Plan evaluation in Ca Cervix Focus on target coverage and reducing toxicities

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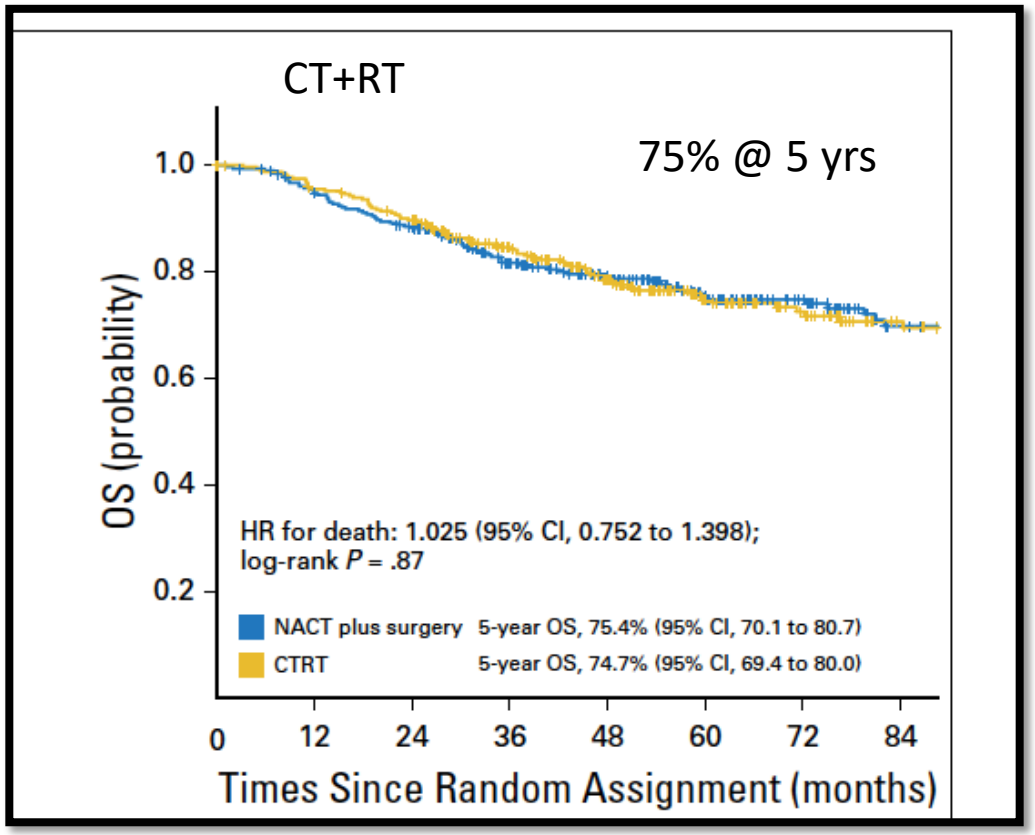
Overview

- External Radiation for Node Negative (IB1-IIIB,IVA) and Node Positive Cervix Cancer (IIIC1-IIIC2)
- Comprehensive Dose evaluation EBRT+BT: Tumour Control and Toxicity
- Postoperative Radiation: Tumour Control and Toxicity
- Post Surgical Recurrent Cancers
- Late Morbidity and Dose Response Relationship

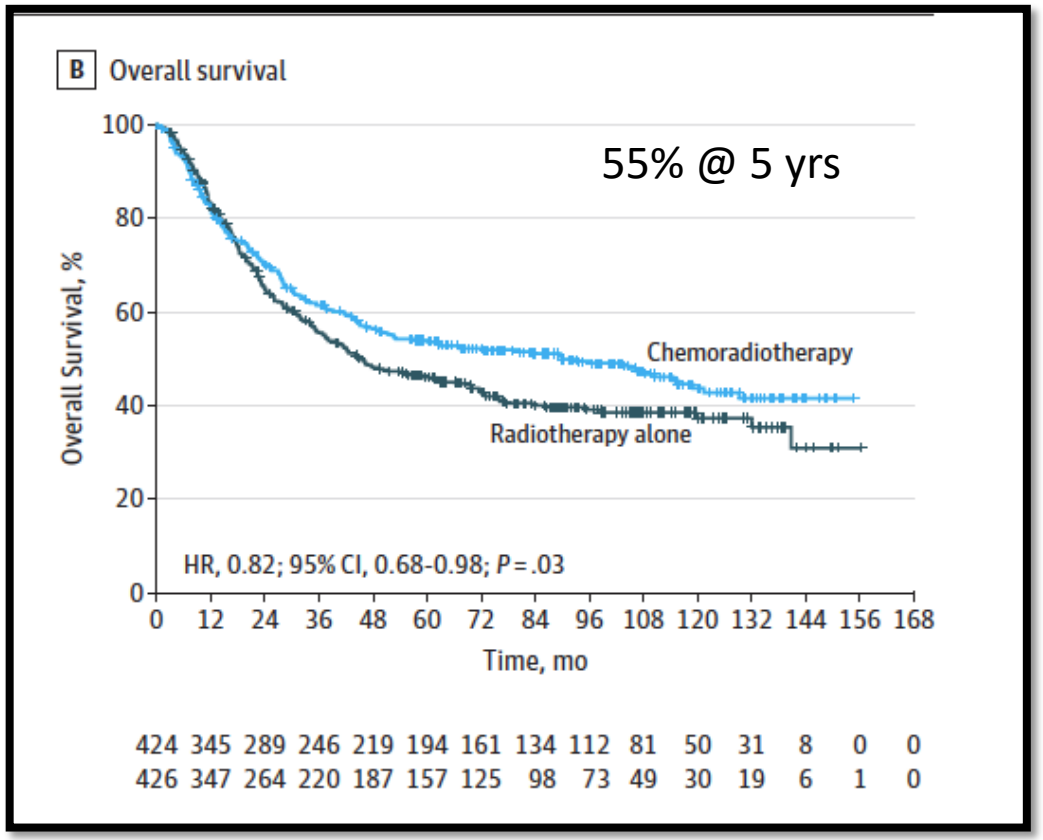
Outcomes of 2D RT (Con Chemo) and 2D BT in Randomized Trials 2003-2011

Stage IB2-IIB



Gupta et al, JCO 2018

Stage IIIB



Shrivastava et al, JCO 2018

70-75 Gy EQD2 Point A

Pelvic Failure Rates following Chemoradiation

	n	Stage	IB	IIB	IIIB	Overall[4]	Concomitant Chemotherapy
RetroEMBRACE 2016	731	IB: 17% IIB: 50% IIIB: 20%	4%	11%	25%	13%	77%
Perez 1998[1]	1499	IB: 33% IIB: 29% IIIB: 23%	12%	21%	41%	23%	0%
Barillot 1997[1]	1875	IB: 26% IIB: 29% IIIB: 25%	13%	24%	49%	NA	0%
Vale 2010[1]	471	IB: 11% IIB: 51% IIIB: 23%	NA	NA	NA	22%	100%
Vale 2008[2]	3.128	IB: <24% IIB: 36% IIIB: 38%	NA	NA	NA	23%	50%
Rose 1999[3]	176	IIB: 58% IIIB: 39%	NA	NA	NA	19%	100%
Whitney 1999[3]	169	IIB: 61% IIIB: 34%	NA	NA	NA	>25%	100%
Eifel 2004[3]	195	IB2: 33% IIB: 36% IIIB: 25%	IB2 + IIB: 13%		29%	17%	100%
TATA 2018[3]	317	IB2: 18% IIB: 57%	IB2 + IIB: 14%		-	14%	100%
TATA 2018[3]	424	All IIIB	–	–	29%	29%	100%

Increasing Pelvic Failure Rate as a function of FIGO Stage.

11-24% pelvic failure rate in Stage II B

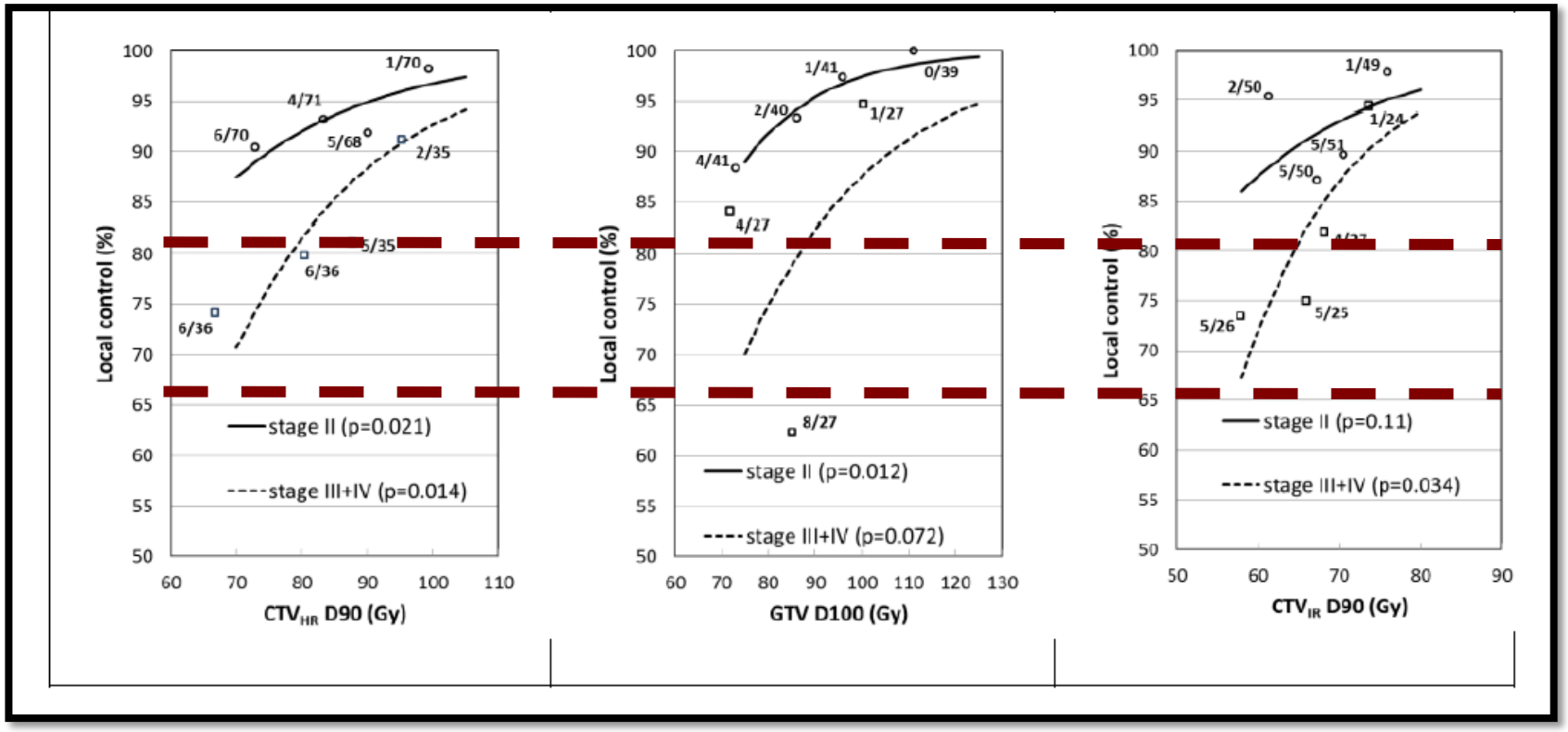
25-49% failure rate in stage III B

Limited correlation with point A dose.

Conventional Brachytherapy Associated with Pelvic Failure Rate of 11-49%

Distant Failure Rate of 25-49%

Primary Tumour Dose vs. Local Control

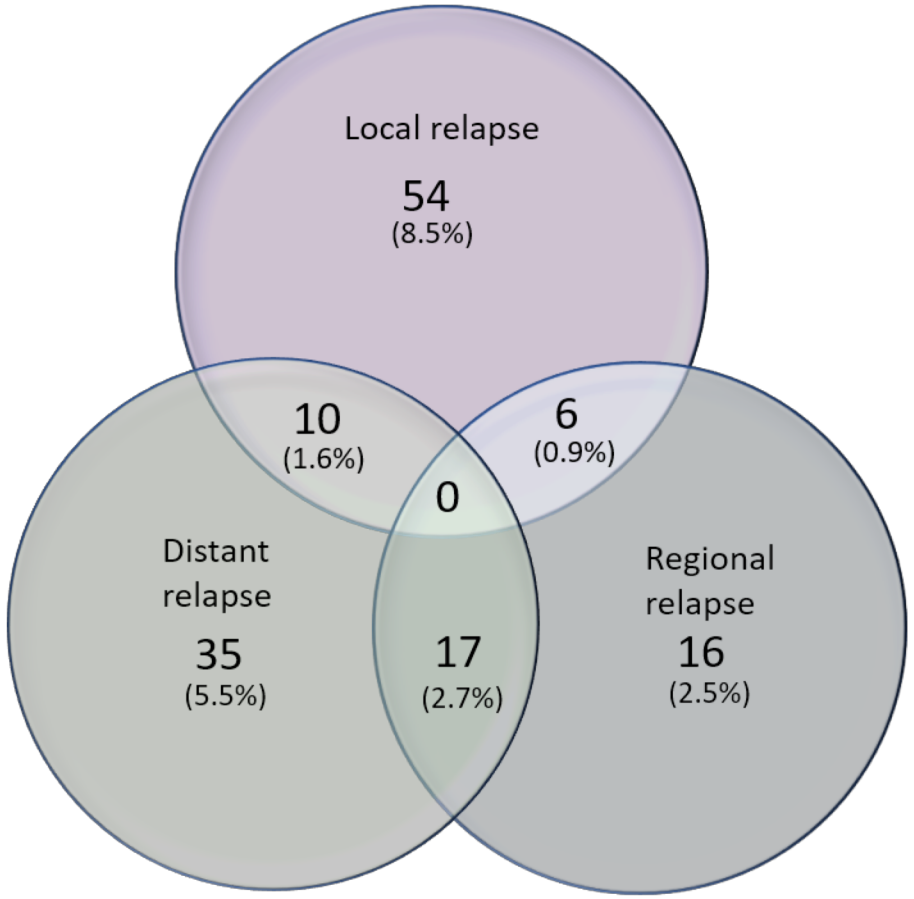


Maximum increment in Stage IIB- III B tumors and with large residual volume: Aim HRCTV D90 (85 Gy EQD2). Further dose escalation to 95 Gy under investigation

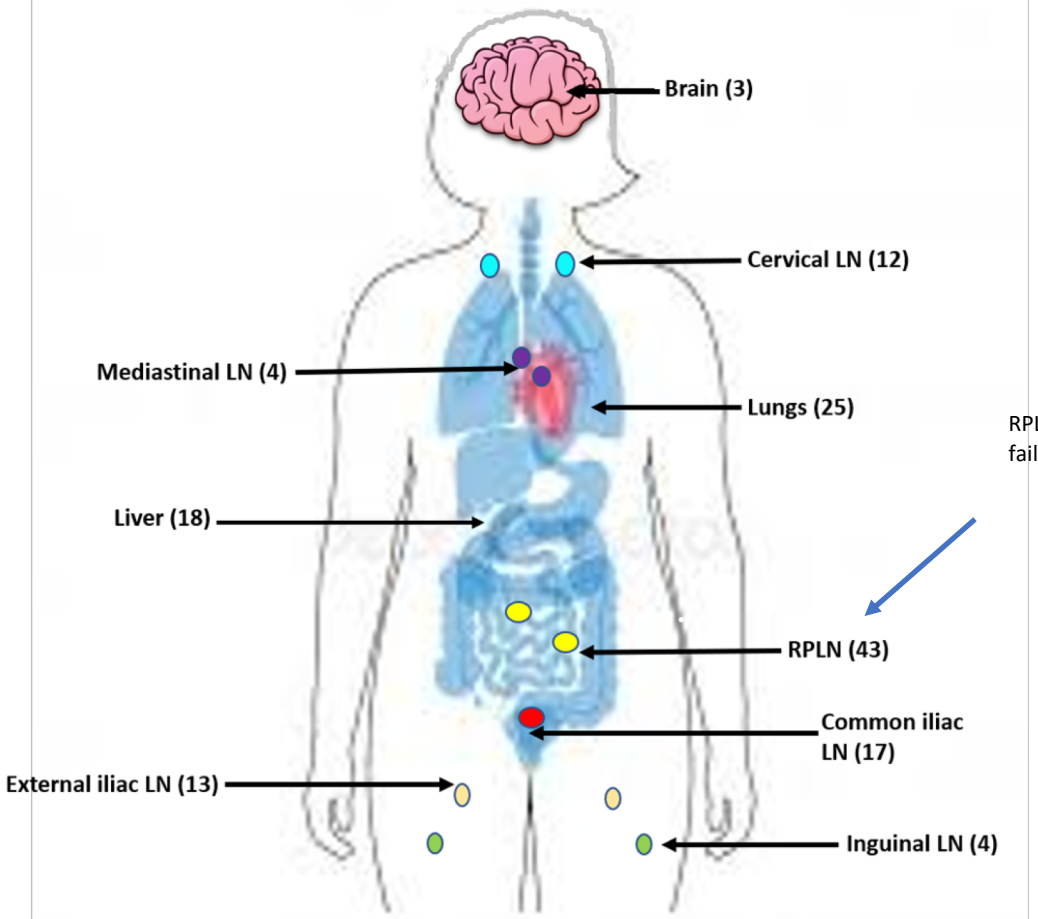
One can expect that outside the setting of. Advanced image guidance this may be associated with higher morbidity and doses to OARs

Potter, R, CTRO 2018

Pattern of Failure of patients treated with Dose escalated Point A based treatment (80-84 Gy)



Venn diagram depicting patterns of relapse.



RPLN most common site of failure

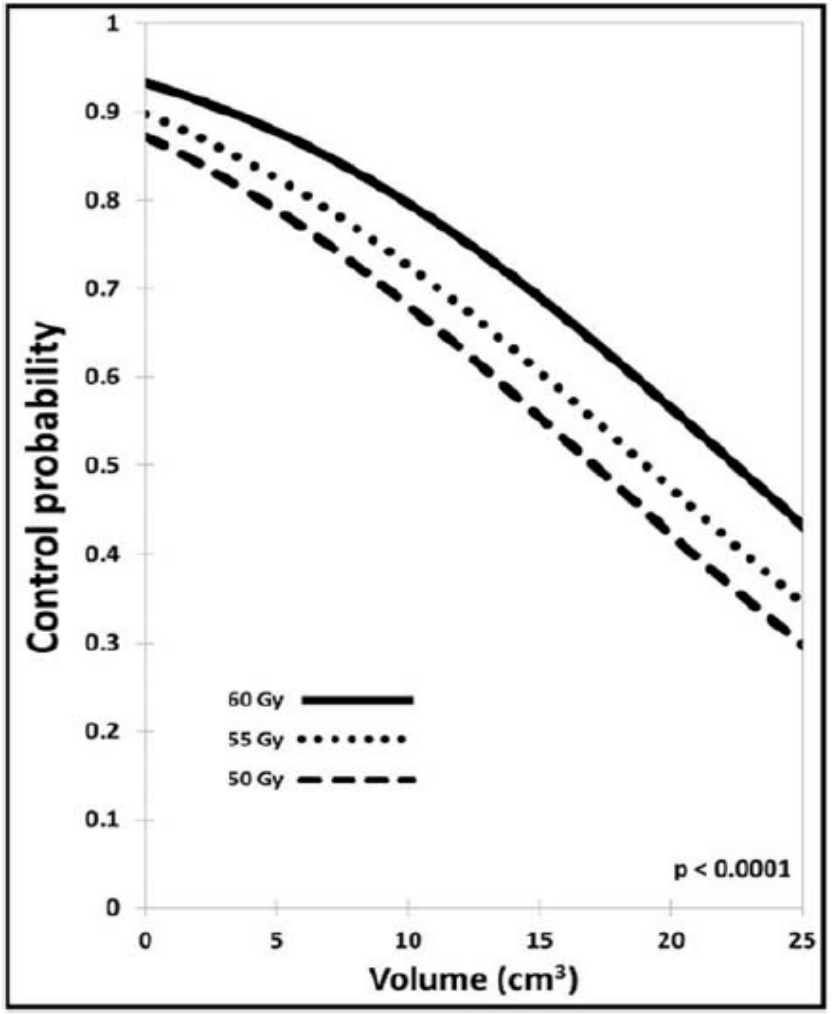
Diagram showing pattern of relapse- Total cases with distal/ distal+ nodal/ regional relapse- 84(excluding local relapse)

Raut, Mittal, Chopra, IJROBP 2020

Nodal Dose Escalation

- Investigated nodal control probability (NCP) according to dose/volume parameters.
- Nodal boost in 75 patients, with 254 unresected pathological nodes.
- SEB→ 63 patients → 1.8-2Gy/#
- SIB→ 12 patients → 50-55Gy/25#
- Overall nodal recurrence rate was 9.1%.
- Nodal volume (threshold: 3 cm3, $p<0.0001$) and LN dose (≥57.5 Gy, $p=.039$) were significant for nodal control.
- Use of SIB was borderline for significance ($p=.07$).

