Landmark trials on advanced technology for cervical cancer

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Learning objectives ....

- To list the available trials on advanced technology
- To identify the limitations of conventional radiation
- To list the benefits of advanced technology
- To define the selected role of advanced technology for cervical cancer

Indian scenario...

- More than one lakh women are diagnosed with cervical cancer every year
- More than 90% of newly diagnosed patients require radiotherapy
- Huge burden of patients per machine and unequal distribution of facilities
- Only 25% of Indian population are medically insured
- Cost of the 3DCRT treatment is 40% more than that of 2DCRT but still 40% less than that of IMRT
- Brachytherapy contributes to the success of radiotherapy for cervical cancer

Standard treatment …

- Concurrent chemoradiation with CDDP infusion… followed by ICBT/ISBT
- Mostly 3 DCRT and wherever not available conventional four field technique..

outcome with standard treatment ....

- Control: 69-78 %
- Acute GI,gr III-IV:7-16%,49%,81% for pelvic,extended pelvic and adding chemo..RTOG 0116
- Acute haemat..76%
- Acute GU...17%
- Chronic proctitis & cystitis...gr III & IV upto 40% with chemo

Landmark data…

- Ana Fernandes-Ots et al.The role of IMRT in Gynaec cancer.Present and Future :RPOR:18 (2013).363-370.
  - comprehensive review

Where do we stand as far as IMRT for cervical cancer….

- Loiselle et al,The emerging role of IMRT for treatment of cervical cancer:Jou of NCCN:2010:8(12),1426-34
  - dosimetric evolution ….still in the nascent stage
- IntERTECC over 20 institutes from all over the world,Survey of IMRT practice, Red Jou 81,2S 2011
  - Half of the participants saw only <50 cases a year
  - Majority used IMRT in the last 5 years.

Landmark trials mainly dosimetric....

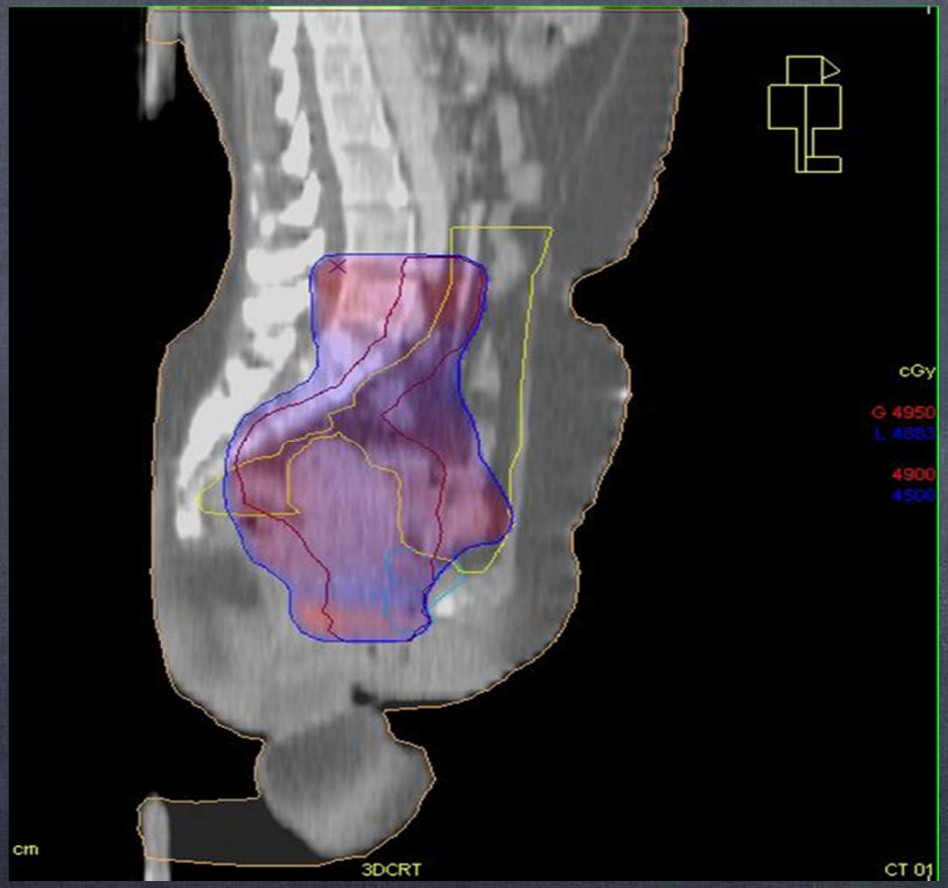
- Roeske et al. IMRT in patients with gynecologic malignancies. Red Jou 2000;48(5):1613–21.
  - Small bowel
- Mell LK et al. Dosimetric comparison of bone marrow-sparing IMRT vs conformal for cervical cancer. Red Jou 2008;71(5):1504–10.
  - Marrow
- Simpson DR et al. NTCP analysis of acute GI toxicity in cervical cancer undergoing IMRT and CDDP. REd Jou 2012;83(1):e81–6
  - GI toxicity
- Daniel et al, Red Jou,74,2,2009
  - SCR estimation

