

# **RADIOTERAPIJA RAKA PROSTATE**

## **Raznolikost tehnoloških mogućnosti**

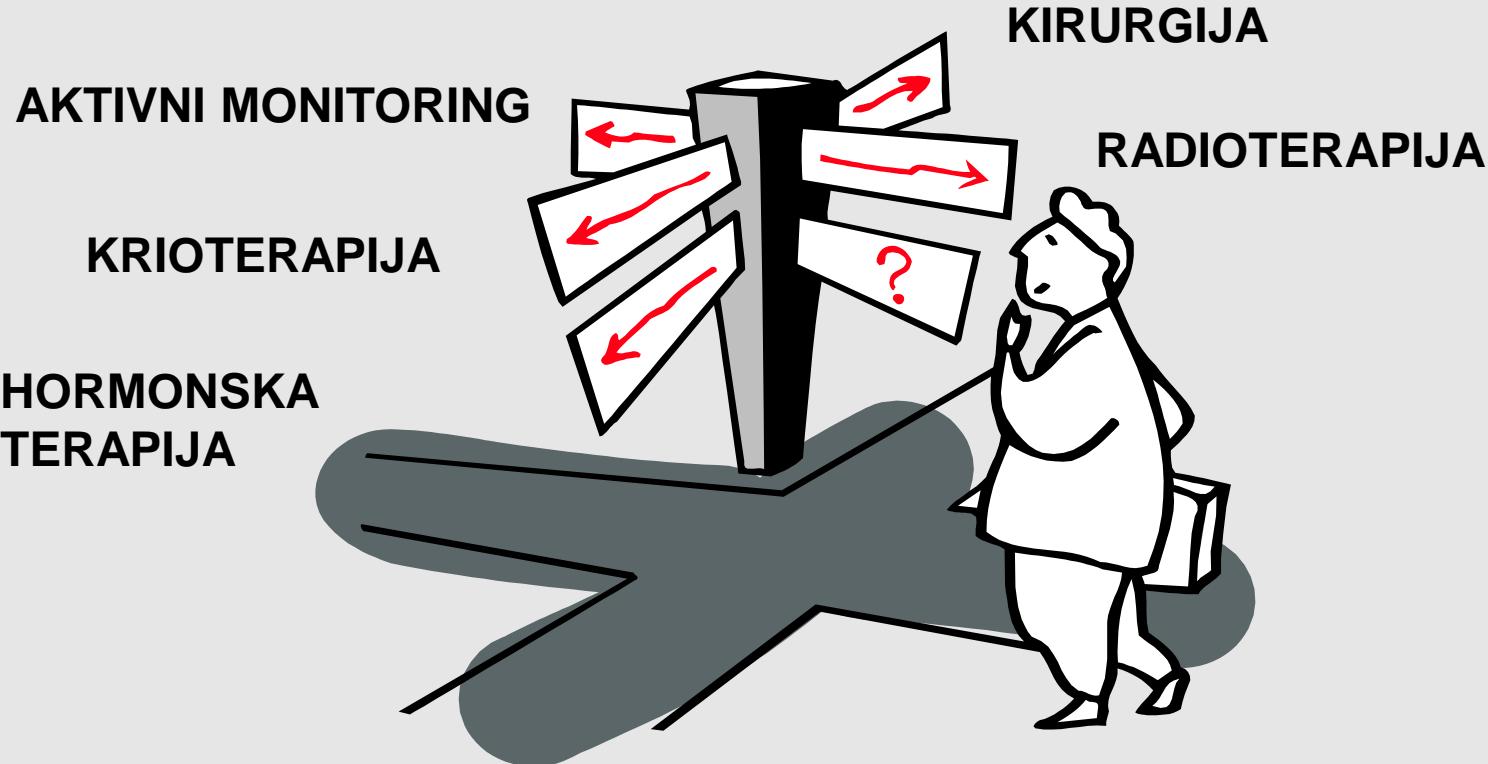
2. KONGRES RADIOLOŠKE TEHNOLOGIJE, VUKOVAR 23.-25.9.2016.

**Doc.dr.sc. Josip Grah**

**Klinika za onkologiju**

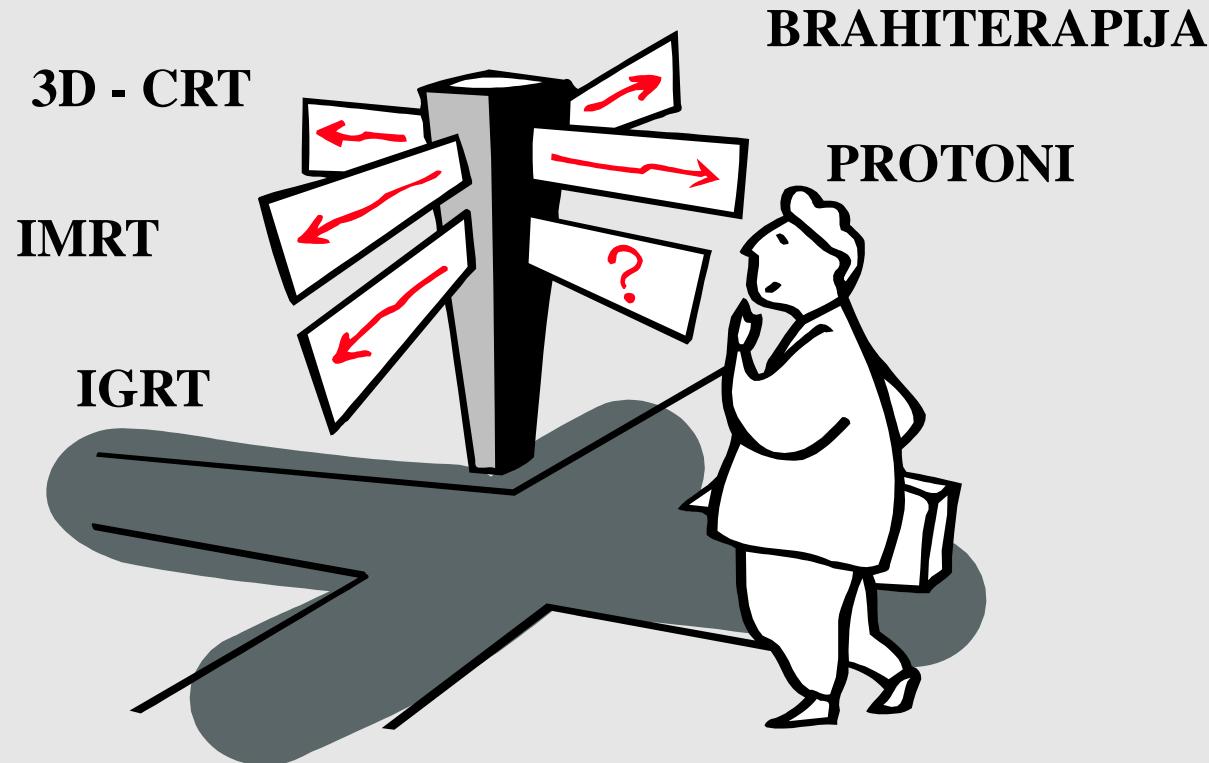
**KBC Zagreb**

# KARCINOM PROSTATE – ŠTO DALJE ?



Nilsson et al. Acta Oncologica 43:4 316-381 2004 (152.654 Patient)

# RADIOTERAPIJA ? – KAMO DALJE ?



# **Kurativne terapijske opcije**

## **Suvremena kirurgija**

## **Suvremena radioterapija**

# TEHNIČKI NAPREDAK

## KIRURGIJA

**PROSTATEKTOMIJA**

nerve sparing 1998

**PROSTATEKTOMIJA**

laparoskopska 2000

**PROSTATEKTOMIJA**

robotic prostatectomy 2003

## RADIOTERAPIJA

**LDR SEEDS** 1984

**BT HDR** 1986

**EBRT** 3D-konformalno

1994

**EBRT IGRT** 1997

**EBRT IMRT** 2000

**PROTONI**

# **PROSTATEKTOMIJA VS RADIOTERAPIJA**

**UROLOZI**

**Kirurgija je bolja!**

**RADIJACIJSKI ONKOLOZI**

**Zračenje je bolje!**

D`Amico : J Clin Oncol 2003, 12:2163

Biochemical disease-free survival from prostate cancer • S. H. STOKES

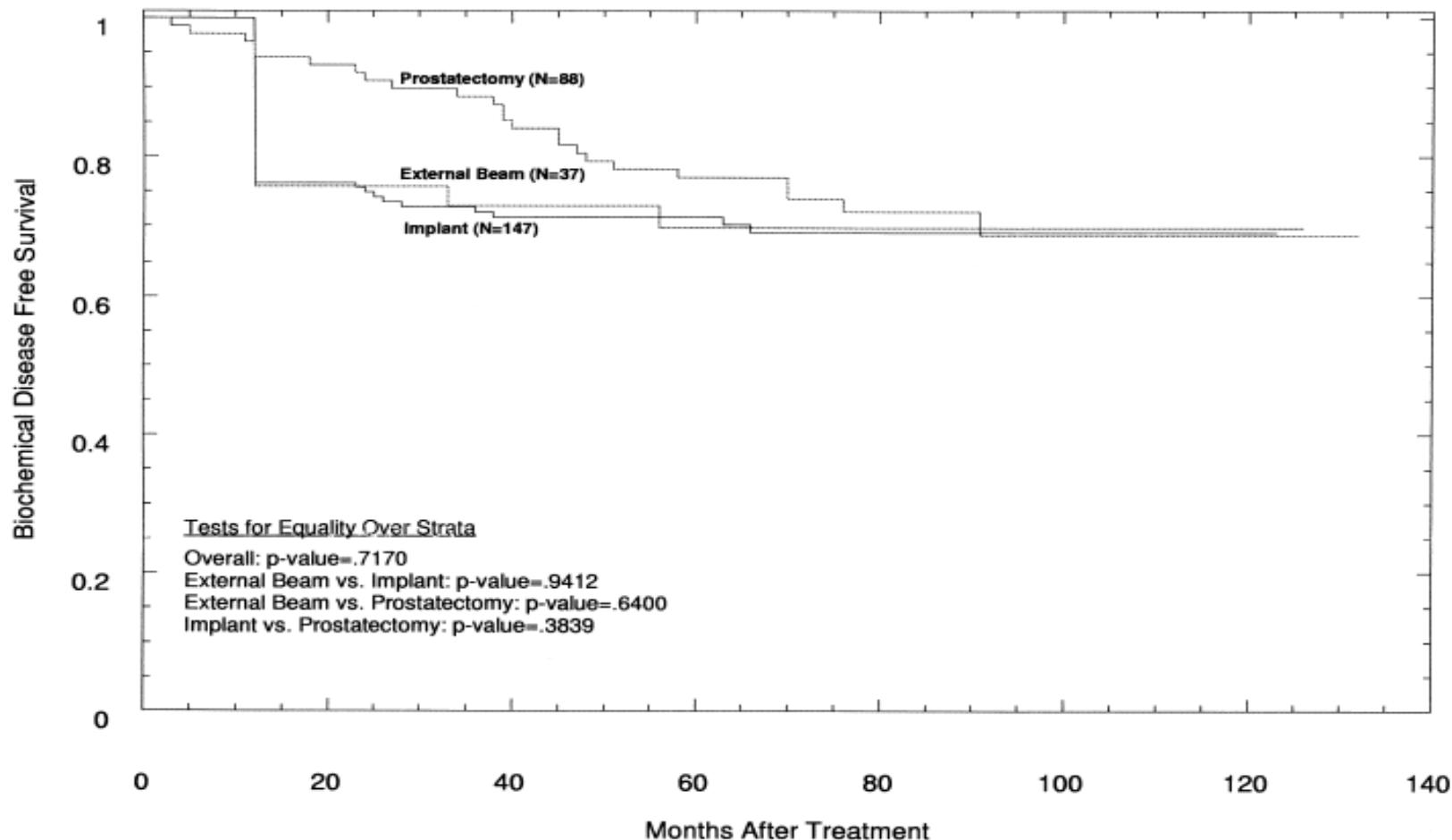


Fig. 5. Actuarial biochemical disease-free survival for low to intermediate risk group undergoing external irradiation, implant, or prostatectomy.

# AUA Prostate Cancer clinical guidelines panel

Middleton RG et al: J Urol 1995 154(6): 2144-8

**“ recommend as a standard that patients  
with newly diagnosed,  
clinically localised prostate cancer  
should be informed of all  
commonly accepted treatment  
options by directly involved specialist”**

**Prije 15 - 20 godina**

**Radikalna prostatektomija**

ili

**Konvencionalna perkutana radioterapija**

**Radikalna prostatektomija**

**PRIJE 10 GODINA**

ili

**Konvencionalna perkutana radioterapija**

ili

**3D Konformalna perkutana radioterapija**

ili

**Brahiterapija**

ili

**CRT + Brahiterapija**

# Radikalna prostatektomija

DANAS

ili

Konvencionalna perkutana radioterapija

ili

Konformalna perkutana radioterapija

3-D

IMRT

IGRT

Low dose rate

High dose rate

Brahiterapija

ili

CRT + Brahiterapija

ili

Protonska radioterapija

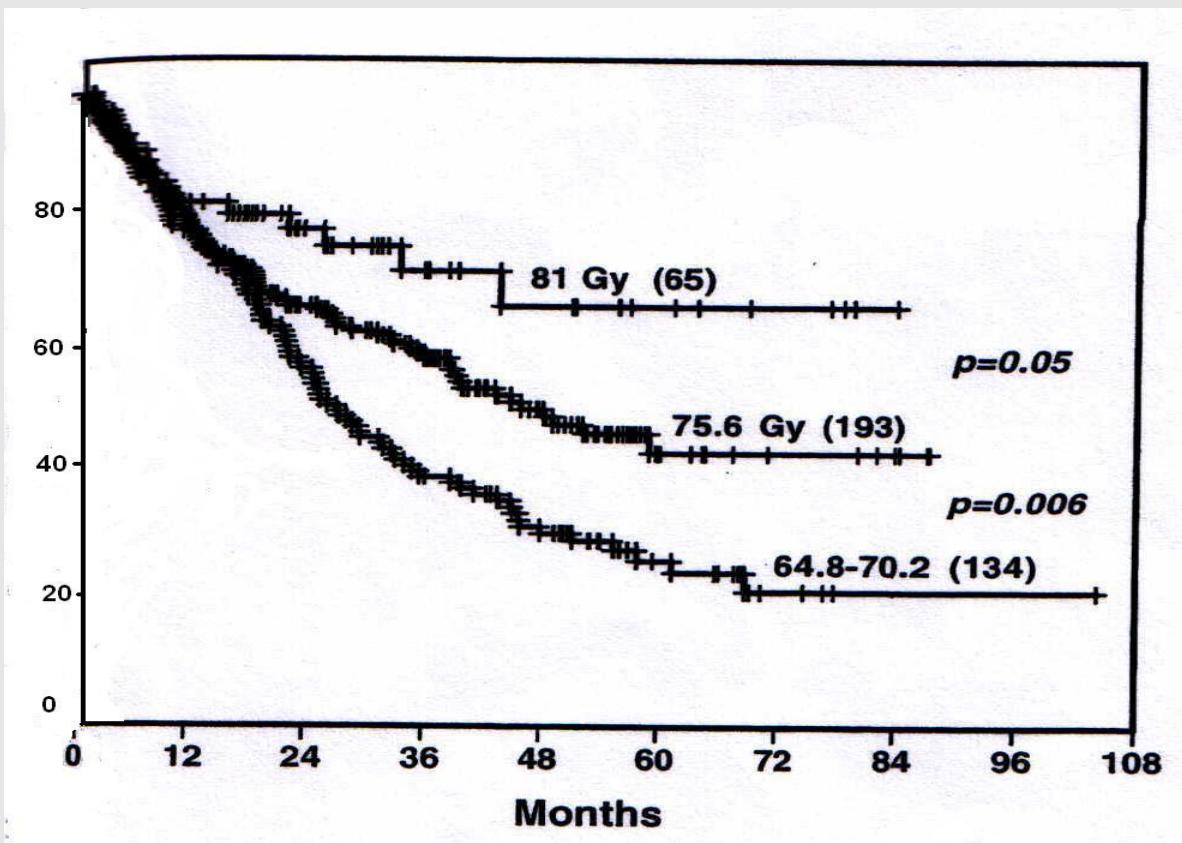
Sa ili bez androgene blokade

# Eskalacija doze

- U ovom trenutku se još neznaju limiti eskalacije doze
- Novija nastojanja usmjereni u povećanje BED (biološki ekvivalentne doze)
- Velika važnost zaštite normalnih tkiva



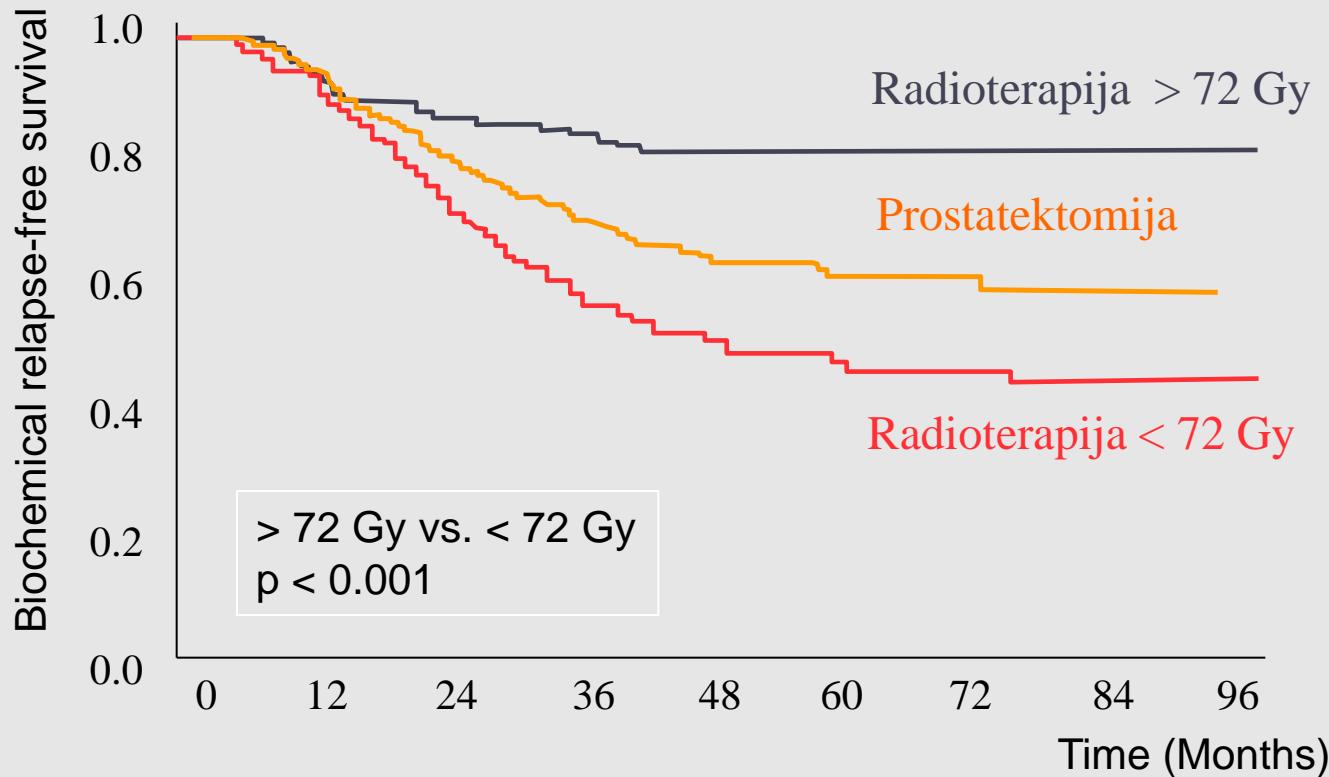
# Pitanje eskalacije doze



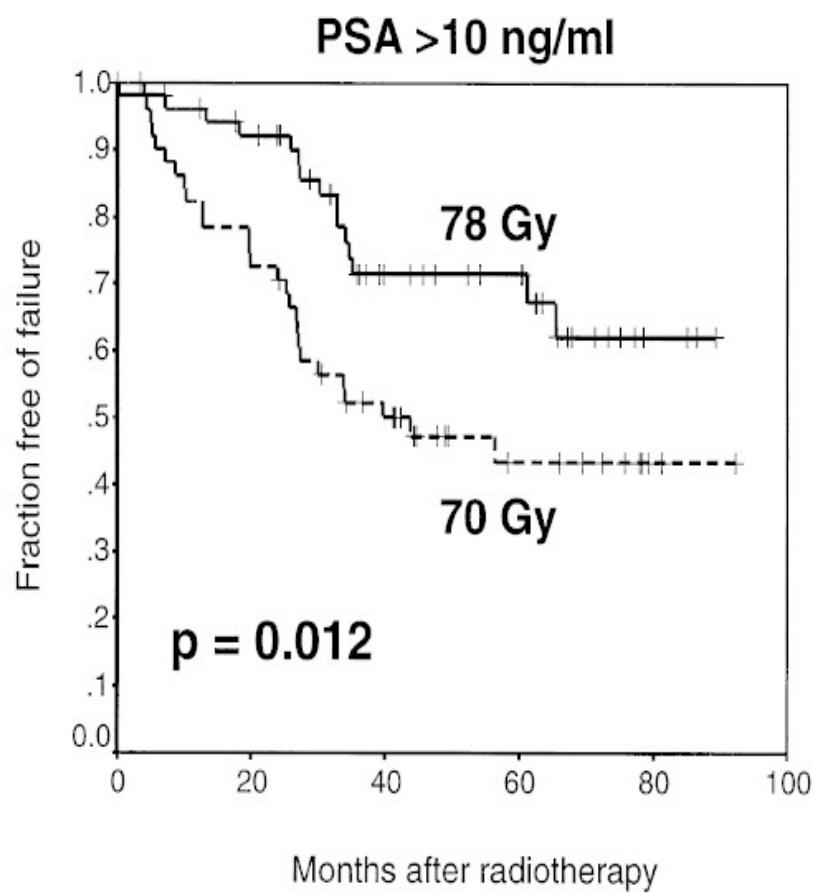
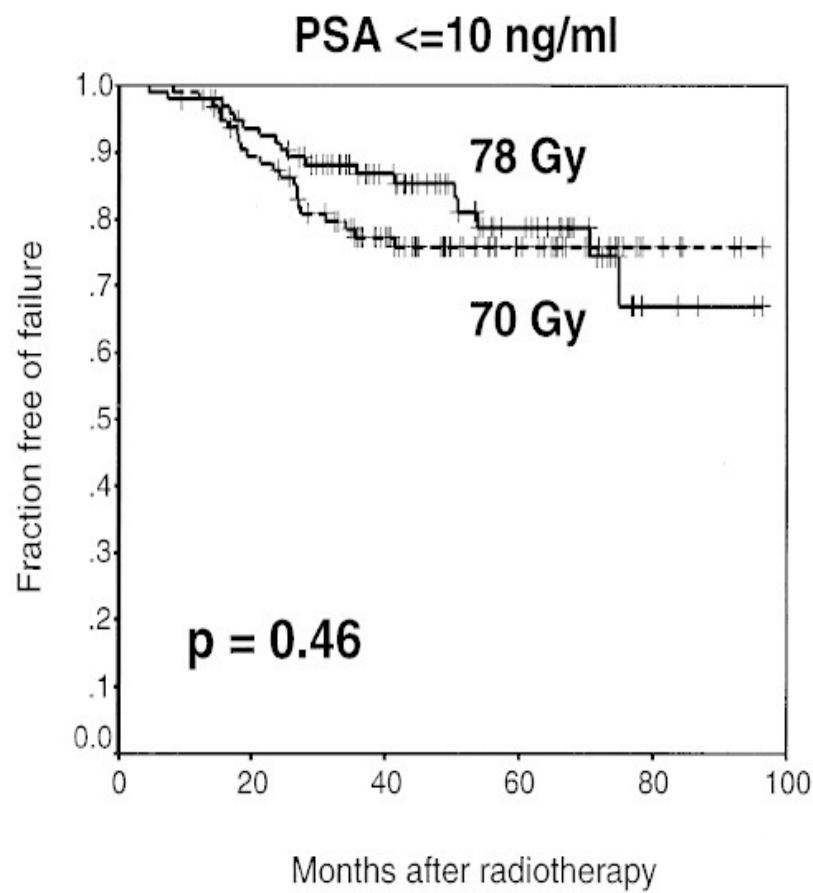
Preživljenje bez biokemijskih znakova bolesti u 392 bolesnika s nepovoljnim prognostičkim pokazateljima

# Eskalacija doze

## srednji/visoki rizik



Kupelian (2002); J Clin Oncol 20:3376

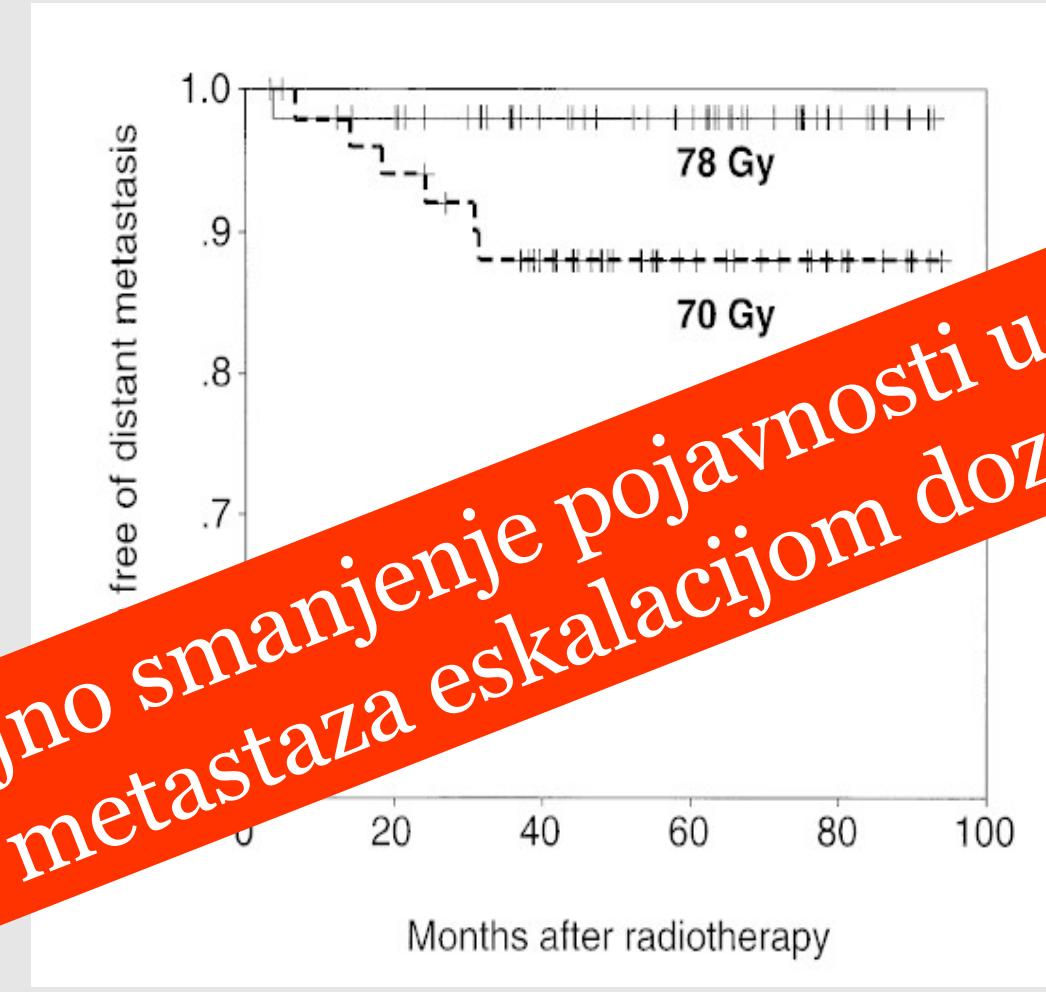


I. J. Radiation Oncology • Biology • Physics

Volume 53, Number 5, 2002

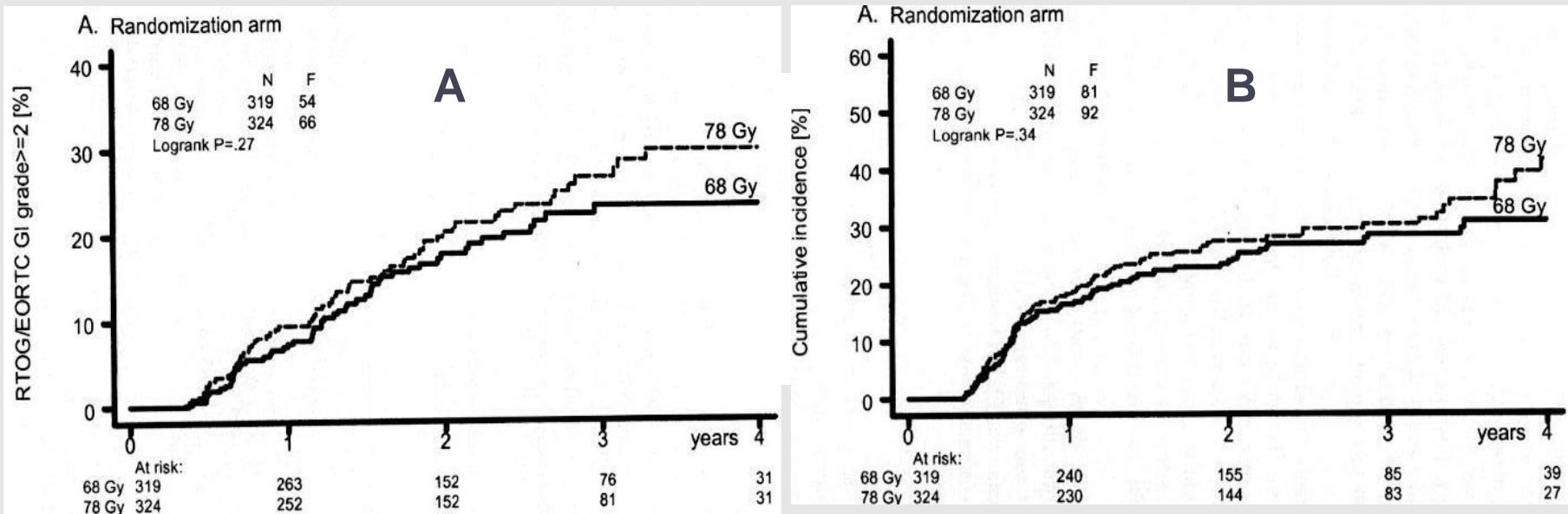
Dose escalation: POLLACK et al. IJRTBP, Vol. 53, 2002

Značajno smanjenje pojavnosti udaljenih metastaza eskalacijom doze!!!