55-57.5 Gy/25# Nodal Dose



Bacarro, Chargari, J Gyn Onco 2017

Pooled Toxicity Results following chemoradiation for cervix cancer and conventional BT

Author	Odd's Ratio (Acute Grade III-IV)
Green,2001	Hemat : 8.6 GI: 2.2
Cochrane, 2005	Hemat : 8.6 GI: 2.2
IPD,2008	Hemat=2-10 GI: Significant Increase
Cochrane,2010	Hemat : 8.6 GI: 2.2
Cochrane IPD,2010	Hemat=2-10 GI Significant Increase

- Increase in Acute Hematological and Gastrointestinal Morbidity with concurrent chemoradiation.
- Suboptimal documentation of Late Effects across chemoradiation trials.
- Traditionally 70-75 Gy has been delivered to point A.
- Dose escalation recommended within setting of Image Guided Brachytherapy
- Nodal Dose escalation use is increasing

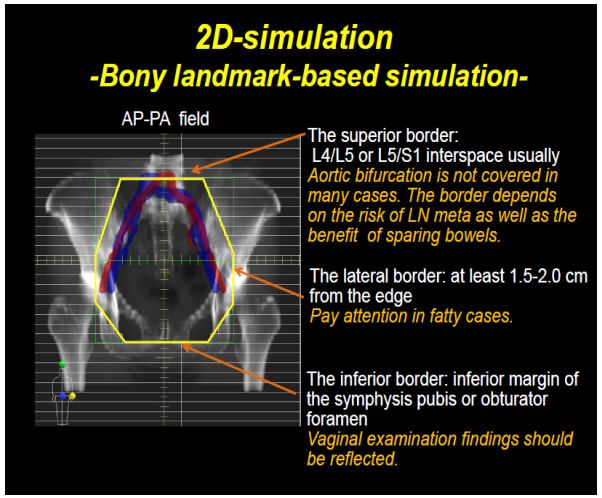
Clear need to reduce GI and Hematological Toxicity with IG-IMRT

Definitive PA Nodal RT +Chemo (Conventional)

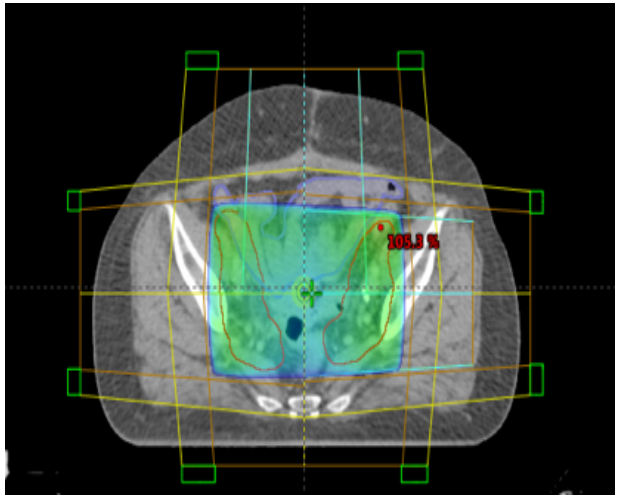
Study	N	Dose (Gy)	Technique	Chemotherapy	Acute Grade III/IV	Late Grade III-IV
Sood	54	45/25	3DCRT	CDDP wk 1/4/BT	77.5%	10%
RTOG 9210	29	54-58	HFRT 3DCRT (1.2 BID)	5FU/CDDP 3 wkly	80%	24%
GOG 125	86	45/30	3DCRT HFRT	5 FU/CDDP/3wkly CDDP 50mg	33.7%	14%
RTOG0116 Arm 1	26	55.8-64.8	3DCRT	CDDP Wkly	84%	40%
RTOG0116 Arm 2	16	55-64.8	3DCRT + AMF	CDDP wkly	87%	20%

Very High Rates of Grade III-IV Acute as well as late toxicity

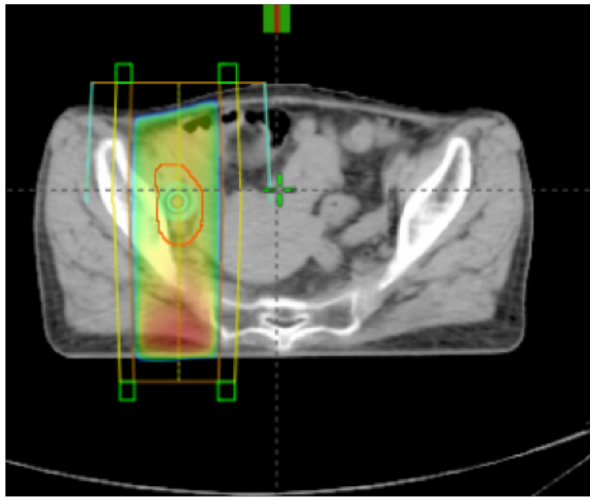
2DRT



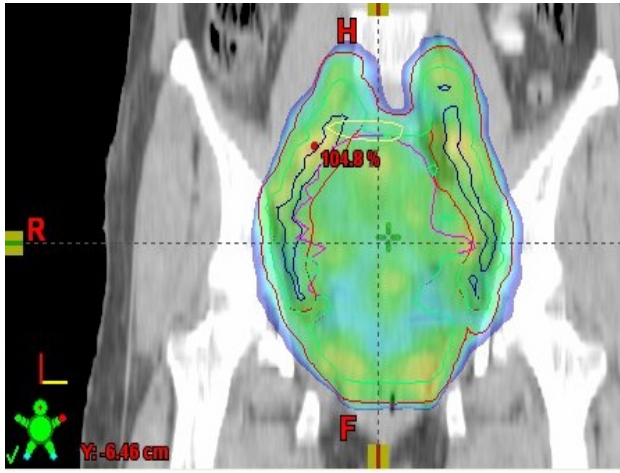
3DCRT



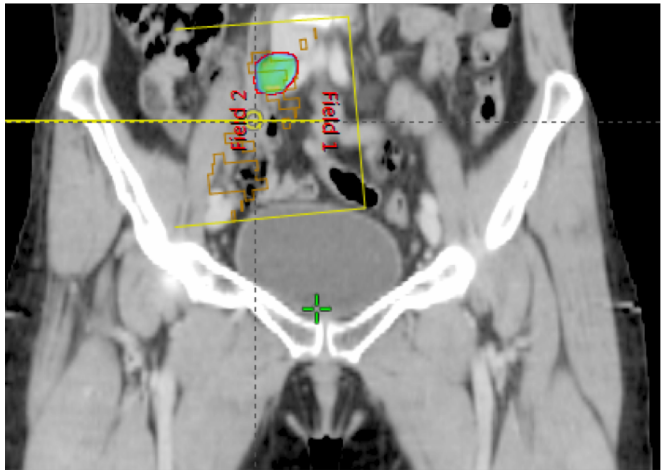
3DCRT with Nodal SEB



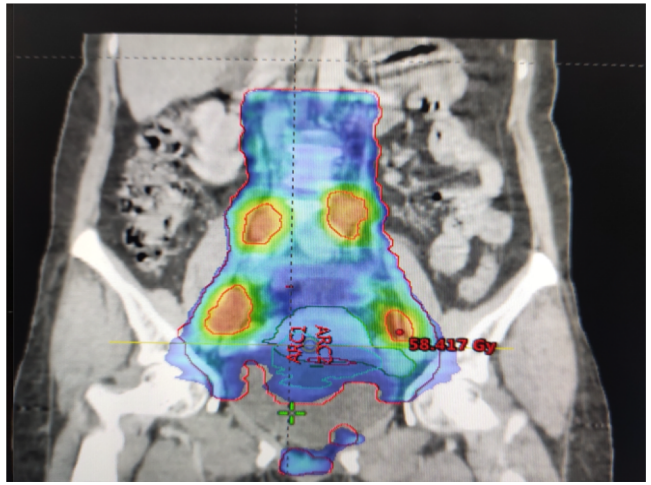
IMRT



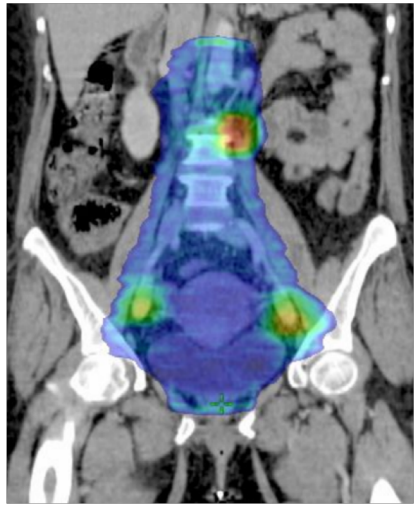
IMRT with Nodal SEB



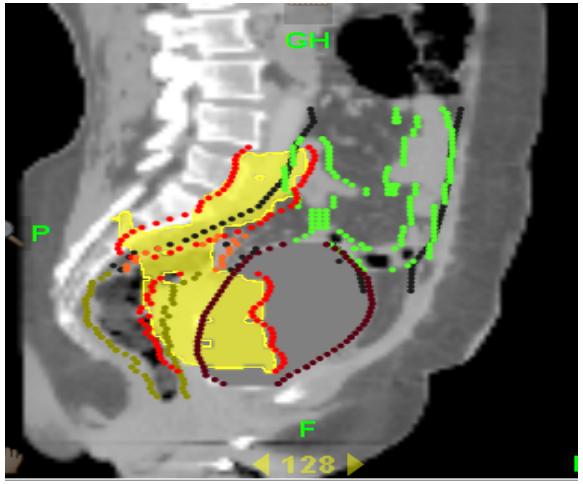
IMRT with Nodal SIB



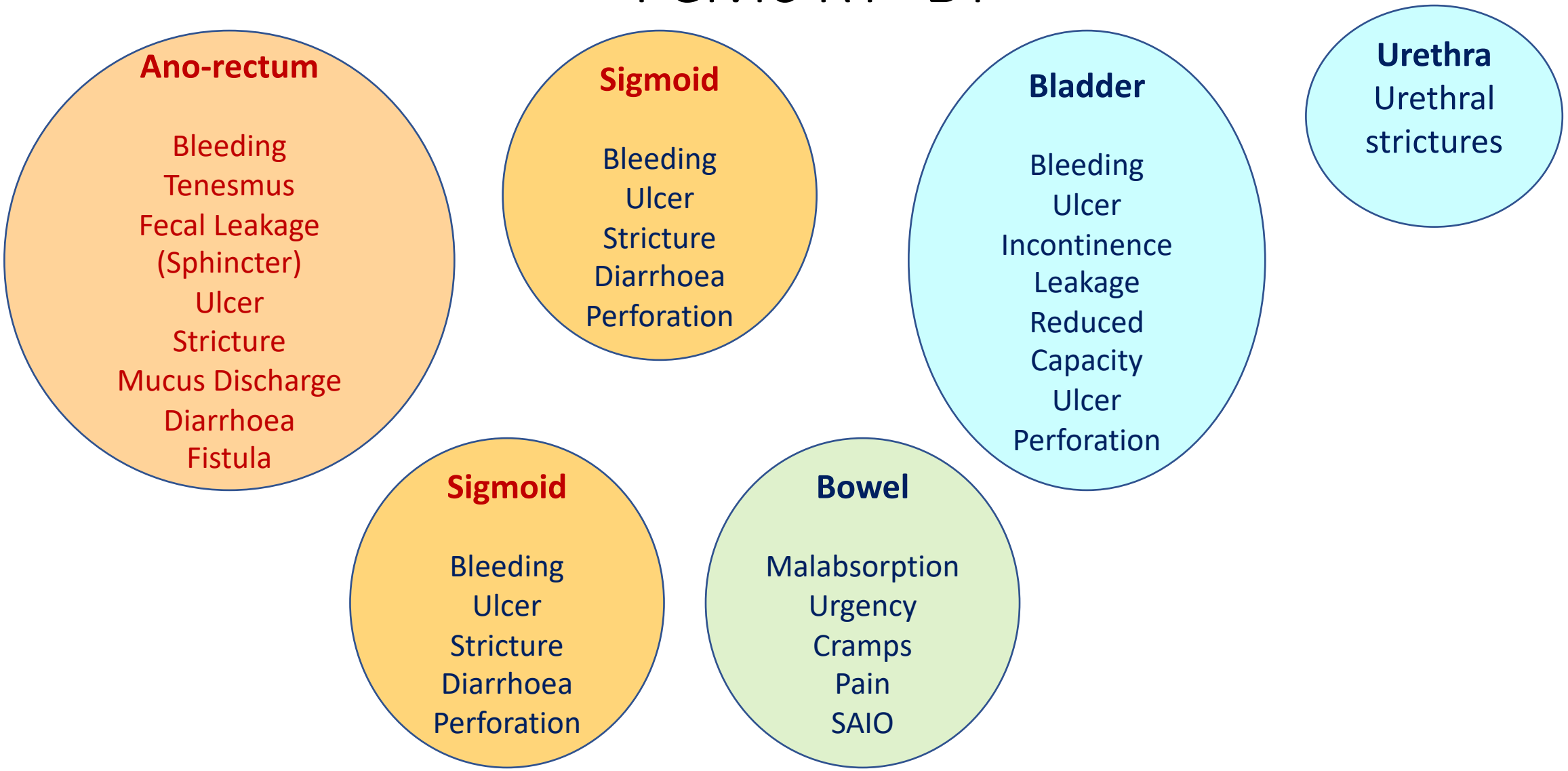
Extended Field RT with SIB



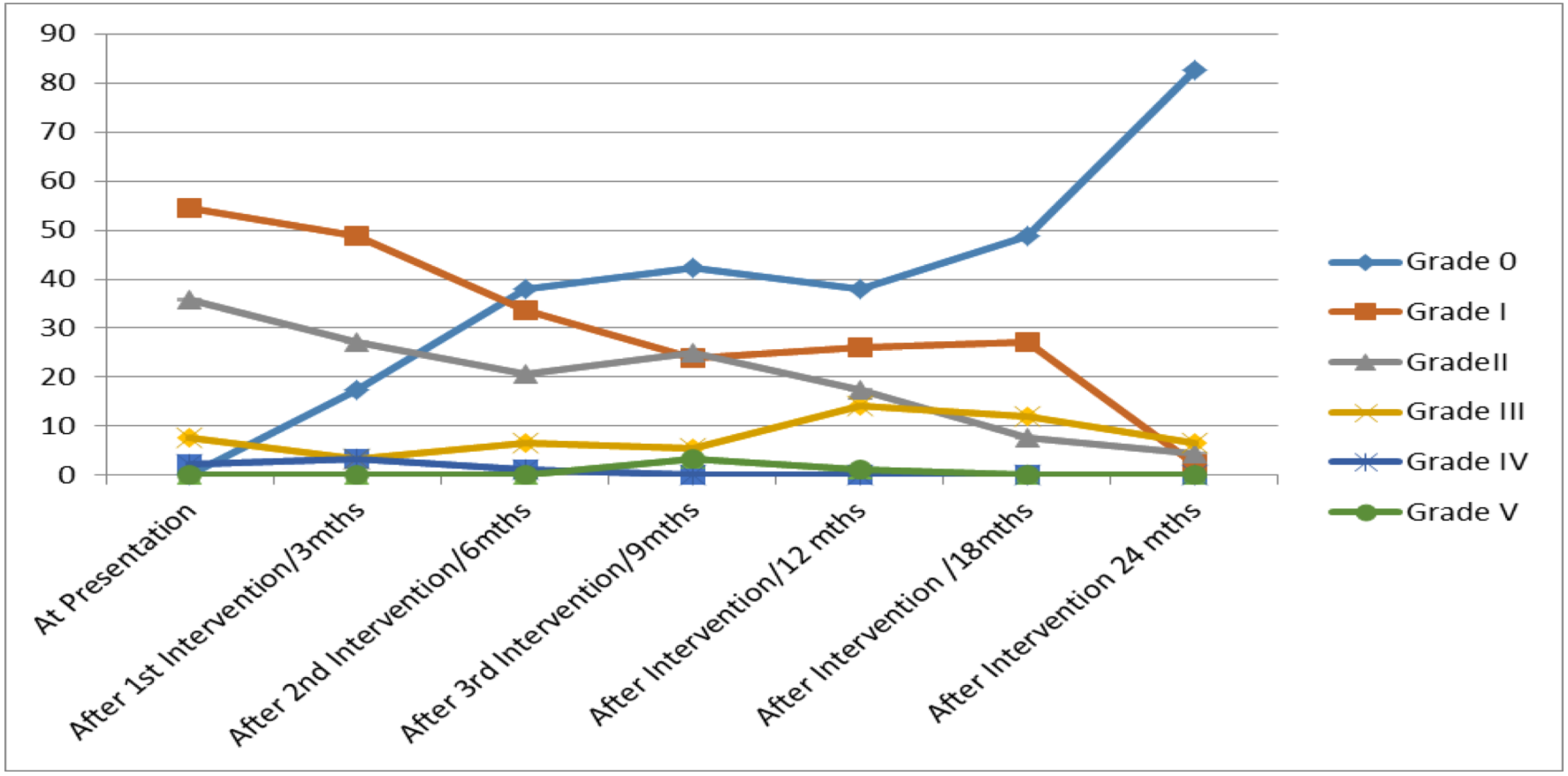
Postoperative IMRT



Pelvic OAR and Symptom Complex Morbidity of Pelvic RT+BT



Persistence Patterns of Late Toxicity

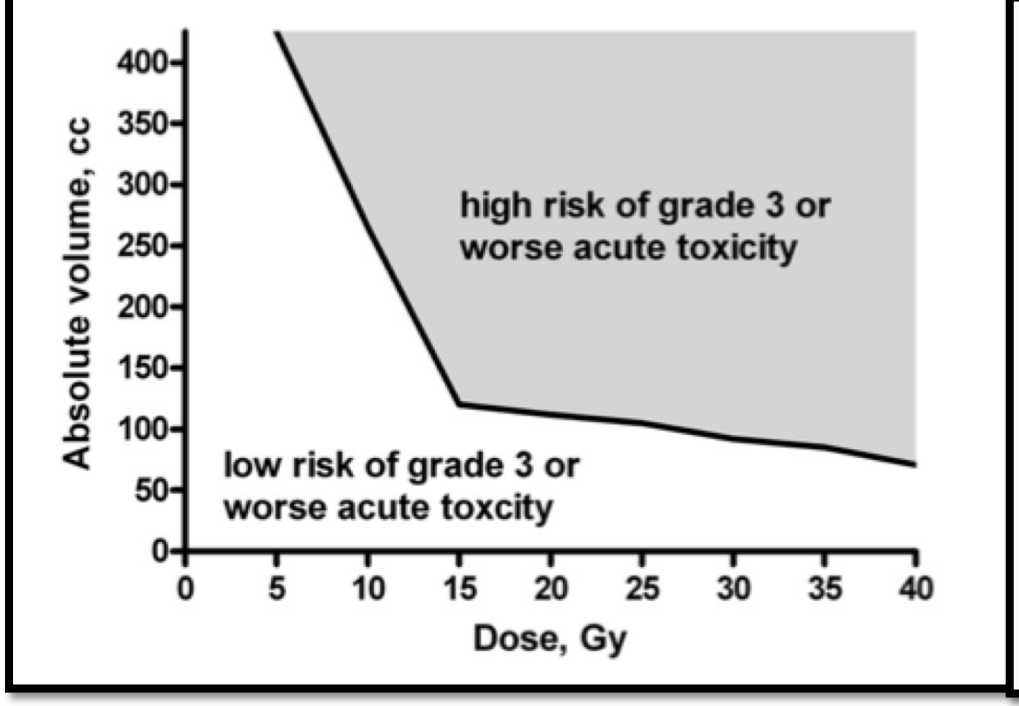


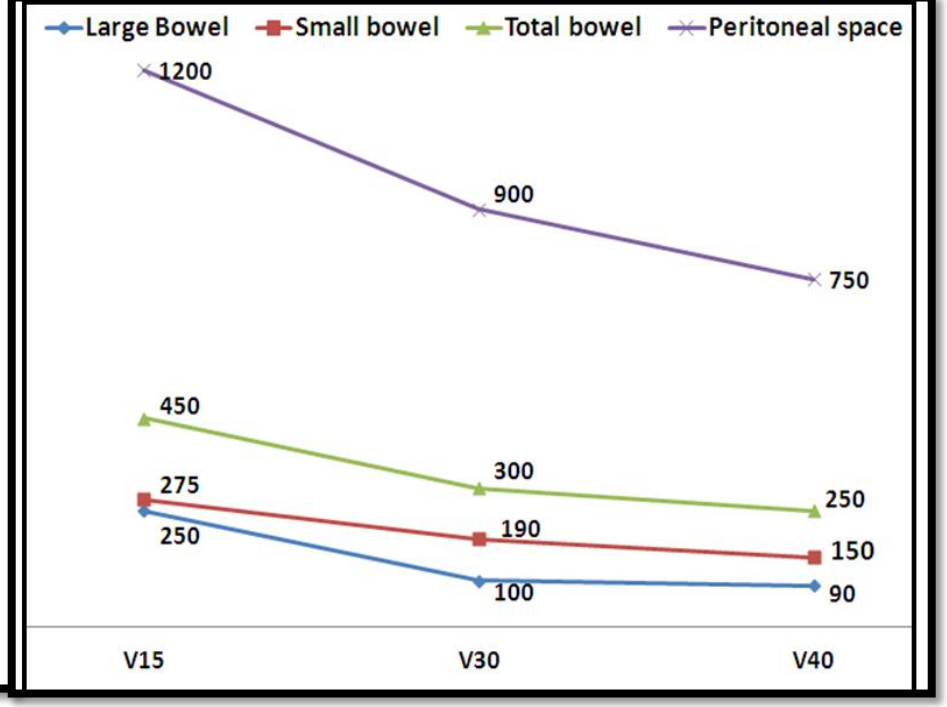
Graph Depicting overall temporal course of all grades of rectal toxicity over a period of 24 months in patients presenting wi
rectal toxicity: Tata Memorial Centre (N=90; 2011-2016)

Shejul, Chopra, Ranjan, Manuscript Peer review

EBRT and BT recommendations from various guidelines: Definitive and Adjuvant Setting

- Level I evidence for use of IG-IMRT for postoperative setting (PARCER/NRG 1203)
- IG-IMRT recommended as the preferred treatment approach by ASTRO,ESTRO guidelines in definitive setting (Gandhi,2013)
- NCG 2020 guidelines IG-IMRT as the preferred treatment approach for for stage III C1 and III C2 (Phase II studies)
- Image guided volume based brachytherapy should be the preferred approach when available. (ICRU 89)





QUANTEC

Rectal Cancer Patients

Baseline Bowel Symptoms

Non Homogenous Contouring Methods.

Correlates with Acute GI Toxicity.

Kavanagh, IJROBP 2010

ACTREC, TMC

Cervical Cancer: Adjuvant RT

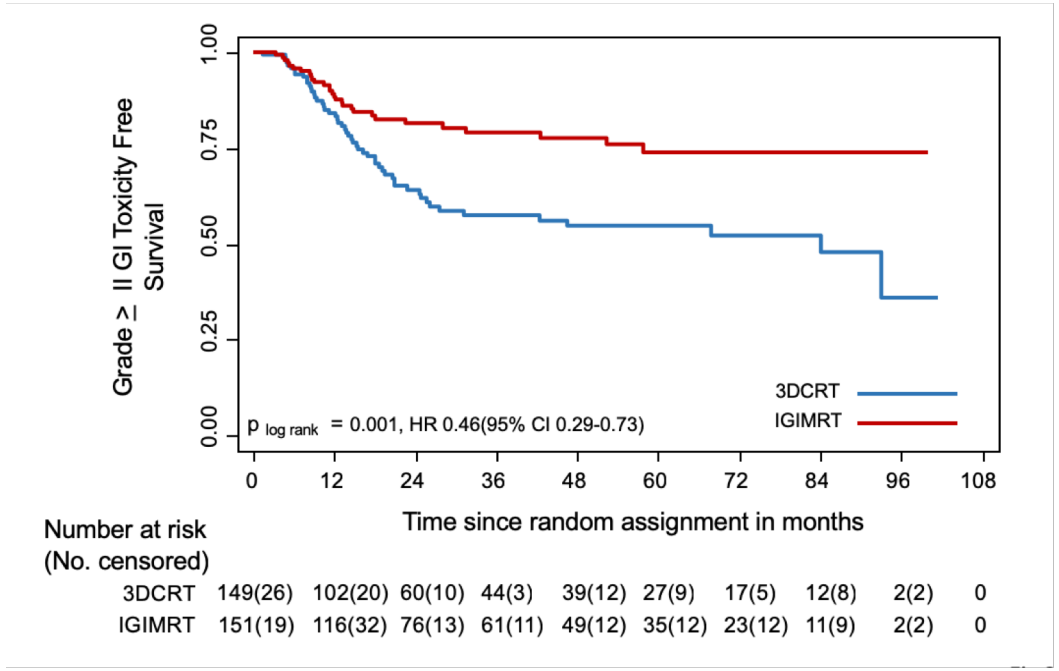
Minimal/No Baseline Bowel symptoms.

