Tailored radiation therapy: IMRT/Proton therpay

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Techniques in RT

Brachytherapy

Radioactive isotope

Tele-therapy

Accelerator

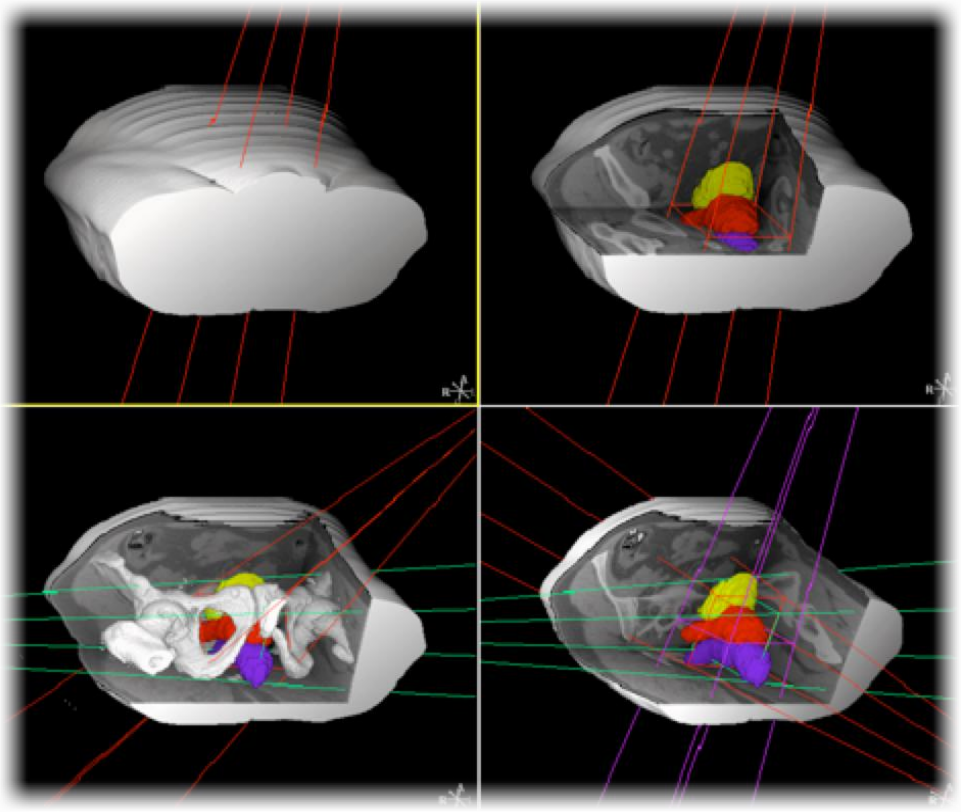
2D RT

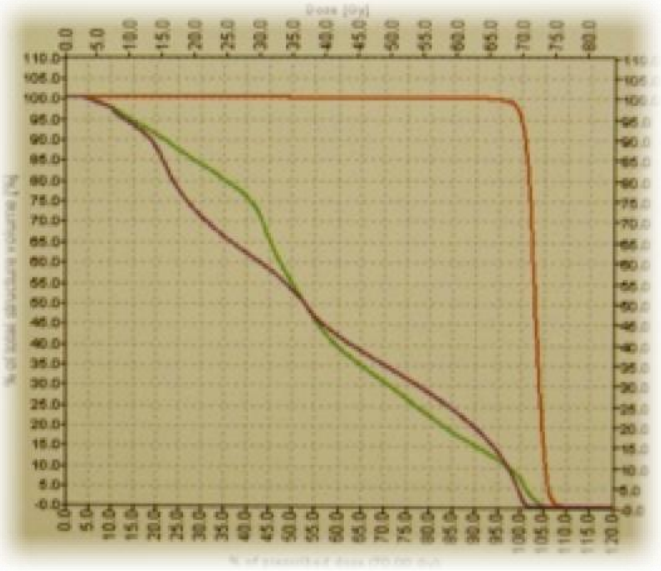
3D CRT

IMRT

Proton therapy

3D Conformal RT

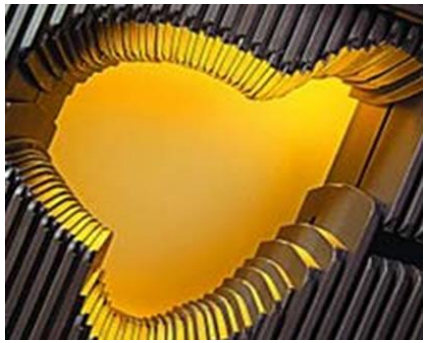




- Using CT images, multiple beam of various angle is arranged to irradiate
- DVH (Dose Volume Histogram) is useful to evaluate the dose distribution
- Irradiated dose to target volume and OAR is measureable quantitatively

IMRT

Intensity Modulated RT
Multi-Leaf Collimator
Intensity Modulation



http://www.cancercenter.com/

- Use of intensity-modulated beams that can provide two or more intensity for any angle beam direction
- Generate concave dose distributions and dose gradients with narrow margins
- Increase tumor control through escalated dose and reduce normal tissue complication through organs at risk sparing

IMRT survey in US

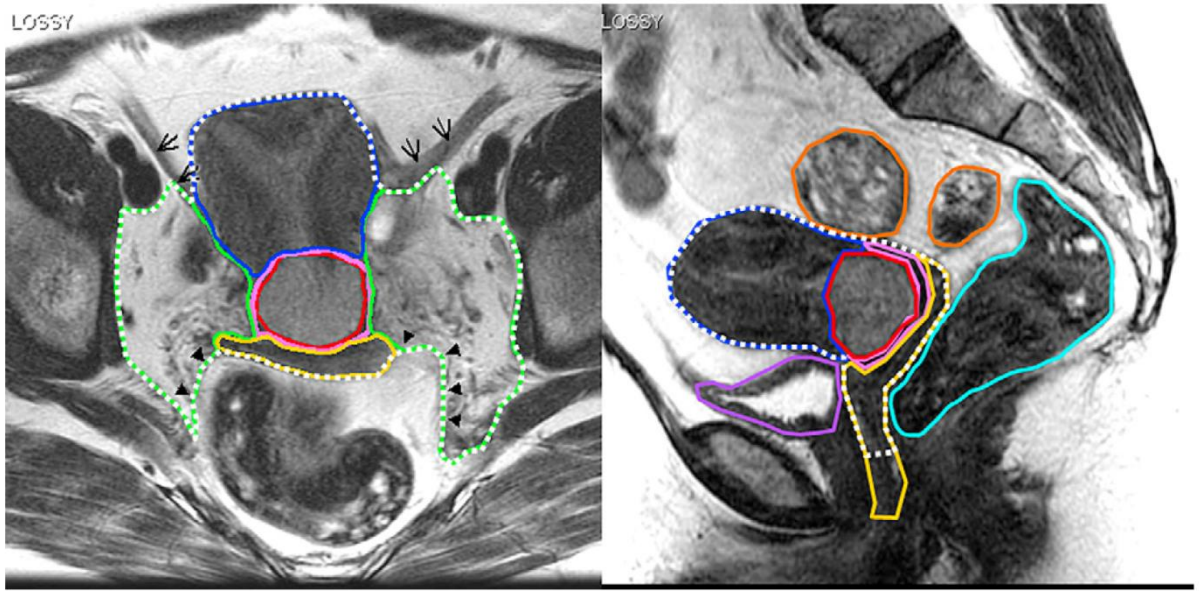
- IMRT utilization

Variable	No. of academics (%)	No. in private practice (%)	Total (%)	*P* value
Disease sites treated				
Genitourinary	28 (60.9)	119 (93.0)	147 (84.5)	< 0.01
Head and neck	35 (76.1)	105 (82.0)	140 (80.5)	0.38
Central nervous system	32 (70.0)	85 (66.4)	117 (67.2)	0.70
Gynecology	12 (26.1)	35 (27.3)	47 (27.0)	0.87
Breast	12 (26.1)	34 (26.6)	46 (26.4)	0.95
Gastrointestinal	13 (28.3)	33 (25.8)	46 (26.4)	0.74
Lung	12 (26.1)	20 (15.6)	32 (18.4)	0.12
Sarcoma	8 (17.4)	22 (17.2)	30 (17.2)	0.97
Pediatrics	14 (30.4)	8 (0.6)	22 (12.6)	< 0.01
Lymphoma	5 (10.9)	16 (12.5)	21 (12.1)	0.77
Other	3 (6.5)	2 (1.6)	3 (1.7)	0.08

Mell et al. Cancer 2005

Target delineation

- RTOG consensus for definitive treatment



Red: GTV

Pink: cervix

Blue: uterus

Yellow: vagina

Green: parametrium

Purple: bladder

Light blue: rectum

Orange: sigmoid

Dashed white line: CTV

- Clinical Target Volume

  Gross tumor

  Cervix: entire cervix

  Uterus: entire uterus

  parametrium: entire parametrium, including ovaries

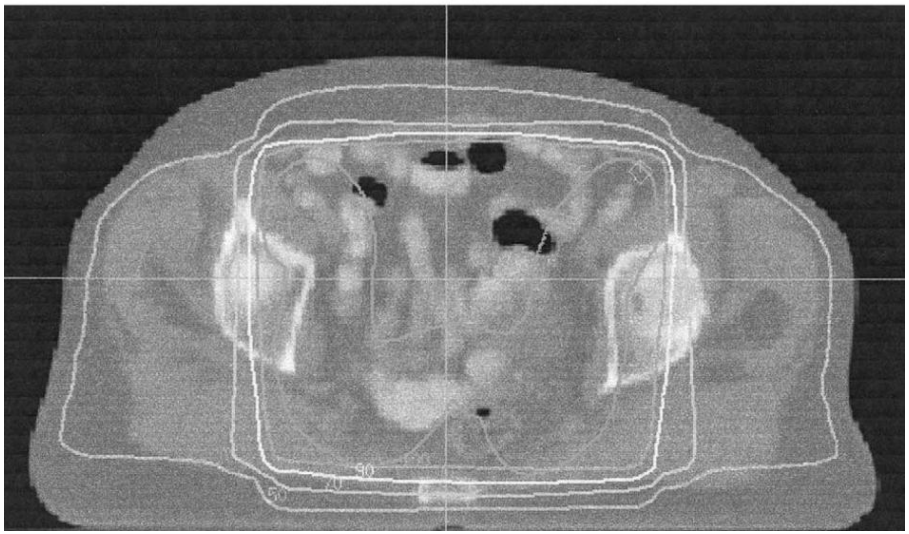
  vagina: upper half to entire vagina according to tumor extent

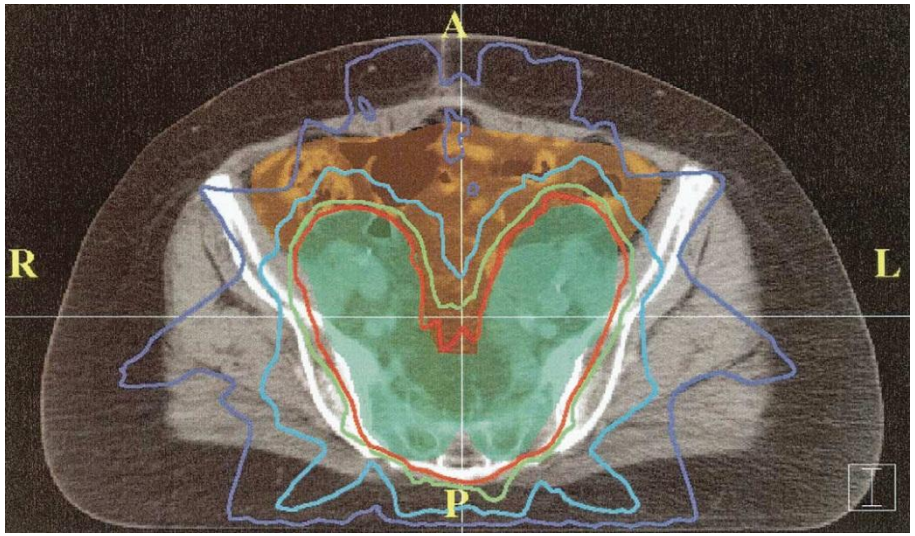
  pelvic nodes: common, internal, external, obturator, presacral

Lim et al. Int J Radiat Oncol Biol Phys 2010

IMRT

- 40 gynecology patients, 2000-2001
- IM-WPRT 45 Gy + ICR 20-25 Gy to vaginal surface or 30-40 Gy to point A using LDR
- 35 previous treated conventional WPRT patients