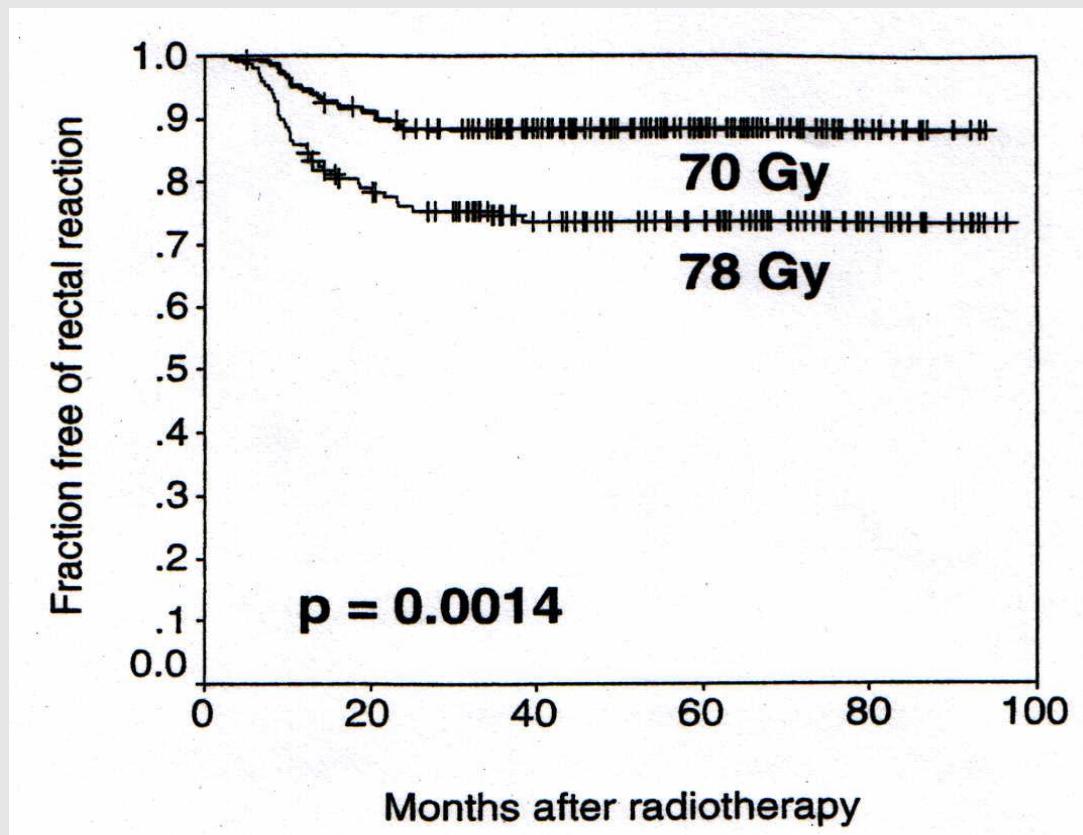
Dose escalation: POLLACK et al. IJRTBP, Vol. 53, 2002

# Kasne nuspojave radioterapije



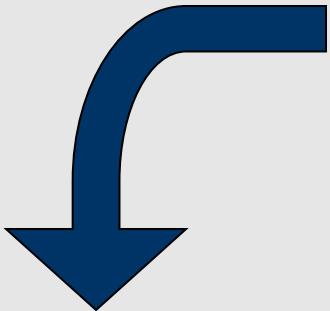
**Kasne intestinalne (A) i genitourinarne (B) nuspojave u 669 bolesnika zračenih dozom do 78 Gy konformalnom ili 68 Gy konvencionalnom radioterapijom**

# Kasne nuspojave radioterapije 2D vs 3D





## ZAKLJUČAK



**Bolja tumorska kontrola raka prostate postiže se eskalacijom doze zračenja  
Rektalne nuspojave ovise o apliciranoj dozi i volumenu ozračenog rektuma  
Izbjegavanje rektalne toksičnosti zračenja uz istodobnu eksalaciju doze moguća je samo uz bolju **konformalnost****