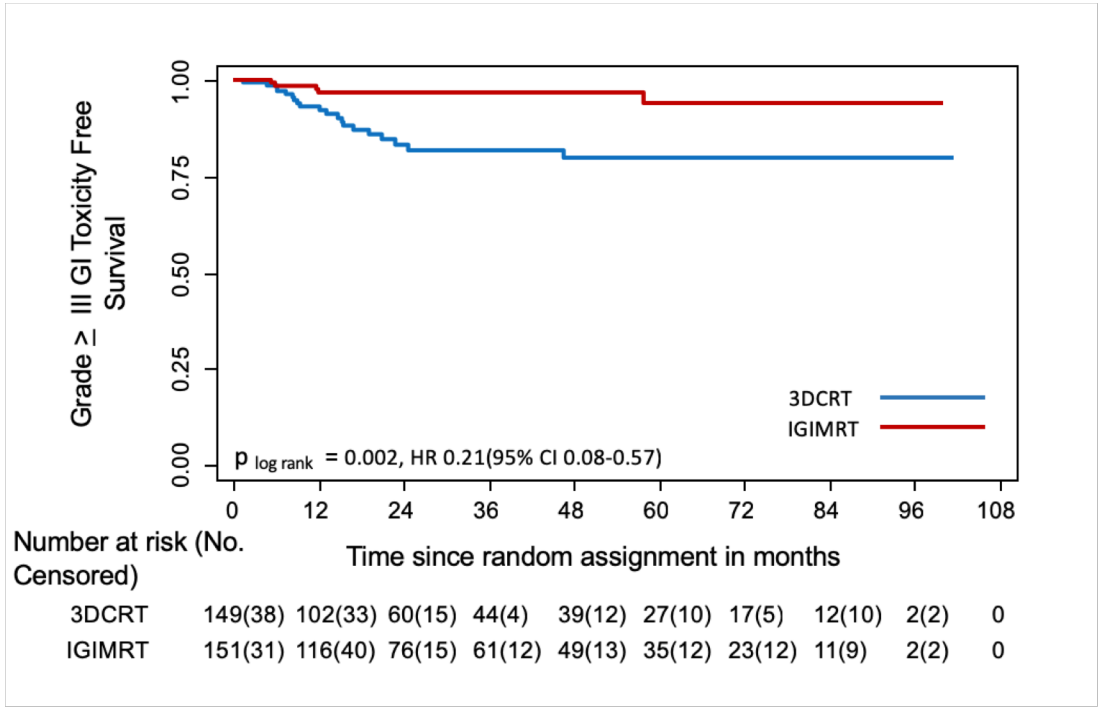
Applicable across contouring methods.

Correlates with late GI toxicity.

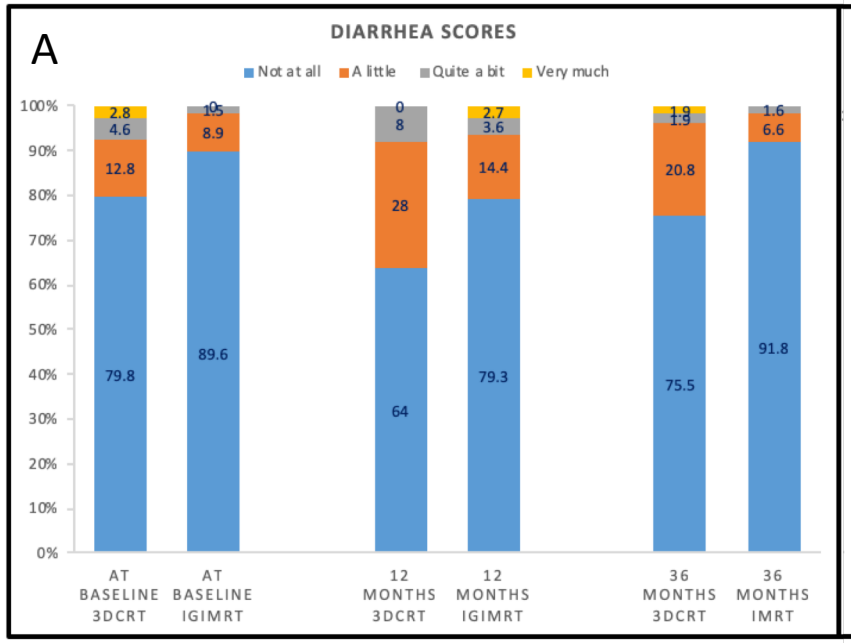
Chopra, S , Tapas Dora IJROBP 2014,
Chopra, S, R Krishnatry, BJR 2015

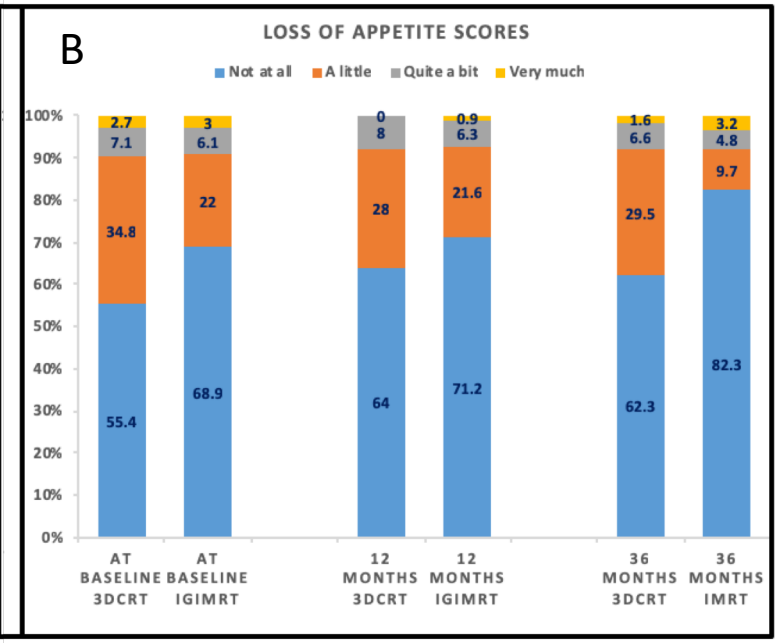
Final Analysis: PARCER Trial

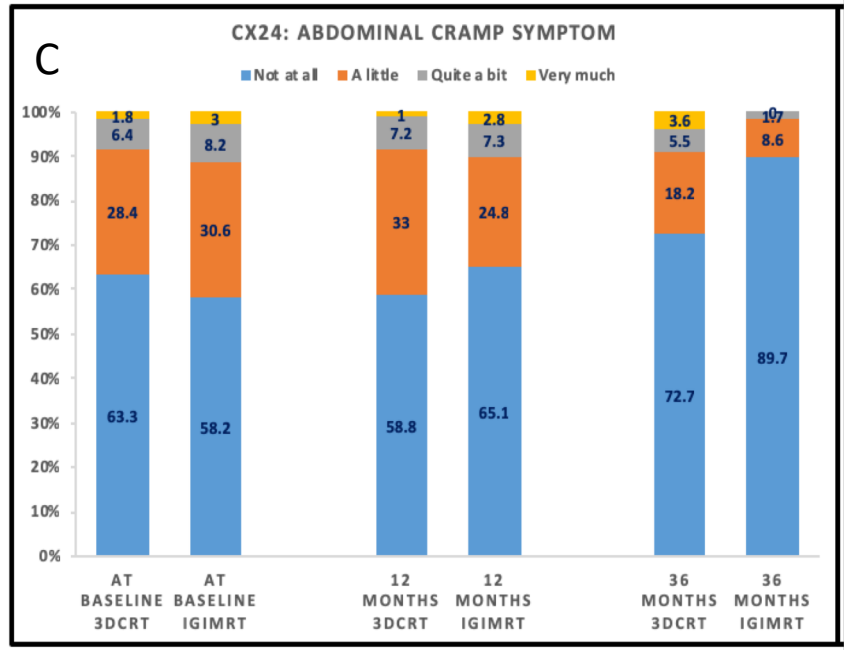


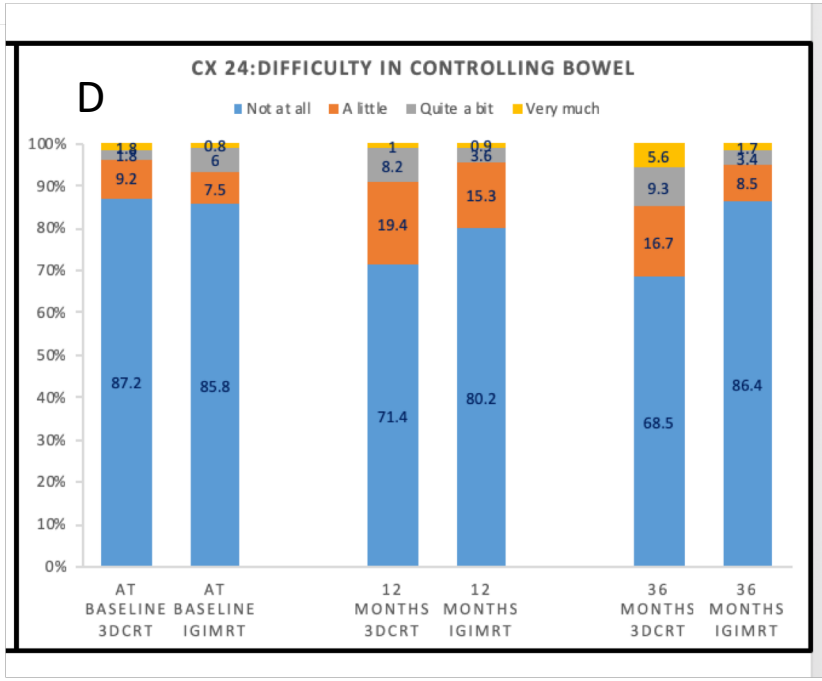


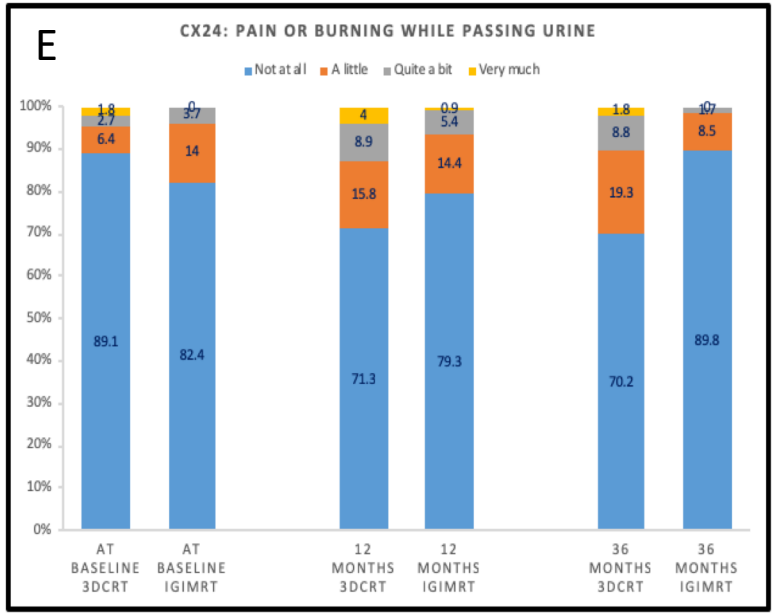
Chopra S, ASTRO 2020

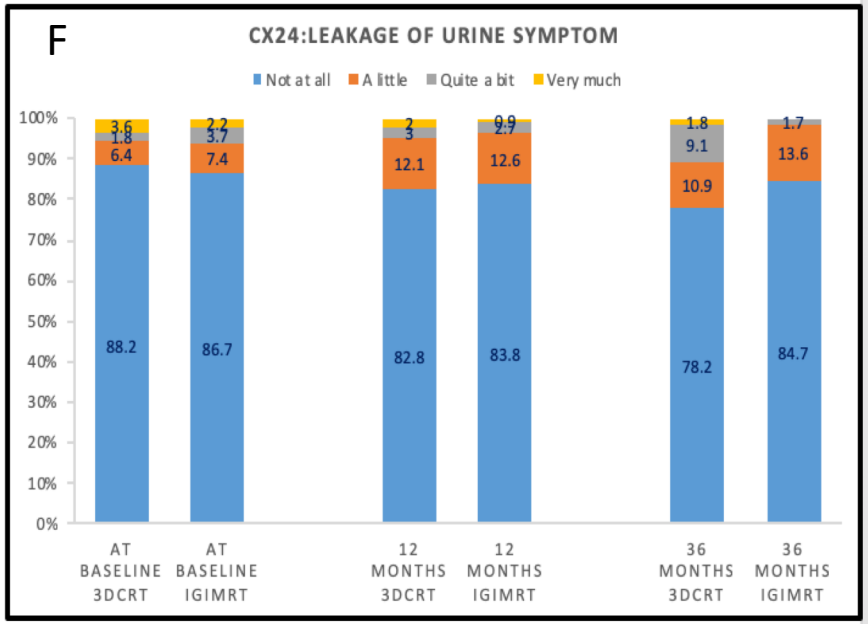












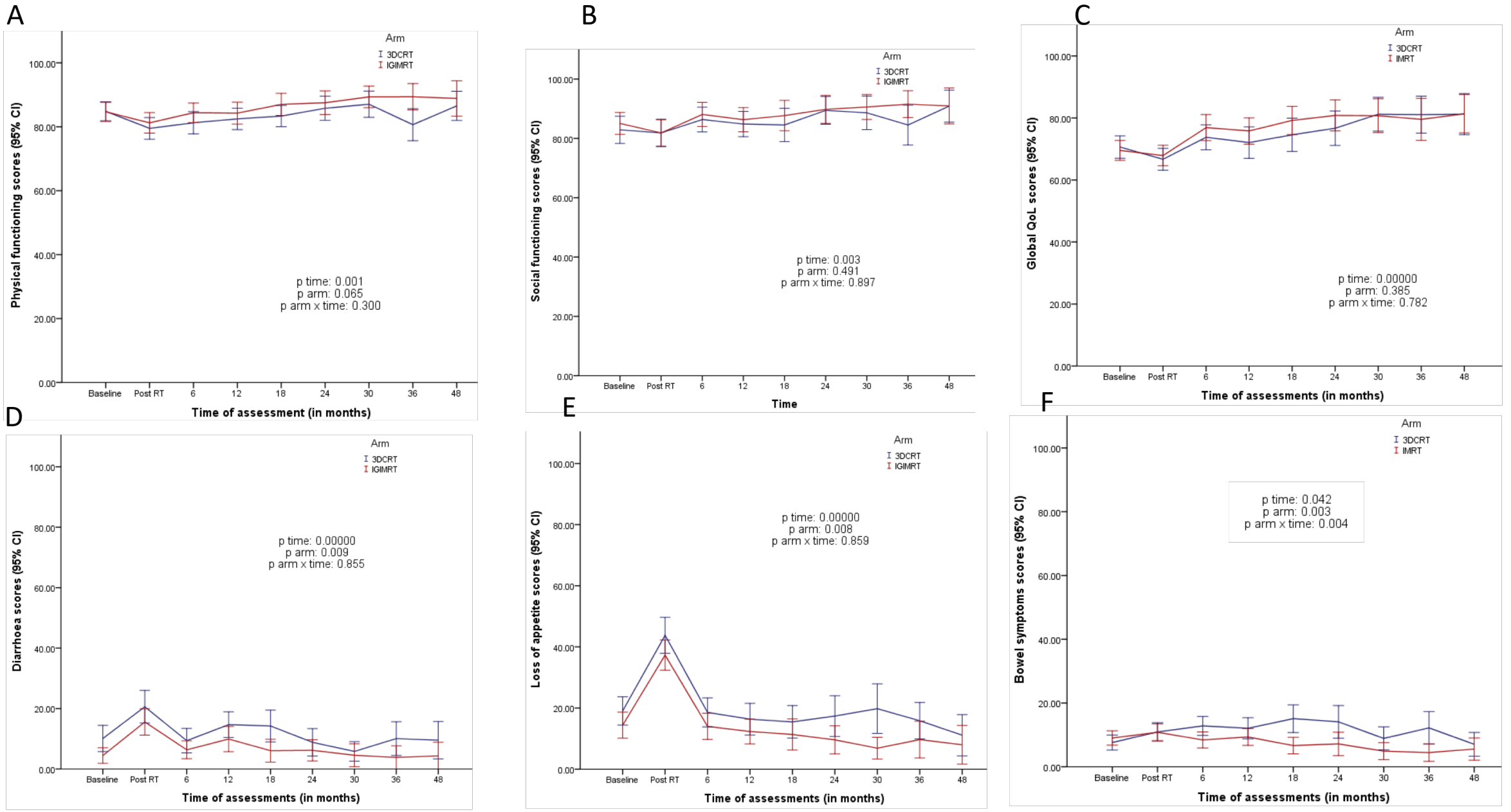


Fig 3 A-F

Dose Constraints for Target during Radical EBRT

		Hard dose constraints	Soft dose constraints
Targets	PTV45	V95% > 95% Dmax<107%*	
	ITV45	Dmin> 95%	
	PTV-N(#)	D98% > 90% of prescribed LN dose Dmax < 107% of prescribed LN dose	
	CTV-N(#)	D98% > 100% of prescribed LN dose	D50% > 102%
Help contour	CTV-HR +10mm		Dmax < 103%
OARs	Bowel	Dmax < 105% (47.3Gy)*	When no lymph node boost: • V40Gy < 100cm3** • V30Gy < 350cm3** When lymph node boost or para-aortic irradiation: • V40Gy < 250cm3** • V30Gy < 500cm3** Dmax < 57.5Gy
	Sigmoid	Dmax < 105% (47.3Gy)*	Dmax < 57.5Gy
	Bladder	Dmax < 105% (47.3Gy)*	V40Gy < 75%** V30Gy < 85%** Dmax < 57.5Gy
	Rectum	Dmax < 105% (47.3Gy)*	V40Gy < 85%** V30Gy < 95%** Dmax < 57.5Gy
	Spinal cord	Dmax < 48Gy	
	Femoral heads	Dmax < 50Gy	
	Kidney	Dmean < 15Gy	Dmean < 10Gy
	Body	Dmax < 107%*	
	Vagina PIBS-2cm		When vagina not involved: $D_{PIBS-2cm}$<5Gy
Optional	Ovaries	<5-8 Gy	
	Duodenum***	V55<15cm^3	

EMBRACE II pprotocol

PTV: Aim 95% coverage to 95% (Not 100%)

Internal Target Volume: Aim coverage of 99% by 95%

Nodal SIB: Large Volumes can lead to excessive Toxicity

Aim: Nodal Dose escalation to Gross Nodes/CTV

PTV: 10% cooling at the periphery

Additional : Bone Marrow

AVOID SIB HOTSPOTS in HELP CONTOUR

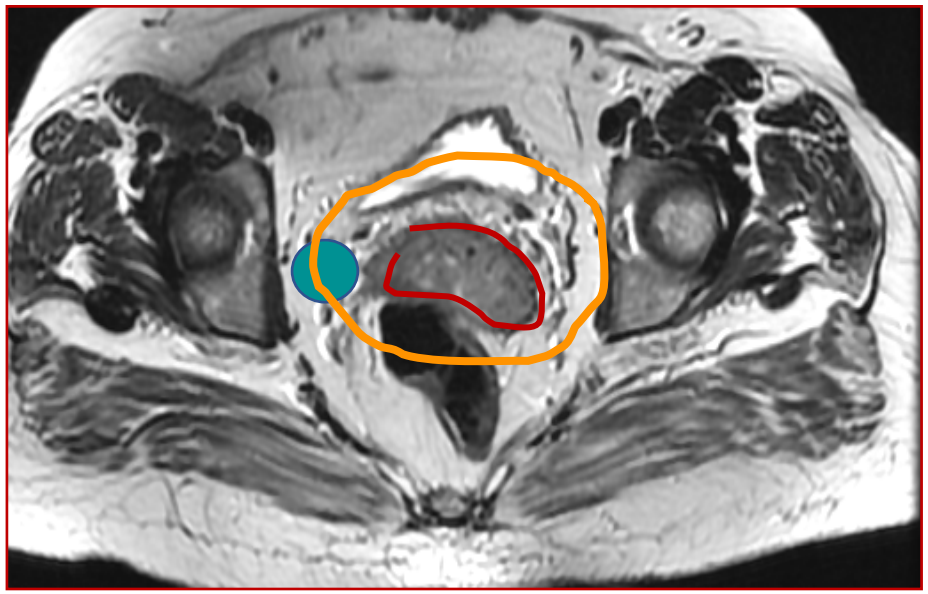
Plan Evaluation: Useful Multi-objective plans