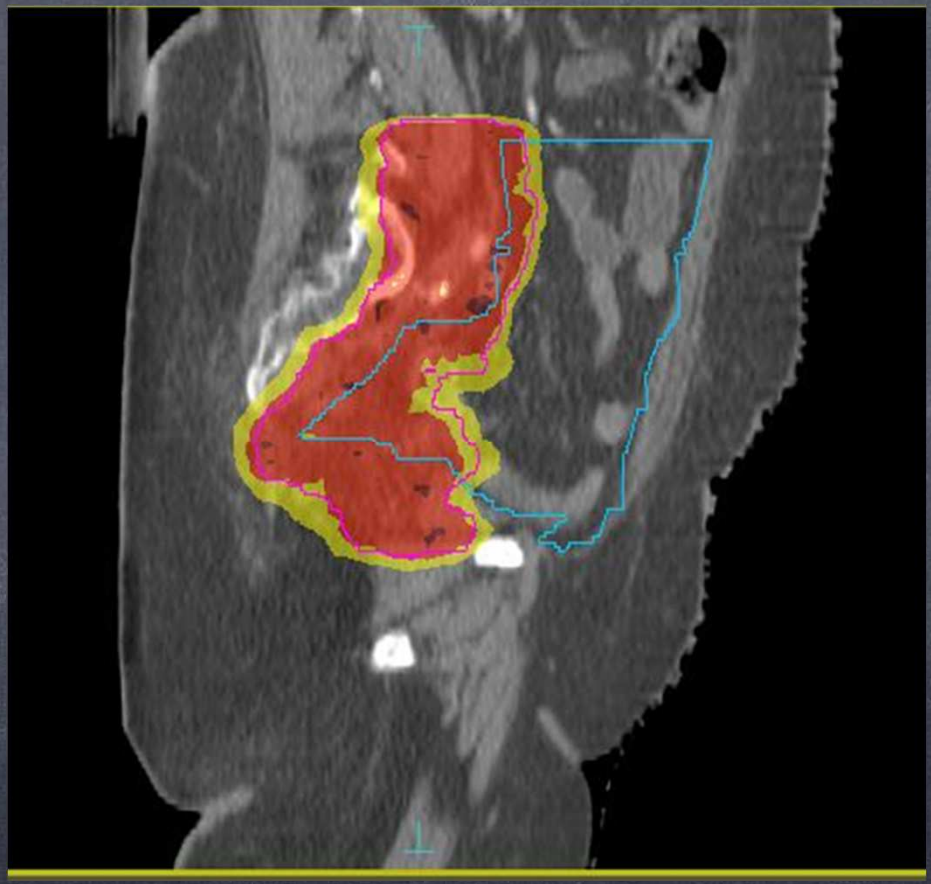
Results

Bowel	**V100**	**reduced by 50 %**
Bladder	**V100**	**reduced by 23 %**
Rectum (as an IMRT Boost)	**V66**	**reduced by 22%**
Bladder (as an IMRT Boost)	**V66**	**reduced by 19%**
Bone marrow (BMS IMRT vs 3DCRT vs AP/PA)	**V20**	**72 vs 97.8 vs 99 % (lesser gr 3 & 4 toxicity)**

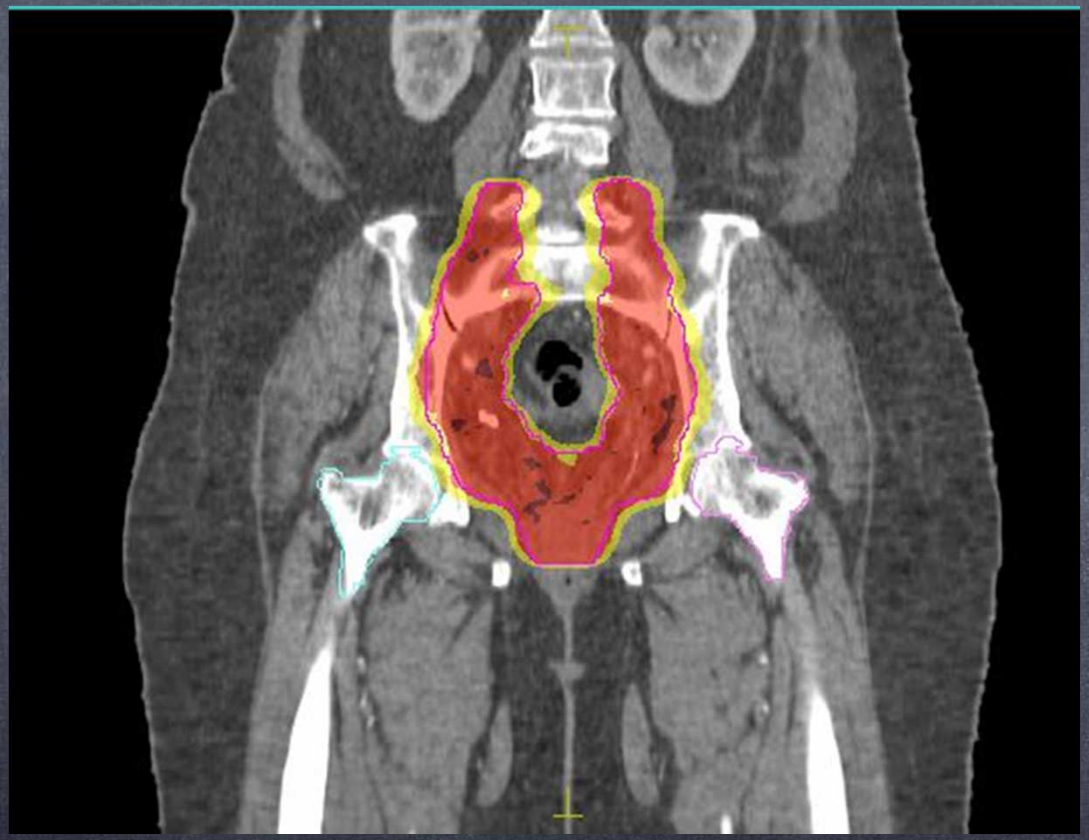
- Simpson et al suggested that a decrease in V45 bowel by 100 CC reduces the gr 2 toxicity by 50 %
- Mell suggested vol of marrow receiving 10-20 Gy predicts haematological toxicity