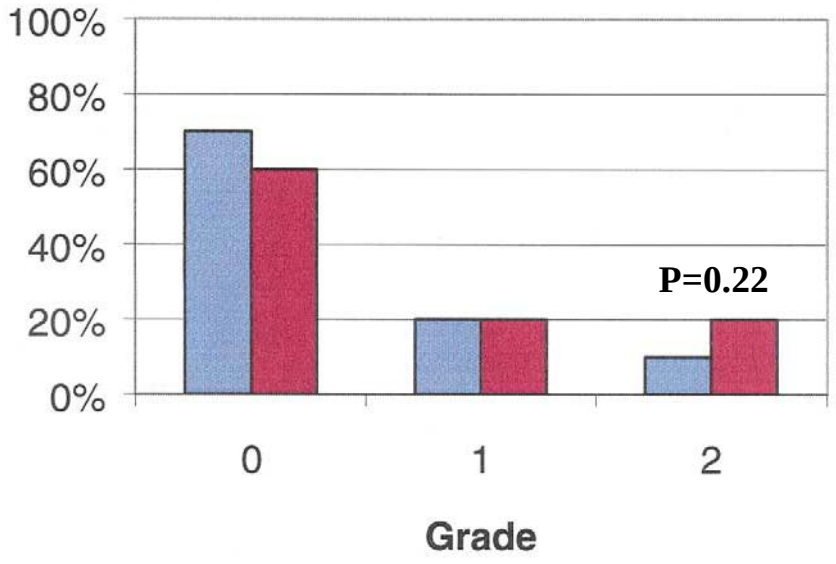




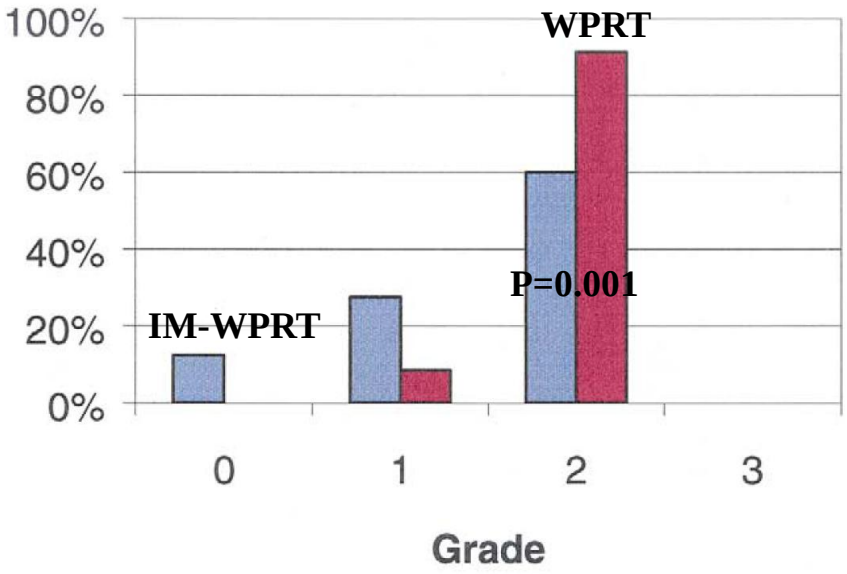
Mundt et al. Int J Radiat Oncol Biol Phys 2002

IMRT

Acute GU toxicity



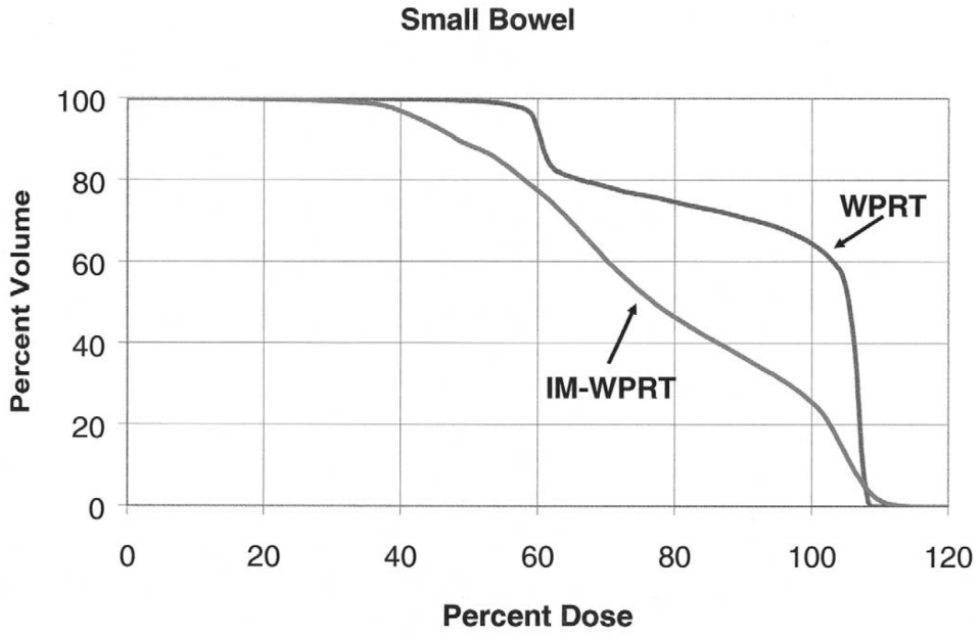
Acute GI toxicity

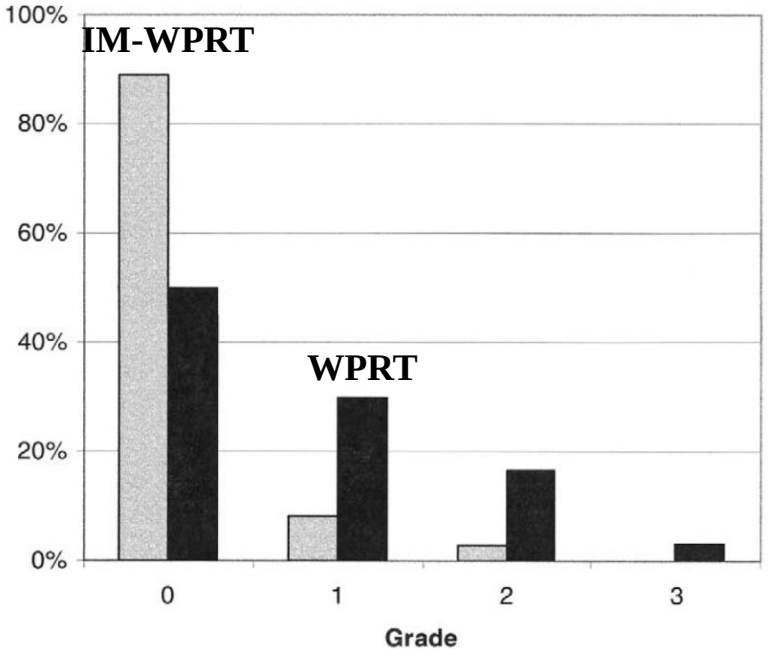


Mundt et al. Int J Radiat Oncol Biol Phys 2002

IMRT

Chronic GI toxicity





Mundt et al. Int J Radiat Oncol Biol Phys 2003

IMRT

- 68 high risk cervix cancer patients, 2002-2006
- Hysterectomy, followed by CCRT
- 33 patients: IMRT

  35 patients: Box-RT

Table 4. Summary of dose–volume histogram statistics for rectum, bladder, and small intestine

	Rectum			Bladder			Small intestine		
	Box-RT	IMRT		Box-RT	IMRT		Box-RT	IMRT	
D_{mean} (Gy)	52.4 ± 1.0	44.35 ± 3.5	$p < 0.001$	52.84 ± 0.9	47.15 ± 3.33	$p < 0.001$	44.79 ± 5.5	32.52 ± 2.8	$p < 0.001$
$V_{100\%}$ (%)	95.5 ± 5.5	34 ± 16	$p < 0.001$	97 ± 3	52 ± 20	$p < 0.001$	53 ± 25	4 ± 3	$p < 0.001$
$V_{90\%}$ (%)	98 ± 2	58 ± 16	$p < 0.001$	99 ± 1	70 ± 18	$p < 0.001$	64 ± 21	12 ± 6	$p < 0.001$
$V_{70\%}$ (%)	99.4 ± 0.6	83 ± 14	$p < 0.001$	99.5 ± 0.5	89 ± 10	$p < 0.001$	75 ± 18	35 ± 11	$p < 0.001$
$V_{50\%}$ (%)	100 ± 0	98 ± 1.5	$p = 0.01$	99.9 ± 0.1	99 ± 0	$p = 0.064$	93 ± 5	78 ± 12	$p < 0.001$

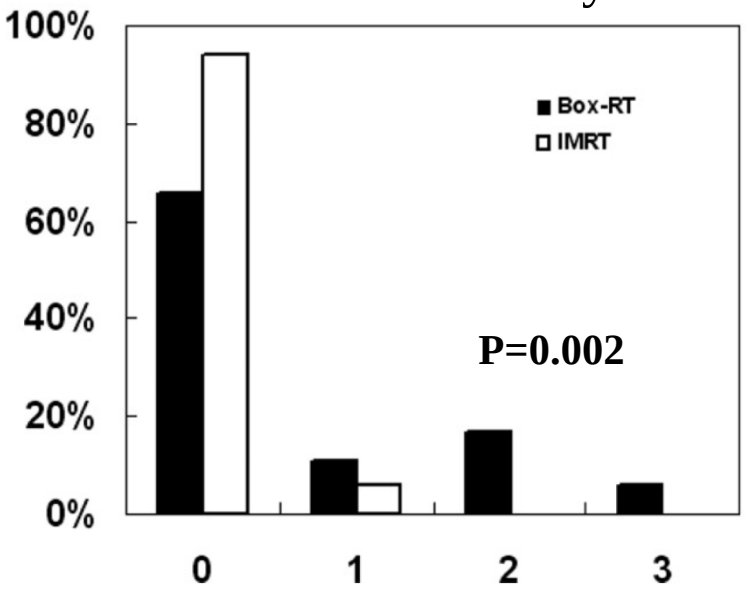
Chen et al. Int J Radiat Oncol Biol Phys 2007

IMRT

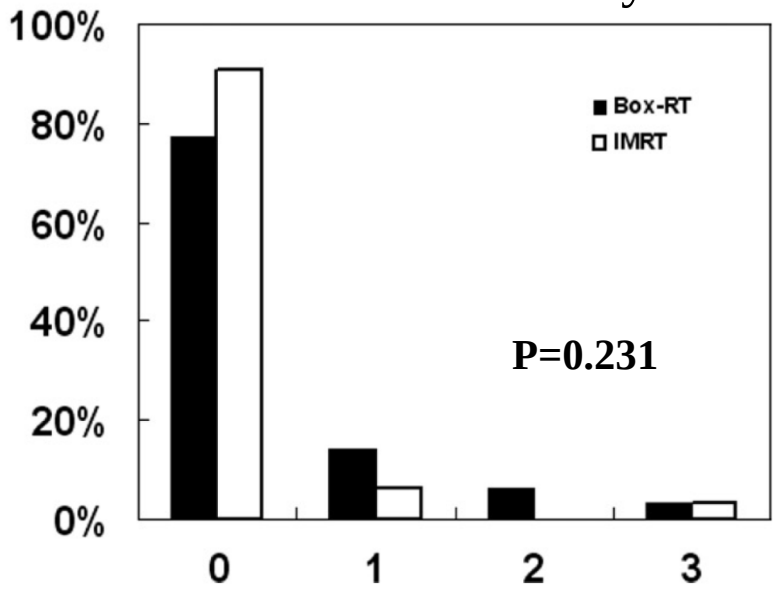
Table 2. Acute toxicities in Box-RT and IMRT patients

	GI (%)		GU (%)		Hematologic (%)	
Acute Grade	Box-RT	IMRT	Box-RT	IMRT	Box-RT	IMRT
0	7 (20%)	21 (64%)	14 (40%)	23 (70%)	16 (46%)	14 (43%)
1	8 (23%)	4 (12%)	12 (34%)	6 (18%)	5 (14%)	8 (24%)
2	20 (57%)	8 (24%)	9 (26%)	4 (12%)	11 (31%)	9 (27%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (9%)	2 (6%)
	P=0.00012		**P=0.022**			

