Role of IMRT in the Treatment of Gynecologic Malignancies

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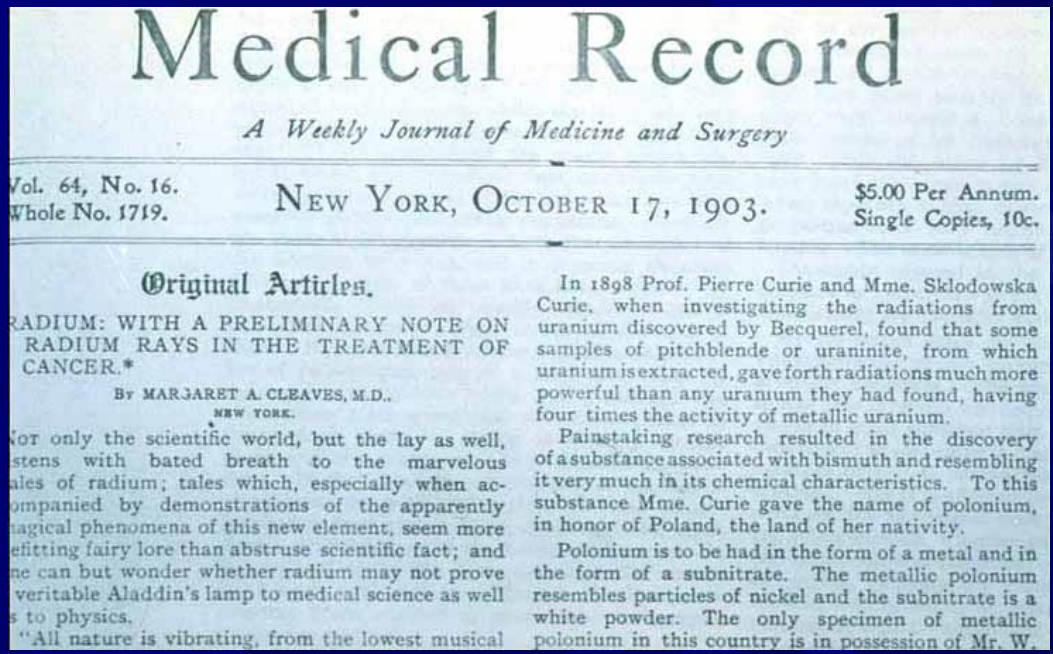
Acknowledgements

- B Aydogan, PhD – Univ of Chicago
- P Chan, MD – Princess Margaret
- P Georg, MD – Med University Vienna
- X. Allen Li, PhD – Med College of Wisconsin
- R Miralbell, MD – Instituto Oncologico Teknon, Barcelona and Hopitaux Universitaires, Geneva Switzerland
- AJ Mundt, MD – Univ of California, San Diego

Background

- RT has a long history in the treatment of gynecologic malignancies, notably cervical and endometrial cancer
- The 1st gynecology patient was treated with RT a century ago



Medical Record

A Weekly Journal of Medicine and Surgery

Vol. 64, No. 16. Whole No. 1719. NEW YORK, OCTOBER 17, 1903. $5.00 Per Annum. Single Copies, 10c.

Original Articles.

RADIUM: WITH A PRELIMINARY NOTE ON RADIUM RAYS IN THE TREATMENT OF CANCER.*

By MARJARET A. CLEAVES, M.D., NEW YORK.

Not only the scientific world, but the lay as well, stens with bated breath to the marvelous ales of radium; tales which, especially when ac- mpanied by demonstrations of the apparently agical phenomena of this new element, seem more efitting fairy lore than abstruse scientific fact; and ne can but wonder whether radium may not prove veritable Aladdin's lamp to medical science as well s to physics.

"All nature is vibrating, from the lowest musical

In 1898 Prof. Pierre Curie and Mme. Sklodowska Curie, when investigating the radiations from uranium discovered by Becquerel, found that some samples of pitchblende or uraninite, from which uranium is extracted, gave forth radiations much more powerful than any uranium they had found, having four times the activity of metallic uranium.

Painstaking research resulted in the discovery of a substance associated with bismuth and resembling it very much in its chemical characteristics. To this substance Mme. Curie gave the name of polonium, in honor of Poland, the land of her nativity.

Polonium is to be had in the form of a metal and in the form of a subnitrate. The metallic polonium resembles particles of nickel and the subnitrate is a white powder. The only specimen of metallic polonium in this country is in possession of Mr. W.

RT in Gynecologic Tumors

- Typically a combination of external beam whole pelvic RT (WPRT) and intracavitary brachytherapy (ICB)
- WPRT is used to treat the primary tumor/tumor bed plus the regional lymphatics
- ICB is used to boost the primary tumor/tumor bed safely to high doses

Gynecologic RT

- Highly efficacious and well tolerated in most patients
- Excellent pelvic control particularly in early stage cervical and endometrial cancer
- Adjuvant RT improves outcome of women with high risk features following surgery

IMRT Rationale

- RT →potential toxicities due to the treatment of considerable volumes of normal tissues
  - Small bowel→ diarrhea, SBO, enteritis, malabsorption
  - Rectum → diarrhea, proctitis, rectal bleeding
  - Bone Marrow → ↓WBC, ↓platelets, anemia
  - Pelvic Bones → Insufficiency fractures, necrosis
- Reduction in the volume of normal tissues irradiated with IMRT may thus ↓risk of acute and chronic RT sequelae
- ↑dose in “high risk” pts, e.g. node+ disease
- An alternative (or replacement) for conventional brachytherapy

Goals

- To discuss the current status of IMRT treatment planning for gynecologic patients receiving whole-pelvic IMRT.
- To describe emerging areas of research and development in the use of IMRT for gynecologic patients.

Treatment Planning Process

Simulation – Prone vs. Supine; Type of immobilization

↓

Target and Tissue Delineation – Multiple imaging modalities

↓

Treatment Planning/Optimization – Number of beams/orientation

↓

Plan Evaluation – High conformity vs. dose homogeneity

↓

Quality Assurance – Verification of calculated dose

↓

Treatment Delivery/Verification – Verification scheme/IG-IMRT

Immobilization

- Patient in supine position
- Immobilized using alpha cradles indexed to the treatment table

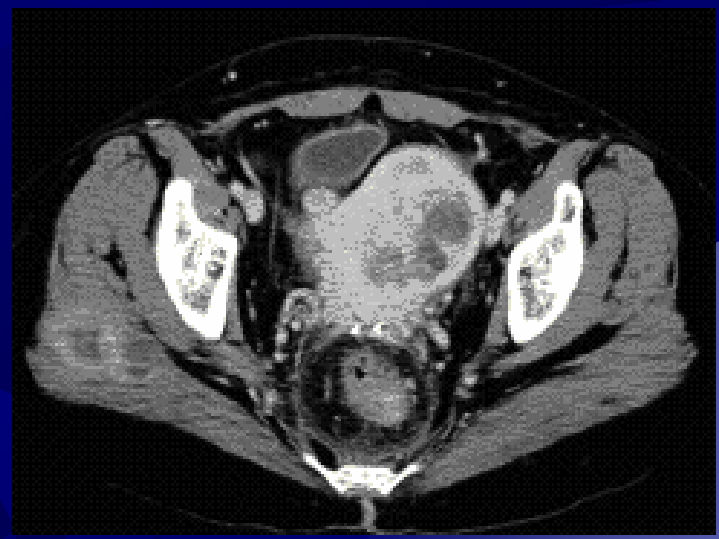
Immobilization

- Others favor the prone position
- Data from the U Iowa suggest ↑dosimetric benefits to the prone position (Adli et al. Int J Radiat Oncol Biol Phys 2003;57:230-238)
- However, may not be possible in patients treated with pelvic-inguinal IMRT

Schefter T, Kavanagh B.
Cervical Cancer: Case Study
IMRT: A Clinical Perspective 2005

Planning CT Scan

- Scan extent: L3 vertebral body to 3 cm below ischial tuberosities
- Typically use 3 mm slice thickness
- Larger volumes used only if treating extended field whole abdomen or pelvic-inguinal IMRT



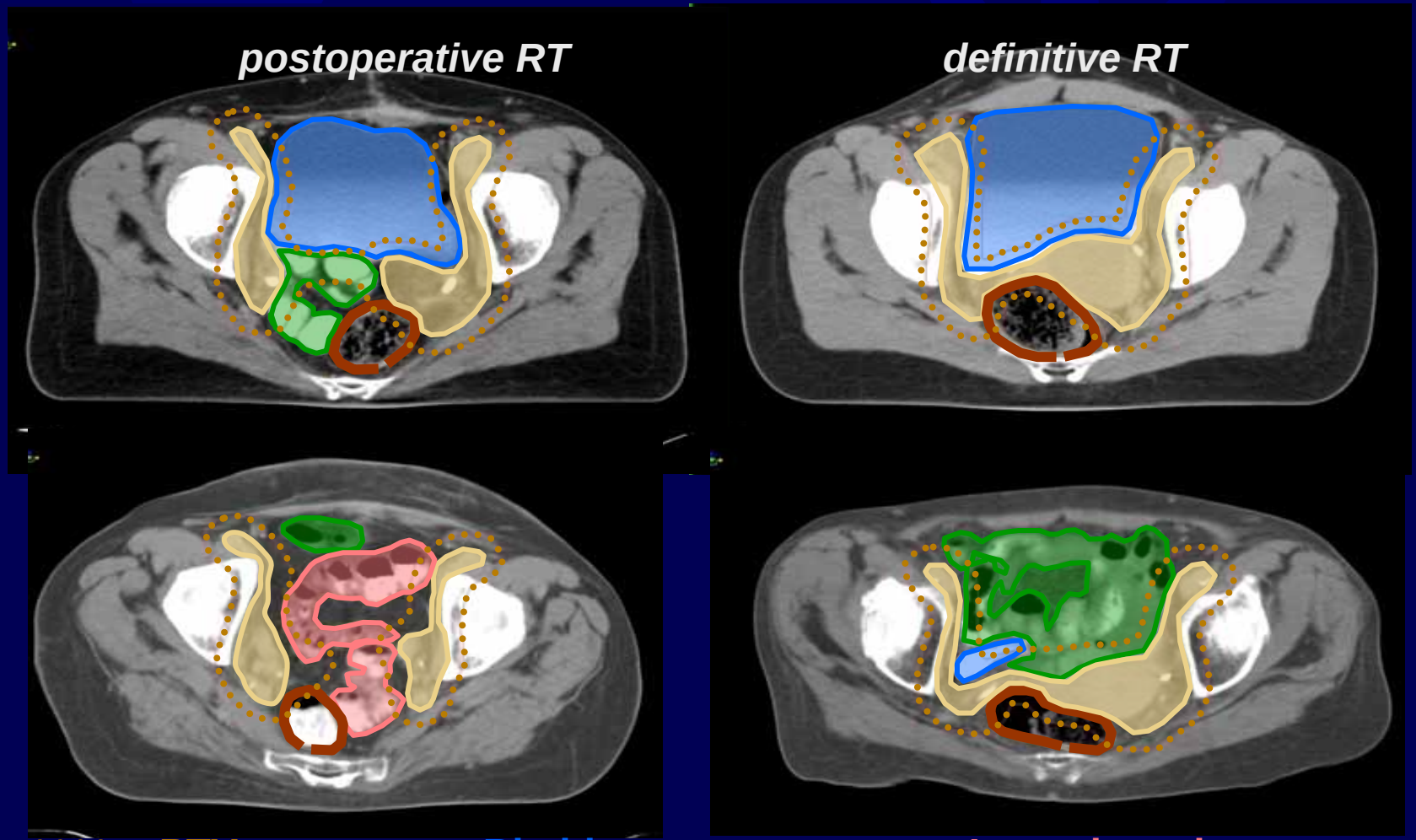
Contrast Administration

- Oral, IV and rectal contrast are commonly used
- Bladder contrast is not needed
- IV contrast is important to delineate vessels which serve as surrogates for lymph nodes
- A vaginal marker is also placed

Target Definition

- Clinical target volume (CTV) drawn on axial CT slices
- CTV *components* depend on the pathology
- In all patients:
  - Upper ½ of the vagina
  - Parametria tissues
  - Pelvic lymph nodes regions (common, internal and external iliacs)
- In cervical cancer and endometrial cancer patients with positive cervical involvement, include the presacral region

CTV and Normal Tissues



Roeske – AAPM 2006

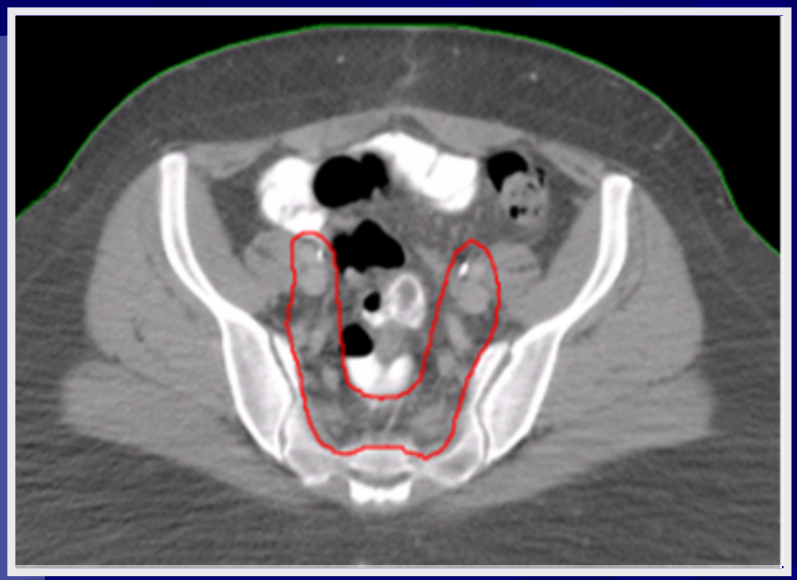
P Georg, MD – Med University Vienna

3D Visualization of the CTV

Target Delineation

- Until recently, no consensus existed regarding target delineation in gynecologic IMRT
- Lack of guidelines or consensus impedes widespread adoption of this approach
- Also impedes development of national cooperative group trials

Consensus Guidelines



Guidelines based on participants' opinions and published data

- Post-operative pelvic IMRT
- GOG-RTOG-NCIC Target Consensus Meeting, June 2005
- www.rtog.org/gynatlas/main.html (accessed July 24, 2006).

Normal Tissues

- Normal tissues delineated depends on the clinical case
- In most cases, include:

  Small bowel, rectum, bladder
- In patients receiving concomitant or sequential chemotherapy, include the bone marrow
- Others include the femoral heads
- Kidneys and liver included only if treating more comprehensive fields

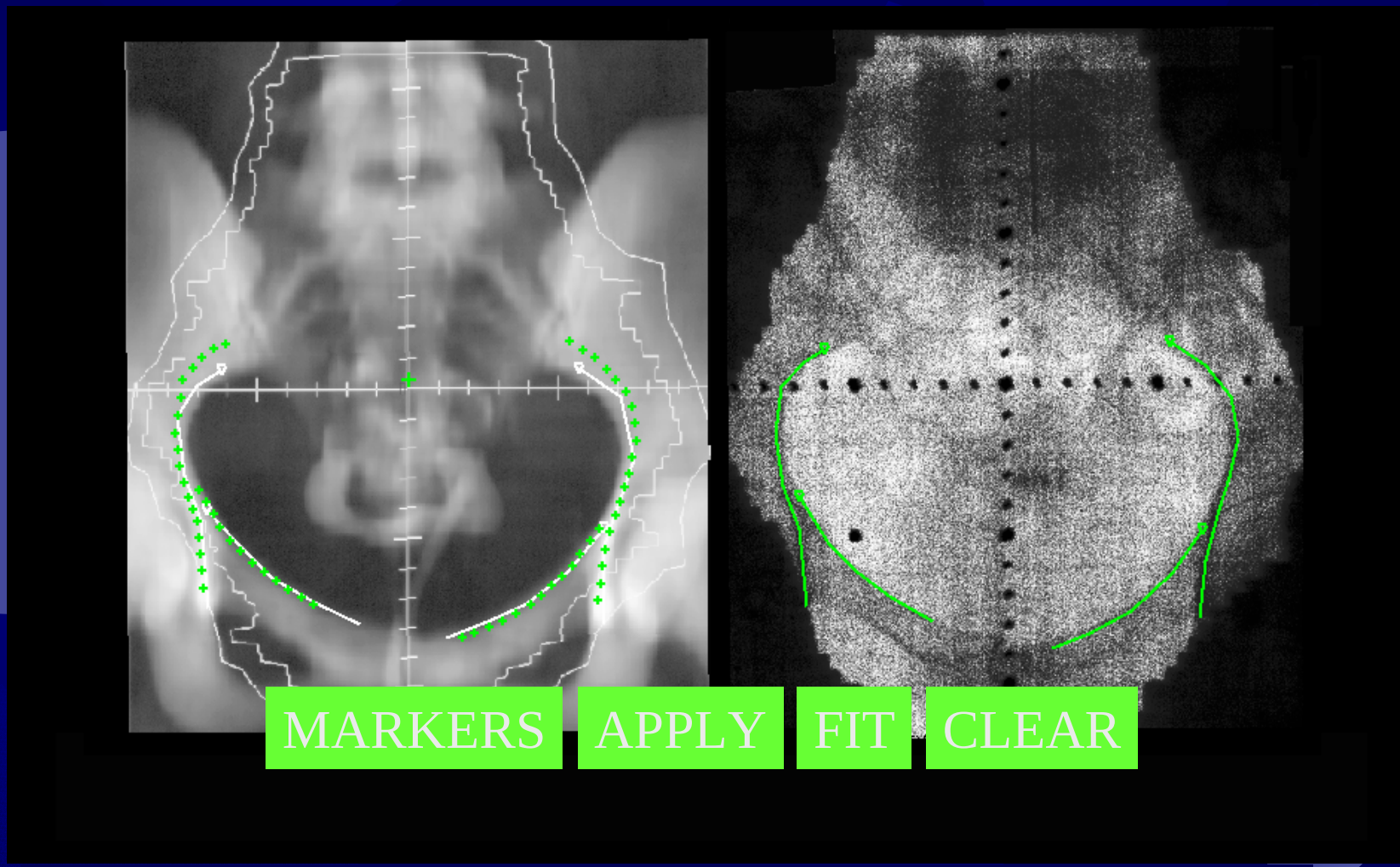
PTV Considerations

- Organ motion in the inferior portion of the CTV due to differential filling of the bladder and rectum
- Set-up uncertainty
- Appropriate expansion remains unclear; various reports ranging from 0.5 – 1.5 cm
- At Univ of Chicago, we use a 1 cm expansion
- Less is known about normal tissues
- Other centers (e.g., MD Anderson) routinely expand normal tissues