Bowel sparing……

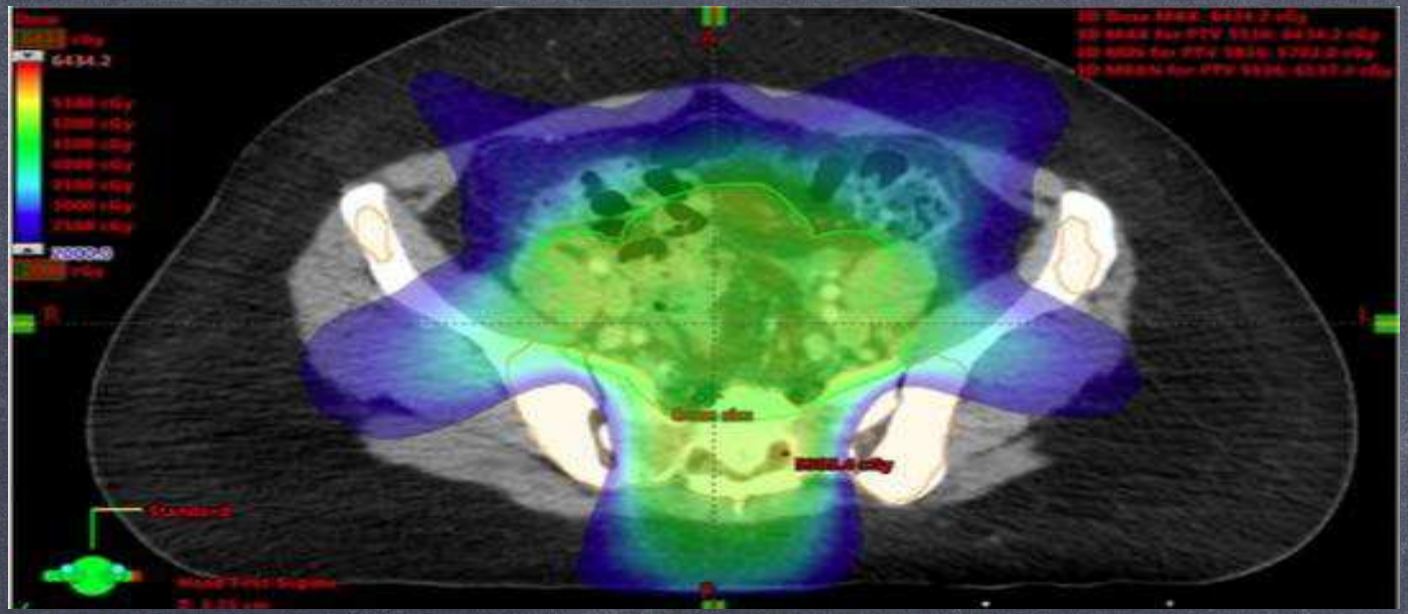




Femora….spared



30 Gy sparing iliac crest and 45 Gy colour wash showing adequate coverage with sparing the marrow..



Ramaiah data….Avinash et al

	2DCRT (A) Median % (IQR)	3DCRT (B) Median % (IQR)	IMRT (C) Median % (IQR)	*p value	Statistical Significance (p value)#		
					(A) - (B)	(A) - (C)	(B) - (C)
V40Gy (%) Bladder	98.7 (14.3)	91.2 (12.2)	69.9 (19.8)	<0.001	0.078	<0.001	<0.001
V40Gy (%) Rectum	87.3 (11.7)	100 (0.8)	99.2 (15.3)	<0.001	<0.001	0.477	0.012
V40Gy (%) Bowel Bag	20.05 (14.4)	28.9 (20.3)	22.6 (12.6)	<0.001	<0.001	0.132	<0.001
V20Gy (%) Bone marrow	84.6 (4.8)	93.0 (5.7)	72.04 (4.5)	<0.001	<0.001	<0.001	<0.001
V40GY (%) Left Femur	68.4 (13.7)	41.0 (19.0)	15.0 (12.4)	<0.001	<0.001	<0.001	0.001
V40GY (%) Right Femur	63.7 (16.6)	35.9 (26.5)	13.5 (10.4)	<0.001	<0.001	<0.001	0.001

Table 2: Dose Volume Parameters of Bladder, Rectum, BowelBag, Femur and Bone Marrow in 2DCRT, 3DCRT and IMRTTreatment plans.

***p value** indicates the p value from Friedman test

#p value from post hoc Wilcoxon signed rank test after adjusting for multiple comparisons using Bonferroni adjustment

Landmark trials of dosimetric and clinical...

- Mundt et al. IMRT for gynecologic malignancies.Red jou.2002;52(5):1330–7.
  - Bowel toxicity
- EA Kidd etal, PET simulated IMRT, Red Journal,Volume 77, Number 4, 2010,1085-1091.
  - Change in institutional policy
  - dose escalation, bowel toxicity
- Chen MF et al. Adjuvant concurrent chemoradiotherapy with IMRT after surgery for high-risk, early stage cervical cancer patients. Cancer J 2008;14:200–206.(54 pts)
- Klopp et al. Pt reported QOL Red Jou,2016,96,S3
- Loren et al.INTERTECC 2,Red Jou.2017::97.3.
  - multicentric single arm phase II

Results….

GU gr II	**IMRT vs 4 field**	**reduced from 91 to 60 %**
Chronic GI	**IMRT vs 4 field**	**reduced from 20 to 3 %**
Hematological (gr III)	**IMRT vs 3 DCRT**	**24 % for pelvic** **28 % for para aortic** **(similar)**

Better sparing of bowel, bladder, rectum, bone marrow (especially as CDDP is also given)

Probably translates to a better QOL

IMRT in terms of bone marrow sparing…

- InterTECC 2 ≥ gr III neutropenia 19.3% vs 40 % (historical comparison),improved QOL at 4 mths
- Korean retrospective study..anaemia (21 vs 40 % and gr I and II 56 vs 79 % for IMRT and conventional respectively)
- Brixley..No significant sparing of iliac crest for doses > 30 Gy

Studied gr II-IV…however gr II is really not worrisome

Landmark trials for efficacy..

No randomised trials…Most are for adjuvant setting..

- Hasselle et al,Red Jou,Clinical outcome of IMRT for cervical cancer,2011:80:1436-1445.
- Zhang G et al. Extended-field IMRT and CDDP for postop cervical cancer with common iliac or para-aortic lymph node metastases: a retrospective review in a single institution. Int J Gynecol Cancer 2012;22(7):1220–5.
- Chen MF et al. Clinical outcome in postop cervical cancer patients treated with CT IMRT: comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2007;67(5):1438–44.
- Chen CC et al. Definitive IMRT/Chemo for locally advanced cervical cancer. Gynecol Oncol 2011;122(1):9–13.

Results….

- No difference compared to 3DCRT as far as local failure, OS and DFS goes.
- Higher distant failure with IMRT...up to 27 %

Suggestion…

- With lesser toxicity, similar outcome, higher distant failure...is there a place for more chemo?
- Molecular biology?

Landmark trials for planning….