Chronic GI toxicity



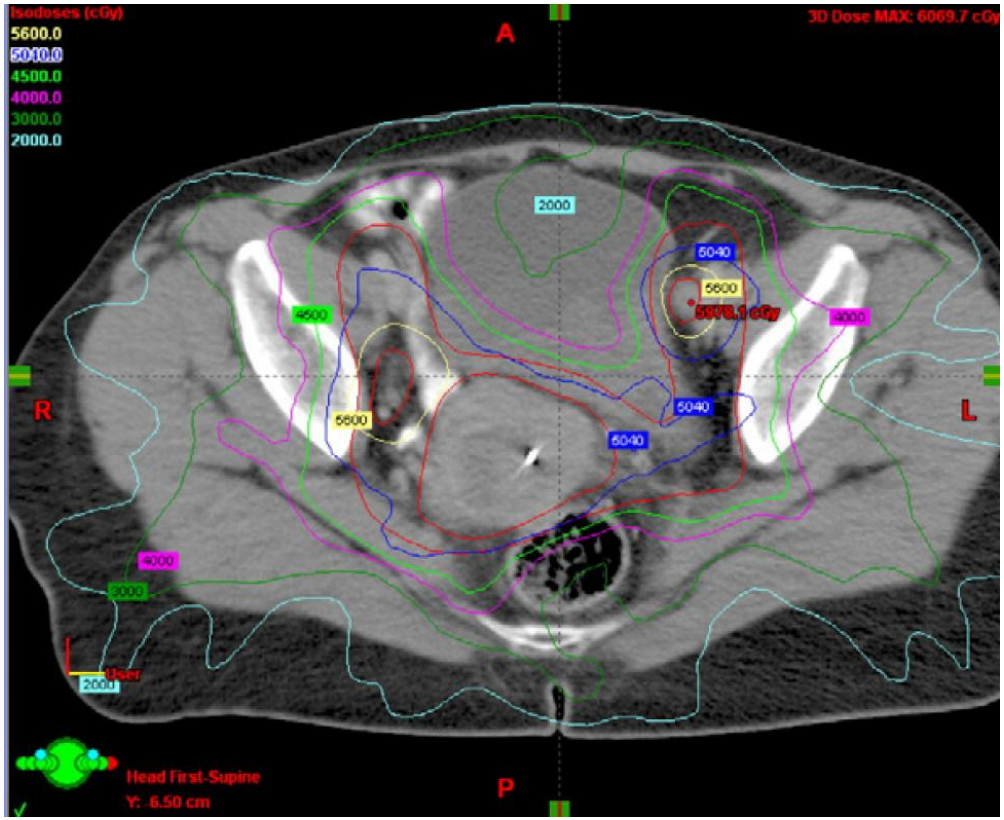
Chronic GU toxicity



Chen et al. Int J Radiat Oncol Biol Phys 2007

IMRT

- Taiwan, 2004-2008
- 109 stage IB2 – IVA cervical cancer patients
- IMRT and HDR of 20-33.5 Gy with concurrent cisplatin-based CTx



- IMRT

  50.4-54 Gy to GTV

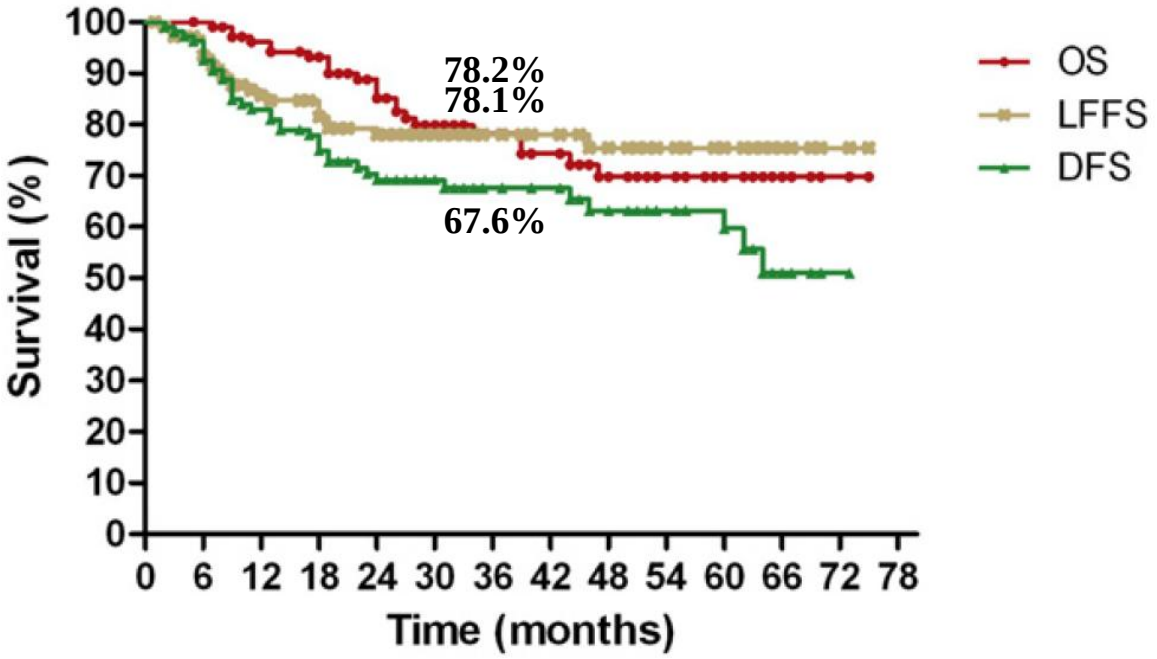
  concomittant IMRT boost to

  54-60 Gy to involved LNs

  45-48 Gy to CTV

Chen et al. Gynecol Oncol 2011

IMRT



Late side effect of IMRT with concurrent chemotherapy (n = 109).

	GI system		GU system		Vagina	Lymphedema
Grade 1	5		1		0	1
2	8		2		0	0
3	1	**4.5%**	3	**6.4%**	0	0
4	4		4		1	0
Total	18		10		1	1

Chen et al. Gynecol Oncol 2011

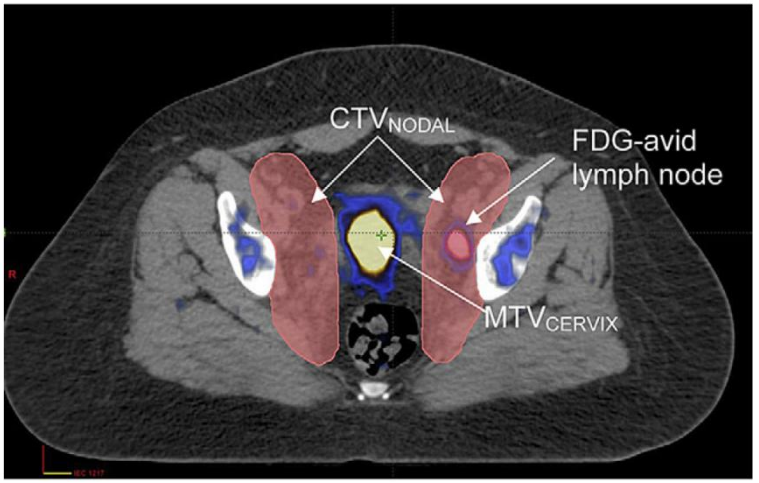
IMRT

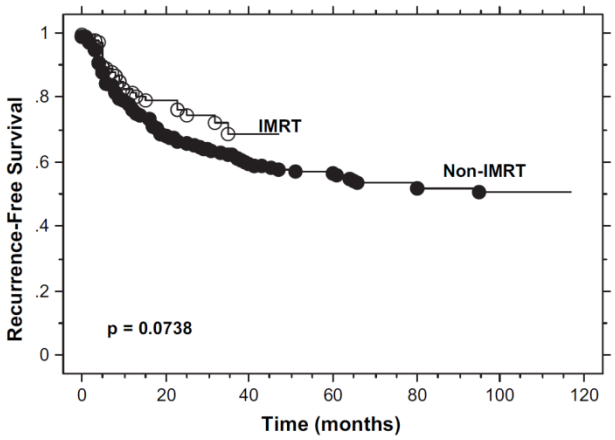
- Cervix cancer with definitive intent, 1997-2008, Washington University
- 135 IMRT patients (2005-)

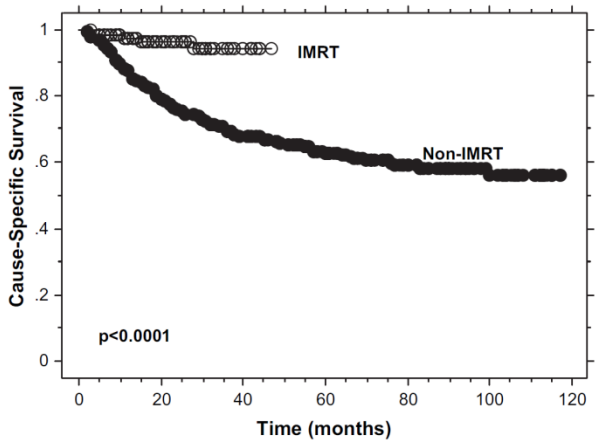
  317 non-IMRT patients (1997-2004)
- 50 Gy whole pelvis + 20 Gy central pelvis

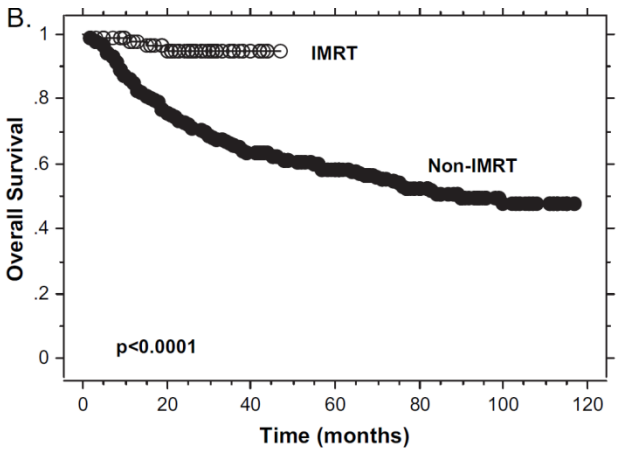
  + brachytherapy

Recurrence	IMRT	Non-IMRT	Total	*p* Value
Overall	39 (28.9%)	139 (43.8%)	178	0.036
Pelvic	11 (8.1%)	33 (10.4%)	44	
Distant	21 (15.6%)	78 (24.6%)	99	
Both	7 (5.2%)	28 (8.8%)	35	







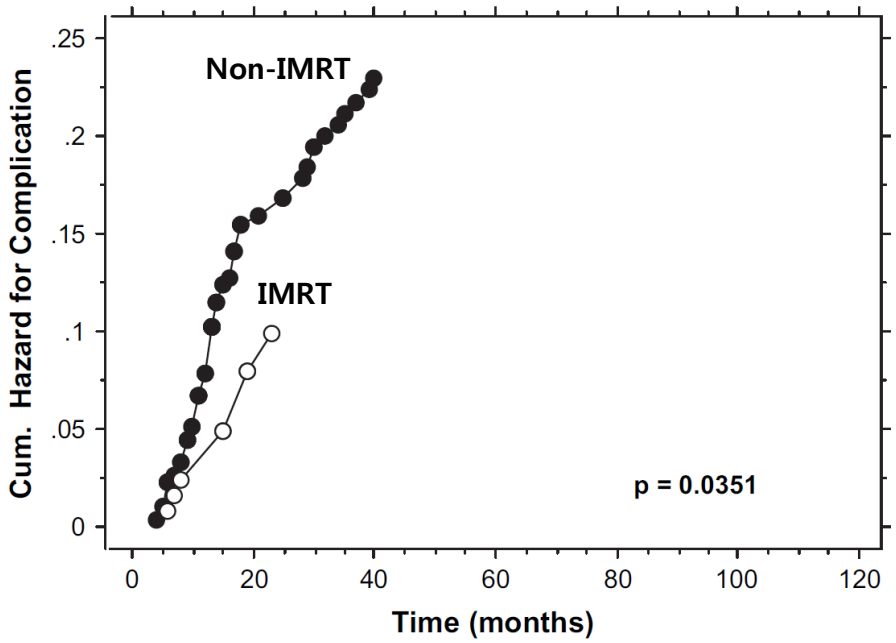


Kidd et al. Int J Radiat Oncol Biol Phys 2010

IMRT

Table 4. Grade 3 or greater gastrointestinal and genitourinary complications in study group

Complication	IMRT group	Non-IMRT group	Total
Rectovaginal fistula	2	12	14
Vesicovaginal fistula	0	11	11
Small bowel obstruction	2	7	9
Large bowel obstruction	2	5	7
Cystitis, Grade 4	1	5	6
Rectal ulcer	1	5	6
Ureteral stricture	0	4	4
Rectal stricture	0	2	2
Proctitis, Grade 4	0	2	2
Ischemic colitis	0	1	1