Setup Uncertainties

- Well-characterized in prostate patients
- Only a few studies in gynecologic patients
- Highly dependent upon immobilization devices, therapists experience and positioning (prone vs. supine)

Characterization of Set-up Uncertainties



dx: 0.0 mm dy: 3.0 mm RMS: 29.2

Set-Uncertainties

Single Alpha-Cradle under Patient

σ_{LR} = 5.4 mm
σ_{SI} = 4.7 mm
σ_{AP} = 5.0 mm

Multiple Alpha-Cradles (indexed to table – current system)

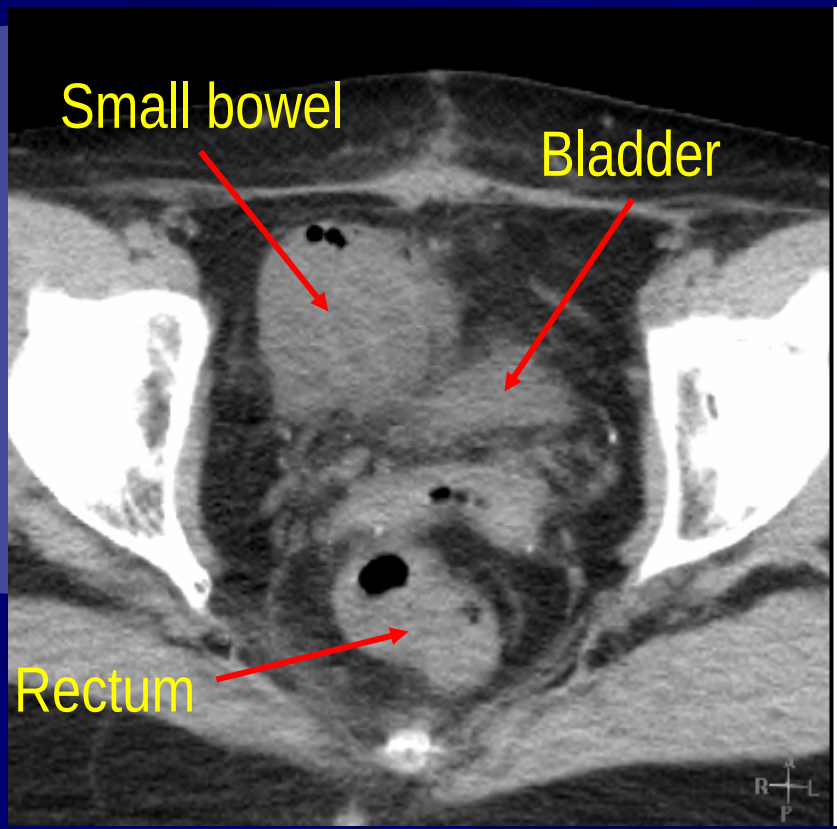
σ_{LR} = 3.2 mm
σ_{SI} = 3.7 mm
σ_{AP} = 4.1 mm

Haslam JJ, et al. Setup errors in patients treated with intensity-modulated whole pelvic radiation therapy for gynecologic malignancies. Med Dosim 30(1): 36-42, 2005.

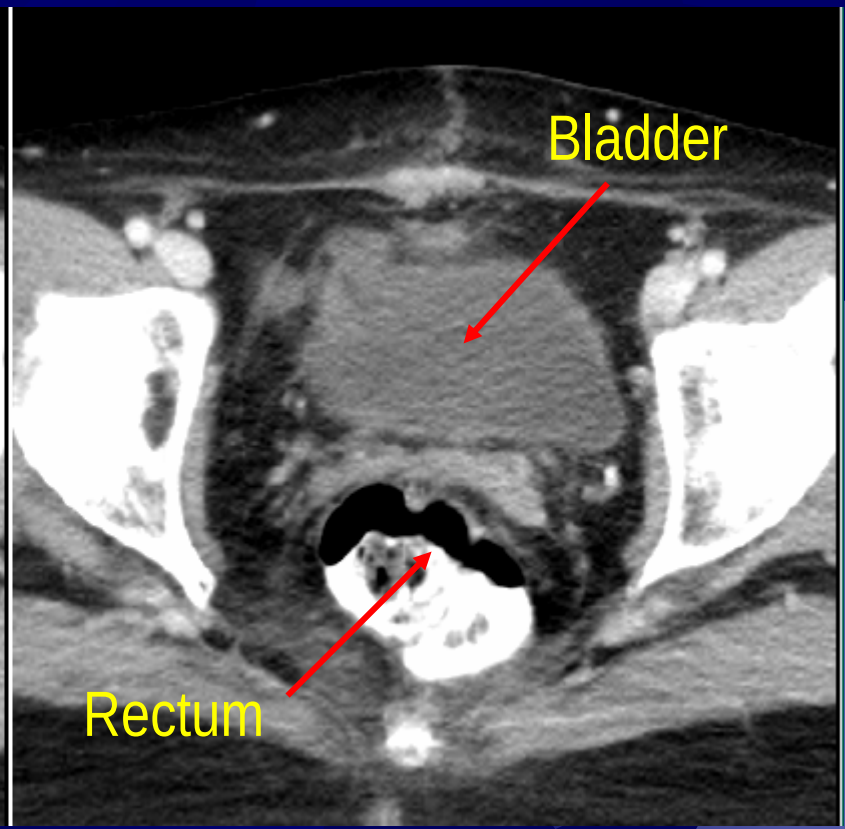
Organ Motion

- A concern in the region of the vaginal cuff
- Two approaches are being studied at our institution to address this:
  - IGRT
  - Vaginal immobilization
- Now we simply avoid *tight* CTV volumes and use a 1 cm CTV→PTV expansion
  - Produces very generous volumes around the vaginal cuff

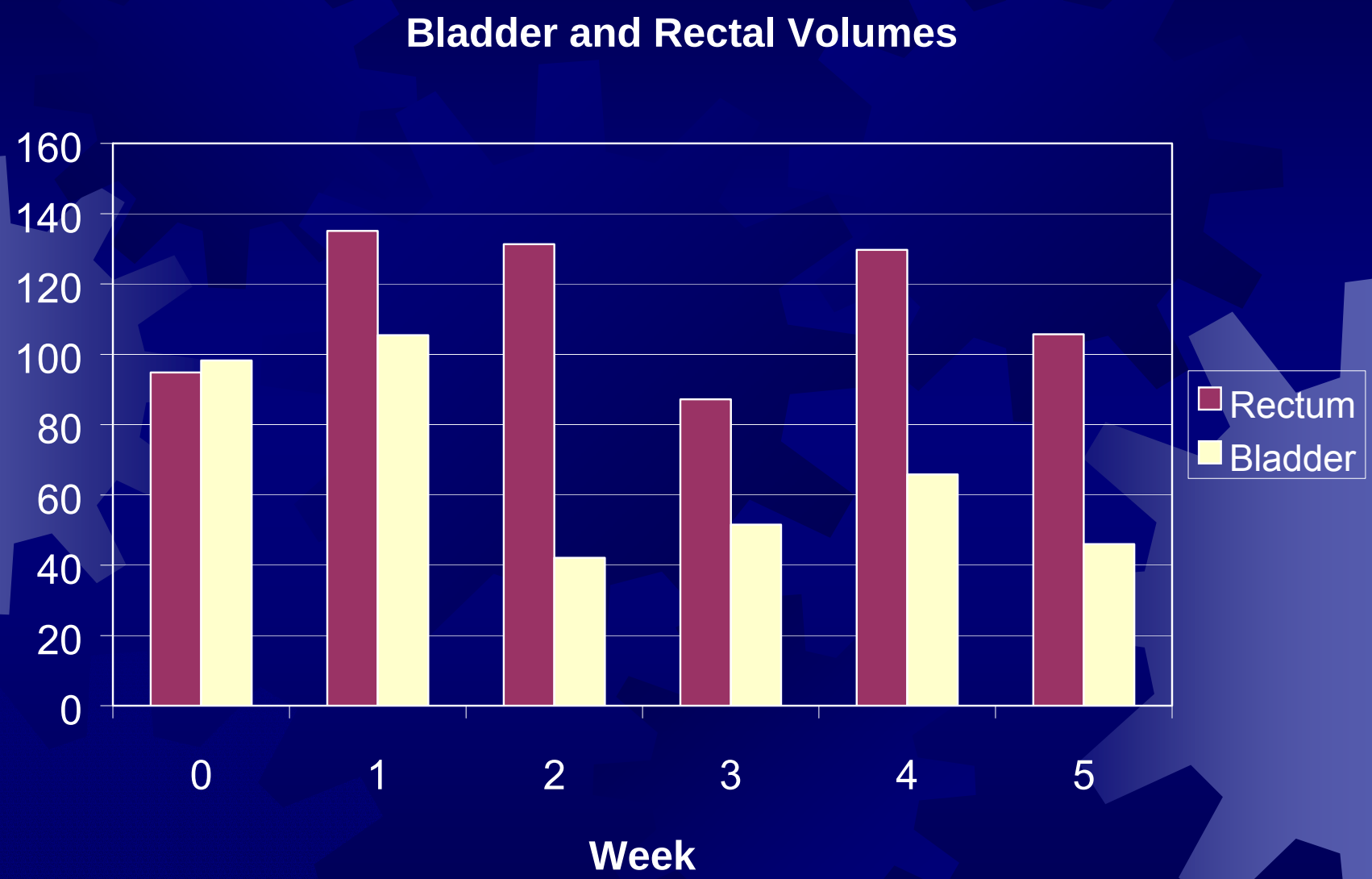
Comparison of CT Scans



Week 3 scan



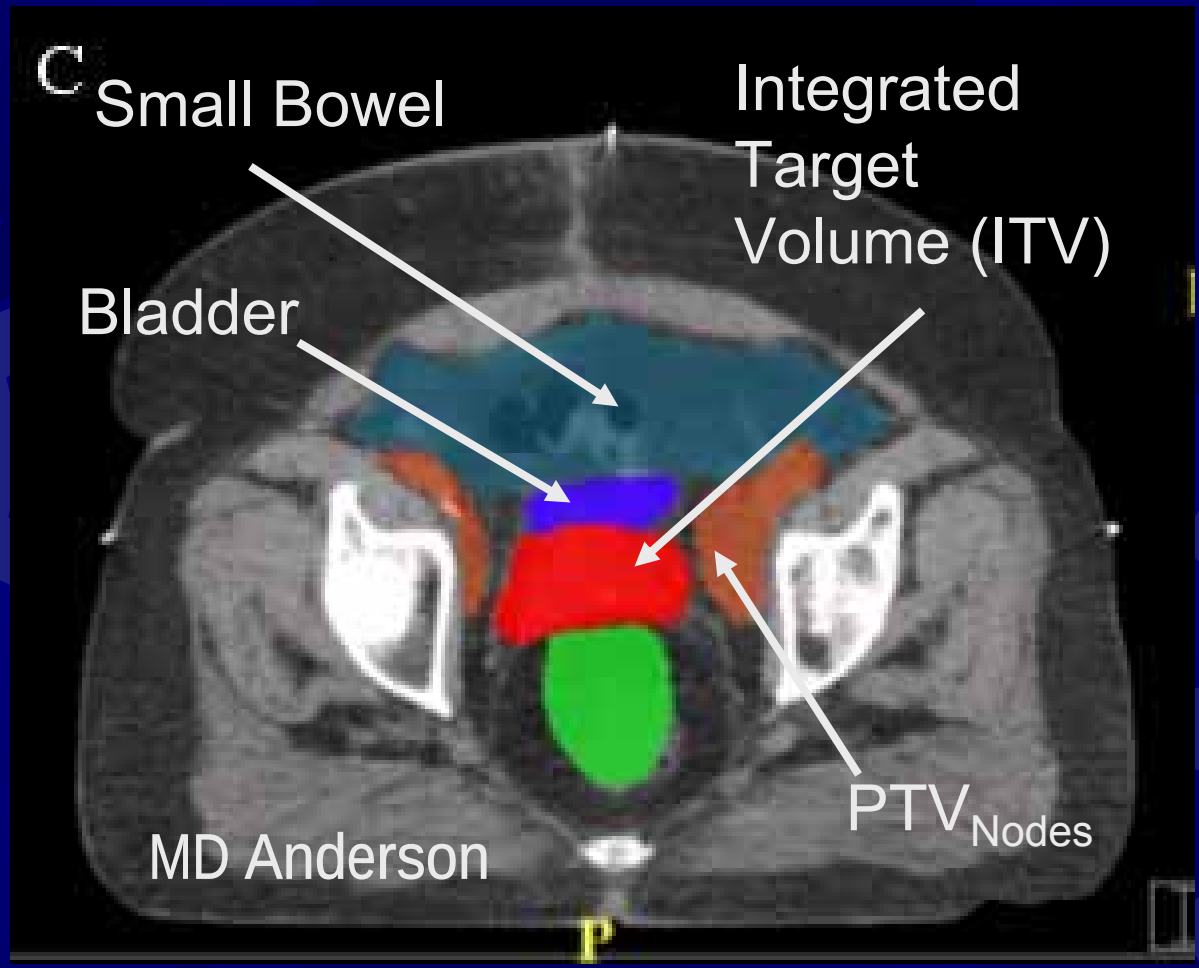
Treatment planning scan


Bladder and Rectal Volumes
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
Week
Rectum
Bladder

“Integrated Target Volume”

- A creative solution to the organ motion problem developed at MDAH
- Two planning scans: one with a full and one with an empty bladder
- Scans are then fused
- An *integrated target volume* (ITV) is drawn on the *full* bladder scan (encompassing the cuff and parametria on both scans)
- ITV is expanded by 0.5 cm → PTV_{ITV}

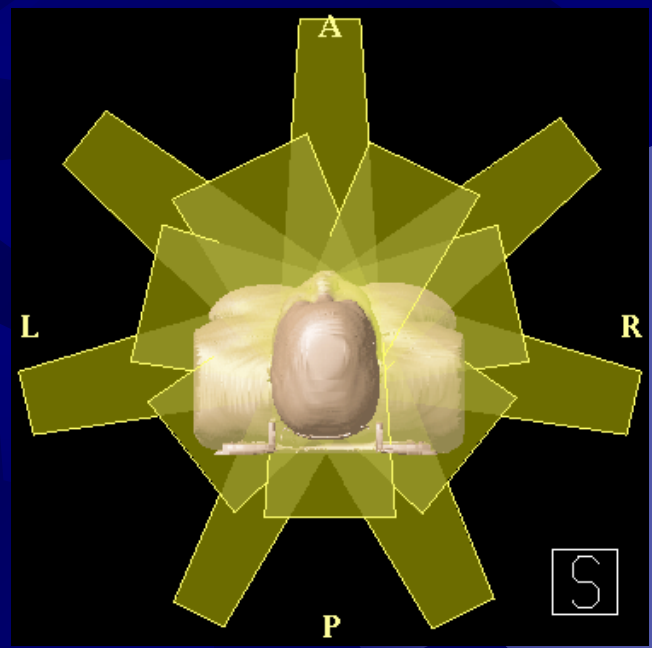
Illustration of ITV



Jhingran A, et al. Endometrial Cancer: Case Study
IMRT: A Clinical Perspective BC Decker 2005