*Bolja konformalnost*

**Bolja slikovna potpotra:**

**MRI-CT fuzija, Molekularni Imaging (?)**

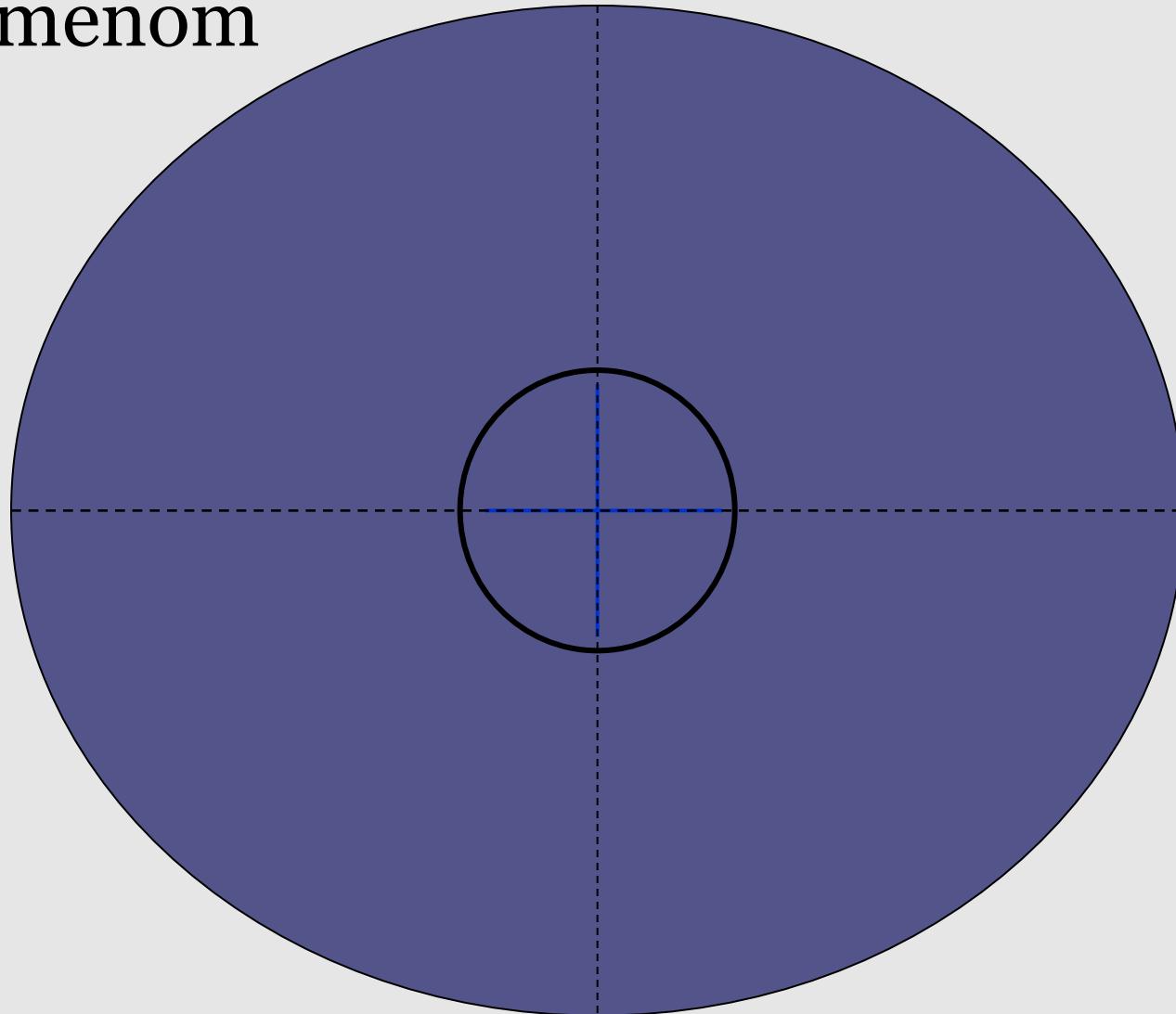
**Bolje tehnike aplikacije zračenja:**

**IMRT, Brahiterapija, Protoni**

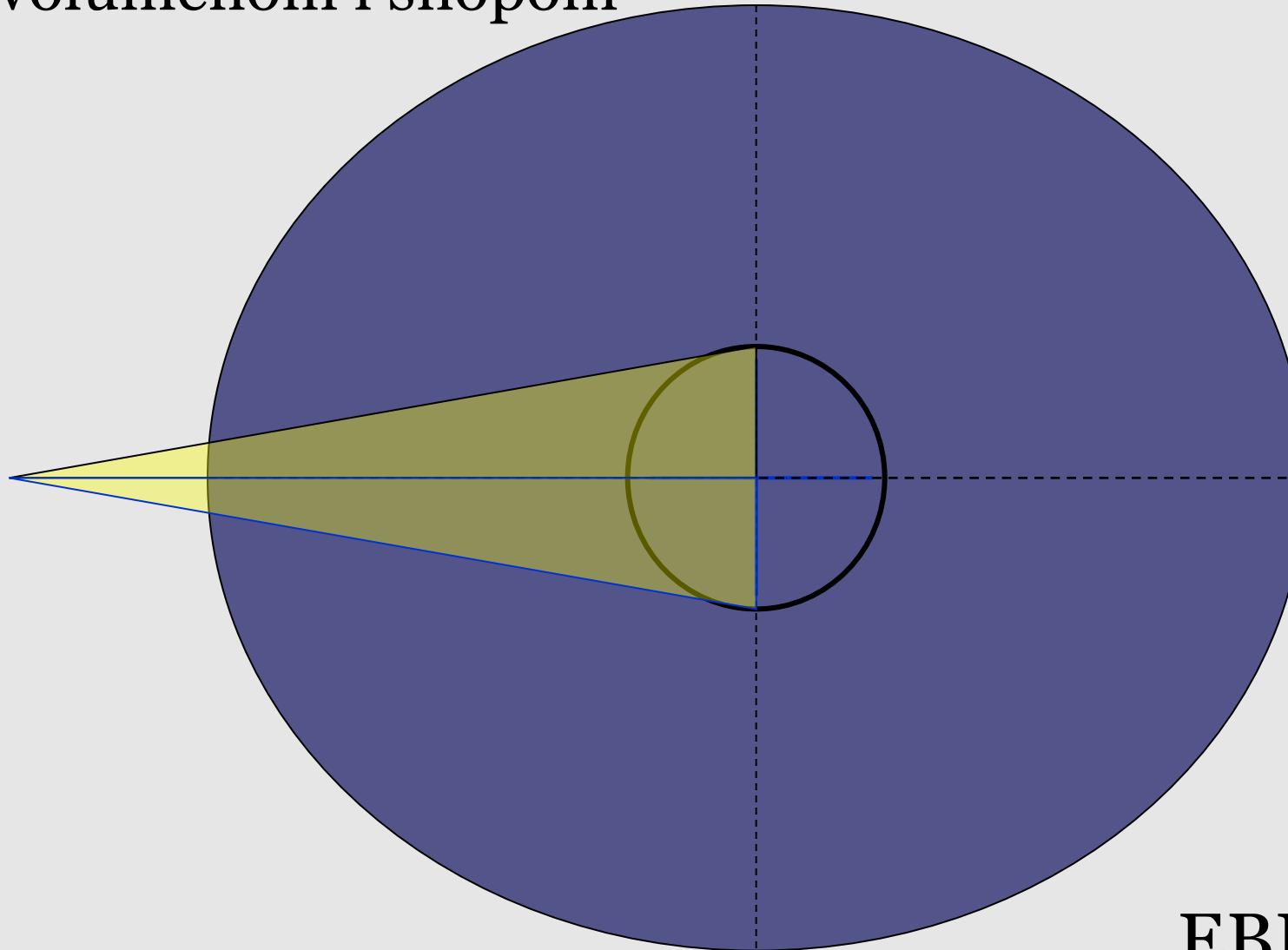
**Bolje pozicioniranje:**

**Adaptativna RT kod mobilnih ciljnih volumena**

# Model bolesnika sa ciljnim volumenom

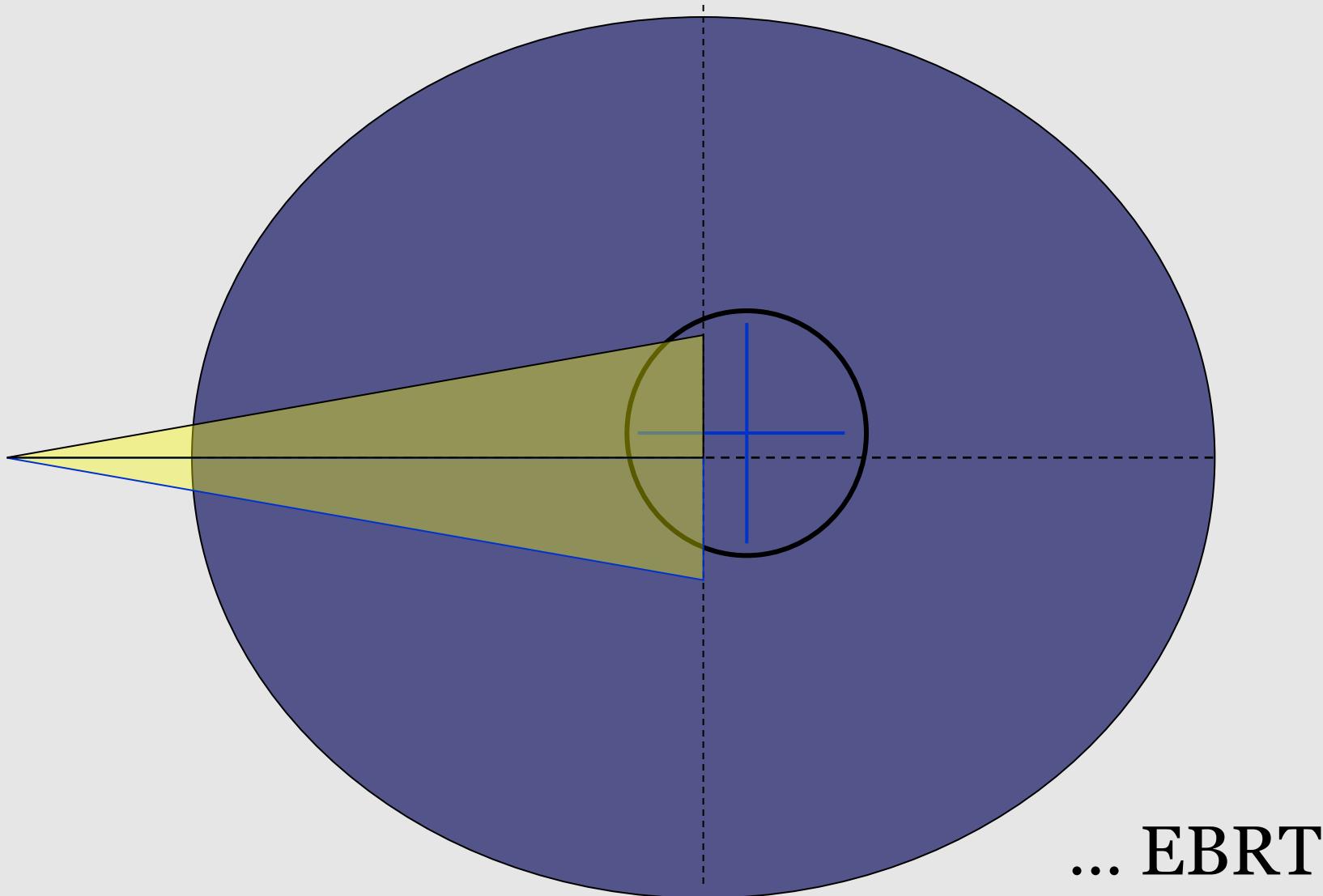


# Model bolesnika sa ciljnim volumenom i snopom

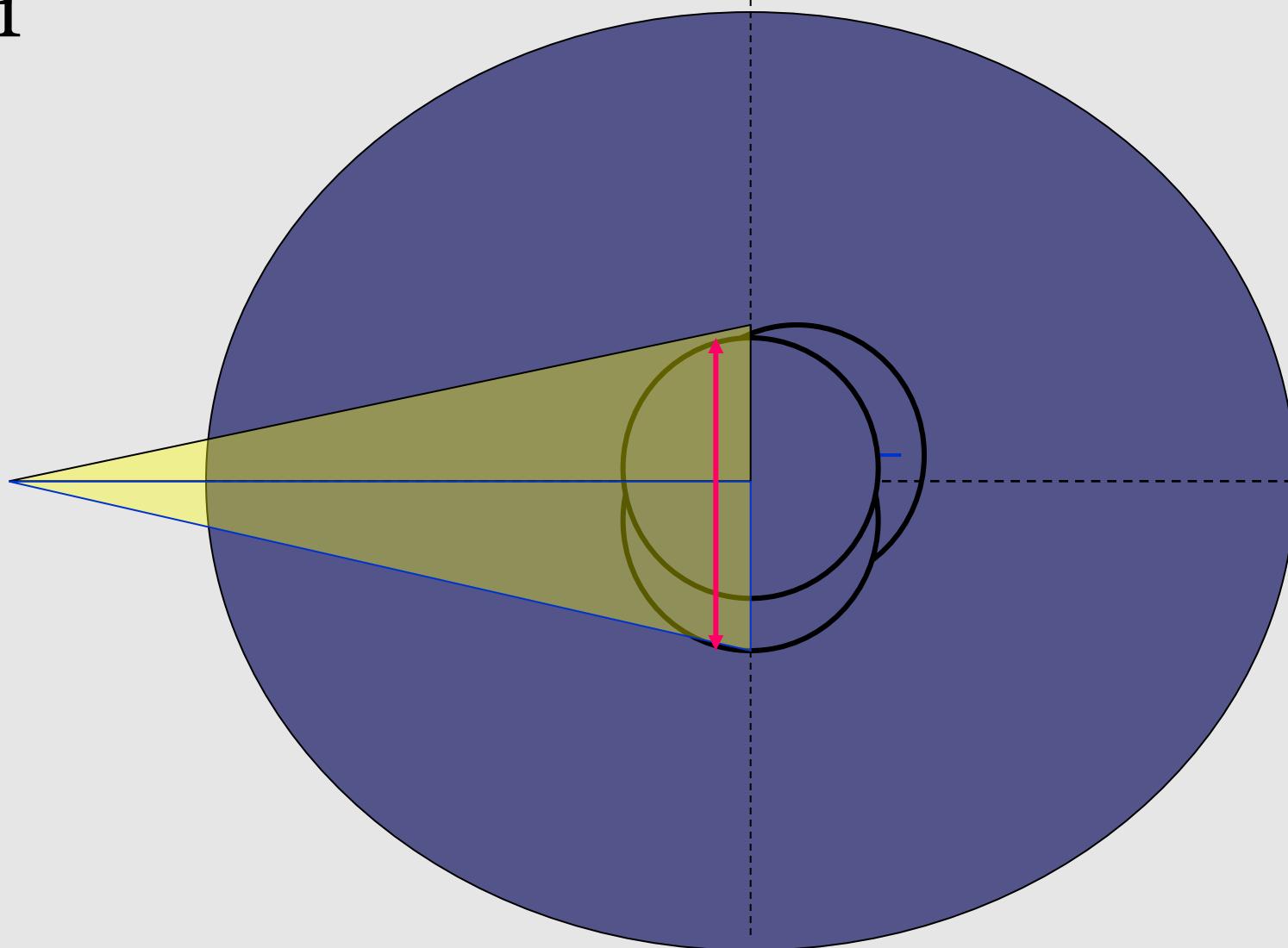


... EBRT

# Problem: pomični ciljni volumen

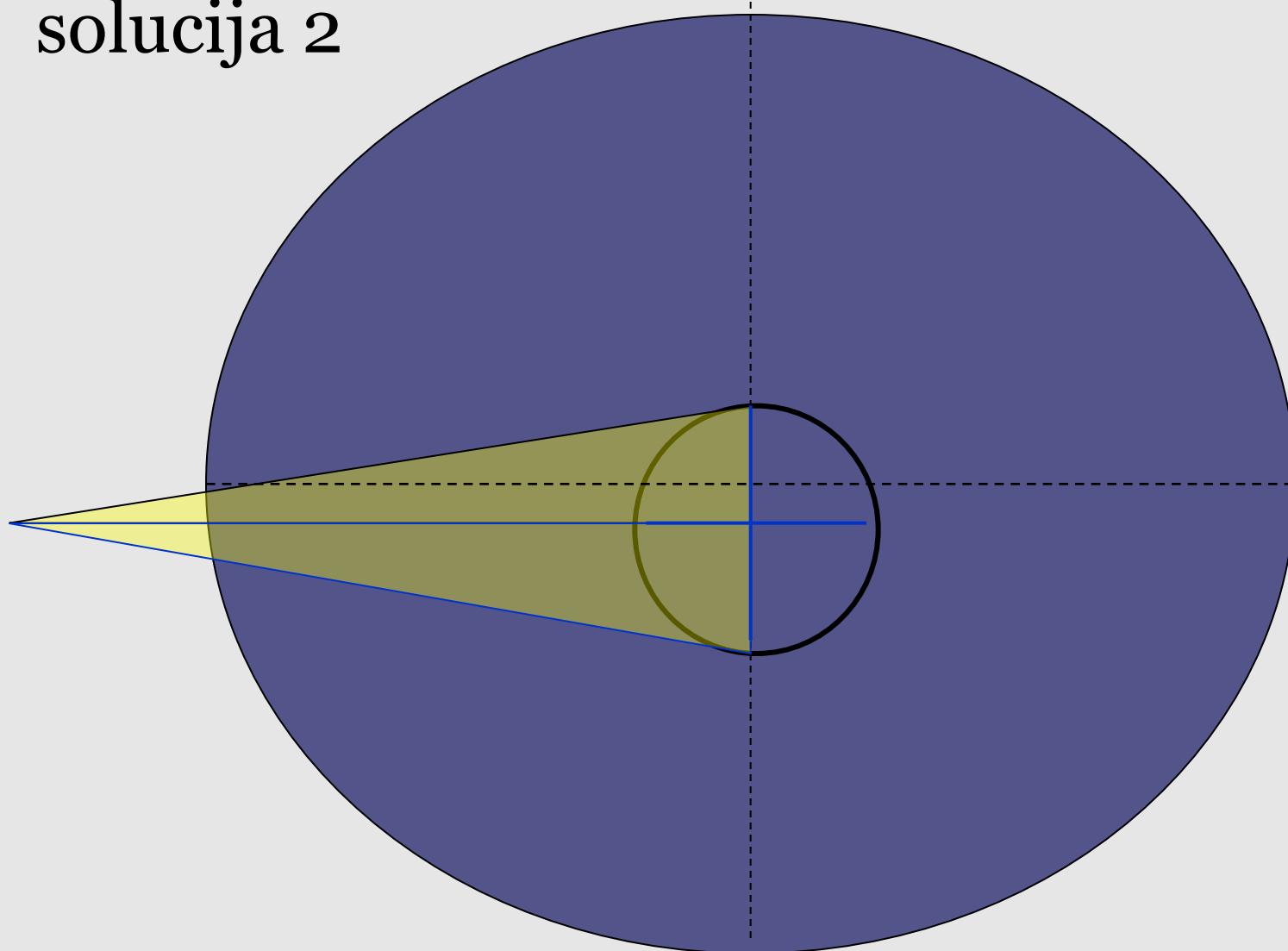


# Problem pomičnog ciljnog volumena: solucija 1



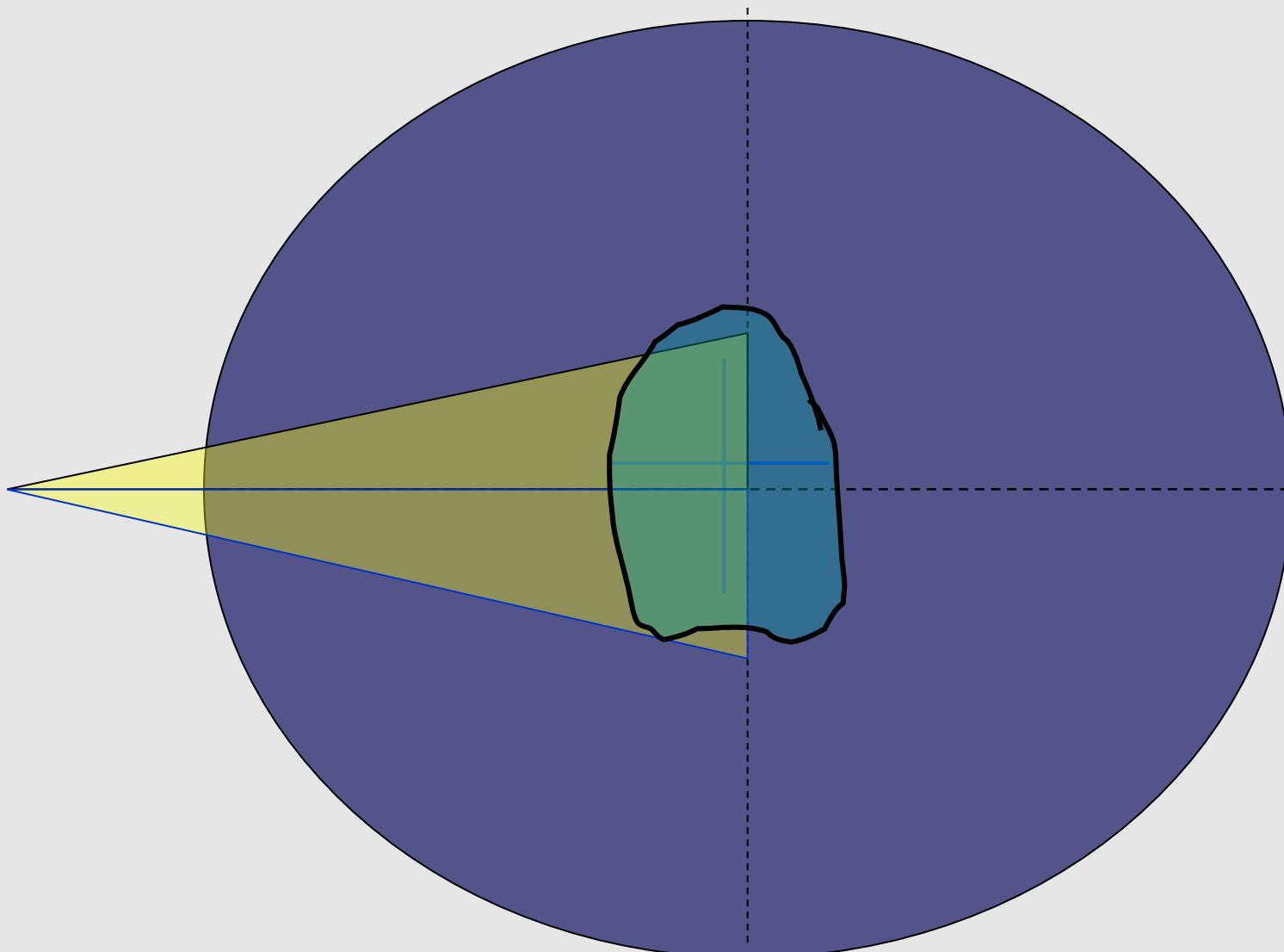
Proširenje snopa

## 2 Problem pomičnog ciljnog volumena: solucija 2



Korekcija greške slikovnim navođenjem (IGRT)

Ali problem je složeniji...!

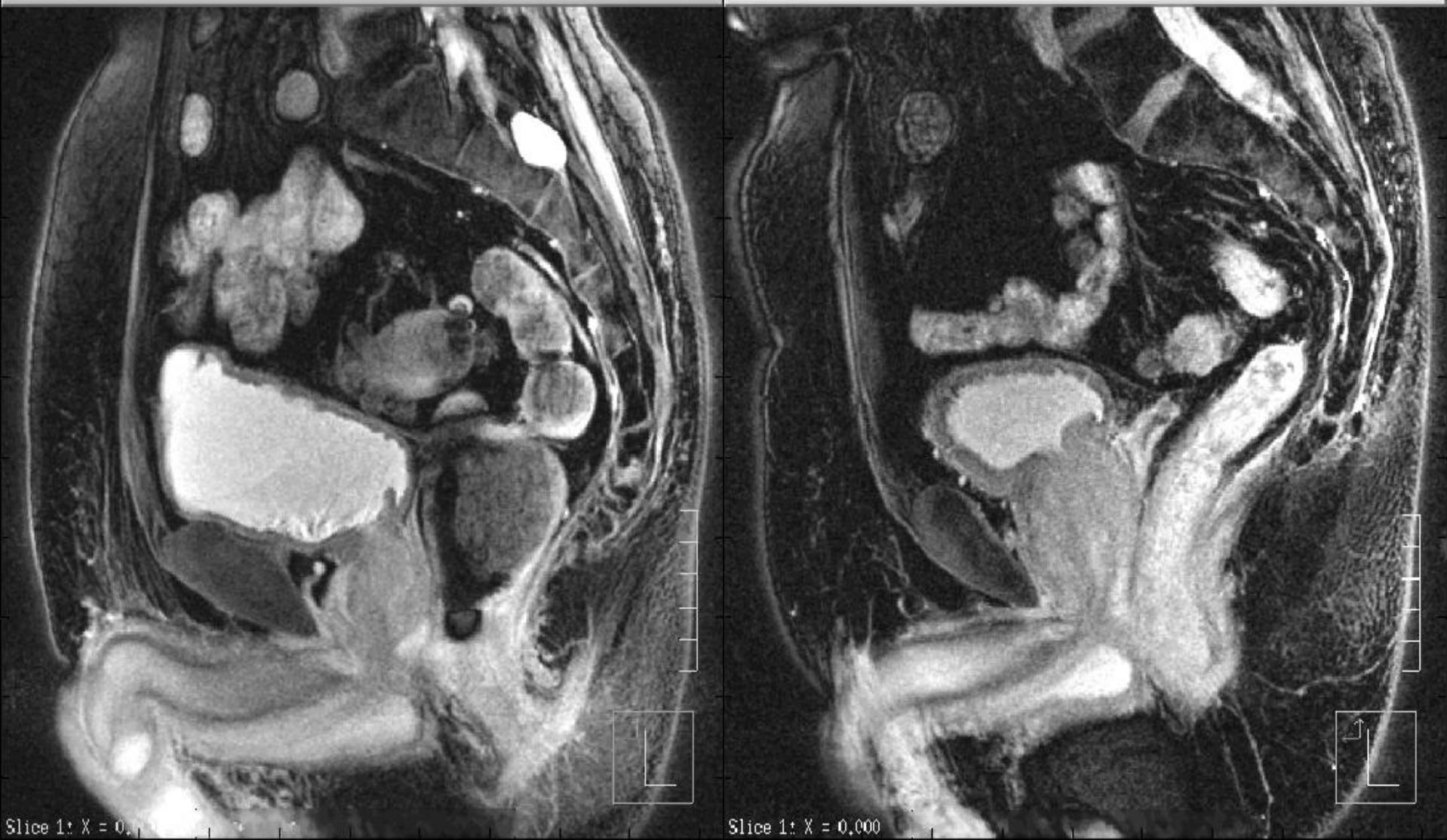


Pokretni ciljni volumen te promjene oblika i veličine

# Sagitalna snimka MR: promjene oblika prostate

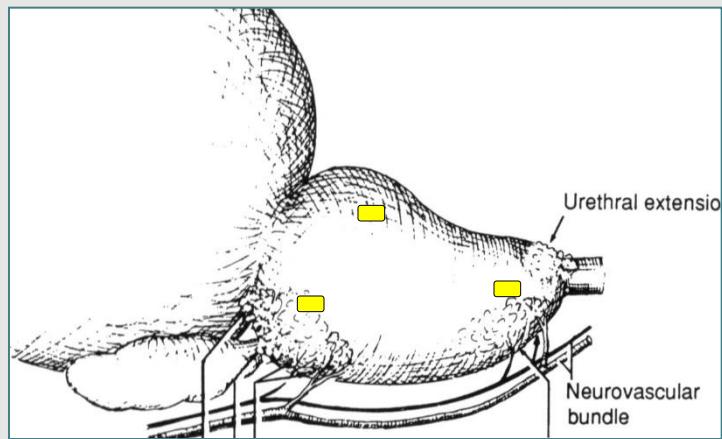
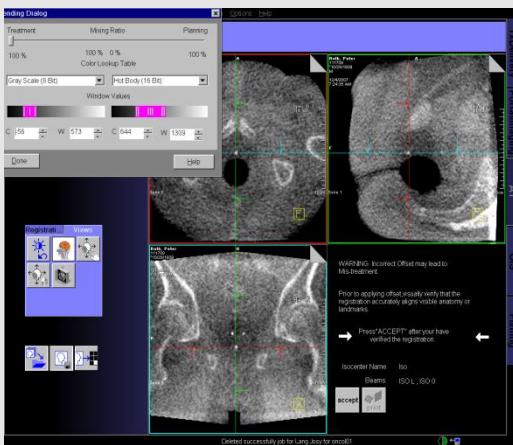
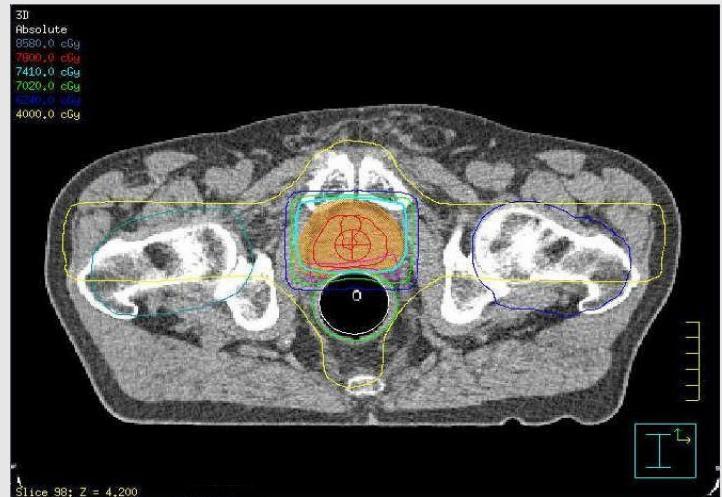
Rektum pun

Rektum prazan

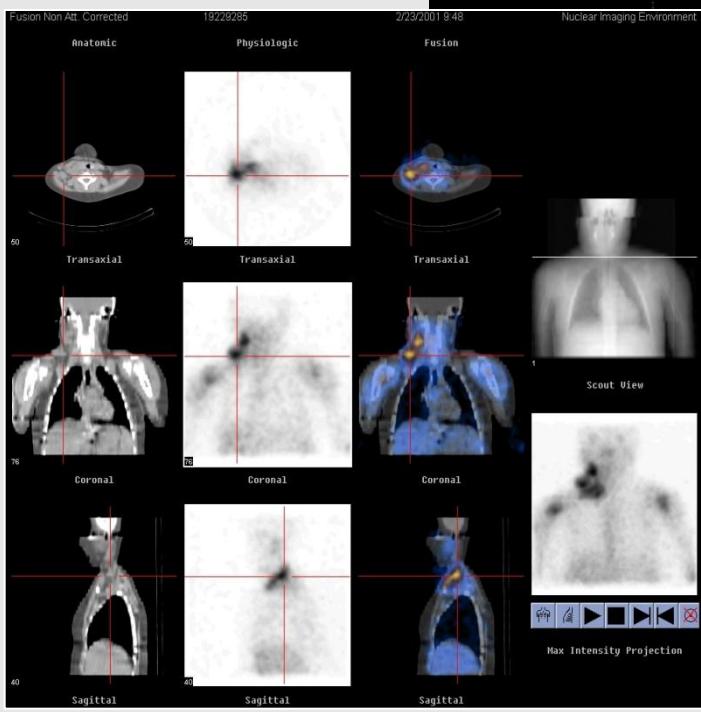
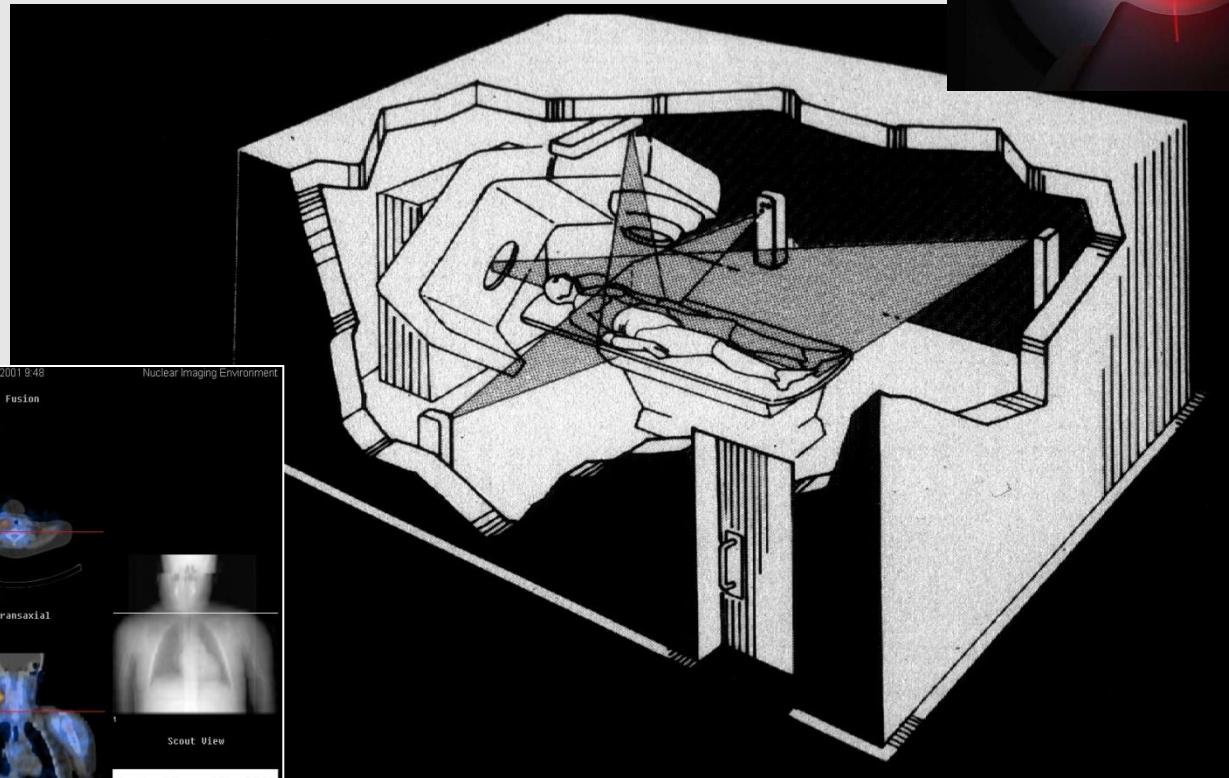


# Moguće opcije za precizno lokaliziranje prostate

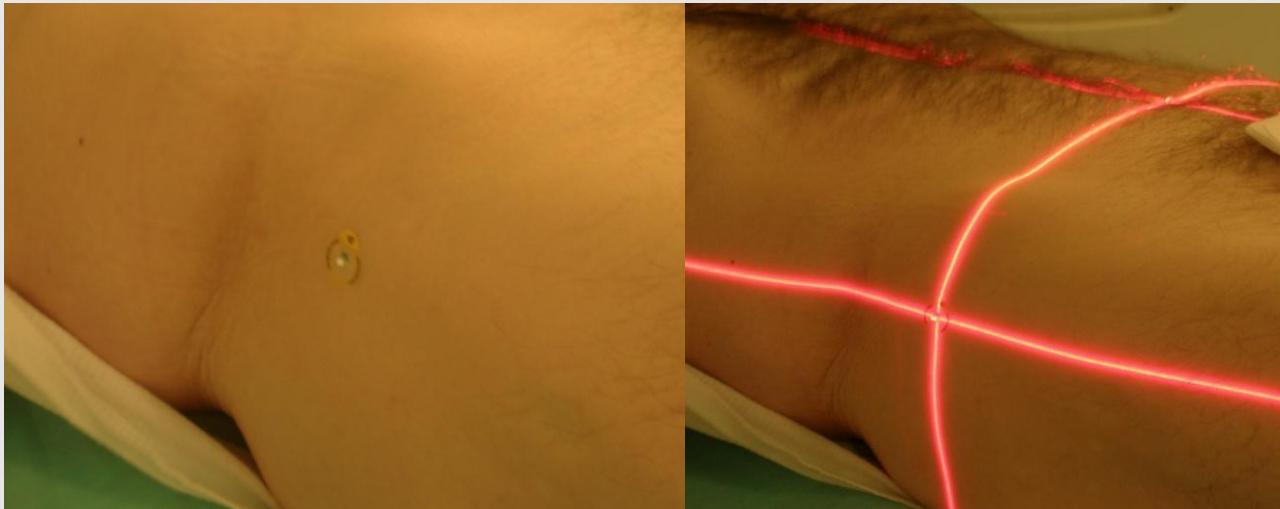
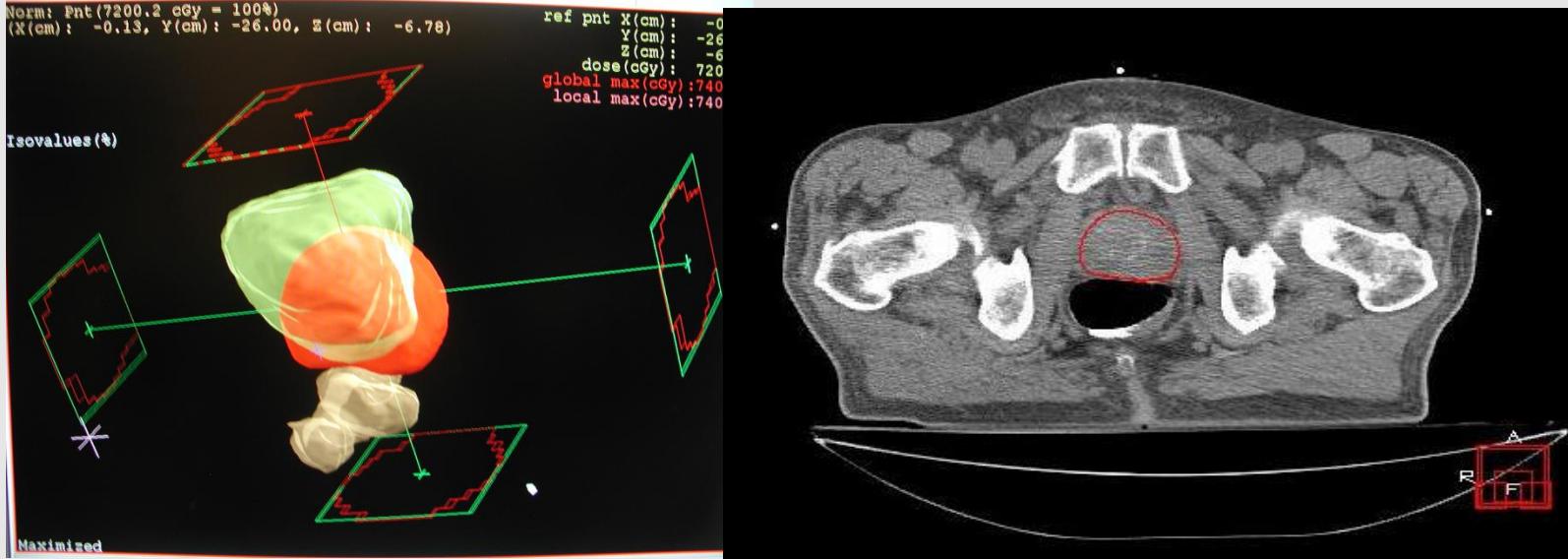
- Laseri
- Fuzija CT-MR
- Rektalni-balon
- MV-CT
- Zlatni markeri (IGRT)



# SUSTAV POZICIONIRANJA BOLESNIKA LASERIMA



# Fizičko osiguravanje točnog položaja bolesnika za zračenje



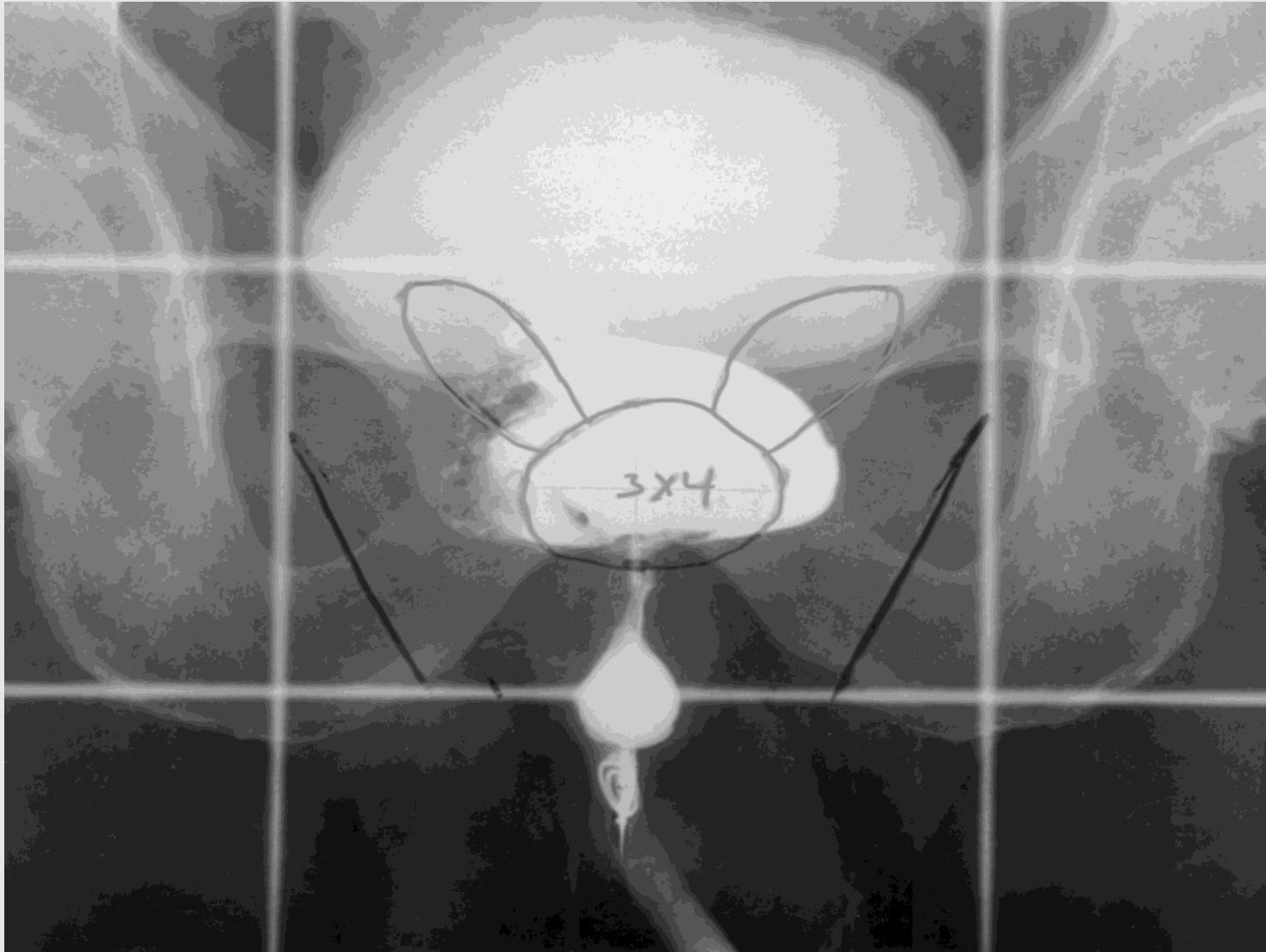
...radi se o površini bolesnika, a što se zbiva unutar zračene regije?