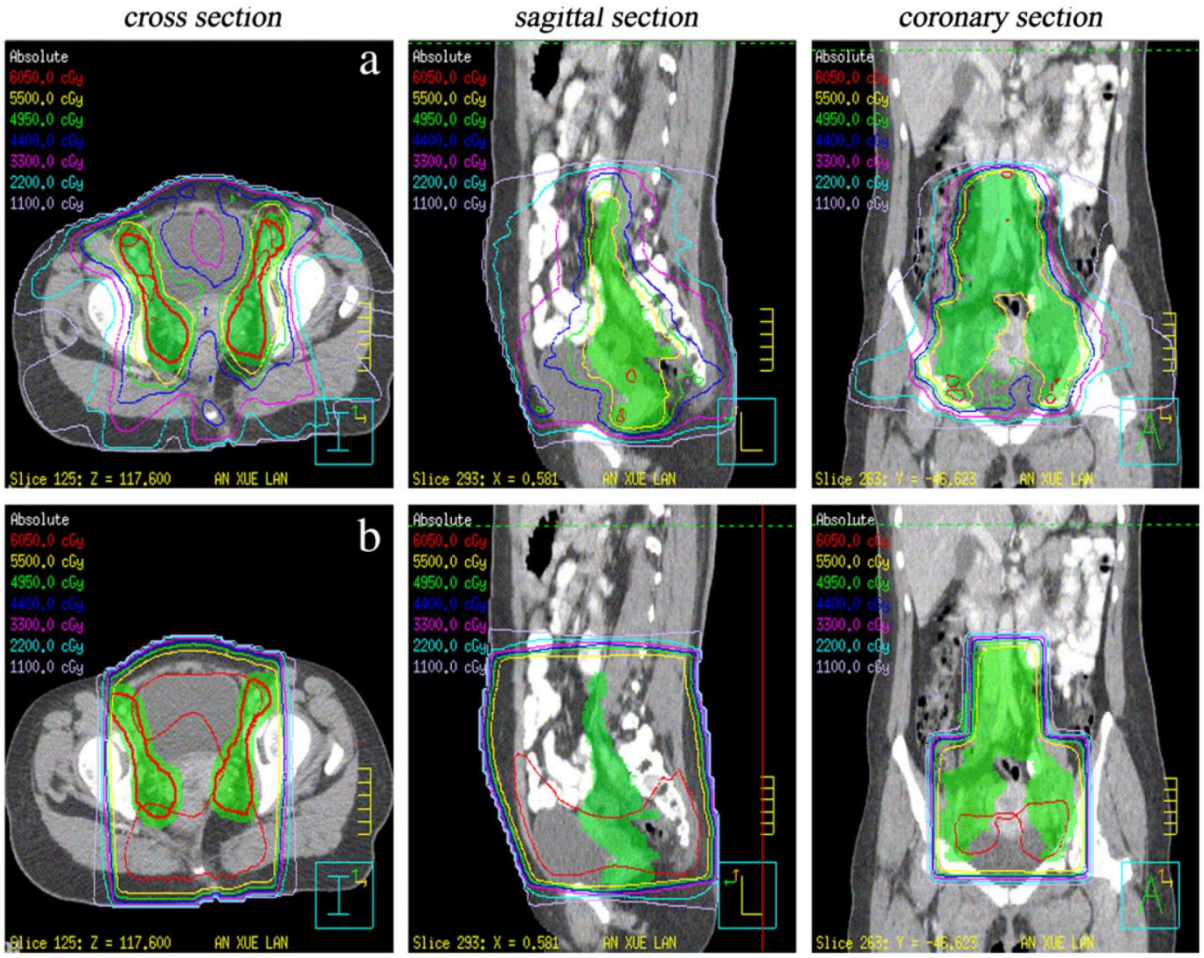


Kidd et al. Int J Radiat Oncol Biol Phys 2010

IMRT

- IIB-IIIB cervix cancer, 2005-2010, Shandong Cancer Hospital
- 60 patients: reduced field IMRT (RF-IMRT)

  62 patients: conventional RT (c-RT)



PTV dose

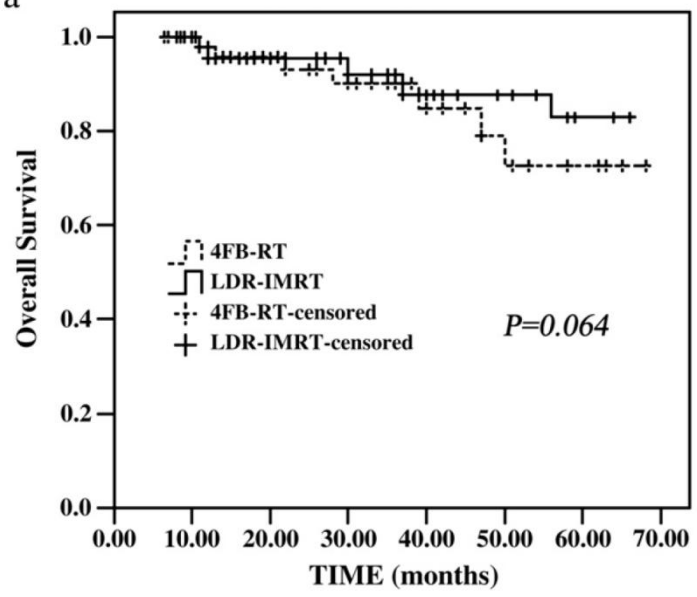
61.5 Gy vs 50.8 Gy

P=0.046

Du et al. Gynecol Oncol 2012

IMRT

a



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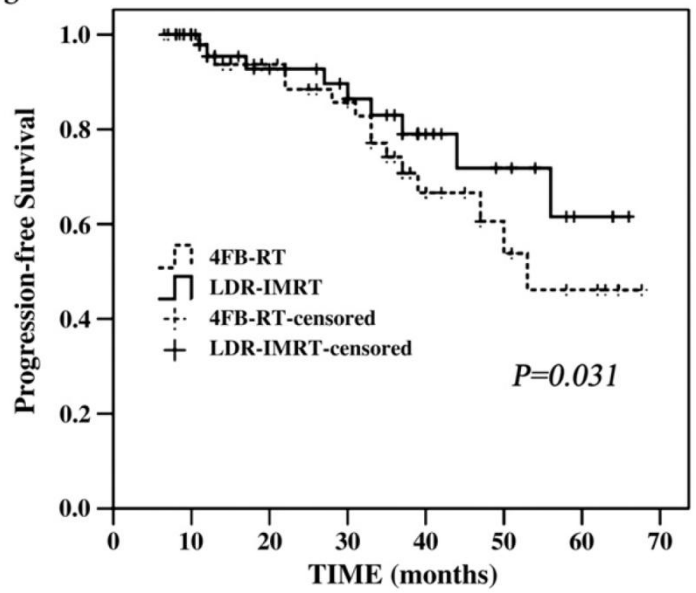


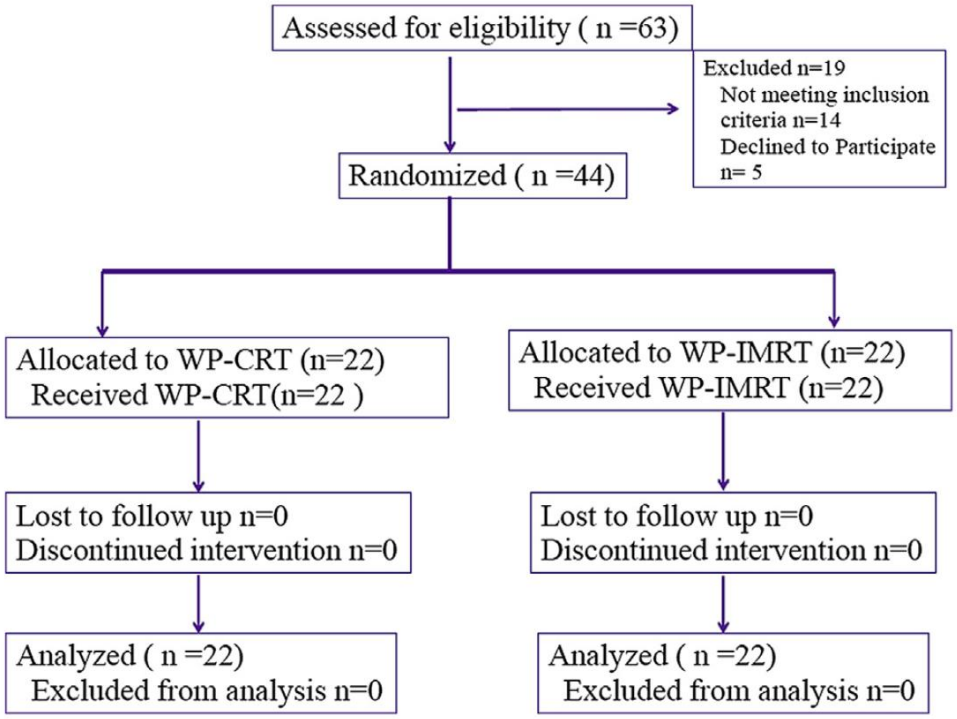
Chronic toxicities

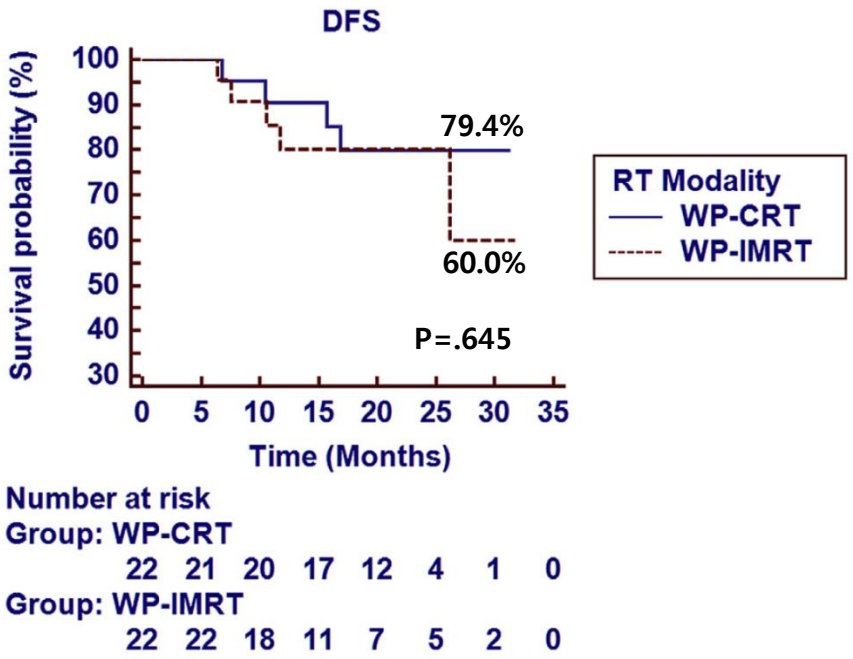
Grade	RF-IMRT group (n = 57)	c-RT group (n = 60)	*P* value
Enterocolitis			0.017
0	32 (56.1%)	20 (33.3%)	
1	17 (29.8%)	11 (18.3%)	
2	8 (14.1%)	18 (30.0%)	
3	0 (0%)	8 (13.4%)	
4	0 (0%)	3 (5.0%)	
5	0 (0%)	0 (0%)	
Cystitis			0.044
0	41 (71.9%)	29 (48.4%)	
1	11 (19.3%)	11 (18.3%)	
2	5 (8.8%)	11 (18.3%)	
3	0 (0%)	6 (10.0%)	
4	0 (0%)	3 (5.0%)	
5	0 (0%)	0 (0%)	

Du et al. Gynecol Oncol 2012

IMRT

- Prospective randomized trial, India
- Cervix cancer, 2010-2012, 44 patients, IIB-IIIB





Gandhi et al. Int J Radiat Oncol Biol Phys 2013

IMRT

Table 2 Dose–volume histogram characteristics for target coverage and OARs

Characteristic	WP-CRT arm	WP-IMRT arm	*P* value
Mean CTV D_{95}, Gy	51.95 ± 0.85	51.26 ± 0 .28	.42
Mean CTV Nodal D_{95}, Gy	52.01 ± 1.1	51.52 ± 0.26	.243
Mean PTV D_{95}, Gy	49.44 ± 4.37	50.68 ± 0.40	.438
Mean rectum V_{40}, % volume	98.37 ± 4.58	42 ± 2.78	.0001
Mean bladder V_{40}, % volume	97.54 ± 3.78	42.44 ± 2.74	.0001
Mean small bowel V_{40}, % volume	61.21 ± 14.63	31.66 ± 3.56	.001
Mean small bowel V_{90}, volume in cm^3	417.54 ± 42.16	199.89 ± 47.08	.005
Mean small bowel V_{100}, volume in cm^3	336.22 ± 37.88	102.47 ± 29.09	.001
Mean bone marrow V_{10} , % volume	99.44 ± 2.85	96.05 ± 3.61	.619
Mean bone marrow V_{20}, % volume	98.95 ± 3.71	87.24 ± 4.70	.618

