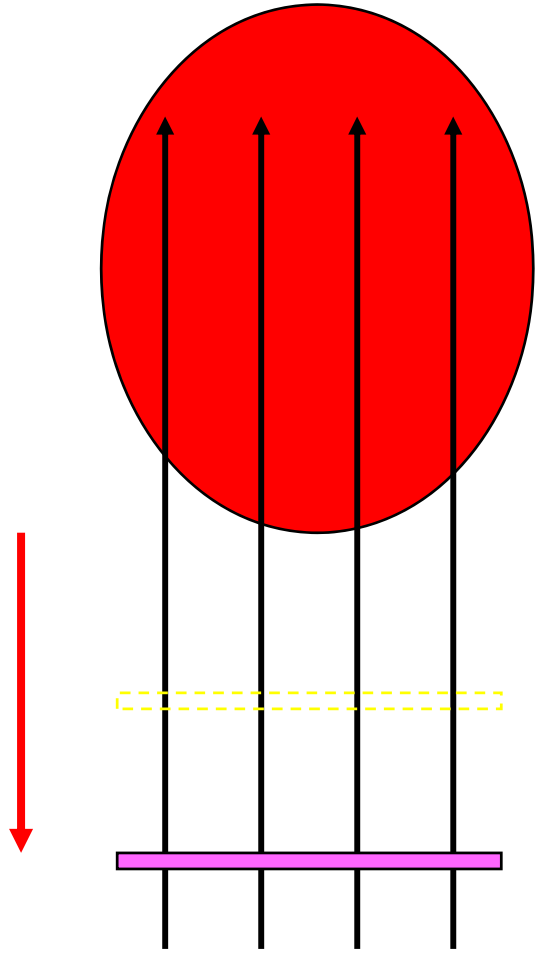
HDR implant: verification for multiple fractions

Repeat skin to hub measures

Repeat limited CT

Adjust catheters

Recalculate dose distribution



Prostate movement from CT before 1st and 2nd fractions

Mean 11.5mm

Median 9.7mm

Range 0-42mm

Prostate cancer brachytherapy

Justification for inter-fraction correction of catheter movement in fractionated high dose-rate brachytherapy treatment of prostate cancer

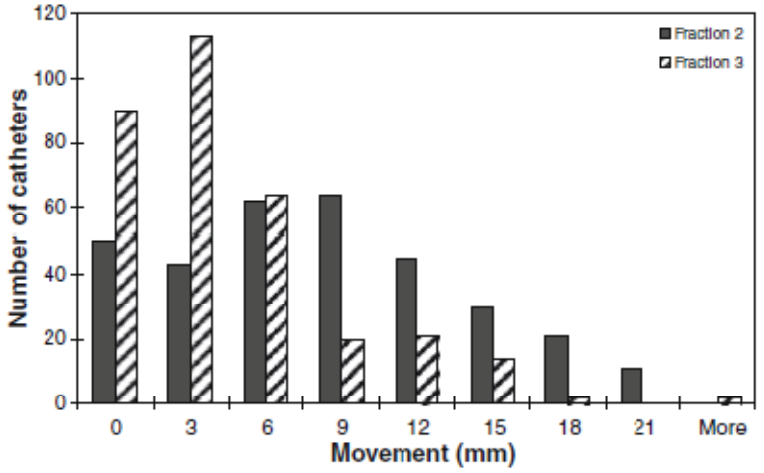
Tania Simnor *, Sonia Li, Gerry Lowe, Peter Ostler, Linda Bryant, Caroline Chapman, Dave Inchley, Peter J. Hoskin

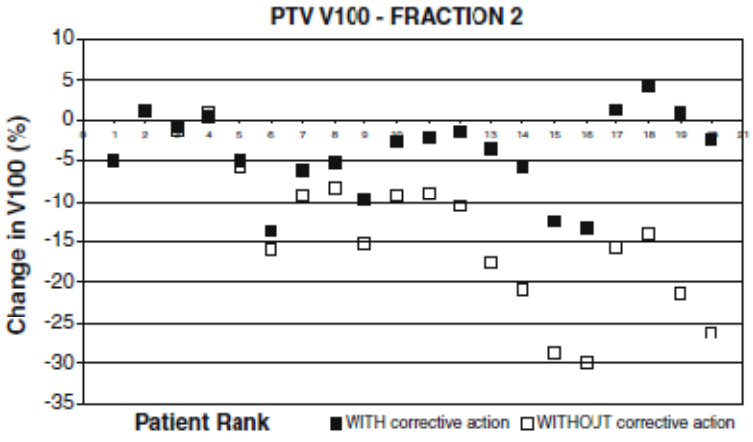
Mount Vernon Centre for Cancer Treatment, Middlesex, UK

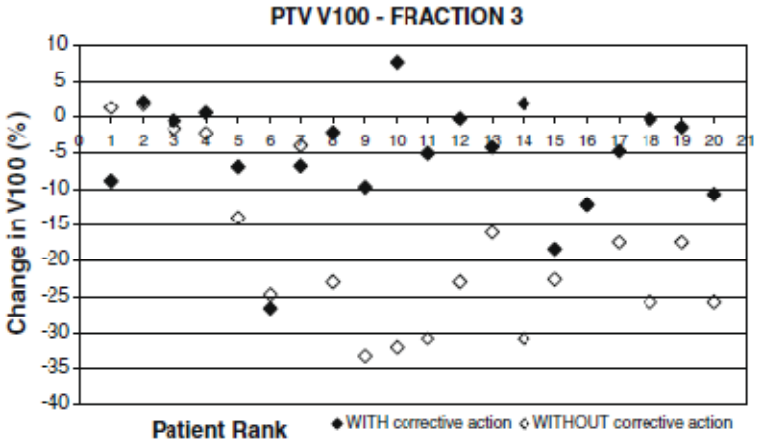
RT&O 2009

20 consecutive monotherapy implants

31.5Gy in 3 fractions in 2 days







Minimal displacement of novel self-anchoring catheters suitable for temporary prostate implants

Bradley R. Pieters[a,*], Johan N.B. van der Grient[a], Leo E.C.M. Blank[a], Kees Koedooder[a], Maarten C.C.M. Hulshof[a], Theo M. de Reijke[b]

[a]*Department of Radiation Oncology, and* [b]*Department of Urology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

Table 1
Distribution of absolute displacement of catheters on day 2 and 3

	Number of catheter position comparison	Number of catheter displacement (%)			
		0 mm	2 mm	4 mm	6 mm
Day 2	311	177 (57%)	111 (36%)	20 (6%)	3 (1%)
Day 3	291	150 (52%)	110 (38%)	27 (9%)	4 (1%)

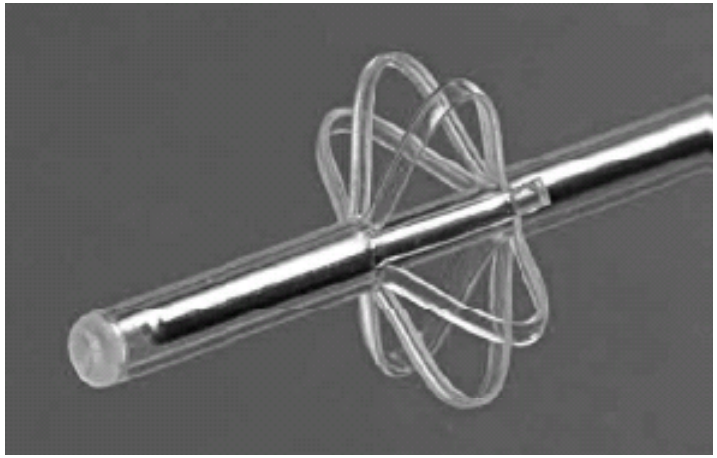


Table 2
Paired differences of dose–volume parameters on day 1 compared to day 3

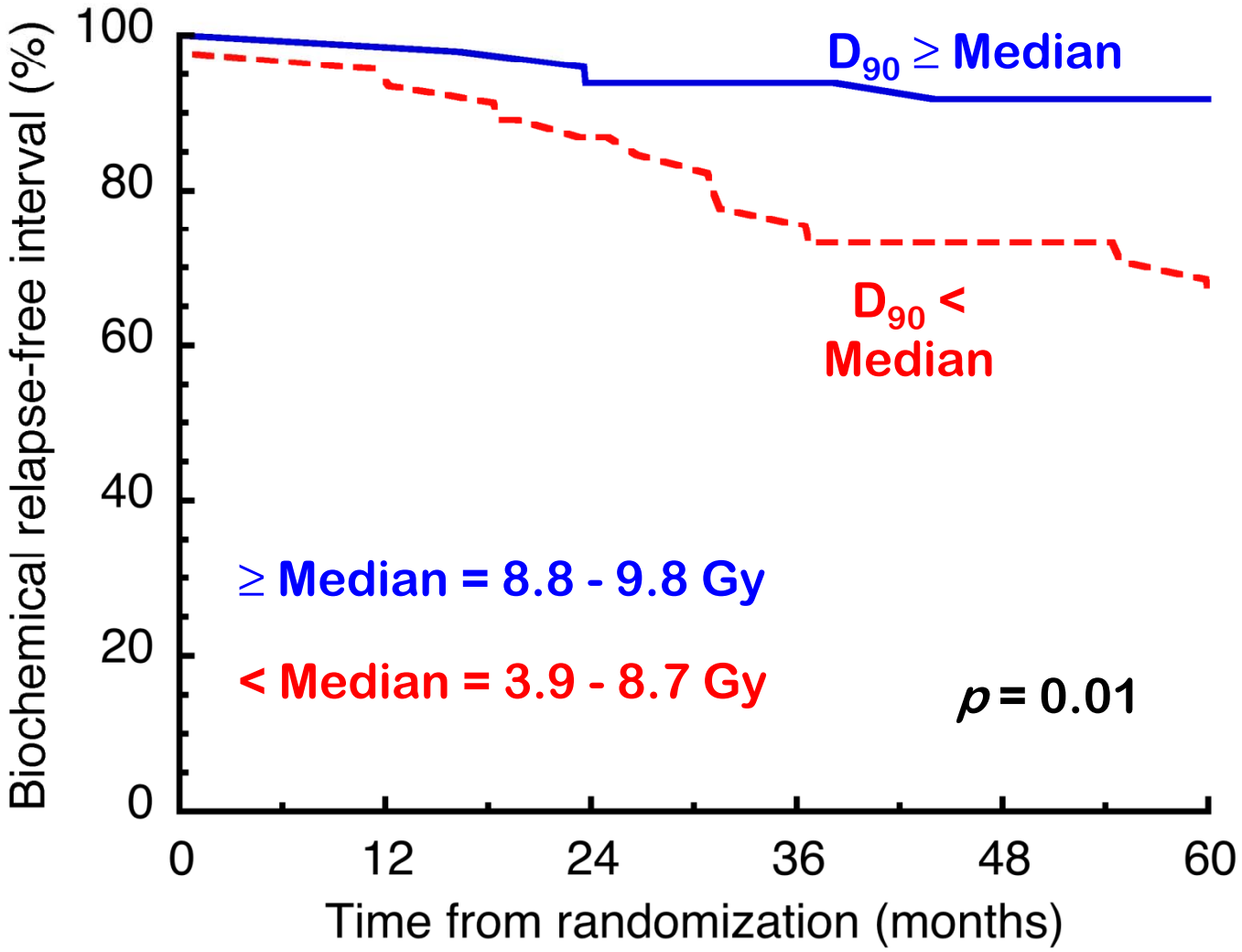
Dose–volume parameters	Mean difference day 1–3	95% CI	*P*
V_{100}	0.25 ml	0.05 to 0.46	0.02[a]
$\ln(V_{150})$	0.04 ml	−0.002 to 0.08	0.06[a]
$D_{0.5\ ml\text{-}u}$	0.99 cGy/pulse	0.02 to 1.96	0.05[a]
$D_{2\ ml\text{-}r}$	0.93 cGy/pulse	0.31 to 1.56	0.01[a]
$\ln(D_{2\ ml\text{-}b})$	−0.01 cGy/pulse	−0.05 to 0.03	0.63[a]
D_{90}			0.002[b]

[a] Paired *t*-test.
[b] Wilcoxon signed ranked sum test.

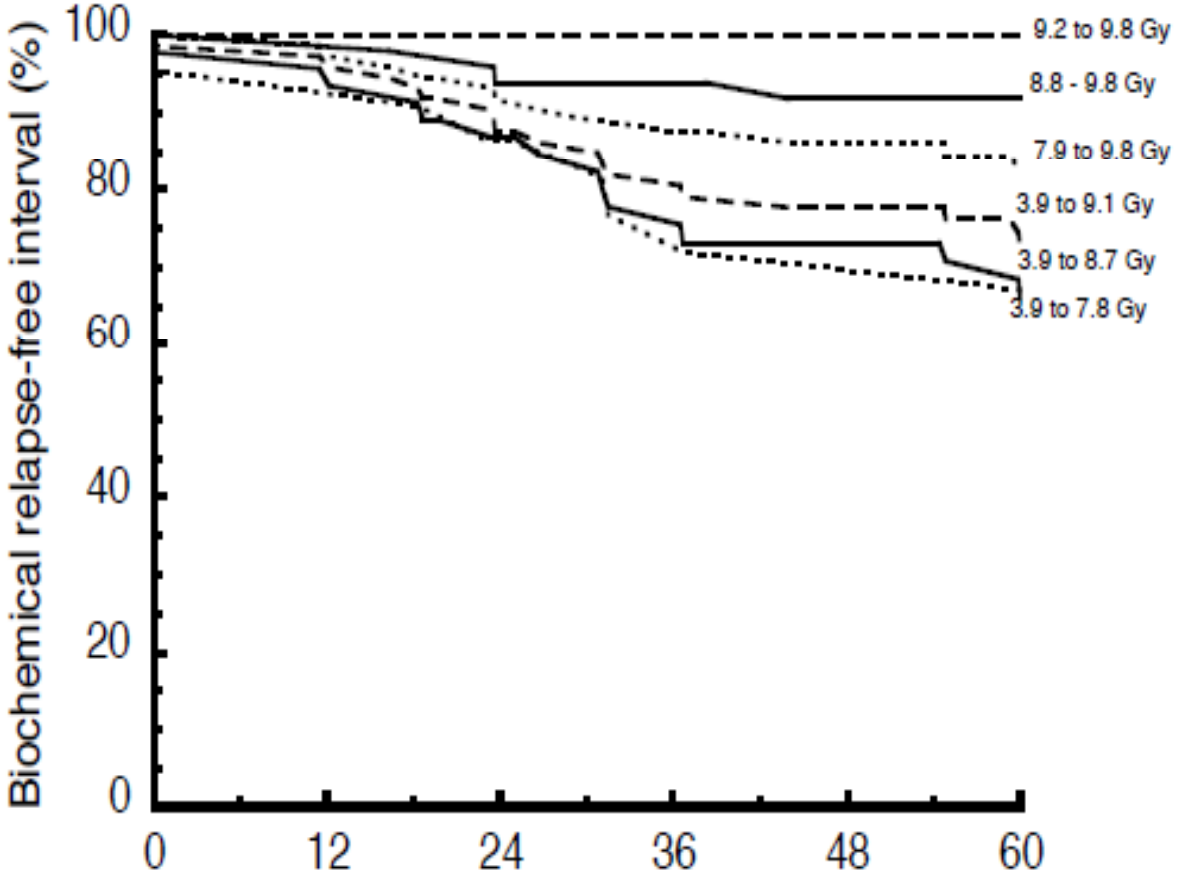
Mean D_{90} and V_{100} in patients with and without biochemical control of disease

D_{90}	Mean (95% CI)	*p*
With relapse (n = 24)	7.9 Gy 7.6 - 8.3	< 0.0001
No relapse (n = 71)	8.6 Gy 8.3 - 8.9 Gy	
V_{100}	Mean (95% CI)	*p*
With relapse (n = 24)	84.7% 81.7 - 87.7%	< 0.0001
No relapse (n = 71)	90.8% 88.8 - 92.7%	

Biochemical Relapse Free Survival by median D_{90}



bRFS shown by median D90 and by quartiles of D90



HDR Brachytherapy

- Meticulous technique
- Individualised dosimetry
- Good QA

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HDR techniques and video demonstration

Frank-André Siebert

UKSK, Campus Kiel, Germany
Clinic of Radiotherapy
Head of Dept. of Medical Physics

- **All equipment must be checked/calibrated**

National / international rules and recommendations

  - Afterloader
  - Source
  - Treatment planning system
  - Ultrasound, tracked stepper
  - Imaging
  - …

- **Personal is trained**

Time schematic for operation room (OR)

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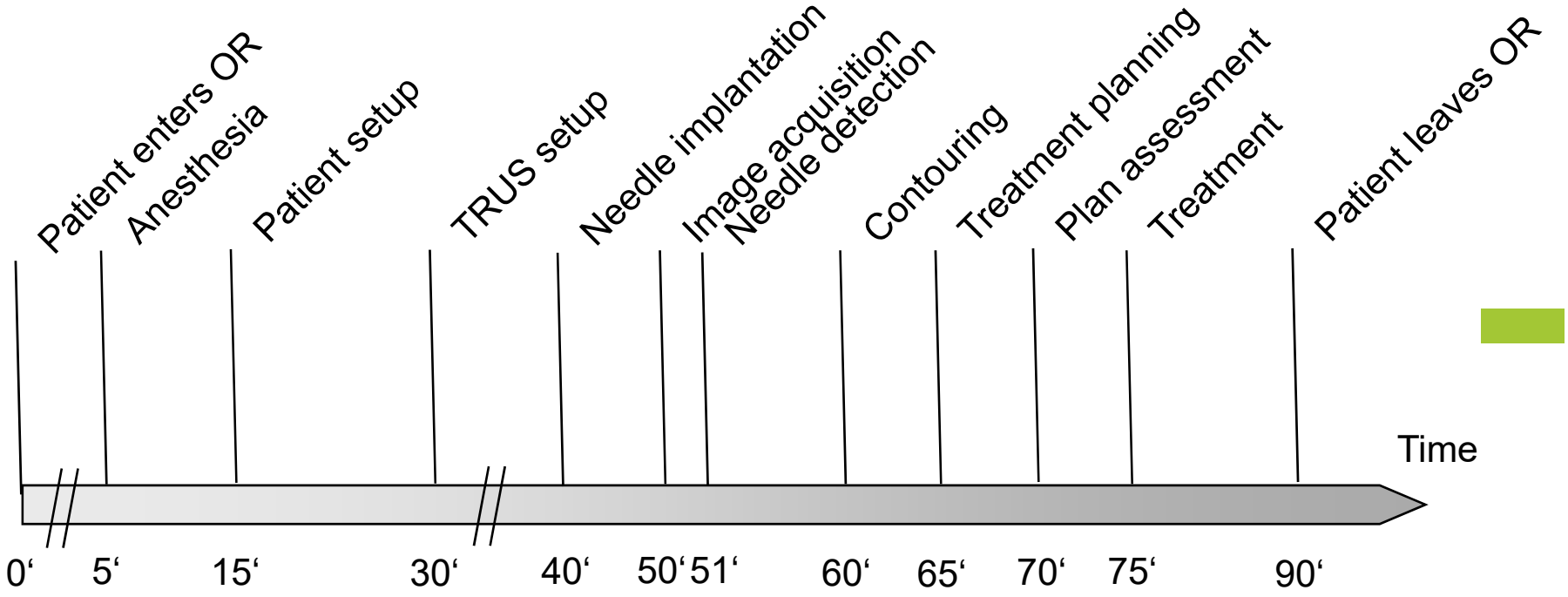

Kiel concept of HDR-BT for prostate cancer

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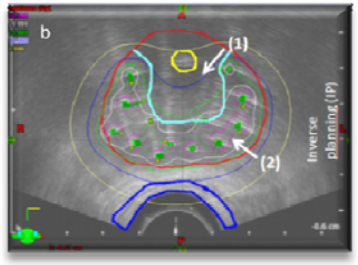
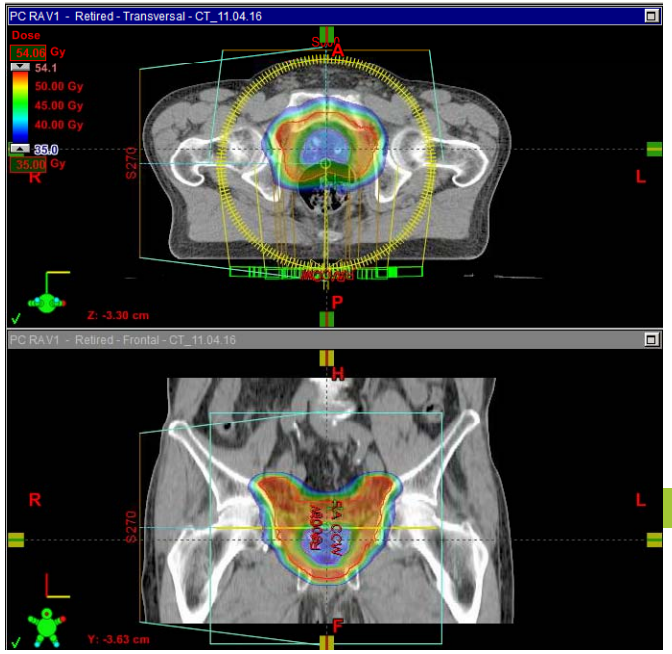
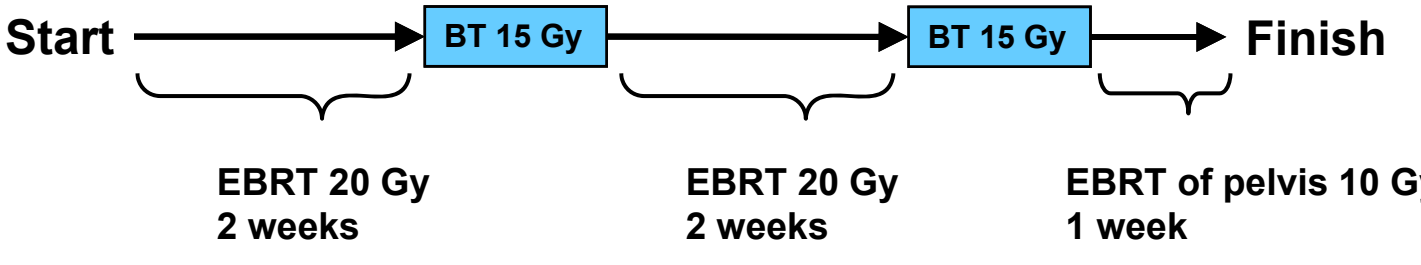
- Staging: T1-T3
- BT: 2 x 15 Gy plus EBRT:

  50 Gy (pelvis), 40 Gy (prostate)

- (Prostate volume < 60 ml)
- (Distance rectum to prostate > 5 mm)







Workflow HDR-Prostate Brachytherapy

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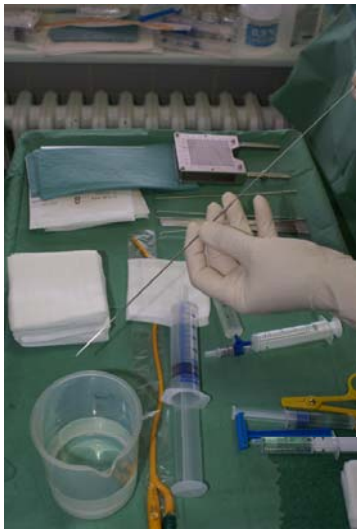
Patient setup → Implant → Image acquisition → Online needle detection → Contouring → Treatment planning → Export, Verification, Treatment



Side table (steril)

Spinal or full anaesthesia

Workflow HDR-Prostate Brachytherapy

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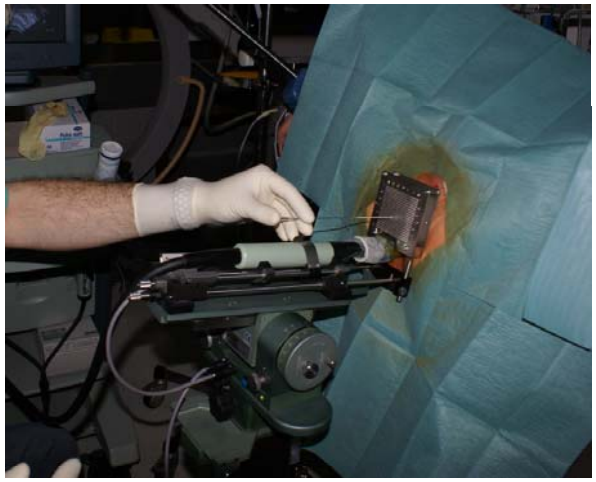
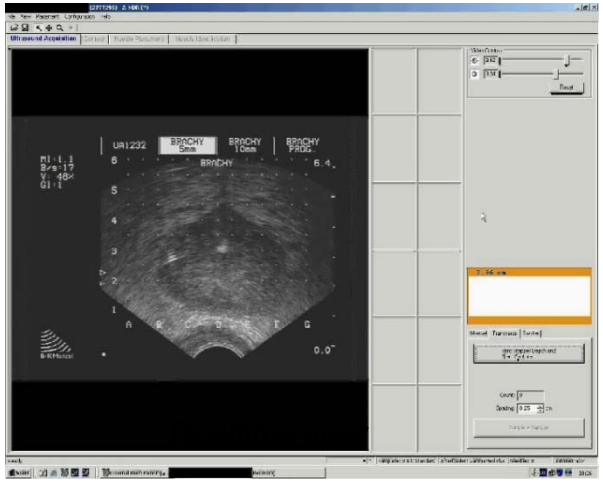
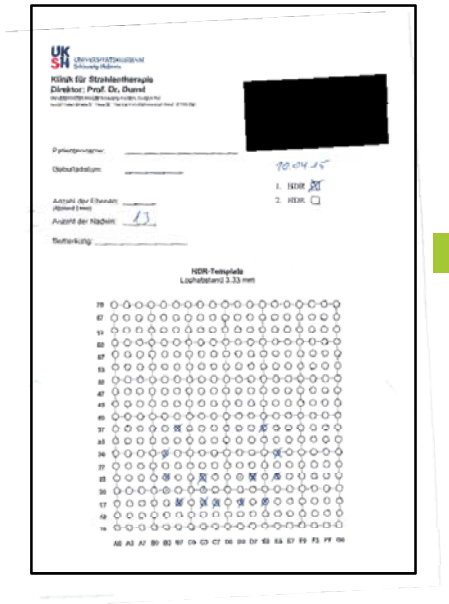
Patient setup → Implant → Image acquisition → Online needle detection → Contouring → Treatment planning → Export, Verification, Treatment



Needle implant



Realtime view



Worksheet

Workflow HDR-Prostate Brachytherapy

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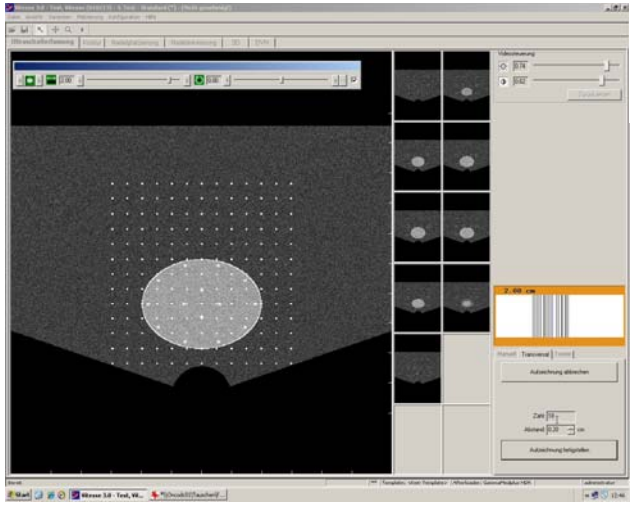
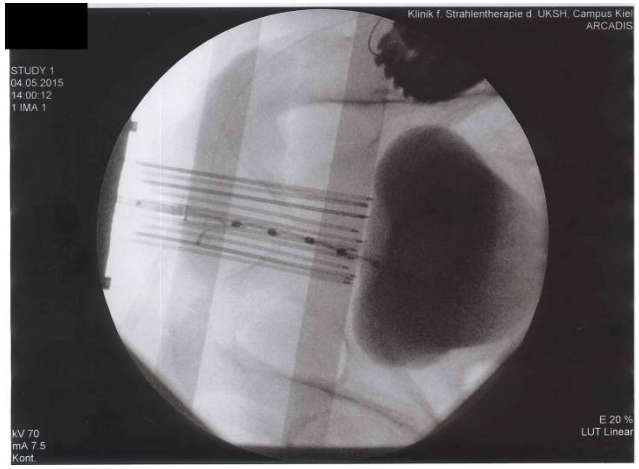
Patient setup → Implant → Image acquisition → Online needle detection → Contouring → Treatment planning → Export, Verification, Treatment



Ultrasound data acquisition

- Manual
- Transversal (autom.)
- Twister (autom.)



C-arm imaging for reporting only

Workflow HDR-Prostate Brachytherapy

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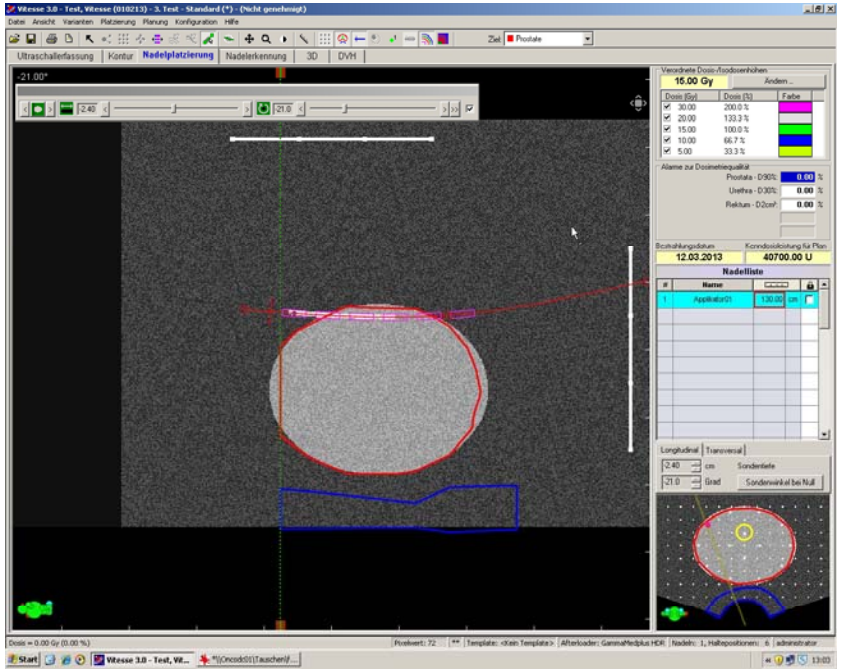
Patient setup → Implant → Image acquisition → **Online needle detection** → Contouring → Treatment planning → Export, Verification, Treatment



- 3D needle detection
- Definition of dwell positions

Workflow HDR-Prostate Brachytherapy

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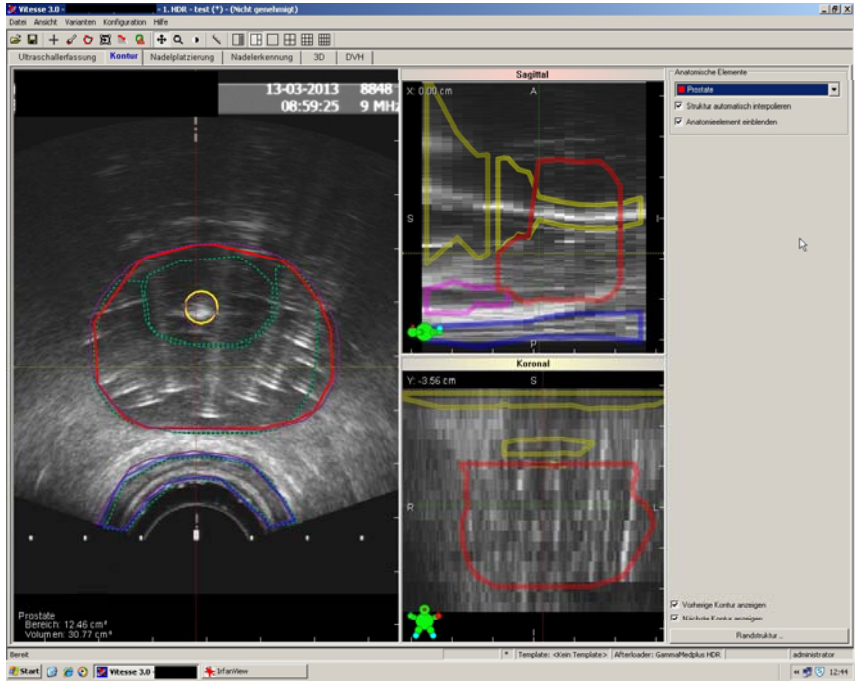
Patient setup → Implant → Image acquisition → Online needle detection → **Contouring** → Treatment planning → Export, Verification, Treatment

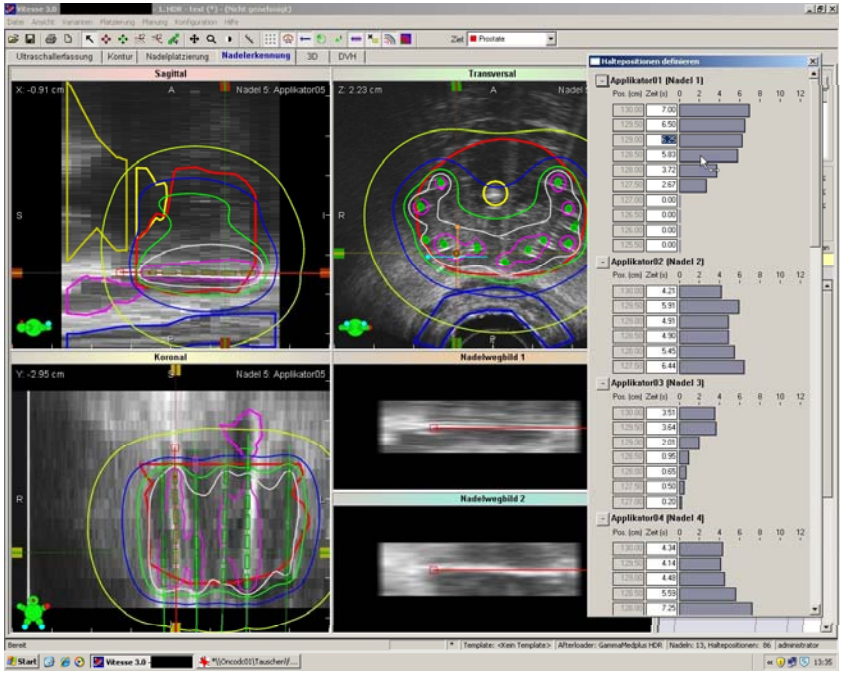


- Delineation of organs

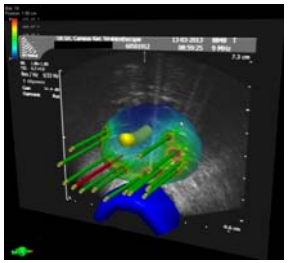
Workflow HDR-Prostate Brachytherapy

Christian-Albrechts-Universität zu Kiel

Patient setup → Implant → Image acquisition → Online needle detection → Contouring → **Treatment planning** → Export, Verification, Treatment



- Manual adjustments of dwell times
- Dose shaping tools
- Adaption of needle curvature



Workflow HDR-Prostate Brachytherapy

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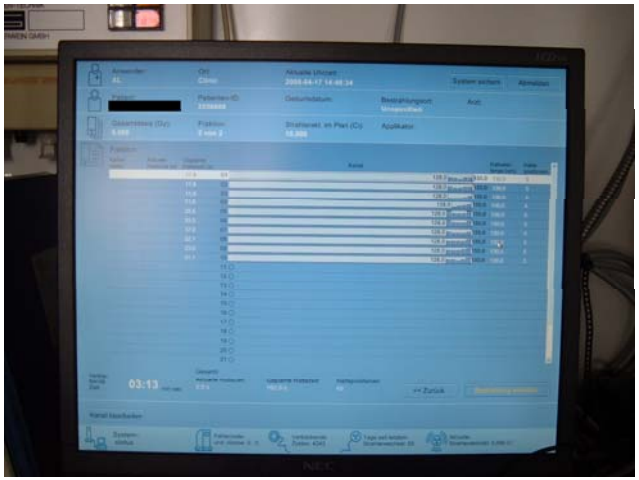
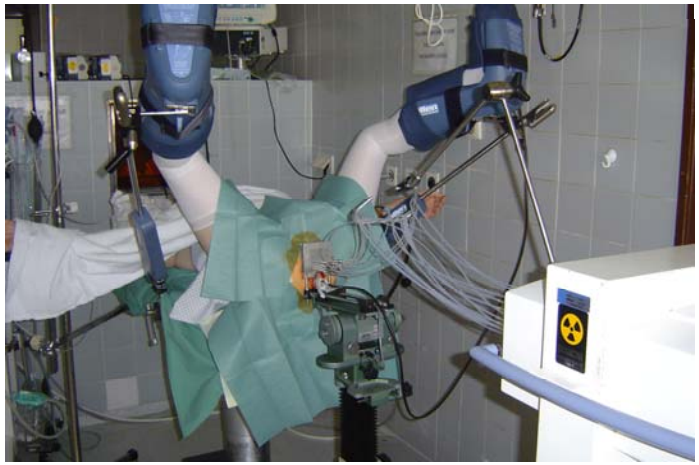
Patient setup → Implant → Image acquisition → Online needle detection → Contouring → Treatment planning → Export, Verification, Treatment



iX control console



Treatment

In-vivo dosimetry

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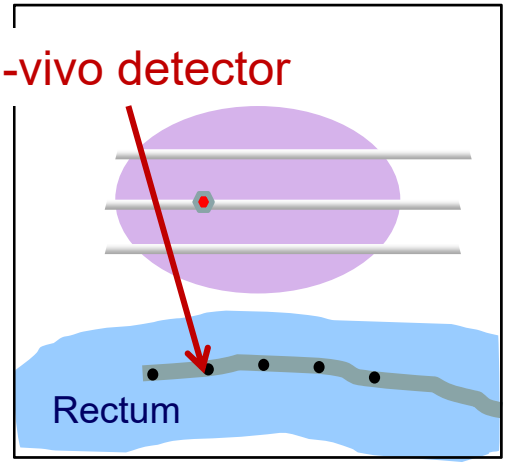
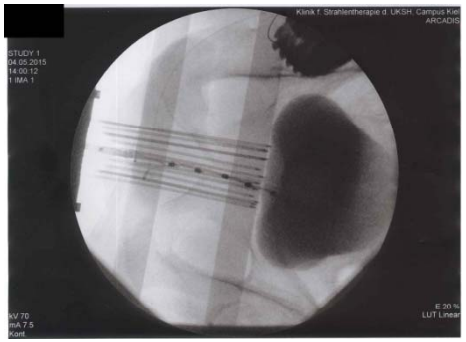
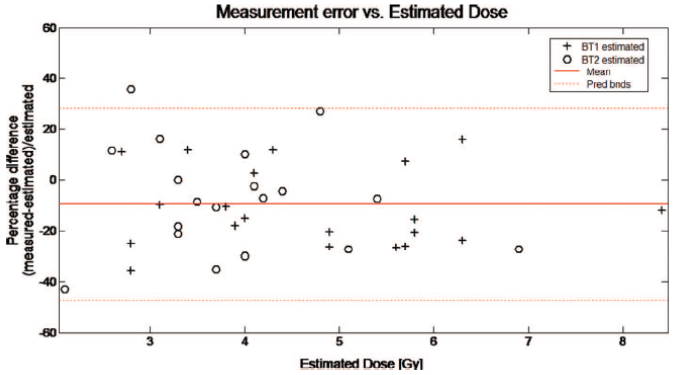


Sagittal view





K. Tanderup et al. 2013

Is rectal in-vivo dosimetry useless?

No, but quite limited.

In-vivo dosimetry

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The missing puzzle piece in brachytherapy…

In vivo dosimetry in brachytherapy

Kari Tanderup[a)]
Department of Oncology, Aarhus University Hospital, Aarhus 8000, Denmark and Department of Clinical Medicine, Aarhus University, Aarhus 8000, Denmark

Sam Beddar
Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030

Claus E. Andersen and Gustavo Kertzscher
Center of Nuclear Technologies, Technical University of Denmark, Roskilde 4000, Denmark

Joanna E. Cygler
Department of Physics, The Ottawa Hospital Cancer Centre, Ottawa, Ontario K1H 8L6, Canada

Med. Phys. 40 (7), July 2013

=> New approaches are under development

New approaches in In-vivo dosimetry

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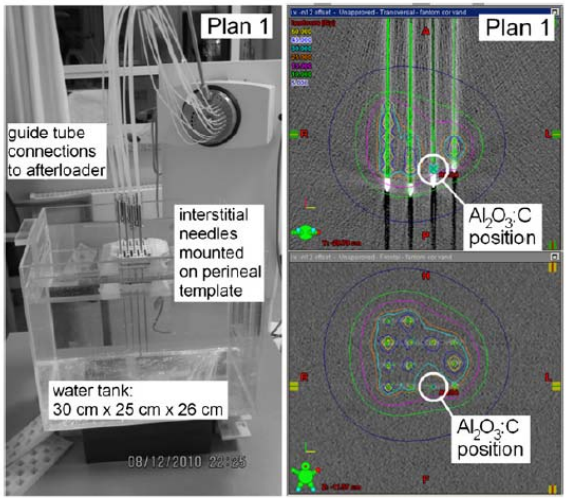
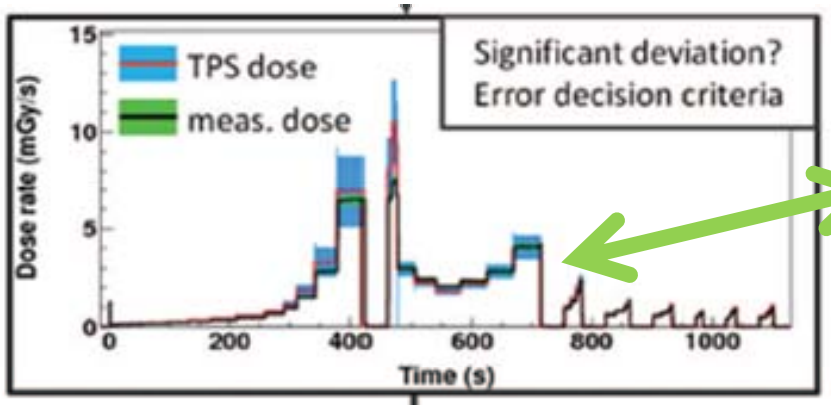


Fig. 1. Experimental setup (left) and a screen shot of the dose plan (right) for the plan 1 simulation. The circled cross-symbols (right), mark the position of the Al_2O_3:C crystal.

Kerztscher et. al. 2011



Dose fingerprint

- Applicator misplacements ≥ 5 mm were detected
- Many channel connection errors were detected (17 out of 20)

New approaches in In-vivo dosimetry

Christian-Albrechts-Universität zu Kiel

Radiotherapy and Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Real-time in vivo dosimetry in high dose rate prostate brachytherapy

Josh Mason [a,*], Arielle Mamo [b], Bashar Al-Qaisieh [a], Ann M. Henry [a,c], Peter Bownes [a]

[a] Leeds Cancer Centre, UK; [b] Sir Anthony Mamo Oncology Centre, San Gwann, Malta; and [c] University of Leeds, UK

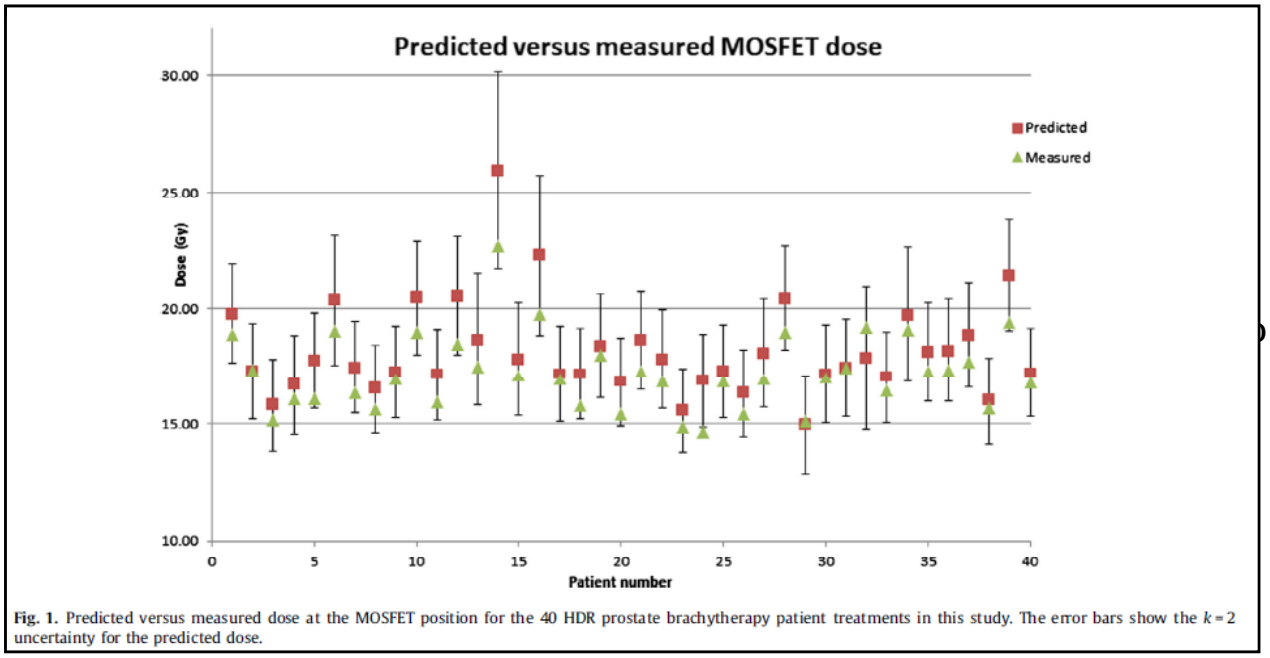


Fig. 1. Predicted versus measured dose at the MOSFET position for the 40 HDR prostate brachytherapy patient treatments in this study. The error bars show the $k = 2$ uncertainty for the predicted dose.

Use of spacers

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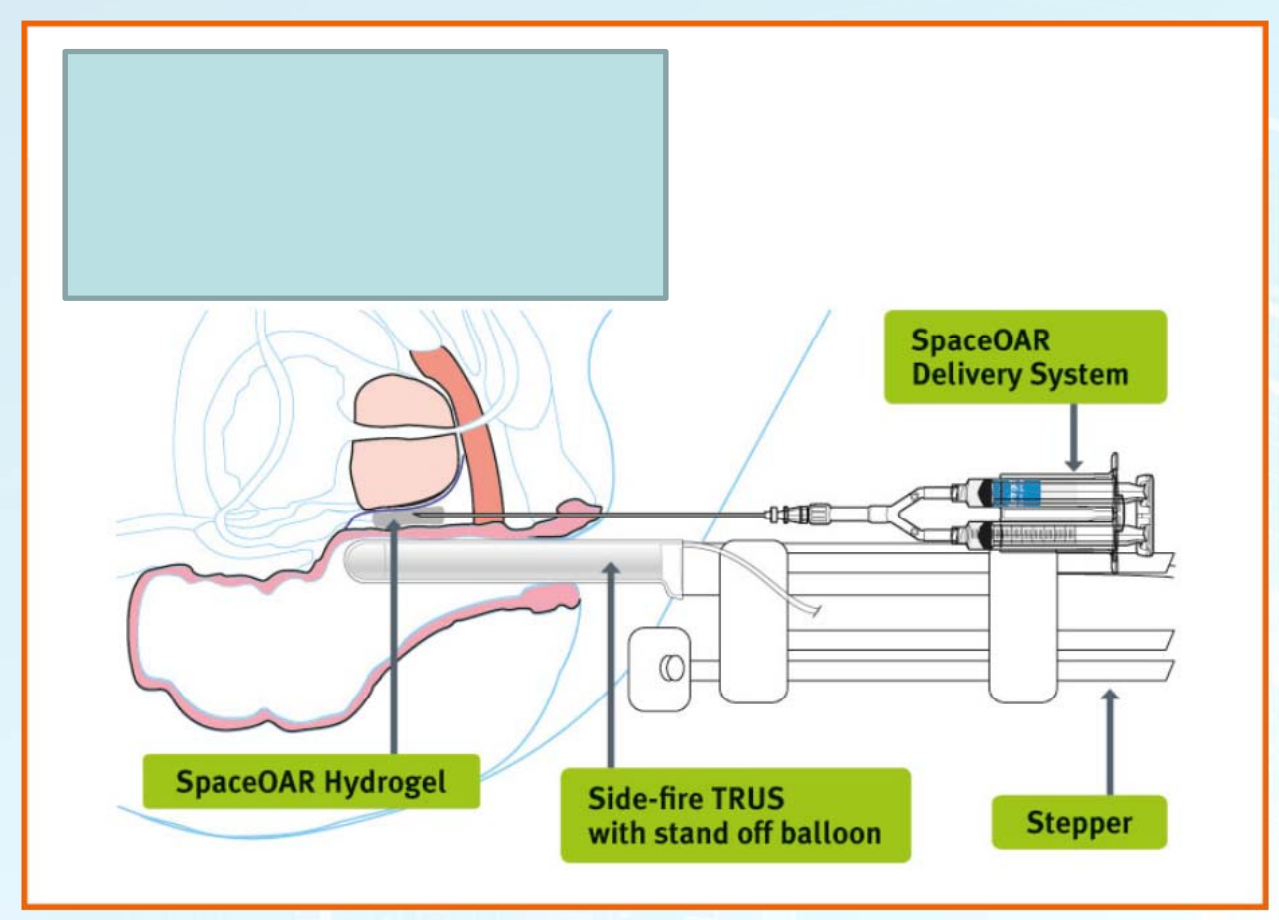

Use of spacers

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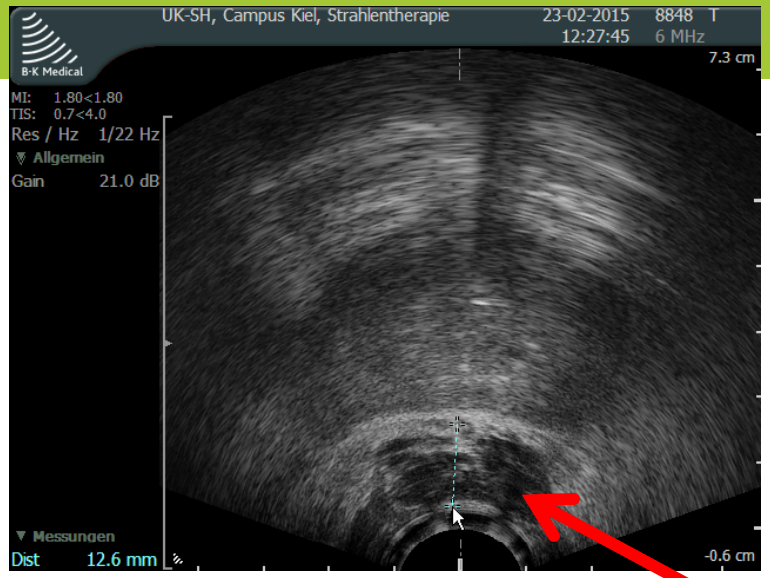
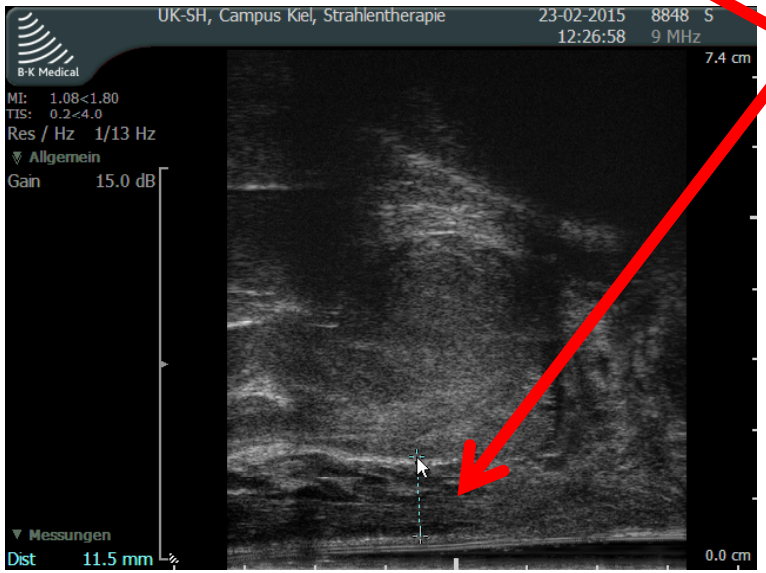
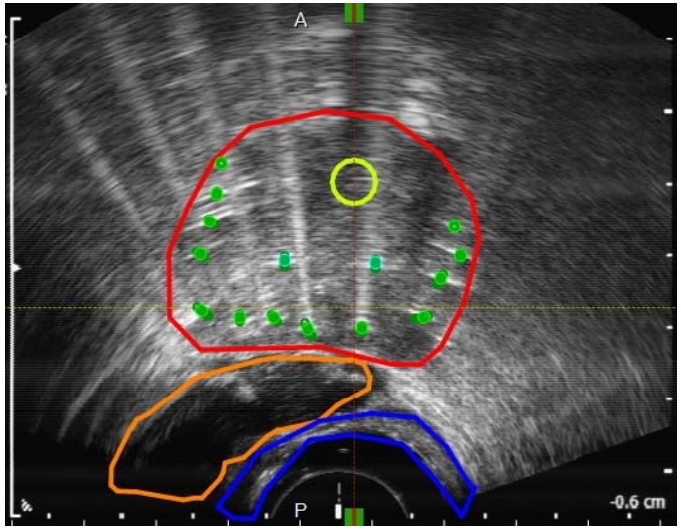




Spacer gel



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Thank you for your attention!

Prostate Brachytherapy Course

“CTV”

C. Salembier

Prostate Brachytherapy Course

"CTV"

C. Salembier

Department of Radiotherapy-Oncology
Europe Hospitals – Brussels - Belgium

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

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

ICRU

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

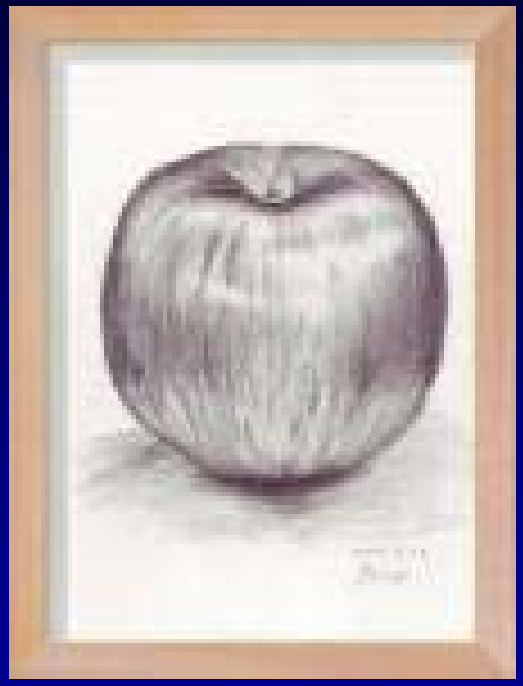
Prostate + 0 mm = 18/49

Prostate + margin = 31/49

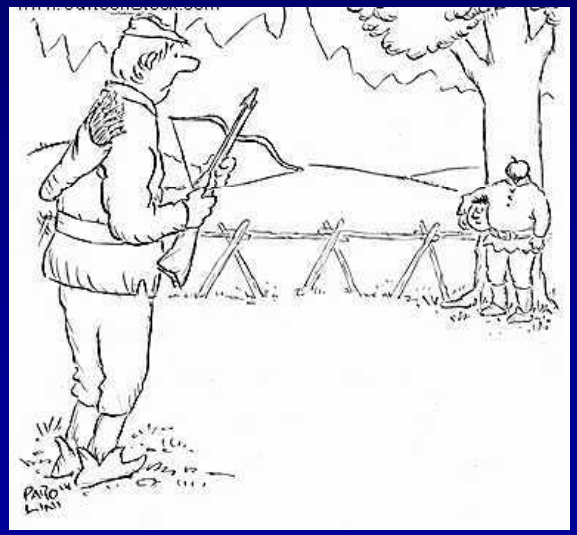
base :	**0 mm = 13**
	3 – 5 mm = 25
	> 5mm = 5
midgland:	**0 mm= 13**
	3 – 5 mm = 28
	> 5 mm = 0
apex :	**0 mm = 13**
	3 – 5 mm = 27
	> 5 mm = 1

peri-prostatic extension ?

CTV = ?



subclinical disease ?

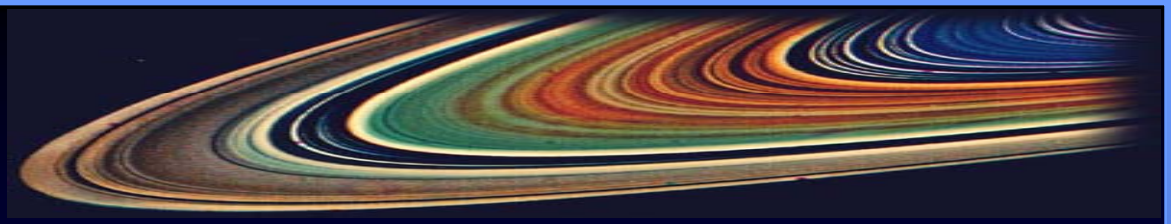


uncertainties in placement ?

PTV = ?

change of position ?

Margins ? ! ?



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

But margins for ……

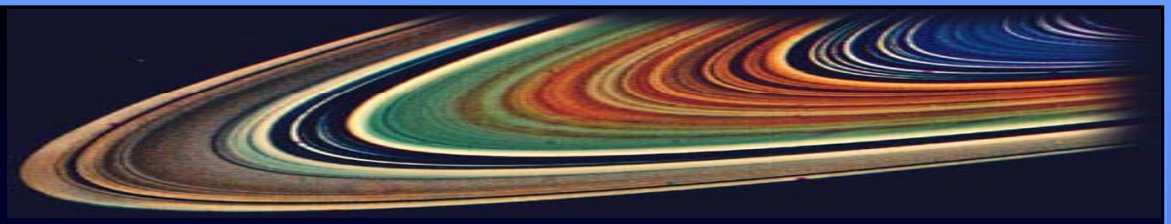
- ***microscopic spread ?***
- ***peri-prostatic extension ?***
- ***subclinical disease ?***

Δ CTV definition

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

Δ PTV definition

Margins ? ! ?

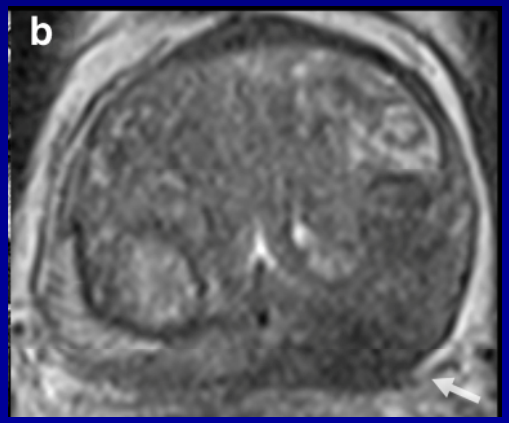


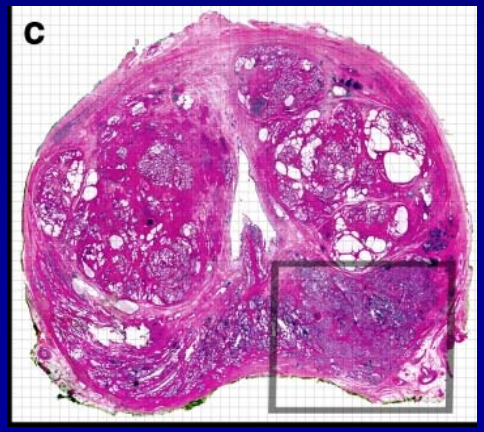
As shown, most centers consider a margin around the drawn prostatic contour for treatment planning.

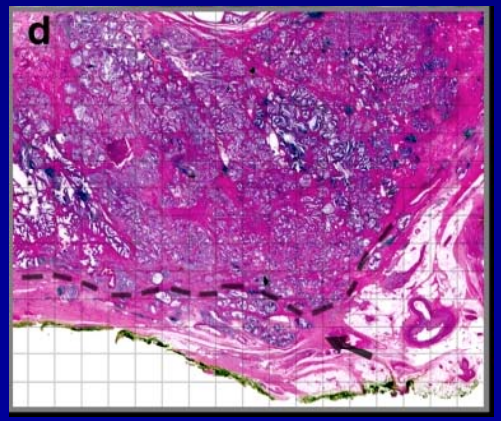
But margins for ……

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

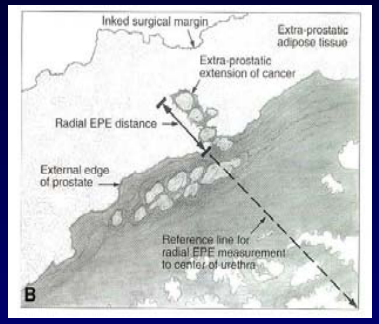
Δ CTV definition





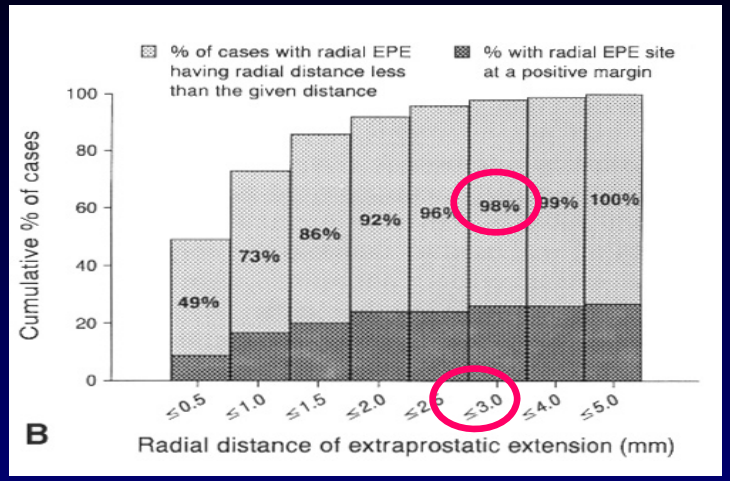


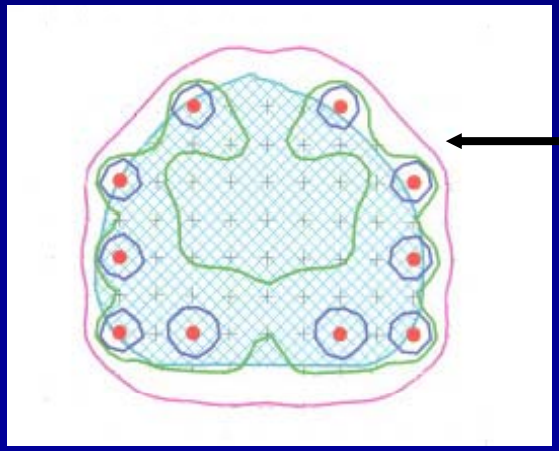
Extra-prostatic disease:



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

Davis et al. Cancer 85(12) 1999



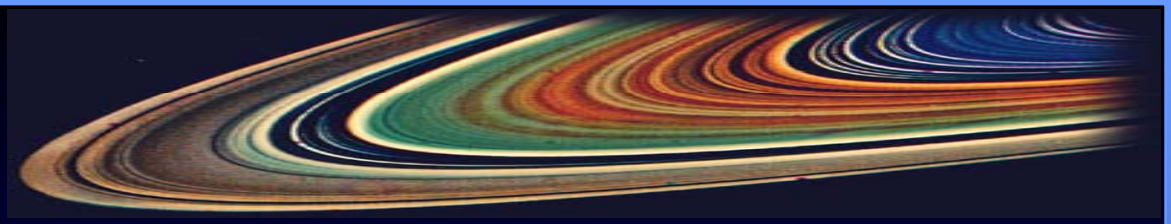


Extraprostatic disease

3 mm margins :

critical to success

Margins ? ! ?



So margins for ……

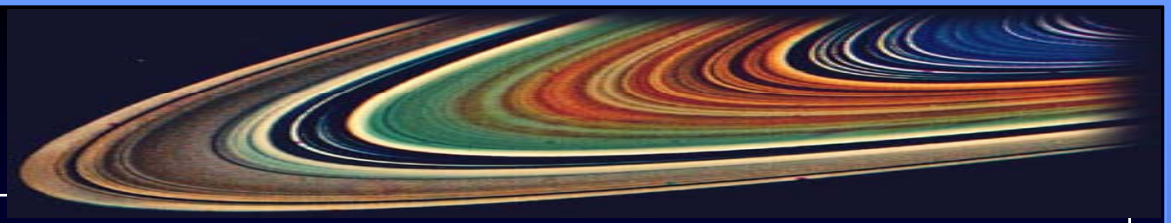
- *microscopic spread ?*
- *peri-prostatic extension ?*
- *subclinical disease ?*

Δ CTV definition

<u>ONE DEFINITION:</u>

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 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]

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 =

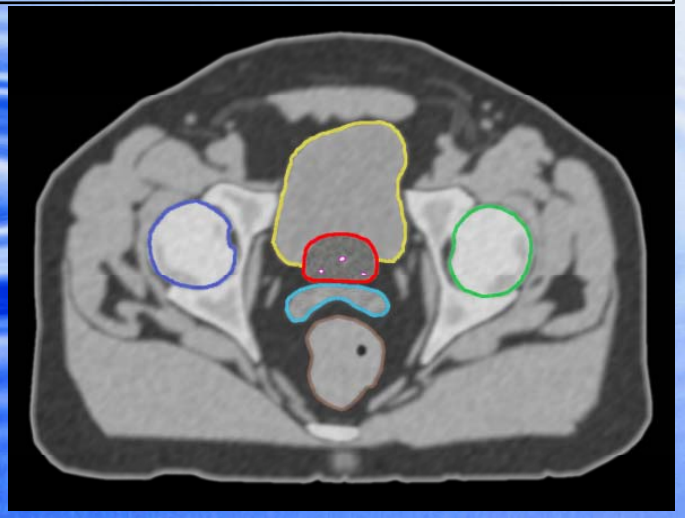
DELINEATION

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

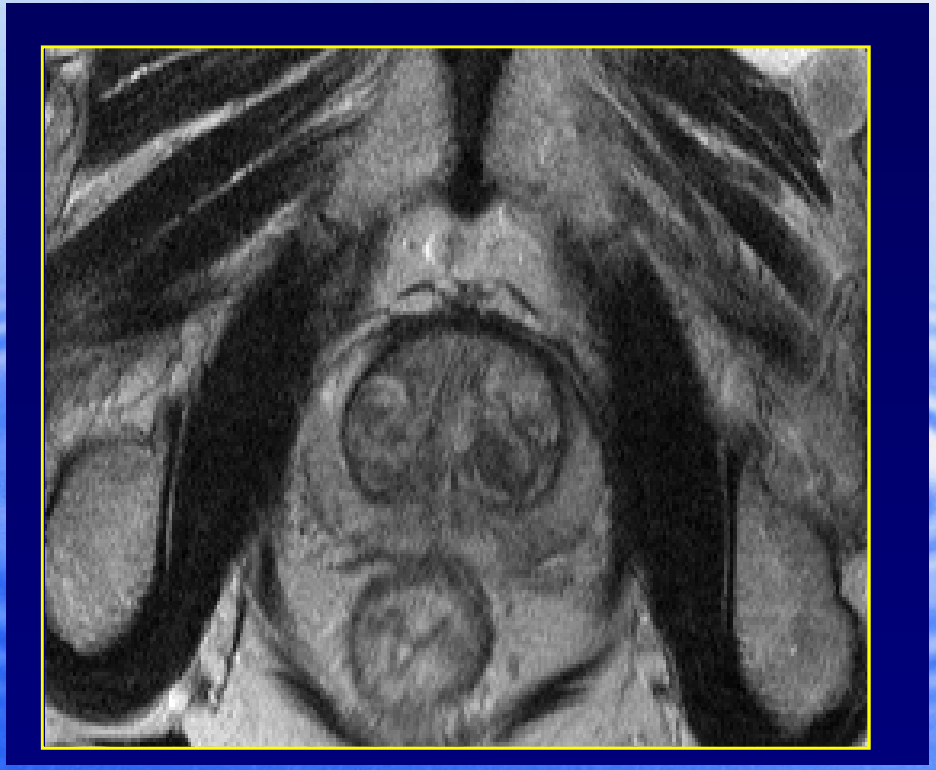


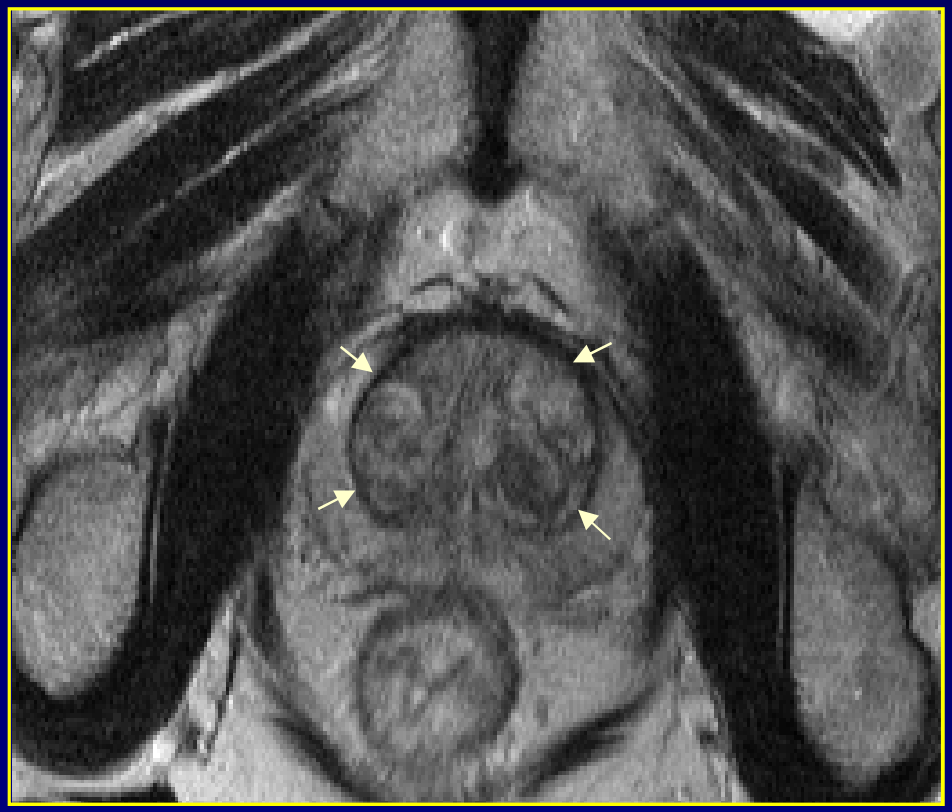

Reality ?

MRI:

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

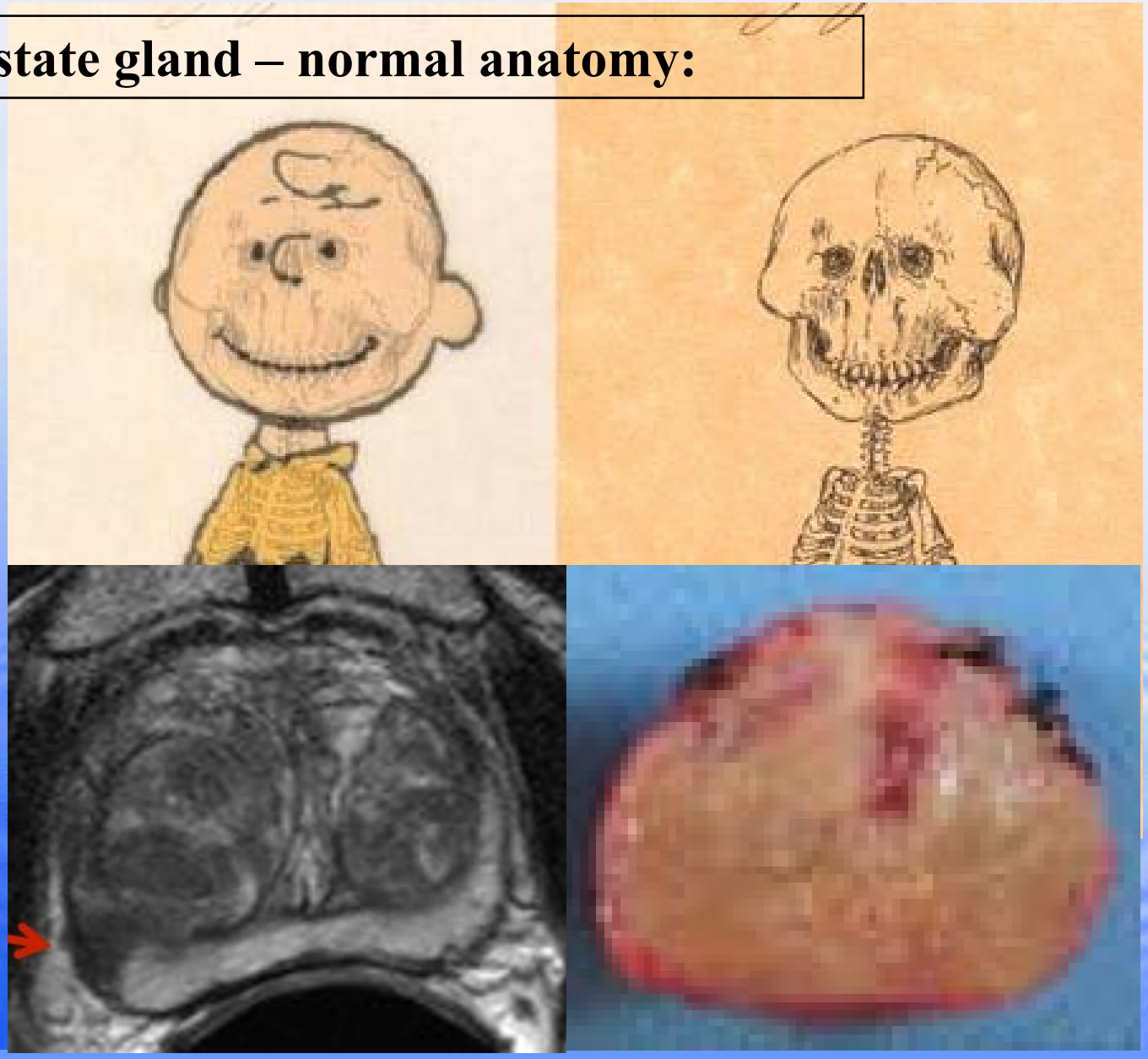
→ more detailed than CT

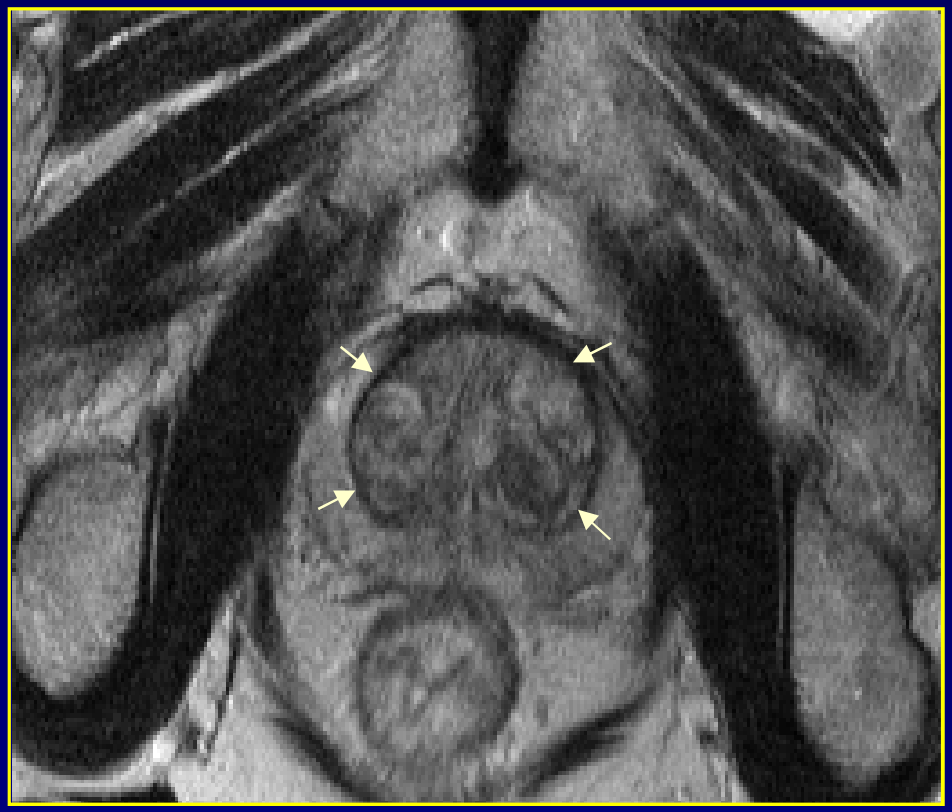




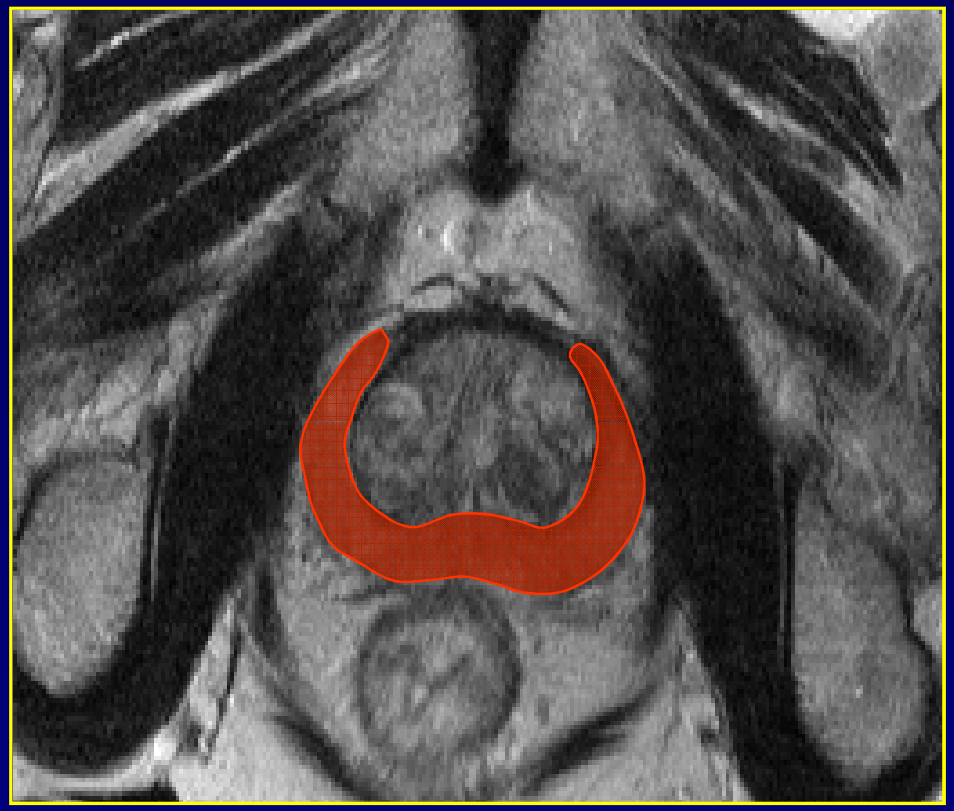
Central Zone =
Surgical Pseudocapsule

Prostate gland – normal anatomy:

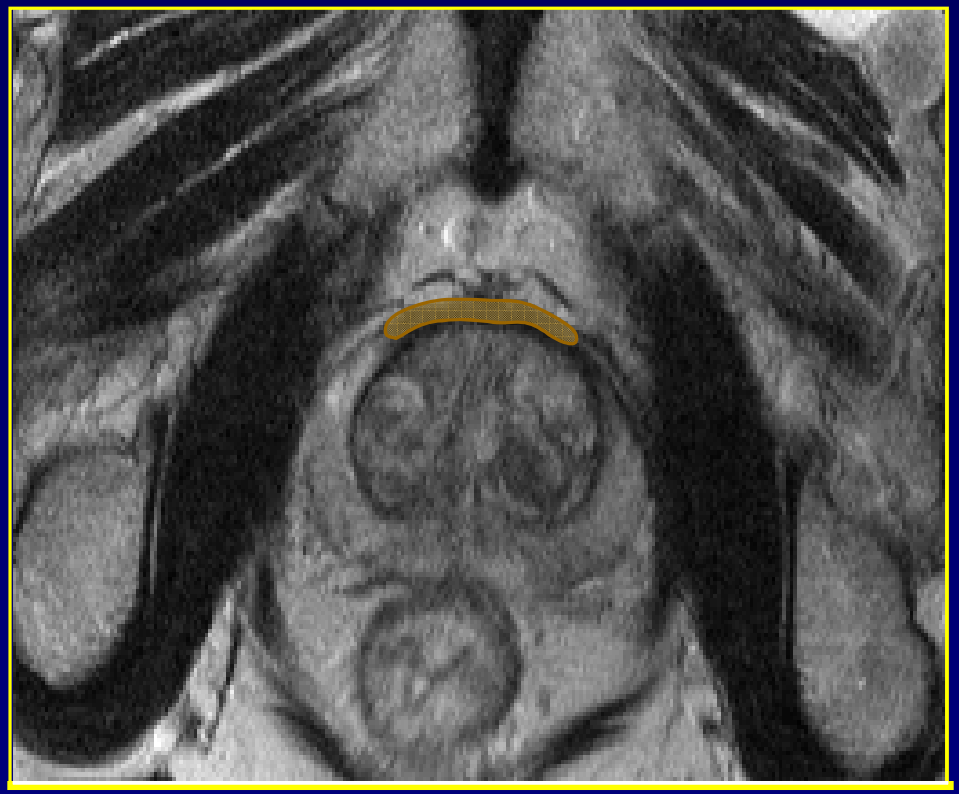




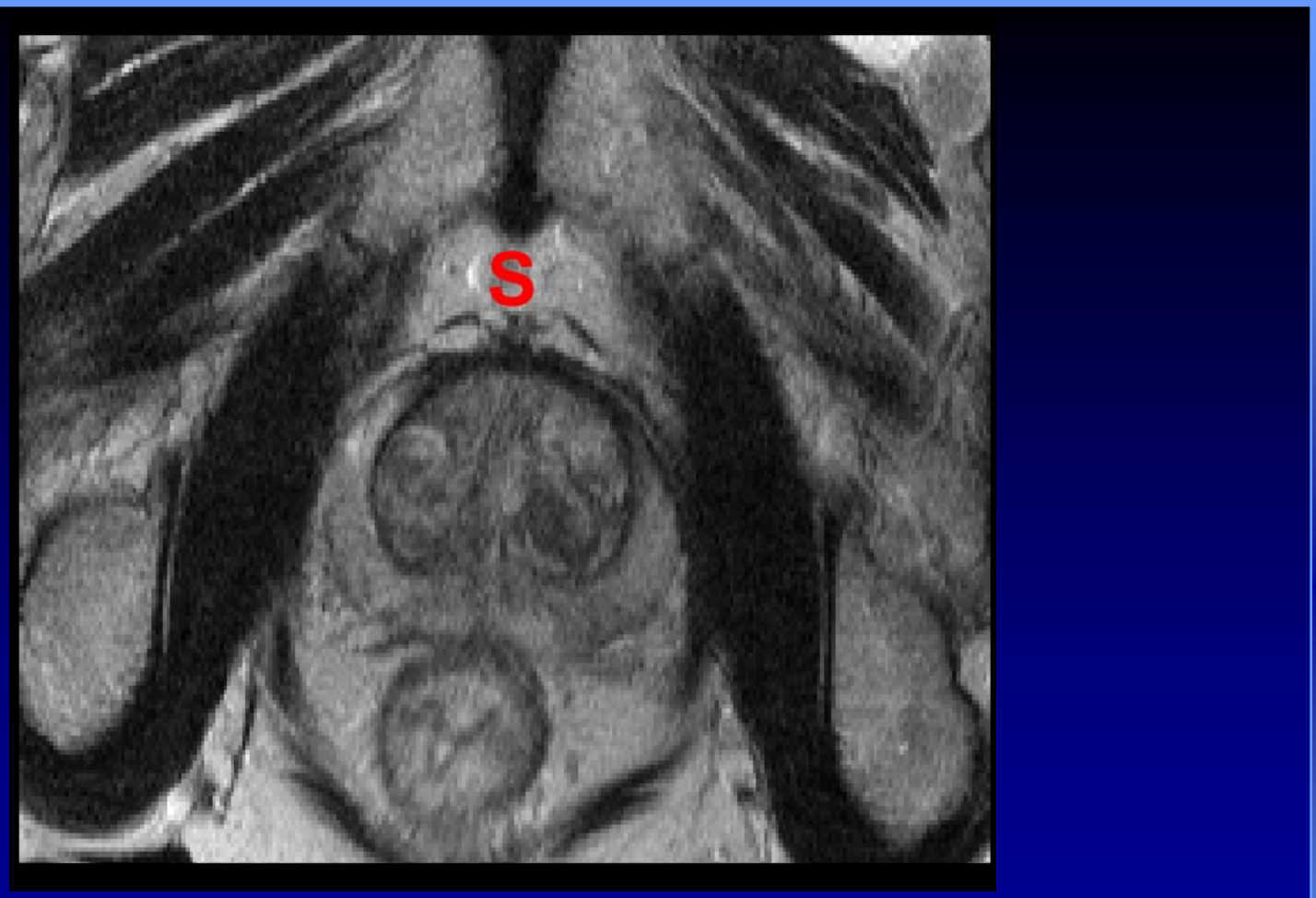
Central Zone =
Surgical Pseudocapsule



Peripheral Zone



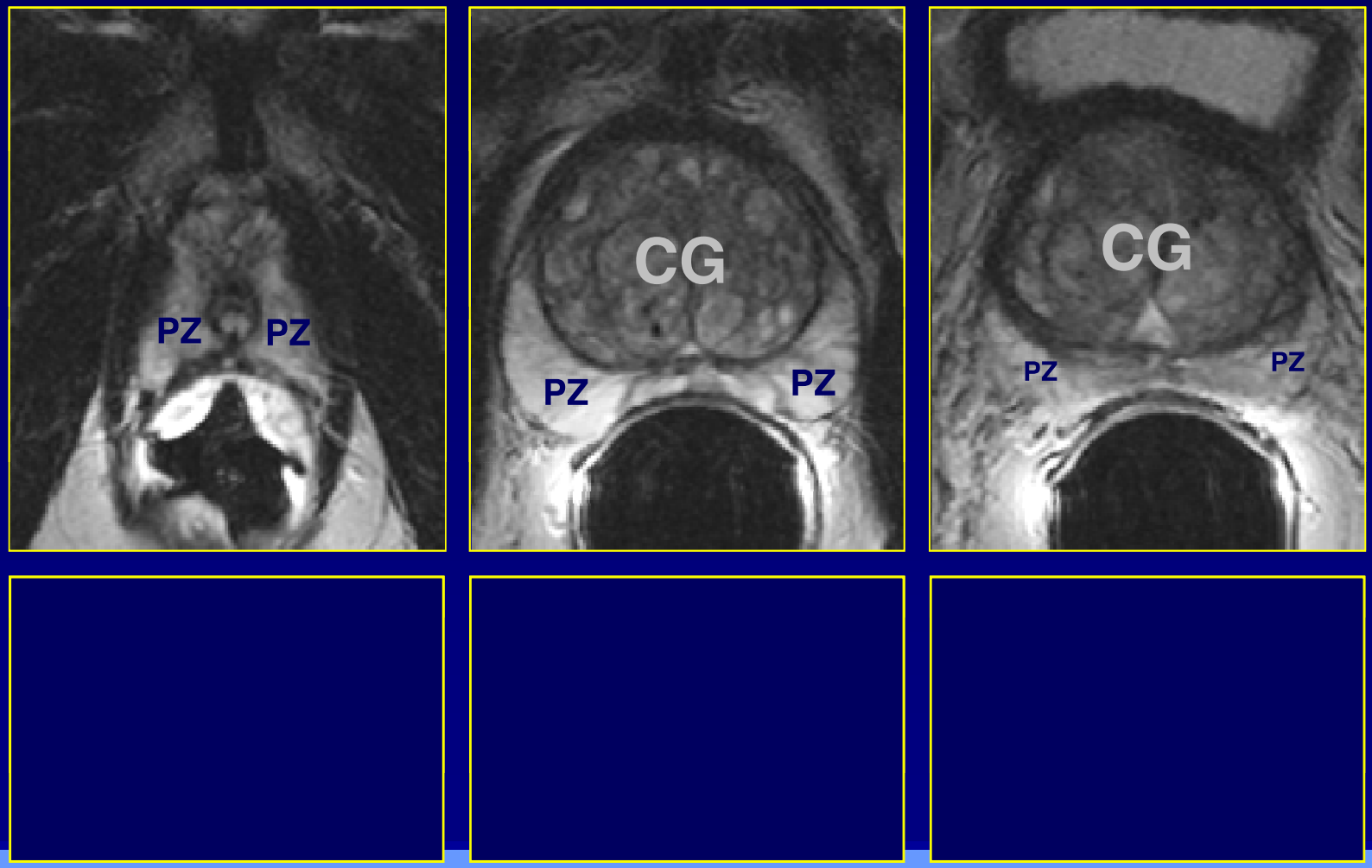
Anterior
Fibromuscular
Stroma

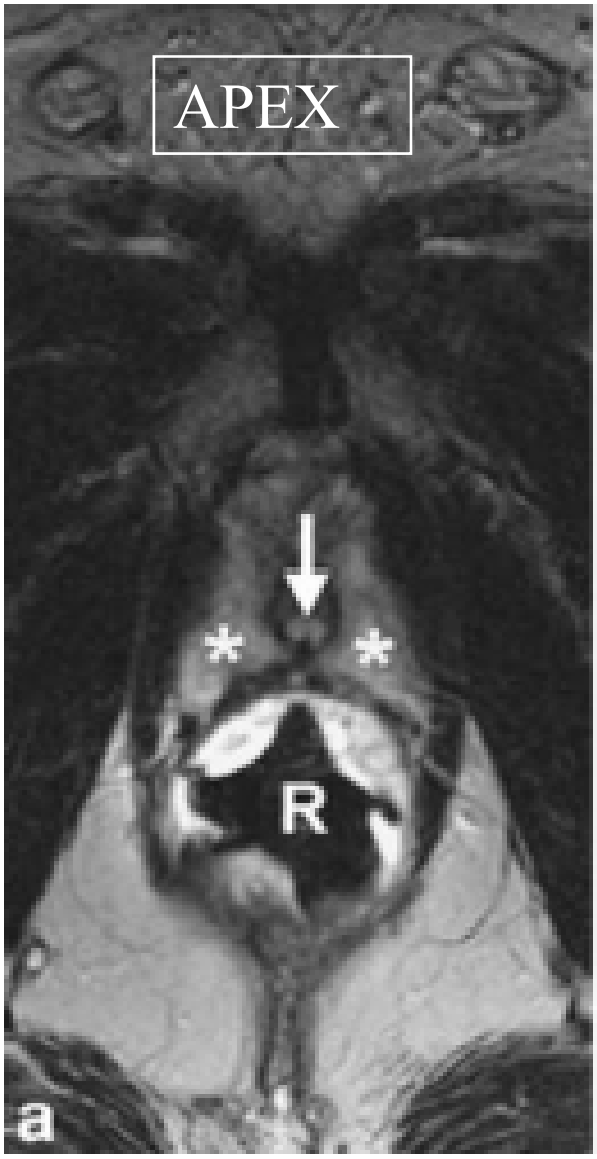


Santorini Plexus

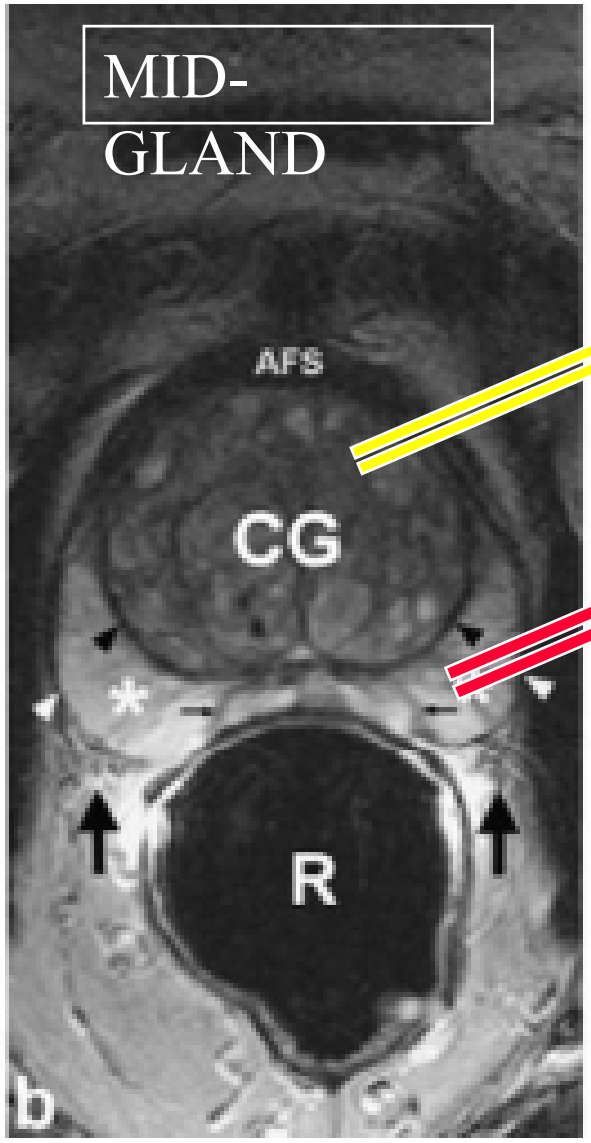
Anatomy

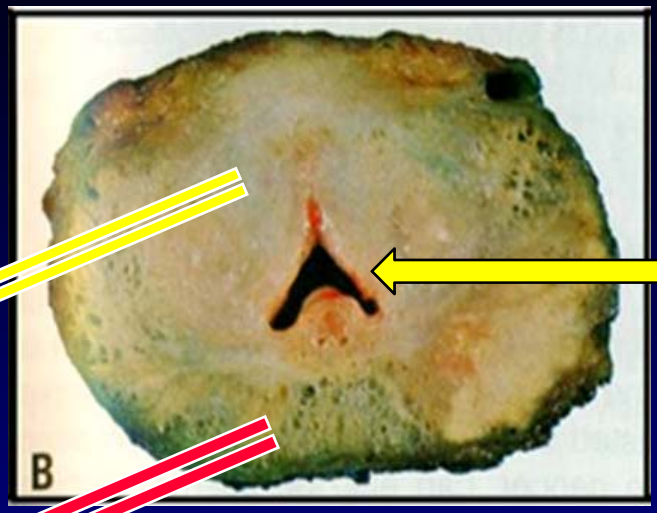
Prostate

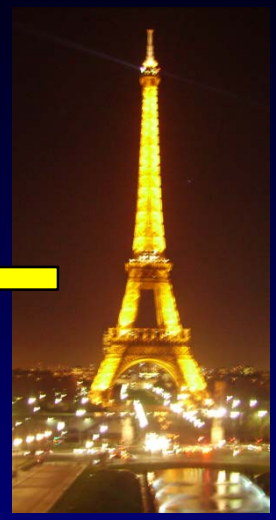




- Distal part of the prostatic urethra
- High signal-intensity peripheral zone tissue



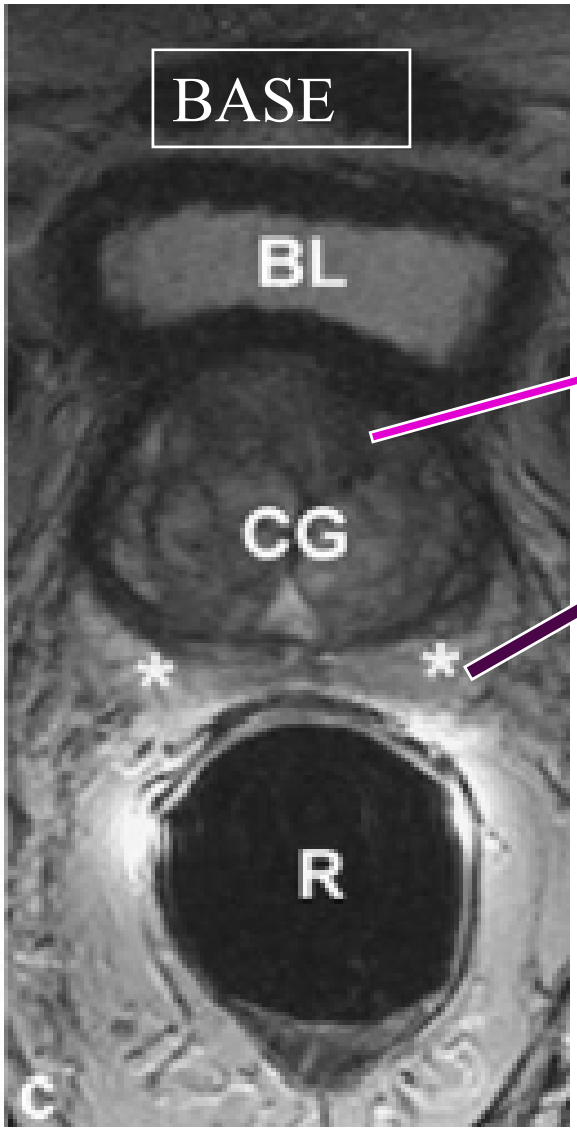


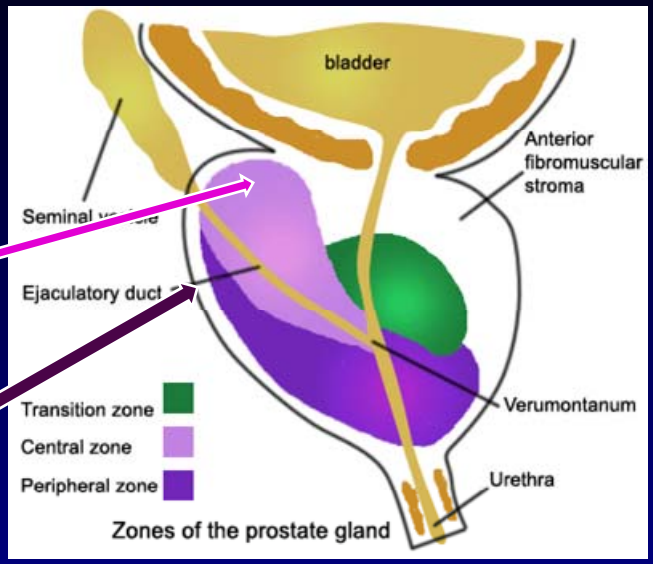


- Mixed signal-intensity central gland

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

- (anterior fibromuscular stroma)
- (neurovascular bundles)

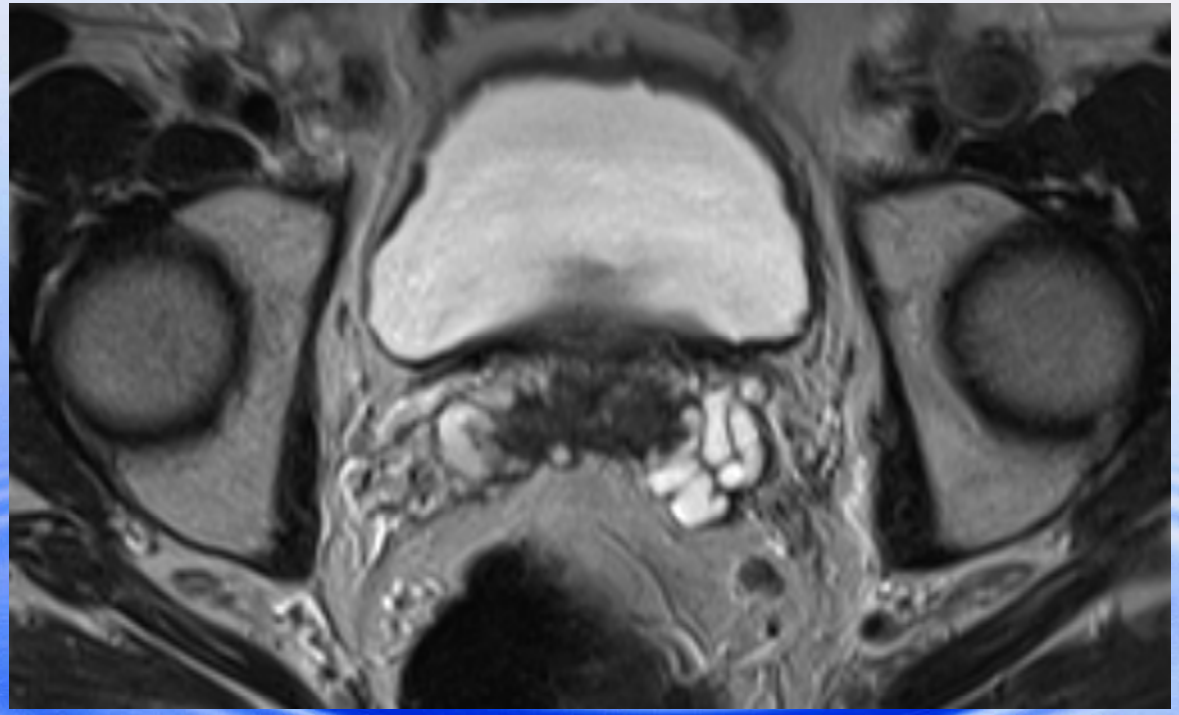


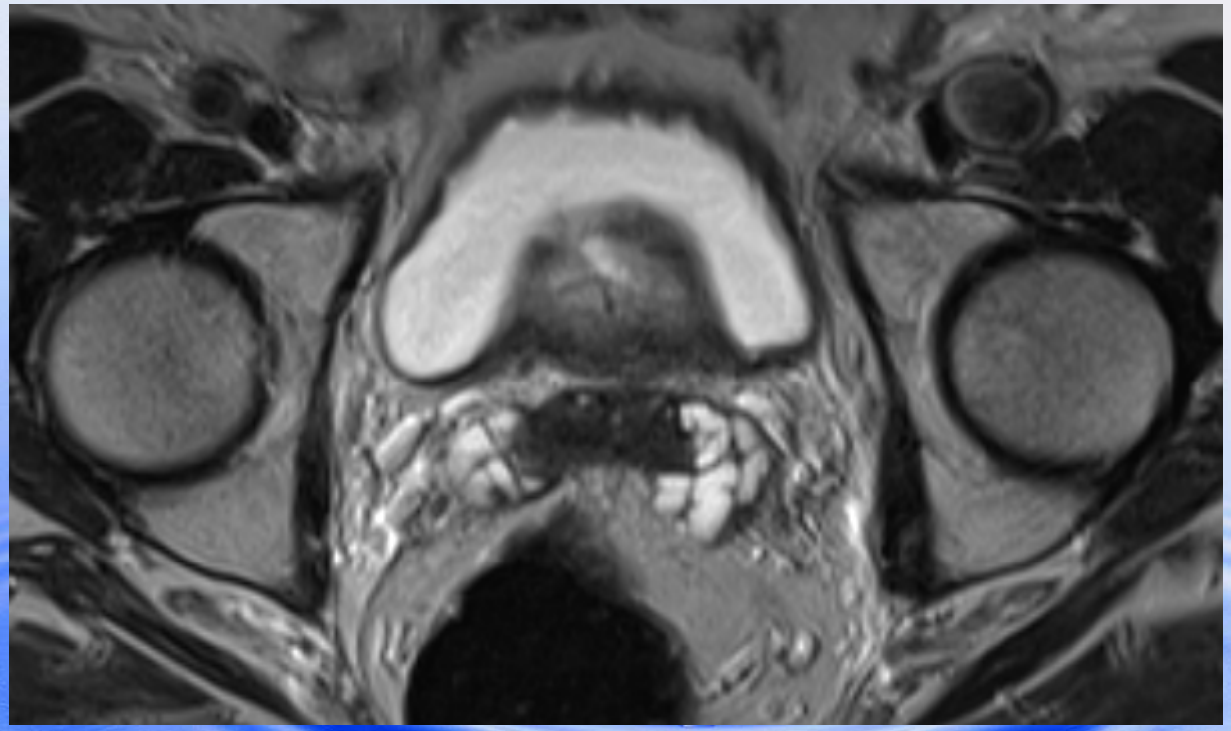


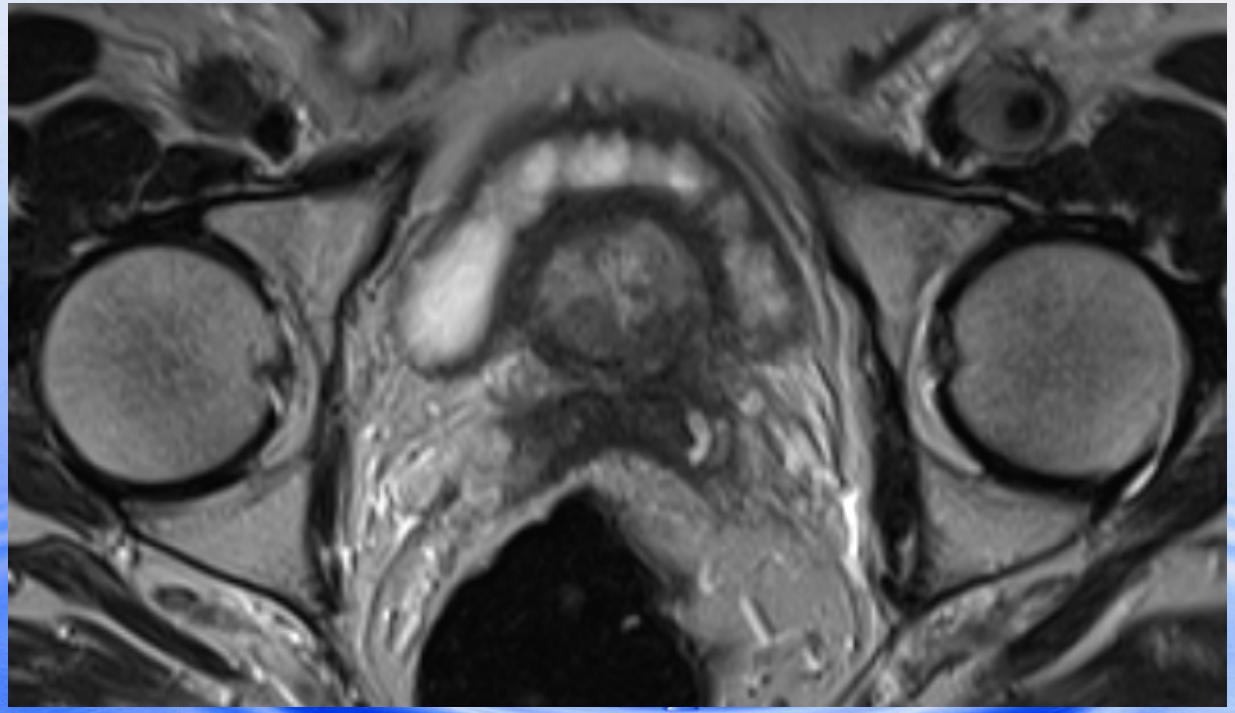
- Almost entirely composed of mixed signal-intensity central gland
- Narrow posterior band of high signal-intensity peripheral zone tissue

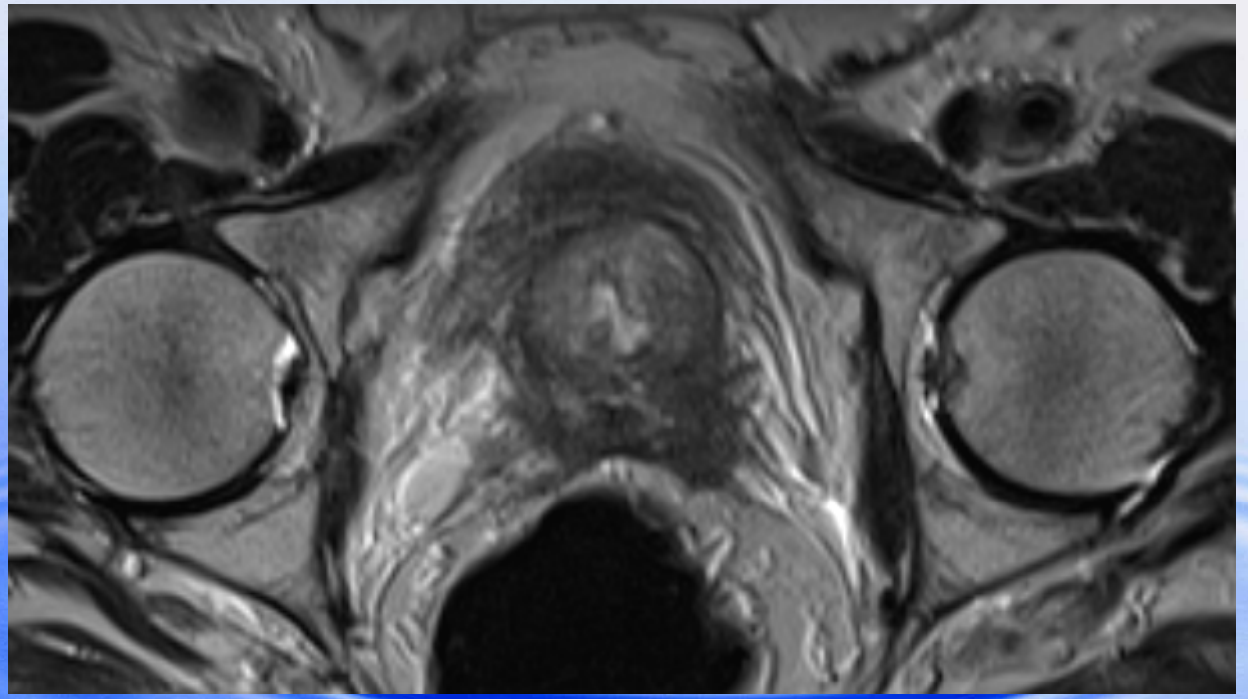
T3-

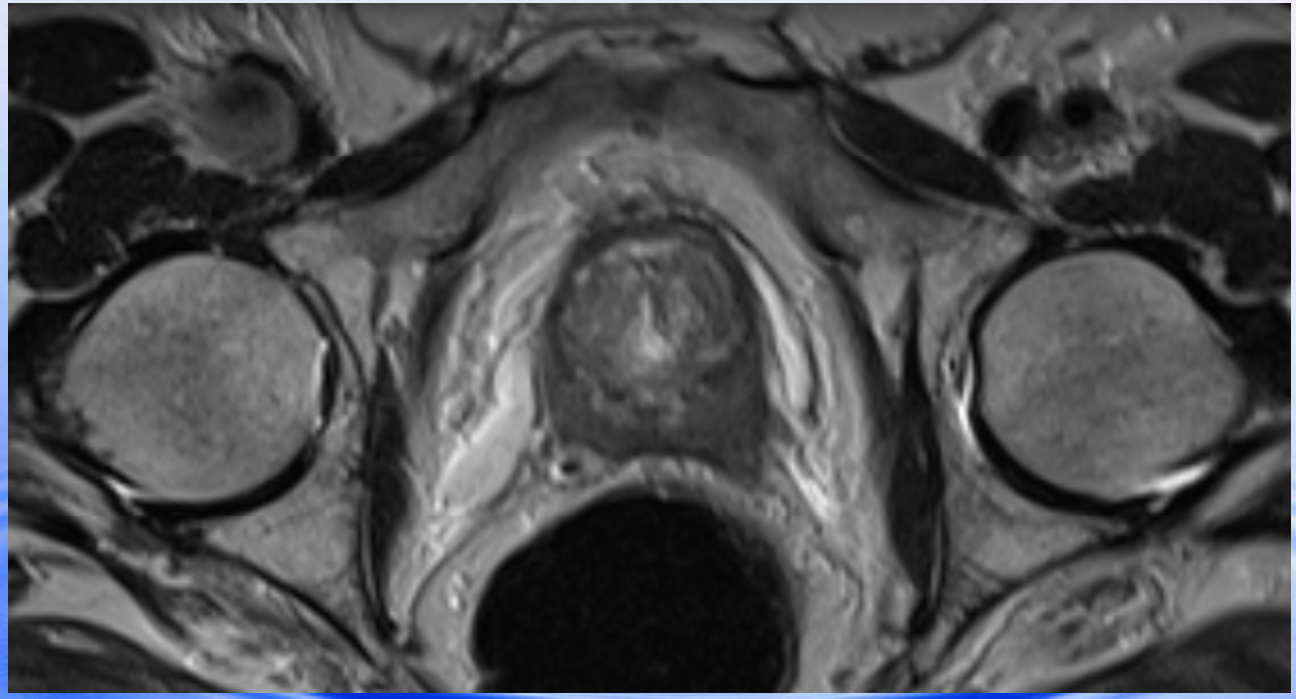
disease:

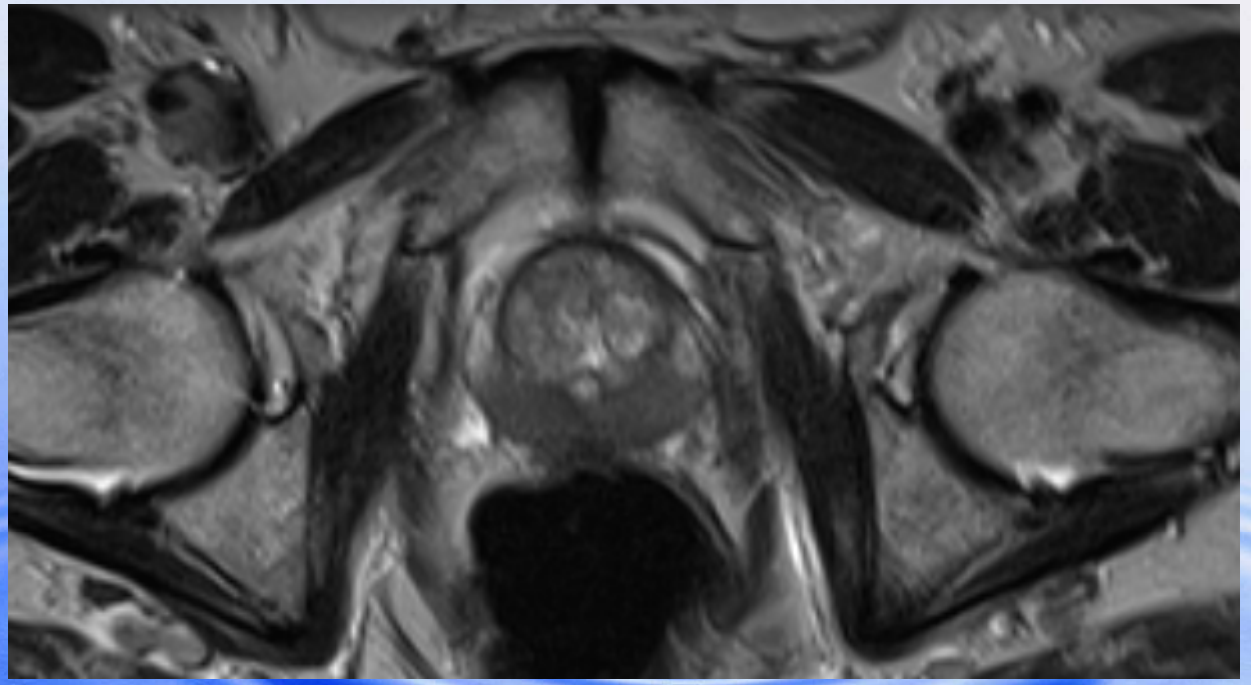


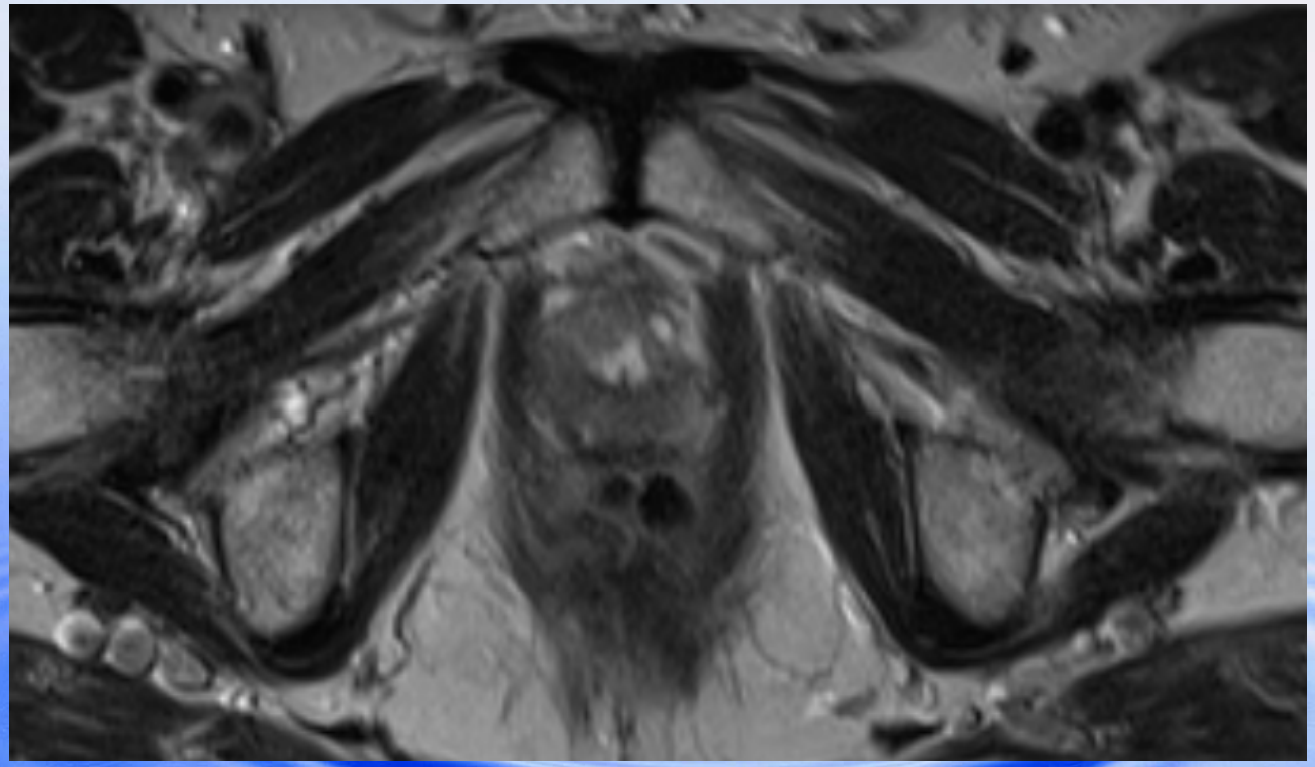










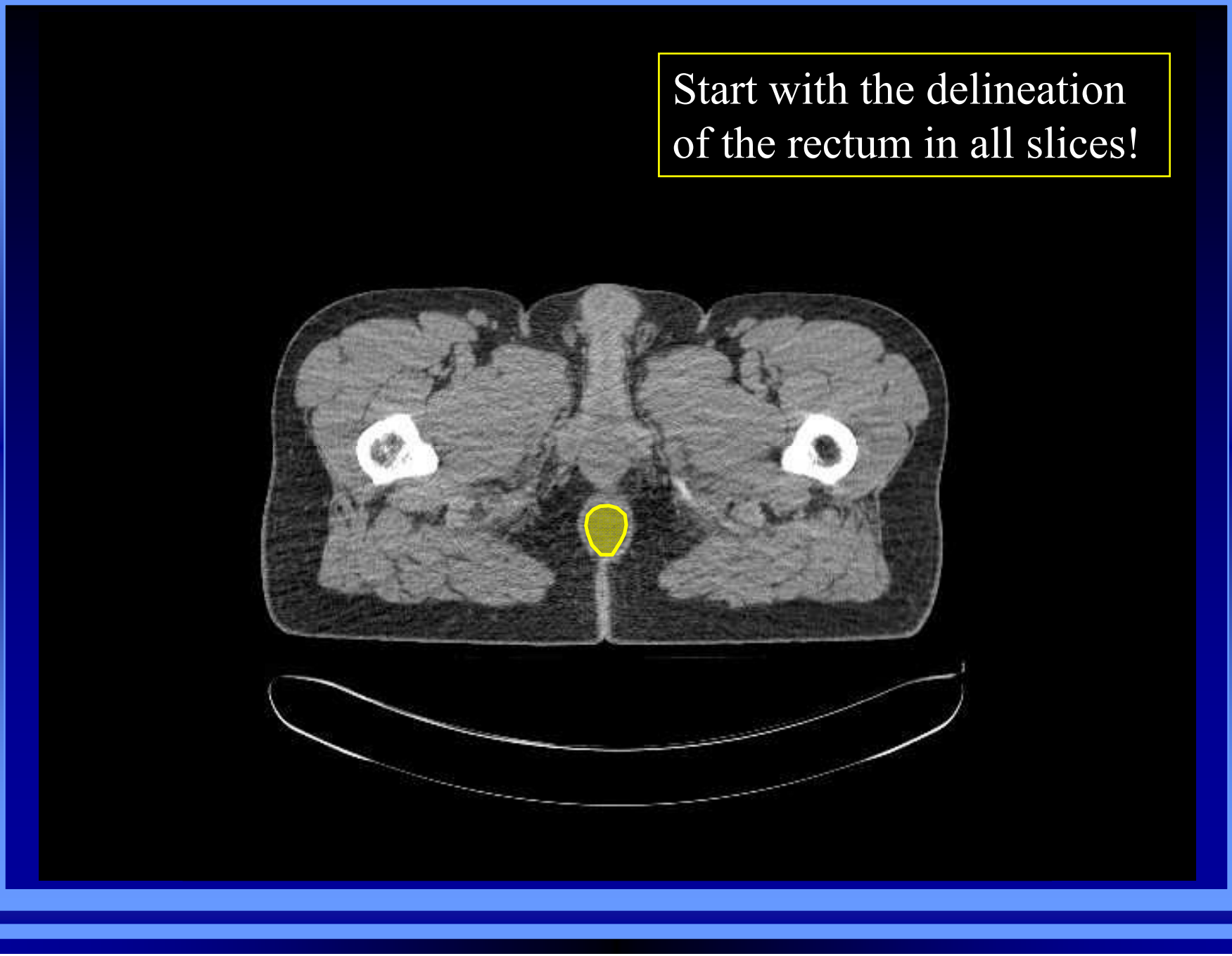


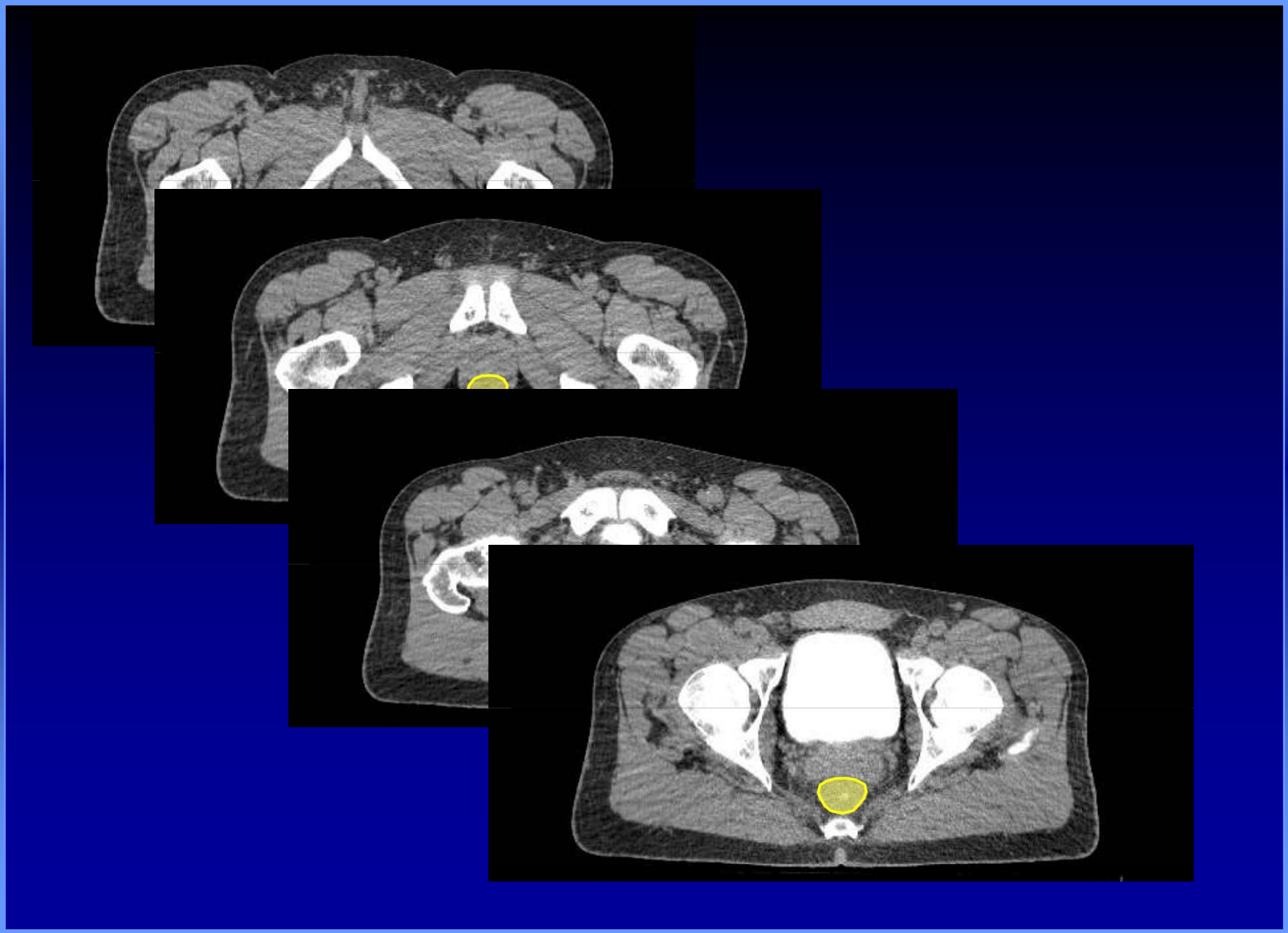
I have no MRI !!!

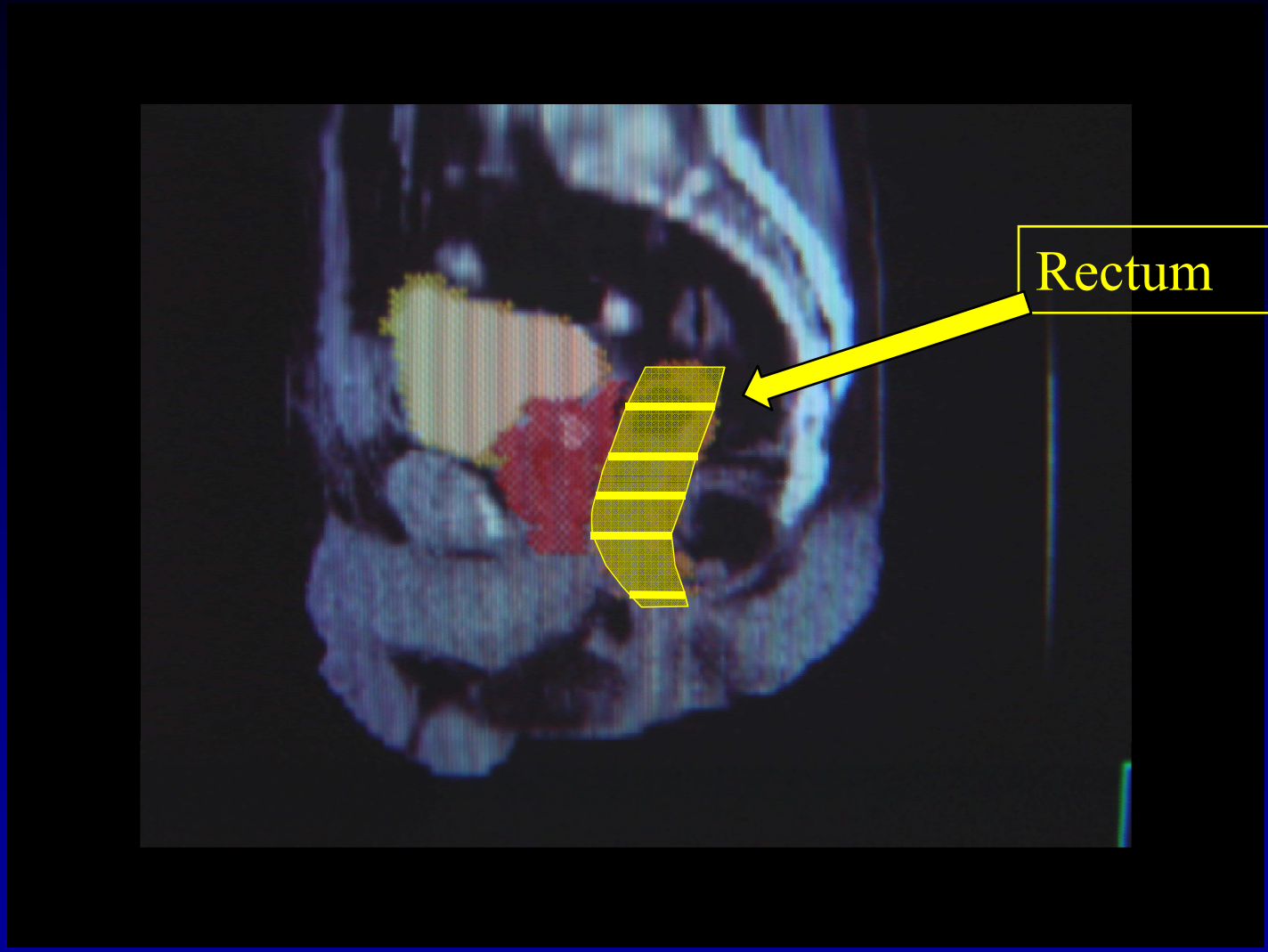
Delineation on CT-scan

Delineation on CT-scan:

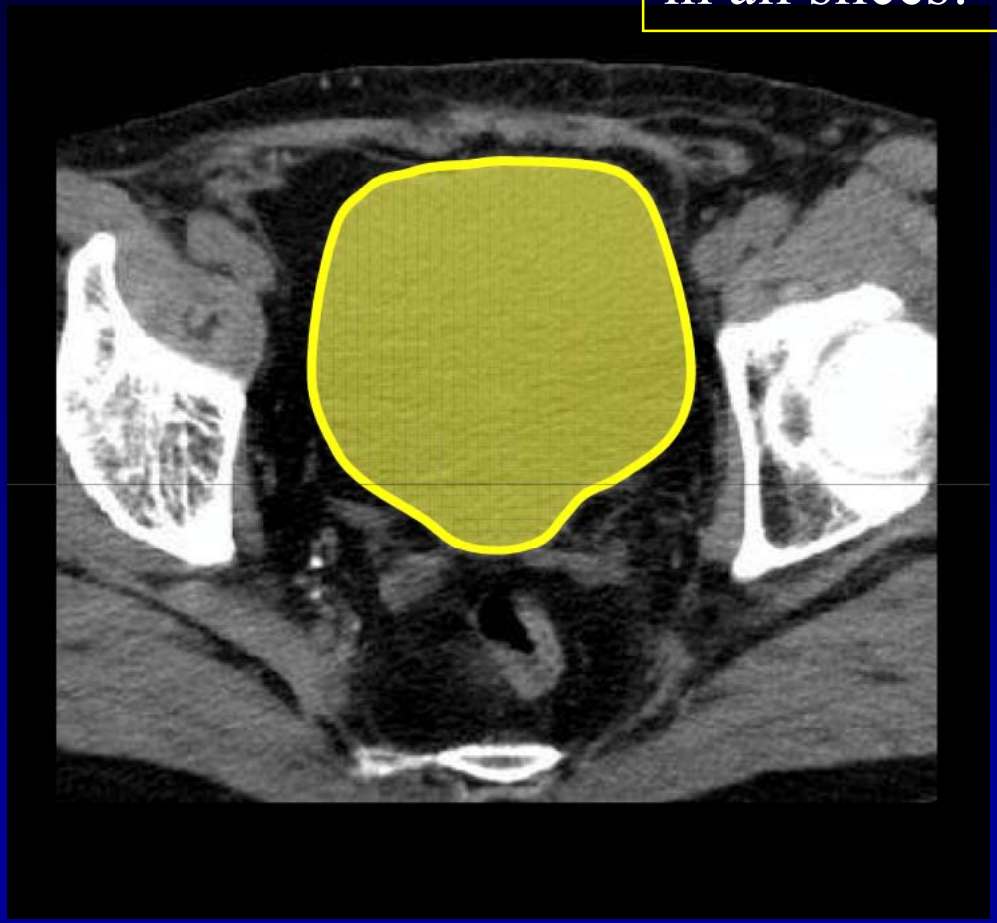
where to start ?


Start with the delineation
of the rectum in all slices!




Rectum

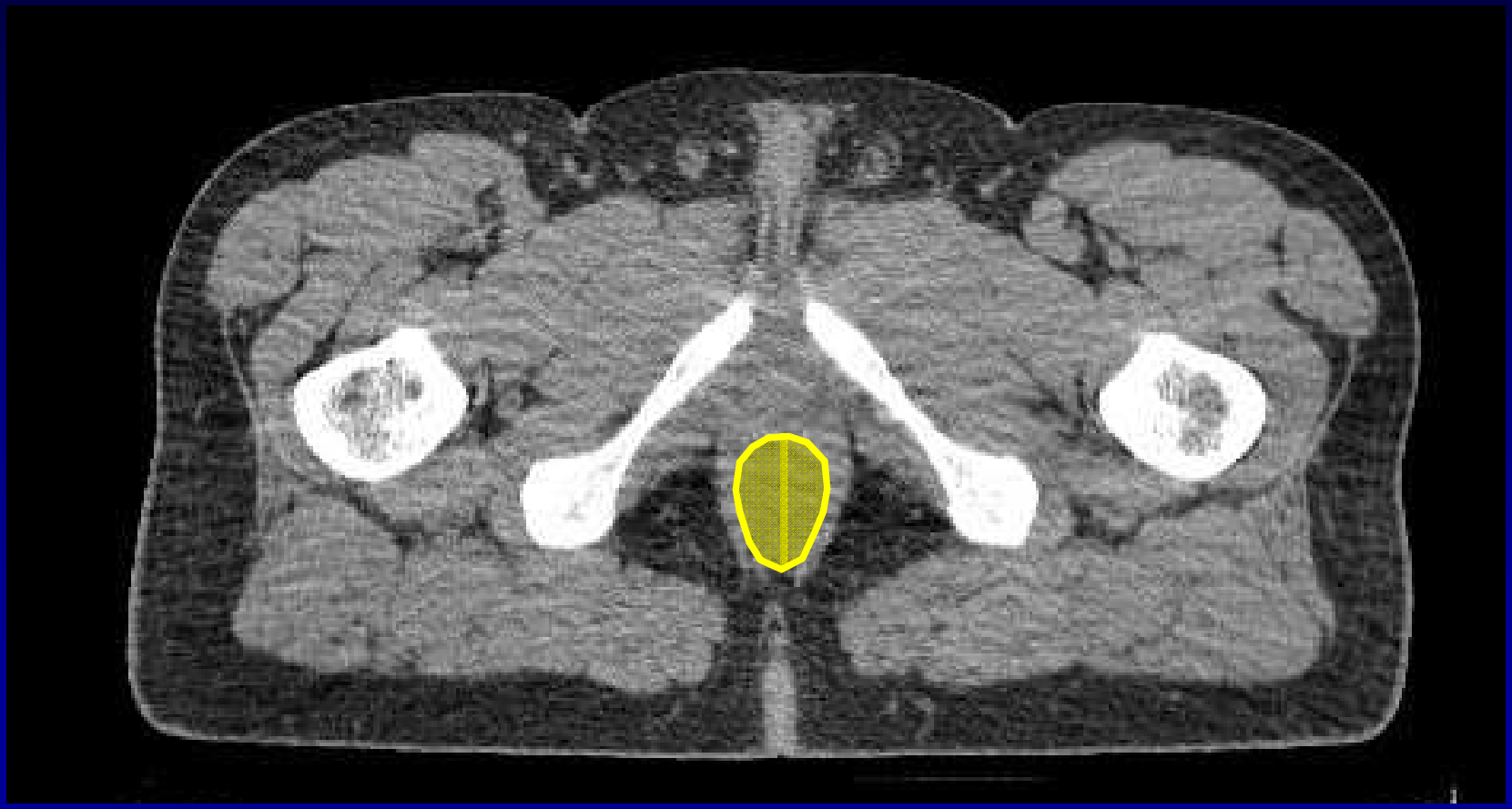
Continue with the delineation of the bladder in all slices!

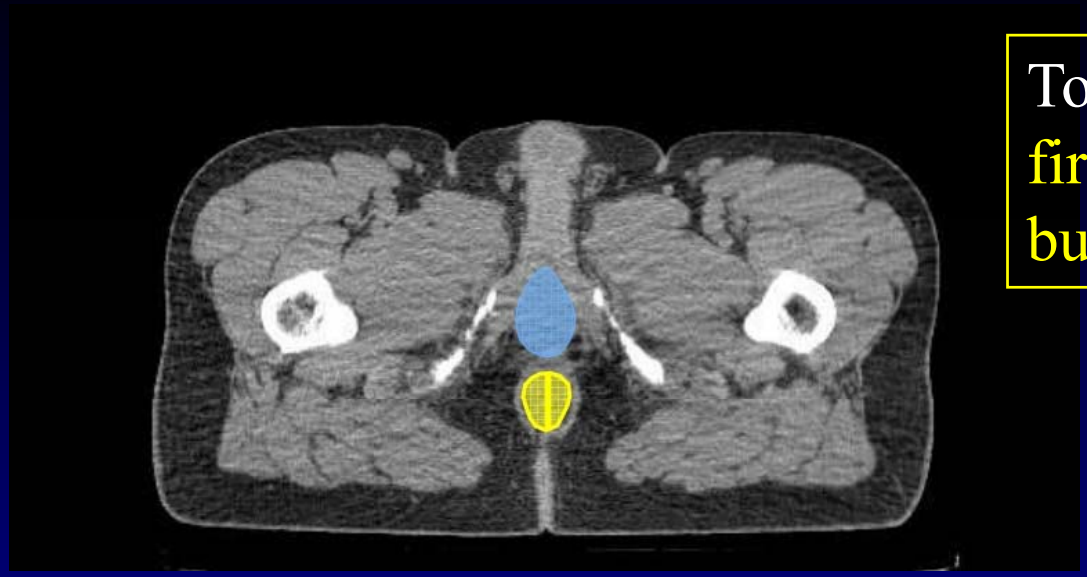


Now we attack the prostate ……

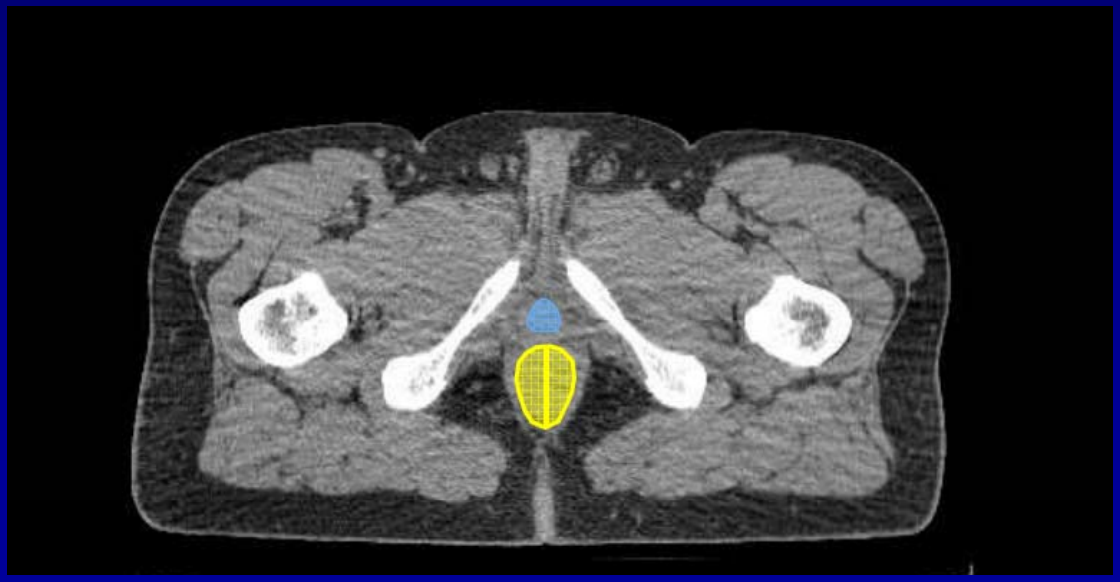
Hey ……

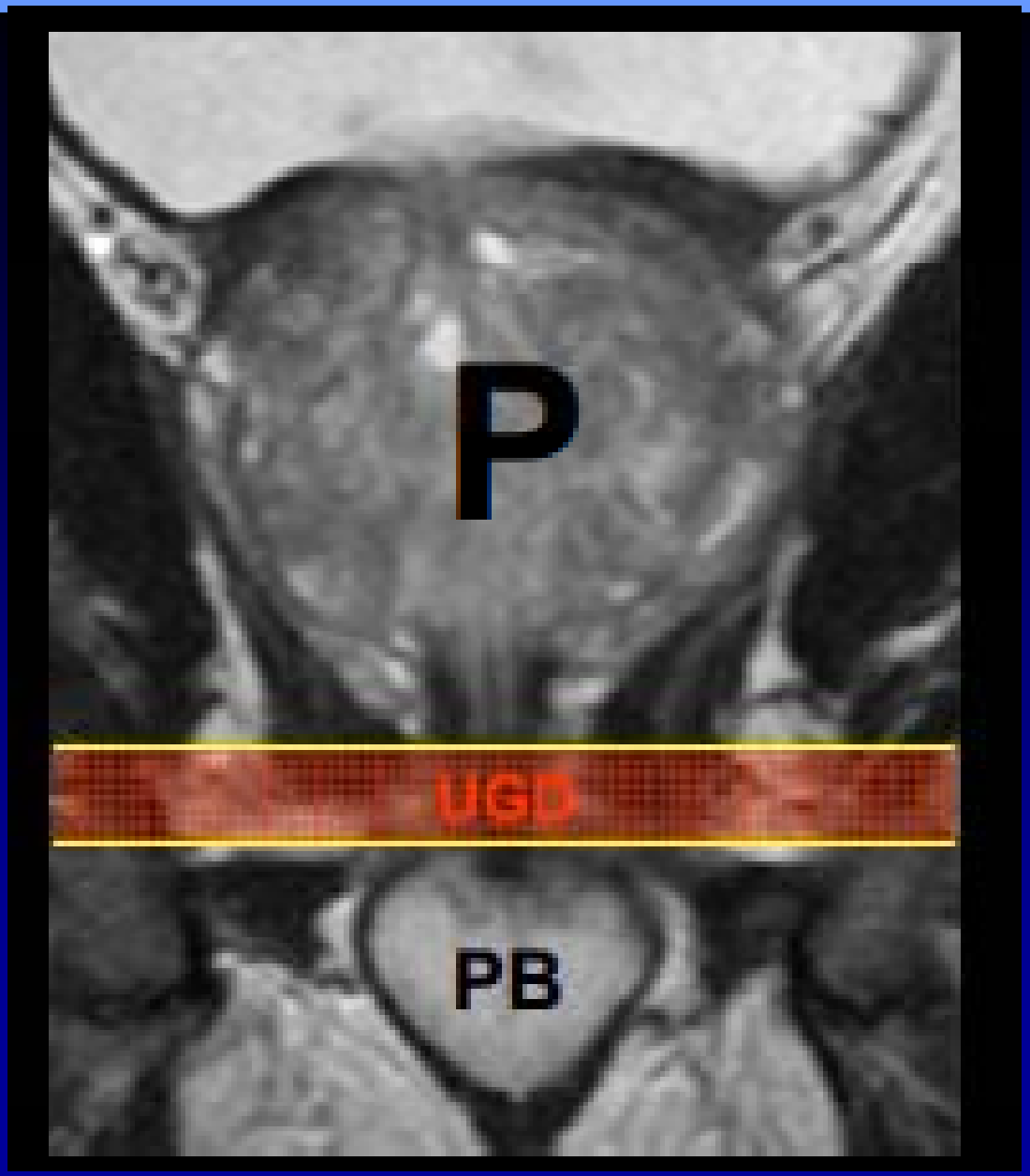
Where is the apex of the prostate ???