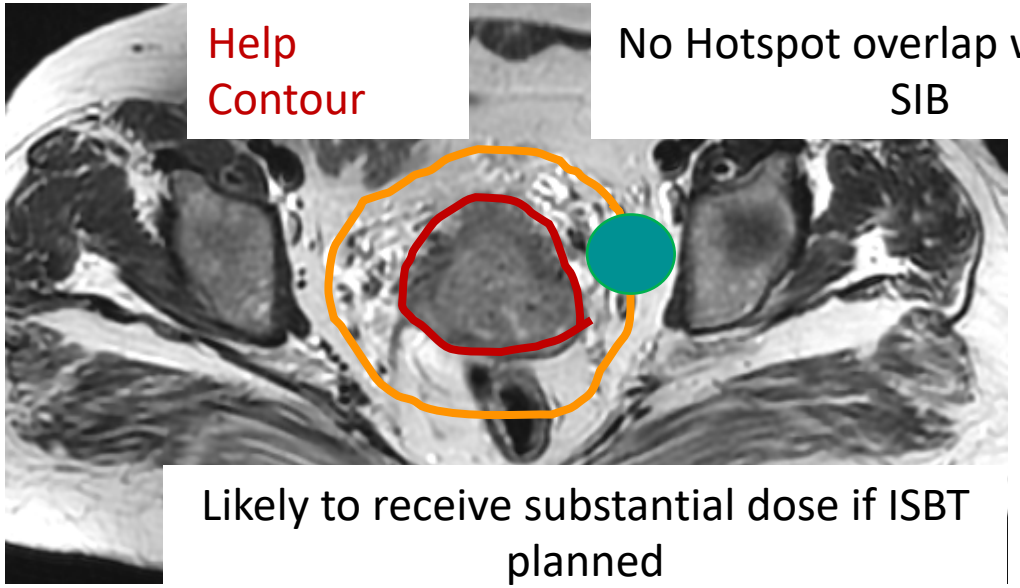
Structure ID	Structure Code	Patient Structure	DVH Objective	Evaluator	Variation	Priority	Met	Achieved
PTV45		PTV45	V43.0Gy[%]	>=95	95.5	2	Goal	96.72 %
PTV45		PTV45	Max[%]	<107	107.5	2	Goal	104.1 %
ITV45		ITV45	D99.9%[%]	>=95	94.5	2	Not met	86.8 %
Help contour		Help contour	Max[%]	<103		2	Goal	94.4 %
PTV-N1		PTV-N1	D98%[Gy]	>=47.25		2	Goal	48.363 Gy
PTV-N1		PTV-N1	Max[%]	<56.2		2	Not met	104.1 %
PTV-N2		PTV-N2	D98%[Gy]	>=47.25		2	Goal	48.631 Gy
PTV-N2		PTV-N2	Max[%]	<56.2		2	Not met	103.4 %
CTV-N1		CTV-N1	D98%[Gy]	>52.5		2	Not met	50.079 Gy
CTV-N1		CTV-N1	D50%[Gy]	>53.6		2	Not met	50.826 Gy
CTV-N2		CTV-N2	D98%[Gy]	>52.5		2	Not met	50.096 Gy
CTV-N2		CTV-N2	D50%[Gy]	>53.6		2	Not met	50.916 Gy
Bowel		Bowel	Max[%]	<=105	105.5	2	Goal	99.3 %
Bowel		Bowel	V40.0Gy[cc]	<250		2	Not met	267.59 cc
Bowel		Bowel	V30.0Gy[cc]	<500		2	Goal	470.79 cc
Sigmoid		Sigmoid	Max[%]	<=105	105.5	2	Goal	92.9 %
Bladder		Bladder	Max[%]	<=105	105.5	2	Goal	94.7 %
Bladder		Bladder	V40.0Gy[%]	<60		2	Goal	54.11 %
Bladder		Bladder	V30.0Gy[%]	<80		2	Goal	77.81 %
Rectum		Rectum	Max[%]	<=105	105.5	2	Goal	92.8 %
Rectum		Rectum	V40.0Gy[%]	<75		2	Goal	27.50 %
Rectum		Rectum	V30.0Gy[%]	<95		2	Goal	56.93 %
Spinal cord		Spinal cord	Max[Gy]	<48		2	Goal	44.662 Gy
Femoral heads_L		Femoral heads_L	Max[Gy]	<50		2	Goal	41.479 Gy
Femoral heads_R		Femoral heads_R	Max[Gy]	<50		2	Goal	42.668 Gy
Kidneys_L		Kidneys_L	Mean[Gy]	<15		1	Goal	8.874 Gy
Kidneys_L		Kidneys_L	Mean[Gy]	<10		2	Goal	8.874 Gy
Kidneys_R		Kidneys_R	Mean[Gy]	<15		1	Goal	11.623 Gy
Kidneys_R		Kidneys_R	Mean[Gy]	<10		2	Not met	11.623 Gy
Body		BODY	Max[%]	<107		2	Goal	104.1 %

- Objective system for patient treatment execution to absolve interindividual dependency.
- Use for Gynecological IMRT

Swamidas J, Chopra S
Work under progress

IMRT-Nodal SIB Planning

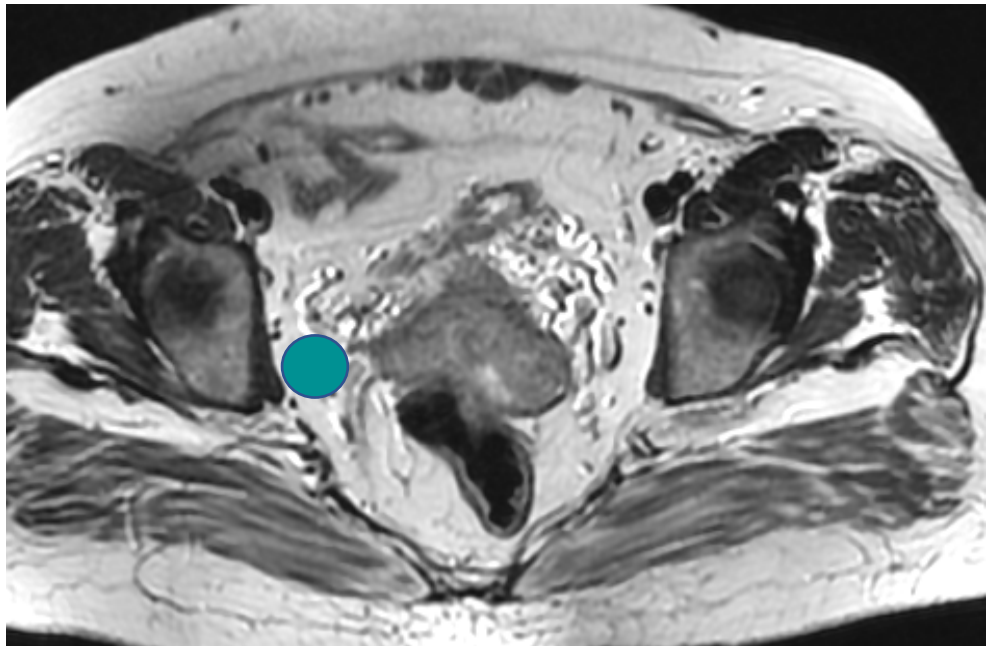




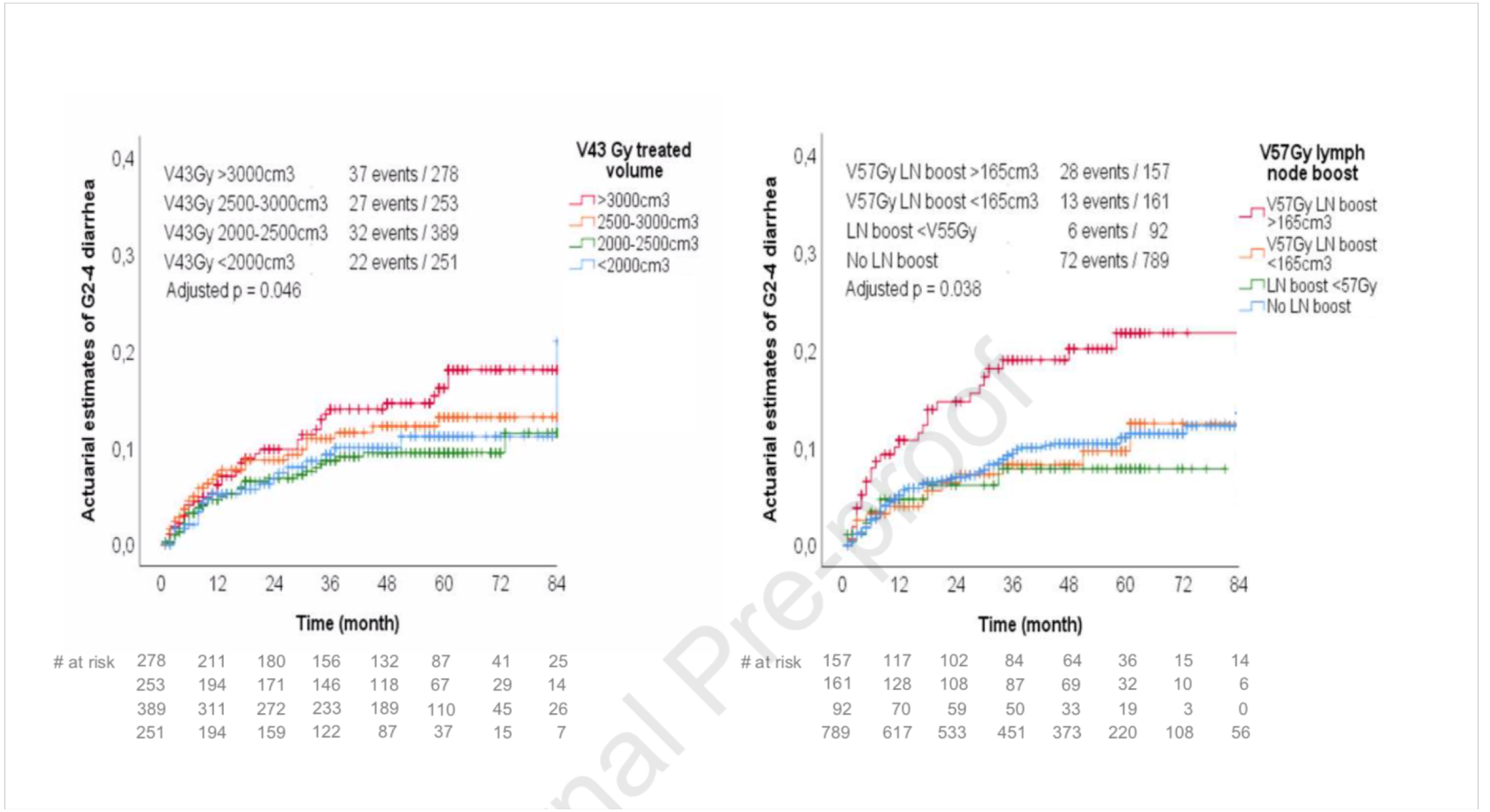
Help Contour

No Hotspot overlap with Nodal SIB

Likely to receive substantial dose if ISBT planned



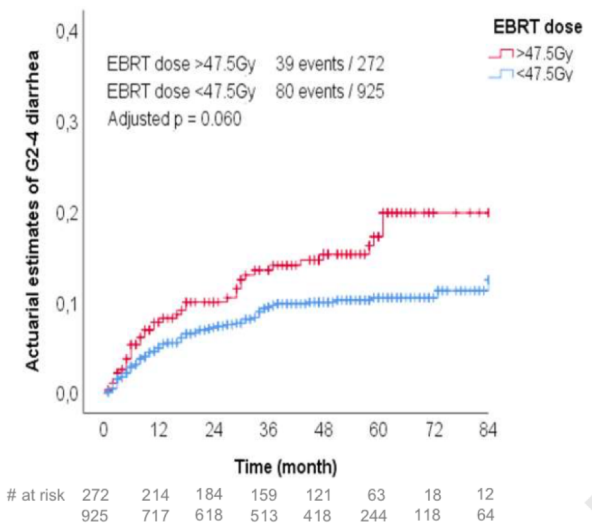
Overall Volume Irradiated/ Nodal Boost and Diarrhoea

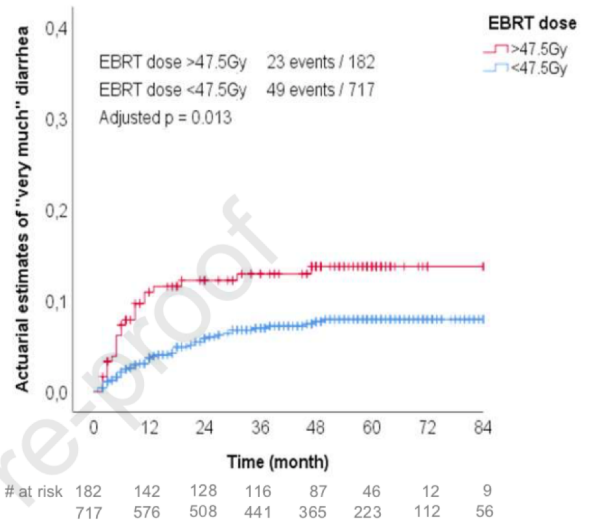


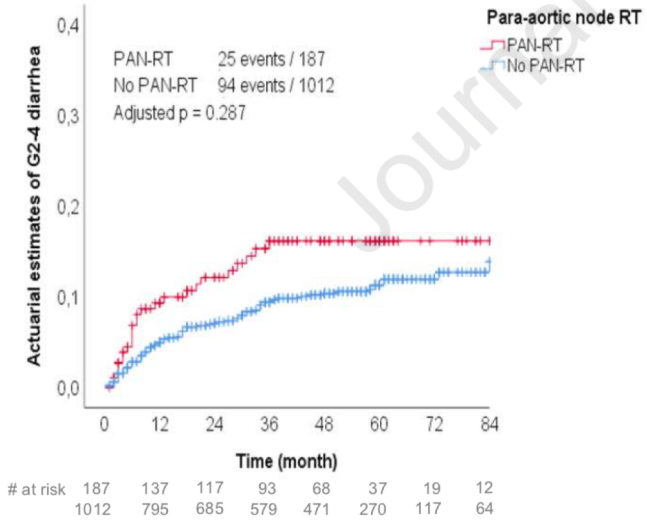
Role of Highly Conformal IMRT plans and Reduced Nodal SIB Volumes

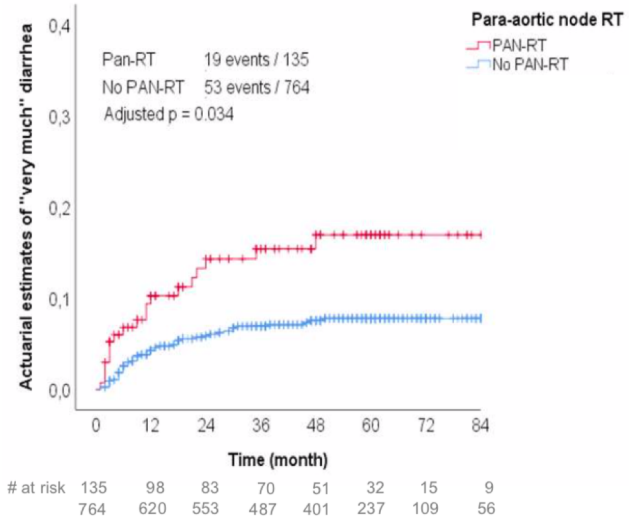
Jensen, IJROBP 2020

Impact of EBRT Dose and Irradiated Volume



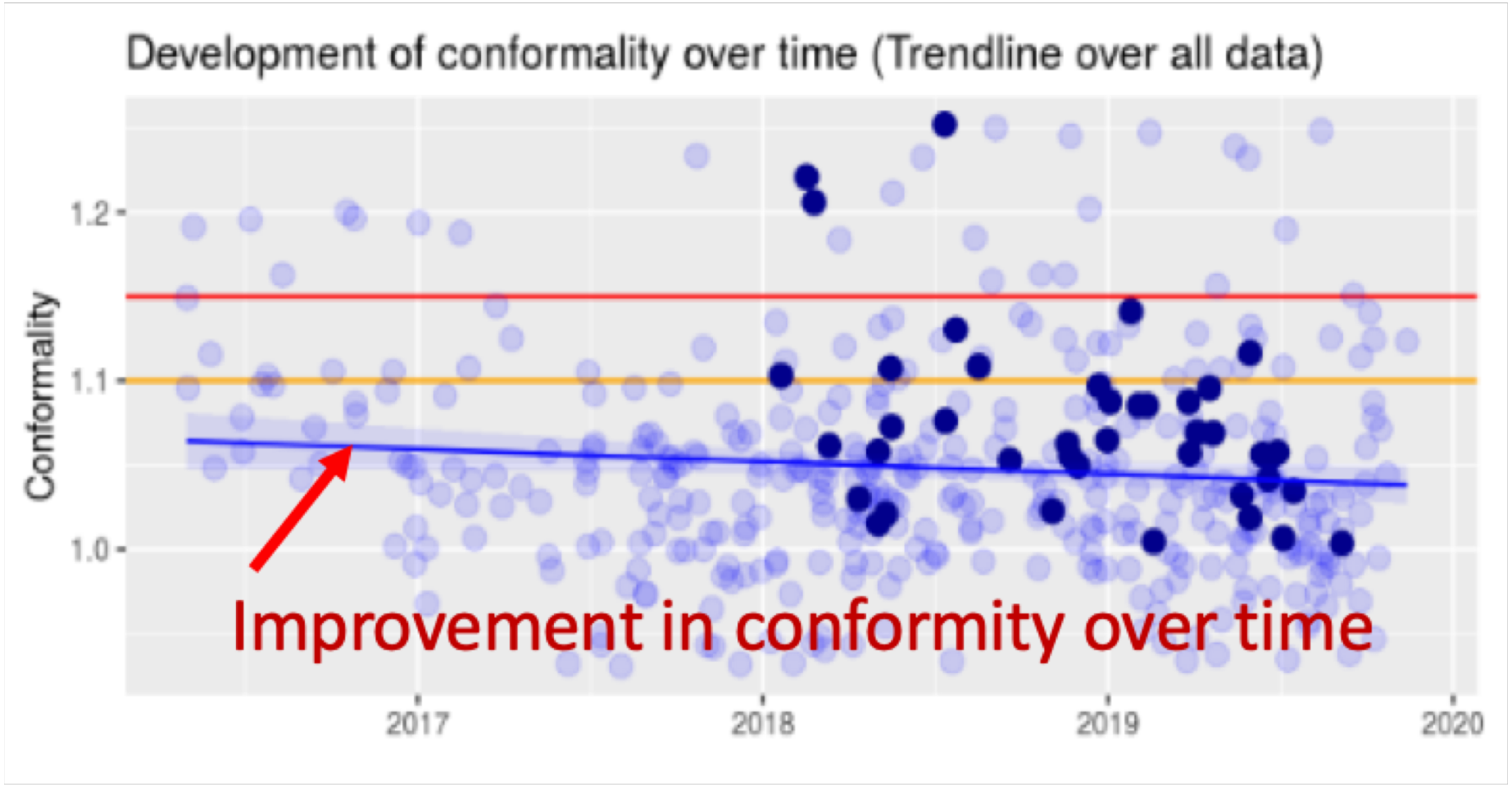






Jensen IJROBP,2020

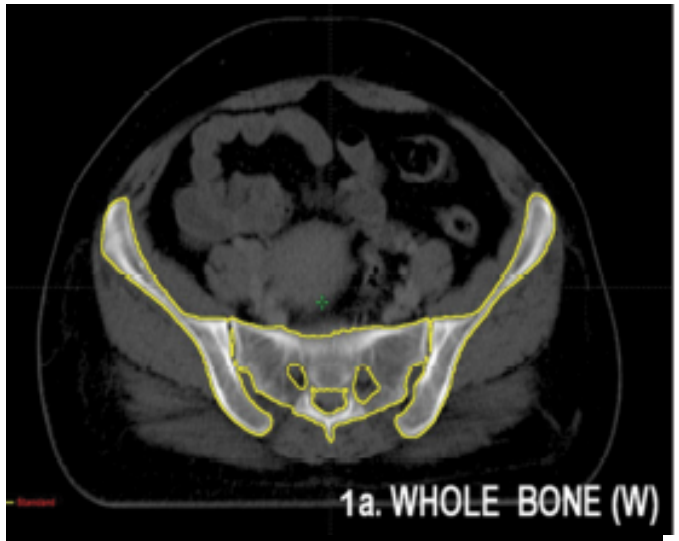
Irradiated Volume Reduction with Conformal Techniques

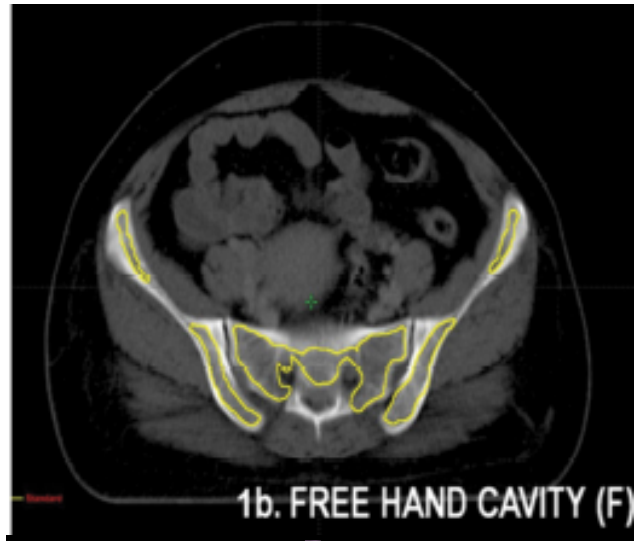


Tata Memorial Data for EMBRACE II.
Slide Content Courtesy Nicole Nescavil, Stefan Ecker, Patients recruited in EMBRACE II study

All treated in Truebeam
Varian

Hematological Toxicity :Bone marrow sub-volume Delineation





Whole Bone

Free Hand

Mahantshetty U,IGCS,2012

Proposed Dose Volume Constraints for BM Sparing IMRT

Author	N	Contouring Method	Treatment Setting	BM volumes correlates ≥ Grade II HT
Mell L	37	Whole bone	Radical	V 10 ≥ 90%
Mahantshetty U	47	Free hand	Radical	V 40 ≥ 40%
Klopp A	40	Whole bone	Post operative	V 40 ≥ 37%

Table 5. Multivariate analysis of whole bone contours with toxicity

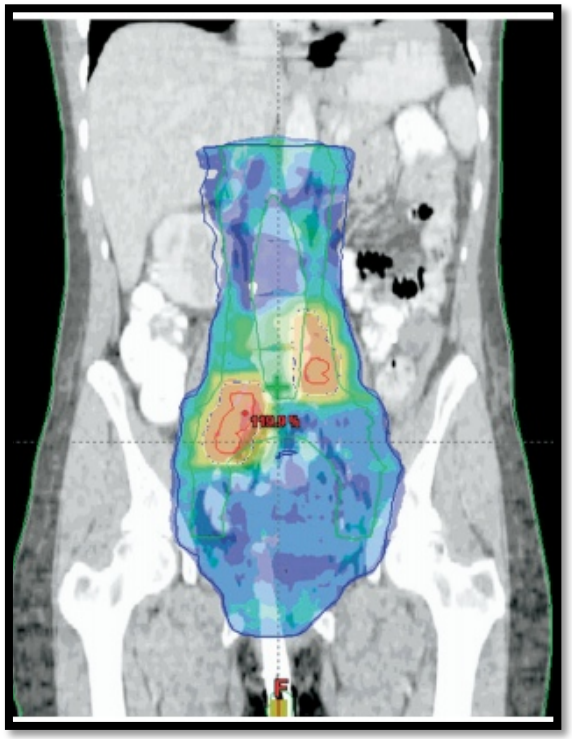
Toxicity	Volume	Percentage	Odds ratio (95% CI)	*P* value
Any HT Grade 2 and above	WP +LS V20	>70%	3.2 (0.3–34.6)	0.32
	WP V20	>75%	0.08 (0.005–1.3)	0.08
	WP V30	>60%	1.04 (0.28–3.7)	0.94
	FHN V40	>5%	0.33 (0.11–1)	0.051
Any HT Grade 3 and above	WP + LS V30	>55%	2.3 (0.14–39.5)	0.54
	WP V30	>60%	2.3 (0.15–36.3)	0.54
	FHN V30	>15%	1.5 (0.18–12.9)	0.68
	FHN V40	>5%	1.68 (0.2–14.08)	0.63
Hemoglobin Grade 2 and above	Ilium V20	>90%	7.15 (1.6–30.3)	0.008
	LP V5	>99%	0.27 (0.06–1.12)	0.07
	LP V40	>25%	0.50 (0.06–3.8)	0.51
	Ischium V40	>45%	0.65 (0.09–4.2)	0.65
WBC Grade 2 and above	WP + LS V30	>55%	2.02 (0.35–11.6)	0.42
	WP V40	>35%	4.7 (0.79–27.8)	0.08
	LP V40	>25%	0.22 (0.02–2.63)	0.23
	Ischium V40	>45%	2.6 (0.39–17.7)	0.31
	FHN V 40	>5%	5.7 (0.98–33.3)	0.05
Neutrophil Grade 2 and above	WP V40	>35%	3.38 (0.6–17.4)	0.14
	Ilium V40	>25%	1.5 (0.36–6.5)	0.57
	LP V40	>25%	0.63 (0.13–3.009)	0.56
	FHN V40	>5%	2.6 (0.69–10.2)	0.15