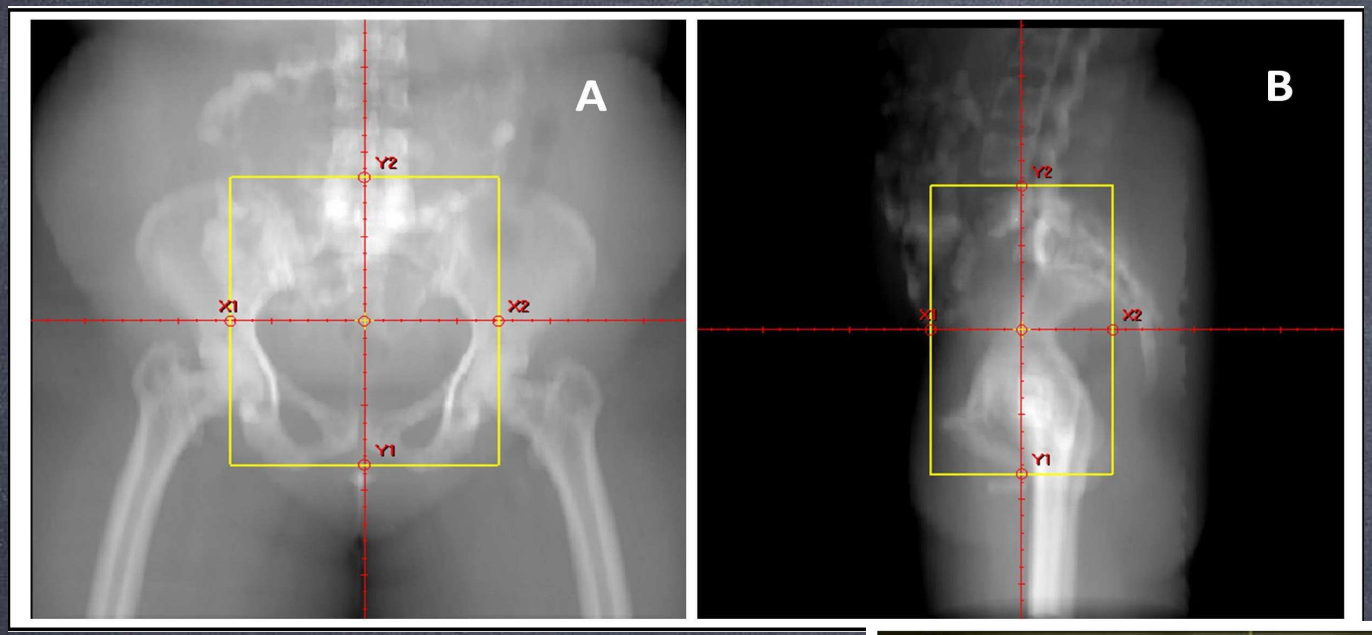
- Lim K et al. Consensus guidelines for delineation of CTV for IMRT for the definitive treatment of cervix cancer. Red Jou. 2011;79(2):348–55
- Taylor A et al. Uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancer. Green jou. 2008;88(2):250–7
- Gordon JJ et al. The effect of uterine motion and uterine margins on target and normal tissue doses in IMRT of cervical cancer. Phys Med Biol 2011;56(10):2887–901

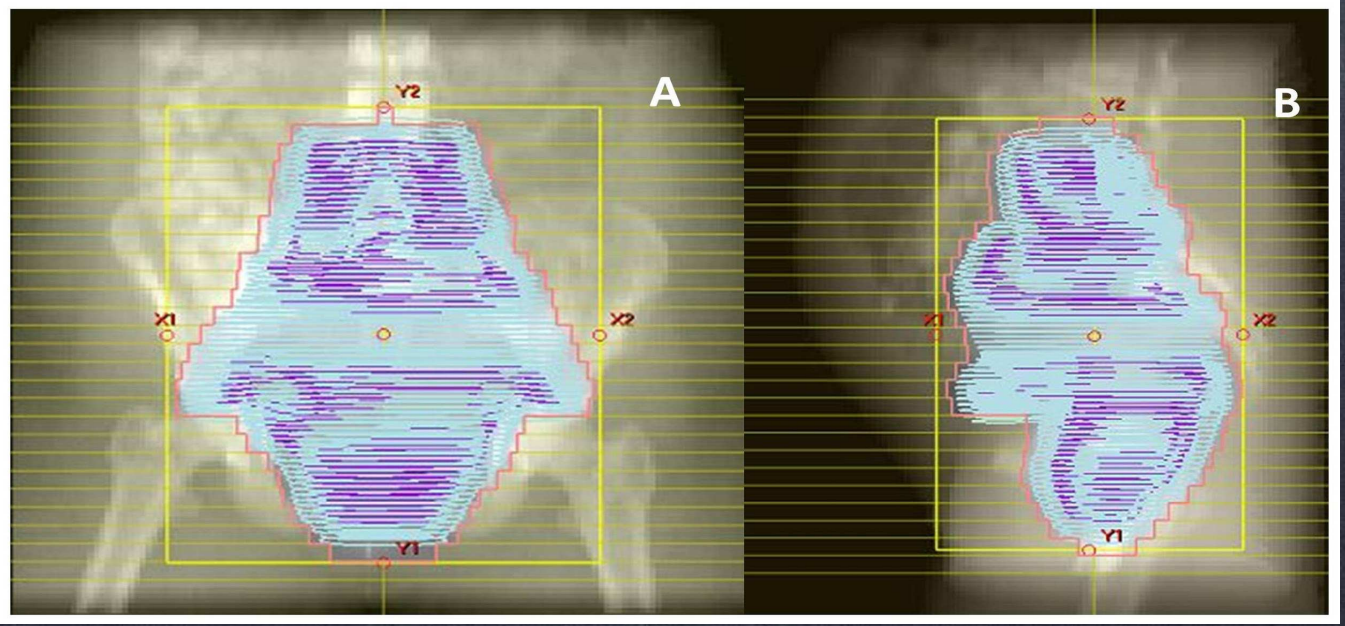
Better coverage…

- around 62 % coverage superiorly and 49 % posteriorly with conventional
- Mundt et al…>110 % by 10% of PTV and >115% by 0.2 % Vs 4 field

Better coverage of PTV /dose escalation

undercoverage.....of PTV





Ramaiah data….Avinash et al

PTV Coverage (%)	2DCRT (A)	3DCRT (B)	IMRT (C)	*p value	Statistical significance(p value)#		
					(A)-(B)	(A)-(C)	(B)-(C)
Min-Max	73.10-90.10 (%)	98.60-100.00 (%)	96.60-100.00 (%)				
Median (IQR)	82.2% (9.6)	99.9% (0.7)	99.3% (1.1)	<0.001	<0.001	<0.001	0.018

Table 1: PTV (Planned Target volume) coverage in 2DCRT, 3DCRT and IMRT.