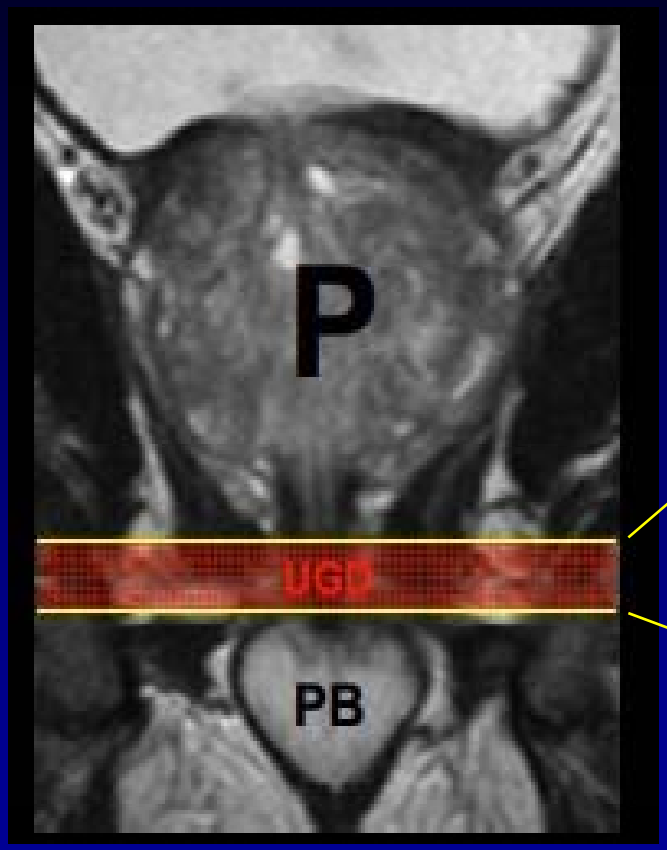




To find the apex:
first delineate the penile bulbus !

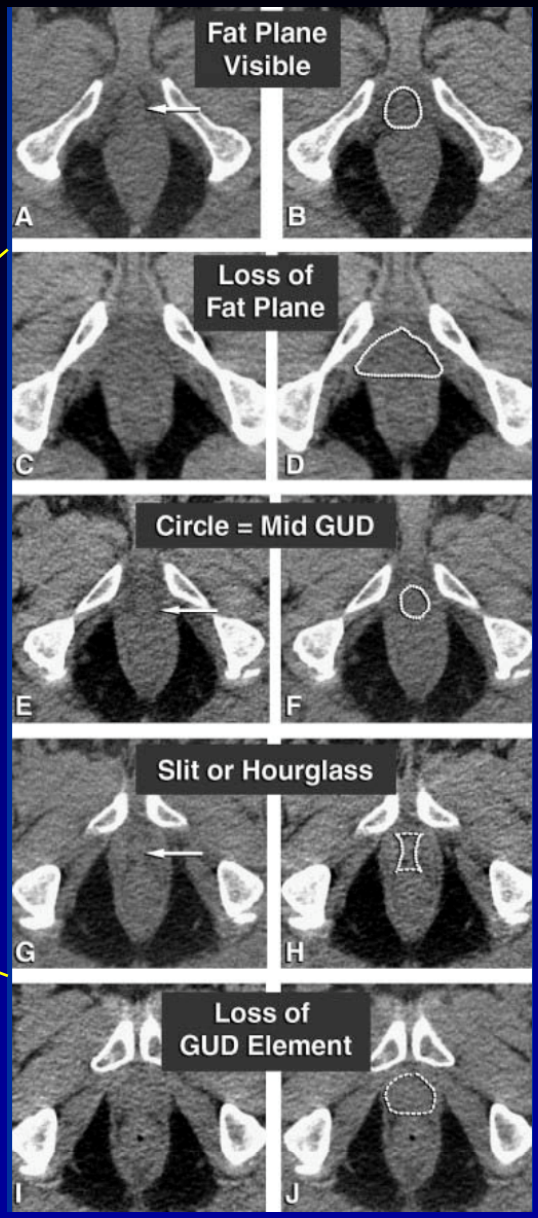



P
UGD
PB



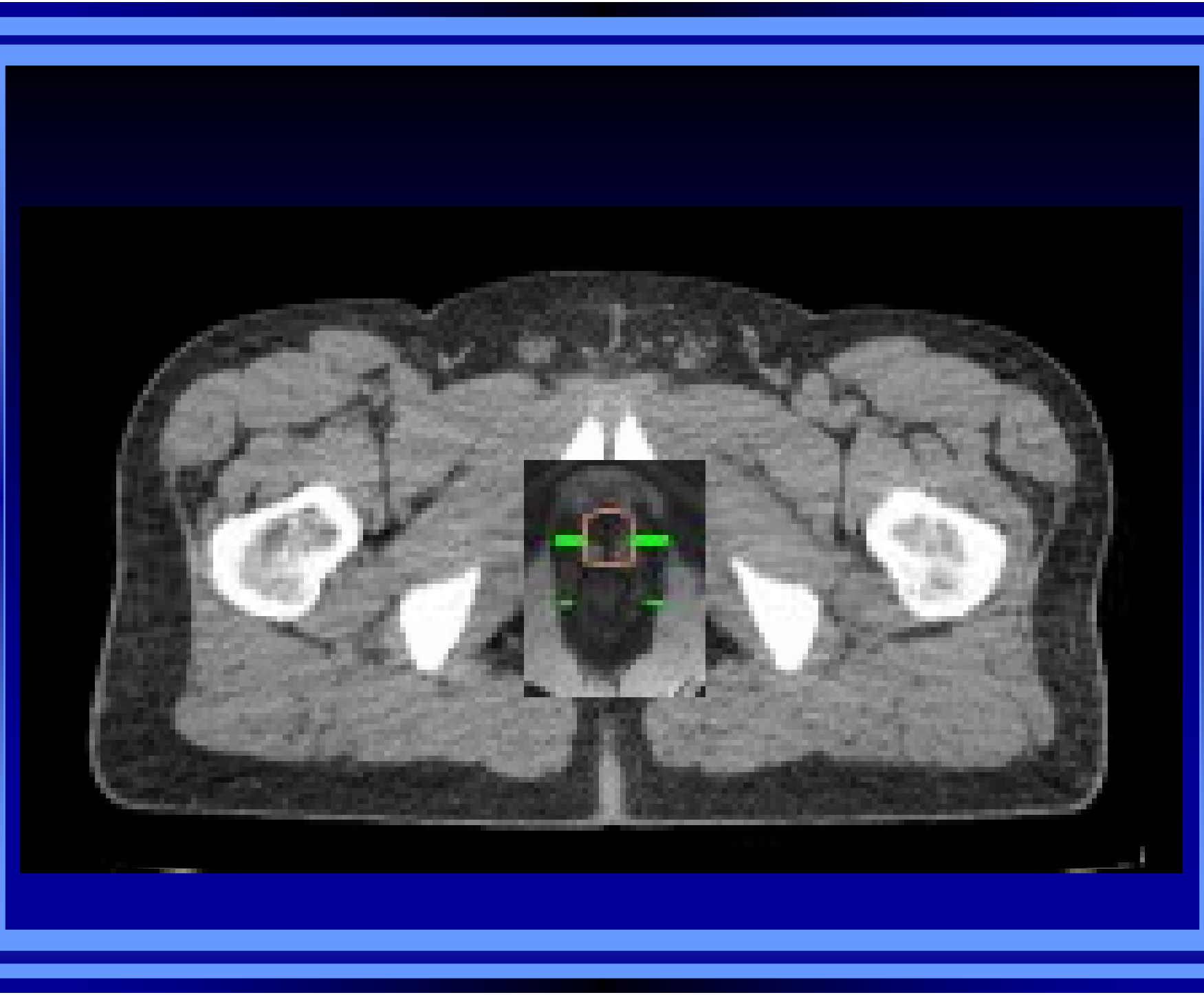
Top

Apex

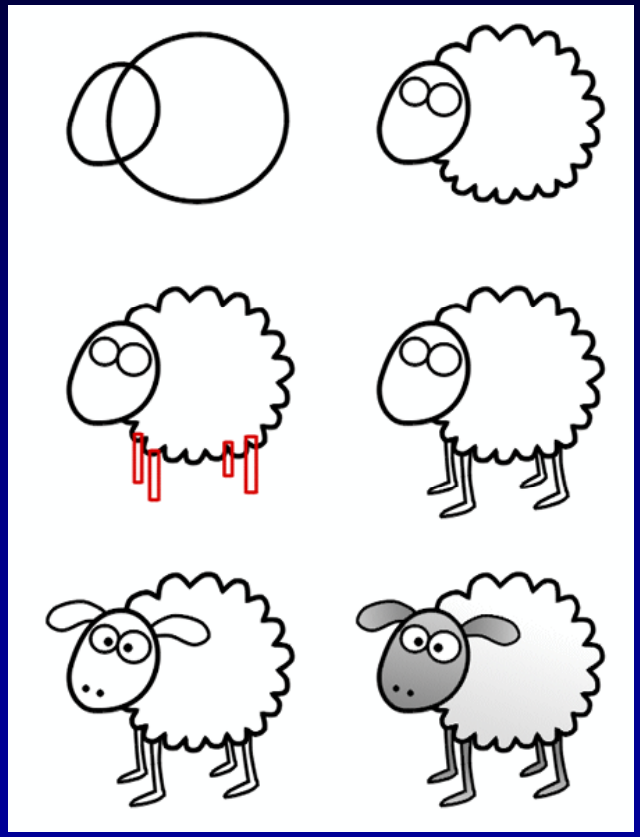


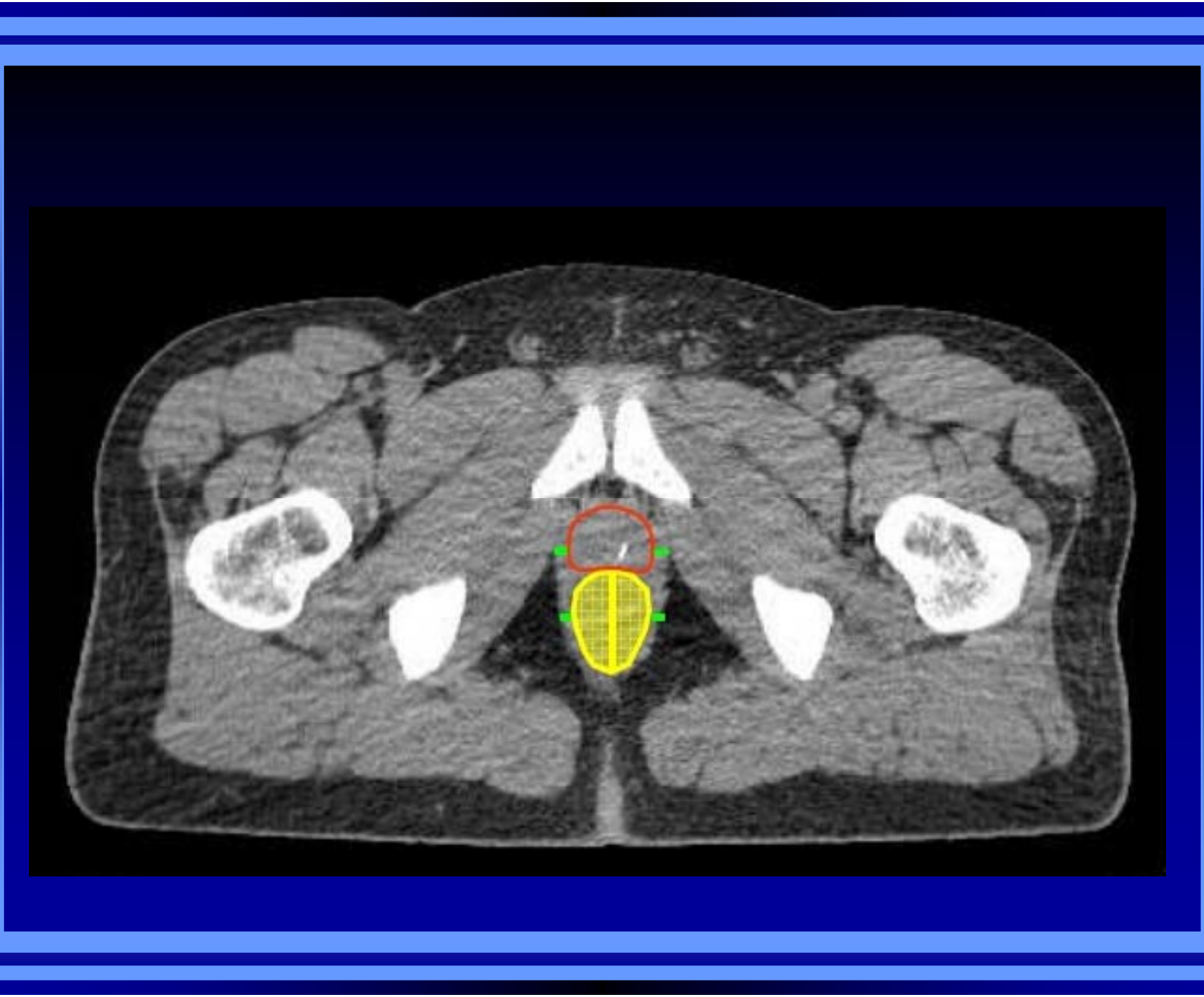
RADIOGRAPHIC AND ANATOMIC BASIS FOR PROSTATE CONTOURING ERRORS AND METHODS TO IMPROVE PROSTATE CONTOURING ACCURACY

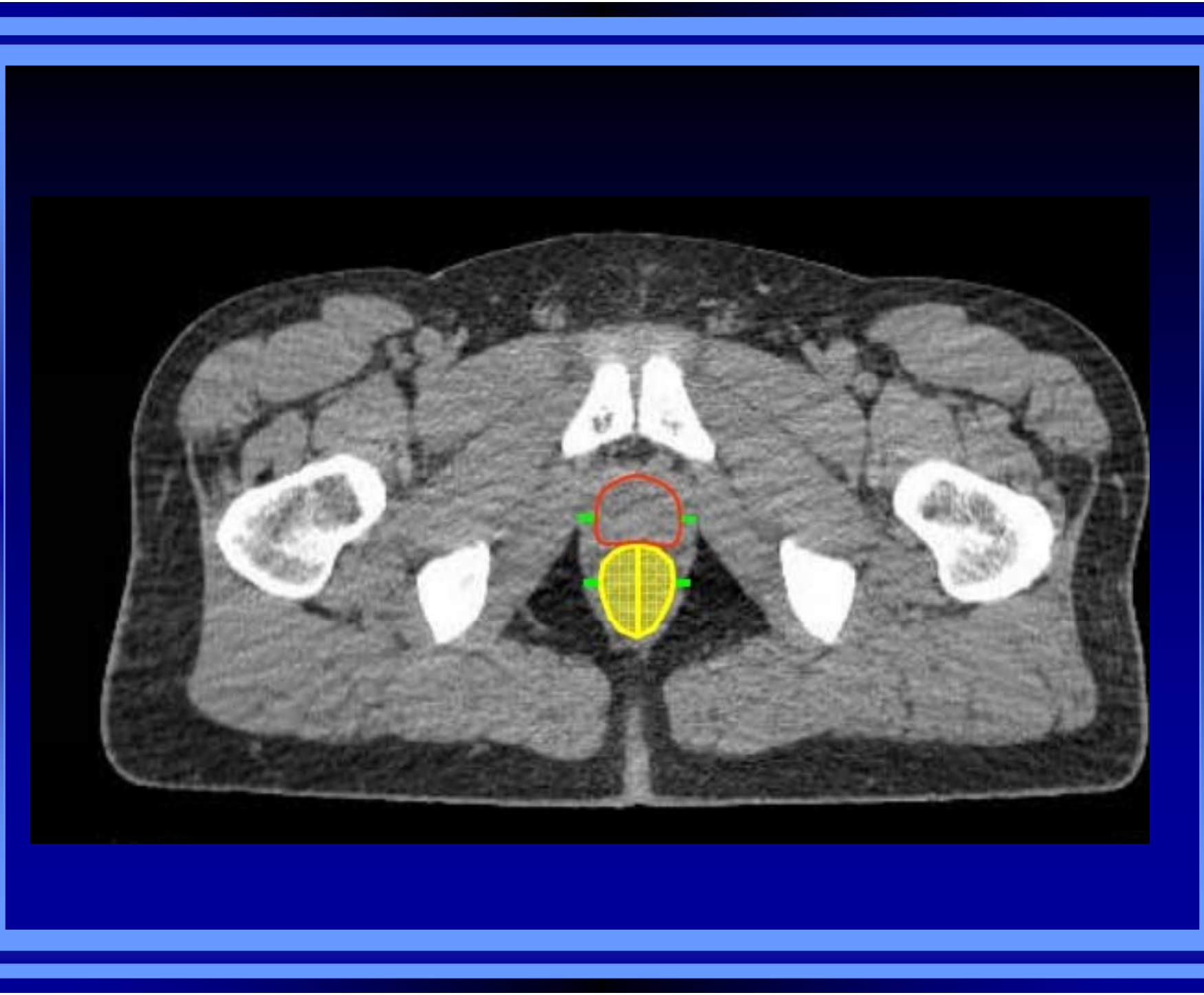
PATRICK W. MCLAUGHLIN, M.D.,*† CHERYL EVANS, M.S.,* MARY FENG, M.D.,* AND VRINDA NARAYANA, PH.D.*†

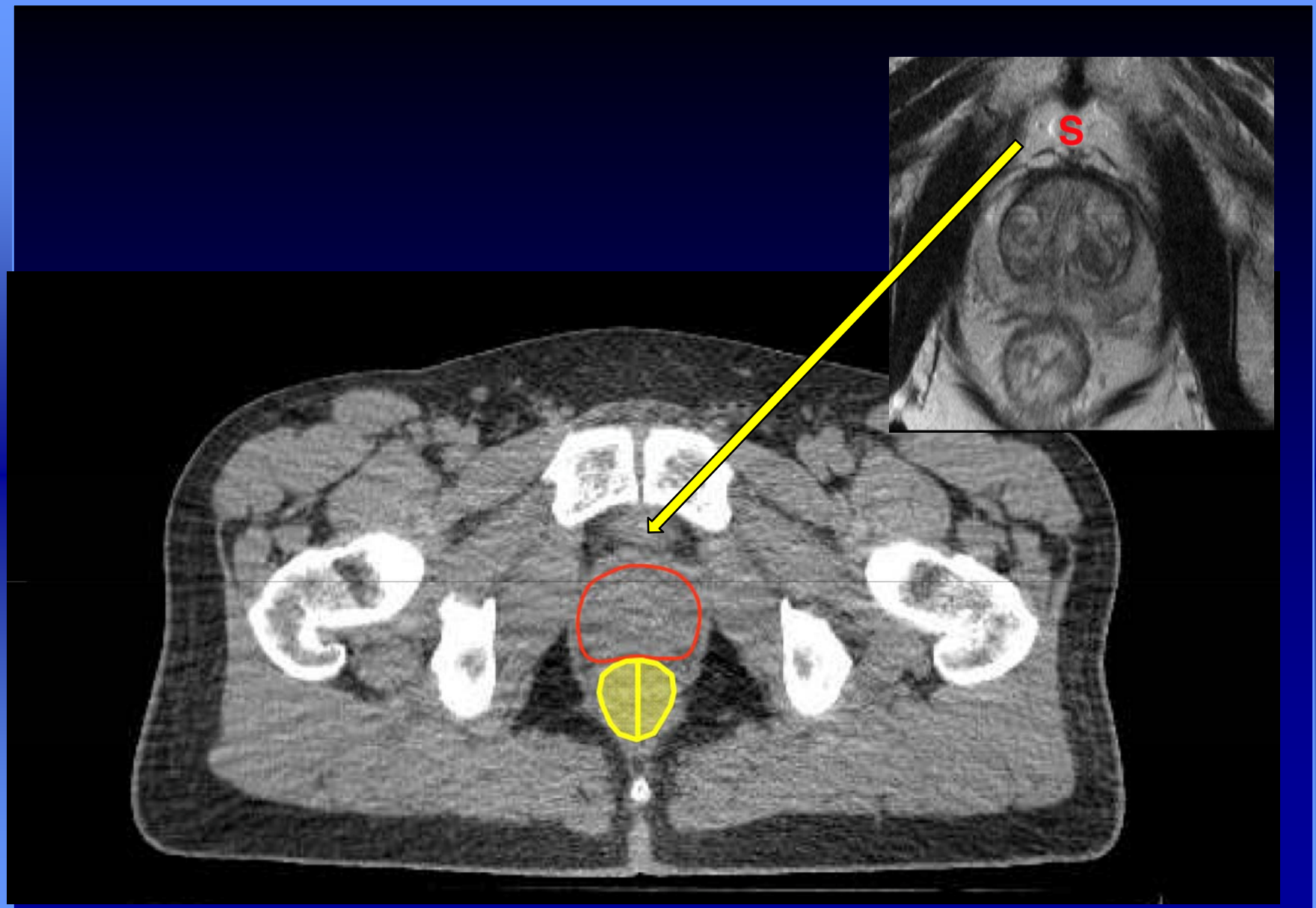


…… And now ???





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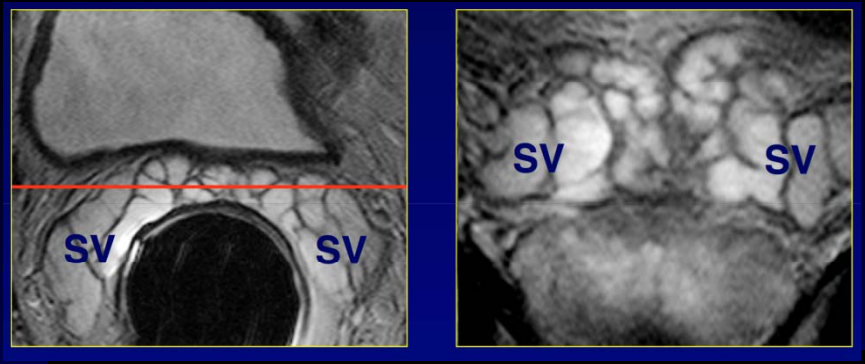
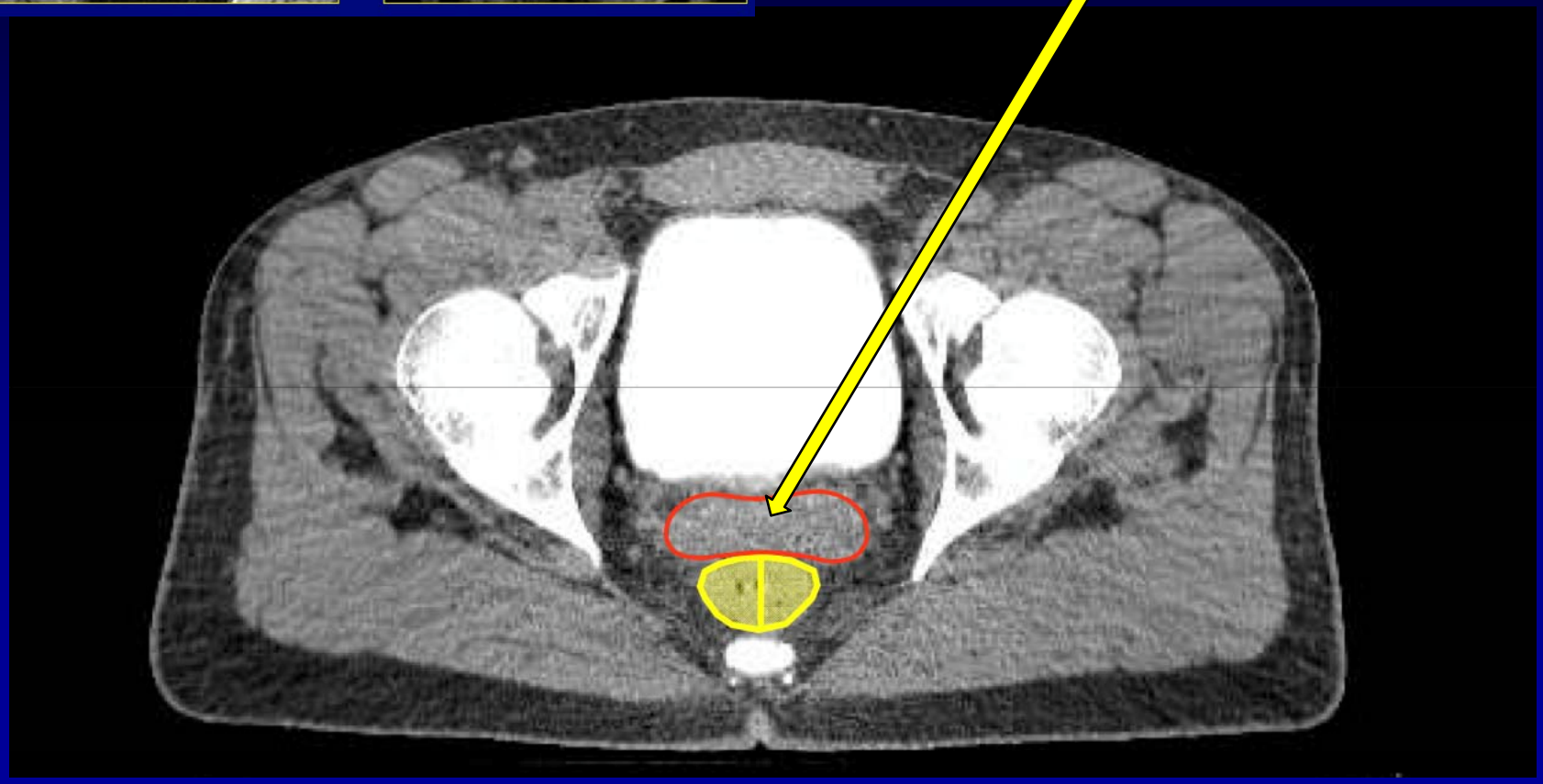
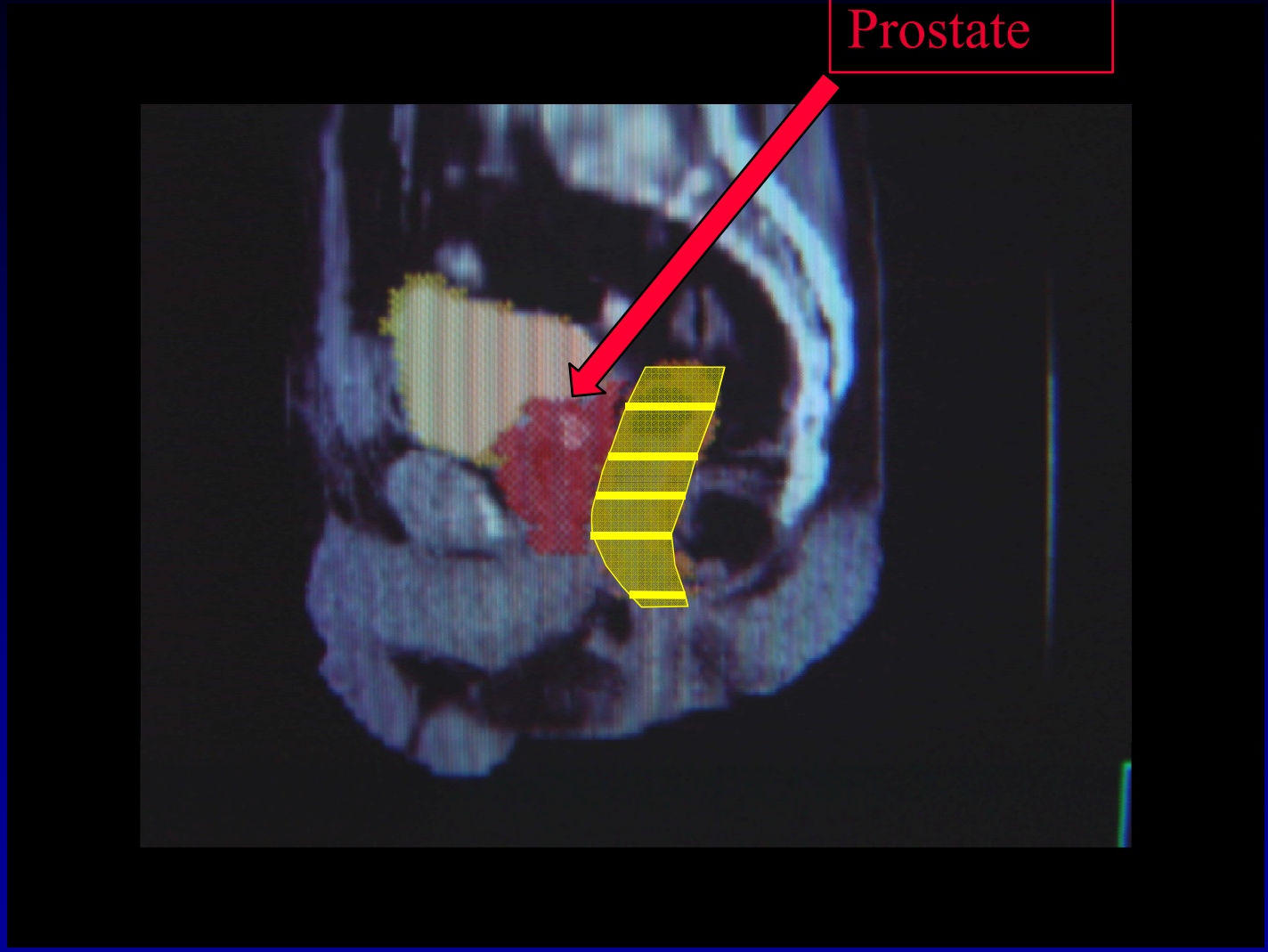


SEMINAL VESICLES

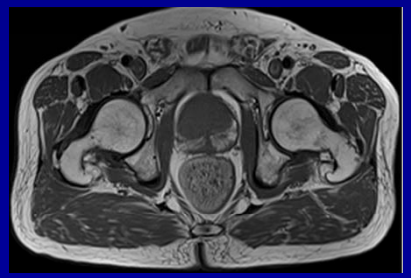
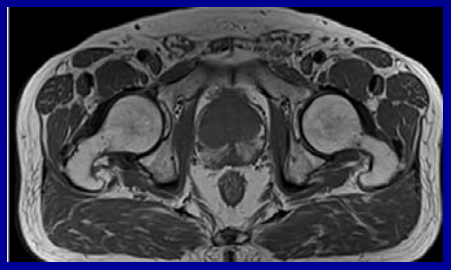
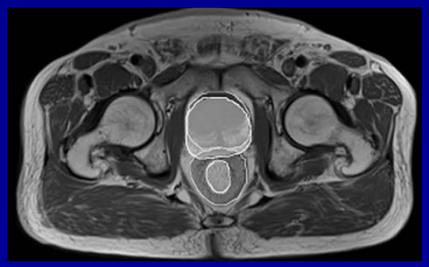


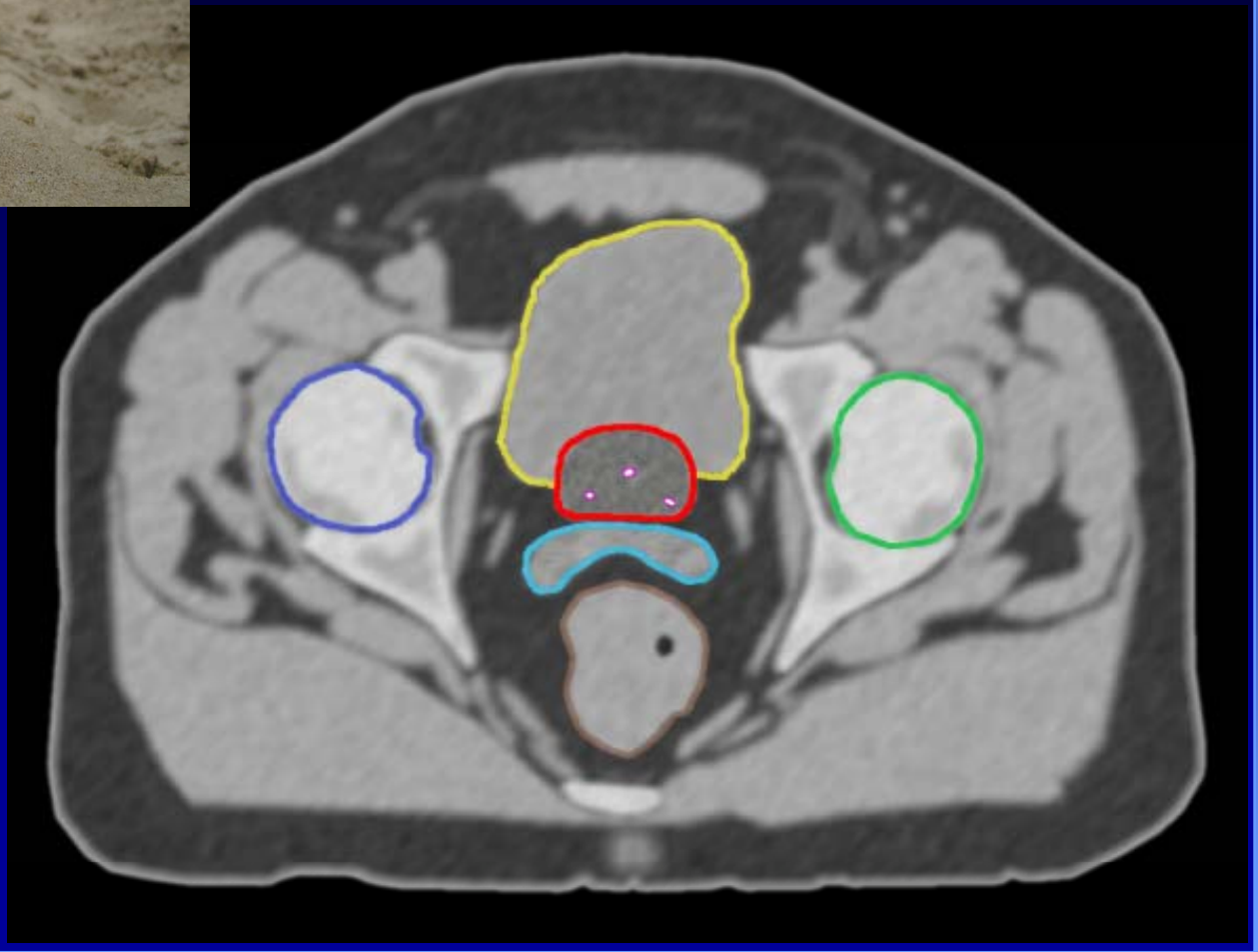

Prostate

Matching between MRI and CT/US

Be aware of possible drawbacks:

-Matching difficulties
-Flat table couch (also on MRI) – patient positioning
-Rectal distension (bowel prep?)
-Variation in bladder volume (bladder prep?)
-P-VS shape and volume differences



During delineation:

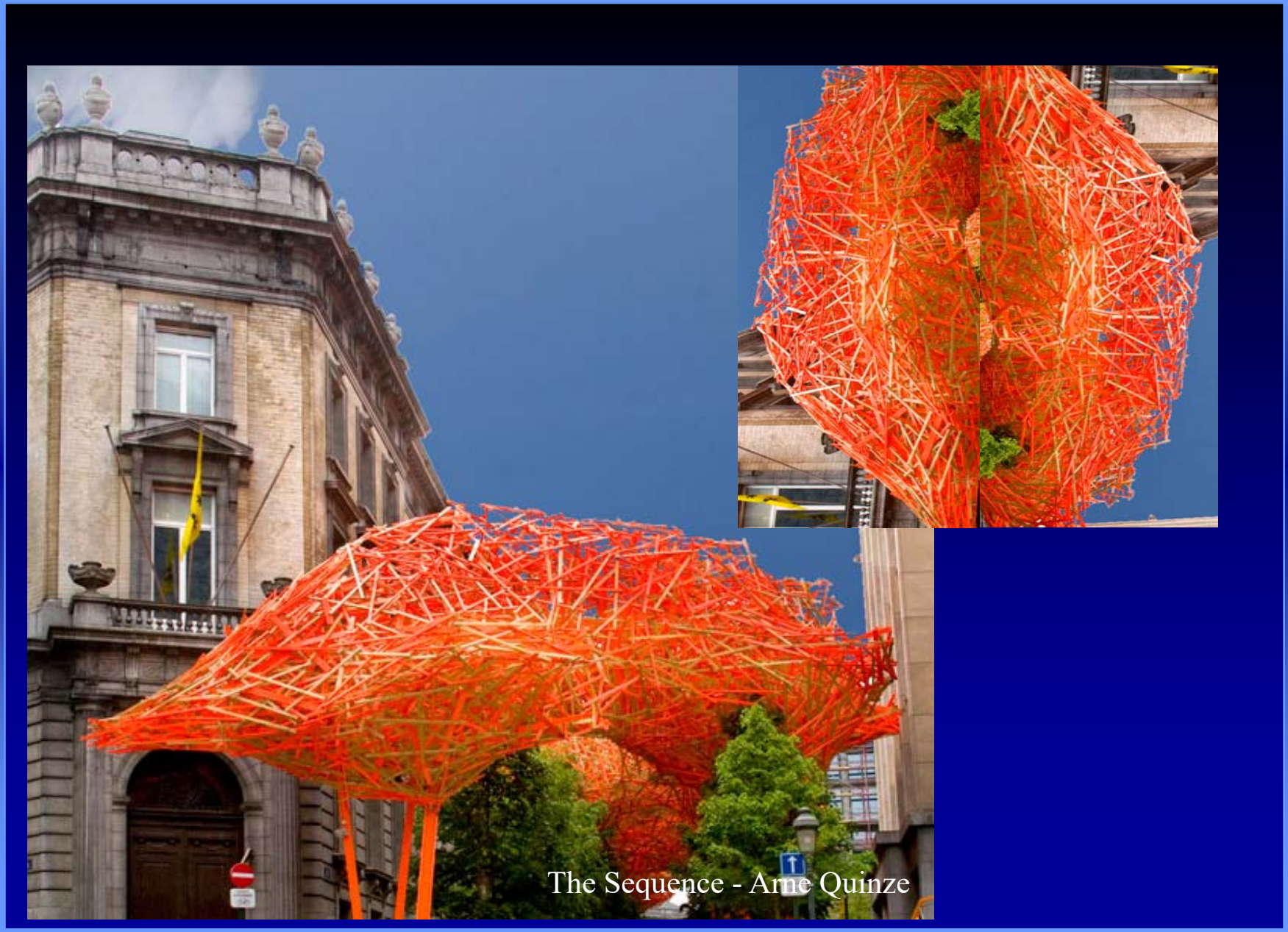
- Apply continuously ‘look ahead and back approach’

- 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...

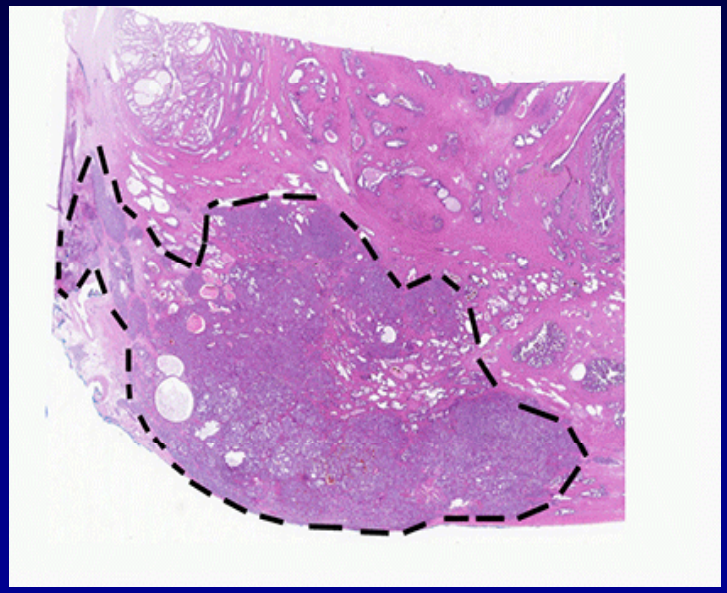

Ceci n’est pas une prostate
Rock Strangers - Arne Quinze

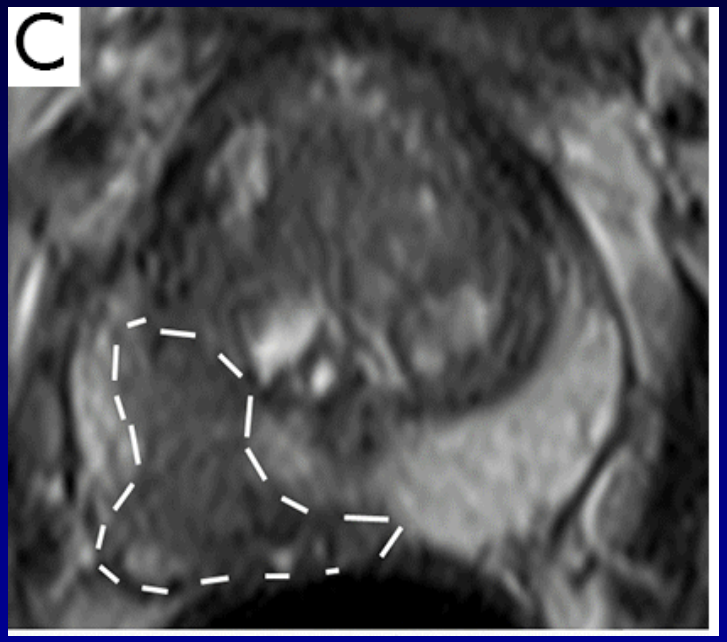

The Sequence - Arne Quinze


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


ADDENDUM: SEQUENCES IN MRI

Prostate: the anatomy…and the radiology..
THE BRIDGE

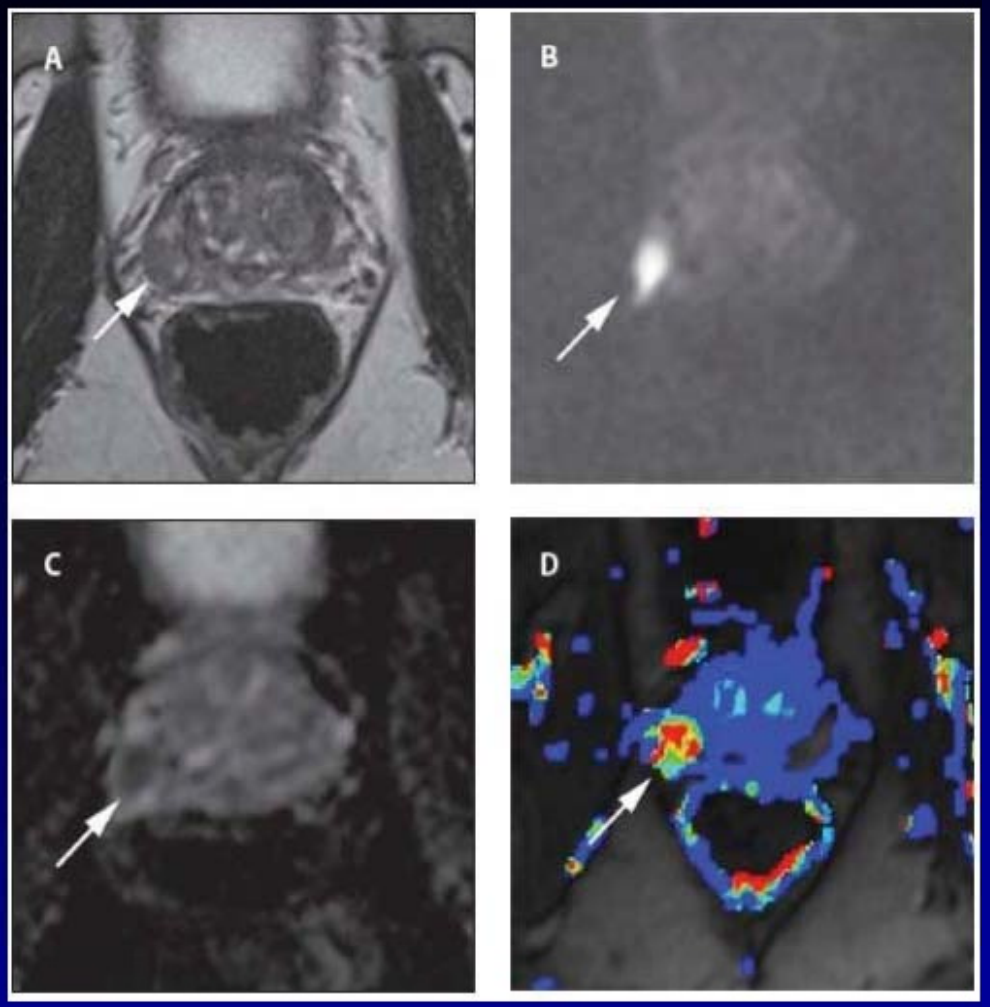




Radtke et al., Transl Androl and Urol. 2015

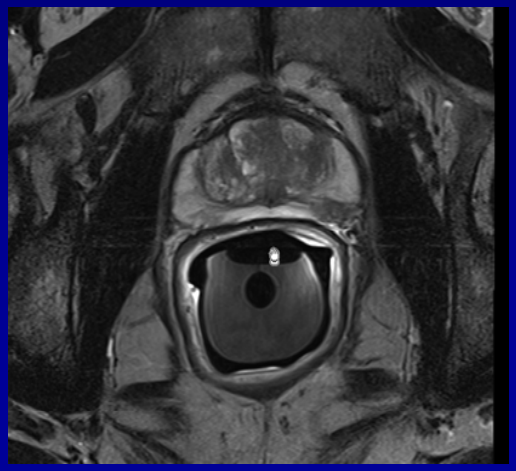
Prostate: the radiological anatomy and MRI which is the best sequence??

Prostate: the radiological anatomy and MRI which is the best sequence??



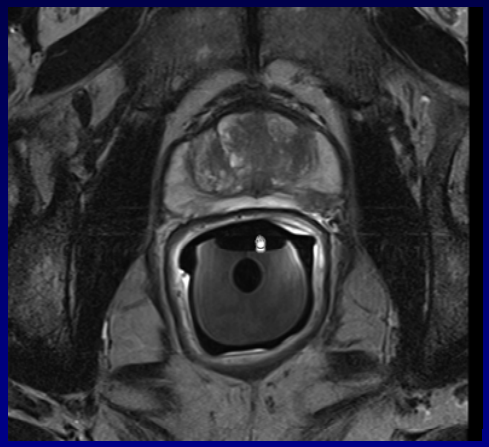
Prostate MRI: some practical points on T2W

- T2-weighted MR imaging is optimal to characterize the prostate
- On T2-wi, the peripheral zone has high signal intensity (quite white), in contrast to the low signal (grey and black) intensity of the central and transitional zones.
- BPH appears as a well-defined and inhomogeneous area with intermediate signal intensity on T2-wi.
- The anterior fibromuscular stroma also appears as an area with low signal intensity on T2-wi.



Prostate MRI: some practical points on T2W

- T2W images are useful to detect prostate cancer in the peripheral zones, as an area of low signal intensity (black).



- Noteworthy, low signal could be:
  - chronic prostatitis,
  - atrophy,
  - scars,
  - post-radiation therapy fibrosis
  - changes after ADT

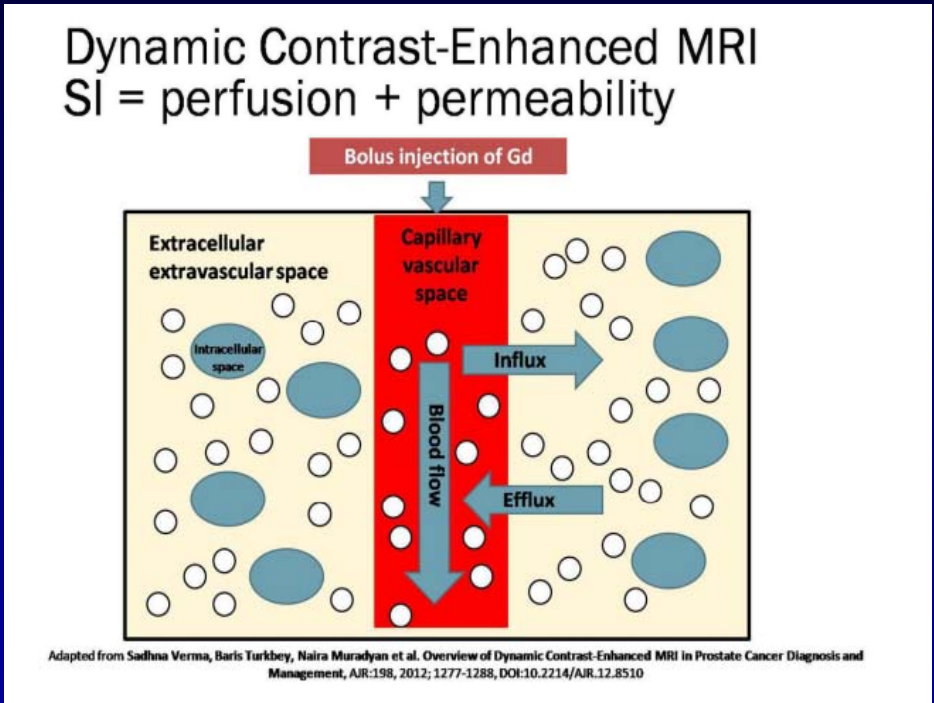
- Difficulties in identify a tumor in the transitional zone….because there is a lot of low signal….

PLEASE, COMMUNICATE WITH YOUR RADIOLOGIST!!

Prostate MRI: some practical points on DWI

- DWI/ADC provide functional information about the behavior of water molecules in tissue.
- Reduced diffusion of water = increased cellularity of malignant lesions that restricts water motion in a reduced extracellular space
- Reduced diffusion of water = prostate cancer
- Low signal intensity on the apparent diffusion coefficient (ADC) maps (dark grey/black)

Prostate MRI: some practical points on DCE

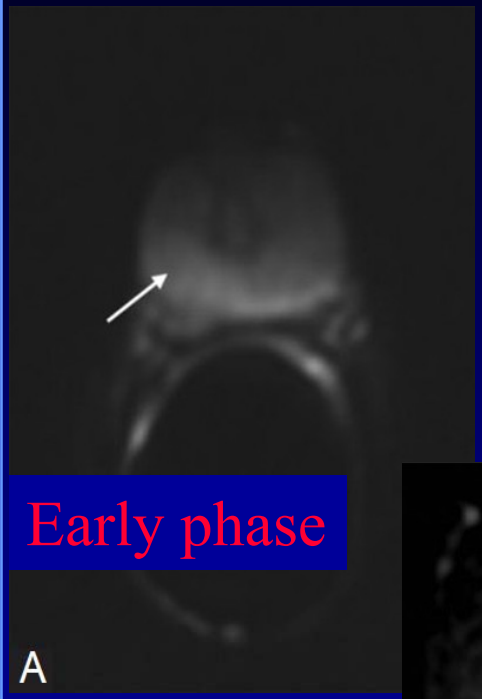


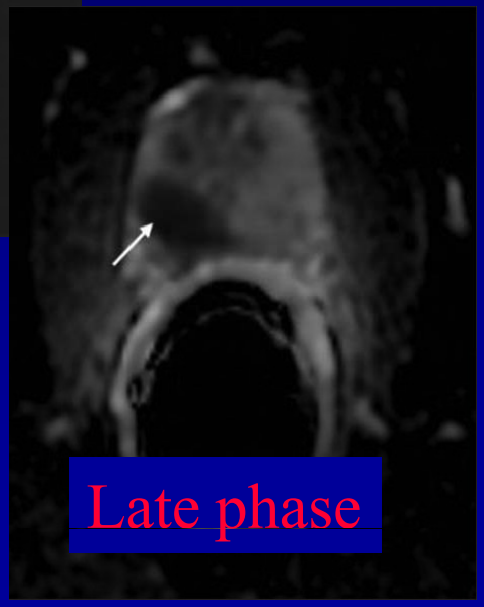
Dynamic Contrast Enhanced MRI =

Based on tumor angiogenesis

Tumor vessels = higher permeability than do normal vessels because of weak integrity of the vessel wall

Prostate MRI: some practical points on DCE

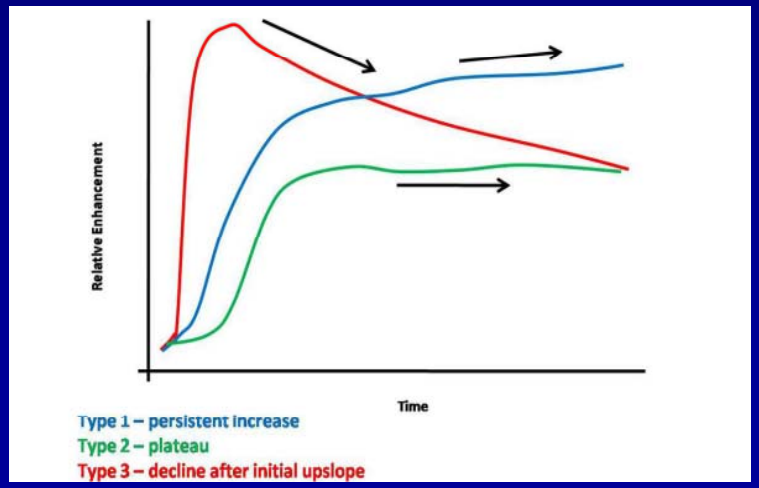




This characteristic tumor environment explains the enhancement pattern of cancerous tissues compared with normal tissues

1. Earlier and faster enhancement

2. Earlier contrast agent washout



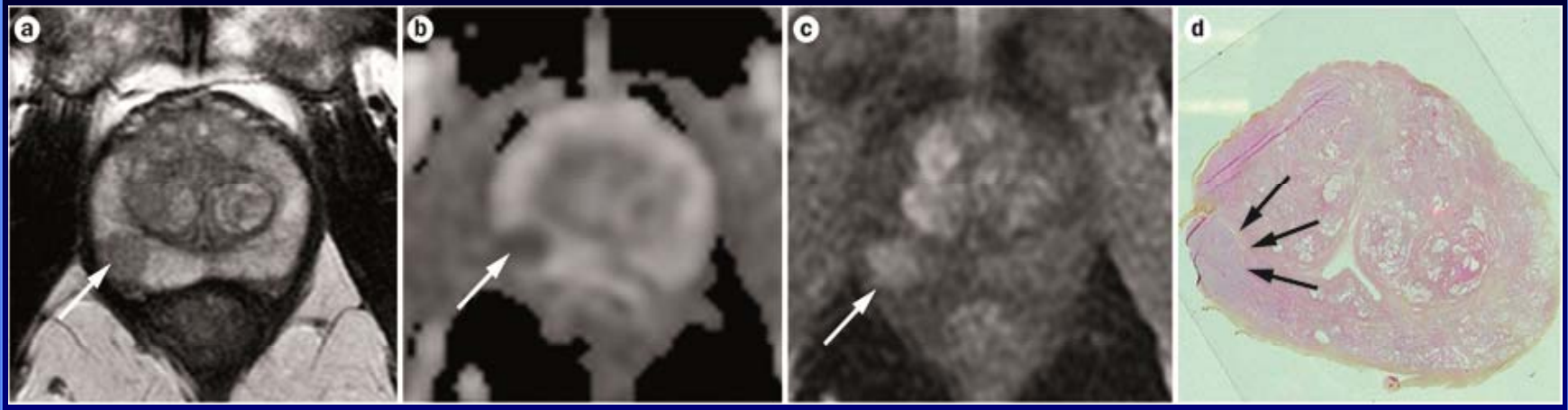
Prostate: the radiological anatomy at MRI which is the best sequence??

The T2W sequence for the Anatomy

The DWI sequence for the Biology

The DCI sequence for the Vascularity

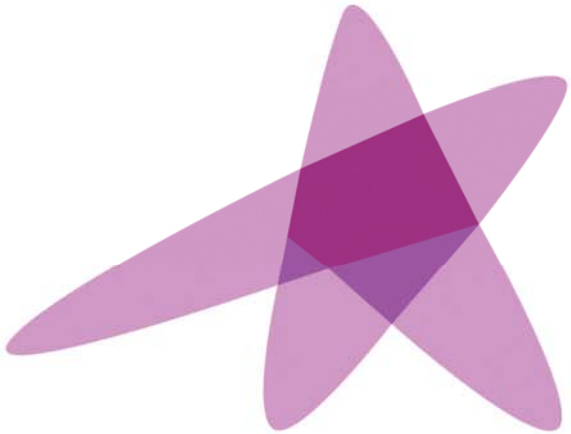
Prostate MRI: some practical points



We look for something DARKER in T2W and in DWI….

….and for something BRIGHTER in late DCE!

Rouvière, O. *et al.* (2012) Prostate focused ultrasound focal therapy—imaging for the future
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2012.136



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WWW.ESTRO.ORG/SCHOOL

Prostate Brachytherapy: Imaging of prostate cancer

S. Machtens

Director of the

Department of Urology and Paediatric Urology

Academic Teaching Hospital

Marien-Hospital Bergisch Gladbach

Teaching Course Brussels 2016

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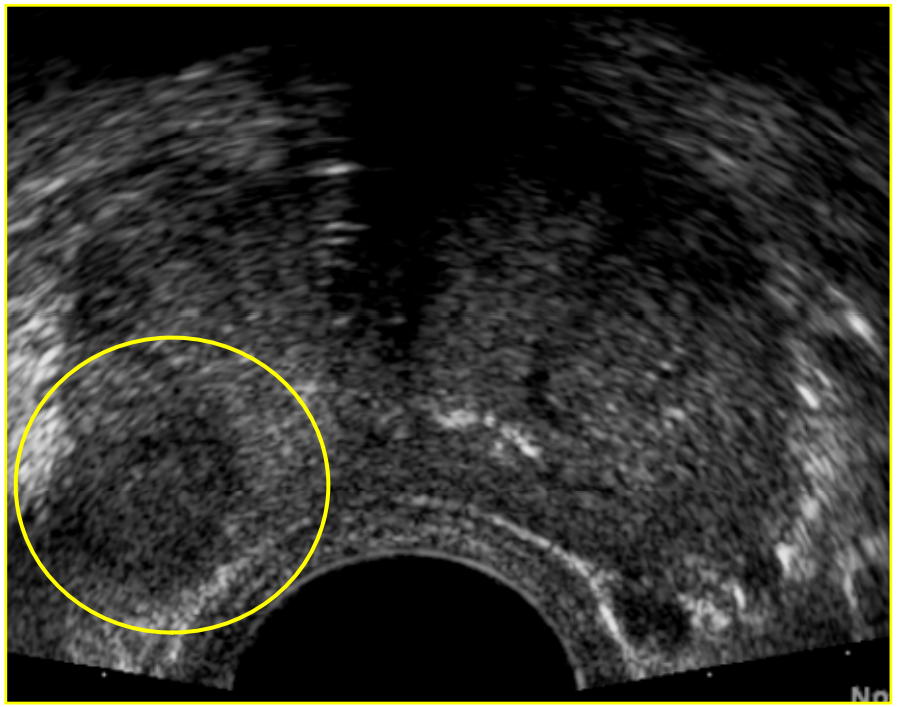
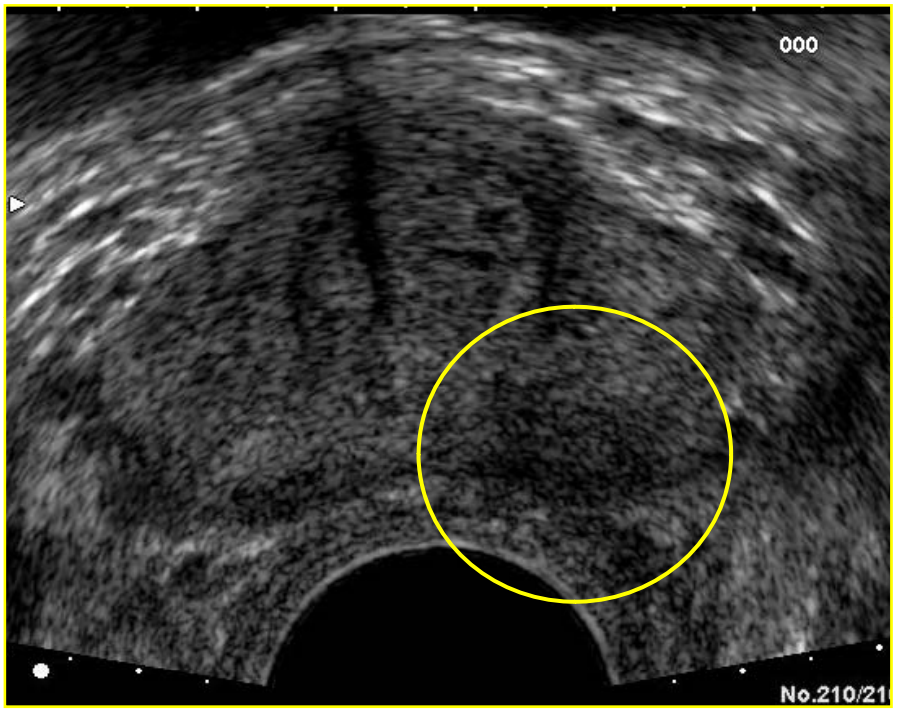
Ultrasound
Prostate Carcinoma





Hypoechoic nodule compared to normal PZ
Low specificity (atrophy, prostatitis, ...)

Ultrasound
Diagnostic Performance

- **Performance in tumour localization**
  - **Sensitivity : 32-85% : false negatives!**
  - **Specificity : 41-79% : false positives!**
- **Inappropriate for screening of general population**

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Ultrasound
Staging Performance

- **Performance in tumour staging**

  - **Extracapsular extension**
    - **sensitivity : 50-90%**
    - **specificity : 50-90%**

  - **Seminal vesicle invasion**
    - **sensitivity : 20-60%**
    - **specificity : 50-90%**

- **Inappropriate for staging**

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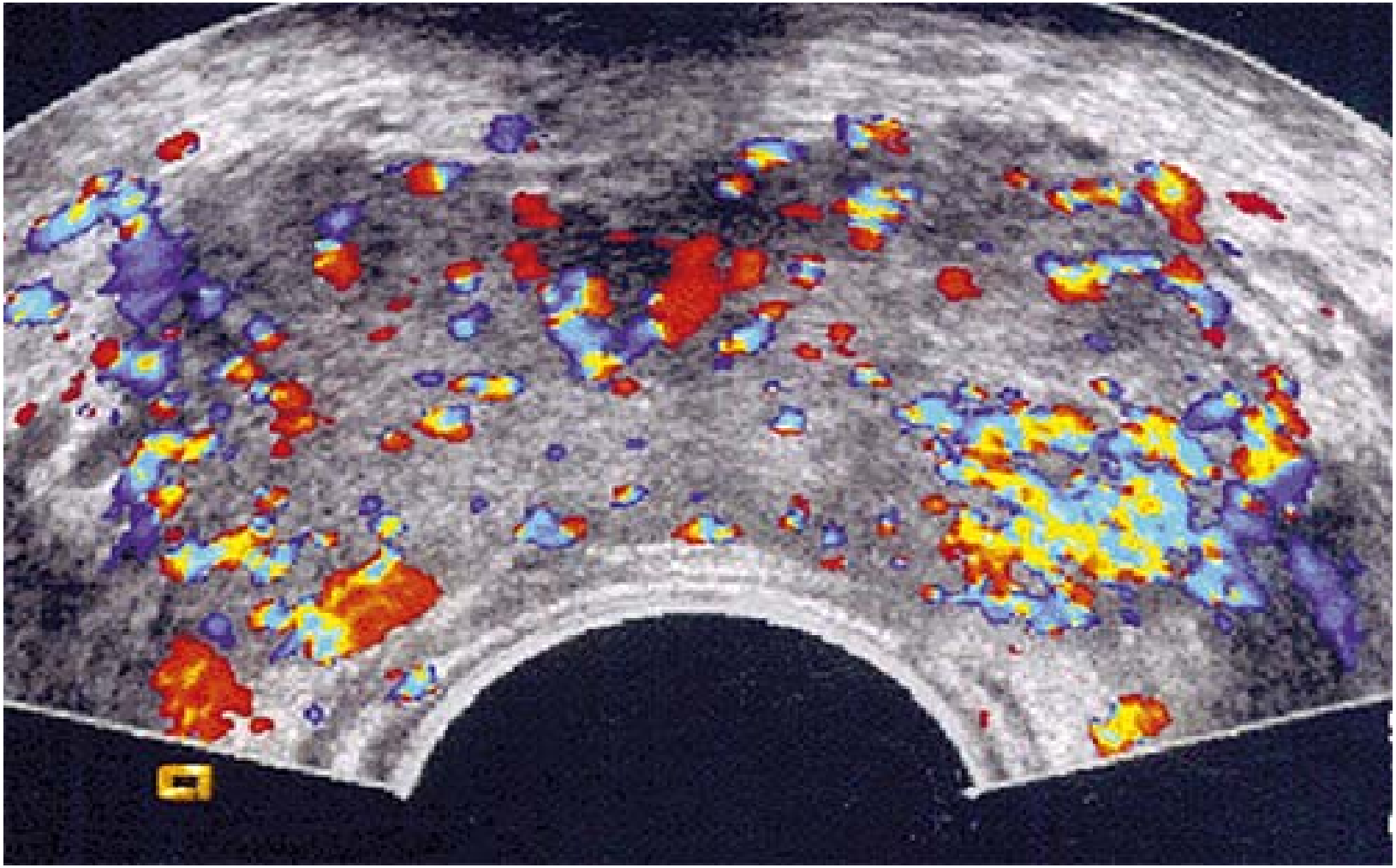
Ultrasound
Value

- **Initial evaluation of patients with elevated PSA and/or abnormal digital rectal examination**
- **Biopsy guidance**
- **Determination of prostate seize**
- **Guidance in brachytherapy**

TRUS with contrast enhancement



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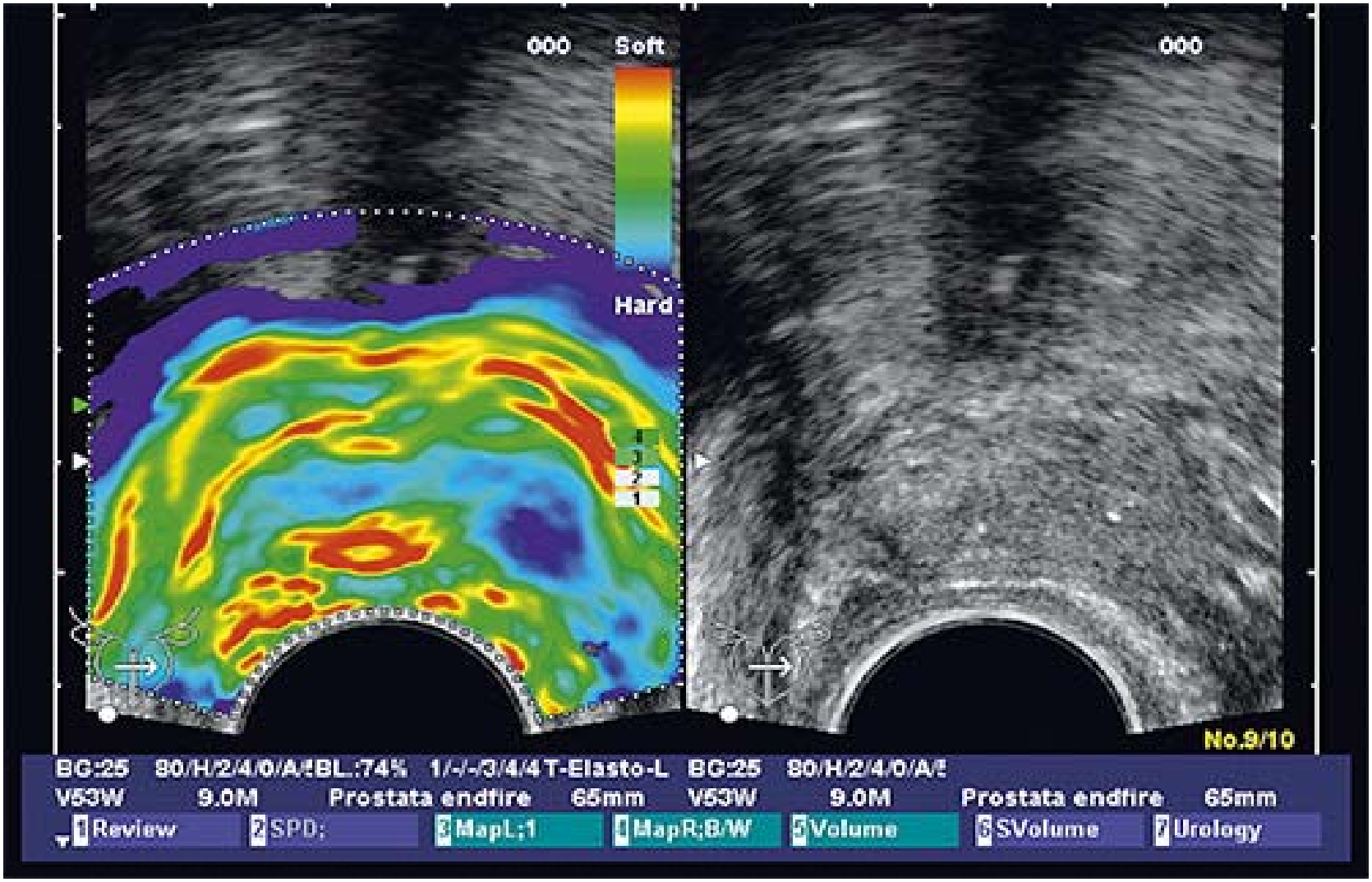
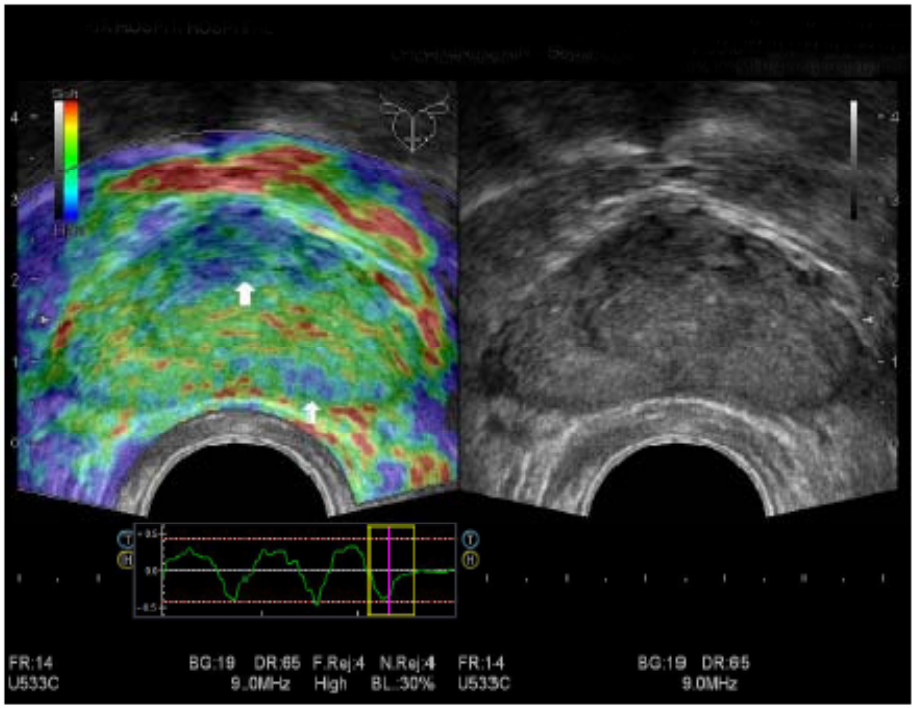
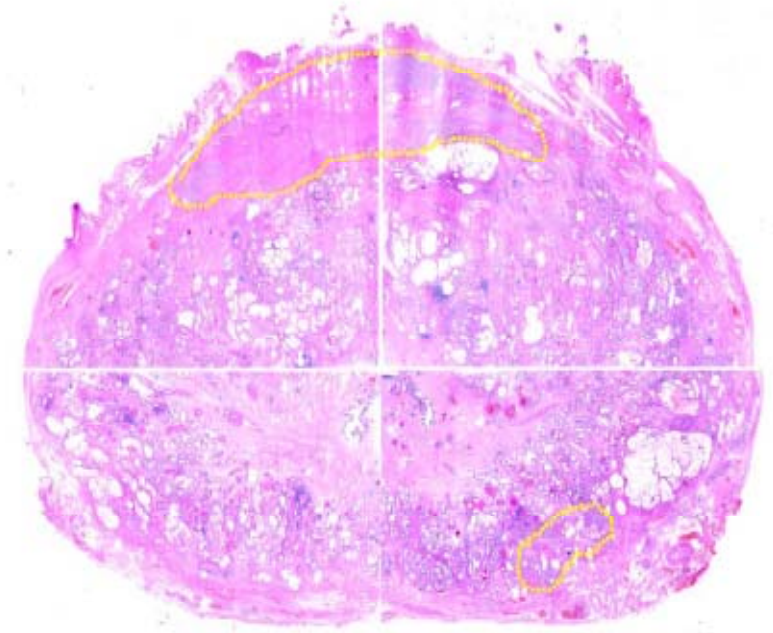
Elastography



Elastography





3. Pallwein L, Mitterberger M, Struve P, Pinggera G, Horninger W, Bartsch G, Aigner F, Lorenz A, Pedross F, Frauscher F (2007) Real-time elastography for detecting prostate cancer: preliminary experience. BJU Int 100:42-46

4. Sumura M, Shigeno K, Hyuga T, Yoneda T, Shiina H, Igawa M (2007) Initial evaluation of prostate cancer with real-time elastography based on step-section pathologic analysis after radical prostatectomy: a preliminary study. Int J Urol 14:811-816

Sensitivität: 69-80%
Spezifität: 78-90%

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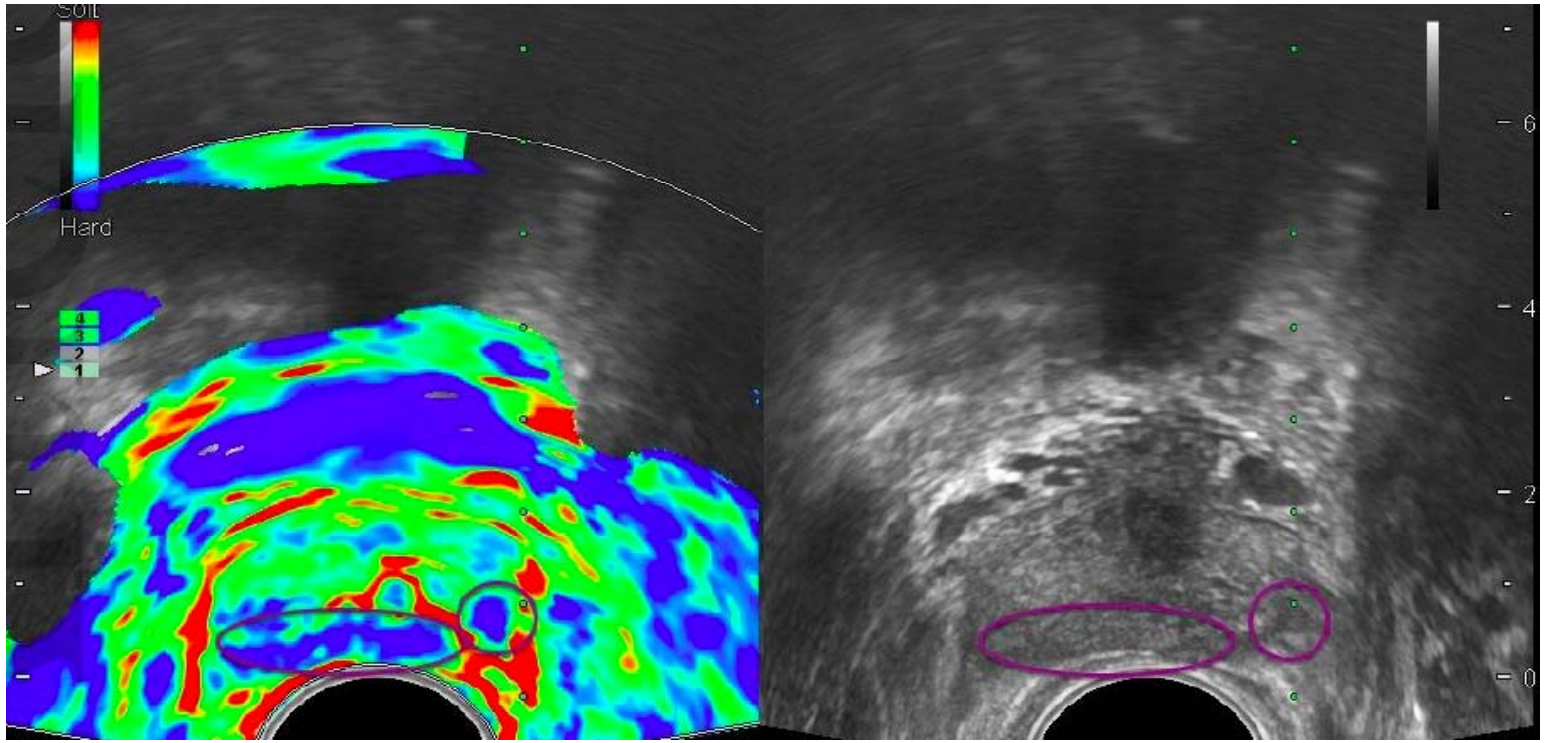
Elastography plus conventional TRUS-Bx

Salomon et al., BJUInt. 2014; 113(4):548-53

1024 men (10+4 cores)

Detektionsrates:

10fach TRUS 39,1%, RTE 29%, Combination 46,2%



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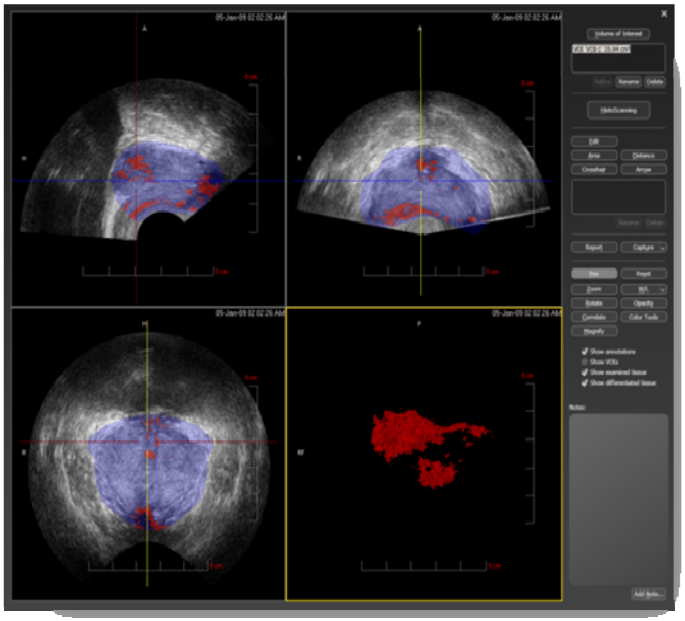
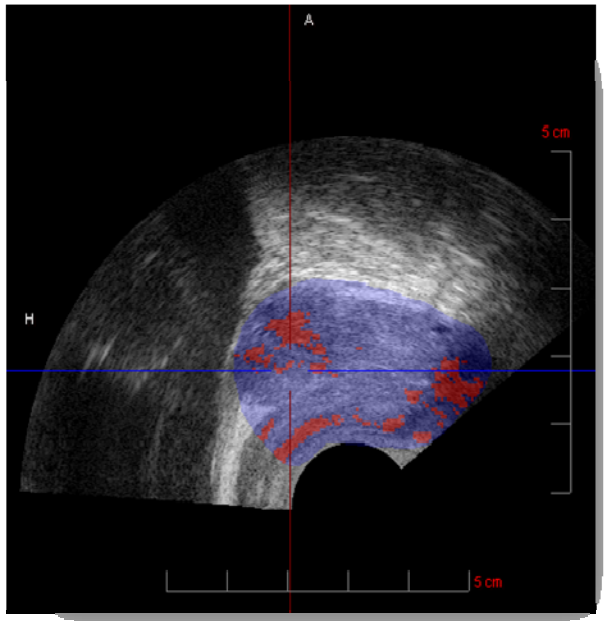
Prostate HistoScanning™

Tissue Differentiation and Visualization

- Computer-based information of 3D data.
- Visualization based on different acustic signals.
- HistoScanning™ signals appear as red pixels.





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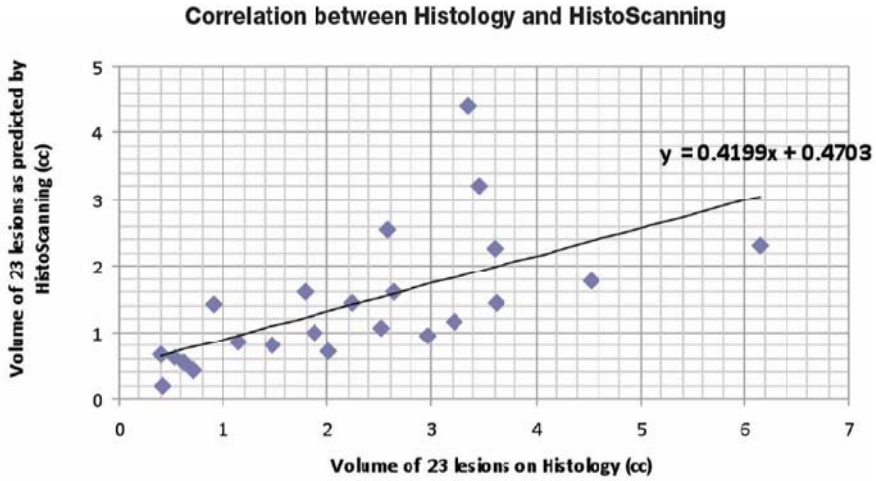
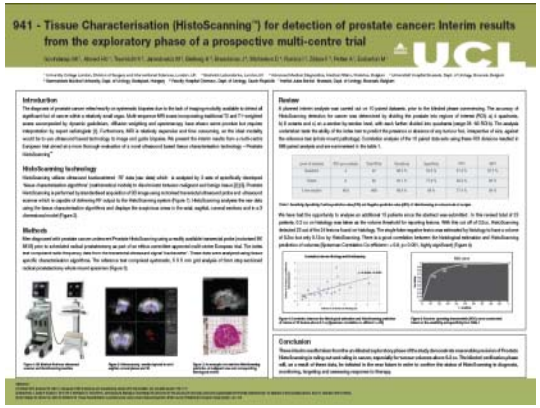
Multicenter clinical study

Results[1] (Govindaraju et al. EAU 2009)

- HistoScanning detected 23 out of the 24 lesions found on histology
- The index lesion was identified in all cases
- The lesion “missed” was estimated by histology to have a volume of 0.2cc but only 0.12cc by HistoScanning (below the reporting threshold)
- There is strong correlation between the histological estimation and prediction of volumes by HistoScanning™ (r = 0.8, p< 0.001)





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EDITORIAL COMMENT

J. Stephen Jones, M.D., Department of Regional Urology, Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, Ohio

tissues. Unfortunately, the data still reveal minimal value from most of these technologies, and those reported in this article are similarly disappointing. HistoScanning demonstrated interesting color images, but coupled with a transperineal-targeted biopsy found exactly one more case of prostate cancer than did the current standard of care—the 14-core extended transrectal biopsy. This "difference" is actually statistically identical ($P > .99$). Exactly the same number of patients ($n = 4$) was found exclusively by both transperineal HistoScan-targeted biopsy as with standard transrectal biopsy, and when targeted using the transrectal approach, the technology actually missed almost half of the cancers that were identified overall.

Furthermore, these data do not support the suggestion that 9 cores are less morbid or traumatic than 14 cores, and the literature is replete with reports demonstrating this is simply not true. This is especially misleading when those 9 cores come at the cost, morbidity, time, and complexity of an operation such as this performed under general anesthesia.

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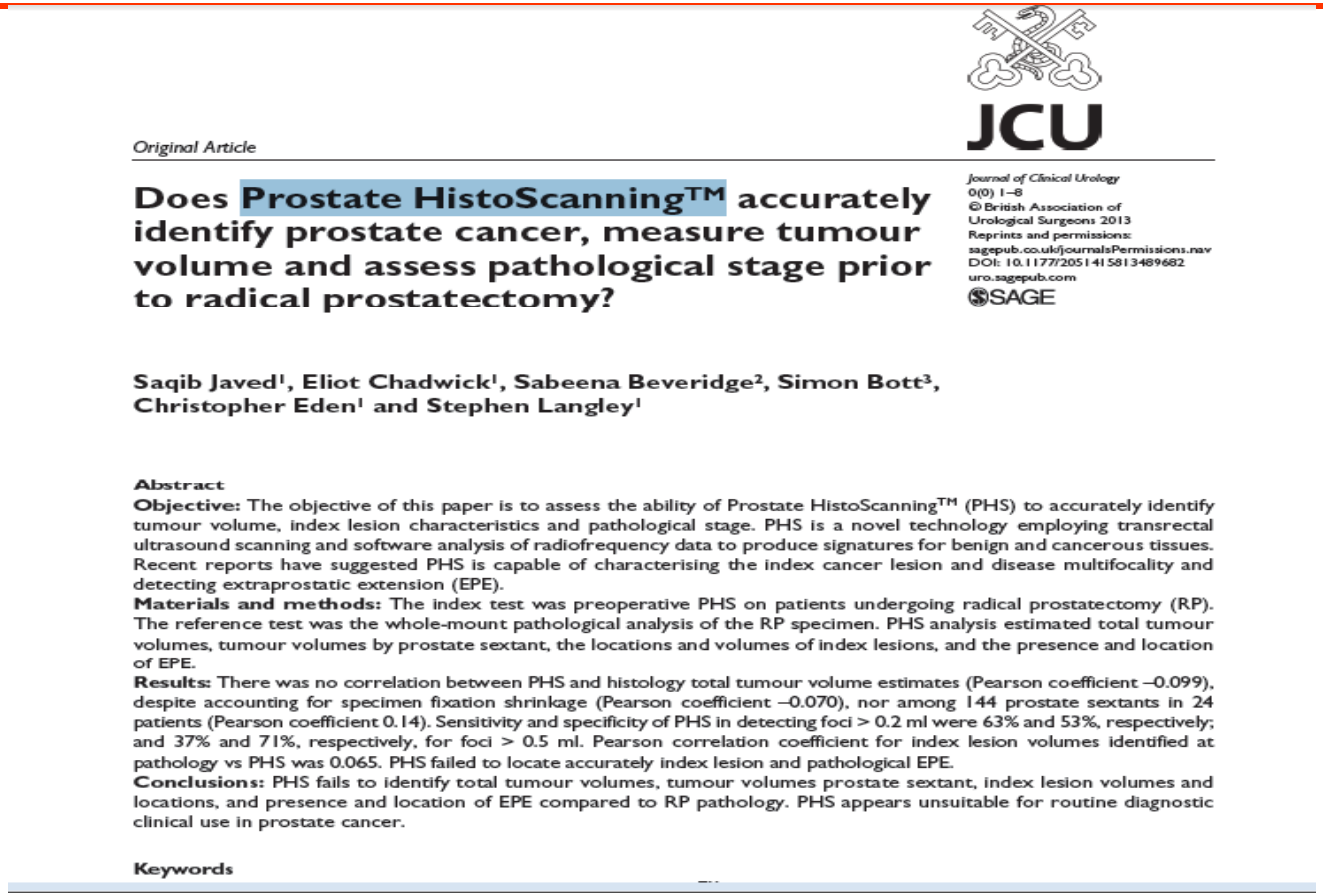
Histoscanning 2013



Original Article

JCU

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DOI: 10.1177/2051415813489682
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Does Prostate HistoScanning™ accurately identify prostate cancer, measure tumour volume and assess pathological stage prior to radical prostatectomy?

Saqib Javed[1], Eliot Chadwick[1], Sabeena Beveridge[2], Simon Bott[3], Christopher Eden[1] and Stephen Langley[1]

Abstract

Objective: The objective of this paper is to assess the ability of Prostate HistoScanning™ (PHS) to accurately identify tumour volume, index lesion characteristics and pathological stage. PHS is a novel technology employing transrectal ultrasound scanning and software analysis of radiofrequency data to produce signatures for benign and cancerous tissues. Recent reports have suggested PHS is capable of characterising the index cancer lesion and disease multifocality and detecting extraprostatic extension (EPE).

Materials and methods: The index test was preoperative PHS on patients undergoing radical prostatectomy (RP). The reference test was the whole-mount pathological analysis of the RP specimen. PHS analysis estimated total tumour volumes, tumour volumes by prostate sextant, the locations and volumes of index lesions, and the presence and location of EPE.

Results: There was no correlation between PHS and histology total tumour volume estimates (Pearson coefficient –0.099), despite accounting for specimen fixation shrinkage (Pearson coefficient –0.070), nor among 144 prostate sextants in 24 patients (Pearson coefficient 0.14). Sensitivity and specificity of PHS in detecting foci > 0.2 ml were 63% and 53%, respectively; and 37% and 71%, respectively, for foci > 0.5 ml. Pearson correlation coefficient for index lesion volumes identified at pathology vs PHS was 0.065. PHS failed to locate accurately index lesion and pathological EPE.

Conclusions: PHS fails to identify total tumour volumes, tumour volumes prostate sextant, index lesion volumes and locations, and presence and location of EPE compared to RP pathology. PHS appears unsuitable for routine diagnostic clinical use in prostate cancer.

Keywords

Conclusions: PHS fails to identify total tumour volumes, tumour volumes prostate sextant, index lesion volumes and locations, and presence and location of EPE compared to RP pathology. PHS appears unsuitable for routine diagnostic clinical use in prostate cancer.

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Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

The PICTURE study – Prostate Imaging (multi-parametric MRI and Prostate HistoScanning™) Compared to Transperineal Ultrasound guided biopsy for significant prostate cancer Risk Evaluation

Lucy A.M. Simmons [a,*], Hashim Uddin Ahmed [a], Caroline M. Moore [a], Shonit Punwani [b], Alex Freeman [c], Yipeng Hu [d], Dean Barratt [d], Susan C. Charman [e], Jan Van der Meulen [e], Mark Emberton [a]

Contemporary Clinical Trials 37 (2014) 69–83

PICTURE: MRI-guided biopsy versus histoscanning

N = 330 men underwent
mpMRI and transperineal mapping biopsy

UCL Advanced Diagnostics
Clinical Trials Service

103 of 249 men had significant PCA (GI pattern 4, core-length > 6 mm)

	sensitivity	specificity	NPP
mpMRI: (PIRADS ≥3)	97.1%	21.9%	91.4%
histoscanning:	93.4%	0.8%	91.4%

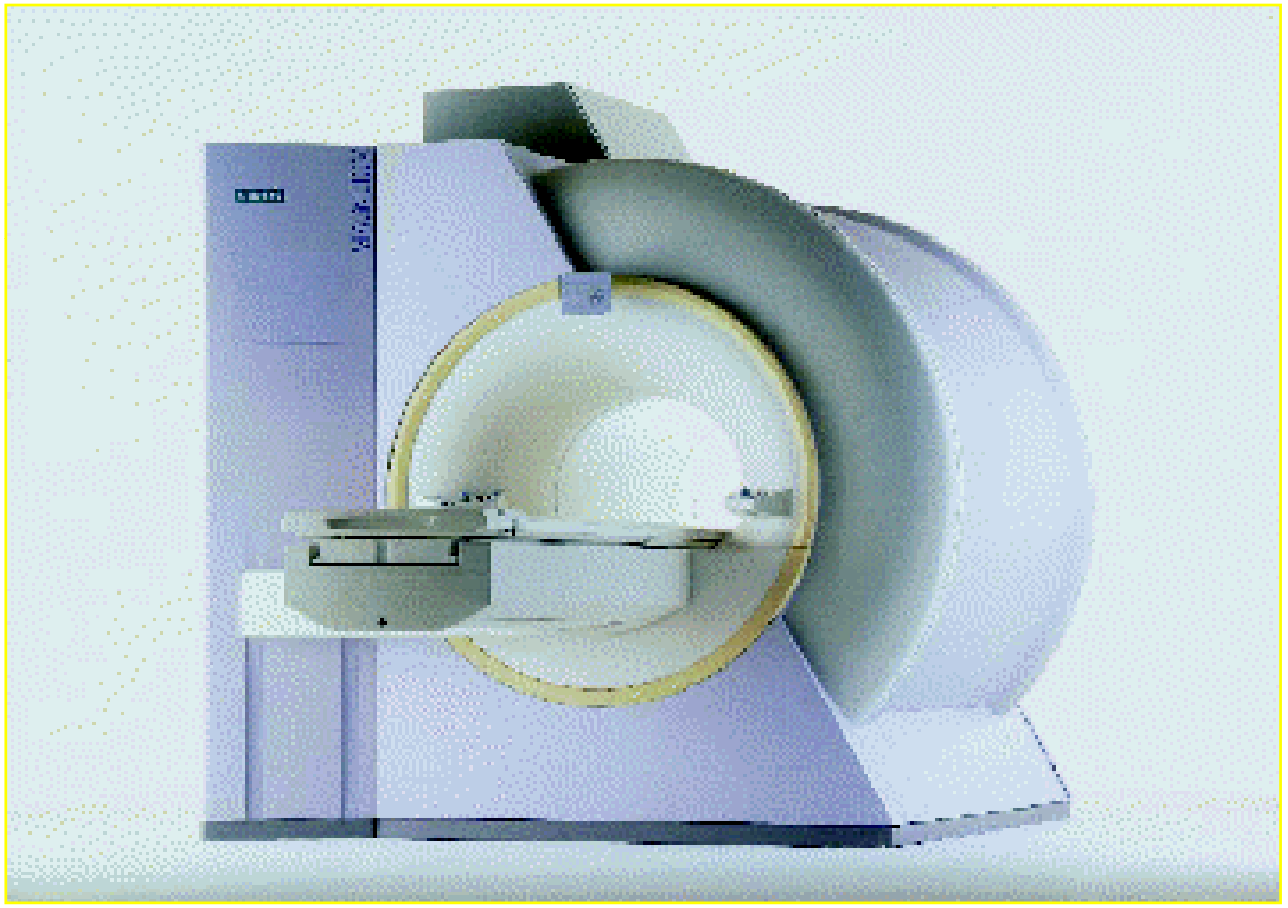
mpMRI outperforms histoscanning in the detection of significant PCA after prior negative TRUS-bx

Abstract # 498

Simmons, L., Kanthabalan, A., Hu, Y., Barrat, D., Punwani, S., Ramachandran, N., Jameson, C., Freeman, A., McCartan, N., Briggs, T., Gelister, J., Charman, S., VanDer Muelen, J., Moore, C., Ahmed, H., Emberton, M.
University College Hospital and Institutes, London

EAU16 MUNICH 11-15 March 2016

Imaging of Prostate Cancer
Body Coil Imaging



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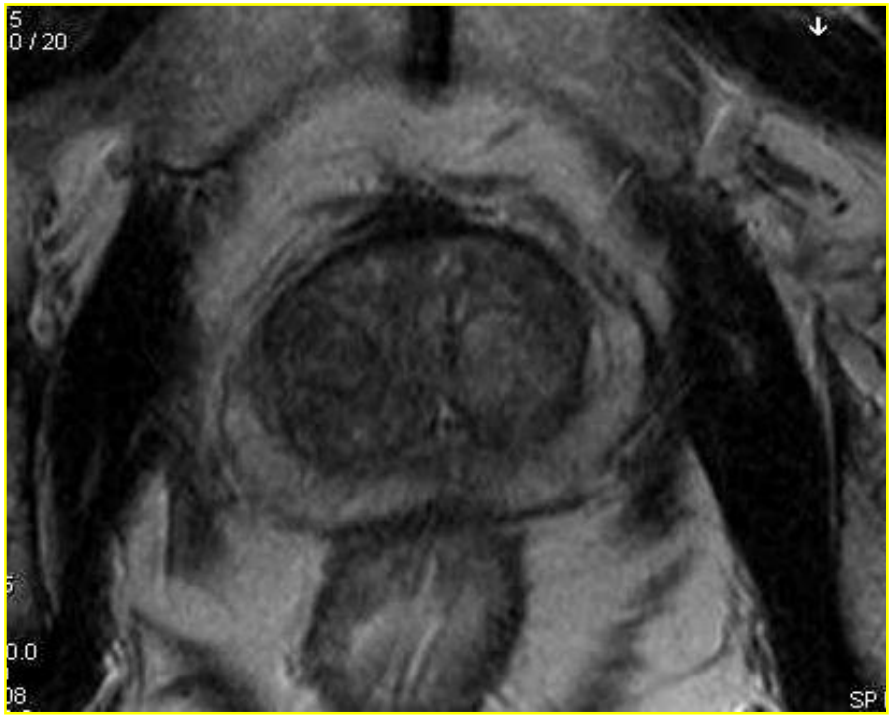
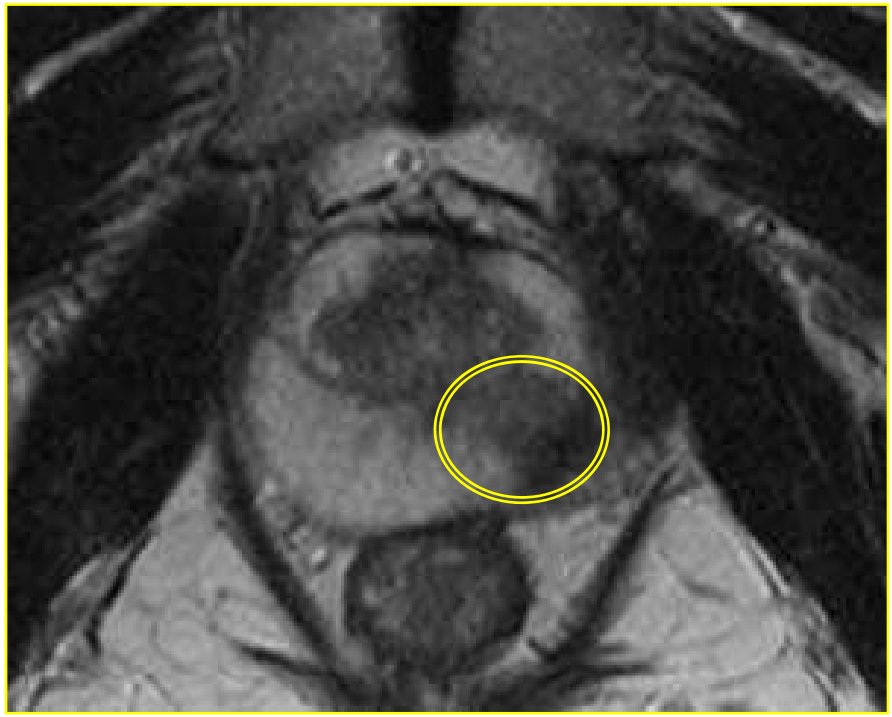
Imaging of Prostate Cancer
Tumour Detection (Body Coil)





Decreased signal intensity relative to normal peripheral zone tissue (70% in peripheral zone)

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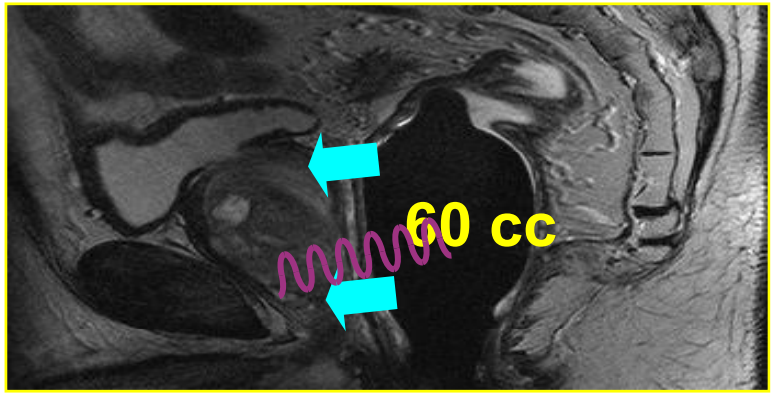
Imaging of Prostate Cancer
Diagnostic Accuracy (Body Coil) (Sensitivity)

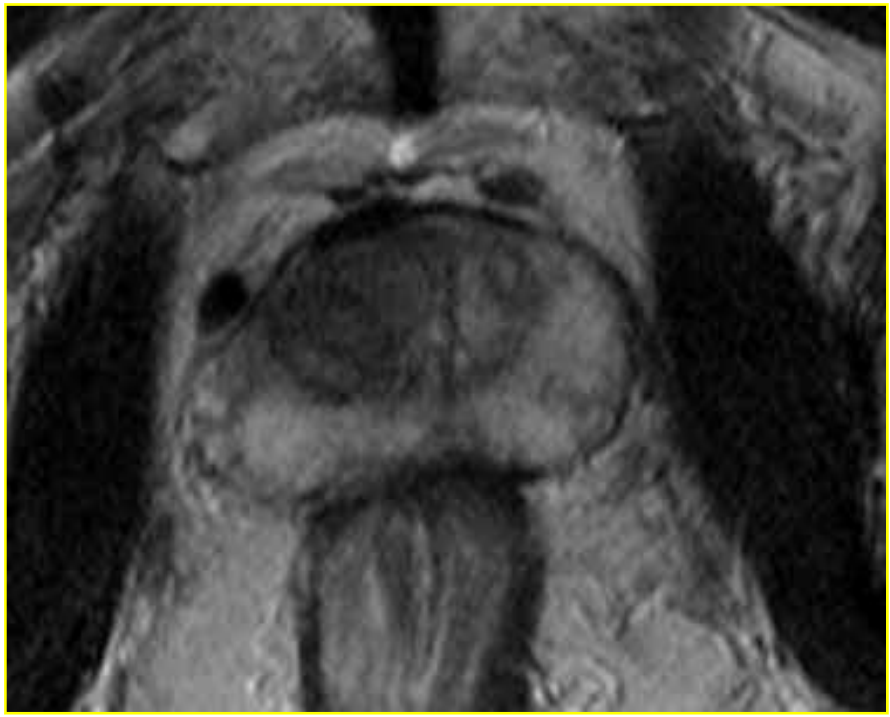
Carter	Radiology 1991;178:523	48%
Tempany	Radiology 1994;192:47	54%
Hricak	Radiology 1994;193:703	68%
Rifkin	N Engl J Med 1990;323:621	69%
Jager	Radiology 1997;203:645	72%
Huch Boni	Clin Radiol 1995;50:593	76%
Kier	AJR 1993;161:601	87%

Imaging of Prostate Cancer
Endorectal Coil Imaging

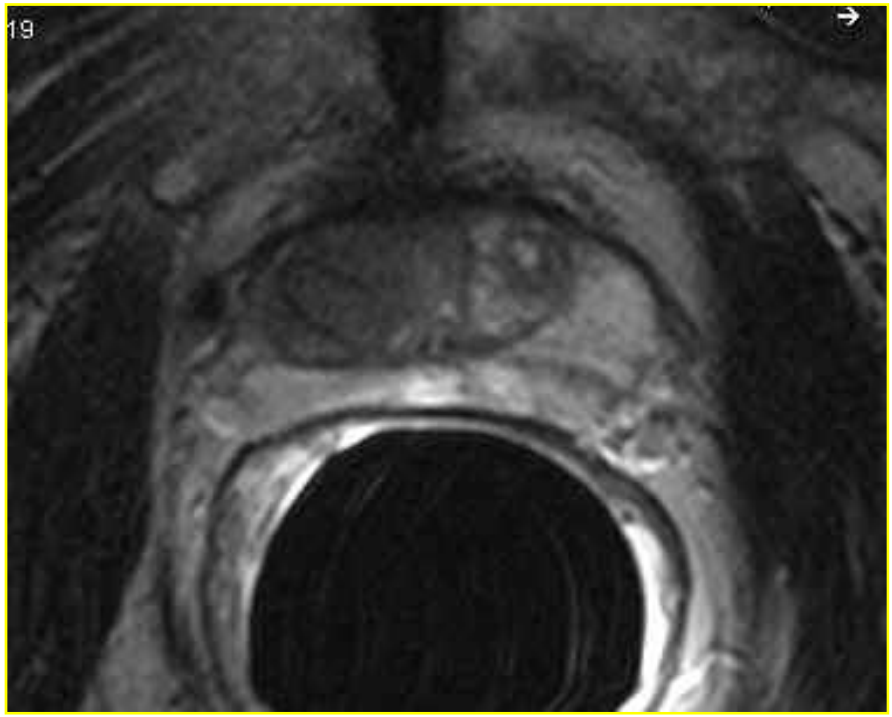
Endorectal Coil



Imaging of Prostate Cancer
Body coil versus Endorectal coil



Normal Prostate with Body Coil



Normal Prostate with Endorectal Coil

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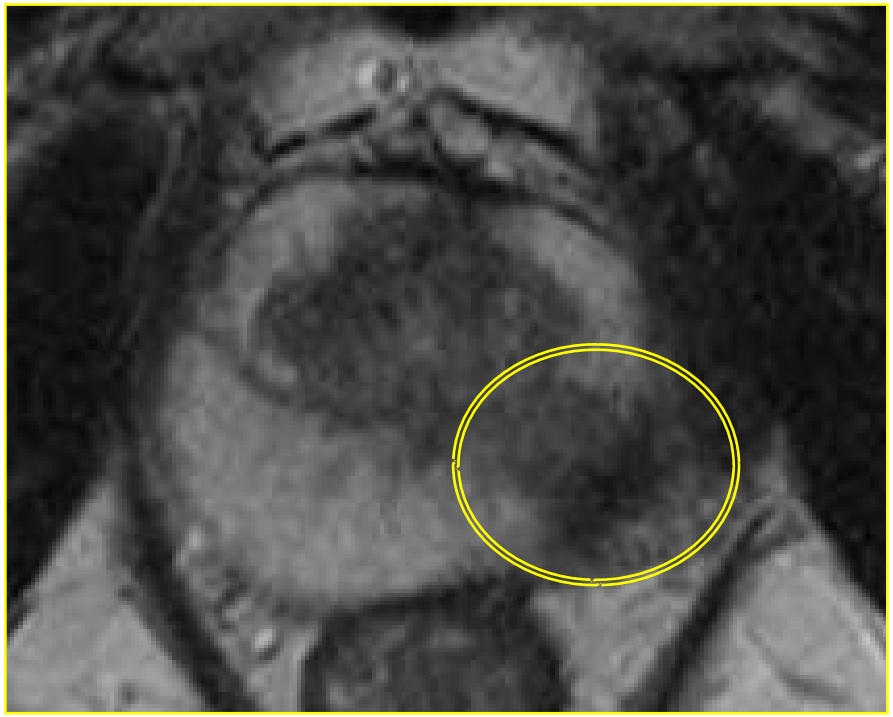
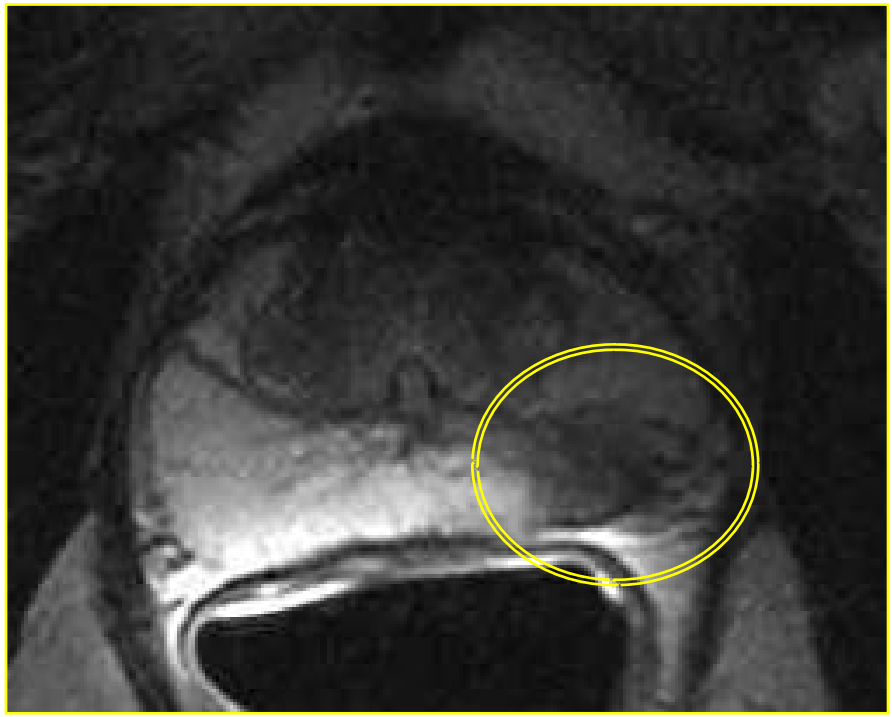
Imaging of Prostate Cancer
Tumour Presence (Endorectal Coil)



Peripheral Zone Tumour with Body Coil

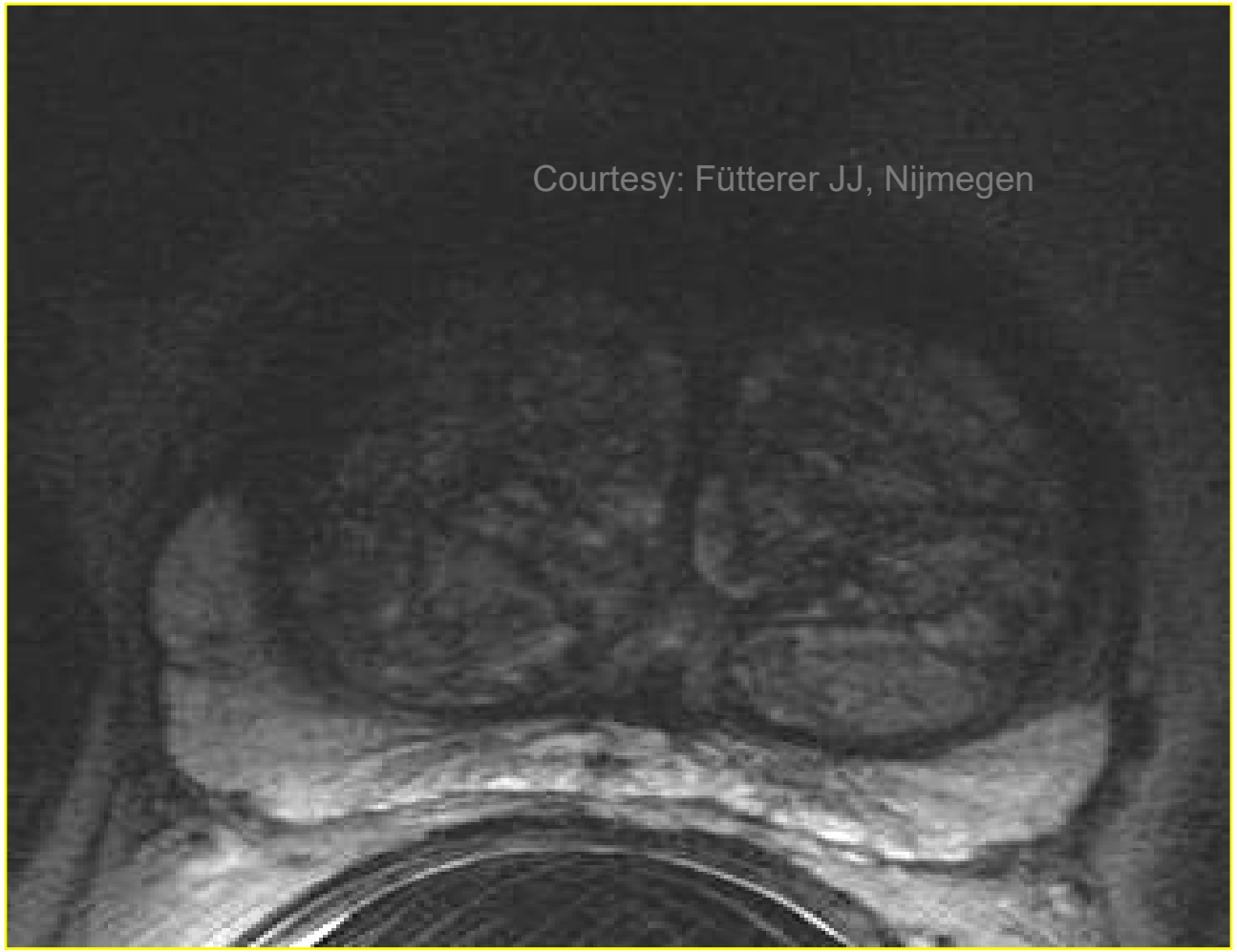


Peripheral Zone Tumour with Endorectal Coil

Imaging of Prostate Cancer
Diagnostic Accuracy (Endorectal Coil)
(Sensitivity

Tempany	Radiology 1994;192:47	61%
Presti	AJR 1996;166:103	63%
Beyersdorff	Radiology 2002;224:701	68%
Perrotti	J Urol 1999;162:1314	70%
Vilanova	Eur Radiol 2001;11:229	71%
Ogura	Urology 2001;57:721	72%
Ikonen	Acta Radiol 2001;42:348	74%
Cornud	Br J Urol 1996;77:843	74%
Bates	Clin Radiol 1996;51:550	77%
Bartolozzi	Eur Radiol 1996;6:339	82%
Huch Boni	JCAT 1995;19:232	82%
Huch Boni	Clin Radiol 1995;50:593	88%

Imaging of Prostate Cancer
Tumour detection @ 3 Tesla



Kim, J Comput Assist Tomogr 2006;30:7-11 (70%)
Heijmink, Radiology 2007;244:184 (ERC > BC)

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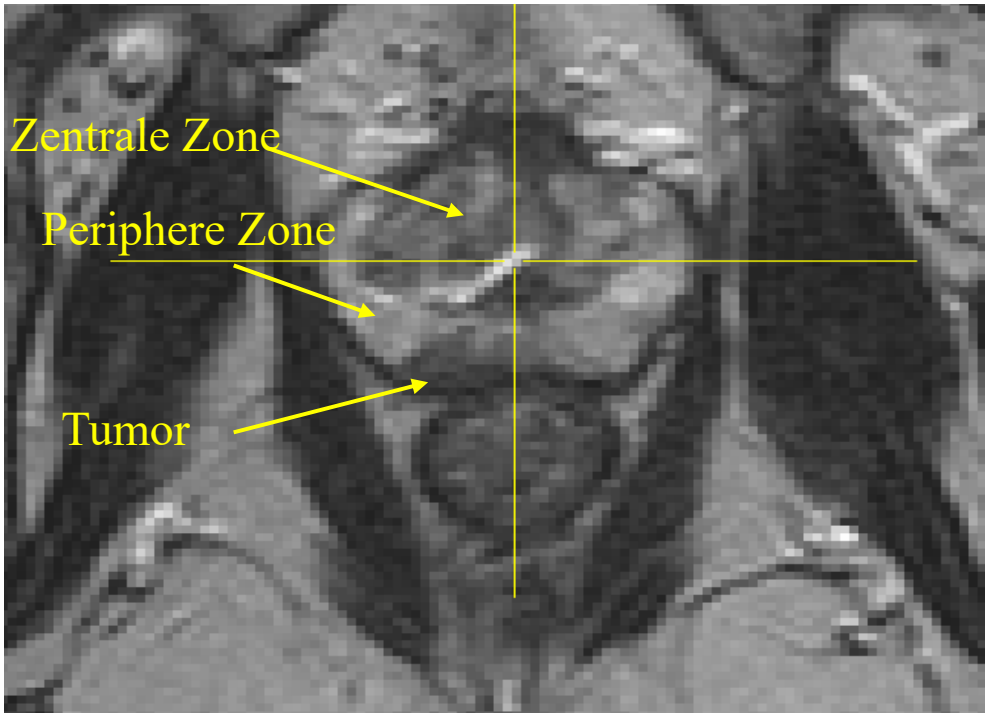
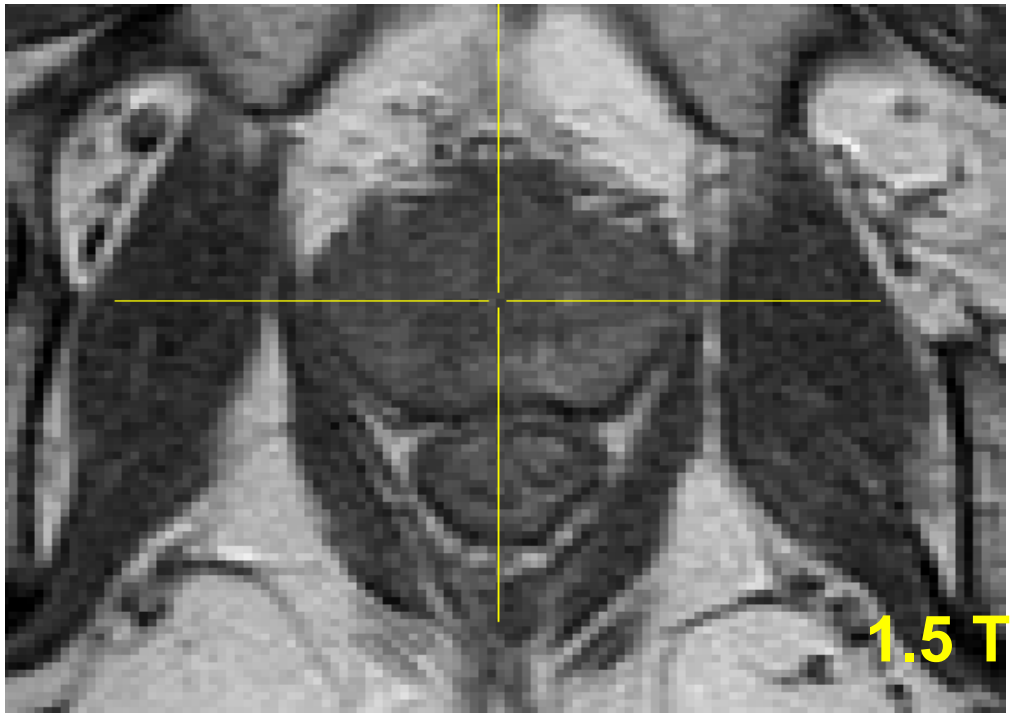
1.5 Tesla MRI

MRI:

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



T2-weigthed



T1-weighted

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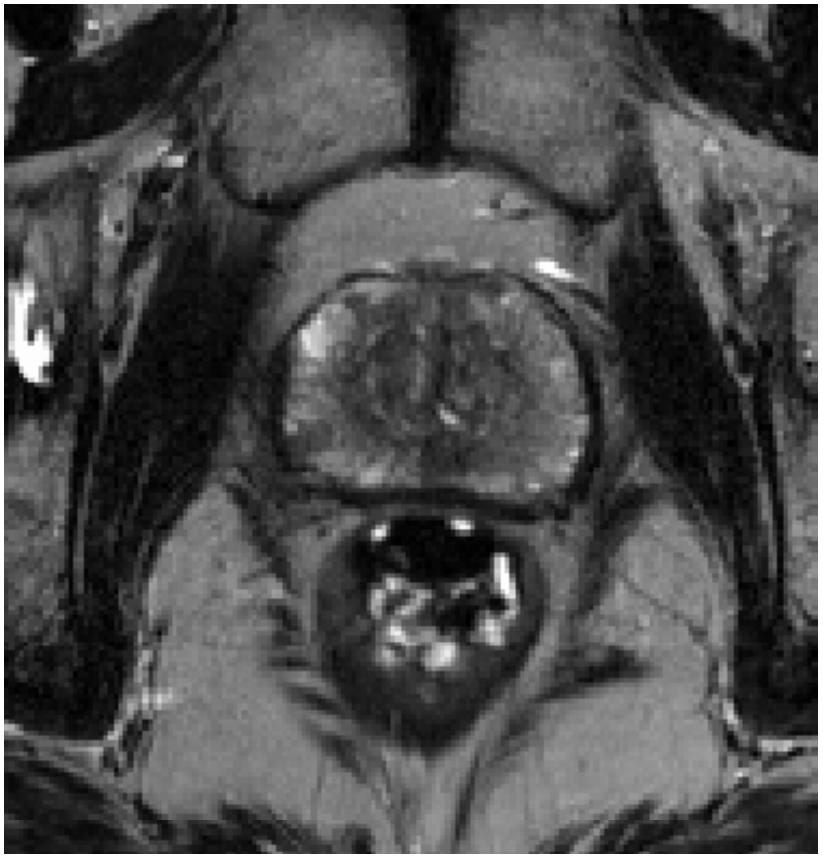
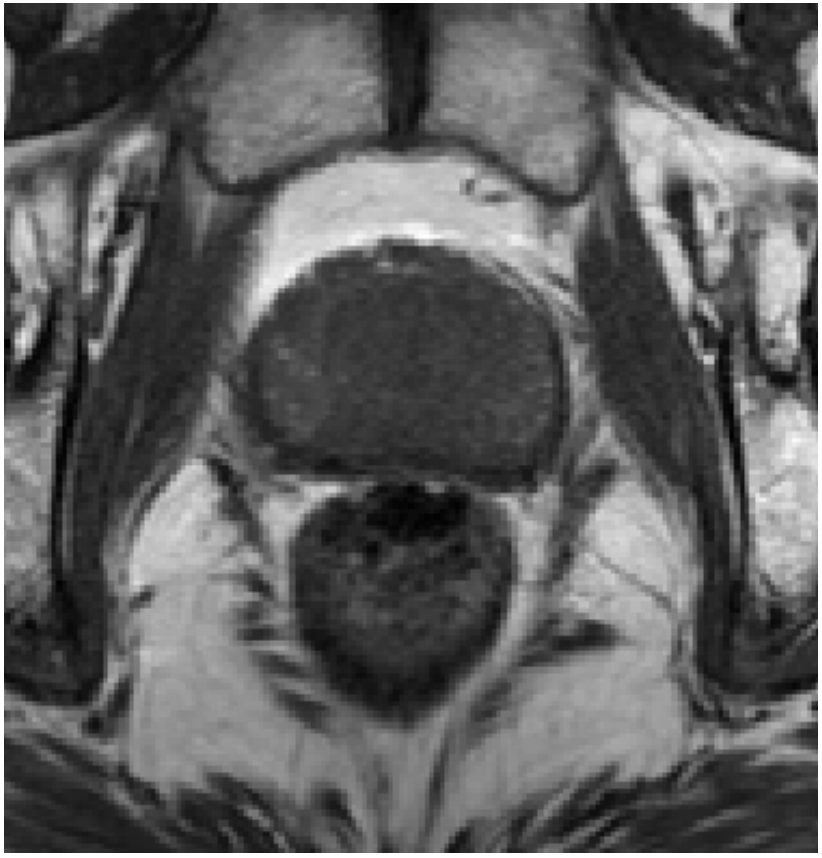
3.0 Tesla MRI



T2 -weighted



T1 weighted

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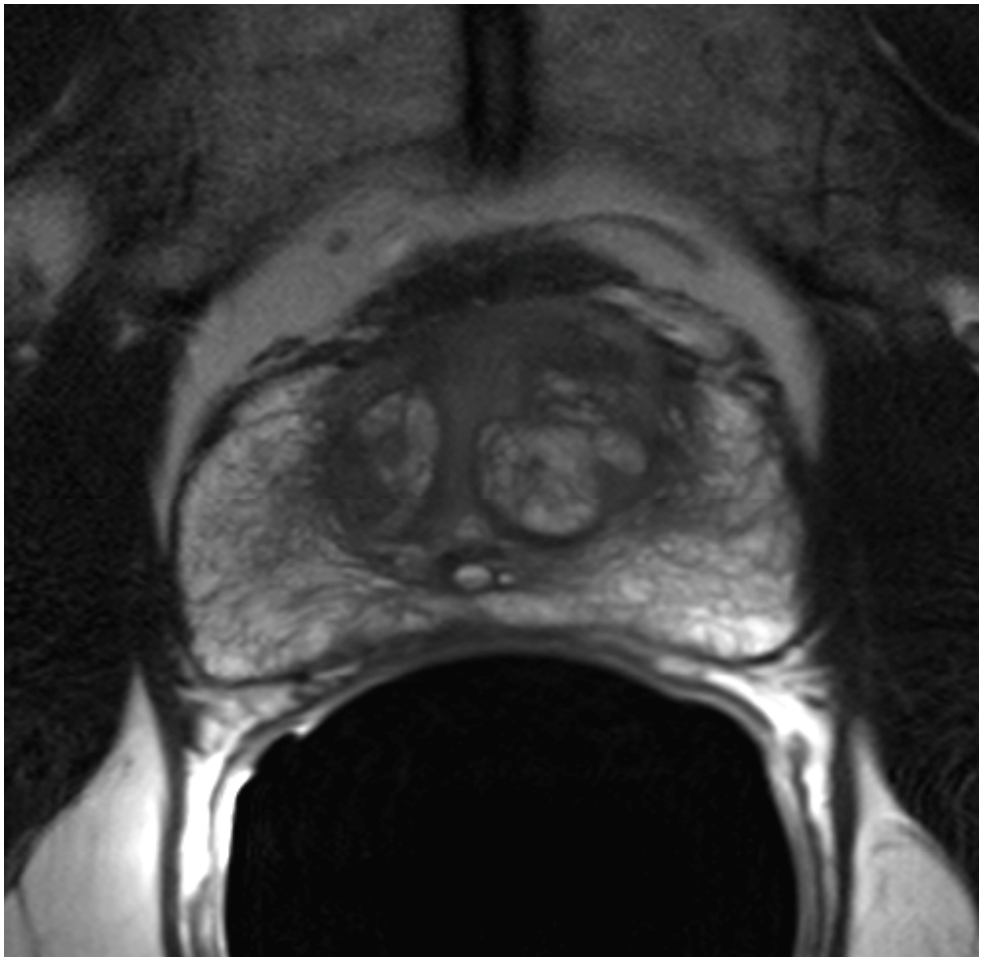
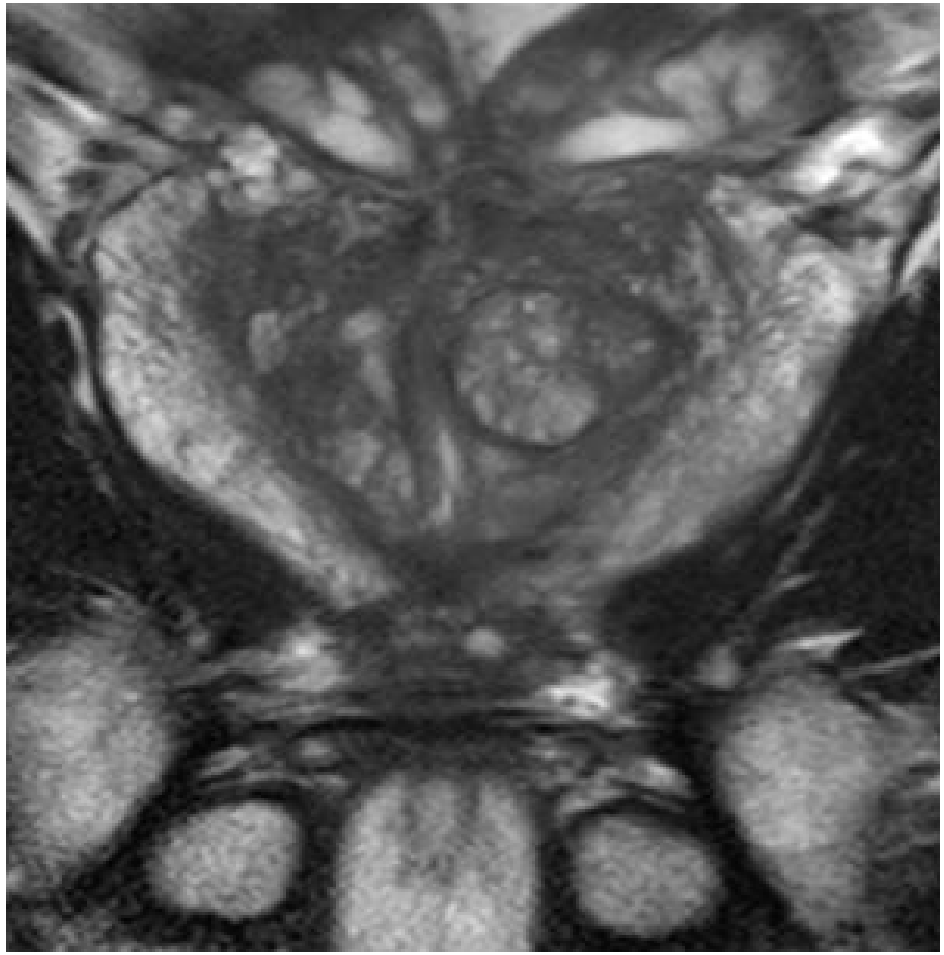
3.0 Tesla MRI + Endorectal coil





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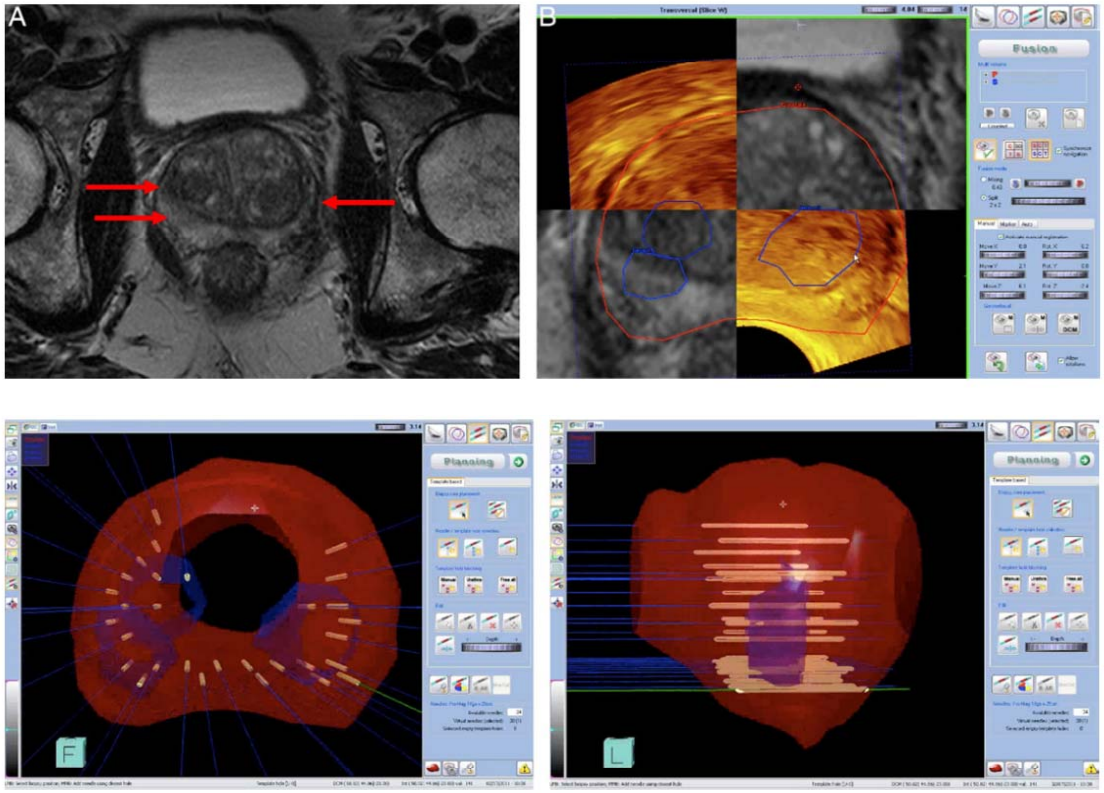
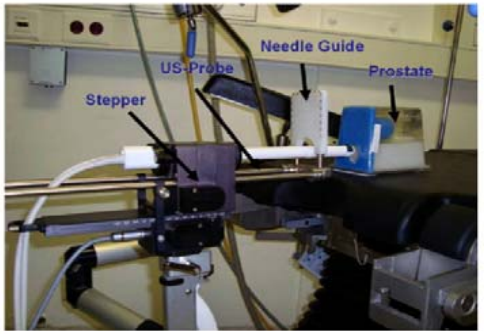
MRT-Ultrasound-Fusion





Hradaschik, J Urol 2012

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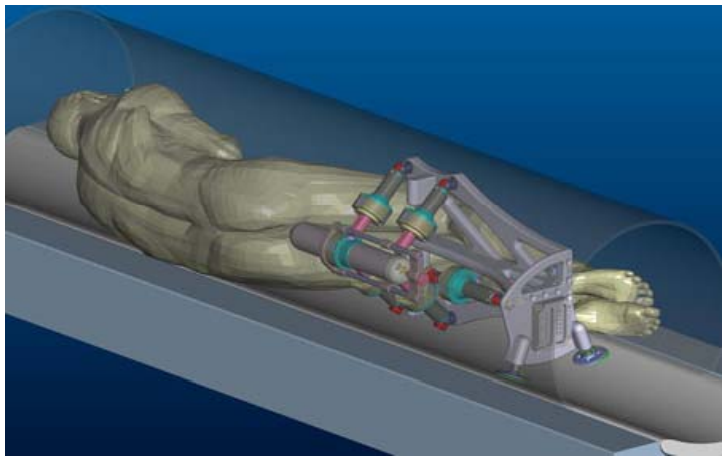
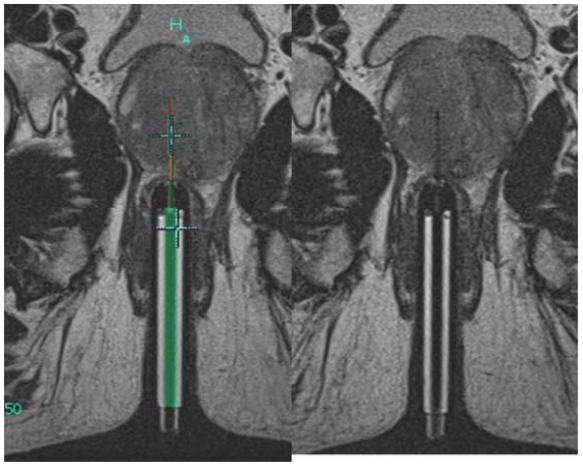
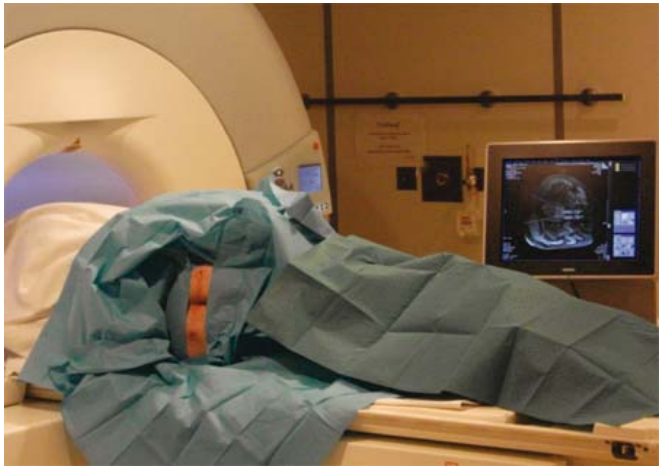
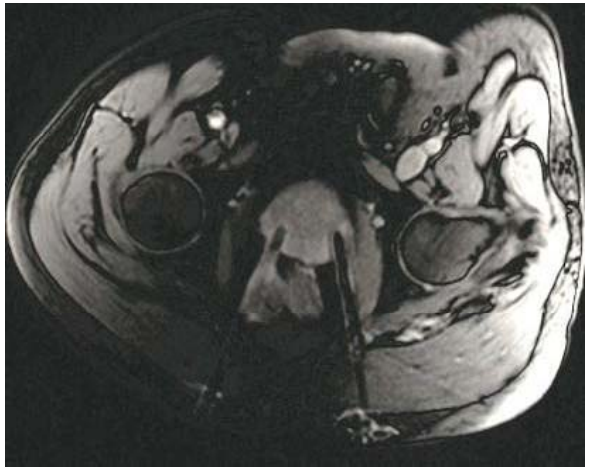
MR-guided Biopsy





Transrectal approach: roboter-guided biopsy





Transgluteal approach in open MR

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Functional Imaging

Functional Imaging

- **Magnetic Resonance Spectroscopy**
- **Dynamic Contrast-Enhanced MRI**
- **Diffusion Weighted Imaging**
- **Cholin PET**

Magnetic Resonance Spectroscopy

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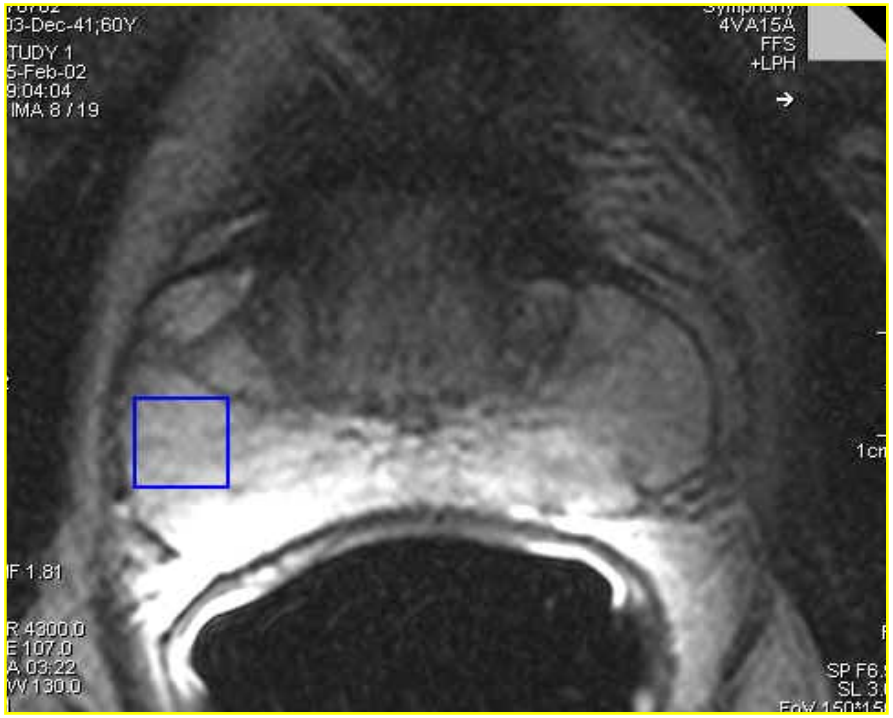
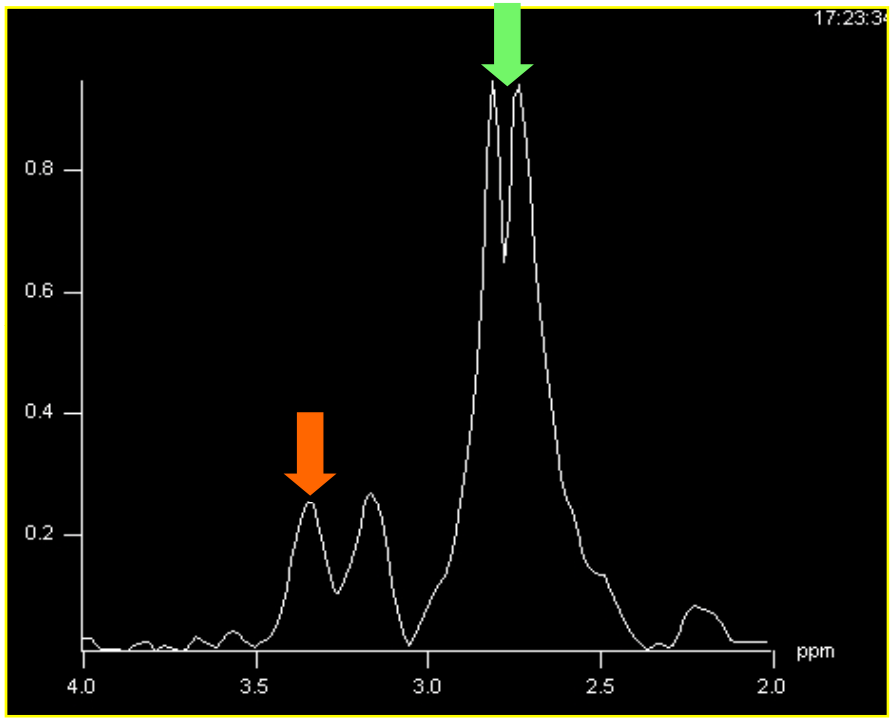
MR-Spectroscopy