... ZATO

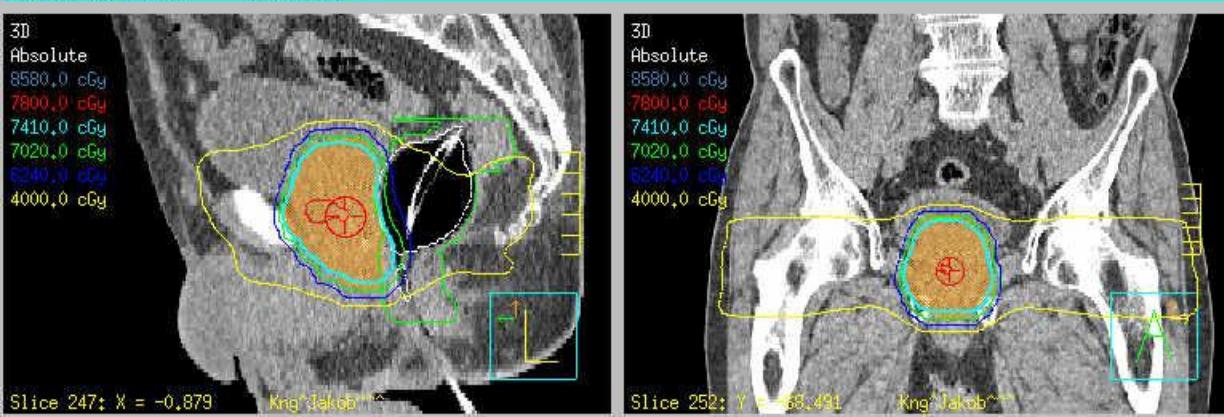
**...POTREBNA JE BOLJA SLIKOVNA  
INFORAMACIJA O POLOŽAJU CILJNOG  
VOLUMENA**

# Zračenje raka prostate

## 1980

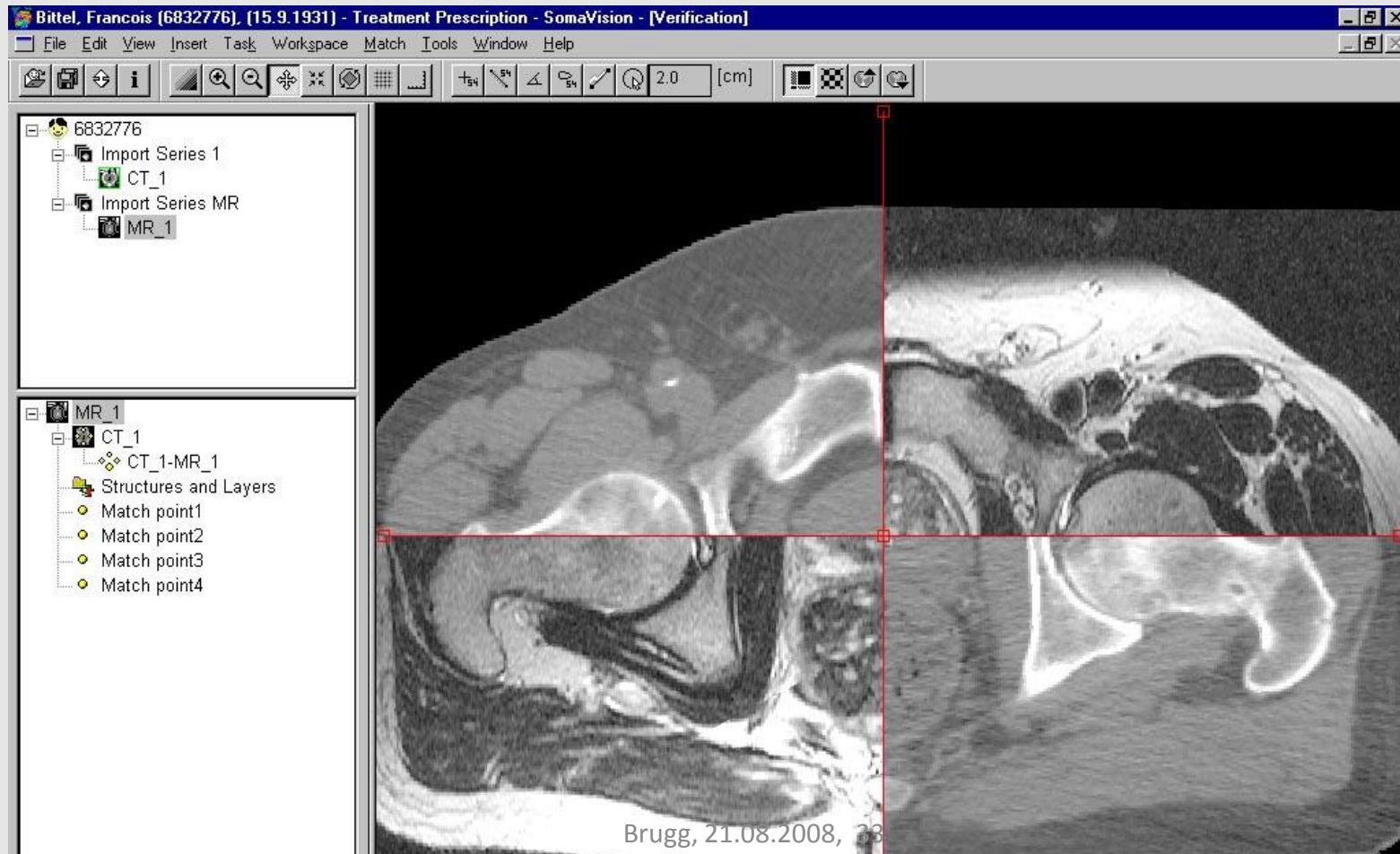


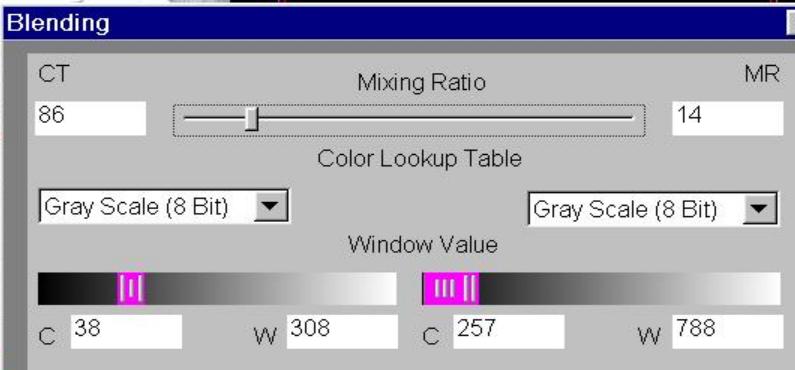
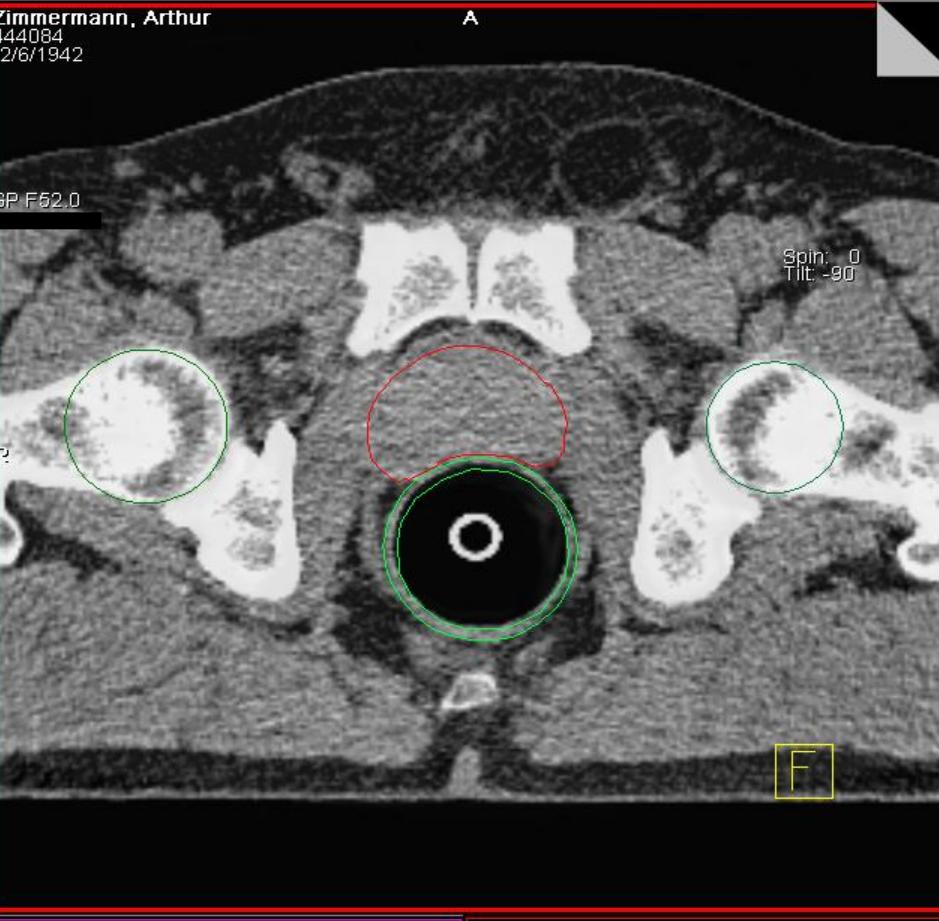
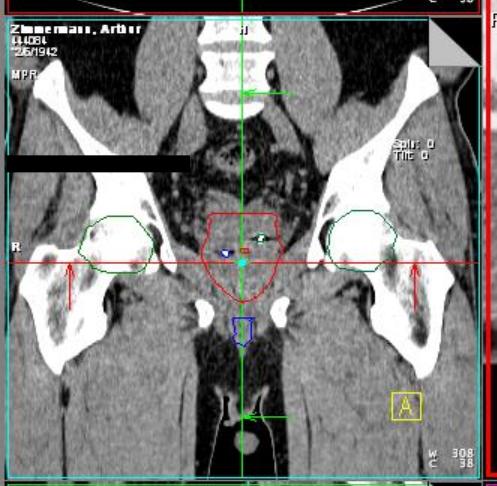
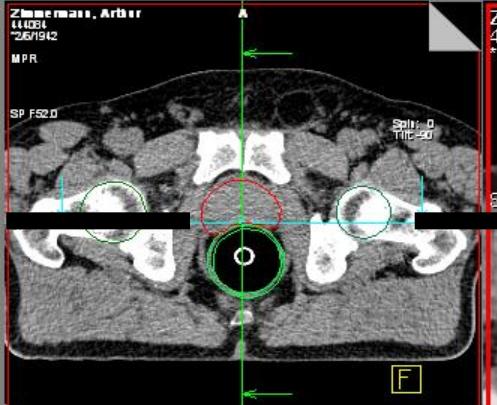
# 3-D konformalna radioterapija sa rektalnim - balonom



# RT planiranje : optimalna slikovna podrška

## CT – MR – Fuzija





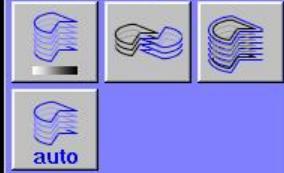
Zimmermann, Arthur



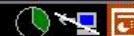
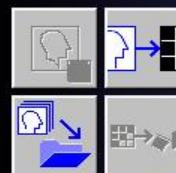
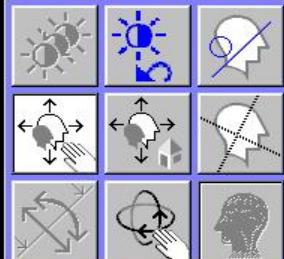
## Structure Display

- Structures
- Skin
- Femur li
- Femur re
- Blase
- Ballon
- Rektum
- Bulbus

## Contour Auto



## Tools View Orientation



Tx Ver

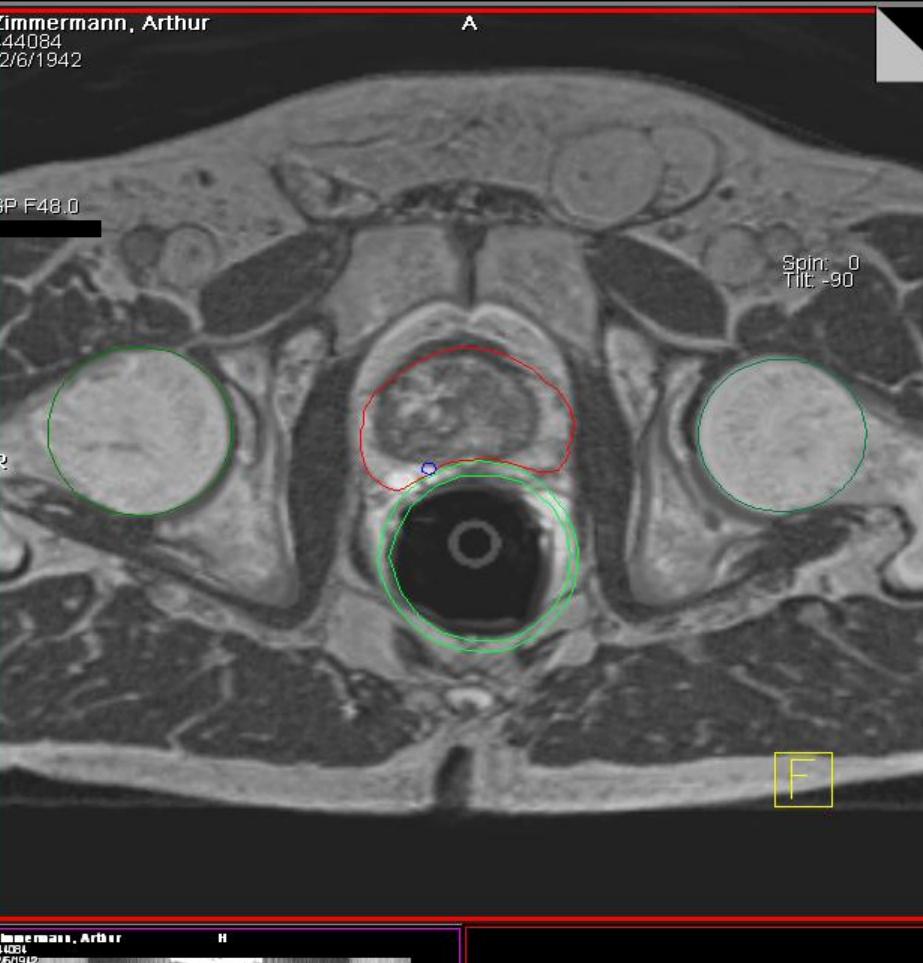
OIS

Localization

Viewing

Filming

3D



**Blending**

CT	Mixing Ratio	MR
21	79	
Color Lookup Table		
Gray Scale (8 Bit)	Gray Scale (8 Bit)	
Window Value		
C 38	W 308	C 257 W 788

Brugg, 21.08.2008, 35

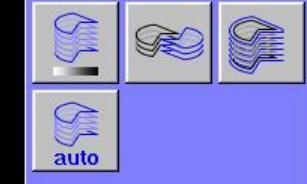
Zimmermann, Arthur



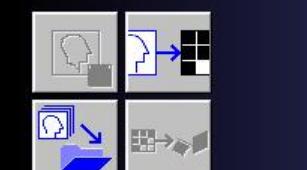
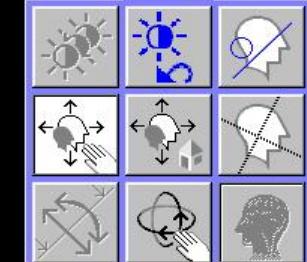
### Structure Display

- Structures
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- Bulbus

### Contour Auto



### Tools View Orient...



Tx Ver

OIS

Localization

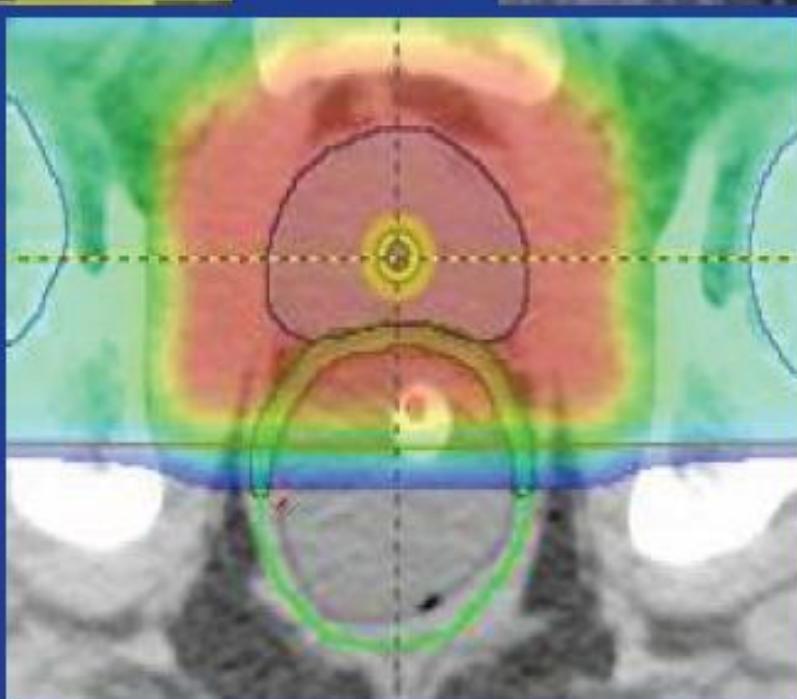
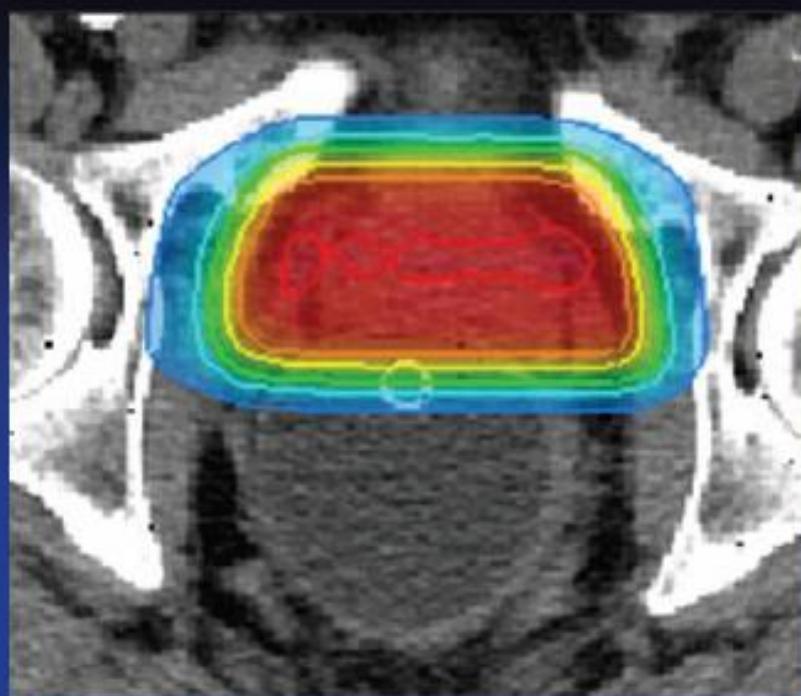
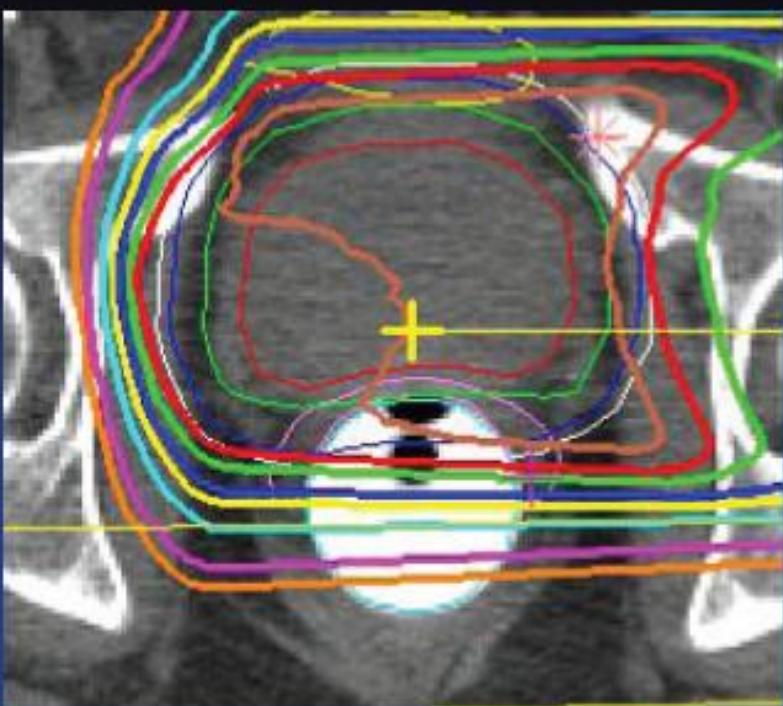
Viewing

Filming

3D

# REKTALNI BALON

- Kod raka prostate veća doza zračenja unaprijeđuje kontrolu bolesti
- Rektalni balon imobilizira prostatu i razmiće zdrava okolna tkiva
- Dobro se tolerira
- Unaprijeđuju dozimetriju kada se primjenjuje zračenje fotonima i protonima



Imobilizira  
prostatu

Razmiće okolne  
strukture

3D CRT  
Protoni  
IMRT

## PHYSICS CONTRIBUTION

## DAILY VARIATIONS IN DELIVERED DOSES IN PATIENTS TREATED WITH RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER

PATRICK A. KUPELIAN, M.D.,\* KATIA M. LANGEN, PH.D.,\* OMAR A. ZEIDAN, PH.D.,\* SANFORD L. MEEKS, PH.D.,\* TWYLA R. WILLOUGHBY, M.S.,\* THOMAS H. WAGNER, PH.D.,\* SAM JESWANI, PH.D.,† KENNETH J. RUCHALA, PH.D.,‡ JASON HAIMERL, PH.D.,‡ AND GUSTAVO H. OLIVERA, PH.D.,‡

Dose recalculation during prostate cancer tomotherapy • P. A. Kupelian et al.

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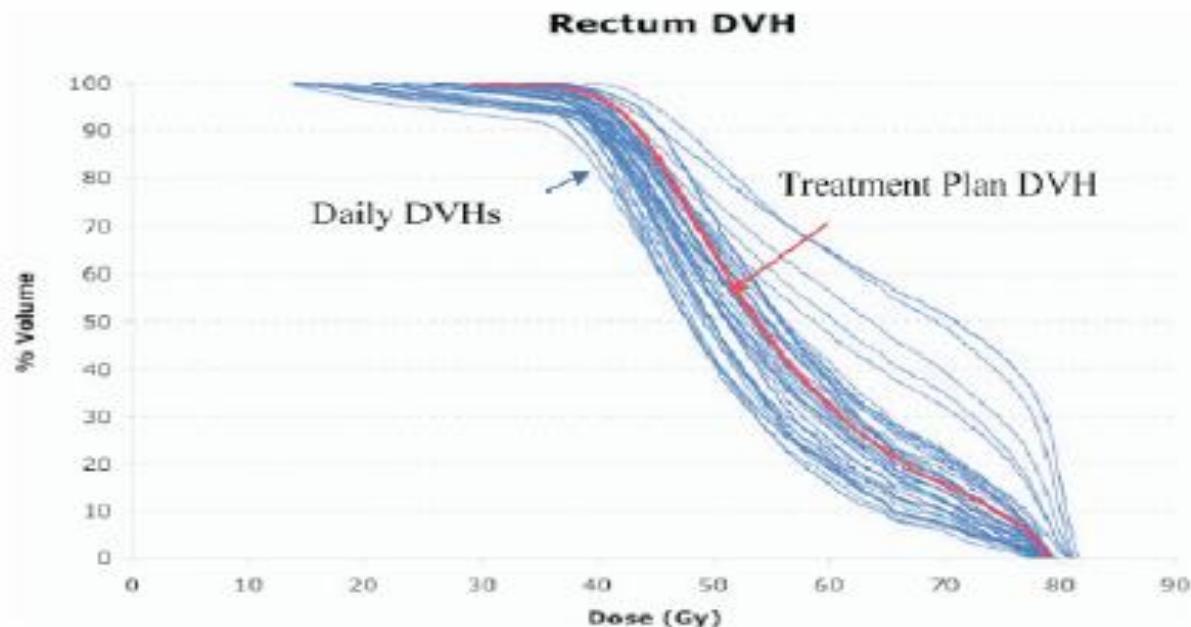


Fig. 4. Rectal dose–volume histogram (DVH) for all 39 treatment fractions in 1 patient. Red line represents the planning computed tomography DVH; thinner blue lines represent daily DVHs.

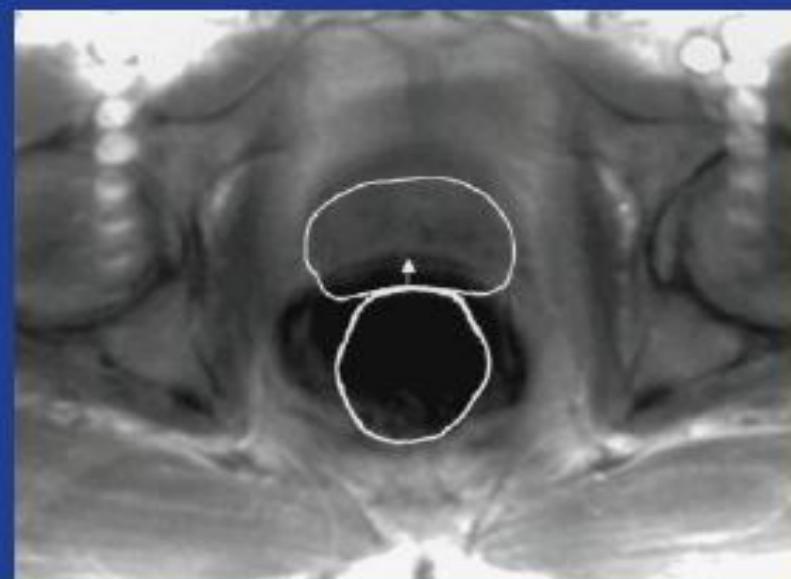
## CLINICAL INVESTIGATION

## Prostate

## EVALUATING THE EFFECT OF RECTAL DISTENSION AND RECTAL MOVEMENT ON PROSTATE GLAND POSITION USING CINE MRI

ANWAR R. PADHANI,\* M.R.C.P., F.R.C.R., VINCENT S. KHOO, F.R.A.C.R.,<sup>†</sup>  
JOHN SUCKLING, B.Sc., M.Sc., Ph.D., MInst.P., \*<sup>‡</sup> JANET E. HUSBAND, F.R.C.P., F.R.C.R., \*  
MARTIN O. LEACH, Ph.D., F.Inst.P., F.I.P.E.M.B., \*  
AND DAVID P. DEARNALEY, M.A., M.D., F.R.C.P., F.R.C.R.<sup>†</sup>