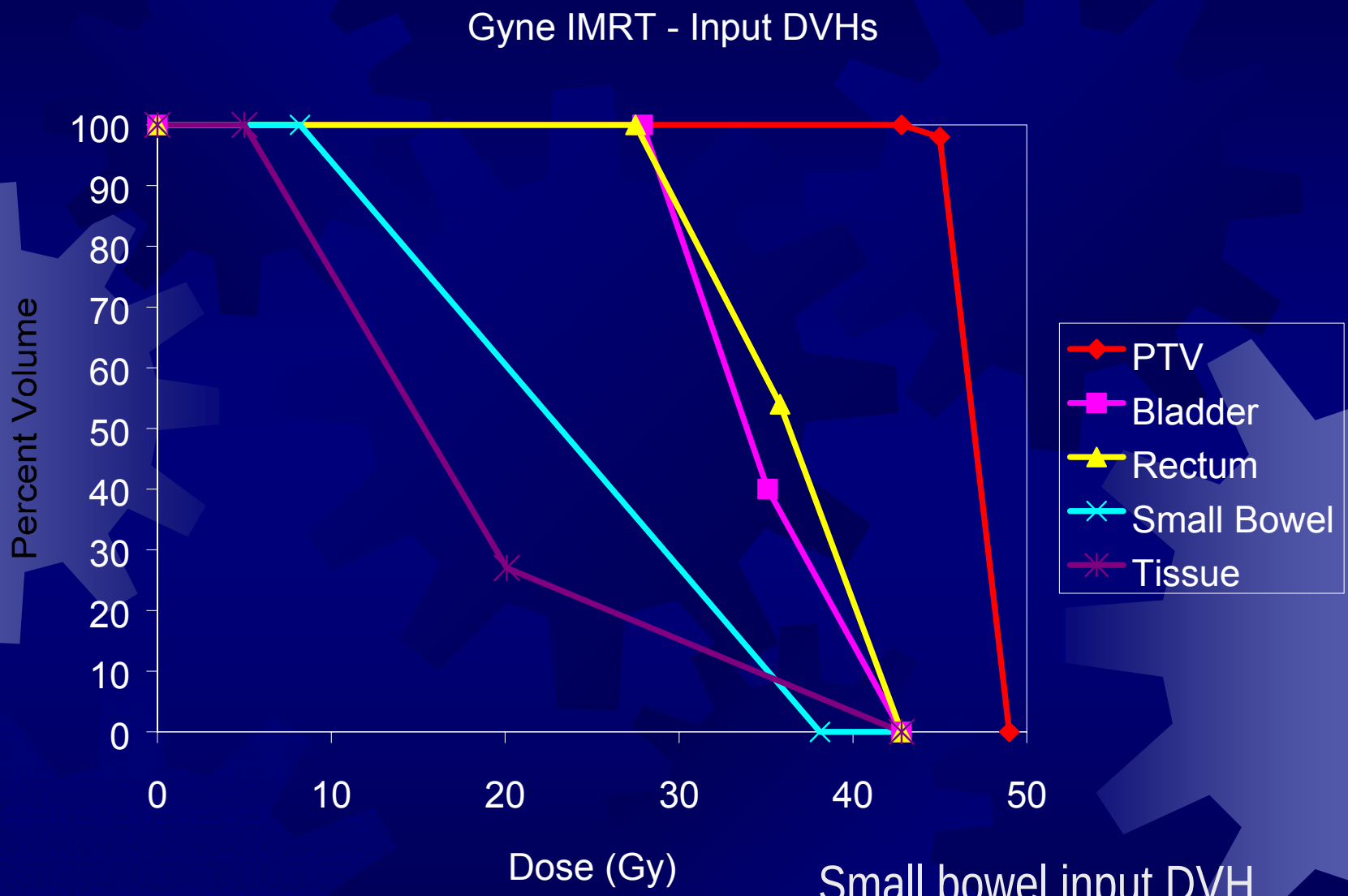
Treatment Planning

- 7-9 co-axial beam angles (equally spaced)
- Most centers use 6 MV
- Comparative plans of 6 vs. 18 MV show little or no difference
- However, 18 MV associated with higher total body doses



Treatment Planning

- Prescription dose: 45-50.4 Gy
  - 45 Gy in pts receiving vaginal brachytherapy
  - 50.4 Gy if external beam alone
- 1.8 Gy daily fractions
  - Given inherent inhomogeneity of IMRT
  - Avoids hot spots > 2 Gy
- “Dose painting” (concomitant boosting) remains experimental
  - Potentially useful in pts with high risk factors (positive nodes and/or margins)

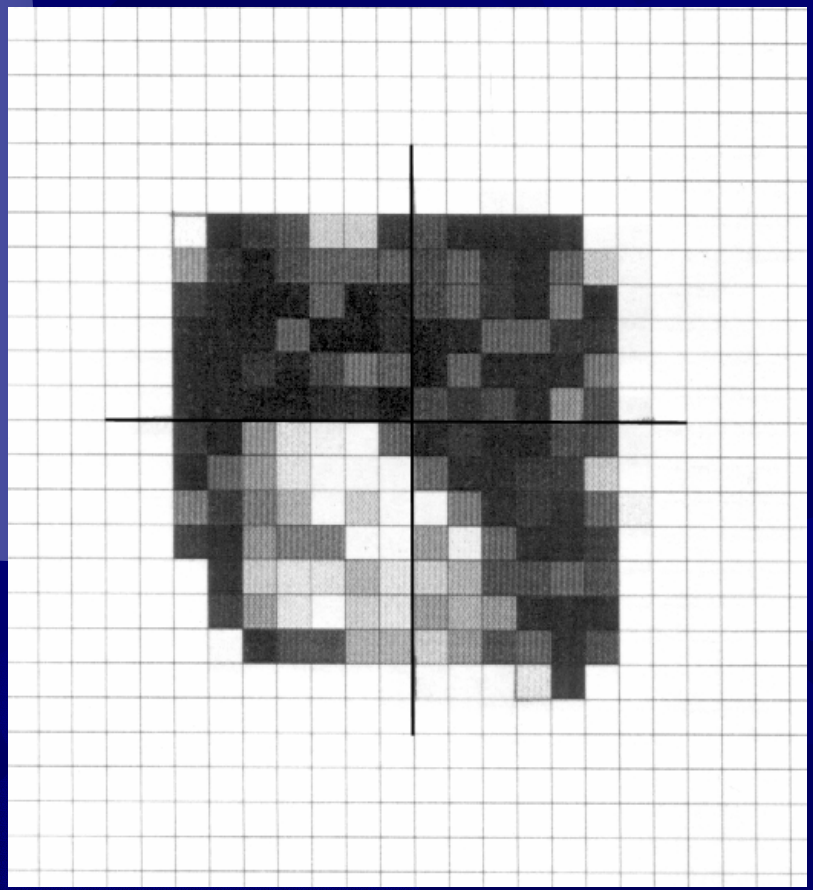


Small bowel input DVH based on NTCP data

IM-WPRT Plan Optimization Current PTV-Specific Criteria

	Acceptable	Unacceptable
Conformity	Good	Poor
PTV Coverage	> 98%	< 96%
Hot Spots		
Location	Within CTV Preferably within GTV	Edge of PTV Rectal or bladder walls in ICB region
Magnitude	<10% (110% dose) 0% (115% dose)	>20% (110% dose) >2% (115% dose)
Cold Spots		
Location	Edge of PTV	Within CTV or GTV
Magnitude	<1% of the total dose	>1% of the dose

IM-WPRT Plan Optimization Normal Tissue Specific Criteria



A more difficult question is *what* makes a normal tissue DVH acceptable.

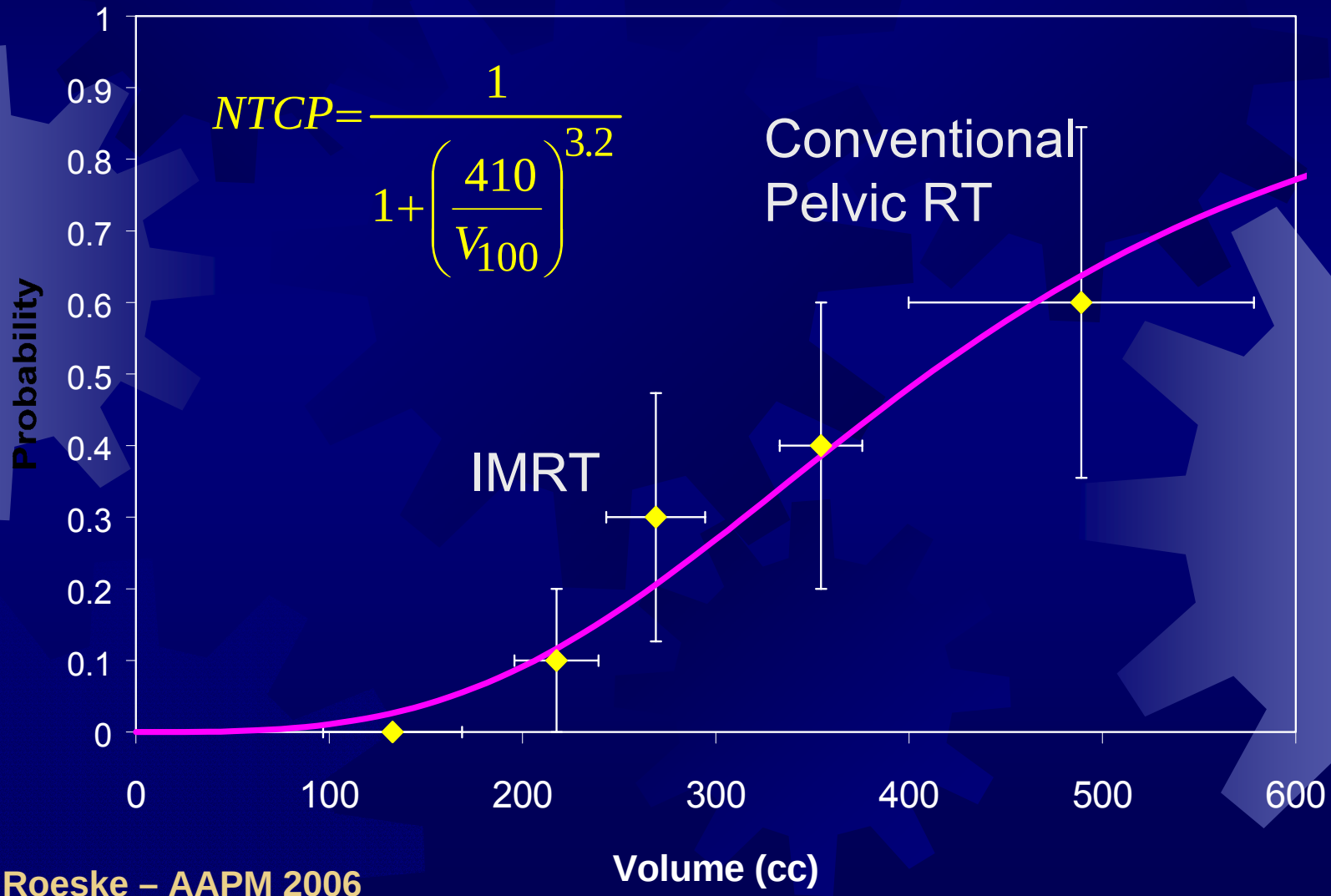
IM-WPRT plans achieve better normal tissue DVHs than WPRT plans. But how good does a normal tissue DVH need to be?

The answer is not clear

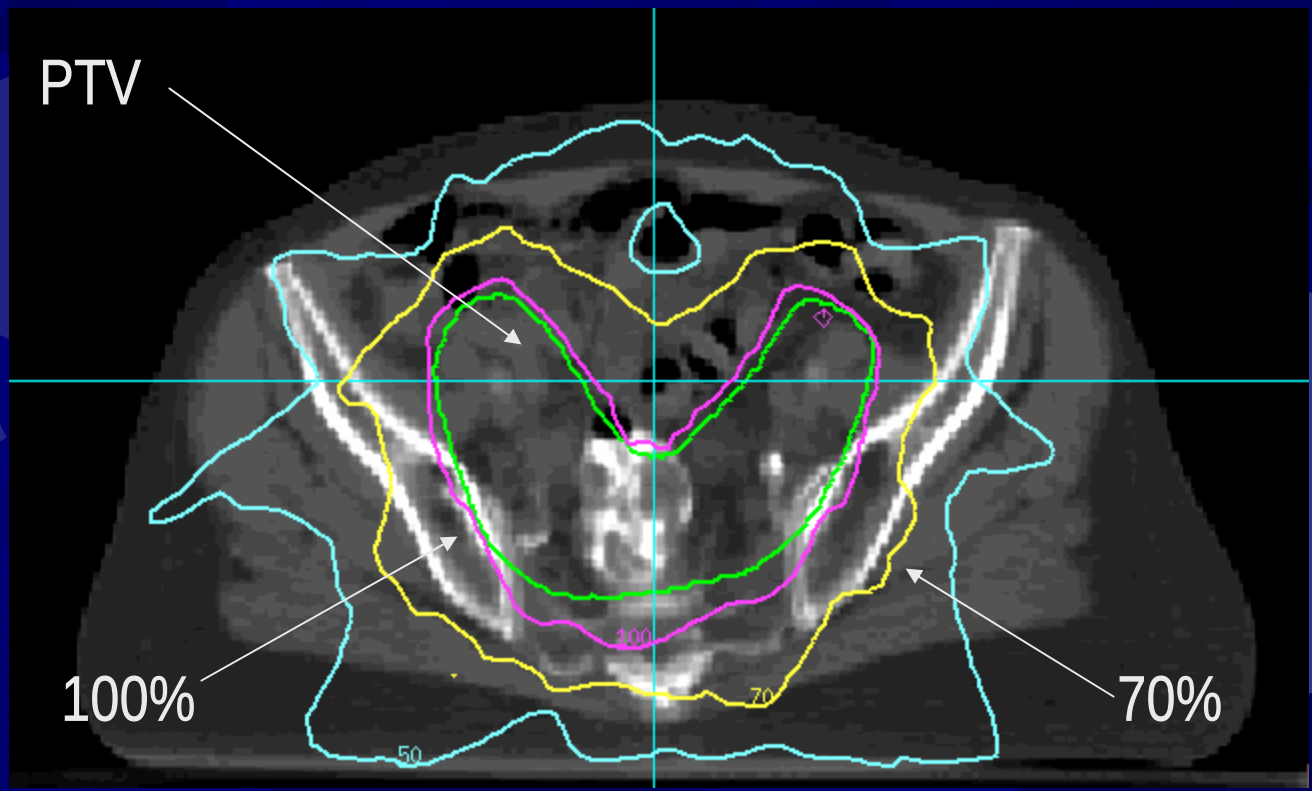
Roeske – AAPM 2006

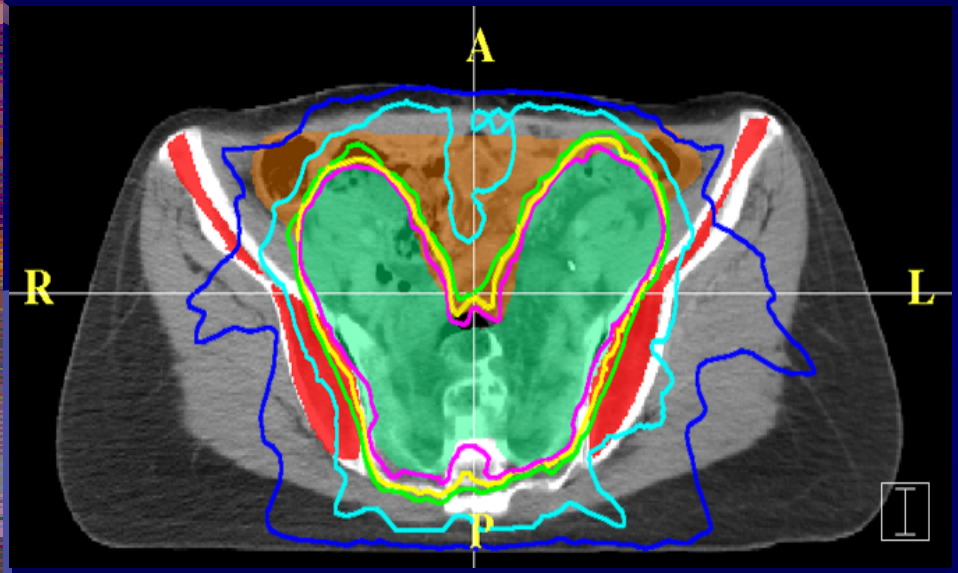
NTCP Analysis
Gynecologic IMRT Patients

Roeske et al. Radiother Oncol 2003;69:201-7.