- **acquisition of spectra from small volumes (voxels) throughout the prostate gland**

- **detection of cellular metabolites**
  - **citrate in normal tissue and BPH**
  - **choline in tumour lesions**

MR-Spectroscopy
Normal Prostate





Normal prostate volume

^{1}H-spectra: dominant citrate peak no elevated choline

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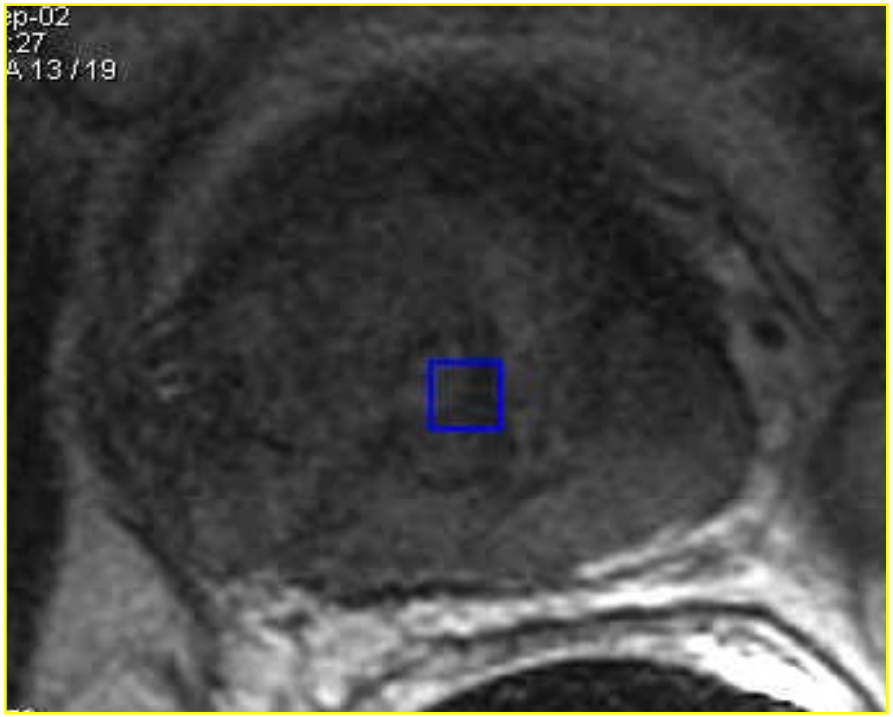
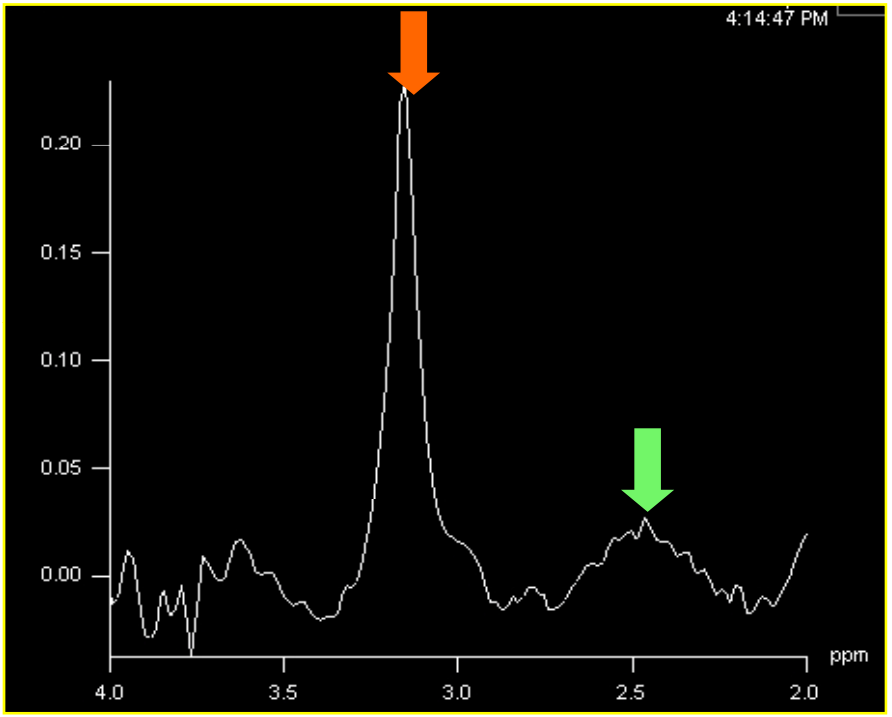
MR-Spectroscopy
Prostate Cancer





Prostate Cancer

^{1}H-spectra:
reduced citrate
elevated choline

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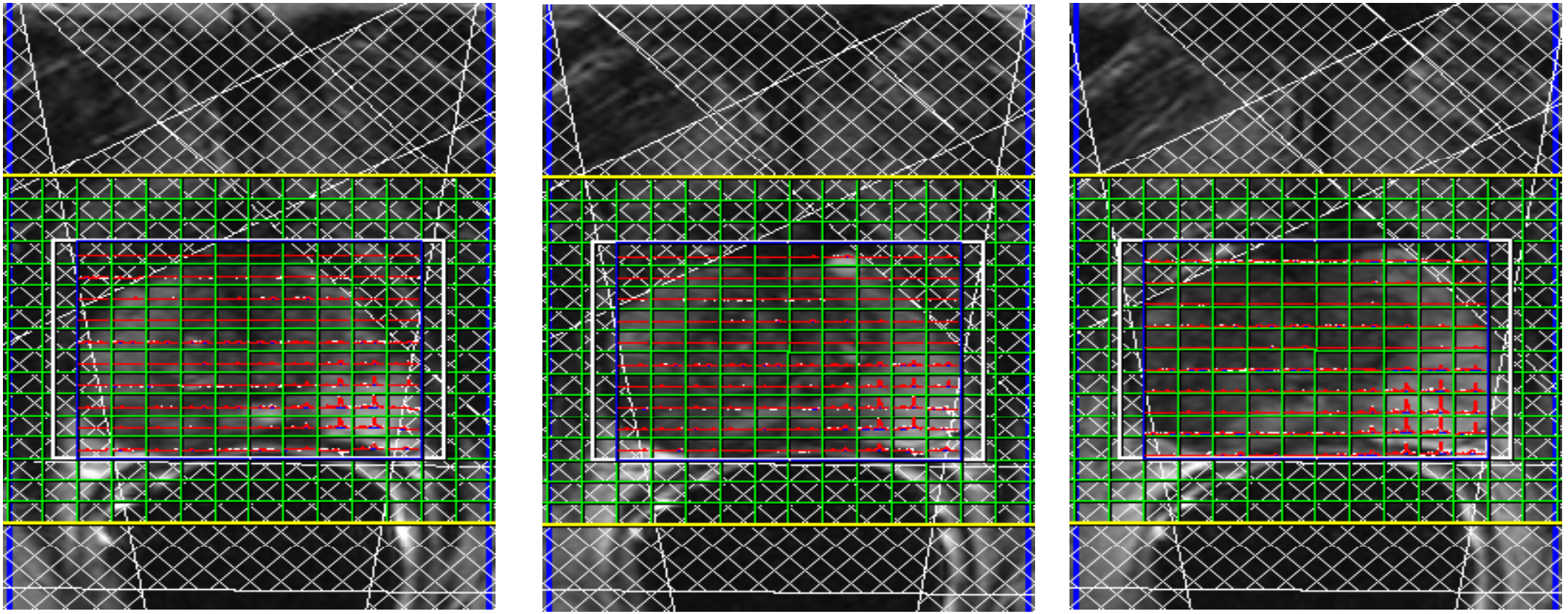
MR-Spectroscopy
Spectral Maps



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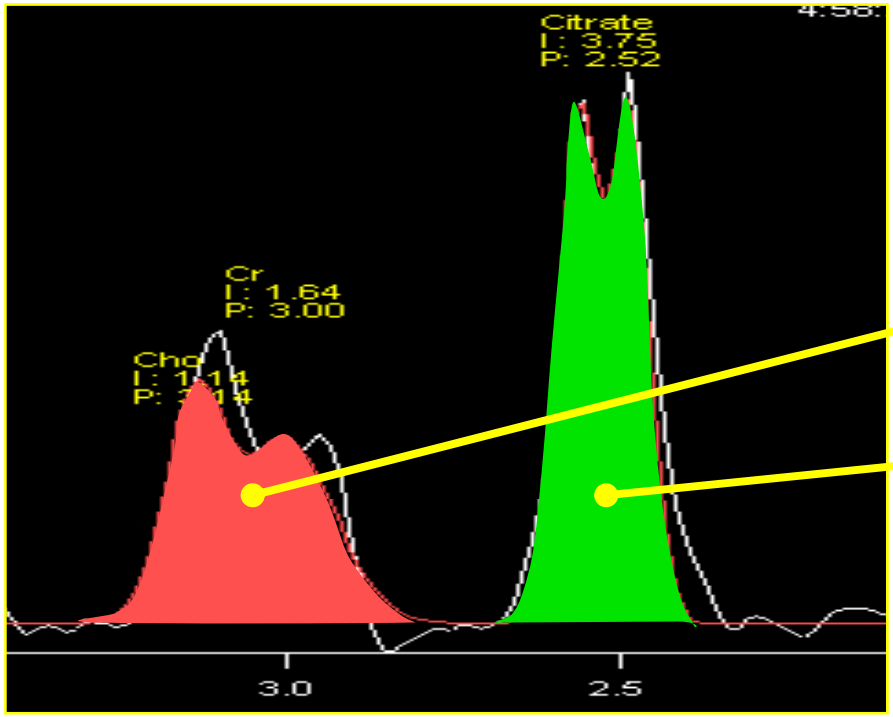
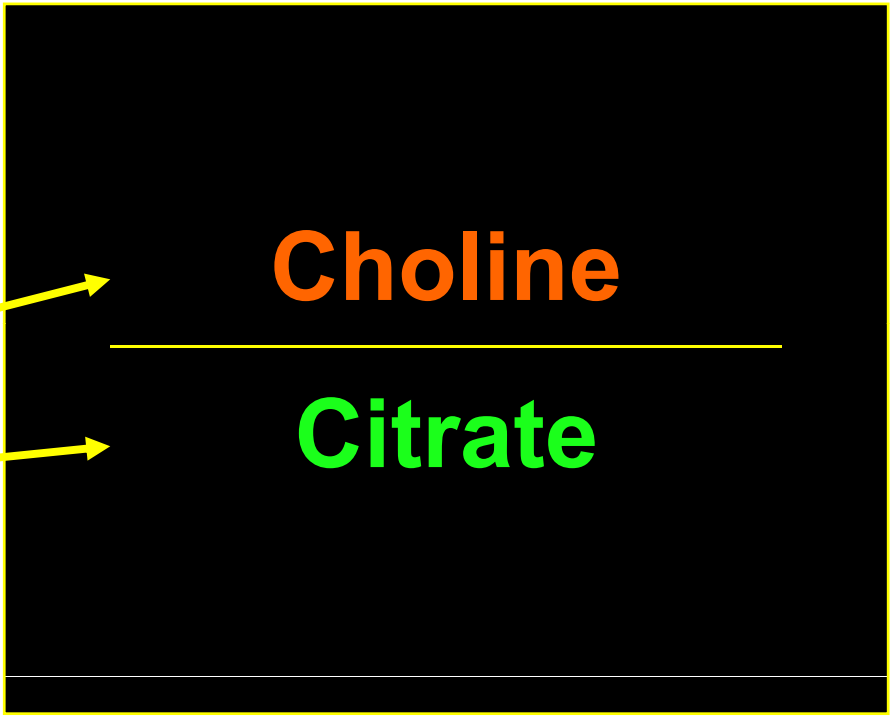
MR-Spectroscopy
Choline/Citrate Ratio Images

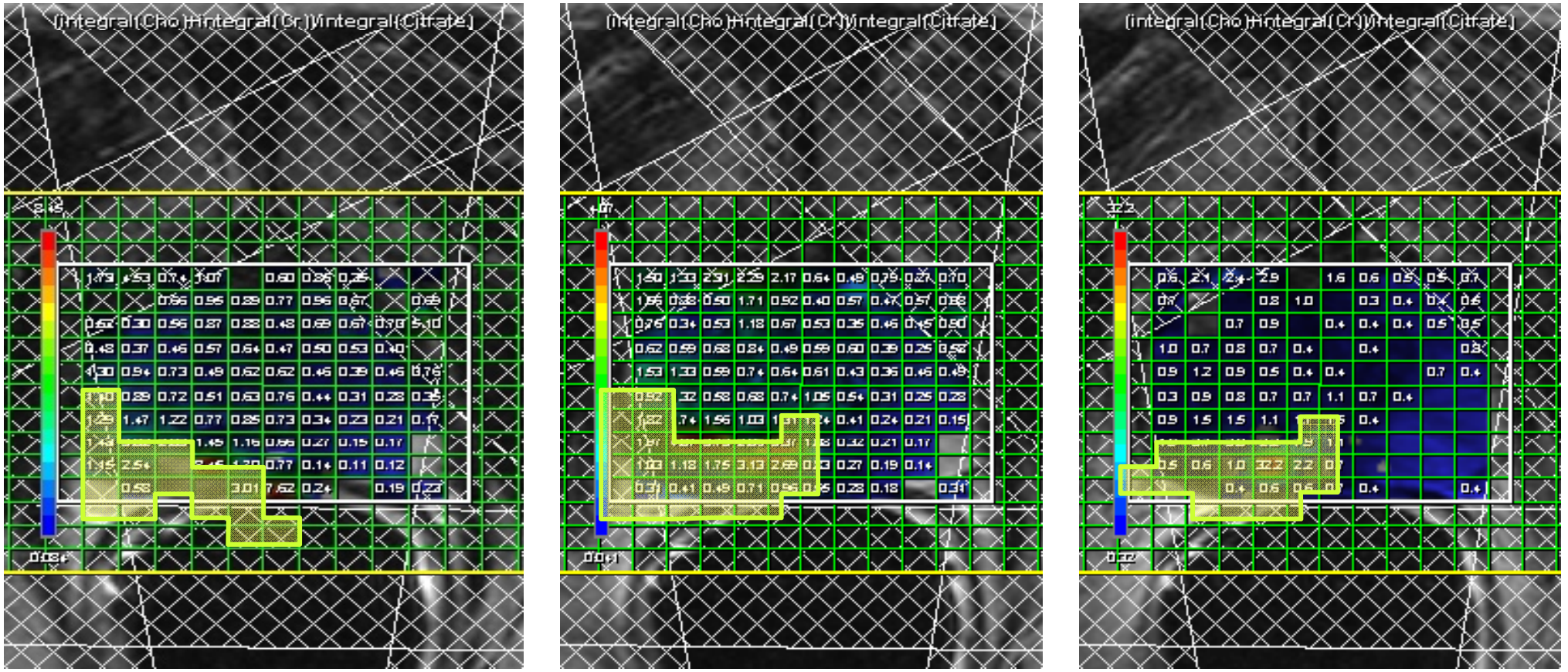




Spectrum

Index

MR-Spectroscopy
Choline/Citrate Ratio Images



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MR-Spectroscopy
Diagnostic accuracy (Sensitivity)

Wefer	J Urol 2000;164:400	69%
Scheidler	Radiology 1999;213:473	67-74%
Zakian	Radiology 2005;234:804	**71%**
Prando	Radiology 2005;236:903	67-79%
Jung	Radiology 2004;233:701	74-85%
Villeirs	Eur J Radiol 2009	78%
Fütterer	Doctoral Thesis 2006	82-85%
Casciani	Radiol Med 2004;108:530	91%

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Dynamic Contrast-Enhanced MRI

Dynamic Contrast-Enhanced MRI
Assessment of Angiogenesis

Lesion Morphology

Angiogenic Factors

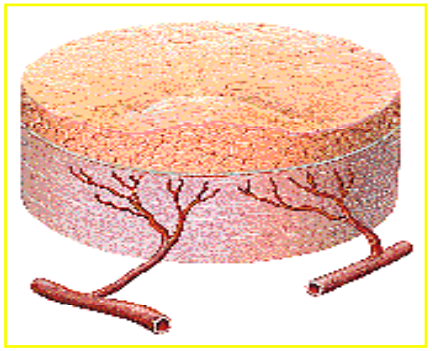
Growth of existing vessels
De novo angiogenesis

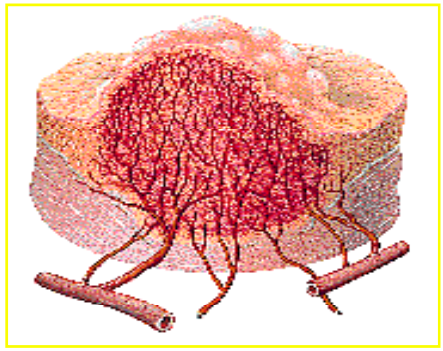
Abnormal configuration:
AV-shunts and defective endothelium

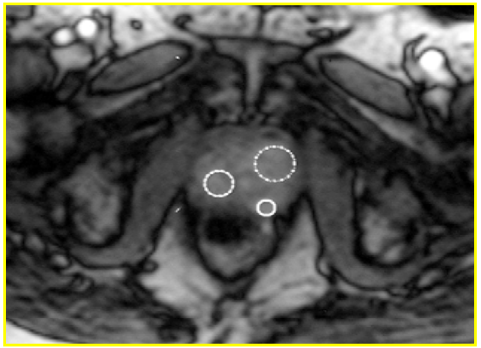
Enhancement

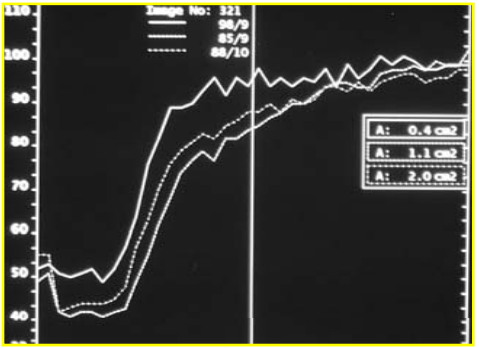
Increased in- en efflux
Expanded extracellular space
Increased extravasation

Earlier onset of enhancement
Increased slope









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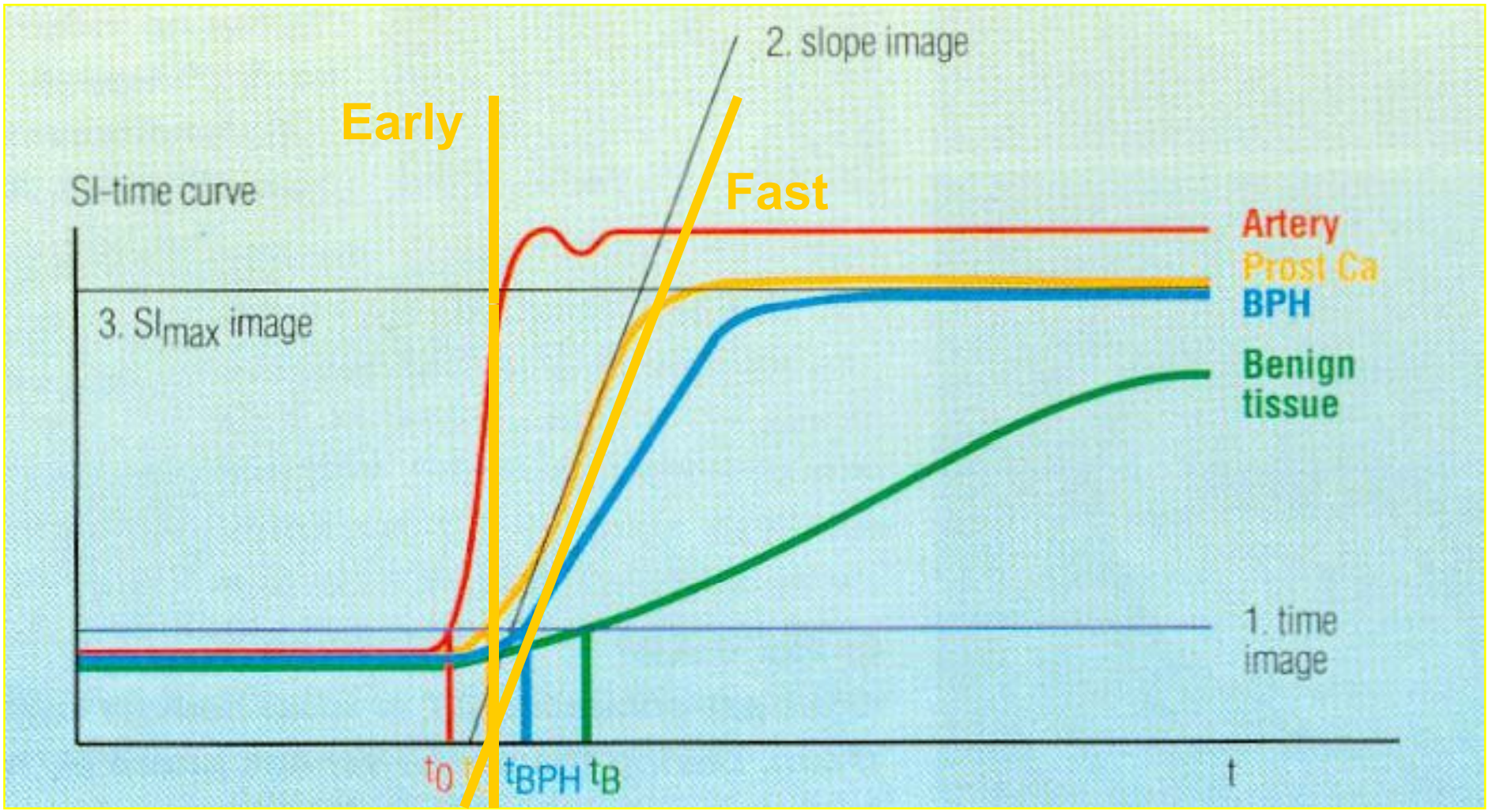
Dynamic Contrast-Enhanced MRI Assessment of Angiogenesis



*G. Jager, J. Barentsz, Nijmegen Group

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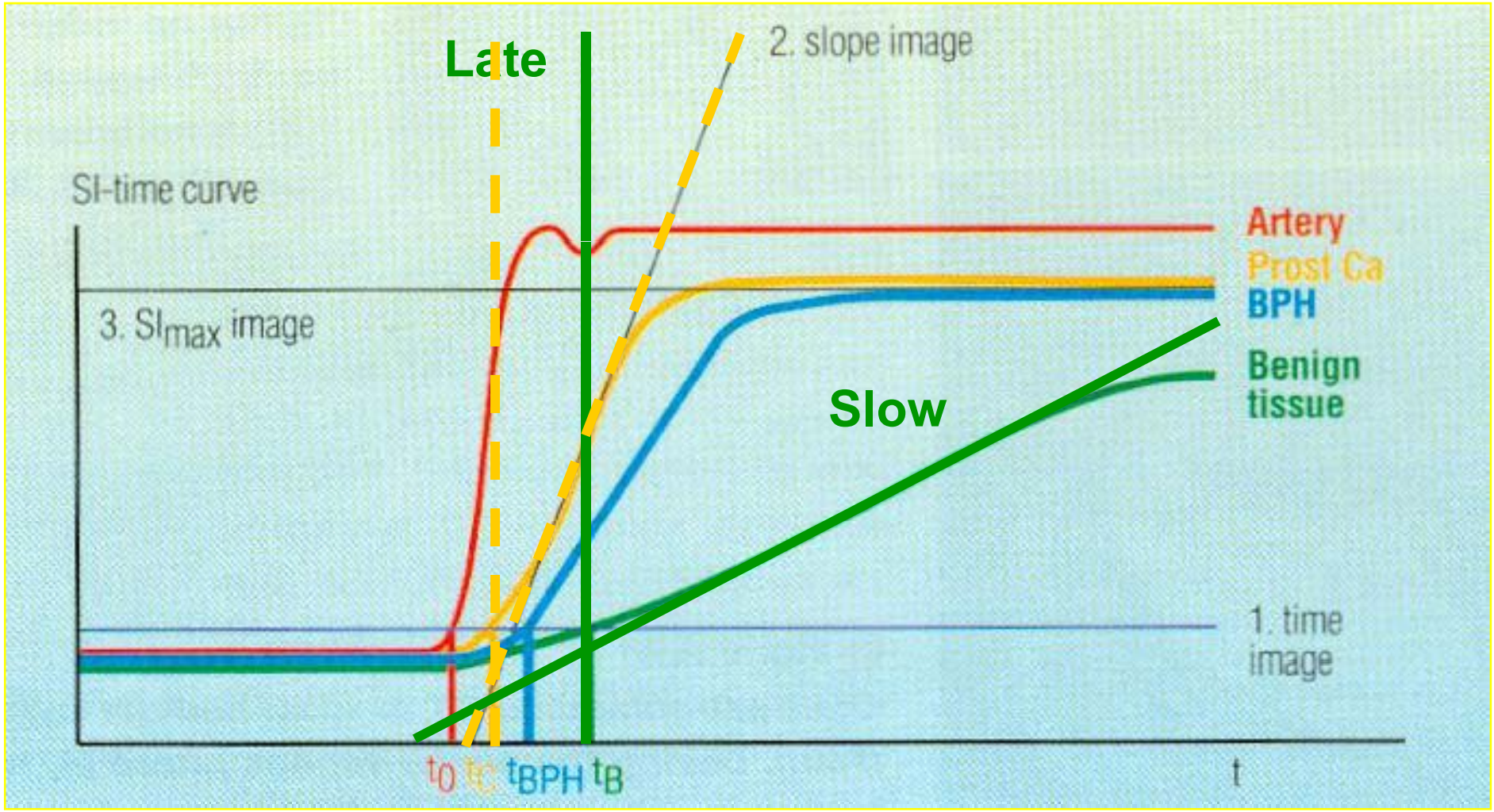
Dynamic Contrast-Enhanced MRI Assessment of Angiogenesis



*G. Jager, J. Barentsz, Nijmegen Group

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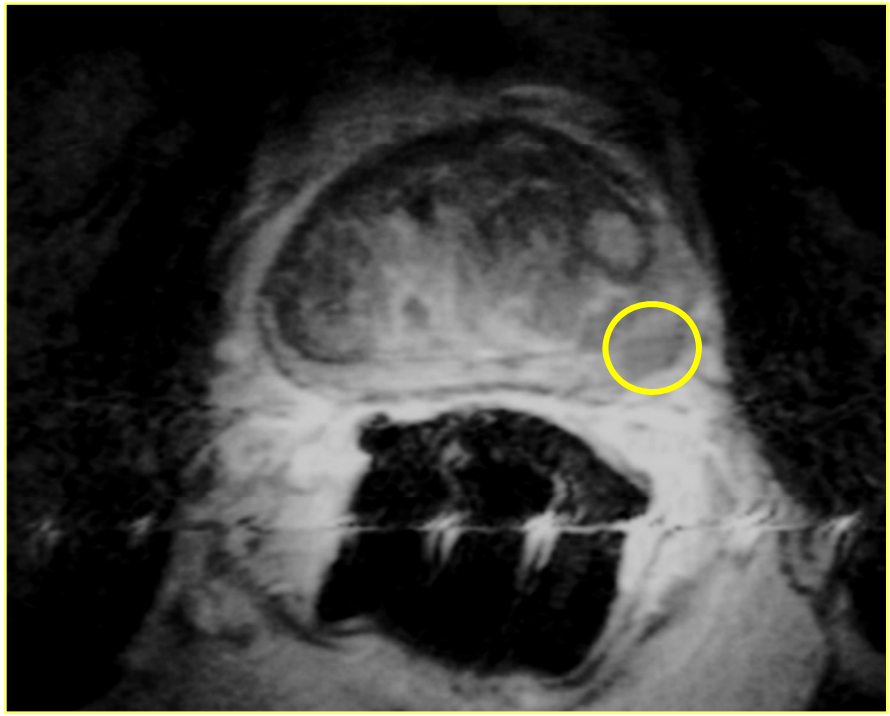
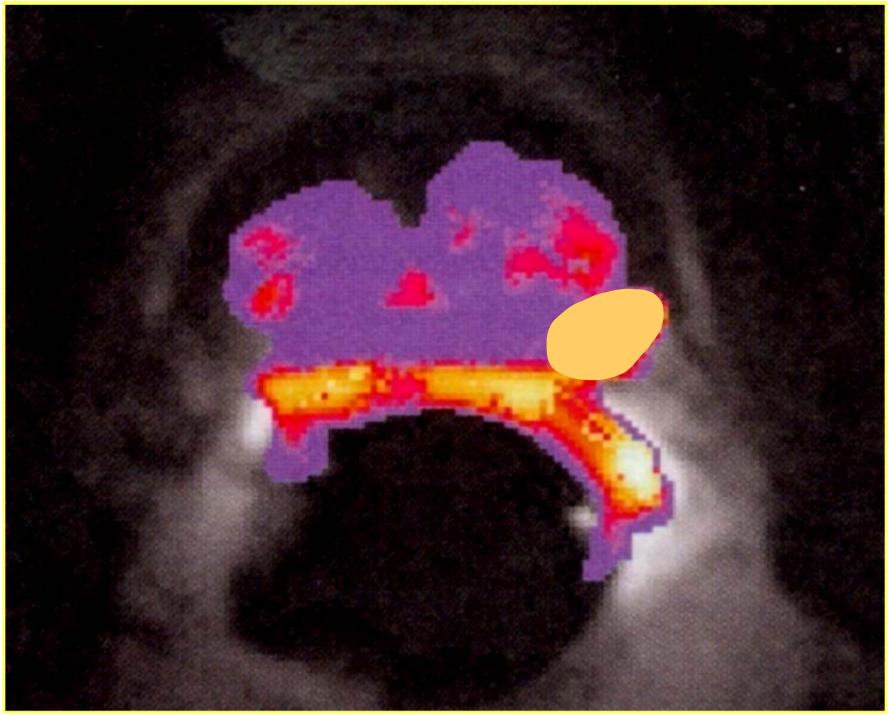
Dynamic Contrast-Enhanced MRI Assessment of Angiogenesis





63-year old man
Suspicious lesion in left peripheral zone

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Imaging of Prostate Cancer
Diagnostic accuracy (dCE MRI)(Sensitivity)

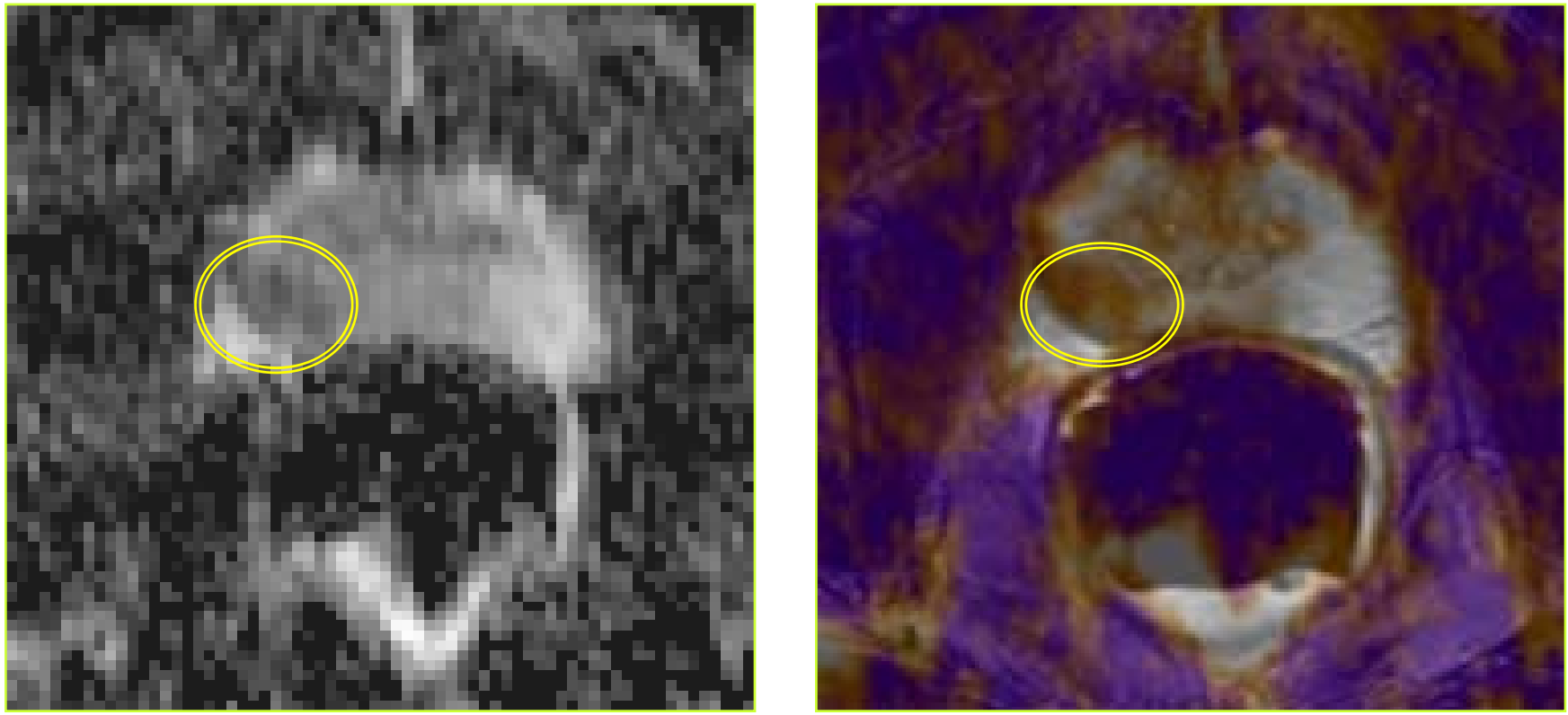
Jager	Radiology 1997;203:645	78%
Namimoto	Co Med Im Gr 1998;22:239	79%
Ogura	Urology 2001;57:721	72%
Muramoto	Eur J Radiol 2002;44:52	92%
Ito	Br J Radiol 2003;76:617	82%
Hara	Prostate 2005;62:140	80%
Kim	J Magn Res Im 2005;22:639	88%
Fütterer	Radiology 2006;241:449	81-91%

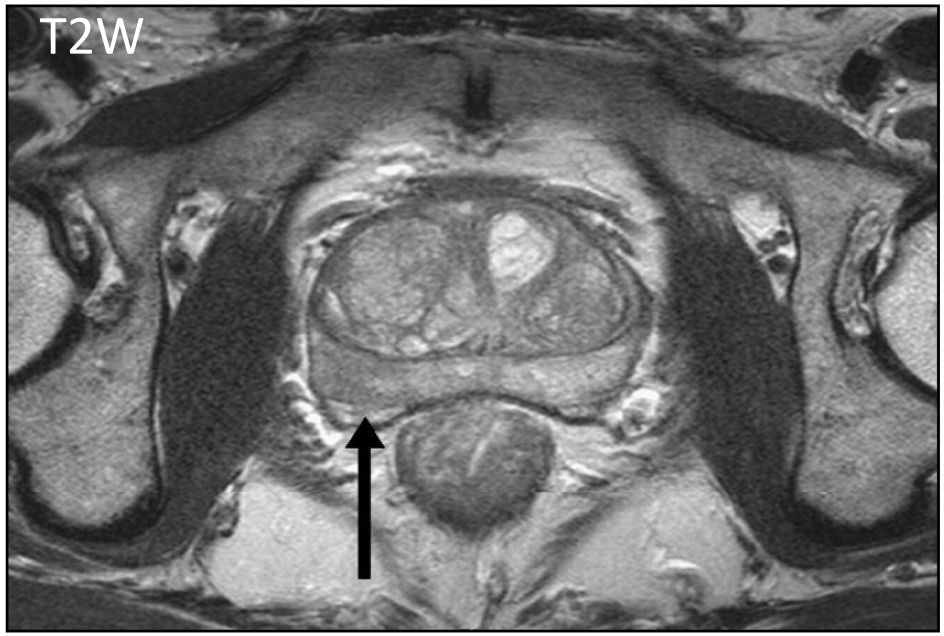
Diffusion Weighted Imaging

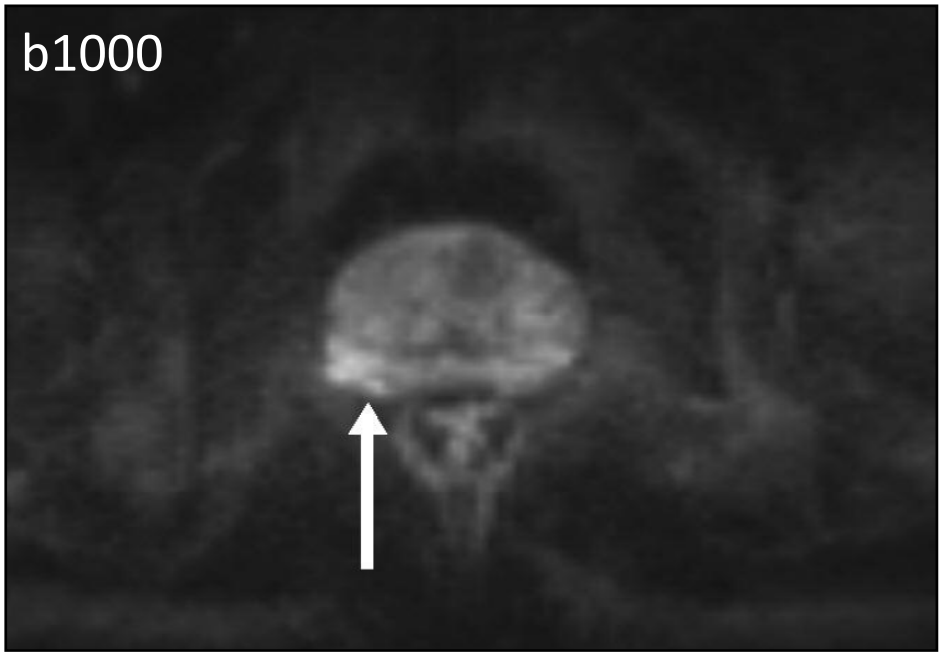
Diffusion Weighted Imaging

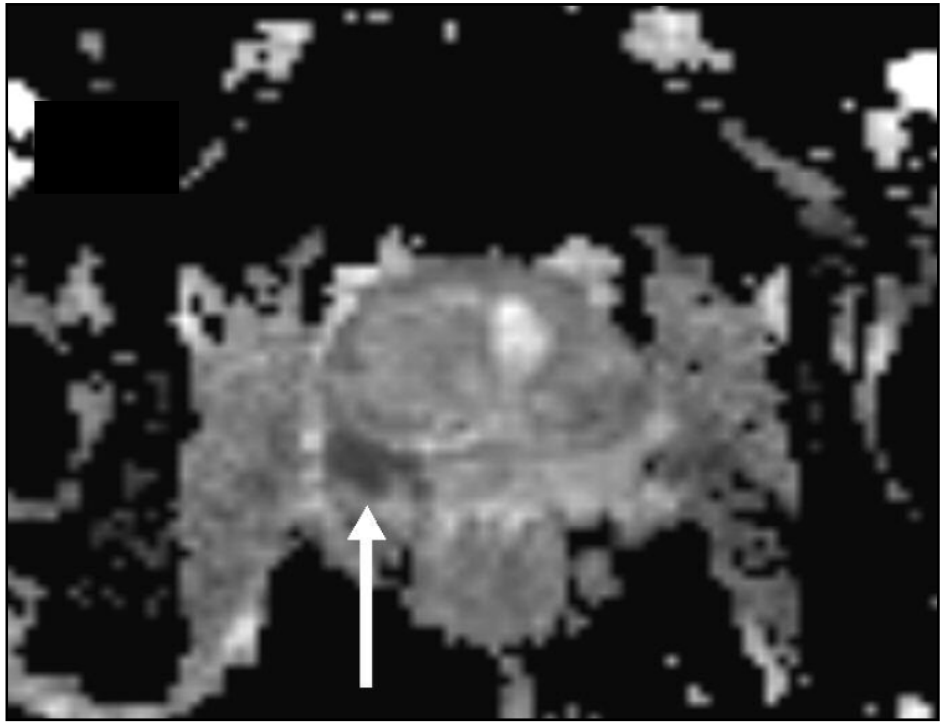
- **visualize the amount of random ('Brownian') movements of water molecules (diffusion)**
- **surrogate for "cellular density"**

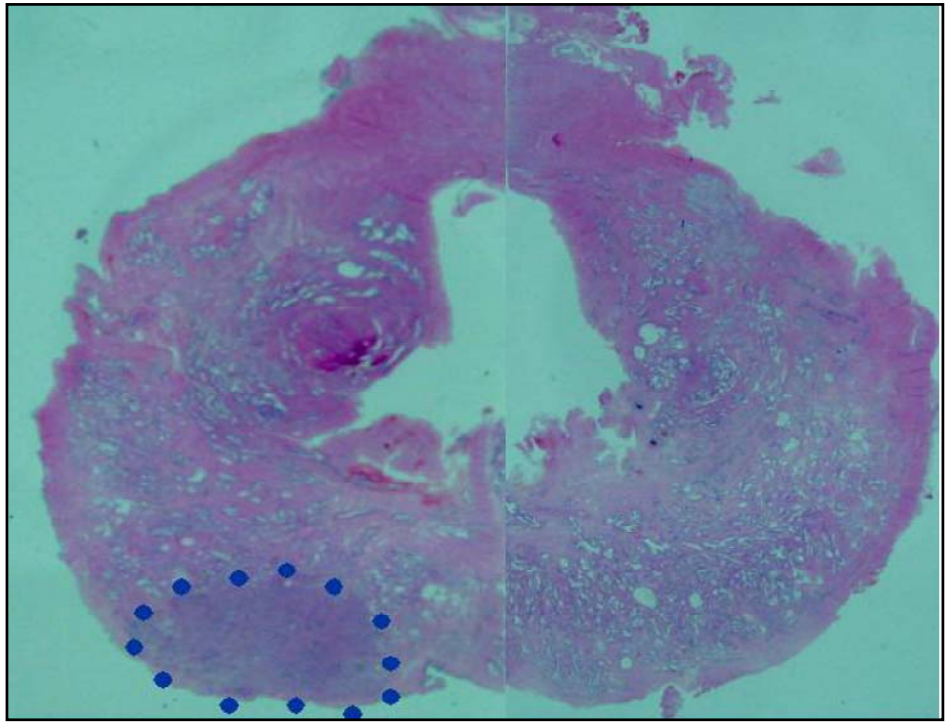
Diffusion Weighted Imaging

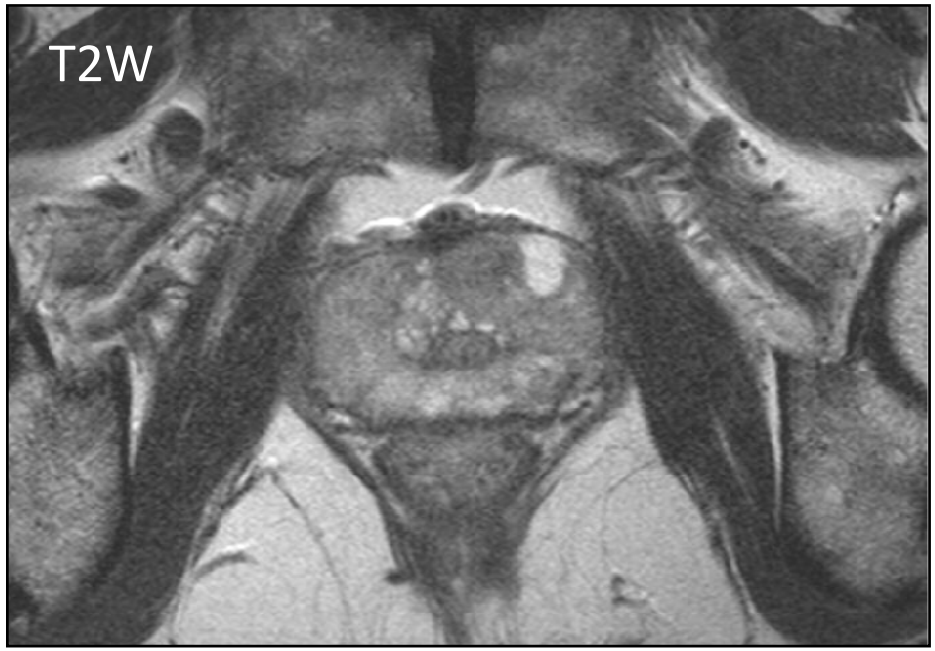


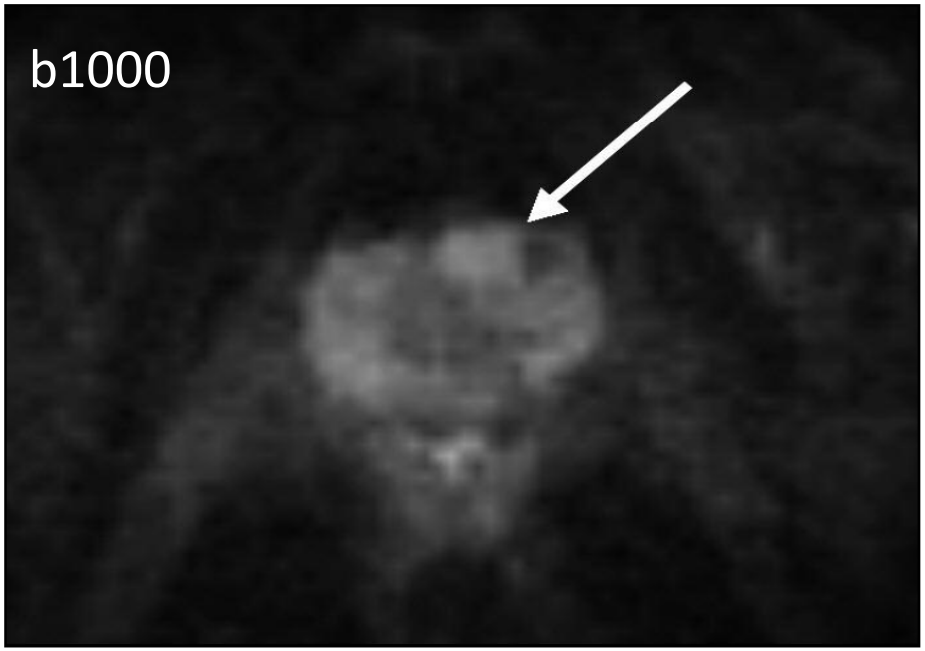


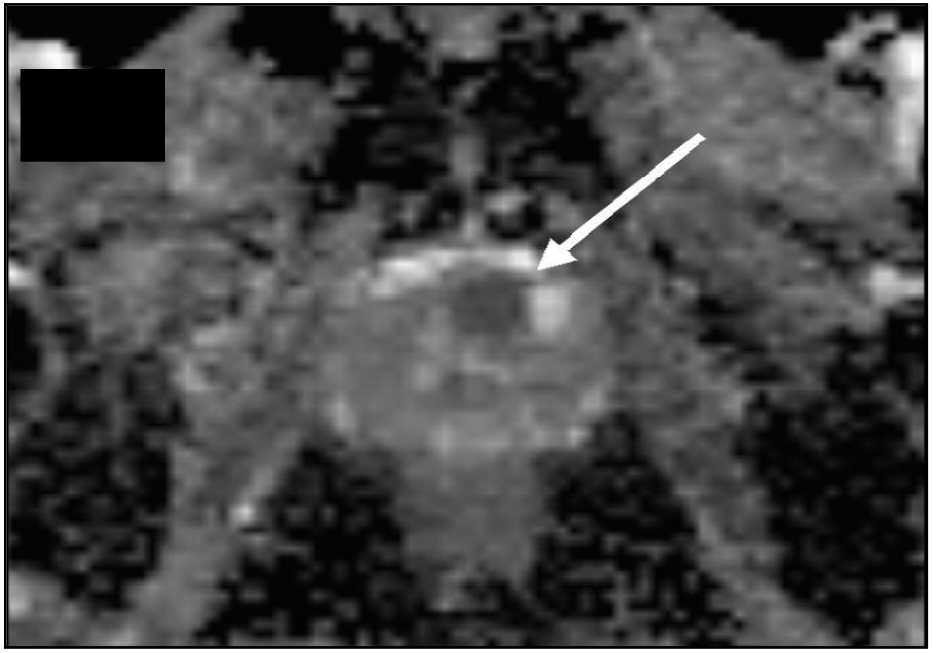


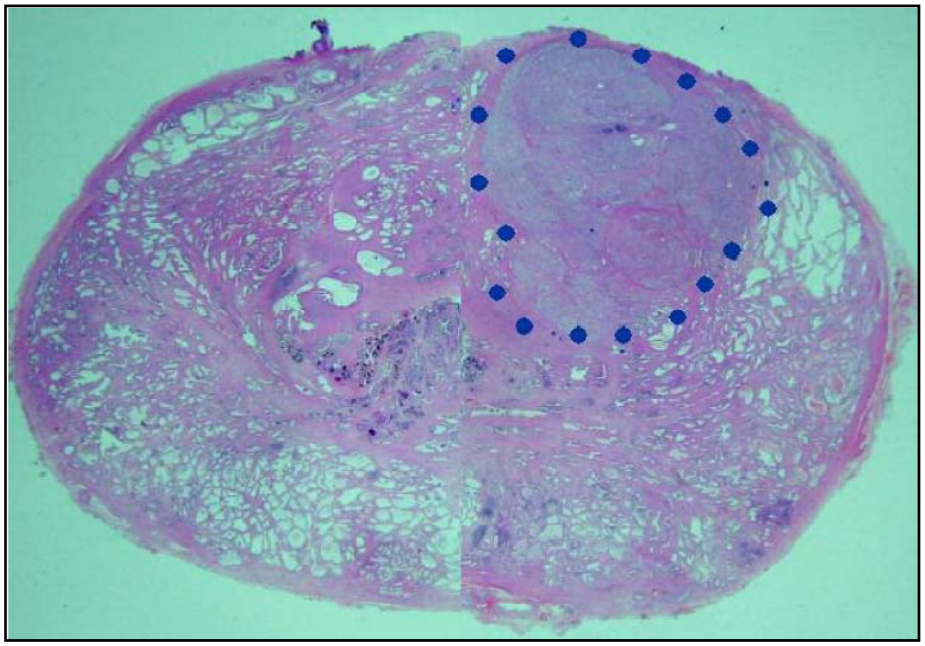












EUROPEAN UROLOGY 59 (2011) 477–494

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Axel Heidenreich on pp. 495–497 of this issue

Magnetic Resonance Imaging for the Detection, Localisation, and Characterisation of Prostate Cancer: Recommendations from a European Consensus Meeting

Louise Dickinson[a,b,c,], Hashim U. Ahmed[a,b], Clare Allen[d], Jelle O. Barentsz[e], Brendan Carey[f], Jurgen J. Futterer[e], Stijn W. Heijmink[e], Peter J. Hoskin[g], Alex Kirkham[d], Anwar R. Padhani[h], Raj Persad[i], Philippe Puech[j], Shonit Punwani[d], Aslam S. Sohaib[k], Bertrand Tombal[l], Arnauld Villers[m], Jan van der Meulen[c,n], Mark Emberton[a,b,c]*

Table 2 – Areas of consensus for general magnetic resonance imaging components

Minimal requirements	Optimal requirements
The data set should include T1-weighted, T2-weighted, diffusion-weighted, and contrast-enhanced MRI but not MR spectroscopy Imaging could be adequately performed at 1.5 T A pelvic phased-array coil is required	The data set should include T1-weighted, T2-weighted, diffusion-weighted, contrast-enhanced MRI Imaging should be performed at 3 T A pelvic phased-array coil, endorectal coil, power injector, and bowel relaxant are required

MR = magnetic resonance; MRI = magnetic resonance imaging.

Dickinson L et al.; Eur Urol 59(2011):477-494

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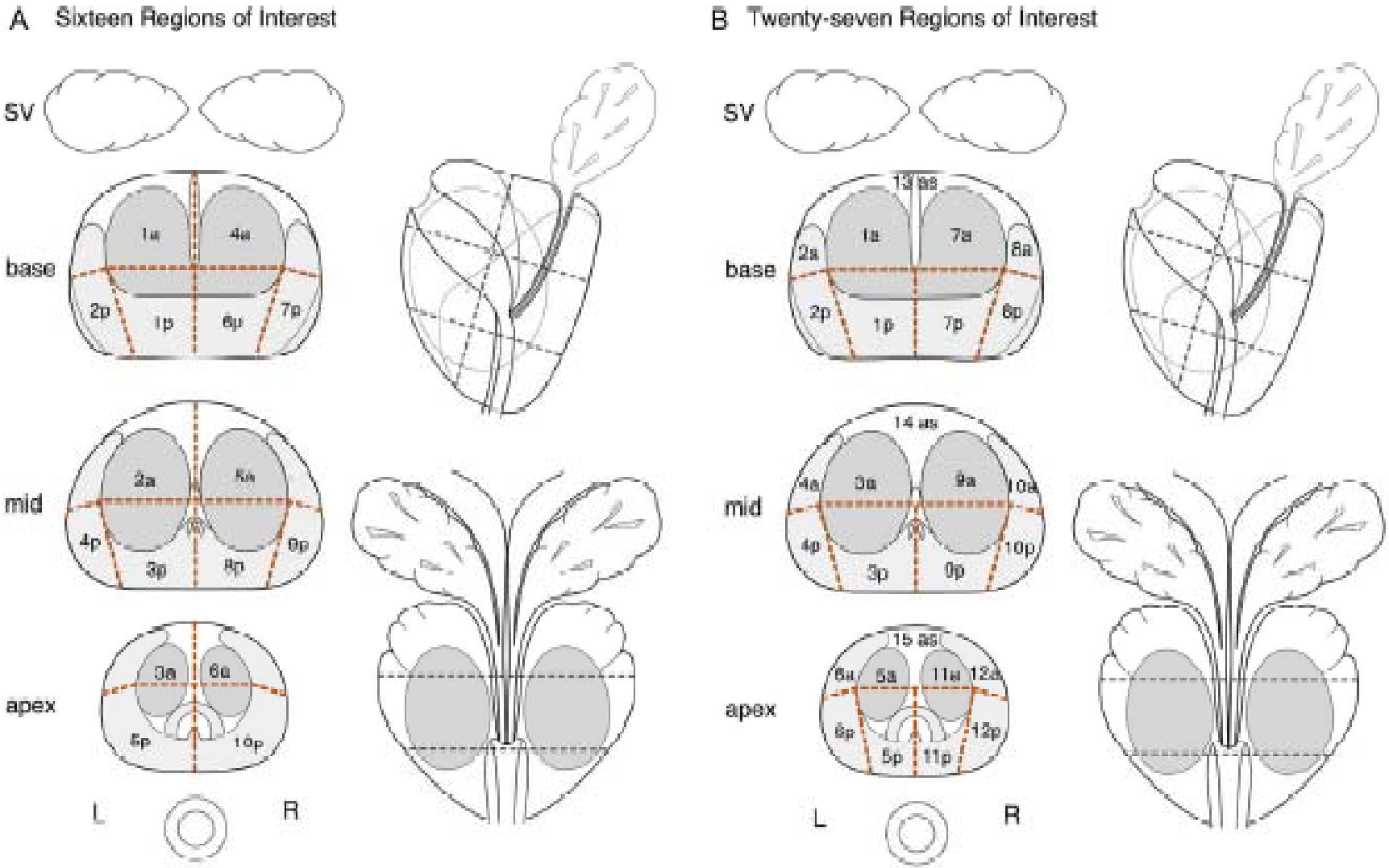

Ten posterior (p) glandular regions - mediolobar and lateral at base and mid; lobar at apex.
Six anterior (a) glandular and stromal regions.

Twelve posterior (p) and twelve anterior (a) glandular regions - mediolobar and lateral at base, mid and apex.
Three anterior stroma (as) central regions.

Dickinson L et al.; Eur Urol 59(2011):477-494

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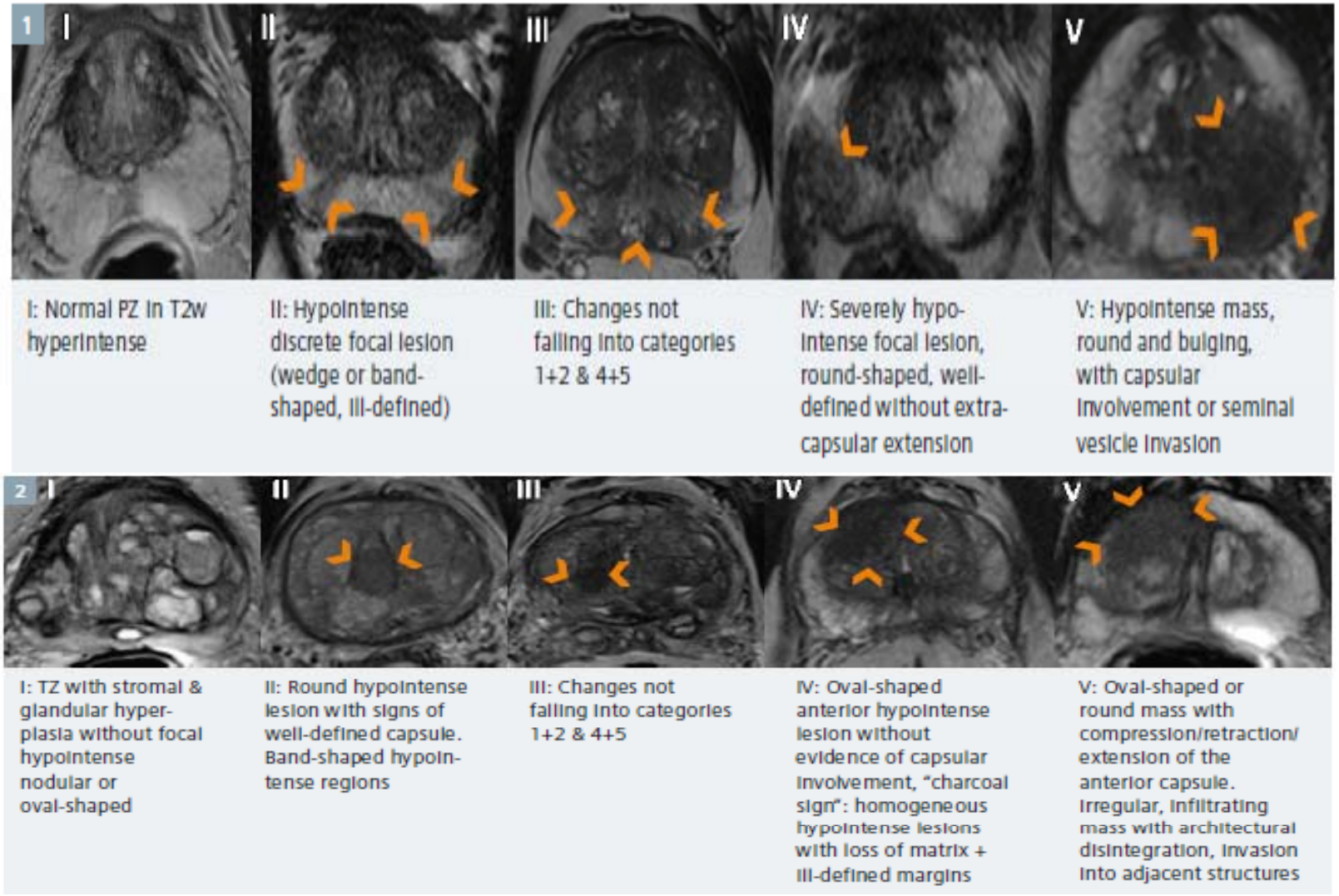
T2w: PI-RADS



Röthke M, Fortschr Röntgenstr 2013; 185: 253–261

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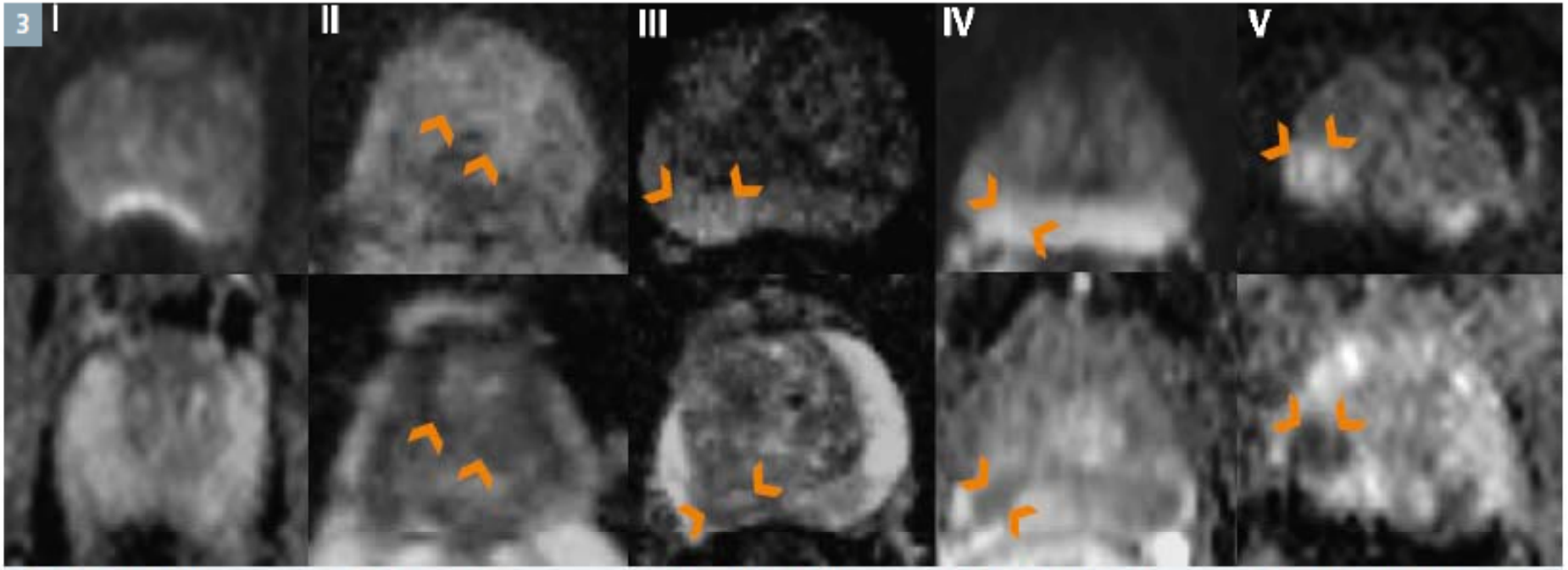
DWI MRI: PI-RADS



3 PI-RADS classification of DWI (high b-values and ADC).

Röthke M, Fortschr Röntgenstr 2013; 185: 253–261

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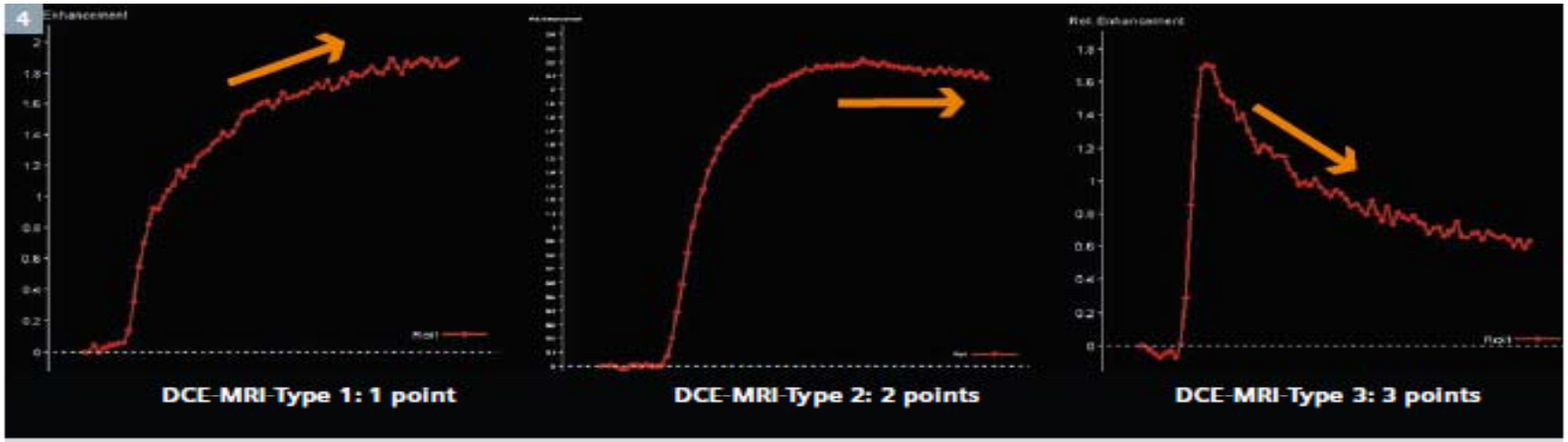
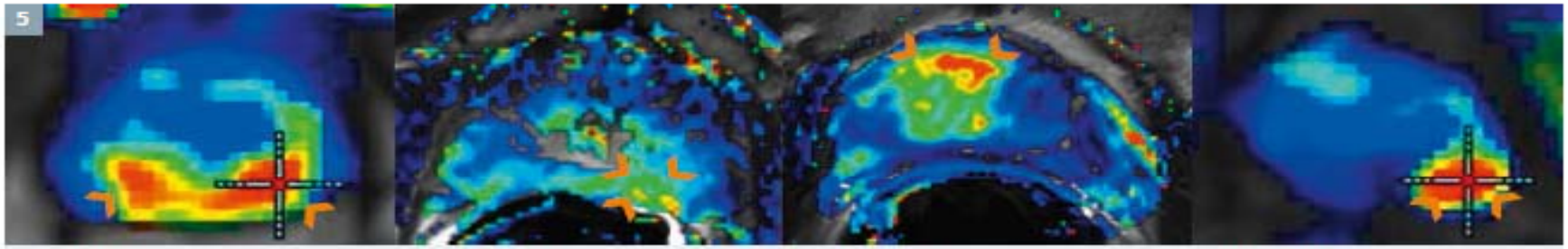
DCE MRI: PI-RADS



4 PI-RADS classification of DCE-MRI, part 1: Curve types.



DCE-MRI – symmetric, non-focal: + 0 points

DCE-MRI – asymmetric, non-focal: + 1 point

DCE-MRI – asymmetric, unusual location: + 2 points

DCE-MRI – asymmetric, focal location: + 2 points

5 PI-RADS classification of DCE-MRI, part 2: Additional points for distribution patterns with curve types II + III.

Röthke M, Fortschr Röntgenstr 2013; 185: 253–261

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Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature.

Fütterer JJ et al., Eur Urol 2015; Epub ahead of print

Table 5 – Performance characteristics of multiparametric magnetic resonance imaging for detection and ruling out of clinically significant cancer

Study (year)	Patients	Overall cancer detection rate, *n*/*N* (%)	Reference	Analysis	Clinically significant disease								
					Accuracy, *n*/*N* (%)	TP (*n*)	TN (*n*)	FN (*n*)	FP (*n*)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
[25] (2014) [a]	129	141/258 [b] (55)	Biopsy	Region	114/258 (44)	72	42	5	139	94	23	34	89
[26] (2014)	115	All	RP	Patient	75/104 (72)	52	23	2	27	96	46	66	92
[27] (2013)	105	36/105 (34)	Biopsy	Patient	24/48 (50)	NR	NR	NR	NR	NR	NR	NR	NR
[28] (2014) [a,c]	54	34/54 (63)	Biopsy	Region	57/108 (53)	26	31	8	43	76	42	38	79
[22] (2013) [a,c]	64	54/64 (84)	Biopsy	Region	183–201/256 (72–82)	41–51	132–154	20–30	29–53	58–73	71–84	49–63	84–89
[29] (2013) [a]	182	144/182 (79)	Biopsy	Patient	103/182 (57)	103	45	27	7	79	87	93	63
[30] (2012)	265	108/265 (41)	Biopsy	Patient	94/265 (35)	NR	NR	NR	NR	NR	NR	NR	NR
[31] (2013)	538	316/538 (59)	Biopsy	Patient	NR	NR	NR	NR	NR	94	28	38	91
[32] (2011) [a]	114	68/114 (60)	Biopsy	Region	217/252 (86)	64	153	3	32	95	84	68	98
[33] (2014)	150	92/150 (61)	Biopsy	Patient	49/150 (33)	49	49	2	50	96	50	50	96
[34] (2014)	125	45/125 (36)	Biopsy	Region	21/28 (75)	NR	NR	NR	NR	NR	NR	NR	NR

Conclusions: mpMRI is able to detect significant PCa in biopsy-naïve males and men with prior negative biopsies. The negative predictive value of mpMRI is important to the clinician because mpMRI could be used to rule out significant disease. This may result in fewer or no systematic or targeted biopsies in patients with PSA suspicious for prostate cancer.

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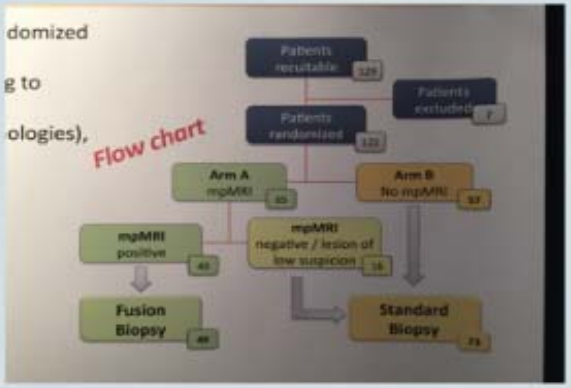
MRI-guided biopsy for primary diagnosis

N = 122 men with mpMRI PIRADS ≥ 3 were randomized

RCT

	arm A	arm B
	= MRI-GB (fusion) with 3 samples per lesion	= TRUS-bx
PCa	61.2%	29.8%
sign PCa	100%	58.8%



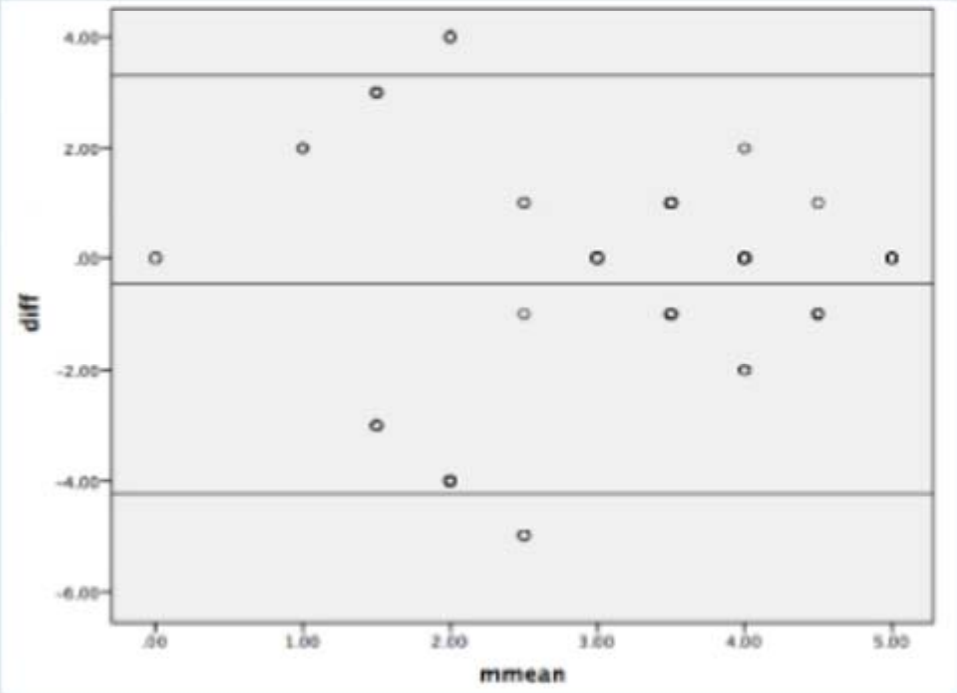
Abstract # 499

Porpiglia, F., Mele, F., Manfredi, M., Aimar, R., Checcucci, E., Cossu, M., Bollito, E., Russo, F., Gned, D., De Pascale, A., Cirillo, S., Fiori, C.
San Luigi Gonzaga Hospital, Depts. of Urology, Radiology, Pathology
University of Turin, Orbassano, Turin, Italy,

How reliable is a MRI ?

N = 126 men with two mpMRIs at different institutions within 4 wks

significant inter-observer variation
in PIRADS grading



Abstract
504

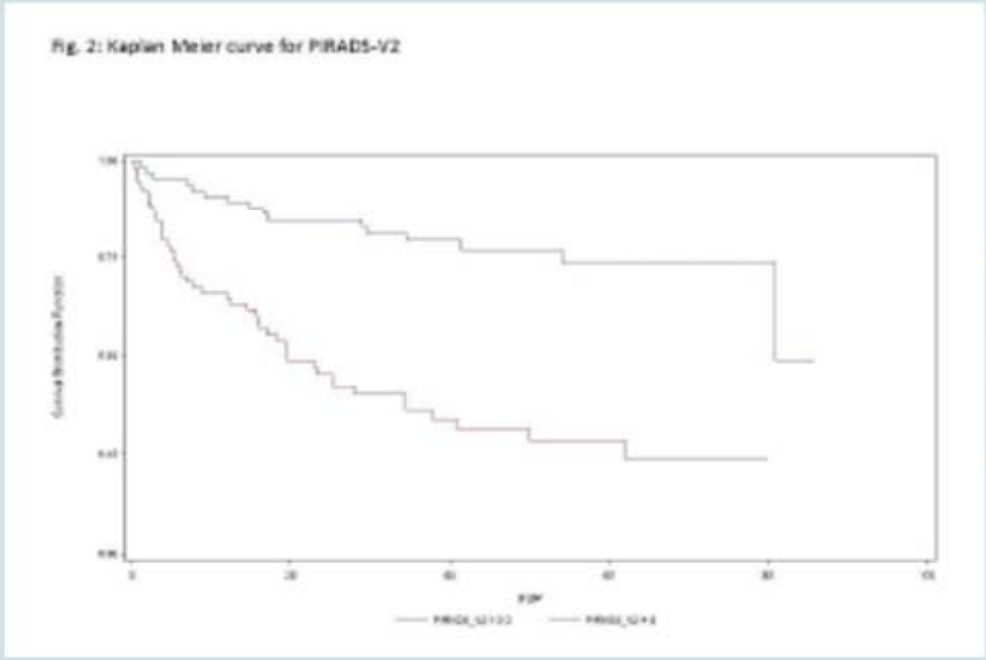
Müller, S., Løfsgaard, L., Estop-Garanto, M., Sand, T.E., Helgø, D.,
Sund, P., Mygland, V.
Akershus University Hospital, Dept. of Urology, Lørenskog, Norway

mpMRI for active surveillance

N = 150 patients

qualified for active surveillance and received mpMRI within the first 3 ms of AS

PIRADS 4 + 5 disqualified for active surveillance



50%

Abstract # 829

Sanguedolce, F., Petralia, G., Sokhi, H., Tagliabue, E., Anyamene, N., Hellawell, G., Padhani, A.R.
Northampton, Mount Vernon Hospital London, UK / Milan, Italy

mpMRI for active surveillance

N = 149 patients qualified for active surveillance

n = 45 with mpMRI guided and perineal saturation bx

n = 104 conventional 12-core TRUS-Bx

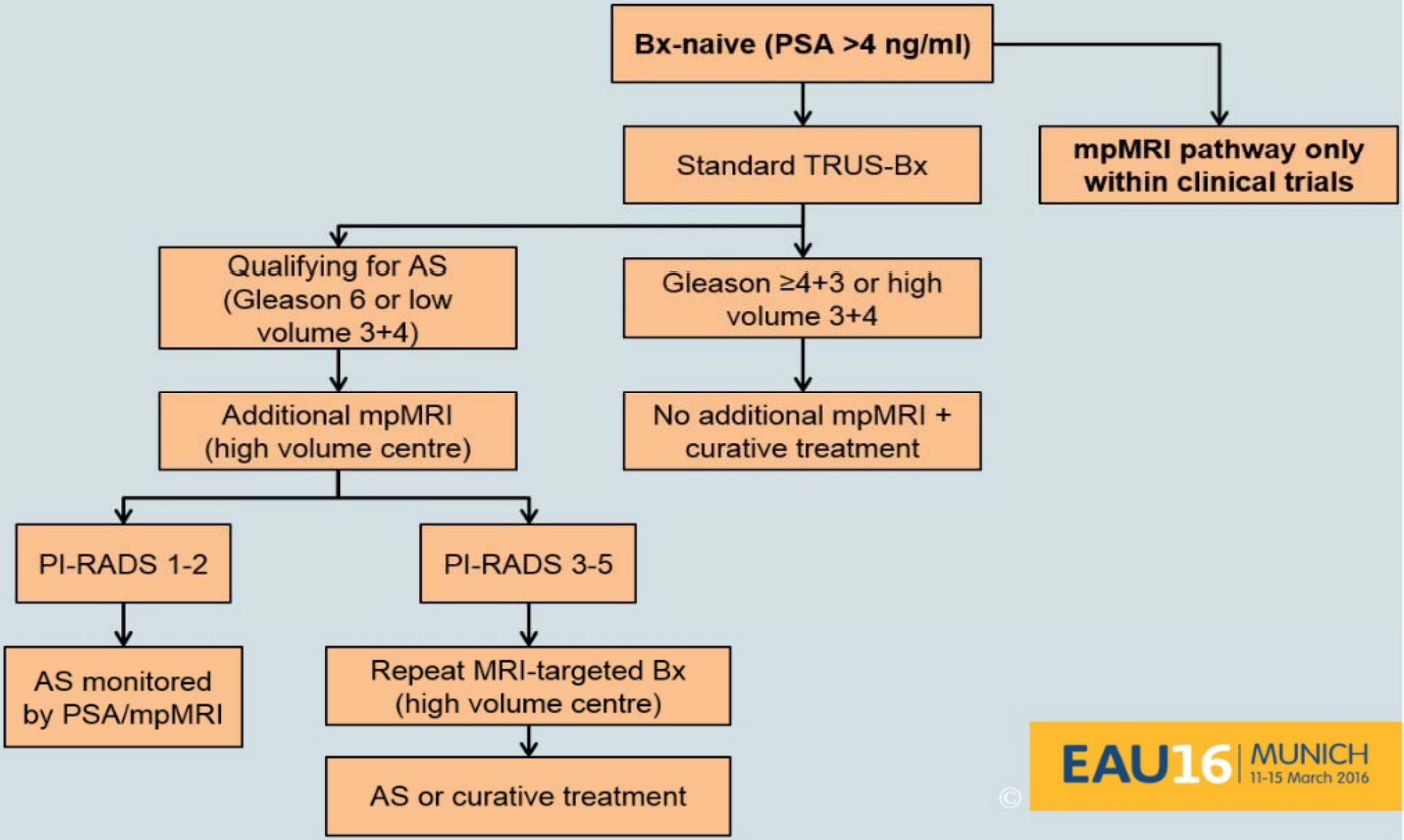
48.1% of patients with conventional TRUS-Bx disqualified after mpMRI

20% of mpMRI patients under AS progressed

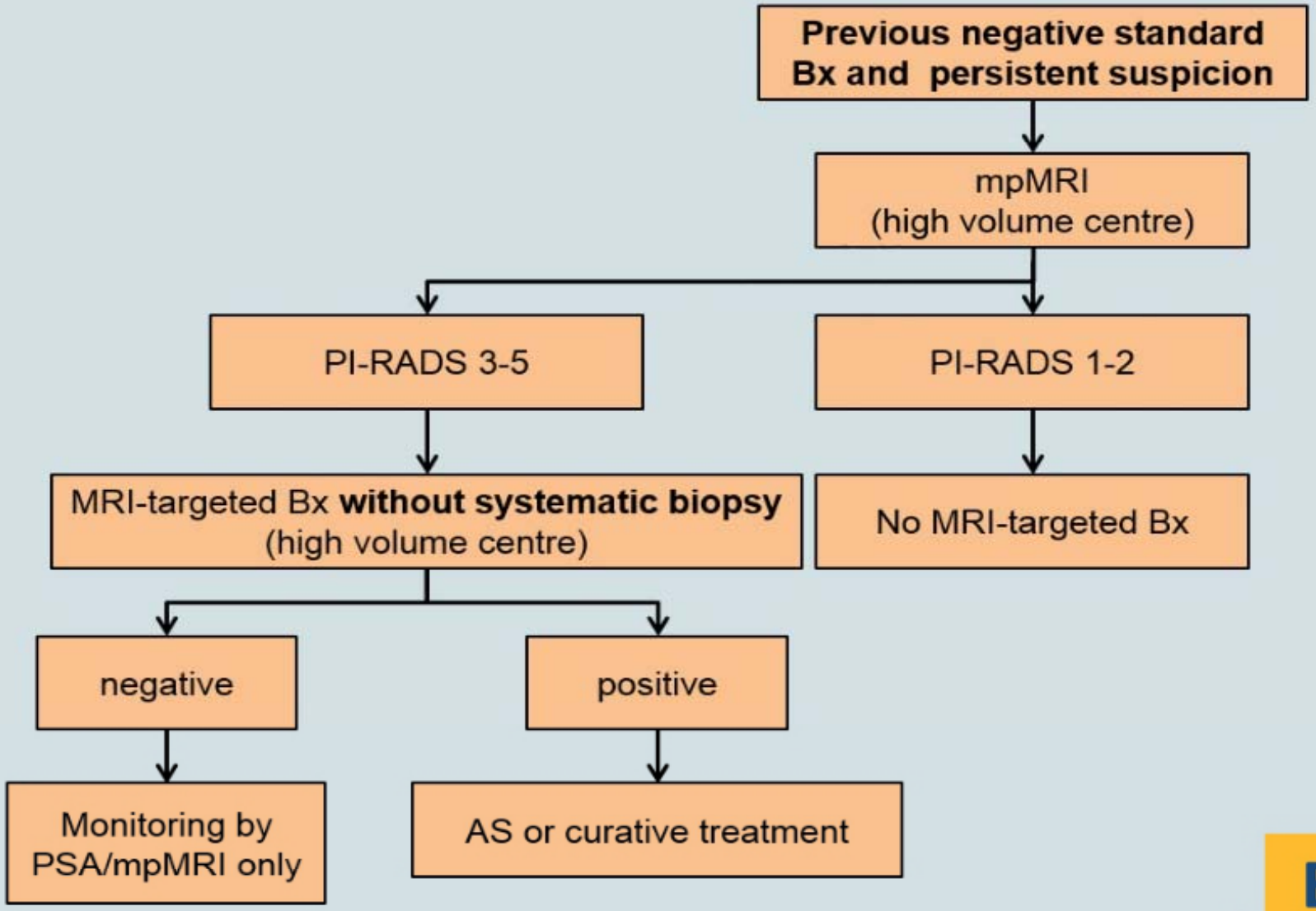
Abstract # 955

Radtke, J.P., Kuru, T.H., Bonekamp, D., Freitag, M., Kesch, C., Wolf, M., Alt, C., Hatiboglu, G., Boxler, S., Pahernik, S., Roth, W., Roethke, M.C., Schlemmer, H-P., Hohenfellner, M., Hadaschik, B.
Depts. of Radiology and Urology, Heidelberg University, Germany

Diagnostic pathway for mpMRI and MRI-targeted Bx (primary indication) 2016



Diagnostic pathway for mpMRI and MRI-targeted Bx (secondary indication) 2016



Hospital admissions after transrectal ultrasound-guided biopsy of the prostate in men diagnmosed with prostate cancer: a database analysis from England.

Anastasiadis E et al., Int J Urol 2015; 22: 181 - 186

- n = 198.361 men between 2000 – 2008
- 30-days complicationrate: 3.7%
  - 1.1% Urinary infection / Sepsis
  - 1.4% Hematuria
  - 1.3% Urinary retention
- Increase 1998 => 2008
  - HR = 1.20, 95% confidence interval 1.08-1.34
  - HR = 1.72, 95% confidence interval 1.41-2.10 for infectin/sepsis

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Biopsy: transrectal vs transperineal

Complication	Transrectal[1]	Transperineal[2]
Pain	43,6%	0%
Urinary infection	17,5%	0%
Prostatitis	4.5%	0.4%
Urosepsis	0.7%	0%
Hematuria	65,8%	41,8%
Hematospermia	92,6%	N/A
Hematochezie	36,8%	0%
Urinray retention	n.k.	13,4%

[1] DJ. Rosario et al.BMJ 2012;344

[2] Porres D et al., DGU 2014

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Biopsy PCA-Detectionrates – Comparison Literature

	PCA-Detectionrates
Transrectal Saturation (TRUS)[1]	30% – 43%
Transperineal (TRUS)[2]	**62.5%**
MRT-supported (biopsynaiv)[3]	66%

[1] EAU Guidelines on PCA
[2] Porres D et al., DGU 2014
[3] CM. Moore et al. Eur Urol 63 (2013), 125-140

Neue Tracer und ihre Anknüpfungspunkte beim PET

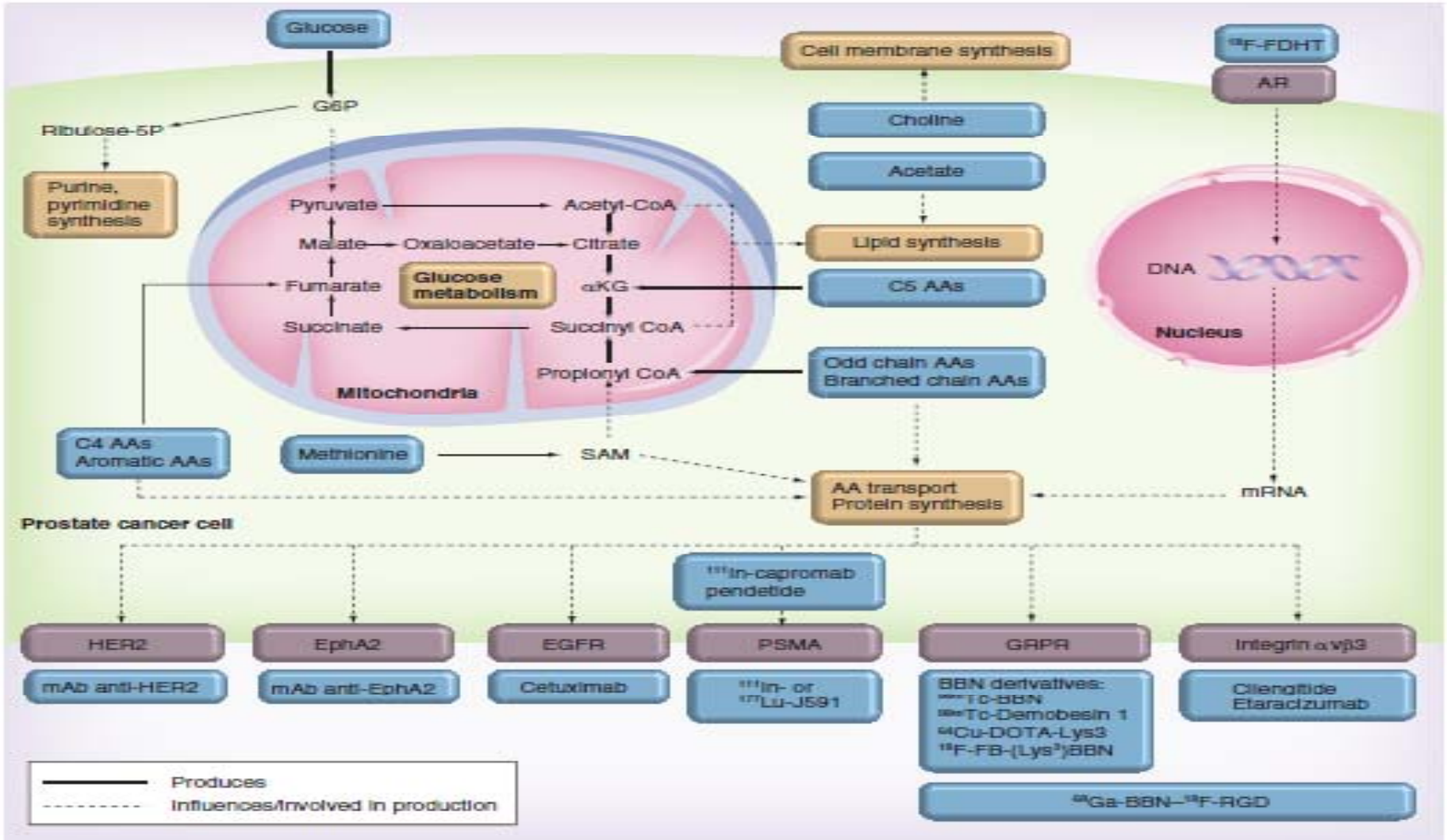
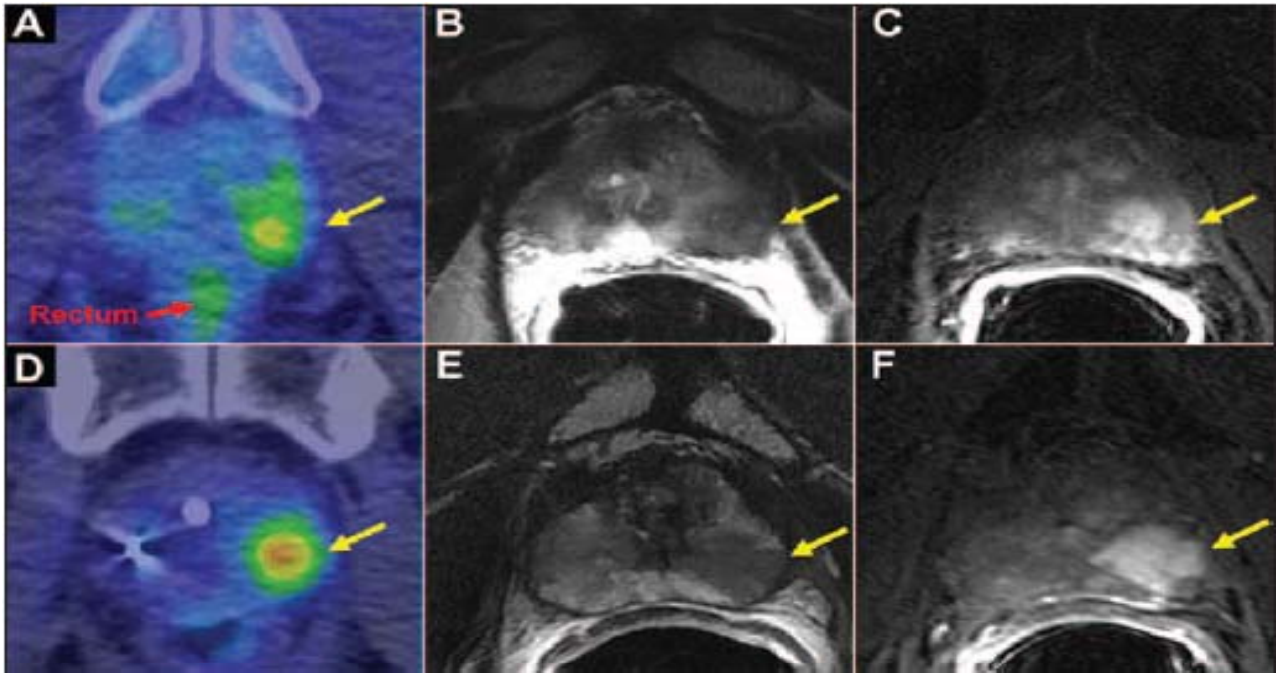
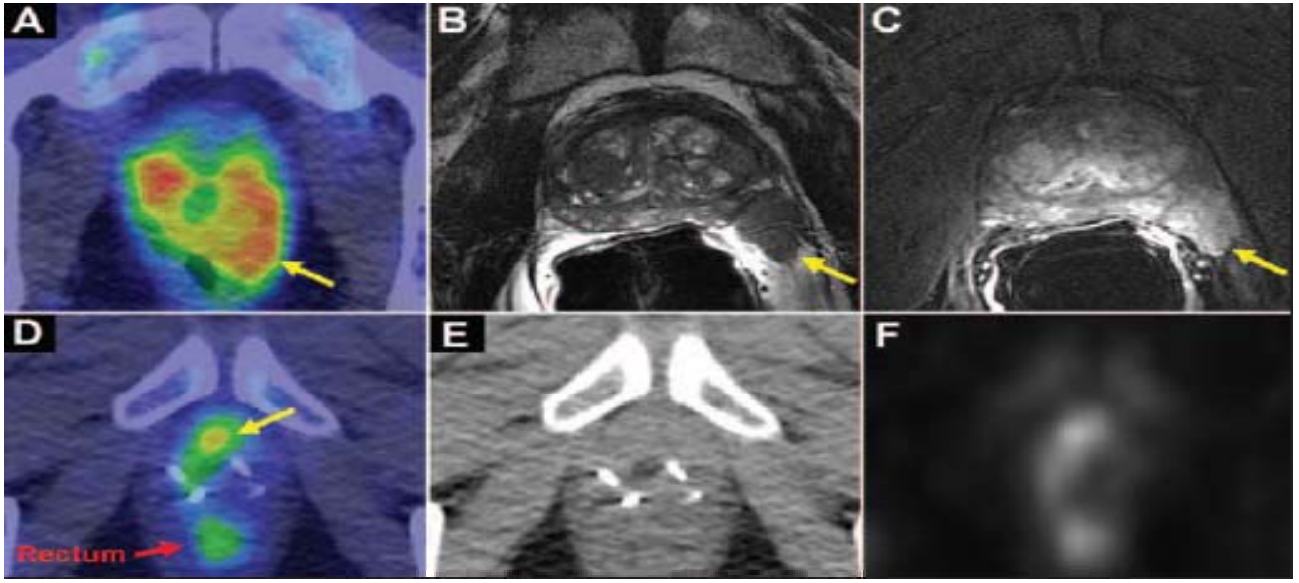


Figure 2. Novel radiotracers used in the detection of recurrent prostate cancer. Novel radiolabeled PET tracers (blue boxes) are used in the detection of metabolic processes (orange boxes) and expressed proteins (purple boxes) of prostate cancer cells.
5P: 5-phosphate; α-KG: α-ketoglutarate; AA: Amino acid; AR: Androgen receptor; BBN: Bombesin; C: Carbon; CoA: Coenzyme A; DOTA: 1,4,7,10-tetraazadodecane-N,N',N'',N'''-tetraacetic acid; FB: Fluorobenzoate; FDHT: Fluoro-5α-dihydrotestosterone; G6P: Glucose-6-phosphate; mAb: Monoclonal antibody; RGD: Arginine–glycine–aspartate; SAM: *S*-adenosyl methionine.
For color image, please see www.futuremedicine.com/doi/full/10.2217/fon.13.196

Nicholas G Zaorsky[*1,2], Kosj Yamoah[2], Madhukar L Thakur[3], Edouard J Trabulsi[4], Timothy N Showalter[5], Mark D Hurwitz[2], Adam P Dicker[2] & Robert B Den[2]
Future Oncol. (2014) 10(3), 457–474





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Urologic Oncology: Seminars and Original Investigations xx (2011) xxx

UROLOGIC ONCOLOGY

Review article

Imaging of prostate cancer with PET/CT and radioactively labeled choline derivates

Bernd Joachim Krause, M.D.[a], Michael Souvatzoglou, M.D.[a], Uwe Treiber, M.D.[b,*]

Table 1
Diagnostic efficacy of ^{18}F- and ^{11}C-choline PET and PET/CT in patients with primary prostate cancer

Tracer	Ref.	Author	Year	Modus	Pts. (*n*)	Local tumor		Lymph nodes	
						Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
^{18}F-FCH	[26]	Kwee	2005	PET	17	100	—	—	—
	[31]	Schmid	2005	PET/CT	19	100	—	—	—
	[27]	Kwee	2006	PET	26	100	—	—	—
	[54]	Husarik	2008	PET/CT	43	98	—	33	100
^{11}C-Cho	[6]	Kotzerke	2000	PET	23	100	—	50	90
	[23]	de Jong	2002	PET	25	100	—	80	95
	[35]	de Jong	2003	PET	67	—	—	80	96
	[32]	Sutinen	2004	PET	14	100	—	—	—
	[33]	Yamaguchi	2005	PET	20	100	—	—	—
	[34]	Yoshida	2005	PET	13	—	—	—	—
	[24]	Farsad*	2005	PET/CT	36	66	81	—	—
	[29]	Reske*	2006	PET/CT	26	100	—	—	—
	[30]	Scher	2007	PET/CT	58	86	70	—	—
	[28]	Martorana*	2006	PET/CT	43	66	84	—	—
	[25]	Giovacchini*	2008	PET/CT	19	72	43	—	—
	[36]	Schiavina	2008	PET/CT	57	—	—	60	98
	[66]	Li†	2008	PET/CT	49	90	86	—	—
Sum					555				
Mean						91	73	61	96
Median						100	81	60	96

FCH = fluoromethylcholine; Cho = choline.
* Sextant-based comparison with histology.
† Uptake ratio of lesion to muscle is compared with histology.

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Urologic Oncology: Seminars and Original Investigations xx (2011) xxx

UROLOGIC ONCOLOGY

Review article

Imaging of prostate cancer with PET/CT and radioactively labeled choline derivates

Bernd Joachim Krause, M.D.[a], Michael Souvatzoglou, M.D.[a], Uwe Treiber, M.D.[b,*]

Table 2
Diagnostic efficacy of ^{18}F- and ^{11}C-choline PET and PET/CT in patients with recurrent prostate cancer

Tracer	Ref.	Author	Year	Pts. (*n*) All	Pts. (*n*) RP	Pts. (*n*) RT	Pts. (*n*) ADT	Time (Mo) Tx-PET/CT	PSA (ng/ml)	Sensitivity (%)	Specificity (%)	Localization
^{18}F-FCH	[53]	Heinisch	2006	34	31	3	4	—	17.1	41	—	LR, LNM, BM
	[31]	Schmid	2005	9	8	1	—	49	14.1	100	—	LR, LNM, BM
	[60]	Cimitan	2006	100	58	21	21	—	48.3	54	—	LR, LNM, BM
	[54]	Husarik	2007	68	68	—	13	—	10.8	87	—	LR, LNM, BM
	[67]	Vees	2007	20	20	—	—	35	0.4	50	—	LR
	[68]	Pelosi	2008	56	56	—	—	—	—	43	—	LR
	[69]	Steiner	2009	47	17	30	—	67	3.3	81	—	LR, LNM
^{11}C-Cho	[56]	Picchio*	2003	100	77	23	—	—	6.6	47	—	LR, LNM, BM
	[52]	de Jong*	2003	36	20	16	—	—	12	55	100	LR, LNM
	[70]	Ohlmann	2007	45	0	45	—	—	7.8	65	—	LR, LNM
	[58]	Rinnab	2007	50	40	10	4	22	3.6	95	40	LR
	[59]	Scattoni	2007	25	25	—	—	—	4.0	100	66	LR, LNM
	[71]	Breeuwsma*	2010	80	0	70	—	—	12.3	81	100	LR, LNM, BM
	[55]	Krause	2008	63	42	21	17	47	5.9	56	—	LR, LNM
	[72]	Rinnab	2008	15	15	—	—	24	2.3	100	0	LNM
	[57]	Reske	2008	49	49	—	9	59	2.0	73	88	LR
	[73]	Rinnab	2009	41	41	—	—	24	2.8	93	36	LR, LNM
	[51]	Castellucci	2009	190	190	—	—	46	4.2	39	—	LR, LNM, BM, LUM
	[74]	Giovacchini	2010	358	358	—	155	—	3.8	85	93	LR, LNM, BM, LUM
Sum				1386	1115	240	223					
Mean								41	8.9	70.7	65.3	
Median								46	5.0	73	77	

FCH = luoromethylcholine; Cho = choline; LR = local recurrence; LNM = lymph node metastases; BM = bone metastases; LUM = lung metastases; RP = radical prostatectomy; RT = radiotherapy; ADT = androgen deprivation therapy; Tx = therapy.

* PET only.

68-Ga-PSMA PET for PCA diagnosis

N = 53 patients with 68-Ga-PSMA PET and simultanous mpMRI before RP

	PCA detection rate in the prostate (sixtants)
68-Ga-PSMA PET	92%
mpMRI	66%
combination of both	98%

Abstract # 557

Eiber, M., Weirich, G., Nguyen, N., Holzapfel, K., Souvatzolgou, M., Haller, B., Rauscher, I., Beer, A., Wester, H.-J., Westenfelder, K., Gschwend, J., Schwaiger, M., Maurer, T.
Dpts. of Urology, Nuclear Medicine and Radiology, TU Munich

Simultaneous 68 Ga-PSMA HBED-CC PET/MRI improves the Localization of Primary Prostate Cancer
Eiber et al; Eur Urol (16), 2016

N=66 Patienten

12/30 mit Lymphknotenmetastasen

Sensitivität PET: 66%
Sensitivität mpMRI: 92%
Sensitivität PET/MRI: 98%

Schlußfolgerung: Höchste diagnostische Genauigkeit bei PET/MRI im Vergleich zu PET und mpMRI

ESTRO School

68-Ga-PSMA PET for LN diagnosis

N = 130 patients with 68-Ga-PSMA PET before RP

11/130 without PSMA signal

N = 36 of 119 eligible patients (30%) had lymph node metastases

sensitivity	75%
specificity	99%
PPV	96%
NPV	90%

Abstract # 557

Eiber, M., Weirich, G., Nguyen, N., Holzapfel, K., Souvatzolgou, M., Haller, B., Rauscher, I., Beer, A., Wester, H.-J., Westenfelder, K., Gschwend, J., Schwaiger, M., Maurer, T.
Dpts. of Urology, Nuclear Medicine and Radiology, TU Munich

Initial Experience of 68Ga-PSMA PET/CT imaging in High-risk Prostate Cancer Patients prior to Radical Prostatectomy.

Budäus et al; Eur Urol (15), 2015

N=30 Patienten

12/30 mit Lymphknotenmetastasen

4 Patienten (33%) richtig positiv
8 Patienten (66,7%) als falsch negativ

Sensitivität: 33%
Spezifität: 100%
Positiv prädiktiver Wert: 100%
Negativ prädiktiver Wert: 69,2%

ESTRO School

68-Ga-PSMA PET for PSA relapse

PSA level	N = 175 detection rate (PSMA positive signal)	N = 38 detection rate (PSMA positive signal)
< 0.2	17%	31%
0.2-0.5	38%	94%
0.5-1.0	63%	57%
1.0-2.0	75%	
2.0-10.0	86%	

Abstract # 560
Paffen, M.L.J.E., Murphy, D., Costello, A, Hicks, R., Hoffman, M.
Dpts. of Urology and Nuclear Medicine, Royal Melbourne Hospital, Australia

Abstract # 548
Van Leeuwen PJ, Emmett L, Hruby G, Kneebone A, Stricker P
Amsterdam

Conclusions

- **Ultrasound**
  - **initial assessment of patients with increased PSA and/or abnormal DRE, but low diagnostic yield**
  - **excellent for biopsy guidance**
  - **no screening**
  - **no staging**

Conclusions

- **CT**
  - **no value for local tumor detection**
  - **lymph node staging**
  - **targeted imaging after bone scan**
  - **(detection of visceral metastases)**

Conclusions

- **MRI**
  - **optimally depicts prostatic anatomy**
  - **primarily detects peripheral zone carcinoma**

Conclusions

- **Tumour detection**

  - **T2-weighted imaging**
    - **baseline examination!**

  - **MR-spectroscopy**
    - **primarily detects higher grade tumours**

  - **dynamic contrast enhanced MRI**
    - **imaging of tumor neovascularisation**

  - **diffusion weighted imaging**

    Minimal requirement in MRI imaging

ESTRO School

Conclusions

- **MRI**
  - **Still not recommended before primary biopsy**
  - **Recommendation before secondary biopsy**
  - **Rising importance in follow-up under active surveillance**

Conclusions

- **PET**
  - **Indication in primary tumour detection unclear.**
  - **Unclear indication during staging.**
  - **No indication in case of recurrence with PSA<1ng/ml**
  - **Unclear indication and evidence in case of recurrence with PSA>1ng/ml**

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a) Image Registration
b) Planning Principles (HDR)

Frank-André Siebert

University Medical Center of Schleswig-Holstein,
Clinic of Radiotherapy
Head of Dept. of Med. Physics
Kiel, Germany

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a) Image Registration

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ELSEVIER

Brachytherapy 12 (2013) 38–43

BRACHYTHERAPY

Ultrasound–CT fusion compared with MR–CT fusion for postimplant dosimetry in permanent prostate brachytherapy

David Bowes[1], Juanita M. Crook[2,*], Cynthia Araujo[3], Deidre Batchelar[3]

[1]*Department of Radiation Oncology, Nova Scotia Cancer Center, Halifax, Nova Scotia, Canada*
[2]*Department of Radiation Oncology, British Columbia Cancer Agency, Center for the Southern Interior, Kelowna, BC, Canada*
[3]*Department of Radiation Physics, British Columbia Cancer Agency, Center for the Southern Interior, Kelowna, BC, Canada*

20 patients (I-125):

pre-implant TRUS
CT (1 month)
MRI (1 month)

→ Urethral position (catheter)
→ Seed positions

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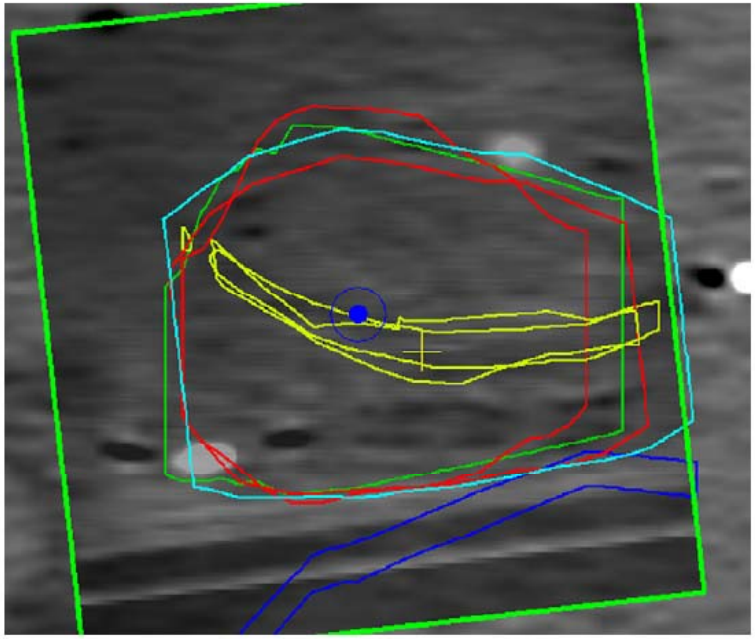

Fig. 1. Overlaying the sagittal images in the plane of the urethra superimposes the urethral curvature and brings the base and apex into alignment.

TRUS-CT fusion

Table 1
Median volume and dosimetric parameters as calculated using CT–TRUS fusion and CT–MRI fusion

Median value (IQ range)	CT–TRUS	CT–MRI
Volume (cc)	32.8 (25.8–42.6)	31.1 (25.8–37.6)
D_{90} (%)	120.0 (117.4–132.2)	122.8 (115.0–132.4)
V_{100} (%)	97.8 (95.4–98.9)	97.8 (94.9–98.8)
V_{150} (%)	71.5 (64.7–75.6)	72.6 (62.7–77.5)
V_{200} (%)	37.2 (28.9–41.2)	36.0 (26.6–42.4)

TRUS = transrectal ultrasound; IQ = interquartile.

CT and TRUS may be a reasonable alternative to MR-based dosimetry in patients where MRI is not available.

Radiotherapy and Oncology 104 (2012) 192–198

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate brachytherapy

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

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

[a] University Hospital Gasthuisberg, Leuven, Belgium; [b] Mount Vernon Cancer Centre, Middlesex, UK; [c] University Hospital of Schleswig-Holstein, Kiel, Germany

- 3 LDR Patients from Leuven
- MRI (T1 and T2), CT, radiographs
- Prostate volumes: 38, 21, 42 ml
- Seeds: 76, 62, 87 (single sources, Oncura 6711)
- VariSeed 8.0

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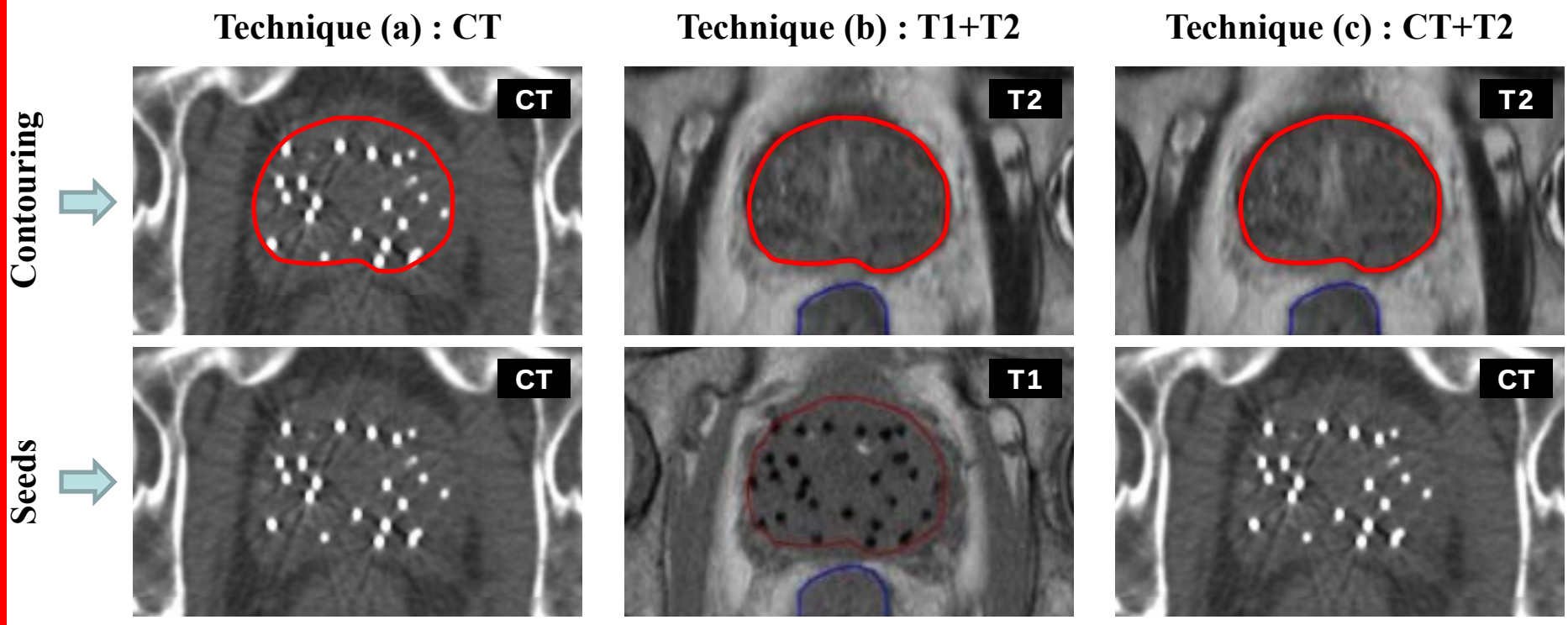
→ Image Fusion T1+T2, CT+T2



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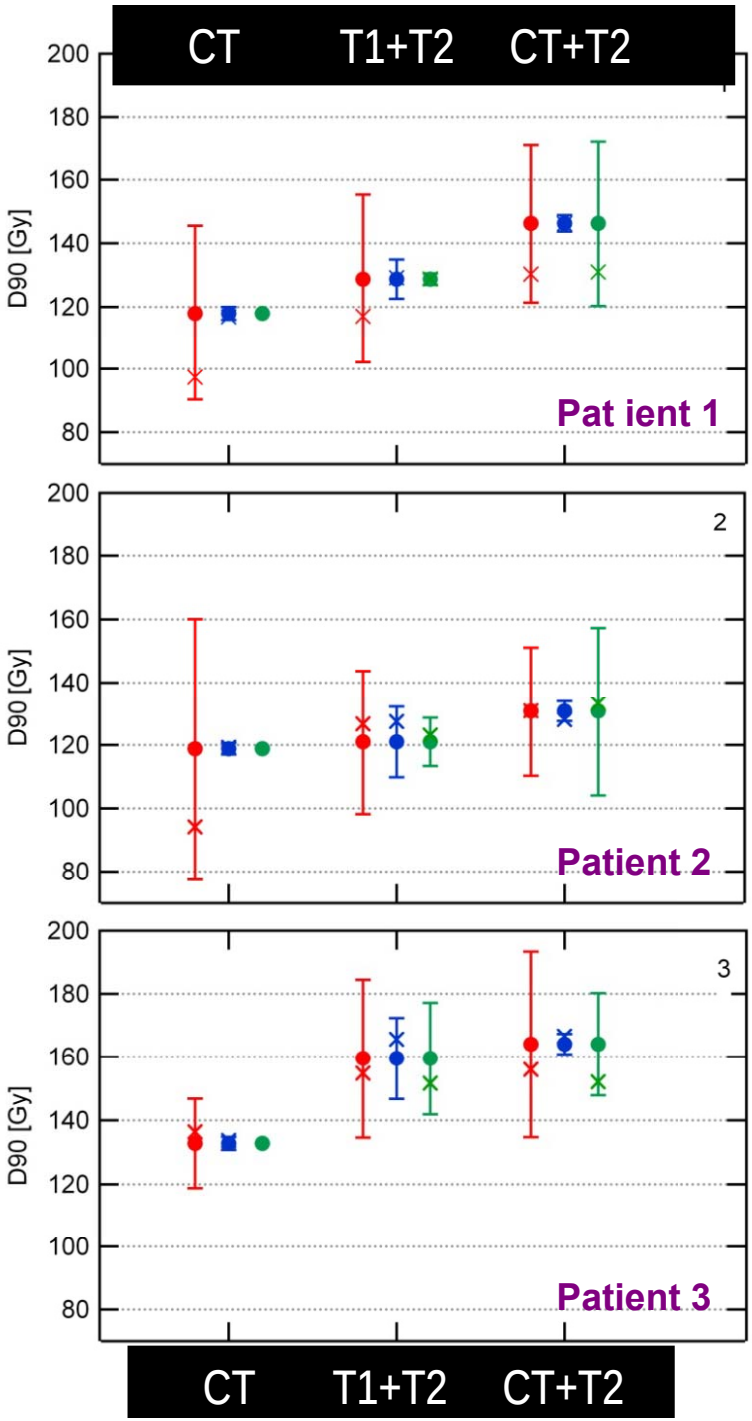

Impact of interobserver variability on D90

- ● Ref_D90
- × MeanObs_D90
- | SD_{ref} interobserver variability with respect to reference (1SD)

Contouring
large interobserver variability for D90 for all techniques

Seeds
- CT: small interobserver spread for D90
- slightly larger for technique (b), using T1 for seeds

Fusion
- T1 + T2 : interobserver variability relatively small, but patient dependent
- CT + T2 : large interobserver variability

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b) Planning principles (HDR)

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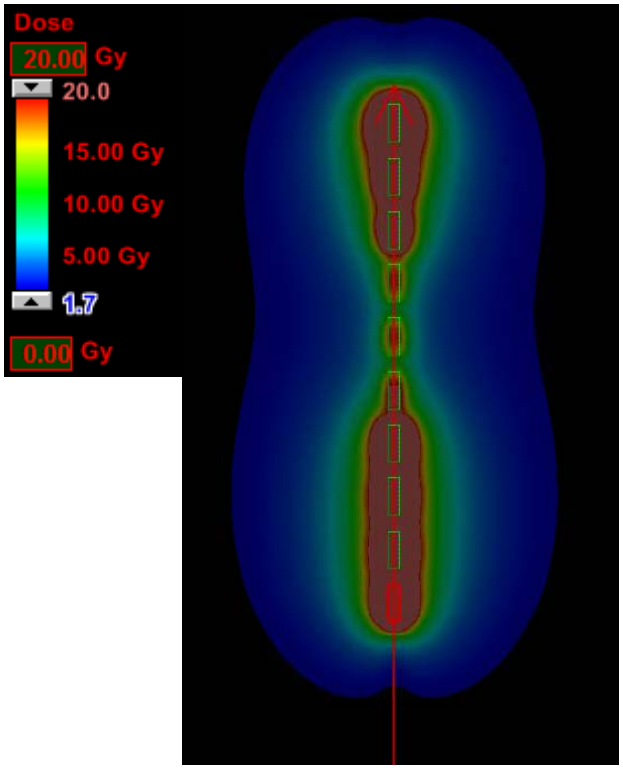
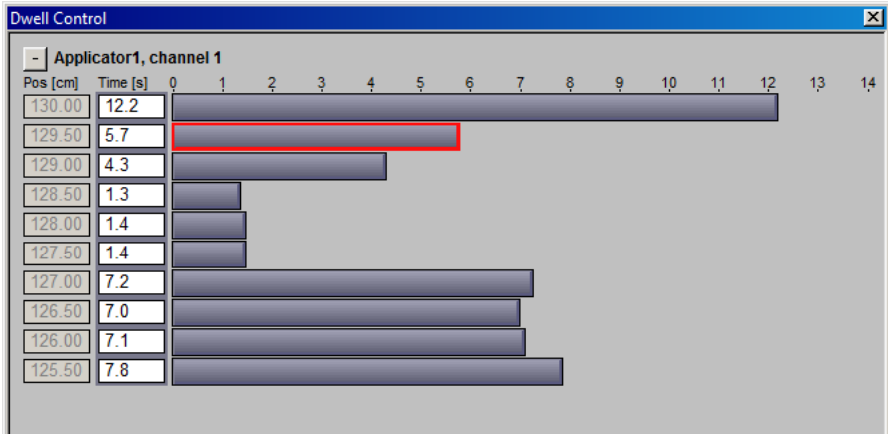
→ Two variables: dwell times and dwell positions





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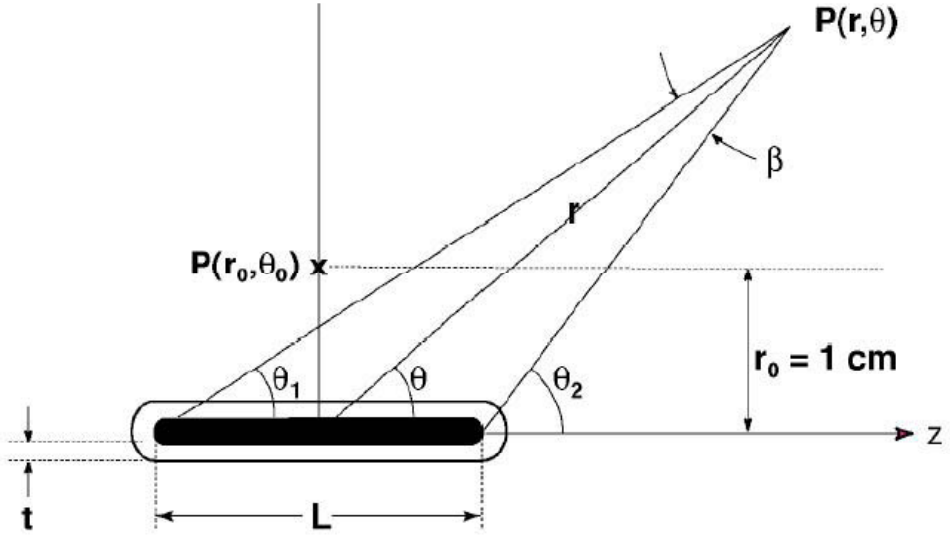
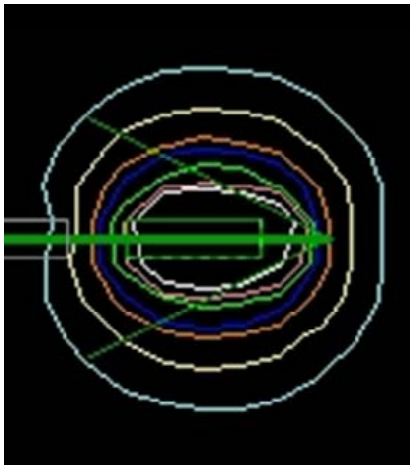
→ TG-43 Formalism

$$\dot{D}(r,\theta) = S_K \cdot \Lambda \cdot \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} \cdot g_L(r) \cdot F(r,\theta)$$

S_k: Air-Kerma-Strength
Λ: Dose-Rate constant
G_L: Geometry function
g_L: Radial Dose function
F: Anisotropy function





Rivard et al. Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations. Med Phys 2004

→ The evolution of brachytherapy treatment planning

TABLE I. Sensitivity of commonly treated anatomic sites to dosimetric limitations of the current brachytherapy dose calculation formalism. Items flagged as "Y" indicate the authors opinion that significant differences between administered and delivered dose are possible due to the highlighted dosimetric limitation.

Anatomic site	Source energy	Absorbed dose	Attenuation	Shielding	Scattering	Beta/kerma dose
Prostate	High	N	N	N	N	N
	Low	Y	Y	Y	N	N
Breast	High	N	N	N	Y	N
	Low	Y	Y	Y	N	N
GYN	High	N	N	Y	N	N
	Low	Y	Y	N	N	N
Skin	High	N	N	Y	Y	N
	Low	Y	N	Y	Y	N
Lung	High	N	N	N	Y	Y
	Low	Y	Y	N	Y	N
Penis	High	N	N	N	Y	N
	Low	Y	N	N	Y	N
Eye	High	N	N	Y	Y	Y
	Low	Y	Y	Y	Y	N

Rivard et al. Med Phys 36(6), 2009

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→ HDR technique: CT or Ultrasound ???

TRUS-based preplanning

before implantation
(not really necessary with experience)

Intra-operative planning (TRUS)

in the operation theatre

CT-based preplanning

before implantation
(not really necessary with experience)

CT-based procedure

Implant the needles then scan

- Different timing
- Different images
- **Same treatment planning techniques**

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Treatment planning techniques

How can I persuade the planning computer to calculate a proper plan?

1. Forward planning
2. Geometrical optimization
3. Inverse planning (volume optimization)

4. Combinations 1.-3.

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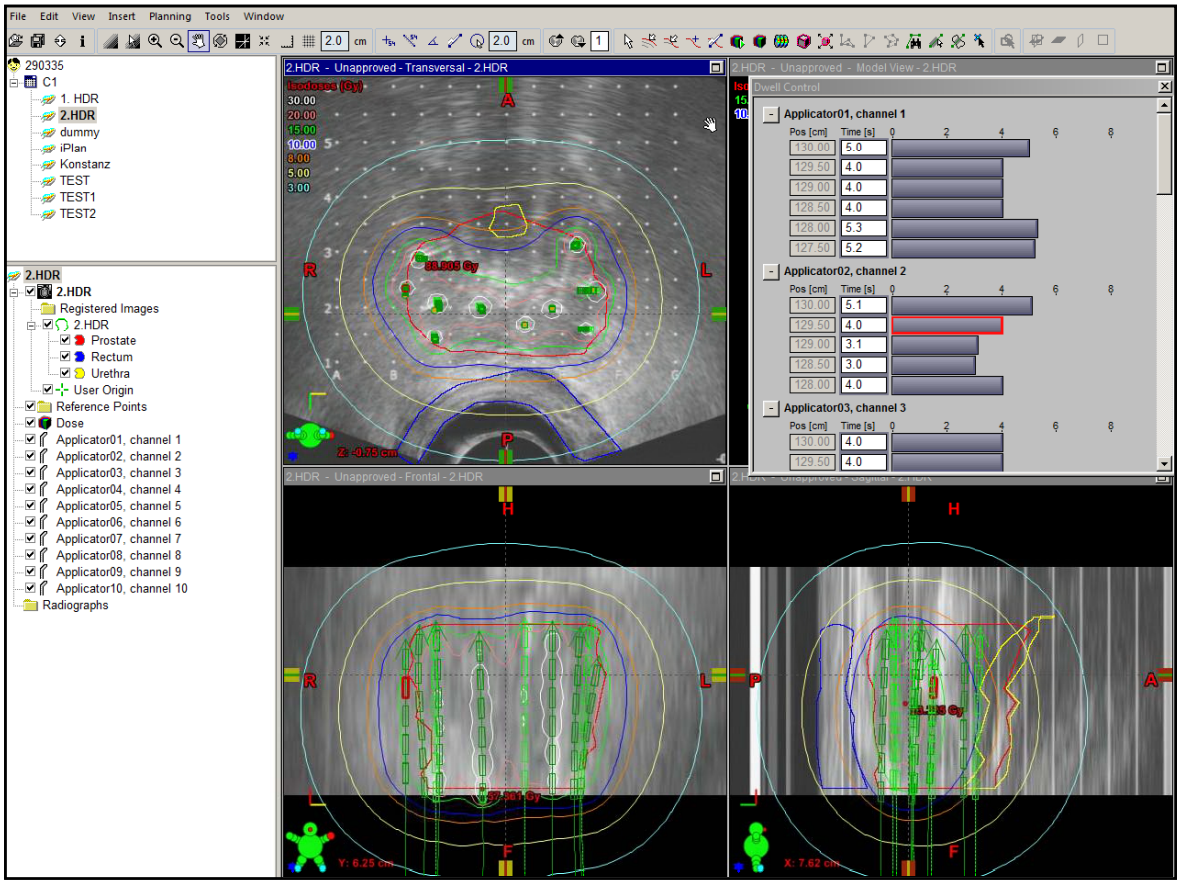
→ Forward planning



- User biased
- Needs experience
- Fast

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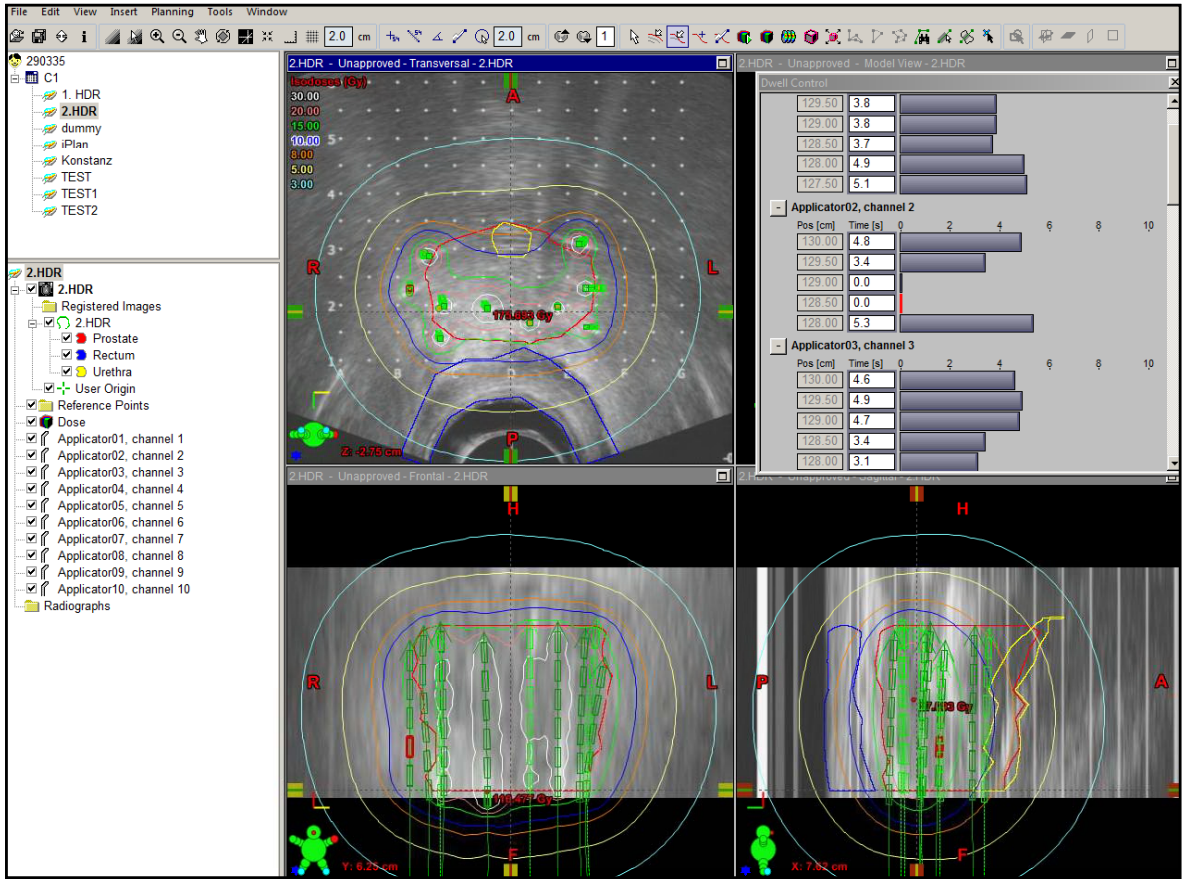
→ Forward planning, *shaping* tools



- Good tools, but check dwell times!

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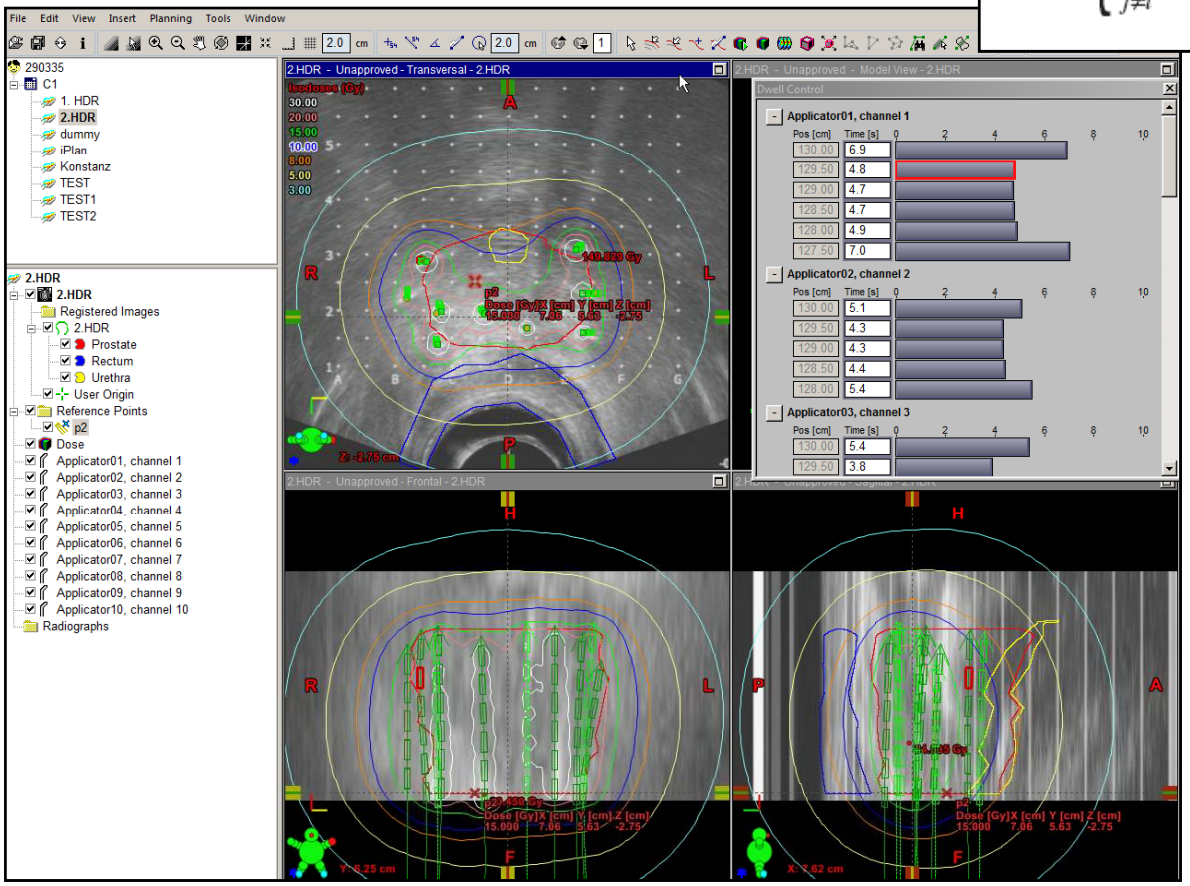
→ Geometrical optimization

$$T_i = \left\{ \sum_{\substack{j=1 \\ j \neq i}}^{n} T_j [(x_j - x_i)^2 + (y_j - y_i)^2 + (z_j - z_i)^2]^{-1} \right\}$$



- Easy to use
- Fast
- Not anatomy based

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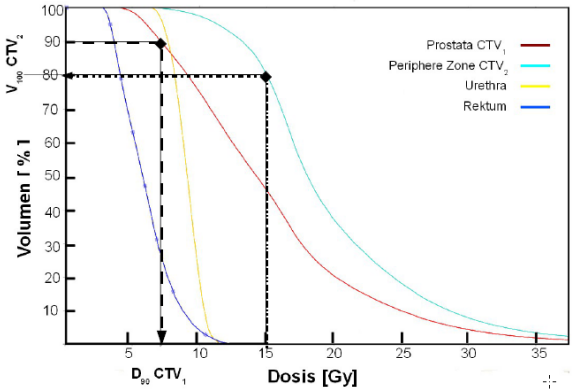
→ Inverse Planning

Is like…

Christmas!

But before we get presents,
we have to write a wish list

In Inverse Planning wishes are normally expressed in terms of dose constraints



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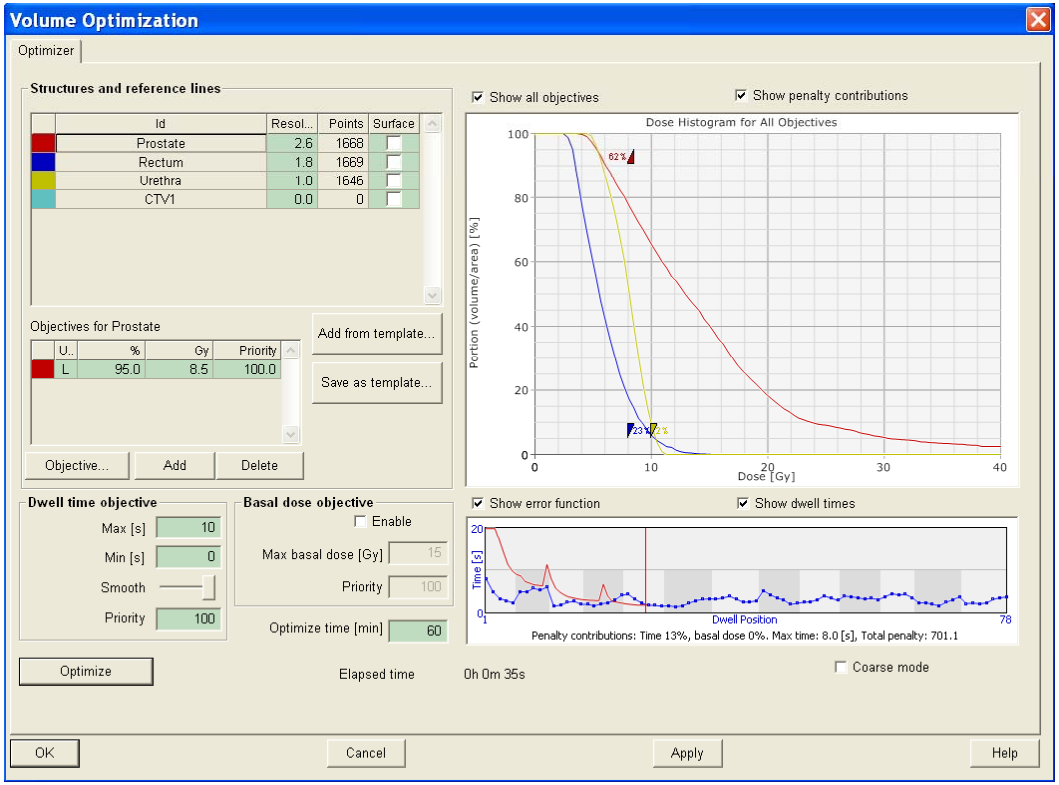
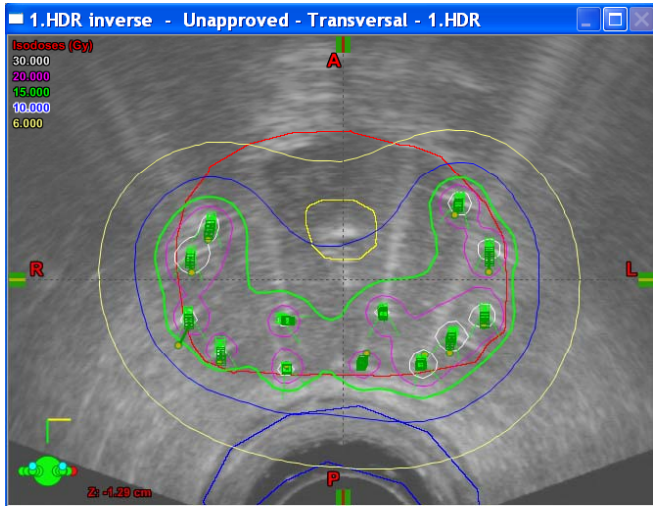
→ Inverse Planning

Dose constraints for individual organs needed





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→ Inverse planning

Convert dose distribution D_i to penalty value w_i
(d_{ij}: dose rate matrix)

$$D_i = \sum_j d_{ij} t_j$$

$$w_i = \begin{cases} m_L(D_i - L) & \text{if } D_i < L \\ m_R(D_i - R) & \text{if } D_i > R, \\ 0 & \text{if } L \leqslant D_i \leqslant R, \end{cases}$$

$$E_n = \sum_i^m \frac{w_i}{m}.$$

(Summation over all dose points)

$$E(k) = \sum_{n=1}^{4} E_n(k).$$

(Summation over clinical criteria)

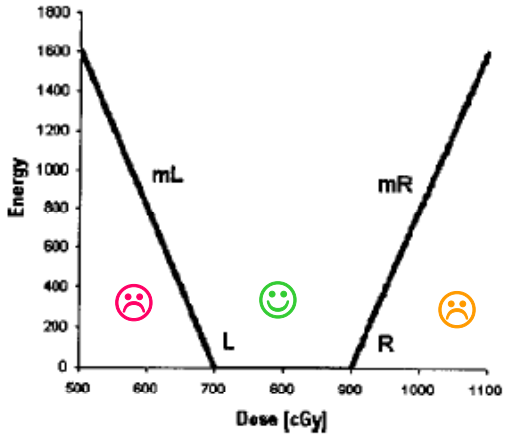
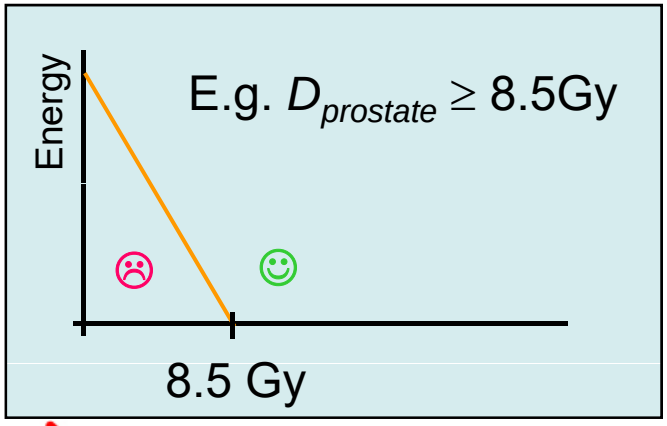


FIG. 4. Dose potential defined by the Eq. (5).



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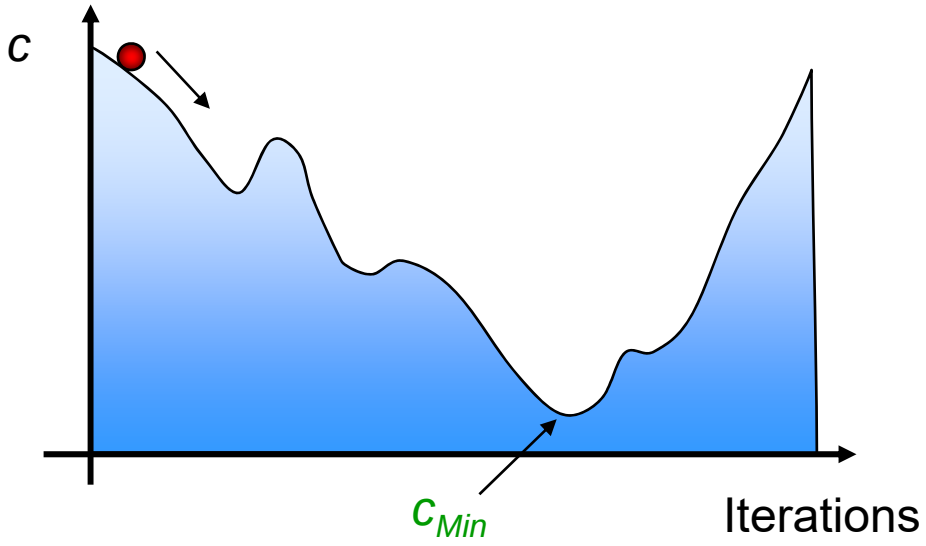
→ Inverse planning

Dwell times t_j change until
global minimum c_{Min} is reached.