Cine-MR over 7 minutes: up to 1.2 cm movement





**PHYSICS CONTRIBUTION**

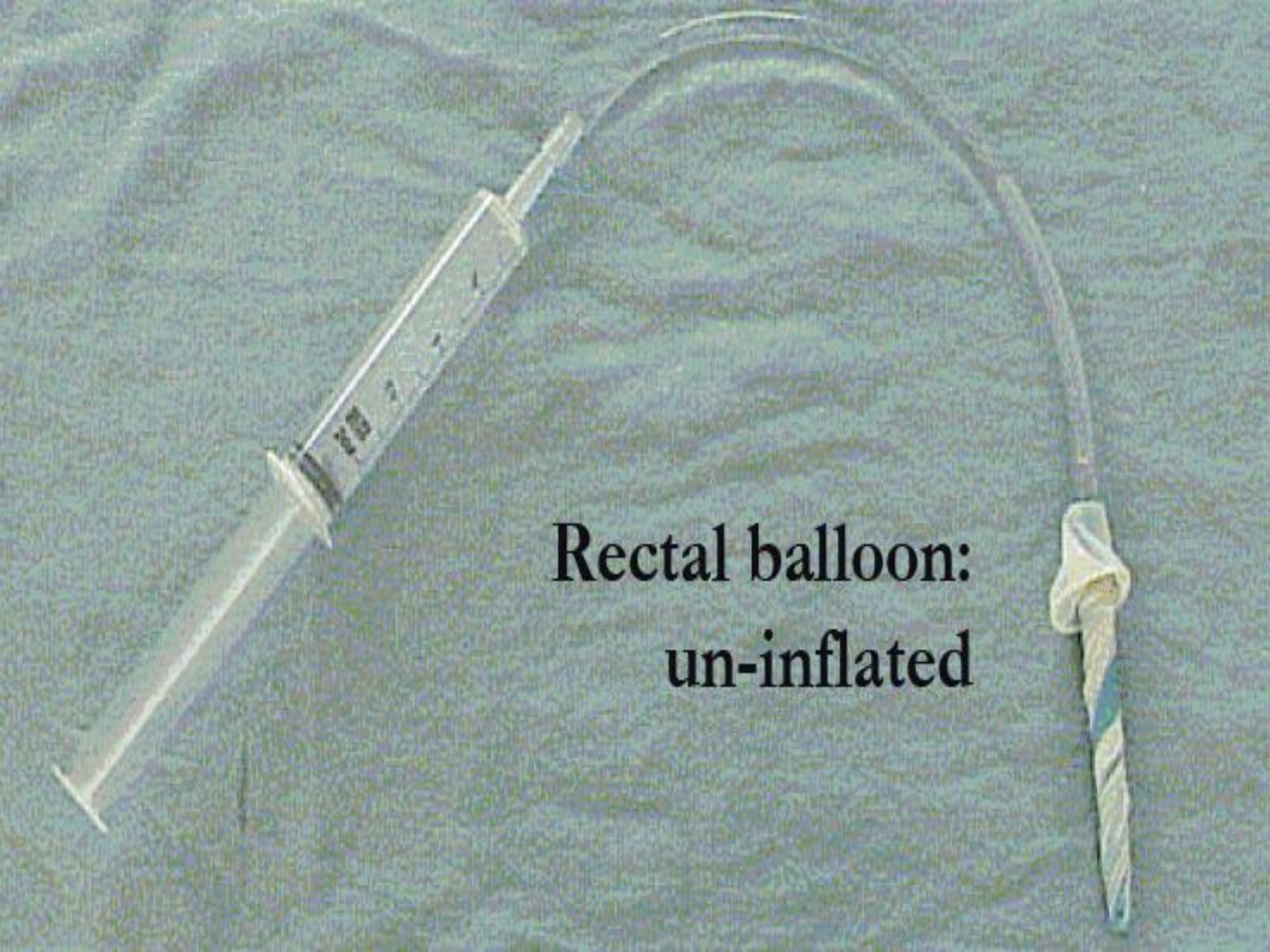
**A PRACTICAL METHOD TO ACHIEVE PROSTATE GLAND  
IMMOBILIZATION AND TARGET VERIFICATION FOR DAILY TREATMENT**

ANTHONY V. D'AMICO, M.D., Ph.D.,\* JUDI MANOLA, Ph.D.,<sup>†</sup> MARIAN LOFFREDO, R.N., O.C.N.,\*  
LYNN LOPES, R.N.,\* KRISTOPHER NISSEN, B.S., R.T.T.,\* DESMOND A. O'FARRELL, C.M.D.,\*  
LEAH GORDON, B.A.,\* CLARE M. TEMPANY, M.D.,<sup>‡</sup> AND ROBERT A. CORMACK, Ph.D.\*

Departments of \*Radiation Oncology, <sup>†</sup>Biostatistics, and <sup>‡</sup>Radiology, Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA

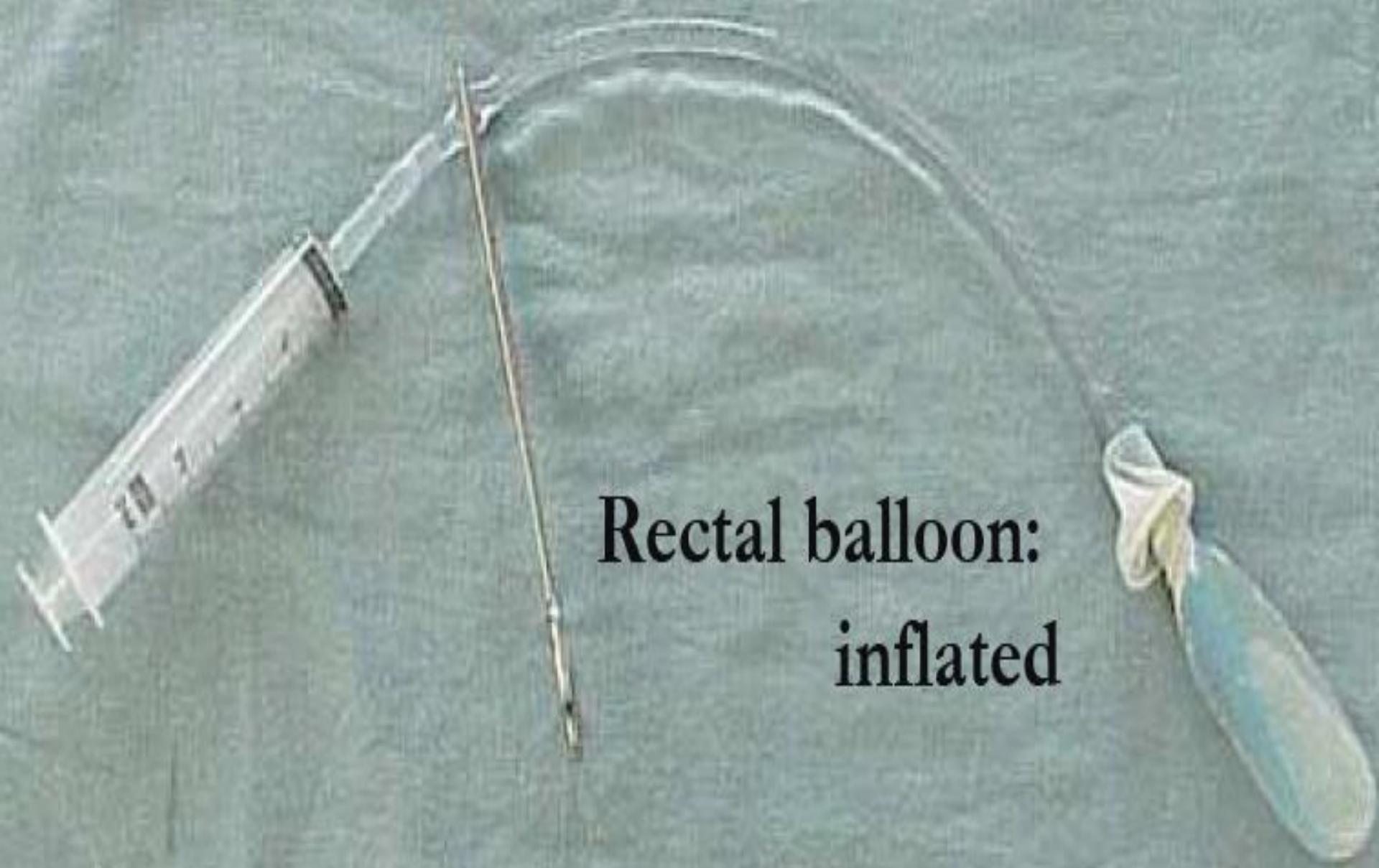
## **Maksimalno pomicanje prostate u bilo kojem smjeru**

- bez rektalnog balona : više od 4 mm**
- sa rektalnim balonom ≤ 1mm**



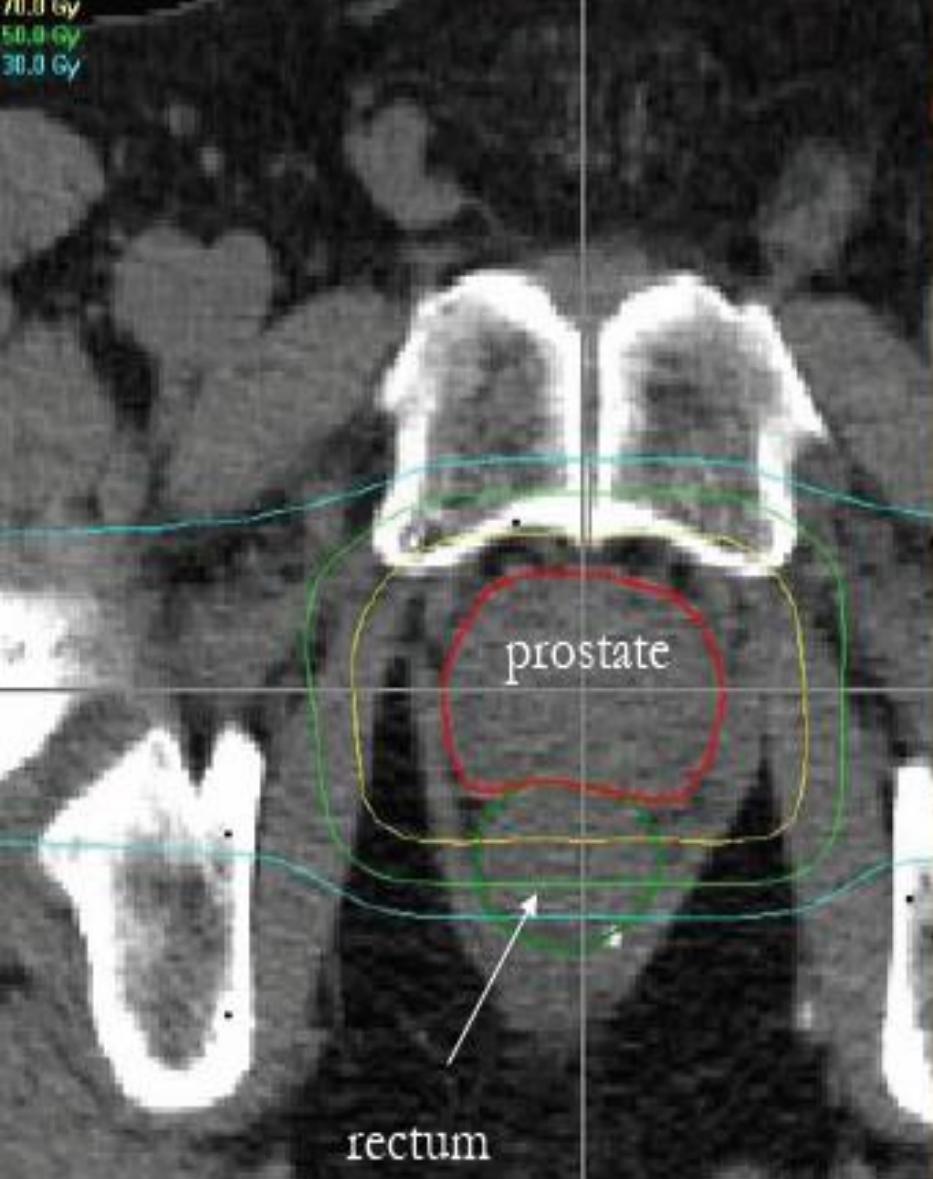
A clear plastic rectal enema catheter is shown lying on a light blue, textured surface. The catheter has a tapered tip and a flared balloon at the distal end. A small amount of white lubricating gel is visible at the junction of the balloon and the catheter tube. The tube features a scale with markings for 10, 20, and 30 milliliters.

**Rectal balloon:**  
**un-inflated**

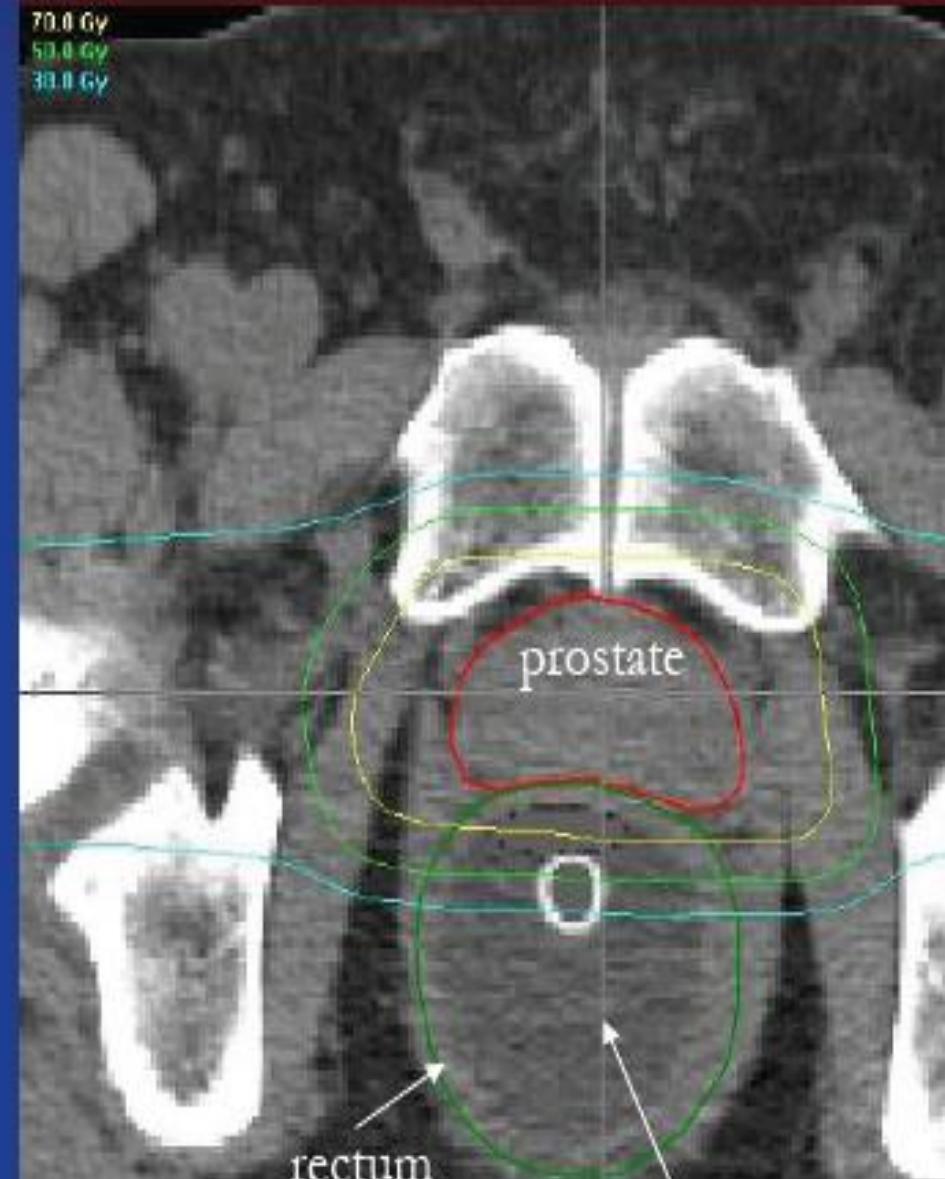


**Rectal balloon:  
inflated**

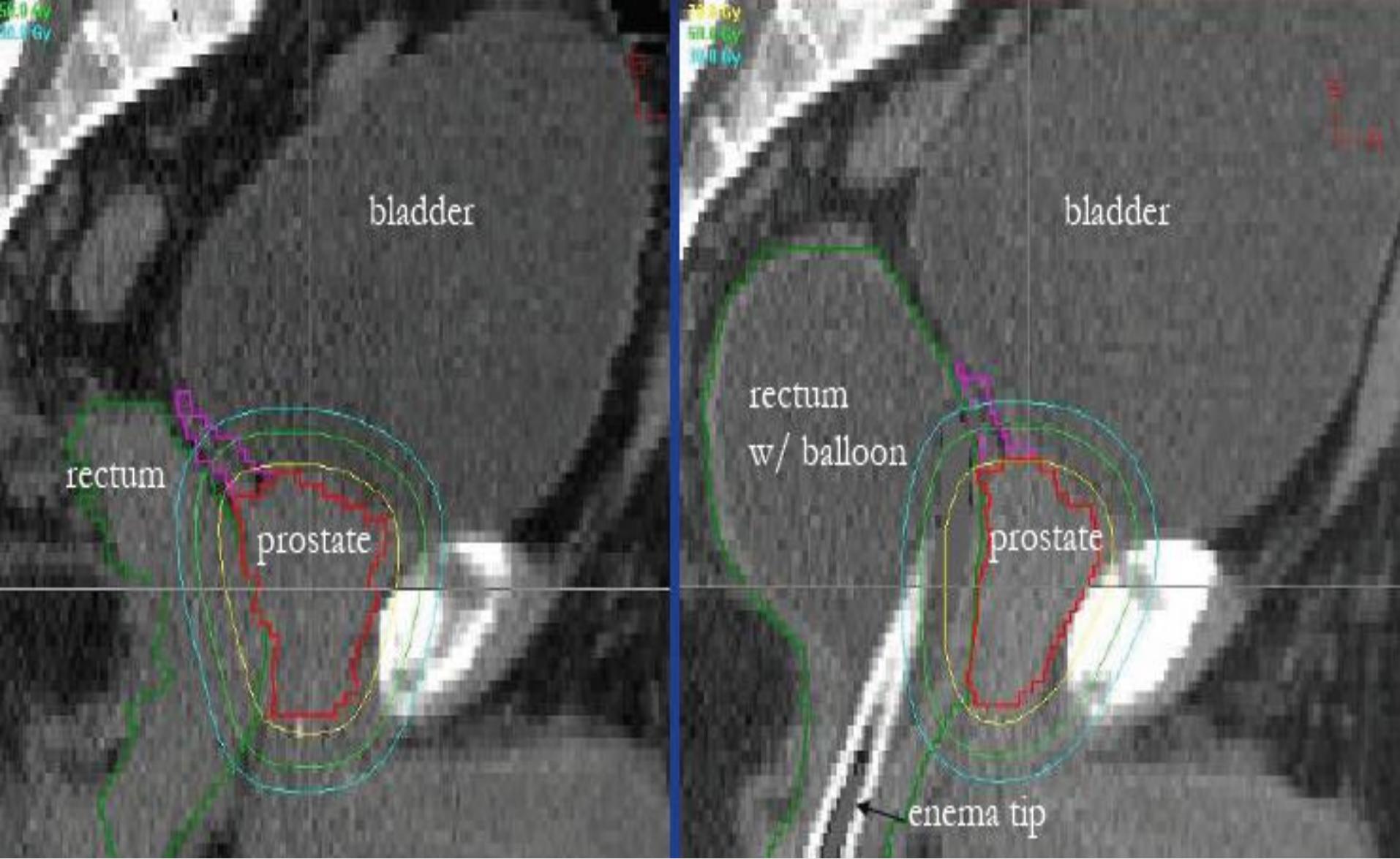
**Prije CT simulacije i svakog zračenja balon se stavi u rektum i napuni sa 120 ml vode**