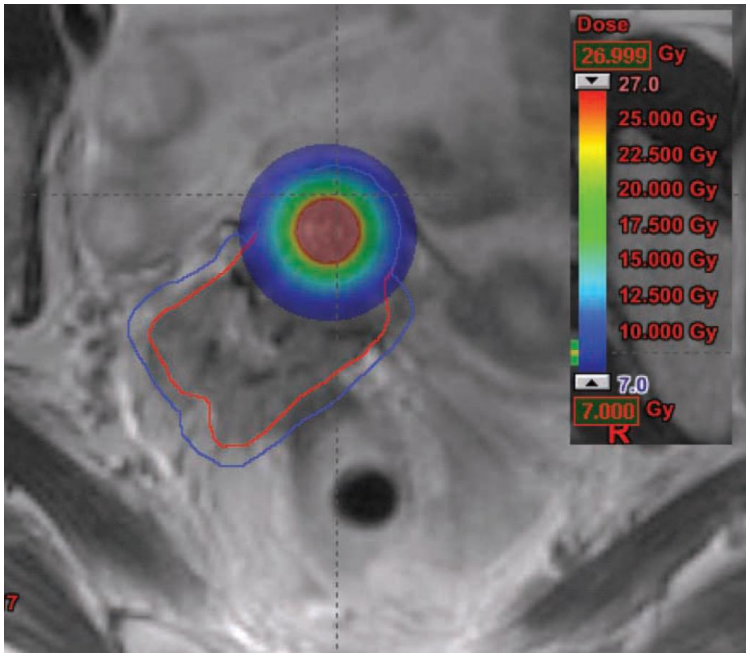
Table 3 Acute gastrointestinal and genitourinary toxicity in WP-CRT and WP-IMRT arms

Toxicity	WP-CRT arm, n (%)	WP-IMRT arm, n (%)	*P* value	Effect size	95% CI of the difference
Vomiting grade ≥2	8 (36.4)	2 (9.1)	**.034**	**0.273**	**0.016 to 0.521**
Vomiting grade ≥3	1 (4.5)	1 (4.5)	.756	0	−0.135 to 0.131
GI grade ≥2	14 (63.6)	7 (31.8)	**.034**	**0.318**	**0.002 to 0.604**
GI grade ≥3	6 (27.3)	1 (4.5)	**.047**	**0.228**	**0.003 to 0.447**
GU grade ≥2	7 (31.8)	5 (23.8)	.404	0.08	−0.202 to 0.361
GU grade ≥ 3	3 (13.6)	0 (0)	.125	0.136	−0.019 to 0.291

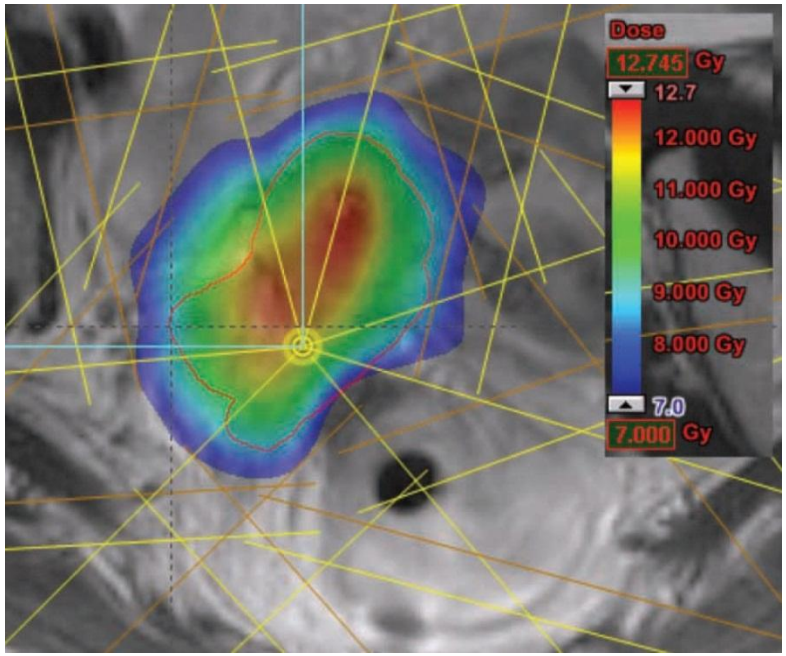
Gandhi et al. Int J Radiat Oncol Biol Phys 2013

IMRT vs brachytherapy

- Brachytherapy: excellent efficacy and tolerance
- IMRT could provide a potential fallback for patients unable or unwilling to receive brachytherapy
- Multiple dosimetric studies suggest IMRT boost is feasible
- Clinical outcome data is limited



Intracavitary brachytherapy



IMRT boost plan

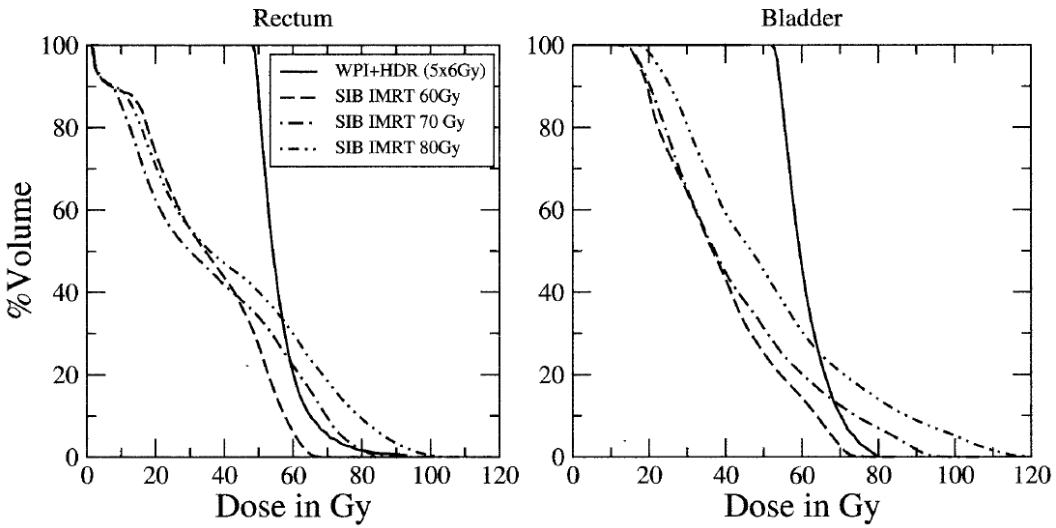
IMRT vs brachytherapy

- IMRT Simultaneous Integrated Boost (SIB)
- SIB boost

  - 45 Gy in 1.8 Gy fractions (whole pelvis)

  - 77.5 Gy in 3.1 Gy fractions (GTV)

- Radiobiologically equivalent to 45 Gy whole pelvic RT + 30 Gy brachytherpay
- Sparing of bladder and rectum is significantly improved with SIB
- SIB treatment can reduce the treatment time to 5 weeks



Guerrero et al. Int J Radiat Oncol Biol Phys 2005

IMRT vs brachytherapy

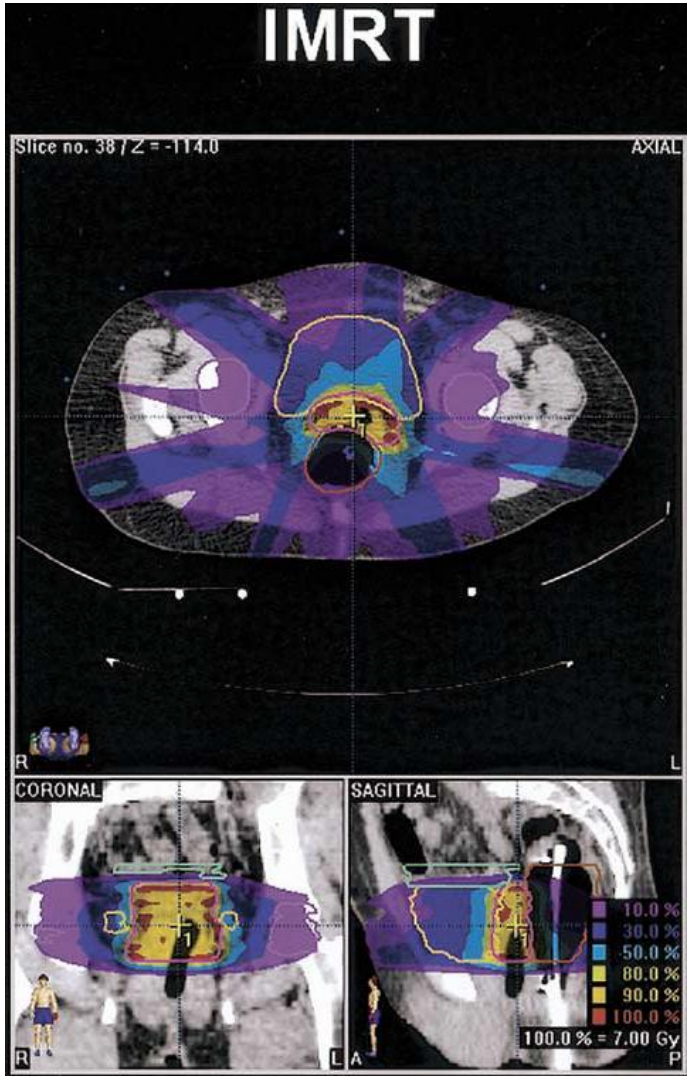
- Fractionated Stereotactic RT boost

- 16 patients with endometrial or cervical cancer
- Treated with final boost to the areas at higher risk for relapse
- Hypofractionated boost (IMRT)
    - Intact uterus 7 Gy X 2 fractions (4-7 days interval)
    - postoperative 4 Gy X 5 fractions (2-3 days interval)
- Body stereotactic RT system
- Rectal balloon for internal immobilization

Molla et al. Int J Radiat Oncol Biol Phys 2005

IMRT vs brachytherapy

- Fractionated Stereotactic RT boost



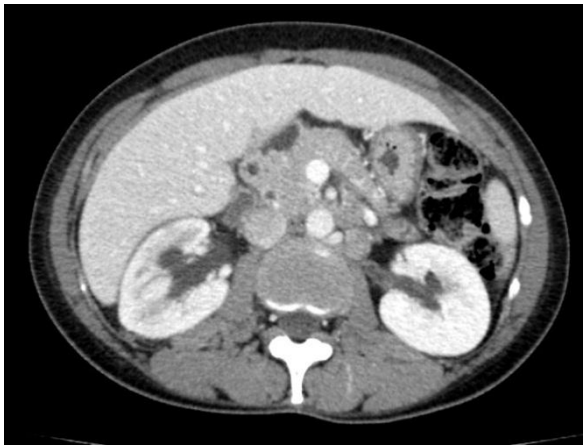
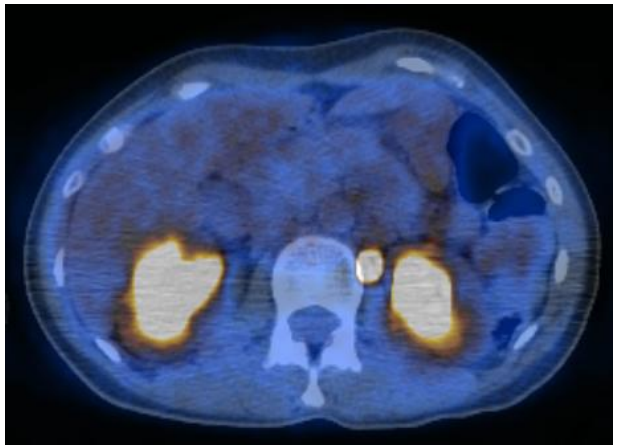
- Median follow-up 12.6 months
- 93% local control
- No ≥ grade 3 acute toxicity
- 1/16 (6%) grade≥ 2 late GI toxicity

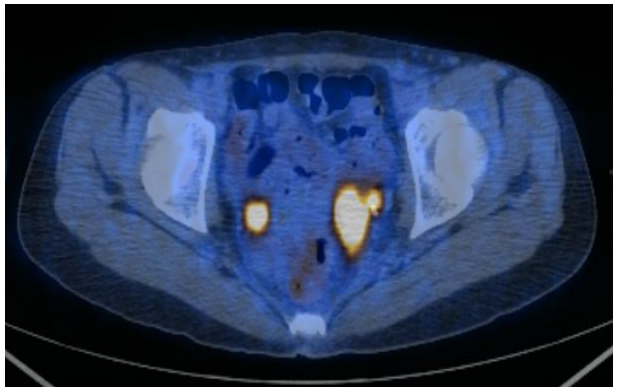
Molla et al. Int J Radiat Oncol Biol Phys 2005