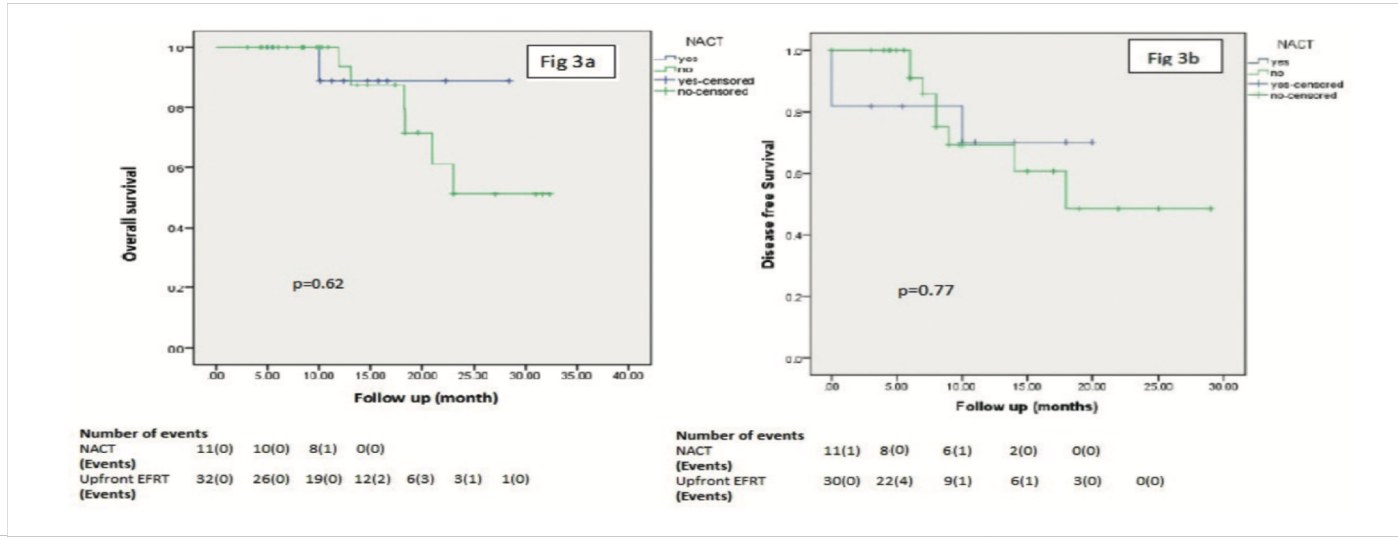
HT, hematological toxicity ; WP, whole pelvis; LP, lower pelvis;LS, lumbar spine; WBC, white blood cells;

Lack of Prospective Validation of Bone Marrow Dose Threshholds

Lewis, Chopra, BJR 2018

EFRT with or without systemic chemotherapy

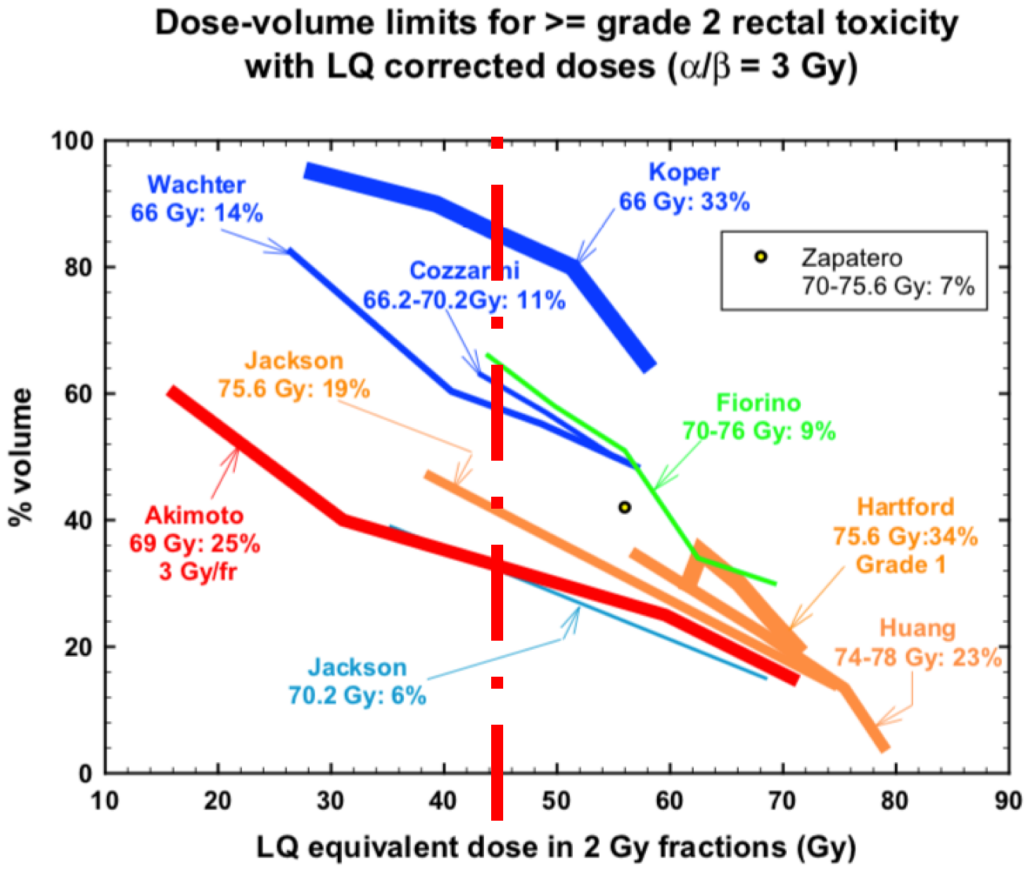




	NACT cohort	Non NACT cohort	*p*-value
Leukopenia ≥ Grade II	7 (58%)	17 (55%)	0.83
Leukopenia ≥ Grade III	7 (58%)	6 (19%)	**0.01**
Neutropenia ≥ Grade II	9 (75%)	8 (25%)	**0.003**
Neutropenia ≥ Grade III	7 (58%)	3 (9.6%)	**0.002**
Thrombocytopenia ≥ Grade II	5 (42%)	4 (13%)	**0.04**
Thrombocytopenia ≥ Grade III	2 (17%)	1 (3%)	0.12
Any ≥ Grade II HT	10 (83.3%)	18 (58%)	**0.11**
Any ≥ Grade III HT	8 (67%)	7 (22.6%)	**0.007**
Acute vomiting > Grade II	5 (45.5%)	5 (18%)	**0.07**
Diarrhoea ≥ Grade II	3 (25.0%)	4 (12.9%)	0.33
Diarrhoea ≥ Grade III	2(16.7%)	3 (9.7%)	0.40
Acute Grade II or higher GI	6 (50%)	9(29%)	0.19
Acute Grade III GI	2 (16.7%)	3 (9.7%)	0.52
Any grade III or higher toxicity (HT/GI)	8 (66.7%)	9 (29%)	**0.02**

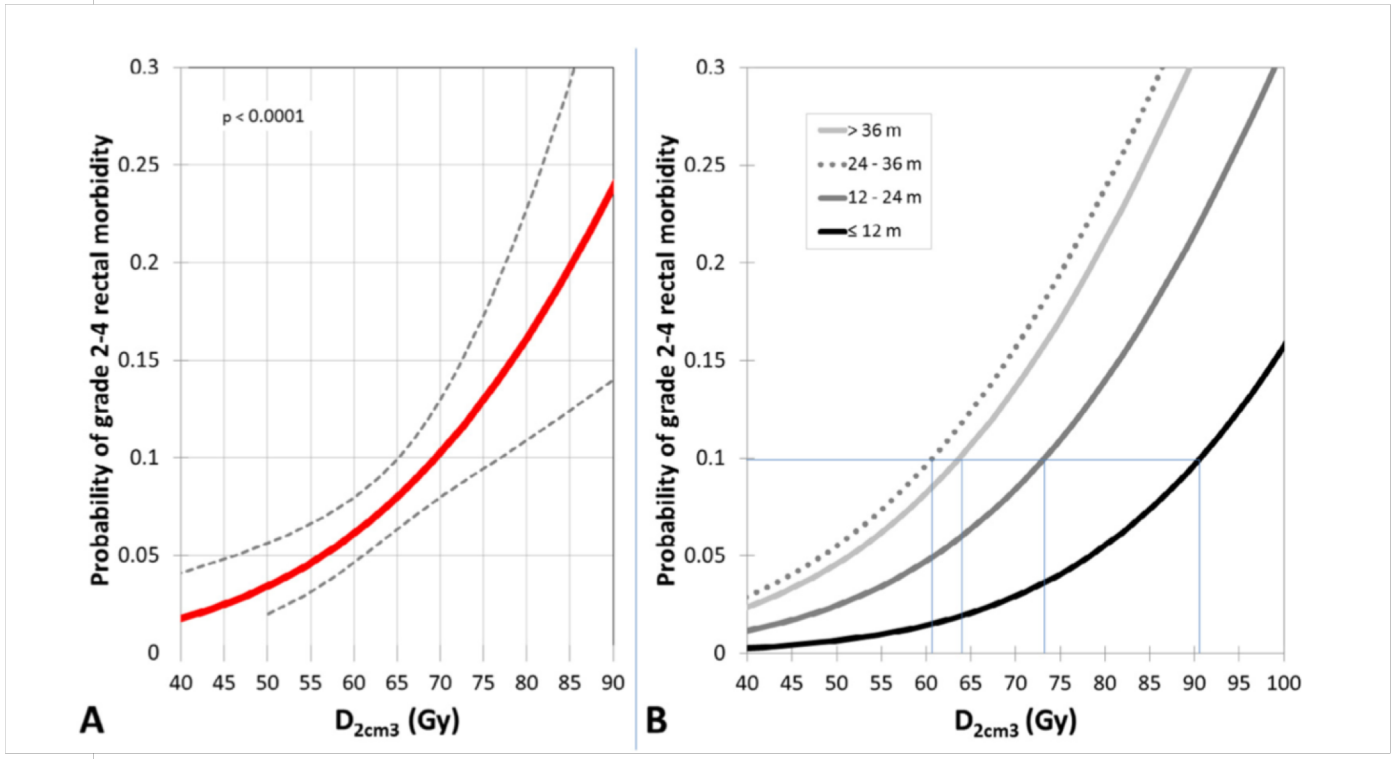
Gupta, Chopra
Ecancer med 2018

Rectum: EBRT



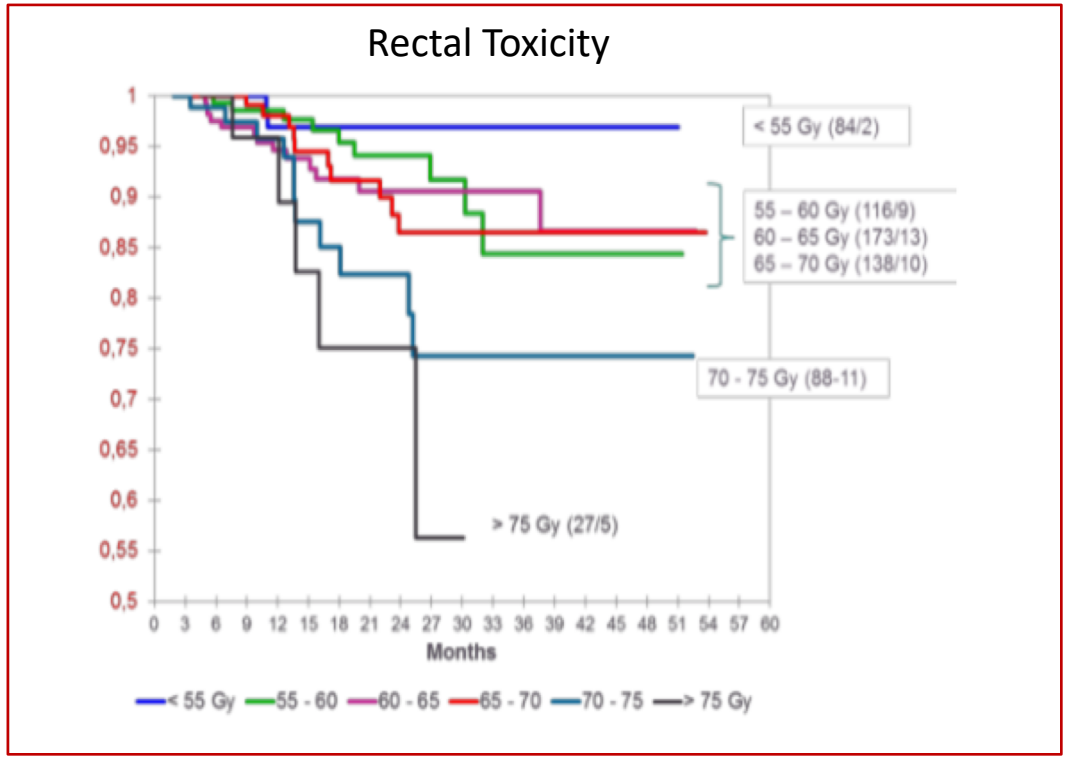
QUANTEC, 2010

Rectum: EBRT +BT



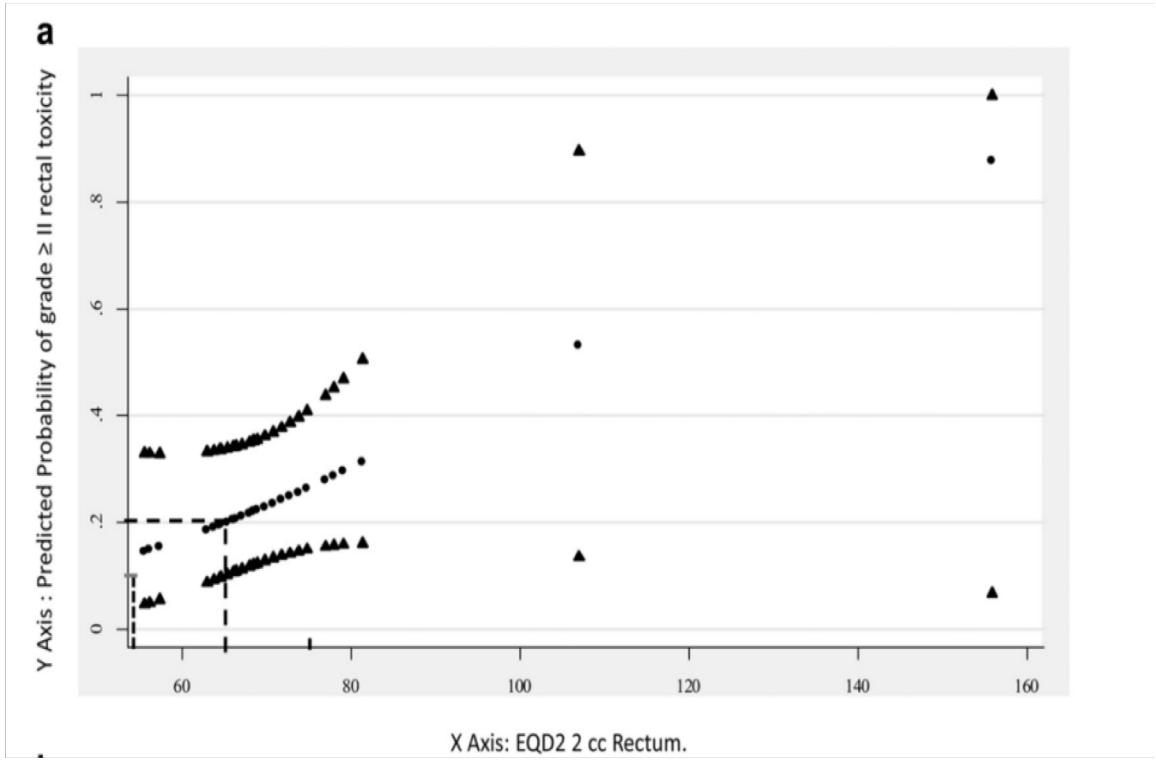
Mazeron, Radiotherapy and Oncology,

Intracavitory/IC-IS Brachytherapy



EMBRACE 1 Results, Potter, Tanderup,2020

Interstitial Brachytherapy BID Continuous Fractionation



Dora, Chopra, Brachytherapy 2015

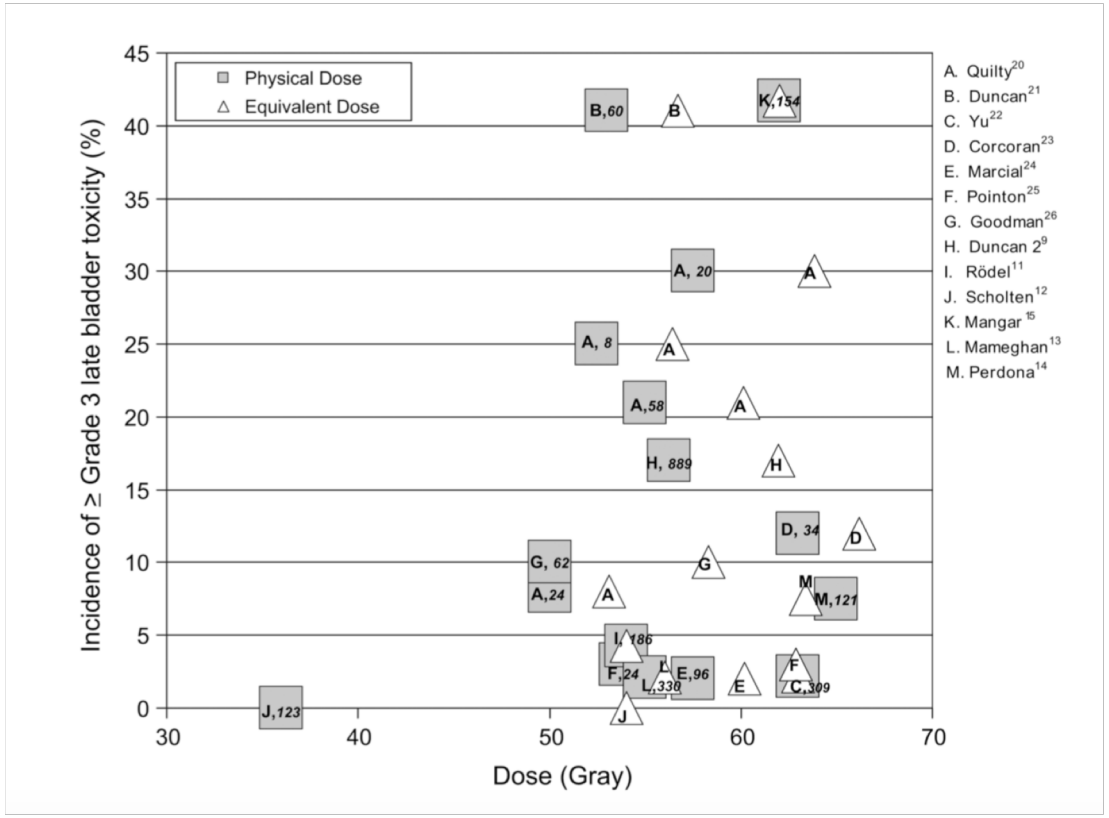
Anal Canal : Dose Constraints

Table 5 Anal canal Dmean results

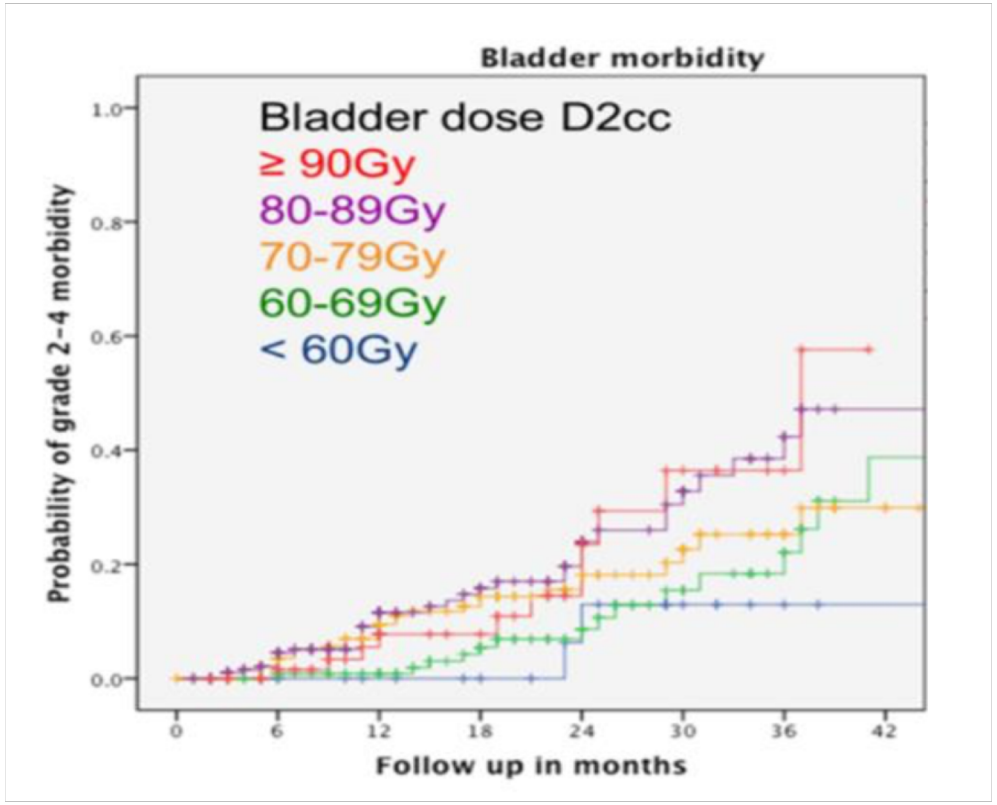
Study	No of pts	OAR	Endpoint	Dmean (in EQD2) constraint	Risk of endpoint below this constraint	Risk of endpoint above this constraint
Al-albany [18]	65	Anal sphincter region	Incontinence >2X/week	43.2	8%	52%
Alsadius [19]	403	Anal canal	Incontinence > 1x/month	40	5.2%	21%
Buettner [20]	388	Anal sphincter region	Incontinence: moderate/ severe (gr2)	47, though <30Gy ideal	5% (approx; read from graph)	
Smeenk [22]	36	Anal canal wall	Urgency present	41.8	15%	62%
Peeters [21]	641	Anal canal wall	Incontinence requiring pad >2x/week	No constraint specified	16% at 19Gy	31% at 52Gy