**Bez balona**

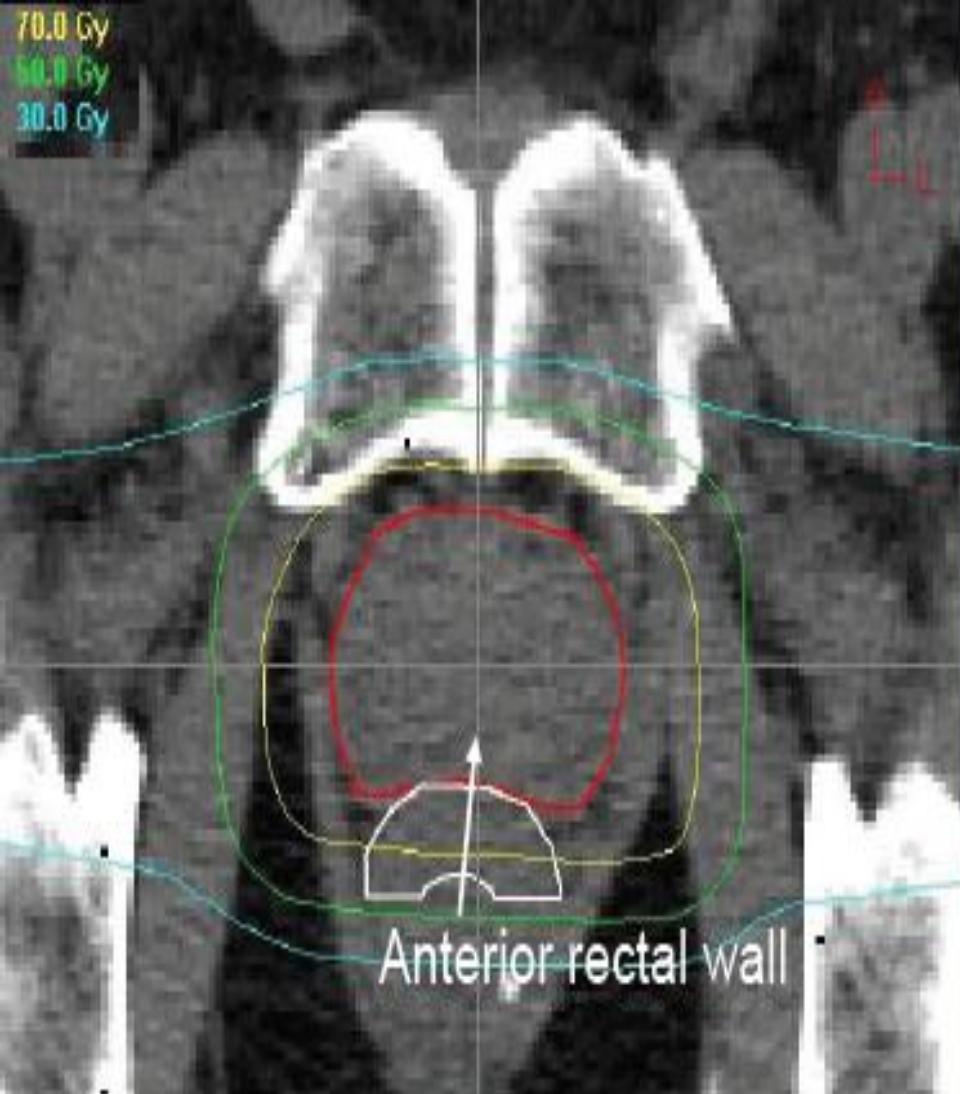


**Sa balonom**

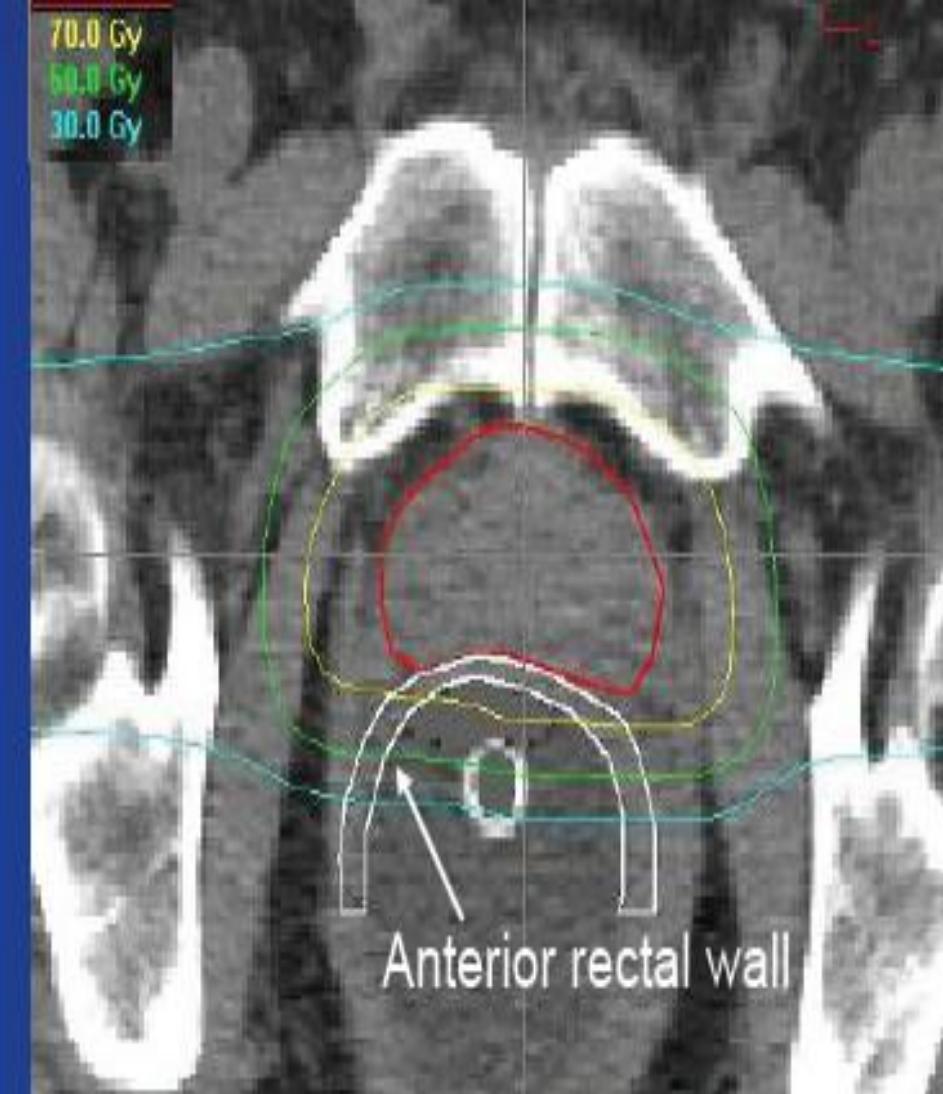


**Bez balona**

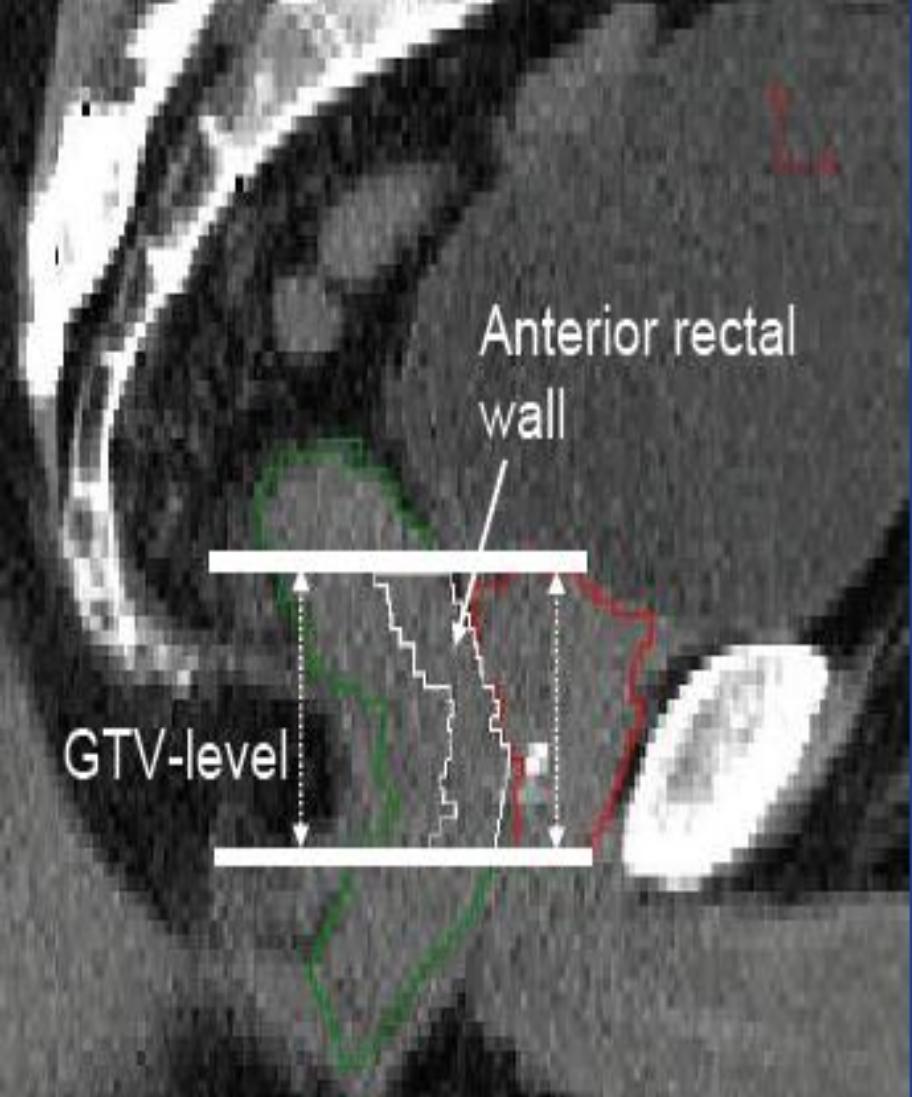
**Sa balonom**



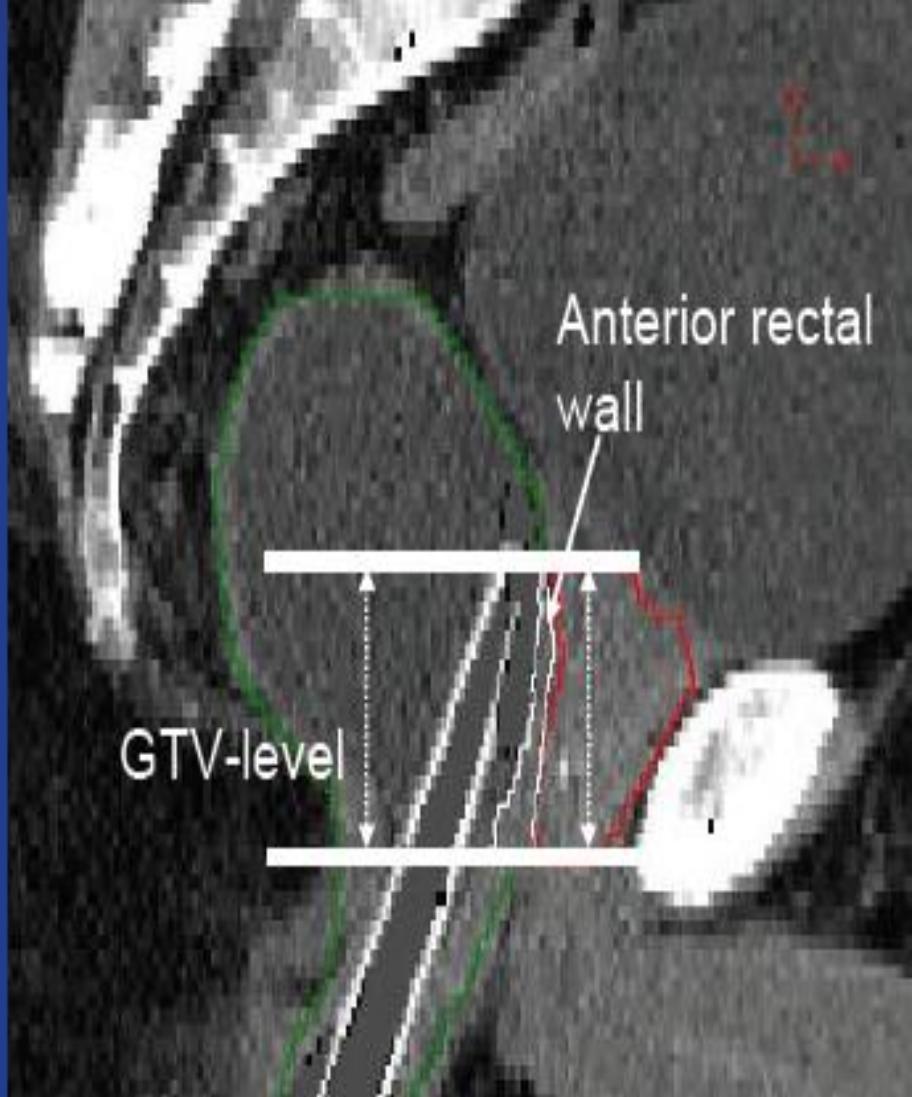
Bez balona



Sa balonom



Bez balona



Sa balonom

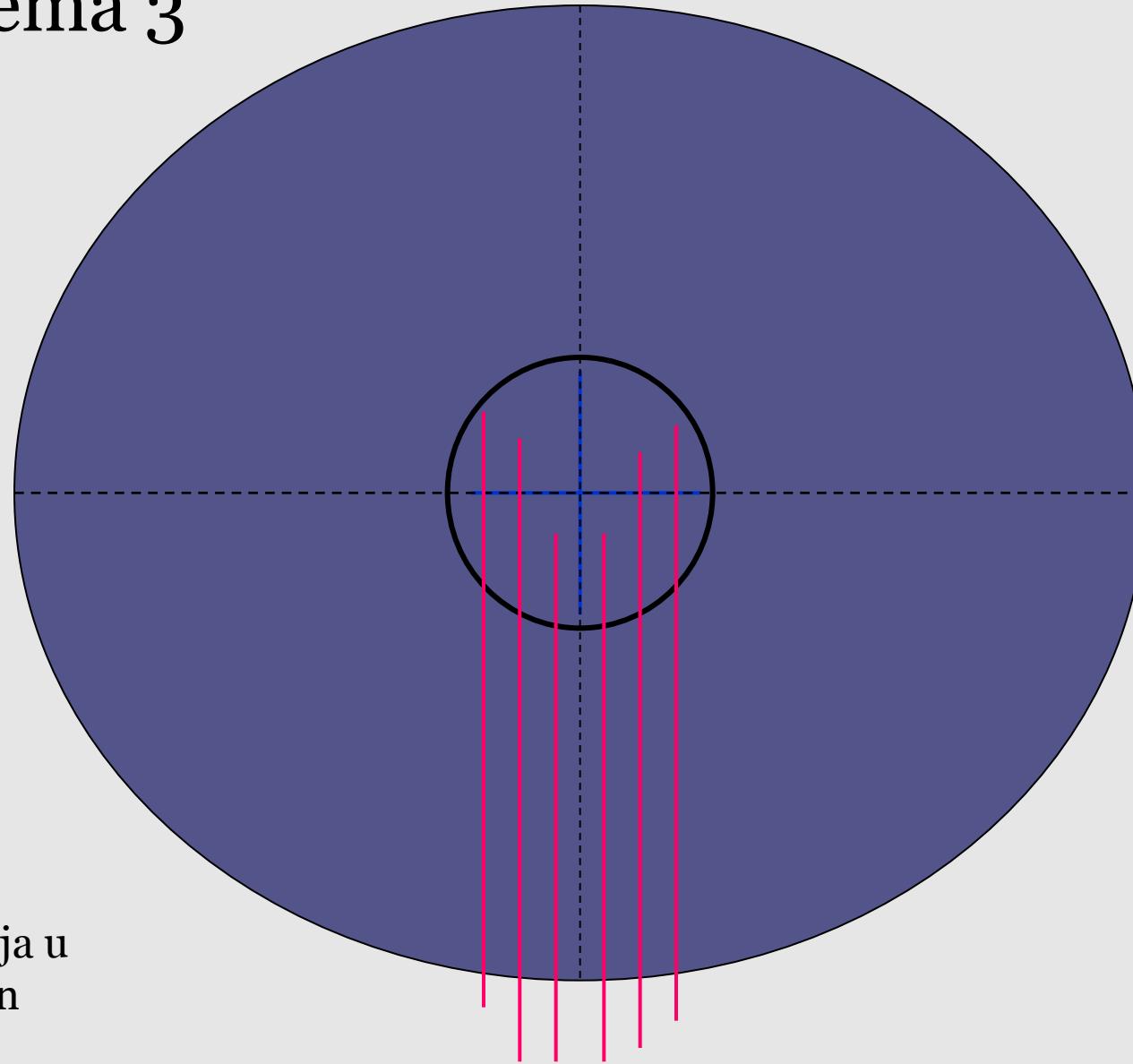
# Brahiterapija raka prostate

- O'Leary et al J. Urol 168:649-652, 2002

Zaključak sastanka AUA iz 2002.g. pokazao je da 51% američkih urologa ponudi bolesniku brahiterapiju kao alternativu radikalnoj prostatektomiji...

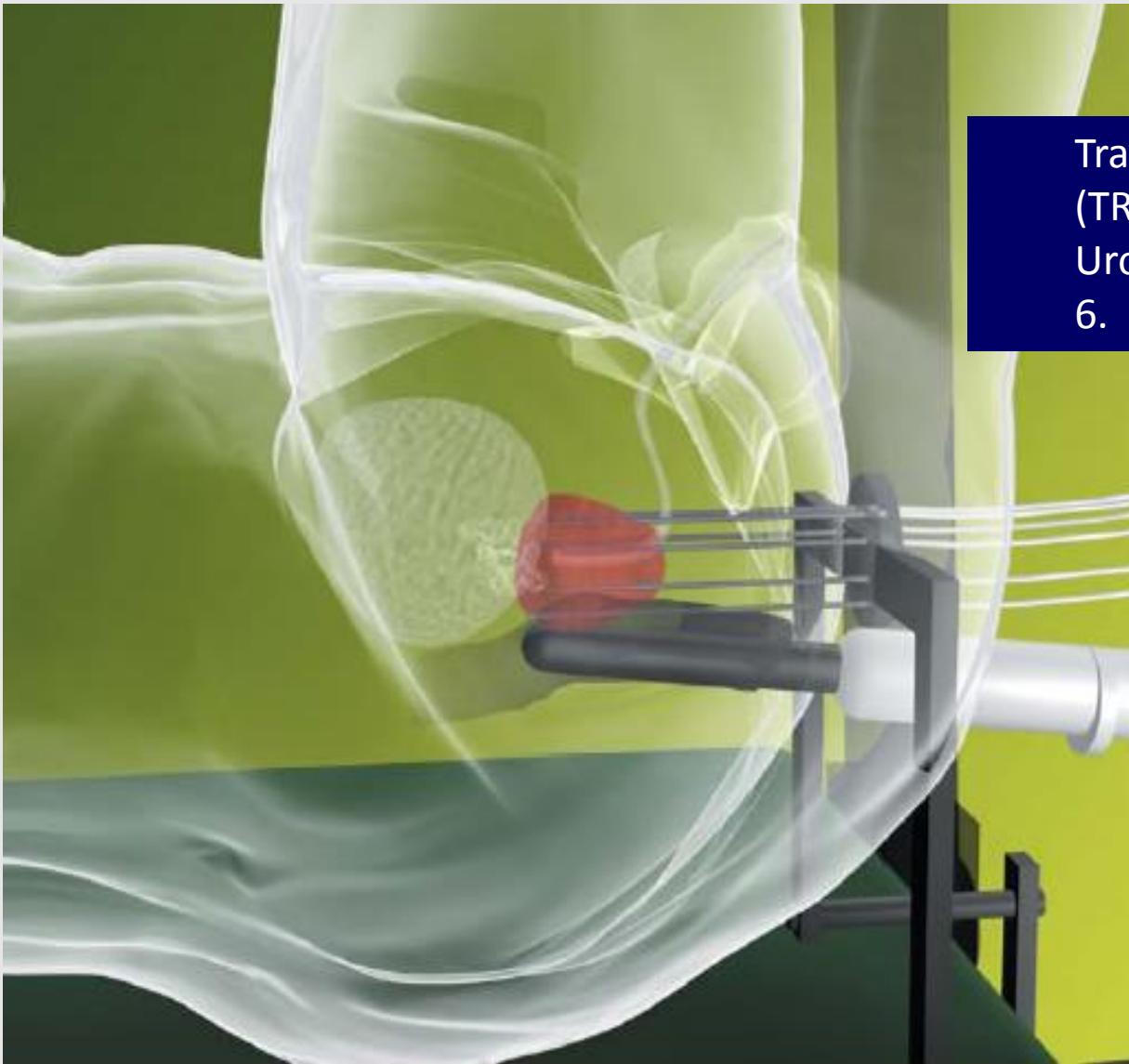
→ značajna promjena u obrascu liječenja

# Problem pomićnog ciljnog volumena: rješenje problema 3



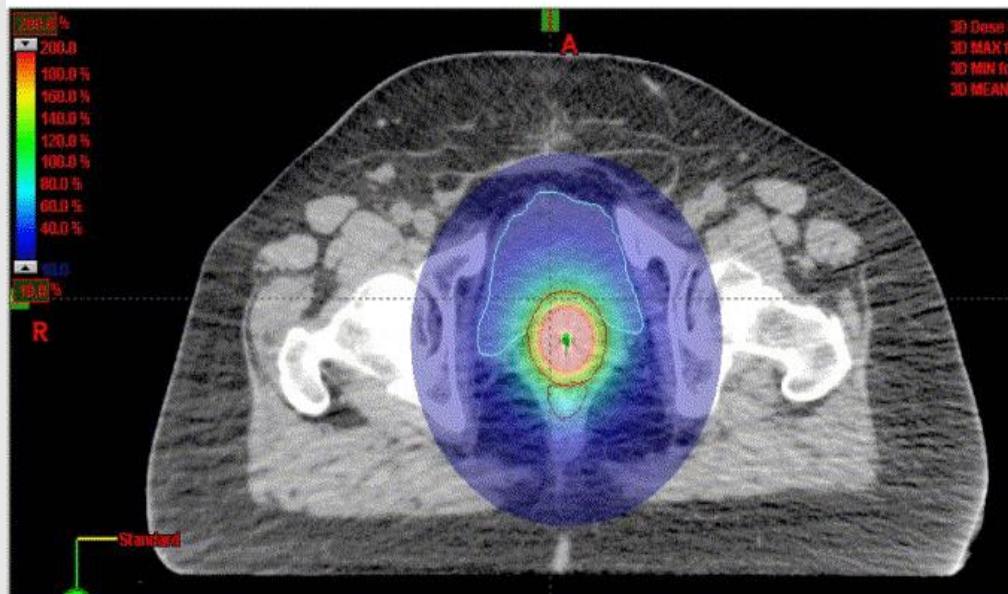
Aplikacija  
minijaturnih  
izvora zračenja u  
ciljni volumen

# Intersticijska brahitherapija



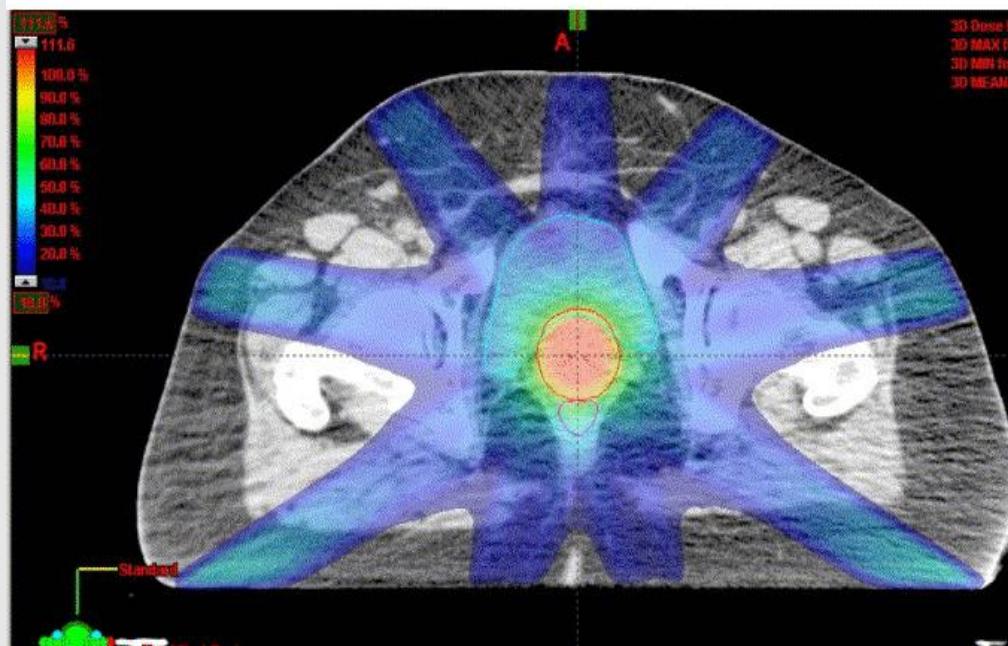
Transrekタルni ultrazvuk-  
(TRUS ) Holm HH et al. J  
Urol. 1983 Aug;130(2):283-  
6.

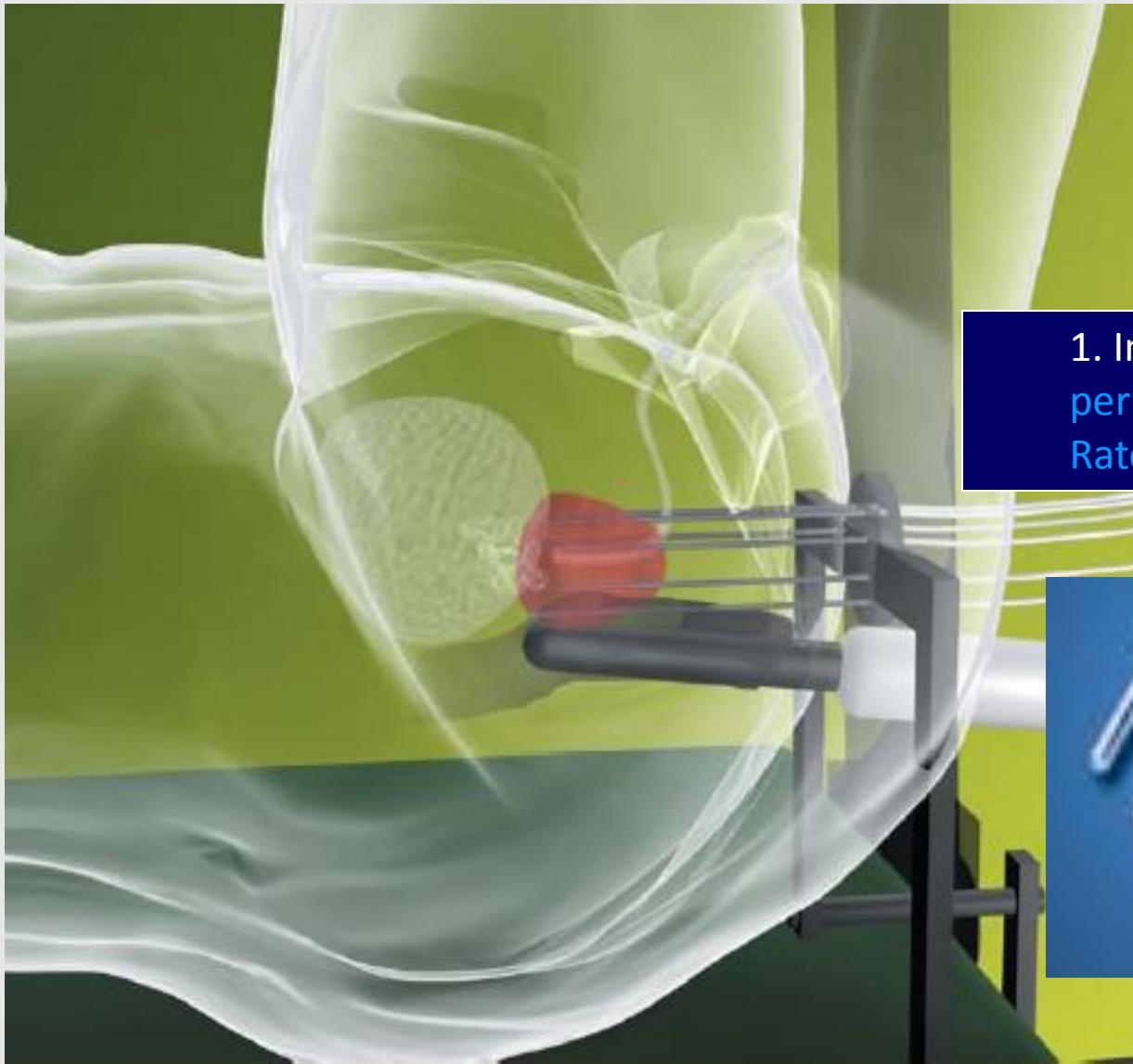
(a) HDR dose distribution



Aydogan et al.  
IJROBP, 2006,  
65: 266-73

(b) IMRT dose distribution

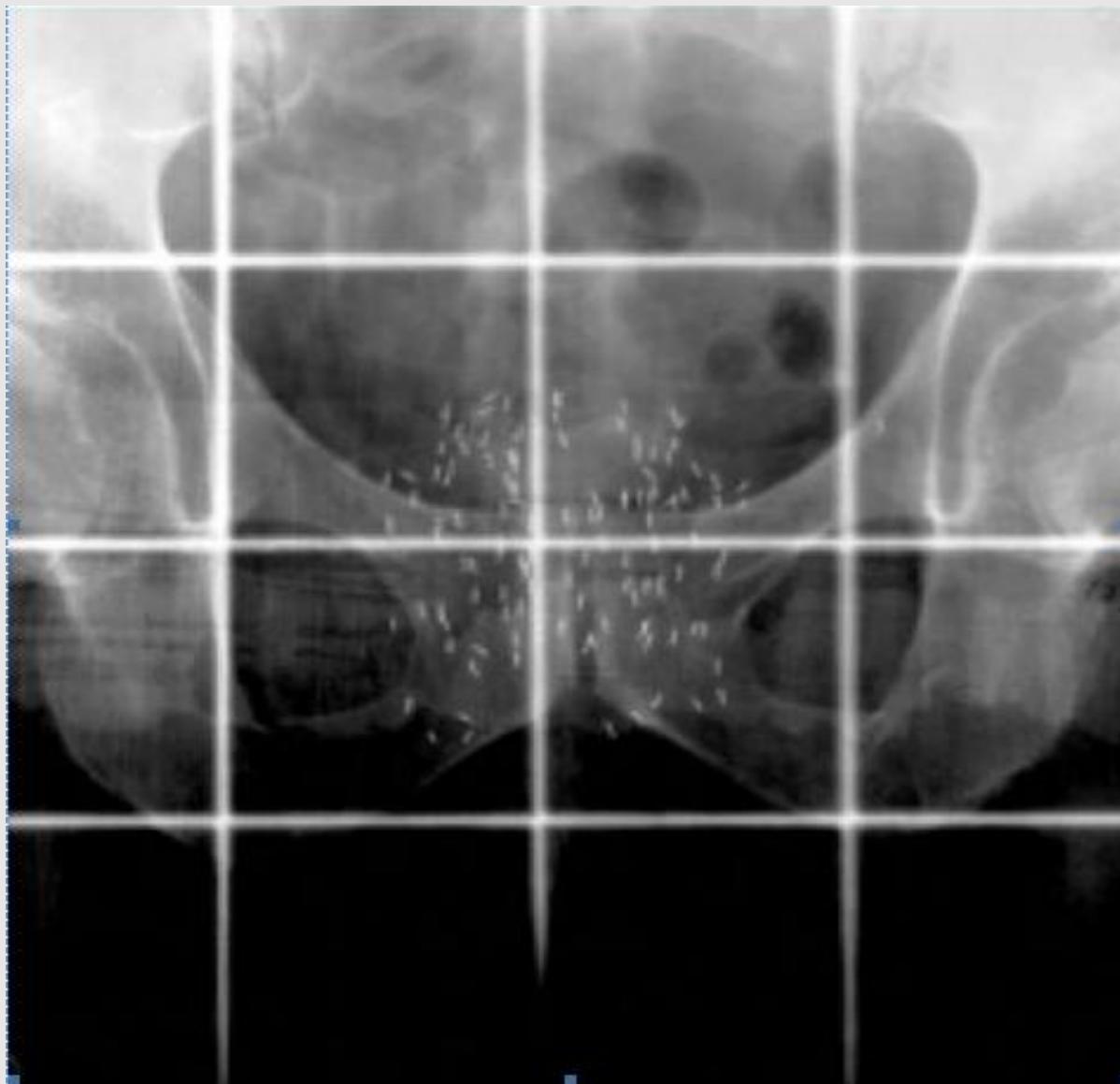




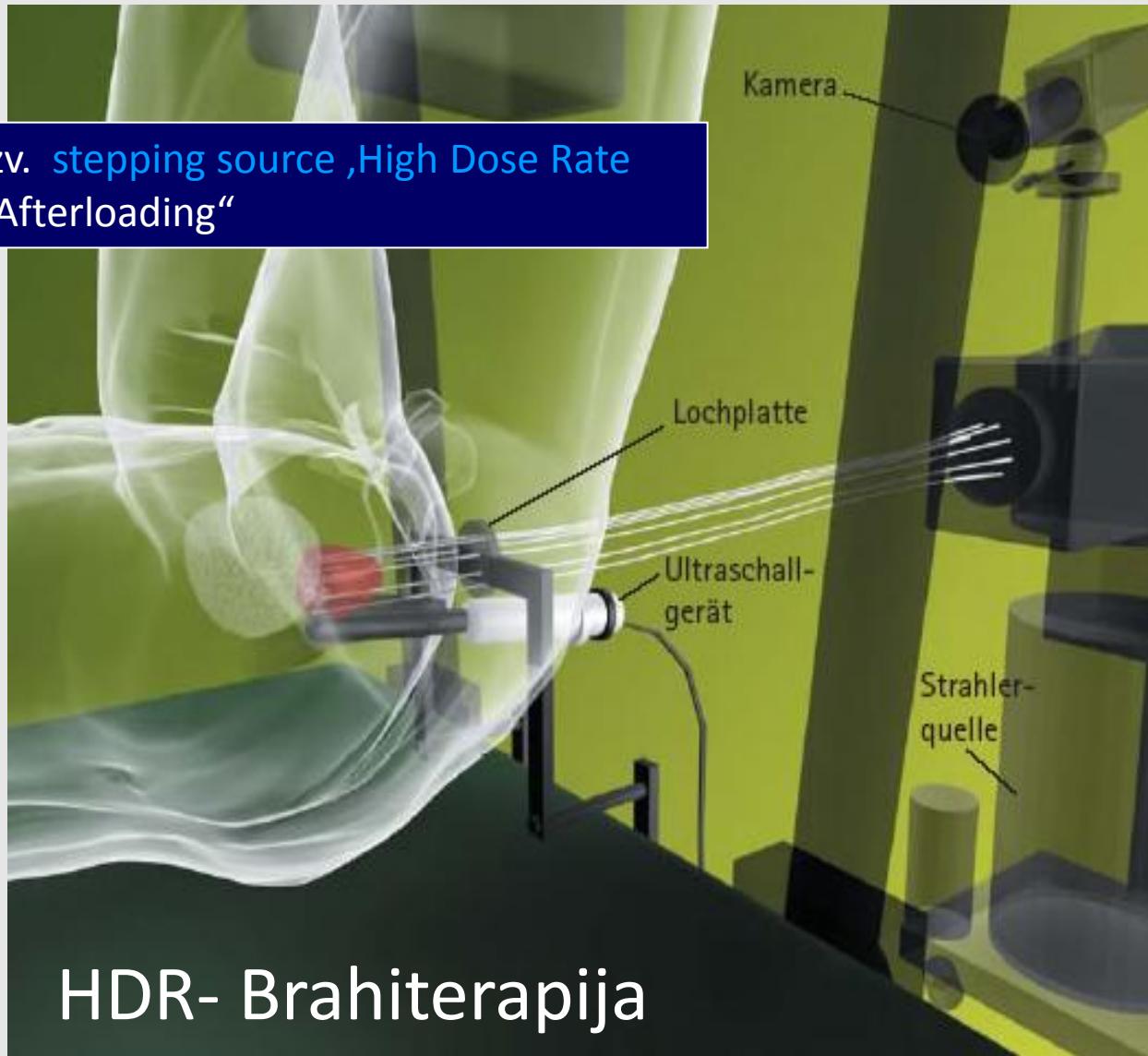
1. Implantacija  
permanentnih Low Dose  
Rate izvora („Seeds“)