Case

- 35/F, recurrent cervix cancer -> salvage RT

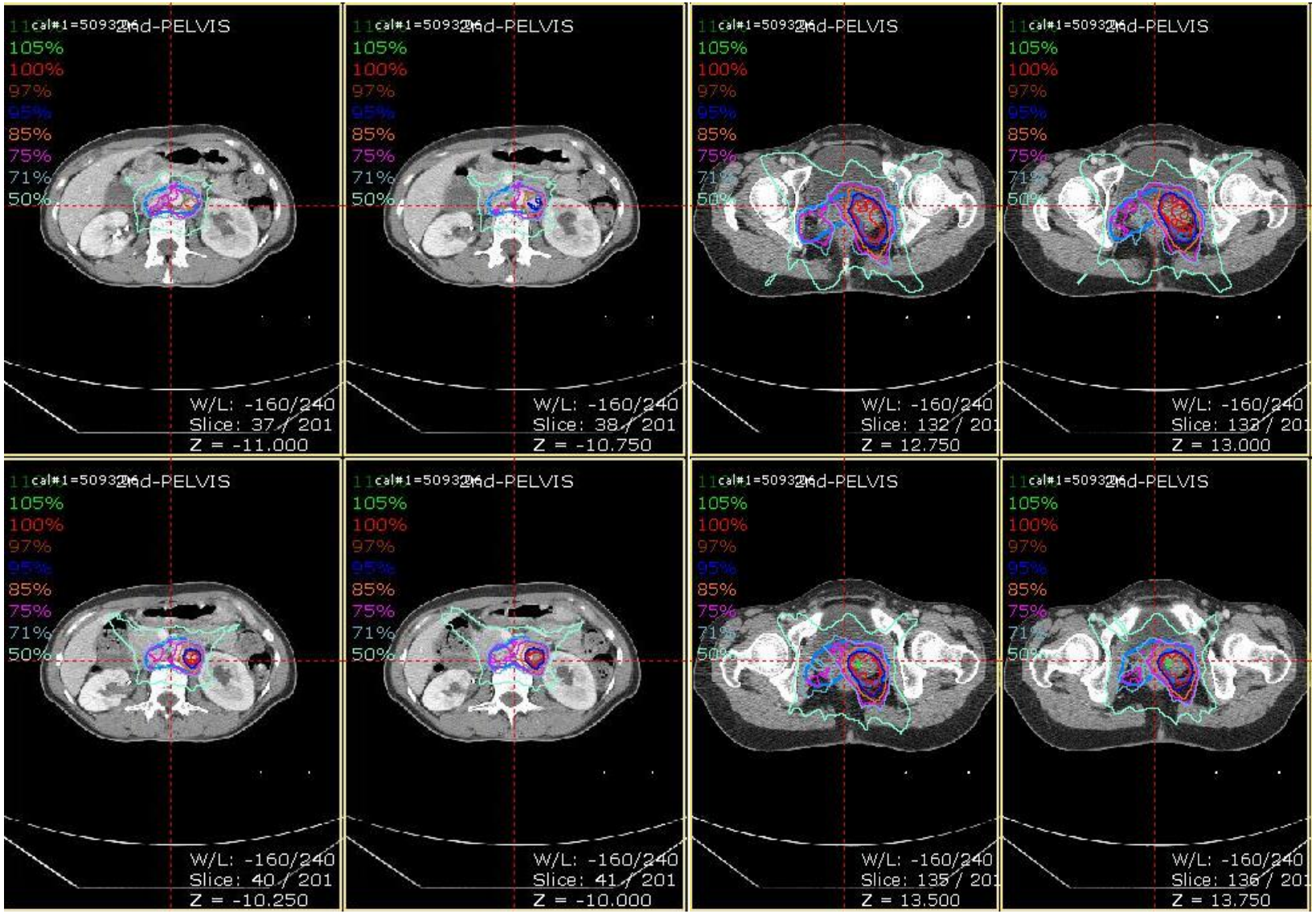
2010. 7 RH with PLND, FIGO IB, 1.9cm, > half, LVI(+)
-> RTx refusal
2011.12 multiple pelvic and RPLN recurrence



Case

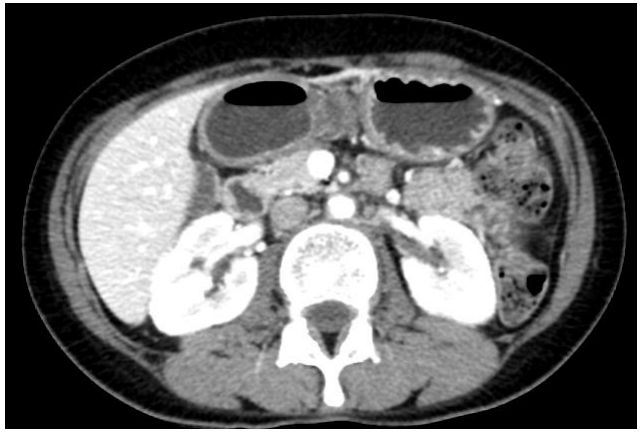
2011.12-2012.1 salvage IMRT SIB 60Gy/25frs to pelvis and RPLN