***p value** indicates the p value from Friedman test

#p value from post hoc Wilcoxon signed rank test after adjusting for multiple comparisons using Bonferroni adjustment

Results...contouring

- Agreement as far as cervix, uterus and nodes are considered.
- No agreement as far as margins, para, vaginal length, dose to OARs and acceptable homogeneity are considered.
- Taylor..uterus moves more than cervix (MRI based)

Suggestion…

- GTV to CTV 1.5-2 Cm, CTV to PTV 0.7 cm with soft tissue verification on all days.
- Best is to have empty rectum and full bladder on all days

Large tu shrinkage…

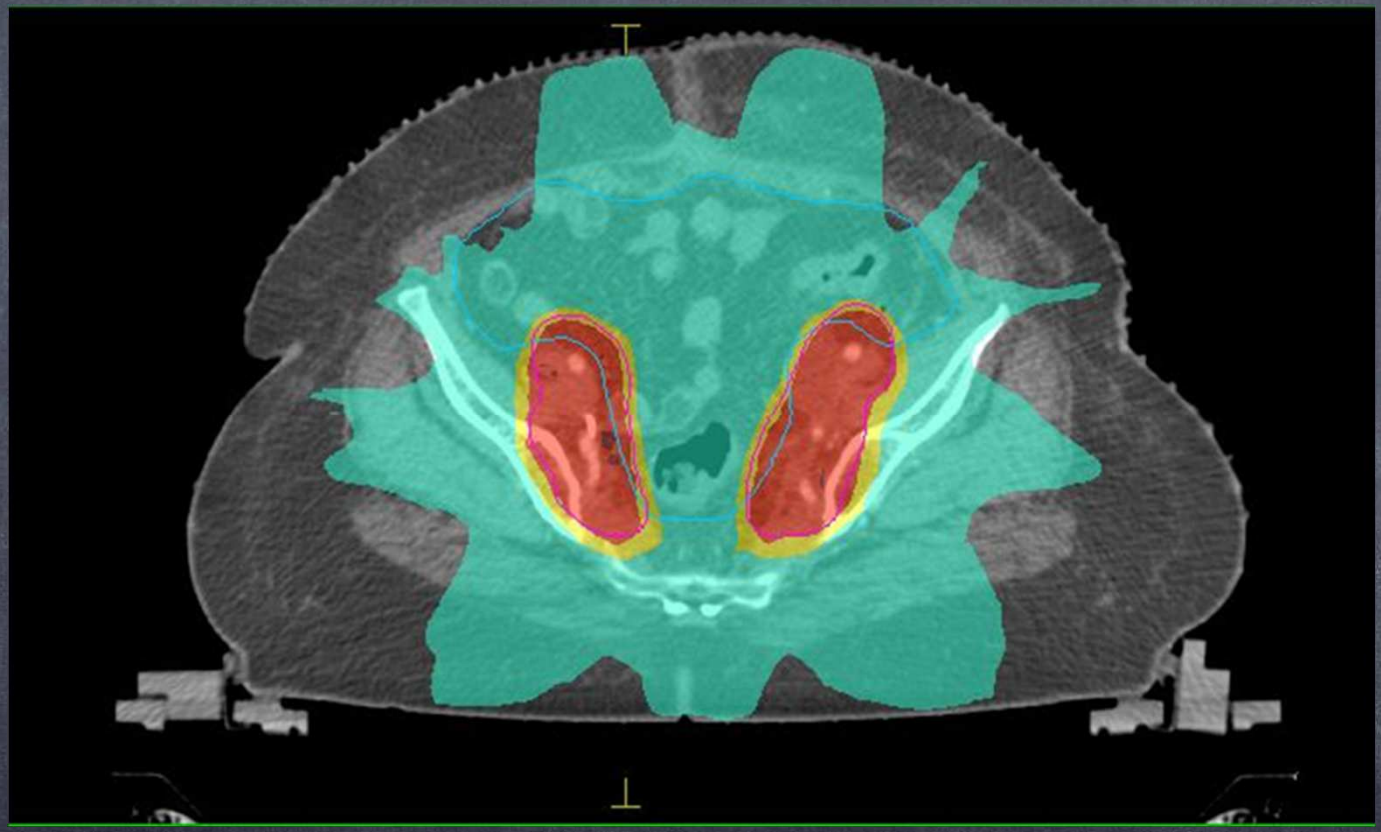
- Chen et al, Red Jou vol 87,2S 2013
  - repeat CT scan at mid treatment
  - Reduction in size by 42 %

Suggestion...
Needs to be replanned

Risk of second cancer...

- Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys 2003;56(1):83–8. 36.
- Hall EJ. Intensity-modulated radiation therapy protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys 2006;65(1):1–7
- Daniel et al,Second cancer risk estimation.Red Jou,74,2,2009.

Smaller area of high dose and larger area of smaller dose…



Secondary cancer risk estimation:....
(common in large areas of smaller dose than small areas of larger dose)

- dosimetric,CT based estimation

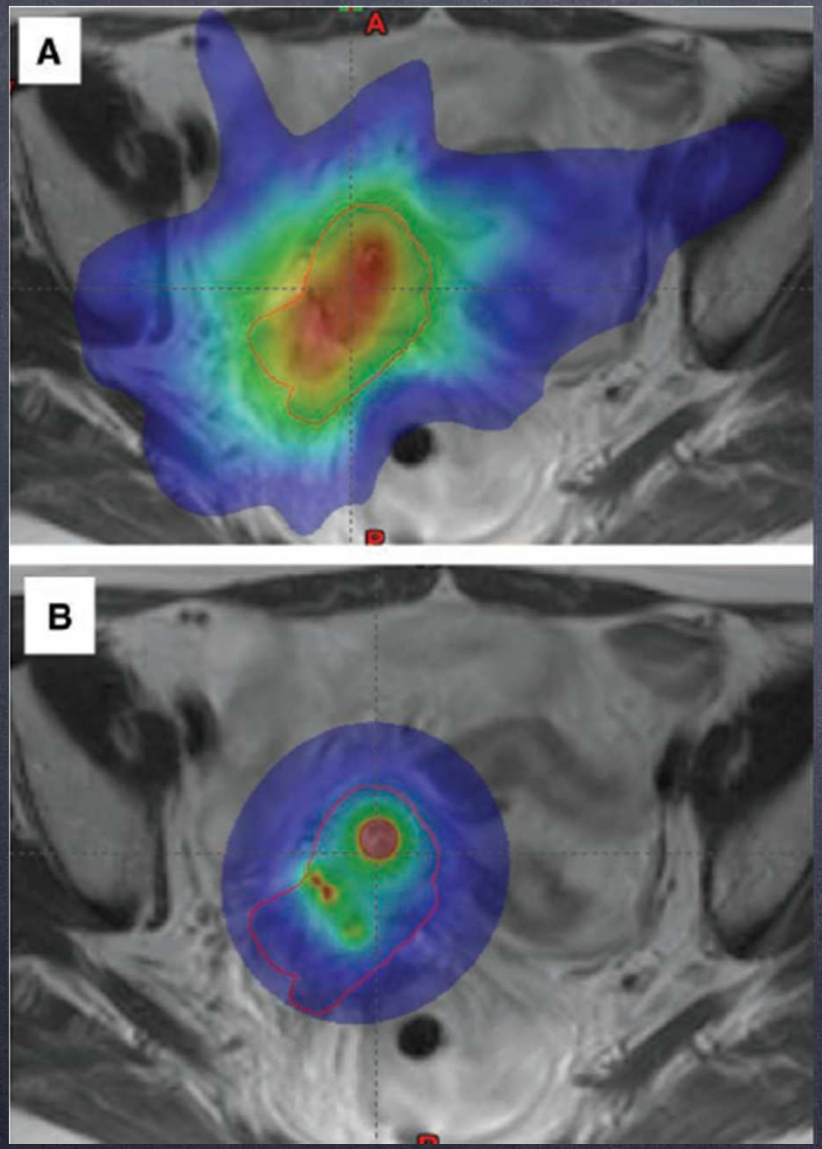
- Effective dose X tissue weighting factor, models for risk calculation
- Compared 3DCRT(4 beams),IM 6 MV(9 beams) and IM 18 MV(9 beams)- kept upper and lower borders same
- 0%,2% and 12 % for 3DCRT,6 MV and 18 MV respectively
- Large volume, higher MU,head leakage,collimator scatter,secondary neutrons (>10 MV)