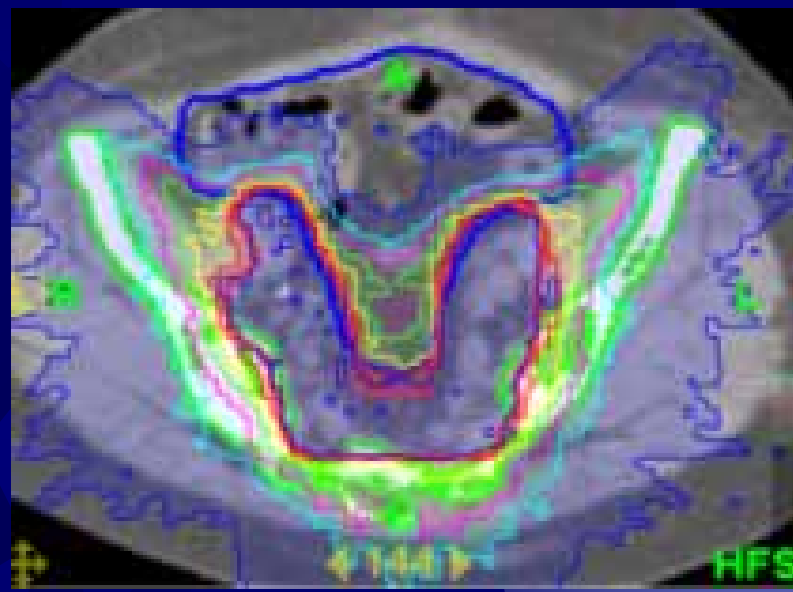


IMRT Isodose Distribution





CORVUS
North American Scientific
NOMOS



Hi-Art
Tomotherapy, Inc

Eclipse
Varian Medical Systems

IM-WPRT Planning Studies

	↓Volume Receiving Prescription Dose		
Author	Bowel	Bladder	Rectum
Roeske	↓50%	↓23%	↓23%
Ahamad	↓40-63%*	NS	NS
Chen	↓70%	↓**	↓**
Selvaraj	↓51%***	↓31%***	↓66%***

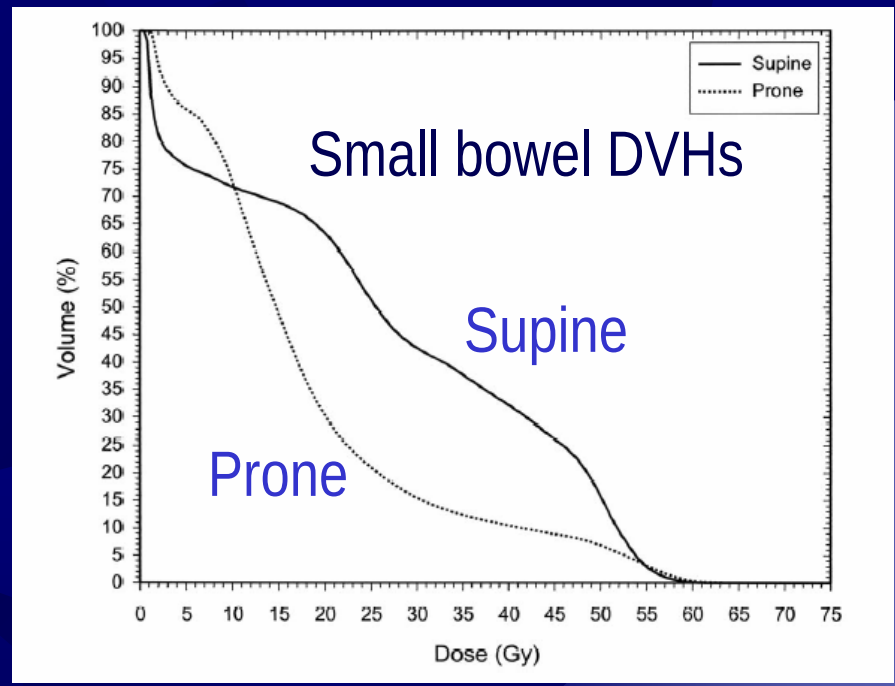
*dependent on PTV expansion used

**data not shown

***reduction in percent volume receiving 30 Gy or higher

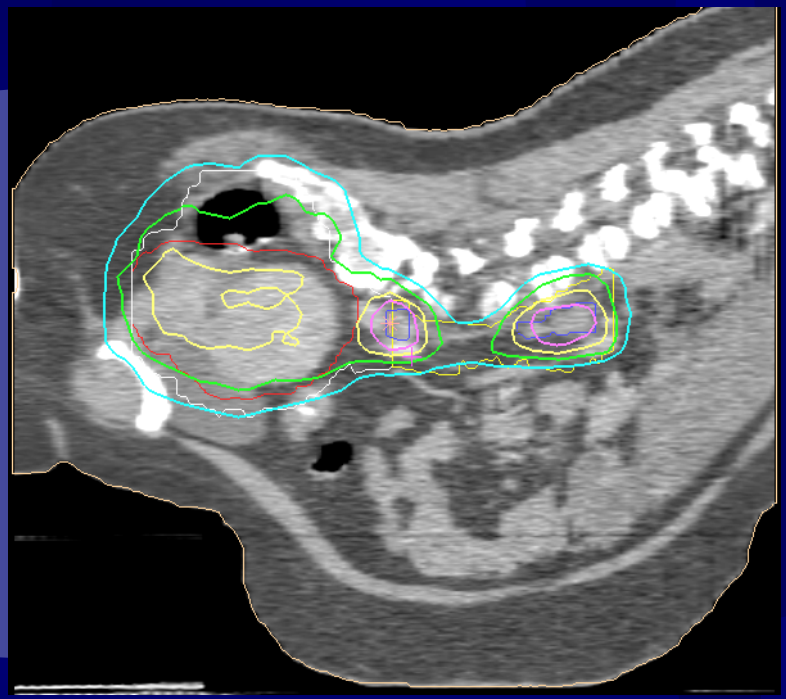
Positioning

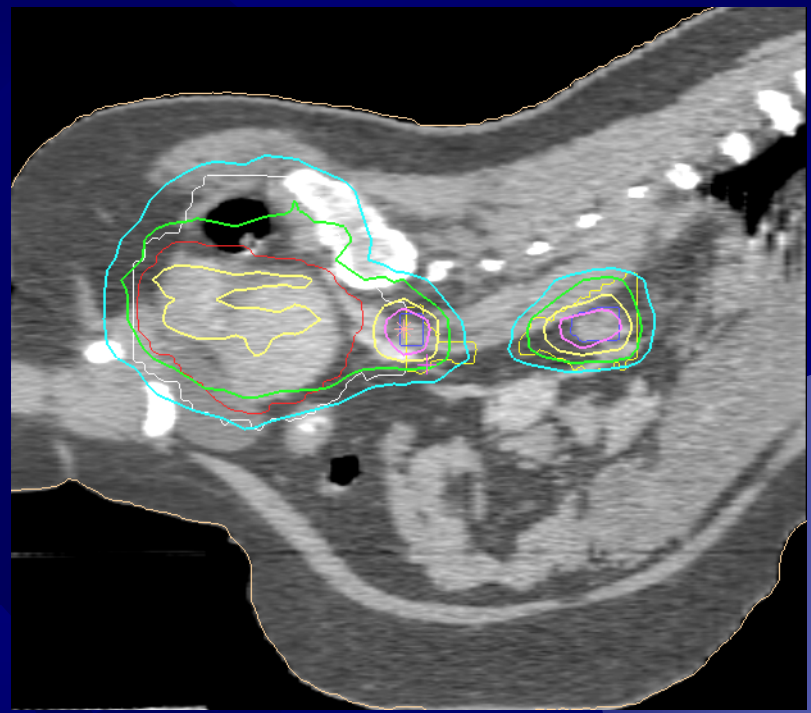
- All of our studies (set-up uncertainty, organ motion) are based on patients in the supine position
- The *prone* position may offer some additional dosimetric sparing



Adli N, Mayr N *et al*. *Int J Radiat Oncol Biol Phys* 57: 230-238, 2003.

Prone Positioning





Schefter TE and Kavanaugh BD. (Colorado) In Mundt and Roeske, *Intensity Modulated Radiation Therapy: A Clinical Perspective* BC Decker, April 2005.

Clinical Experience

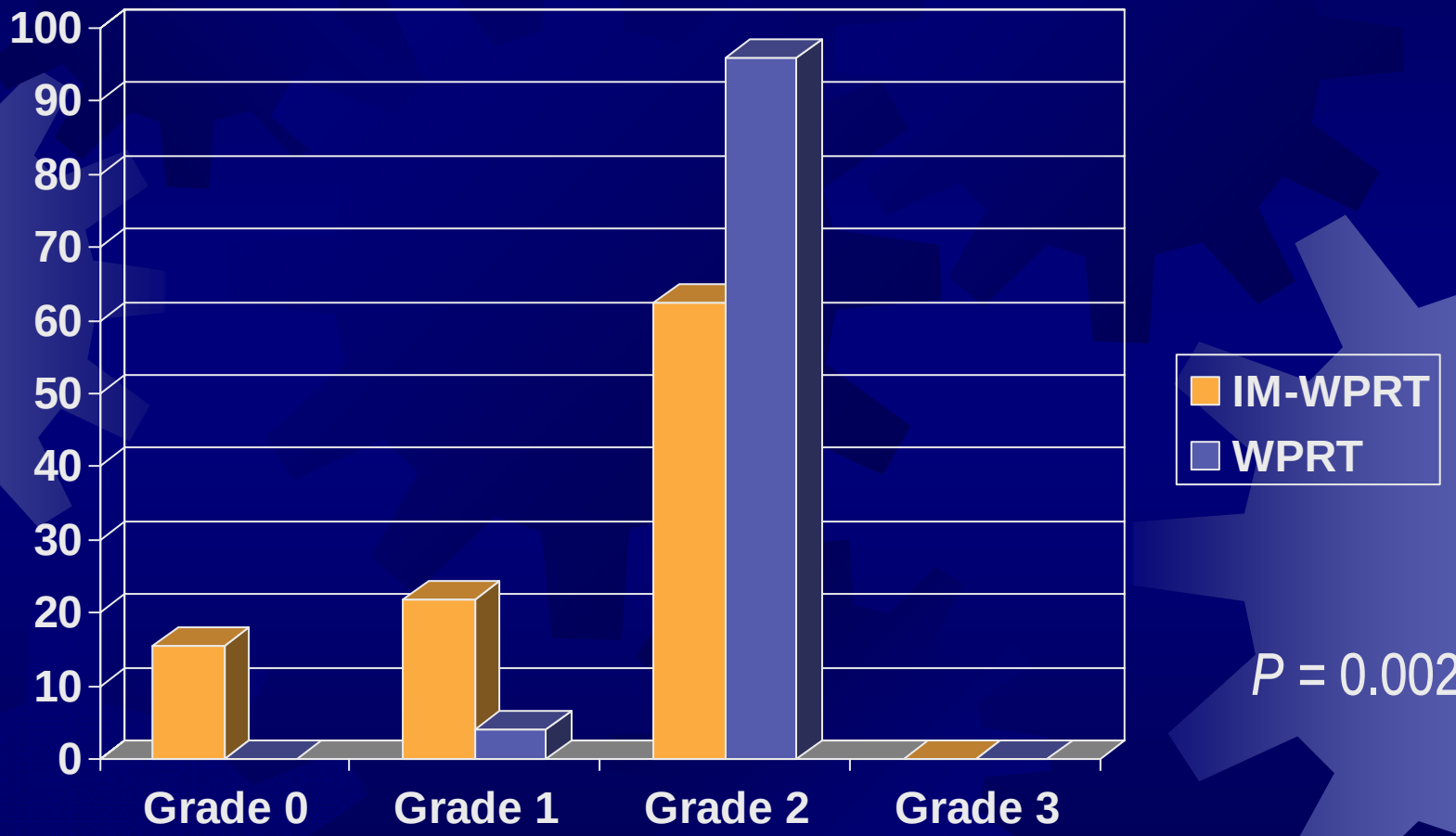
- Between 2/00 and 7/06, >200 women were treated with IM-WPRT in our clinic
- Most had cervical cancer, primarily stage IB
- Most underwent definitive RT and, in stages IB2-IIIB, concomitant cisplatin-based chemotherapy
- Endometrial cancer patients were treated *following* primary surgery
- ICB was administered in ~50% of women following IM-WPRT

Mundt, Roeske, *et al*. *Gyne Oncol* 82(3): 456-463, 2001.
Mundt *et al*. *Int J Radiat Oncol Biol Phys* 52(5):1330-1337, 2002.

Clinical Experience

- Monitored weekly for *acute* side effects
- Worst toxicities were graded on a 4-point scale
  - 0 = none
  - 1 = mild, no medications required
  - 2 = moderate, medications required
  - 3 = severe, treatment breaks, hospitalizations
- Toxicity evaluated in a matched cohort of previous gynecology patients treated with conventional pelvic RT
- Balanced in terms of age, site, radiation dose, chemotherapy and brachytherapy

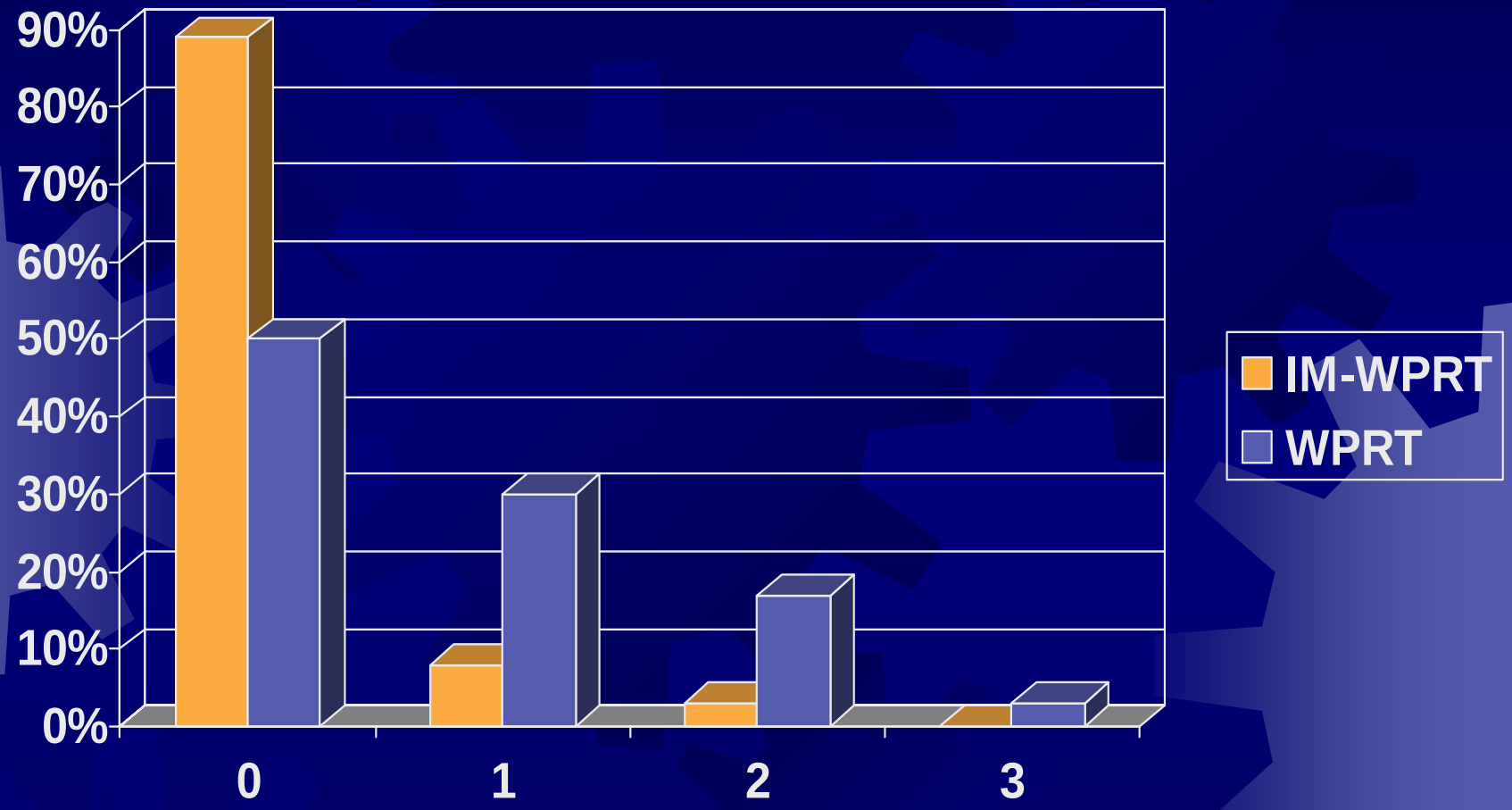
Acute GI toxicity
IM-WPRT vs. WPRT



P = 0.002

Mundt et al. *Int J Radiat Oncol Biol Phys* 52:1330-1337, 2002

Chronic GI Toxicity



On multivariate analysis controlling for age, chemo, stage and site, IMRT remained statistically significant
(p = 0.01; OR = 0.16, 95% confidence interval 0.04, 0.67)

Roeske – AAPM 2006

What about tumor control?