LDR- Brahiterapija



2. Implantacija tzv. stepping source ,High Dose Rate  
(Iridium 192) = „Afterloading“



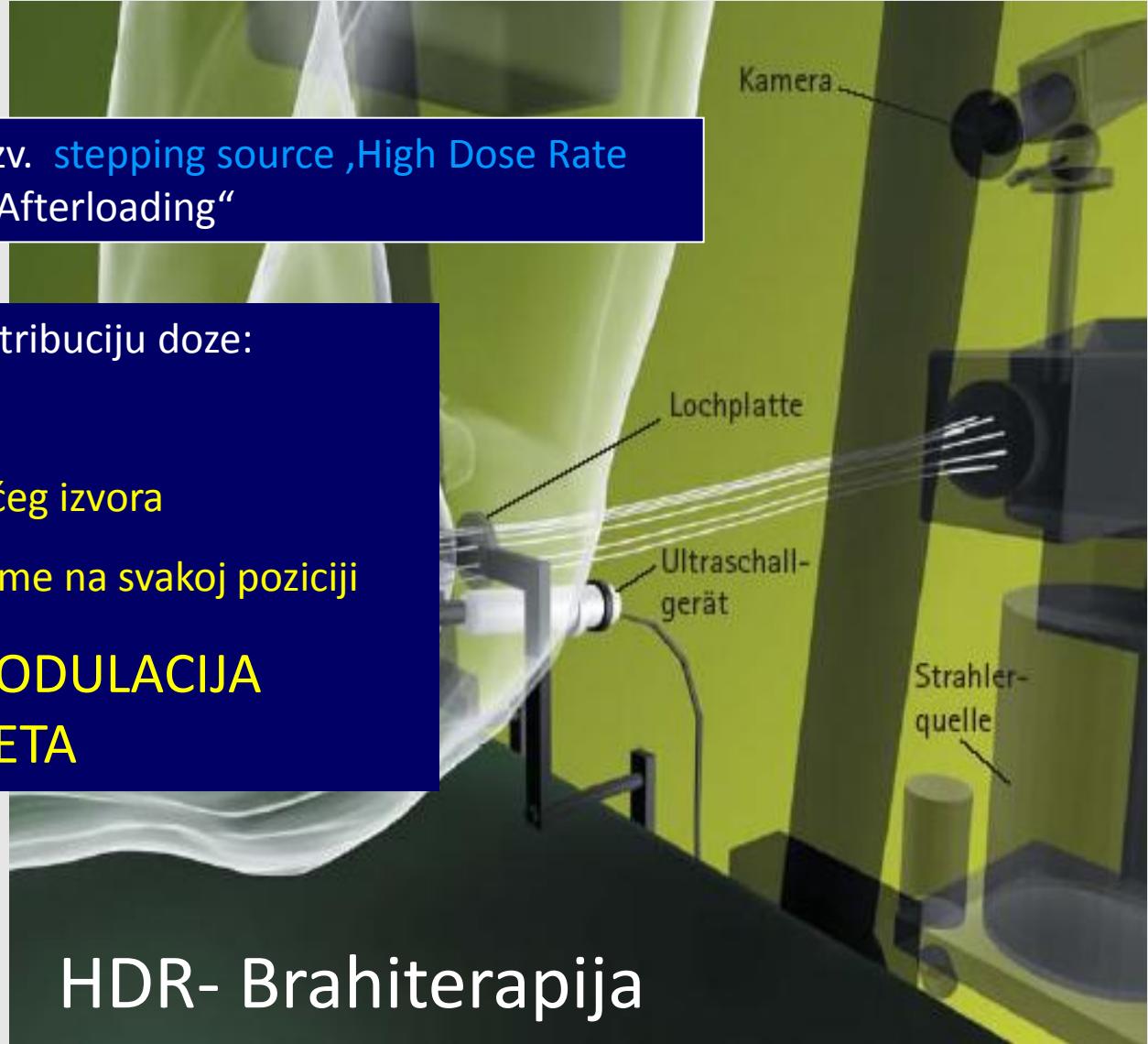
2. Implantacija tzv. stepping source ,High Dose Rate  
(Iridium 192) = „Afterloading“

Tri varijable za distribuciju doze:

1. Geometrija
2. Pozicija putujućeg izvora
3. Određeno vrijeme na svakoj poziciji

= PRAVA MODULACIJA  
INTENZITETA

HDR- Brahiterapija





# Usporedba intersticijskih brahiterpijskih metoda

Karakteristika	Implantacija zrnaca	HDR-BT
Optimizacija	ograničena	vrlo dobra
Vrijeme terapije	dugo (tjedni)	minute
Utjecaj post implantacijskog-edema na distribuciju doze	značajan	nije značajan
Pošteda organa rizika	dobra	vrlo dobra
Pomicanje izvora zračenja	moguće	nije moguće
Opasnost za ozračivanje okoline	moguće (ograničeno)	nije moguće
Frakcioniranje	nije potrebno	potrebno
Nizak a/b-Ratio	nedostatak ?	prednost ?

# (Oxford Centre for Evidence-based Medicine Levels of Evidence 1+ to 2+)

Intersticijska BT je superiorna u odnosu na EBRT u smislu točnosti aplikacije – pomičnost ciljnog volumena

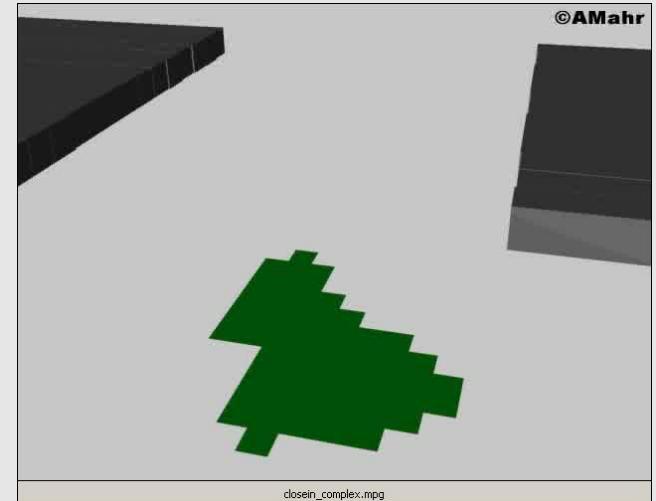
Putujući izvor je superiorniji u odnosu na zrnca u smislu aplikacije vrlo visokih doza

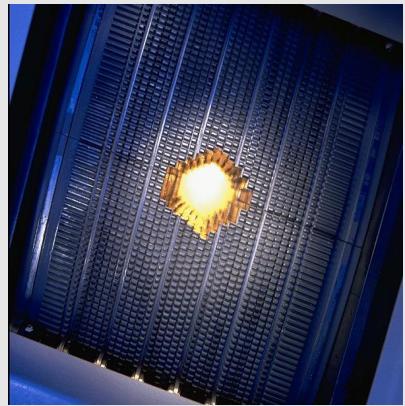
Intensity modulated HDR-BT je danas najbolja metoda eskalacije doze : visoka doza / dokazano bolje preživljenje i manja toksičnost

# **IMRT**

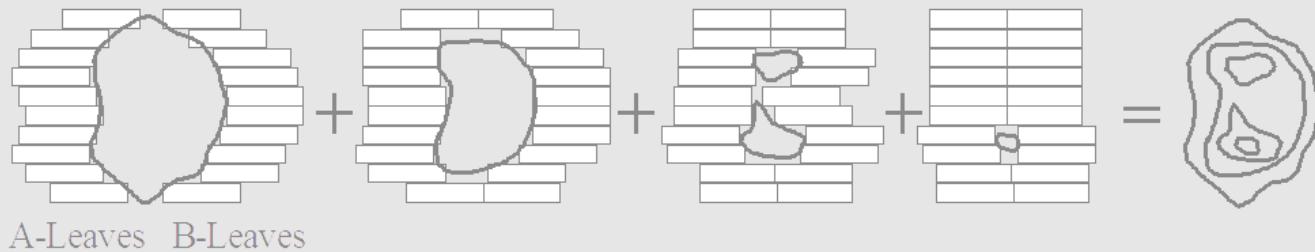
- **Perkutano zračenje**
- **Bolja konformalnost**
- **Veća pošteda organa rizika**
- **Tehnička zahtjevnot**
- **Konzumacija više vremena**

1. 2D nadogradnja intenziteta pojedinačnim različitim snopovima – usporedivo sa građenjem tornja LEGO kockama
2. Tijekom pomicanja MLC ne provodi se zračenje pa je cijeli proces lako kontrolirati
3. Veliki broj pojedinačnih snopova iz različitih smjerova ostvaruje 3D raspodjelu intenziteta zračenja





## "Step-and-shoot" (digital) technique

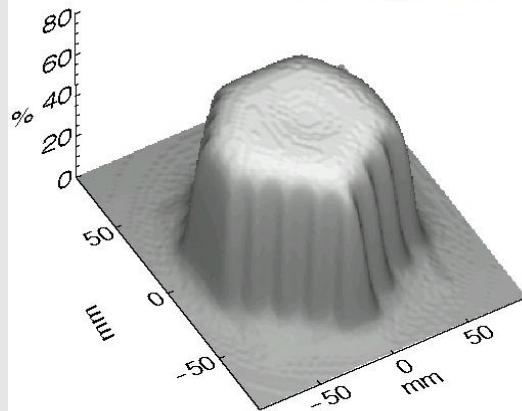


A-Leaves B-Leaves



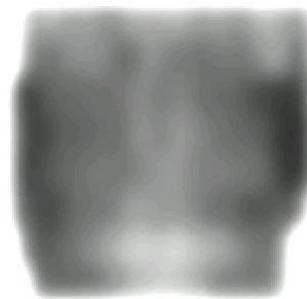
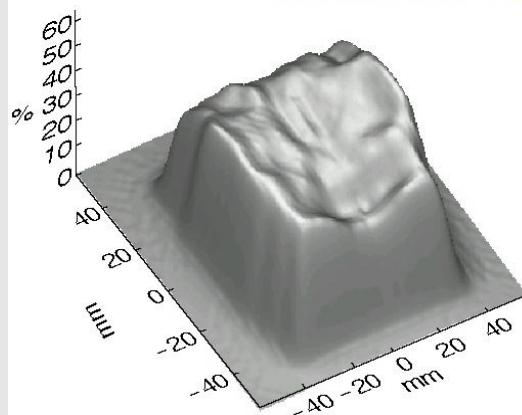
IMRT – moguć boost na dominantnu  
intraprostatičnu tumorsku leziju i do  
90 Gy (uz pomoć MRSI)

### **Homogene Dosisintensität**



**3D**

### **Modulierte Dosisintensität**



**IMRT**

# IMRT raka Prostate

## Prednosti

- Moguća provedivost u svakom stadiju bolesti
- Moguće postizanje velike preciznosti zračenja
- Dobra svakodnevna reproducibilnost
- Dopušta eskalaciju doze uz manje nuspojava

## Nedostatci

- složenost izrade plana (vrijeme, know-how, high-tech uređaji)
- terapija koja se provodi relativno kratko vrijeme
- unaprijeđenje lokalne kontrole i preživljjenja još nisu sigurno dokazani

# **IGRT**

- **Poznate činjenice:**

1. bolesnika je teško svakodnevno namjestiti u točnan položaj za zračenje

2. ciljni volumen se pomiče između frakcija i za vrijeme frakcija

3. Tumor i bolesnik mijenjaju se tijekom zračenja

# IGRT

- Nije novost u radioterapiji
- Negativni utjecaj netočnosti namještanja bolesnika te pomicanje ciljnog volumena i promjene samog tumora – odavno su prepoznati problemi
- Prevladavanje tih problema - tehnologijom

# Rane IGRT tehnologije



- Johns (1959)  
Princess Margaret  
Hospital  
**kV “portal imaging” na  
Co60 uređaju**

Unaprijeđenje točnosti  
namještanja bolesnika

# Moderne IGRT tehnike omogućuju češču primjenu i veću točnost

## Current IGRT Technologies



# IGRT u liječenju raka prostate

- Još se uvijek bazira na planarnom (kV) IGRT

Najčešće implantacijom zrnaca za orijentaciju

Novije – volumetrijska IGRT (CBCT), bez implantacije zrnaca

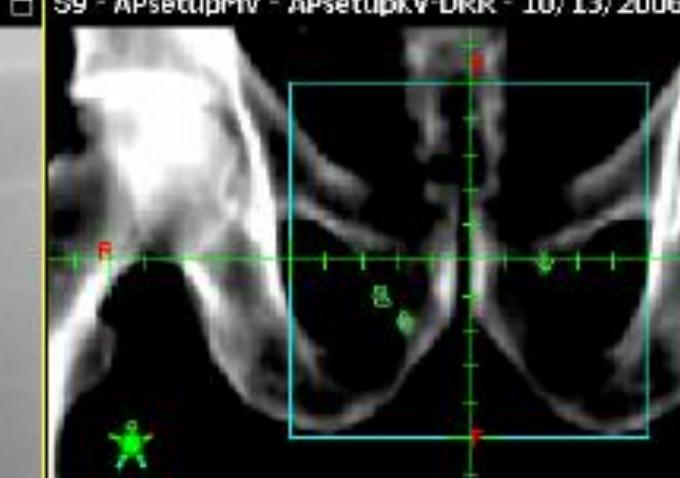
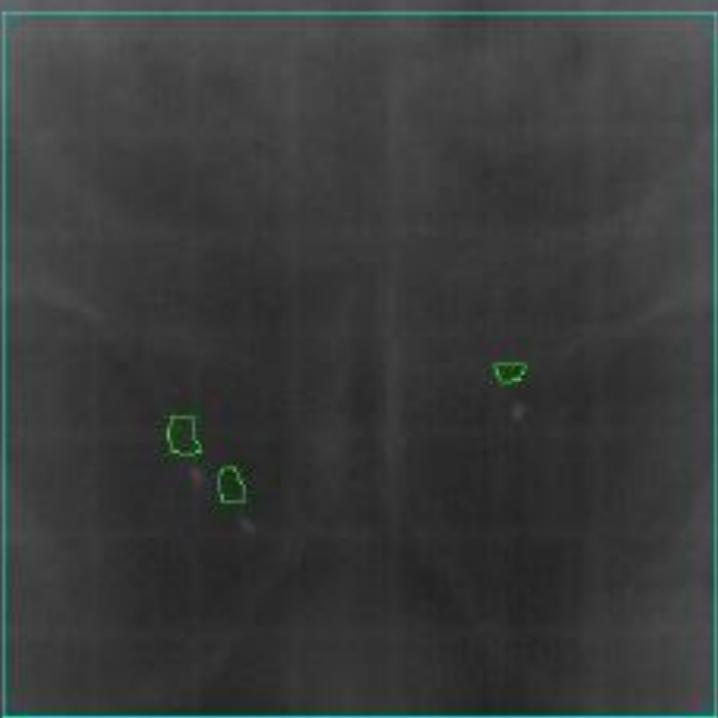
- Uključivanje urologa u tim za radioterapiju

Implantacija zrnaca – dva lateralno i jedno u apeks

Simulacija 1 tjedan nakon implantacije

Ne implantirati zrnca do završetka neoadjuvantne hormonske terapije

Isocenter: Acquisition



S9 - APsetupMV - APsetupMV-24\_8\_8 - 10/26/2006



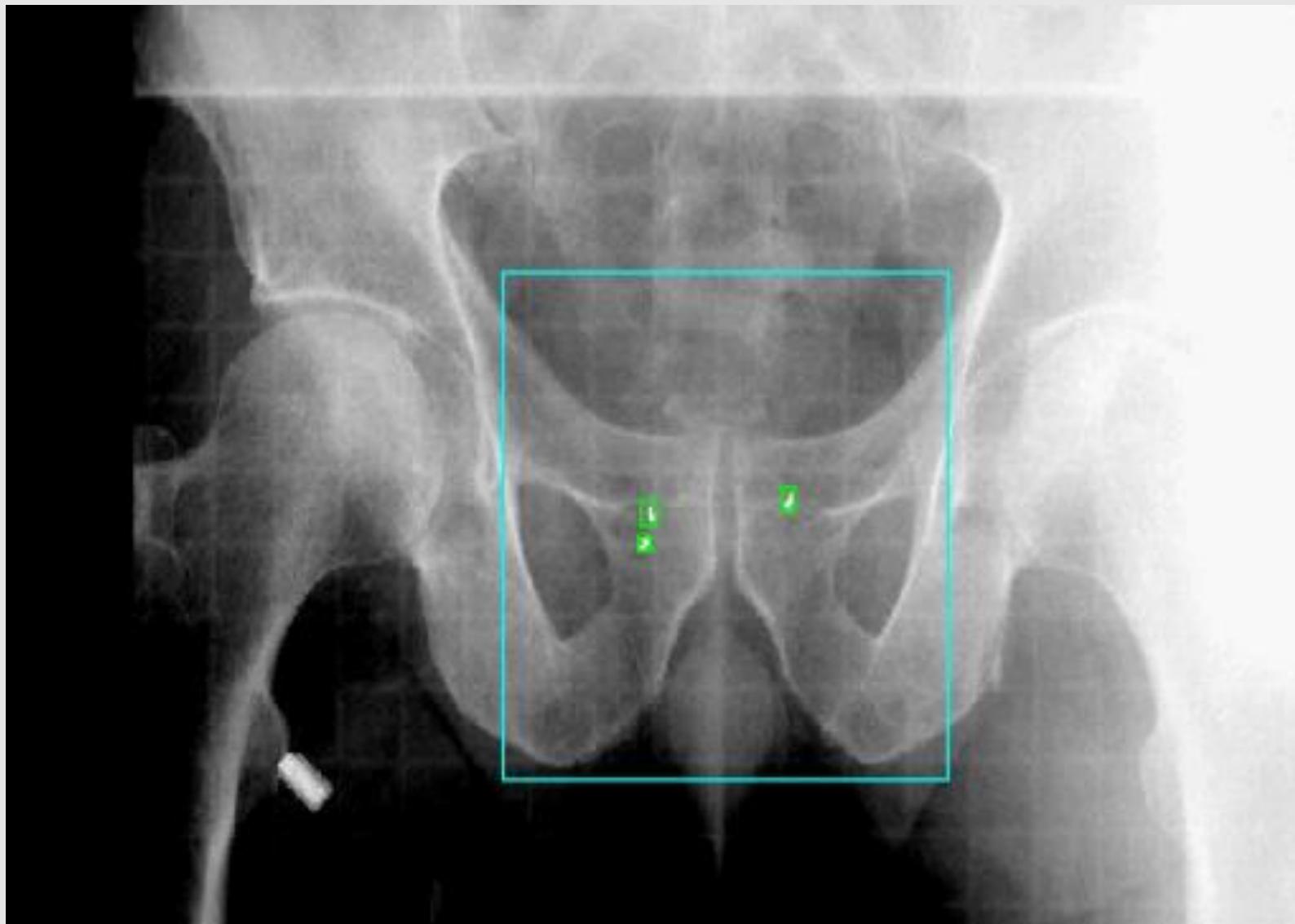
Summary: Images (2 App) / Douch Corrections (VAR\_IEC scale)

RIsetupKV APsetupMV-24\_8\_8

Patient alert from pnoibiensky, display date 10/27/2006

Status: Open Signed off date: <empty> Signed off by: <empty>

## PORAVNANJE POLOŽAJA ZRNACA



U početku 30-ak min, nakon 3-4 mj. oko 5 min. (bolesnici moraju moći zadržati urin i više od 20 minuta)

# Protonska radioterapija raka prostate

- Relativno nova metoda radioterapijskog liječenja zloćudnih bolesti
- Dva važna pitanja ostaju:
  1. Je li radioterapija protonima bolja od standardne radioterapije fotonima?
  2. Treba li ona biti prihvaćena kao standardna metoda liječenja

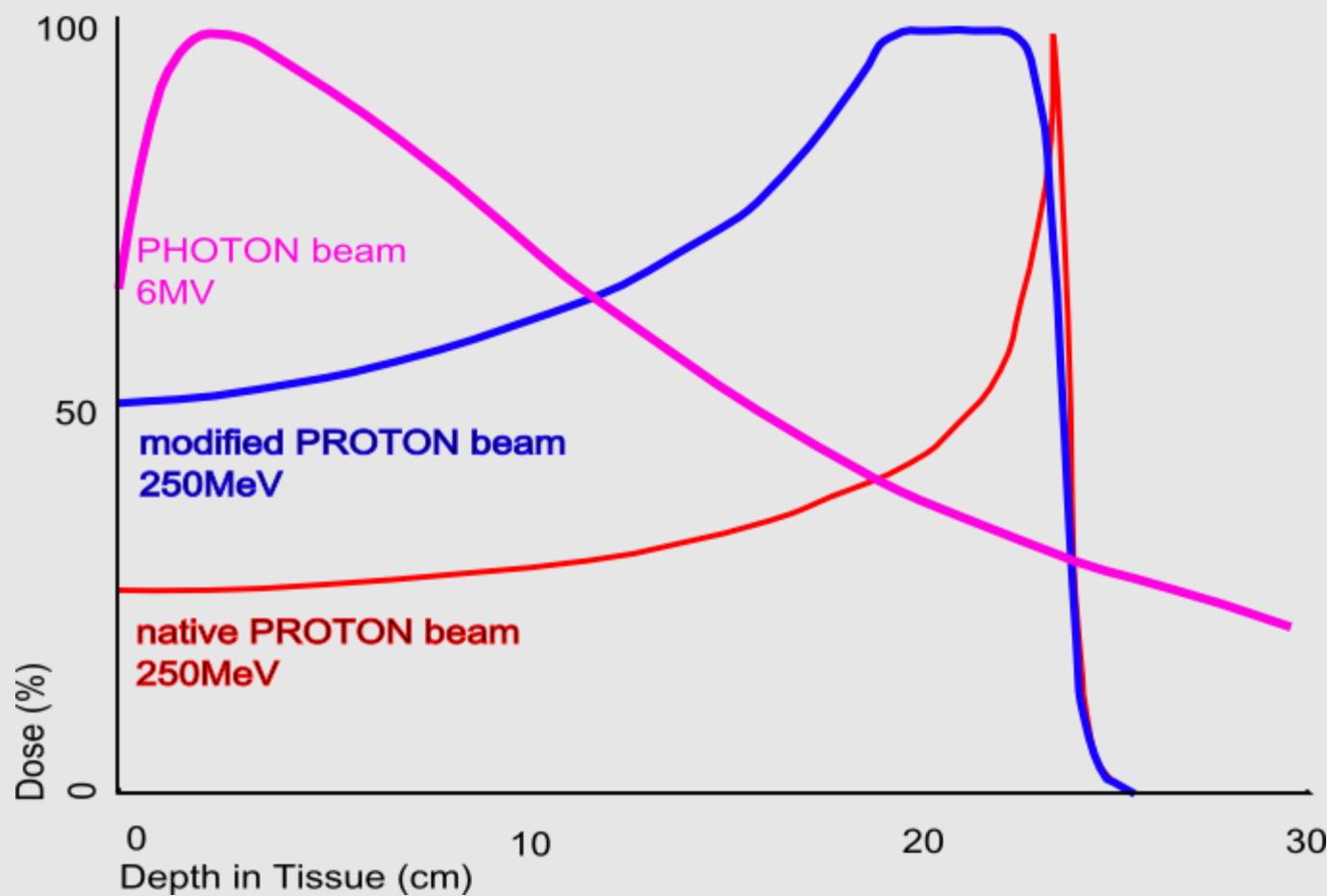
# Radioterapija protonima

- Metoda koja se primjenjuje za eskalaciju doze u radioterapiji raka prostate, ali bez jasnih zaključaka o prednostima nad fotonskom terapijom