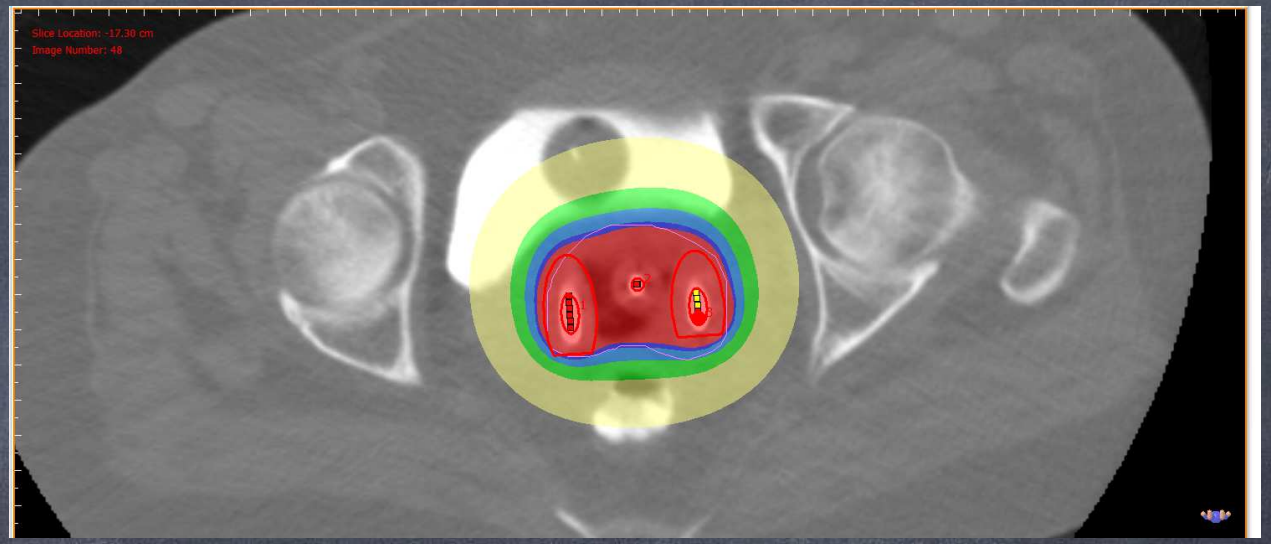
Although theoretical,possibility is still there,everything needs to be looked into and weighed against the expected benefit.

Can IMRT Replace Brachy ?

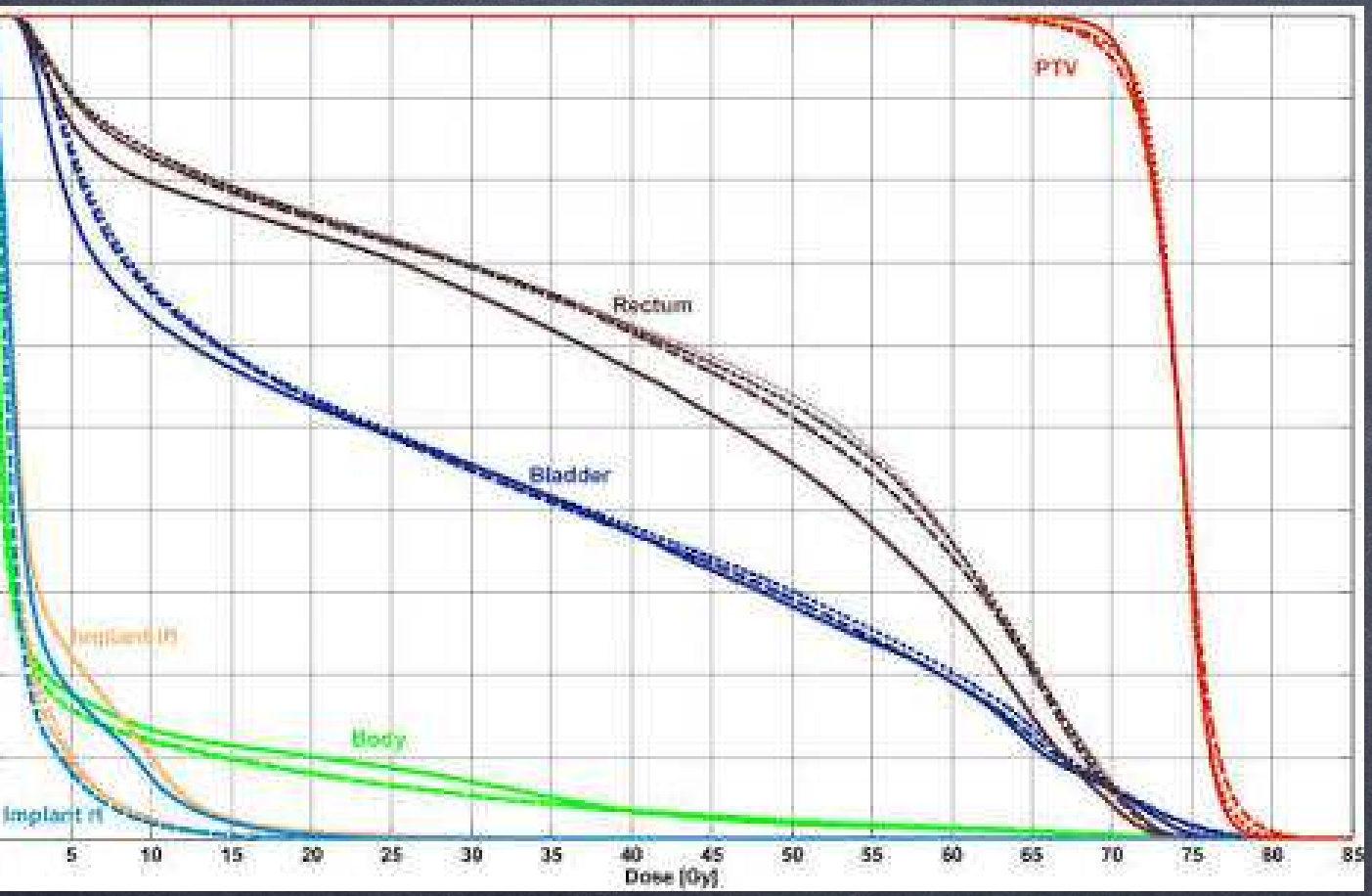
- Wahab et al et al, AGIMRT (Applicator guided IMRT),dosimetric,mean percent tumor volume getting the prescription dose was higher for the AGIMRT (90 vs 58, p = 0.005)
  - conceptual advantages?
- Roeske,Mundt et al…
  - only upto 77-80 Gy can be delivered with IMRT, with increased rectal toxicity