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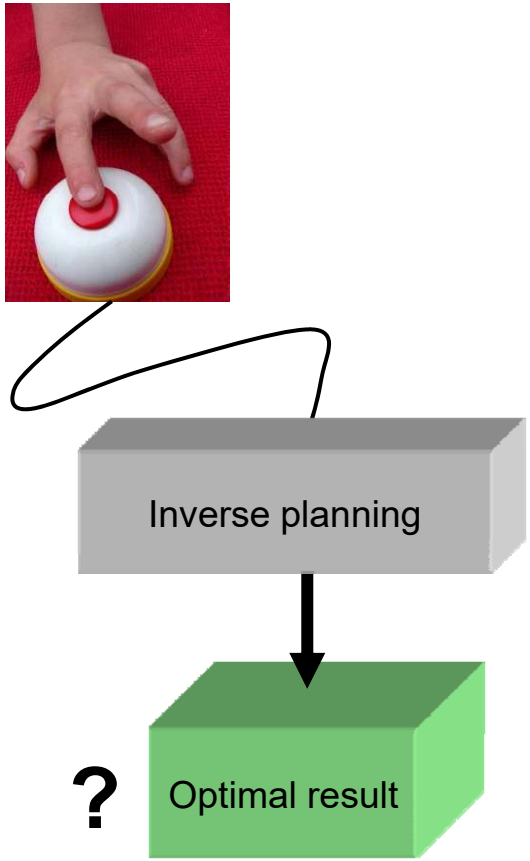
→ Inverse planning

- No *one-click* solution
- Constraints must be adapted
- User-independant solution
- Can save time
- Check the results



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Uncertainties in Brachytherapy

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

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

Kirisits et al. Radiother Oncol. Jan 2014; 110(1): 199–212.

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→ Checklist: HDR program (new / improvement)

- ✓ Literature research, courses (e.g. ESTRO)
- ✓ Patient selection
- ✓ Equipment: hardware, software, imaging
- ✓ Radiation protection
- ✓ Configure TPS
- ✓ Prescription dose, dose constraints
- ✓ Training
- ✓ Dummy run (phantom)
- ✓ Establish QA program
- ✓ …

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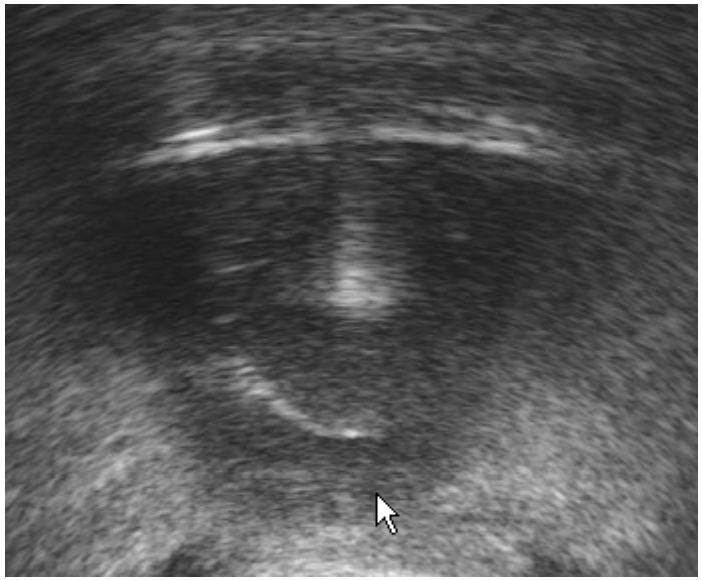

Thank you for your attention !

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Extra Slides

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Kiel experience with BrachyVision (v8.8) for HDR prostate

- 38 implants tested

  Conventional vs. Inverse planning

Table 2
Dosimetric and quantitative parameters used for analysis

Parameters	Conventional planning	Inverse planning	*p*-Value
D_{90} CTV_1 (Gy)	5.62	5.63	0.67
D_{90} CTV_2 (Gy)	11.03	10.89	0.38
V_{200} CTV_1 (%)	29.83	29.87	0.80
V_{200} CTV_2 (%)	5.76	8.14	<0.01
DNR CTV_1	0.70	0.68	0.87
DNR CTV_2	0.34	0.36	<0.01
COIN CTV_1	0.26	0.30	0.17
COIN CTV_2	0.54	0.52	0.86
$D_{2\ cc}$ rectum (Gy)	6.04	6.12	0.09
$D^*_{2\ cc}$ rectum (Gy)	6.04	6.00	0.32
$D_{0.1\ cc}$ urethra (Gy)	9.57	9.02	0.34
$D^*_{0.1\ cc}$ urethra (Gy)	9.57	8.94	<0.01

CP = conventional planning; IP = inverse planning optimization; CTV = clinical target volume; DNR = dose nonhomogeneity ratio; COIN = conformity index.

The means of 38 plans considered are shown. Statistically significant is the difference in V_{200} CTV_2 and the reduction of the urethral dose of $D^*_{0.1\ cc}$ urethra.

Siebert et al. Brachytherapy 2014; 13(3)

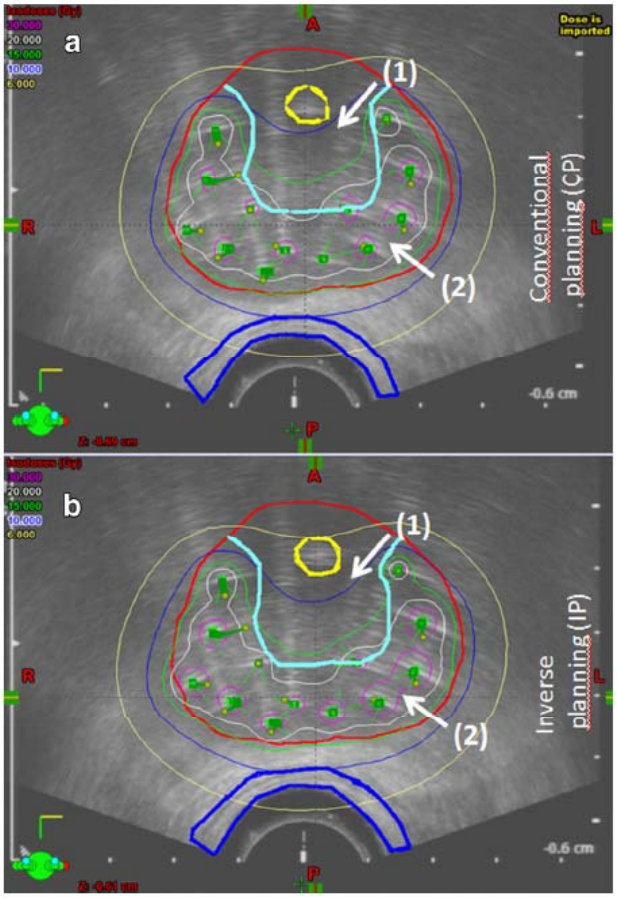


Fig. 1. Comparison of the dose distribution of an arbitrary patient using conventional planning (CP; a) and inverse planning (IP; b). White arrows outline the major differences between those two planning types: The CP leading to more dosage to the organs at risk (1), the IP creating hot spots within the clinical target volume (2).

St James's Institute of Oncology

Functional MRI guided HDR prostate brachytherapy tumour boost

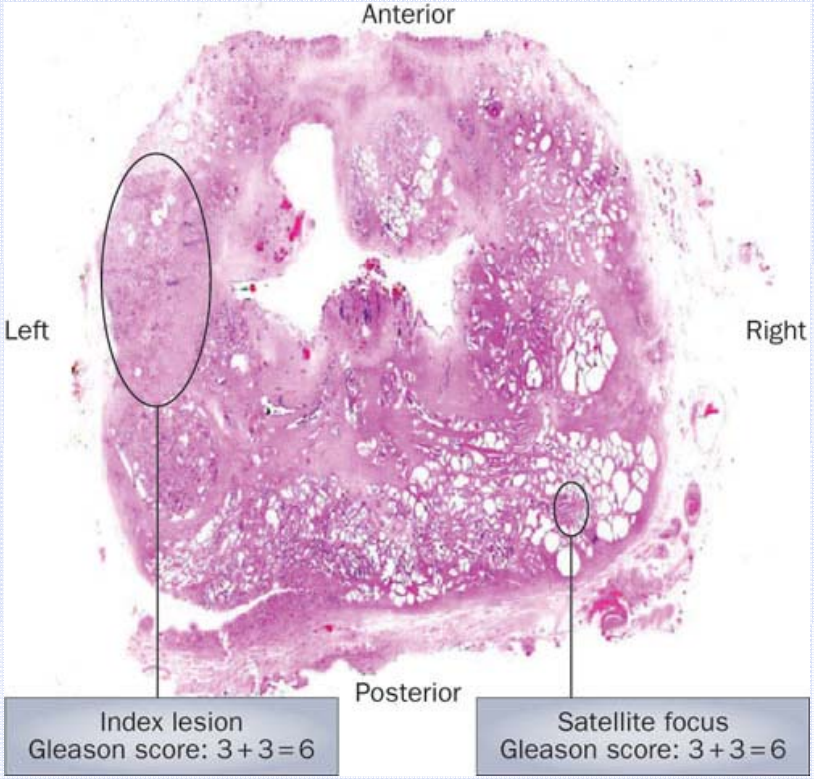
The Leeds Teaching Hospitals NHS
NHS Trust

Background

- 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

Rationale for study

- High dose/fraction may be radiobiologically advantageous
- Multiple randomised controlled trials demonstrate increased prostate cancer cure rates with higher doses of radiation
- Studies have shown that biological behaviour of prostate cancer may be driven by dominant lesion



Karavitakis, M. *et al.* (2010) Tumor focality in prostate cancer: implications for focal therapy *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2010.190

MR acquisition/processing

- 15 pts, T2c or T3a disease, 12/15 patients had neo-adjuvant hormone therapy
- T2 weighted (T2W), diffusion weighted (DWI) and dynamic contrast enhanced (DCE) MRI
- Phased-array pelvic and spine coils
- DWI (b-values 0, 150, 500 s/mm^2) - ADC map generated by scanner
- DCE (200 x 2-s 3D acquisitions) - generated Ktrans map from 1-compartment model and arterial input function, using PMI[1]

1 - PMI: Platform for research in medical imaging: see Quantification of cerebral blood flow, cerebral blood volume, and blood-brain-barrier leakage with DCE-MRI. Sourbron S, Ingrisch M, Siefert A, Reiser M, Herrmann K. Magn Reson Med. 2009 Jul;62(1):205-17.

F-GTV delineation

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

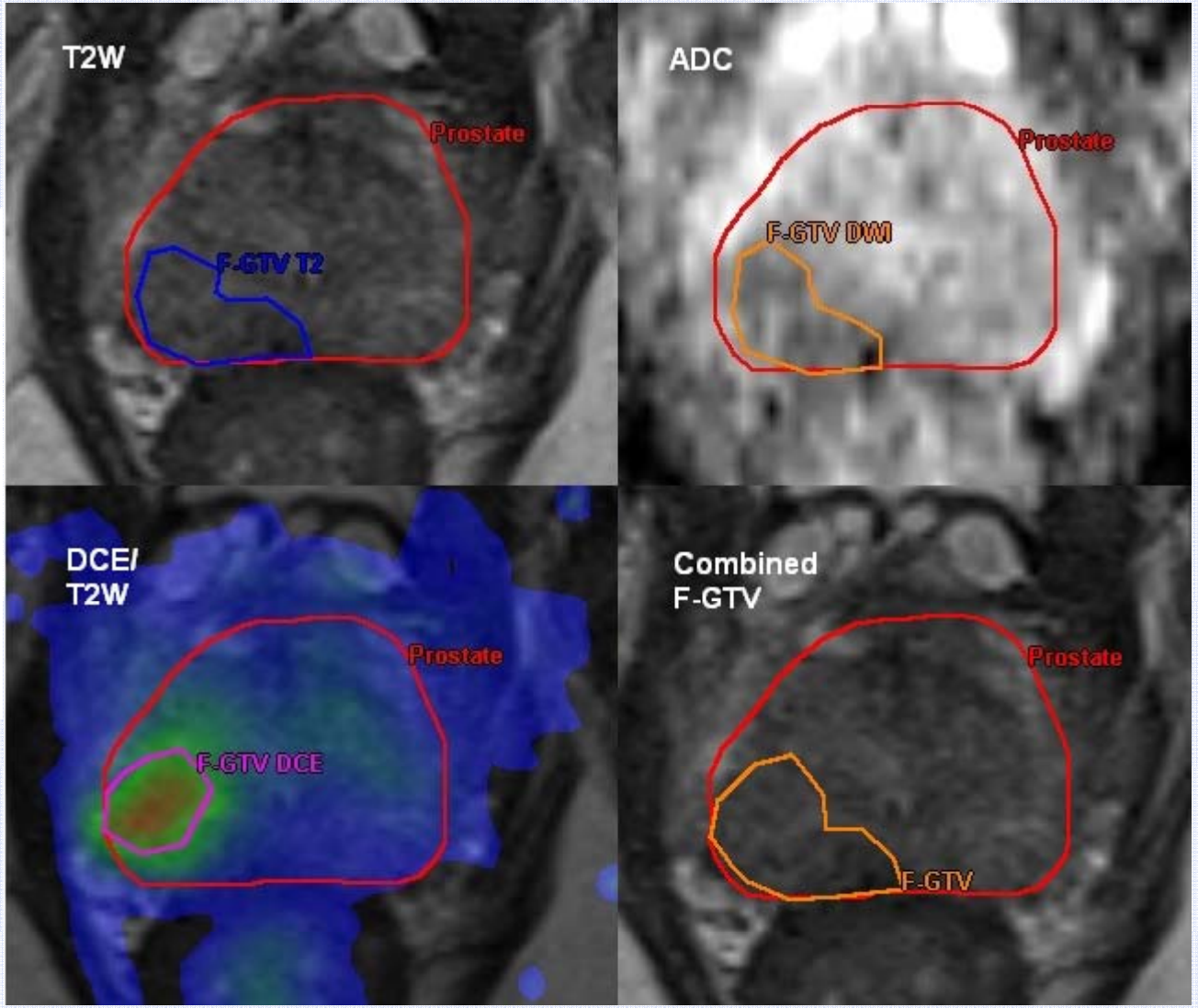
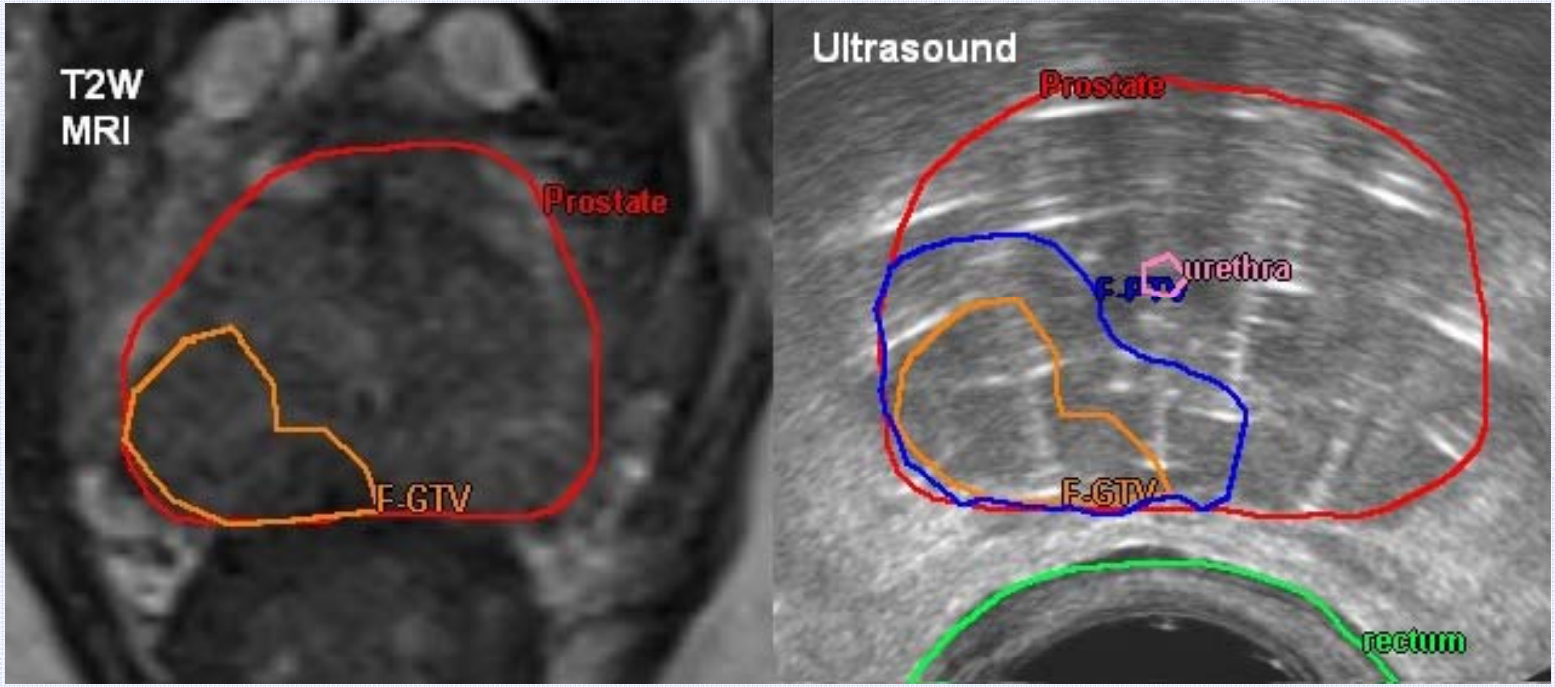


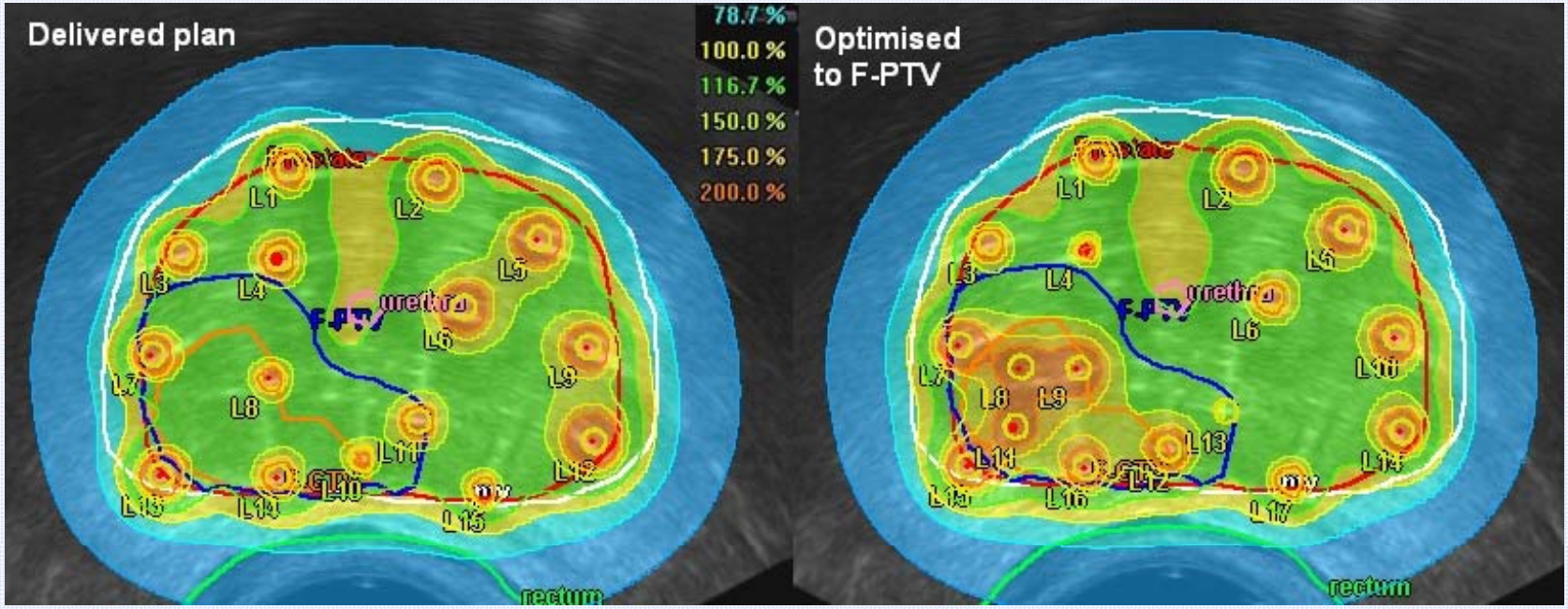
Image registration MRI-TRUS

- 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

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	Intermediate Risk	High Risk
Stage: T1 or T2a,b Gleason Sum ≤ 6 PSA ≤ 10 ng/ml	Stage T1 or T1-2 Gleason Score 7 PSA < 10 or Stage T1-2 Gleason 6 PSA 10-20	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

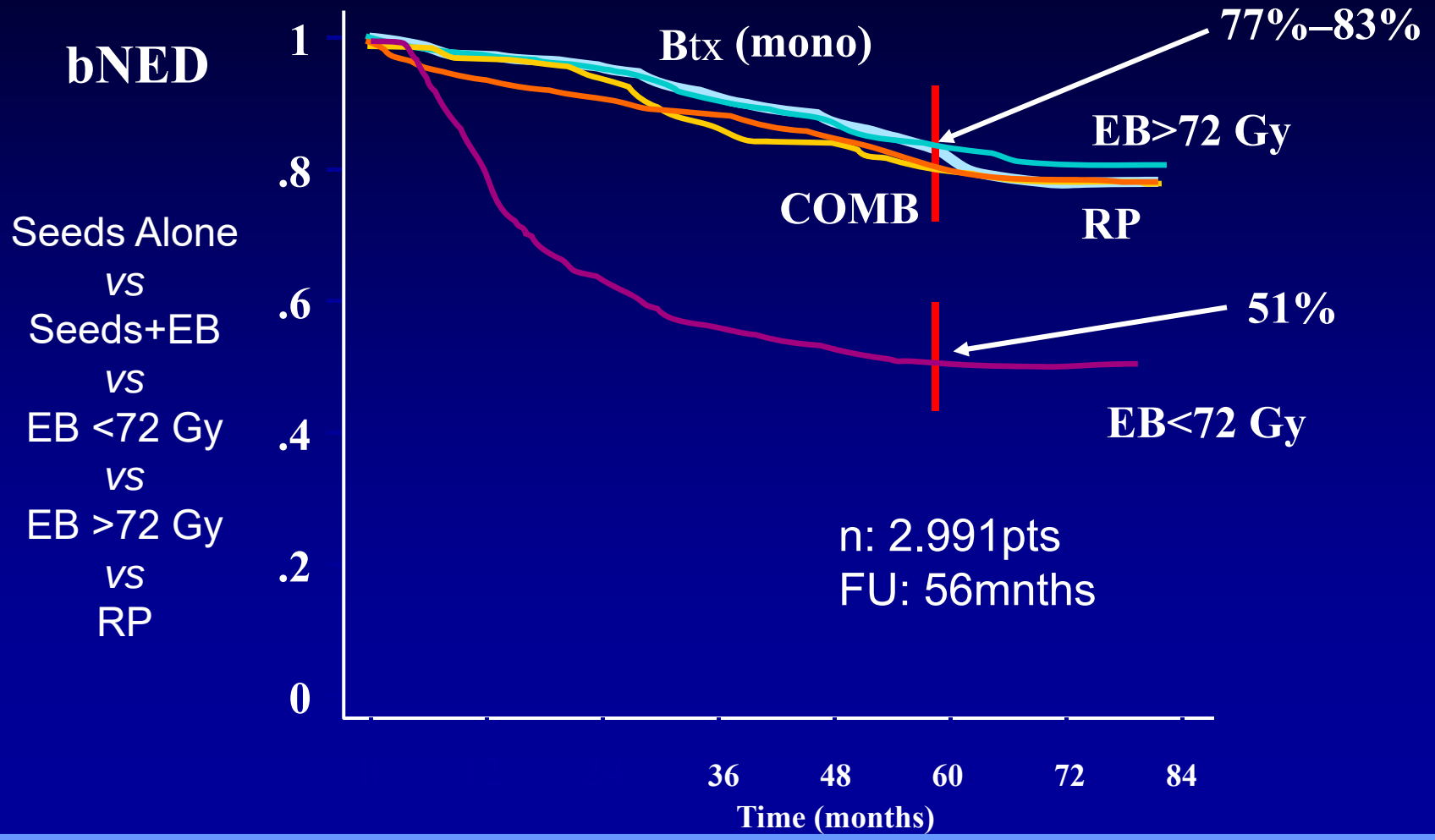
PATRICK A. KUPELIAN, M.D.,* LOUIS POTTERS, M.D.,† DEEPAK KHUNTIA, M.D.,‡
JAY P. CIEZKI, M.D.,‡ CHANDANA A. REDDY, M.S.,‡ ALWYN M. REUTHER, M.P.H.,‡
THOMAS P. CARLSON, M.D.,‡ AND ERIC A. KLEIN, M.D.‡

*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

BJUI SUPPLEMENTS

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]

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

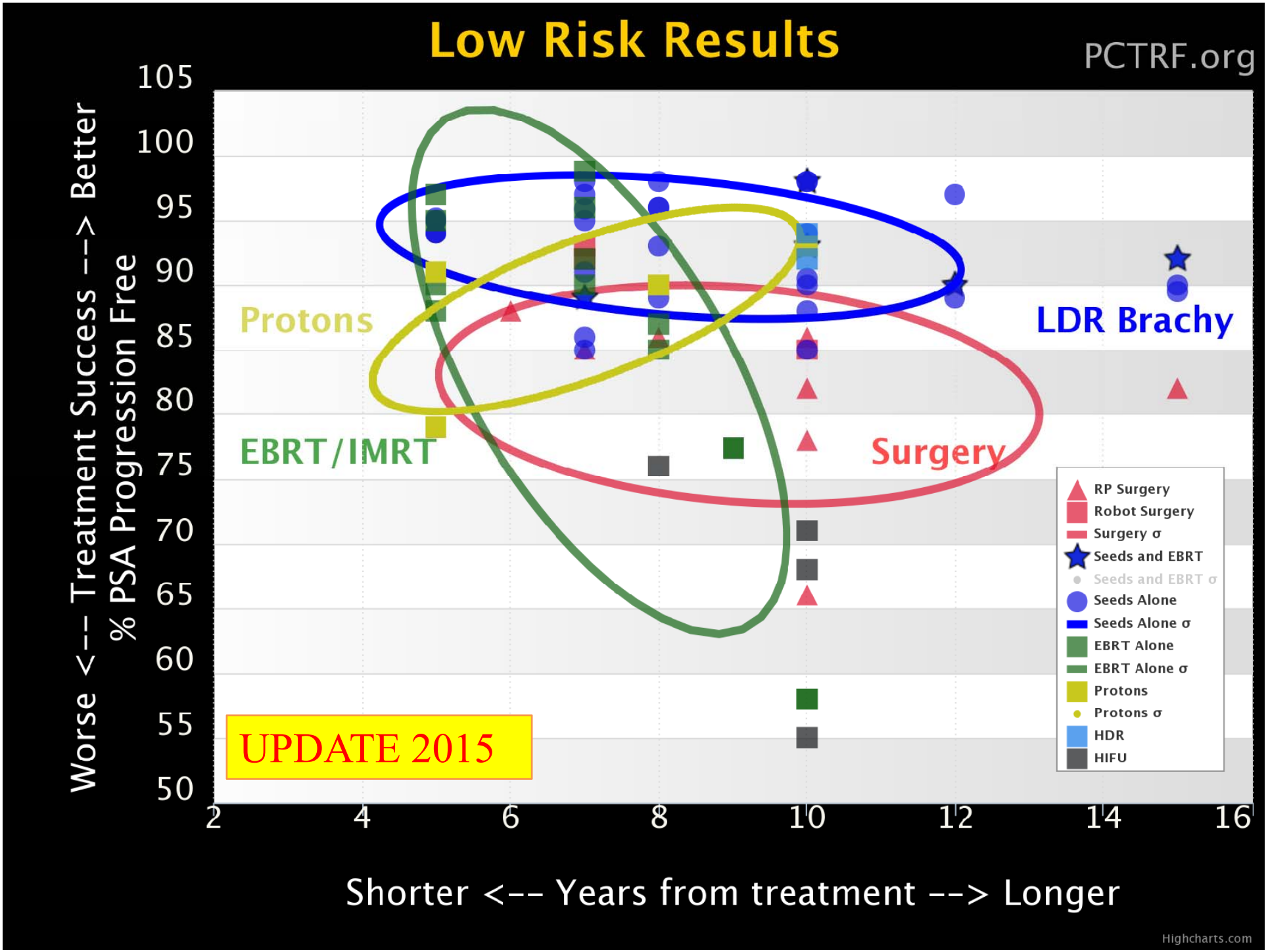
Prostate Cancer Results Study Group
Updated June 2015

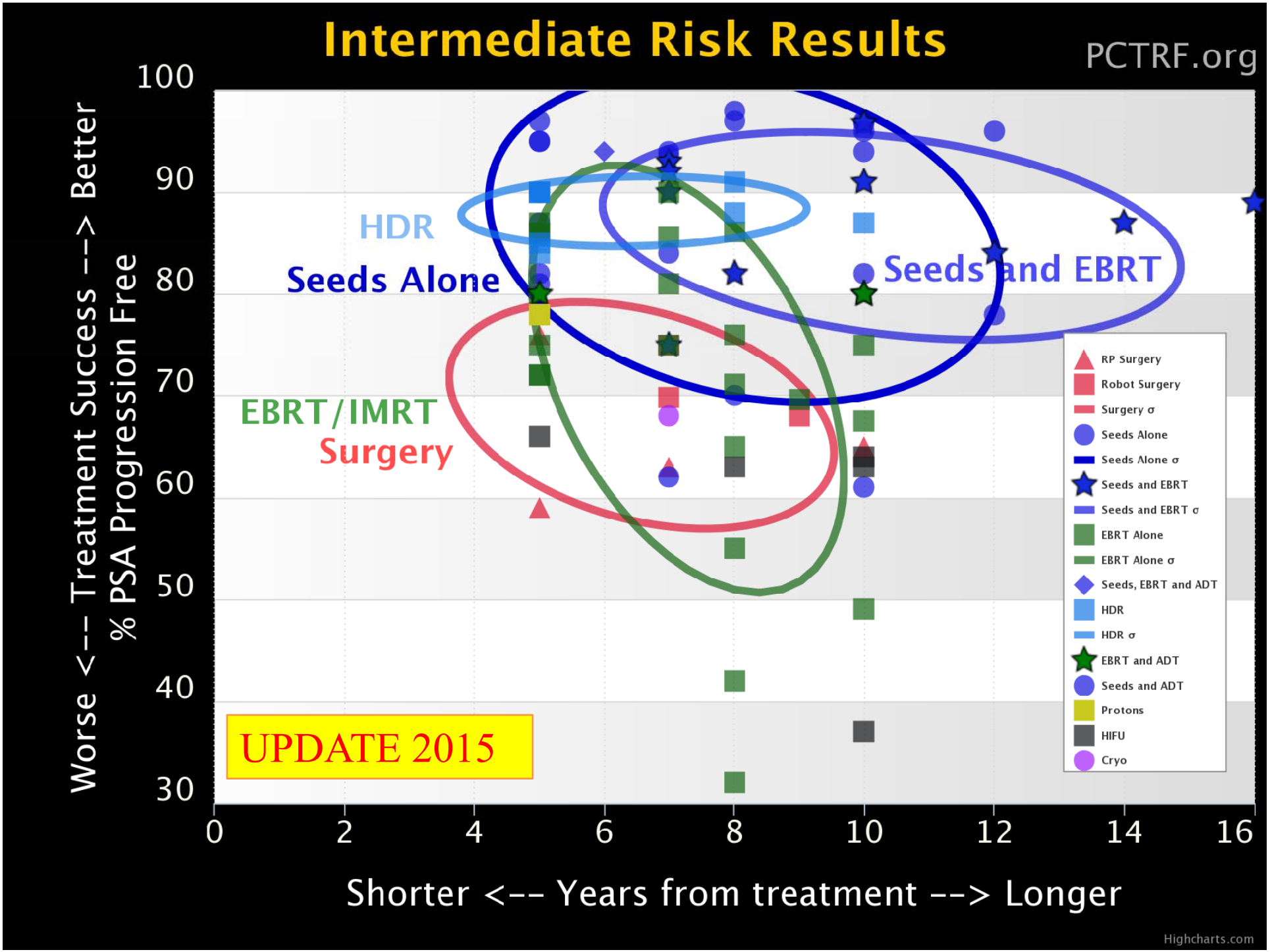
Peter Grimm, DO
Prostate Cancer Center of Seattle

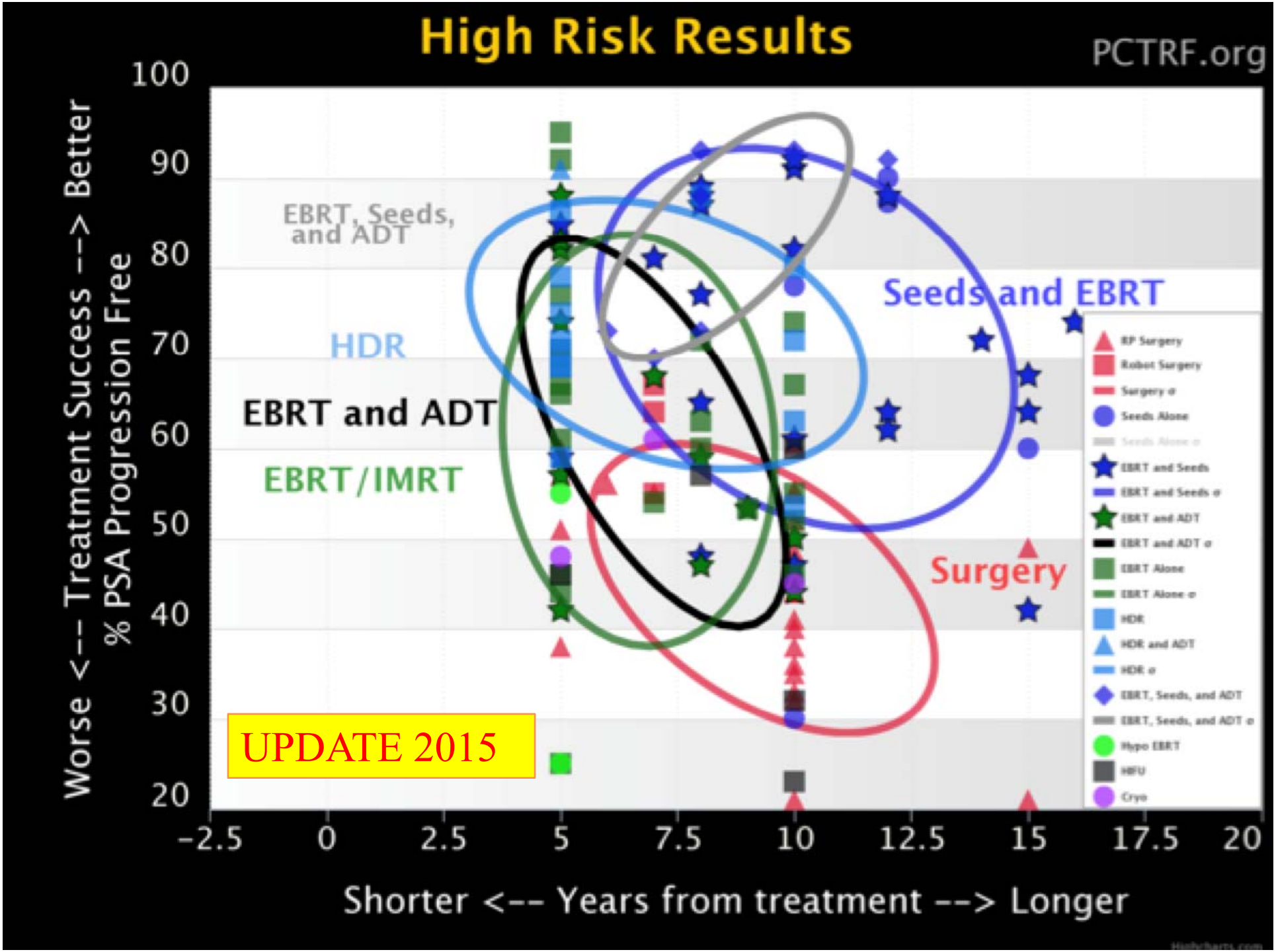
% Articles Meeting Criteria

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
EBRT/IMRT
Surgery
LDR Brachy
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

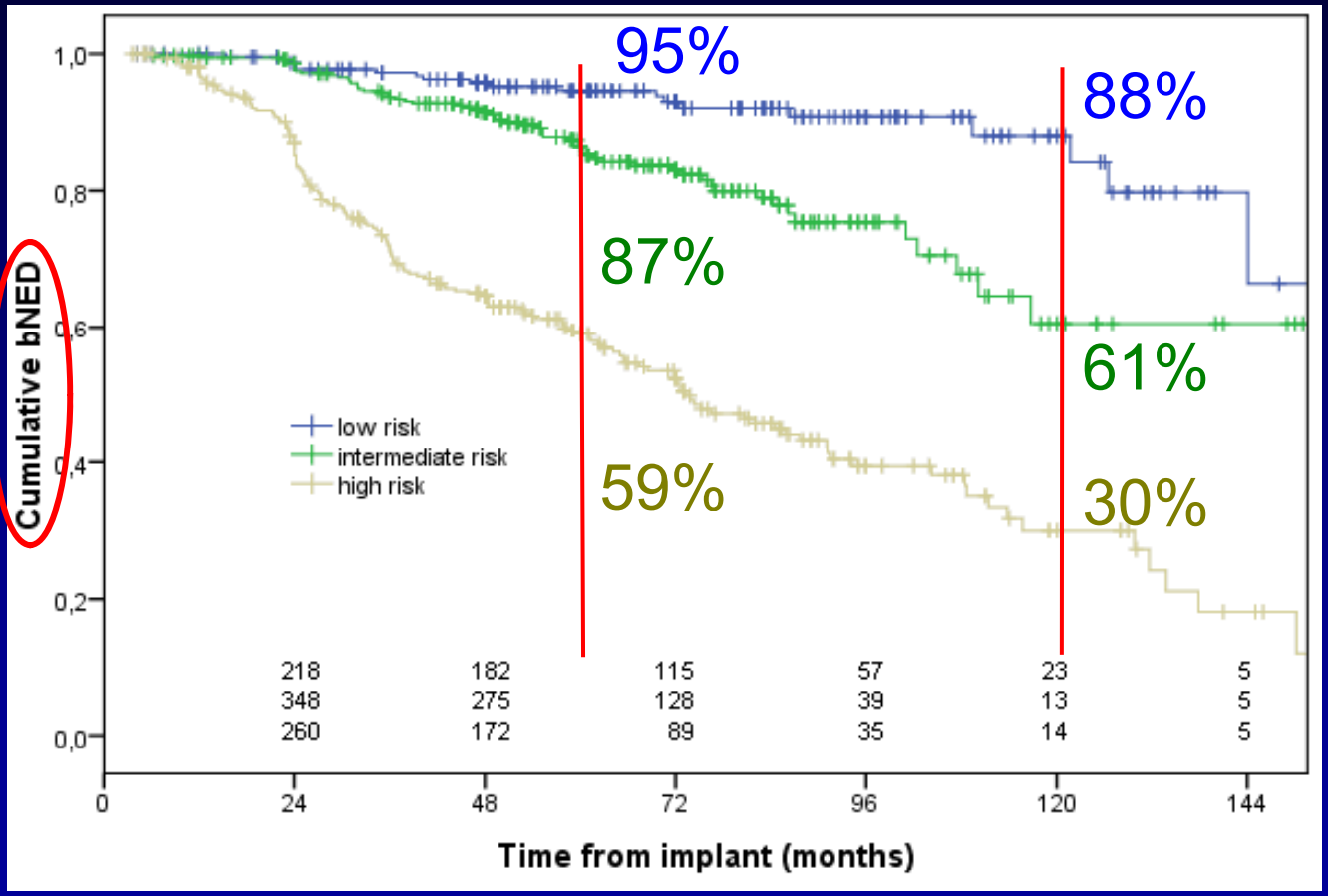

Intermediate Risk Results
PCTRF.org
Worse <-- Treatment Success --> Better
% PSA Progression Free
100
90
80
70
60
50
40
30
0
2
4
6
8
10
12
14
16
Shorter <-- Years from treatment --> Longer
HDR
Seeds Alone
Seeds and EBRT
EBRT/IMRT
Surgery
UPDATE 2015
RP Surgery
Robot Surgery
Surgery σ
Seeds Alone
Seeds 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 o
Seeds Alone
EBRT and Seeds
EBRT and Seeds o
EBRT and ADT
EBRT and ADT o
EBRT Alone
EBRT Alone o
HDR
HDR and ADT
HDR o
EBRT, Seeds, and ADT
EBRT, Seeds, and ADT o
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.

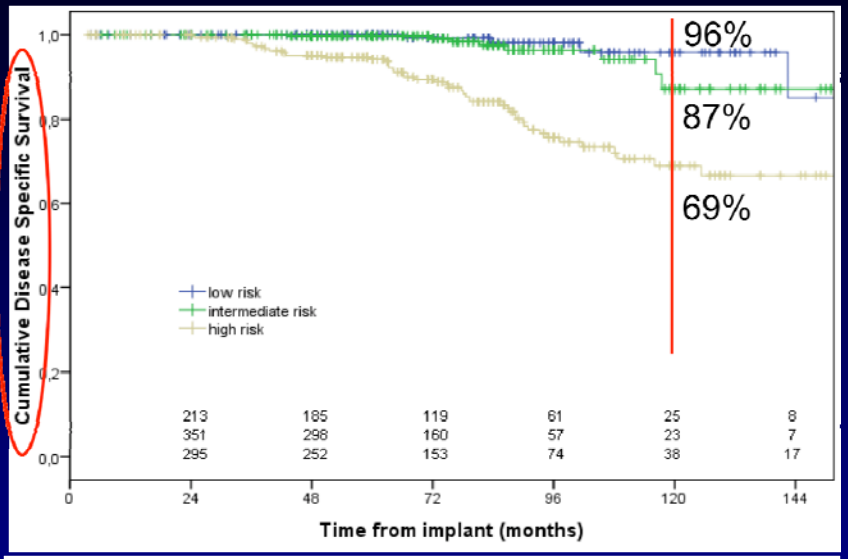
Hinnen et al.



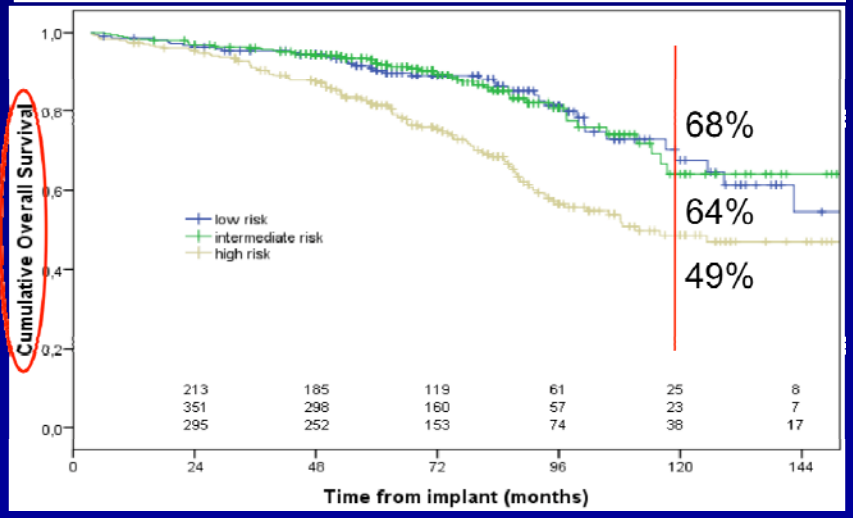
bNED

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

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.§

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

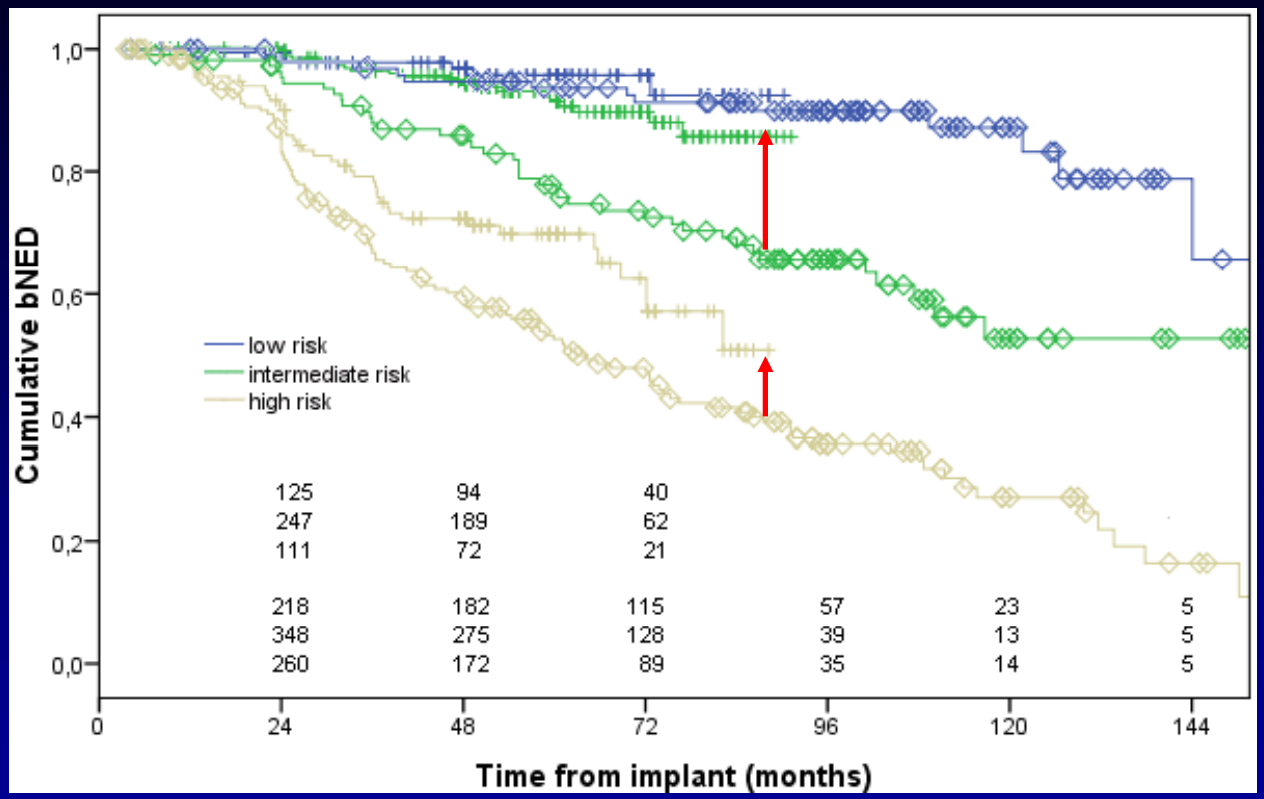
Seeds: factors that might or might not influence outcome

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. …

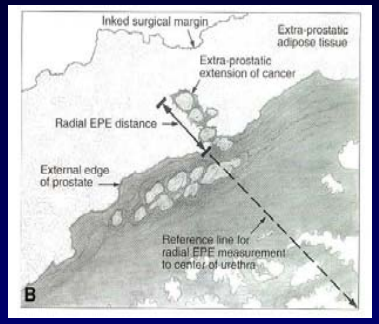
UMC database: bNED before and after 2000



n=921 - 1989-2004

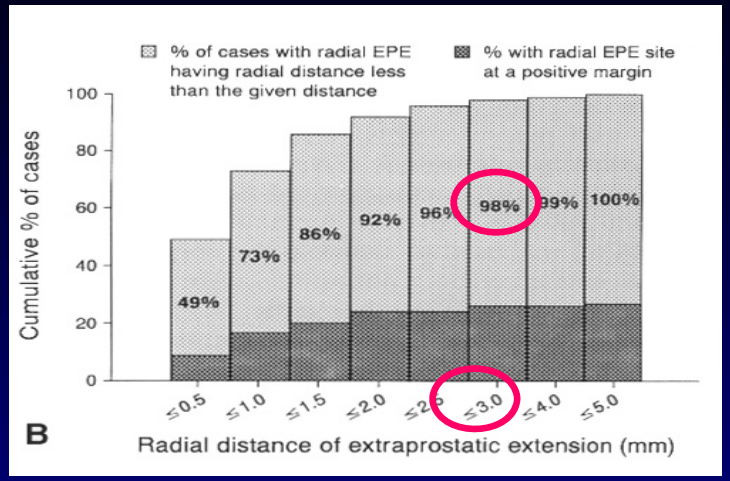
- There seems to be a trend for improved outcome in time
- Raison: technique? patient selection? learning curve? other factors?

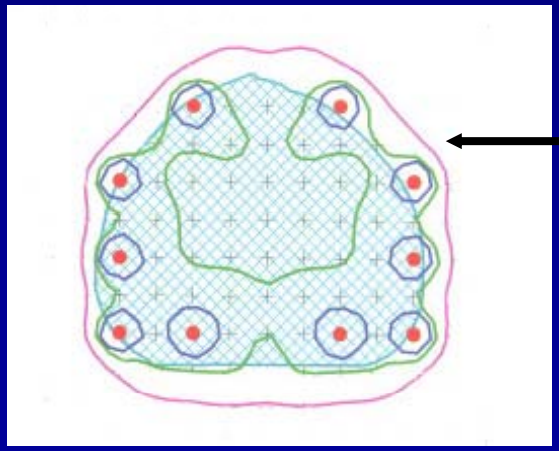
Implant related: Margins:



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

Davis et al. Cancer 85(12) 1999



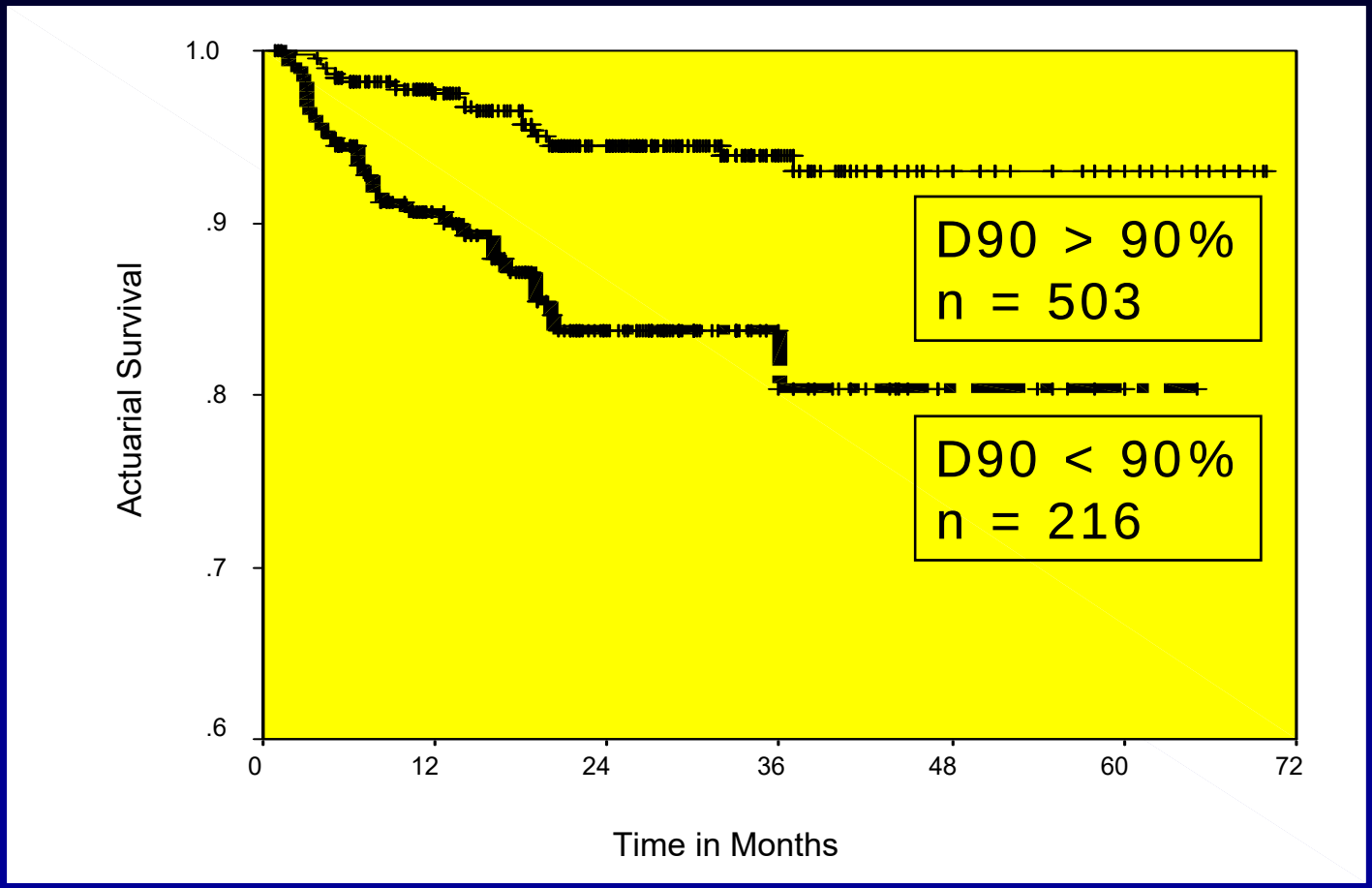


Extraprostatic disease

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

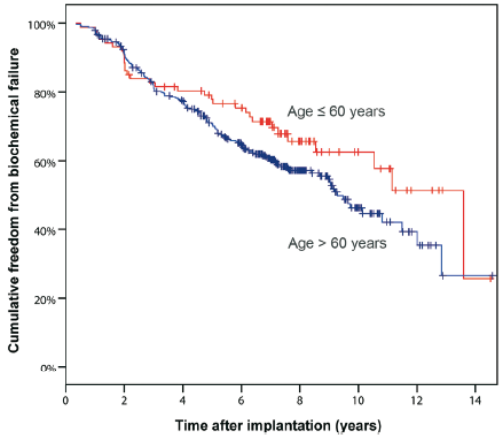


Figure 2. Kaplan–Meier curve for disease-specific survival in patients with aged ≤60 years versus > 60 years. Log-rank test p=0.1

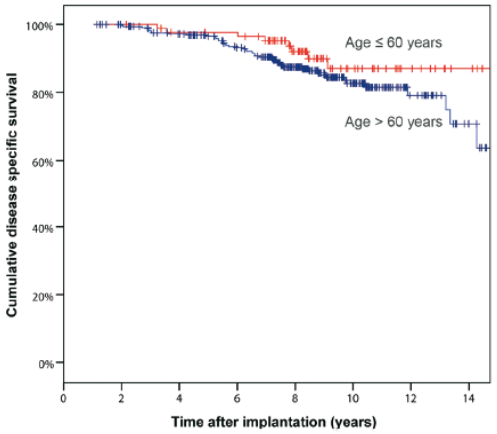
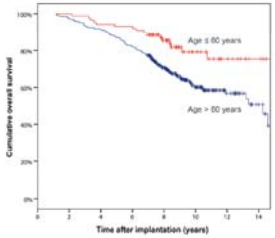
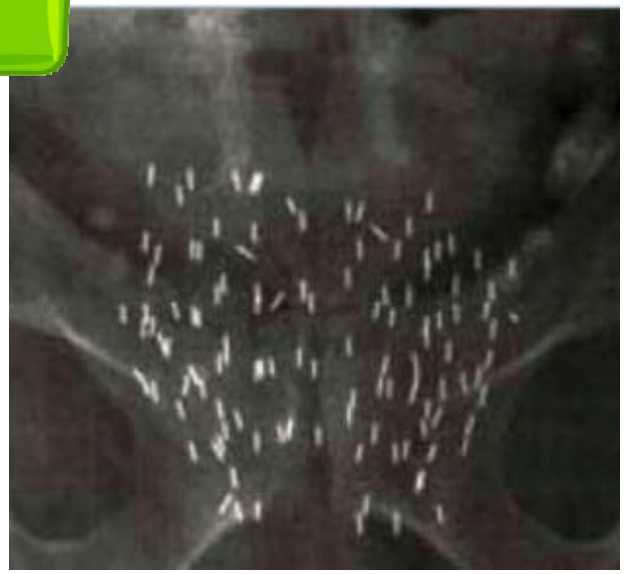


Figure 3. Kaplan–Meier curve for overall survival in patients aged ≤60 years versus >60 years. Log-rank test p<0.01



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)

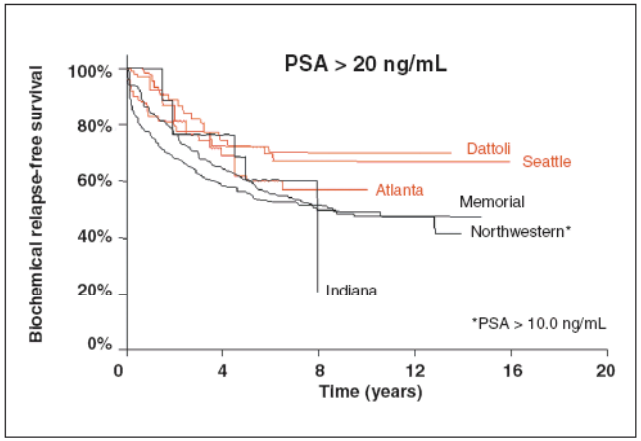


Figure 5: Survival After Brachytherapy vs Prostatectomy, by PSA Level—Biochemical relapse-free survival among patients with prostate-specific antigen (PSA) > 20 ng/mL treated definitively with brachytherapy and supplemental external-beam radiation (red) or radical prostatectomy (black).

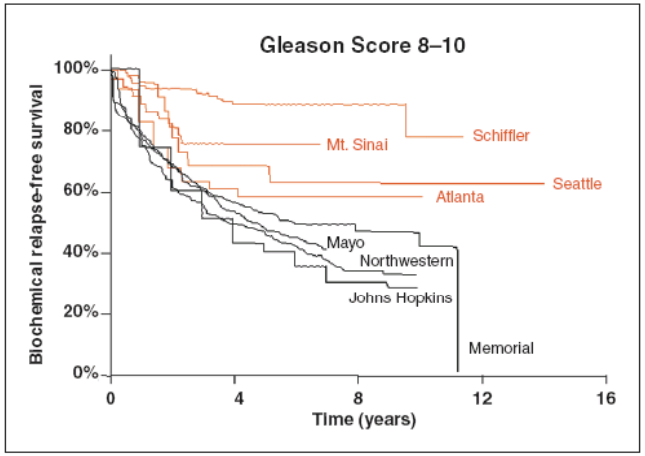
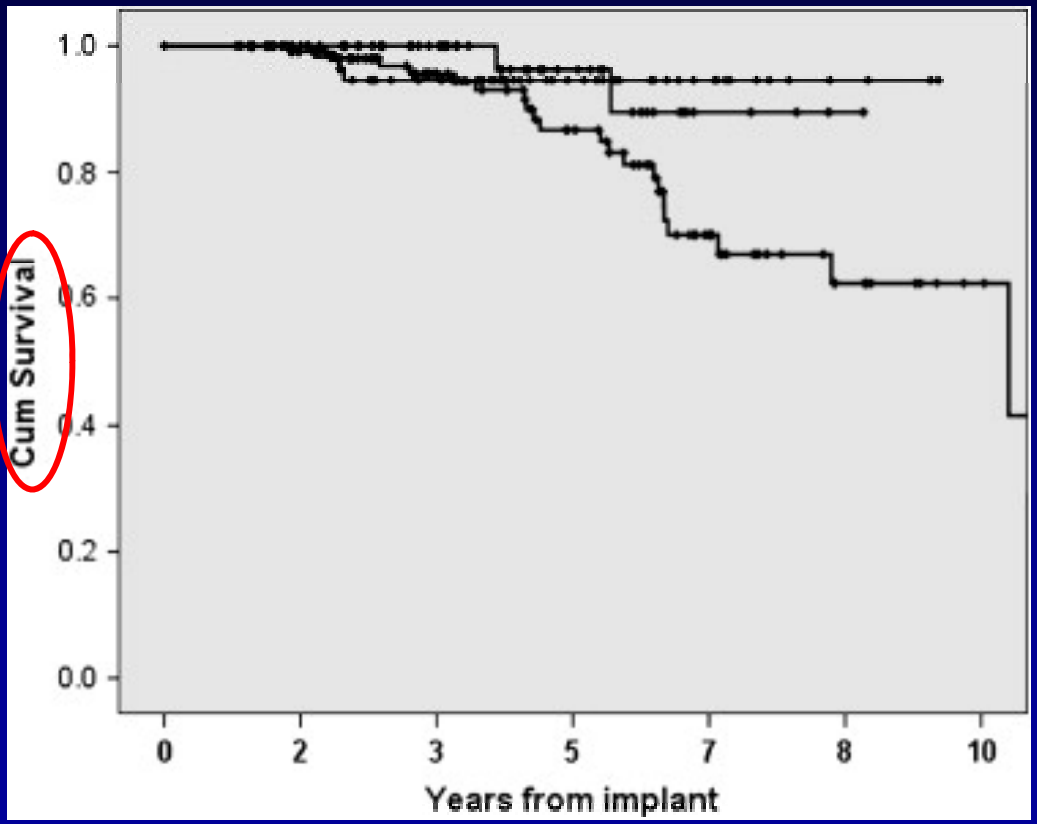


Figure 4: Survival After Brachytherapy vs Prostatectomy, by Gleason Score—Biochemical relapse-free survival among patients with Gleason score 8–10 treated definitively with brachytherapy and supplemental external-beam radiation (red) or radical prostatectomy (black).

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.

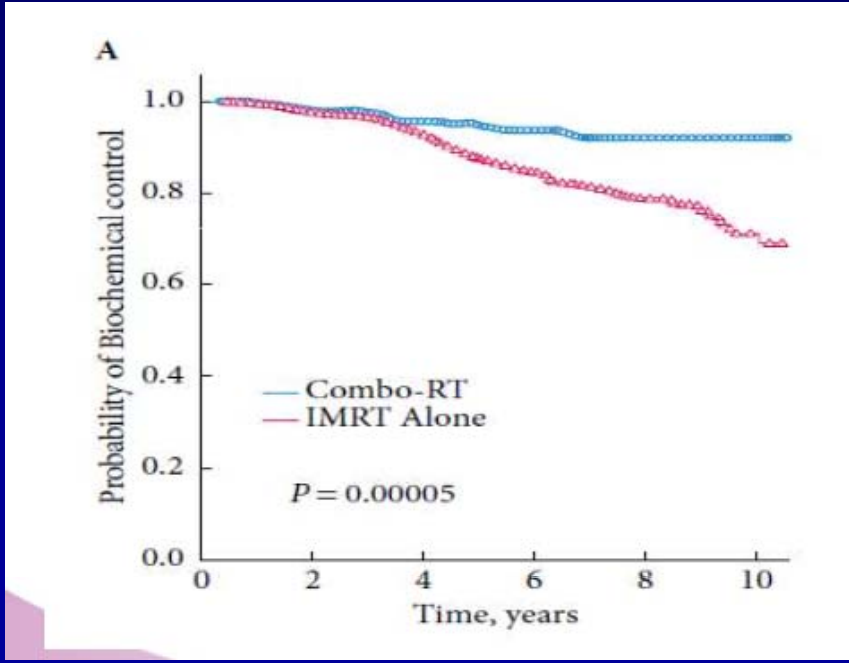
Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer

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)



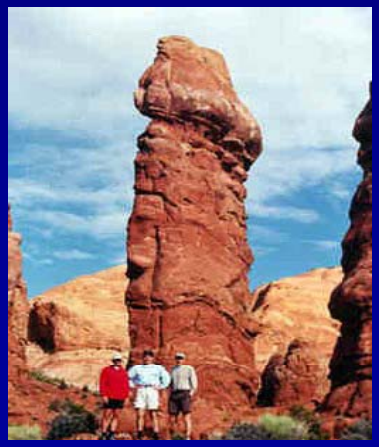
RTE + HDR or Seeds

>

Escalated dose RTE

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

Quality of Life – Side Effects



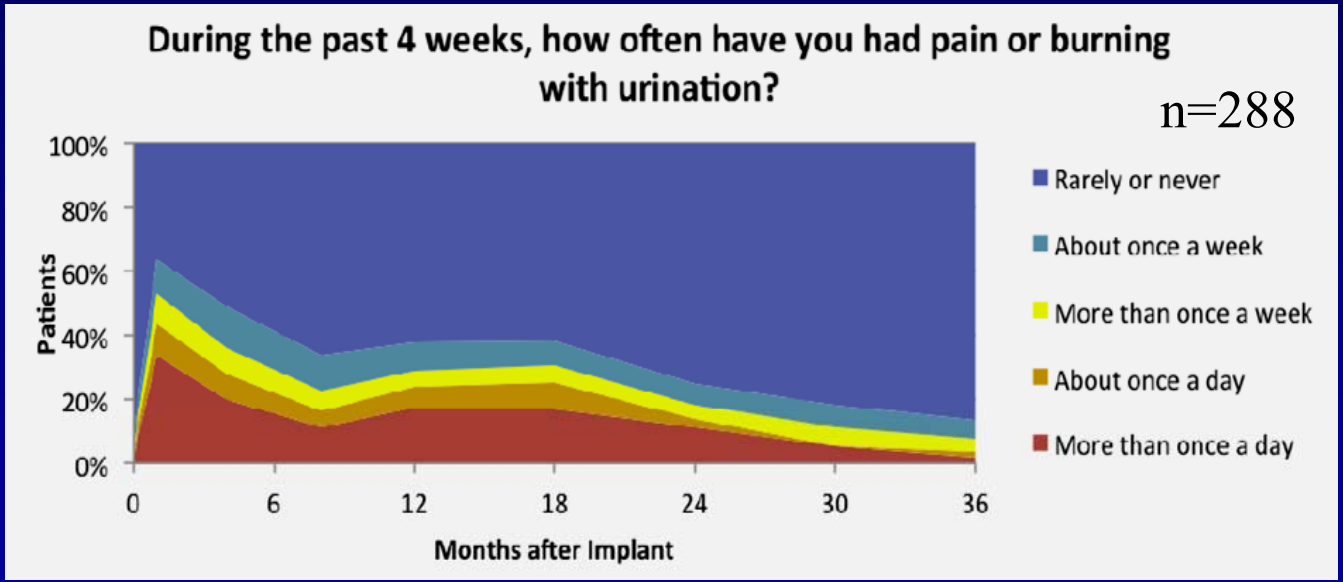
Toxicity grading:

- 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

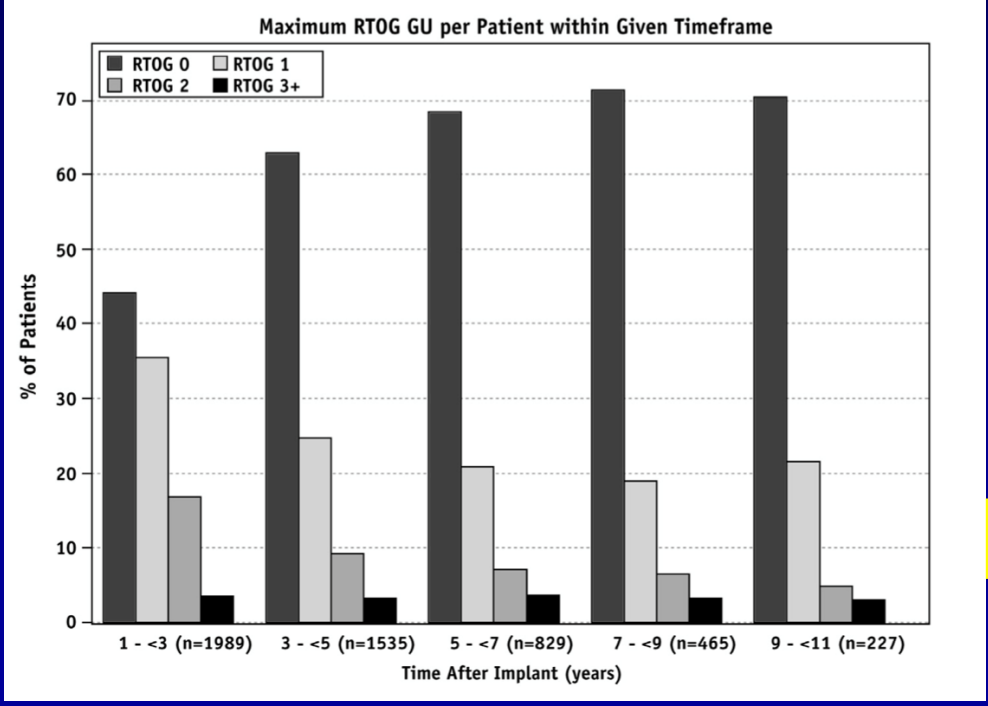
Urinary Bother

- 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*

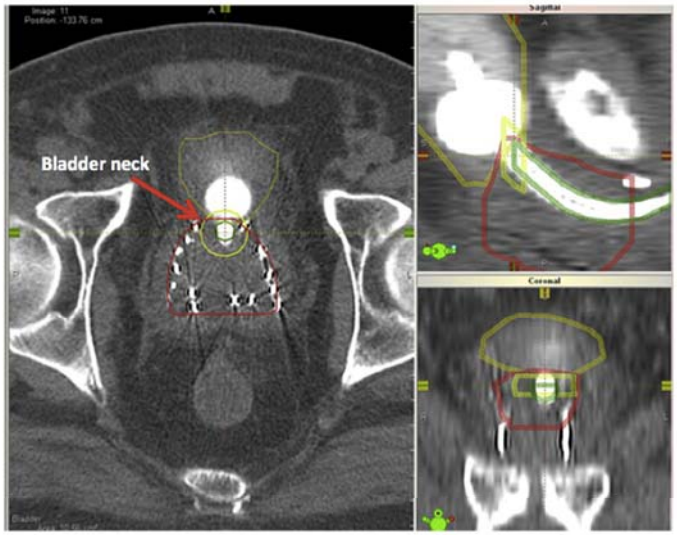


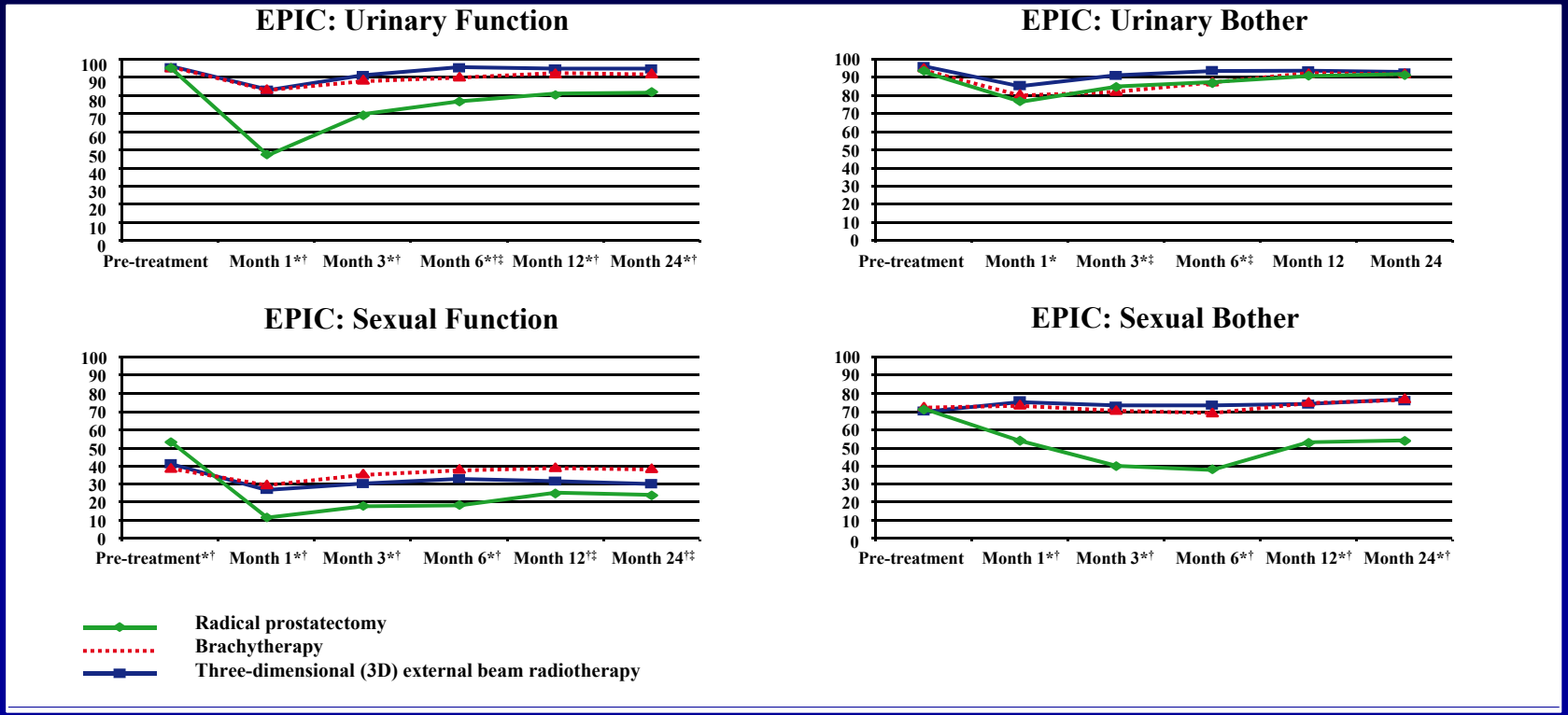
Fig. 1. Contour of bladder neck on computed tomographic scan on day 0 after implantation.

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

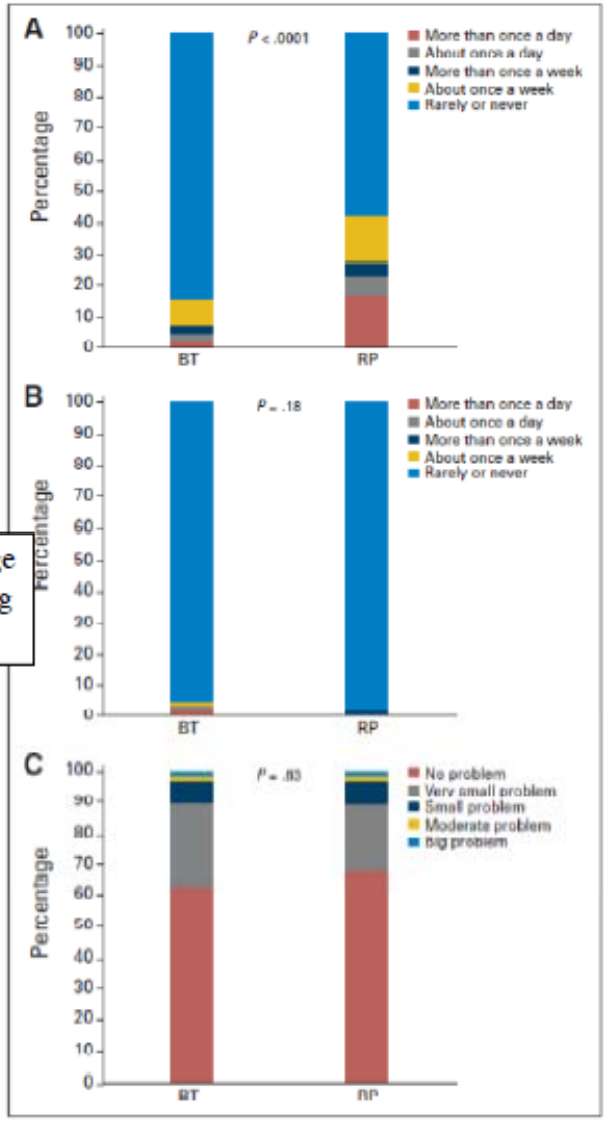
Quality of life following prostate cancer treatment

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

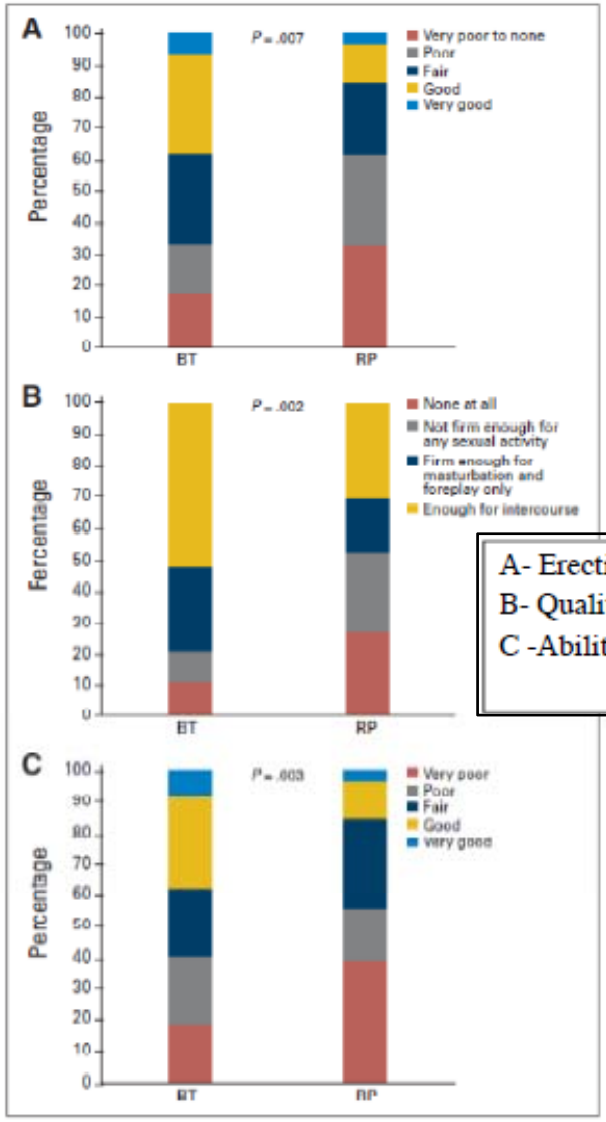


Ferrer M et al. *Int J Radiat Oncol Biol Phys* 2008; 72: 421–32.

- 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

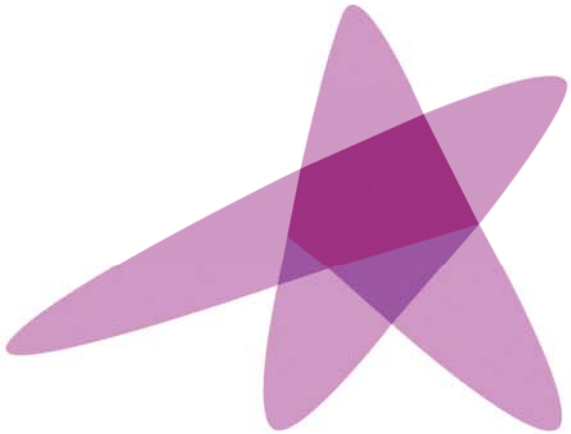
Brachytherapy	External Beam	Surgery
Less time of work	8 weeks of treatment + recuperation	6 -12 weeks recovery
Continence unaffected Mild LUTS in 70% Moderate LUTS in 30%	Continence unaffected Mild LUTS in majority Moderate LUTS in 50%	50% immediate continence 75% by 3 months 90-95% by 6 months
Very 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 intermediate-risk patients
- High-risk patients may benefit from combined EBRT and seed treatment
- Toxicity is low and acceptable
- No decrease in long term QoL
- Quality assurance very important
- Anti-androgen therapy does not seem to influence outcome in seed monotherapy


THANK
YOU!



ESTRO School

WWW.ESTRO.ORG/SCHOOL

High dose rate brachytherapy for prostate cancer: RESULTS

Peter Hoskin
Mount Vernon Cancer Centre
Northwood, UK

ESTRO School

HDR prostate brachytherapy

- HDR Boost
- HDR Monotherapy

	α/β 1.5	α/β 3.5	α/β 10
Ext beam			
74Gy/37f	74	74	74
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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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

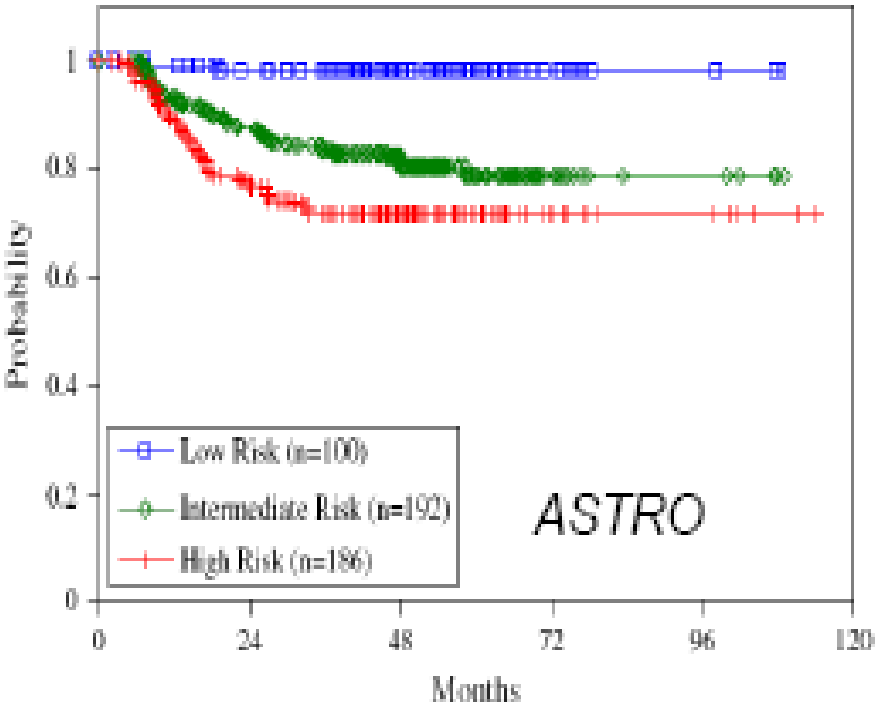
611 patients:
Seattle:
Kiel:
WBM:

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

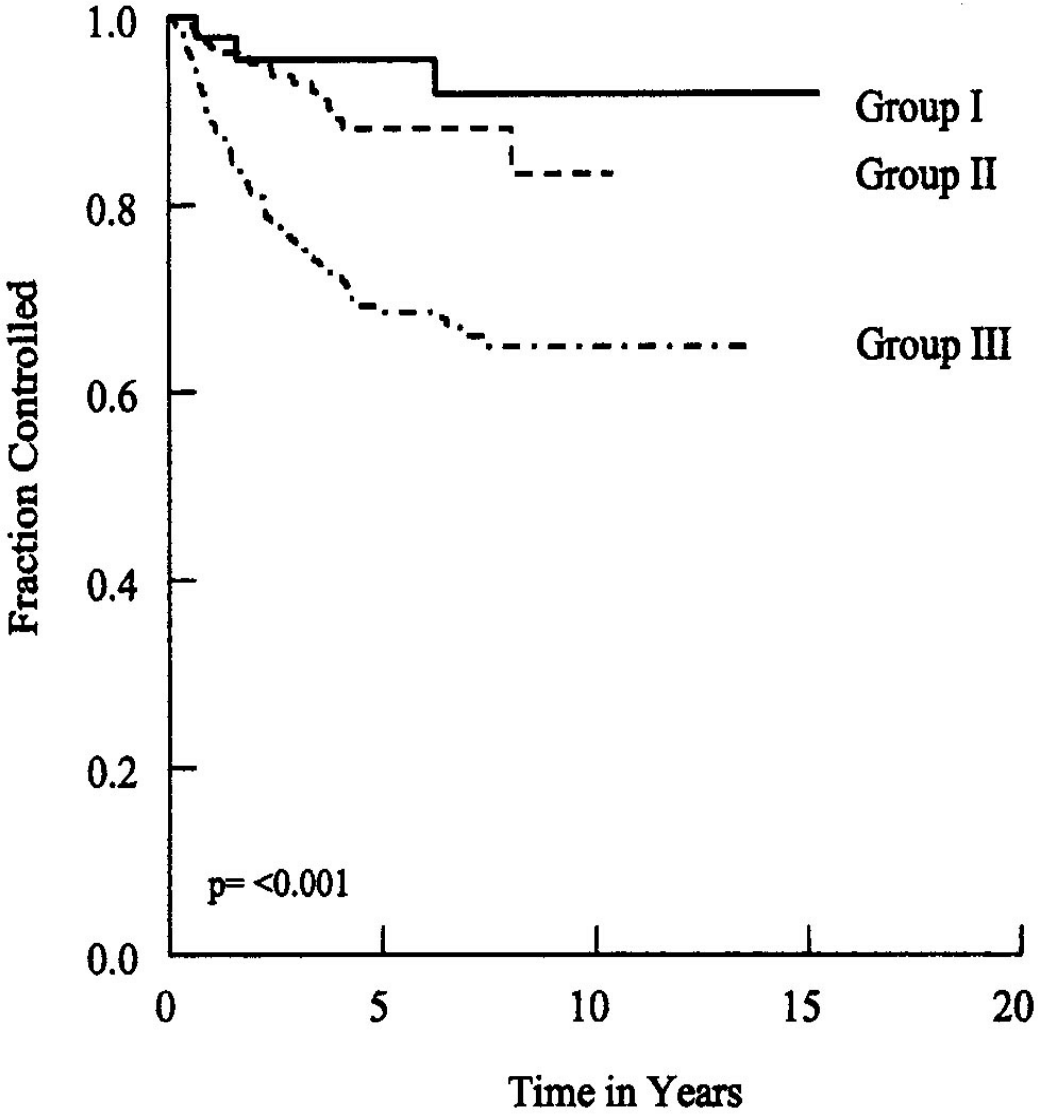
CTV= Prostate + pelvic LN

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



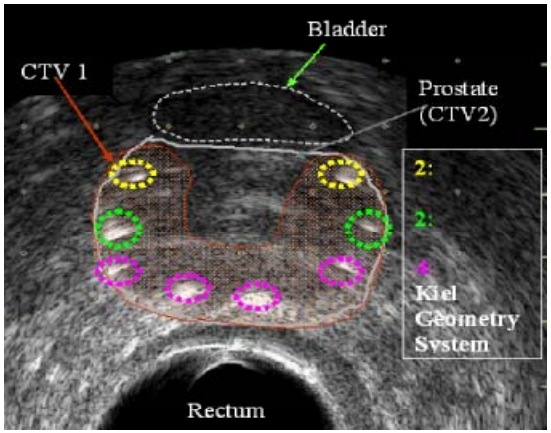
School

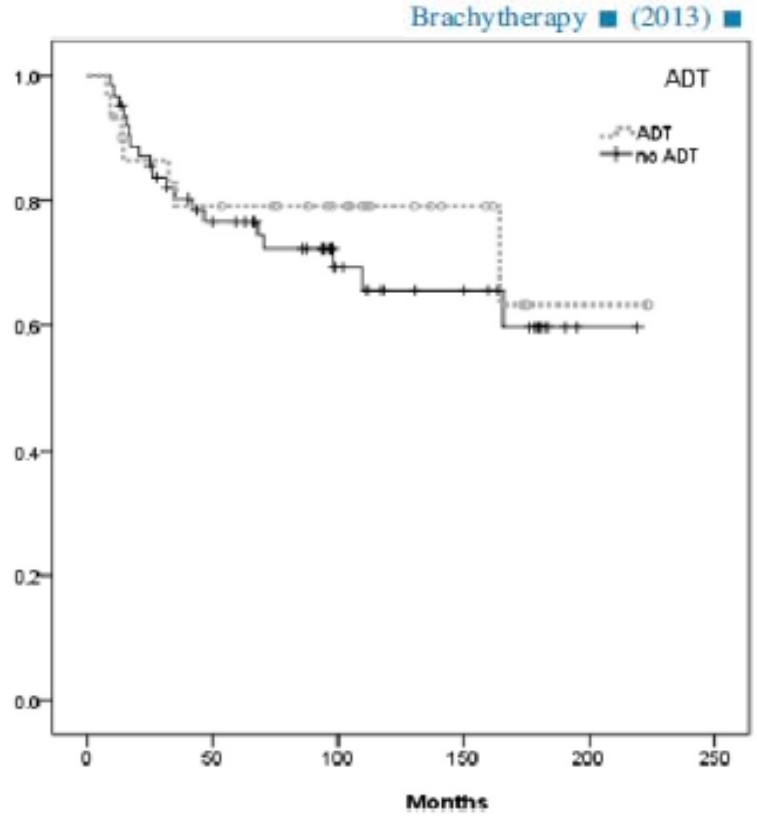
The 15-year outcomes of high-dose-rate brachytherapy for radical dose escalation in patients with prostate cancer—A benchmark for high-tech external beam radiotherapy alone?

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

ESTRO School

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 High-dose group	EBRT 46 HDR-BT 23	4	87
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

ESTRO School

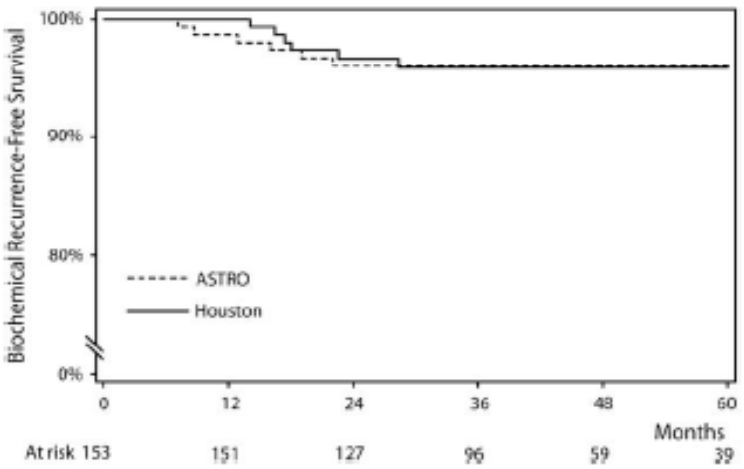
AN EIGHT-YEAR EXPERIENCE OF HDR BRACHYTHERAPY BOOST FOR LOCALIZED PROSTATE CANCER: BIOPSY AND PSA OUTCOME

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

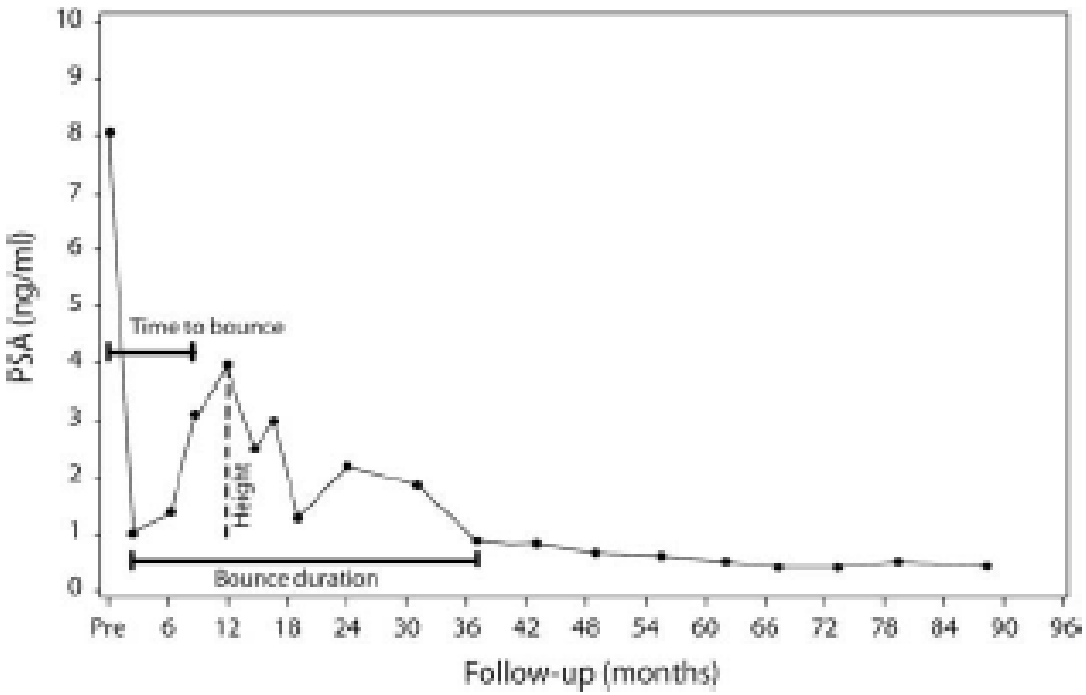
IJROB 2009

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



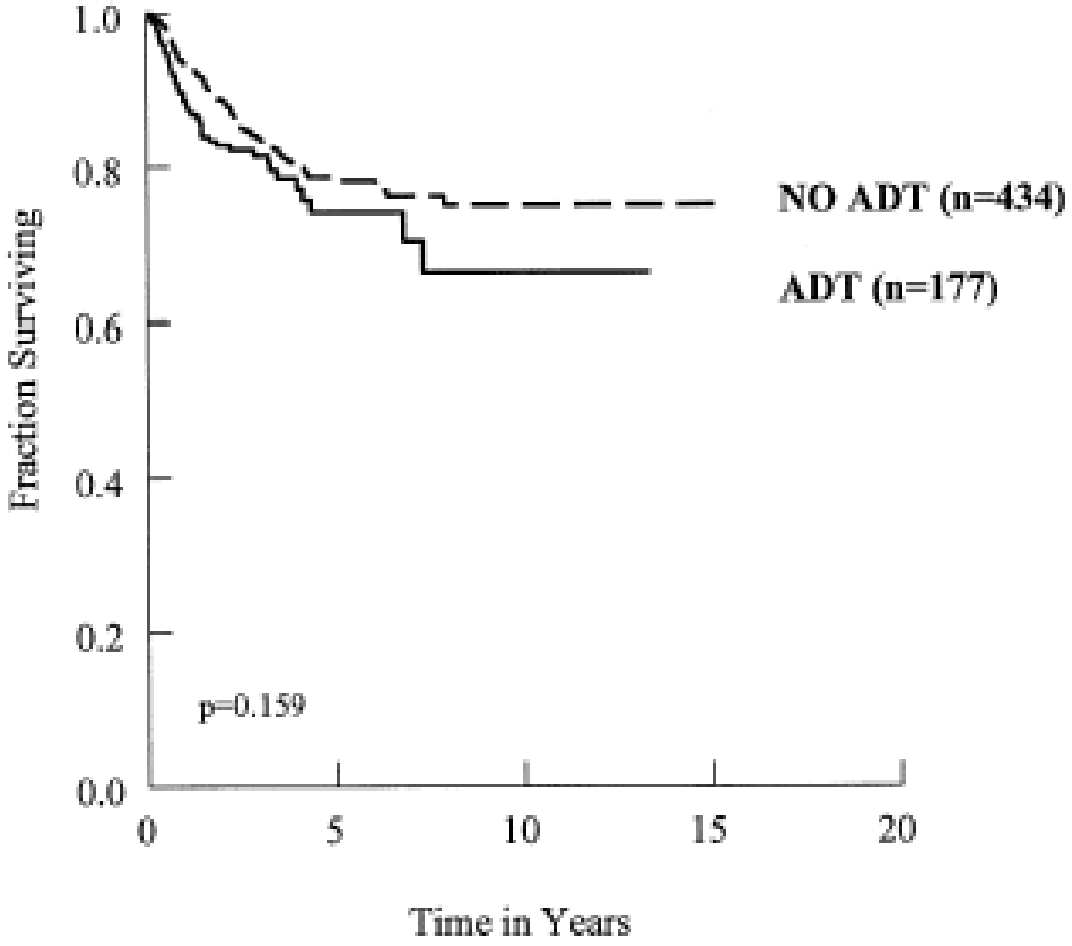
n=153

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)



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.*



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

ESTRO School

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

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.*

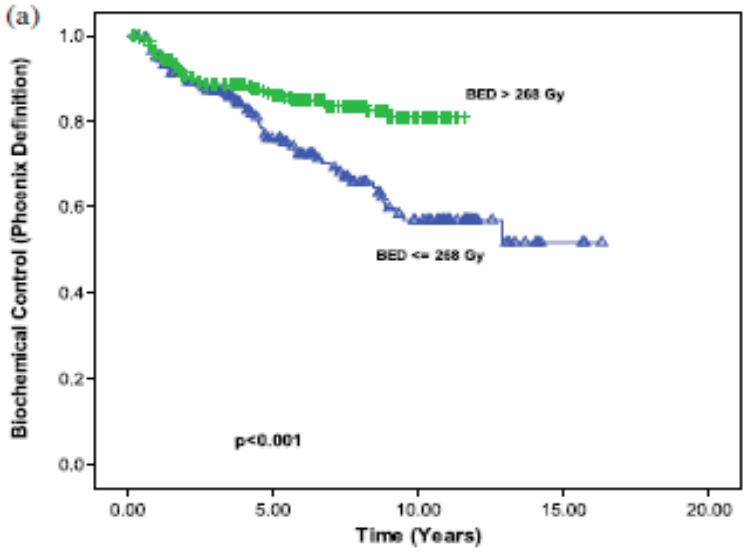
IJROB 2010

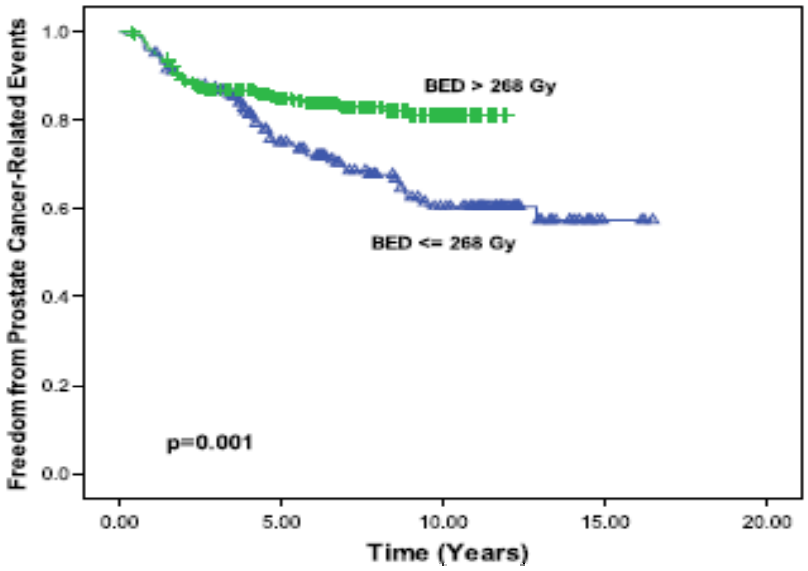
472 patients: 1992-2007: inter/high risk

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)

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

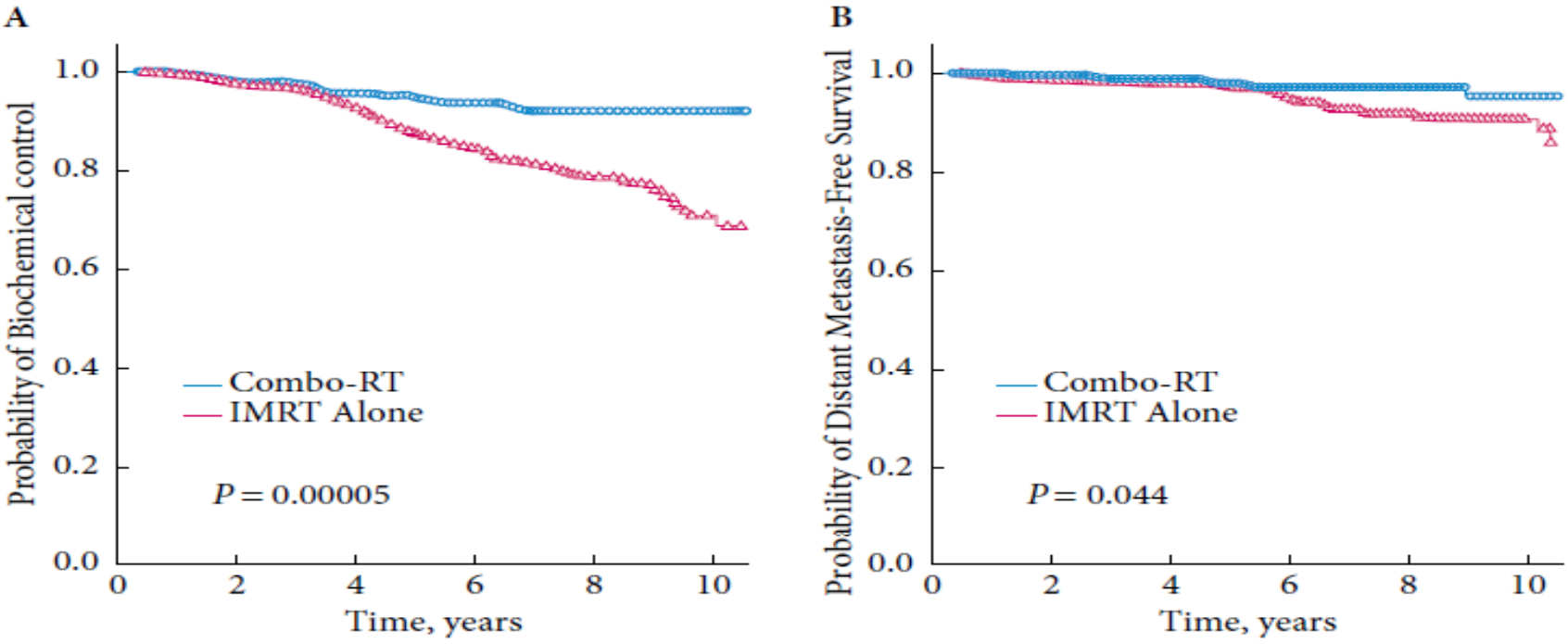
Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer

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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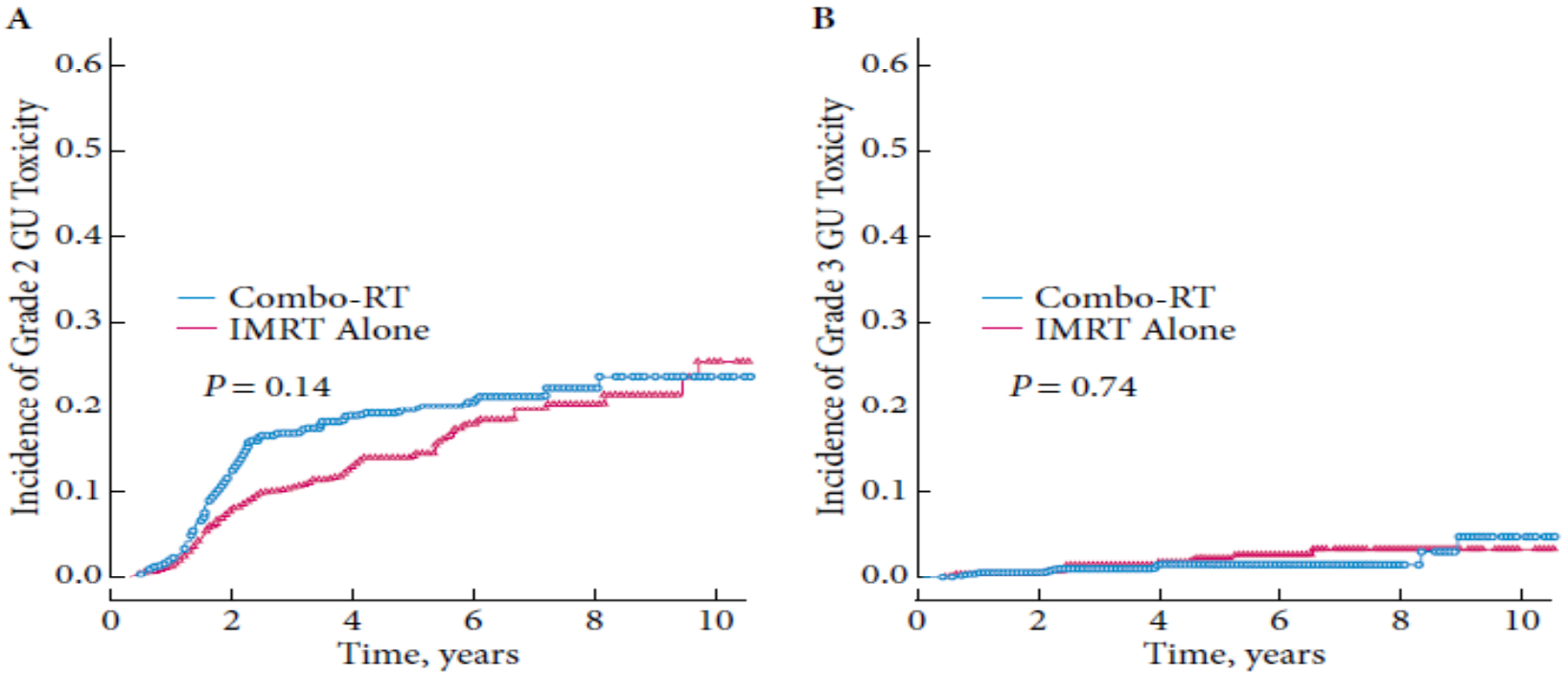


ESTRO School

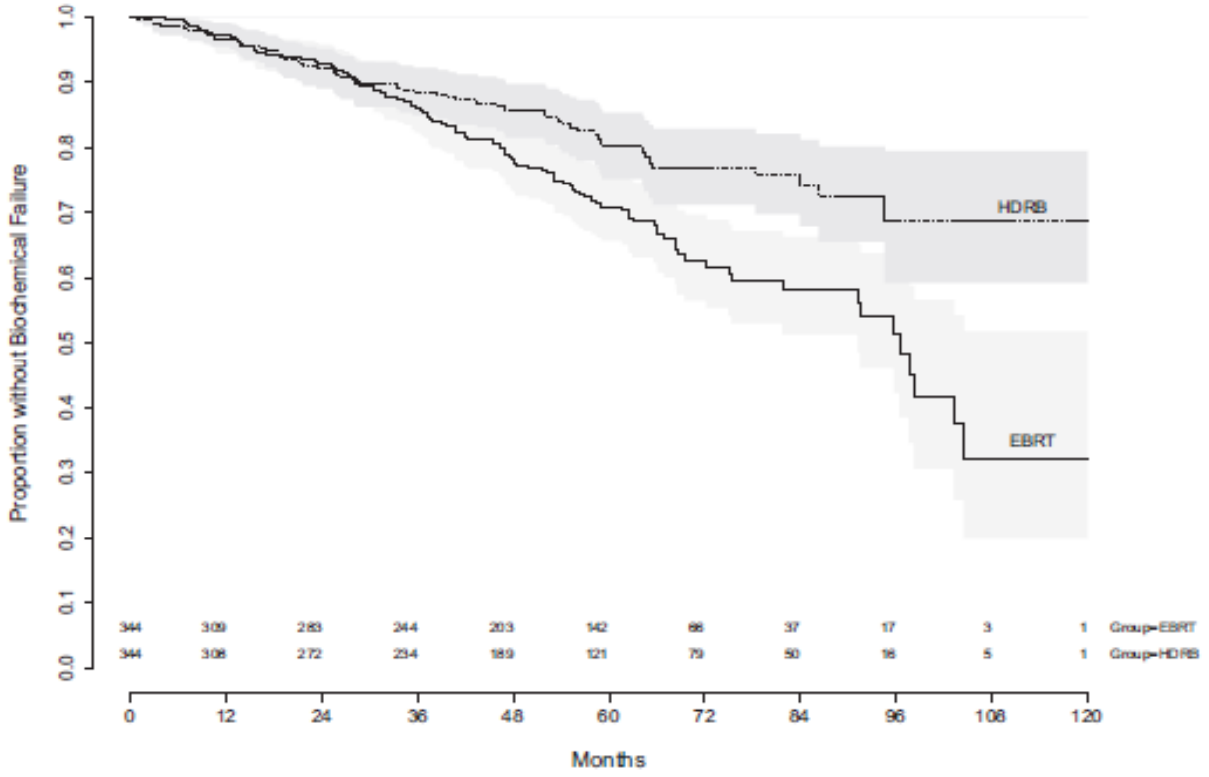
Direct 2-Arm Comparison Shows Benefit of High-Dose-Rate Brachytherapy Boost vs External Beam Radiation Therapy Alone for Prostate Cancer

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.

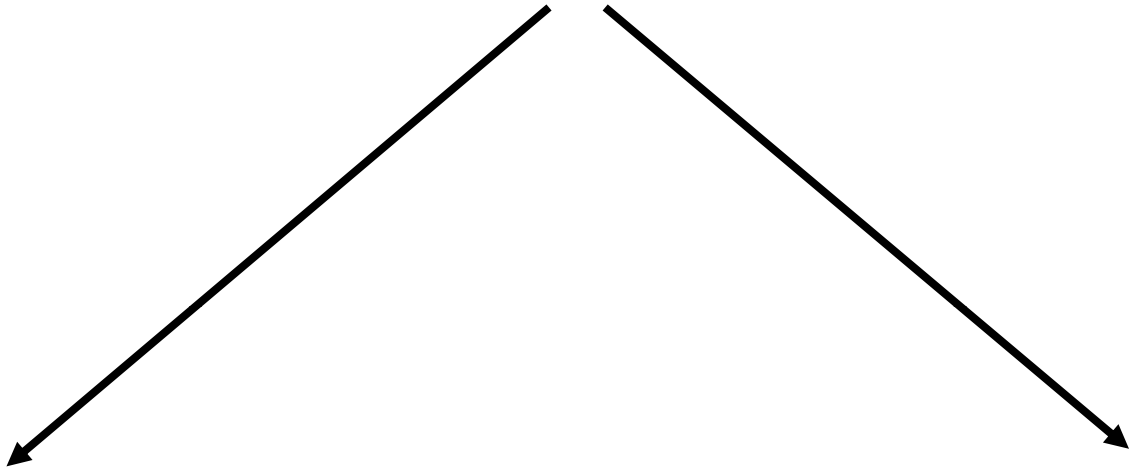
ESTRO School

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)



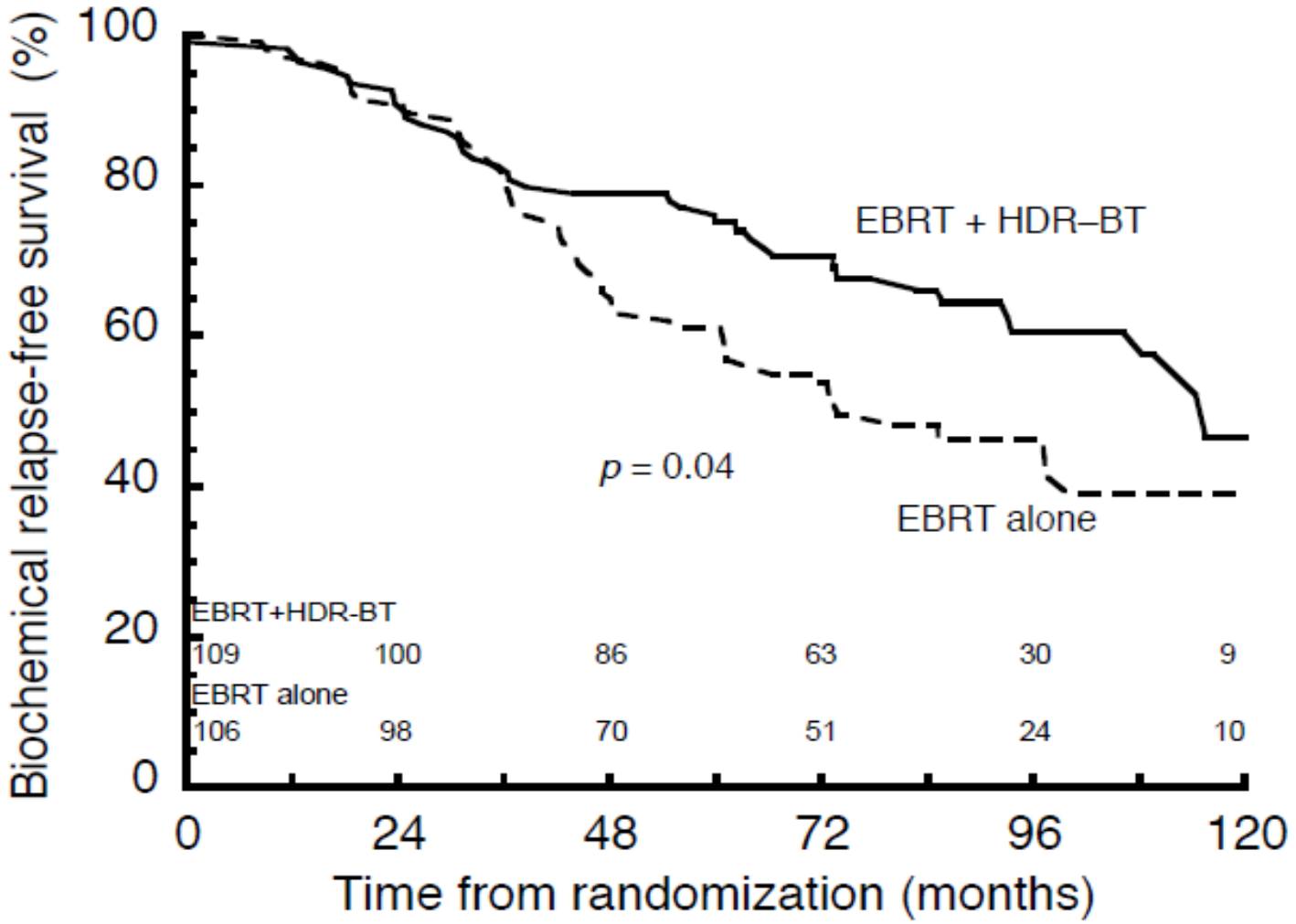
55Gy/20f
Ext beam

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

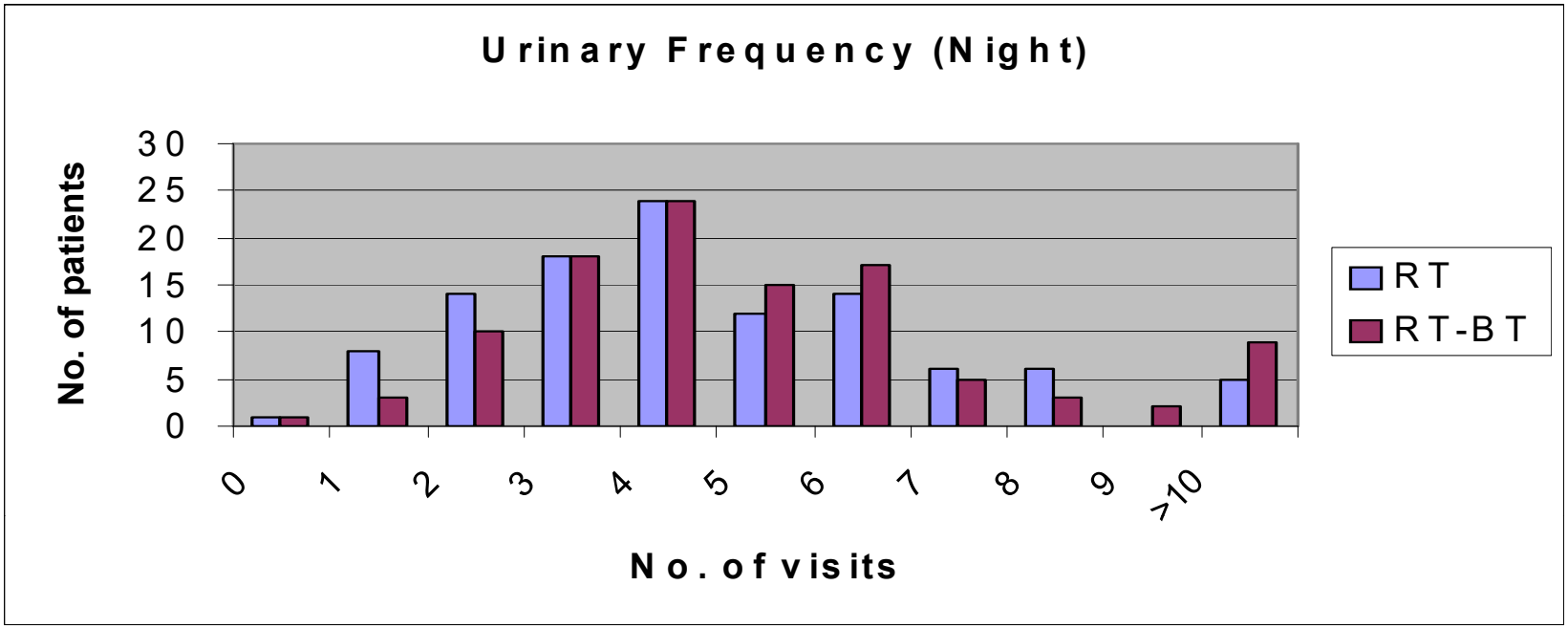
Closed 08/05: 220 patients randomised

ESTRO School

MV RCT HDR Boost



Acute toxicity:



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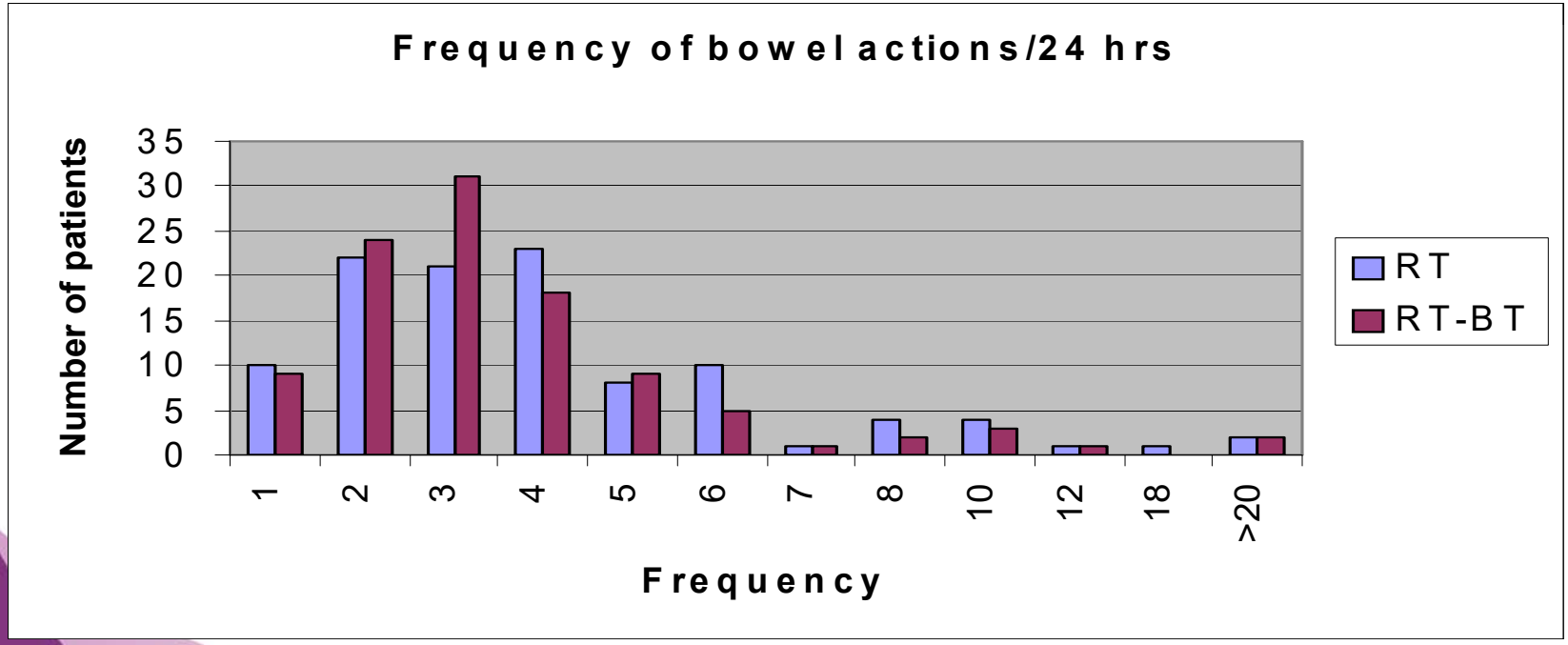

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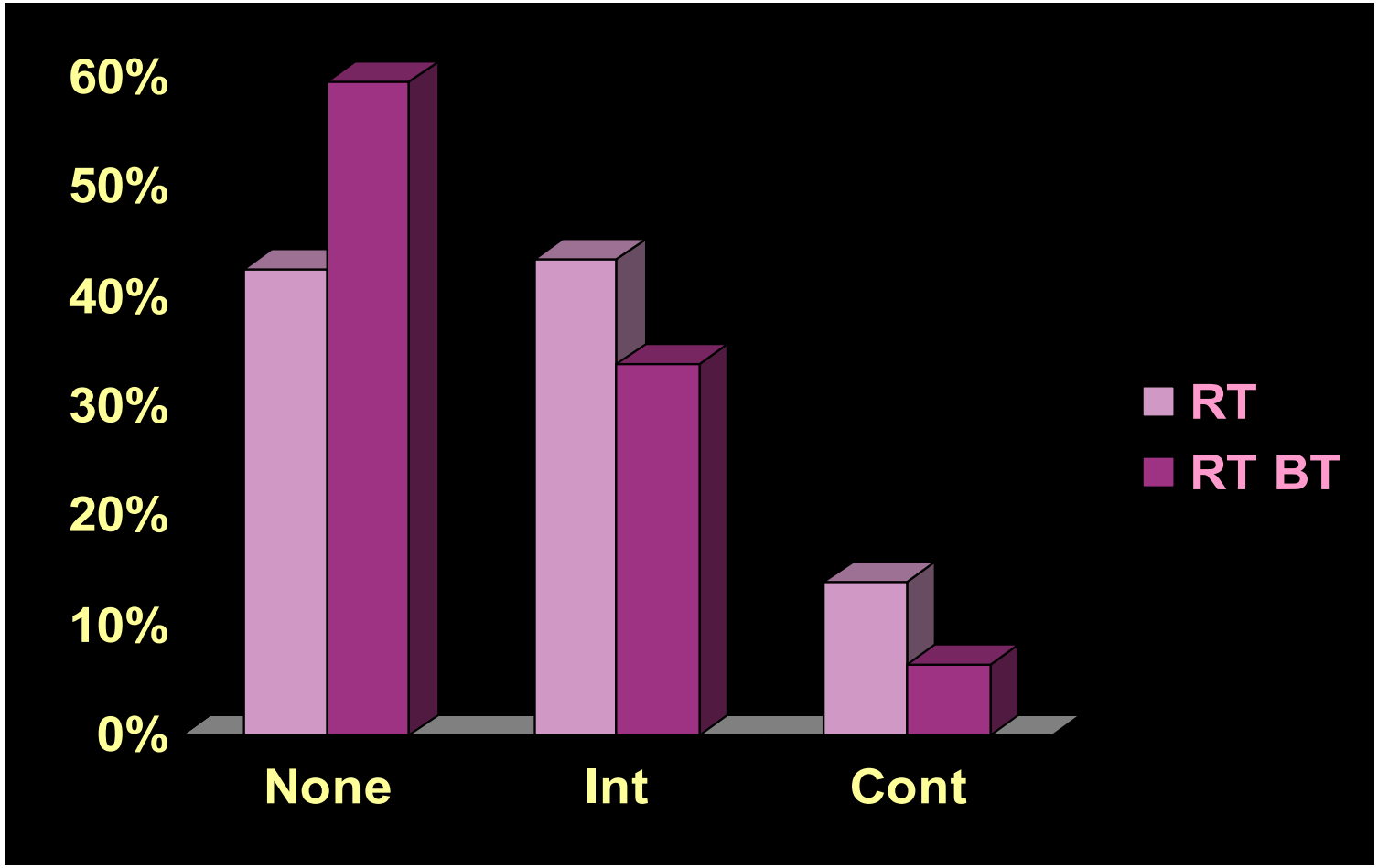
Acute toxicity: rectal discharge



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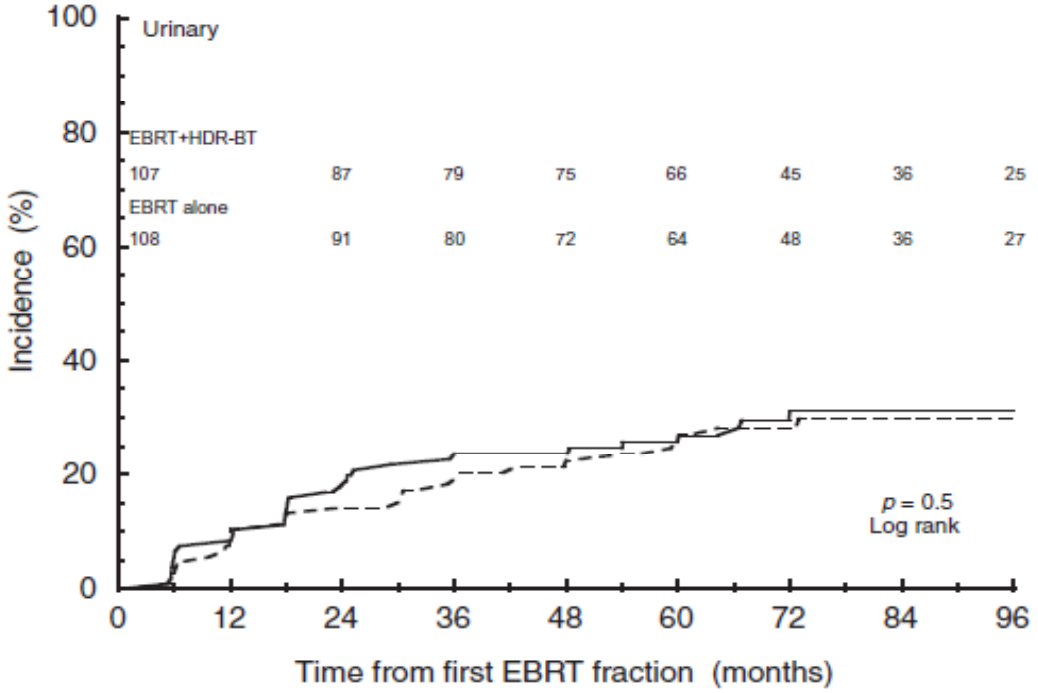
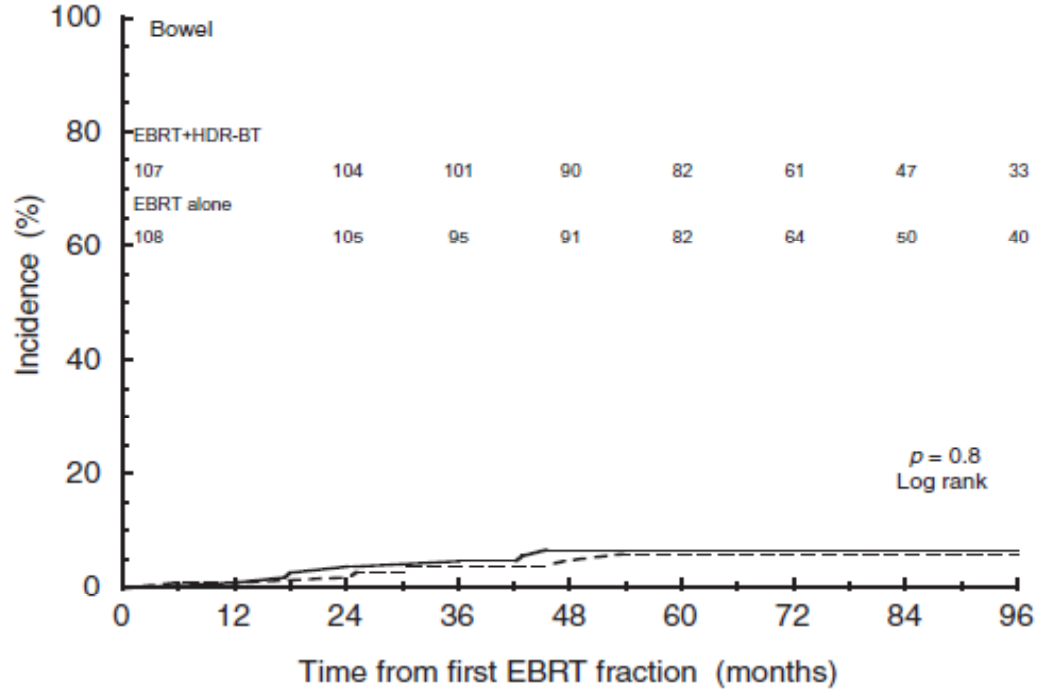
MV RCT
Late toxicity





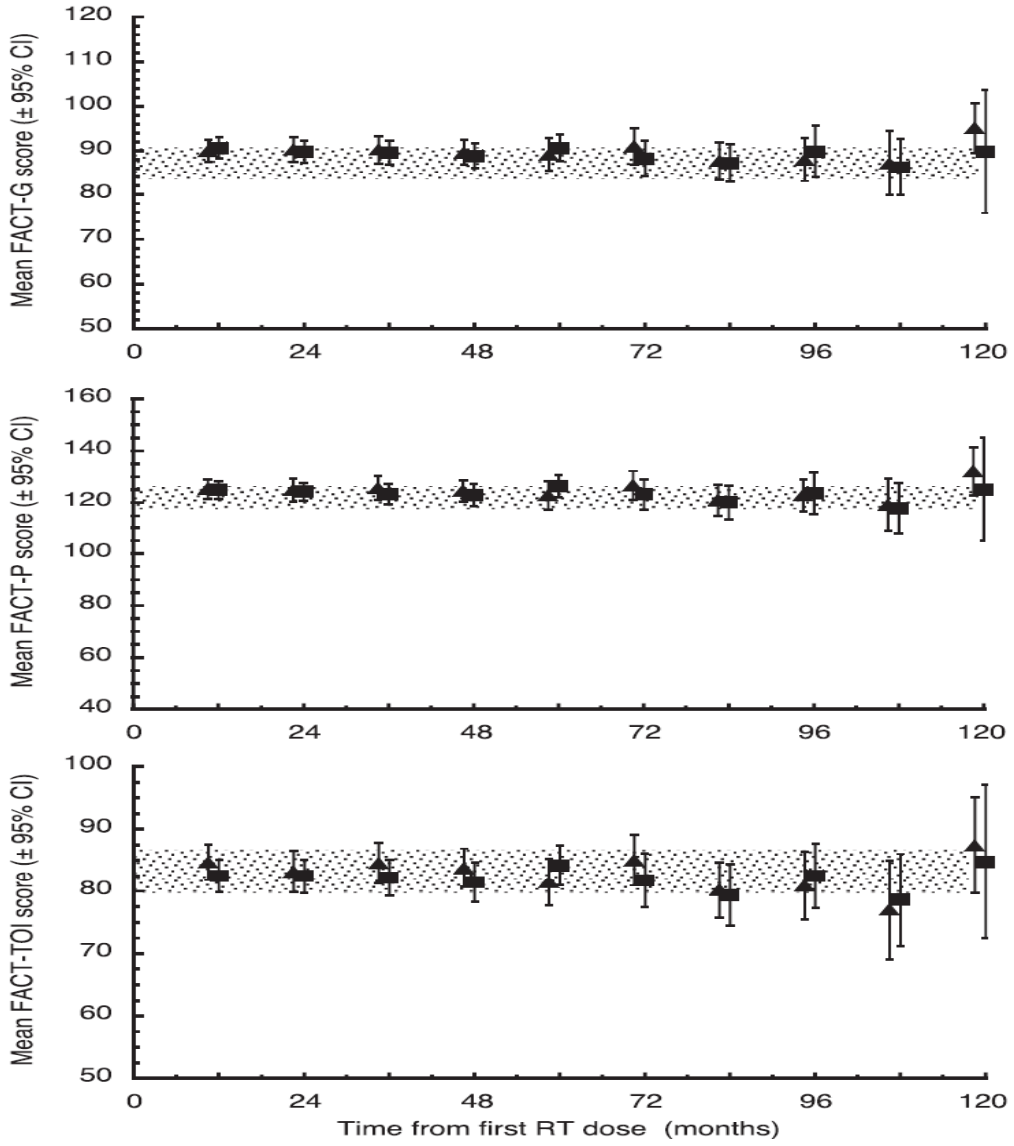
TRO School

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

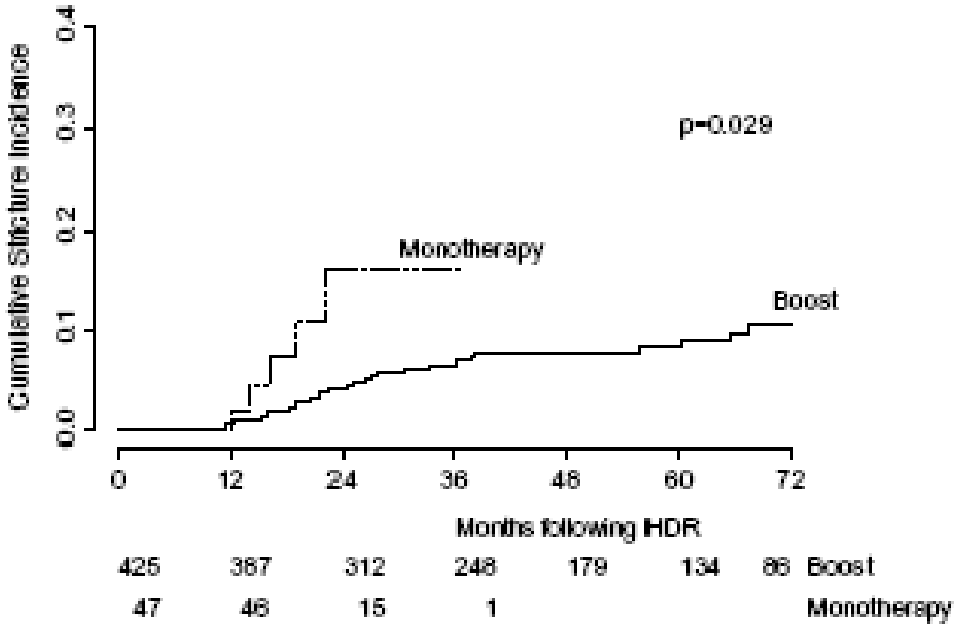
Prostate cancer brachytherapy

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

ESTRO School

Prostate cancer brachytherapy

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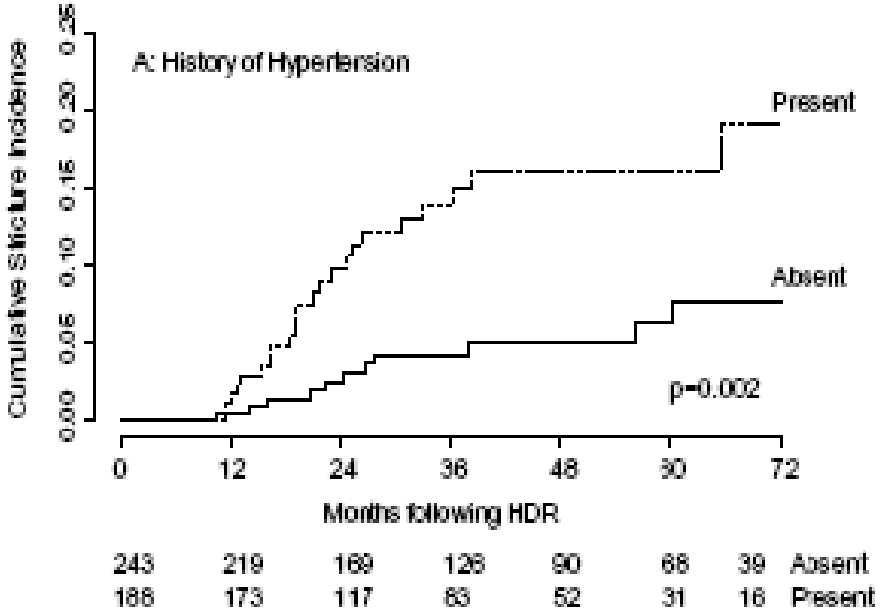
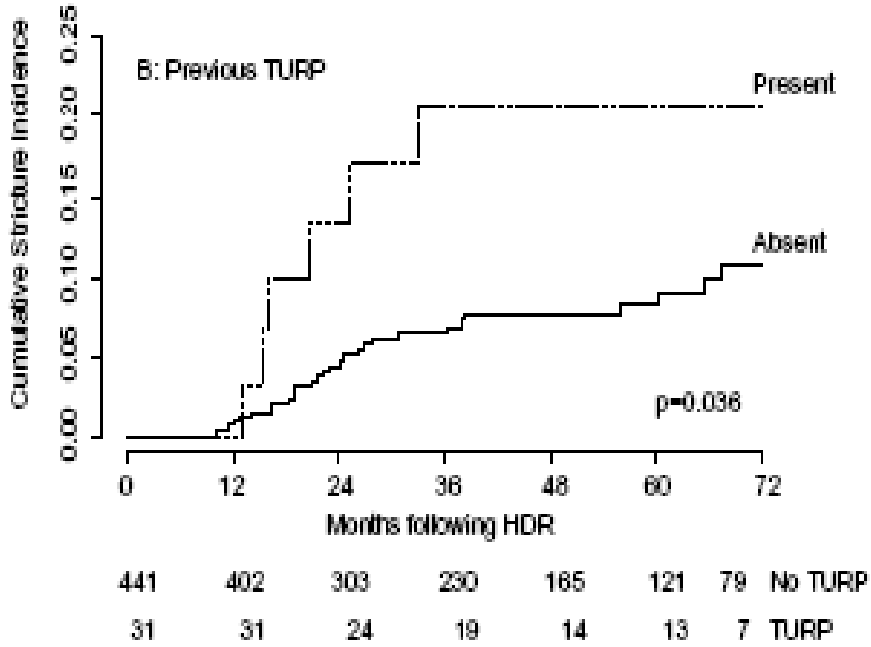




PHASE II TRIAL OF COMBINED HIGH-DOSE-RATE BRACHYTHERAPY AND EXTERNAL BEAM RADIOTHERAPY FOR ADENOCARCINOMA OF THE PROSTATE: PRELIMINARY RESULTS OF RTOG 0321

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		

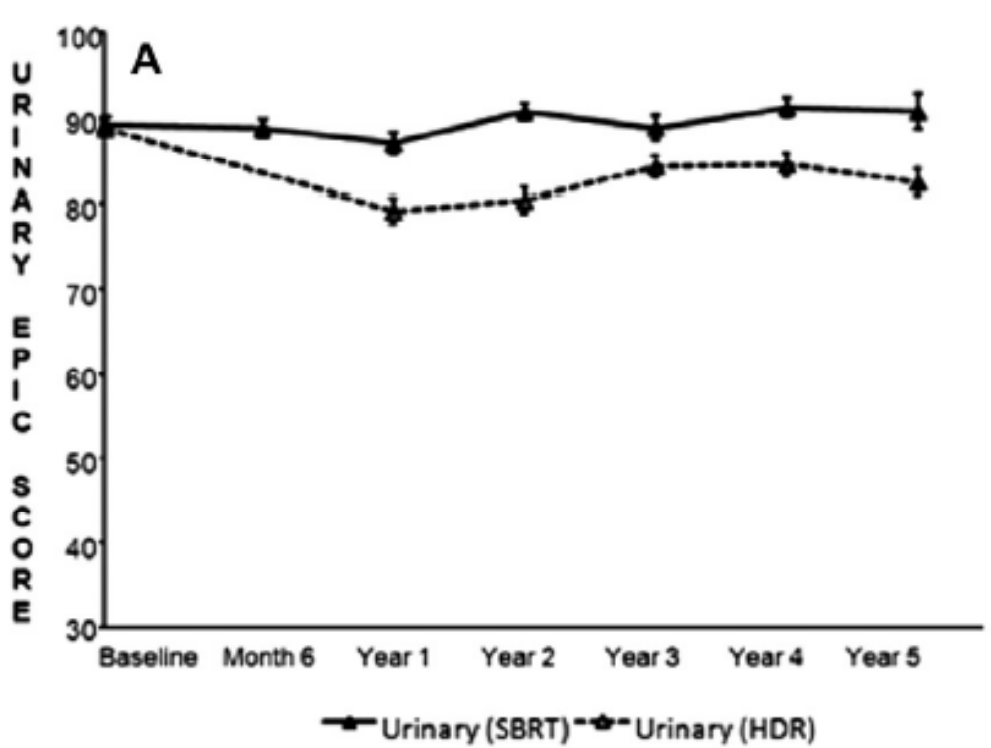
A comparative study of quality of life in patients with localized prostate cancer treated at a single institution: Stereotactic ablative radiotherapy or external beam + high dose rate brachytherapy boost

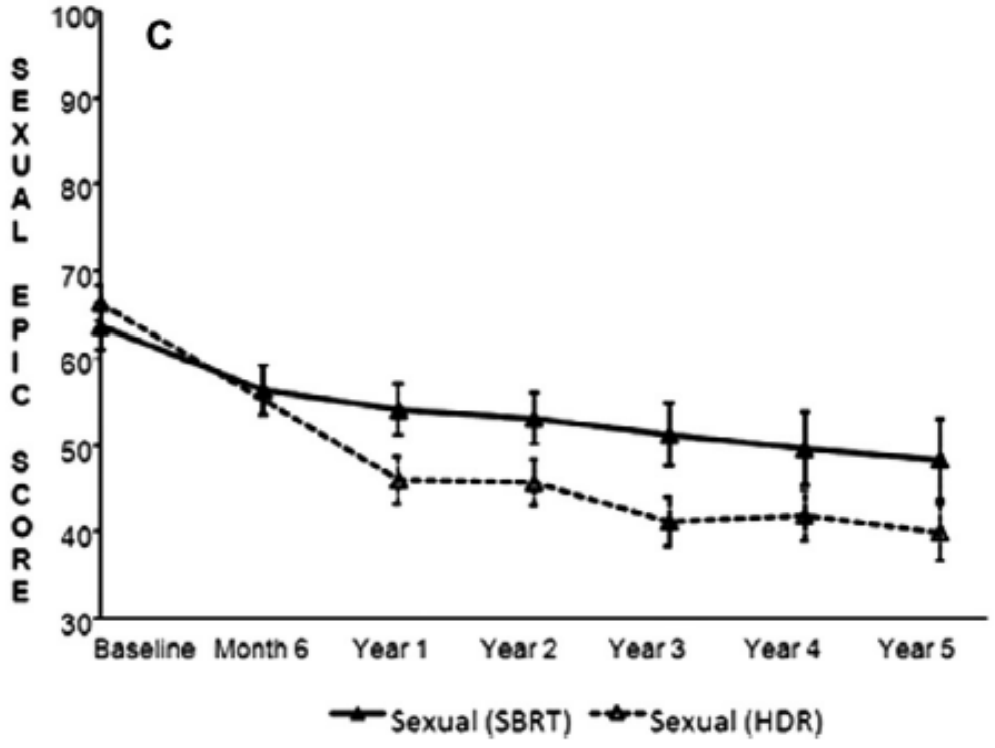
Joelle Helou [a,b], Gerard Morton [a,b], Liying Zhang [a], Andrea Deabreu [a], Laura D'Alimonte [a,b], Evelyn Elias [a], Hima Bindu Musunuru [a,b], Alexandre Mamedov [a], Ananth Ravi [a,b], Hans Chung [a,b], Patrick Cheung [a,b], Andrew Loblaw [a,b,c,*]

[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

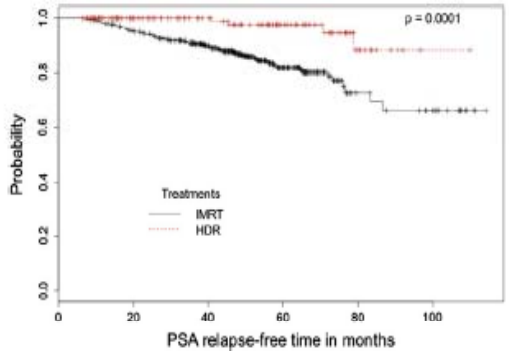
	Treatment groups		
	HDR boost *n* (%)	SABR *n* (%)	*p*-Value*
	N = 117	*N* = 84	
Urinary	68 (58)	15 (18)	**<0.0001**
Urinary function	63 (54)	16 (20)	**<0.0001**
Urinary bother	55 (47)	11 (13)	**<0.0001**
	N = 117	*N* = 84	
Bowel	51 (44)	27 (32)	0.2466
Bowel function	43 (37)	26 (31)	**0.0216**
Bowel 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**

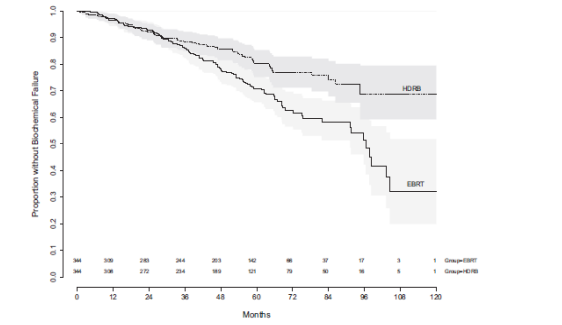
Evidence for HDR boost with external beam

Prospective series >1000 patients

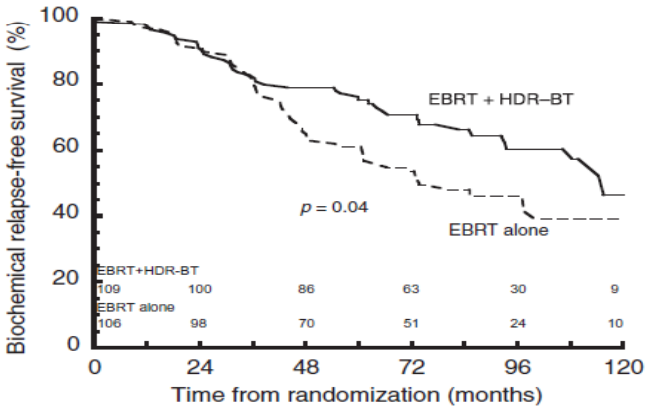
Case control studies

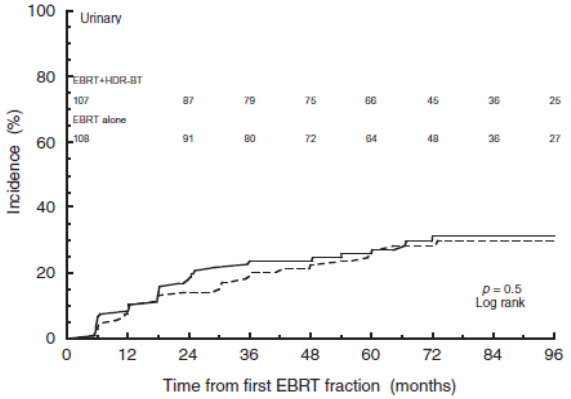
RCT





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





ESTRO School

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

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,*]

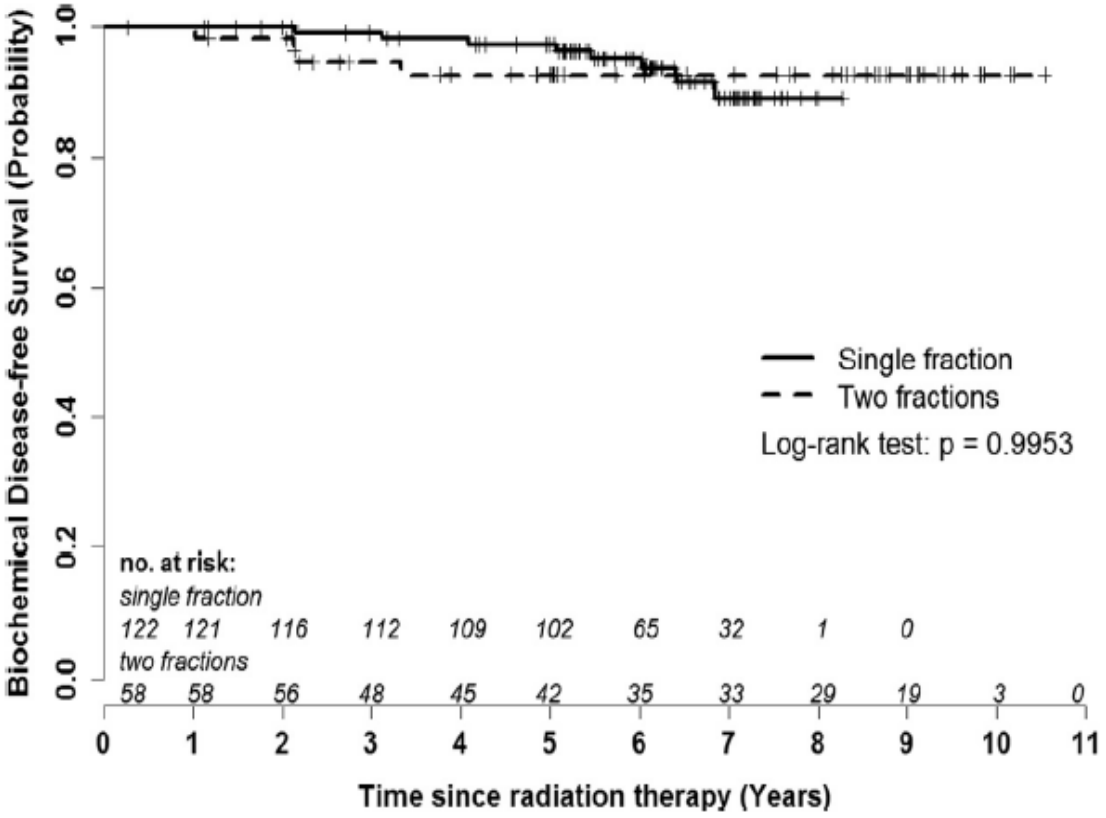
[a] *Sunnybrook Odette Cancer Centre; and* [b] *University of Toronto, Canada*

Radiotherapy and Oncology xxx (2015)

ESTRO School

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



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			
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**

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MONOTHERAPEUTIC HIGH-DOSE-RATE BRACHYTHERAPY FOR PROSTATE CANCER: FIVE-YEAR RESULTS OF AN EXTREME HYPOFRACTIONATION REGIMEN WITH 54 GY IN NINE FRACTIONS

YASUO YOSHIOKA, M.D., PH.D.,* KOJI KONISHI, M.D.,* IORI SUMIDA, PH.D.,* YUTAKA TAKAHASHI, PH.D.,* FUMIAKI ISOHASHI, M.D.,* TOSHIYUKI OGATA, PH.D.,* MASAHIKO KOIZUMI, M.D., PH.D.,* HIDEYA YAMAZAKI, M.D., PH.D.,† NORIO NONOMURA, M.D., PH.D.,‡ AKIHIKO OKUYAMA, M.D., PH.D.,‡ AND TAKEHIRO INOUE, M.D., PH.D.*

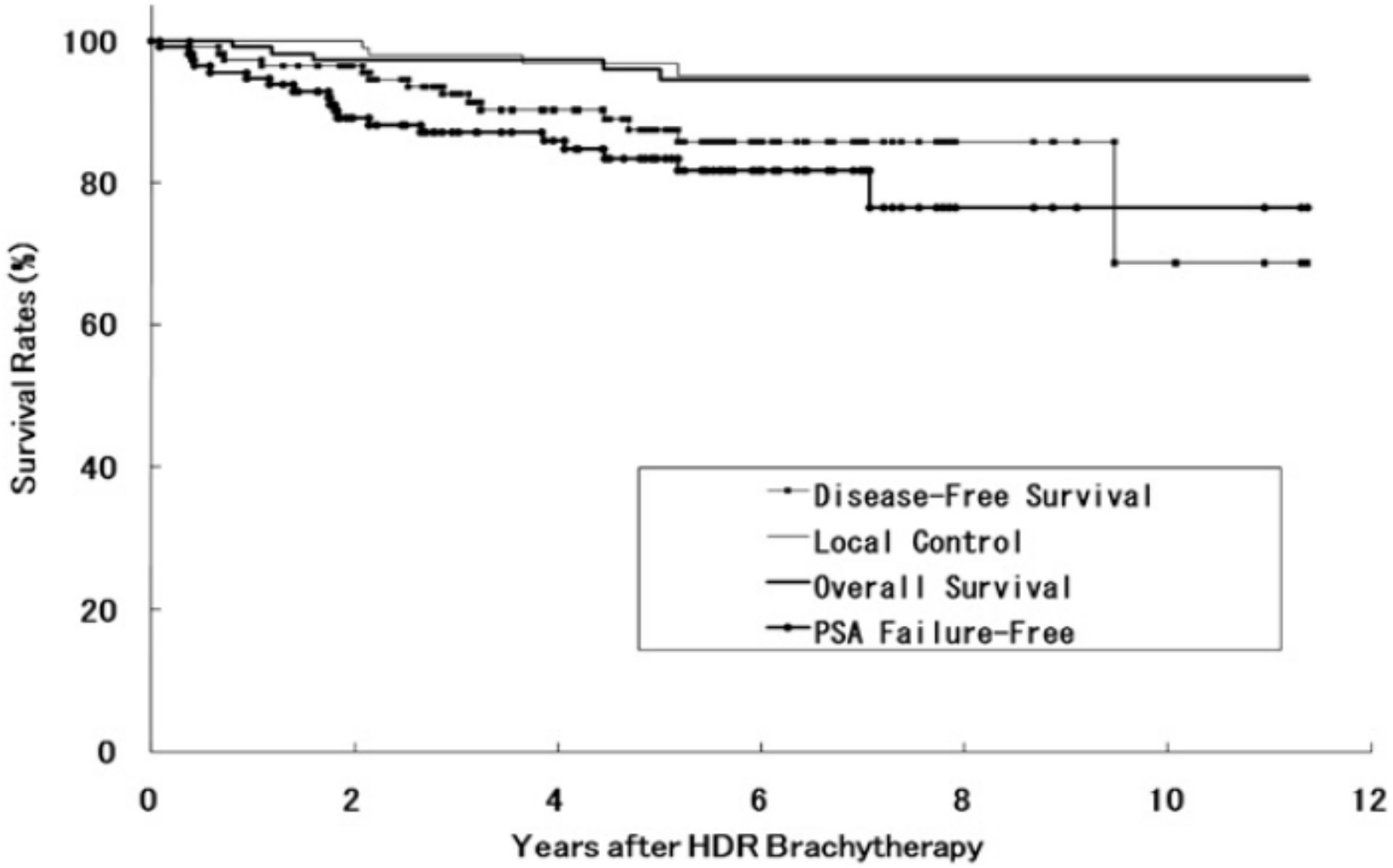
*Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan; †Department of Radiology, Kyoto Prefectural University of Medicine, Kyoto, Japan; ‡Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan

IJROB 2011

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

  - Neoadjuvant hormones in 94

HDR brachytherapy results: monotherapy [Yoshioka et al 2011]



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High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer

Yasuo Yoshioka[a,*], Koji Konishi[a], Ryoong-Jin Oh[a], Iori Sumida[a], Hideya Yamazaki[a], Satoaki Nakamura[a], Kazuo Nishimura[b], Norio Nonomura[b], Akihiko Okuyama[b], Takehiro Inoue[a]

[a]*Department of Radiation Oncology, and* [b]*Department of Urology, Osaka University Graduate School of Medicine, Japan*

Table 2
Acute toxicities ($n = 111$)

Grade	Adverse event	n
Grade 4		0
Grade 3	Urinary frequency/urgency	3
	Hemorrhage – bladder or urethra	1
	Urinary retention	1
	Pain – urethra	1
	Total	6
Grade 2	Urinary frequency/urgency	16
	Hemorrhage – bladder or urethra	3
	Urinary retention	3
	Obstruction – urethra	2
	Pain – anus	2
	Pain – urethra	2
	Pain – perineum	1
	Total[a]	23
Grade 1		56

Grade, CTCAE v3.0.
[a] Some patients showed multiple events.