Jadon, Radiation Oncology, 2019

Bladder Toxicity: EBRT+ Image Guided BT

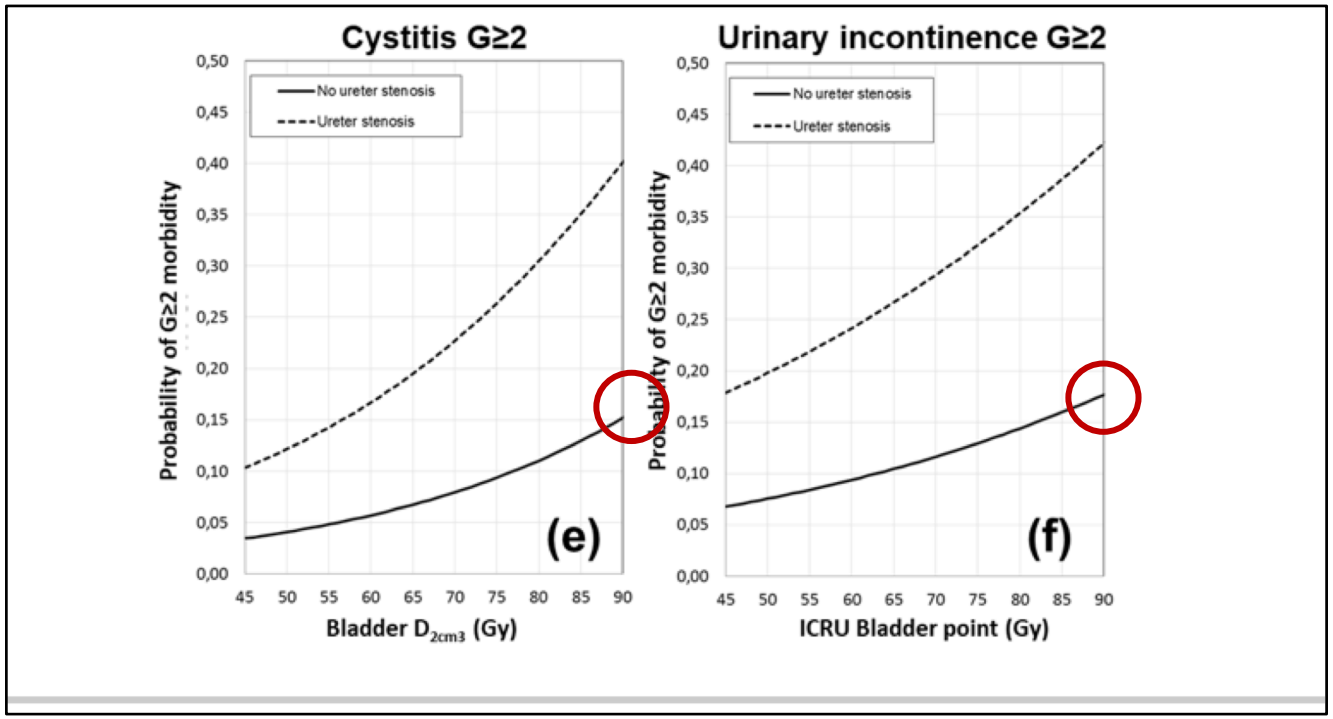


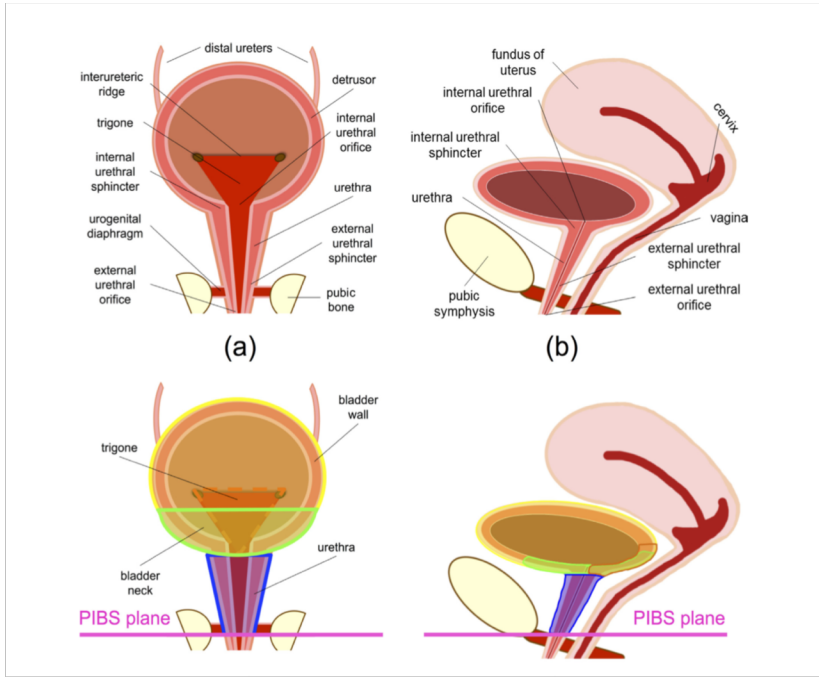
Viswanathan, QUANTEC,2010



EMBRACE II Protocol, 2016
Tanderup, Potter

Bladder: Dose Volume Correlation Toxicity (Primary Setting)





10-15% Grade II toxicity expected

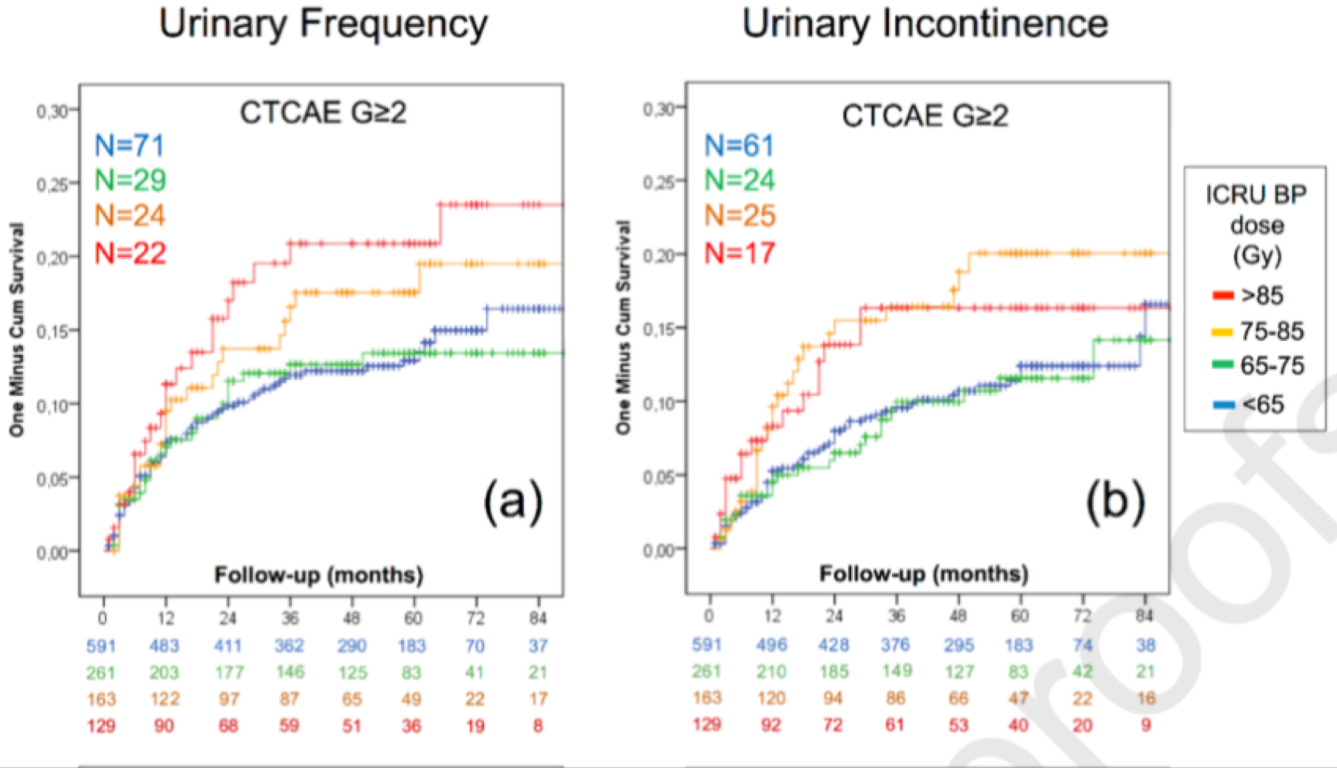
Median follow up short for Bladder Toxicity

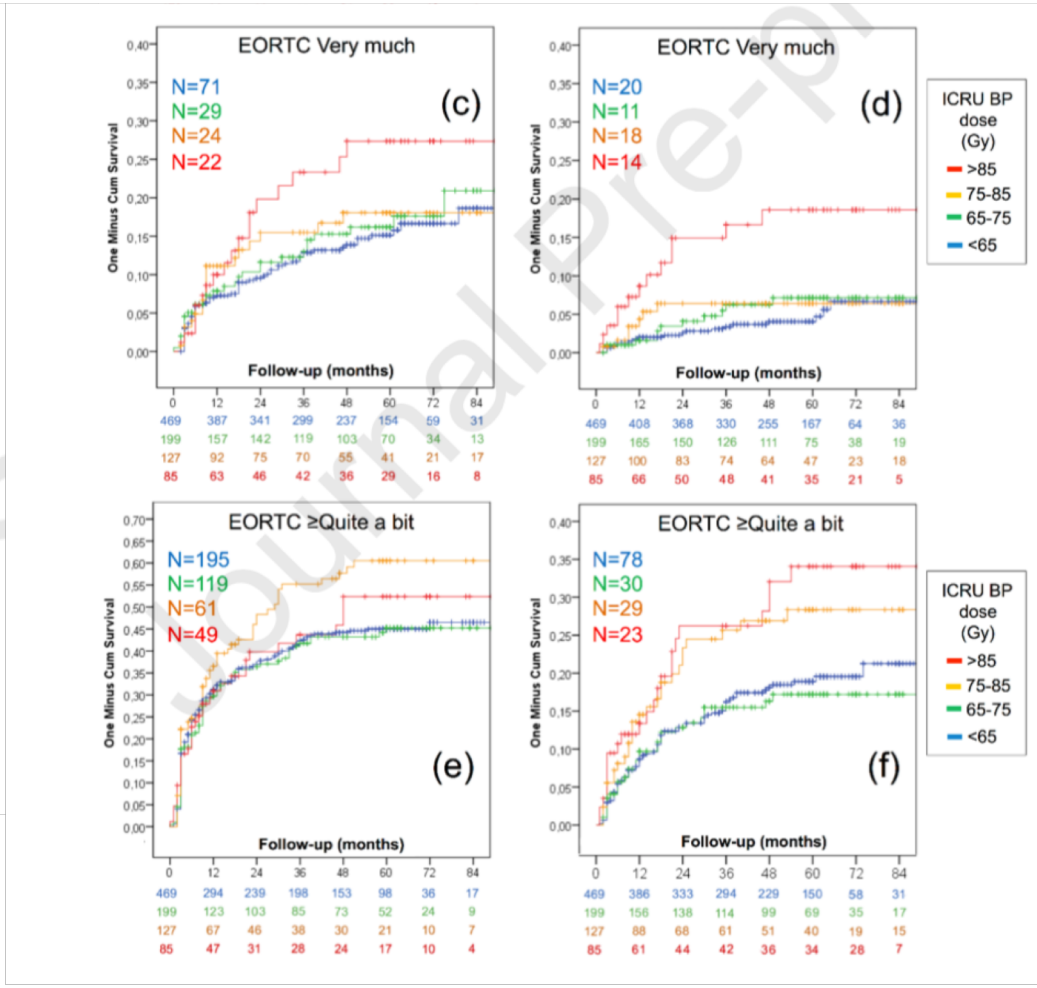
Trigonum, Detrusor, Bladder wall, Urethra may be related to various endpoints

Tanderup, Seminars in Radiation Oncology, 2020

Tanderup, Seminars in Radiation Oncology, 2020

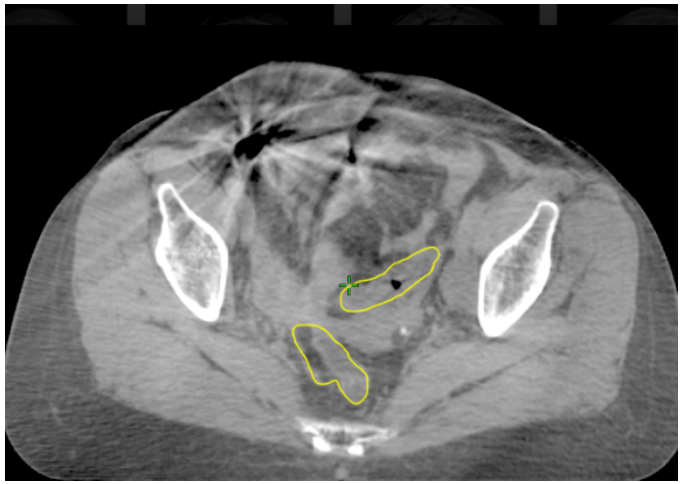
ICRU Bladder Point and Dose Volume Effects

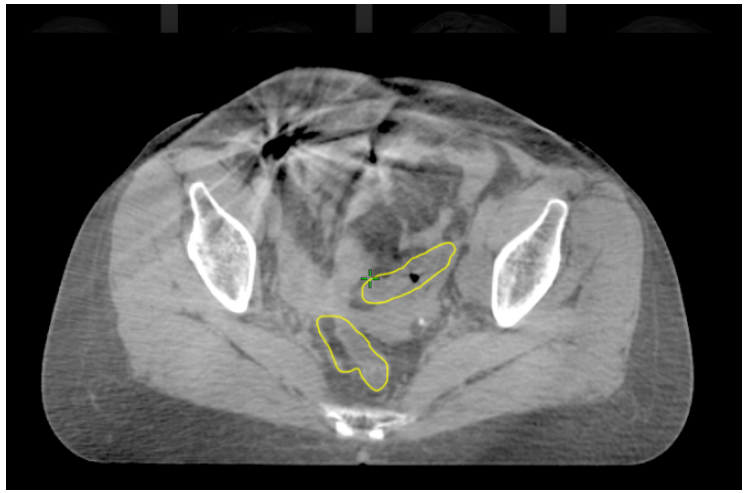


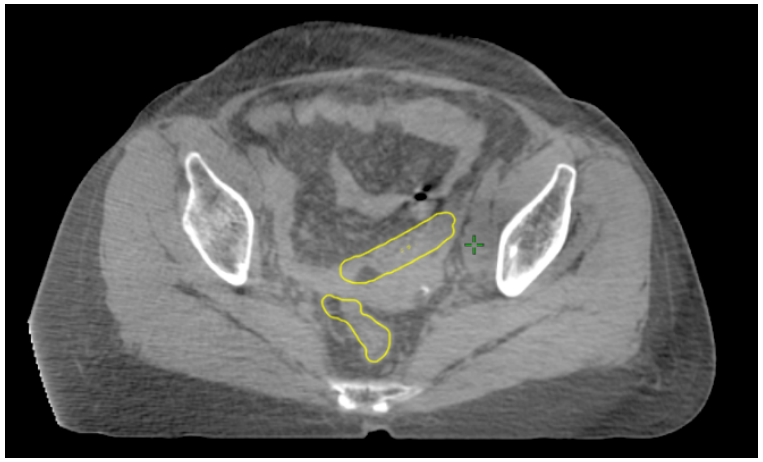


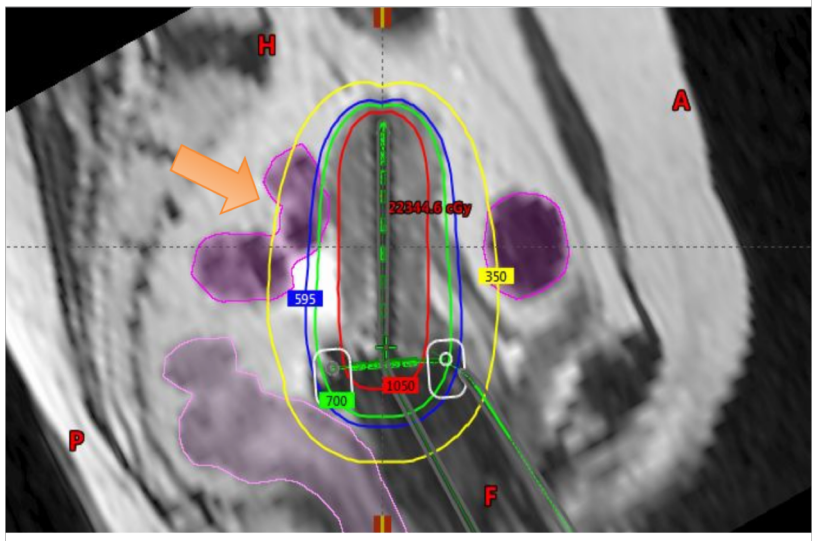
Spampinato, Radiotherapy and Oncology 2020

Sigmoid :OAR Displacement Intrafraction and Intercourse Re RT

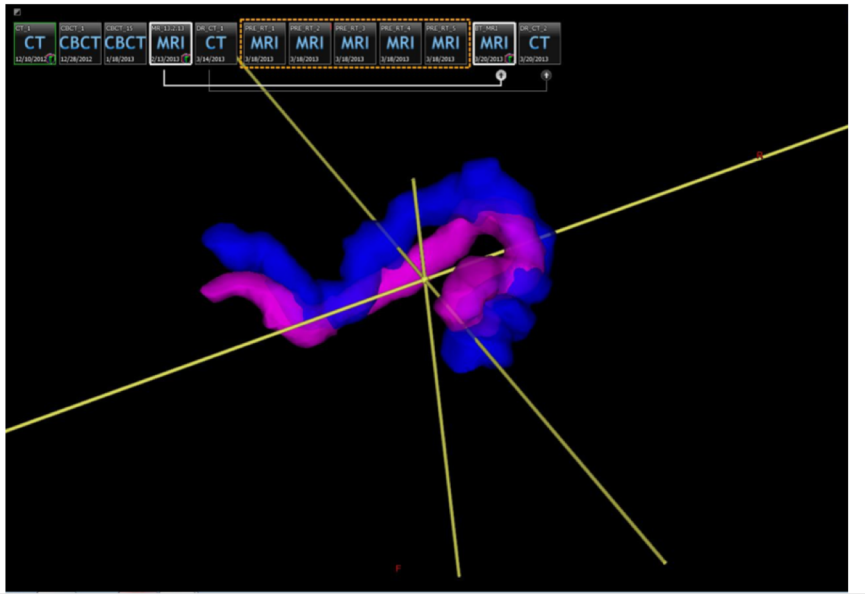


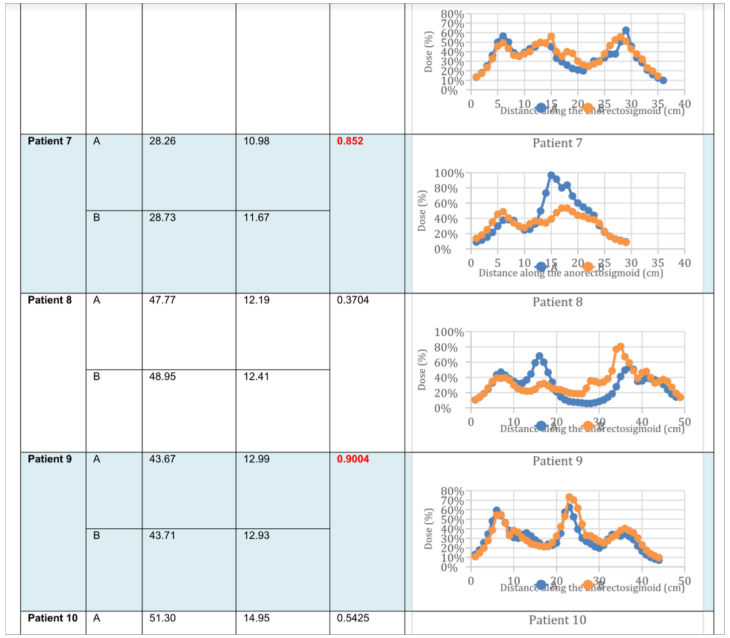






gure 8 Sagittal reconstruction of MRI showing isodose from HDR Brachytherapy. The arrow (orange) points to the gion of sigmoid receiving high dose from brachytherapy. This region usually lies 14-15 cm from the anal verge at a oint located 4 cm cranial and 2.5 cm posterior to the flange.