*Olsen et al. Radiother Oncol 2007.*

- Protonska radioterapija je terapijska opcija, ali nije superiorna fotonima

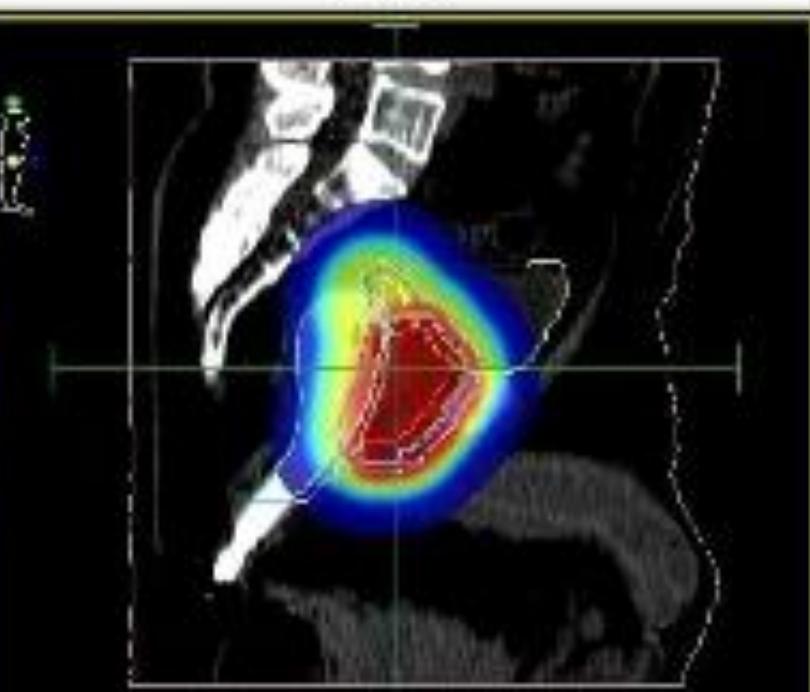
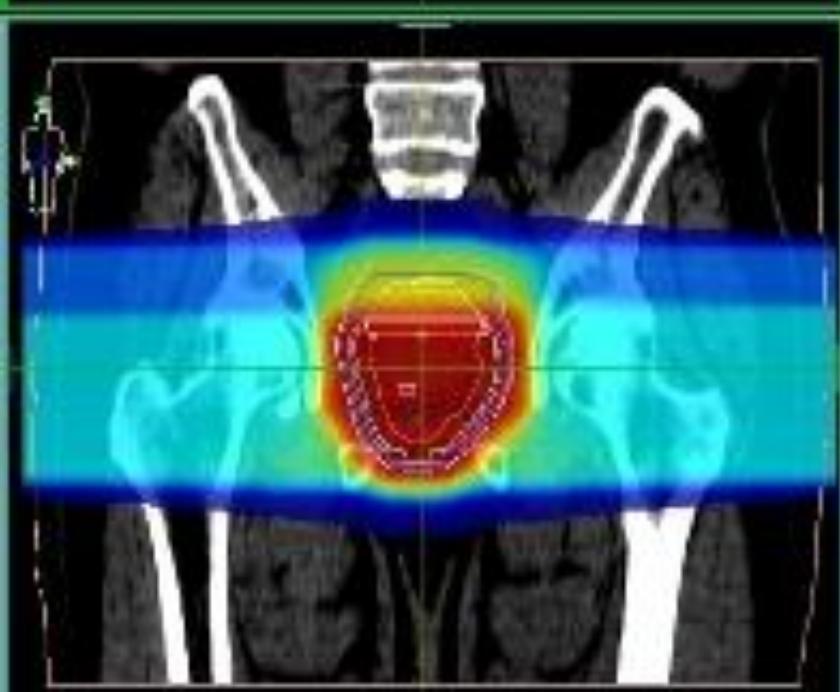
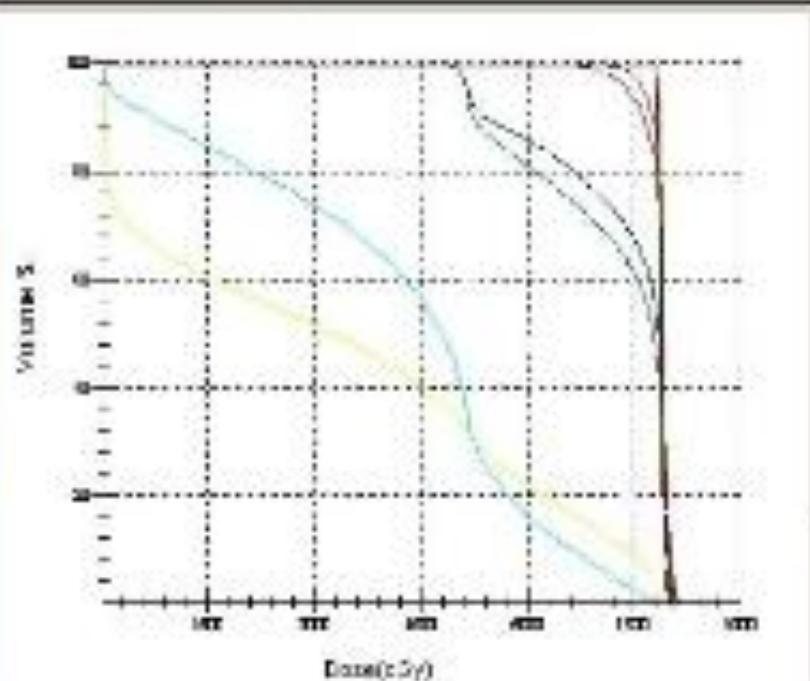
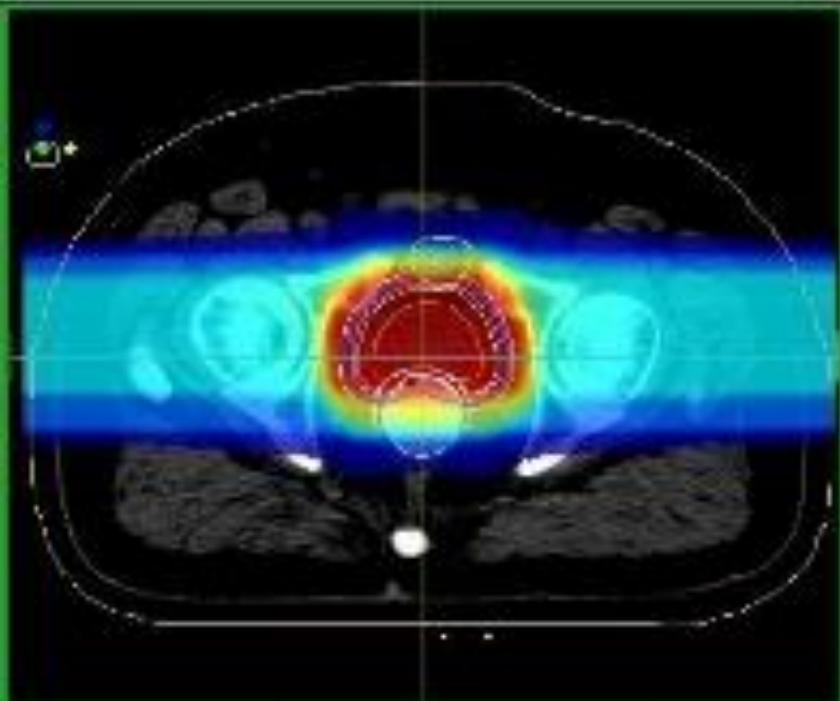
*Lodge et.al. Radiother Oncol 2007.*



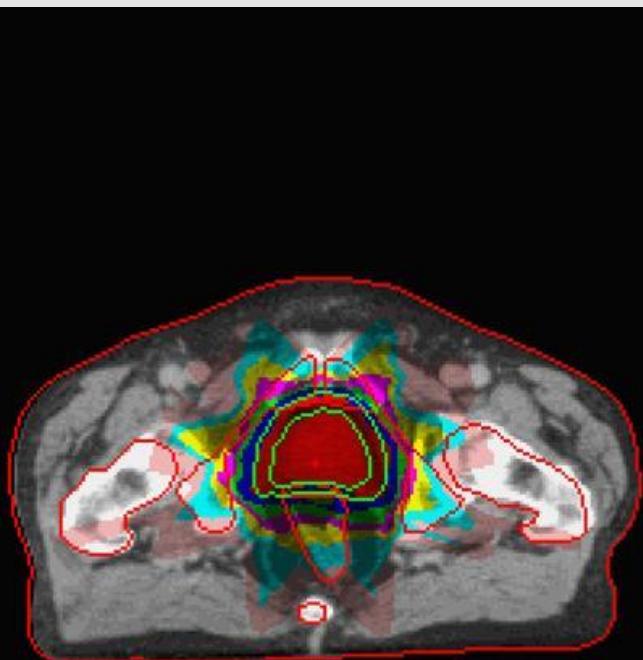
PLAN1COMPOSITE

Global Max = 8119 cGy

Dose (cGy)



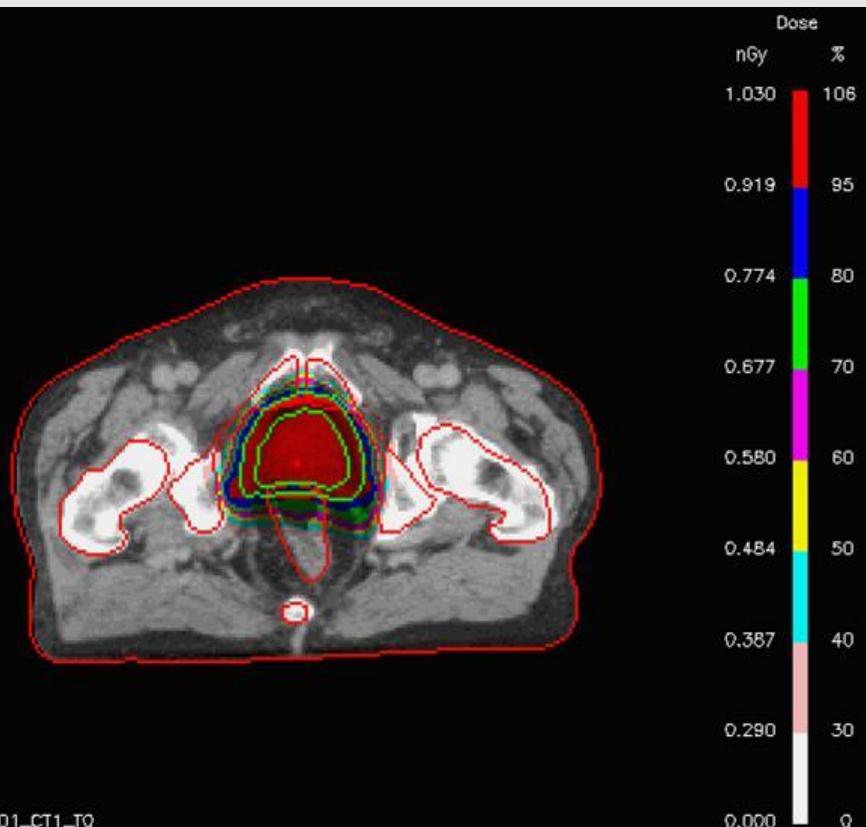
# IMRT i PT



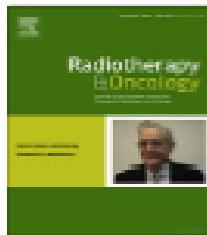
G99001\_CT1\_T0



G99001\_CT1\_T0



# Cijena radioterapije



## Cost of particle therapy

### How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons

Andrea Peeters<sup>a,e</sup>, Janneke P.C. Grutters<sup>a,d</sup>, Madelon Pijls-Johannesma<sup>a,b,\*</sup>, Stefan Reimoser<sup>c</sup>, Dirk De Ruysscher<sup>a,b</sup>, Johan L. Severens<sup>d,e</sup>, Manuela A. Joore<sup>d,e,1</sup>, Philippe Lambin<sup>a,b,1</sup>

<sup>a</sup>Maastricht Radiation Oncology (MAASTRO Clinic), The Netherlands; <sup>b</sup>GROW Research Institute, University Medical Center, Maastricht, The Netherlands;

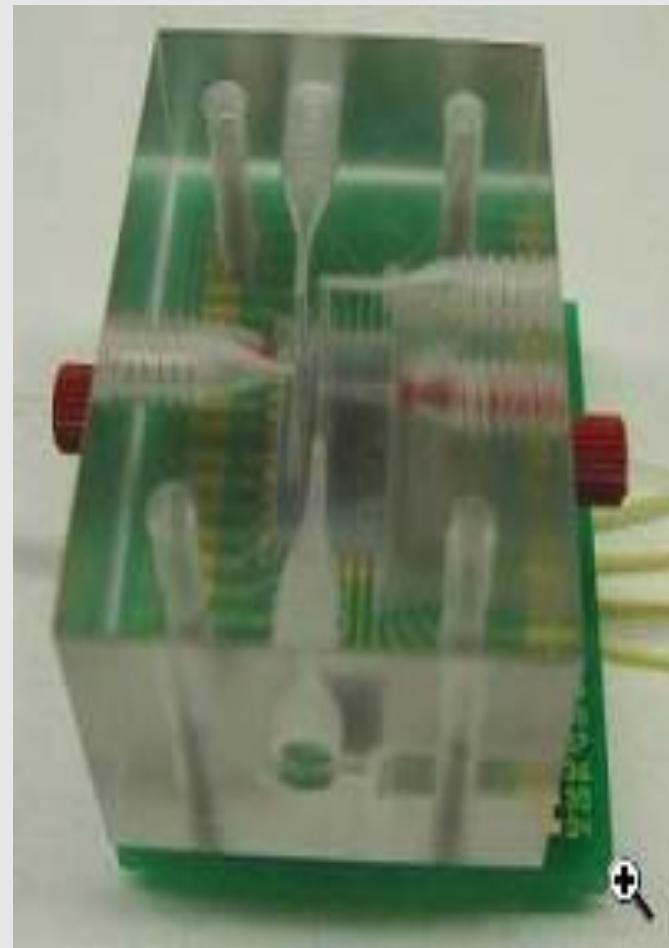
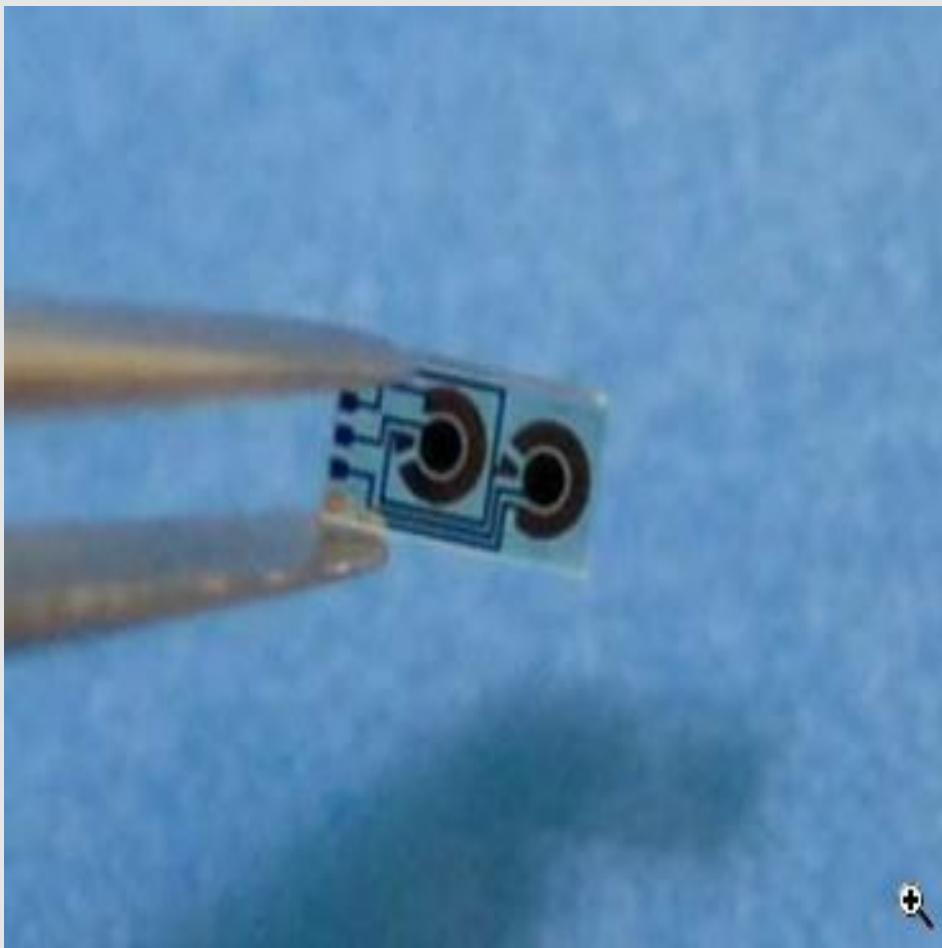
<sup>c</sup>Turner & Townsend, München, Germany; <sup>d</sup>Department of Health Organization, Policy & Economics, Maastricht University, The Netherlands;

<sup>e</sup>Department of Clinical Epidemiology and Medical Technology Assessment, University Hospital Maastricht, The Netherlands

Cijena po frakciji – uračunati troškovi izgradnje prostorije, uređaja u punoj funkciji i protok (broj) bolesnika

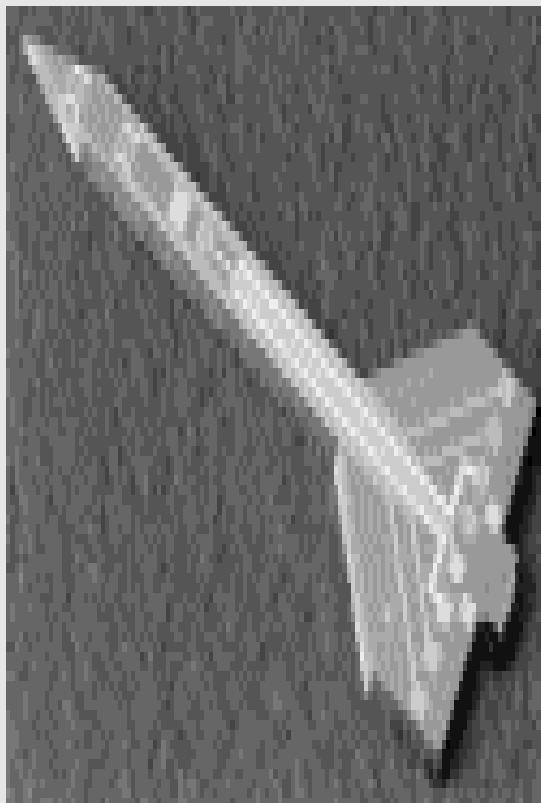
1. 1128 Eura (877-1974) – protoni i ioni ugljika
2. 743 Eura (578-1300) – protoni
3. 233 Eura (190-407) -fotoni

# ‘Lab-on-chip’ tehnologije

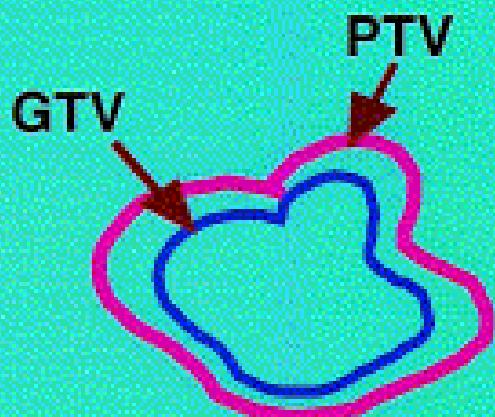


# Minijaturiziranje implantiranih biosenzora

- Mikro/nanofabrikacija
- Implantacija putem ultrafine igle u smislu redukcije oštećenja tkiva



# Biological Target Volume?



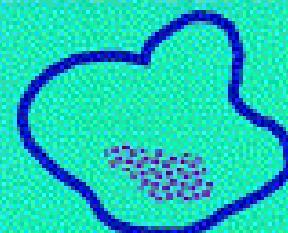
- PET
  - IUDR
- Tumor growth**



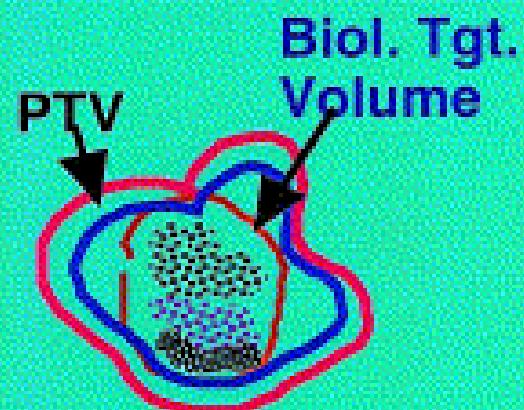
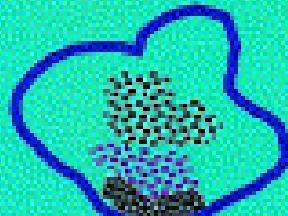
- PET
  - F-miso
- Hypoxia**



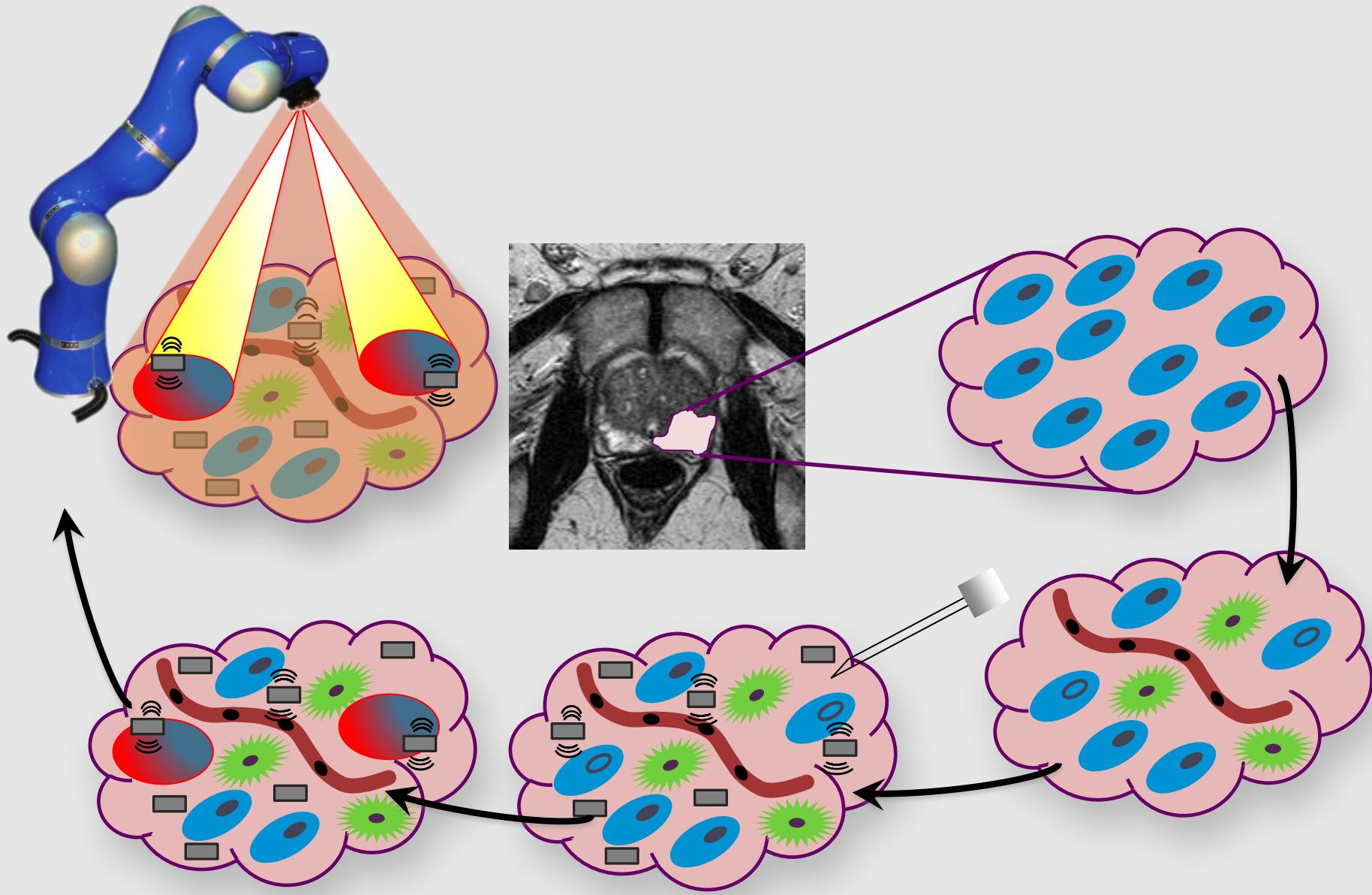
- MRI/MRS
  - choline/citrate
- Tumor burden**



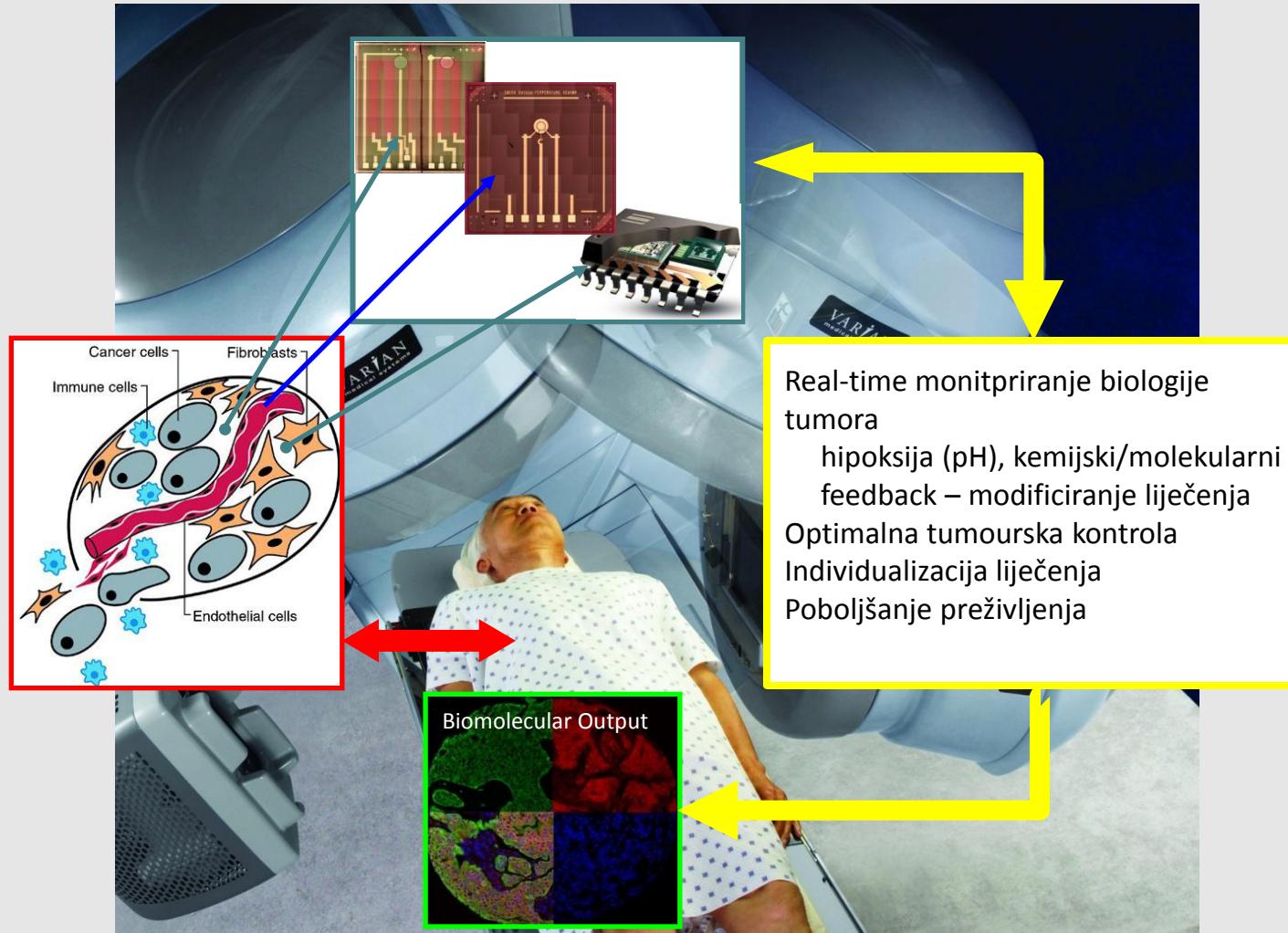
**Biological Eye View**



# Biosenzorski Adaptirana Radioterapija



# Real Time monitoriranje tumora In vivo



# **Što je istina ?**

**Znanstveno dokazane činjenice  
– na najvišoj mogućoj razini  
dokaza**

# **Što je istina ?**

**Znanstvena istina je  
promjenjiva**

**... i ima svoj rok trajanja**