Table 3
Late toxicities ($n = 111$)

Grade	Adverse event	n
Grade 4		0
Grade 3	Perforation – colon	1[a]
Grade 2	Hemorrhage – rectum	8
	Urinary frequency/urgency	3
	Hemorrhage – bladder or urethra	2
	Obstruction – urethra	1
	Total[b]	12
Grade 1		29

Grade, CTCAE v3.0.
[a] This patient developed a sigmoid-colon perforation 7 years after brachytherapy and underwent colostomy.
[b] Some patients showed multiple events.

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

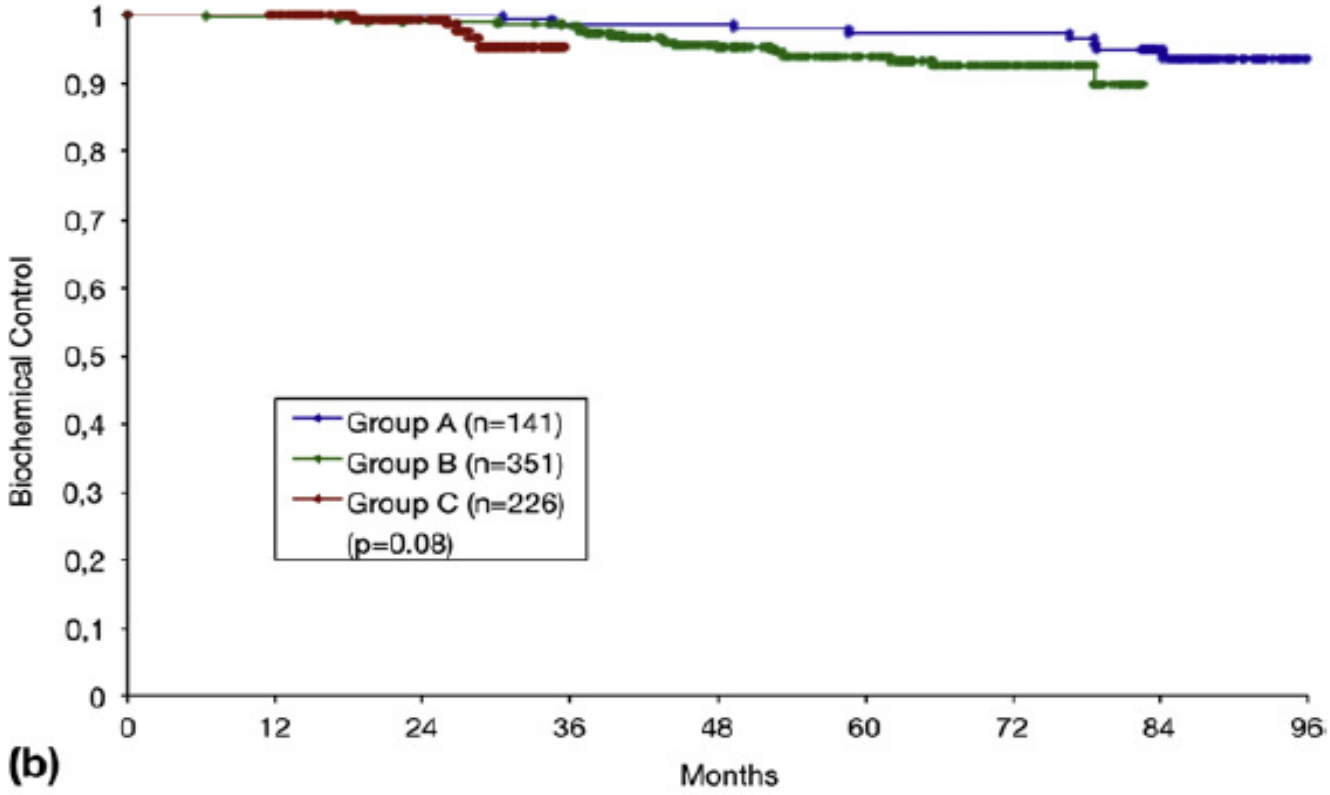
High-Dose-Rate Interstitial Brachytherapy as Monotherapy for Clinically Localized Prostate Cancer: Treatment Evolution and Mature Results

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



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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,† et al

Acute toxicity

	No. of occurrences (%) in group A (n=141)		No. of occurrences (%) in group B (n=351)		No. of occurrences (%) in group C (n=226)	
Grade	Gastrointestinal	Genitourinary	Gastrointestinal	Genitourinary	Gastrointestinal	Genitourinary
Grade 5	0%	0%	0%	0%	0%	0%
Grade 4	0%	0%	0%	0%	0%	0%
Grade 3	1 (0.7%)	13 (9.2%)	0%	17 (4.8%)	0%	9 (3.9%)
Grade 2	0%	22 (15.6%)	6 (1.7%)	58 (16.5%)	8 (3.5%)	40 (17.6%)
Grade 1	26 (18.4%)	66 (46.8%)	55 (15.7%)	169 (48.1%)	28 (12.3%)	83 (36.7%)

Late toxicity

	No. of occurrences (%) in group A (n=141)				No. of occurrences (%) in group B (n=351)				No. of occurrences (%) in group C (n=225)			
	Grade				Grade				Grade			
Toxicity	1	2	3	4	1	2	3	4	1	2	3	4
Genitourinary												
Frequency/ urgency	48 (34.0%)	13 (9.2%)	3 (2.1%)	-	105 (29.9%)	17 (4.8%)	2 (0.6%)	-	61 (27.1%)	17 (7.5%)	0	-
Dysuria	9 (6.3%)	1 (0.7%)	1 (0.7%)	0	17 (4.8%)	4 (1.1%)	2 (0.6%)	0	18 (8.0%)	4 (1.7%)	1 (0.4%)	0
Incontinence	7 (4.9%)	11 (7.8%)	1 (0.7%)	1 (0.7%)	30 (8.6%)	18 (5.1%)	1 (0.3%)	0	26 (11.5%)	17 (7.5%)	1 (0.4%)	1 (0.4%)
Retention	22 (15.6%)	39 (6.3%)	4 (2.8%)	0	59 (16.8%)	19 (5.4%)	7 (2.0%)	0	26 (11.5%)	10 (4.4%)	2 (0.8%)	0
Erectile dysfunction	45 (31.9%)	30 (21.2%)	17 (12.0%)	-	85 (24.2%)	55 (15.7%)	58 (16.5%)	-	53 (23.5%)	41 (18.2%)	43 (19.1%)	-
Gastrointestinal (rectum)												
Pain	2 (1.4%)	1 (0.7%)	1 (0.7%)	0	7 (2.0%)	1 (0.3%)	1 (0.3%)	0	6 (2.6%)	0	0	0
Mucositis/ necrosis	0	1 (0.7%)	5 (3.5%)	0	0	3 (0.8%)	4 (1.2%)	0	0	1 (0.4%)	1 (0.4%)	0
Diarrhea	1 (0.7%)	0	0	0	0	0	0	0	1 (0.4%)	0	0	0

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

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

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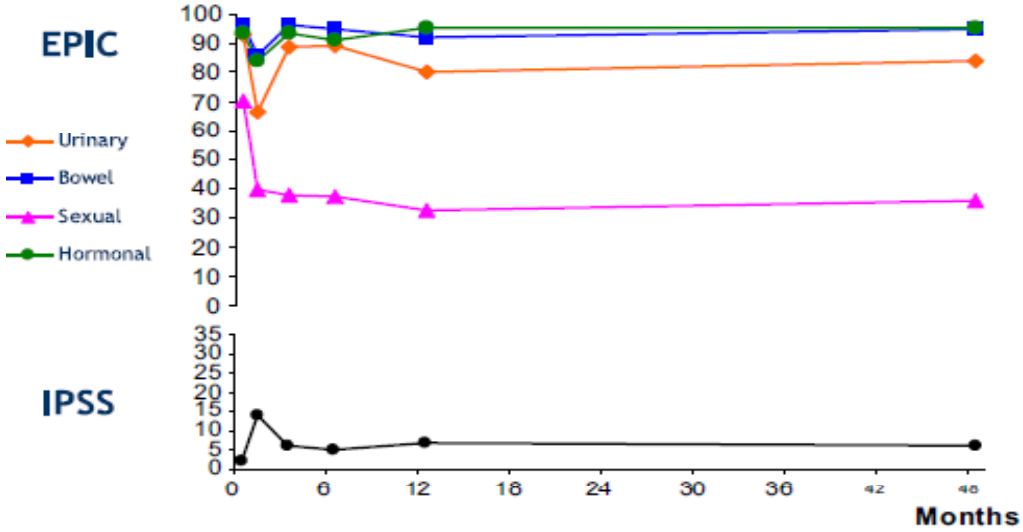
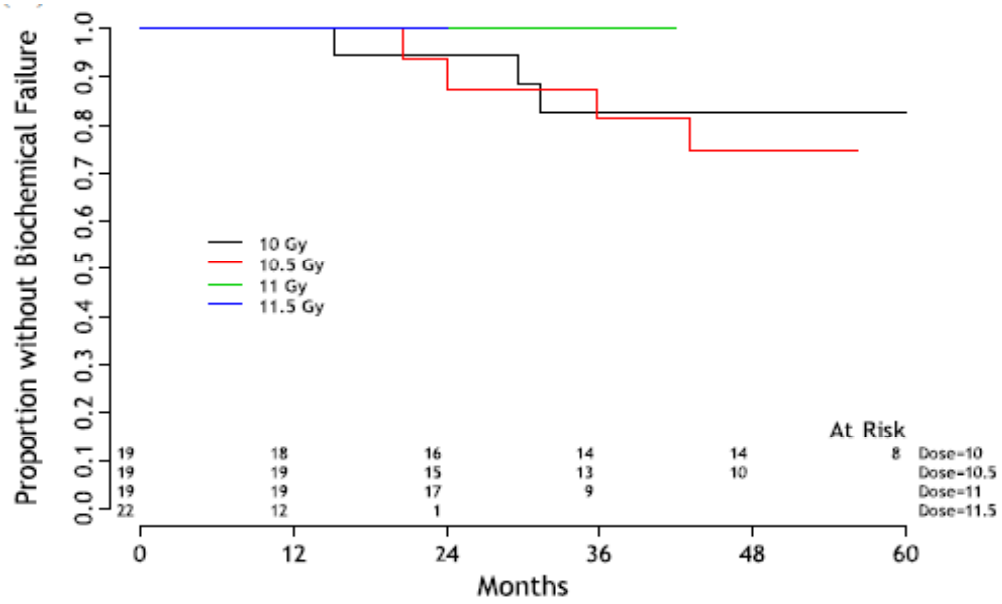
FARSHAD FOROUDI, F.R.A.N.Z.C.R.,*‡ KEEN HUN TAI, F.R.A.N.Z.C.R.,*‡
SARAT CHANDER, F.R.A.N.Z.C.R.,*‡ SYLVIA VAN DYK, D.APP.SC.,* ANDREW SEE, F.R.A.N.Z.C.R.,†
AND GILLIAN M. DUCHESNE, M.D., F.R.C.R., F.R.A.N.Z.C.R.*‡

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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HDR Monotherapy: toxicity

Author (reference)	Year	*N*	Risk groups	GU Grade 2 (%)	GU Grade 3 (%)	GI Grade 2 (%)	GI Grade 3 (%)	ED (%)
Barkati *et al.* (50)	2012	79	Low–interm.	2–6	2–4	0–3	0	43
Demanes *et al.* (42)	2011	157	Low–interm.	10	3	1	0	n/a
Ghadjar *et al.* (48)	2009	36	Low–interm.	25	11	6	0	25
Ghilezan *et al.* (52)	2012	50	Low–interm.	16	1	1	1	n/a
		44						
Hoskins *et al.* (49)	2012	55	Interm.–high	33–40*	3–16,*	4–13*	0–1*	n/a
		109			3–6 strictures			
		33						
Komiya *et al.* (41)	2013	51	Low–high	QoL (IPSS, FACT-P & IIEF) at baseline after 12 wk				
Mark *et al.* (46)	2010	317	Low–high	3.2	0	1.3	1%	n/a
							0.6% (Grade 4)	
Martinez *et al.* (45)	2010	141	Low–interm.	Grade 1–3, 15–43	0	6.5	0	20
Prada *et al.* (53)	2012	40	Low–interm.	0	0	0	0	NR
Rogers *et al.* (47)	2012	284	Interm.	1.5	0.6	0	0	17.4
Yoshioka *et al.* (39)	2011	112	Low–high	7	1	6	2	NR
Zamboglou	2013	141	Low–high	15.6	9.2	0	0.7	11.1
et al. (51)		351		16.5	4.8	1.7	0	
		225		17.6	3.8	3.5	0	

From Demanes and Ghilezan 2014

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

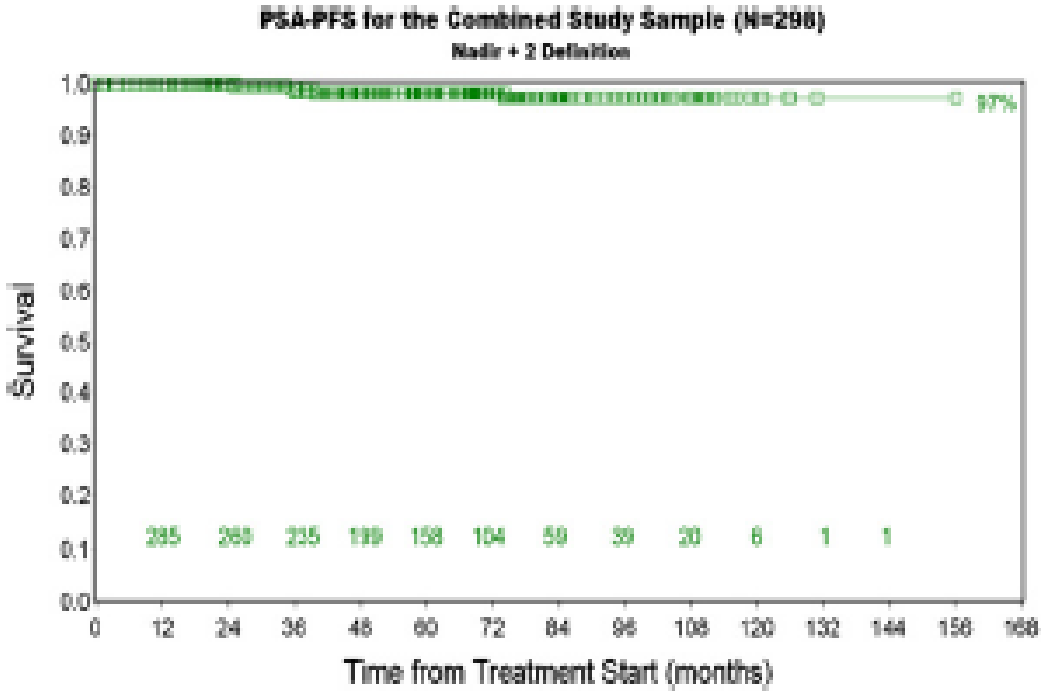
HIGH-DOSE-RATE MONOTHERAPY: SAFE AND EFFECTIVE BRACHYTHERAPY FOR PATIENTS WITH LOCALIZED PROSTATE CANCER

D. Jeffrey Demanes, M.D.,* Alvaro A. Martinez, M.D.,† Michel Ghilezan, M.D.,†
Dennis R. Hill, M .D.,‡ Lionel Schour, M.D.,‡ David Brandt, M .S.,‡ and Gary Gustafson, M.D.†

*California Endocurietherapy at UCLA, Department of Radiation Oncology, David Geffen School of Medicine of the University of California at Los Angeles, Los Angeles, CA; †William Beaumont Hospital, Royal Oak, MI; and ‡California Endocurietherapy, Oakland, CA

298 PATIENTS 1996-2005 38Gy in 4 FRACTIONS (WBH)
42Gy in 6 FRACTIONS (CET)

293 Low risk (Biologically equivalent)



Genitourinary toxicity	Grade 2	Grade 3
Dysuria	4%	0.3%
Retention	5%	3%
Hematuria	4%	1%
Incontinence	1%	0.3%
Frequency/urgency	10%	0.3%

*Crude 5 year rates scored per event not per patient.

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

MICHEL GHILEZAN, M.D., PH.D., ALVARO MARTINEZ, M.D., GARY GUSTASON, M.D., DANIEL KRAUSS, M.D., PETER CHEN, M.D., JAMES FONTANESI, M.D., MICHELLE WALLACE, R.N., HONG YE, M.S., ALYSE CASEY, R.N., EVELYN SEBASTIAN, B.S., KIM LEONARD, M.S., AND AMY LIMBACHER, B.S.

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 μg/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

HDR implant: biological advantage 2Gy EQD

	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

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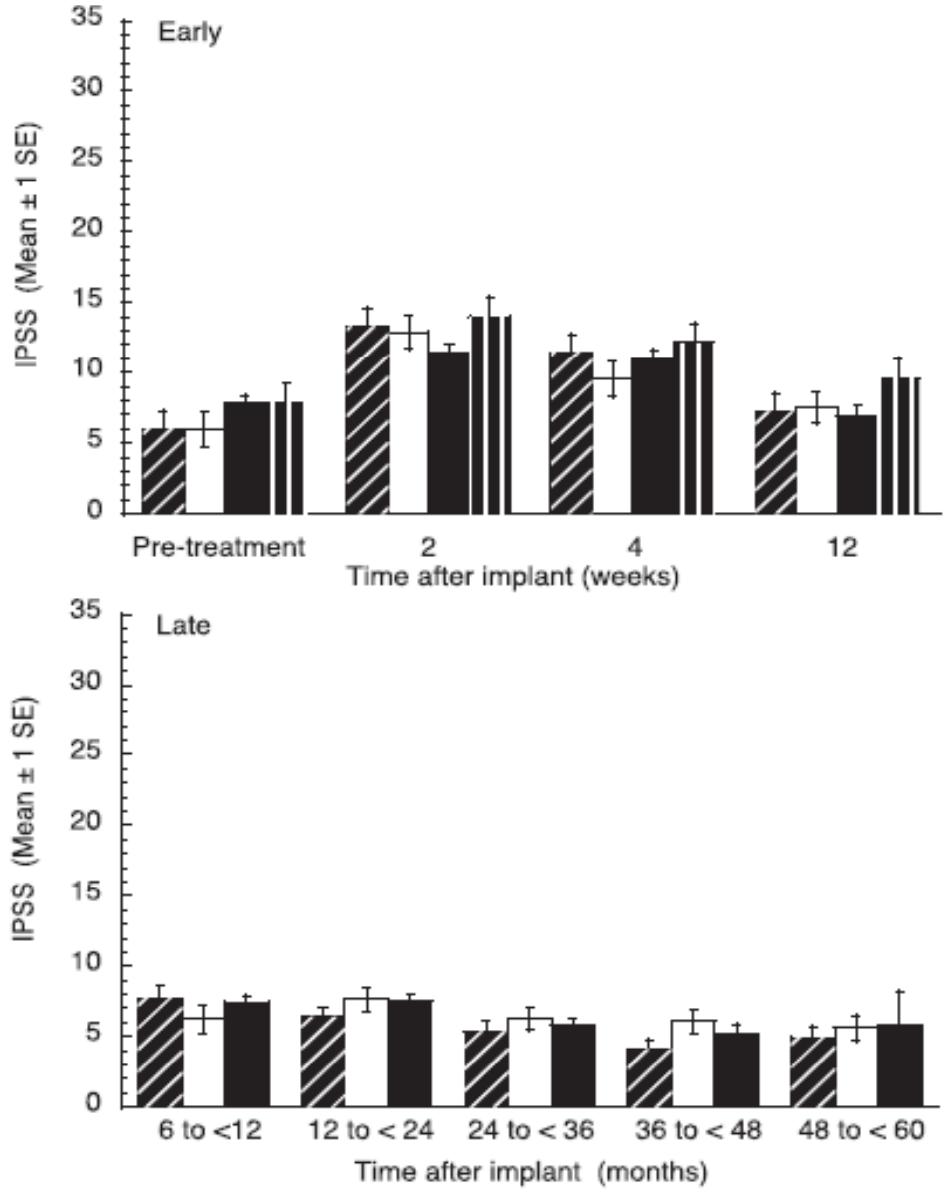
HIGH-DOSE-RATE BRACHYTHERAPY ALONE FOR LOCALIZED PROSTATE CANCER IN PATIENTS AT MODERATE OR HIGH RISK OF BIOCHEMICAL RECURRENCE

doi:10.1016/j.ijrobp.2011.04.031

Urinary symptom scores



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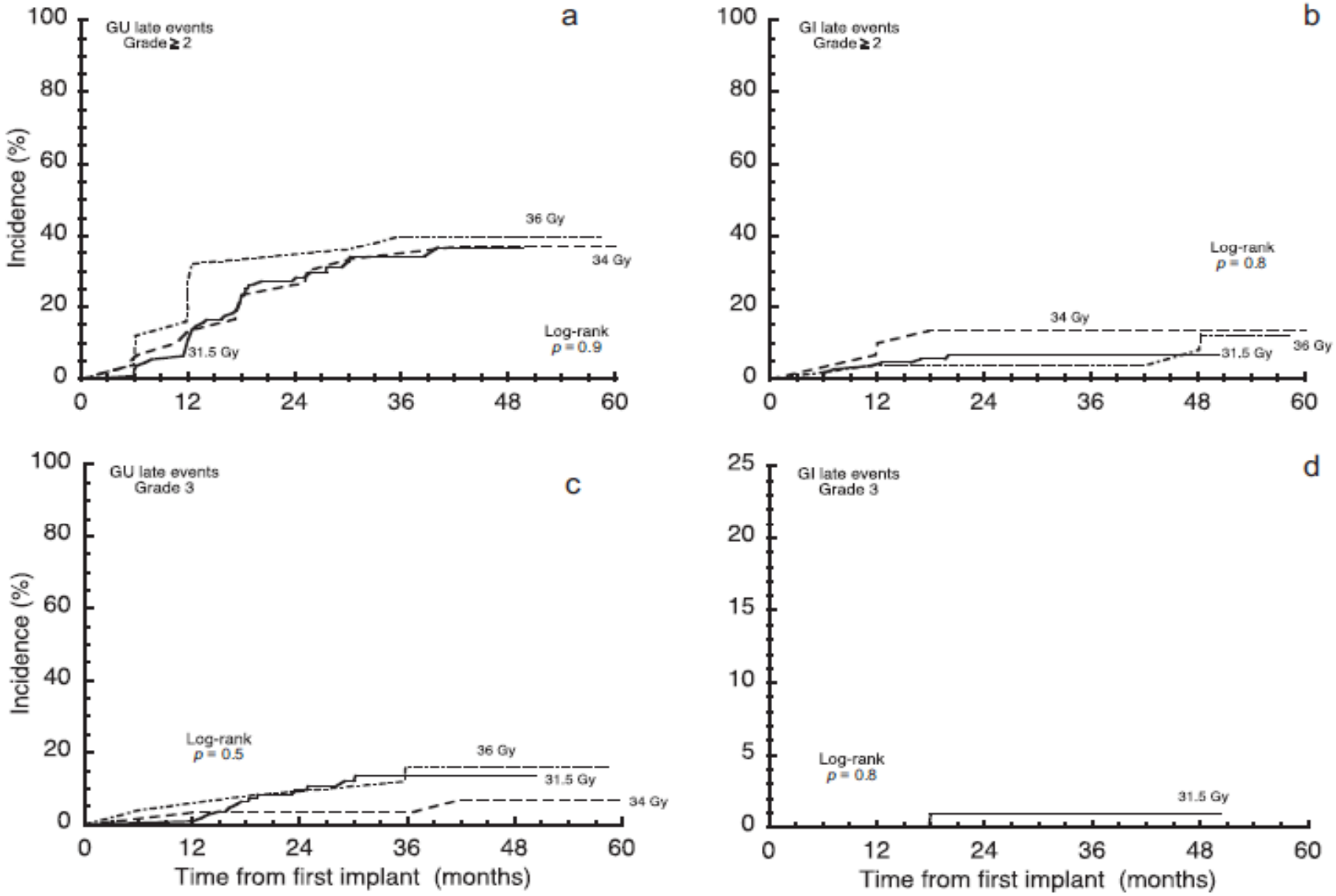
HIGH-DOSE-RATE BRACHYTHERAPY ALONE FOR LOCALIZED PROSTATE CANCER IN PATIENTS AT MODERATE OR HIGH RISK OF BIOCHEMICAL RECURRENCE

doi:10.1016/j.ijrobp.2011.04.031

Late toxicity (>6 months)



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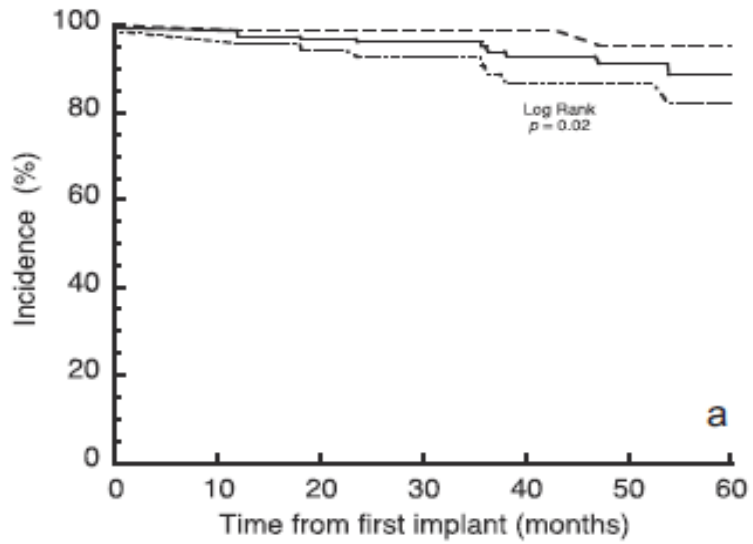
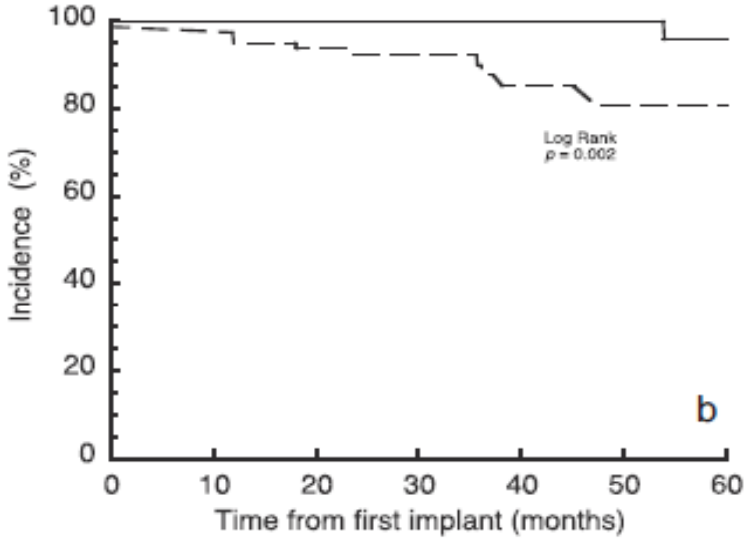
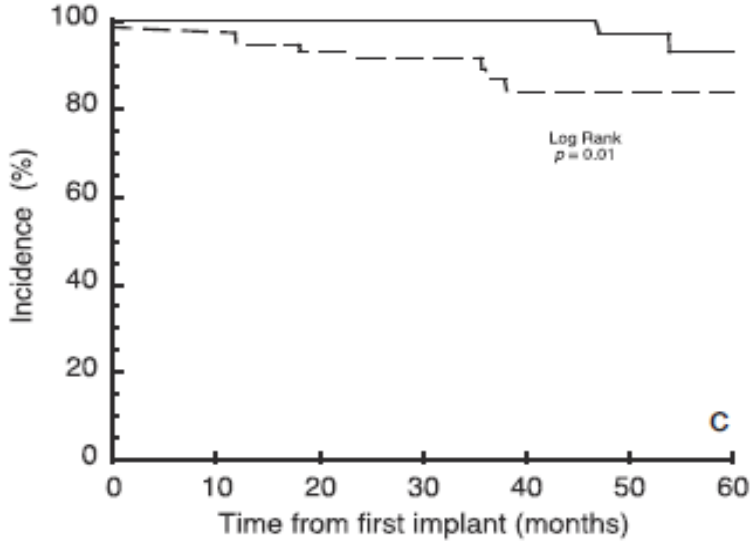
HIGH-DOSE-RATE BRACHYTHERAPY ALONE FOR LOCALIZED PROSTATE CANCER IN PATIENTS AT MODERATE OR HIGH RISK OF BIOCHEMICAL RECURRENCE

doi:10.1016/j.ijrobp.2011.04.031

Freedom from biochemical failure







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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

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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]

[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

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)

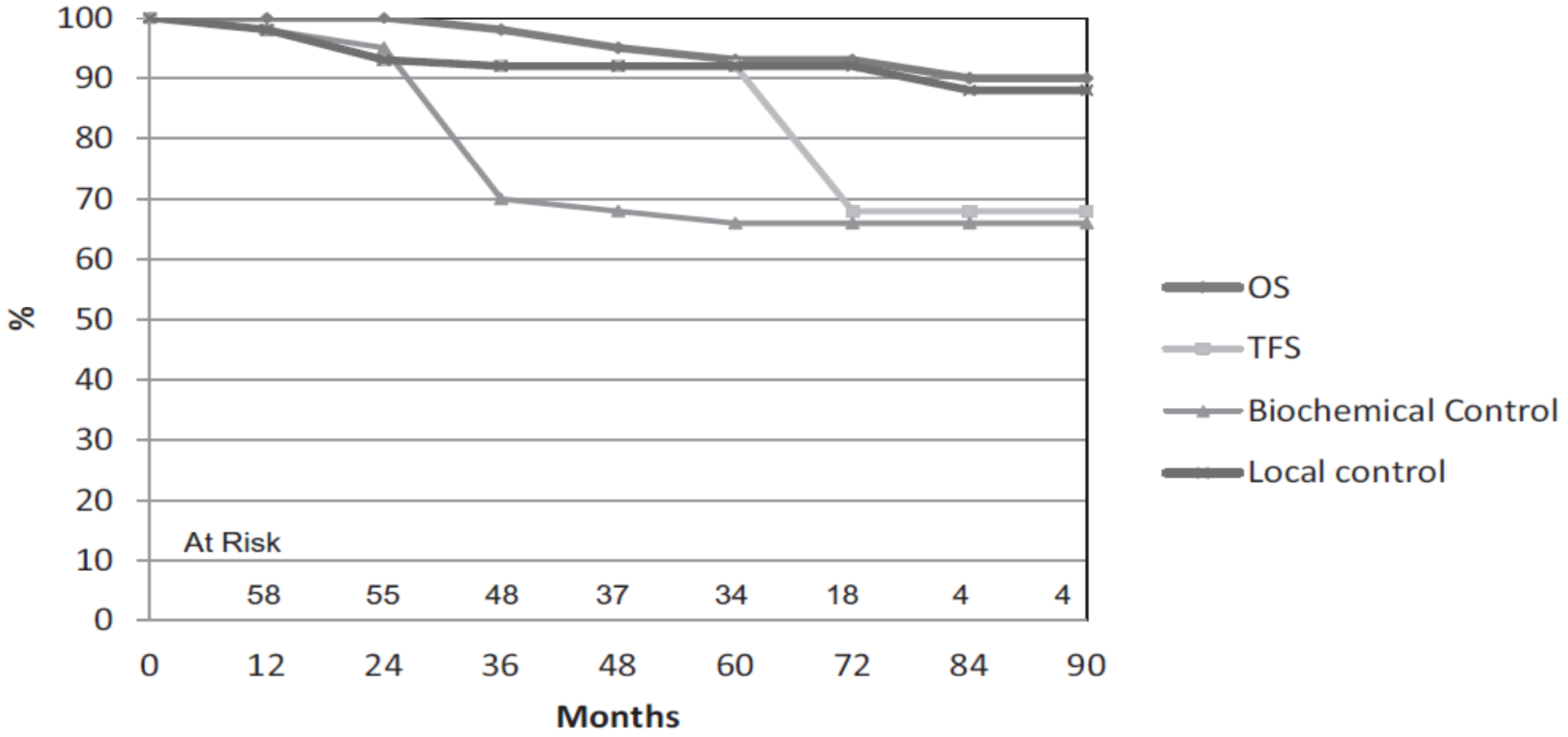
ESTRO School

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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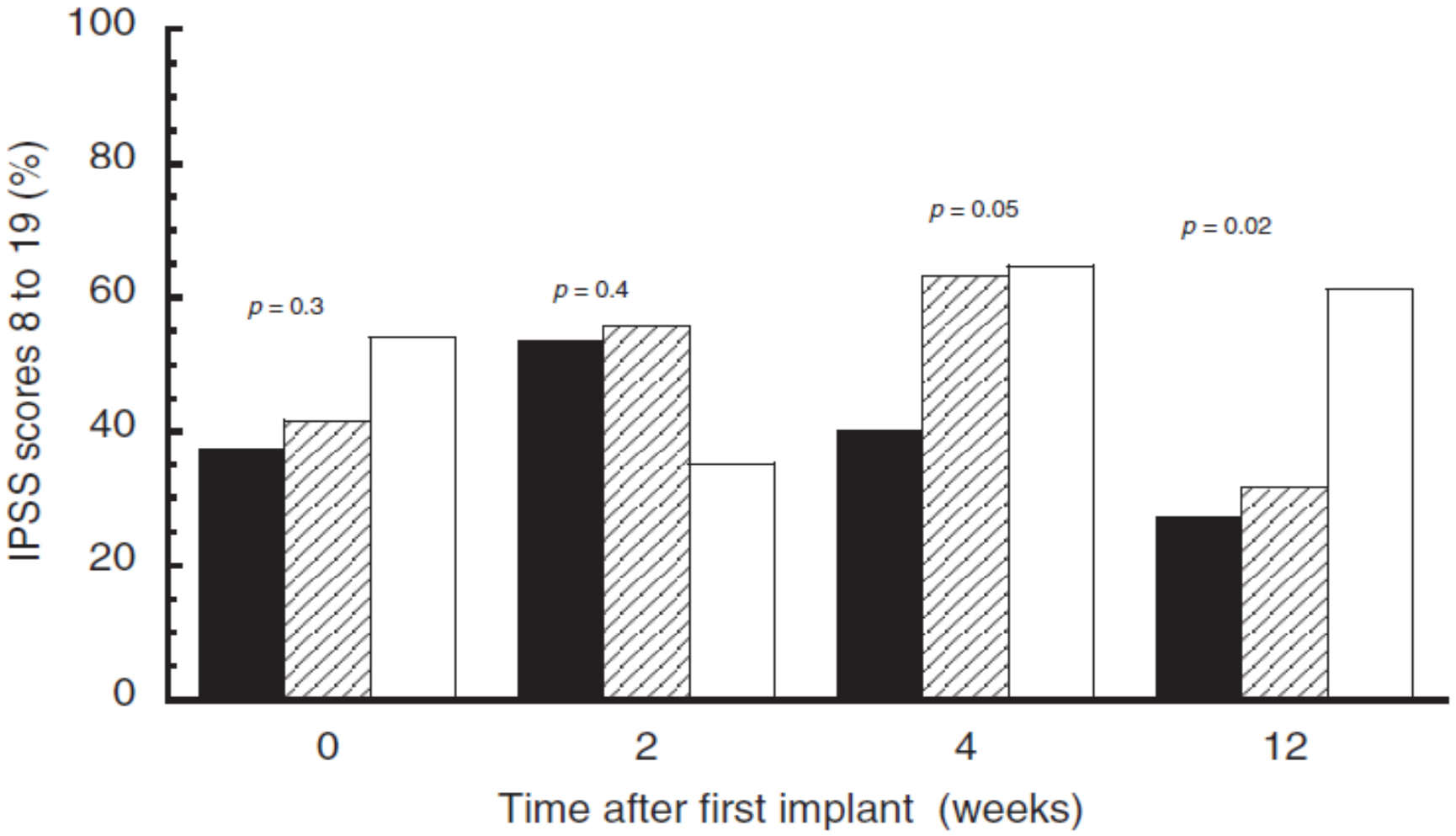
High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: Acute toxicity

Peter Hoskin, Ana Rojas *, Peter Ostler, Robert Hughes, Roberto Alonzi, Gerry Lowe, Linda Bryant

Cancer Centre, Mount Vernon Hospital, Middlesex, UK

Radiotherapy and Oncology 110 (2014) 268–271



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High-dose-rate brachytherapy alone given as two or one fraction to patients for locally advanced prostate cancer: Acute toxicity

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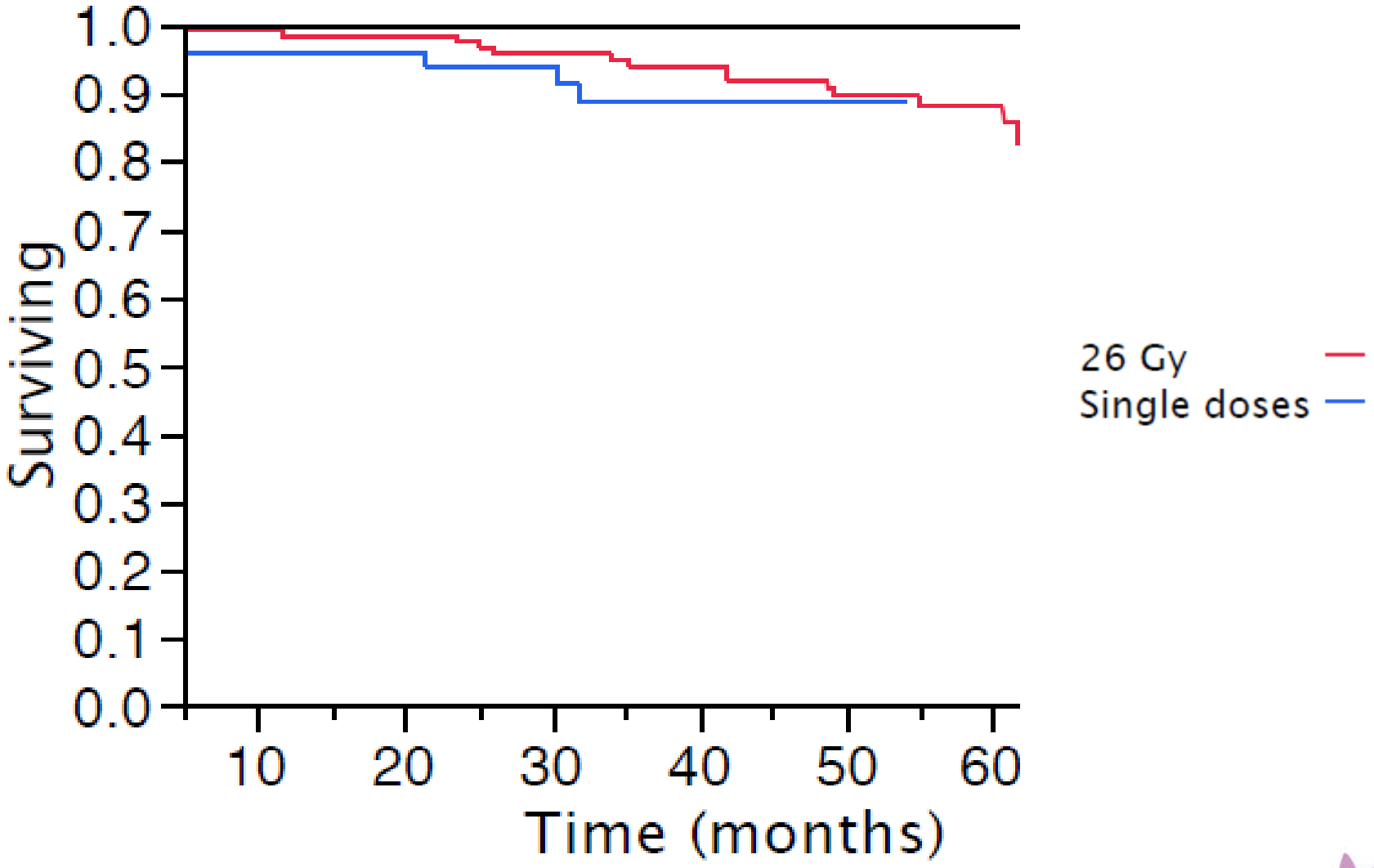
Cancer Centre, Mount Vernon Hospital, Middlesex, UK

Radiotherapy and Oncology 110 (2014) 268–271

Prevalence of RTOG early urinary and bowel adverse events.

	Dose	Week 2	[1]p	Week 4	[1]p	Week 12	[1]p
Urinary							
Grade 1	26 Gy	30% (33/111)	0.2	26% (30/114)	0.05	14% (13/93)	0.5
	19 Gy	22% (5/23)		17% (4/23)		5% (1/21)	
	20 Gy	13% (3/23)		4% (1/24)		14% (3/22)	
Grade 2	26 Gy	13% (14/111)	0.04	6% (7/114)	0.2	3% (3/93)	0.5
	19 Gy	0		0		0	
	20 Gy	0		0		0	
Grade 3	26 Gy	6% (7/111)	0.4	4% (5/114)	0.6	2% (2/93)	0.2
	19 Gy	0		0		0	
	20 Gy	9% (2/23)		4% (1/24)		9% (2/22)	
Bowel							
Grade 1	26 Gy	18% (20/111)	0.2	18% (21/114)	0.9	10% (9/93)	0.5
	19 Gy	9% (2/22)		17% (4/23)		19% (4/21)	
	20 Gy	30% (7/23)		17% (4/24)		14% (3/22)	
Grade 2	26 Gy	3% (3/111)	0.5	0		1% (1/93)	0.4
	19 Gy	0		0		0	
	20 Gy	0		0		5% (1/22)	

MVCC Biochemical RFS



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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

- **Early experience in advanced cases suggests high rates of biochemical control**
- **Optimal indication yet to be defined: ?intermediate/high risk…?low risk**

- **Acute toxicity less than seed brachytherapy**
- **Late toxicity profile may also be favourable with lower rates of late urinary and erectile dysfunction**

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Post plan imaging and dosimetry

Frank-André Siebert

Campus Kiel, Clinic of Radiotherapy

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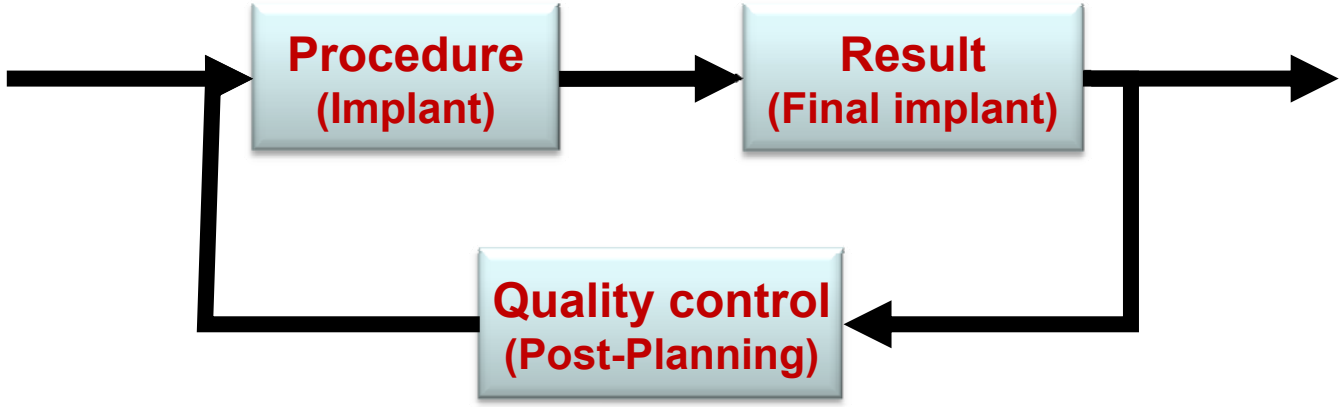
→ Why post-planning ?

Quality control feedback loop



- Detection of severe under-/ overdosage
- Important for systematic treatment
- Feed-back of the results, benefit for future patients

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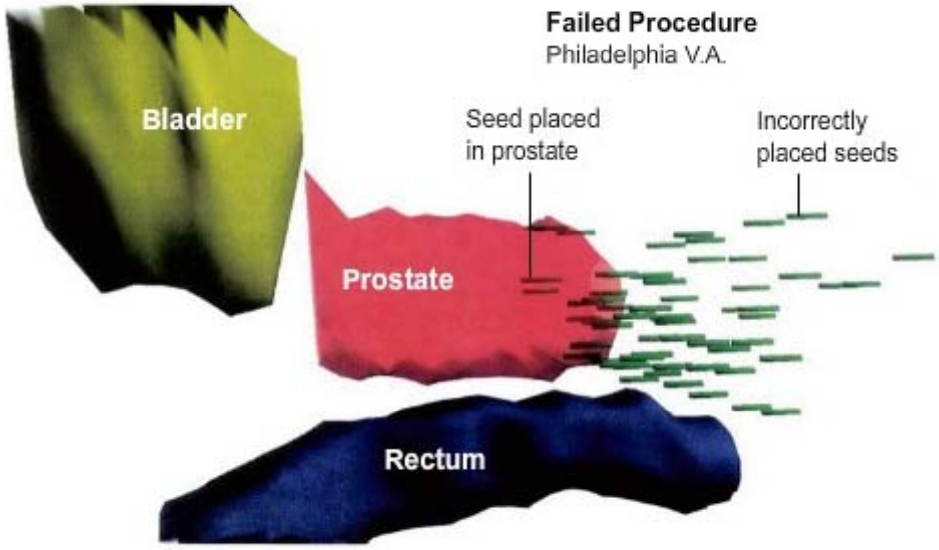
→ Why post-planning ?



In this case, nearly all of the seeds have been placed outside of the prostate, in the perineum. Of the prescribed dose of 160 gray, the prostate received only 24. This means that the patient's prostate cancer was only minimally treated by the procedure.

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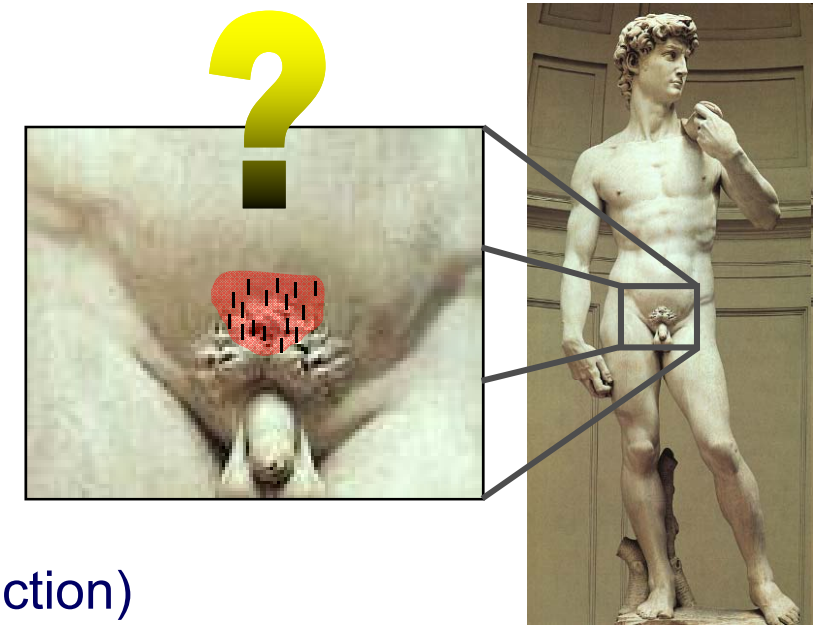
→ Aim of post-planning dosimetry

Determination of

- Dose to organs at risk
- Dose at target



Knowledge of

- Organs (-> Contouring)
- Position of seeds (-> Detection)

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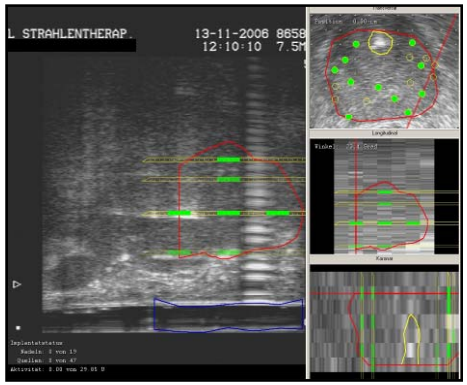
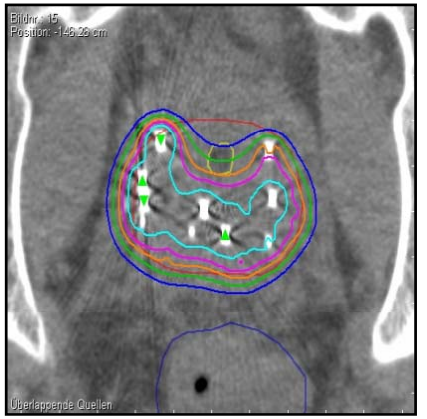
→ Image modality

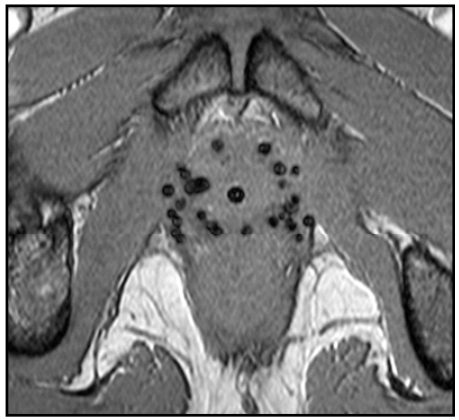
TRUS



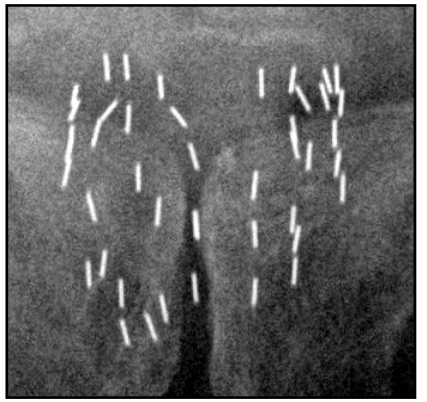
CT



MRI



X-ray



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→ CT post-planning

Volume 26, Number 1, 1993

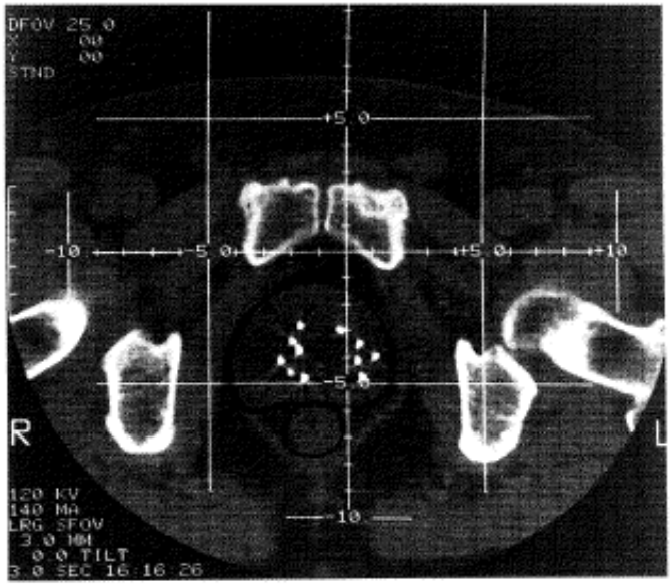
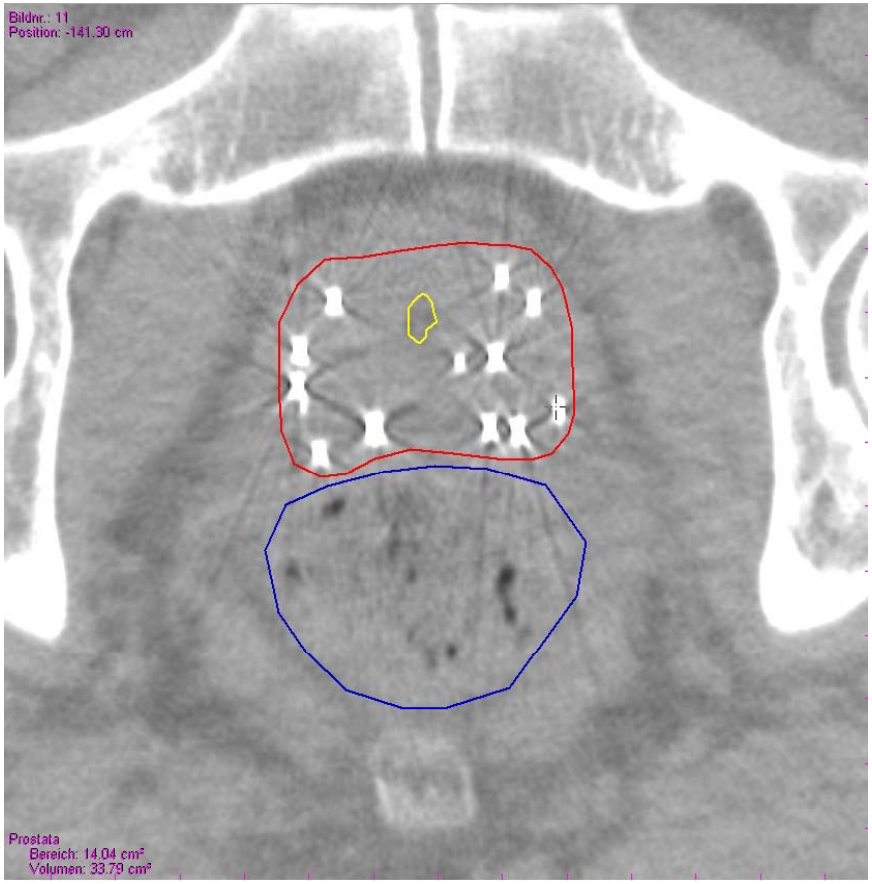


Fig. 1. The seed-images (white dots) on a transverse CT scan.

Roy et al. IJROBP 1993 (26) 163-169



„gold standard“

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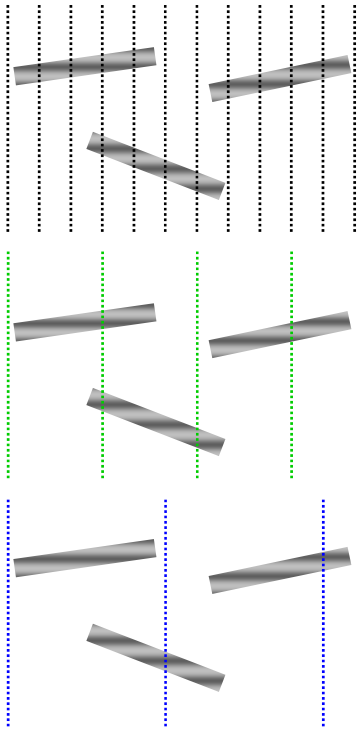
→ CT post-planning

1. **Source detection**
2. **Anatomical information**



1 mm spacing

3 mm spacing

5 mm spacing
(under sampling,
seed sorting)

Scan parameters varies widely:

- Slice spacing, 1-5 mm
- Field of view
- Axial/spiral scan

Accurate detection of seed orientation in CT difficult.

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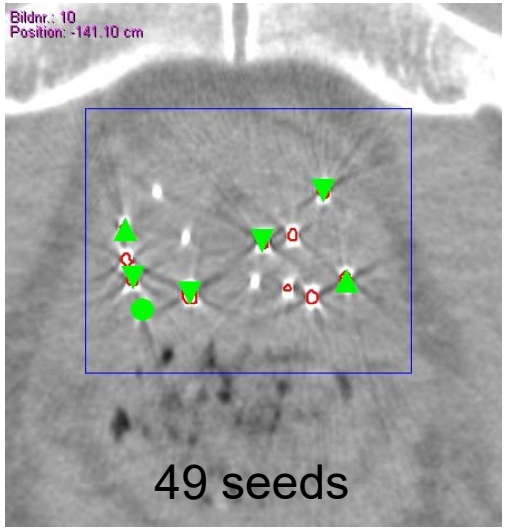
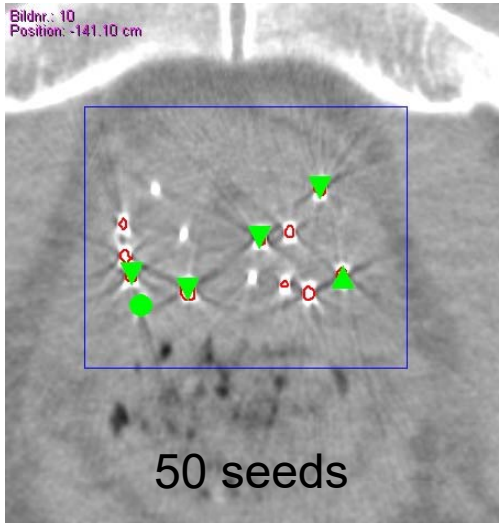
→ Automatical seed finding

Advantage: Time saving, reproducible method

But…check the results!



49 seeds



50 seeds

Problems may occur with

- Calcifications
- Close sources
- Unknown seed number

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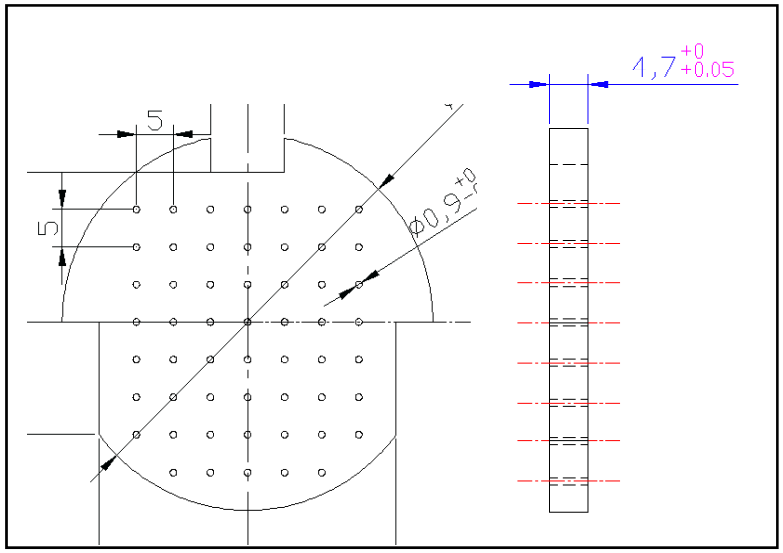
→ CT post-planning

Can we trust the CT post-planning results?

Two questions:

1. Is CT post-planning of different centers comparable?
2. What is the influence of CT parameters and seed models?

=> Phantom check



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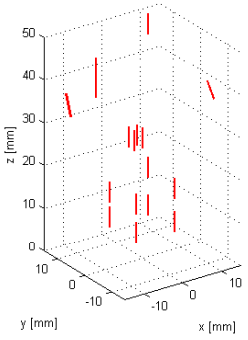
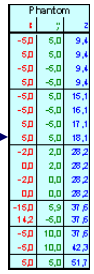
Braphyqs multi-center study



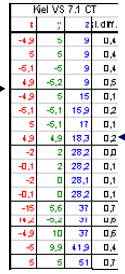
Test configuration
(17 inactive *IBt*-Seeds



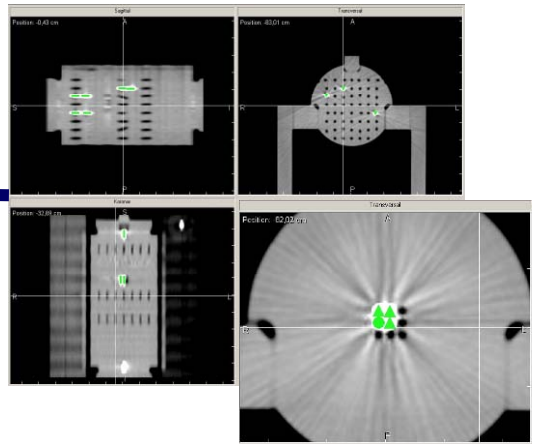
Seed positions
in phantom

Comparison

$$\sigma = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(d_i - \bar{d})^2}$$



rekonstructed
seed positions



Center	TPS	CT-Param.	σ (x) [mm]	σ (y) [mm]	σ (z) [mm]
A	5	Ax 2 / 2	0,1	0,1	0,3
B	5	Sp 4 / 1	0,2	0,2	1,2
B	1	Sp 4 / 1	0,2	0,3	1,3
C	5	Sp 2 / 2.5	0,2	0,2	1,2
C	5	Sp 2 / 1	0,1	0,1	0,3
…	…	…	…	…	…

Siebert et al. Radiother Oncol 85 (2007) 316-323

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→ Imaging of different seed models

Oncura EchoSeed 6734

IBt Intersource-125

AnchorSeed

Theragenics TheraSeed 200

Bebig IsoSeed S17

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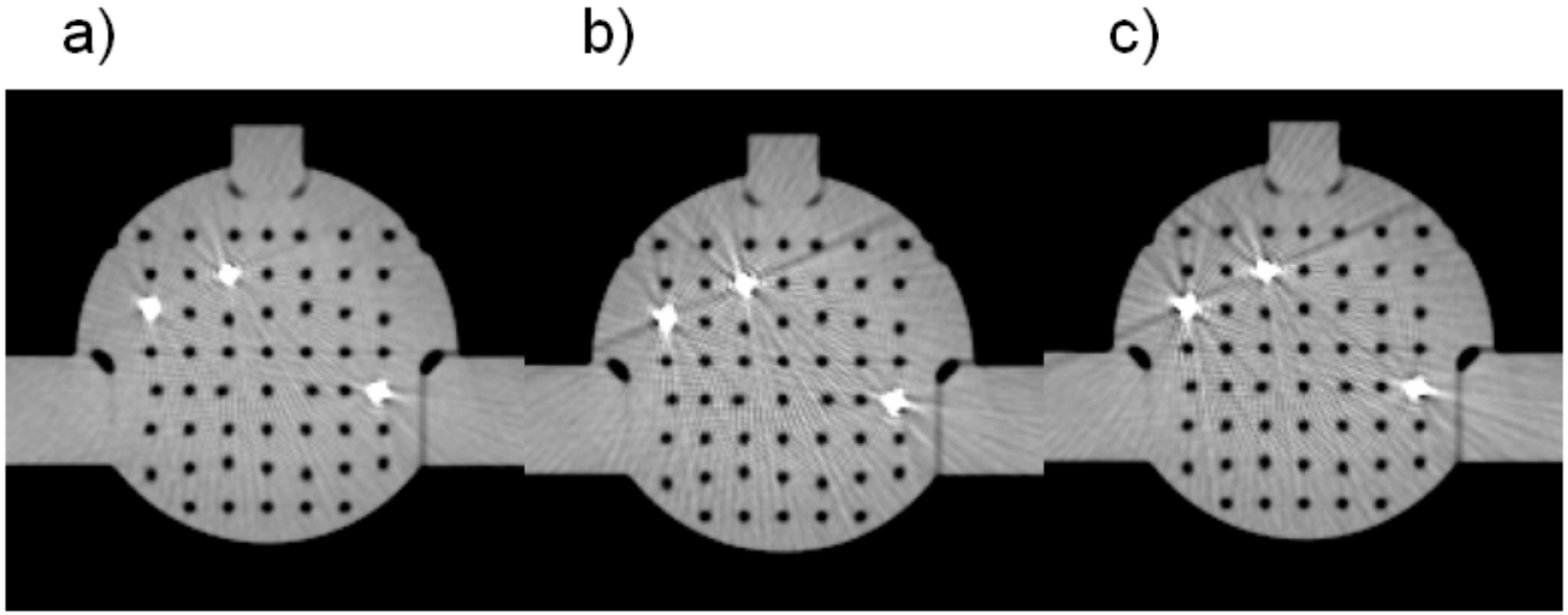

a) Bebig IsoSeed® I25.S06
b) Mentor ProstaSeed® I-125
c) Oncura EchoSeed® 6734

Scan protocol: “Onc Medium Body”, axial scan, kV_p=130, 125 mA,
2 mm slice thickness, 2 mm index, SFOV 200 mm, 2.560 pixels/mm

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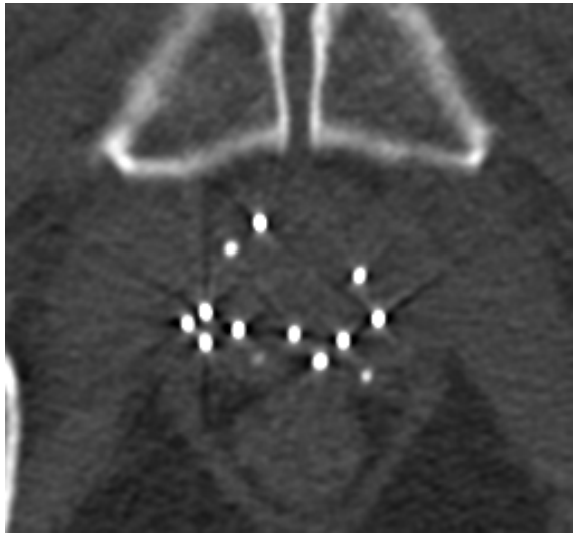
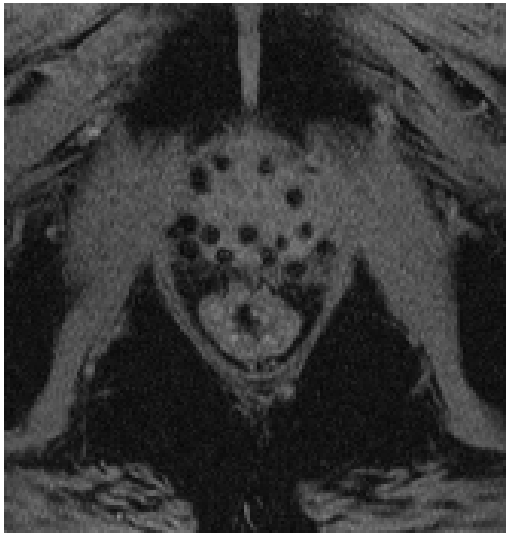
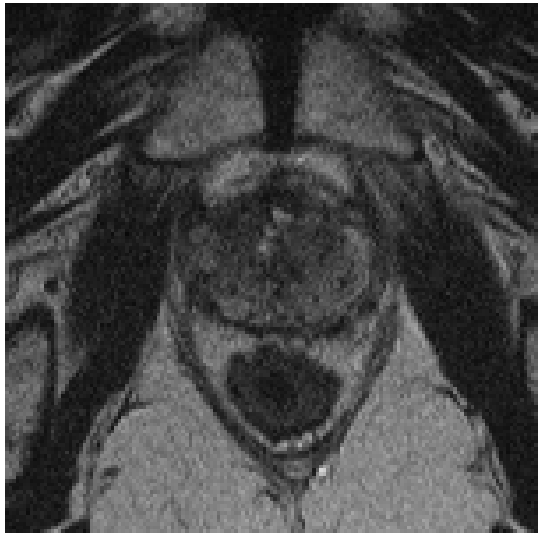
→ MRI post planning



CT



MRI (T1)



MRI (T2)

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UK SH

→ MRI post planning

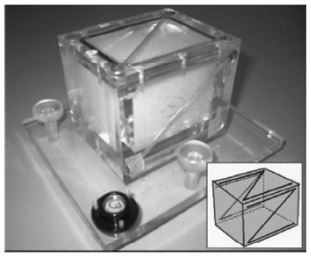

Fig. 1. Prostate phantom consisting of PMMA container filled with agarose gel. Three N-shaped coordinate axes are integrated in the container walls as indicated in the schematic diagram.

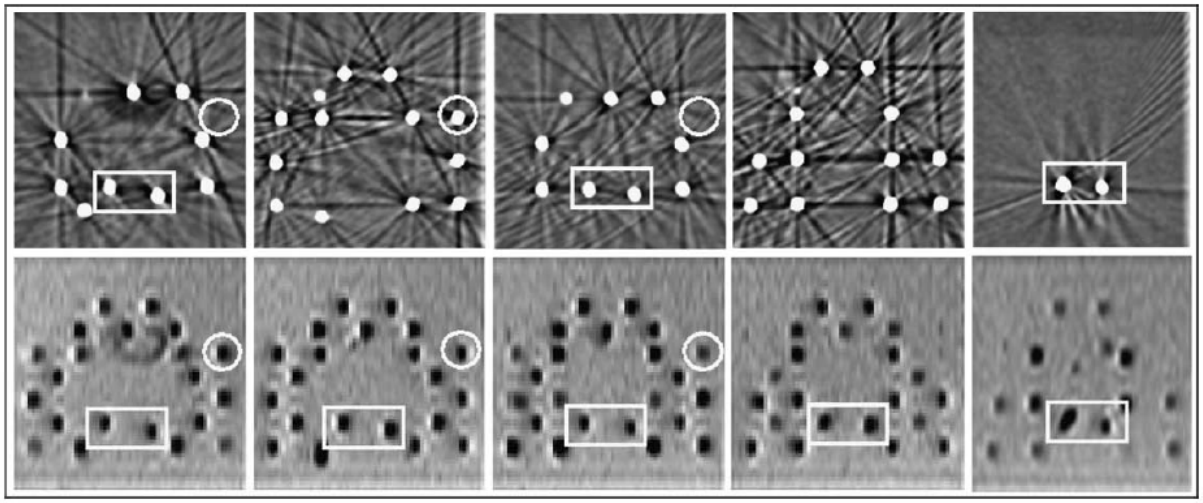

Fig. 4. Five consecutive slices for CT (Siemens) and MRI (Philips 1.5T) taken with 5 mm slice thickness. MR images are displayed below the corresponding CT slices. For the same geometry, more seed signal voids are visible on MRI than CT. Some examples are marked with a circle and rectangle.

De Brabandere et al. Radiother Oncol, 2006

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→ TRUS post-implant dosimetry

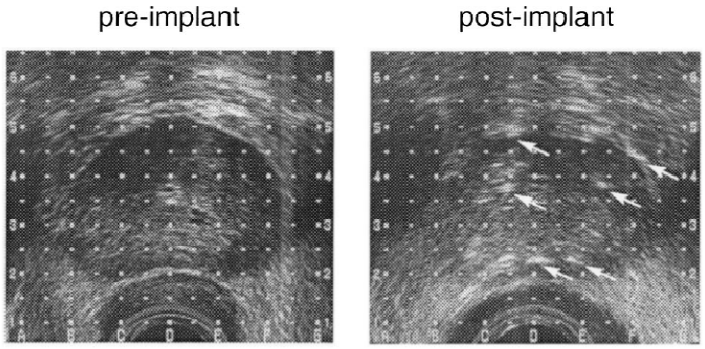

FIG. 1. Pre and post-implant TRUS images. Placement of sources partially obscures the prostatic margin. There are many bright spots that might be interpreted as sources (small arrows), but many could also be an air artifact, leading to false positive source identifications. And some sources might not produce enough signal to be seen, leading to false negative source identifications.

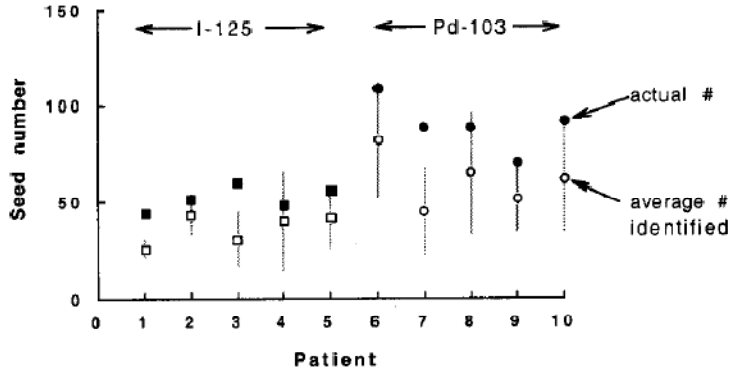

FIG. 3. The actual number of seeds implanted versus the average number identified by observers. Note that the I-125 patients are on the left, and the Pd-103 patients are on the right. Error bars represent the standard deviations of the number of seeds identified (alleged).

The average percent of the seeds allegedly identified per patient ranged from 51% to 83% ~mean: 74%!

Stored images used in this study.

Han et al. Med Phys 30 (2003) 898-900

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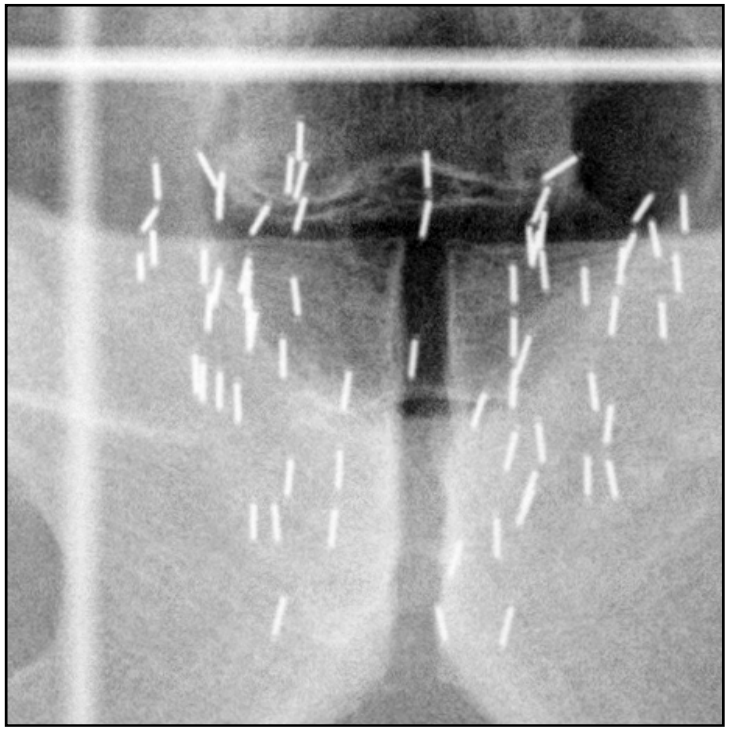
X-Ray seed reconstruction

- Determination of source locations only
- No anatomical information
- Good for source counting



Different algorithms for reconstruction exist, e.g.:

Tubic et al. Med Phys 28 (2001) 2272-2279
Tutar et al. Med Phys 30 (2003) 3135-3142
Siebert et al. Med Phys 34 (2007) 967-975

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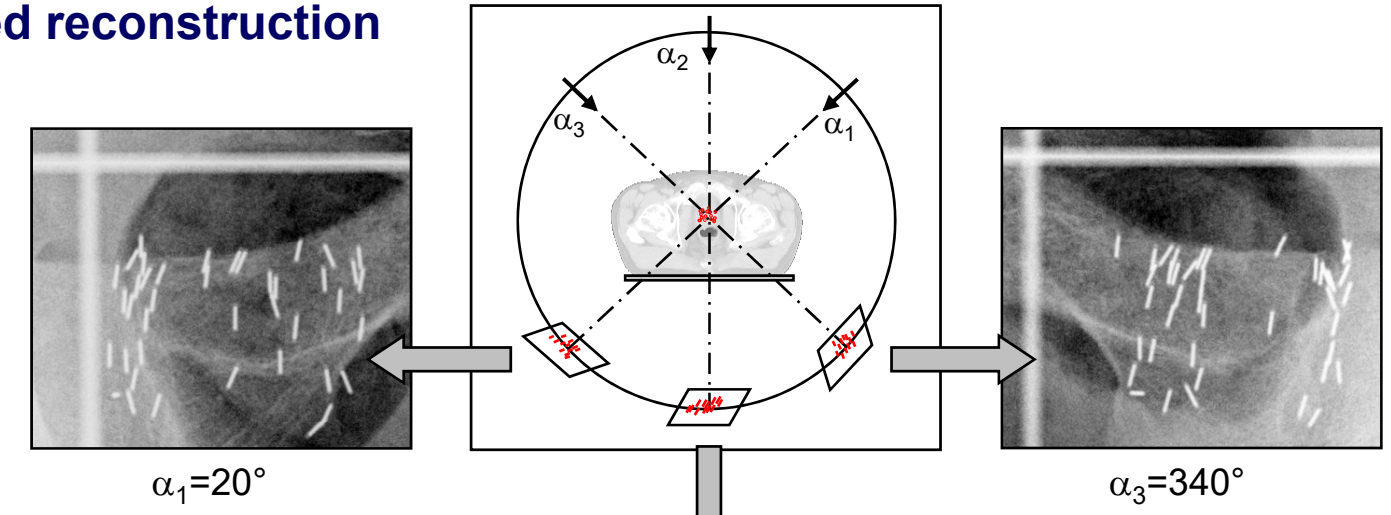
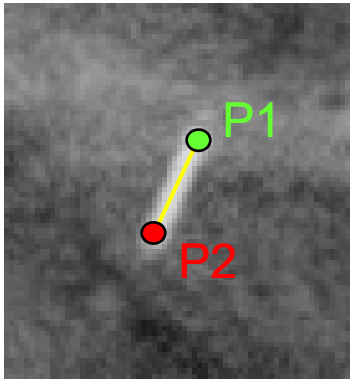
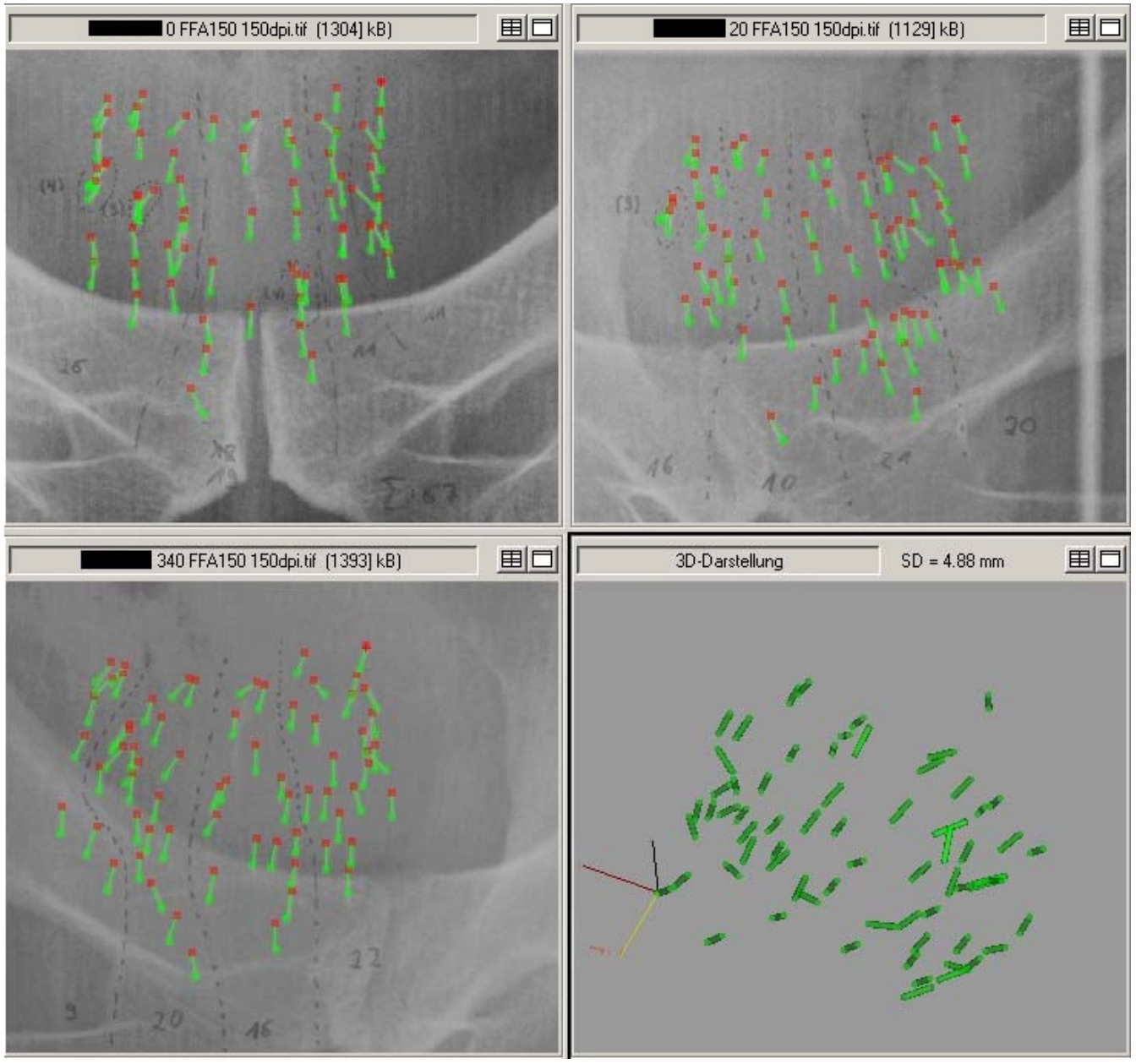
→ X-Ray seed reconstruction





Avoid patient movement between radiograph exposition.


0 FFA150 150dpi.tif (1304] kB)
20 FFA150 150dpi.tif (1129] kB)
340 FFA150 150dpi.tif (1393] kB)
3D-Darstellung
SD = 4.88 mm

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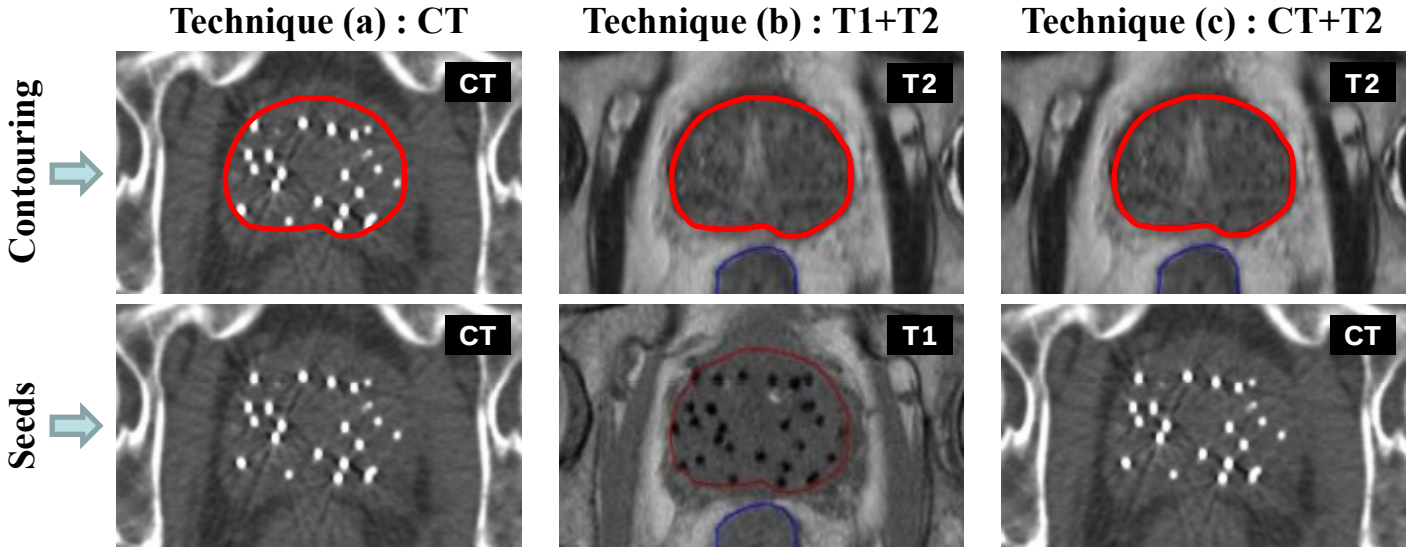
→ M. De Brabandere et al.: BRAPHYQS/PROBATE study

Prostate post-implant dosimetry:
a comprehensive interobserver study to investigate uncertainties introduced by seed localization, contouring and image fusion



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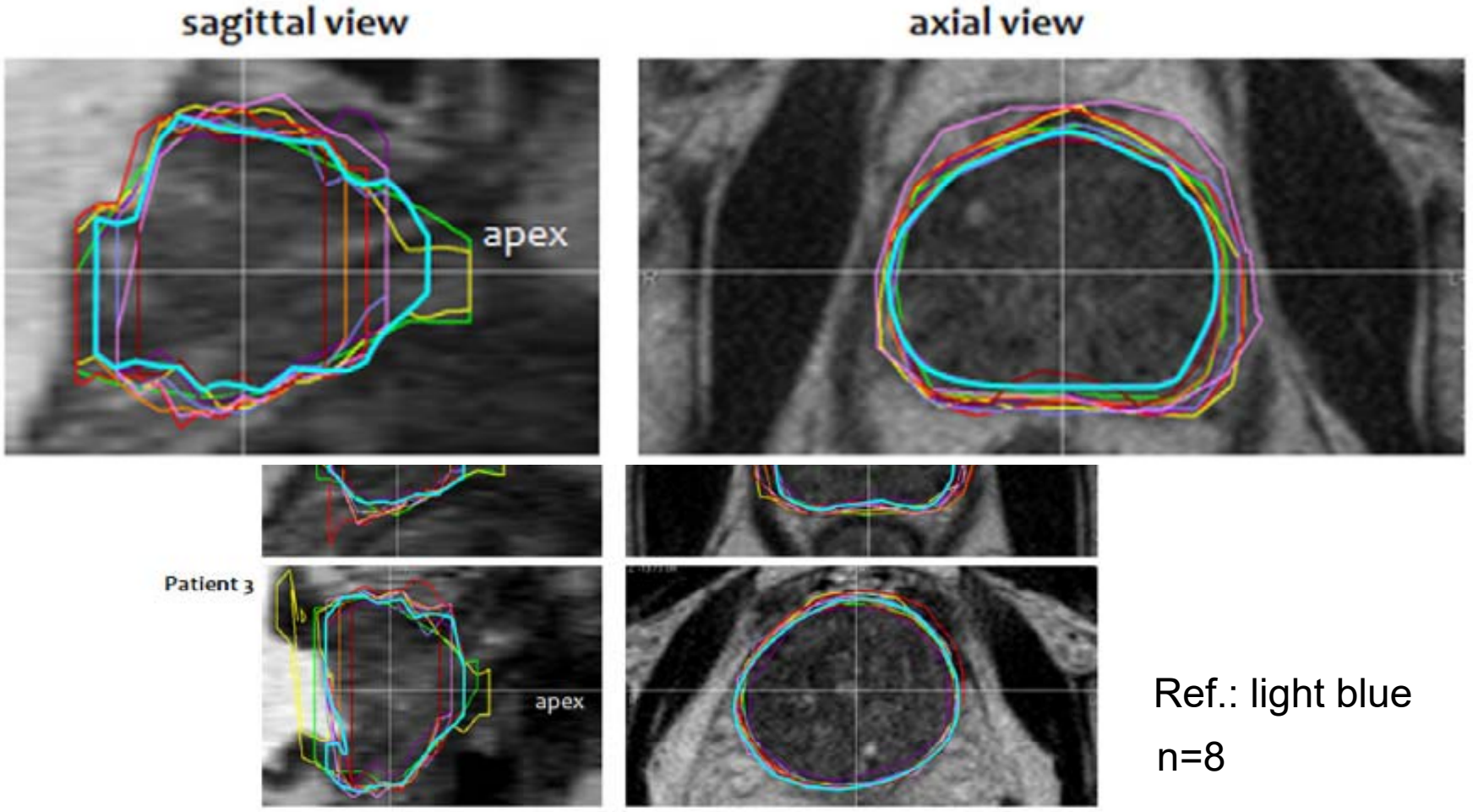
→ Delineation in T2 data

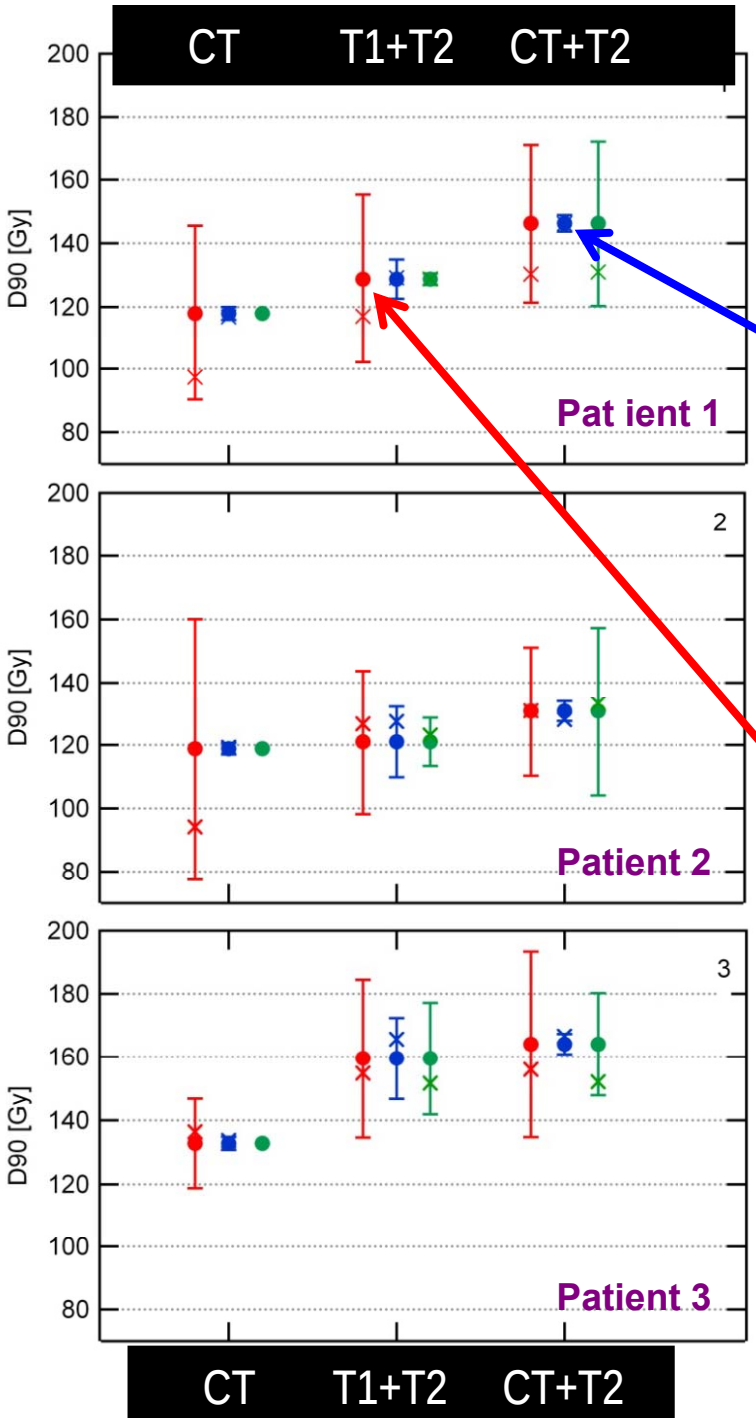


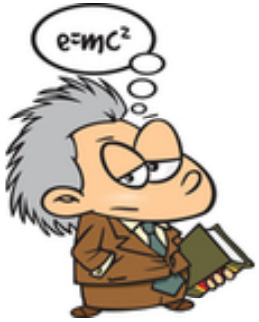
Ref.: light blue

n=8

Fig. 1. Post-implant CTV-P contours as delineated on (a) CT and (b) T2 by eight observers and a reference (blue) for three patients.

Impact of interobserver variability on D90





Physicists

Clinicians

- erver variability with
- o reference (1SD)

Co
large interobserver variability for D90
for

Se
- server spread for D90
- technique (b), using

Fu
- T1 + T2 : interobserver variability relatively small, but patient dependent
- CT + T2 : large interobserver variability

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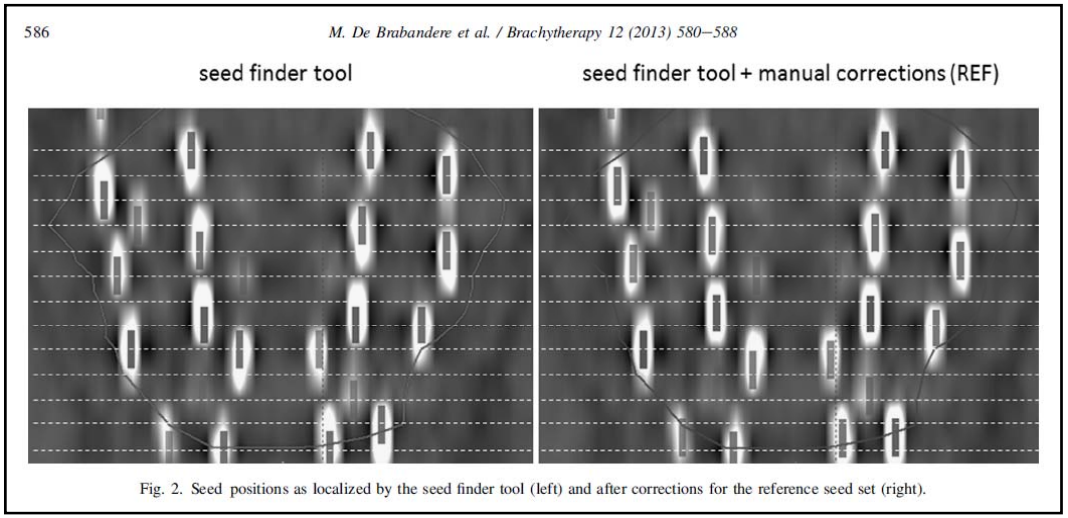
→ Seed reconstruction accuracy



- CT: deviations 1.1 mm (1 SD)
- Effect on D90 (CT, CT+T2) < 2%

- T2: deviations 3.0 mm (1 SD)
- Effect on D90 (T1 +T2) 7%

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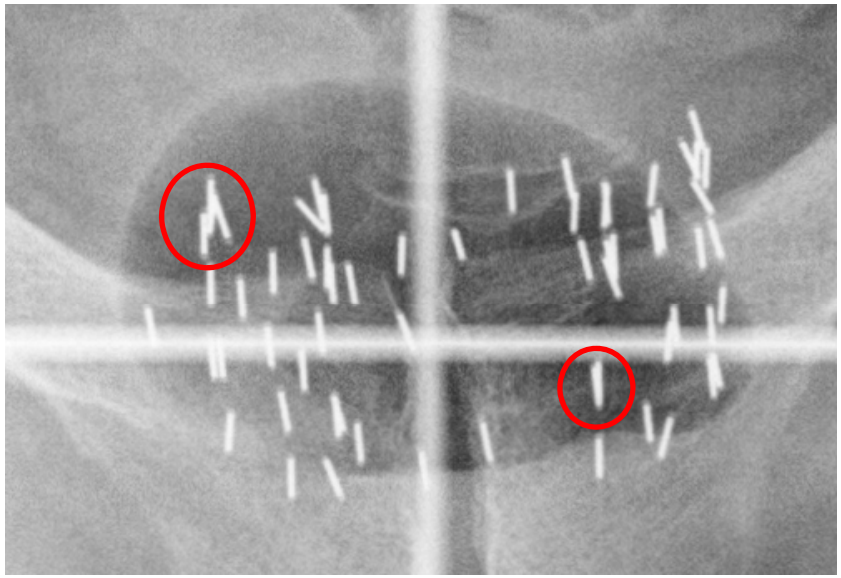
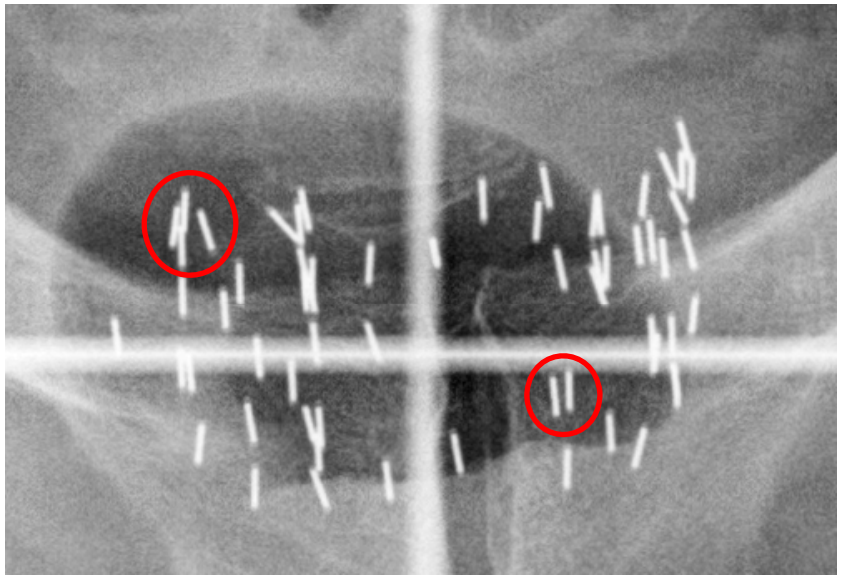
Flouroscopies: counting the seeds



0°



5°

Two flouroscopies with Δ≈5° can help to identify and count seeds

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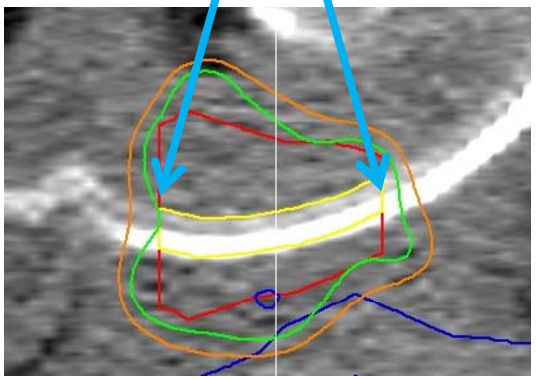
→ Contouring...

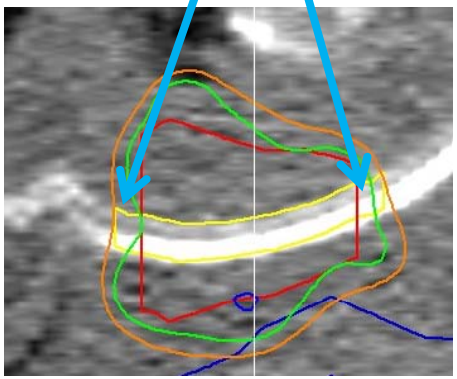
- Should be consistent within a clinic or study
- Careful selection of parameters

0 mm



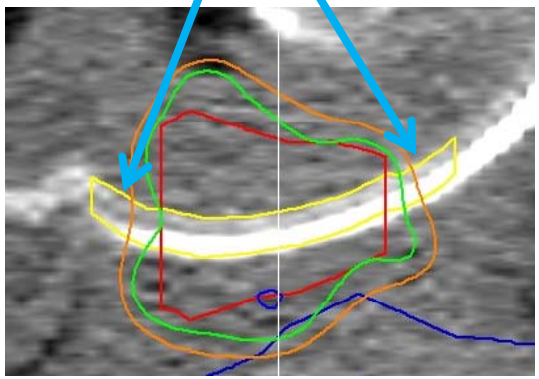
Urethra
Vol= 0.87cc
D10=178.03Gy
D0.1cc = 176.53Gy

±4 mm



Urethra
Vol= 1.12cc
D10=175.93 Gy
D0.1cc = 176.50Gy

±10 mm



Urethra
Vol= 1.37cc
D10=174.58 Gy
D0.1cc = 176.54Gy

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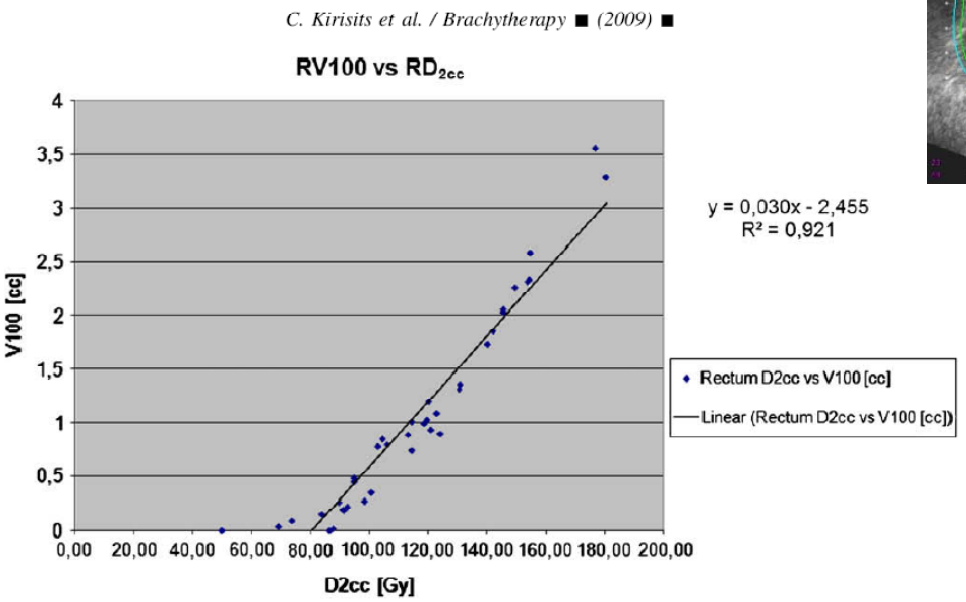
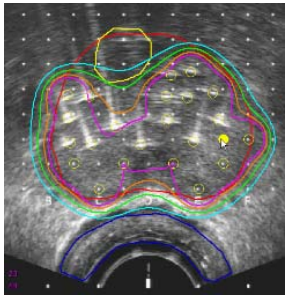
„Only absolute volume parameters are stable in relation to different contouring concepts.“

High correlation between D_R1, D_{R2cc}, $D_{R0.1cc}$ (<5%).

Reporting D_u5, D_u10, D_u30 is redundant.





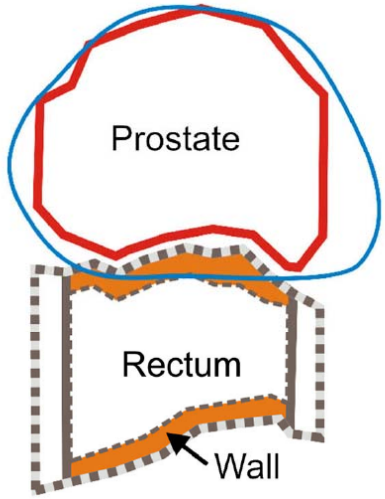


Fig. 1. Sagittal view showing the prostate and different rectum contours. The initial rectum structure is extended by additional contours (dotted line) in the next cranial and caudal slice, respectively. The shaded region indicates the rectum wall contour, if a second inner contour is delineated. The isodose is related to the RD_{2cc}, which will remain at a constant value for all variations of contours shown in this example. A detailed discussion of this figure can be found in the text.

Kirisits et al. 2009 Brachytherapy 8(4):353-60

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→ Timing of post-planning dosimetry

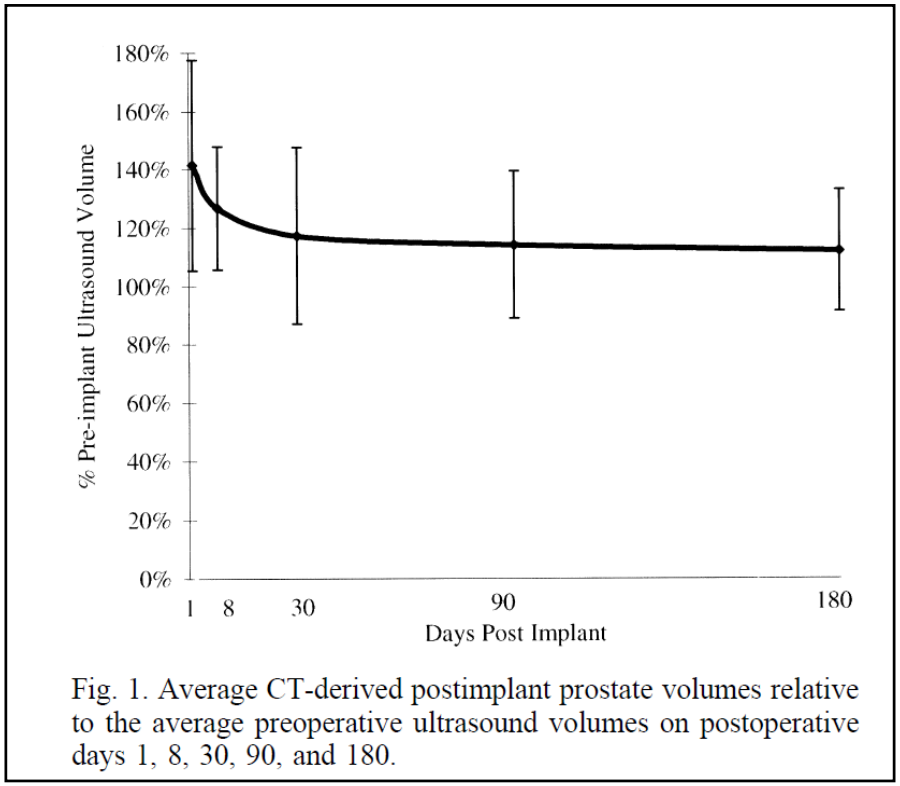

Fig. 1. Average CT-derived postimplant prostate volumes relative to the average preoperative ultrasound volumes on postoperative days 1, 8, 30, 90, and 180.

One month after implant gives the most accurate prostate volume.

Prestidge et al. Med Phys 40 (1998) 1111-1115

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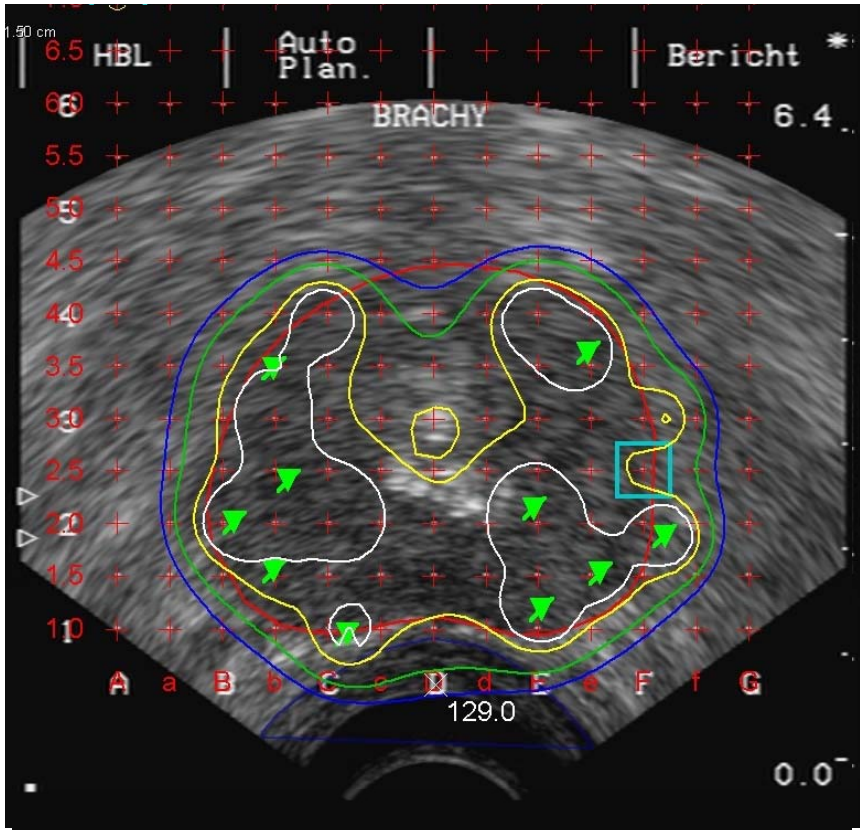
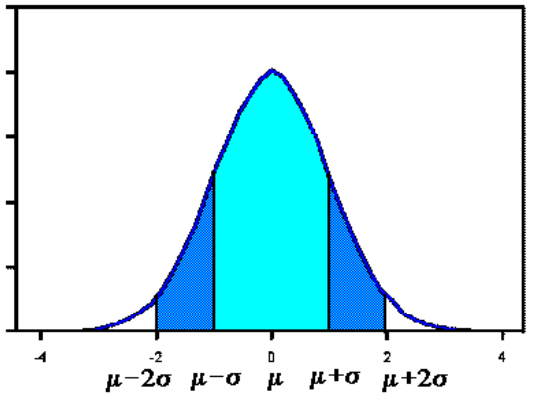
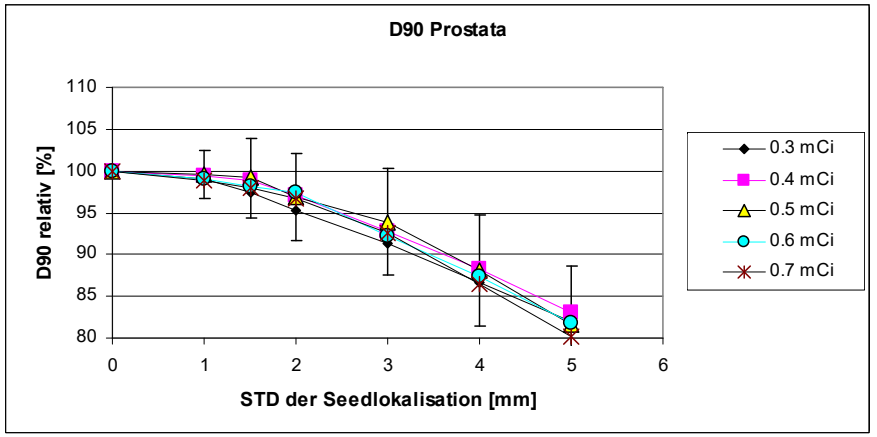
→ Simulation of seed displacements

24 ml, σ: 1.5 mm, 0.5 mCi







=> Robust dose distribution

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→ Seed migration

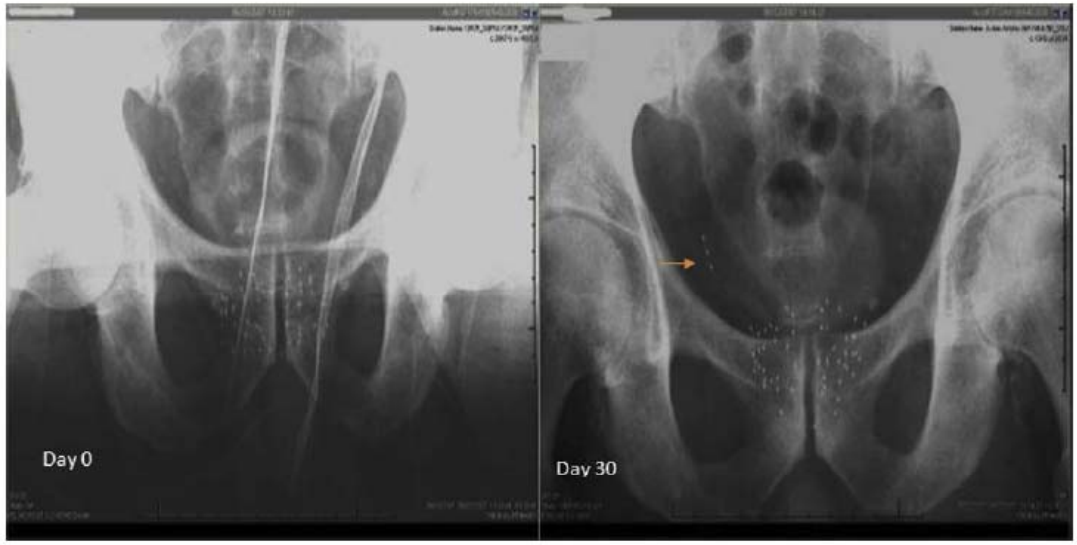
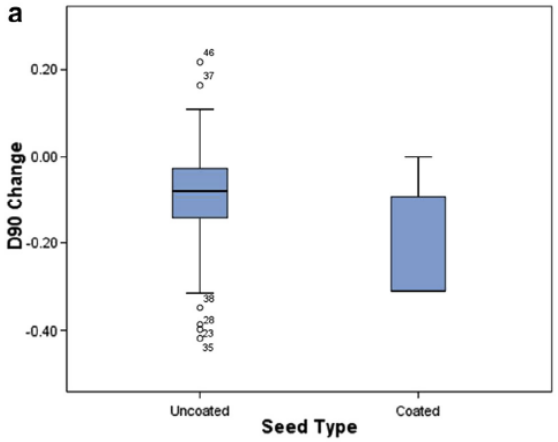


Fig. 1. Day 0 and day 30 comparison of post implant pelvic radiographs of a patient showing significant pelvic migration of the seed strand when real-time source stranding was used.

Fig. 2. Photo of an actual AnchorSeed.



Sarkar et al. Brachytherapy 12 (2013) 356-361

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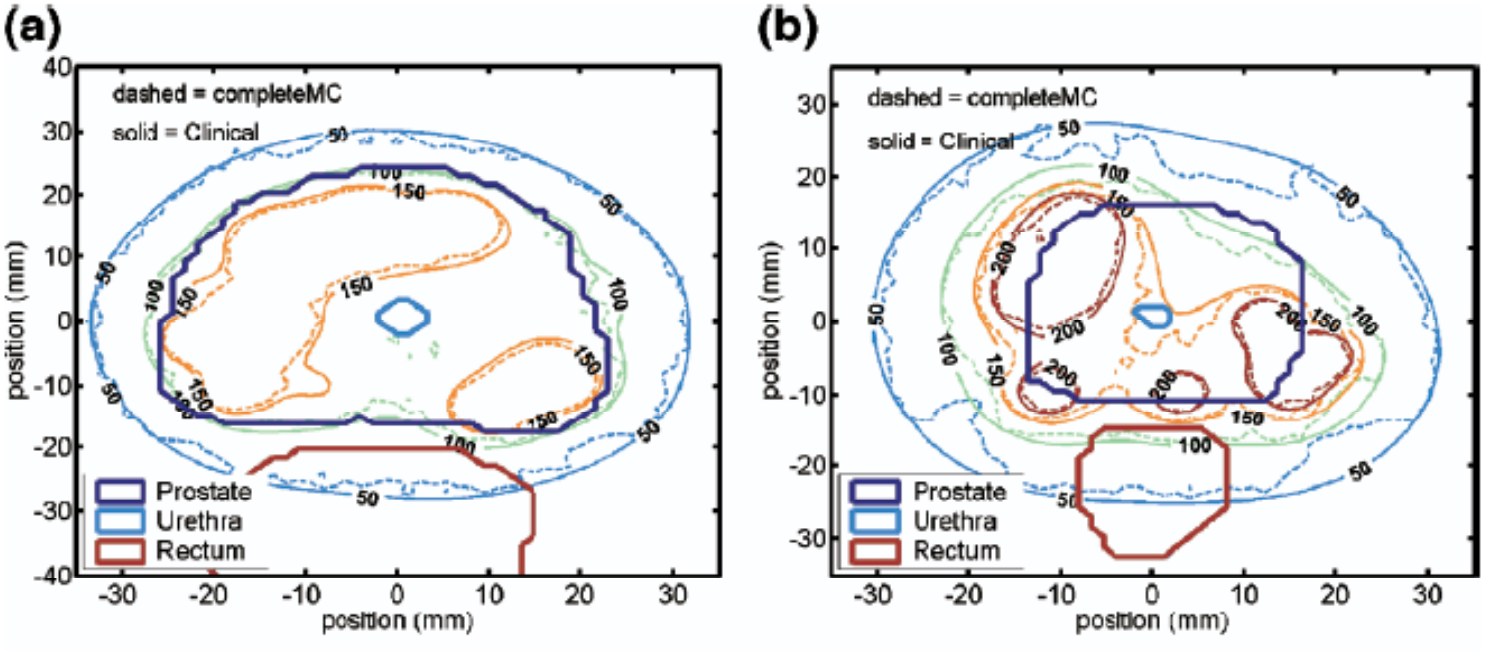
→ Postimplant dosimetry using a MC dose calculation engine



Isodose comparisons between TG-43 and Monte-Carlo

Carrier et al. 2007, IJROBP

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IOP Publishing | Institute of Physics and Engineering in Medicine
Physics in Medicine & Biology
Phys. Med. Biol. 60 (2015) 5455–5469
doi:10.1088/0031-9155/60/14/5455

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A simple analytical method for heterogeneity corrections in low dose rate prostate brachytherapy

Fernando Hueso-González[1,5], Javier Vijande[1,2], Facundo Ballester[1], Jose Perez-Calatayud[3] and Frank-André Siebert[4]

$$\dot{D}_{\mathrm{het}}(r) = S_{\mathrm{K}} \Lambda g_{\mathrm{p,het}}(r) \varphi_{\mathrm{an}}(r) \left(\frac{r_0}{r} \right)^2$$

$$g_{\mathrm{eq}}(r) = \frac{\rho_{\mathrm{w}}}{\rho(r)} \frac{1}{\Delta r} \int_{r_{\mathrm{eq}}}^{r_{\mathrm{eq}}+\Delta r_{\mathrm{eq}}} g_{\mathrm{w}}(r') \mathrm{d}r'$$

Calcification

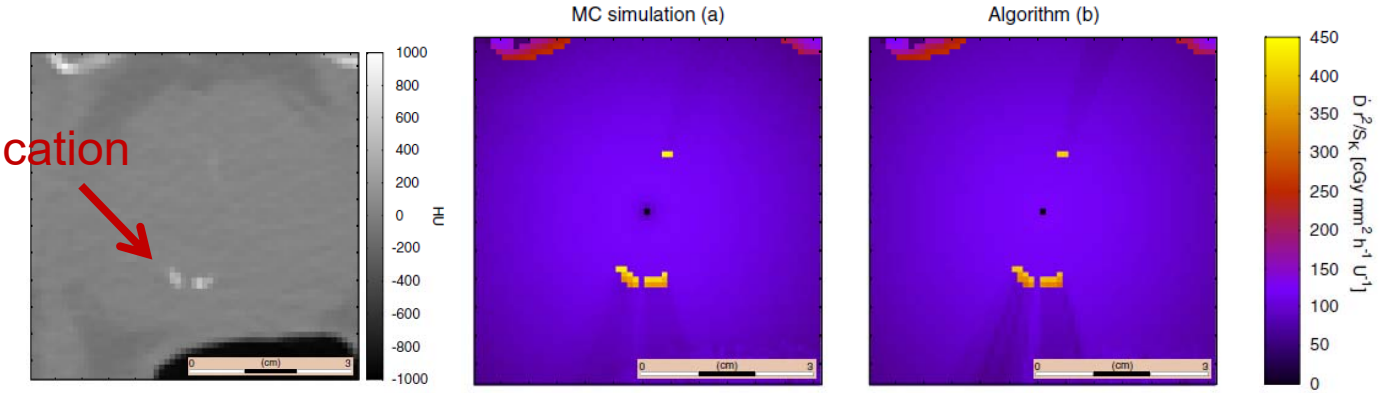

Figure 3. Dose rate by air kerma strength multiplied by the squared distance to the radioactive seed (located at the image center) for (*a*) MC simulation, and (*b*) analytical algorithm *RayStretch*. Heat maps are shown in a common color scale range for a reliable comparison.

- Potential to incorporate any type of heterogeneities
- Real-time speed

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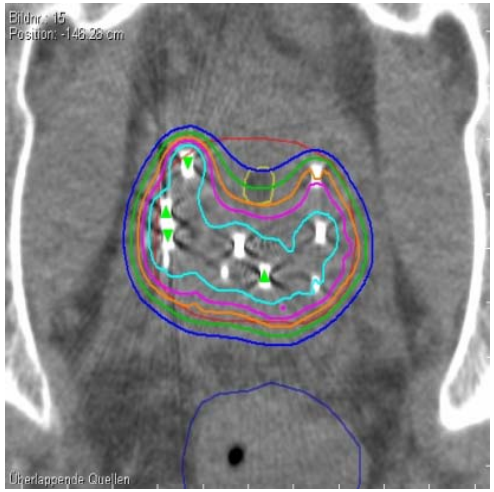
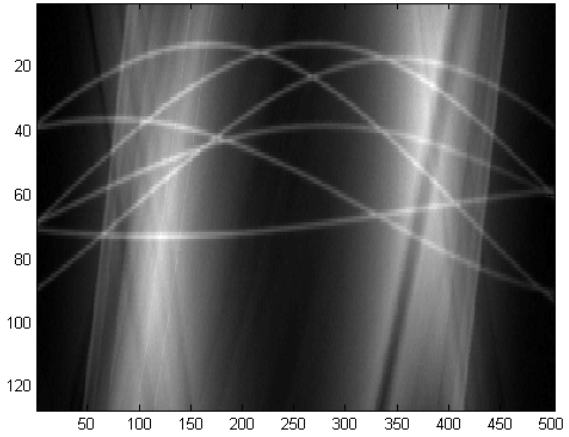
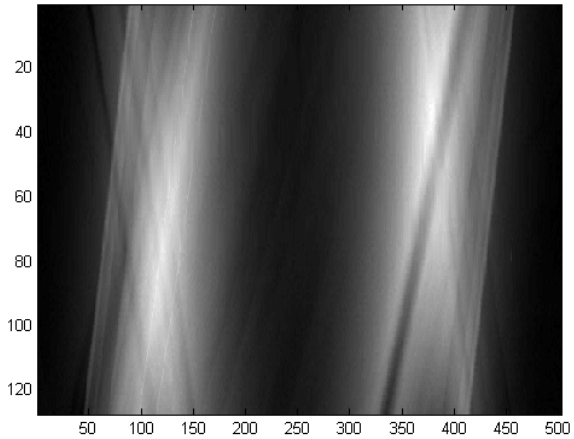
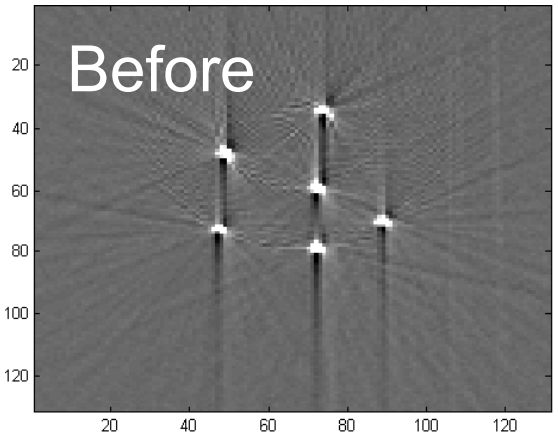
→ CT artefact reduction

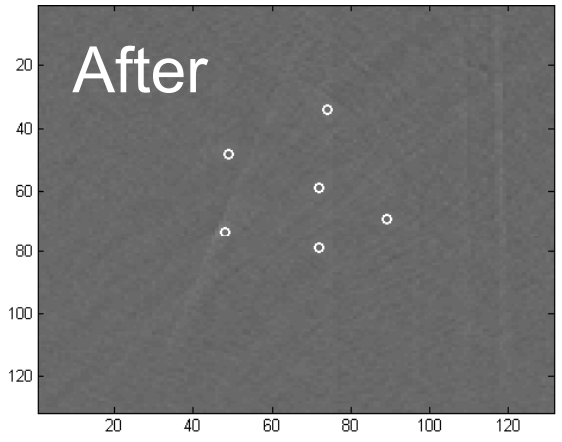


Sinogram correction









Xu et al. Med Phys 2011

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→ DVH constraints for permanent prostate brachytherapy (I-125)

Prostate:

- **V100 ≥ 95%** of CTV.
- **D90 > 100%** of prescription dose.
- **V150 ≤ 50%** of CTV.

Rectum:

- Primary parameter: **D_{2cc} ≤ 145 Gy**.
- Secondary parameter: **$D_{0.1cc}$ (~D_{max}) < 200 Gy**.

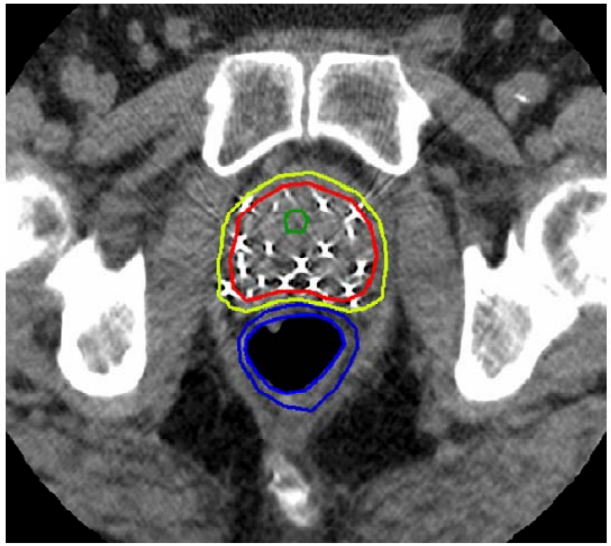

Fig. 2. Post-plan definitions of CTV. Legend: ——, CTV-P = CTV-prostate; ——, CTV-PM = CTV-prostate margin; ——, urethra prostatica; ——, rectum (outer and inner wall).

Urethra:

- Primary parameter: **D_{10} < 150%** of the prescription dose.
- Secondary parameter: **D_{30} < 130%** of the prescription dose.