- Preliminary data suggests that our IMRT patients have a low rate of pelvic failure
- Majority of recurrences within the GTV; only 1 in the CTV in uninvolved nodes
- None of the stage IB-IIA cervix or stage IB-IIB endometrial patients relapsed in the pelvis
- However, longer follow-up and more patients needed to truly evaluate the impact of IMRT on tumor control

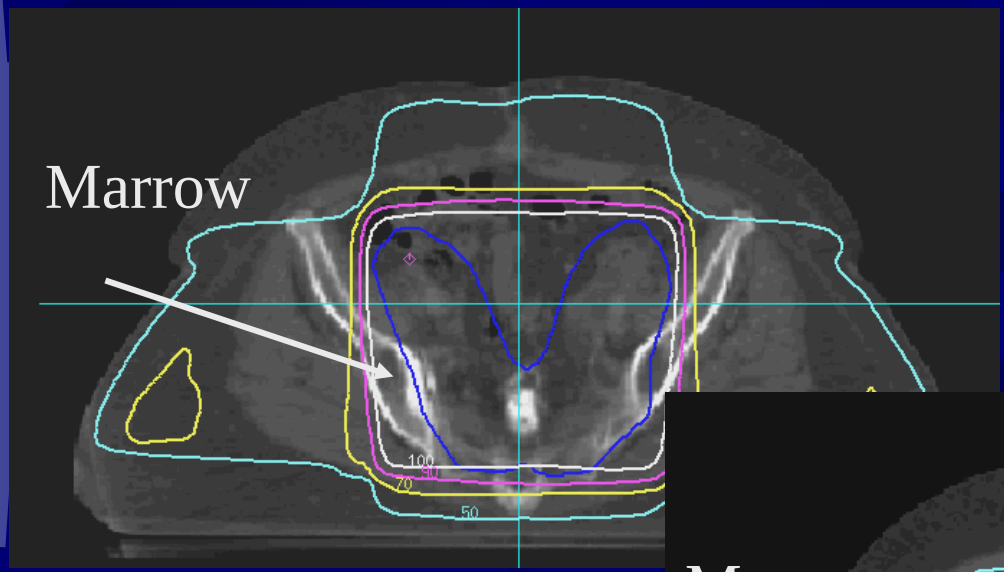
Future Directions

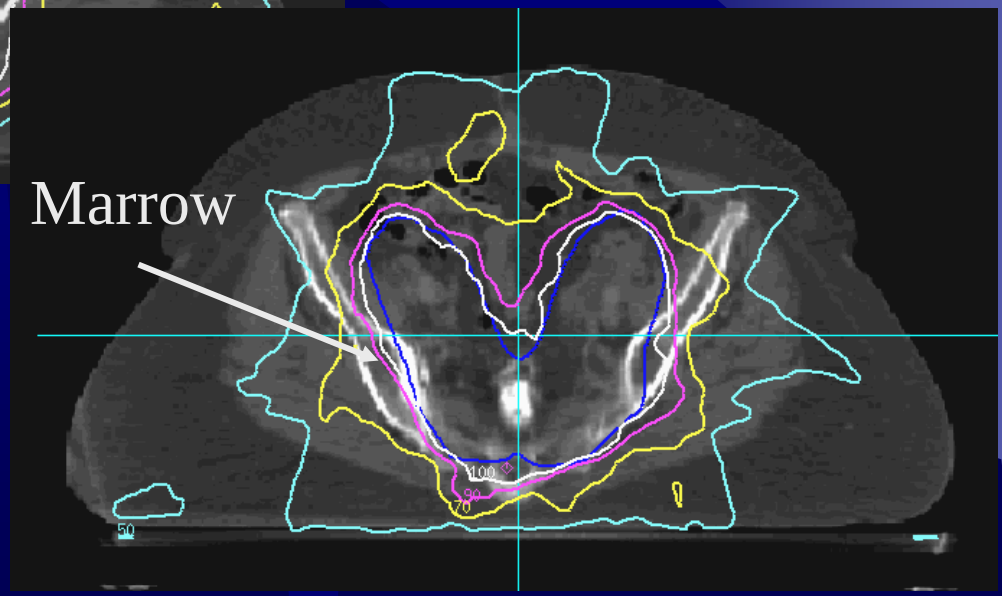
- Bone marrow sparing IMRT
- IGRT and adaptive radiotherapy in gynecologic IMRT
- IMRT as a replacement of brachytherapy

Gynecologic IMRT
Bone Marrow Sparing Approach

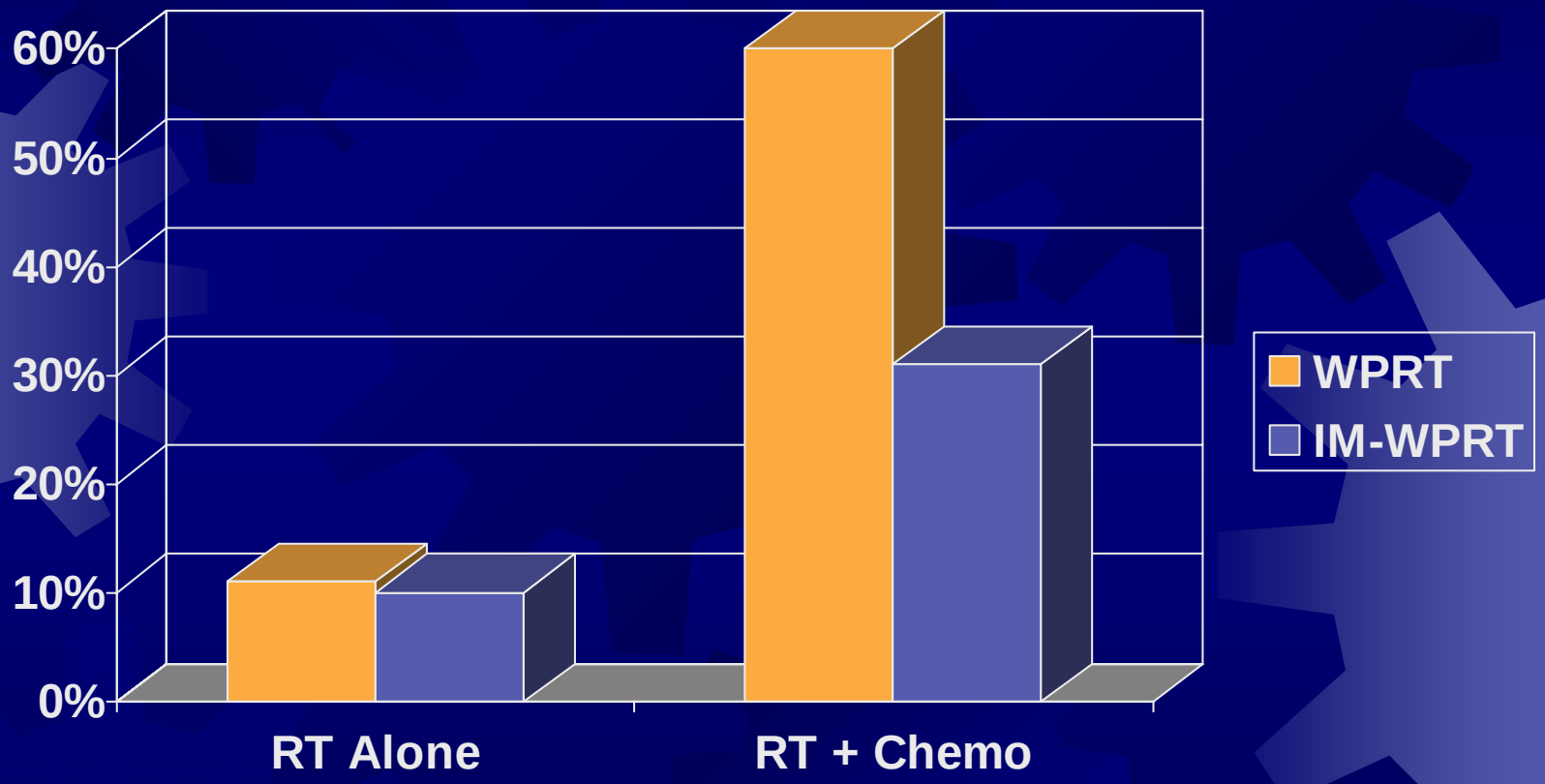
- Focus is on the small bowel and rectum
- Additional important pelvic organ is the bone marrow
- 40% total BM is in the pelvis (within the WPRT fields)
- ↓pelvic BM dose may ↑tolerance of concurrent chemotherapy and the chemotherapy at relapse

Increased Dose Conformity with IMRT Reduces Volume of Pelvic Bone Marrow Irradiated





Grade ≥ 2 WBC Toxicity WPRT versus IM-WPRT Patients



p = 0.82 *p* = 0.08

Brixey et al. *Int J Radiat Oncol Biol Phys* 52:1388-93, 2002

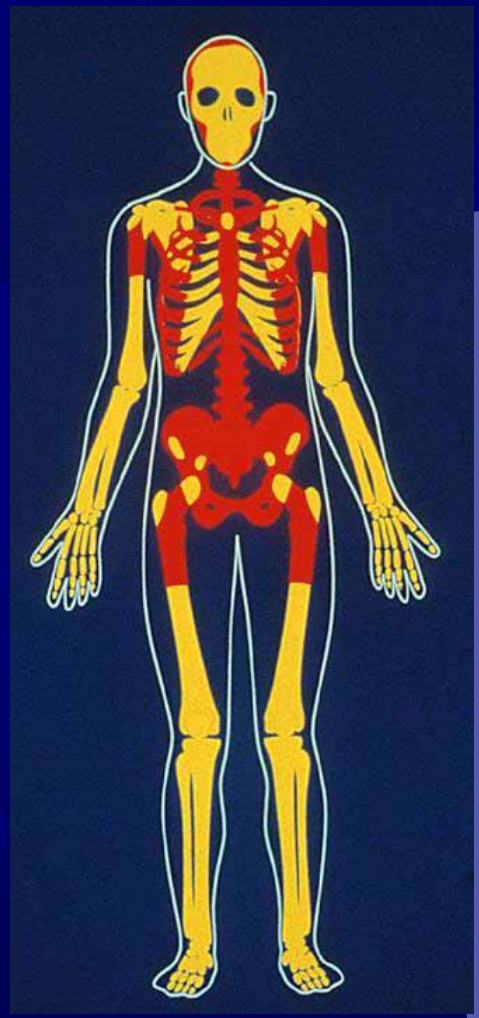
BM-Sparing IMRT

- Dosimetric analysis of factors associated with acute hematologic toxicity
- 37 cervical cancer pts treated with IM-pelvic RT plus CDDP (40 mg/m^2/week)
- Major predictors of hematologic toxicity:
  - Total pelvic BM V-10 and V-20
  - Lumbar sacral spine V-10
- Not volume of the iliac crests

Mell LK, Kochanski J, Roeske JC, et al.
Int J Radiat Oncol Biol Phys (In press)

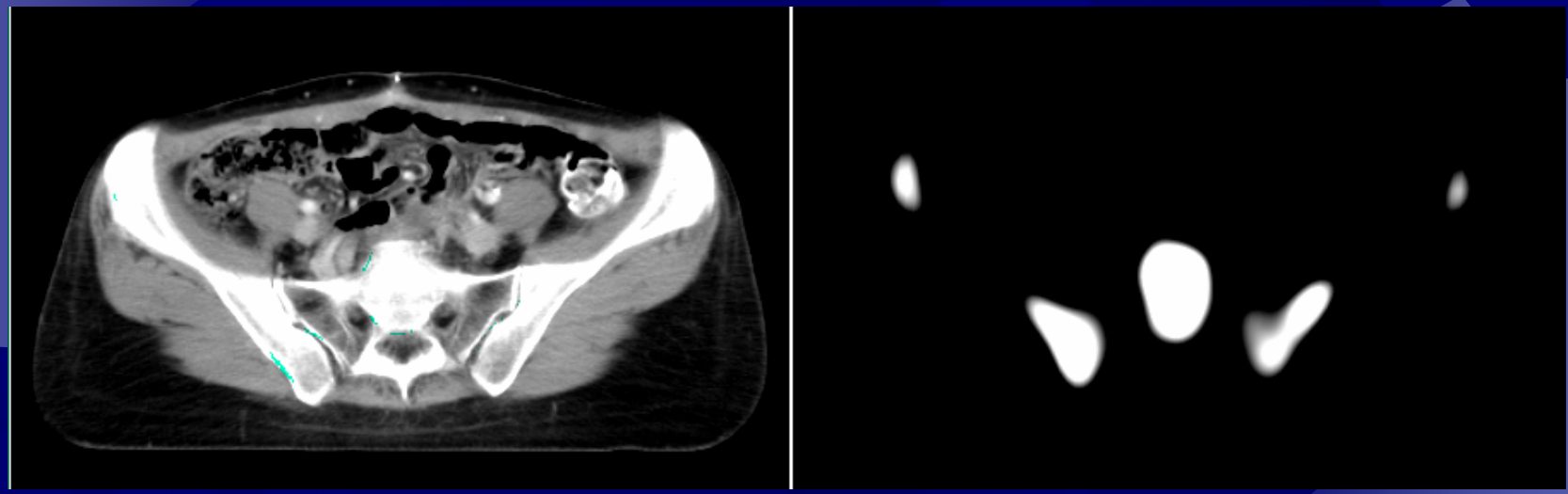
A Bone Marrow Primer for Physicists

- Two type of marrow:
  - Red Marrow – Active
  - Yellow Marrow - Inactive
- Nearly 40-50% of red marrow is located in the pelvis.
- Distribution of red marrow depends on age and sex.
- With age, conversion of red to yellow marrow occurs.



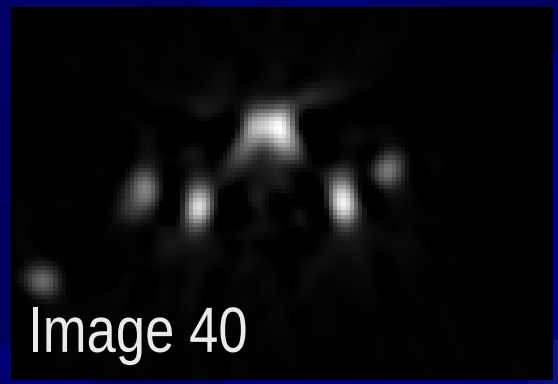
Functional Bone Marrow Imaging - SPECT

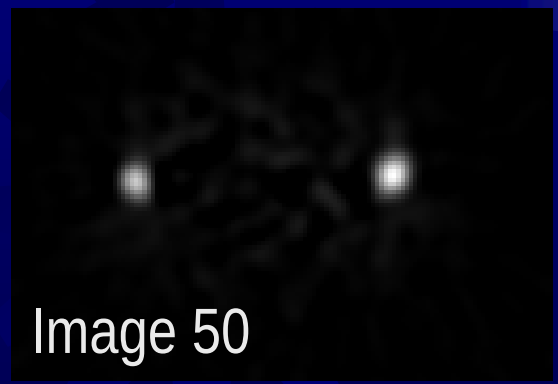
- Use Tc-99m sulfur colloid SPECT imaging to define active bone marrow



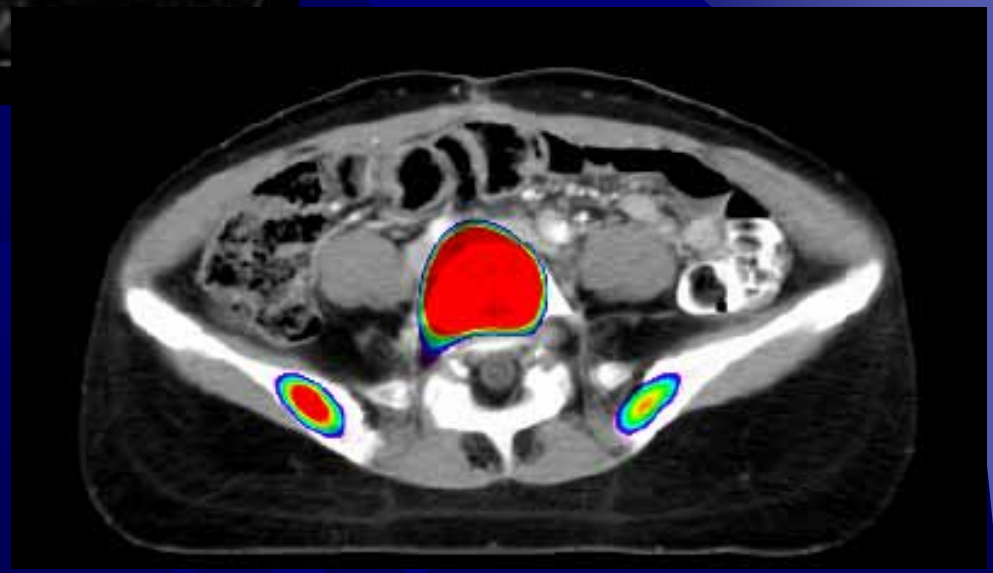
Roeske JC, Lujan AE, Reba R, et al. Radiother Oncol. 2005 Oct;77(1):11-7.