IMRT vs Brachy….





DVH....


PTV
Rectum
Bladder
Body
Implant #1
5
10
15
20
25
30
35
40
45
50
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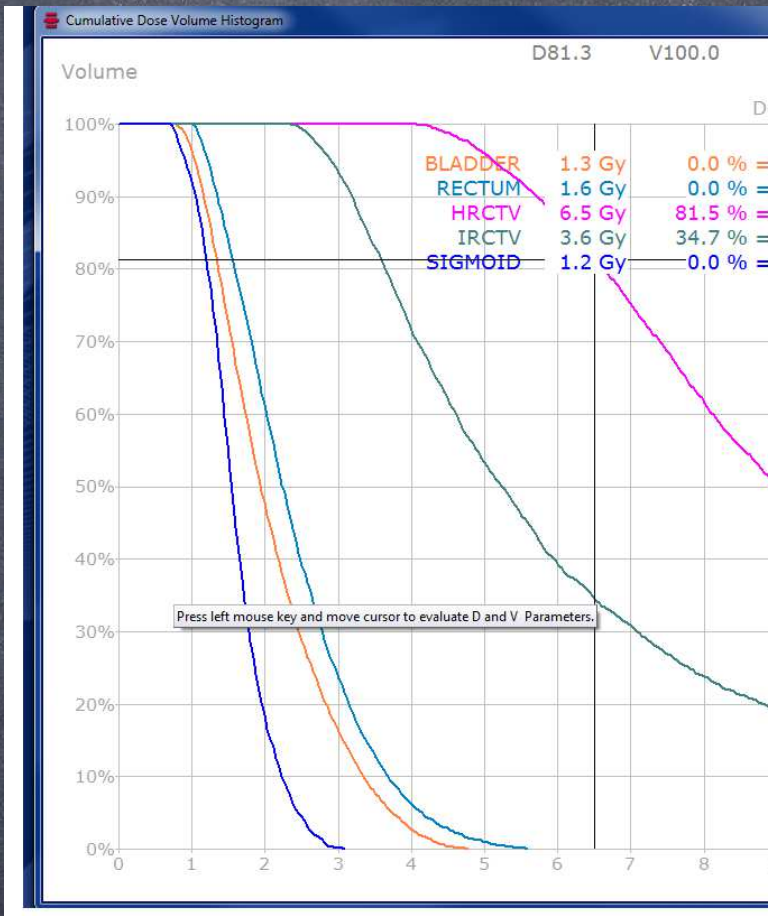
60
65
70
75
80
85
Dose [Gy]


Cumulative Dose Volume Histogram
D81.3
V100.0
Volume
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
BLADDER 1.3 Gy 0.0 % =
RECTUM 1.6 Gy 0.0 % =
HRCTV 6.5 Gy 81.5 % =
IRCTV 3.6 Gy 34.7 % =
SIGMOID 1.2 Gy 0.0 % =
Press left mouse key and move cursor to evaluate D and V Parameters.
0
1
2
3
4
5
6
7
8

Other aspects of planning...

- Simulation related…not possible in prone and with immobilization, frog leg position..
- Longer time, higher MU
- Problems of inverse planning Vs human planner
- Stringent QA/expertise/cost
- Relatively lesser dose from EBRT (mostly from brachy)

When should IMRT be used...

- Postop
- gross nodes - pelvic & para aortic
- cases medically unfit for brachy
- Vault ca
- IBS
- residual and recurrent