Parameters should be reported => Comparison possible

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GEC ESTRO Recommendations, Salembier et al 2007

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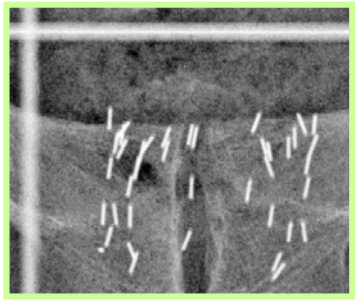
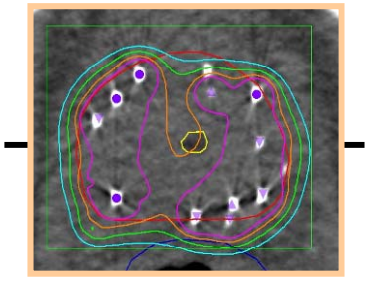
→ Post-implant dosimetry: typical procedure

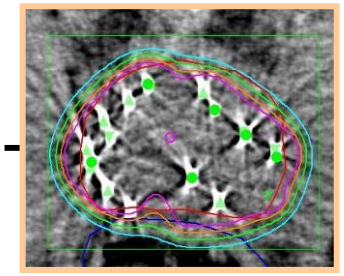
Check number of seeds during implant

Count seeds in X-ray images



CT based post-planning:
seed detection, contouring





CT day 0

CT after 4 weeks


Thank you for your attention…

ESTRO

School

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ncidence of Complications of Prostate Brachytherapy

S. Machtens

Director of the

Department of Urology and Paediatric Urology

Academic Teaching Hospital

Marien-Hospital Bergisch Gladbach

ching Course Brussels 05.-07.06.2016

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

athophysiology

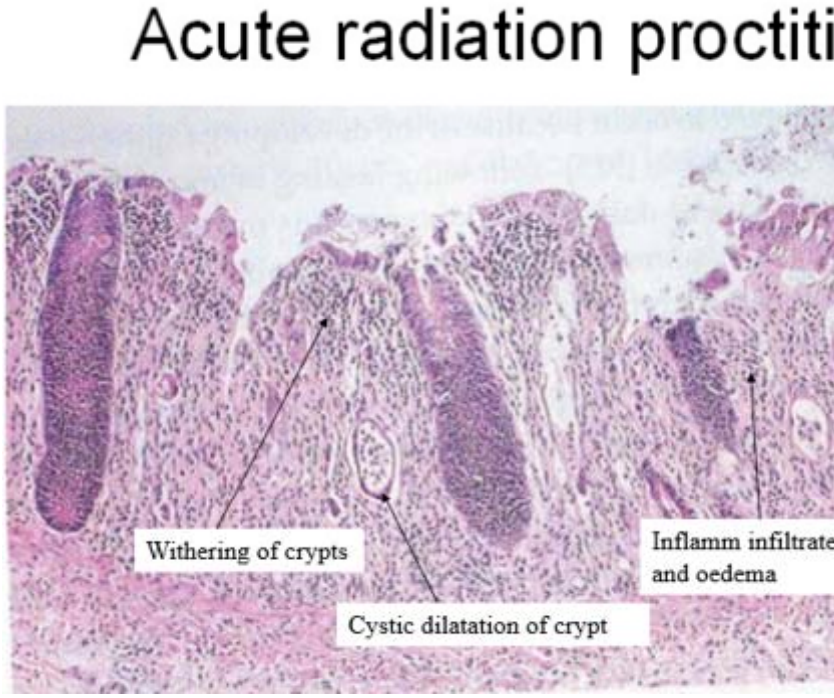
istopathology findings

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

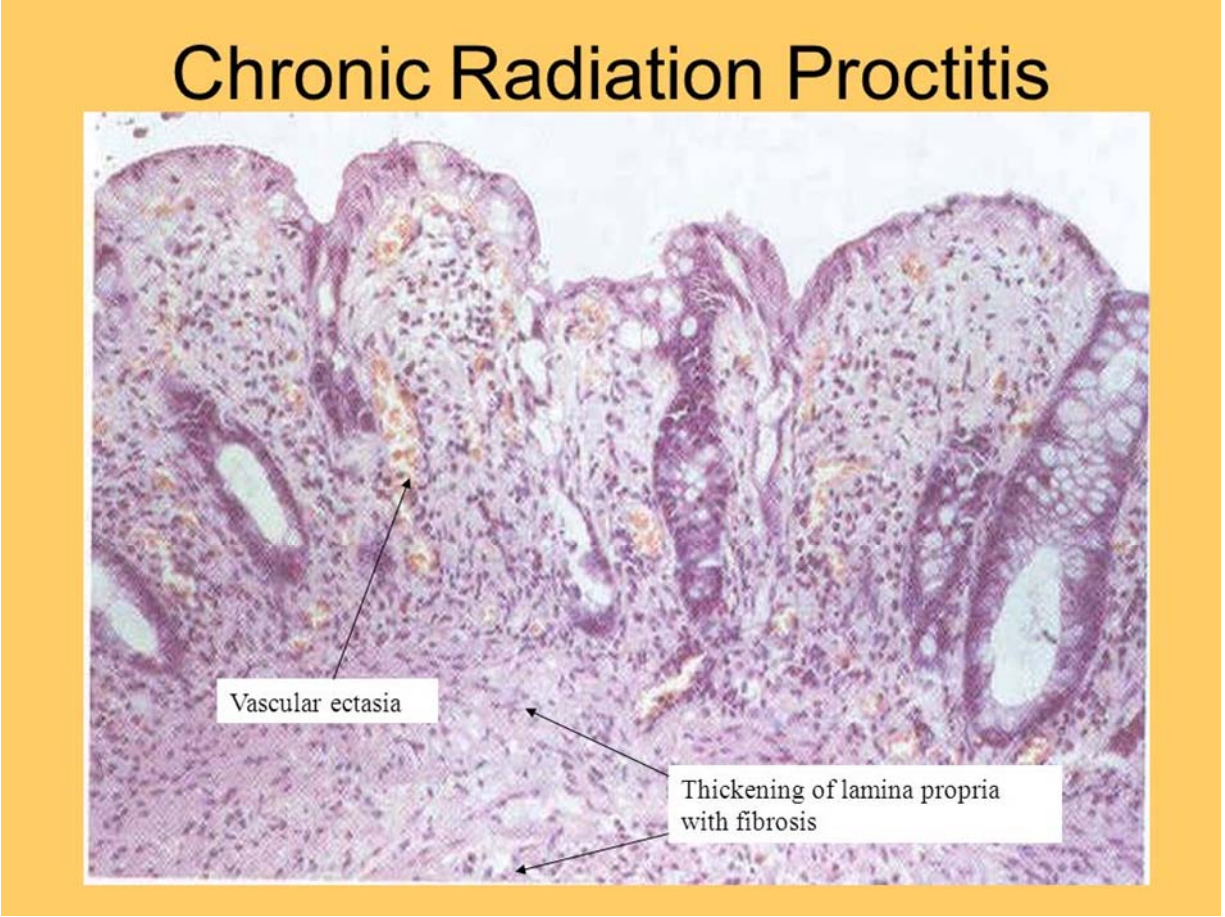
- If the submucosal damage is not prominent, the epithelial cells regenerate and the changes regress.
- Severe submucosal changes leads to progression of mucosal injury, ulcerations, and erosion of the villi.
- histologic findings in the acute phase correlate poorly with clinical symptoms.

Normal tissue effects and injury – **Acute effects** – LDR prostate brachytherapy – **rectal mucosa**

	Acute effects	symptoms	outcome	management
tal cosa	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

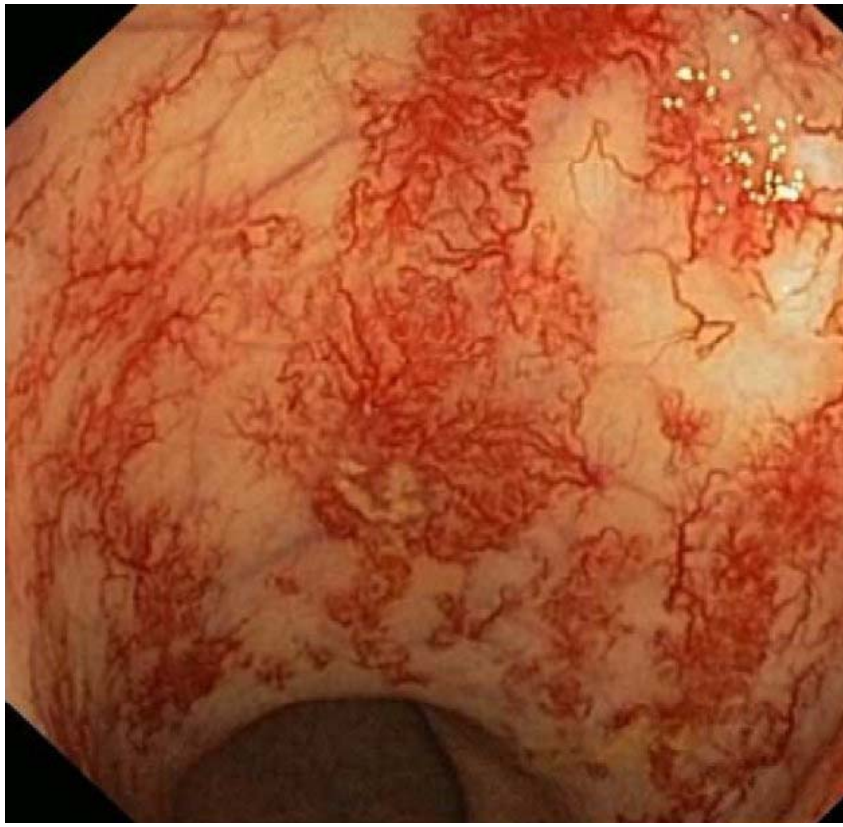
- Repopulation of the mucosal cells occurs in the later stage of the acute phase
- The severity of the damage to supportive connective tissue limits the degree of reepithelialization
- Fibrosis of the underlying connective tissue causes patchy ischemia of the mucosa, which may cause ulceration
- Local 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

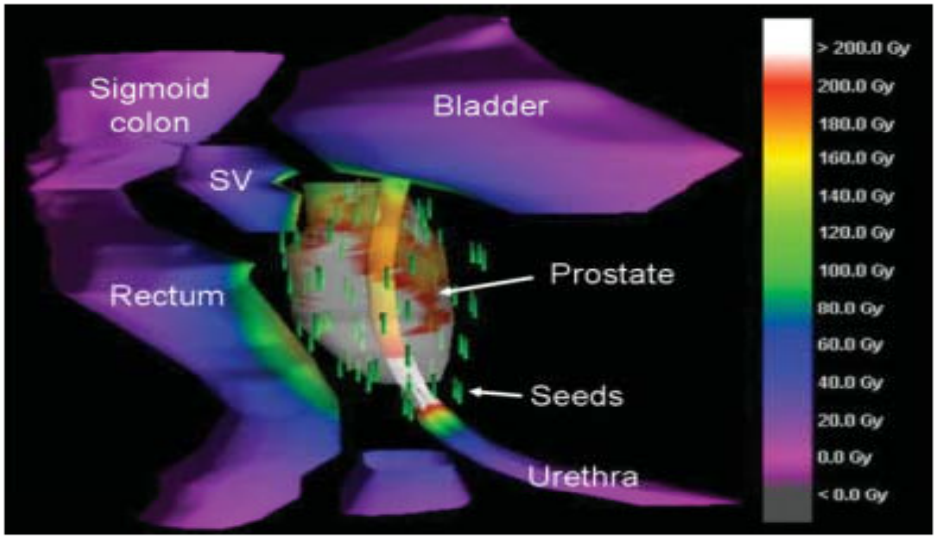
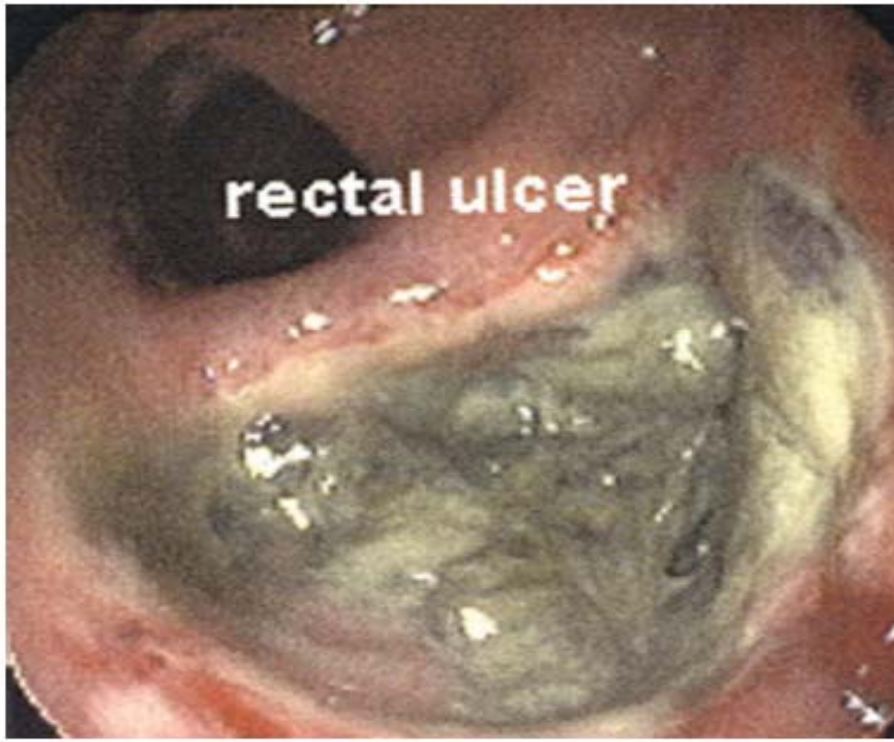


FIGURE 1. A typical 3-dimensional-rendered plan (lateral view) of a stranded seed implant. The close proximity of the anterior rectal makes it difficult to limit radiation dose to this area without compromising prostate dose coverage. Stranded seeds were used to maintain better seed spacing and alignment. SV indicates seminal vesicle; Gy, grays.



Cancer 2009;115:1827–39. © 2009 American Cancer

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.

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

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 3, pp. 817–824,

0360-3016/06/$–see front

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
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, 2

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, 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 ($p = 0.027$).

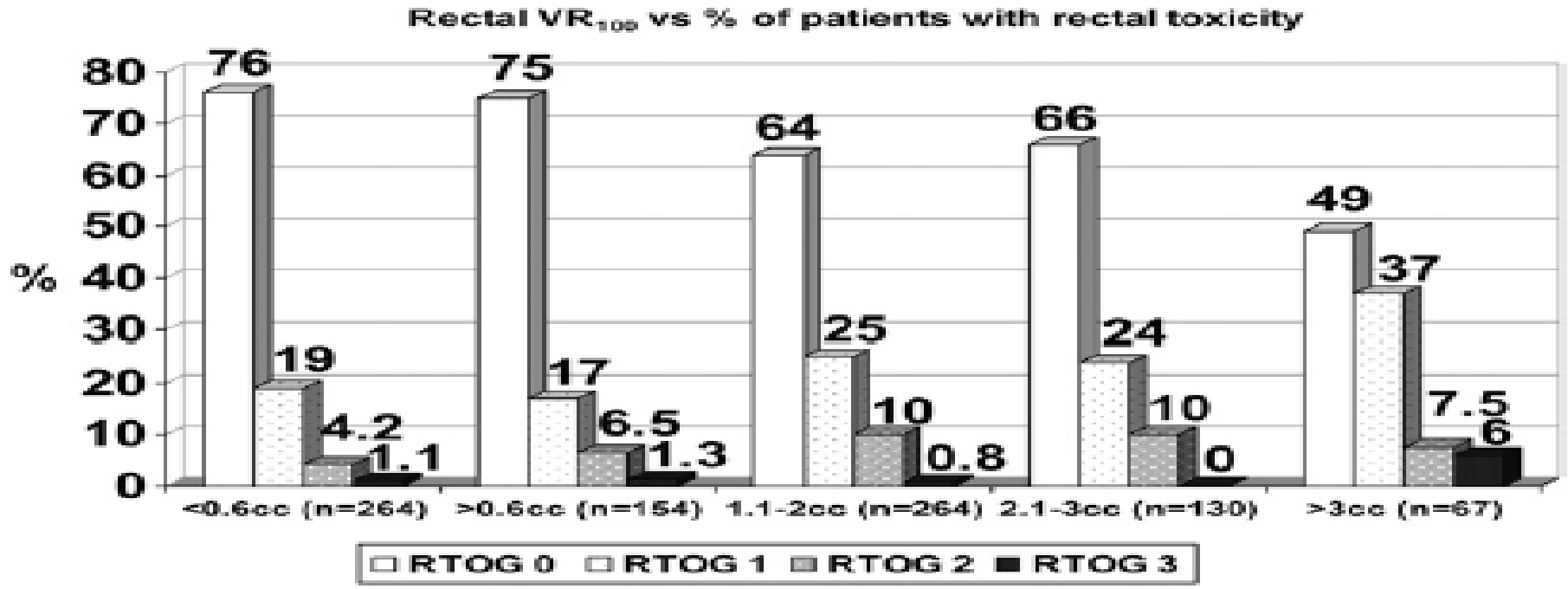
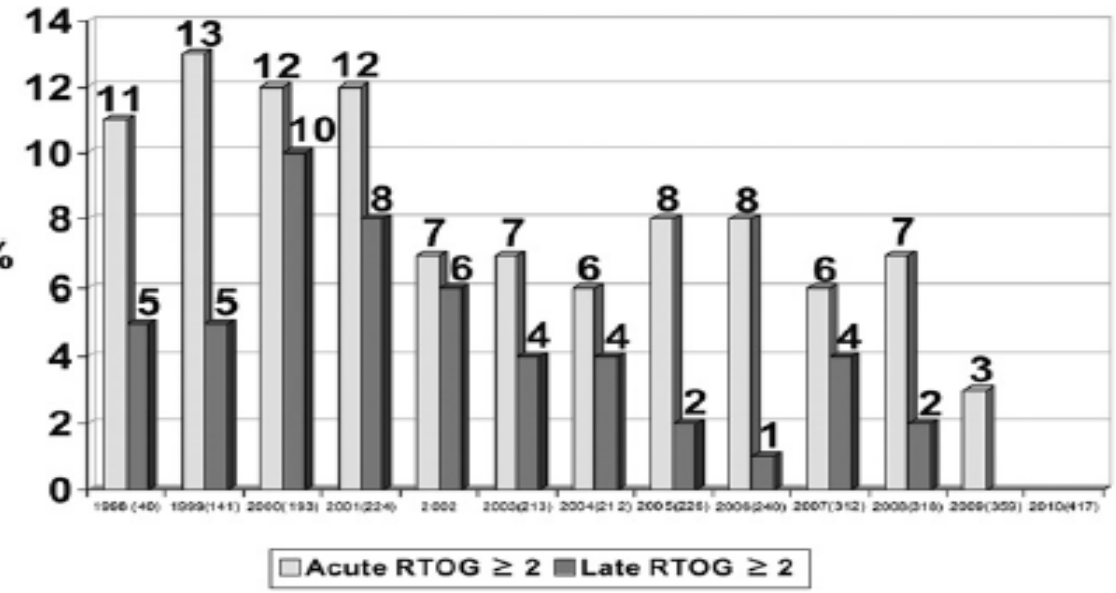


Fig. 1. Percentage of patients with late rectal toxicity by rectal V_{100cc}, patients with available toxicity data ($\geq$12 months followup) and available rectal dosimetry ($n = 879$). For each dose—volume histogram group, we gave number of patients and percentage of patients in the group with Radiation 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%.



g. 3. Institutional crude Radiation Therapy Oncology Group ≥2 acute
d late rectal toxicity, expressed as a percentage of patients wit
xicity recorded for each implant year 1998–2009.

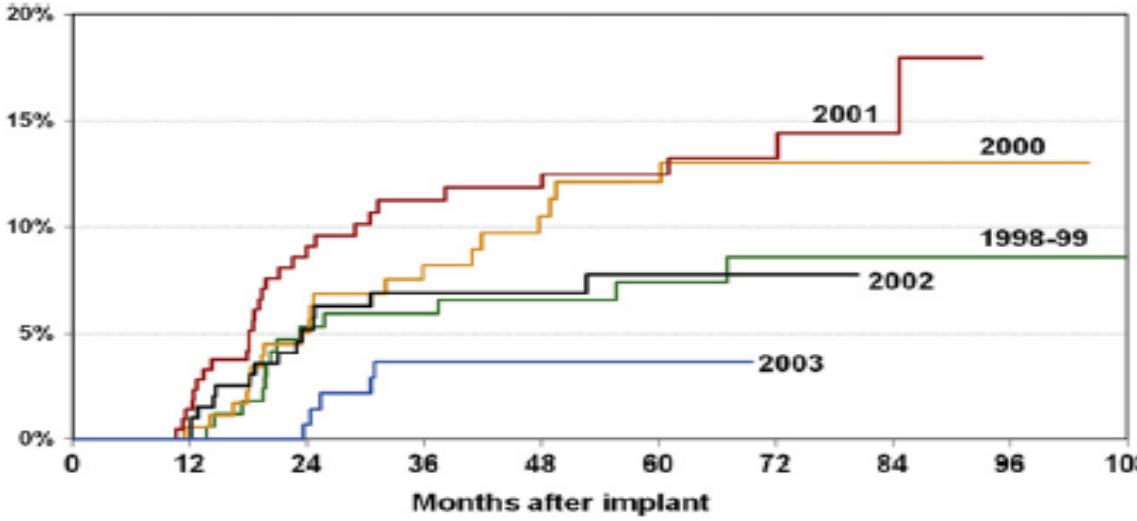
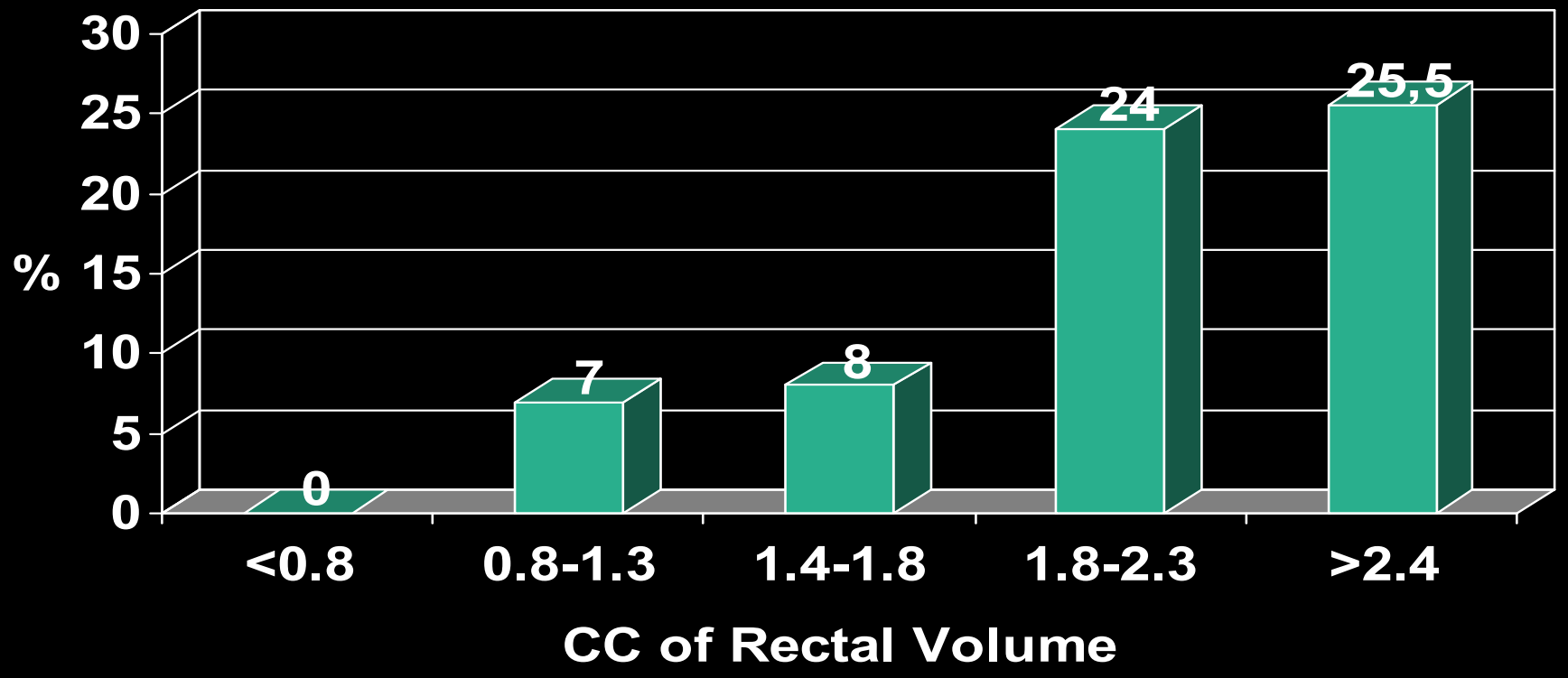


Fig. 2. Kaplan–Meier curves for late rectal Radiation Therapy Oncolog
Group ≥2, illustrating the institutional learning curve.

ctitis rate for rectal volume irradiated with 160Gy



[Snyder et al., Int J Radiat Oncol Biol Phys, 2001]

dose constraints - Rectum

J Radiat Res. 2012 Nov; 53(6): 923–929.
Published online 2012 Aug 1. doi: 10.1093/jrr/rrs059
PMCID: PMC3483856

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]

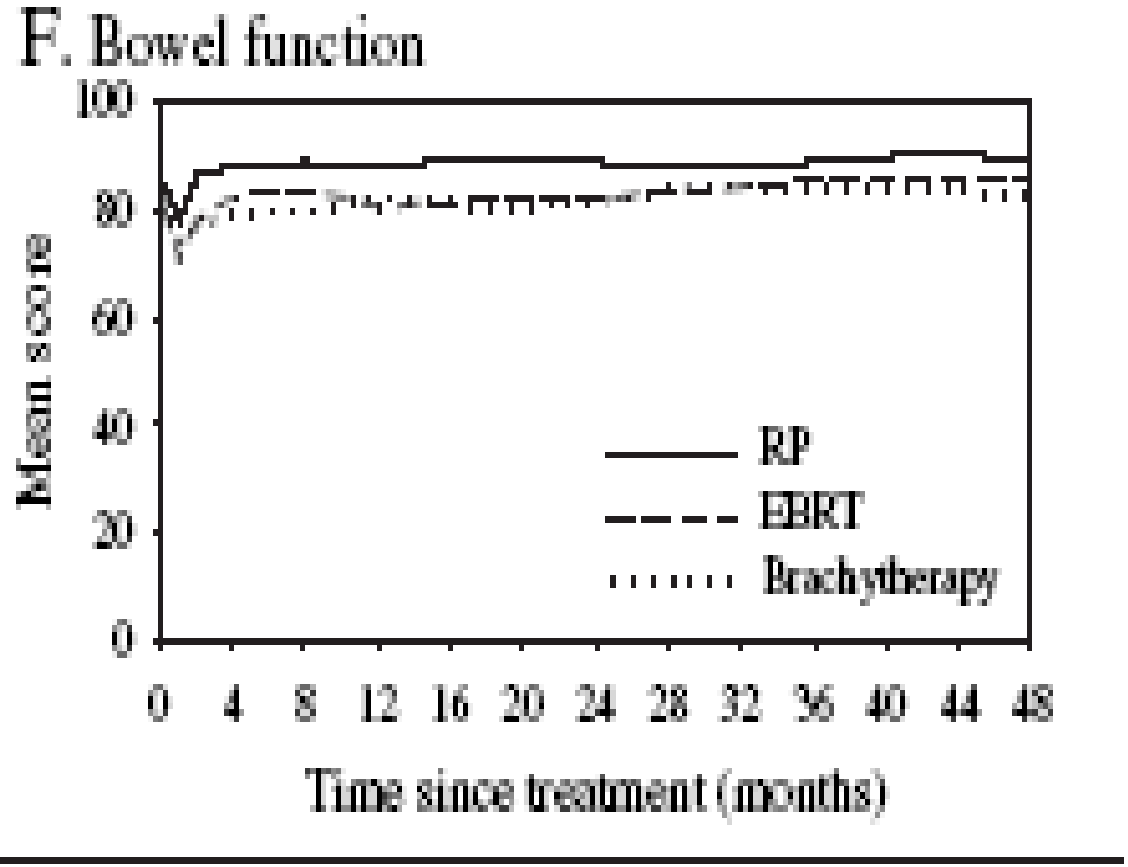
Rectum RV100 (145Gy)	Gr 1 bleed Median 20 months *p=0.02*	Grade 2 or higher
>1cm³	36%	0
<1cm³	14%	0

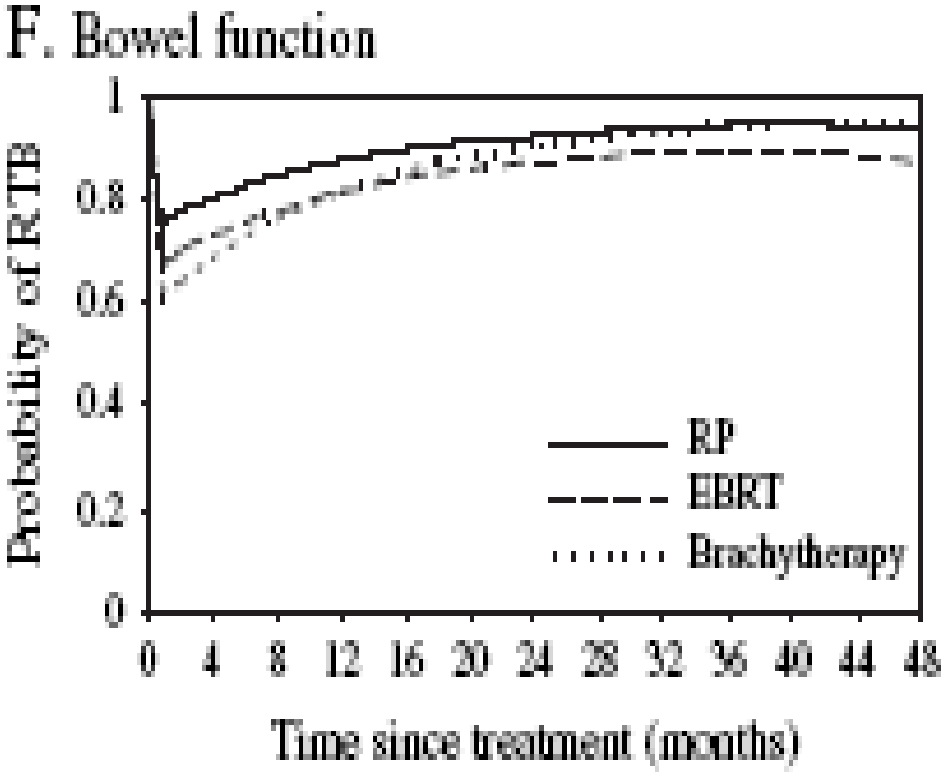
Caution! Dose constraint for 145Gy not 160Gy

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 RO/EAU/EORTC recommendations on prostate brachytherapy

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

ELSEVIER

Brachytherapy 11 (2012) 6–19

BRACHYTHERA

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, Gregory S. Merrick[6], Wayne M. Butler[6], Peter D. Grimm[7], Nelson N. Stone[8], Louis Potters, 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]

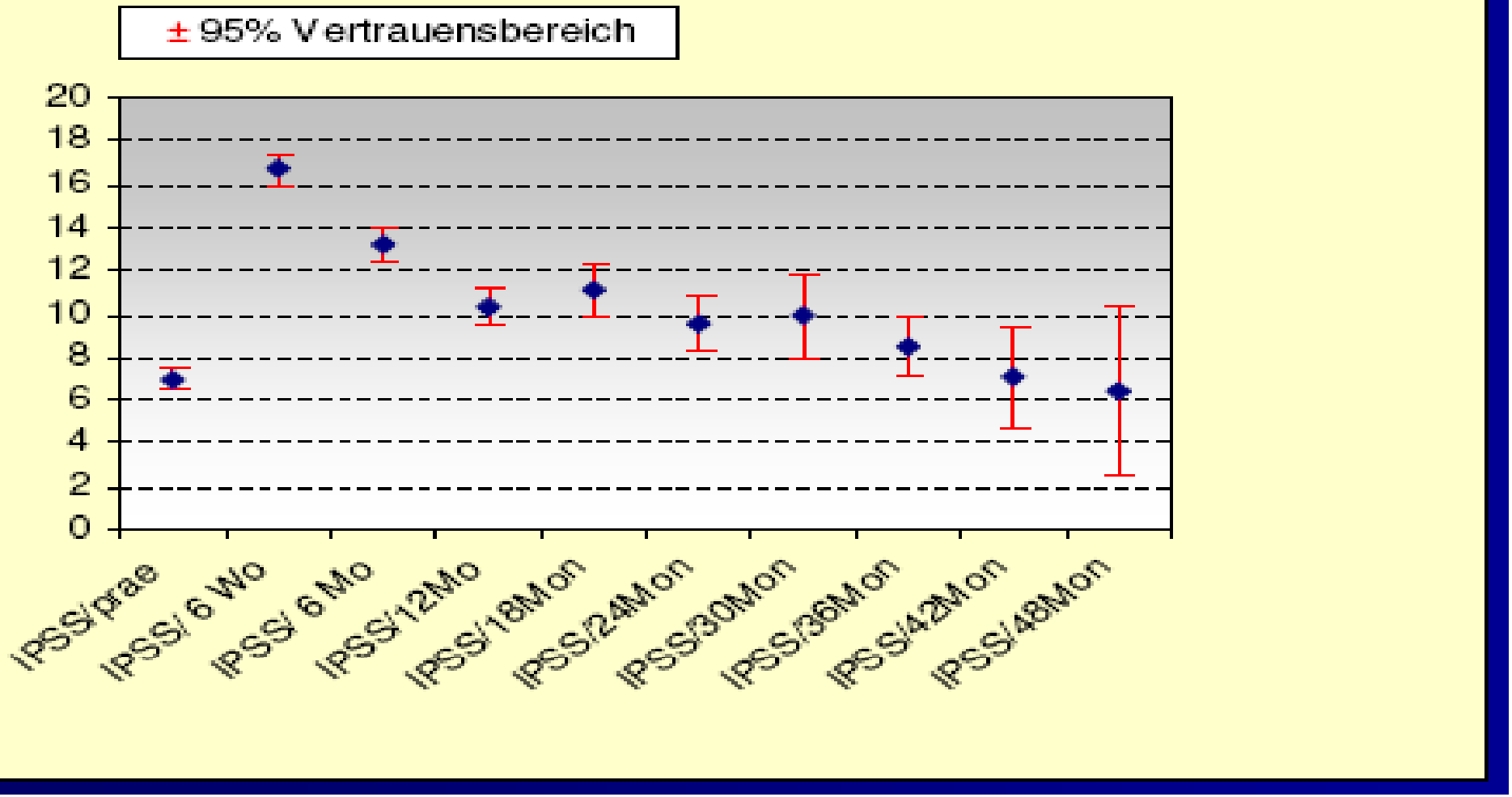
Normal tissue effects and injury – Acute effects
LDR prostate brachytherapy - urothelium

	Acute effects	symptoms	outcome	management
thelium	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
thelium	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*

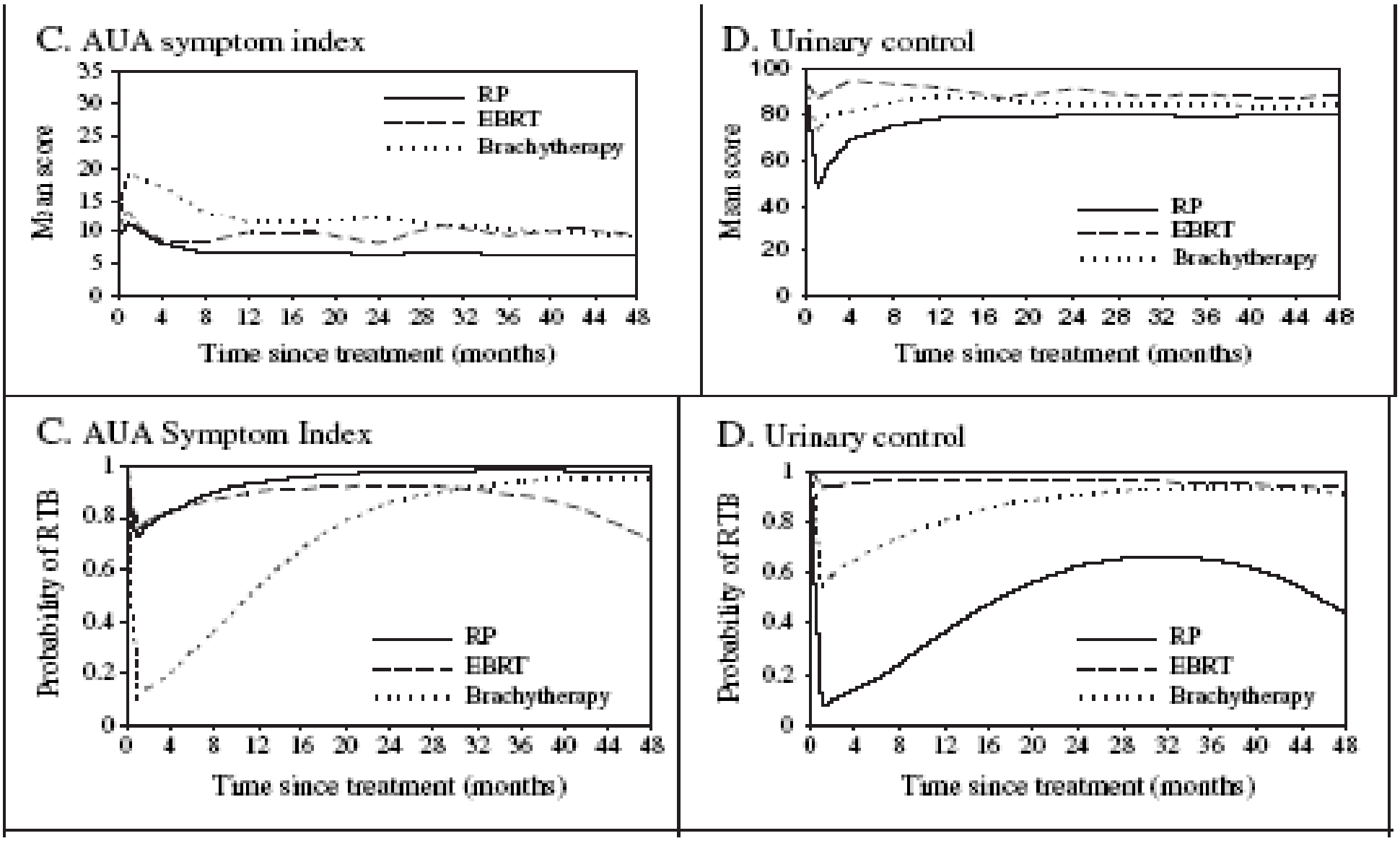
- **667 patients with a median follow-up of 31 months**

Table 2
ncontinence after treatment ($n = 667$)

ollow-up period	*n* (%)
re-treatment	9 (1.4%)
ost-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

J Natl Cancer Inst 2009;10

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

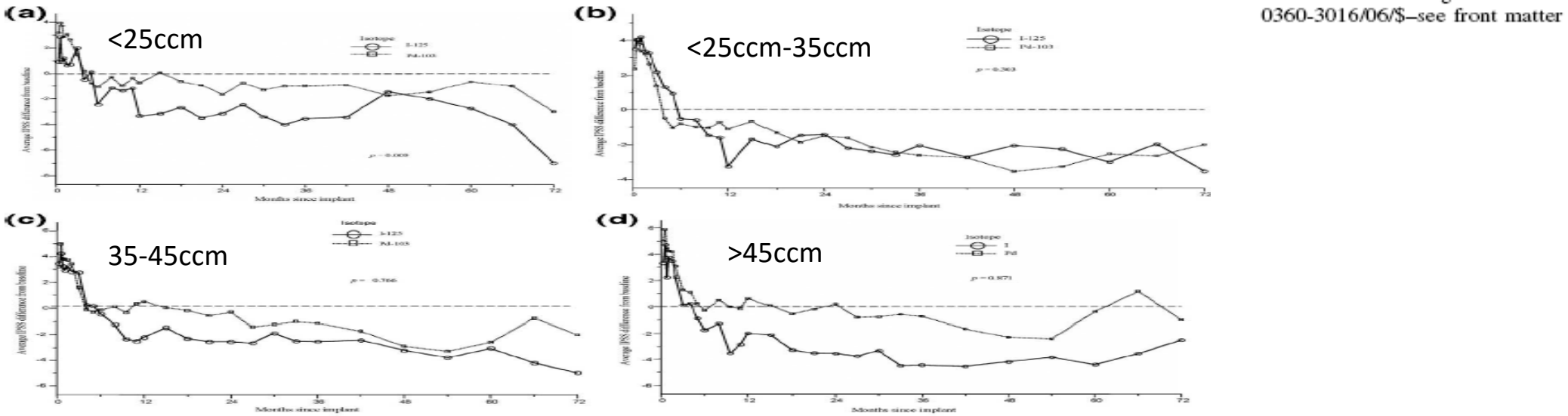
THE INFLUENCE OF ISOTOPE AND PROSTATE VOLUME ON URINARY MORBIDITY AFTER PROSTATE BRACHYTHERAPY

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

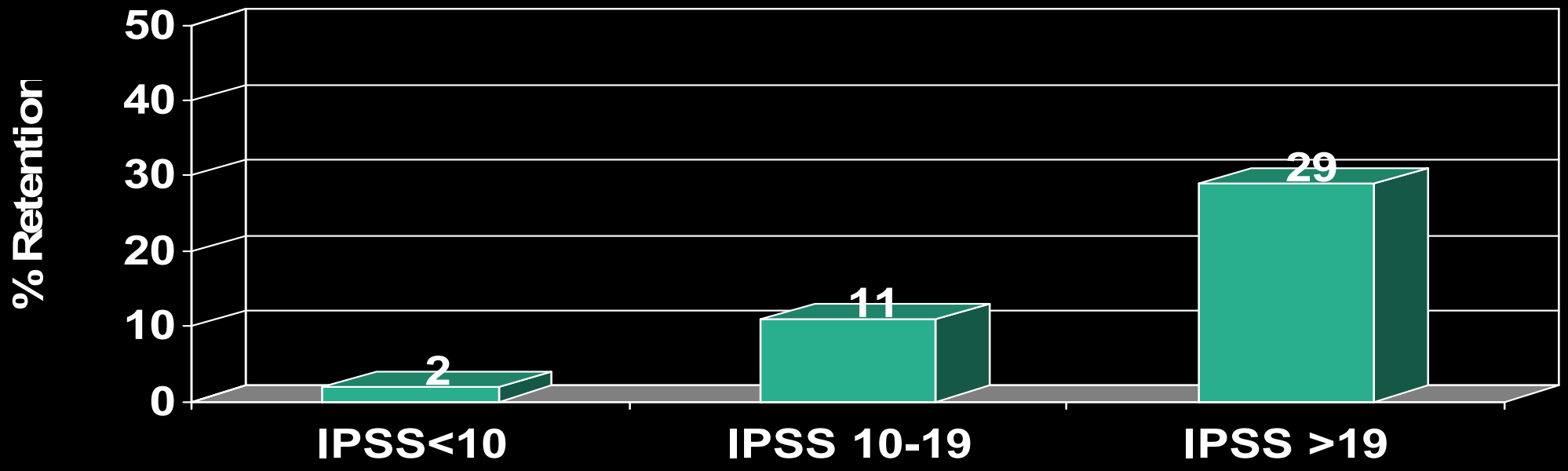
0360-3016/06/$–see front matter

76; median Follow-up: 41,2months



Conclusion: Higher acute retention (<5days), but equal resolution

dentification 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, 2

0360-3016/10/$–see front ma

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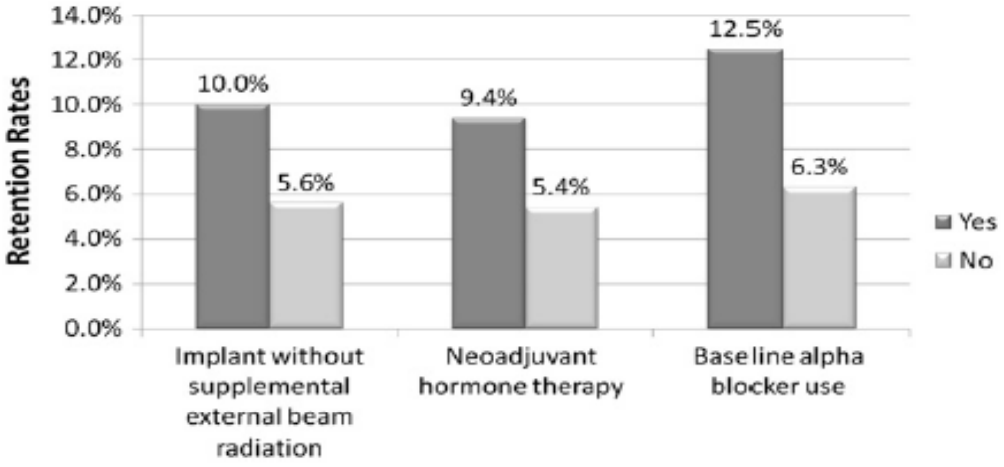
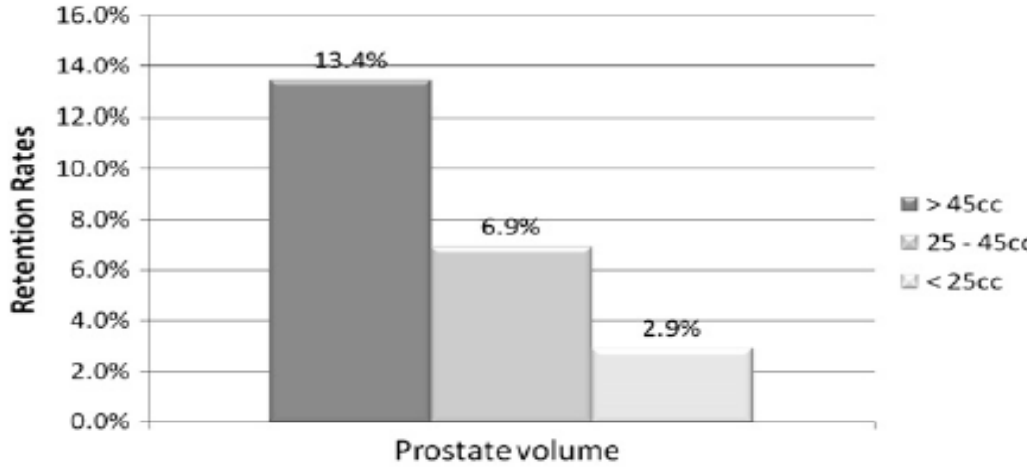
doi:10.1016/j.ijrobp.2009.04.008

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



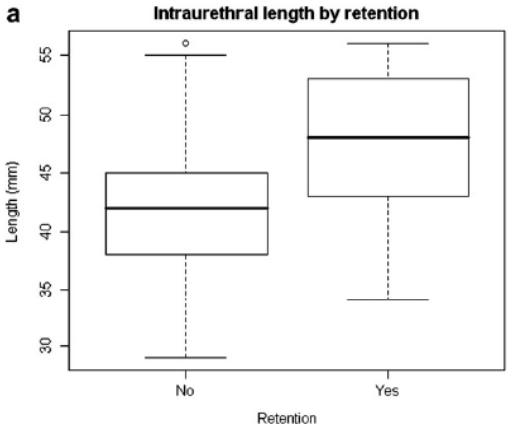


Prostatic length predicts functional outcomes after iodine-125 prostate brachytherapy

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]

[1]*Department of Urology, Northampton General Hospital, Cliftonville, Northampton, UK*
[2]*Department of Medical Physics, Northampton General Hospital, Cliftonville, Northampton, UK*
[3]*Department of Oncology, Northampton General Hospital, Cliftonville, Northampton, UK*

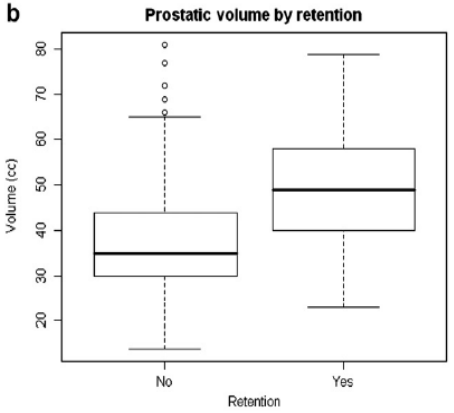
a



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

ods and Materials: From July 2002 to January 2013, 927 patients with prostate
er (median age, 66 years) underwent LDR brachytherapy with Iodine 125
753) or Palladium 103 (n=174) as definitive treatment (n=478) and as a boost
449) followed by supplemental EBRT (median dose, 50.4 Gy). Structures contoured

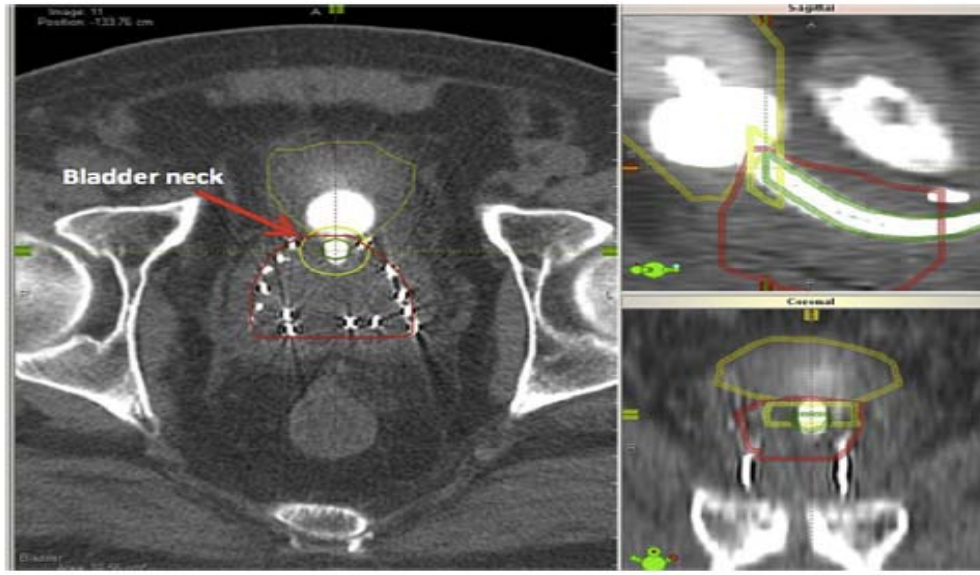


Fig. 1. Contour of bladder neck on computed tomographic scan on day 0 after impl

linical 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

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

epartments of *Radiation Oncology and †Medical Physics, Memorial Sloan Kettering Cancer Center, ew York, New York

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

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

able 3 Receiver operator curve analysis for acute and late rinary toxicity

Variable	Area under the curve	*P* value	(95% CI)
cute 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
ate 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.

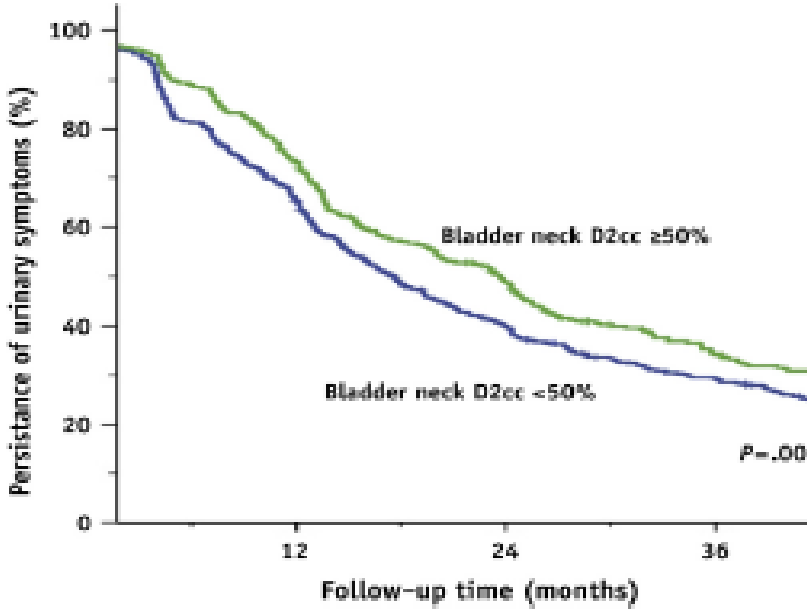


Fig. 2. Kaplan-Meier survival curves: time to Int tional Prostate Symptom Scores resolution according t bladder neck D2cc dose.

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 5, pp. 1445–1449, 2

0360-3016/10/$–see front ma

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doi:10.1016/j.ijrobp.2009.04.008

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%

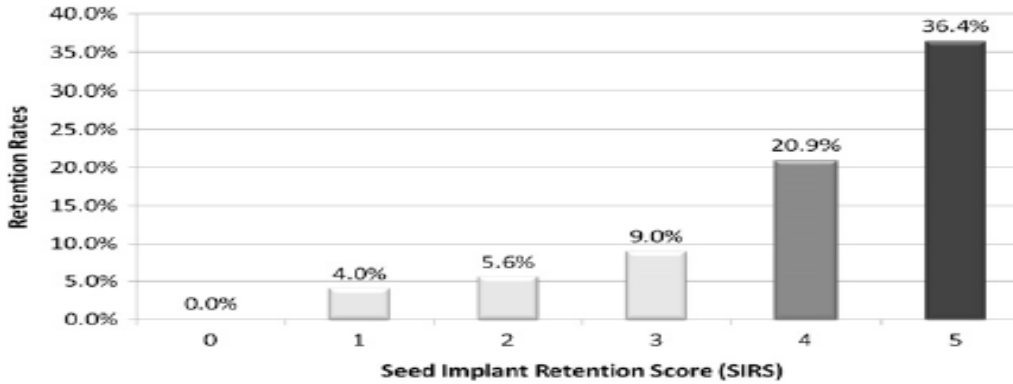

Fig. 3. Seed implant retention score and retention.

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 1, pp. 76–84, 2011

0360-3016/$–see front matter

ELSEVIER

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*

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 patients 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

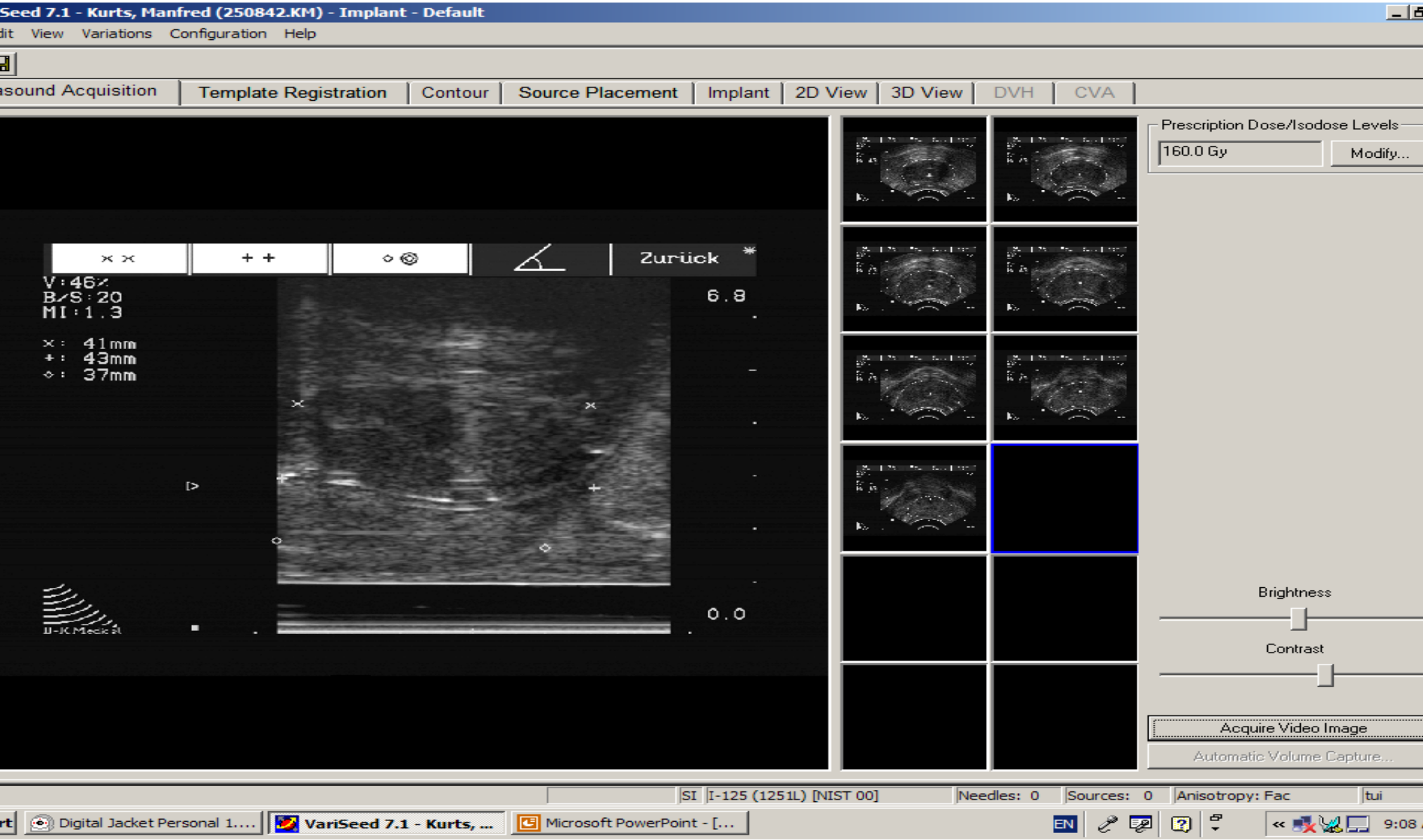
One-step customized transurethral resection of the prostate and permanent implant brachytherapy for selected prostate cancer patients: Technically feasible but too toxic

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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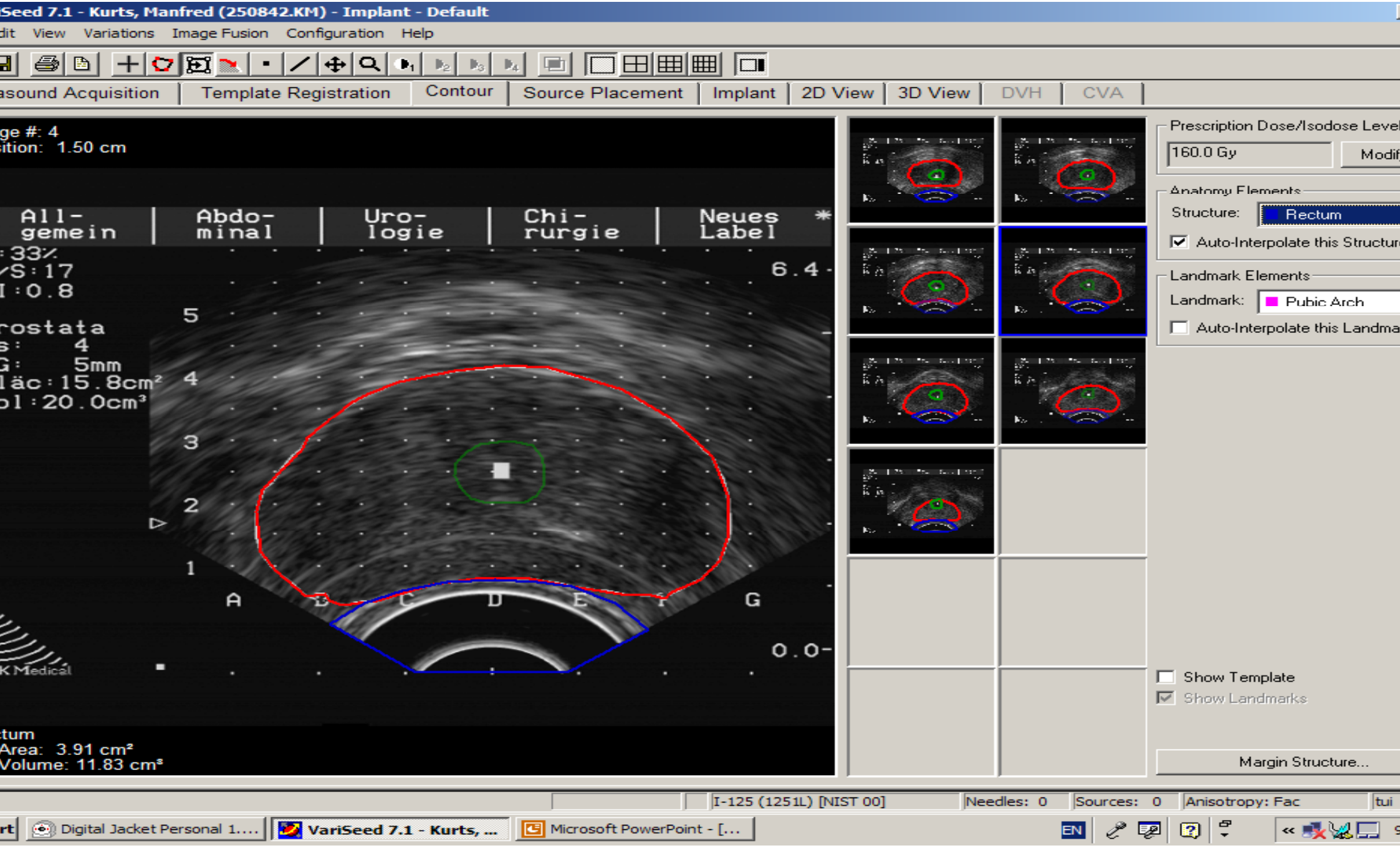
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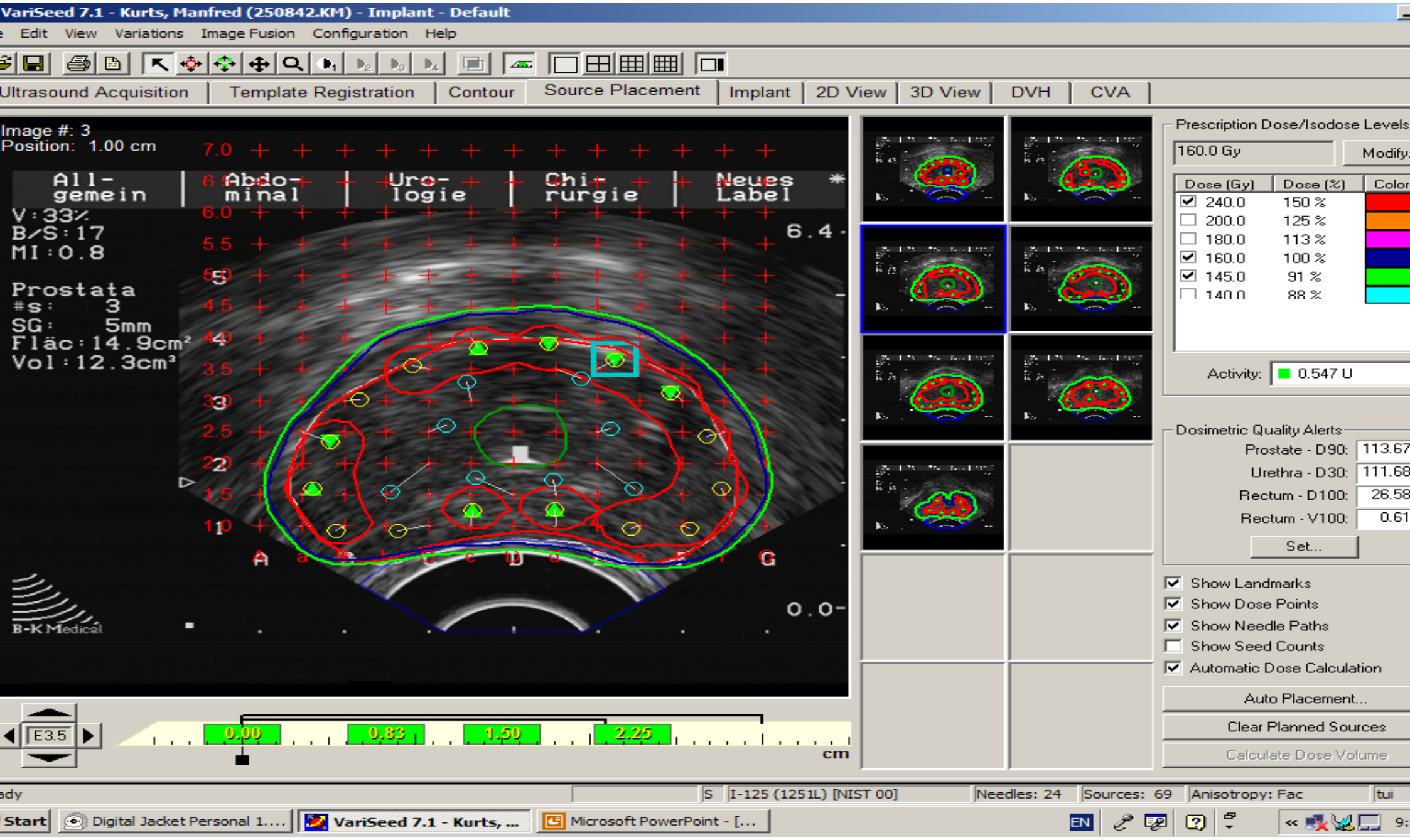
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ESTRO and ABS dose constraints - Urethra

urethra	GEC-ESTRO	ABS
uV5		<150%
uV10	<150%	
uV30	<130%	<125%

Urethral volume getting 30% of the dose (uV30)<125-130% of prescription

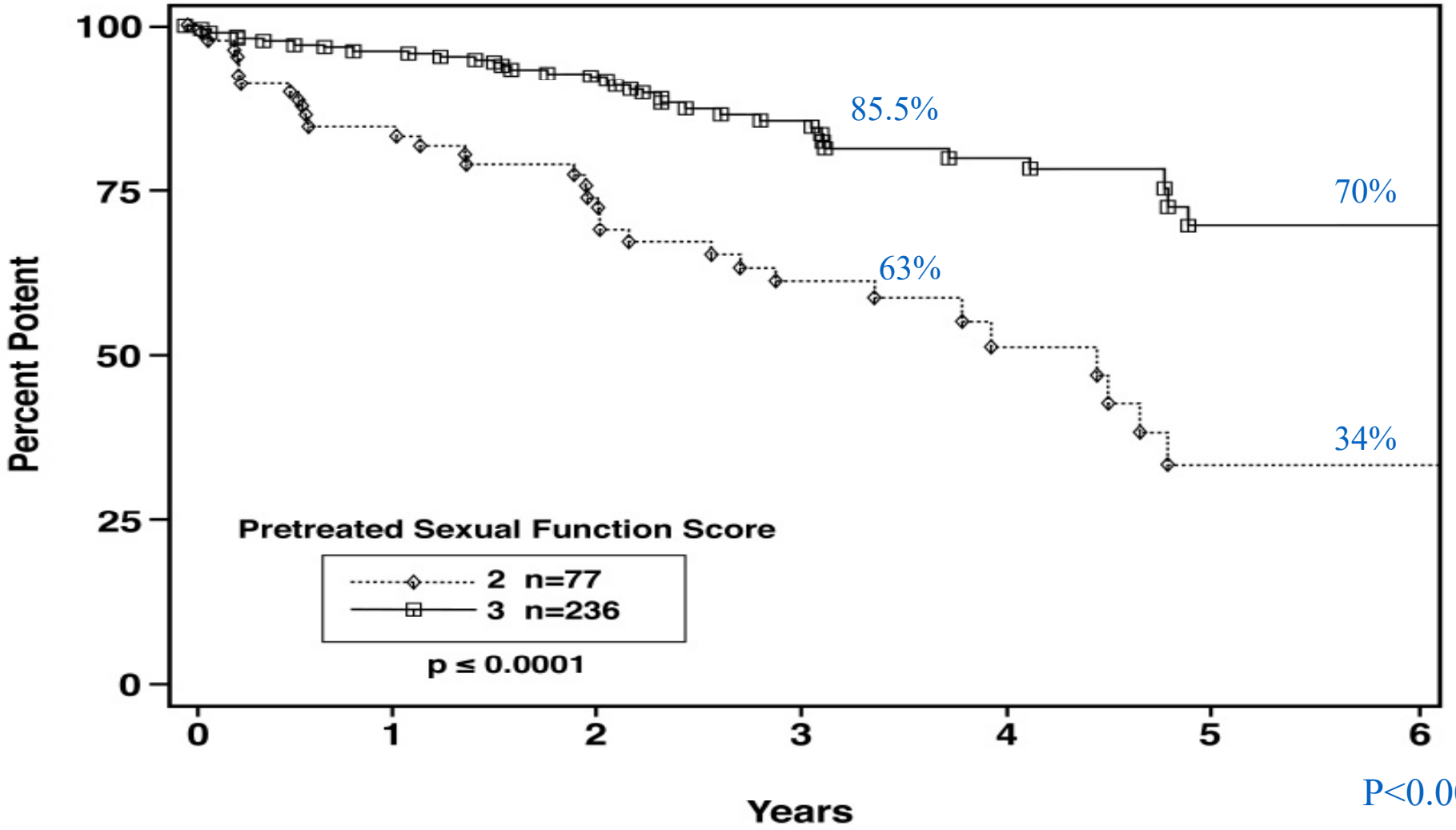
Urethral volume getting 10% of the dose (uV10) <150% of prescription

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)



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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.**

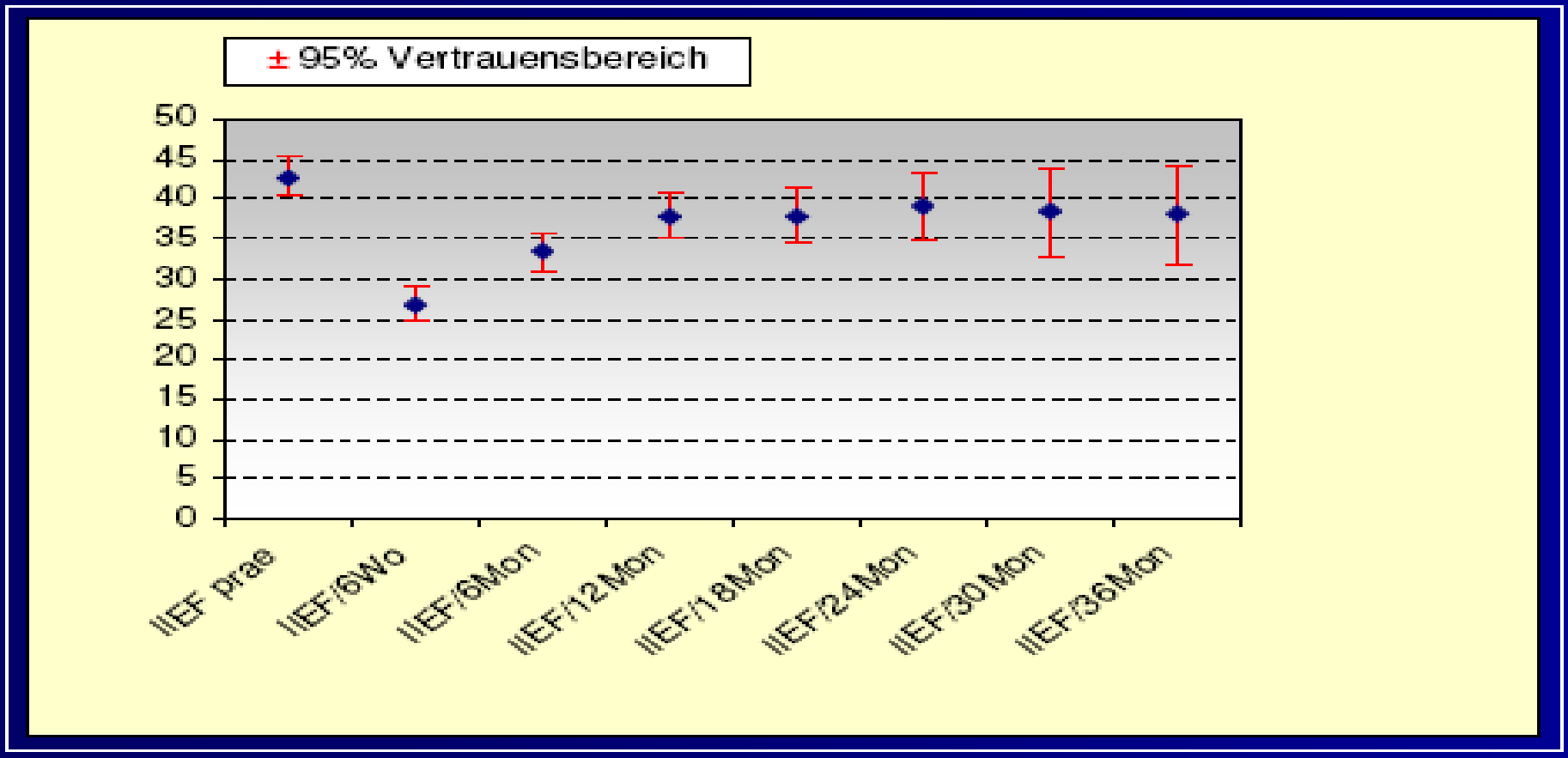
Table 4
Sexual function of 521 patients prior and after treatment

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%)

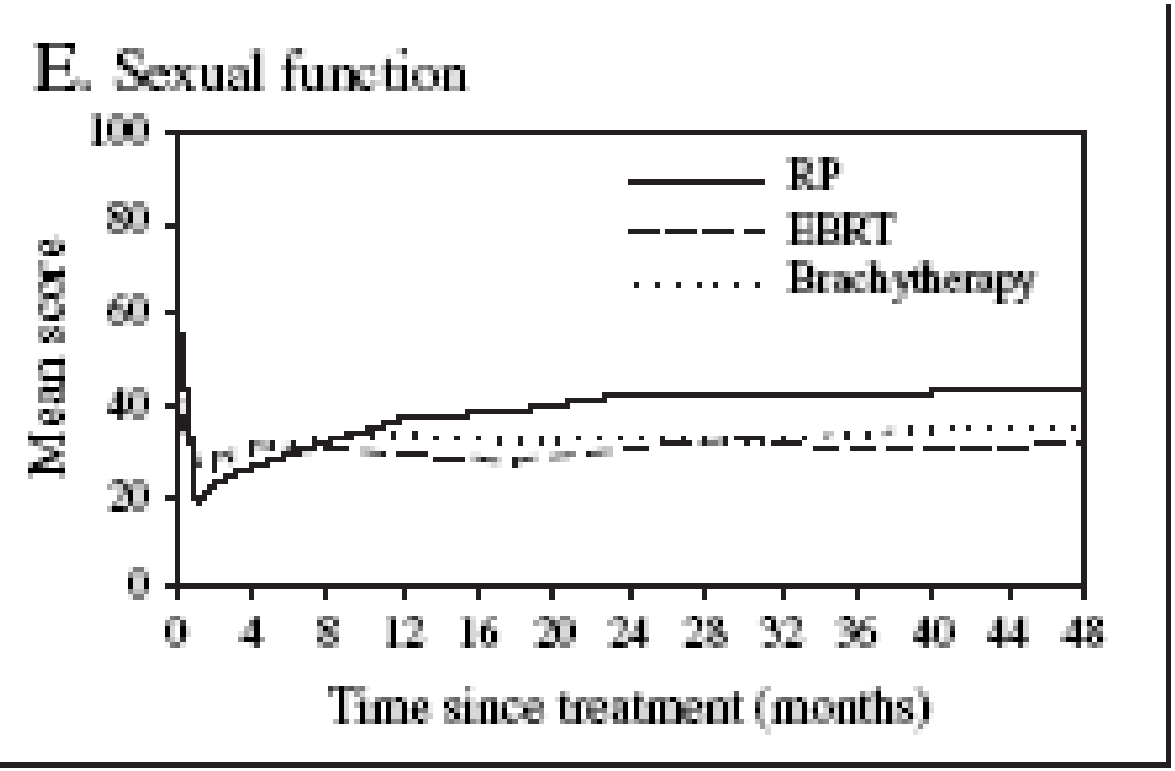
IIEF (International Index of Erectile Function) im Zeitverlauf

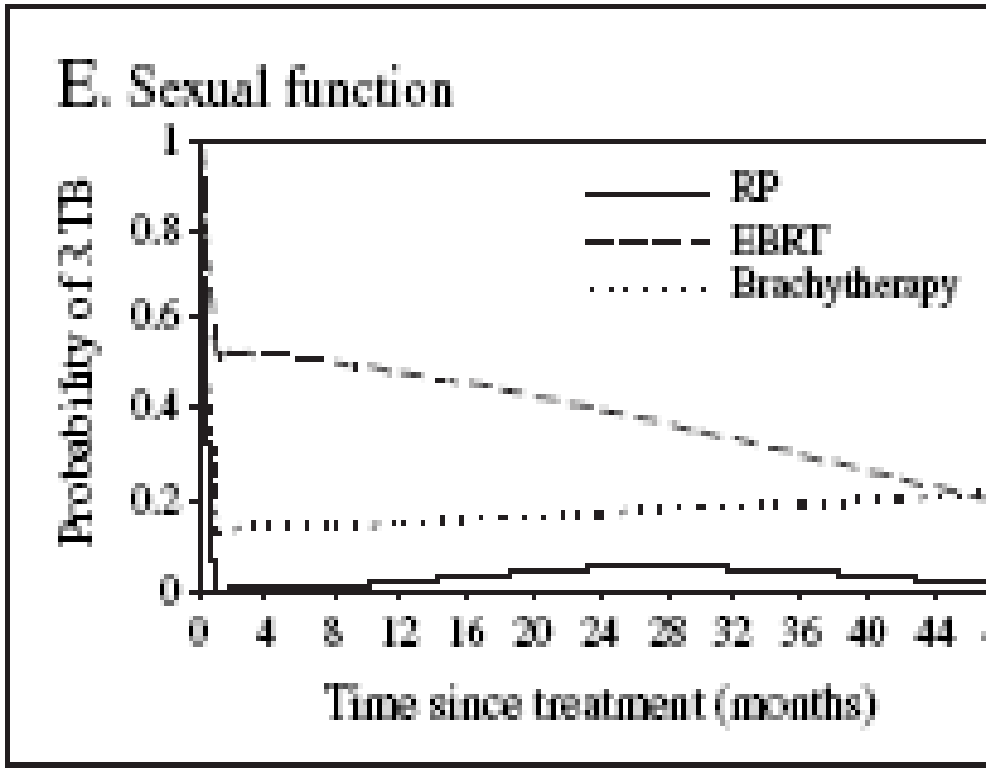


Survivorship Beyond Convalescence: 48-Month Quality-of-Life Outcomes After Treatment for Localized Prostate Cancer

J Natl Cancer Inst 2009;101:888–8

John L. Gore, Lorna Kwan, Steve P. Lee, Robert E. Reiter, Mark S. Litwin





Second 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

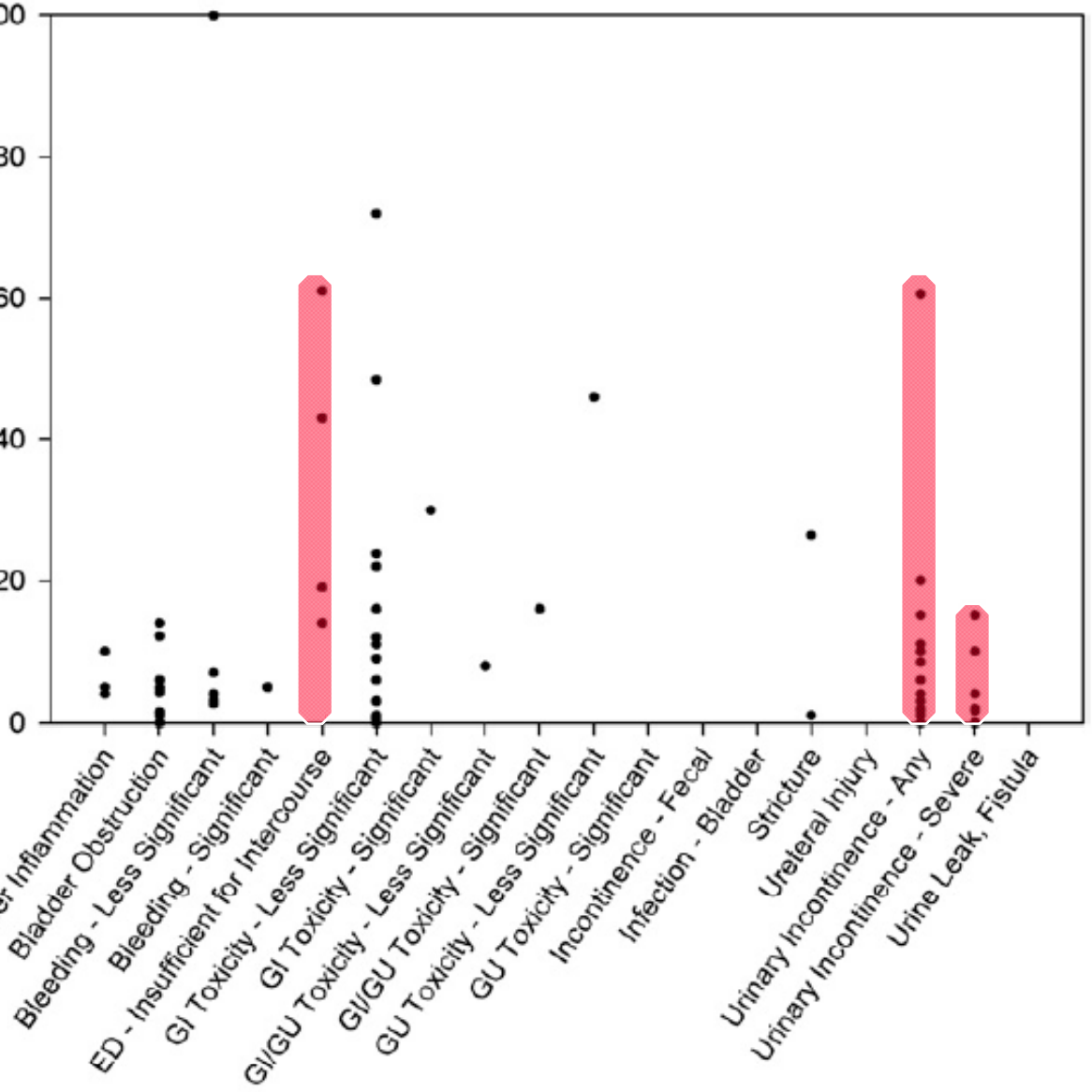
CaP conveys increased risk of developing second malignancy regardless of treatment

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.



3. Rate of complications reported with interstitial prostate nytherapy.*

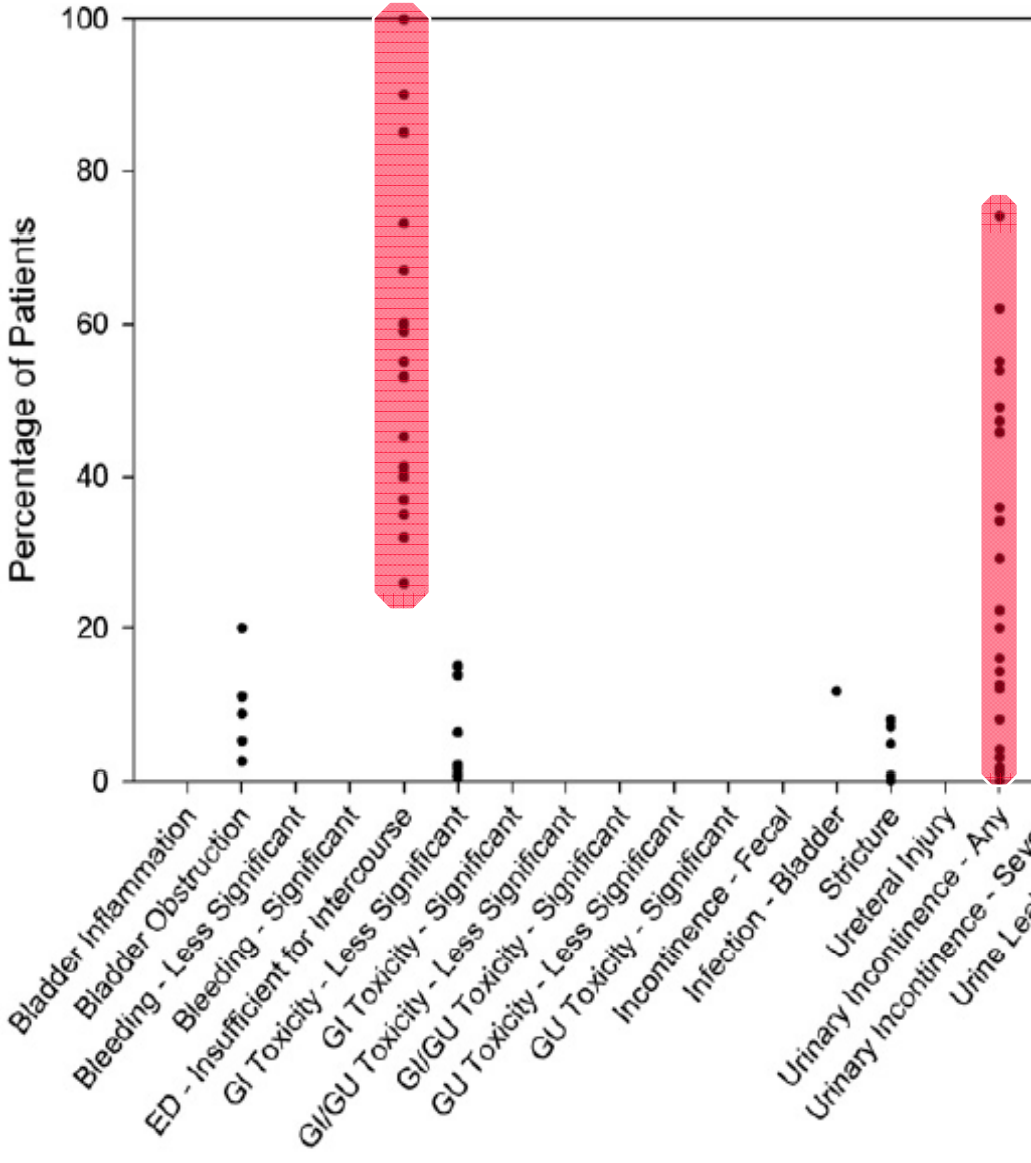
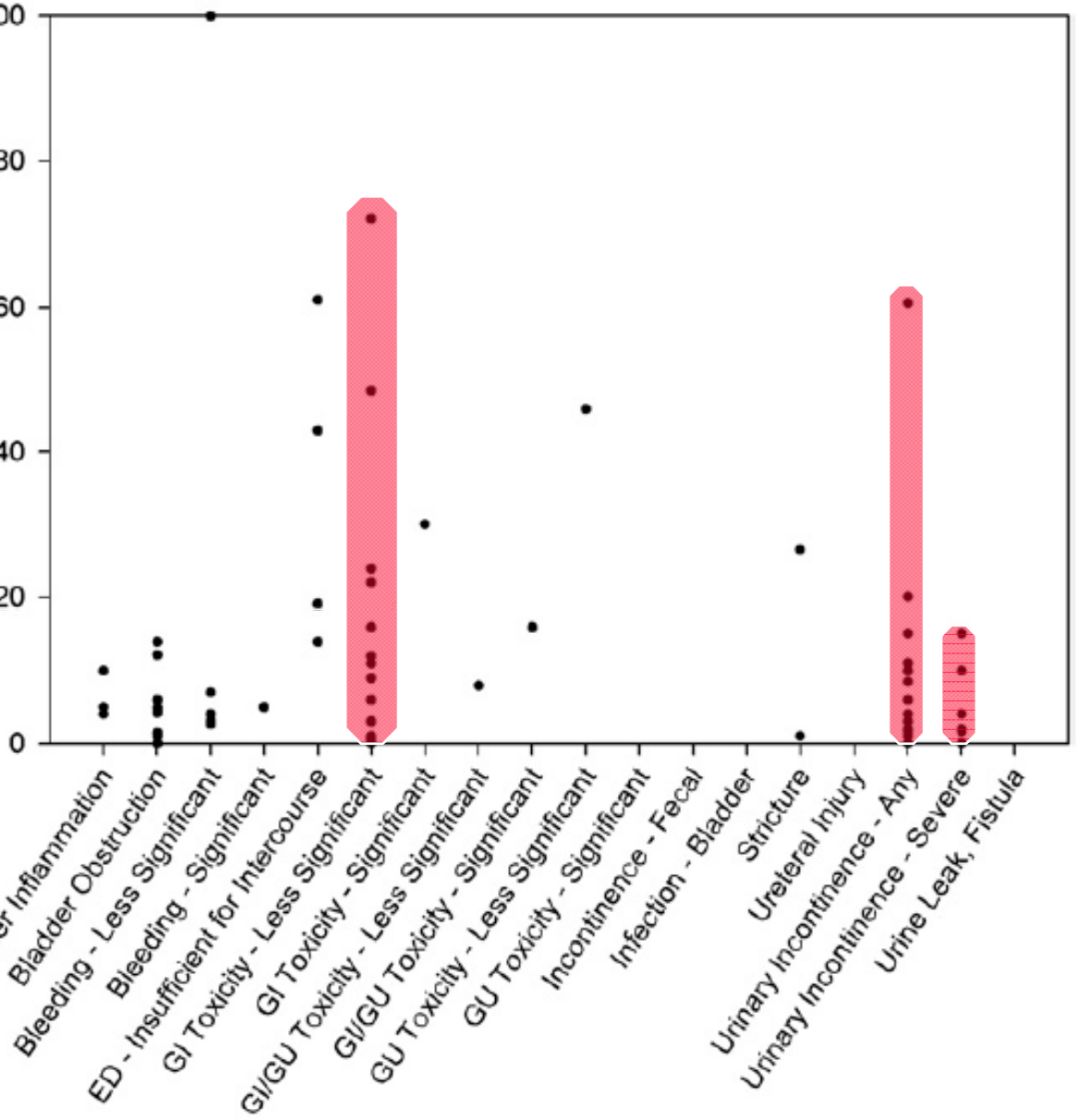


FIG. 5. Rate of complications reported with radical p tomy.*



3. Rate of complications reported with interstitial prostate
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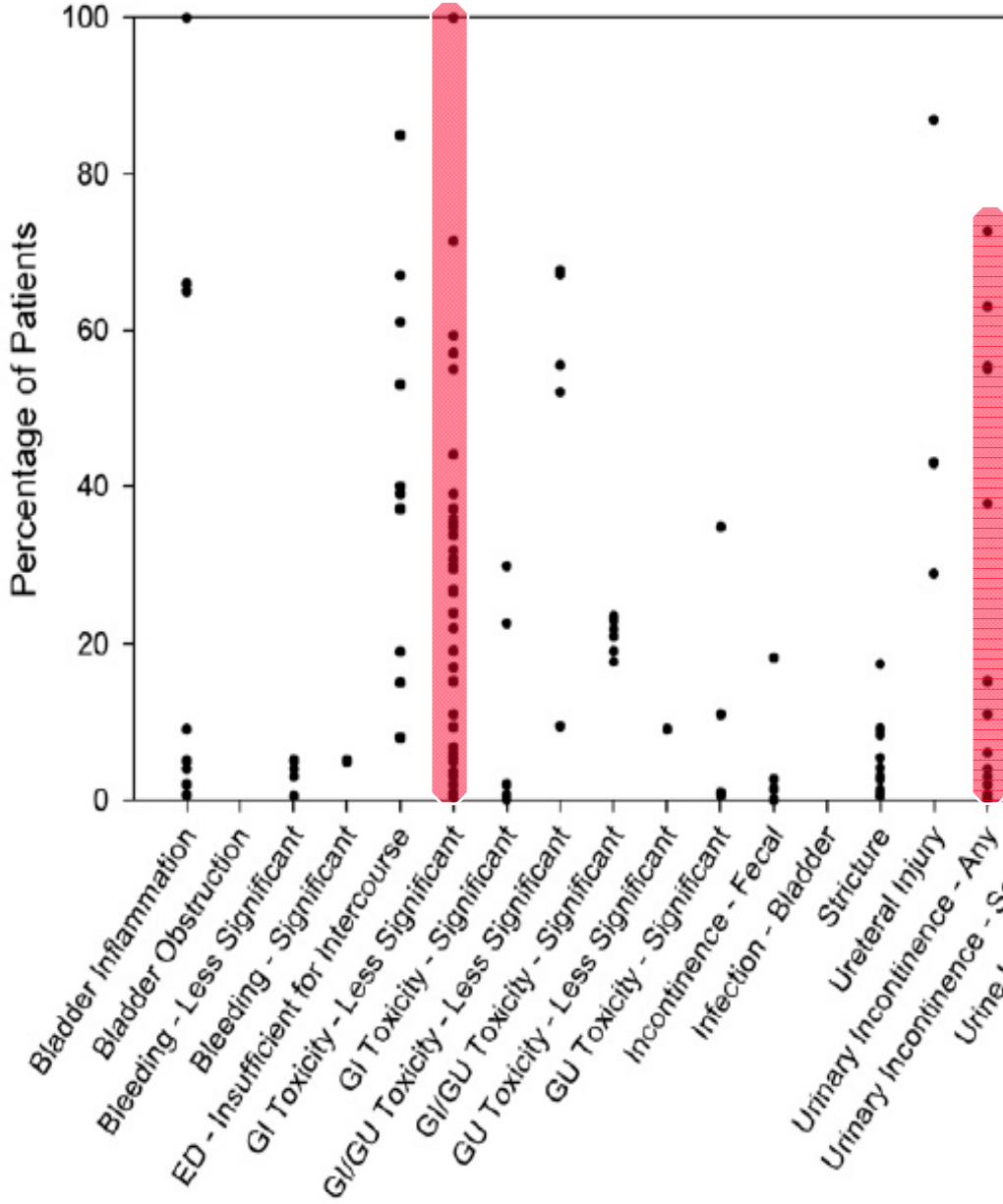


FIG. 4. Rate of complications reported with external bea
therapy.*

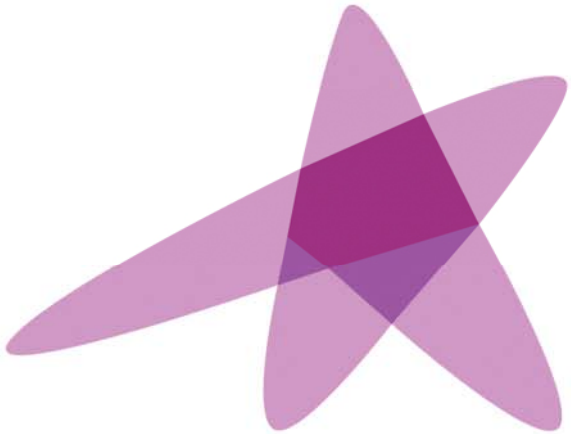
ummary

- 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



ESTRO School

WWW.ESTRO.ORG/SCHOOL

Management of toxicity and complications

S. Machtens

Director of the

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Academic Teaching Hospital

Marien-Hospital Bergisch Gladbach

Teaching Course Brussels 05.-07.06.2016

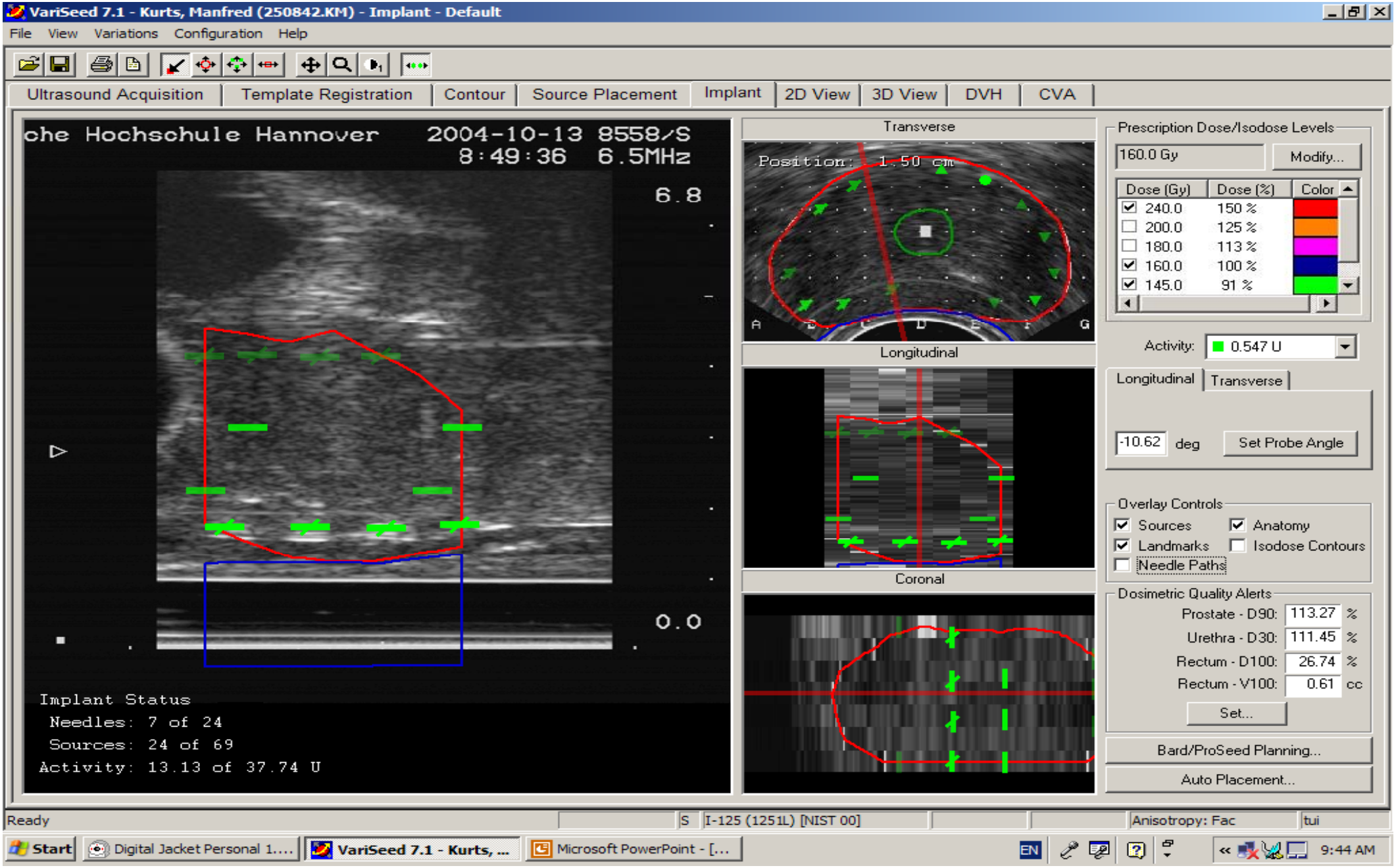
ESTRO School

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]

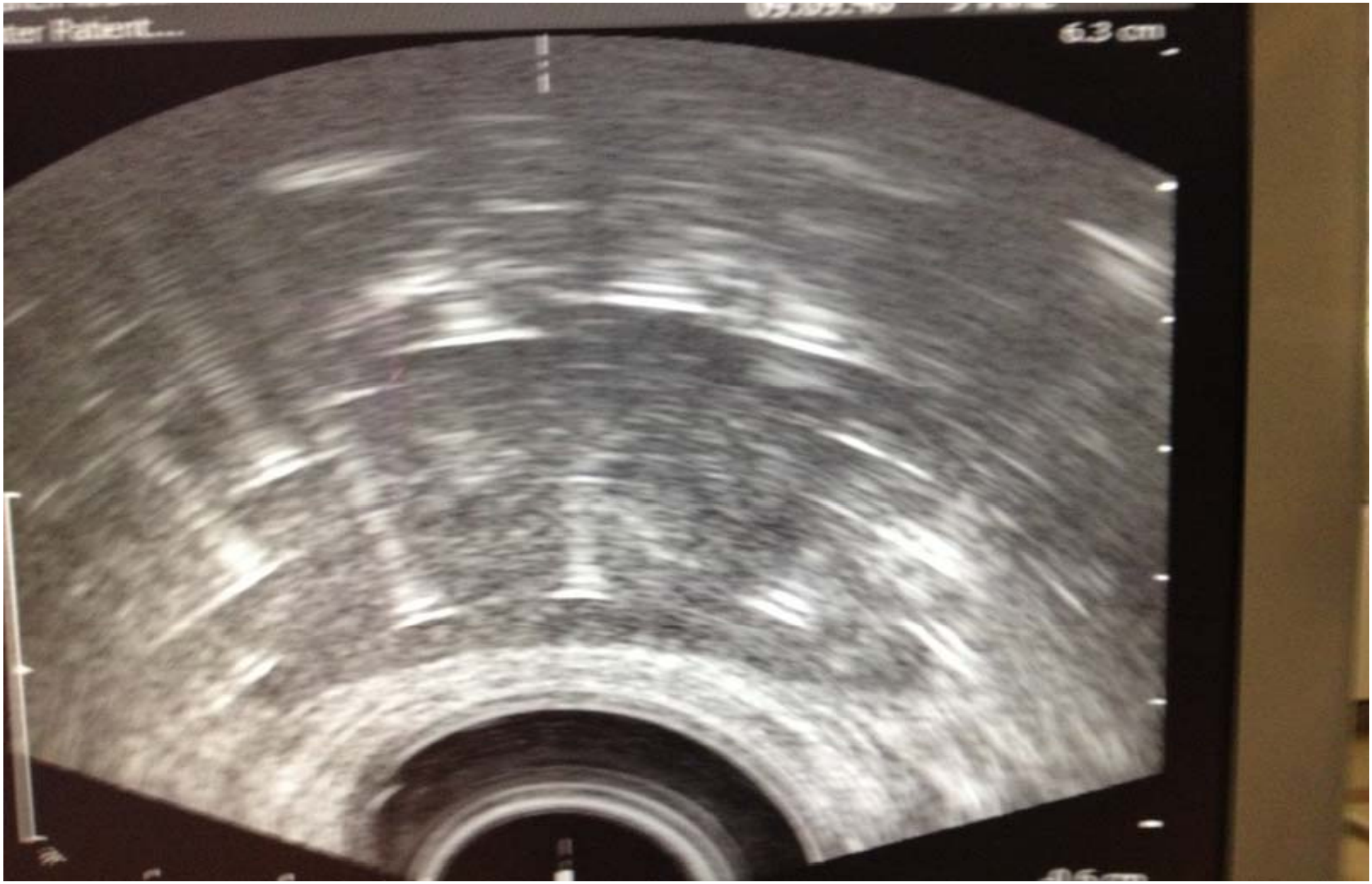
Reduction of rectal morbidity

- **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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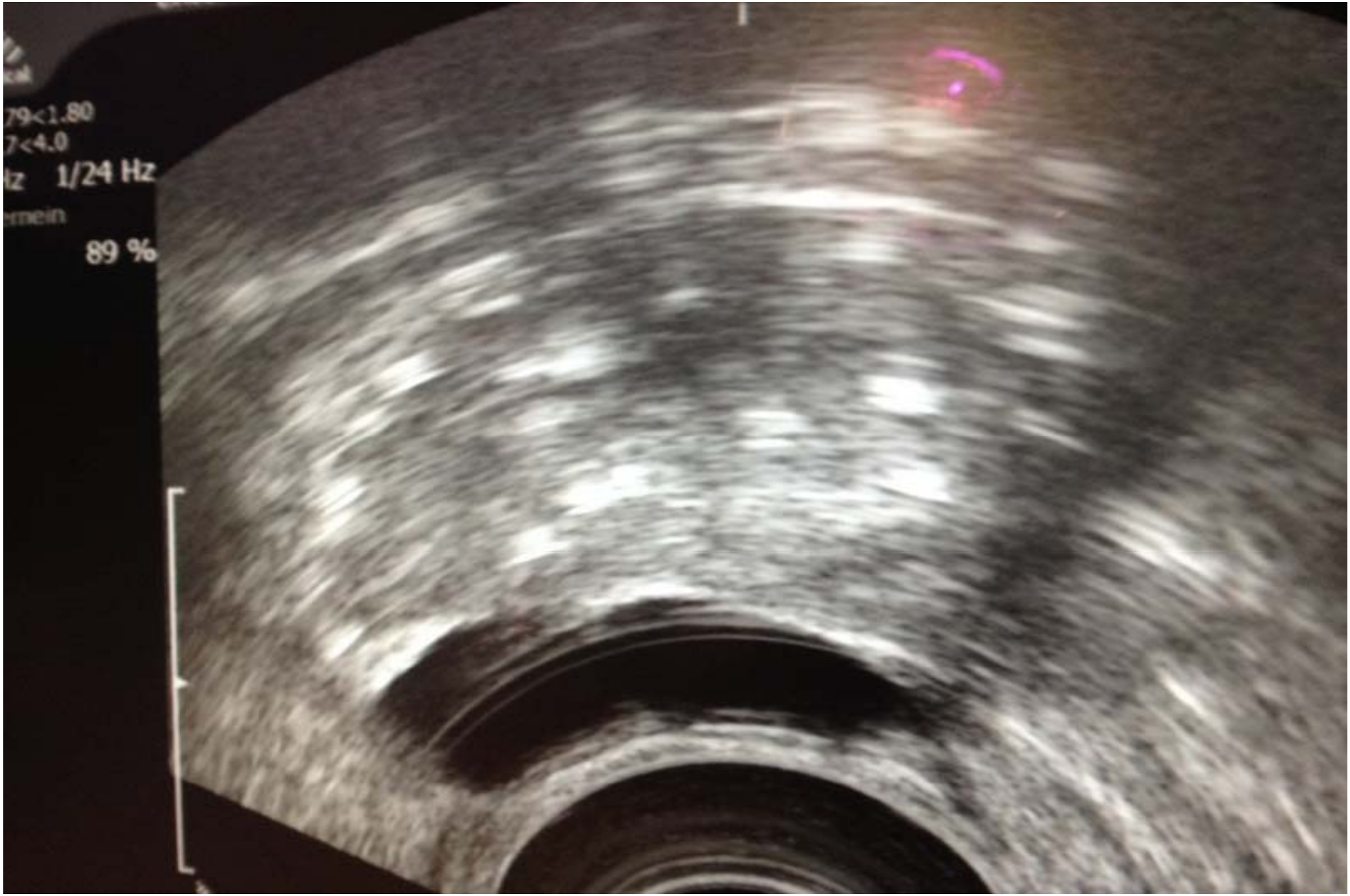
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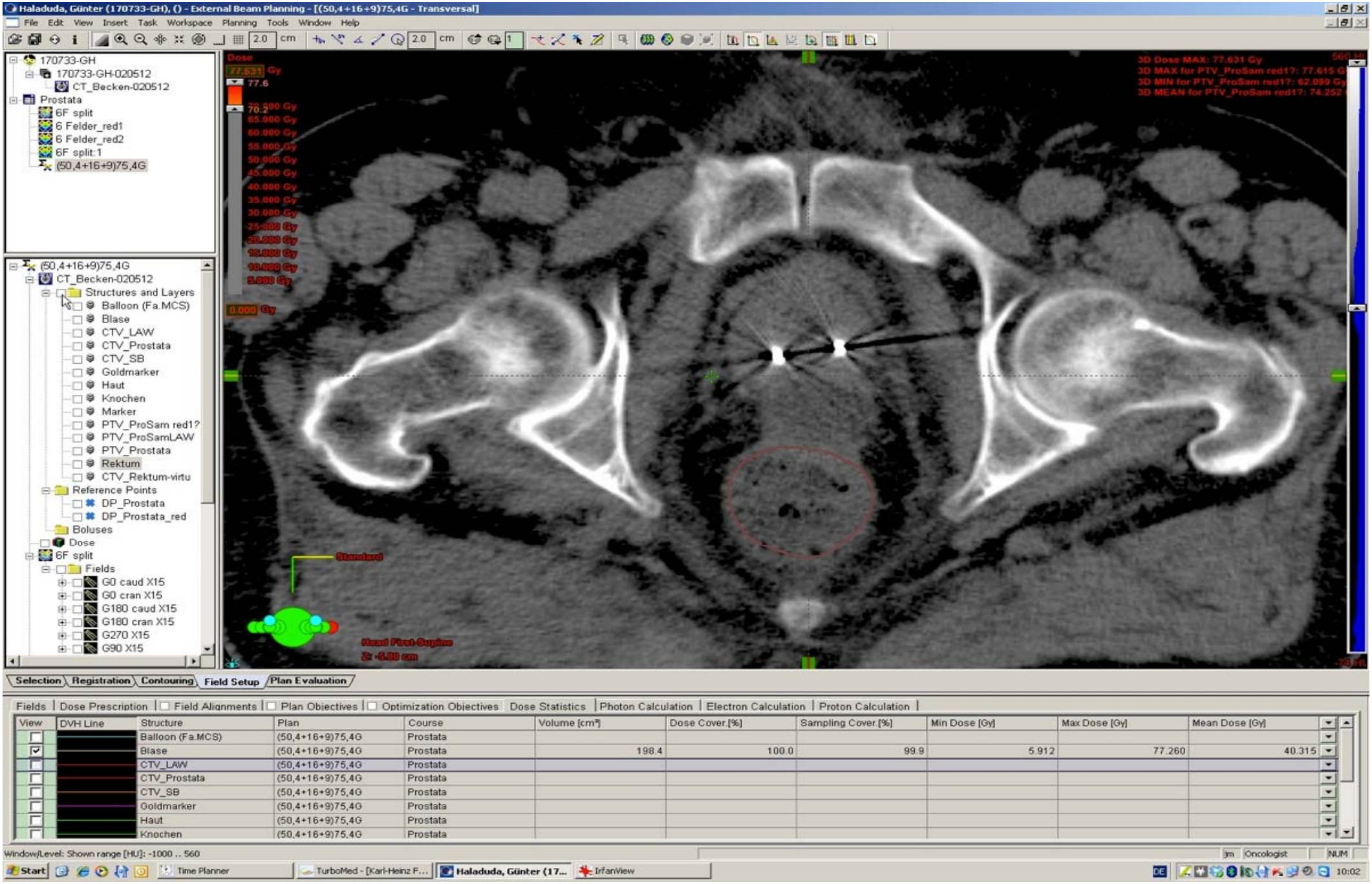

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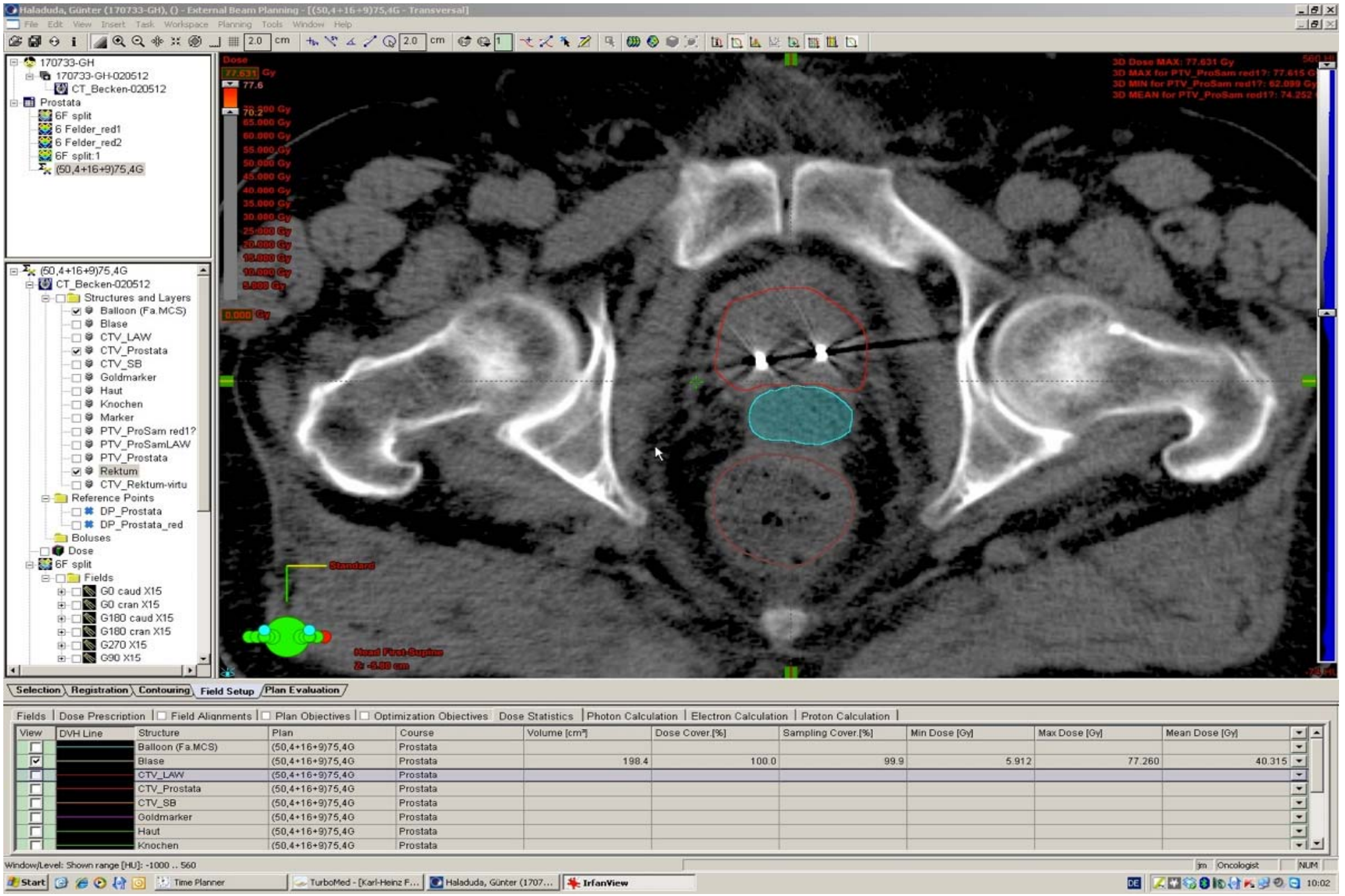

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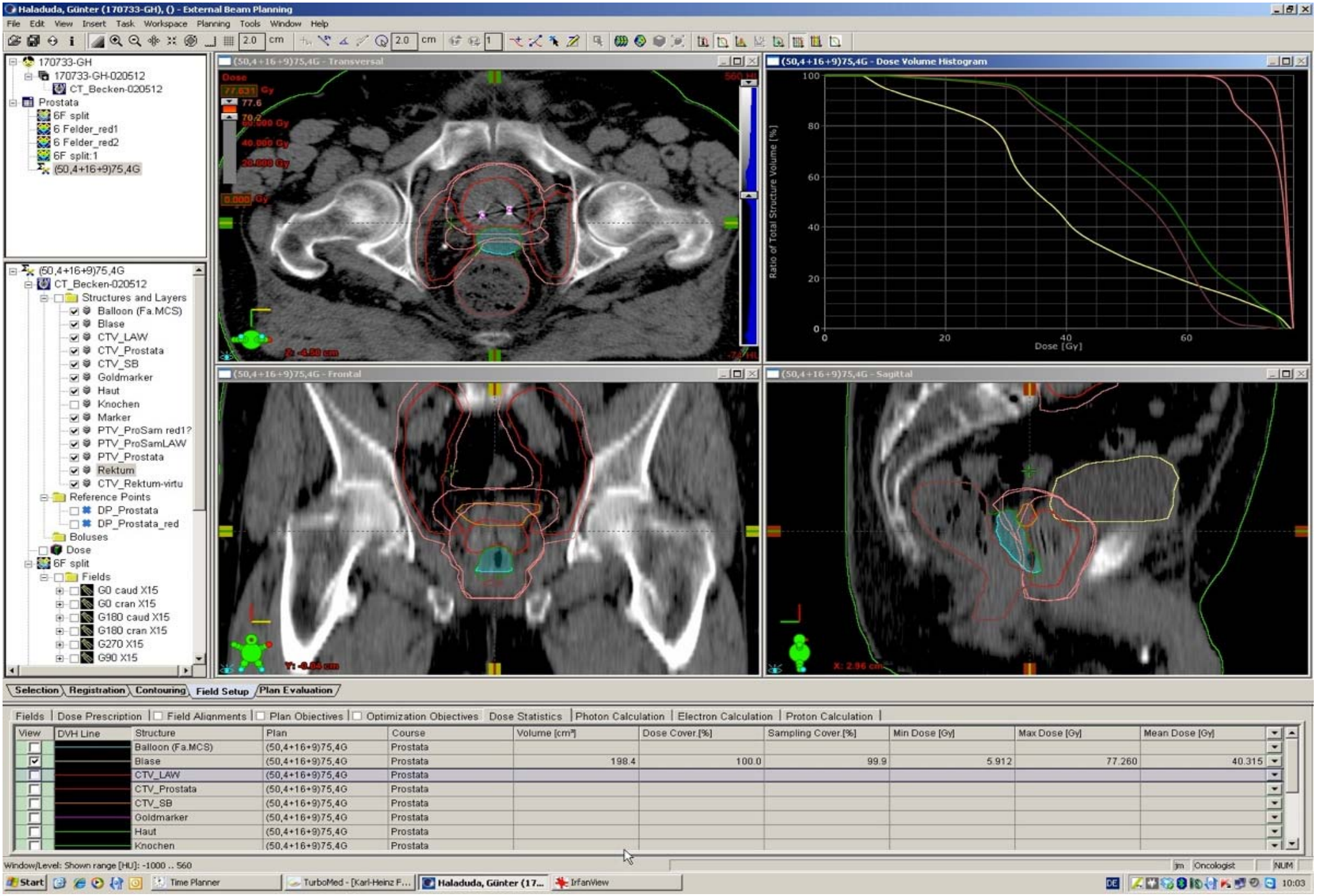

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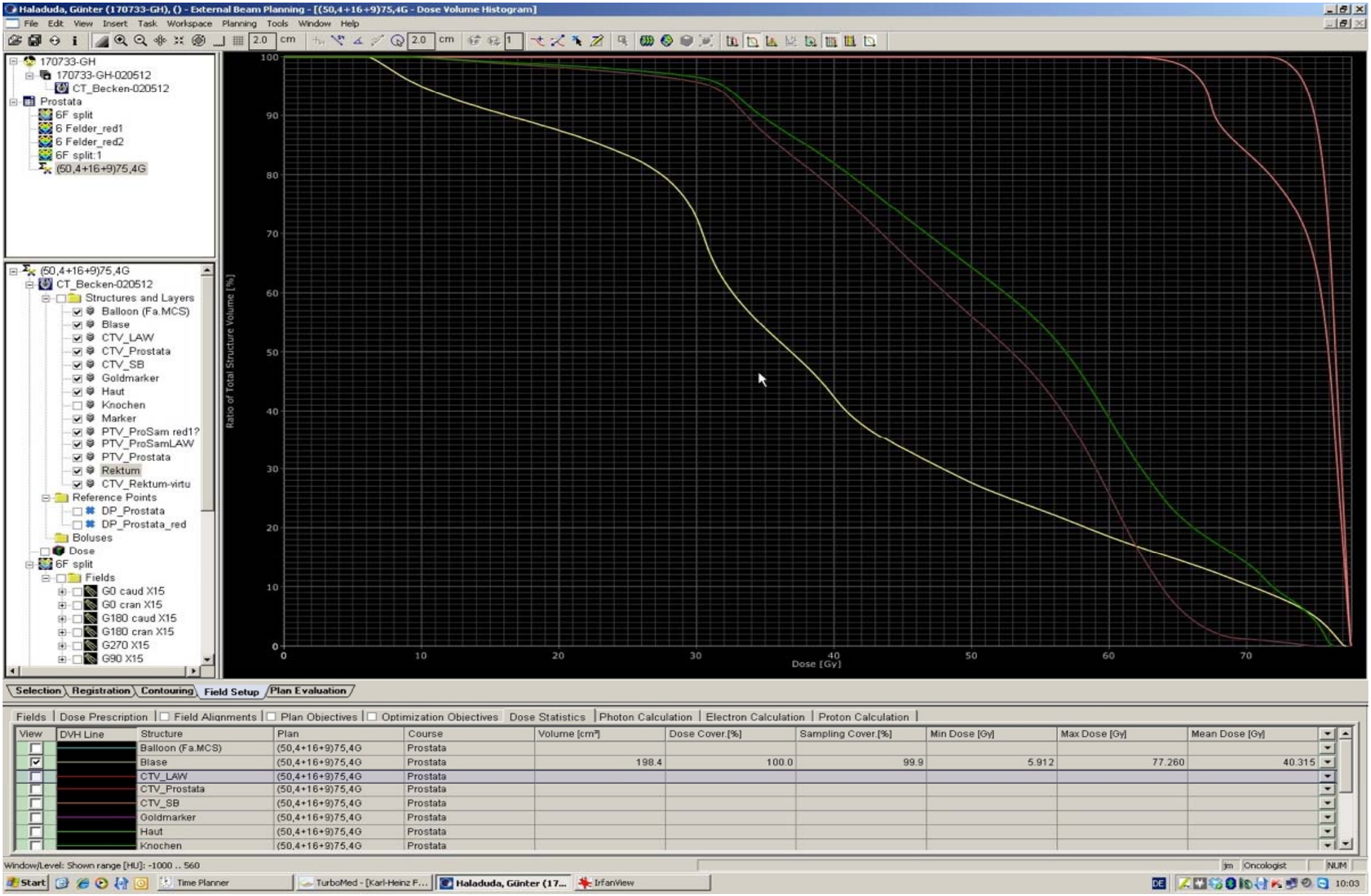
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Prostata
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Structures and Layers
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CTV_SB
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PTV_Prostata
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Reference Points
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Fields
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G0 cran X15
G180 caud X15
G180 cran X15
G270 X15
G90 X15
Ratio of Total Structure Volume [%]
Dose [Gy]
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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
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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
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Haladuda, Günter (17...
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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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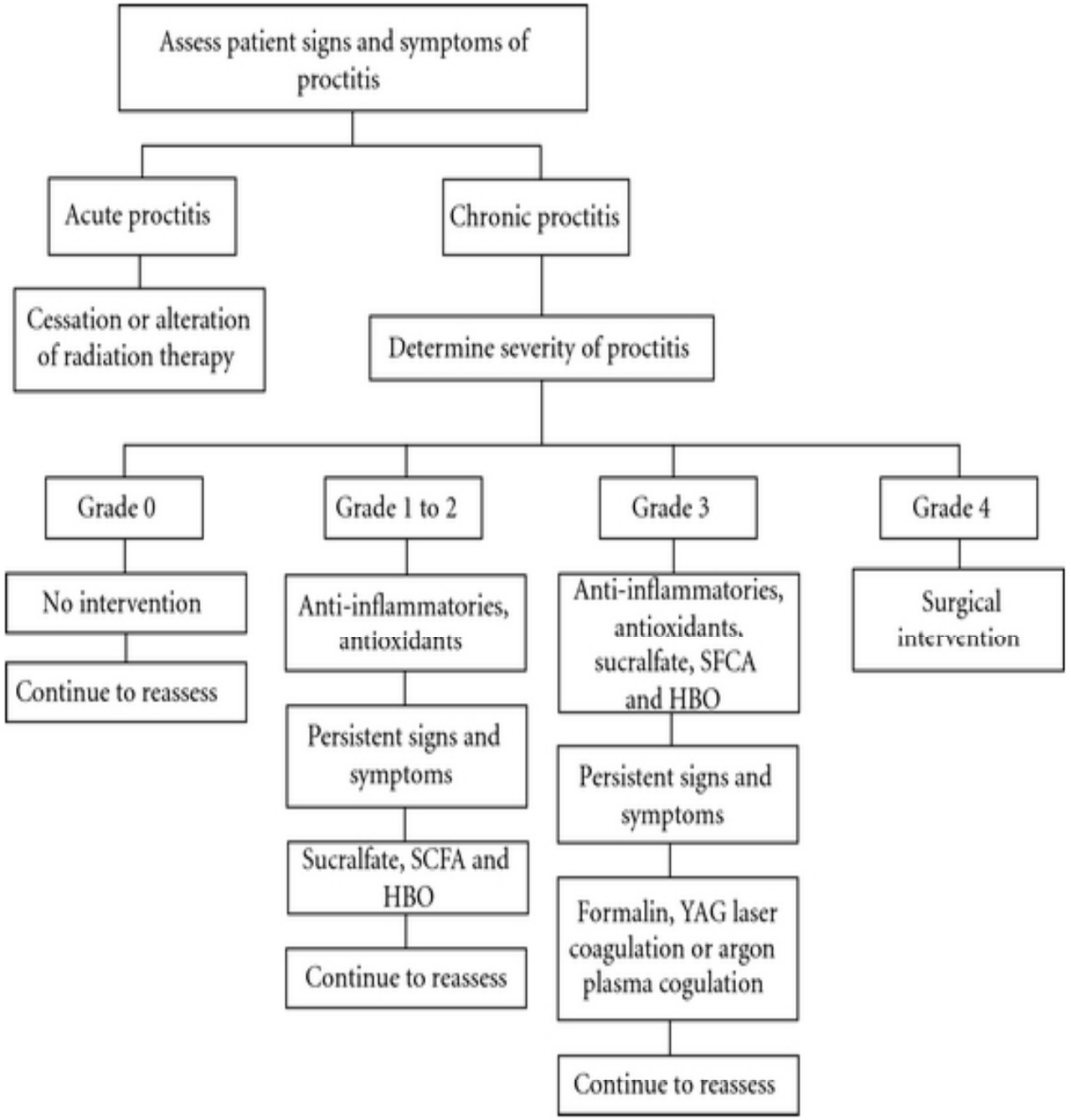
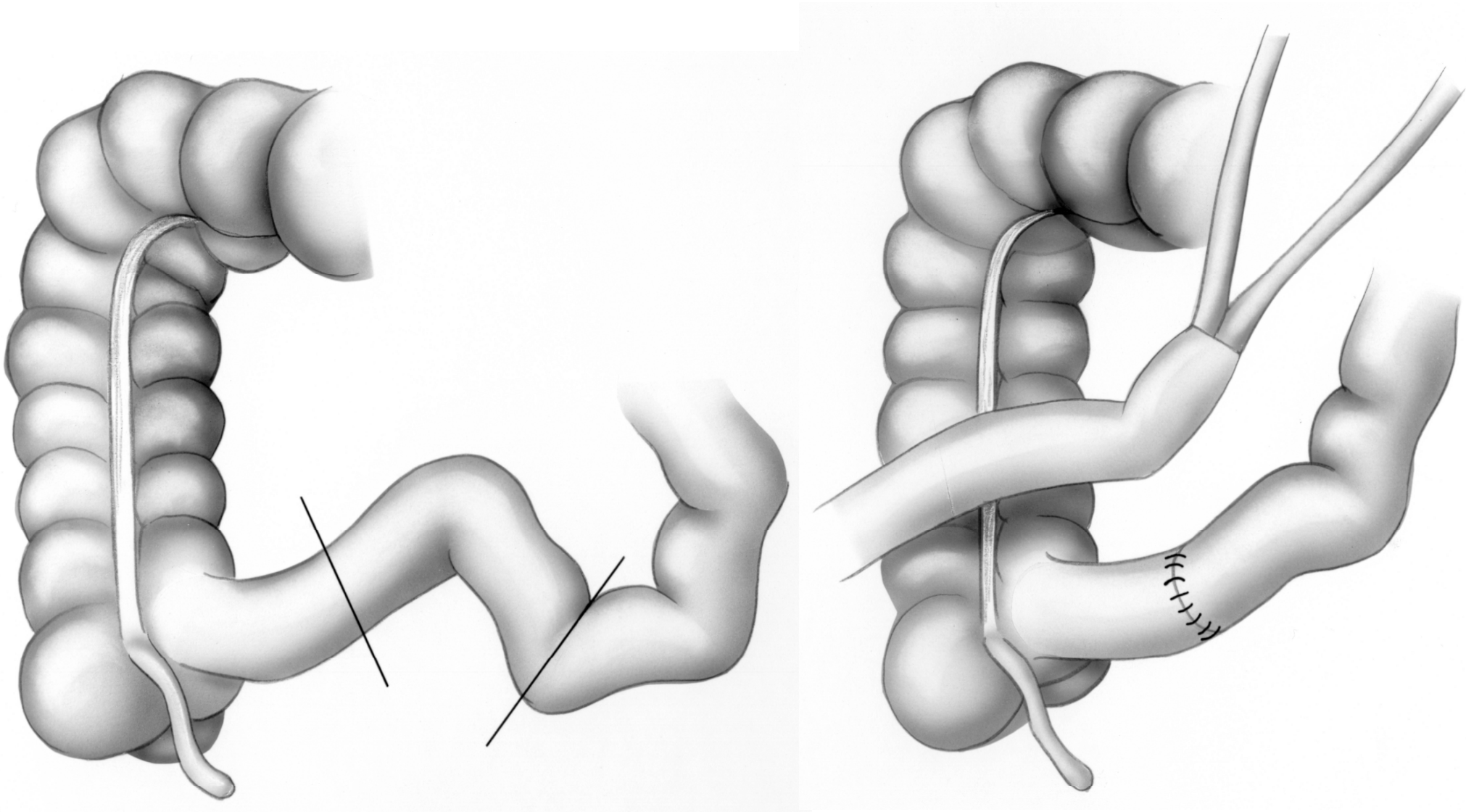
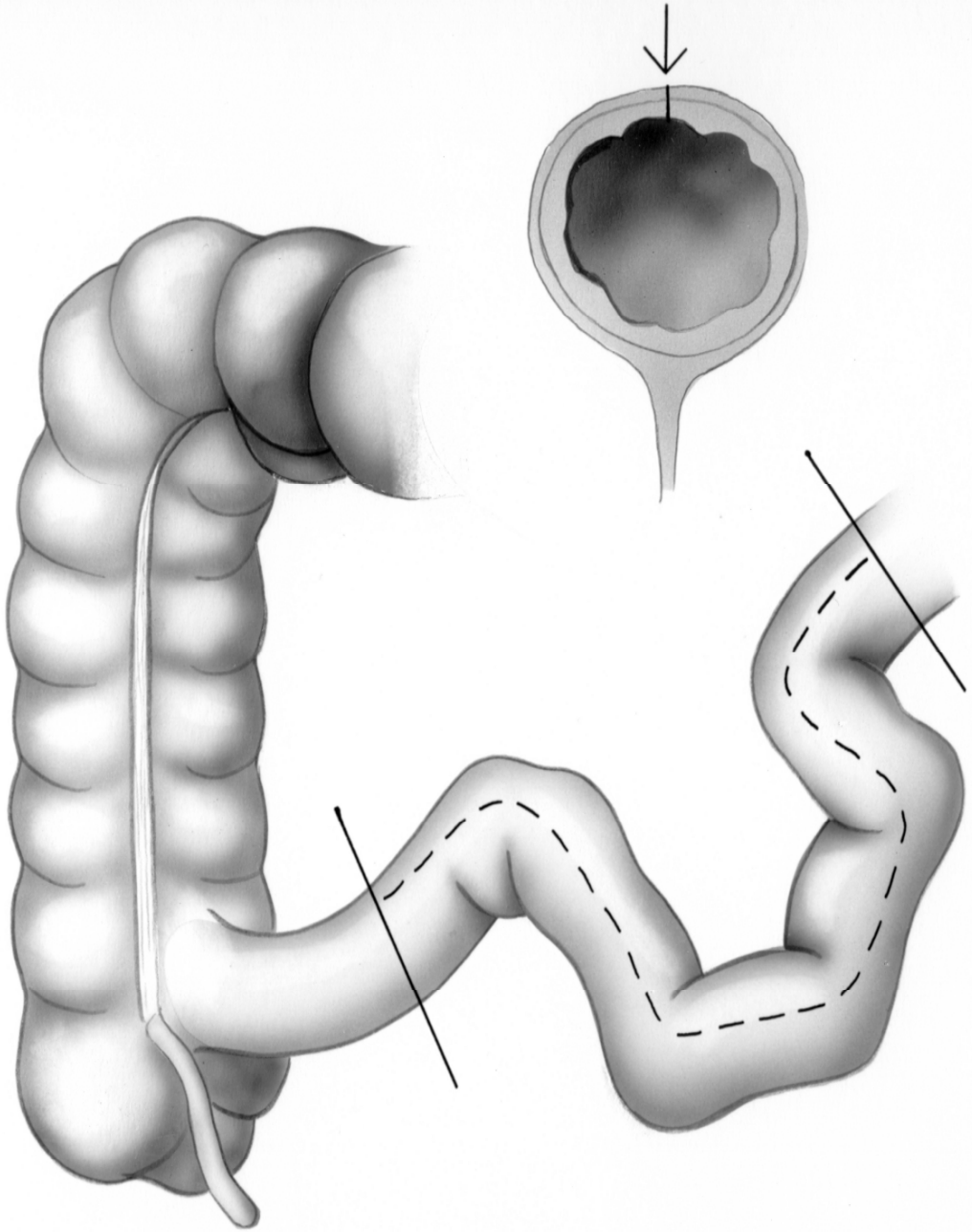
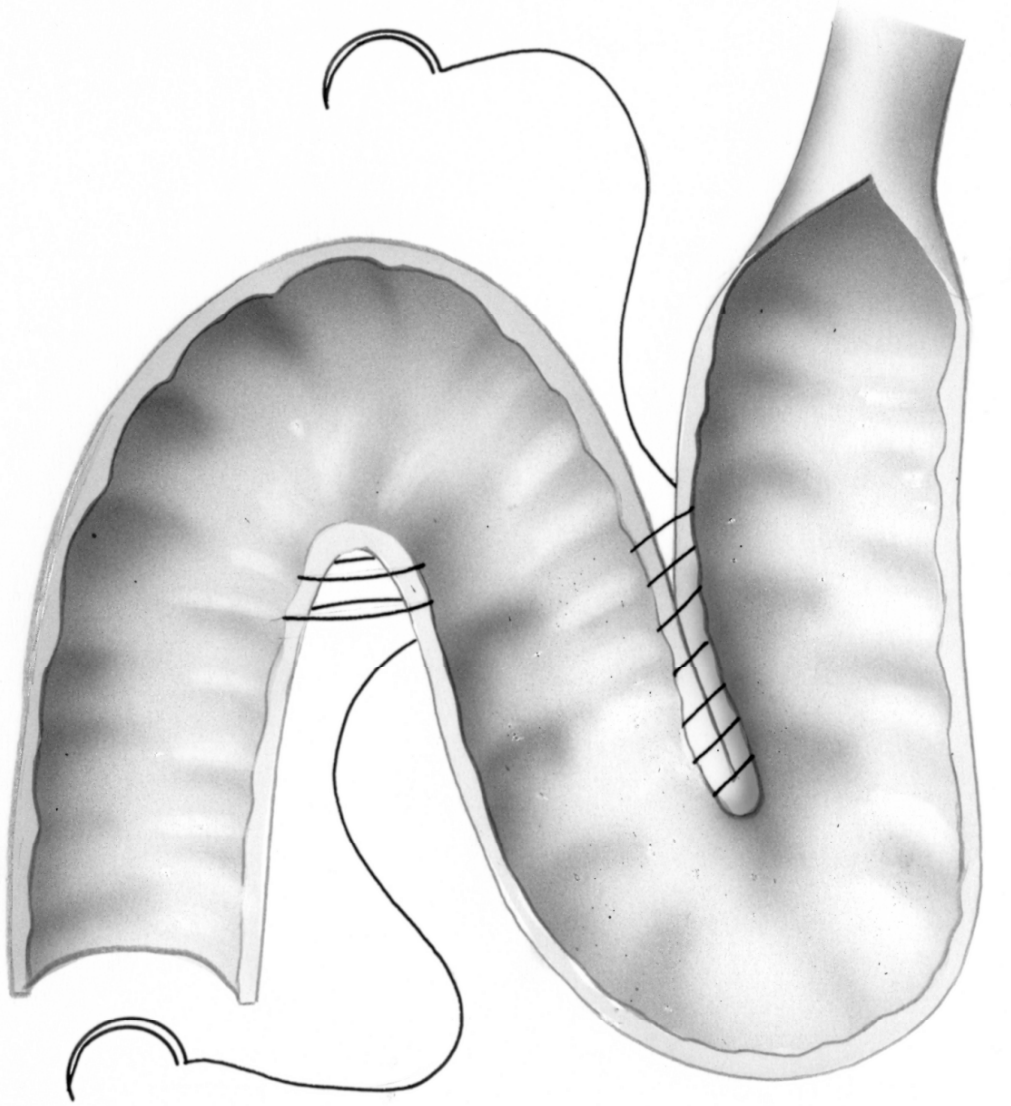

Assess patient signs and symptoms of proctitis
Acute proctitis
Chronic proctitis
Cessation or alteration of radiation therapy
Determine severity of proctitis
Grade 0
Grade 1 to 2
Grade 3
Grade 4
No intervention
Continue to reassess
Anti-inflammatories, antioxidants
Persistent signs and symptoms
Sucralfate, SCFA and HBO
Continue to reassess
Anti-inflammatories, antioxidants, sucralfate, SFCA and HBO
Persistent signs and symptoms
Formalin, YAG laser coagulation or argon plasma cogulation
Continue to reassess
Surgical intervention

Treatment of rectal complications

- **Plastic reconstruction of the rectal wall with gracilis muscle.**
- **Radical operation with construction of neobladder.**







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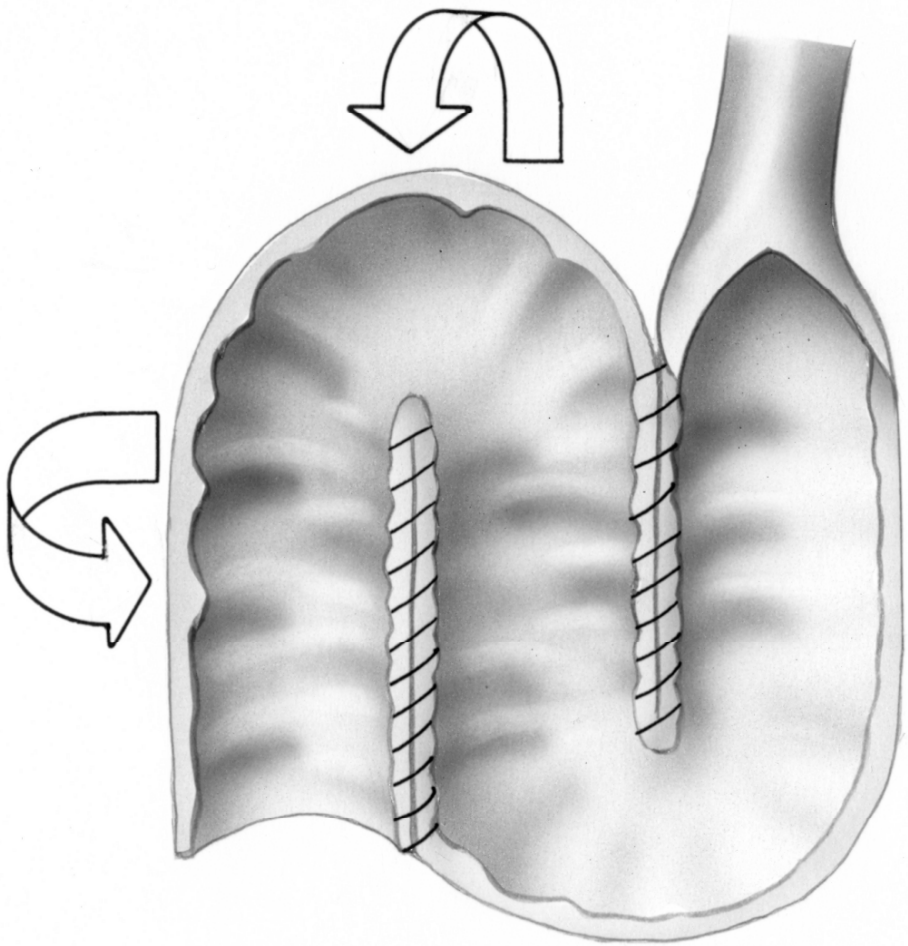

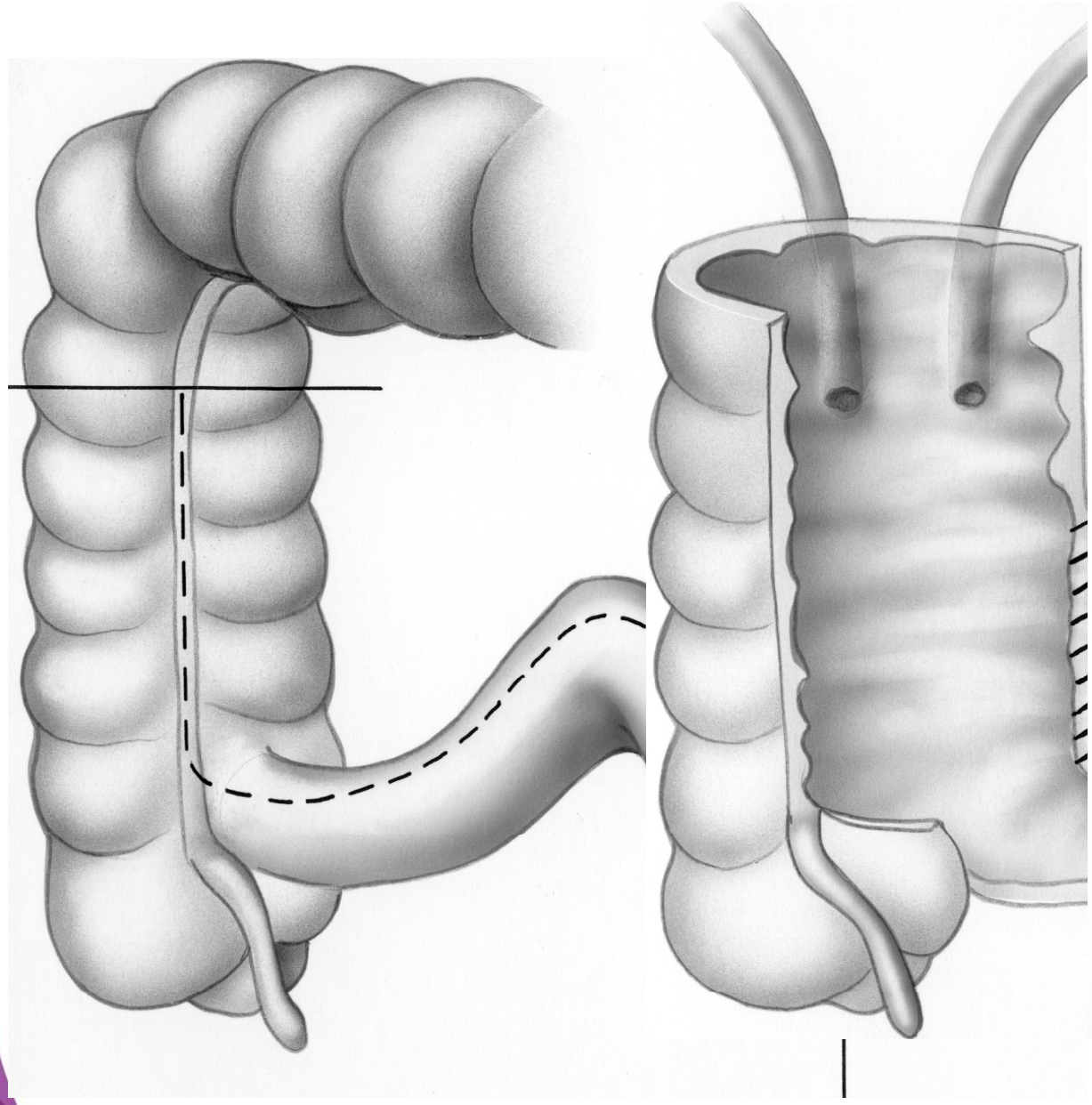

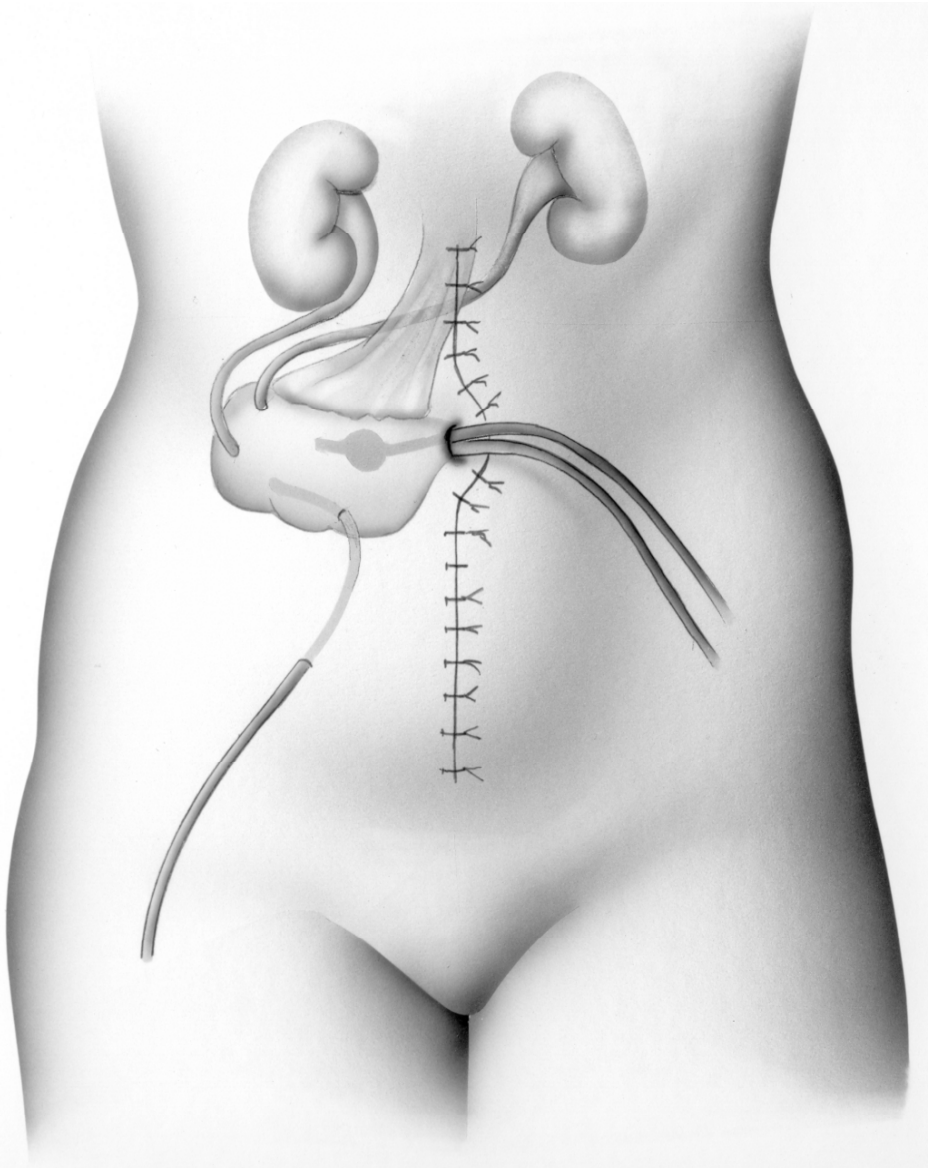

Reduction of urinary morbidity

- **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.**

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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

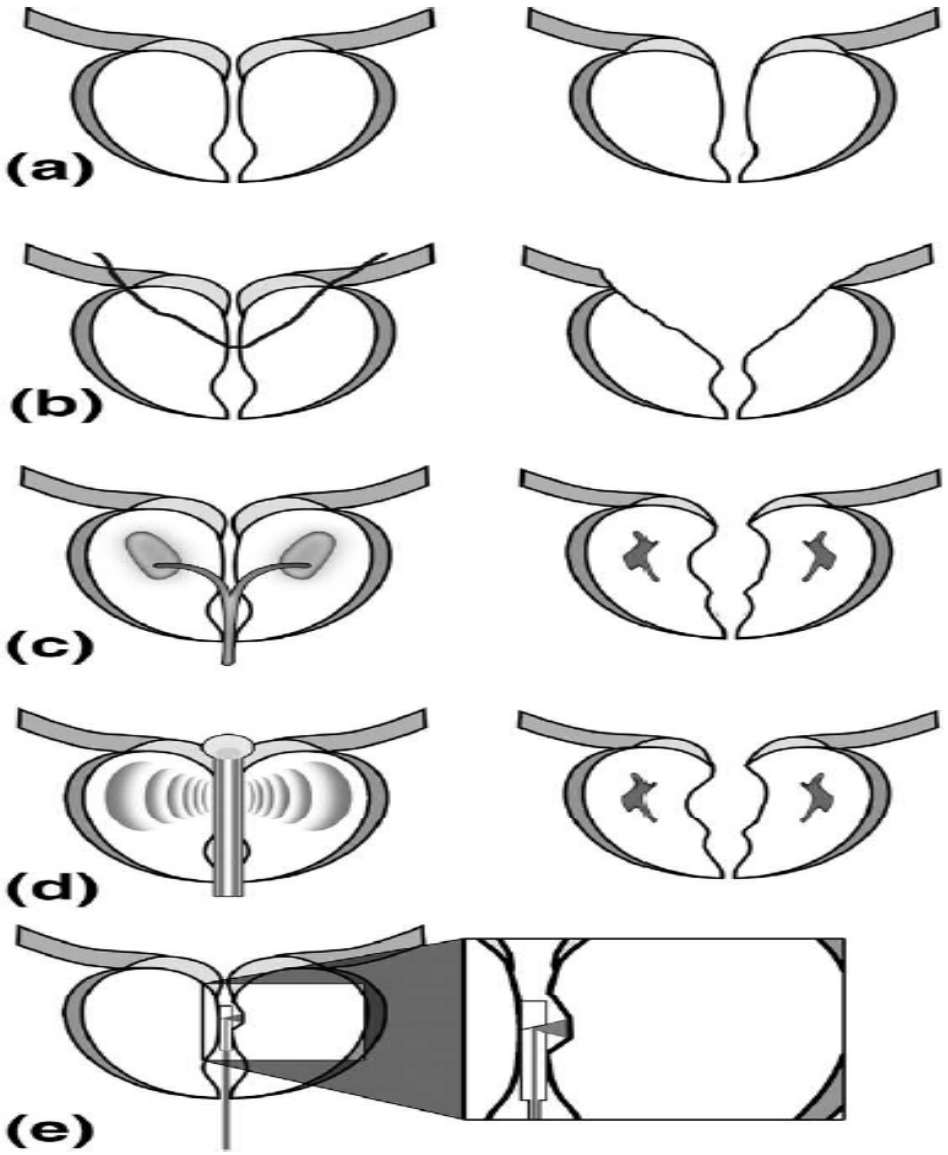


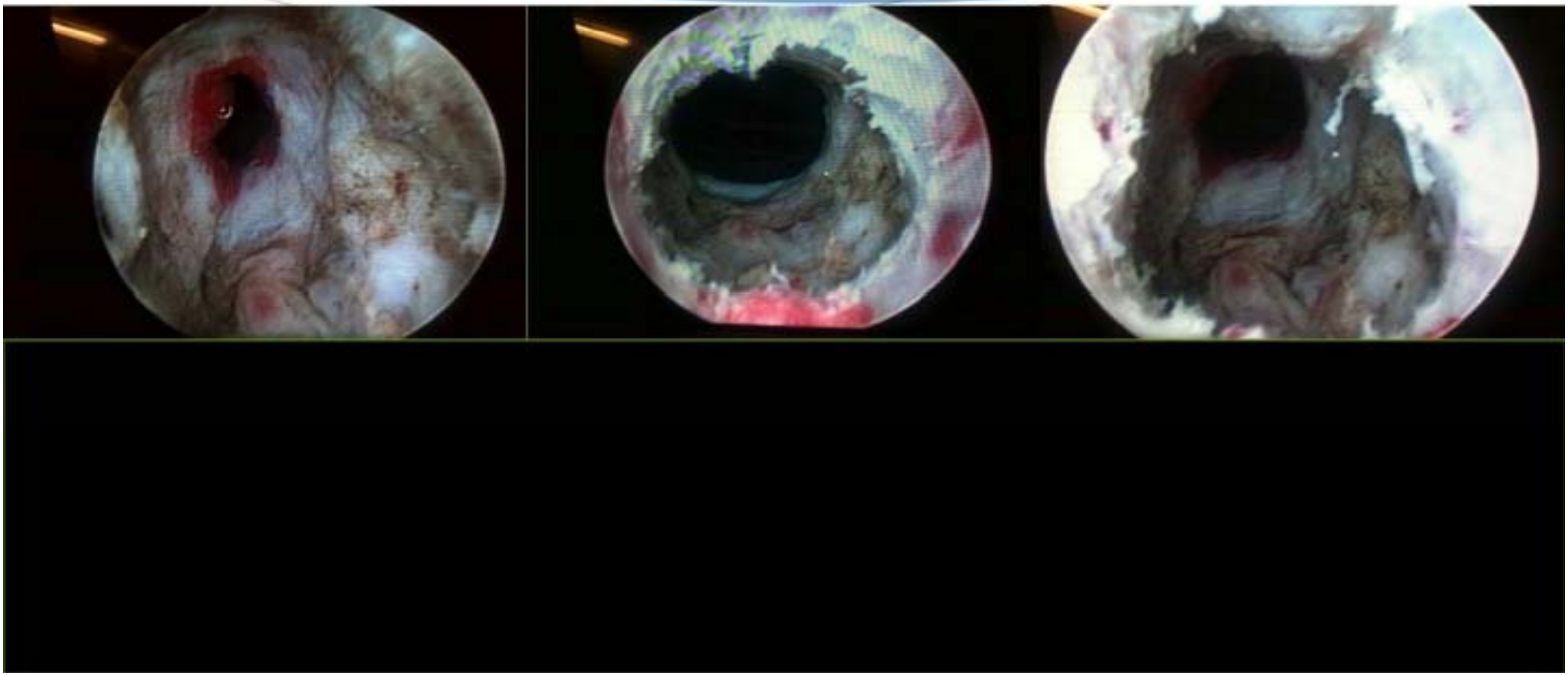
Fig. 9. Surgical procedures to relieve obstruction. (a) Transurethral incision. (b) transurethral prostatectomy. (c) Interstitial (laser or ultrasound). (d) Microwave. (e) Superficial (holmium) laser.