Tc-99m Bone Marrow Images

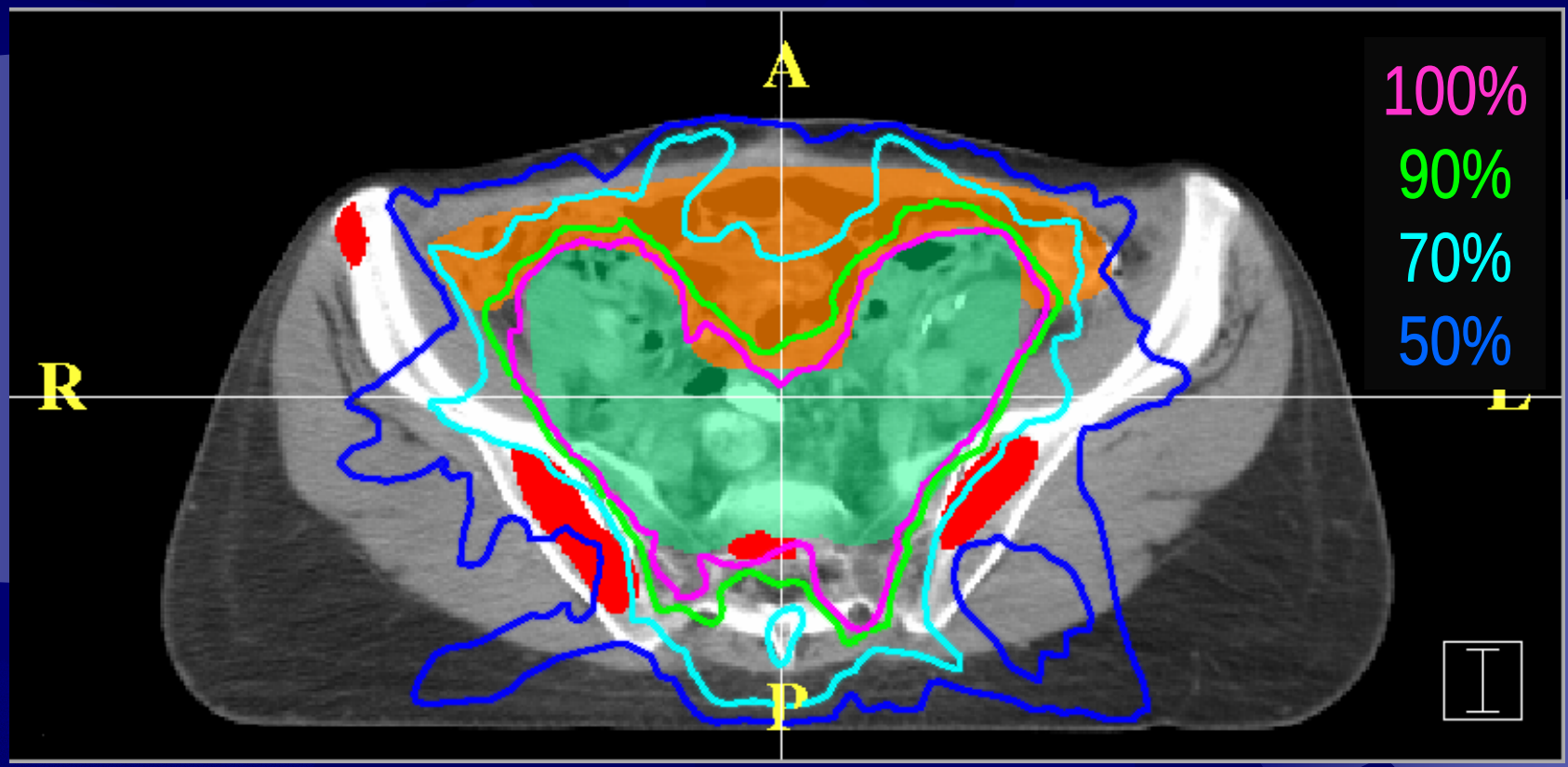




SPECT/CT Fusion



SPECT-based BM Sparing

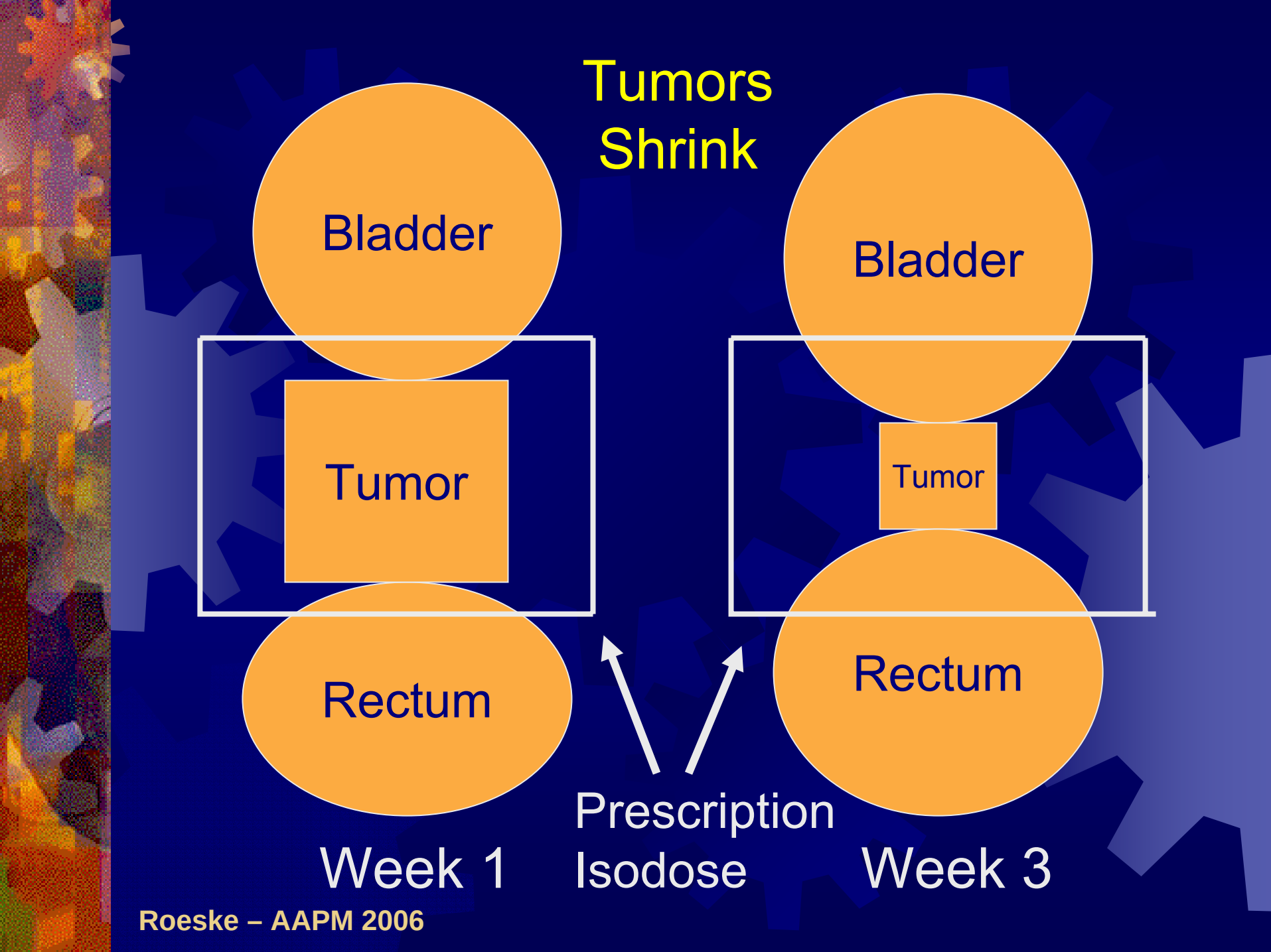


Bone Marrow Sparing

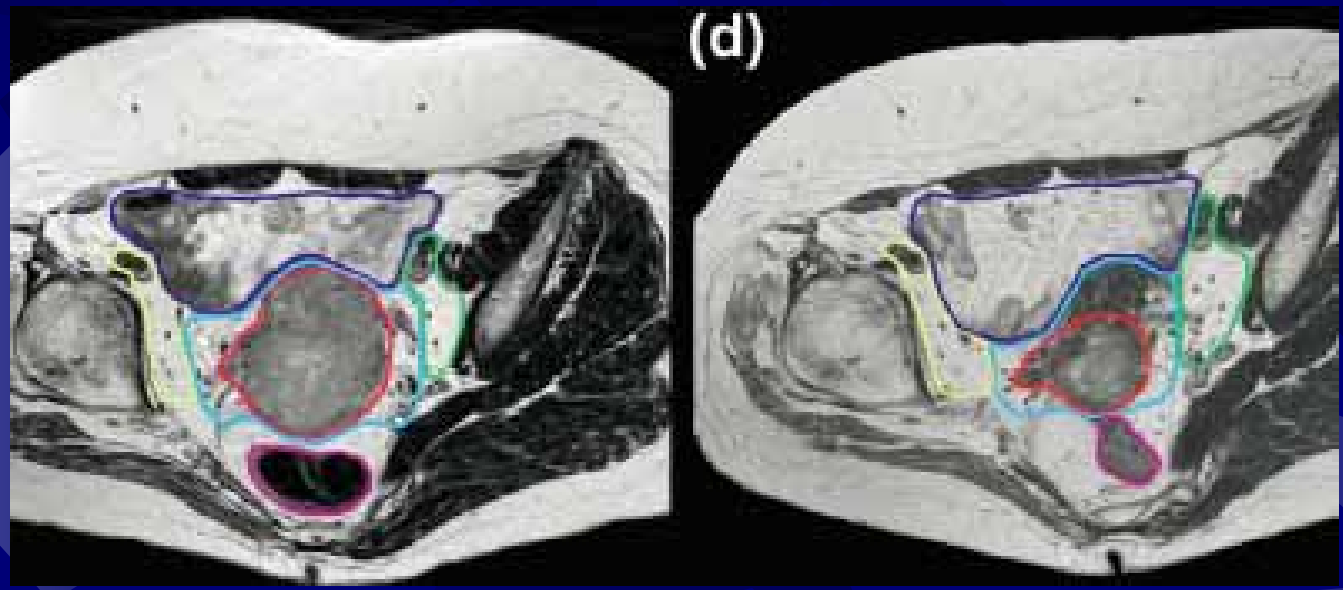
- Patients treated using IM-WPRT have a demonstrated reduction in AHT compared to patients treated with WPRT.
- Further improvements may be achieved by incorporating BM into the planning process.
- Functional BM imaging may have an important role for identifying areas of active BM.
- Future investigations are being designed to determine if functional BM imaging can reduce hematologic toxicities in these patients.

IGRT in Gynecologic IMRT

- Many cervical tumors rapidly shrink during RT (especially with concomitant chemotherapy)
- Tight margins (CTV-to-PTV expansions) early on may be too large by the end of treatment


Tumors
Shrink
Bladder
Tumor
Rectum
Bladder
Tumor
Rectum
Prescription
Isodose
Week 1
Week 3

Impact of Tumor Regression in Cervical Cancer Patients

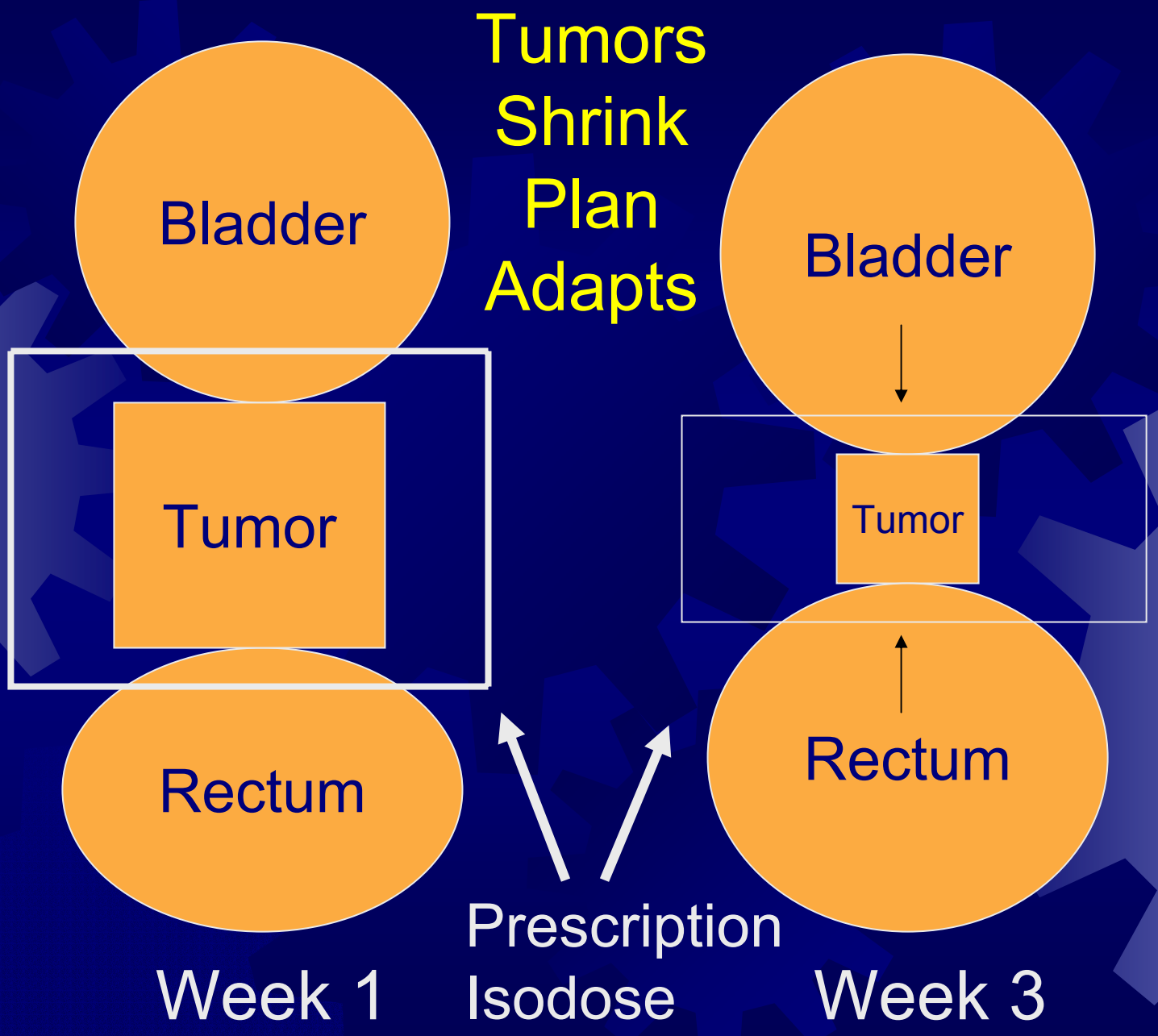


- 14 cervical cancer pts
- MRI before RT and after 30 Gy
- 46% ↓GTV

Van de Bunt et al. Int J Radiat Oncol Biol Phys 64(1):189-96, 2006.

IGRT/Adaptive RT

- IGRT techniques (cone beam CT) may allow plans to be adapted as tumors respond
- ↑ Bladder and rectal sparing
- No changes made in coverage of the parametrial tissues
- Also allow management of organ motion

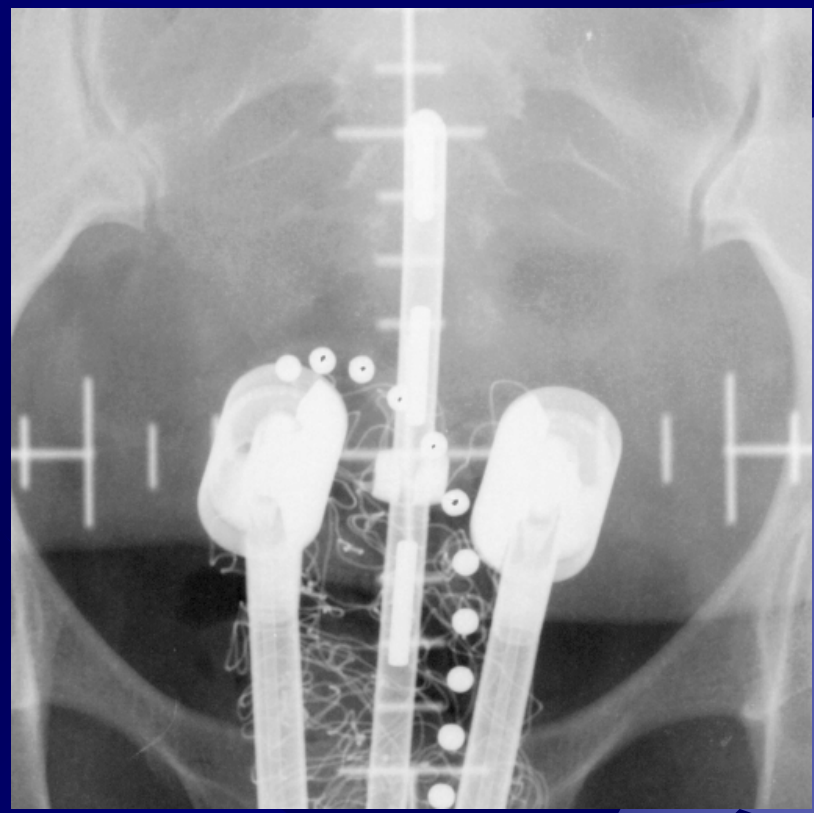

Tumors
Shrink
Plan
Adapts
Bladder
Tumor
Rectum
Bladder
Tumor
Rectum
Prescription
Isodose
Week 1
Week 3

IGRT/Adaptive RT

- University of California San Diego: Clinical trial in gynecology patients assessing
  - Feasibility of on-board imaging (cone beam CT) to improve delivery of IMRT plans
  - Impact of adapting treatment plans to tumor response

Can IMRT Replace ICB?

- IMRT has been used to reduce volume of normal tissues irradiated
- In selective sites (e.g., head and neck, prostate), IMRT has been used to deliver *higher* than conventional doses
- Can the same paradigm be applied to cervical cancer?



Stereotactic Boost Approach

- High dose rate brachytherapy (HDR-BT) boost to the vaginal vault for endometrial cancer or to the primary tumor in cervical cancer are current treatment approaches in gynecologic oncology.
- Goal: To challenge this paradigm by using high-precision extracranial stereotactic radiotherapy with the *Novalis*.

Molla et al. Int J Radiat Oncol Biol Phys 62: 118-24, 2005.