Case

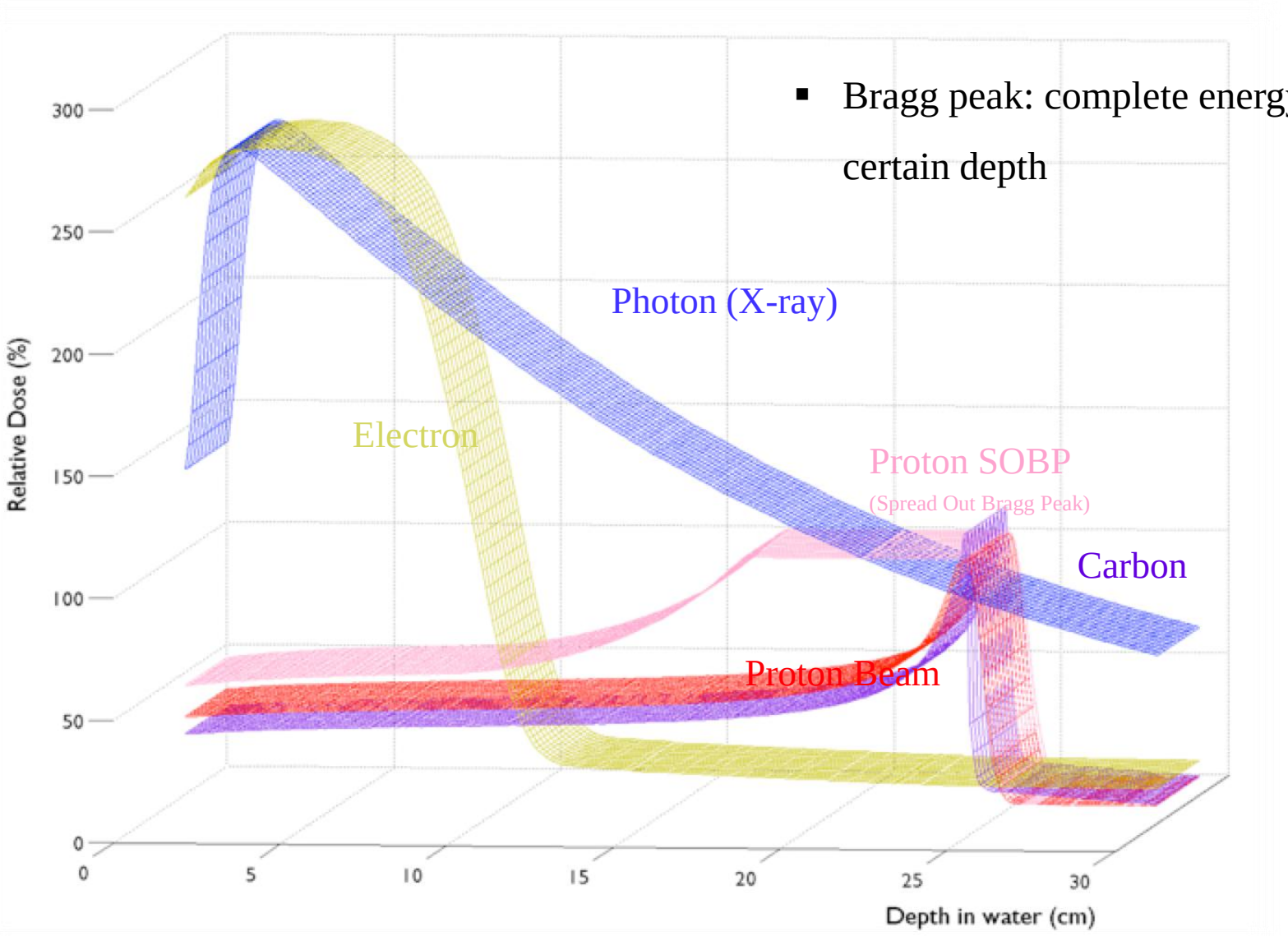
Post-RT 6months

Post-RT 2yr 4months



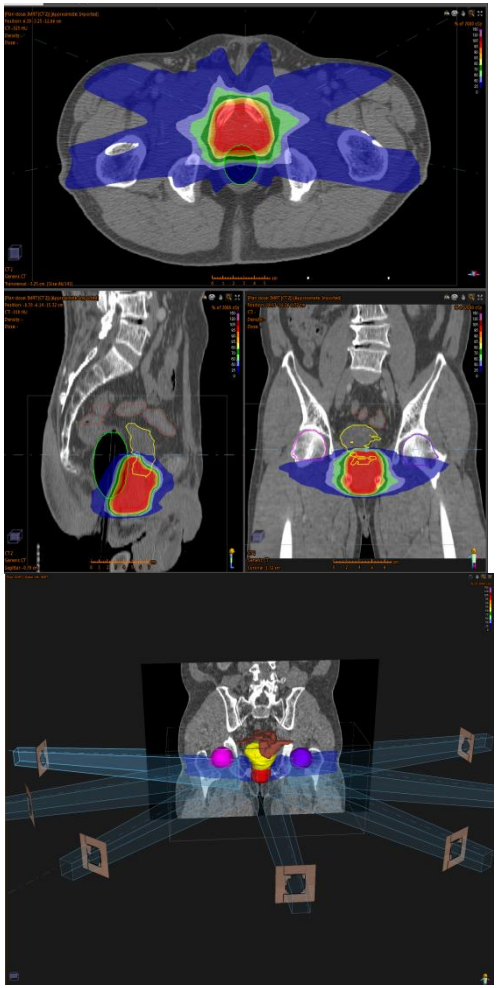
Proton therapy

- Bragg peak: complete energy delivery at certain depth

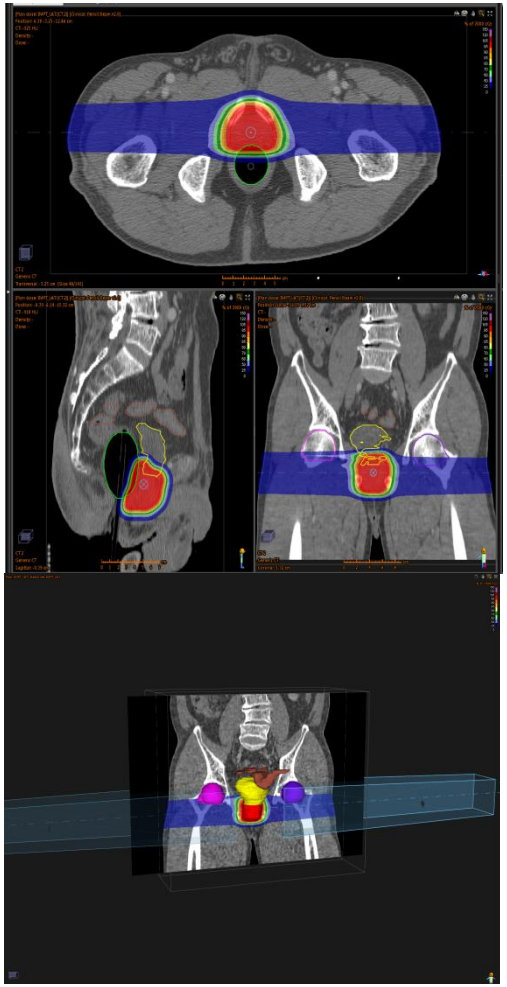


3D CRT

IMRT



Proton



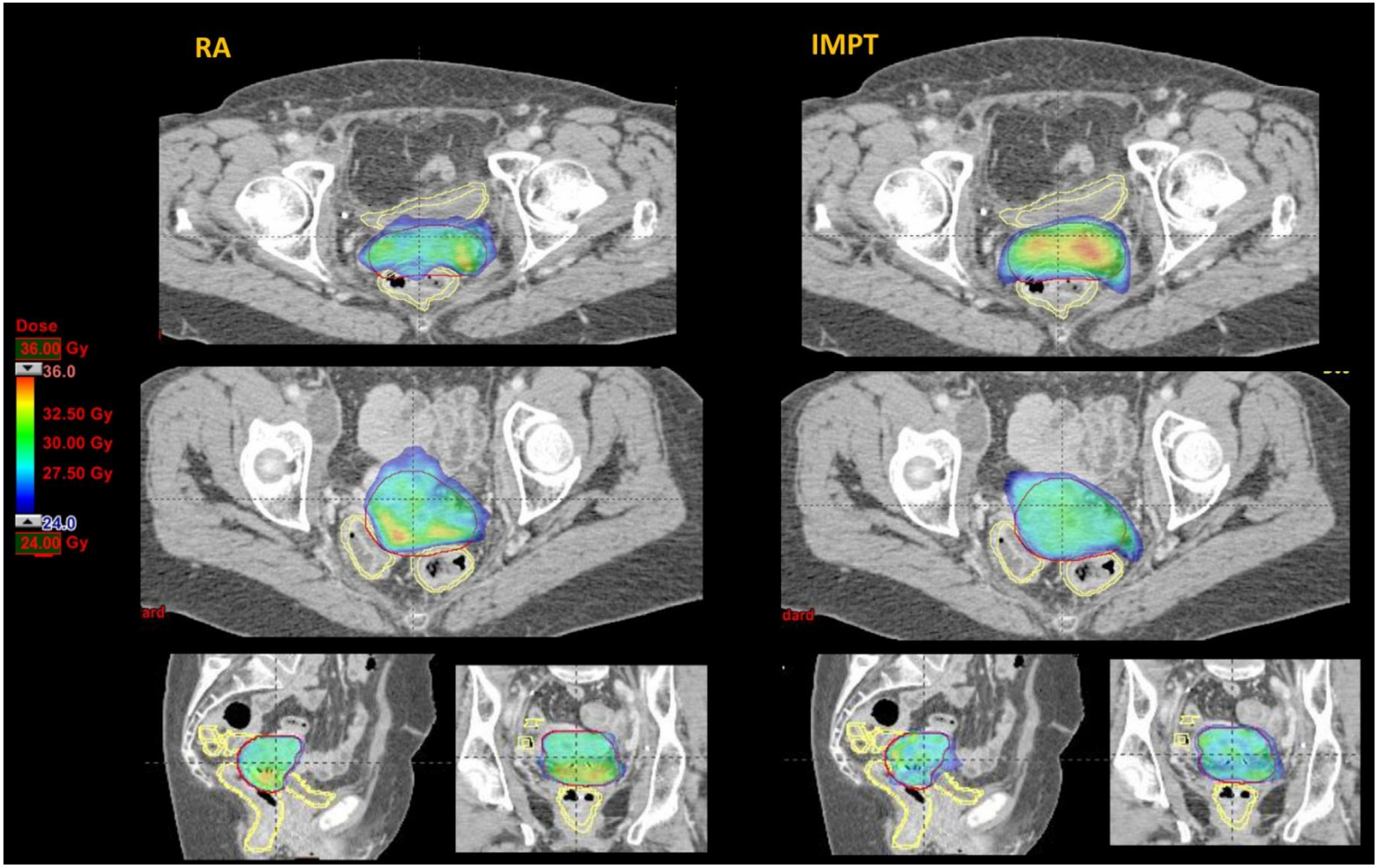
prostate cancer, liver cancer, head and neck cancer,

pediatric tumor, brain tumor, sarcoma

Re-RT…….

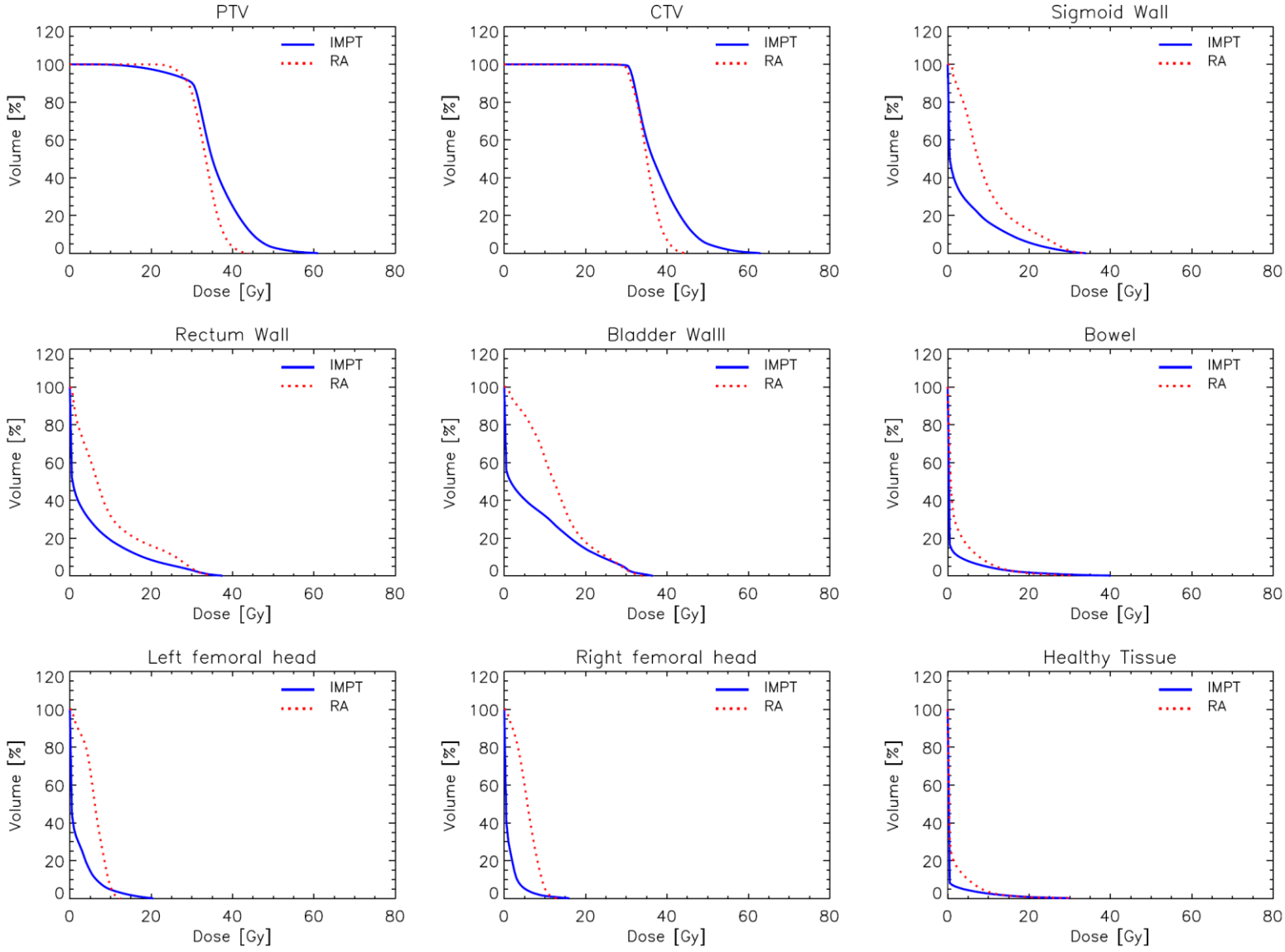
Proton therapy

- Cervix cancer, 11 patients who were unable to undergo brachytherapy
- whole pelvic RT 50.4 Gy + IMPT boost 6 Gy x 5 frs



Clivio et al. Int J Radiat Oncol Biol Phys 2013

Proton therapy

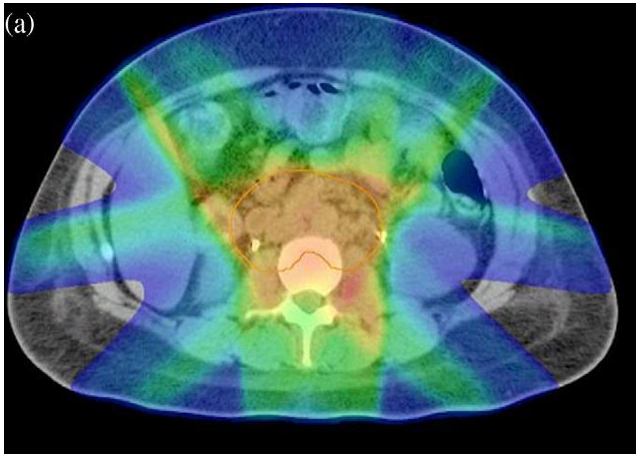


Clivio et al. Int J Radiat Oncol Biol Phys 2013

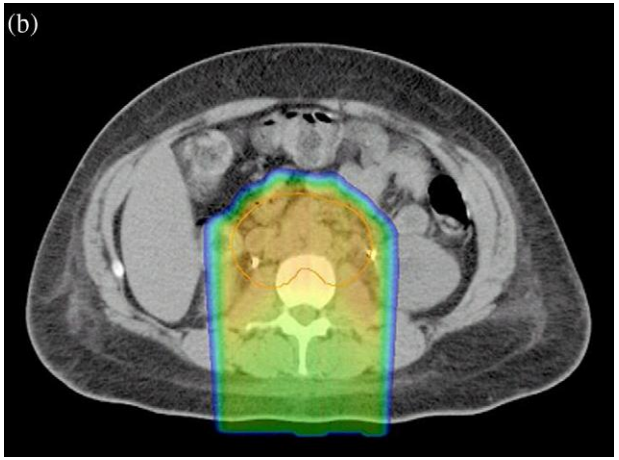
Proton therapy

- Gynecologic cancer, 10 consecutive patients
- IMRT, IMPT, PSPT (passive scattering proton therapy) planning comparison
- IMRT to pelvic nodes with PSPT to PA nodes (PSPT/IMRT)

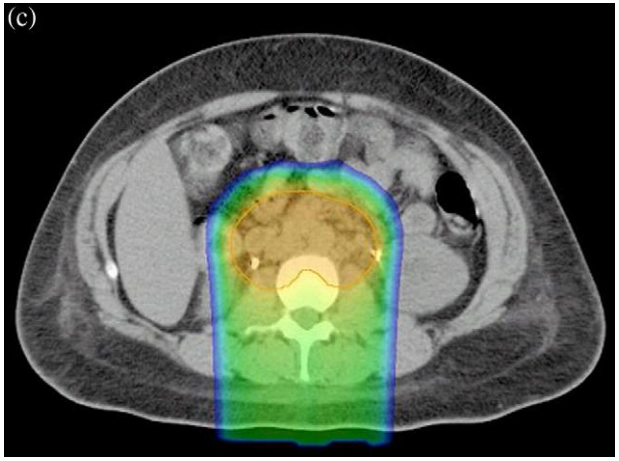
  IMRT to pelvic nodes with IMPT to PA nodes (IMPT/IMRT)



IMRT/IMRT



PSPT/IMRT



IMPT/IMRT

Milby et al. Int J Radiat Oncol Biol Phys 2011

Proton therapy

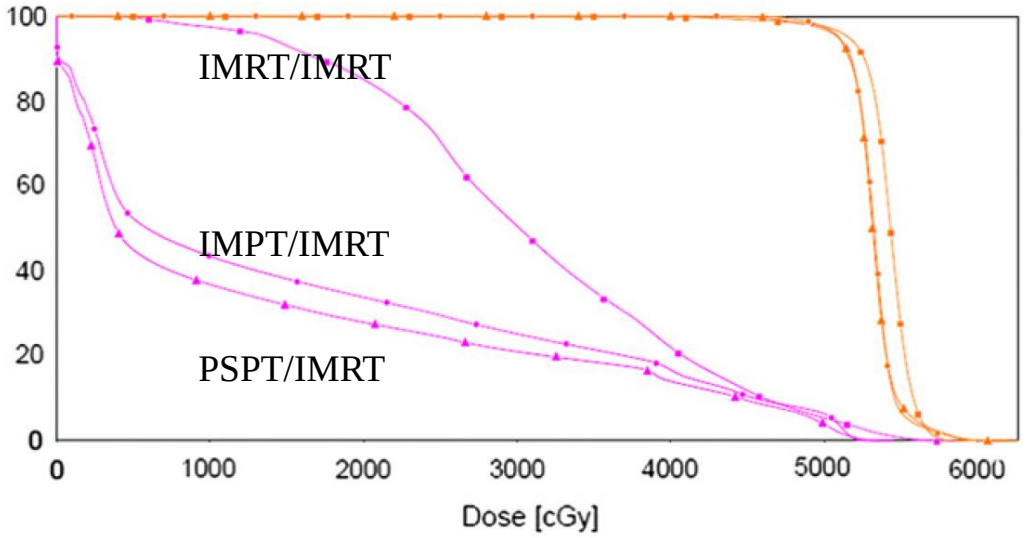


Table 3 Dose–volume histogram comparisons for the small bowel

Small bowel	IMRT/IMRT	PSPT/IMRT	*p* value IMRT/PSPT vs. IMRT/IMRT	IMPT/IMRT	*p* value IMRT/IMPT vs. IMRT/IMRT
Mean, Gy (RBE)	32.7 ± 5.3	22 ± 8.4	<0.001	23.4 ± 8.4	<0.001
V_{50}	14.7 ± 11.9	13.8 ± 11.9	0.5	15.1 ± 10.5	0.8
V_{45}	24.4 ± 14.4	23.0 ± 14.1	0.2	24.3 ± 14.4	0.9
V_{40}	32.8 ± 16.1	29.1 ± 16.0	0.01	36.2 ± 19.5	0.5
V_{35}	42.0 ± 16.3	34.3 ± 16.8	0.001	41.9 ± 19.1	1
V_{30}	53.3 ± 15.3	38.7 ± 17.1	<0.001	46.8 ± 18.2	0.3
V_{20}	82.5 ± 11.9	49.7 ± 19.3	<0.001	56.0 ± 16.7	0.001