FUNCTIONAL ANATOMY OF THE PROSTATE: IMPLICATIONS FOR TREATMENT PLANNING

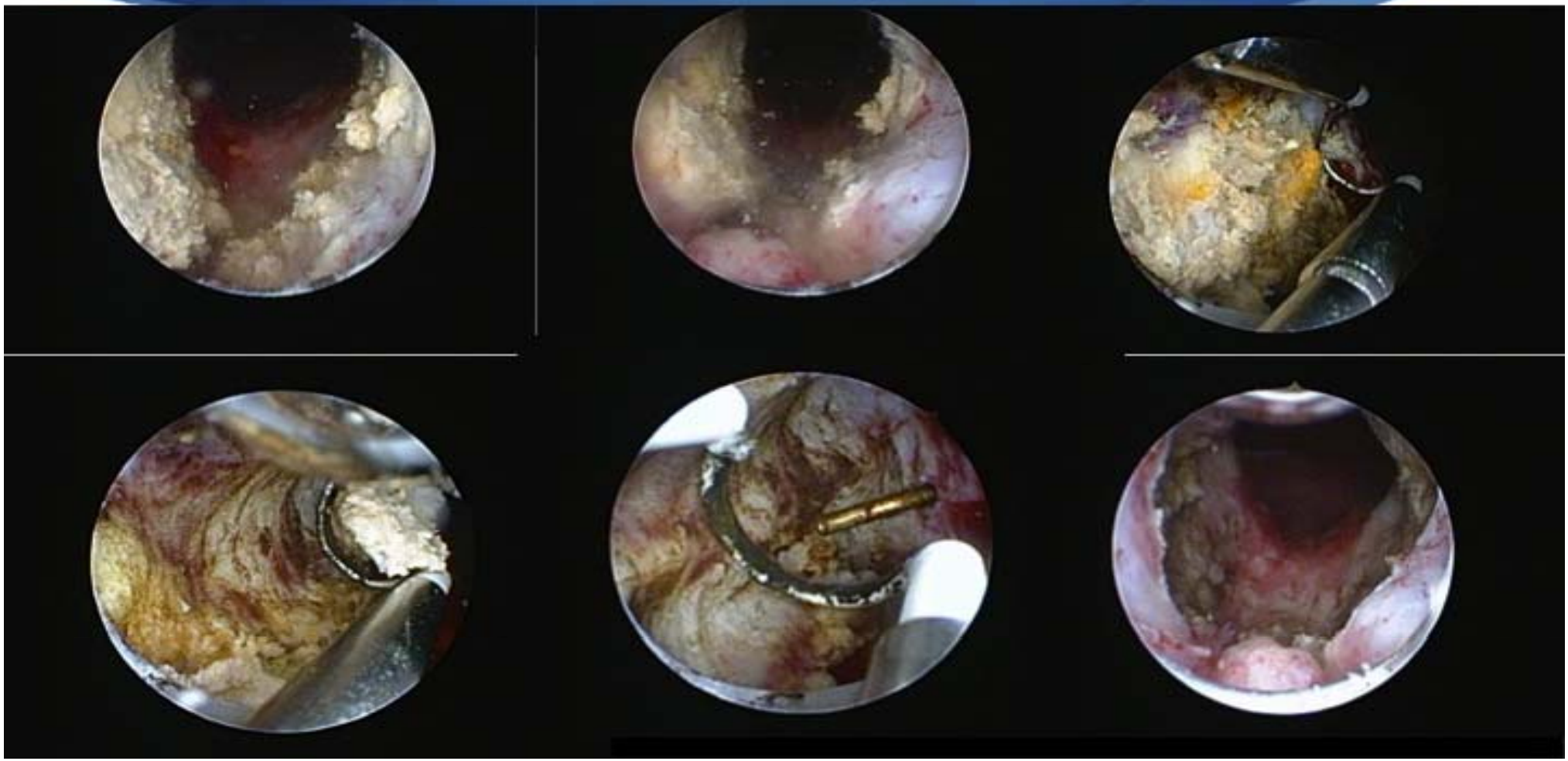
PATRICK W. MCLAUGHLIN, M.D.,*† SARA TROYER, B.S.,† SALLY BERRI, M.D.,† VRINDA NARAYANA, PH.D.,*† AMICHAY MEIROWITZ, M.D.,† PETER L. ROBERSON, PH.D.,† AND JAMES MONTIE, M.D.‡

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 2, pp. 479–491, 2005

TURP 6 M after IPB



TURP 12 M after IPB



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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

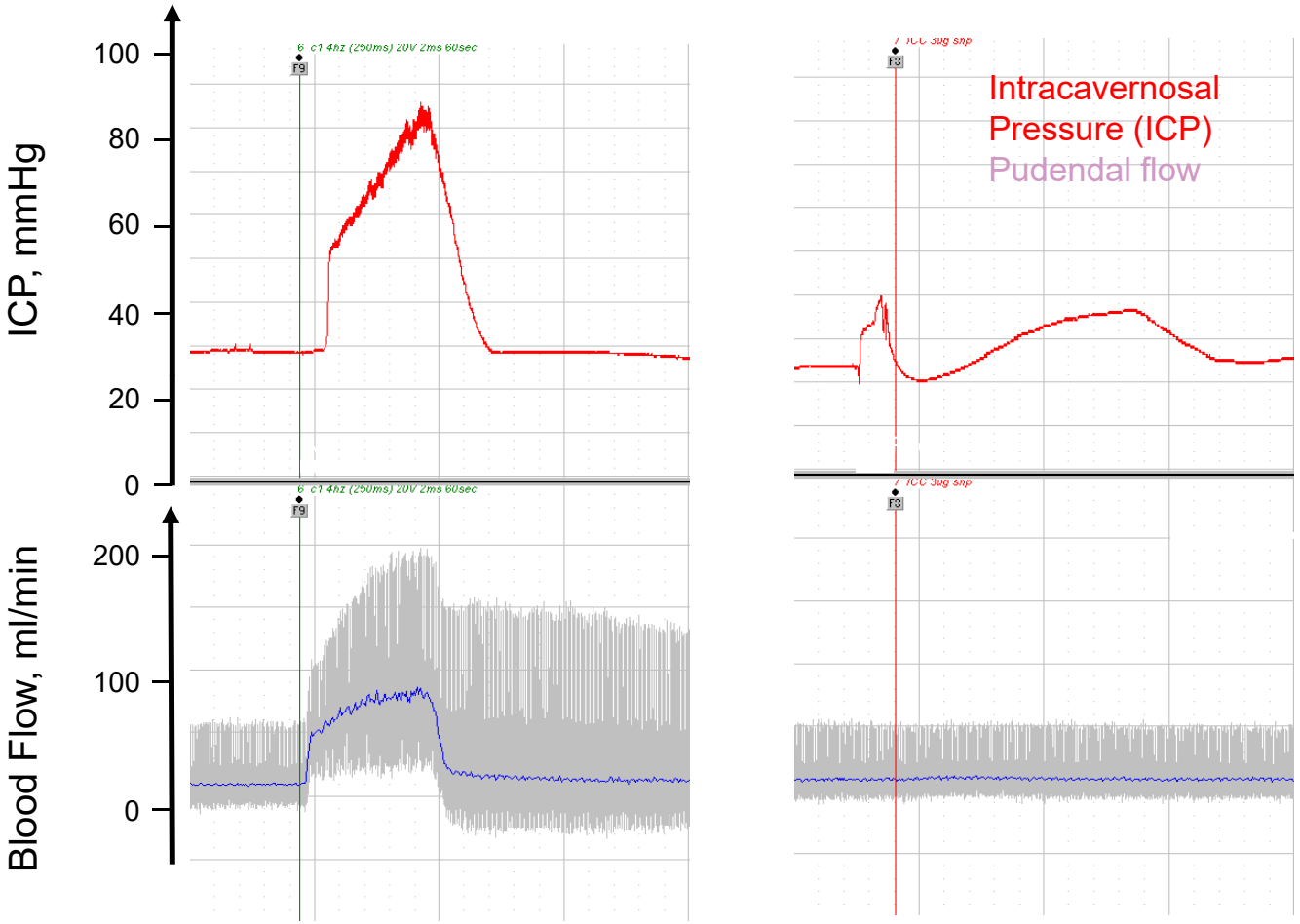
M. A. KOLLMEIER,* R. G. STOCK, J. CESARETTI AND N. N. STONE
From the Departments of Radiation Oncology and Urology (NNS), Mount Sinai School of Medicine, New York, New York

- **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 5cm^2 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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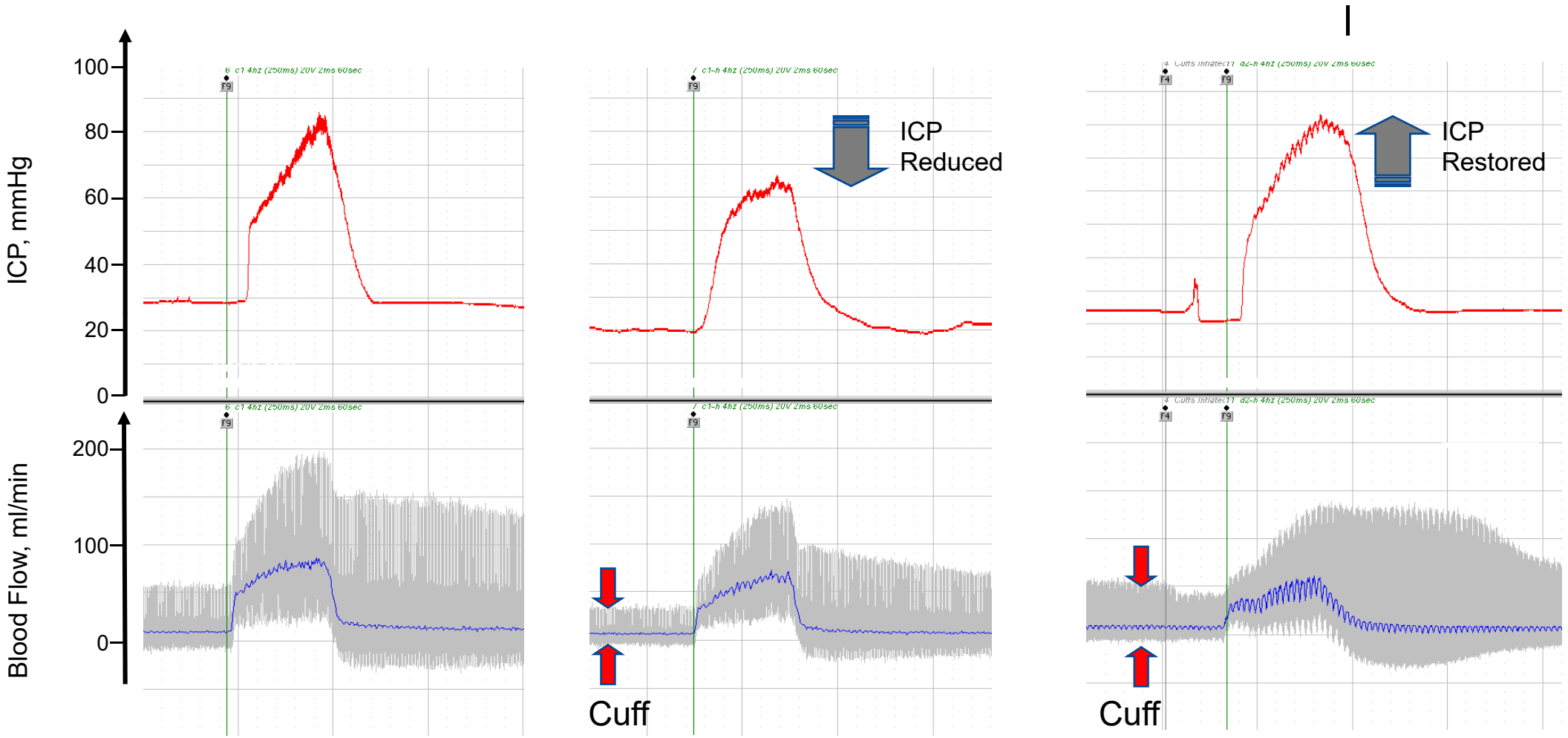
Sildenafil Restores Erection Hardness (ICP)



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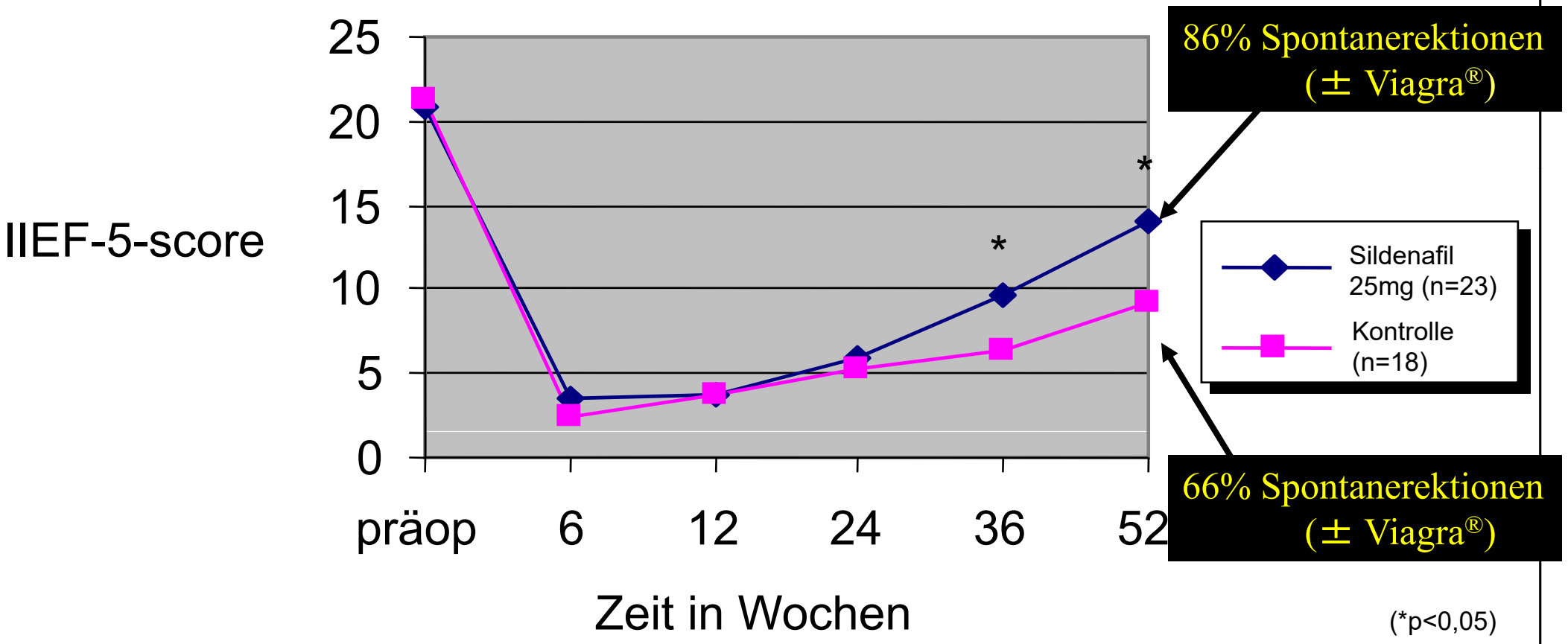
Erholung der erektilen Funktion "Kieler Konzept" nach nsRRP (n=41)



(*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

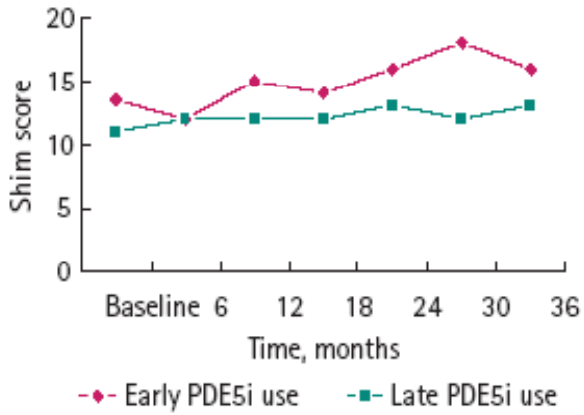
JOURNAL COMPILATION © 2006 BJU INTERNATIONAL | 98, 1255–1258 | doi:10.1111/j.1464-410X.2006.06441.x

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

	n	≤ pT3a	SV+	LN+	SM+	Gleason ≥ 8
Gheiler	40	42%	28%	15%	13%	No data
Stephenson	100	36%	17%	7%	6%	17%
Heidenreich	118	79%	20%	14%	11%	20%

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

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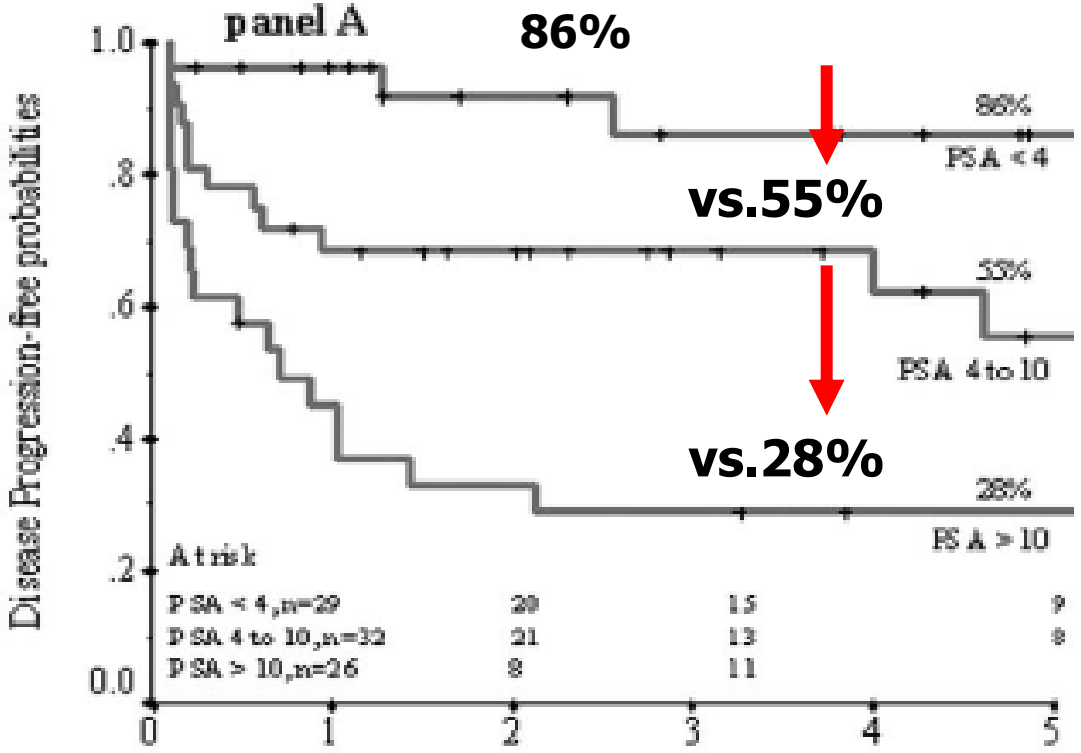
Significant prognostic risk factors for organ-confined disease at salvage therapy

	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

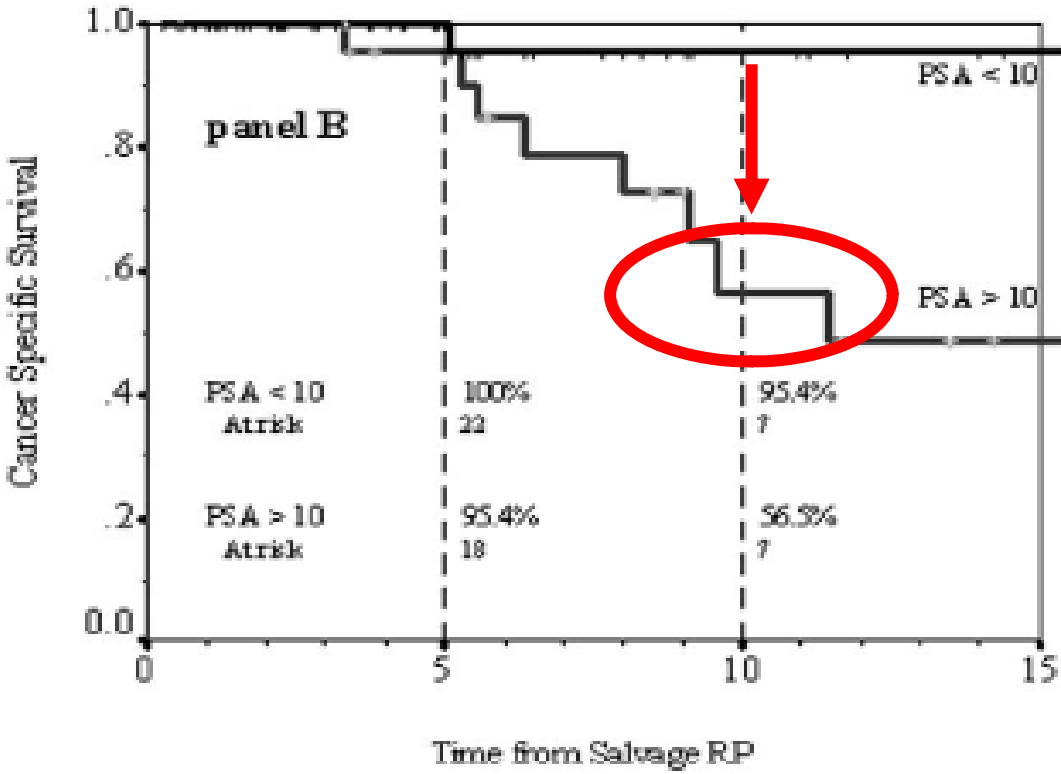


Fig. 3. (A) Disease progression-free probabilities by preoperativ serum PSA strata. (B) Cancer survival categorized by preoperativ serum PSA level (<10 vs. ≥10 ng/mL). PSA = prostate-specifi antigen.

Bianco FJ IJROBP 2005

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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

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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

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ESTRO Course Brussels 2016

RADIOPROTECTION ISSUES

Jean-Marc Cosset

Part I ; Accidents in HDR and LDR prostate brachytherapy

Part II ; Radioprotection aspects of permanently implanted sources for prostate cancer

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Accidents in HDR and LDR Brachytherapy

Jean-Marc Cosset
Institut Curie
ICRP Committee 3

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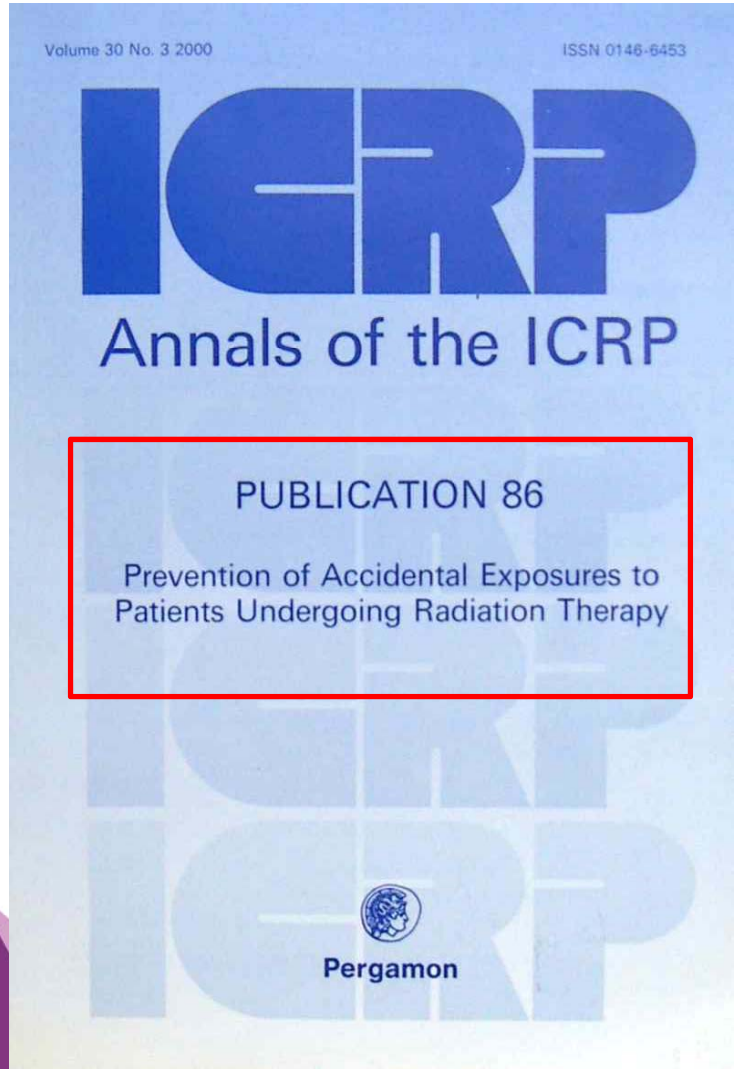
Presentation based on three successive ICRP Publications



Chairman ;
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Members of the task group:
A.Dutreix
P.Andreo
T.Landberg
JM.cosset

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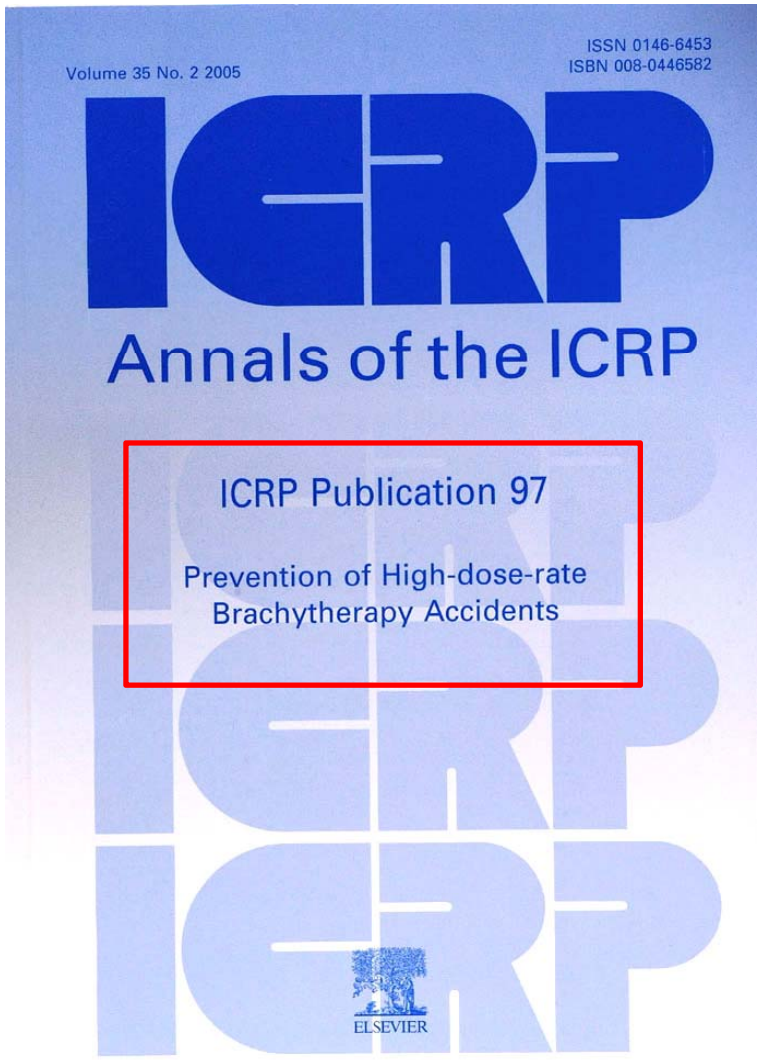

Chairman;
Luis Pinillos-Ashton
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S.Nag
V.Levin

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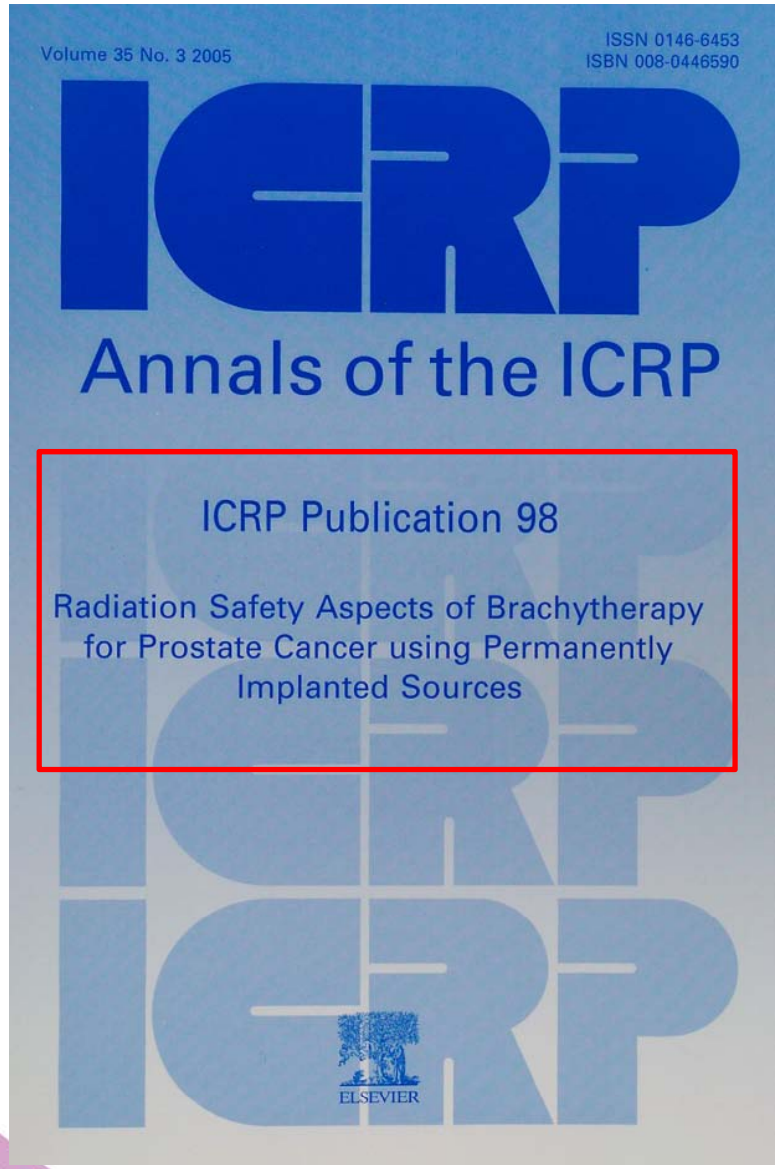

Chairman:
Jean-Marc Cosset
members of the task group
D.Ash
T.Mc Kenna
L.Pinillos-Ashton
M.Hiraoka
M.Zelefsky
L.Dauer

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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

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The main chapters

- Equipment problems
- Source ordering, delivery, calibration and acceptance
- Treament planning
- Source preparation
- Treatment delivery
- Source removal
- Accidents involving public exposure and environmental contamination

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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).*

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- Radioactive materials in recycled metals ; an update
- Lubenau JO , Yusko,JG
- Health physics, 1998 ,74(3):293-9

- *« The steel manufacturer Association made available data collected by its members beginning in 1994, that expanded the database for* ***radioactive materials found by the metal recycling industry in recycled metal scrap to over 2,300 reports as of 30 June 1997…*** *»*

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

- Again, the reported accidents were analyzed ...

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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 ...

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- 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 .....)
- The catheter with the source felt at that time with necrotic tissues,
- ... and was disposed in a waste container, without identification of the source ...

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- 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 ...

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.

- Strahlenther Onkol. 1999 Oct;175(10):524-9.
- **Emergency rescue in accidents with HDR afterloading units.**
- Kaulich TW, Becker G, Lamprecht U, Nüsslin F, Bamberg M.

- **Abstract**
- HDR brachyradiotherapy has minimized the exposure to radiation of the personnel working in this field. Nonetheless there are periodically reported troubles with afterloading units concerning the retraction of sources that require **immediate action** for the limitation of possible damage

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- “…The quickest possible rescue of a patient in an emergency demands an unequivocal definition of responsibilities….
- …The organizational structure of the clinic allowing, the emergency physician should invariably be the physician who placed the applicator
- … A well-practiced emergency management can be of life-saving importance for the patient.”

ICRP 98 :

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

published in 2005

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- **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 »

- Actually : not a real « accident »
- But a succession of « malpractices » leading to ***97 medical errors out of 116 prostate cancer implantations***
- ***During 6 years,*** from 2002 to 2008 !! ....

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

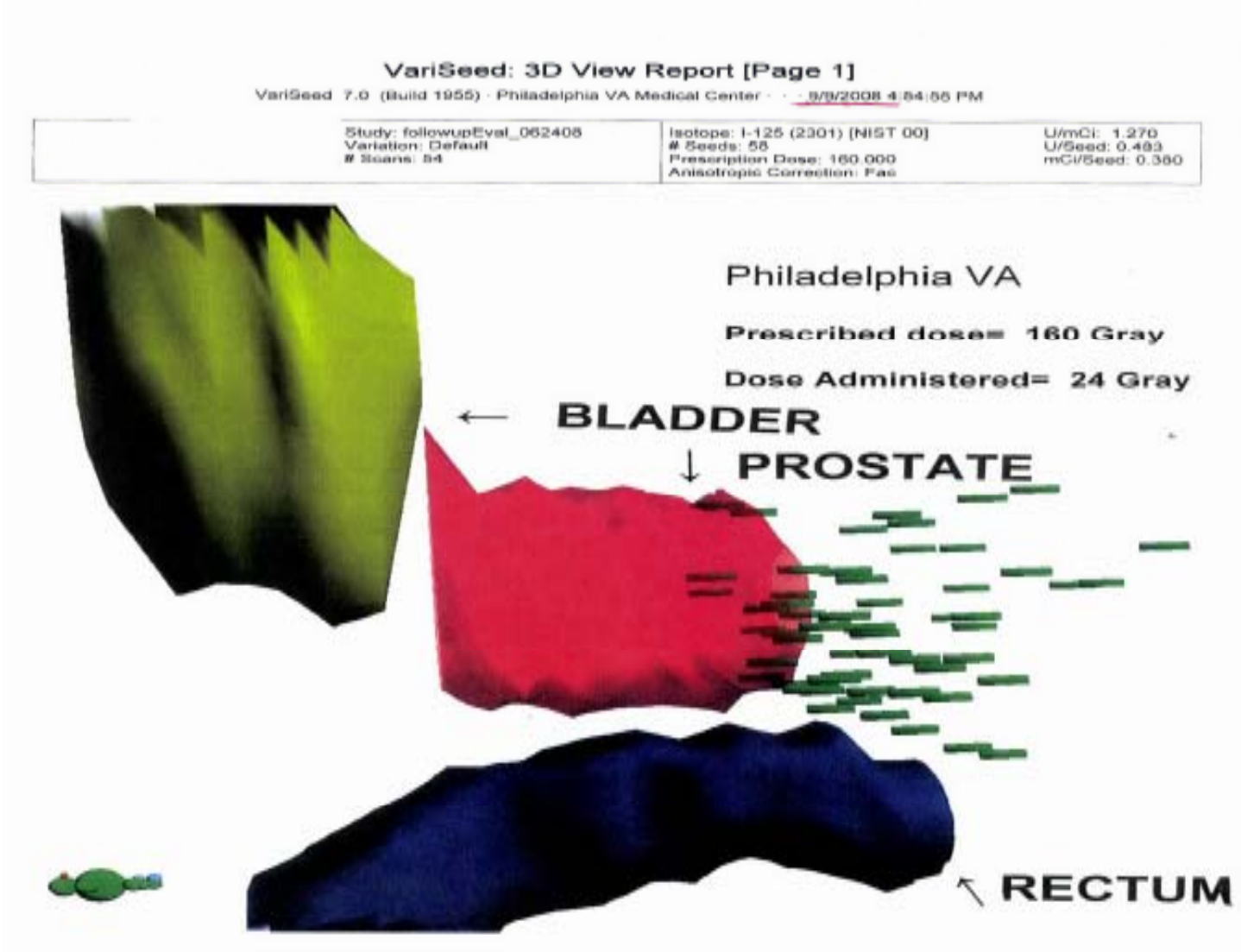
- February 2003 ; during a seed prostate implant**, 40 out of 74 seeds were « implanted » in the patient's bladder**; they were subsequently expelled and recovered ...

- 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 0.5 Sv
  (Overdoses of rectum, bladder wall or prostate surrounding tissues)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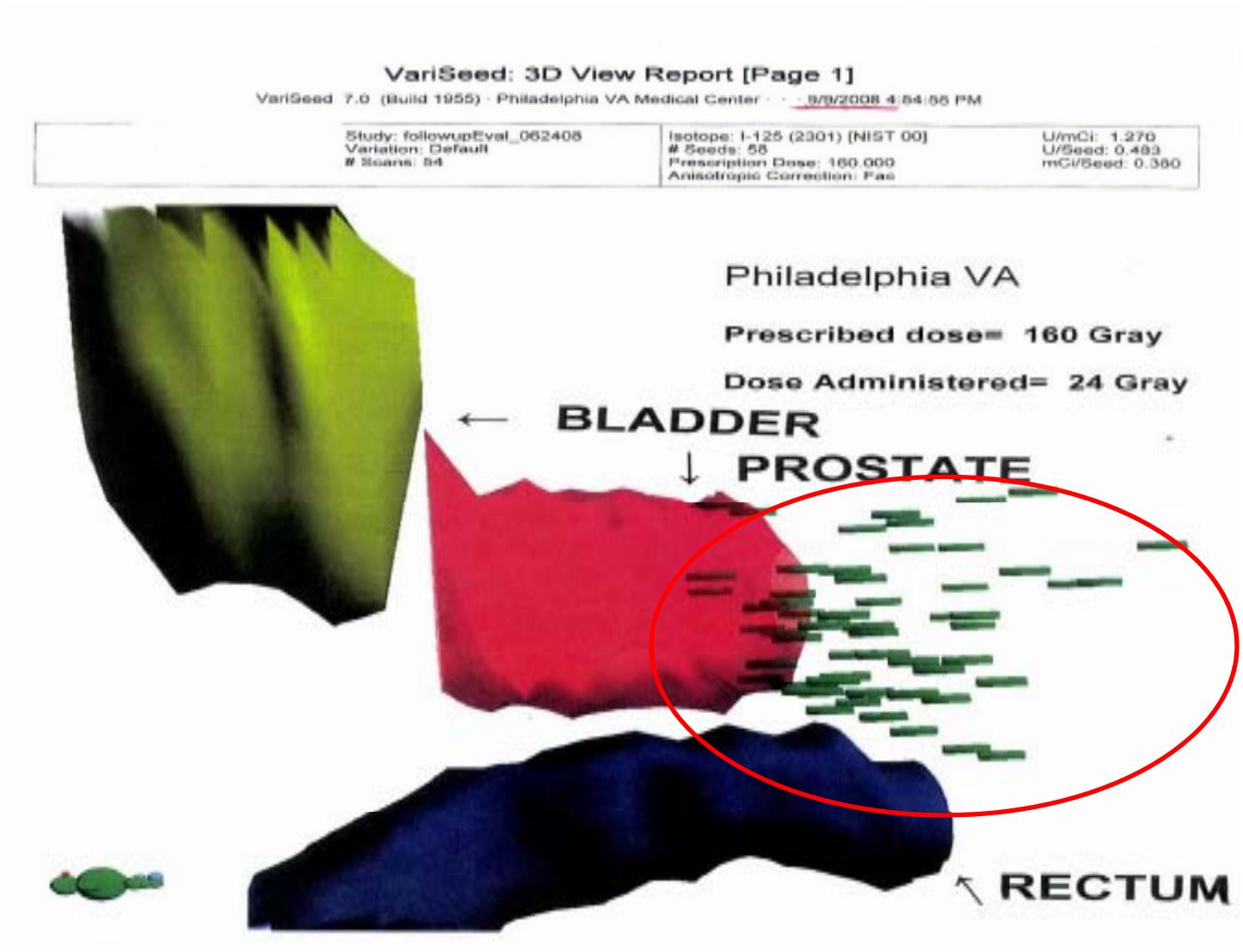
Study: followupEval_062408
Variation: Default
Scans: 84
Isotope: I-125 (2301) [NIST 00]
Seeds: 58
Prescription Dose: 160.000
Anisotropic Correction: Fas
U/mCi: 1.270
U/Seed: 0.483
mCi/Seed: 0.380
Philadelphia VA
Prescribed dose= 160 Gray
Dose Administered= 24 Gray
BLADDER
PROSTATE
RECTUM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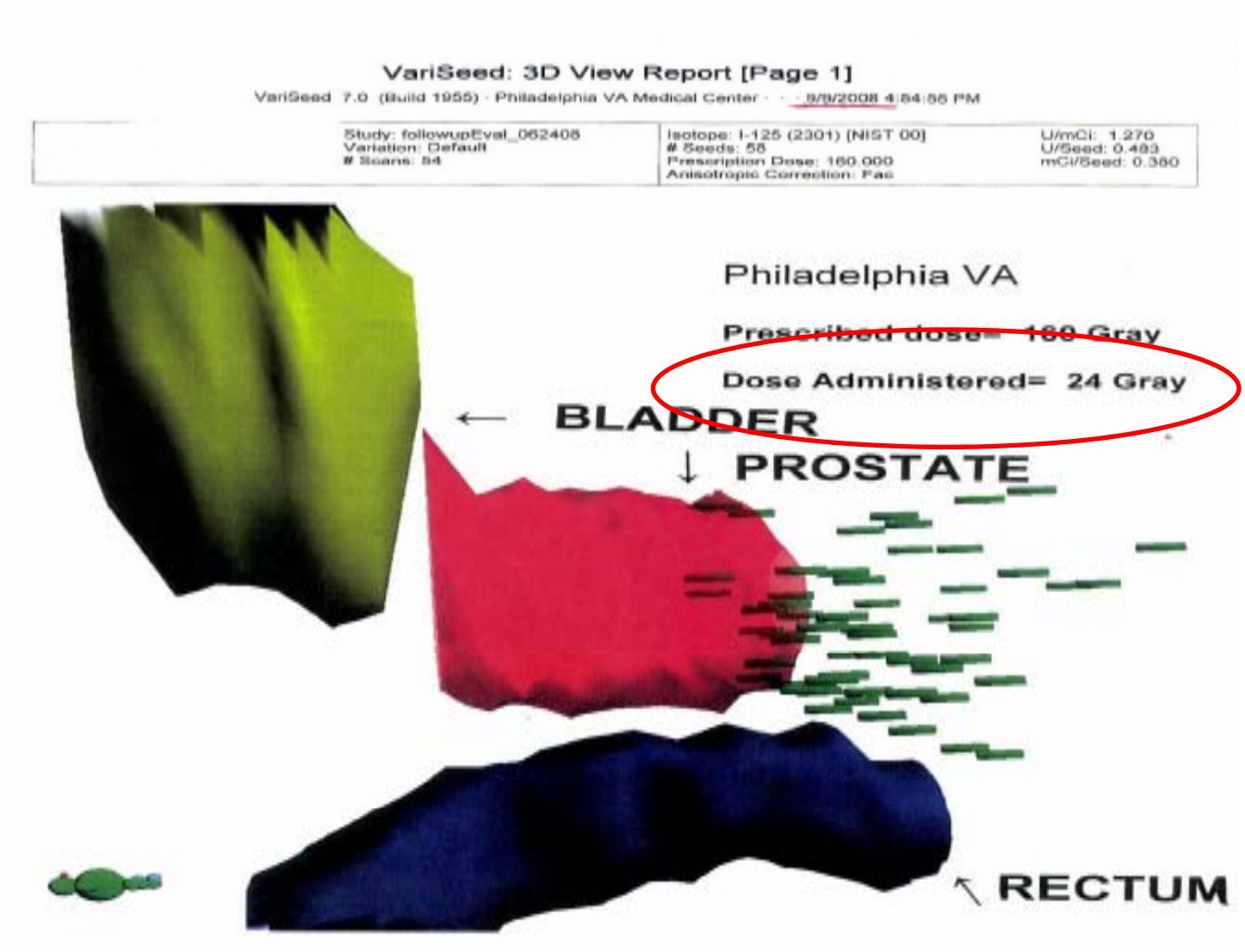
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Prescribed dose= 160 Gray
Dose Administered= 24 Gray
BLADDER
PROSTATE
RECTUM

- 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

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Received September, 2011:

- Event Number: 47279
- Rep Org: ILLINOIS EMERGENCY MGMT. AGENCY
  Licensee: SWEDISH AMERICAN HOSPITAL
  Region: 3
  City: ROCKFORD State: IL
  County:
  License #: IL-01067-01
  Agreement: Y
  Docket:
  NRC Notified By: DAREN PERRERO

- Notification Date: 09/19/2011
  Notification Time: 18:00 [ET]
  Event Date: 09/13/2011
  Event Time: 07:00 [CDT]
  Last Update Date: 09/19/2011
- Emergency Class: NON EMERGENCY
  10 CFR Section:
  AGREEMENT STATE

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- **AGREEMENT STATE REPORT - MEDICAL EVENT INVOLVING THE MISADMINISTRATION OF I-125 SEEDS IN A PROSTATE CANCER TREATMENT**
-

  "On Thursday, September 15, the Radiation Safety Officer (RSO) for the licensee called [the state] to make a preliminary advisement that a medical event involving a prostate cancer treatment had occurred at their facility".

- 71 seeds planned to be implanted in the prostate
- **Actual number of seeds implanted in the prostate : 3 (!) .....**
- The other seeds ; in the bladder, in the bladder and rectal wall, in the perineum etc .....

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 ...

Frequently forgotten accidents !

- Actually, the main risk of « accident » in permanent implant prostate brachytherapy could be ...
- The accidental puncture (and blood contamination) of the finger(s) of the operator !
- Therefore ; take care of you !
- And beware of seropositive patients ...

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Conclusions

- Accidents in LDR and HDR brachytherapy are rare (++) but may occur ...
- But should not !
- *« The majority of the accidental exposures that occurred with brachytherapy can be linked to sources parameters, to dose calculation procedures and to insufficient training of personnel » (ICRP 86)*

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A last (important) point

- In the same way it has to be done in external radiotherapy, all precursor events, incidents or accidents in brachytherapy ***have to be immediately reported and analyzed***, in order to rapidly propose corrective measures, to circulate the information and to learn from experience !

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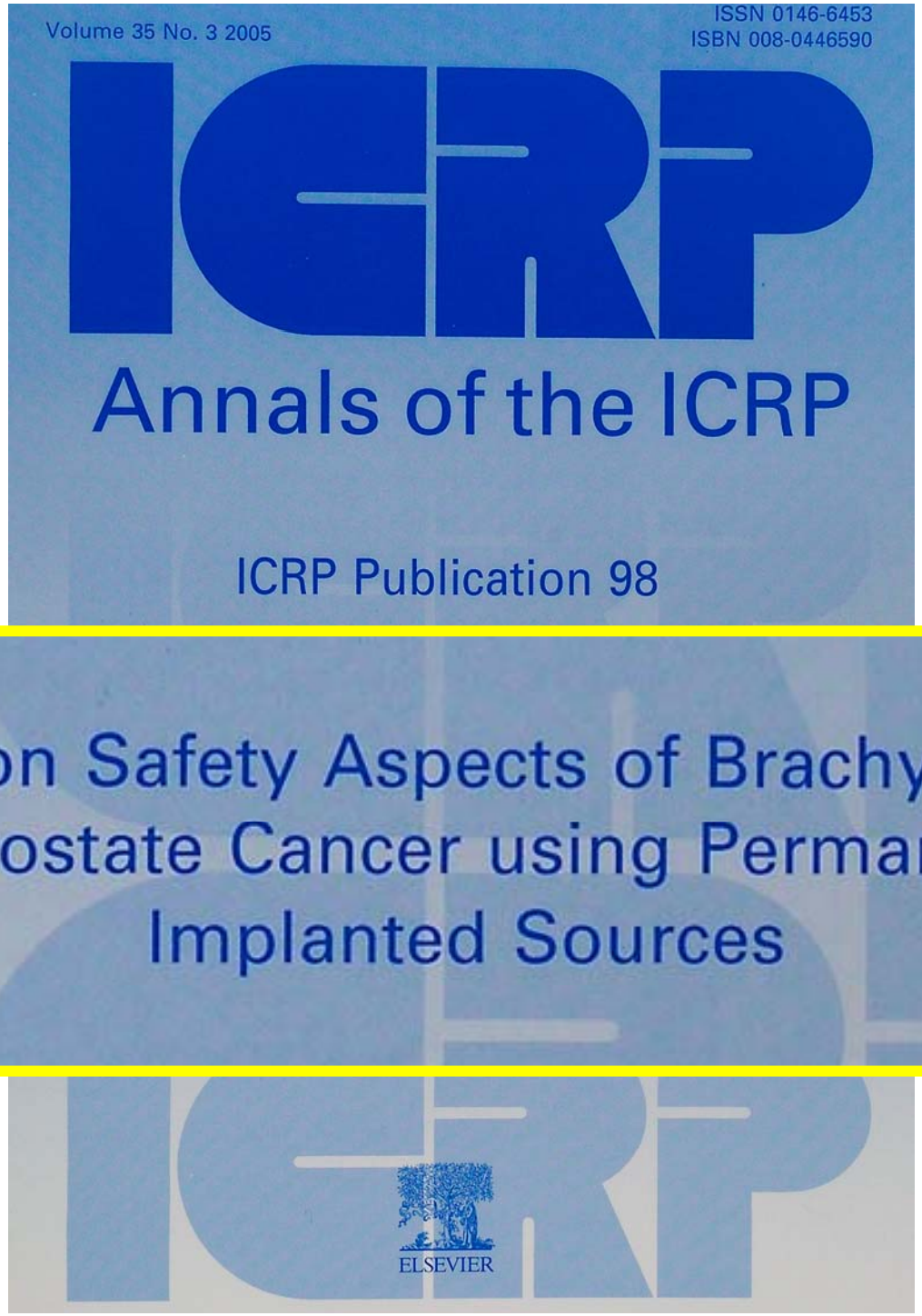

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ICRP 98 ; the general background :

- Prostate cancer ; now the first cancer in males (in terms of incidence) in most developed countries
- More and more localized stages (screening)
- Able to benefit from brachytherapy ...
- In the US ; 30 to 40 000 (more ?) implantations each year
- In Europe (and in some other countries) several thousands cases already treated annually, and rapid increase ...
- (very) encouraging results

ICRP 98 ; the radioprotection background :

- Permanent seed implantation;
- No adverse effects to medical staff and/or the patient's family reported so far ...
- However, ICRP felt necessary to address a number of Radioprotection issues raised by the procedure.

ICRP 98 writing Committee :

- *Chairman* : **JM COSSET (Paris, France)**
- *Full members* : **D.ASH (Leeds, UK)**
- **L.PINILLOS-ASHTON (Peru)**
  T.McKENNA (IAEA)
  M.ZELEFSKY (New-York, USA)
  M.HIRAOKA (Kyoto, Japan)
- *Corresp. members* : **W.YIN (Beijing, China)**
  L.DAUER (New-York, USA)
  C.PEREZ (USA)
  JC.ROSENWALD (France)

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- When this study started, surprisingly few precise data in the literature …
- The Task Group in charge actually « triggered » some complementary measurements ; MSKCC, Leeds (UK), Institut Curie (France)…

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Table 1

	Nb of Patients	Anterior μSr/h						Lateral μSr/h					
		Surface	20cm	25cm	30cm	50cm	100cm	Surface	20cm	25cm	30cm	50cm	100cm
Smathers I 125	19	50 (22-89)					< 0.3	0.06					< 0.3
Leeds I 125	62	26.75 (2-67)				2.6 (0.2-5.1)	0.75 (0-1.6)	1.43 (0.1-17.4)				0.3 (0-1.9)	0.1 (0-0.5)
Curie I 125	47	115 (17-350)	22 (4-61)					0.8 (0.2-1.5)					
MSKCC I 125	545	37.3 (0.9-221)			6.0 (0.2-32.7)		< 0.9	1.9 (0.9-16.8)					< 0.9
Smathers PD 103	19	17 (5-49)					< 0.3	0.19					< 0.3
MSKCC PD 103	72	8.2 (0.9-63.6)			2.9 (0.2-15)		< 0.3	1.4 (0.9-6.2)					< 0.9

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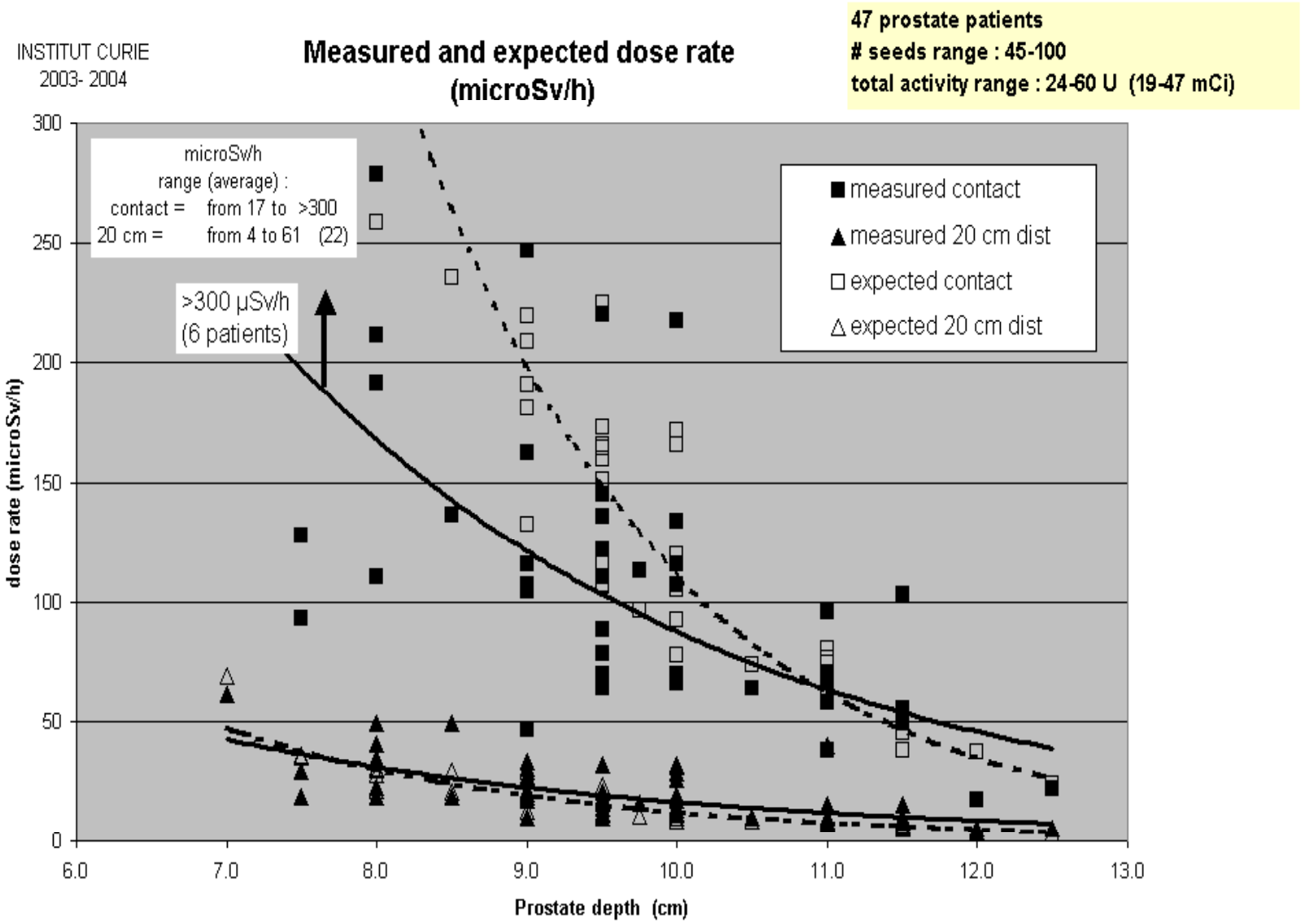
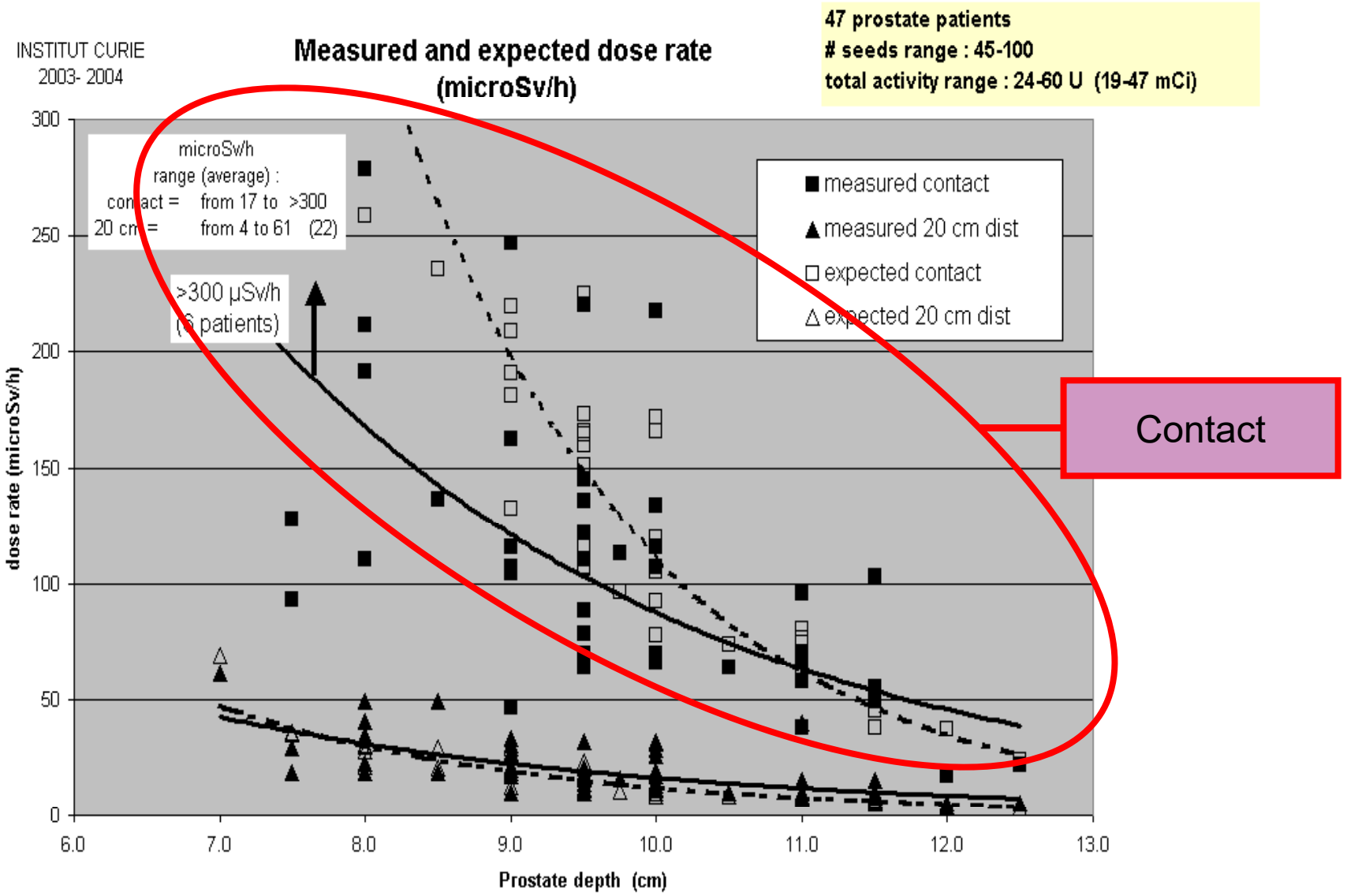


Figure 1 : Dose rate at abdomen surface (squares) and at 20 cm distance (triangles) for a series of 47 patients of Institut Curie for various patient thickness (the prostate depth was assumed to be half of the patient thickness).



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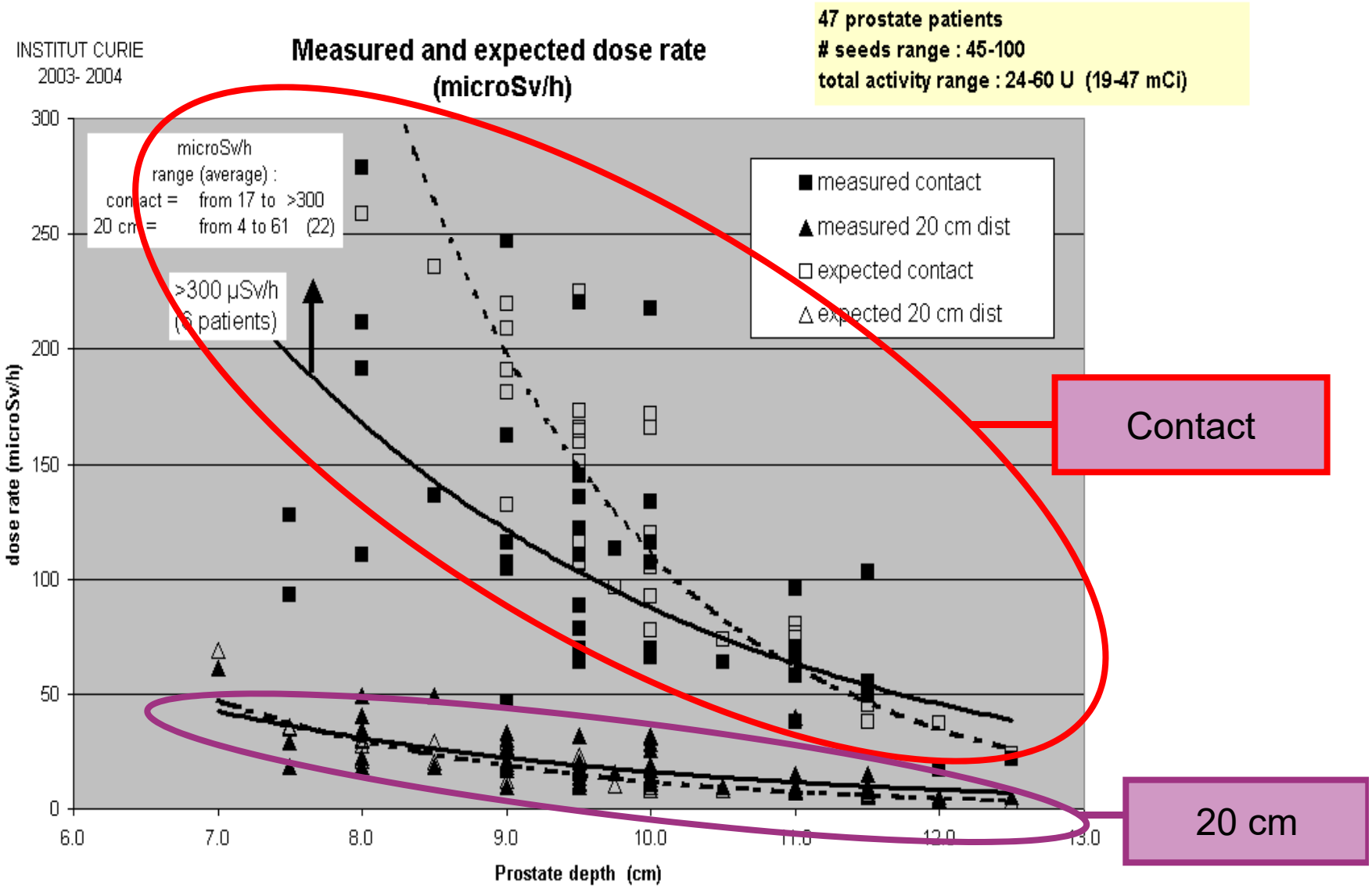

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One large-scale study in the literature;

- Michalski et al; (2003):
- For 44 patients ;
- Dosimeters to the patient, spouse, children, pets (!), and monitoring of 4 rooms frequently occupied by the patient
- *Very low levels of exposure :*
- Example; Calculated mean lifetime dose to a spouse; 0.1 mSv for a ^{125}I implant ...

To make a long story short ;

- ***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)...

- **A New recent study (paper submitted in 2016):**

- **Prospective study of direct radiation exposure measurements for family members living near patients with prostate iodine-125 seed implantation: Proof of radiation safety**
- Takashi Hanada, Ph.D.*1, 2, Atsunori Yorozu, M.D., Ph.D.2, Yukiko Shinya, M.D.2, et al.

- MATERIAL AND METHODS: Twenty-five patients who underwent 125I seed implantation, along with their family members, were provided dosimeters to measure direct radiation 10 exposure. The estimated lifetime exposure dose (ELED) and precaution time for holding children near the patient's chest were calculated.

- **“According to findings, our sample size was large enough to suggest that no precautions are necessary for most family members who 194 are approaching implanted patients”**

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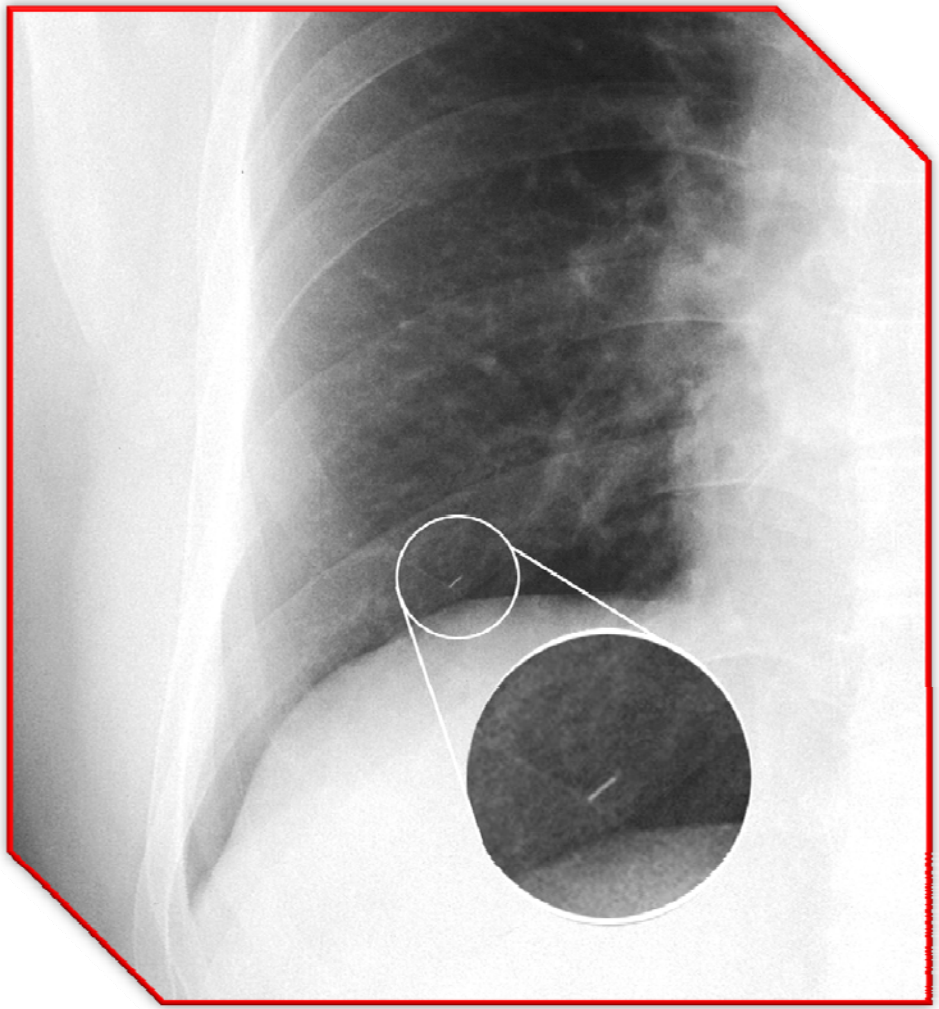
Seeds may migrate to the lungs (no radioprotection problem …)



- And may be expelled from the patient's body in three ways ; urine, semen, and gastro-intestinal tract (this last case very rare !)
- More frequent with « free » seeds than with « stranded » seeds .

In experienced teams, those migrations are now very rare (even with free seeds), but :

- Recommandations should be given to the patients:
- Sieving the urine at least for a few days
- Use of a condom for the first five ejaculates
- Recommandations also for the brachytherapists; they should adapt their technique in order to reduce the number of migrations !

Result of the discussions within the task group :

... " Expelled seeds may represent a hazard for people finding them if unaware of the (small) risk of touching them (particularly young children), this is the reason why sieving the urine is often recommended.

However, one has to keep in mind that two risks have to be balanced : the risk of a patient dealing inadequately with a (or several) seed(s) found by sieving their urine , and the risk (actually negligible) of flushing a source in the toilets." ...

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… "Therefore, identification of migrating sources is useful from a medical point of view (at least to try and improve the technique in order to reduce those migrations)…

…while from a radiation safety perspective it is better to have the seeds flushed down the toilet instead of stored by the patient and transported back to the physician." …

- **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

4. CREMATION 27
4.1. Current national recommendations 27
4.2. Activity remaining in patients' ashes 28
4.3. Potential airborne releases 29
4.4. Recommendations for cremation 29

4. CREMATION 27
4.1. Current national recommendations 27
4.2. Activity remaining in patients' ashes 28
4.3. Potential airborne releases 29
4.4. Recommendations for cremation 29

A difficult topic …

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Cremation

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

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)

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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) »*

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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)

6. FATHERING OF CHILDREN 33

- 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 !

A recent paper (Mydlo 2004), after an extensive review of the literature and an estimation of only 20 cGy for the dose to testis, speculates that *the effects of prostate brachytherapy on spermatogenesis in prostate cancer patients are minimal.*

What about the genetic risk ?
(Collaboration with ICRP Committee 1)

- *Current estimates of the genetic risks from radiation (UNSCEAR 2001) suggest that a paternal testicular dose of 1 Gy to a patient would result in an excess of around 1 case in 300 live born offspring…"*

What about the genetic risk ?

- *“ This is a small percentage increase (~4 %) over the natural incidence of these genetic effects and these figures may serve to reassure patients on the relatively low risk of genetic effects in their children.”*

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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 +++

8. SECONDARY CANCERS 37
8.1. Secondary cancers after prostate brachytherapy 37
8.2. Secondary cancers after treatment of prostate cancer 37
8.3. Secondary cancers after external irradiation for prostate cancer 37
8.4. Secondary cancers: conclusions 38

- Almost no case of second cancers reported after prostate brachytherapy
- But ; possible problem of follow-up ...

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Secondary cancers: The conclusions of the task group (2005);

- The risk of a second radio-induced cancer (in the life time of a patient) after prostate brachytherapy therefore appears to be either nil , or extremely low
- The benefits of the technique clearly outweigh (by far !) the (limited) risk of second malignancies ...

Cancer. 2006 Sep 1;107(5):991-8. Links

Cancer incidence after localized therapy for prostate cancer.

Moon K, Stukenborg GJ, Keim J, Theodorescu D.
Department of Urology, University of Virginia, Charlottesville, Virginia 22908, USA.

- CONCLUSIONS: Patients who received EBRT had significantly higher odds of developing second cancers both overall and in the areas that were exposed to radiation. It is noteworthy that, to the authors' knowledge, this report shows for the first time that, despite the higher doses of radiation delivered, **patients who received radioactive implants had the lowest odds of developing second cancers.** *(Actually no increase at all for those patients!)*

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Second cancers after prostate cancer RT

- . Strahlenther Onkol. 2007 Nov;183(11):605-9.
- **Risk of second malignancies after prostate irradiation?**
- Müller AC, Ganswindt U, Bamberg M, Belka C.
- **DISCUSSION:**
- Up to now, all available data are highly heterogeneous. Thus, a low risk for secondary cancer cannot be ruled out completely **Nevertheless, it seems very unlikely that there is a relevant risk for secondary cancer since the largest of the published series did not document an increased risk for any secondary cancer.**

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Risk of second primary cancer following prostate cancer radiotherapy : DVH analysis using the competitive risk model »
Takam R. et al.

Phys Med Biol, 2009

- *« The average risk of developing SPC was no greater than 0.6 % for all treatment techniques but* ***was lower with either LDR or HDR brachytherapy alone*** *compared with any EBRT technique. »*

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Second cancers after prostate cancer RT

- Radiother Oncol. 2011 Jan;98(1):81-6.
- **Analysis of second malignancies after modern radiotherapy versus prostatectomy for localized prostate cancer.**
- Huang J, Kestin LL, Ye H, Wallace M, Martinez AA, Vicini FA.
- **CONCLUSIONS:**
- **Radiation-related SPC risk varies depending on the RT technique and may be reduced by using BT, BT boost, or 3DCRT/IMRT.**

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- BJU Int. 2012 Dec;110(11):1696-701.
- **Secondary cancers after intensity-modulated radiotherapy, brachytherapy and radical prostatectomy for the treatment of prostate cancer: incidence and cause-specific survival outcomes according to the initial treatment intervention.**
- Zelefsky MJ[1], Pei X, Teslova T, Kuk D, Magsanoc JM, Kollmeier M, Cox B, Zhang Z.
- [1]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA. Zelefskm@mskcc.org

- **CONCLUSIONS:**
- **The incidence of SM after radiotherapy was not significantly different from that after RP when adjusted for patient age and smoking history.**

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- Clin Oncol (R Coll Radiol). 2014 Apr;26(4):210-5.

Second primary cancers occurring after I-125 brachytherapy as monotherapy for early prostate cancer.

- Musunuru H[1], Mason M[1], Murray L[1], Al-Qaisieh B[2], Bownes P[2], Smith J[3], Franks K[1], Carey B[3], Bottomley D[1], Henry AM[4].

- **AIMS:**
- Prostate brachytherapy may be associated with a lower risk of radiation-induced second primary cancer (SPC) as a significantly smaller volume of normal tissue is irradiated when compared with external beam techniques.
- **MATERIALS AND METHODS:**
- SPC incidence was retrieved by conducting a UK cancer registry search (Northern and Yorkshire Cancer Registry and Information Service) for 1805 consecutive patients with localised prostate cancer who received monotherapy with I-125 brachytherapy from 1995 to 2006 at a single public hospital.
- **RESULTS:**
- In total, 170 patients (10.8%) were diagnosed with second primaries (1 year or more after implant); 20 of these were bladder and 10 rectal cancers.
- CONCLUSIONS:
- Overall, the incidence of SPC after I-125 is comparable with other published data with no significant excess more than 5 years from treatment. Mortality secondary to SPC of the bladder or rectum is unusual.

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- Radiother Oncol. 2014 Feb;110(2):213-228.
- **Second primary cancers after radiation for prostate cancer: A systematic review of the clinical data and impact of treatment technique.**
- Murray L[1], Henry A[2], Hoskin P[3], Siebert FA[4], Venselaar J[5]; PROBATE group of the GEC ESTRO.

- **Abstract**
- The development of a radiation induced second primary cancer (SPC) is one the most serious long term consequences of successful cancer treatment.
- An increased risk of radiation-induced SPC has been identified in several studies, particularly those with longer durations of follow-up.
- **The risk of radiation-induced SPC appears small,** in the range of 1 in 220 to 1 in 290 over all durations of follow-up, and may increase to 1 in 70 for patients followed up for more than 10years,

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Radiother Oncol. 2014 Feb;110(2):213-228.

Second primary cancers after radiation for prostate cancer: A systematic review of the clinical data and impact of treatment technique.

Murray L[1], Henry A[2], Hoskin P[3], Siebert FA[4], Venselaar J[5]; PROBATE group of the GEC ESTRO.

To date there are insufficient clinical data to draw firm conclusions about the impact of more modern techniques such as IMRT and brachytherapy on SPC risk, although limited evidence is encouraging.

In conclusion, despite heterogeneity between studies, an increased risk of SPC following radiation for PCa has been identified in several studies, and this risk appears to increase over time. This must be borne in mind when considering which patients to irradiate and which techniques to employ.

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- Int J Radiat Oncol Biol Phys. 2014 Nov 15;90(4):934-41.
- **Incidence of second malignancies in prostate cancer patients treated with low-dose-rate brachytherapy and radical prostatectomy.**
- Hamilton SN[1], Tyldesley S[1], Hamm J[2], Jiang WN[3], Keyes M[1], Pickles T[1], Lapointe V[4], Kahnamelli A[5], McKenzie M[1], Miller S[6], Morris WJ[7].
- **METHODS AND MATERIALS:**
- From 1998 to 2010, 2418 patients were treated with Iodine 125 prostate BT monotherapy at the British Columbia Cancer Agency, and 4015 referred patients were treated with RP. ...
- **Results :**
- Radical prostatectomy was not associated with a decreased pelvic malignancy risk compared with BT (HR 0.57, P=.082), even when excluding postprostatectomy external beam radiation therapy patients (HR 0.87, P=.56).

- **CONCLUSIONS:**
- **After adjustment for covariates, BT patients did not have an increased second malignancy risk compared with RP patients. Further follow-up of this cohort is needed given the potential latency of radiation-induced malignancies.**

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- Int J Radiat Oncol Biol Phys. 2015 Feb 1;91(2):295-302.
- **Risk of second cancers according to radiation therapy technique and modality in prostate cancer survivors.**
- Berrington de Gonzalez A[1], Wong J[2], Kleinerman R[2], Kim C[2], Morton L[2], Bekelman JE[3].
- **Author information**
- , National Cancer Institute, National Institutes of Health, Bethesda, Maryland. Electronic address: berringtona@mail.nih.gov.
- **METHODS AND MATERIALS:**
- The cohort was constructed using the Surveillance Epidemiology and End Results-Medicare database. We included cases of prostate cancer diagnosed in patients 66 to 84 years of age from 1992 to 2004 and followed through 2009.
- **RESULTS:**
- During an average of 4.4 years' follow-up among 5-year prostate cancer survivors ... 2933 second solid cancers were diagnosed. ...
- Rates of second solid cancers for higher- and lower-energy RT were similar overall (RR = 0.97, 95% CI: 0.89-1.06), as were rates for site-specific cancers.

- **There were significant reductions in colon cancer and leukemia rates in the first decade after brachytherapy compared to those after external beam RT.**

- Comments ; short follow-up ! .....

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APPENDIX C. EXAMPLE OF MINIMUM RECOMMENDATIONS TO BE GIVEN TO PATIENTS UNDERGOING PROSTATE BRACHYTHERAPY WITH PERMANENTLY IMPLANTED SEEDS 45

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A reminder ; the ICRP 98 Main Points

- 1/ The use of permanent radioactive implants .... is rapidly increasing all over the world
- 2/ No adverse effects to the medical staff and/or patient family have been reported so far.
- 3/ The dose from the patients ... remains in almost all cases well below 1 mSv.
- 4/ Expulsion of sources through urine, semen or gastro-intestinal tract is a rare event. Simple recommendations should be given to the patient
- 5/ Cremation can be allowed if 12 months have elapsed since the implantation (more ?)
- 6/ The patient must be provided with specific recommendations (+++)...

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2010 ; A key paper !

Dauer LT, Kollmeier MA, Williamson MJ, St Germain J, Altamirano J, Yamada Y, Zelefsky MJ.

Less-restrictive, patient specific radiation safety precautions can be safely prescribed after permanent seed implantation

- Brachytherapy. 2010.

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Editorial

Prostate brachytherapy patients are (almost) normal people !

Jean-Marc Cosset 1,2

- 1. Department of Oncology/Radiotherapy, Institut Curie, Paris, France
- 2. Vice chairman, International Commission on Radiological Protection (ICRP) committee 3

- “ ….Actually, the precise instructions to be given to the patients were left to the discretion of the facilities performing brachytherapy; those instructions were *frequently amplified* by the hospitals, with recommendations being often more conservative than those published by ICRP… “

- ....Moreover, those radioprotection aspects have also sometimes been reported in the general press, and here again with a significant enhancement of the message (For example *"Avoid all contacts with children for six months" !*...) .

- Such a drift may be responsible for two types of risk;
- first, the risk to induce in some implanted patients the feeling to be somewhat “plague-stricken”,
- and secondly, the risk that some others give up the brachytherapy proposal, simply because they fear to endanger their family...

- In this specific context, Lawrence T. Dauer and his colleagues of the MSKCC have to be commended for the cardinal work published in the present issue of “Brachytherapy”(2), because this study is going to allow *to significantly refine the recommendations to the patients*, in terms of the duration time during which precautions are really required.

- This study is based on a large cohort of patients (1279 cases), for whom precise radiation exposure rate measurements have been obtained between 1995 and 2008.
- The first (important) message of L.T.Dauer and colleagues is that ***no precaution*** (e.g, no precaution at all !) is necessary for a large panel of persons approaching the patients after a prostate implantation ;

- : that is the case for all implantations with Pd 103.
- After a typical implantation with I 125, no precaution at all is required for coworkers and non pregnant adults (even those sleeping with the patient). Only the pregnant adult sleeping with the patient and children can in some situations reach the “limits”.
- *Of note, the limits chosen here are still “conservative”, since set at 50 % only of the ALARA guidelines…*

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- The second message, maybe more important, is that the authors propose an algorithm enabling to determine the precaution time for a given patient, based upon the precise exposure rate measured at 30 cm from the patient. *As mentioned above, those calculations are only useful for the case of a pregnant adult sleeping with the patient, and in case of children in the house and held. The crude result is that it is now possible to customize the precaution time for each patient case.*

- For example, at their median exposure rate of 0.5 mR/h at 30 cm (for I 125) , the authors report that the patient should avoid sleeping “in contact” with a pregnant adult for 84 days, and avoid holding children in the lap for long periods of time (more than 1-3 hours) for 42 days.

- However, direct measurements on the patient and use of the algorithm now allow to refine this precaution time; in the case of a very obese patient, with few seeds implanted, and with consequently a very low measured exposure rate, precaution time may be anticipated *to be much shorter, and even nil in some specific cases.*

- In contrast, for a skinny patient with a large number of implanted seeds, with a higher exposure rate (The authors report a maximum level of 3.6 mR/h), the precaution time can be calculated to be significantly longer.

- Those customized recommendations should serve to reassure both the patients and the authorities.

In conclusion, in almost all cases, prostate brachytherapy patients should be considered as normal people !

Thank You !

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Brussels 2016

FOCAL BRACHYTHERAPY : The French experience

Jean-Marc Cosset

Institut Curie and Institut Mutualiste Montsouris,
Paris, France

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The French experience

- **In Paris, since 2006 : close collaboration between the radiotherapy department of the Institut Curie and the Urology department of the Institut Mutualiste Montsouris (IMM);**
- **To date :**
- **Overall : more than 500 focal treatments performed at the IMM, essentially using:**
- **Photodynamic therapy**
- **HIFU (ultrasounds)**
- **Cryotherapy**
- **Brachytherapy**

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- **Morbidity of focal therapy in the treatment of localized prostate cancer.**
- *Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, Macek P, Durand M, Prapotnich D, Rozet F, Cathelineau X.*
- *Eur Urol. 2013 Apr;63(4):618-22.*
- **TOOKAD(®) Soluble vascular-targeted photodynamic (VTP) therapy: determination of optimal treatment conditions and assessment of effects in patients with localised prostate cancer.**
- *Azzouzi AR, Barret E, Moore CM, Villers A, Allen C, Scherz A, Muir G, de Wildt M, Barber NJ, Lebdai S, Emberton M.*
- *BJU Int. 2013 Oct;112(6):766-74*
- **Focal cryoablation: a treatment option for unilateral low-risk prostate cancer.**
- *Durand M, Barret E, Galiano M, Rozet F, Sanchez-Salas R, Ahallal Y, Macek P, Gaya JM, Cerruti J, Devilliers H, Loeffler J, Amiel J, Vallancien G, Cathelineau X*
- *BJU Int. 2014 Jan;113(1):56-64.*

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- In Paris, **focal brachytherapy was initiated in February 2010**,
- According to a protocol approved by the IMM ethics committee, with all patients receiving detailed information and signing an informed consent.

- **In this Phase II non-randomized study,**
- **Patient selection is based on (at least) two series of prostate biopsies (with a minimum of 20 biopsies overall)**
- **and on a high-resolution endorectal MRI.**

- **Only patients with very limited and localized tumors, according to strict criteria, (*actually almost the same as in the "consensus" paper*), were selected for the procedure.**

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- **The entry criteria being almost identical to the French active surveillance's ones,**
- **All patients were proposed active surveillance, but they expressed their (written) will to choose focal treatment.**
- **Among those patients reffered to our group for discussion of a focal brachytherapy, only 2 chose the surveillance strategy *(but clear selection of patients)*...**

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- **The technique is directly derived from the "real-time" procedure (already published by our team) with the permanent implantation of "free" LDR 125 Iodine seeds,**
- **The reason for the choice of the I 125 seeds:**
- **An experience of more than 3600 patients implanted with 125 I seeds since 1998 by our group,**
- **And the recommendations of the 2012 BJU Consensus paper :**
- ***"When reviewing the characteristics of the different permanent seed isotopes available (125I, 103Pd and 131Cs) it was noted that 125I had the most favourable characteristics"***

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- **The reasons for the choice of a permanent-implant free-seed technique :**
- **Again, our experience of more than 3600 treated patients,**
- **And again, the recommendations of the 2012 consensus paper:**
- ***" The greater flexibility afforded by loose seeds may be important for implanting the central portion of the prostate as in a hemi-gland implant."***
- ***"For the ultra-focal protocol, loose seeds might be preferable."***

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- **We chose to deliver to the focal volume the dose usually recommended by the GEC-ESTRO for the whole prostate (145 Gy).**
- **Sticking to the same dose constraints to the surrounding structures : see :**
- ***Tumour and target volumes in permanent prostate brachytherapy: the ESTRO/EAU/EORTC recommendations on prostate brachytherapy.***
- *Salembier C, Lavagnini P, Nickers P, Mangili P, Rijnders A, Polo A, Venselaar J, Hoskin P; GEC ESTRO PROBATE Group.*
- *Radiother Oncol. 2007 Apr;83(1):3-10*

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Finally,

- **Considering our (severe) selection of patients,**
- **We chose to propose, in most cases, the « ultra-focal » technique, with a margin of about 10 mm around the MRI target.**

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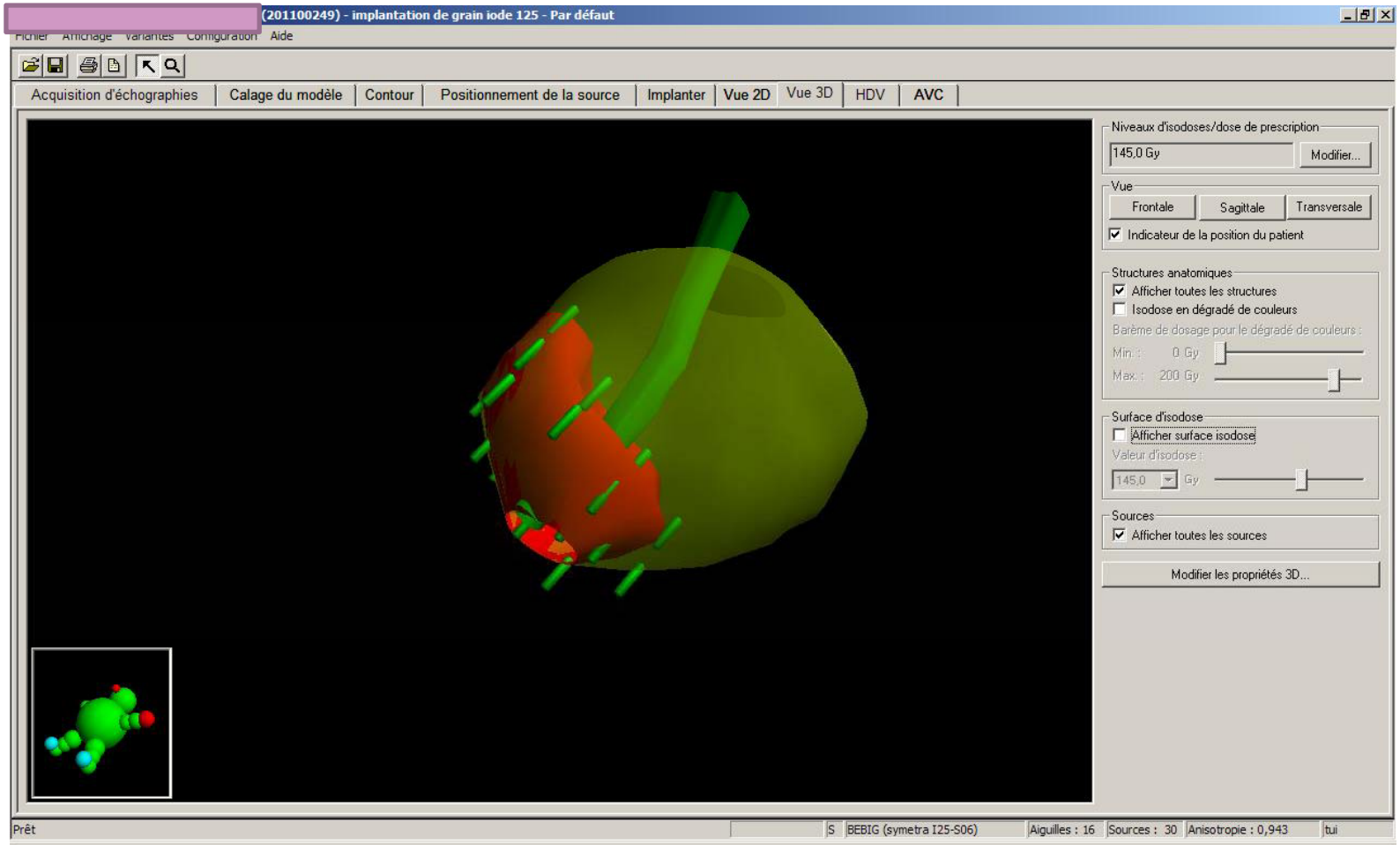
First step ; Choice of the « focal » Volume, based whenever possible on a MRI-echography fusion



- **Second step ; Complete real-time preplanning**
- **Third step : Implantation of needles**
- **Fourth step: Implantation of seeds, according to the preplanning, with continuous feed-back taking into account the real position of each seed (« dynamic dosimetry »).**

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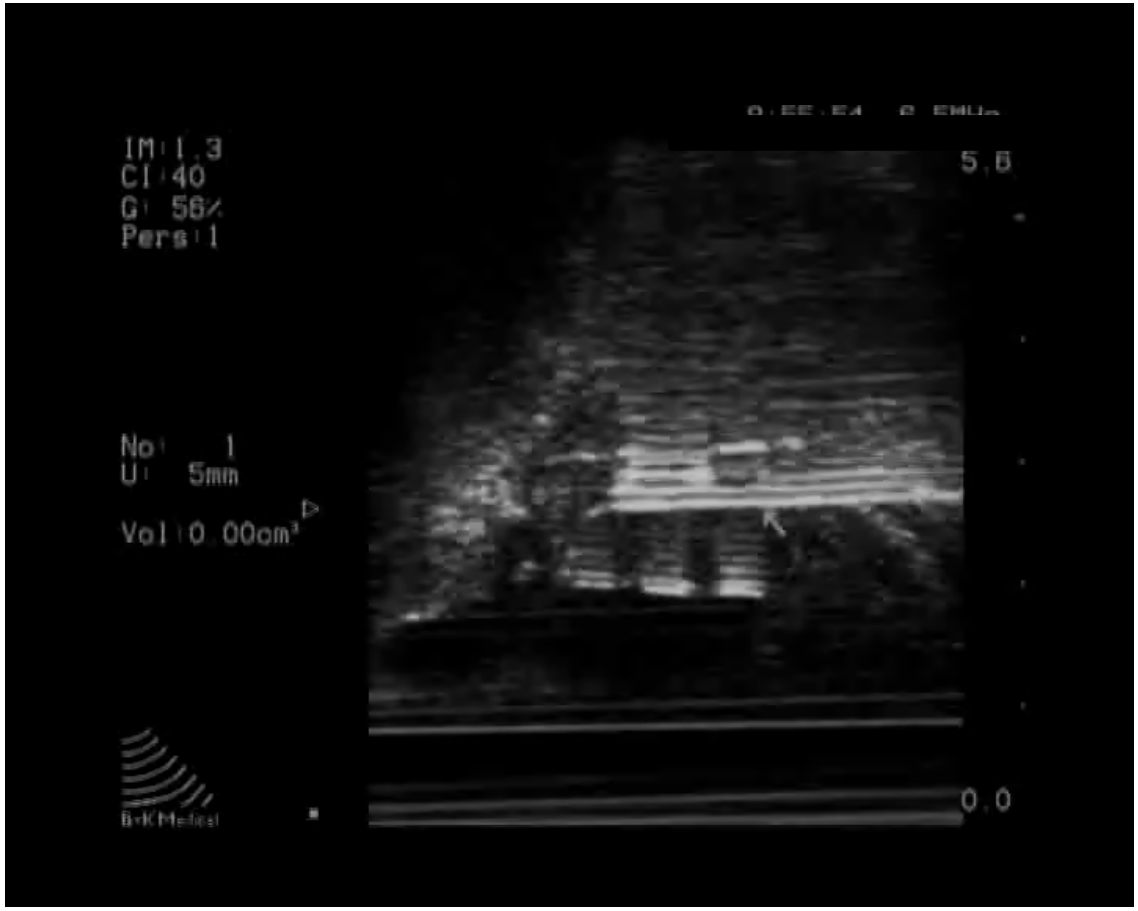
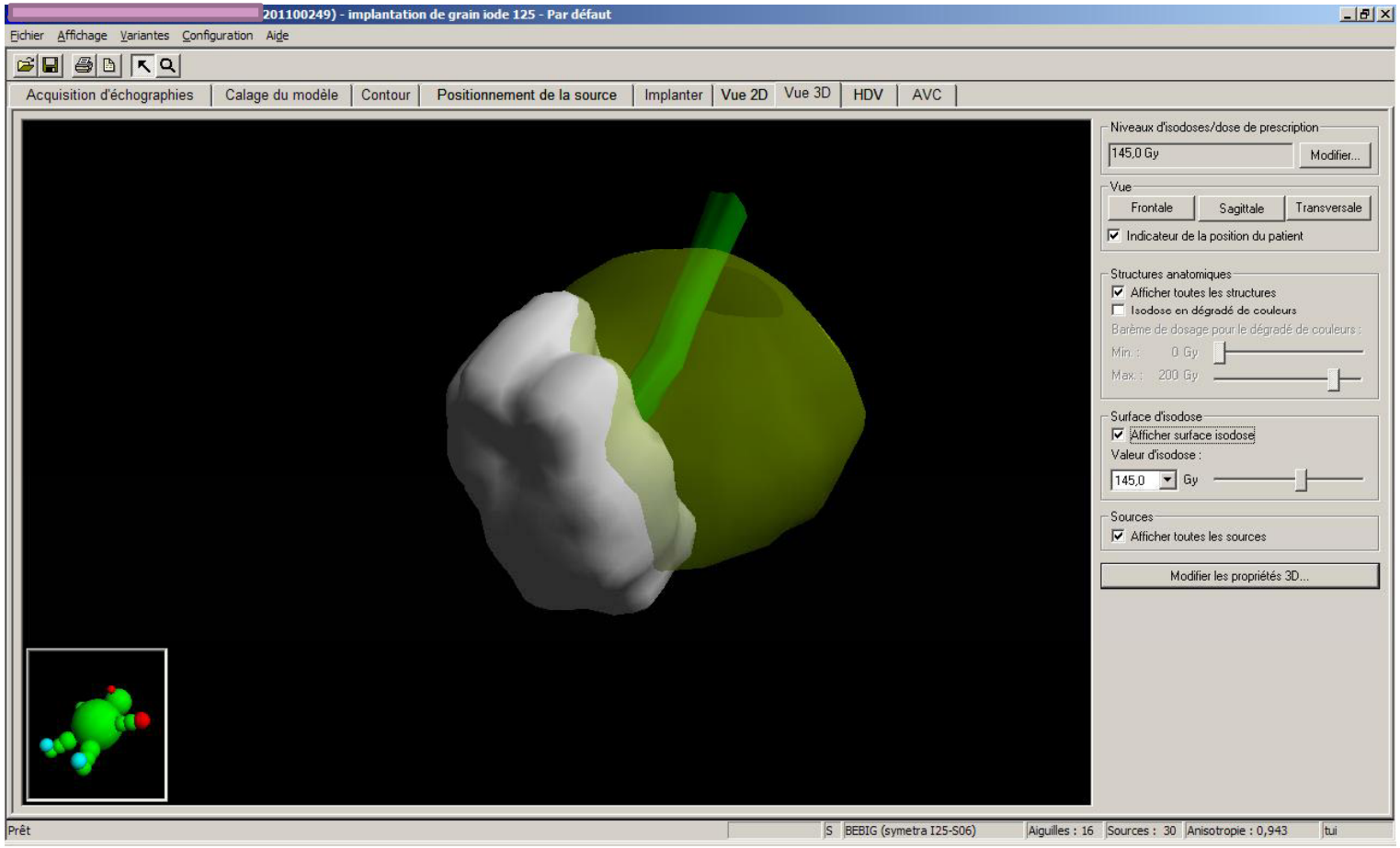

IM 1.3
CI 40
G 56%
Pers 1
No 1
U 5mm
Vol 0.00cm³
5.6
0.0
B-K Medical

Fifth step : Dosimetric results ; In white: the 145 Gy isodose



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Preliminary results

- **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], FrançoisRozet[2,] Marc Galiano[2], Guy Vallancien[2]**
- [1] Department of Oncology/Radiotherapy, Institut Curie, 75005 Paris, France
- [2] Department of Urology, Institut Mutualiste Montsouris, 75013 Paris, France
- 3 Department of Radio-Oncology, Hospital Charles LeMoyne, Montréal, Canada
- 4 Department of Statistics, Institut Curie, 75005 Paris, France

- **Brachytherapy, 2013, 12, 331-337**

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In this first series :

- **21 focal implantations** were performed and analyzed,
- *(Today -June 2016- : 48)*
- The treated volume corresponded to a **mean value of 35% of the total prostatic volume (range 20-48 %).**
- For the focal volume, **mean D90 was 182 Gy, and the mean V100 was 99.6 %.**

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- **In our experience, the technique could be entirely performed in approximately an hour and a half, that is to say not significantly different from a usual "whole prostate" brachytherapy.**

- **Early urinary toxicity (still being evaluated) seems to be somewhat *inferior* to what is usually observed after brachytherapy of the whole prostate.**

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- **Table 1 : Urinary toxicity (scored by IPSS) and sexual toxicity (scored by IIEF5) for focal prostate brachytherapy. *Incontinence score (ICS) and rectal toxicity (almost constantly nil in this series) not shown.***
- Mean (range)
- **Initial IPSS** **5.3** (0-15)
- IPSS at 2 months 11.8 (1-28)
- IPSS at 6 months 6.6 (2-17)
- IPSS at 12 months **5.4** (2-9)

- **Initial IIEF5** **18.2** (1-25)
- IIEF5 at 2 months 16.6 (1-25)
- IIEF5 at 6 months 17.7 (1-25)
- IIEF5 at 12 months **18.3** (1-25)

- **we did compare the toxicities observed in this first 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**
- **(Questionnaires filled in by the patient himself and NOT by the physician).**

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- **Since almost no change in the ICS score nor in the rectal toxicity score was noted in both series, we concentrated on the evolution of IPSS and IIEF.**

- **We first checked that the two groups (“Focal” and “total”) were comparable in terms of initial IPSS (p=0.95) and initial IIEF (p=0.51).**
- **In both groups, we analyzed the mean scores at 2, 6 and 12 months, and also the variations of these scores (comparing the scores at distance with the initial values).**

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- **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).***

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- **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).***

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Update 2016 : A trend ?

- **With now 48 patients implanted (focal):**
- **Possible trend for less early urinary toxicity after focal implantation of the apex**
- **Compared with an implantation of the prostate base (?)**

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Update 2015

	Mean IPSS 2 months	Mean IPSS 6 months
All cases	**11.4**	**8**
Focal base	**13.4**	**10.1**
Focal apex	**9.9**	**6.7**

To be confirmed …

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Update 2016

- **Control biopsies** ; planned between 18 and 24 months post-implantation,
- 35 Patients accepted the control biopsies (10 to 28 cores) :
- 3 patients refused ...
- 1 relapsed before 2 years (lymph node relapse)
- 1 patient living abroad ...
- **In 27/35 cases ; control biopsies were negative,**
- **In 8 cases** ; **positive biopsies (23%)**

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8 positive control biopsies at 2 years

- **(- 1 case** ; **1 controlateral microfocus** ; active surveillance, but MRI suspect image at 4 years ; second series of biopsies ; **negative)**
- **- 1 case** ; 1 controlateral positive biopsy (Gleason 6) ; normal IRM and Pet-cholin and PSA still decreasing : **active surveillance.**
- **- 4 cases :** controlateral (+ homolateral in one case) : ***controlateral complementary focal brachytherapy*** (1 + 1 planned) or ***active surveillance*** (2)
- **- 2 homolateral : <u>above</u>** the focal treated volume ; **salvage treatment being discussed**

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Moreover :

- - **1 <u>nodal</u> (iliac) relapse** at 1 year ½ ; **hormone therapy.**
- - 1 relapse at (controlateral) biopsies performed at 3 years ½ *(while the 2 years control biopsies were negative)*; T3 MRI ; **radio-hormonotherapy.**

- *+ 1 case suspect ++ of homolateral relapse on MRI at 3 years (just above the treated focal volume) with a rising PSA ; Second series of biopsies (24) ; all negative : ?? …*

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Overall : update 2015

- Among 48 patients , 35 with a follow-up > 2 years.
- 10 (11 ?) relapses have been registered:
- A rate of about 21 % at 3 years ?
- Acceptable ?

Conclusion:

- **The French experience on 48 patients :**
- **Focal prostate treatment by brachytherapy is easily feasible,**
- **With apparently little acute urinary toxicity (essentially when treating the apex ?)**
- **No relapse occurred in the treated area (among 48 patients, but 2 “borders”),**
- **10 relapses / 48, with a relatively short follow-up of three years : too much ?**

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- **Therefore : non-negligible relapse rate outside the treated volume ,**
- **In spite of the relatively short follow-up,**
- **and of the severe selection of patients in this series …**
- **Tentative conclusion : PRUDENCE …**
- **Further investigation is needed to more precisely assess the long-term tumor control rate,**
- **Taking into account the possibility and efficacy of salvage therapies …**

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Thank you for your attention

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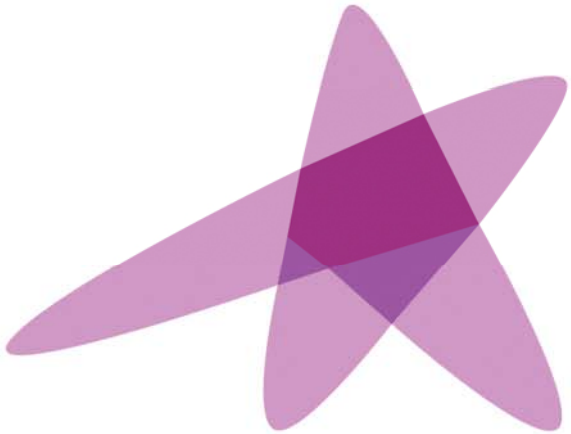

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How can we achieve focal therapy

- 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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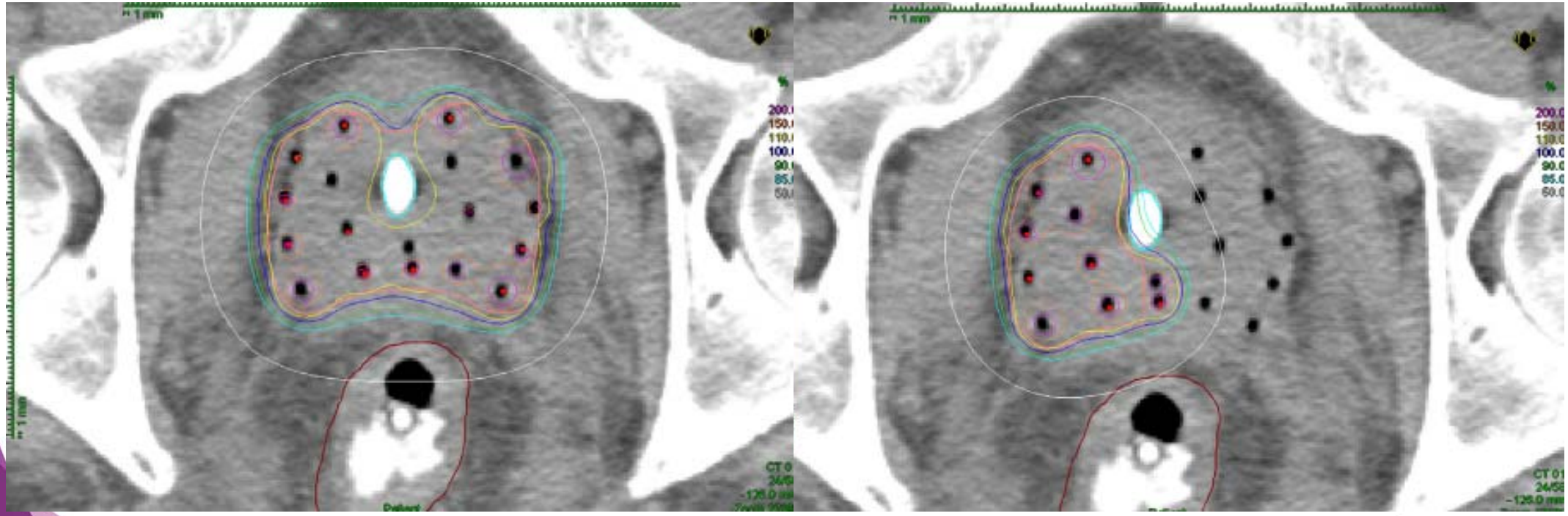
[3]*Department of Urology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA*

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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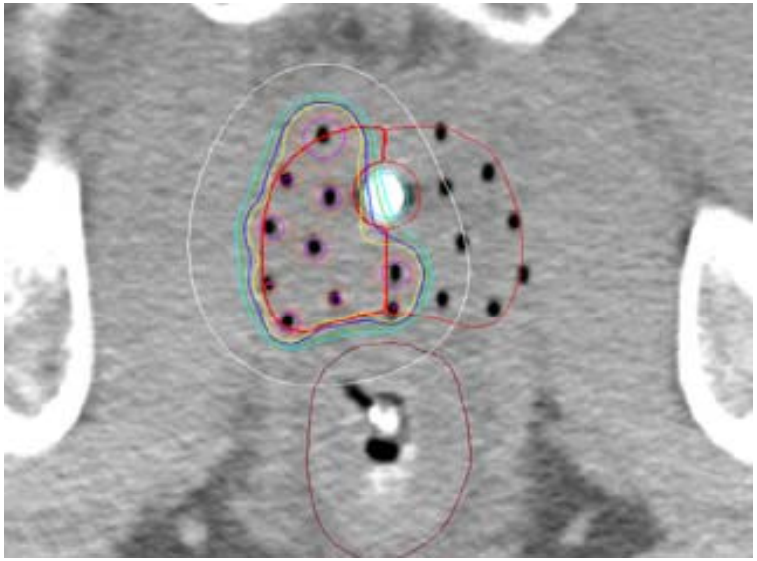

Evaluation of "spill" dose from hemigland treatment to contralateral hemigland

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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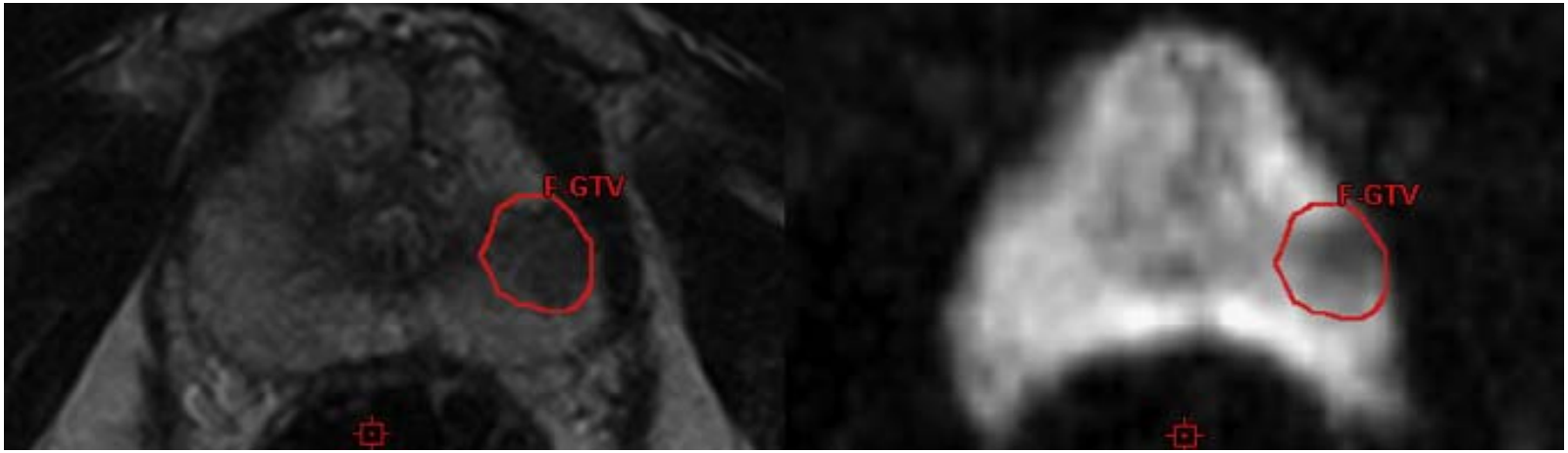
Dosimetry modeling for focal high-dose-rate prostate brachytherapy

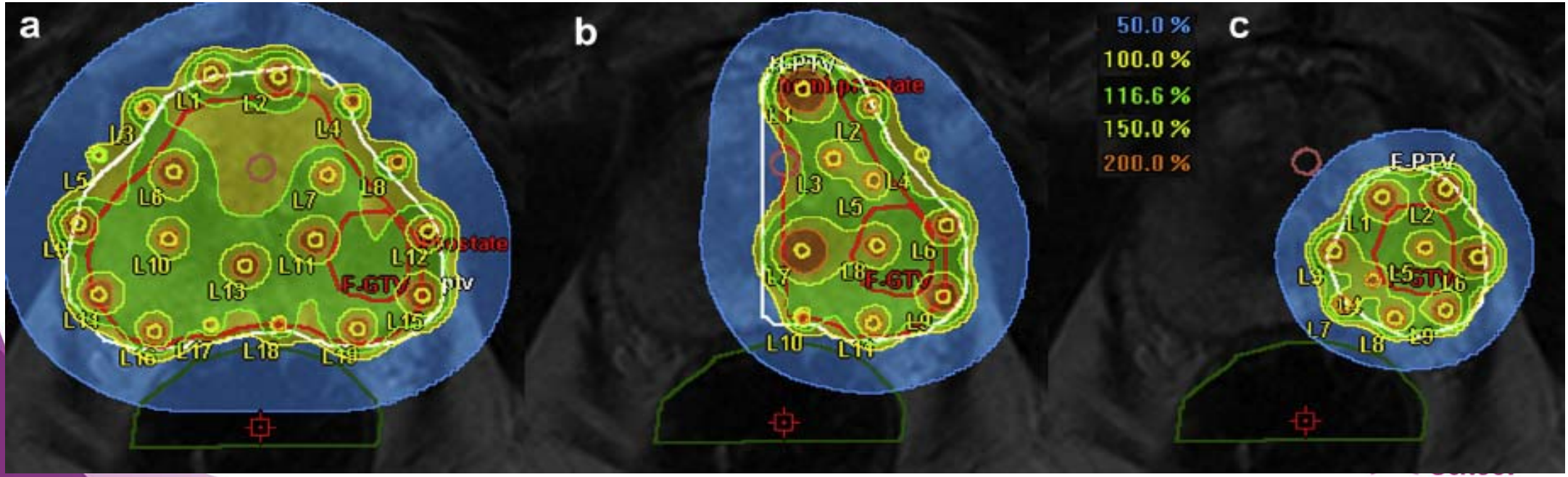
Josh Mason[1,2,*], Bashar Al-Qaisieh[1], Peter Bownes[1], David Thwaites[2,3], Ann Henry[4]

[1]*Department of Medical Physics and Engineering, St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK*

[2]*Academic Unit of Medical Physics, University of Leeds, Leeds, UK*

Brachytherapy 13 (2014) 611–617





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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

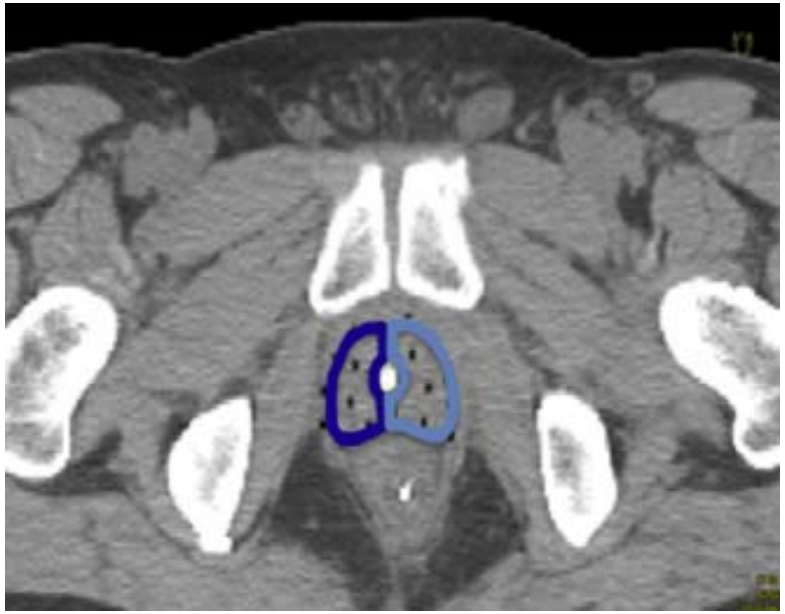
From whole gland to hemigland to ultra-focal high-dose-rate prostate brachytherapy: A dosimetric analysis

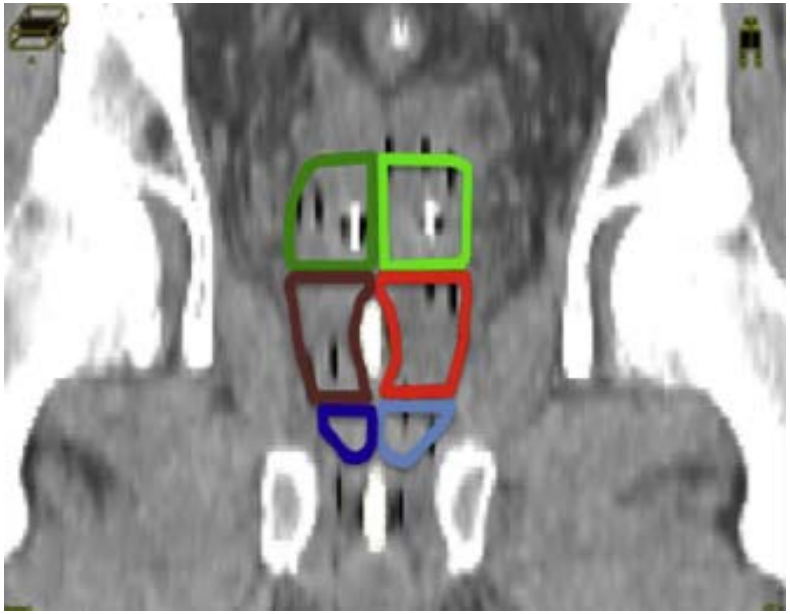
Robyn Banerjee[1], Sang-June Park[2], Erik Anderson[2], D. Jeffrey Demanes[2], Jason Wang[2], Mitchell Kamrava[2,*]

[1]*Department of Oncology, University of Calgary, Calgary, Alberta T2N 4N2, Canada*
[2]*Department of Radiation Oncology, University of California Los Angeles (UCLA), Los Angeles, CA 90095, USA*

Brachytherapy 14 (2015) 366–372

Whole gland vs hemigland vs focal





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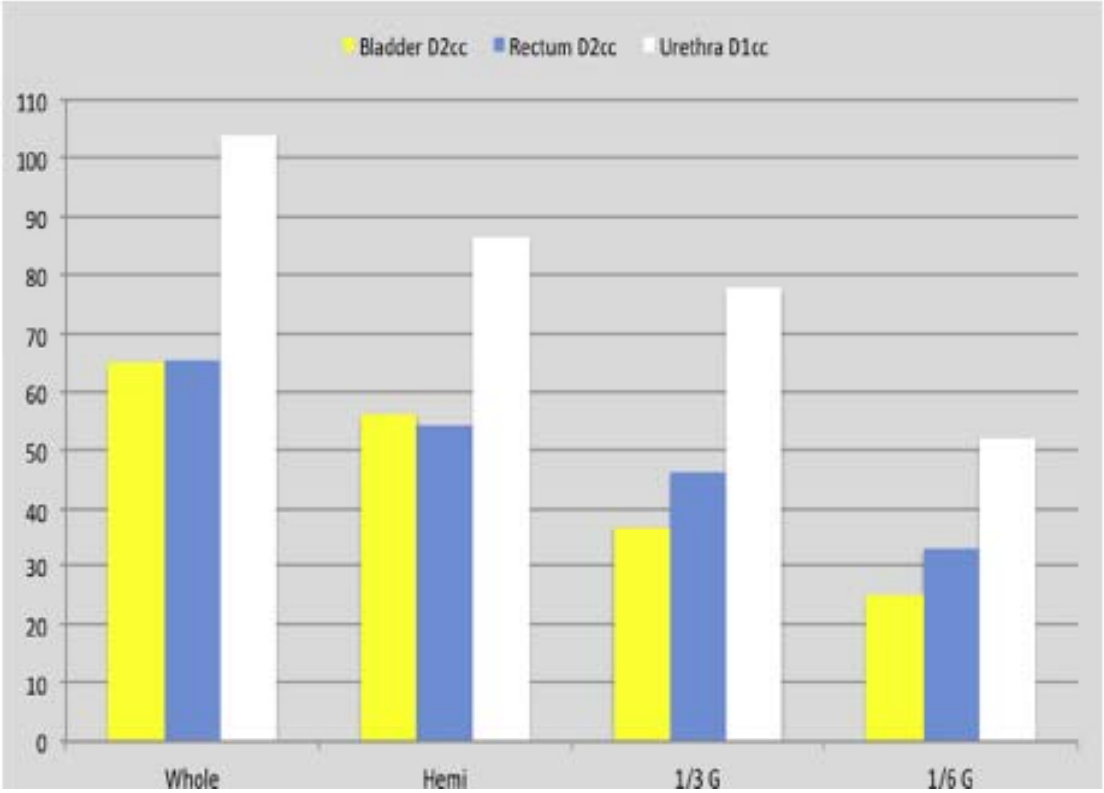
Brachytherapy 14 (2015) 366–372

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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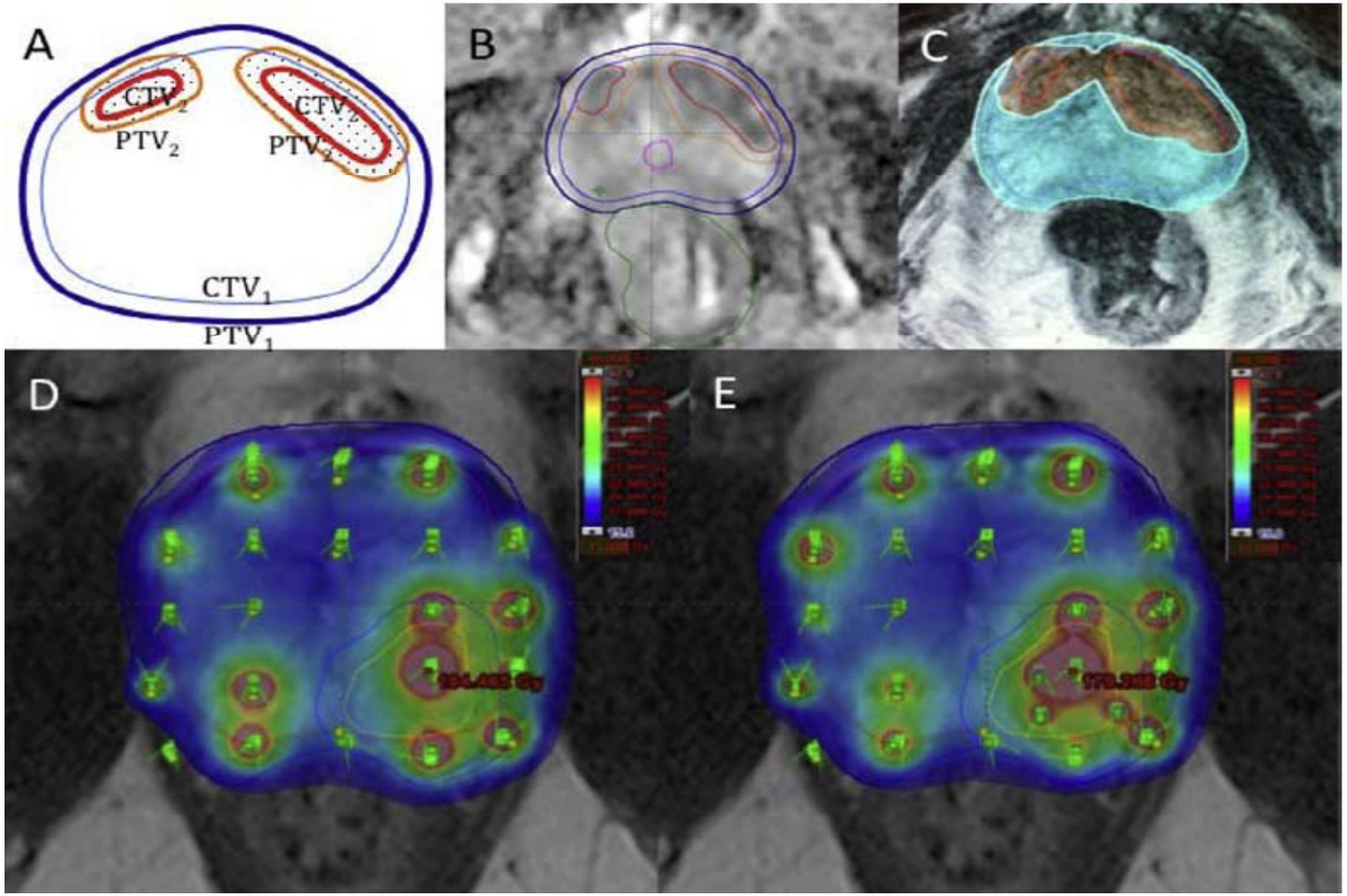
Optimal source distribution for focal boosts using high dose rate (HDR) brachytherapy alone in prostate cancer

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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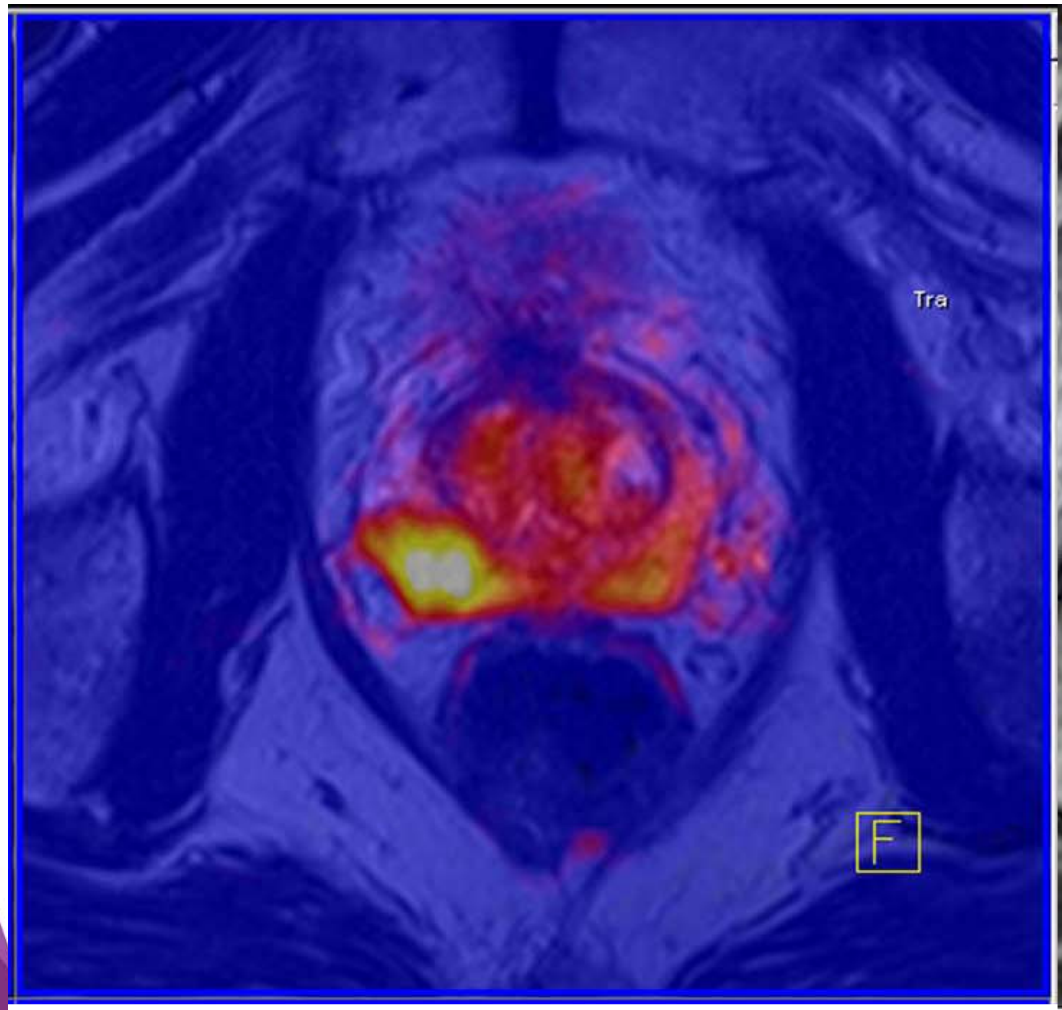
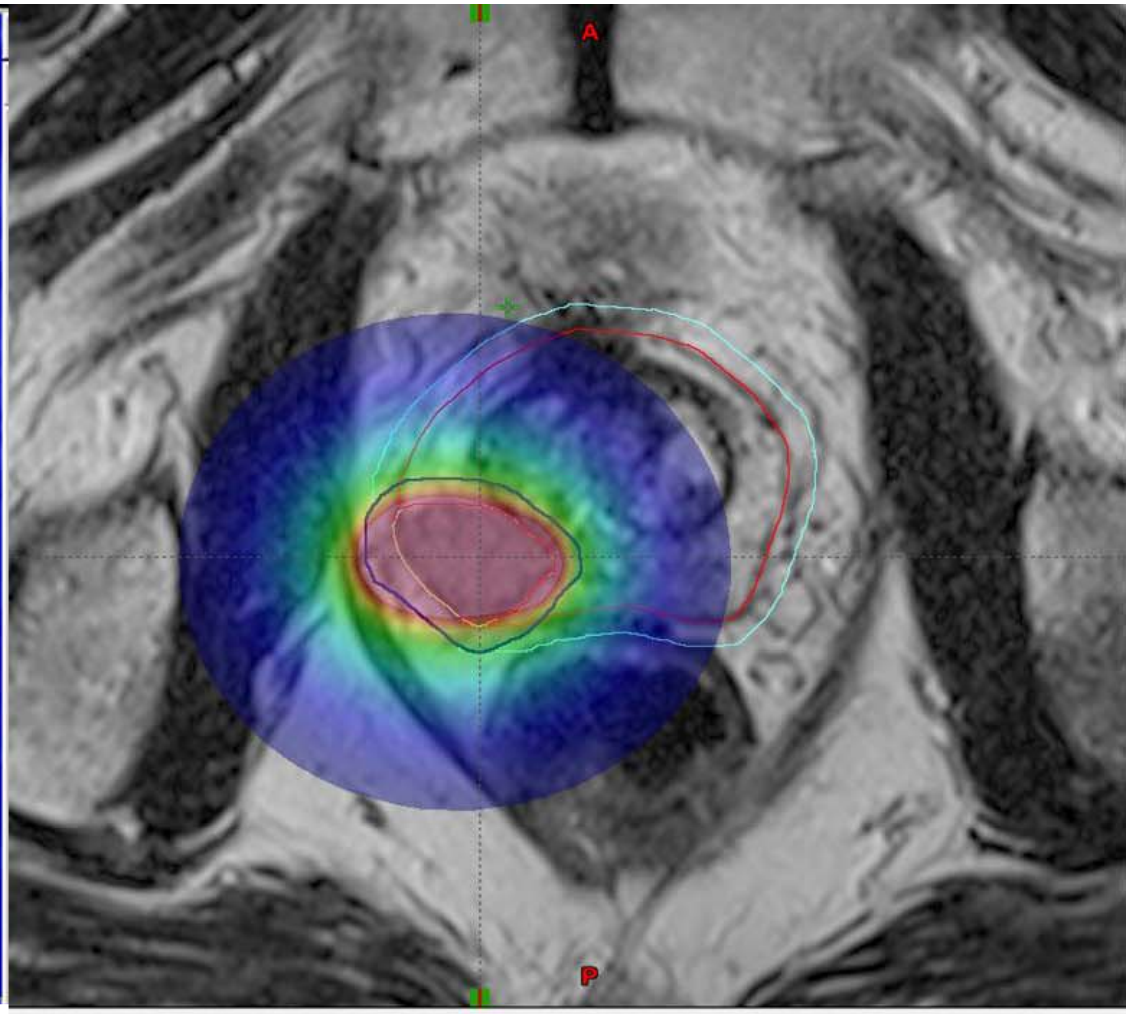
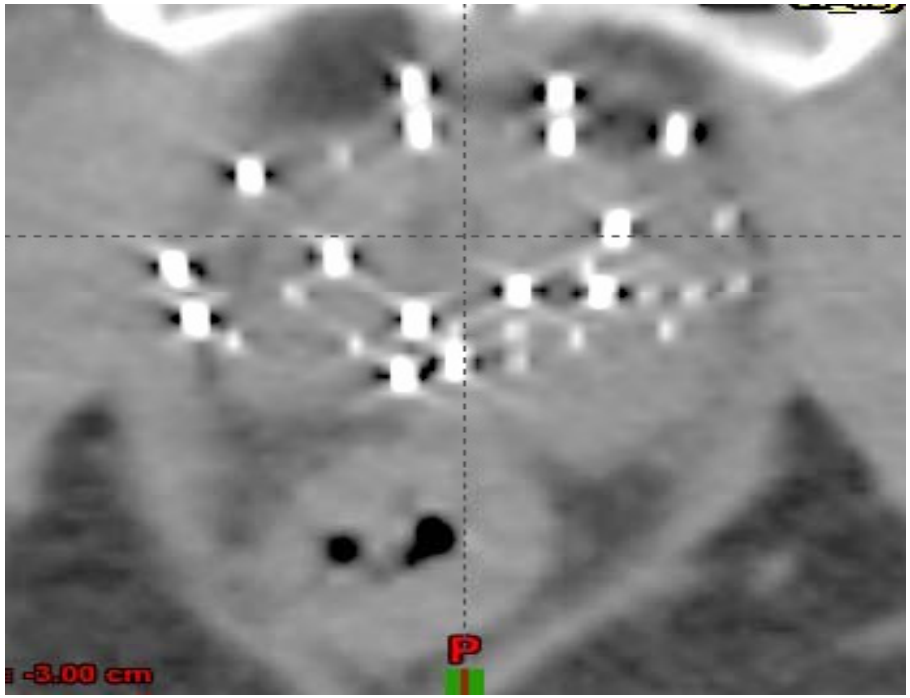
Focal Therapy



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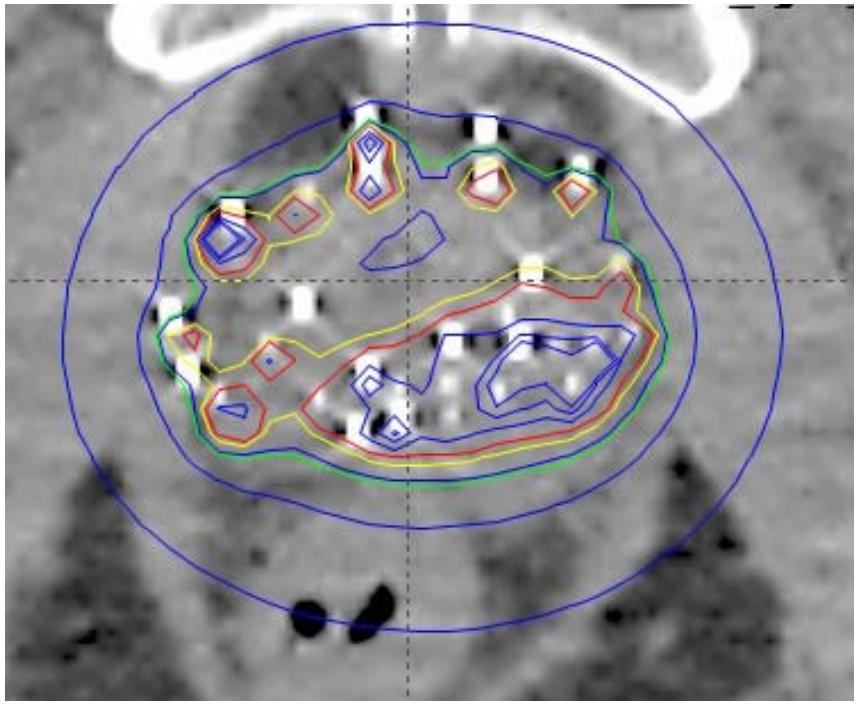
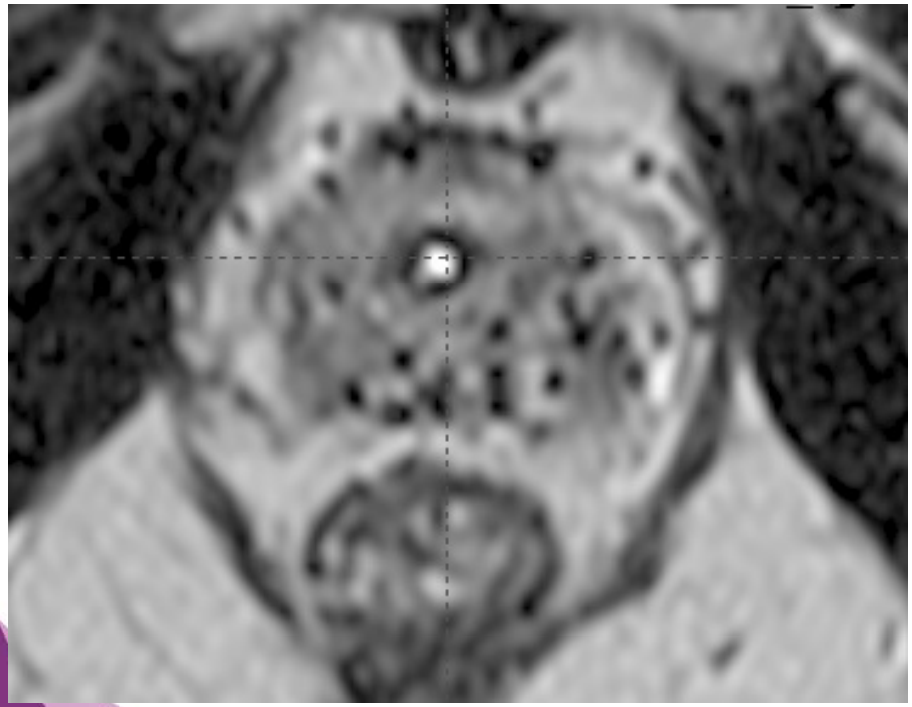
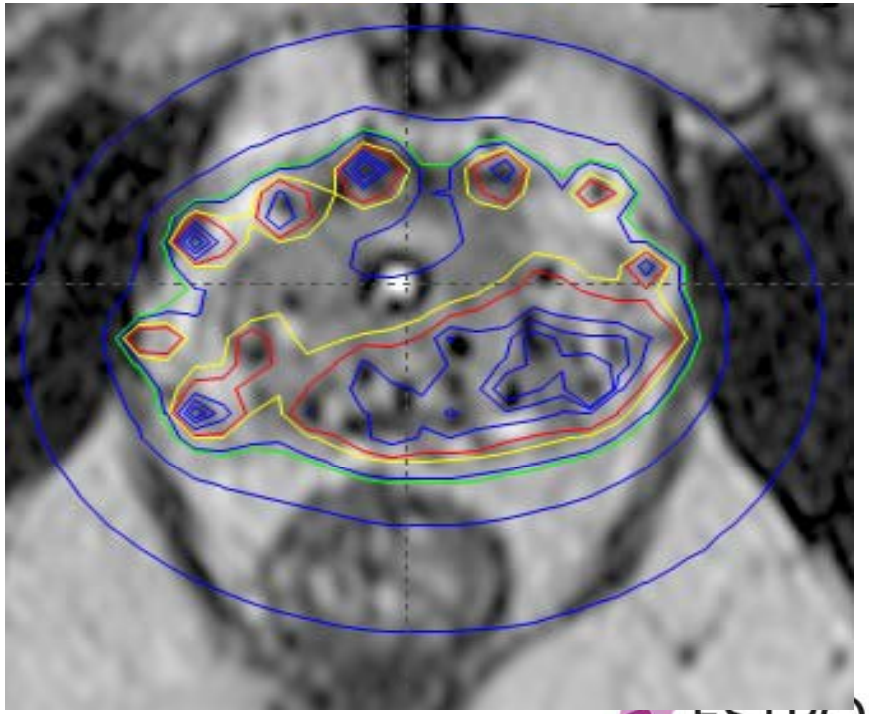




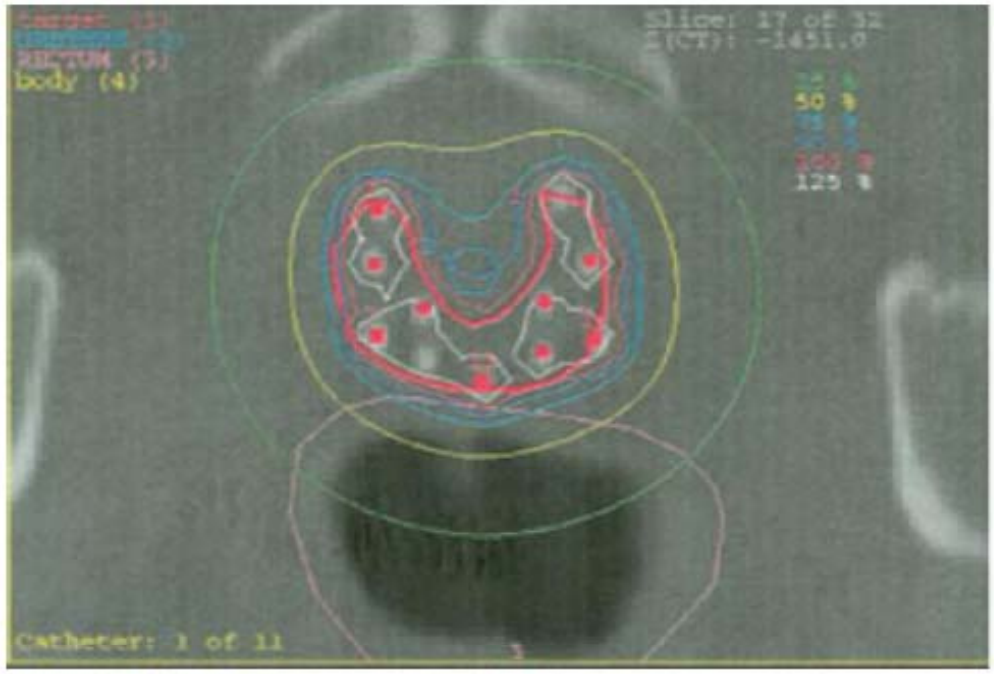


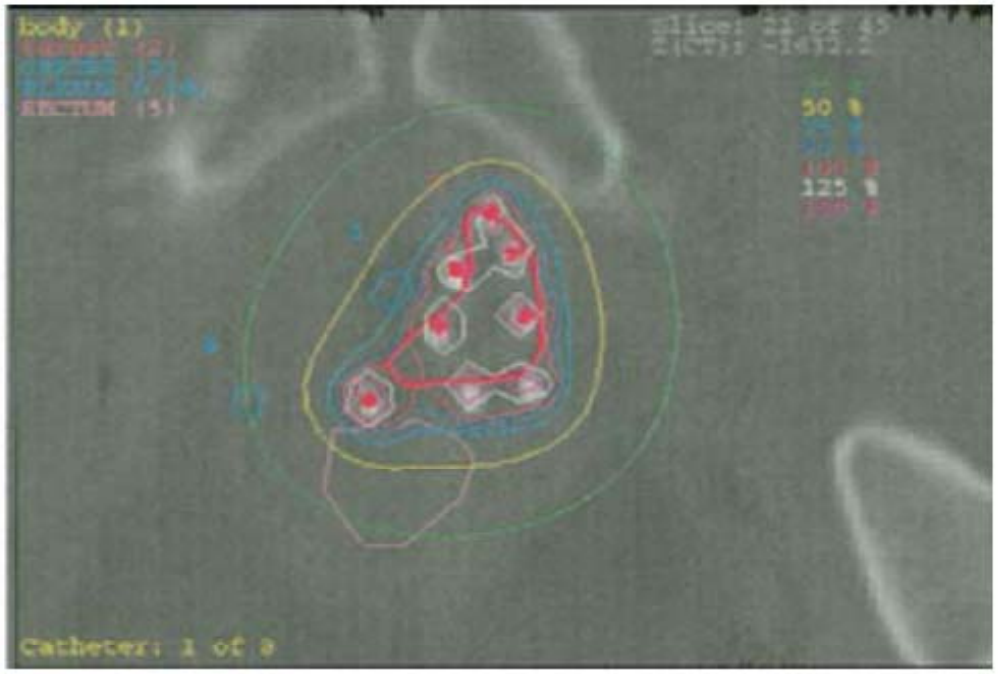
High-Dose-Rate Brachytherapy Boost to the Dominant Intra-Prostatic Tumor Region: Hemi-Irradiation of Prostate Cancer

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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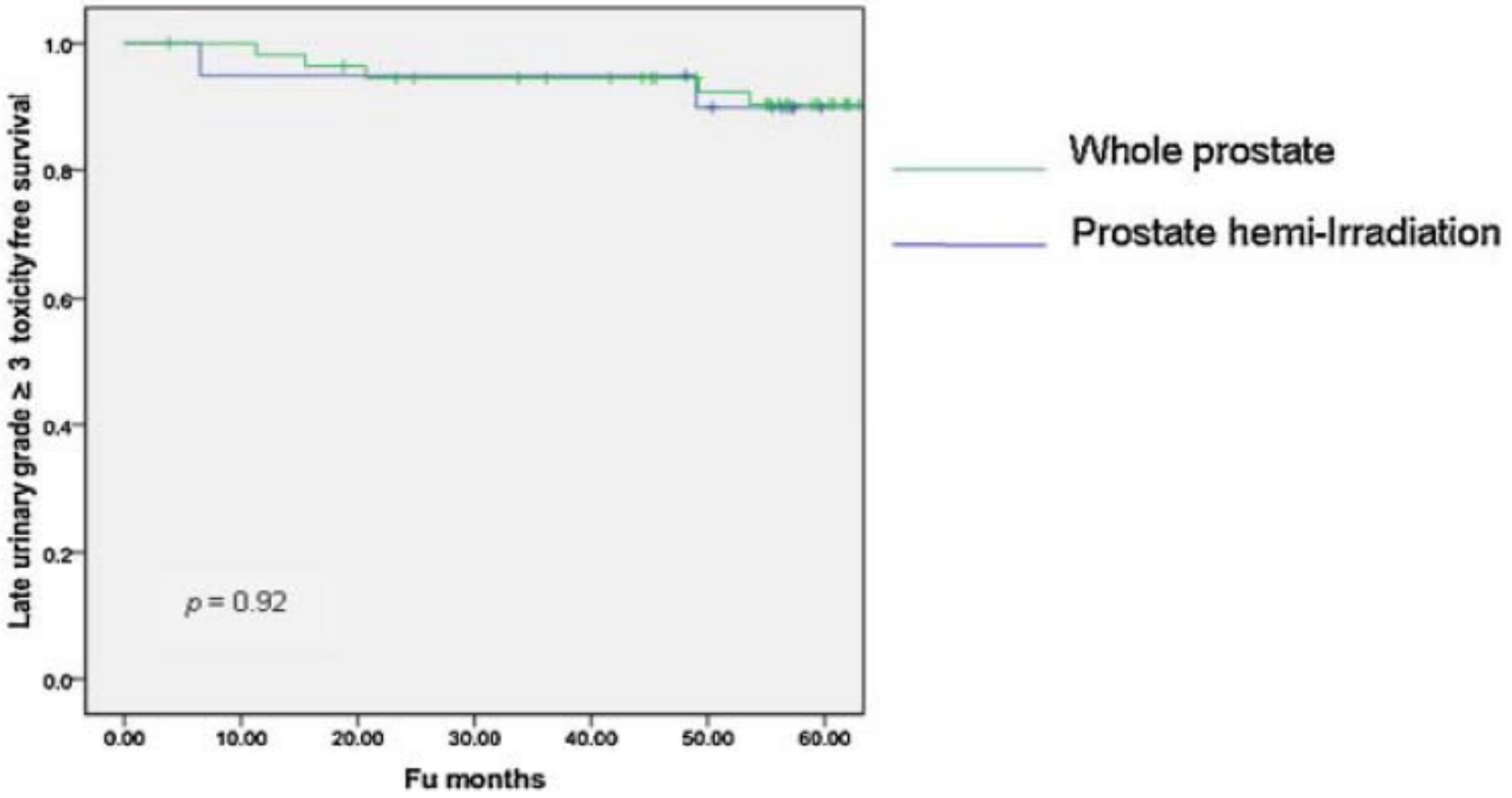

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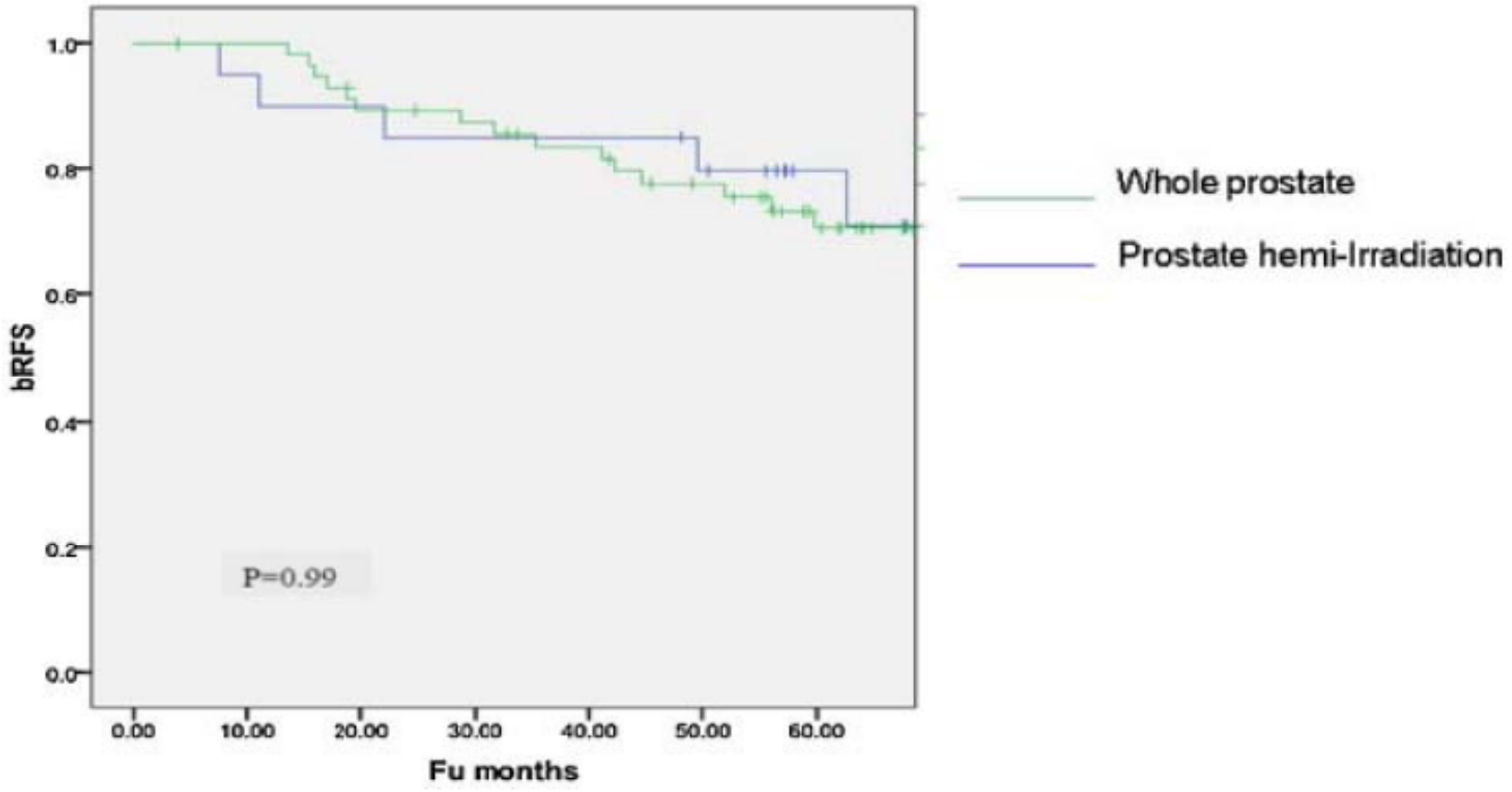

Dose escalation to dominant intraprostatic lesions with MRI-transrectal ultrasound fusion High-Dose-Rate prostate brachytherapy. Prospective phase II trial

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)		

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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

ESTRO COURSE Brussels 2016

New indications of prostate brachytherapy :

Salvage brachytherapy

Jean-Marc Cosset

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The rationale

- **After external irradiation,**
- **20-50 % of patients may experience a biochemical relapse**

- **Such a relapse may be related to microscopic dissemination, but also , in an unknown percentage of cases, to a pure LOCAL relapse.**

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- **The prognosis of such 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.