Patient Immobilization

- Customized vacuum body cast
- A stereoatactic extracranial infrared guided repositioning system *(ExacTrac, BrainLAB)*
- MRI endorectal probe inflated with 60 cc air (for internal immobilization)

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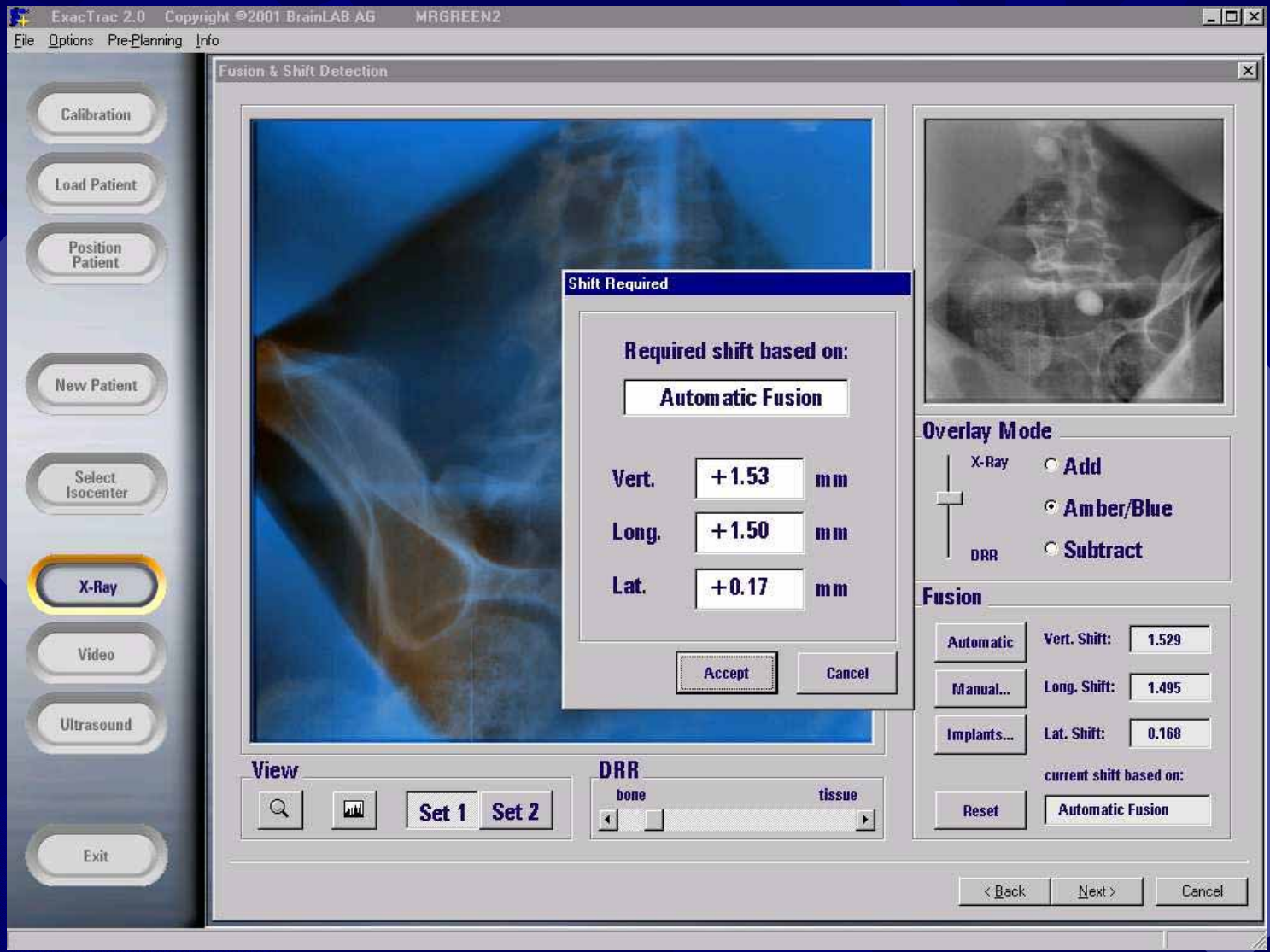
Image Fusion of Bony Landmarks



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Improvement of the PTV margins with bone registration

	Body markers →	Bones
X (Rt-Lt):	9.0	5.1
Y (A-P):	8.0	6.0
Z (Sup-Inf):	6.4	3.1

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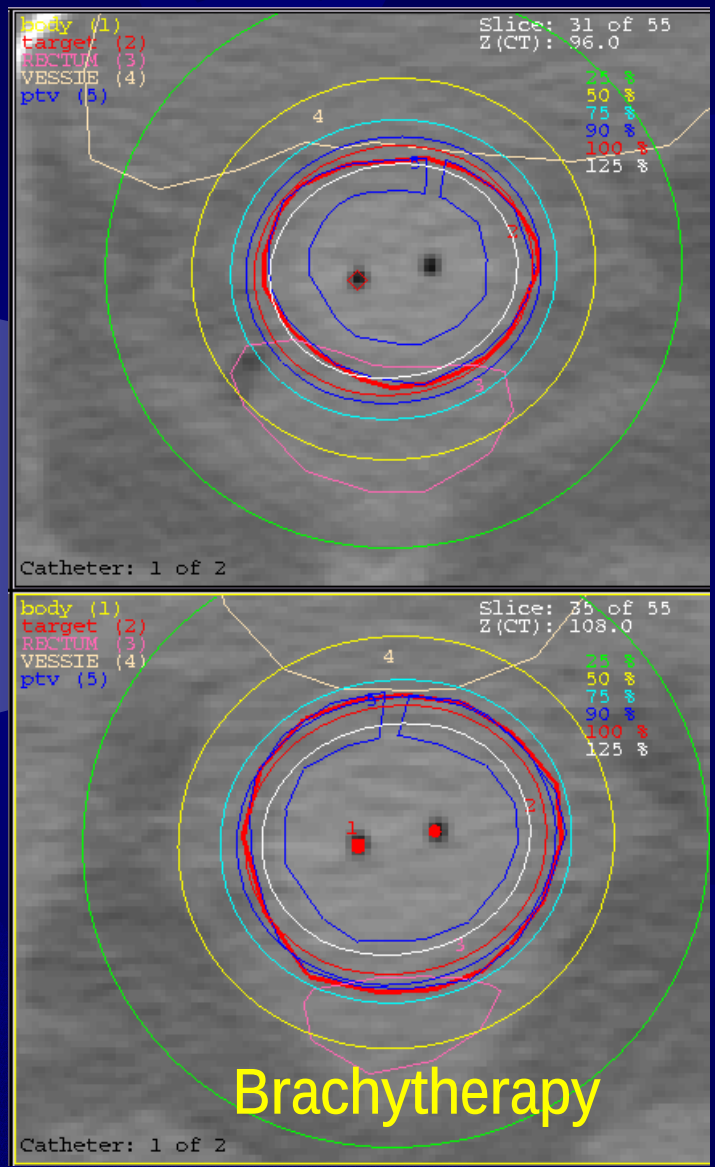
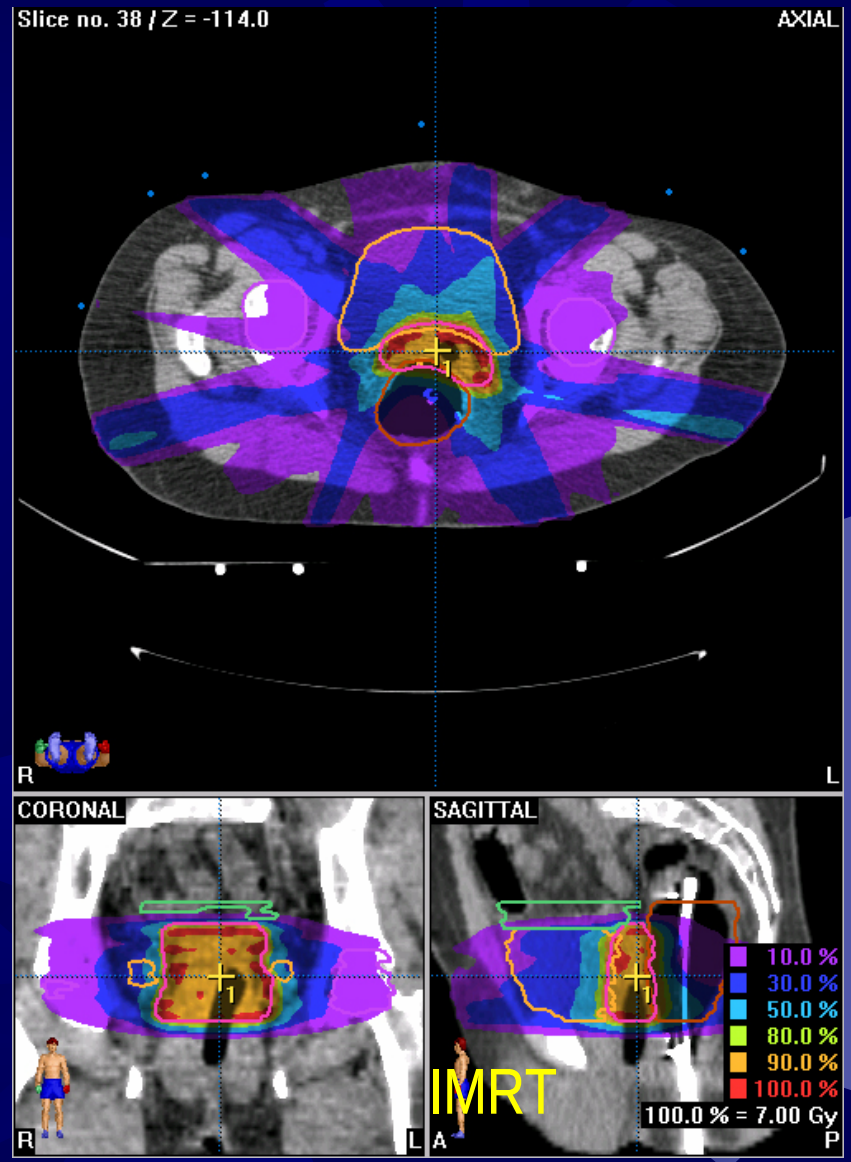
Planning Comparison





Preliminary Results

- Treated 21 women with either cervical (9) or endometrial cancer (12)
- Use of this approach to deliver final boost to areas of high risk (vaginal vault, parametria, cervix, etc.) was feasible, well-tolerated and an acceptable alternative to HDR-BT

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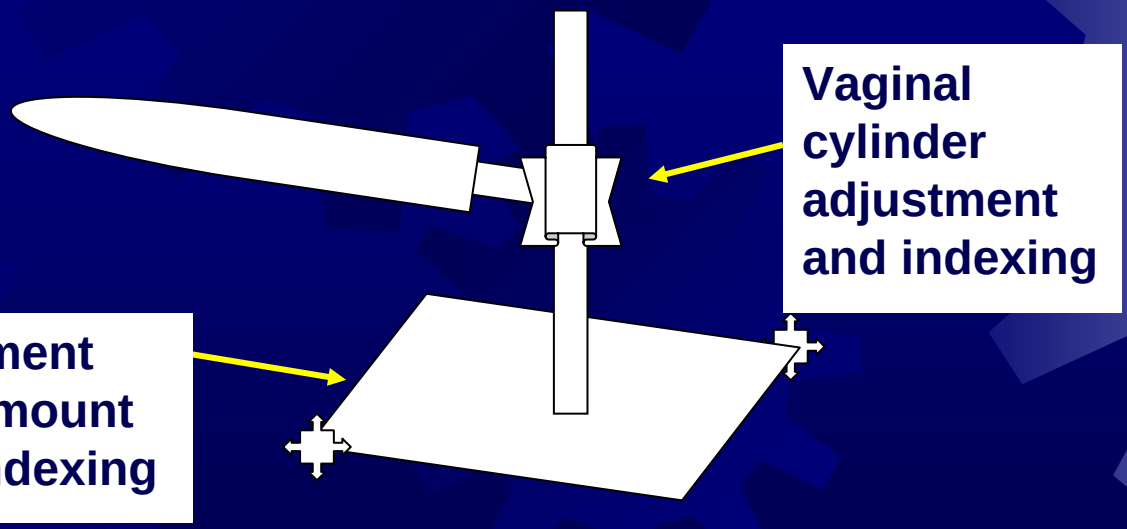
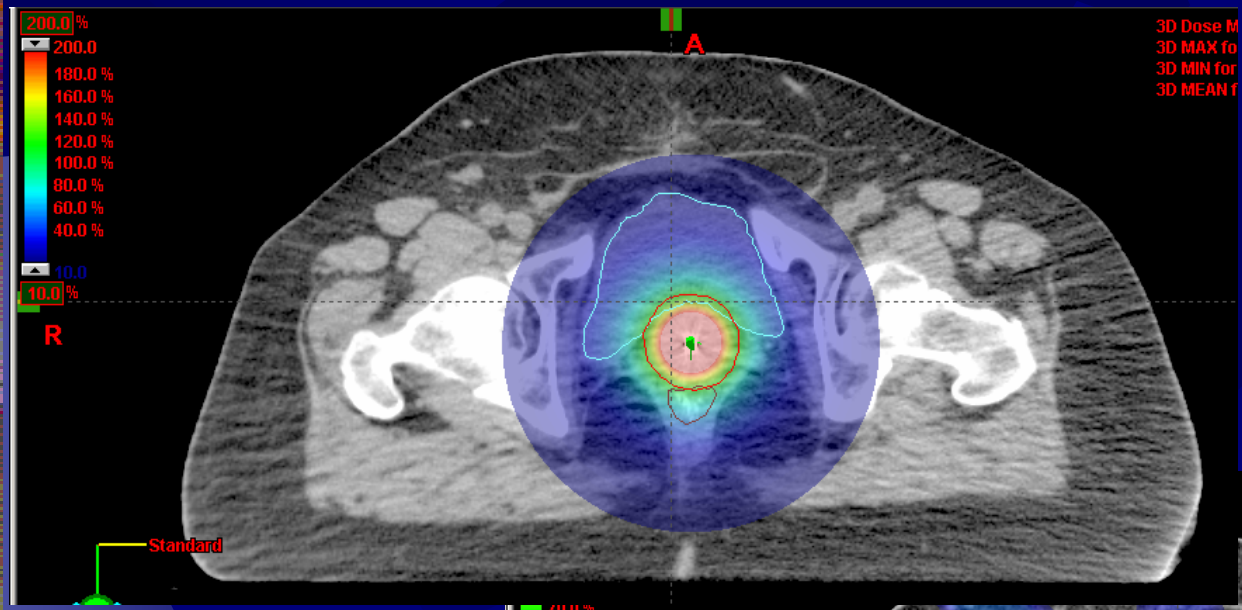
Vaginal Immobilization Device

- Early stage endometrial cancer treated with whole pelvic RT and vaginal (cylinder) HDR
- Goal: Use vaginal cylinder-type immobilization device and IMRT