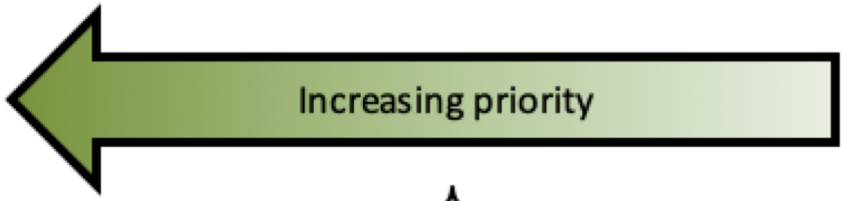


Patient 7	A	28.26	10.98	0.852	Patient 7
	B	28.73	11.67		
Patient 8	A	47.77	12.19	0.3704	Patient 8
	B	48.95	12.41		
Patient 9	A	43.67	12.99	0.9004	Patient 9
	B	43.71	12.93		
Patient 10	A	51.30	14.95	0.5425	Patient 10

Bindal, Shingal, Chopra, Swamidas Work in Progress (Sigmoid Dose Accumulation)

Dose Volume Recommendations Gyn EBRT+BT

EQD2



OAR Dose planning aims	Rectum D_{2cm3} $EQD2_3$	Bladder D_{2cm3} $EQD2_3$	ICRU Recto-vaginal point $EQD2_3$	ICRU bladder point $EQD2_3$	Bowel D_{2cm3} $EQD2_3$	Sigmoid D_{2cm3} $EQD2_3$
Soft constraint*	< 65 Gy	< 80 Gy	< 65 Gy	< 75Gy	< 65 Gy$^{\$}$	< 70 Gy$^{\$}$
Hard constraint**	< 75 Gy	< 85 Gy#	< 75 Gy	< 85Gy	< 75 Gy$^{\$}$	< 75 Gy$^{\$}$

Intra and Interfraction Displacements

Rectum> Bladder>Bowel>SIgmoid

Tanderup, Seminars in Radiation Oncology, 2020

EMBRACE II: Tata Memorial Centre N=50 (2018-2019)

	HRCTV D90	GTV 98	IRCTV D98	Rectum 2cc	Bladder 2 cc	Sigmoid 2cc	Bowel 2cc
Median	96 Gy	106 Gy	63 Gy	62.6	80.2	68	63 Gy
Range	(86-114 Gy)	(90-125 Gy)	(57-70)	(50-75)	(58-91)	(51-78)	(45-81)

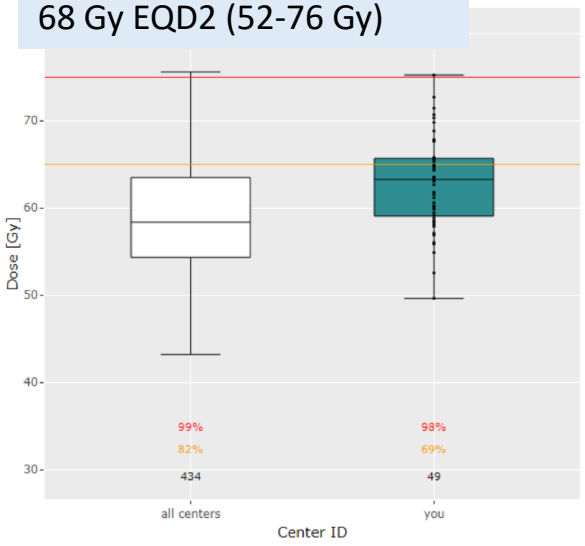
EMBRACE : Tata Memorial Centre N=94 (2009-2013)

	HRCTV D90	GTV 98	IRCTV D98	Rectum 2cc	Bladder 2 cc	Sigmoid 2cc	Bowel 2cc
Median	88.3 Gy	Not Reported	Not Reported	65.7	85.7	67 Gy	Not Reported

Organ at Risk Doses During Cervix Cancer Radiation: IMRT+ IGBT

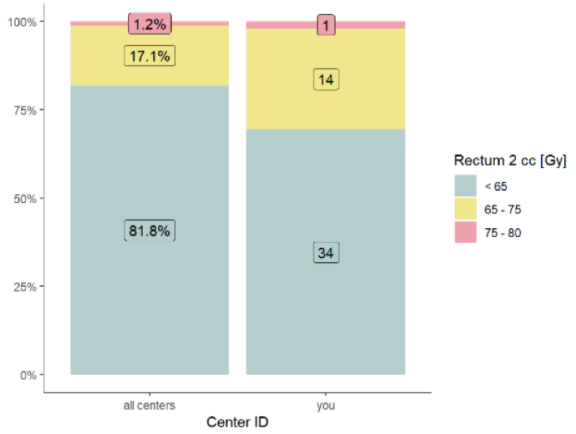
Rectum

68 Gy EQD2 (52-76 Gy)



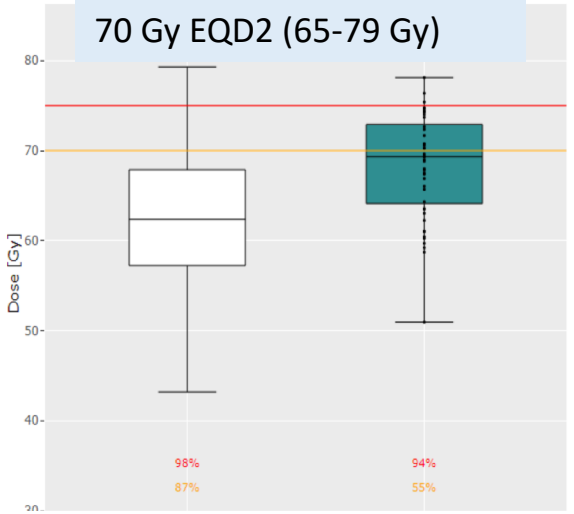
Rectum

25% patients received 65-75 GY



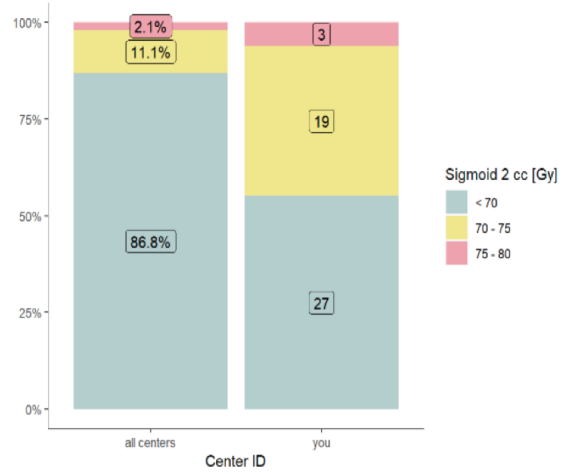
Sigmoid

70 Gy EQD2 (65-79 Gy)



Sigmoid

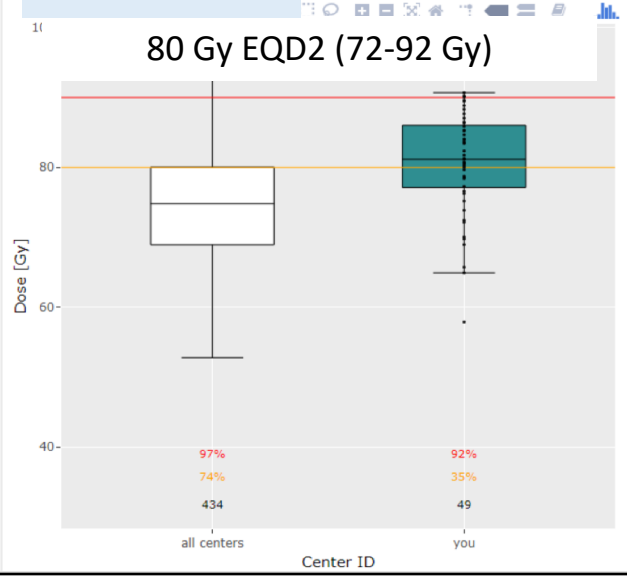
40-45 % patients received > 70 Gy



In 25-30% patients organ tolerance already reaches ED 10

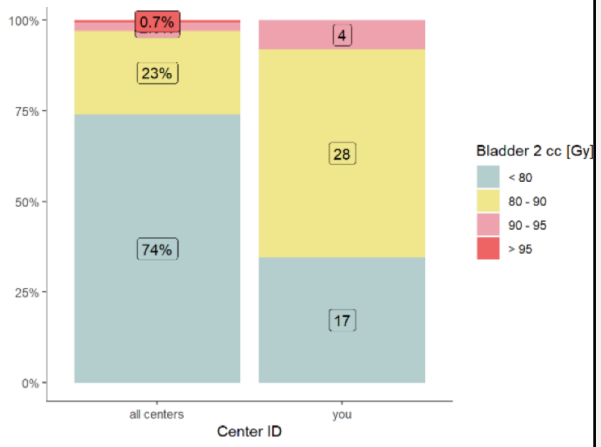
Bladder

80 Gy EQD2 (72-92 Gy)



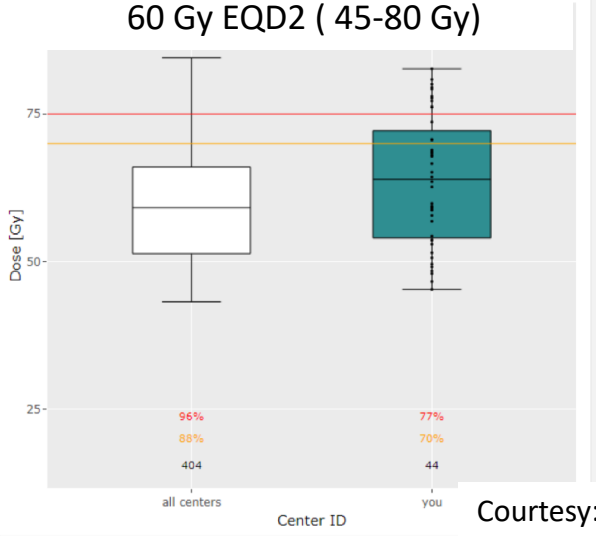
Bladder

70 % patients received > 80 Gy



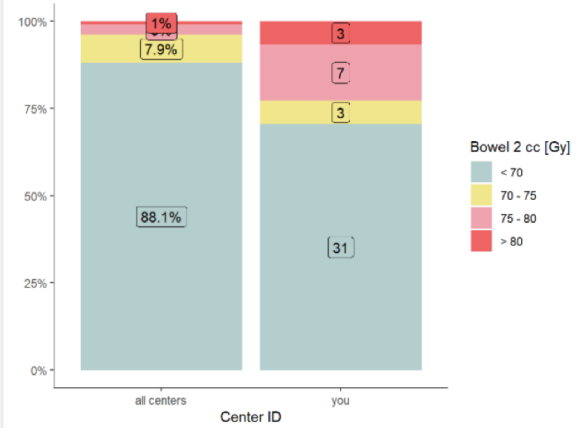
Bowel

60 Gy EQD2 (45-80 Gy)



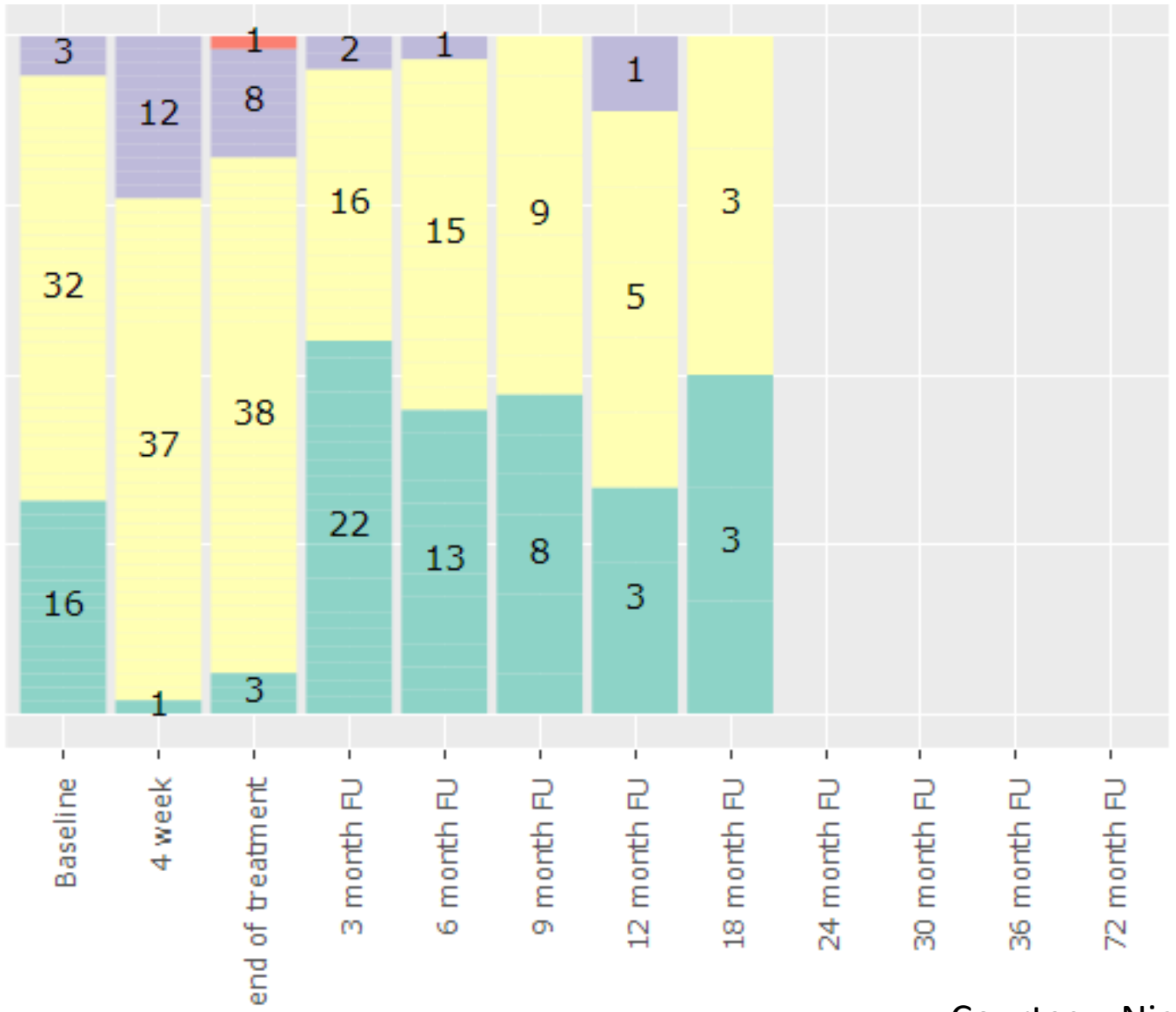
Bowel

20% receive > 70 Gy



Courtesy: RMonitOR Nicole Nescavil, Stephan Ecker

Acute Morbidity: EMBRACE II (Tata Memorial Centre)



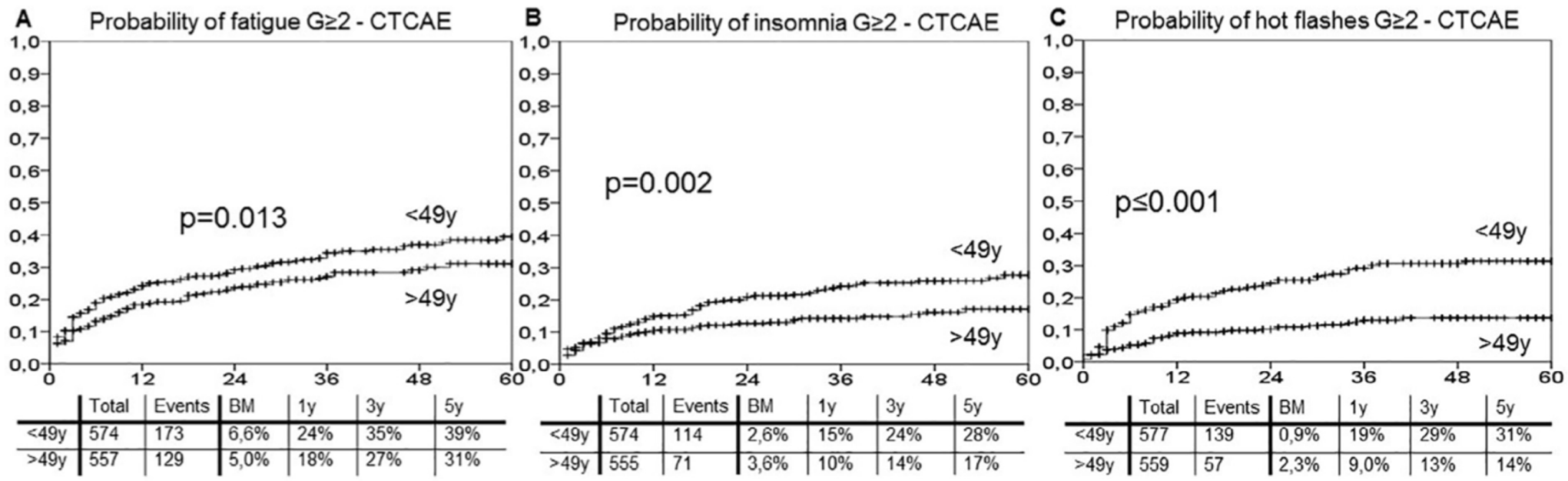
All patients completing IMRT and BT within 50 days without any break due to HT

Low Rate of Grade II-III toxicity

N=50

Courtesy: Nicole Nescavil, Stefan Ecker

Fatigue, Insomnia and Hot flashes



	Total	Events	BM	1y	3y	5y
<49y	574	173	6,6%	24%	35%	39%
>49y	557	129	5,0%	18%	27%	31%

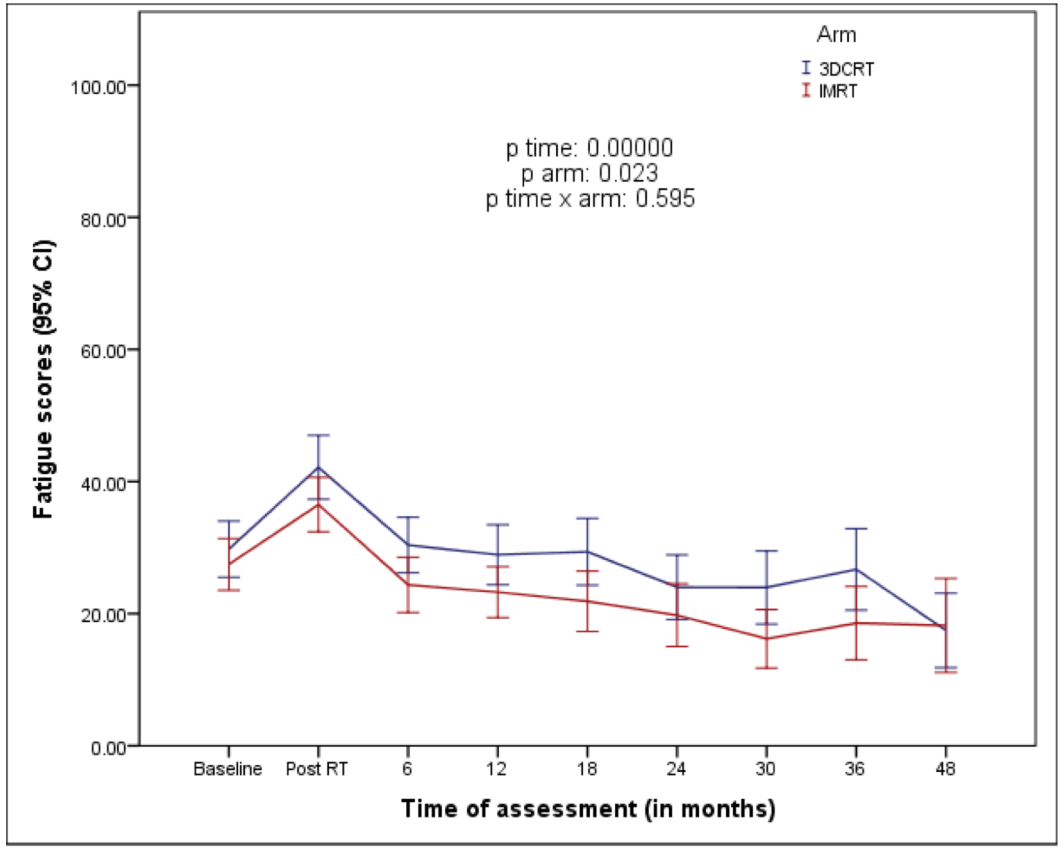
	Total	Events	BM	1y	3y	5y
<49y	574	114	2,6%	15%	24%	28%
>49y	555	71	3,6%	10%	14%	17%

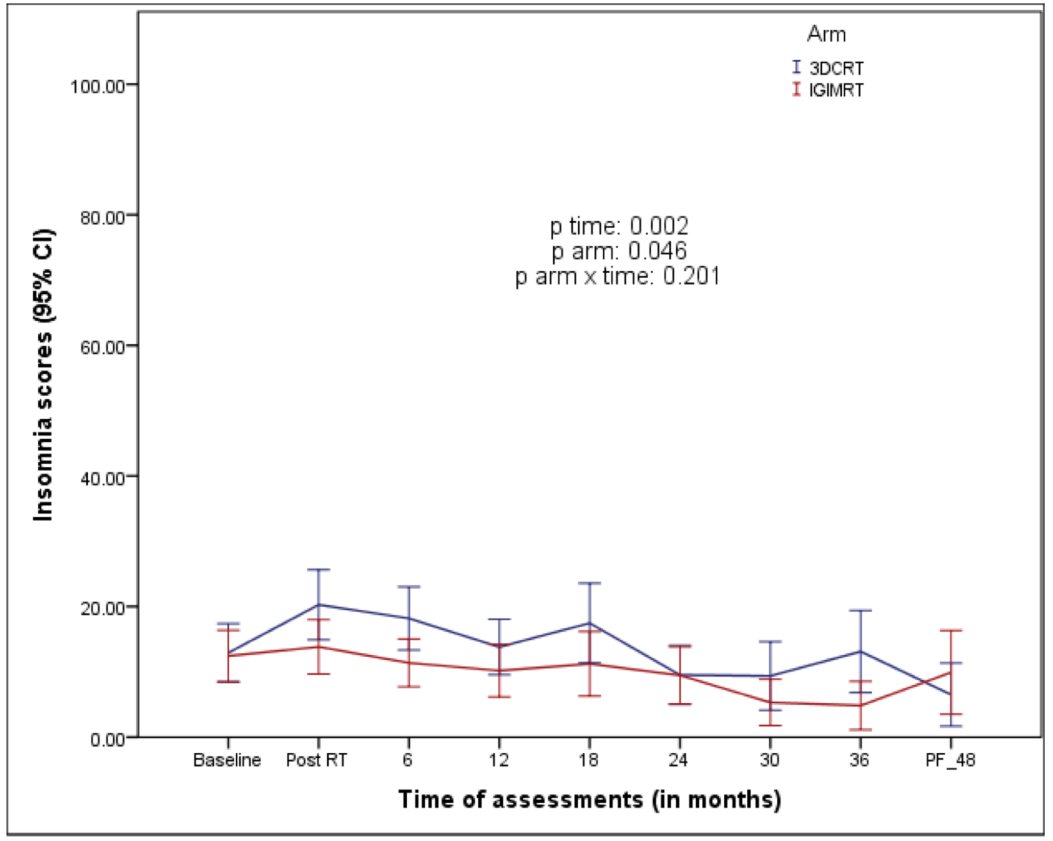
	Total	Events	BM	1y	3y	5y
<49y	577	139	0,9%	19%	29%	31%
>49y	559	57	2,3%	9,0%	13%	14%

Fig. 4. Actuarial estimates, for patients younger and older than 49 years, are shown in the Kaplan–Meier curves: (A) CTCAE G ≥ 2 fatigue, (B) CTCAE G ≥ 2 insomnia, (C) CTCAE G ≥ 2 hot flashes. *Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, BM = baseline morbidity, G = grade, y = year.*