Milby et al. Int J Radiat Oncol Biol Phys 2011

Clinical trials

- On going

  RTOG 1203

  Phase 3

  281 enrollment

  "A Randomized Phase III Study of Standard vs. IMRT Pelvic Radiation for Post-Operative Treatment of Endometrial and Cervical Cancer"

  Objective

  primary: acute gastrointestinal toxicity

  secondary: late GI, GU, hematologic toxicity

  loco-regional control, disease-free survival, overall survival

https://clinicaltrials.gov/

Clinical trials

- On going

  MGH

  Pilot study

  30 enrollment

  "Proton Beam Teletherapy for Post-Hysterectomy Cancers of the Uterus and Cervix"

  Objective

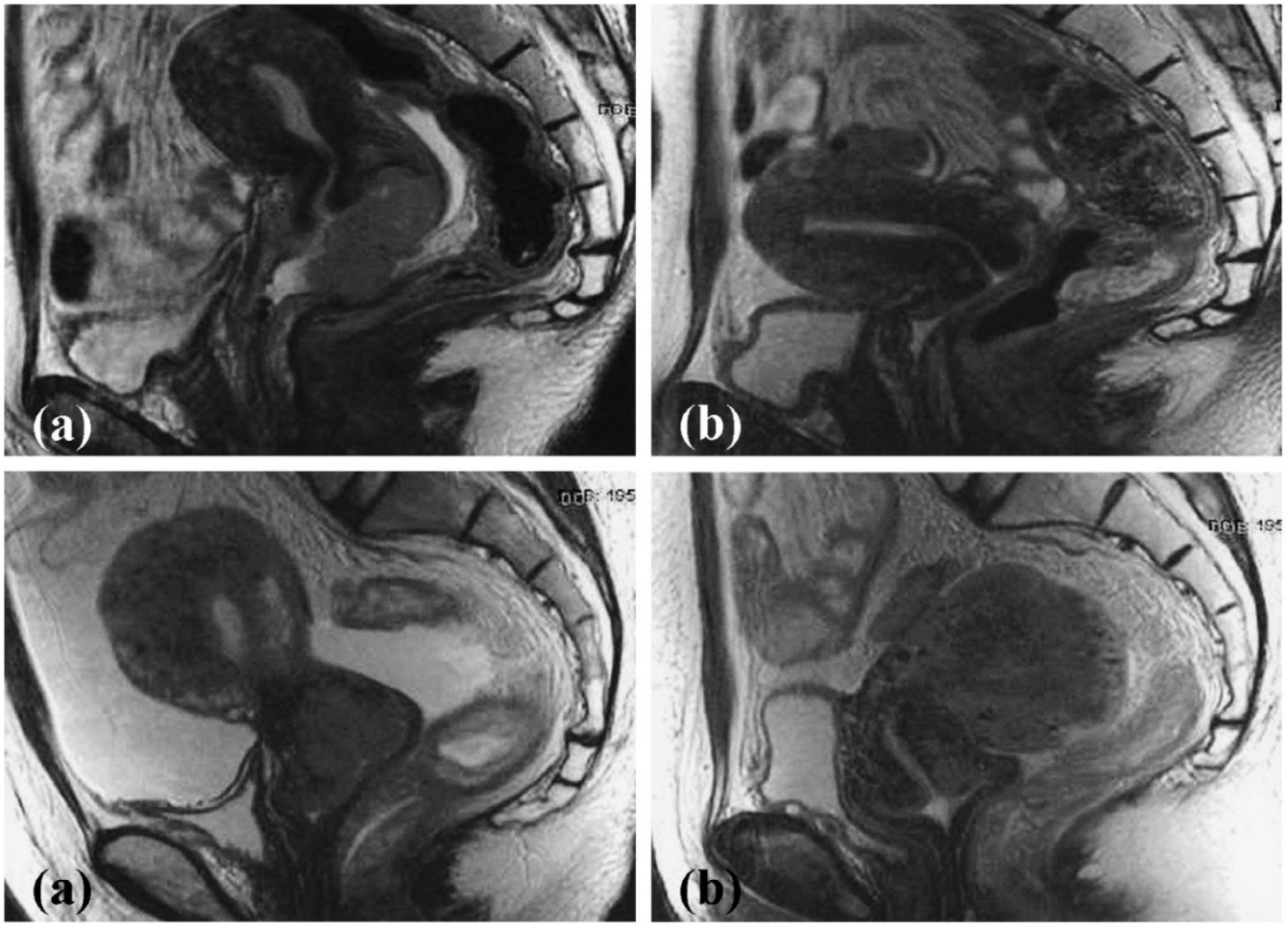
  primary: acute and late side effects

  secondary: QOL, progression-free survival

https://clinicaltrials.gov/

Considerations for IMRT/Proton therapy

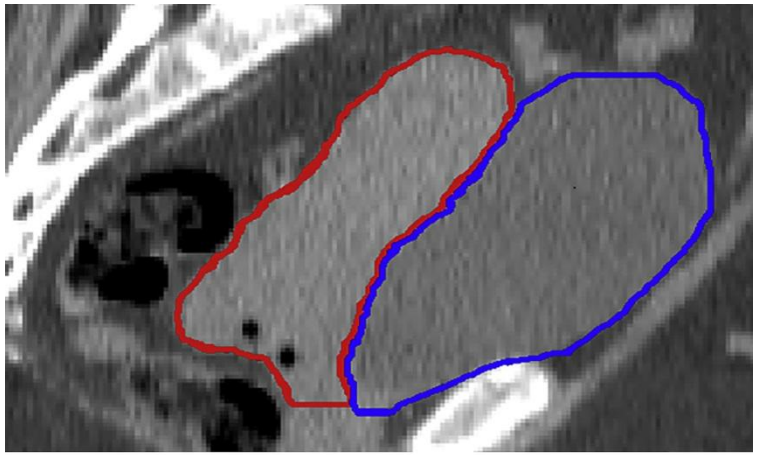
- volume reduction during RT
- unpredictably target movement during RT

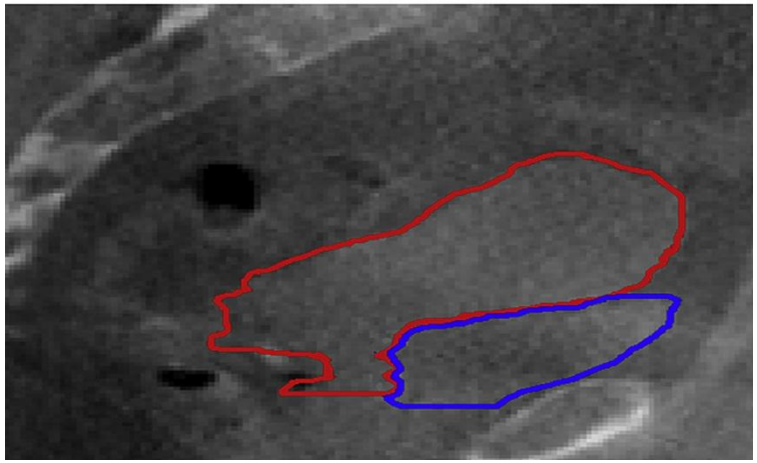


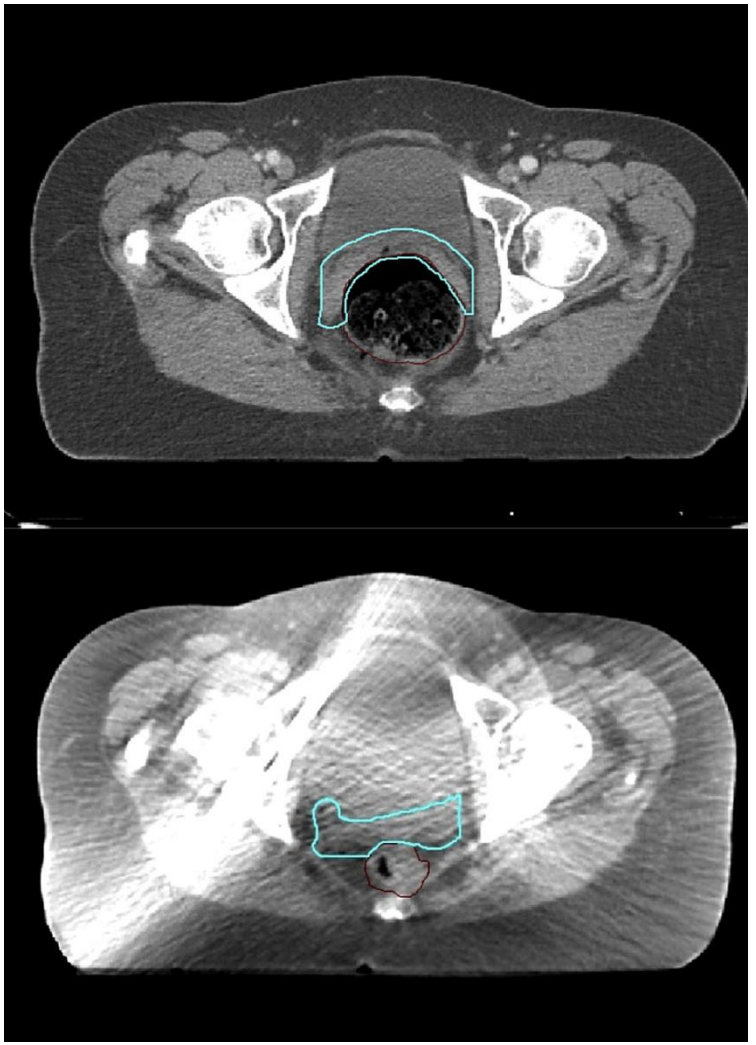
Huh SJ et al. Radiat Oncol 2004

Considerations for IMRT/Proton therapy

- Internal organ volume change





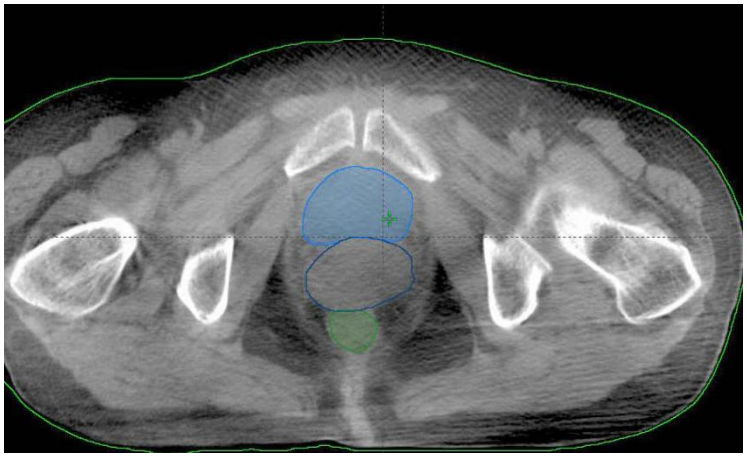


Jadon R et al. Clin Oncol 2014

Adaptive IMRT

- Current work focused on using daily volumetric imaging to adapt IMRT
- Daily imaging addresses concerns of inter-fraction organ motion of the target
- Multiple software tools required
  - automated segmentation: labor-intensive contouring
  - deformable registration: cumulative DVHs

- Cone-beam CT image are sufficient for adaptive IMRT for most patients



  - avoid bladder and rectum based on daily CBCT images
  - addresses tumor shrinkage and inter-fraction organ motion

Summary

-IMRT is a better technique to reduce the delivery of dose to adjacent normal tissue such as rectum, bladder, small bowel, compared with 3D-CRT. However the clinical significances of treatment results are limited.

-Proton therapy for gynecologic cancer is investigational tool. Proton therapy can reduce the radiation exposure to normal tissue than IMRT.

-To do IMRT or Proton therapy for gynecologic cancer, we might be concerning about tumor regression or target movement during treatment.

-Prospective studies are needed to demonstrate the use of IMRT or proton therapy and provide important data on toxicity and survivals.

Thank you for your attention