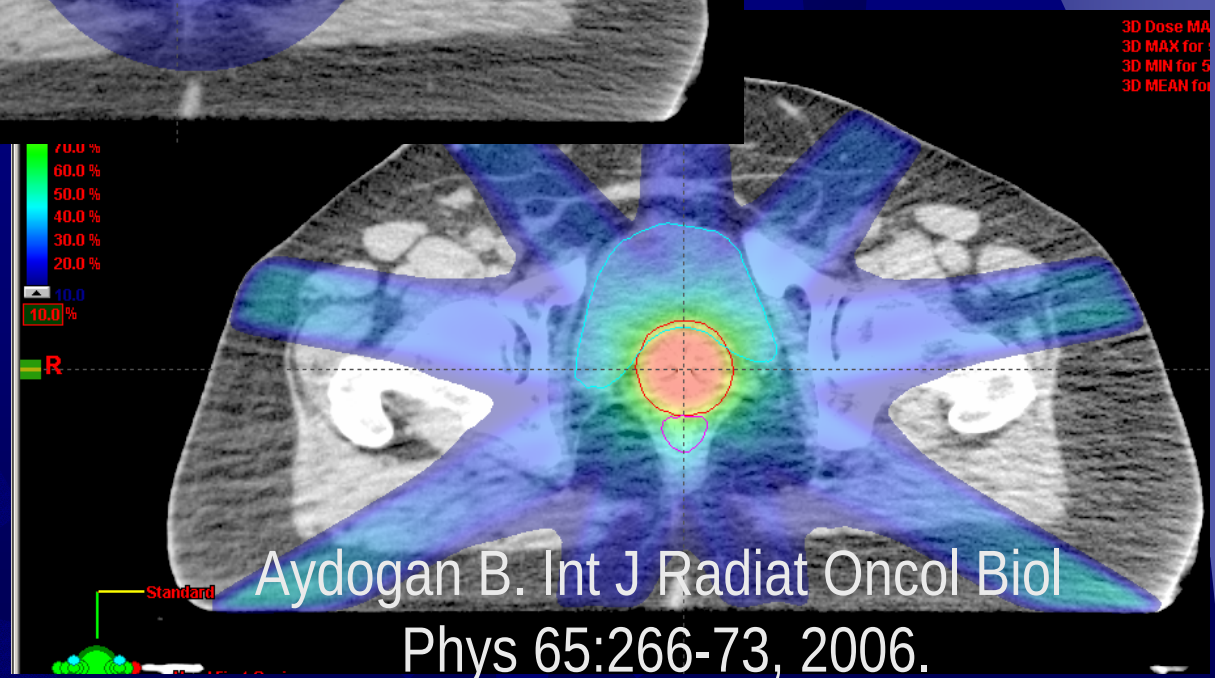


B Aydogan, PhD – Univ of Chicago

Comparison of HDR vs. IMRT



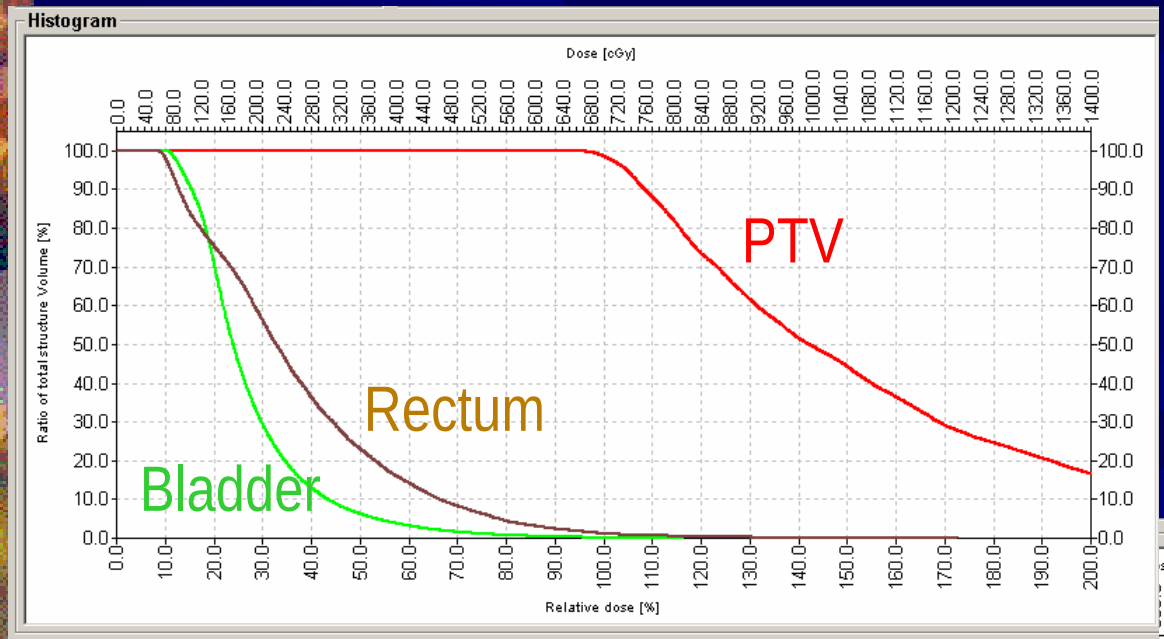
HDR



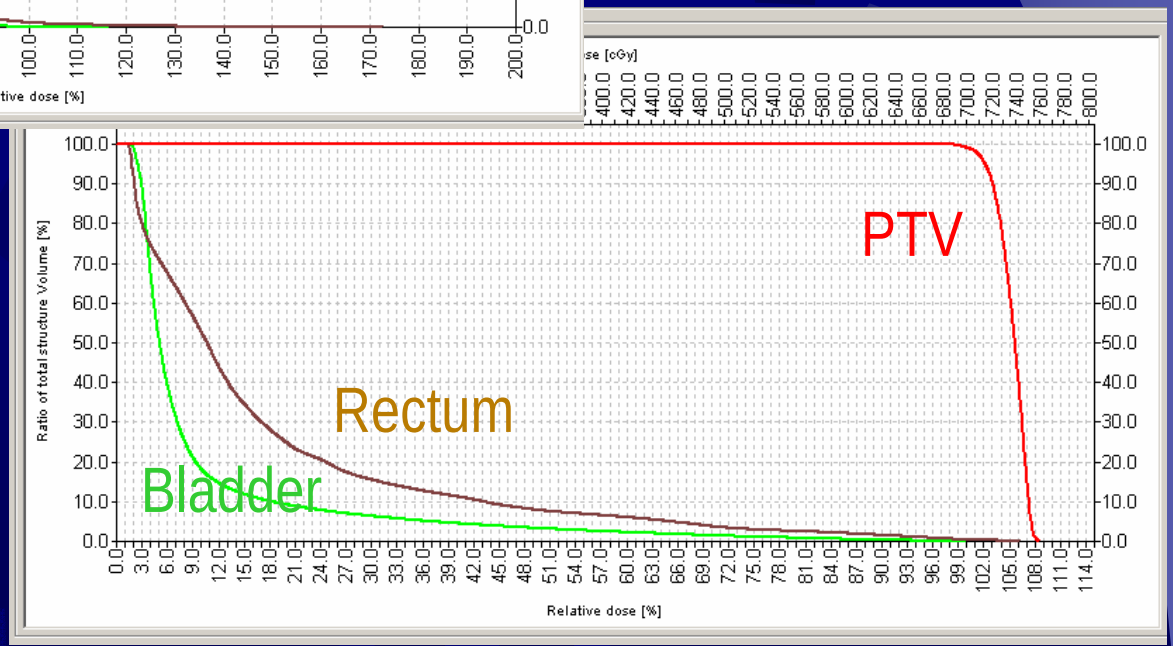
IMRT

Aydogan B. Int J Radiat Oncol Biol Phys 65:266-73, 2006.

Comparison of HDR vs. IMRT



HDR



IMRT

IMRT vs. HDR

- Maximum rectal doses lower with IMRT vs. HDR (89% vs. 143%, $p < 0.05$)
- Mean rectal doses in IMRT also lower than HDR (14.8% vs. 21.4%, $p < 0.05$)
- IMRT also resulted in lower maximum bladder doses (66.2% vs. 74.1%, $p < 0.05$)
- Plans provided comparable coverage to the PTV with IMRT plans resulting in less dose heterogeneity

B Aydogan, PhD – Univ of Chicago

IMRT in Women Unable to Receive Brachytherapy

- Definitive radiotherapy (RT) for cervical cancer relies on intracavitary brachytherapy (ICB) for the final tumouricidal boost.(Grigsby et al. 1991, Coia et al. 1990)
- About 5 – 10% of these patients are not able to receive ICB.(Bachtiary et al. 2005, Eifel et al 1999)
- Delivery of external beam RT boost is limited by normal tissue tolerance.
  - Limiting the boost dose << 40 Gy. (20 - 30)

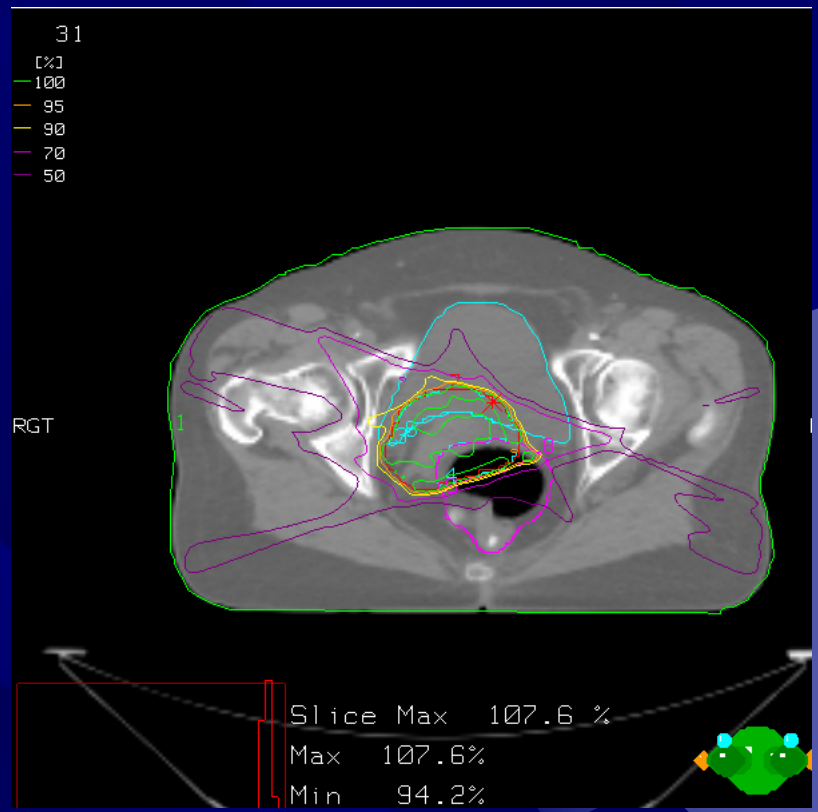
P Chan, MD – Princess Margaret

Analysis

- 12 patients who received CRT boost post large pelvic RT (2001-2003) were retrospectively analyzed.
  - RTOG Toxicity graded.
- The planning target volume (PTV) were as contoured in the original CRT plans.
  - Gross tumour volume (GTV) - the proximal vagina/cervix.
  - Clinical target volume (CTV) = GTV + 10/7 mm margin and clinician modification.
  - PTV = CTV + 5 mm.
- Organs at risk (OAR) - Bladder, rectum, and remaining bowel
- Compared IMRT vs. conventional planning.

P Chan, et al. Radiat Oncol 1:13, 2006.

Comparison of Conventional vs. IMRT Planning



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Dosimetric Impact of IMRT

- IMRT improves PTV conformation by 20%.
- IMRT reduces volume of rectum (22%) and bladder (19%) receiving the highest doses (>66% of prescription).
- However, IMRT increases volume of tissue receiving lower doses which raises the issues of increased secondary cancer risk. (Hall et al. 2003)

P Chan, MD – Princess Margaret

Future Studies

- Prospective IMRT boost trial for gyne-oncology patients not suitable for ICB – GY03.2
  - 7 patients accrued – all tolerated treatment well.
- A 4 mm margin for cervix movement if daily online imaging is available.
  - Daily online soft tissue imaging.
  - Fiducial marker.
- Dose escalation towards ICB dose.

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Can an IMRT-SIB boost be useful?

- Intracavitary brachytherapy (ICB) may not adequately treat bulky tumors
- ICB may not be efficient in cases where the tumor geometry and patient anatomy make application difficult

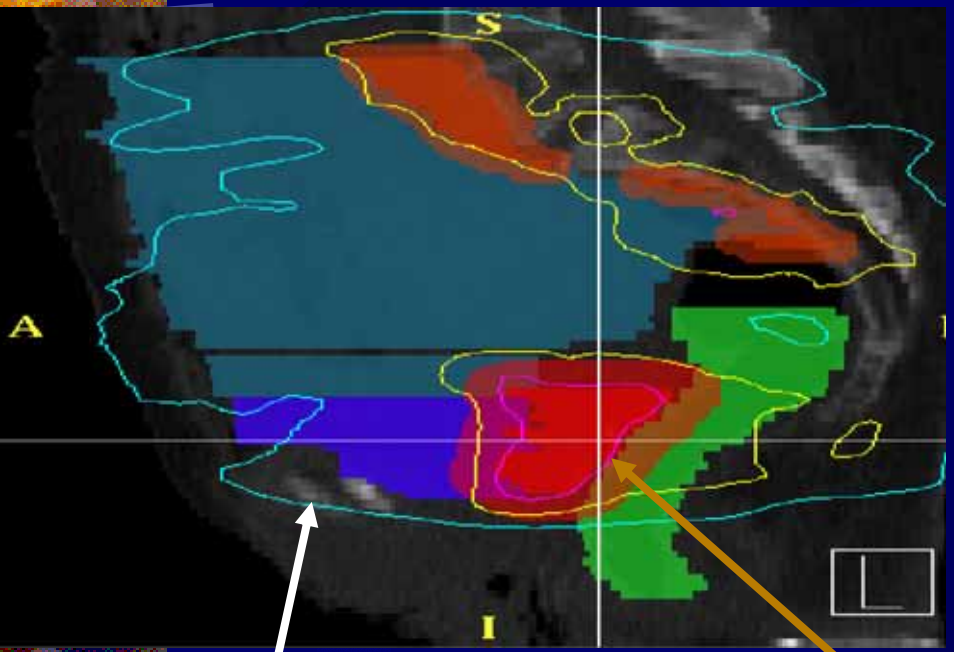
Guerrero M, et al. Int J Radiat Oncol Biol Phys 62(3):933-39, 2005.

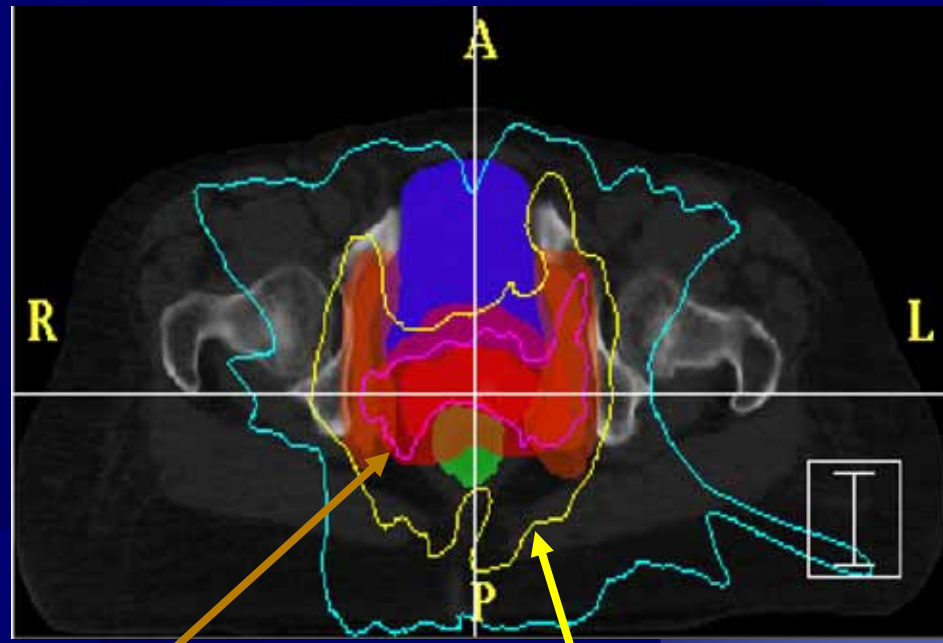
IMRT SIB boost

	Whole Pelvis	Boost	BED Tumor	BED Normal
Conv	45 Gy in 1.8Gy/fr	40 Gy (2 LDR)	78.6	139.3
IMRT1	45 Gy in 1.8Gy/fr	28 Gy in 2.9 Gy/fr	78.6	145.0
IMRT2	45 Gy in 1.8Gy/fr	26 Gy in 2.8Gy/fr	75.6	139.3

X. Allen Li, PhD – Med Col of Wisconsin

IMRT-SIB Planning Approach





20 Gy

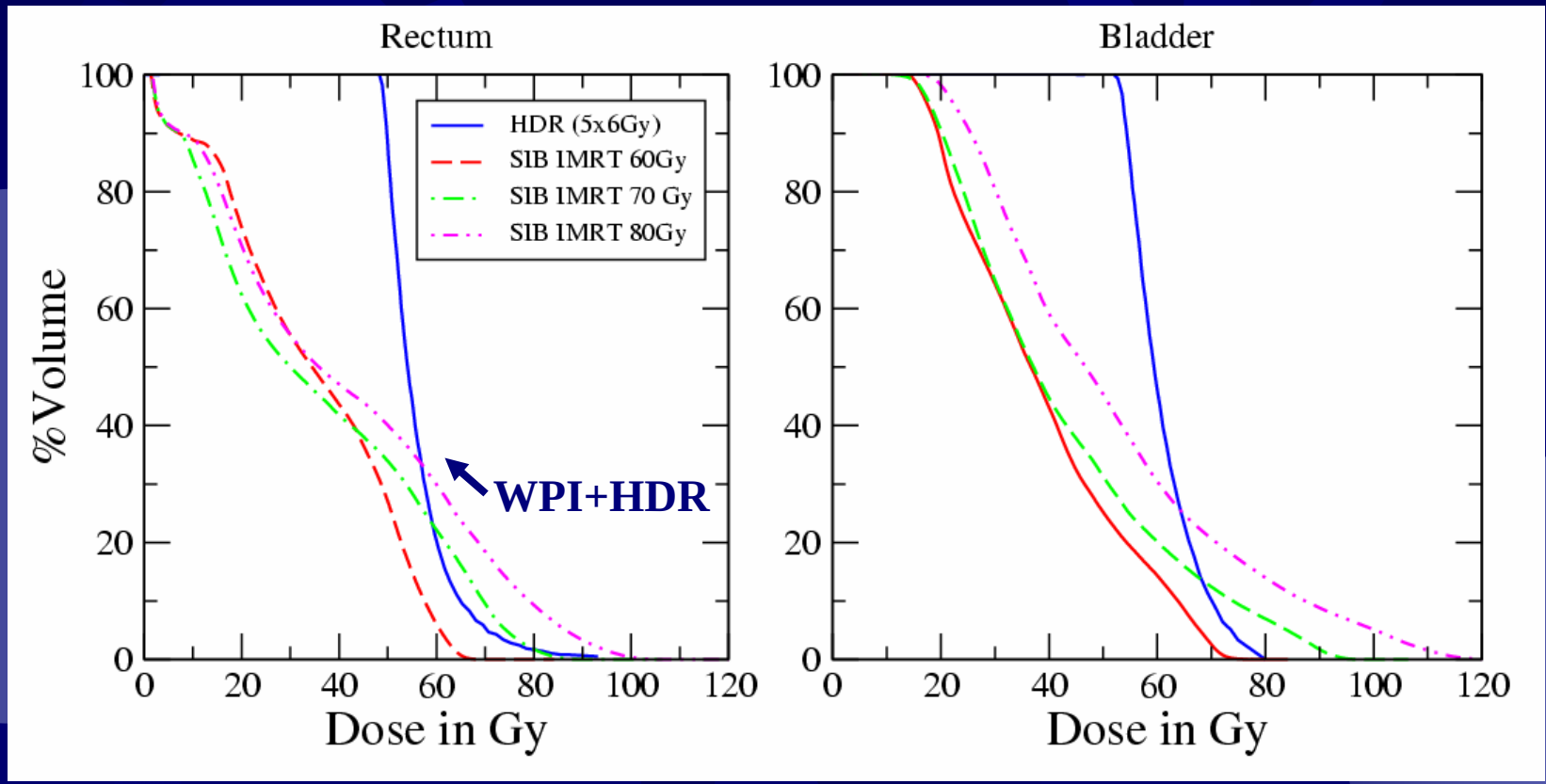
60 Gy

25 x 2.4 Gy

45 Gy

25 x 1.8 Gy

DVH Comparison



- Target coverage ranged from 94-95.5%
- Bladder and rectum doses reduced using 60-70 Gy SIB treatment

Conclusions

- IMRT is a useful means of reducing the volume of normal tissues irradiated in gynecologic patients receiving WPRT
- Our initial evaluation indicate a significant reduction in GI toxicity relative to patients receiving conventional therapy
- Continued follow-up and critical evaluation are required to validate the long term merits of this approach

What about the negatives?

- IMRT results in higher volumes of normal tissue receiving lower doses
- Increased MUs result in higher total body doses
- Target and tissue delineation are *time-consuming*
- Few guidelines exist regarding *how* targets should be contoured and plans optimized
- *Long-term* follow-up is not available assessing tumor control and *unexpected* sequelae
- Clinical data are available from only one institution and while prospective no randomized comparisons have been performed