- **Consequently,**
- **Several attempts to « salvage » those local failure after external irradiation :**
- **Essentially:**
- **Surgery**
- **Cryotherapy**
- **HIFU (ultrasounds)**

- **Until recently ; results usually poor, with frequent complications/Side effects.**

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What about **Salvage brachytherapy** for localized prostate cancer after failure of a previous radiotherapy ?

- The literature :
- In the large majority of cases after failure of an ***external irradiation***
- In rare cases after a ***first-line brachytherapy***…
- Mostly proposed to date with ***permanent implants, but more and more with HDR.***

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- **A review of the papers available in 2016,**
- **Reporting on series of patients treated by permanent implants after external RT** ***(or brachytherapy)***
- **About 500 cases found to date in the literature.**

Author	Nb of cases	Follow-up (months)	BFS	Grade ¾ Toxicity
Beyer (1999)	17	62	53 %	NA
Grado (1999)	49	64	34 %	16 %
Allen (2007)	12	45	63 %	0 %
Nguyen (2007)	25	47	70 %	30 %
Lee (2008)	21	36	38 %	0 %
Aaronson (2009)	24	30	88 %	4 %
Burri (2010)	37	86	54 %	11 %
Battermann (2010)	31	73	23 %	3-6 %
Crehange (2010)	24	25	87.5 %	0 %
Lopez (2010)	42	48	80.6 %	21 %

Author	Nb of cases	Follow-up (months)	BFS	Grade ¾ Toxicity
Peters (2013)	129	29	20%	About 30 %
Sasaki (2013)	7	short	2 relapses	0 % ?
Vargas (2014)	69	60	73,8 % (non-CRPC)	GU 3 : 8,7 %
Henriquez (2014)	56	48 (median)	77 %	GU : 24 %
Rose (2015)	18	31.5	78 %	Role of dose ++

One of the largest experience : Vargas 2014

ELSEVIER

BRACHYTHERAPY

Brachytherapy 13 (2014) 53–58

Salvage brachytherapy for recurrent prostate cancer

Carlos Vargas[1,*], Douglas Swartz[2], Apoorva Vashi[2], Marc Blasser[4], Ali Kasraeian[3], Jamie Cesaretti[1], Kathleen Kiley[1], Jason Koziol[1], Mitchell Terk[1]

[1]*Florida Center for Prostate Care, Jacksonville, FL*
[2]*McIver Urological Clinic, Jacksonville, FL*
[3]*Kasraeian Urology, Jacksonville, FL*
[4]*Urology Associates of Northeast Florida, Orange Park, FL*

ABSTRACT

PURPOSE: To evaluate the role of salvage prostate brachytherapy for locally recurrent prostate cancer after external beam radiation alone.

METHODS AND MATERIALS: Sixty-nine consecutive patients treated with salvage brachytherapy after a local failure were analyzed.

CONCLUSIONS: A subset of failures after definitive radiation is local in nature, and excellent control is possible with salvage brachytherapy.

In addition: literature reviews :

- Can J Urol. 2012 Dec;19(6):6534-41.
- **Salvage therapy for locally recurrent prostate cancer after radiation.**
- Marcus DM, Canter DJ, Jani AB, Dobbs RW, Schuster DM, Carthon BC, Rossi PJ.
- Department of Radiation Oncology, Emory University, Atlanta, Georgia, USA.
- **MATERIALS AND METHODS:**
- A review of the literature was performed to identify studies of local salvage therapy for patients who had failed primary EBRT for localized prostate cancer.

- **Conclusions :**
- ***As there are no randomized trials comparing salvage treatment modalities for localized prostate cancer recurrence after EBRT, the selection of a local treatment modality should be made on a patient-by-patient basis...***

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- World J Urol. 2012 Sep 28.
- **Re-irradiation for salvage of prostate cancer failures after primary radiotherapy.**
- Ramey SJ, Marshall DT.
- **PURPOSE:**
- **To review the literature on use of radiation as a salvage option after local-only failure following initial treatment with radiation.**
- **Results:**
- **Biochemical disease-free survival (bDFS) at four to 5 years ranged from 20 to 75 %. Patient selection may have influenced these varying rates since some studies with lower bDFS had higher risk populations.**
- **the crude rate of grade 3-4 genitourinary toxicities among all studies was 13 % (range 0-47 %), and the crude rate of grade 3-4 gastrointestinal toxicities was 5 % (range 0-20 %). Incontinence rates were low among reviewed studies at 4 % (range 0-29 %).**

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- World J Urol. 2013 Apr;31(2):403-9.
- **Patterns of outcome and toxicity after salvage prostatectomy, salvage cryosurgery and salvage brachytherapy for prostate cancer recurrences after radiation therapy: a multi-center experience and literature review.**
- Peters M, Moman MR, van der Poel HG, Vergunst H, de Jong IJ, Vijverberg PL, Battermann JJ, Horenblas S, van Vulpen M.
- **METHODS:**
- A total of 129 patients from five different centers in the Netherlands were retrospectively analyzed.
- **RESULTS:**
- **BF occurred in 25 (81%) patients in the brachytherapy group (mean follow-up 29 ± 24 months), 29 (66%) patients in the prostatectomy group (mean follow-up 22 ± 25 months) and 33 (61%) patients in the cryosurgery group (mean follow-up 14 ± 11 months). Severe (grade >3) genitourinary and gastrointestinal toxicity was observed in up to 30% of patients in all three groups.**

Peters M, Moman MR, van der Poel Hg et al .

- **CONCLUSION:**
- ***"This overview shows clinical practice of prostate cancer salvage. Significant failure and toxicity rates are observed, regardless of salvage technique. Patients should be selected with great care before offering these salvage treatment strategies."***

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A rough analysis of the available literature :

- Rather short series …
- Sometimes lacking a sufficient follow-up,
- Large heterogeneities ! …
- Large variations in BFS ; from about 20 to 90 % …
- Large variations in grade 3-4 toxicities : from 0 to about sometimes 50 % …
- WHY ?

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- **Why such differences ? tentative explanations:**

- **1/ <u>Differences in follow-up ?</u>** the longer the follow-up, the lower the BFS ?
- Battermann and Grado , publishing at 73 and 64 months, report the lowest BFS ; 23 and 34 % , respectively.
- But Beyer, with a 62 months follow-up, reports a BFS of 53 %,
- And Burri, with a follow-up of 86 months, reports an equivalent BFS of 54 %
- ***Therefore, the variations in follow-up durations do not explain all the differences ...***

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- **2/ <u>Selection of the patients ?</u>**
- **Probably a major (the main ?) problem**
- **Essentially for the first (older) papers …**
- **Today , we should insist on this selection:**

In the French phase II trial « CAPRICUR » (Started in 2013, just completed)

- Biopsy-proven relapse
- With biopsies performed more than 2 years after the first irradiation
- PSA < 10 ng/ml
- PSA doubling time (at relapse) > 8 months
- Endorectal MRI eliminating an extra-capsular extension
- No distant metastases (Negative Bone scan - FNa if possible - , negative CT scan and Choline Pet-Scan)

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- **To make a long story short ;**
- **Selection of patients ;**

- **Everything should be done to eliminate an extra-protatic extension of the disease.**
- **Respecting the classical contra-indications of brachytherapy (prostate volume, previous TURP,IPSS >15, etc ...)**
- **A particular attention for the rectum : no previous post-(external) RT severe rectitis ...**

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- **3/ A problem of dose ?**

- **The salvage brachytherapy dose has been usually reduced : with a D90 of about 120 Gy (Beyer, Burri, Lopez ...)**
- **Some other authors (N'Guyen...) used an almost conventional D90 of 145 Gy...**
- **But N'Guyen reported both *a high BFS (70 %) and the highest rate of grade 3-4 toxicities ...***
- **The optimal dose in this setting thus remains to be precisely defined ...**

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Dose for salvage ; a 2015 paper

- Brachytherapy. 2015 Feb 26.
- **Salvage low-dose-rate permanent seed brachytherapy for locally recurrent prostate cancer: Association between dose and late toxicity.**
- Rose JN[1], Crook JM[2], Pickles T[3], Keyes M[3], Morris WJ[3].
- **RESULTS:**
- "...**These 5 patients with late toxicity had higher dose to the prostate (isodose enclosing 90% [D_{90}] median, 151 Gy; range, 135-185 Gy) compared with those without late complications (median, 134 Gy; range, 105-165; p < 0.04). "**
- **CONCLUSION:**
- "...The goal of planning should be to treat the recurrent disease to an adequate dose with careful attention to maintain a conservative D_{90} "

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Dose chosen in the French trial CAPRICUR :

- D90 prostate: **90 Gy**
- GTV or Index tumor (if identified) **: 144 Gy**

- **4/ <u>A problem of technique ?</u>**

- **The different groups have used rather different techniques of implantation**
- **(Preplanning in one or two steps, stranded or loosed seeds, automatic, semi-automatic or manual implantations etc ...)**

- **This could have played a role in the heterogeneity of the results, in terms of BFS as well as in terms of toxicity ...**

- **What about salvage by HDR brachytherapy ?**

- **More and more authors are reporting an experience of salvage brachytherapy using an HDR technique,**
- **The pioneers; Lee B, 2007, Tharp M , 2008, De Cicco L, 2009**
- **Small series ;**
- **Encouraging (but very) preliminary results .**

ABS 2011

- **The MSKCC experience ; preliminary presentation ;**
- **Salvage High-Dose-Rate Brachytherapy for Recurrent Prostate Cancer After Ultra High Intensity Modulated Radiotherapy: Results of a Prospective Study**
- *Lisa K. Morikawa, MD, Michael J. Zelefsky, MD, Gil'ad N. Cohen, MS, DABMP, Marco Zaider, PhD, Sherri M. Donat, MD, Yoshiya Yamada, MD (MSKCC)*

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The MSKCC experience ; the 2013 paper

- **Brachytherapy. 2013 Dec 24. S1538-4721**
- **A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy.**
- *Yamada Y[1], Kollmeier MA[2], Pei X[2], Kan CC[2], Cohen GN[3], Donat SM[4], Cox BW[2], Zelefsky MJ[2].*
- *[1]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY.*
- ***METHODS:***
- **Forty-two patients with biopsy-proven recurrence were enrolled on a Phase II study of salvage HDR monotherapy** using iridium-192. Median pretreatment EBRT dose was 8100 cGy (6840-8640 cGy) and the median time from completion of EBRT to salvage HDR was 73 months. **The protocol prescription dose of 3200 cGy was delivered in four fractions over 30 hours in a single insertion.** Median follow up after salvage HDR was 36 months (6-67 months).

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- ***RESULTS:***
- **The actuarial prostate-specific antigen biochemical relapse-free survival and distant metastases-free survival rates at 5 years were 68.5% and 81.5%, respectively. Cause-specific survival was 90.3%. Late genitourinary Grade 1and 2 toxicities were found in 38% and 48%, respectively….**
- **No Grade 4 toxicities were observed.**
- ***CONCLUSIONS:***
- **Genitourinary toxicity was the most commonly encountered toxicity observed after salvage HDR but severe toxicities were uncommon.**
- **Salvage HDR is an effective and well-tolerated modality for locally recurrent prostate cancer and should be considered even for patients who have previously been treated with ultra-high dose levels of EBRT.**

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The San Diego experience

- Int J Radiat Oncol Biol Phys. 2013 Jun 1;86(2):324-9.
- **Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes.**
- Chen CP[1], Weinberg V, Shinohara K, Roach M 3rd et al.
- [1]Department of Radiation Oncology, Scripps Clinic, San Diego, California, USA.
- **PURPOSE:**
- Evaluate efficacy and toxicity of salvage high-dose-rate brachytherapy (HDRB) for locally recurrent prostate cancer after definitive radiation therapy (RT).
- **CONCLUSIONS:**
- **Prostate HDRB is an effective salvage modality with relatively few long-term toxicities.**

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A polish experience ; HDR + hyperthermia

- **Strahlenther Onkol. 2014 Feb;190(2):165-70**

- **Salvage prostate HDR brachytherapy combined with interstitial hyperthermia for local recurrence after radiation therapy failure.**
- *Kukiełka AM, Hetnał M, Dąbrowski T, Walasek T, Brandys P, Nahajowski D, Kudzia R, Dybek D, Reinfuss M.*
- *Department of Radiotherapy, Centre of Oncology, M. Skłodowska - Curie Institute, Krakow Branch, ul. Garncarska 11, 31-115, Krakow, Poland, drkukielka@gmail.com.*

- ***CONCLUSION:***
- **IHT in combination with salvage HDR brachytherapy is a well tolerated and effective treatment.**

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The Future ? (1):

- **Phase II trials :**

- **Phase II Radiation Therapy Oncology Group trial n° 0526**

  A Prospective Phase II Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Adenocarcinoma Following External Beam Radiotherapy

- **Closed to accrual (With 100 patients included, January 2014); results awaited.**

- **French CAPRICUR trial (activated 2013; completed end of 2015)**

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The Future ? (2):

- **Trying to reduce toxicity ?**
- **Introducing the systematic injection of hyaluronic acid gel between prostate and rectal wall ?**

What about rectal spacing ?

- **Systematically planned with 10 cc hyaluronic acid gel in the French CAPRICUR trial.**
- ***Also proposed by other groups :***
- Brachytherapy. 2014 Sep-Oct;13(5):442-9..
- **Use of a rectal spacer with low-dose-rate brachytherapy for treatment of prostate cancer in previously irradiated patients: Initial experience and short-term results.**
- Mahal BA[1], Ziehr DR[1], Hyatt AS[1], et al .
- **RESULTS:**
- **the median space between the prostate and rectum was 10.9mm (prior EBRT) vs. 7.7mm (prior brachytherapy), p=0.048.**
- **CONCLUSION:**
- **Hydrogel spacer placements may be feasible in most patients with prior pelvic radiation.**

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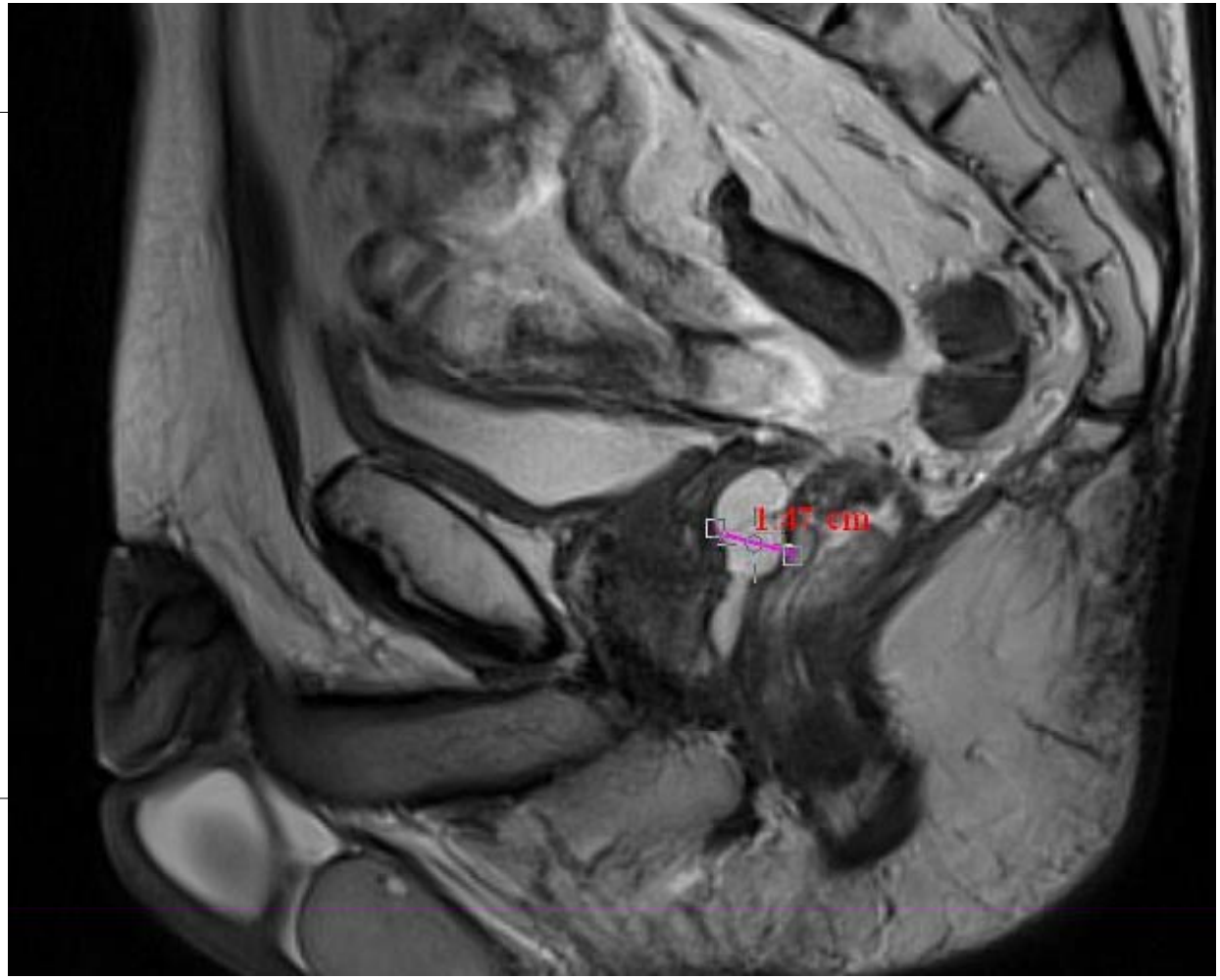
What about rectal spacing ?



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The future (3); ***Focal salvage*** brachytherapy ?

- Int J Radiat Oncol Biol Phys. **2013 Feb 1;85(2):370-7.**
- **Feasibility of MR imaging/MR spectroscopy-planned focal partial salvage permanent prostate implant (PPI) for localized recurrence after initial PPI for prostate cancer.**
- **Hsu CC, Hsu H, Pickett B, Crehange G, Hsu IC, Dea R, Weinberg V, Gottschalk AR, Kurhanewicz J, Shinohara K, Roach M 3rd.**

- Radiother Oncol. **2013 Nov;109(2):246-50.**
- **Cold spot mapping inferred from MRI at time of failure predicts biopsy-proven local failure after permanent seed brachytherapy in prostate cancer patients: Implications for focal salvage brachytherapy.**
- **Crehange G, Krishnamurthy D, Cunha JA, Pickett B, Kurhanewicz J, Hsu IC, Gottschalk AR, Shinohara K, Roach M 3rd, Pouliot J.**

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- J Contemp Brachytherapy. 2014 Oct;6(3):304-10..
- **Salvage low-dose-rate (125)I partial prostate brachytherapy after dose-escalated external beam radiotherapy.**
- Chang L[1], Buyyounouski MK[2].
- [1]Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA.
- [2]Department of Radiation Oncology, Stanford University, Stanford, CA, USA.
- **PURPOSE:**
- **To report outcomes on 5 patients treated with salvage partial low-dose-rate (LDR) 125-iodine ((125)I) permanent prostate seed brachytherapy (BT) for biopsy-proven locally persistent prostate cancer, following failure of dose-escalated external beam radiotherapy (EBRT).**
- **CONCLUSIONS:**
- **In carefully selected patients with local persistence of disease, partial LDR (125)I permanent prostate seed implant appears to be a feasible option for salvage local therapy with an acceptable toxicity profile.**

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The Future (4)

Salvage Brachytherapy *after prostatectomy* ???

- Brachytherapy. 2012 Jun 27.
- Permanent seed brachytherapy for locally recurrent prostate cancer after radical prostatectomy: A case report and review of the literature.
- Gaztañaga M, Crook JM.

- Brachytherapy. 2013 Oct 23. S1538-4721
- High-dose-rate brachytherapy with or without intensity modulated radiation therapy as salvage treatment for an isolated, gross local recurrence of prostate cancer post-prostatectomy.
- Strom TJ, Wilder RB, Fernandez DC, Mellon EA, Saini AS, Hunt DC, Biagioli MC.

- + Gastaldi

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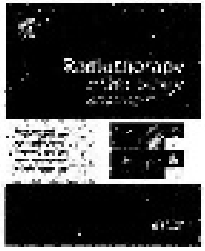
What to do in 2016 ?

Contents lists available at ScienceDirect

Radiotherapy and Oncology

118 (2016) 122-130



Original article

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

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Delphi Study ?

A Delphi study is useful to learn from those who have experience with salvage treatment of the prostate in their clinical practice. The Delphi concept involves multiple rounds of questionnaires in which consensus between these experts is sought [10]. The outcome of a Delphi study is based on opinions and arguments of experts and is not always based on facts. An important aspect of a Delphi study is that it will provide an estimation of future developments, which is not available with contemporary data. Four elements characterize a Delphi study: anonymity, iteration, controlled feedback and statistical analysis.

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Two Conclusions :

- **Consensus or majority agreement for most points dealing with patient selection and work-up … :**

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.

- **Examples ;**

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Table 1
Overview of the surveys and the score in the different rounds (the bold letters show group consensus).

Question	Answers	Agreement level
A. Indication for Salvage		
Should there be a minimum age?	No	**100**
What is the maximum acceptable ECOG/WHO performance score?	1 (Symptomatic but completely ambulatory (Restricted in physically strenuous activity)	**88.9**
	2 (Symptomatic;<50% in bed during the day)	11.1
Should previous Androgen Deprivation Therapy be a contraindication for salvage brachytherapy?	Yes	15.8
	No	**84.2**
What is the maximum acceptable T-classification at primary treatment?	T2	6.2
	T3a	12.5
	T3b	**81.3**

What is the maximum acceptable T-classification at salvage treatment?	T2	5.9
	T3a	5.9
	T3b	**88.2**
Is there to your opinion a part of the prostate inappropriate for re-irradiation?	No	**100**
Is there a maximal tumor lesion diameter that can be implanted?	No	**83.3**
	Hemigland	16.7
What is the maximum Gleason score at primary treatment?	<7	5.3
	<8	**94.7**
Should International Prostate Symptom Score (IPSS) of the patients be known?	Yes	**84.2**
What is the maximum IPSS for salvage?	<8	12.5
	8–15	**87.5**
Should Maximal Urinary flow (Qmax) of the patients be known?	Yes	**88.9**
	No	11.1

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	No	11.1

No consensus neither agreement on :

- LDR or HDR ?
- Which dose ?
- Which fractionation for HDR ?
- Which volume : total or focal ?
- If focal ; « ultrafocal » ou « hemigland » (one lobe) ?

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C. Salvage brachytherapy treatment		
Minimum time interval between primary and salvage treatment	2 years	Majority agreement
Treatment modality	HDR	Consensus Majority
	LDR	agreement
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.

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Conclusions

- **A second-line brachytherapy appears to be able to salvage some selected patients after failure of a previous external irradiation**
- **Long-term BFS could reach up to 50-70 %**
- **With optimal techniques, Grade 3-4 toxicity rates could be low and acceptable**

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- **Complementary trials, such as the RTOG 0526, and French CAPRICUR should allow to better define :**
- **The criterias to propose such a salvage therapy to patients with local relapses,**
- **The dose not to be exceeded (108 Gy ? 120 Gy ? 140 Gy ?)**
- **The technical points allowing to reduce as much as possible the toxicities (urinary and rectal); rectal spacers ?**

- **With a (very) prudent approach, salvage brachytherapy could become a standard in the next years …**

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- **While waiting for complementary data:**
- **Stick to the Delphi Consensus !**

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Thank You

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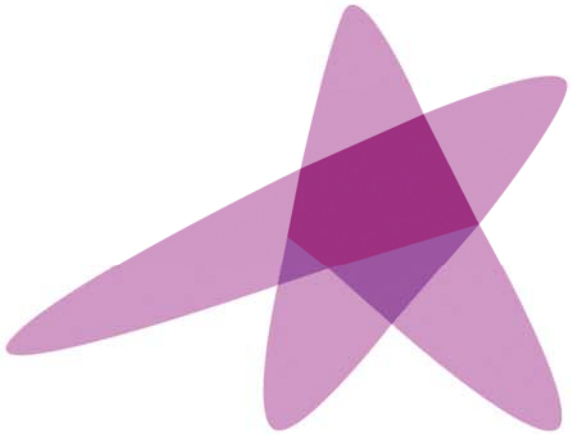

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WWW.ESTRO.ORG/SCHOOL

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

Prostate brachytherapy (LDR or HDR), surgery or IMRT

Peter Hoskin

Mount Vernon Cancer Centre

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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

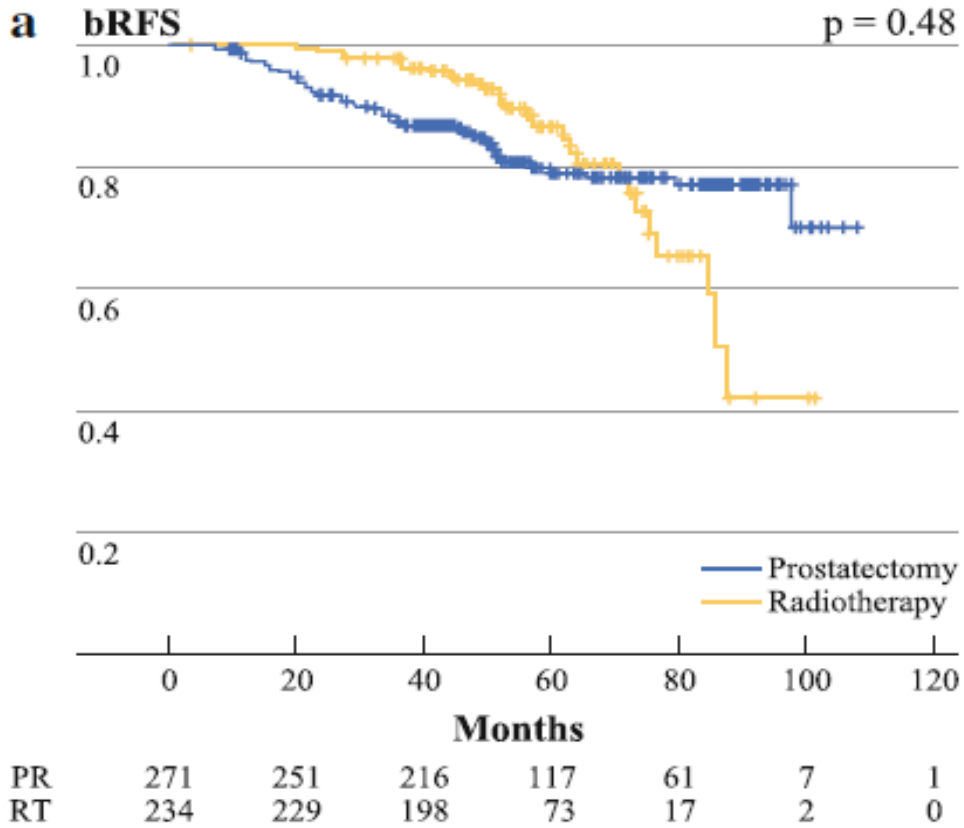
Which is best?

- 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.

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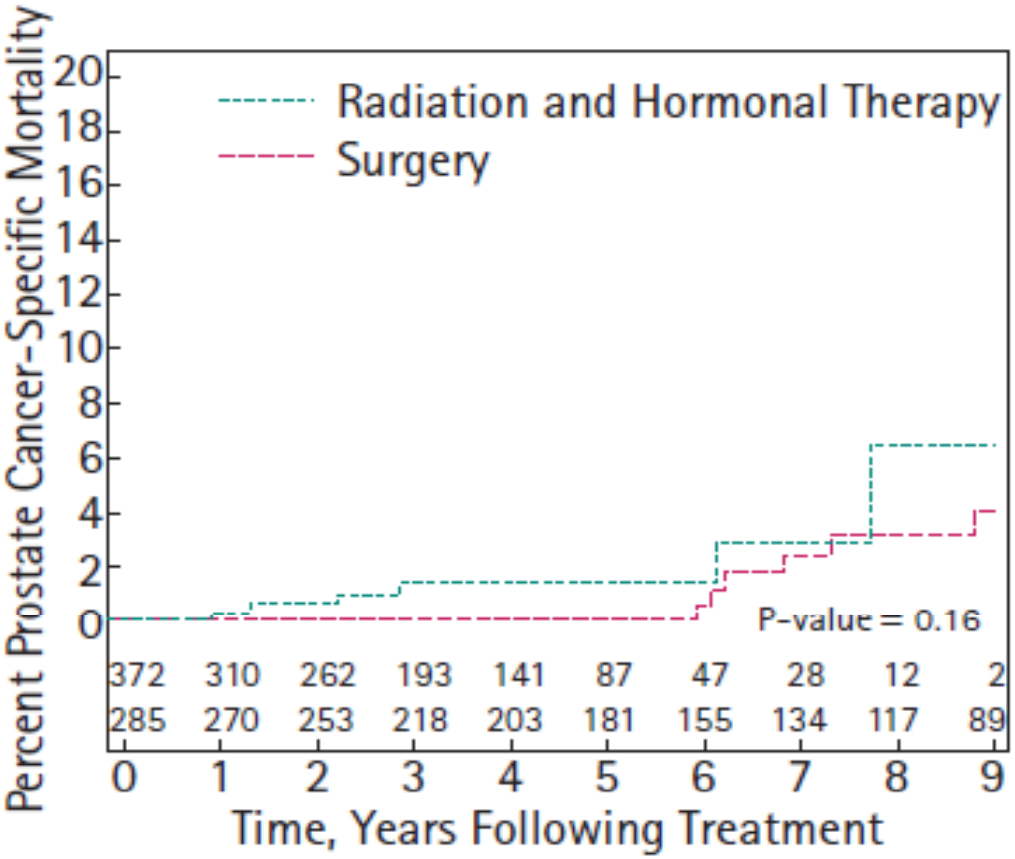
Radical prostatectomy vs radiation therapy and androgen-suppression therapy in high-risk prostate cancer

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

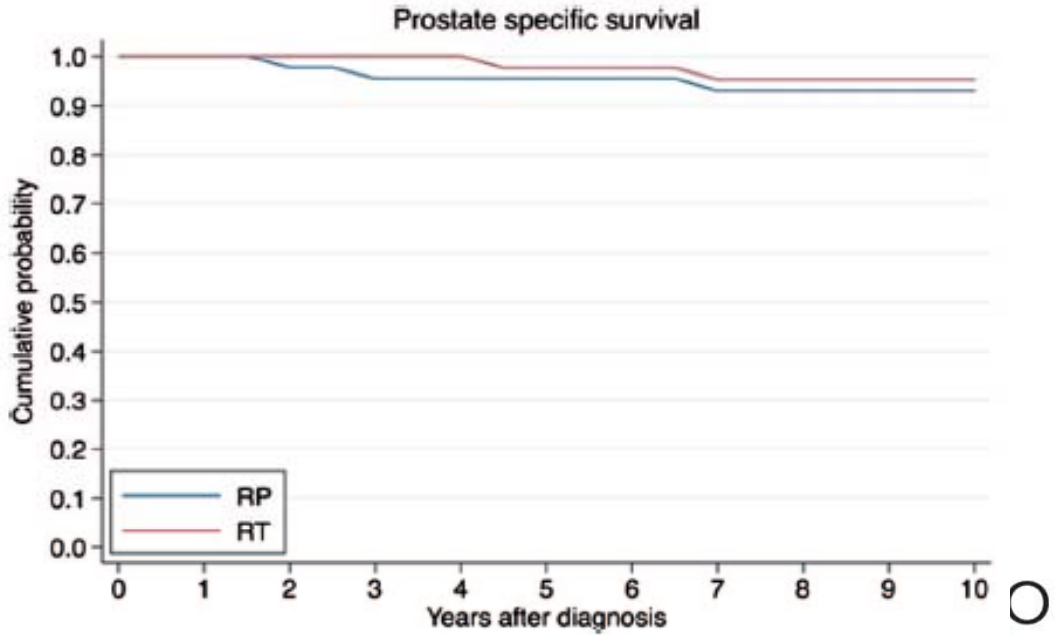
	Randomized to prostatectomy	Randomized to irradiation
T-stadium	n = 45	n = 44
	n (%)	n (%)
T1	18 (40)	17 (39)
T2	17 (38)	16 (36)
T3	4 (9)	3 (7)
Unknown	6 (13)	8 (18)

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

ESTRO School

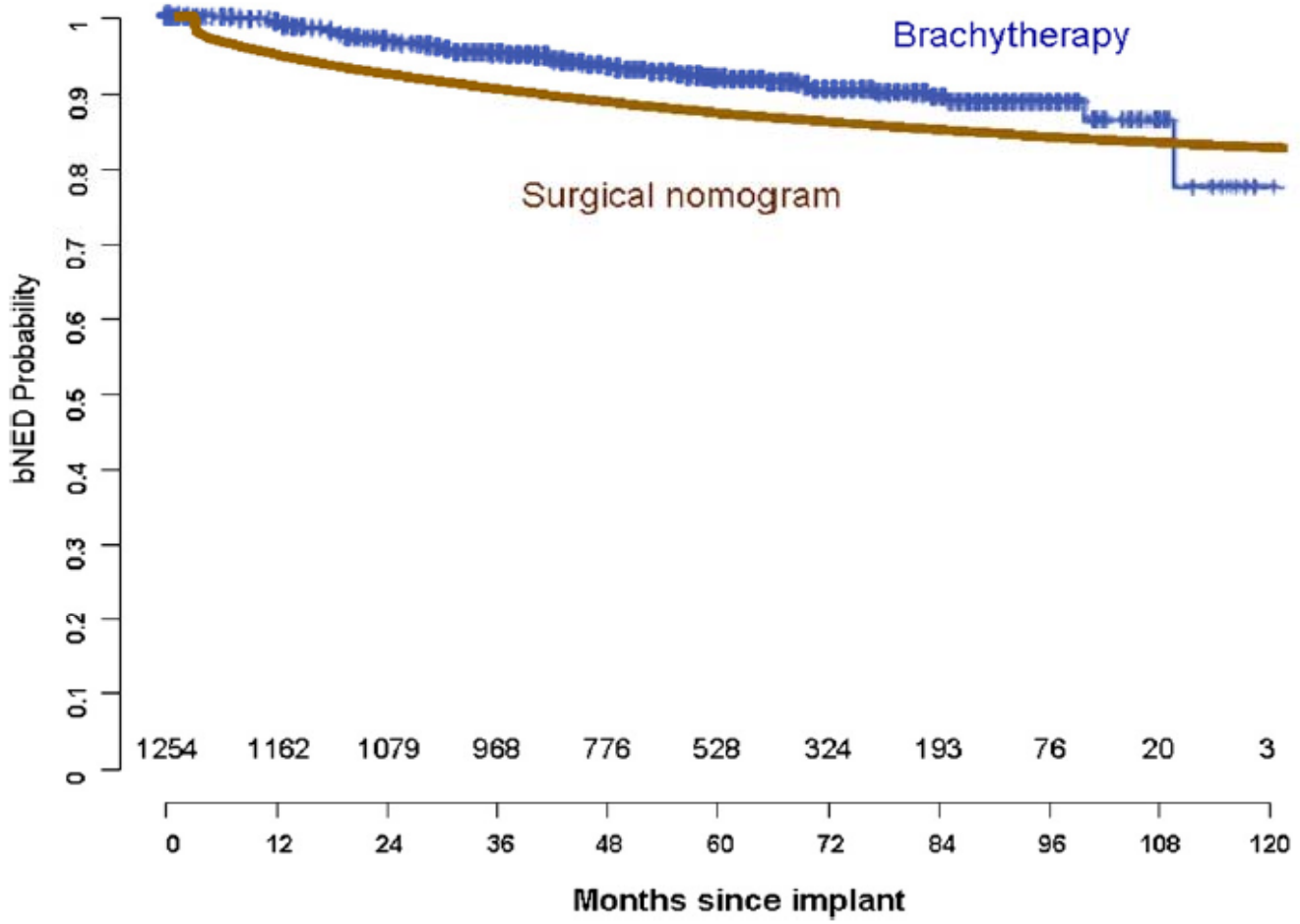
Comparative 5-year outcomes of brachytherapy and surgery for prostate cancer

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



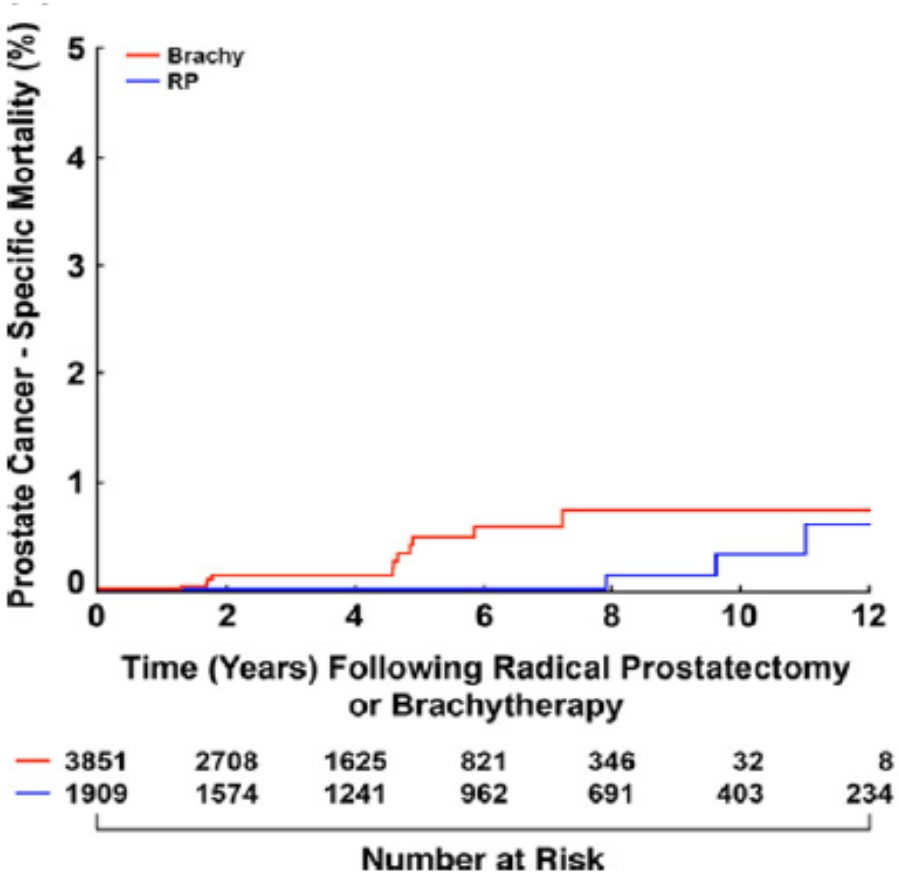
ESTRO School

Risk of Death From Prostate Cancer After Radical Prostatectomy or Brachytherapy in Men With Low or Intermediate Risk Disease

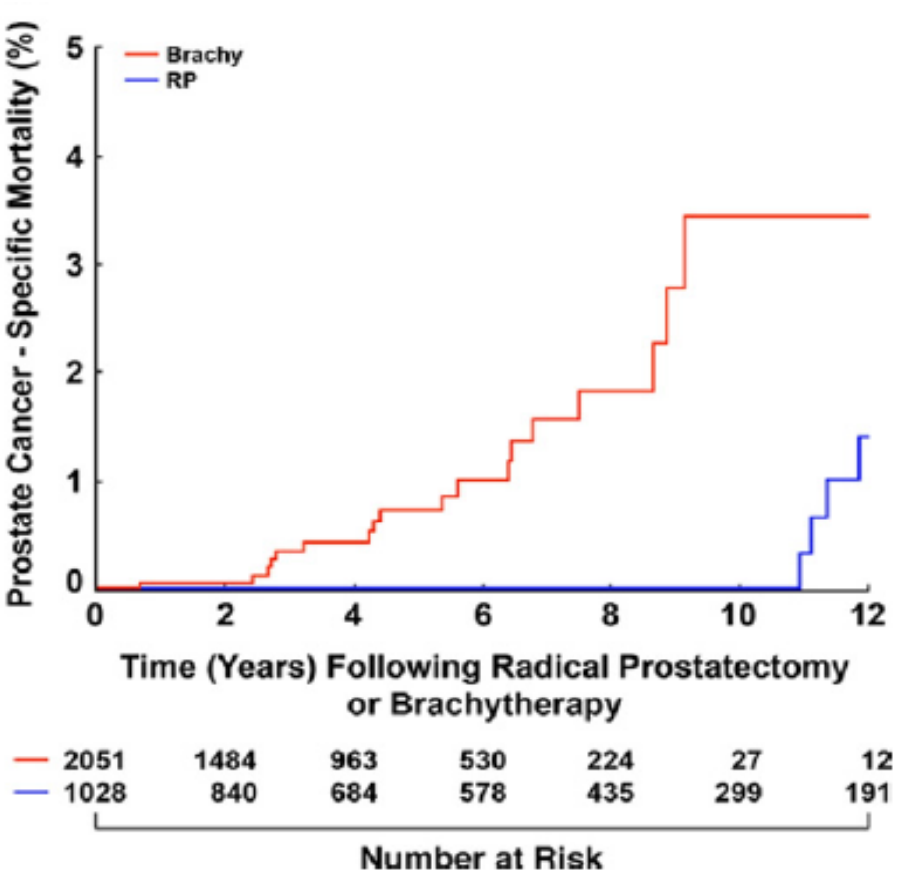
Nils D. Arvold,*,† Ming-Hui Chen,† Judd W. Moul,‡ Brian J. Moran,†
Daniel E. Dosoretz,† Lionel L. Bañez,† Michael J. Katin,† Michelle H. Bracciofortet
and Anthony V. D'Amico†

JOURNAL OF UROLOGY® Vol. 186, 91-96, July 2011

LOW RISK



INTERMEDIATE RISK



ESTRO School

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

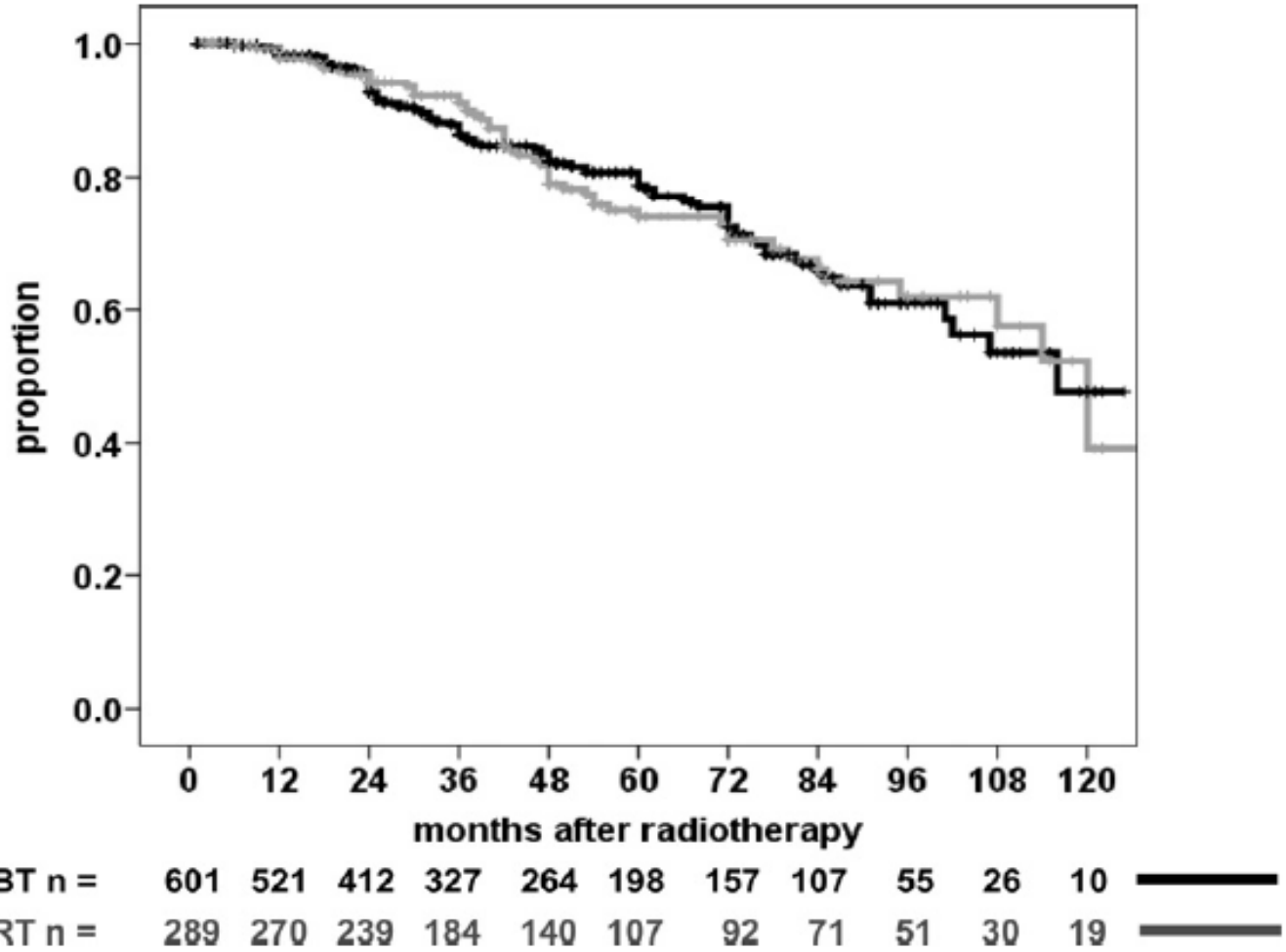
ESTRO School

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



ESTRO School

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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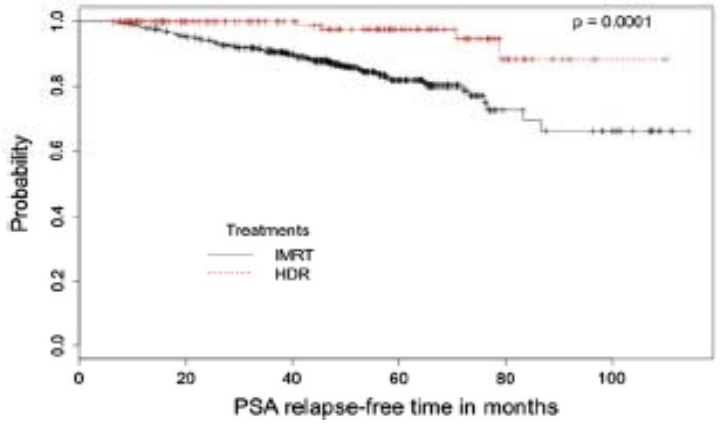
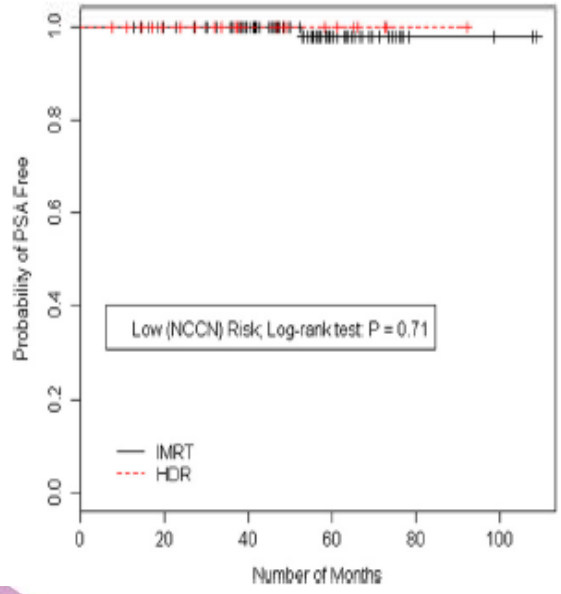
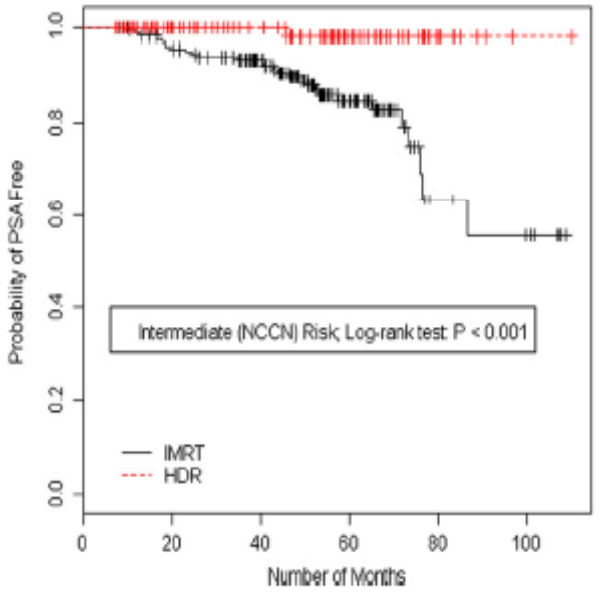
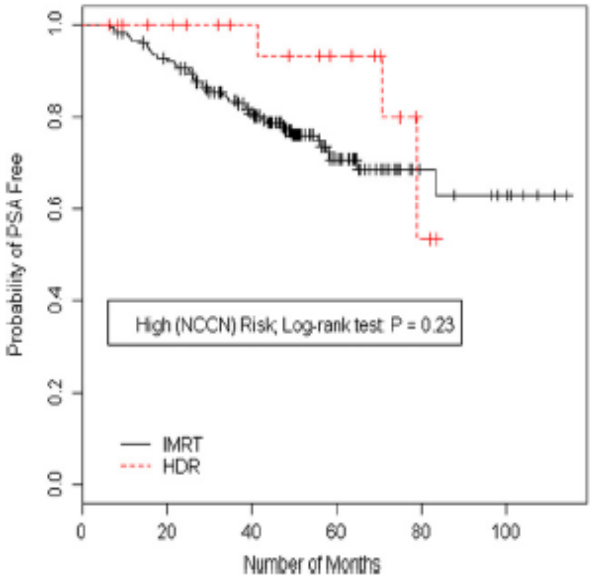
[3]Department of Medical Physics, Memorial Sloan-Kettering Cancer Center New York, New York, NY

Brachytherapy 2010









ESTRO School

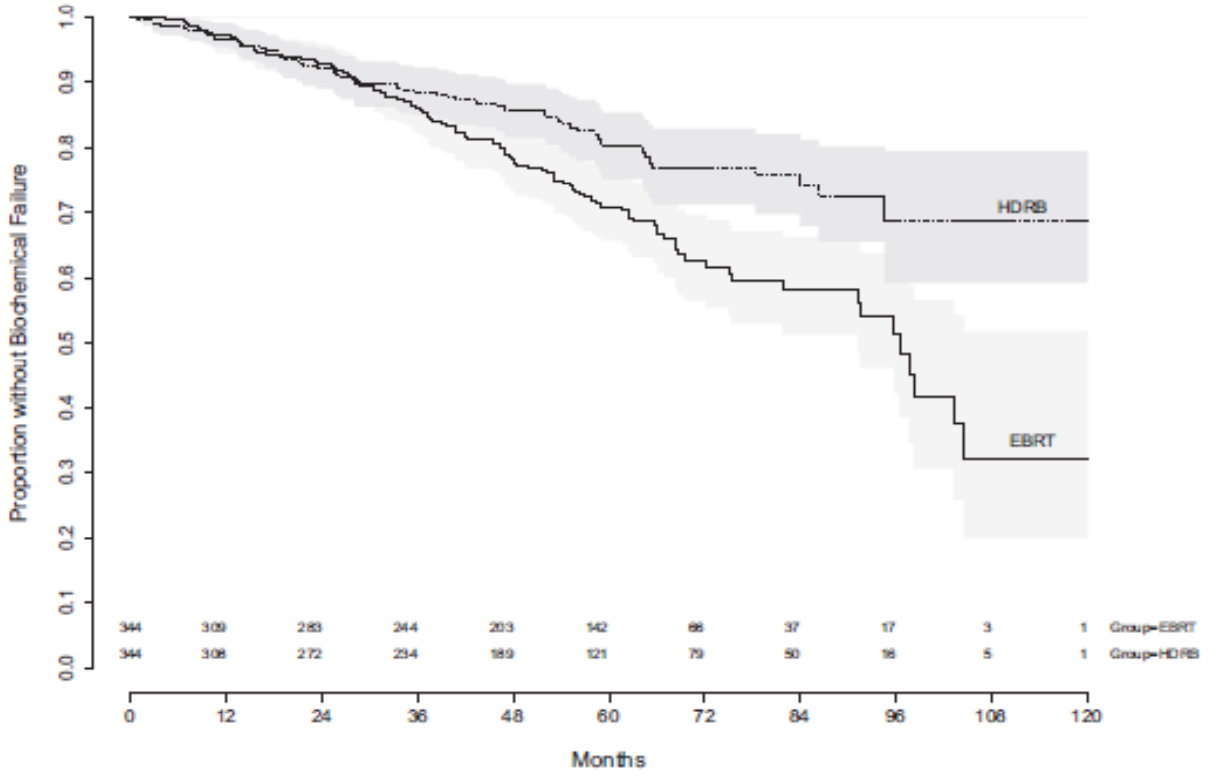
Direct 2-Arm Comparison Shows Benefit of High-Dose-Rate Brachytherapy Boost vs External Beam Radiation Therapy Alone for Prostate Cancer

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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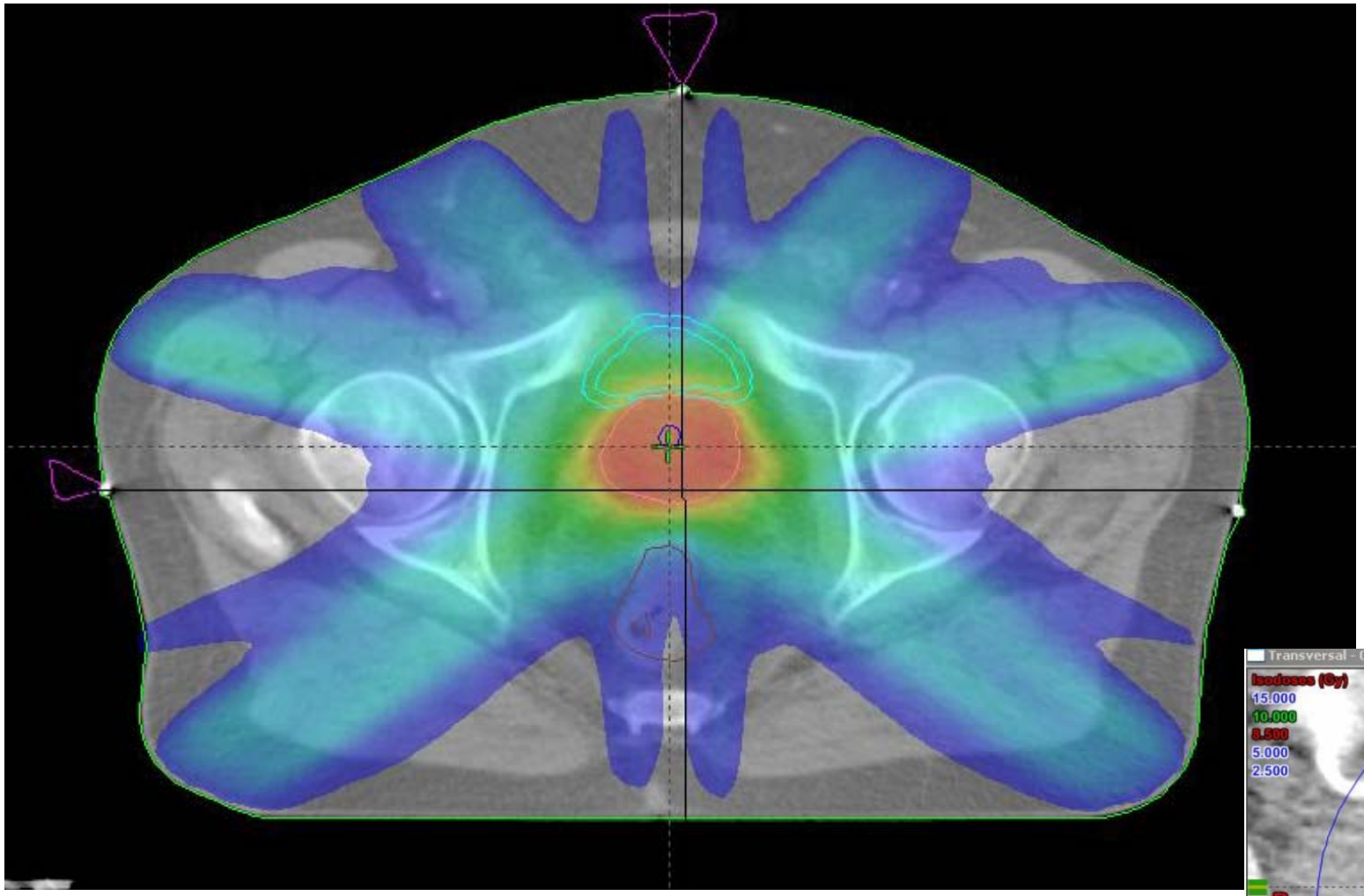
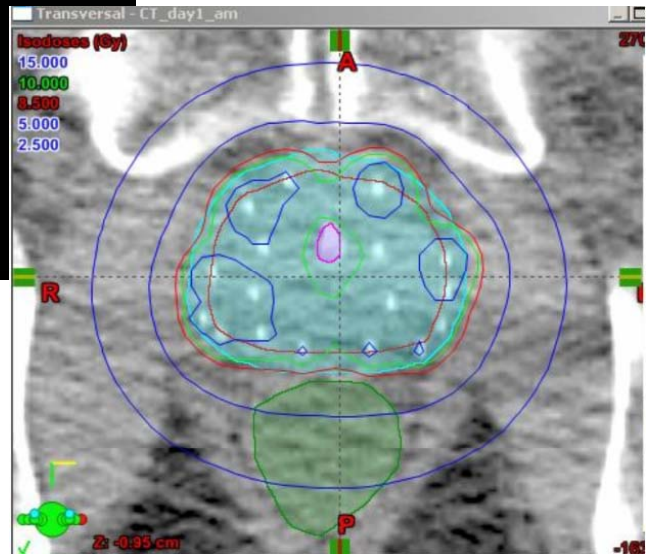




ESTRO School

THE CALCULATED RISKS OF SECOND MALIGNANCIES FROM INTENSITY-MODULATED RADIATION THERAPY

Kry et al 2005

% risk of fatal second malignancy

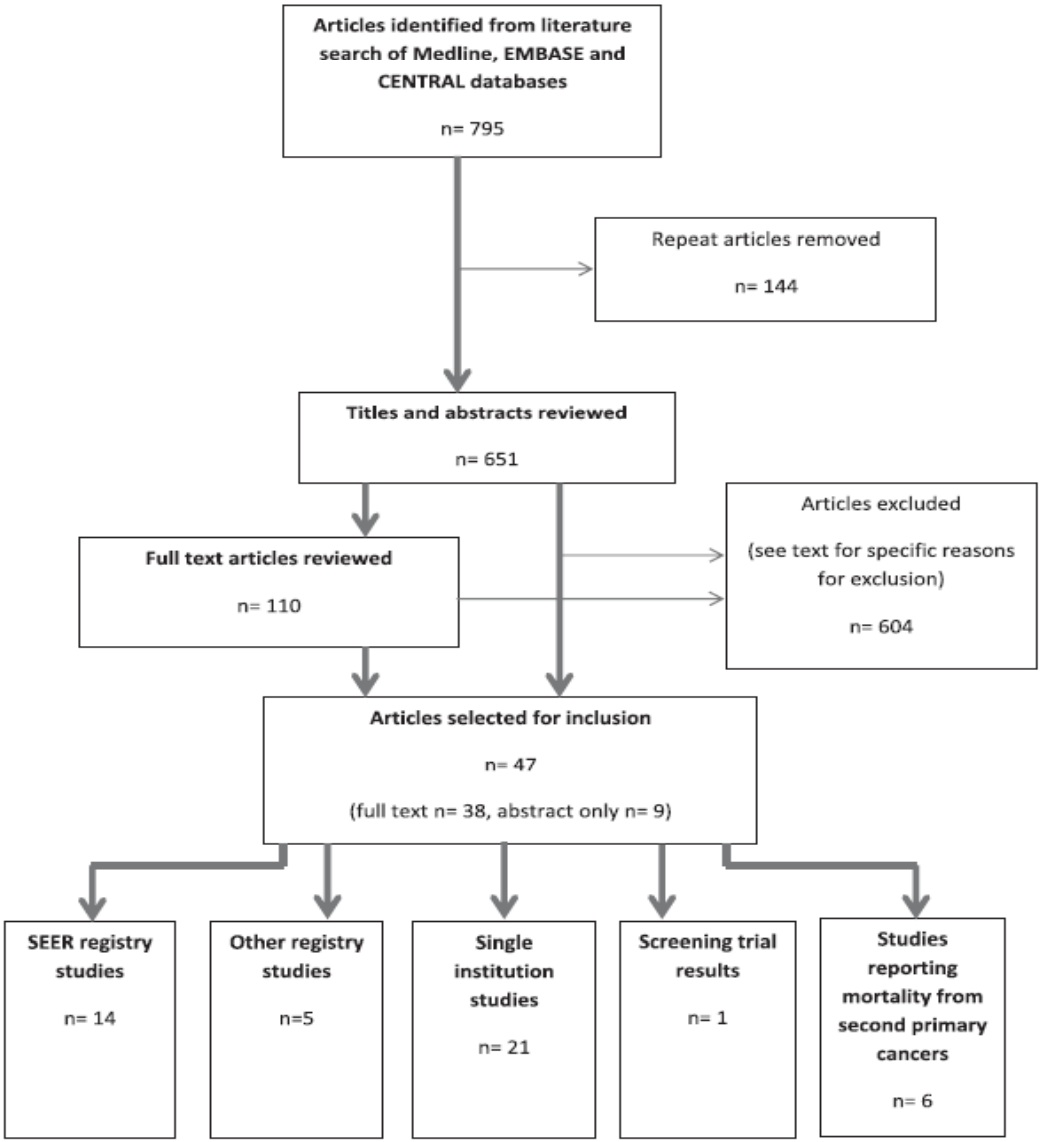
Conventional	IMRT					
18MV	6MV		10MV	15MV		18MV
	V	S	V	V	S	V
1.7%	**2.9%**	**3.7%**	**2.1%**	**3.4%**	**4.0%**	**5.1%**

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

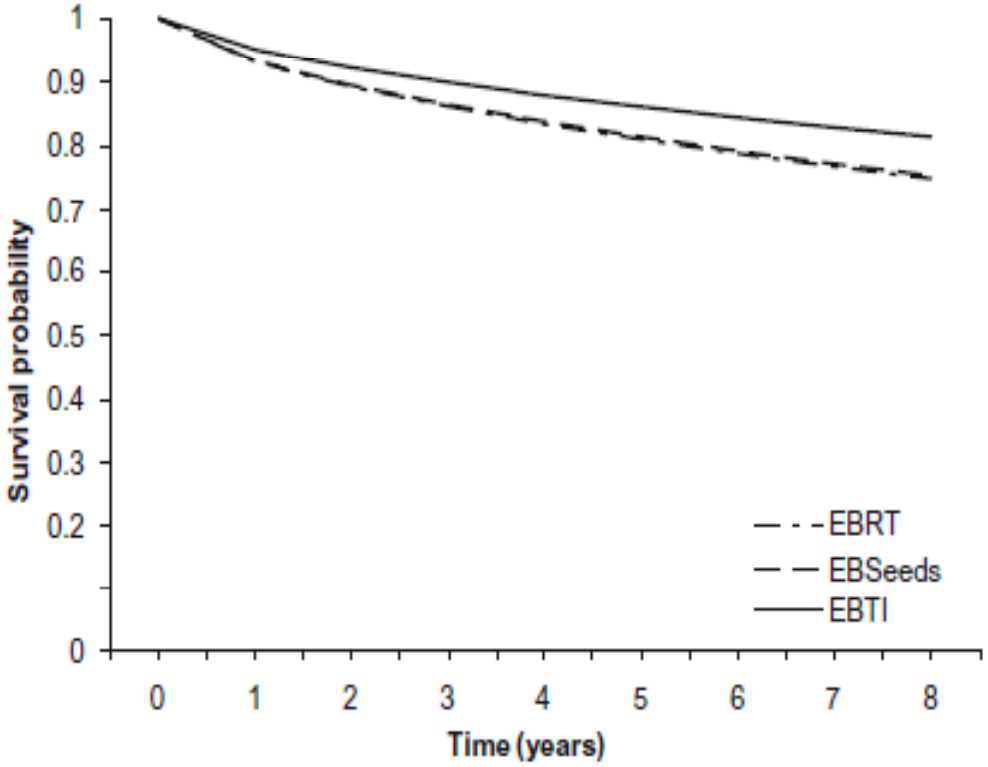
Comparison of three radiotherapy modalities on biochemical control and overall survival for the treatment of prostate cancer: A systematic review

Bradley R. Pieters [a,*], Djuna Z. de Back [a], Caro C.E. Koning [a], Aeilko H. Zwinderman [b]

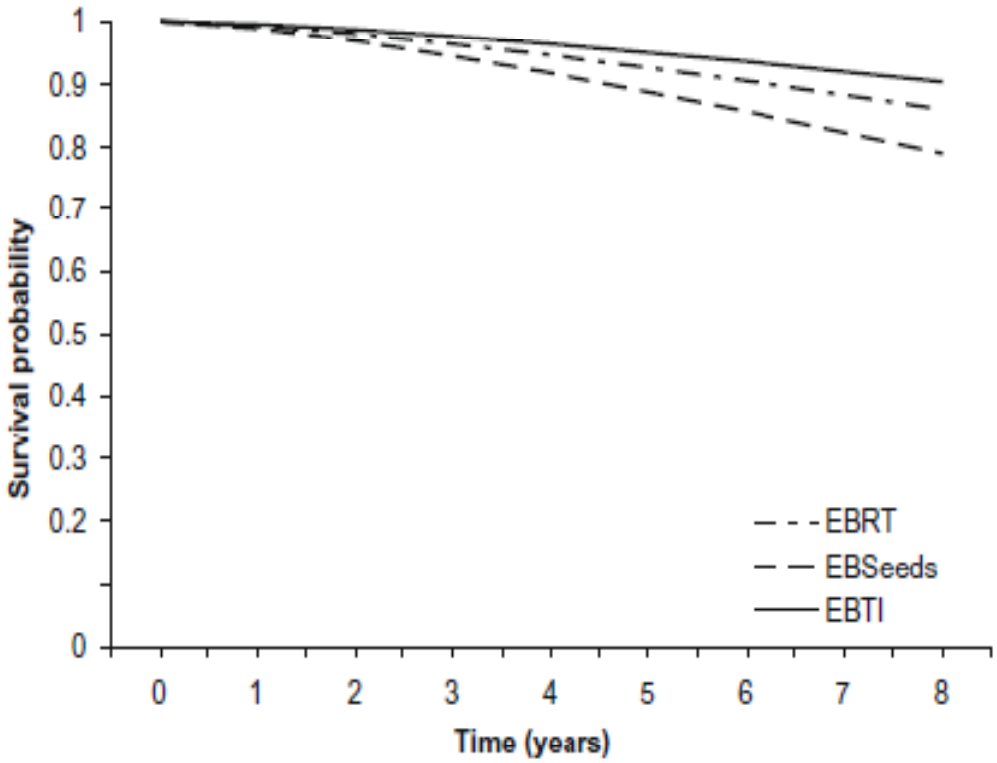
Radiotherapy and Oncology 93 (2009) 168–173

40 papers with 3,5 and 8 year data

bRFS



Overall survival

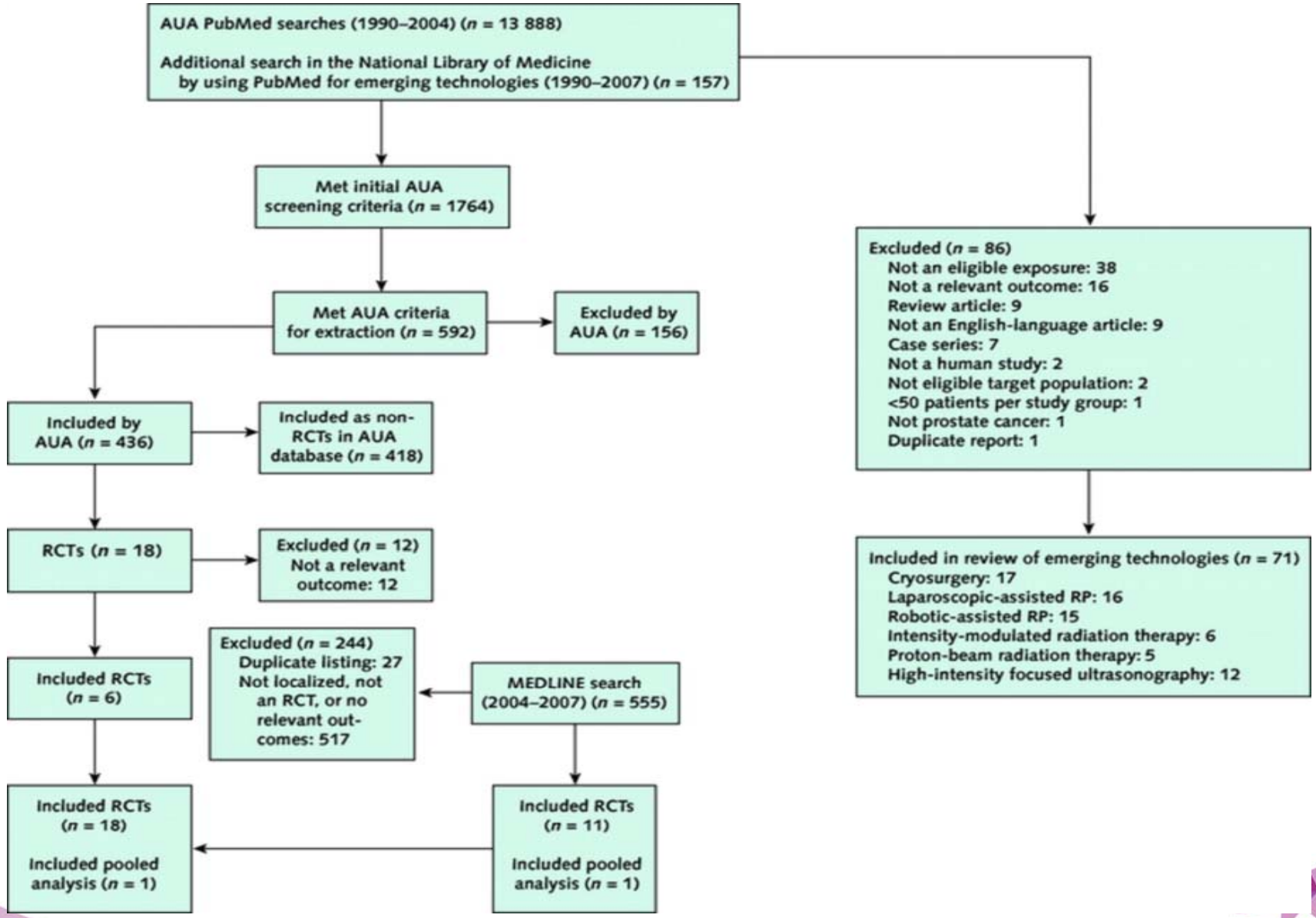


ESTRO School

Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer

Timothy J. Wilt, MD, MPH; Roderick MacDonald, MS; Indulis Rutks, BA; Tatyana A. Shamliyan, MD, MS; Brent C. Taylor, PhD; and Robert L. Kane, MD

Ann Intern Med. 2008;148:435-448.



ESTRO School

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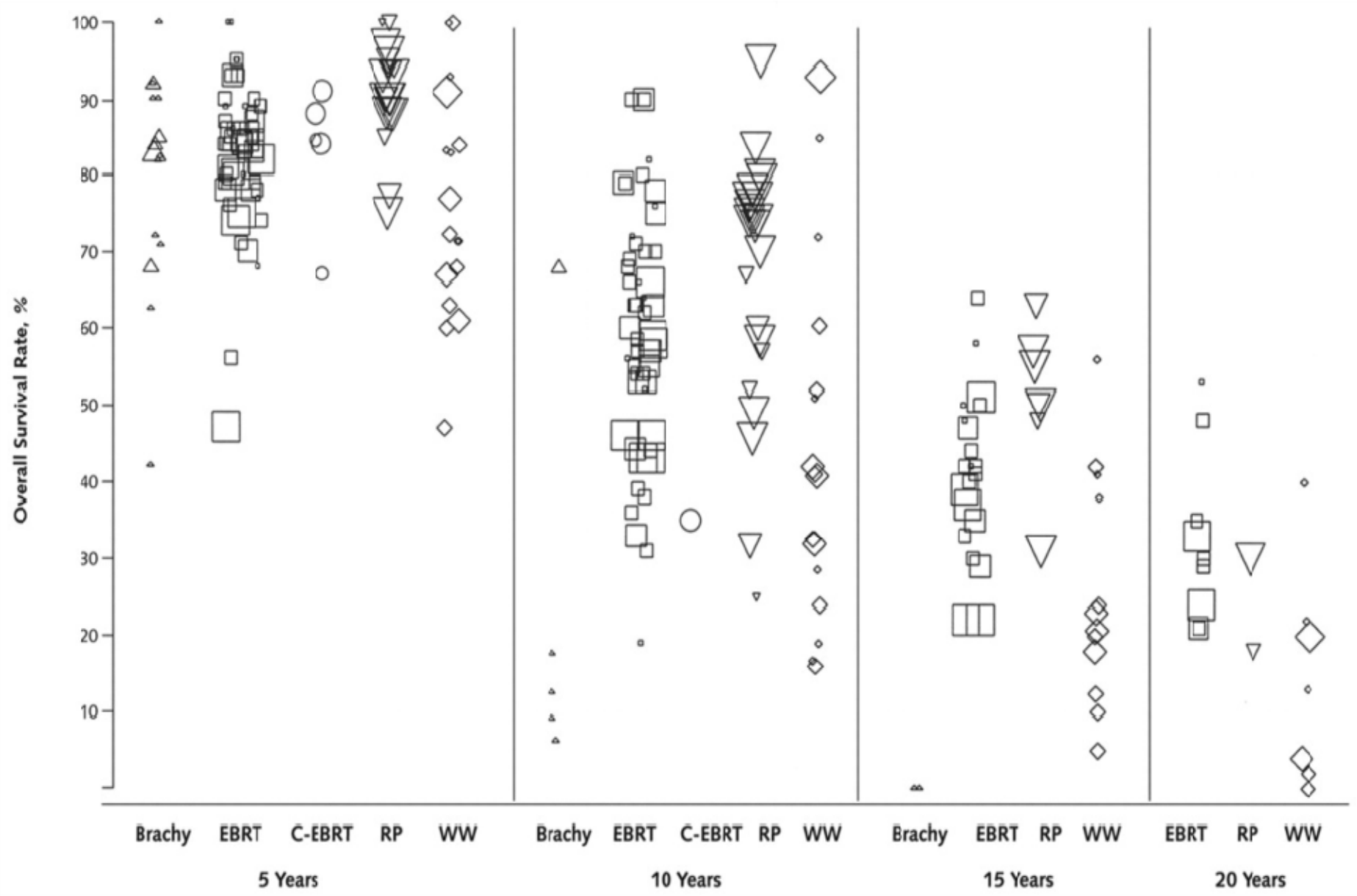

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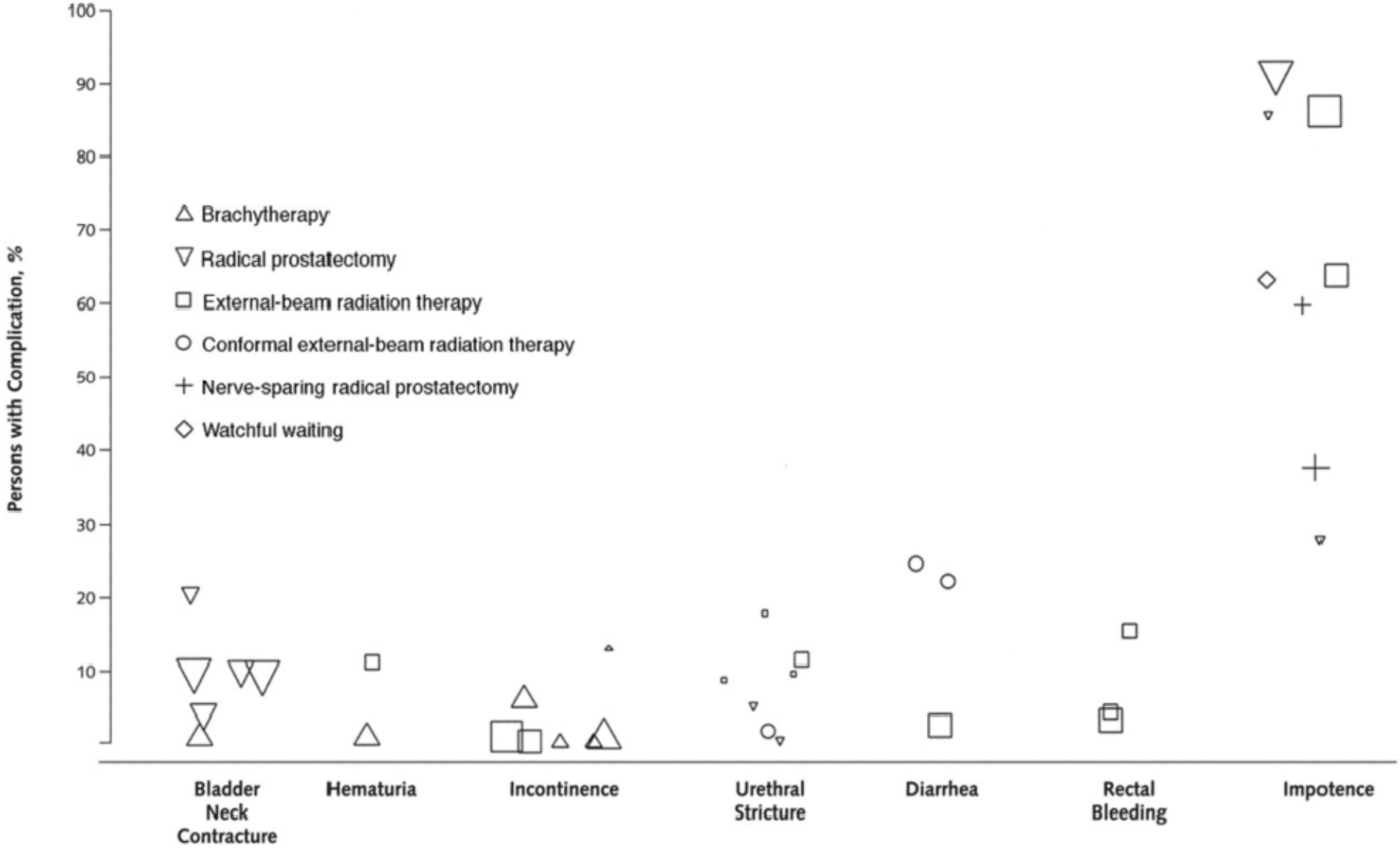

BJUI SUPPLEMENTS

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]

[1]Prostate Cancer Center of Seattle, WA, USA, [2]Urology Centre Kortrijk, Belgium, [3]Bostwick Laboratories, Glen Allen, VA, USA, [4]Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, USA, [5]MD Andersen Center, Houston, TX, USA, [6]The Prostate Clinic, Utrecht, The Netherlands, [7]BC Cancer Agency Vancouver Center, Vancouver, BC, Canada, [8]UCLA, Los Angeles, CA, USA, [9]Duke University Medical Center, Durham, NC, USA, [10]Department of Urology, Marien-Krankenhaus, Bergisch Gladbach, Germany, [11]University of California, Davis, CA, USA, [12]Chicago Prostate Center, Westmont, IL, USA, [13]Urologic Research Institute, Wheeling Jesuit University, WV, USA, [14]Alfred Health and Monash Univeristy, Melbourne, Australia, [15]University of California, San Francisco, CA, USA, [16]Mt Sinai Medical Center, New York, USA, [17]Prostate Cancer Research Institute, Los Angeles, CA, USA, [18]Prostate Cancer Center of Seattle, WA, USA, [19]Harvard Medical School, Boston, MA, USA, [20]Memorial Sloan Kettering Cancer Center, New York, USA, [21]University of California, Irvine, CA, USA, [22]Piedmont Radiation Oncology, Greensboro, NC, USA, [23]Virginia Commonwealth University, Richmond, VA, USA, and [24]Department of Urology, Royal Surrey County Hospital, Guildford, UK

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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

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	No. of patients (no. of studies)		
Treatment type	Low risk	Intermediate	High
RP	6447 (6)	3696 (4)	5149 (11)
Robotic RP	706 (1)	479 (1)	200 (1)
Seeds alone	8133 (17)	5808 (15)	295 (1)
Seeds + EBRT	726 (1)	1554 (6)	2864 (15)
EBRT + seeds + ADT	–	–	1231 (6)
HDR (seeds)	226 (2)	607 (4)	869 (5)
Protons	388 (2)	162 (1)	–
EBRT alone	4735 (9)	2969 (10)	3828 (11)
HIFU	227 (1)	–	–
Cryotherapy	–	175 (1)	357 (2)
Seeds + ADT	–	165 (1)	–

ADT, androgen deprivation therapy; HDR, high dose radiotherapy; HIFU, high intensity focused ultrasound; RP, radical prostatectomy; EBRT, external beam radiation.

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CANCER CONTROL RATES: COMPARISON OF TREATMENT OPTIONS

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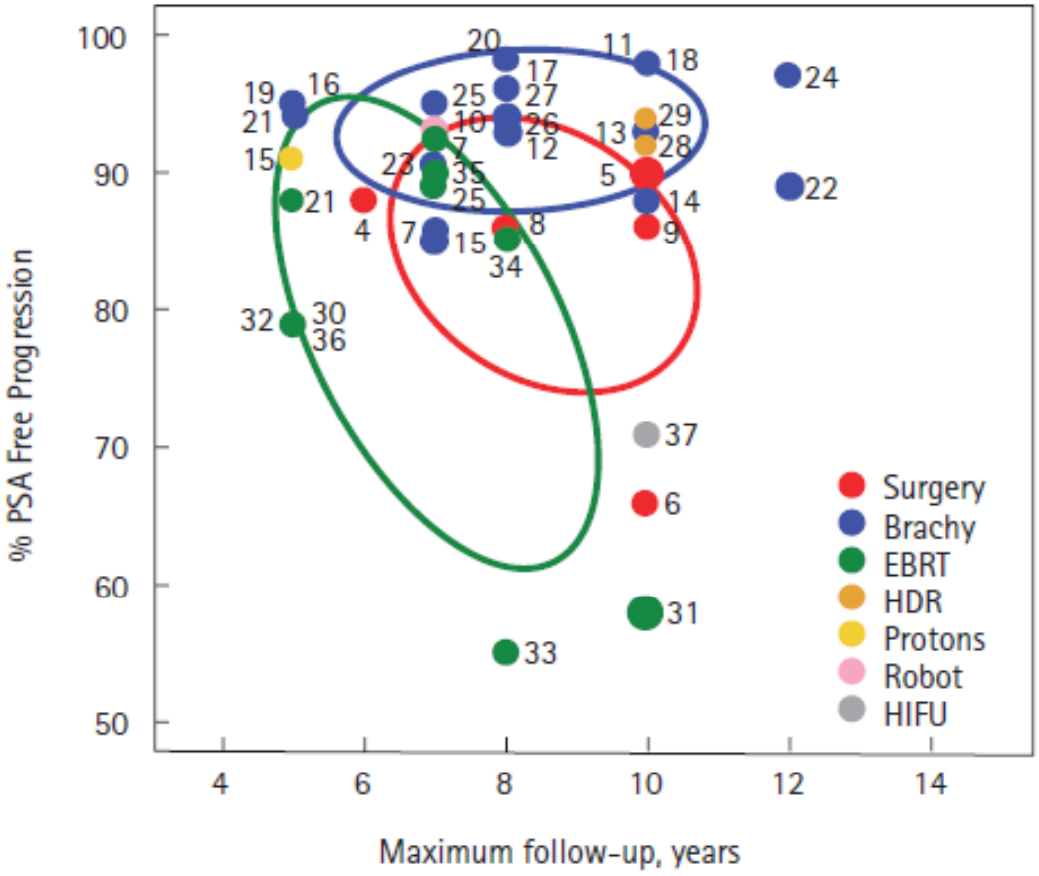
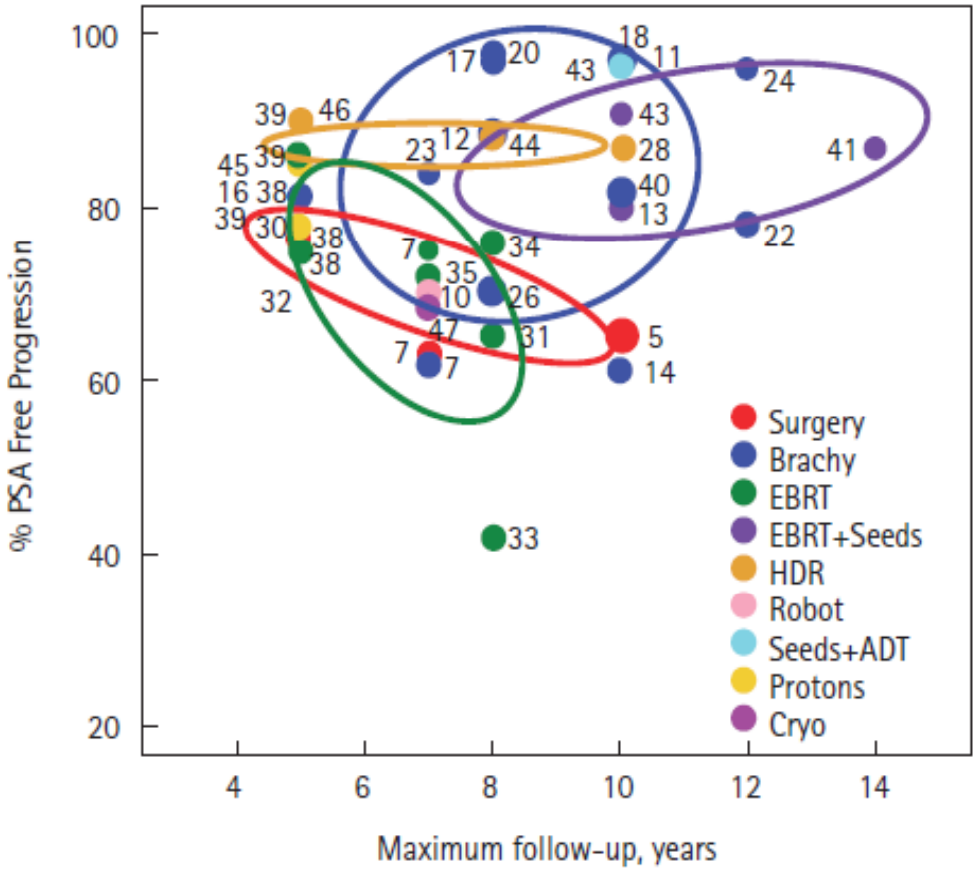
LOW risk



INTERrisk



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CANCER CONTROL RATES: COMPARISON OF TREATMENT OPTIONS

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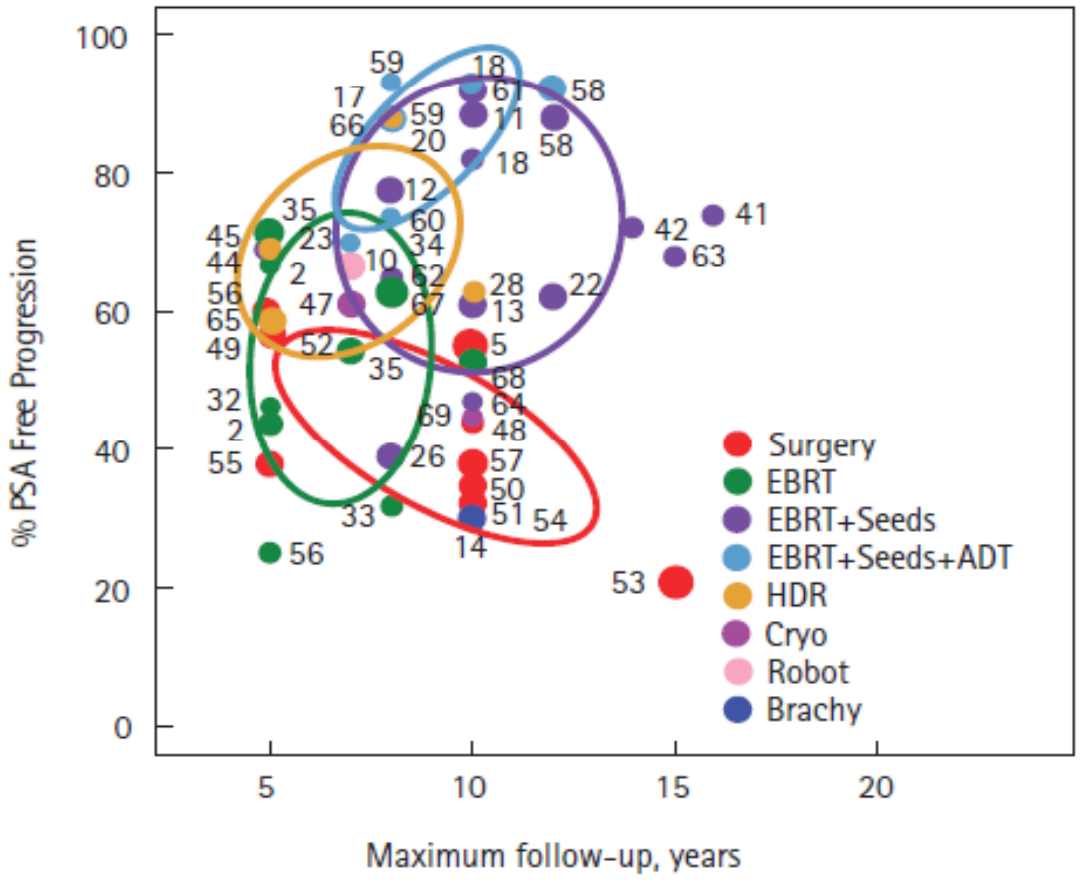
HIGH risk



ESTRO School

Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis

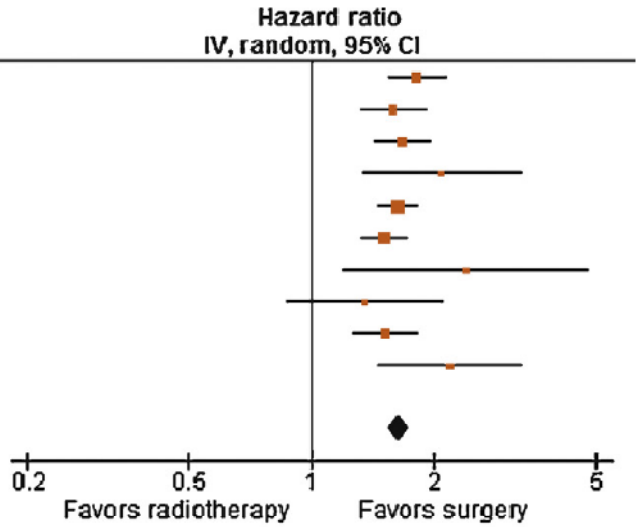
EUROPEAN UROLOGY XXX (2015)

Christopher J.D. Wallis [a,b,c], *Refik Saskin* [c,d], *Richard Choo* [e], *Sender Herschorn* [a,b], *Ronald T. Kodama* [a,b], *Raj Satkunasivam* [a,b], *Prakesh S. Shah* [c,f,g], *Cyril Danjoux* [h], *Robert K. Nam* [a,b,c,*]

a

Study or subgroup	log[hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
Boorjian 2011	0.5988	0.0852	12.1%	1.82 [1.54, 2.15]
Cooperberg 2010	0.4637	0.0911	10.6%	1.59 [1.33, 1.90]
Hoffman 2013	0.5128	0.0792	14.0%	1.67 [1.43, 1.95]
Jeldres 2008	0.7419	0.2255	1.7%	2.10 [1.35, 3.27]
Kibel 2012	0.4886	0.0562	27.8%	1.63 [1.46, 1.82]
Ladjevardi 2010	0.4121	0.0685	18.7%	1.51 [1.32, 1.73]
Merglen 2007	0.8755	0.3537	0.7%	2.40 [1.20, 4.80]
Rice 2013	0.3038	0.2255	1.7%	1.35 [0.87, 2.11]
Sun 2013	0.4187	0.0917	10.5%	1.52 [1.27, 1.82]
Tewari 2007	0.7839	0.2058	2.1%	2.19 [1.46, 3.28]
Total (95% CI)			**100.0%**	**1.63 [1.54, 1.73]**

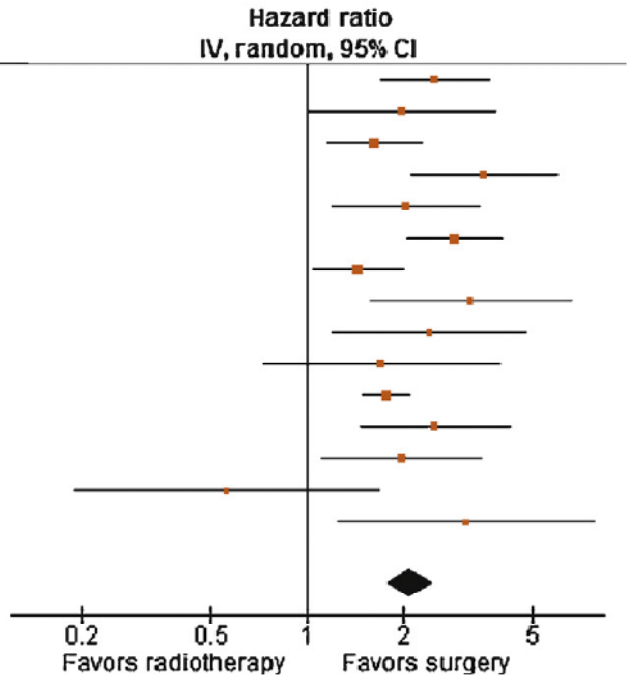
Heterogeneity: Tau² = 0.00; χ^2 = 8.85, df = 9 (p = 0.45); I^2 = 0%
Test for overall effect: Z = 16.56 (p < 0.00001)



b

Study or subgroup	log[hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
Albertsen 2007	0.9163	0.1968	9.0%	2.50 [1.70, 3.68]
Arvold 2011	0.6831	0.3384	4.7%	1.98 [1.02, 3.84]
Boorjian 2011	0.4824	0.1748	9.9%	1.62 [1.15, 2.28]
Cooperberg 2010	1.2698	0.2669	6.4%	3.56 [2.11, 6.01]
DeGroot 2013	0.7031	0.27	6.3%	2.02 [1.19, 3.43]
Hoffman 2013	1.0508	0.1724	10.1%	2.86 [2.04, 4.01]
Kibel 2012	0.3646	0.166	10.4%	1.44 [1.04, 1.99]
Lee 2014	1.1694	0.3665	4.2%	3.22 [1.57, 6.60]
Merglen 2007	0.8755	0.3537	4.4%	2.40 [1.20, 4.80]
Merino 2013	0.5342	0.4331	3.2%	1.71 [0.73, 3.99]
Sooriakumaran 2014	0.5653	0.085	14.5%	1.76 [1.49, 2.08]
Sun 2013	0.9163	0.2709	6.3%	2.50 [1.47, 4.25]
Tewari 2007	0.678	0.2903	5.8%	1.97 [1.12, 3.48]
Westover 2012	-0.5798	0.5575	2.1%	0.56 [0.19, 1.67]
Zelefsky 2010	1.1394	0.4675	2.8%	3.12 [1.25, 7.81]
Total (95% CI)			**100.0%**	**2.08 [1.76, 2.47]**

Heterogeneity: Tau² = 0.04; χ^2 = 26.70, df = 14 (p = 0.02); I^2 = 48%
Test for overall effect: Z = 8.54 (p < 0.00001)



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Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis

EUROPEAN UROLOGY XXX (2015)

Christopher J.D. Wallis [a,b,c], Refik Saskin [c,d], Richard Choo [e], Sender Herschorn [a,b], Ronald T. Kodama [a,b], Raj Satkunasivam [a,b], Prakesh S. Shah [c,f,g], Cyril Danjoux [h], Robert K. Nam [a,b,c,]*

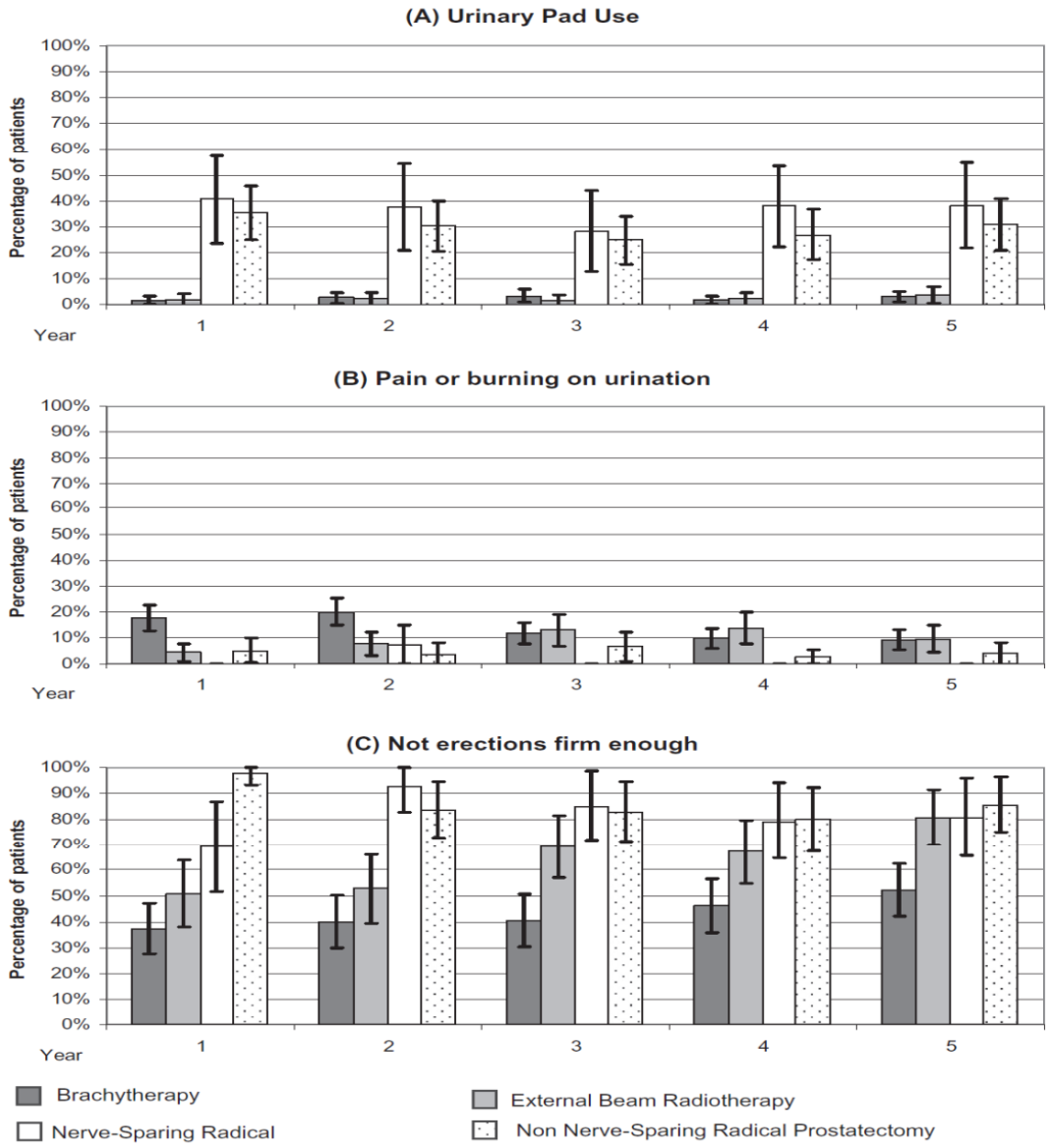
Table 3 – Newcastle-Ottawa Scale for risk of bias assessment of studies included in the meta-analysis

Study	Selection				Comparability	Outcome			Overall
	Representativeness of exposed cohort	Selection of nonexposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequacy of follow-up	
Abdollah (2012)	☆	☆	☆	☆	☆☆	☆			7
Albertsen (2007)	☆	☆	☆	☆	☆☆	☆	☆		8
Arvold (2011)	☆		☆	☆	☆☆				5
Boorjian (2011)	☆		☆	☆	☆☆	☆	☆		7
Cooperberg (2010)	☆	☆	☆	☆	☆☆	☆			7
DeGroot (2013)	☆	☆	☆	☆	☆☆	☆	☆		8
Hoffman (2013)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Jeldres (2008)	☆	☆	☆	☆	☆☆	☆	☆		8
Kibel (2012)	☆	☆	☆	☆	☆☆	☆	☆		8
Ladjevardi (2010)	☆	☆	☆	☆	☆☆	☆		☆	8
Lee (2014)	☆	☆	☆	☆	☆☆	☆	☆		8
Merglen (2007)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Merino (2013)	☆	☆	☆	☆	☆☆		☆		7
Rice (2013)	☆	☆	☆	☆	☆☆	☆	☆		8
Sooriakumaran (2014)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Sun (2013)	☆	☆	☆	☆	☆☆	☆		☆	7
Tewari (2007)	☆	☆	☆	☆	☆☆	☆			7
Westover (2012)	☆		☆	☆	☆☆	☆			6
Zelefsky (2010)	☆		☆	☆	☆☆	☆		☆	7

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

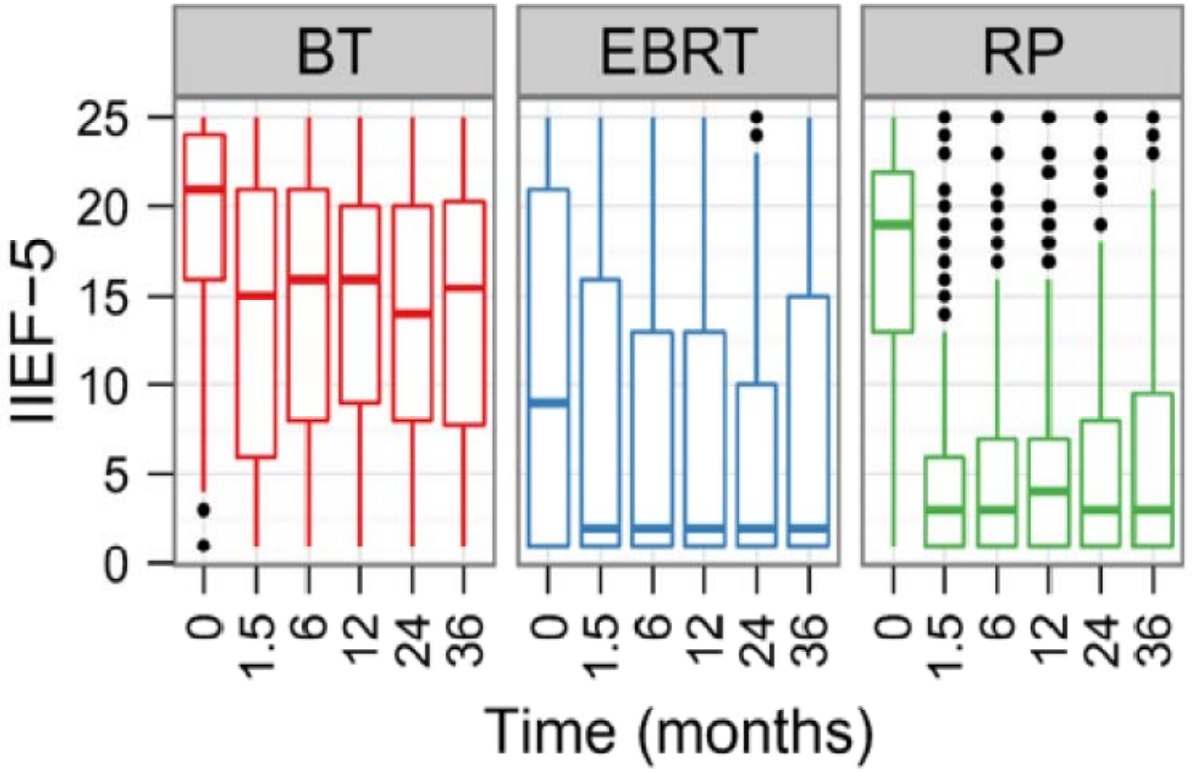


Erectile function following brachytherapy, external beam radiotherapy, or radical prostatectomy in prostate cancer patients

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)	Still on RT (with diarrhoea)
DAY 52:		Try the Vacupump	Finish RT (with diarrhoea)

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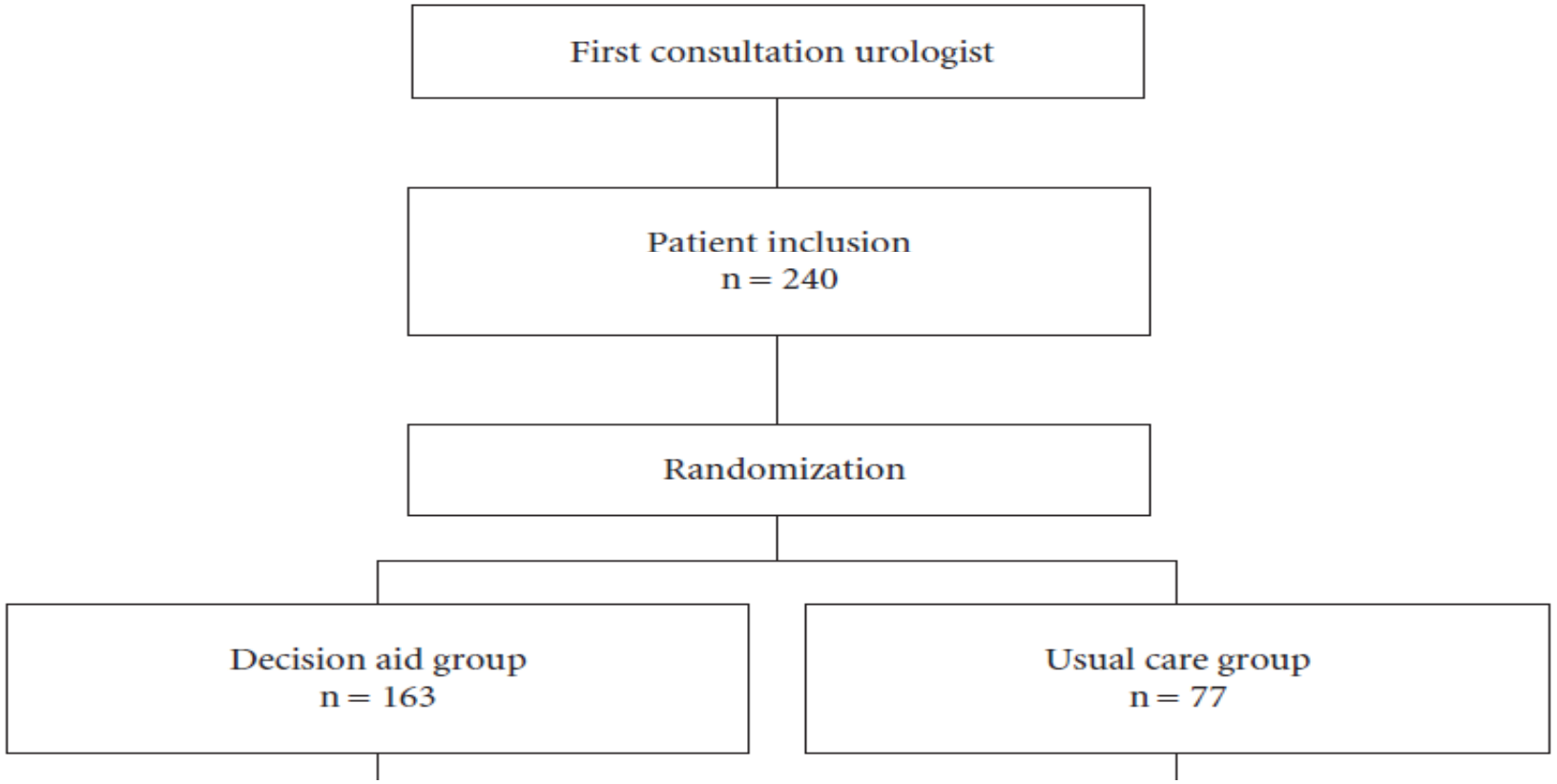
Choice between prostatectomy and radiotherapy when men are eligible for both: a randomized controlled trial of usual care vs decision aid

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

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

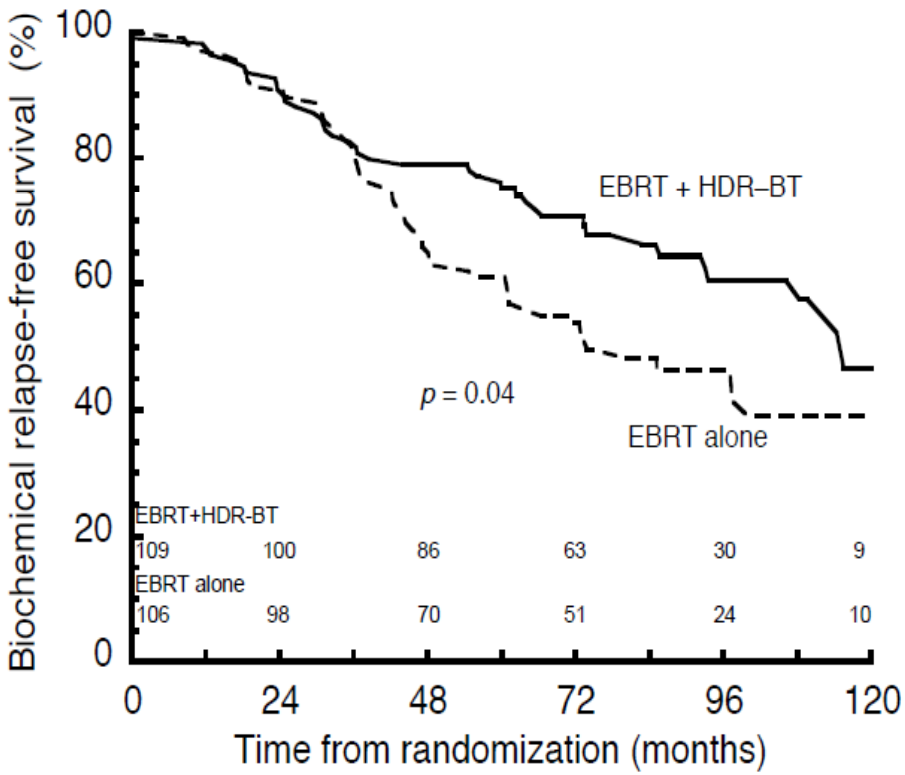
- Volume limited
- Limited cover of ECE/SV
- Dose delivery variable
- Dose limited/fixed
- QA post implant
- Less flexible for boosts

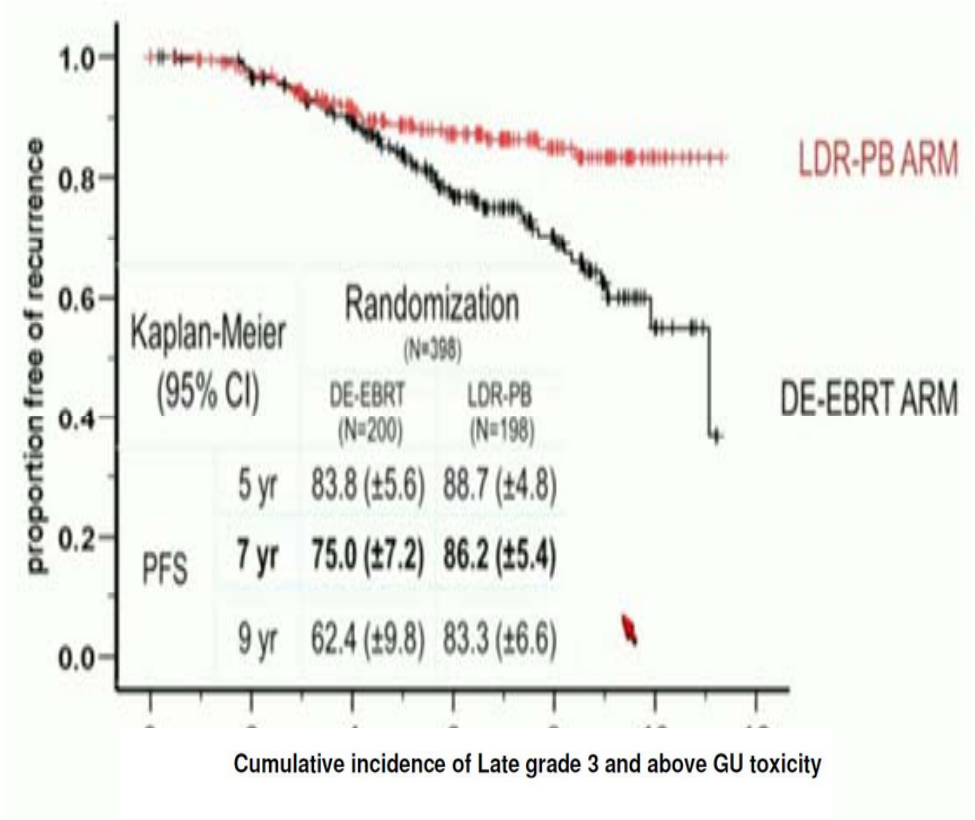
HDR

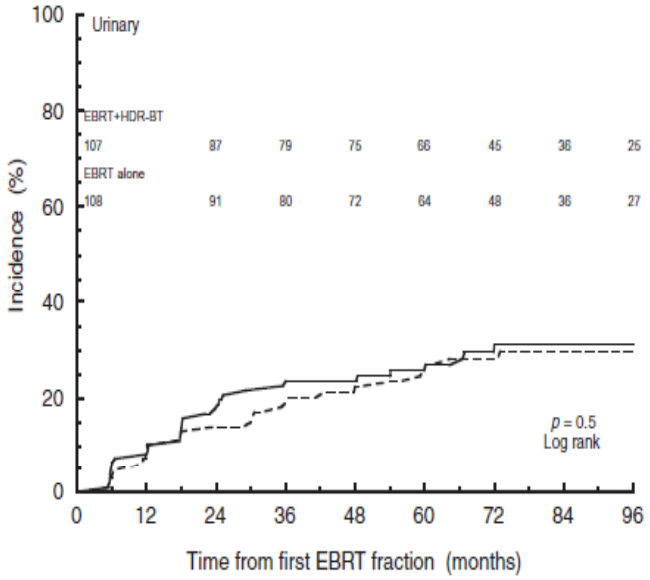
- Fractionation
- Requires HDR facility

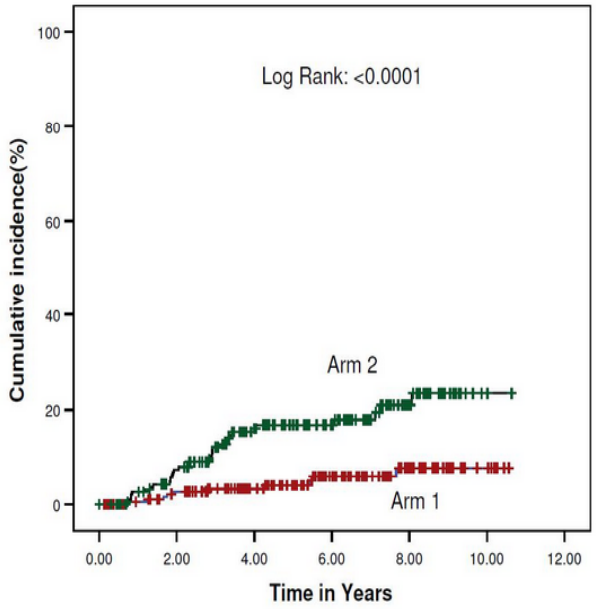
- Can implant large glands
- Can implant ECE and SV
- Accurate dose delivery
- Biologically higher dose
- QA pre delivery
- Focal subvolume boosts

HDR Best Boost ? LDR









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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

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 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

a) 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

a) External beam IMRT + HDR boost

ESTRO School

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

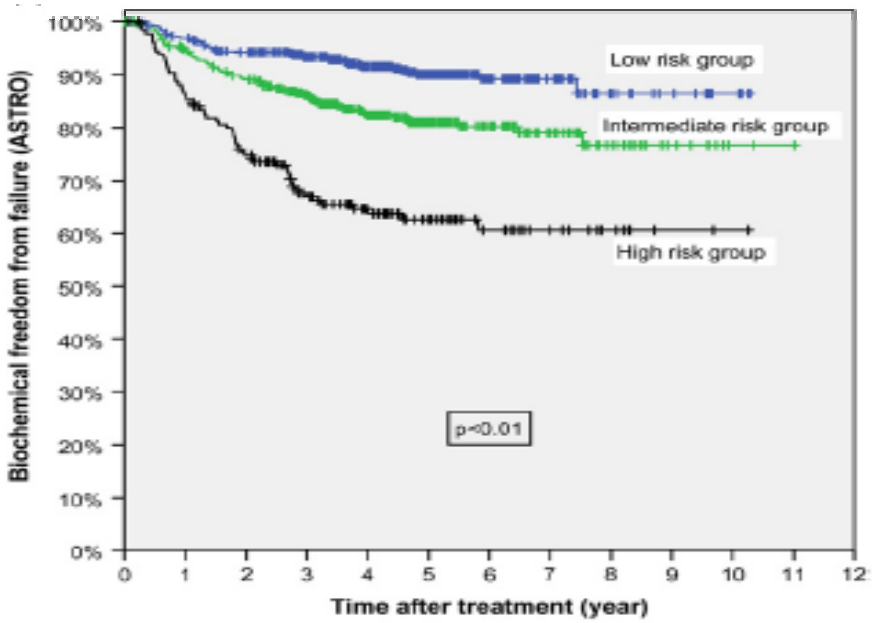
b) Active surveillance

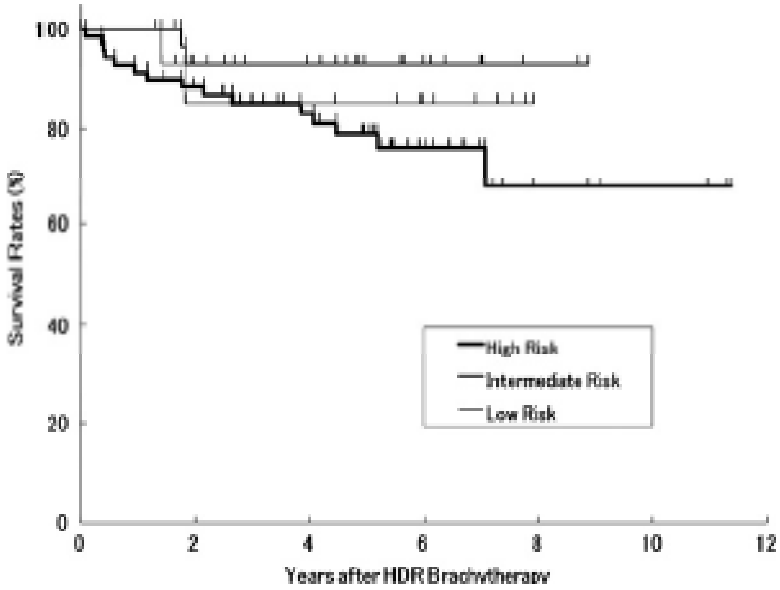
c) External beam IMRT to 78Gy with ADT

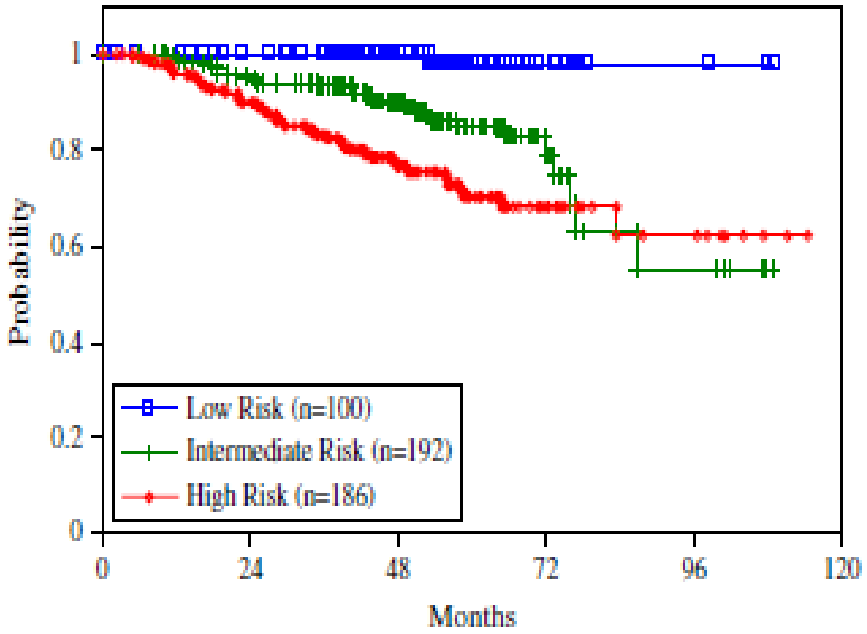
d) LDR seed brachytherapy

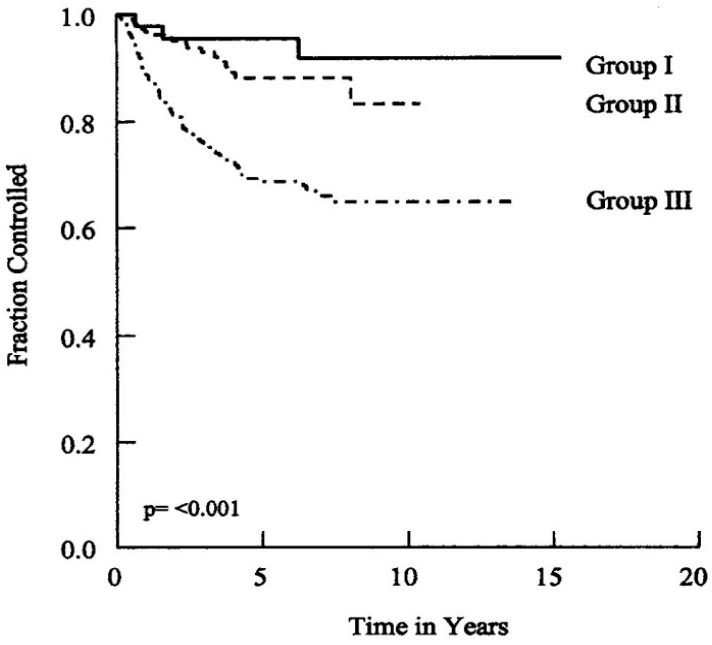
e) External beam IMRT + HDR boost

Does the technique matter?









Prostate brachytherapy has been the subject of heated debate among surgeons and the proponents of the various brachytherapy methods. This very first interdisciplinary book on the subject provides a comprehensive overview of innovations in low dose rate (LDR), high dose rate (HDR), and pulsed dose rate (PDR) interstitial brachytherapy for the management of local or locally advanced prostate cancer. In addition to detailed chapters on patient selection and the use of imaging in diagnostics, treatment guidance, and implantation control, background chapters are included on related medical physics issues such as treatment planning and quality assurance. The results obtained with the different treatment options and the difficult task of salvage treatment are fully discussed. All chapters have been written by internationally recognized experts in their fields who for more than a decade have formed the teaching staff responsible for the successful GEC-ESTRO/EAU Prostate Brachytherapy Teaching Course.

This book will be invaluable in informing residents and others of the scientific background and potential of modern prostate brachytherapy. It will also prove a useful source of up-to-date information for those who specialize in prostate brachytherapy or intend to start an interstitial brachytherapy service.

Radiology

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