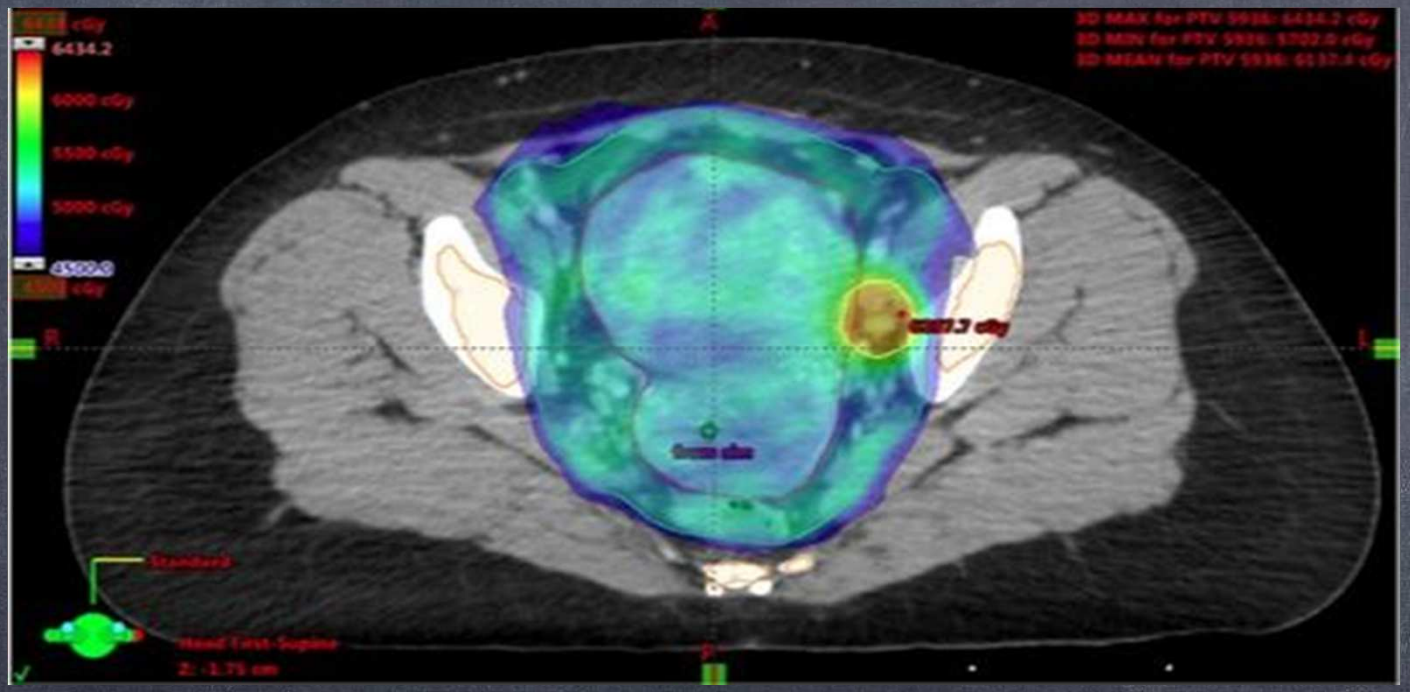
Post op

Portelance L et al. Post-op IMRT with chemotherapy for patients with cervical Carcinoma/RTOG 0418 phase II study. Red jou. 2009;75(3):S640–1.

Extended field

Small Jr W et al. EF RT and ICBT with cisplatin and amifostine for cervical cancer with positive lymph nodes: results of arm II of (RTOG) 0116. Int J Gynecol Cancer 2011;21(7):1266–75.

Pelvic nodal boost.....



Previously treated

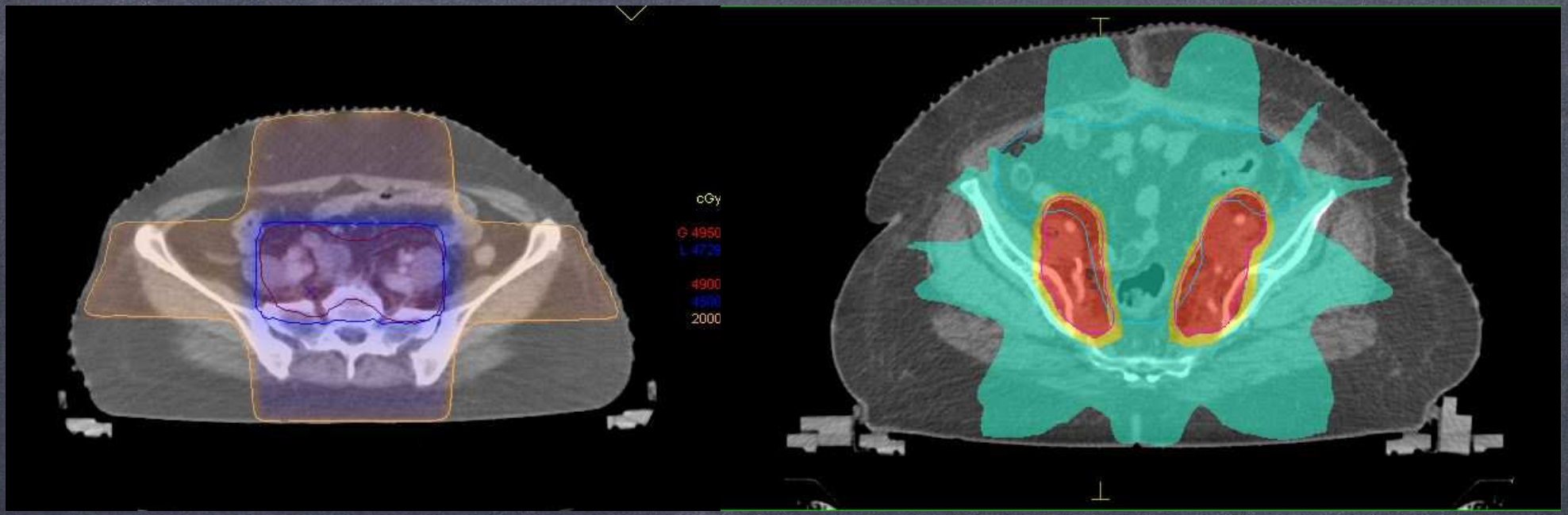
- University of Chicago…

	IMRT	Conventional	P value
Gr II enteritis	60%	91 %	0.002
Gr I	34%	75%	0.001
Rarely needed medication	75%	35%	0.001
GU gr II	10%	20%	0.22
GI symp at 20 mths F/u	11.1%	50%	
≥Gr II haematological	31%	60%	

Dose escalation….MD Anderson…

- For gross nodes..
- Pelvic nodes upto 64 Gy, 2.2 Gy/Fr,50 Gy to microscopic disease
- Para aortic upto 70 Gy
- 5 years NED

3DCRT vs IMRT....



Going forward...

- Sagae,Small et al.Advances & concepts in cervical cancer trials.A roadmap for the future. Int Jou Gynae Ca 2016,26(1):199-207
- GCIG …Gynaec cancer Inter Group formation from all over the world
- Collaborate,identify the problems,fund ,QA and do trials in next 2-3 years.

Ongoing…

- NCI 10-269,LN +ve cervical cancer,
- Protons/3 DCRT/IMRT
- Side effects,QOL,Survival

To Sum Up….

- Trials with longer follow up are slowly coming up
- Dosimetric studies have shown theoretical benefits
- Clinical benefits in terms of reduced enteritis are apparent
- NOT A SUBSTITUTE for brachytherapy
- Beneficial in selected cases.. Postop, gross nodes, para aortic, cases medically unfit for brachy, Vault ca,IBS,residual and recurrent lesions

whenever IMRT is done . . . .

- Make sure your QA is precise
- use adequate margins
- Respect the OARs,evaluate the plan systematically
- If margins are inadequate, do IGRT on all days

Learning objectives ....

- To list the available trials on advanced technology
- To identify the limitations of conventional radiation
- To list the benefits of advanced technology
- To define the selected role of advanced technology for cervical cancer

Any queries???