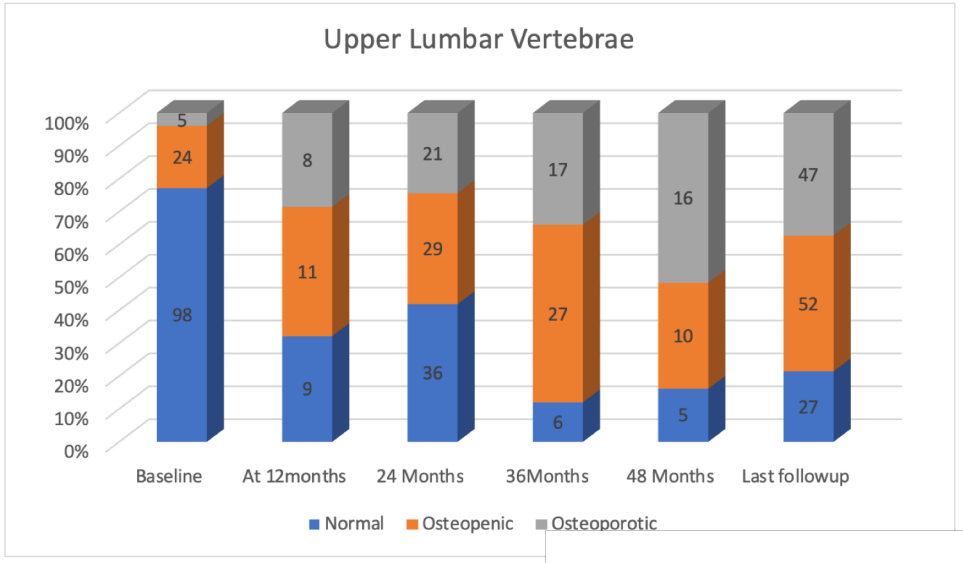
Smet, Radiotherapy and Oncology,2020

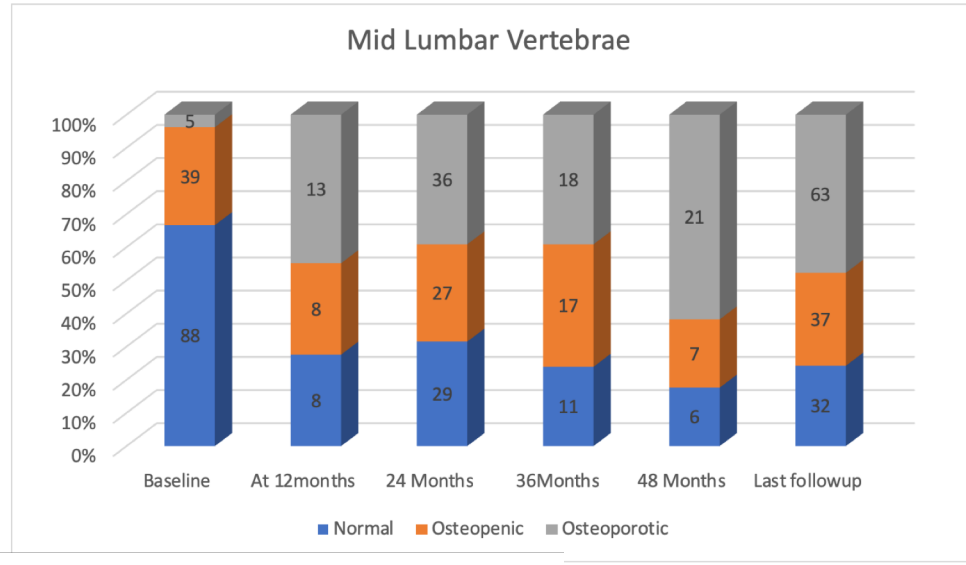
Impact of IG-IMRT on Fatigue and Insomnia

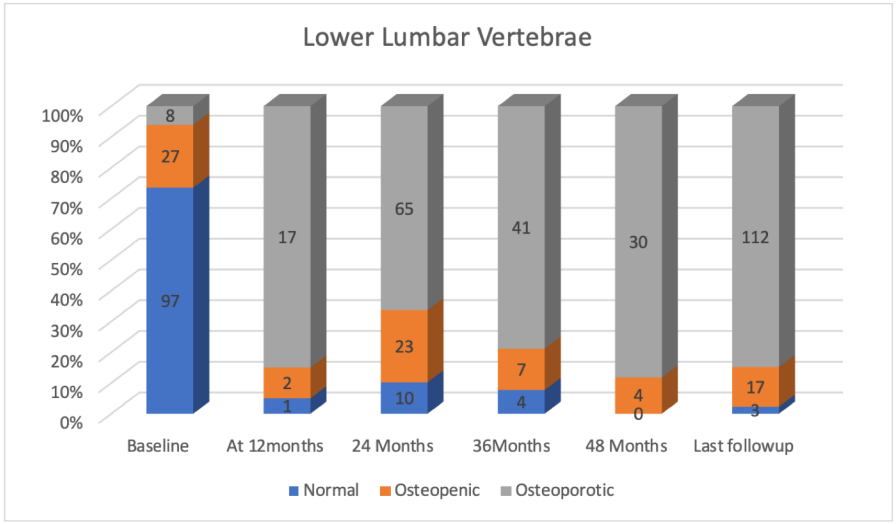




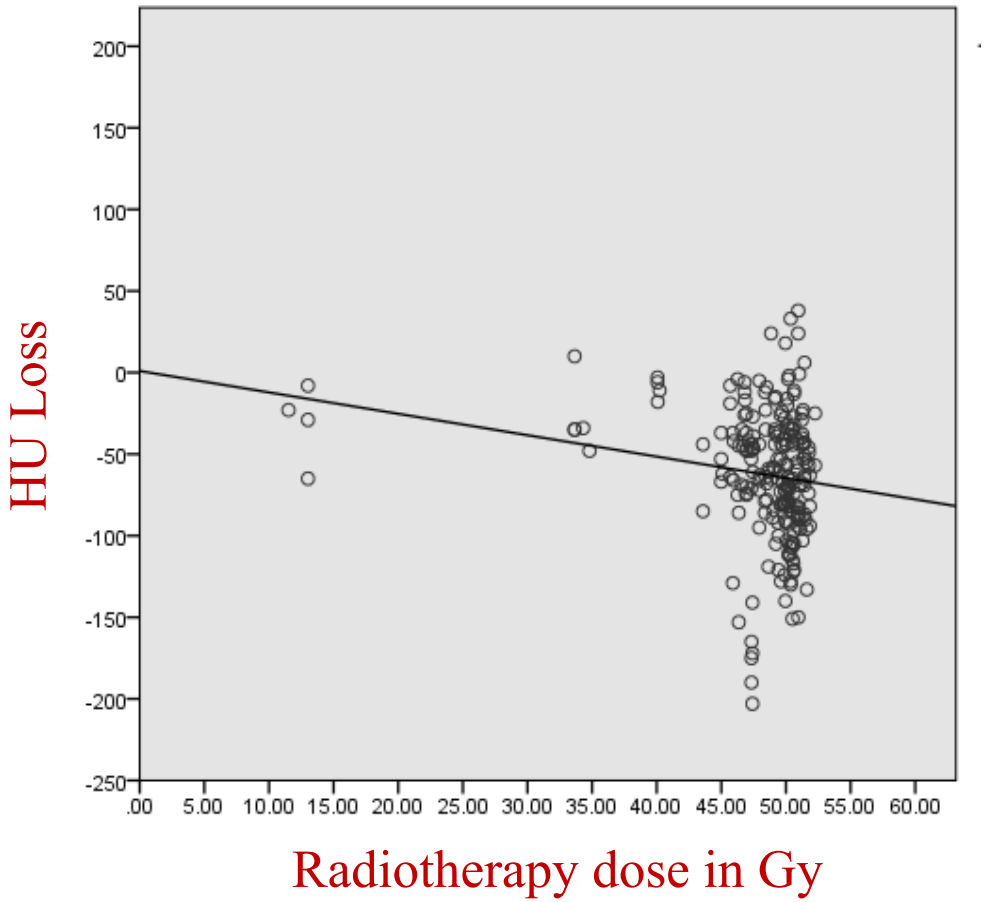
Bone Effects after Pelvic EBRT





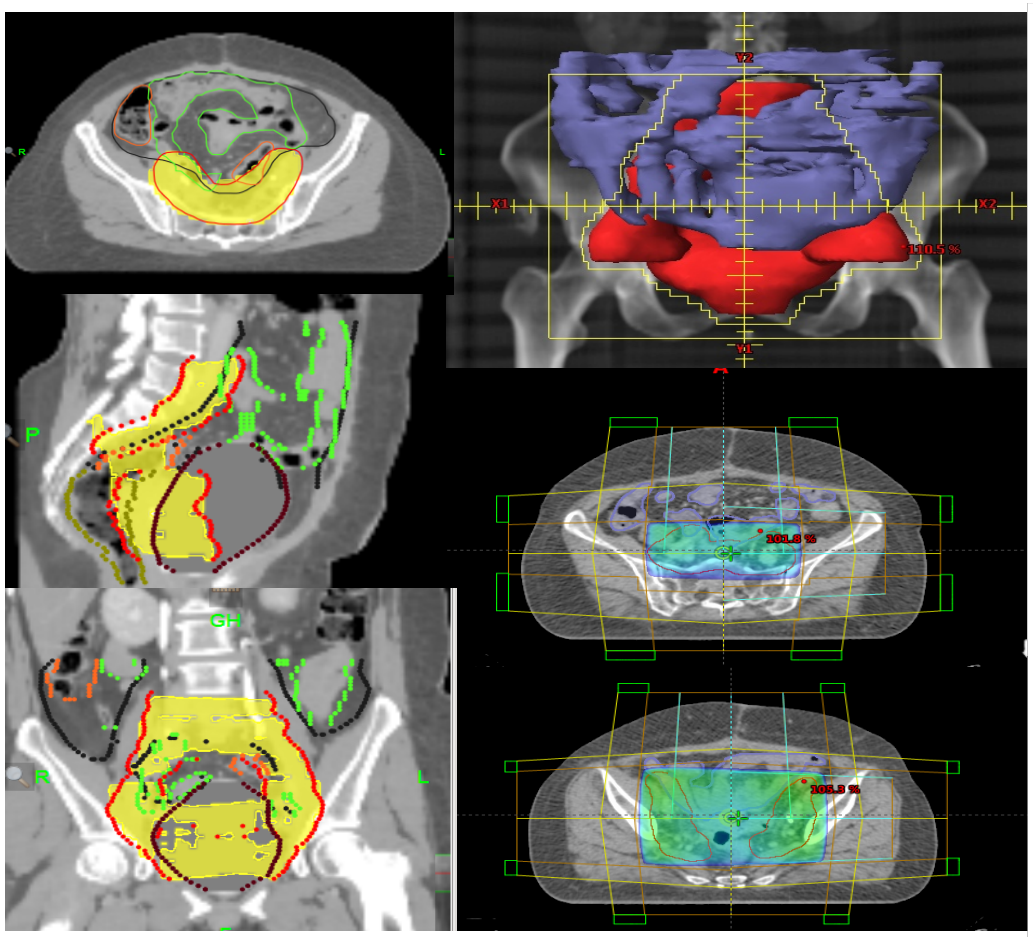


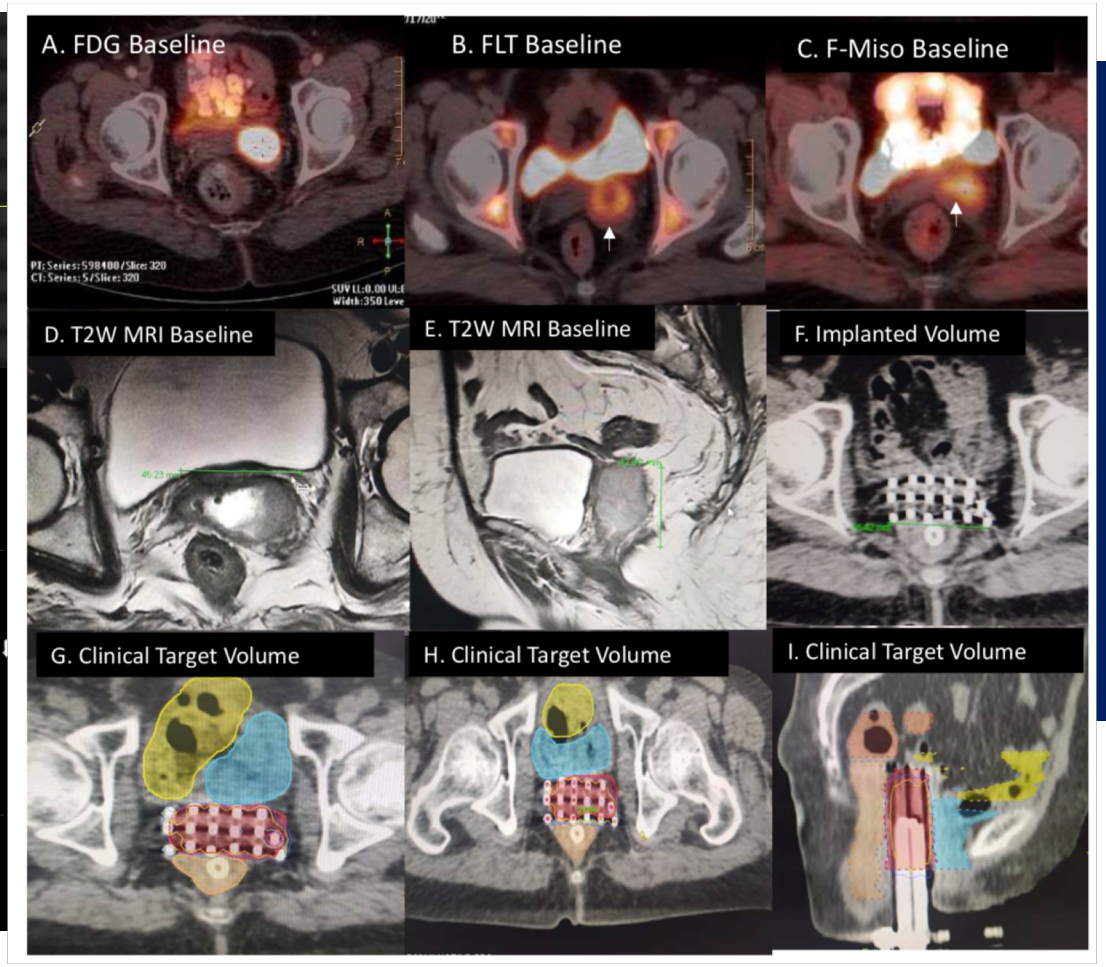
Correlation of Increasing Dose with HU Loss



50-60 HU Loss with Pelvic RT at median follow up of 36 Months (12-60 mths)

EBRT+ Brachytherapy for post surgical recurrences





IG-IMRT/3DRT (50/25)

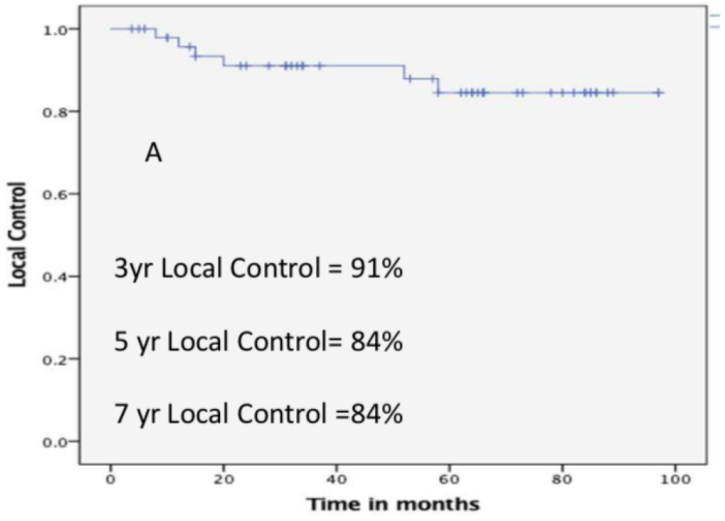
Nodal Boost (6-10 Gy)

Weekly CDDP 40 mg/m2

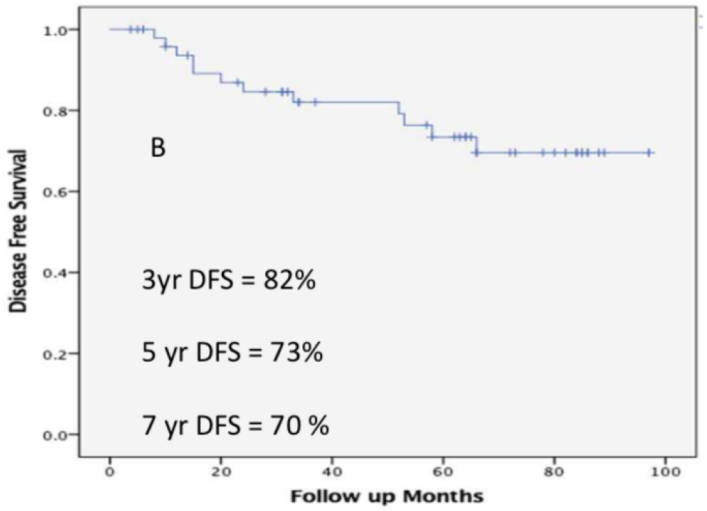
Parameter	Outcomes
Patients recruited on study	N=50
Median Age	47 years (35-65 yrs.)
Gross Tumor Volume Baseline (T2W MRI)	20.7 cc (0-96 cc)
Fluorodeoxyglucose PET Volume (35% SUV Max)	14.8 cc (0-62 cc)
Flouro-Thyidine PET Volume (35% SUV Max)	10.8cc (0-49) (23/34 67% of FDG uptake)
Hypoxic sub volume Flouro Misonidazole	8/34 (23% of those with FDG uptake)
Histology	42 Squamous: 8 Adenocarcinima (84%:16%)
Pelvic Nodal Involvement	19 (38%)
Previous Surgery	Wertheim's Hysterectomy=5 Total abdominal hysterectomy and bilateral salpingoophrectomy=45
Residual Disease After Surgery Recurrent Disease after surgery	N=23 N=27
Average time to presentation	36 mths (1-228 mths)
Dose (EQD2) MUPIT/Small Tandem-Needles Vaginal Brachytherapy (Single/Multisource)	71 Gy (67-74 Gy) 35/ 73 Gy 12/ 67 Gy
Clinical Target Volume at Brachytherapy	38 cc (12-85 cc)
D 90 (Dose Received by 90% of Clinical Target Volume)	71 Gy (50**-74 Gy)
CTV D98 (Dose Received by 98% of Clinical Target Volume)	65 Gy (53**-74 Gy)
Rectum 2 cc/Bladder 2 cc/Sigmoid 2 cc Doses	68 Gy (62-69 Gy)/ 67 Gy (65-71)/62 Gy (57-67 Gy)

Table 1: Table depicting baseline, imaging and treatment details of the study cohort

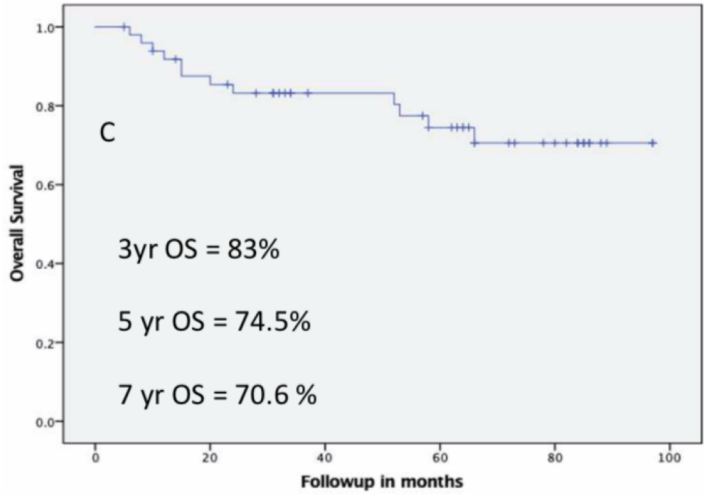
Chopra S, IJROBP,2019



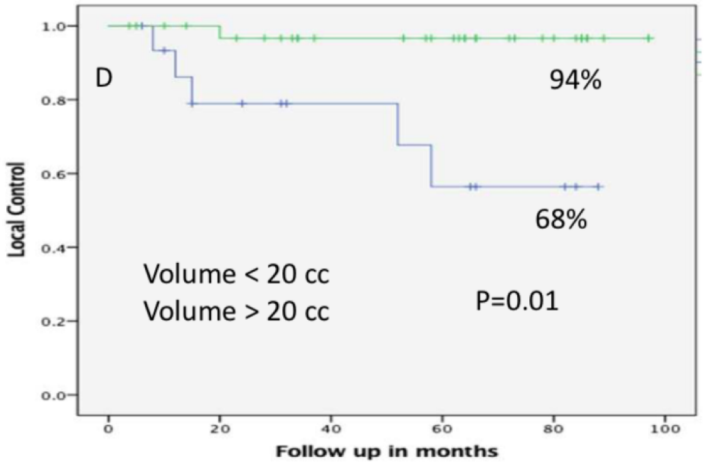
N=	50	41	29	24	13	0
Events	0	4	2	0	0	0



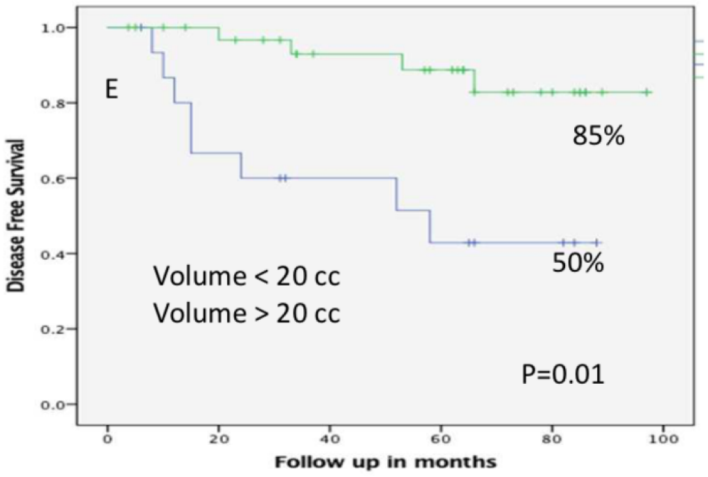
N=	50	41	29.	24.	13	0
Events	0	5	2	4	0	0



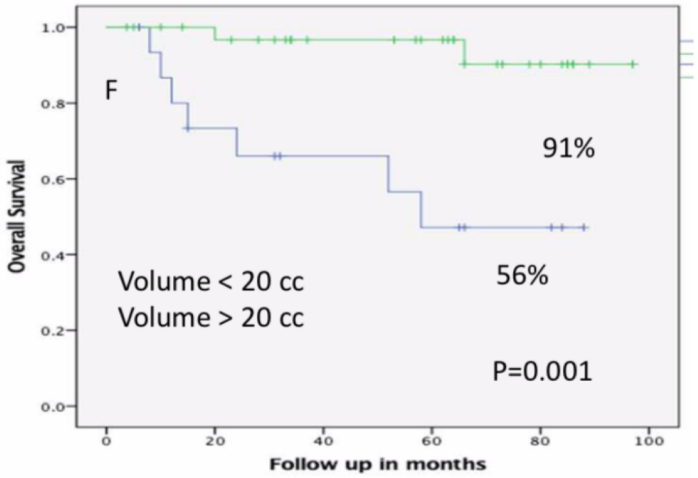
N=	50	41	29.	24.	13	0
Events	0	6	1	3	1	0



N=	50	41	29	24	13	0
Events	0	4	2	0	0	0



N=	50	41	29.	24.	13	0
Events	0	5	2	4	0	0



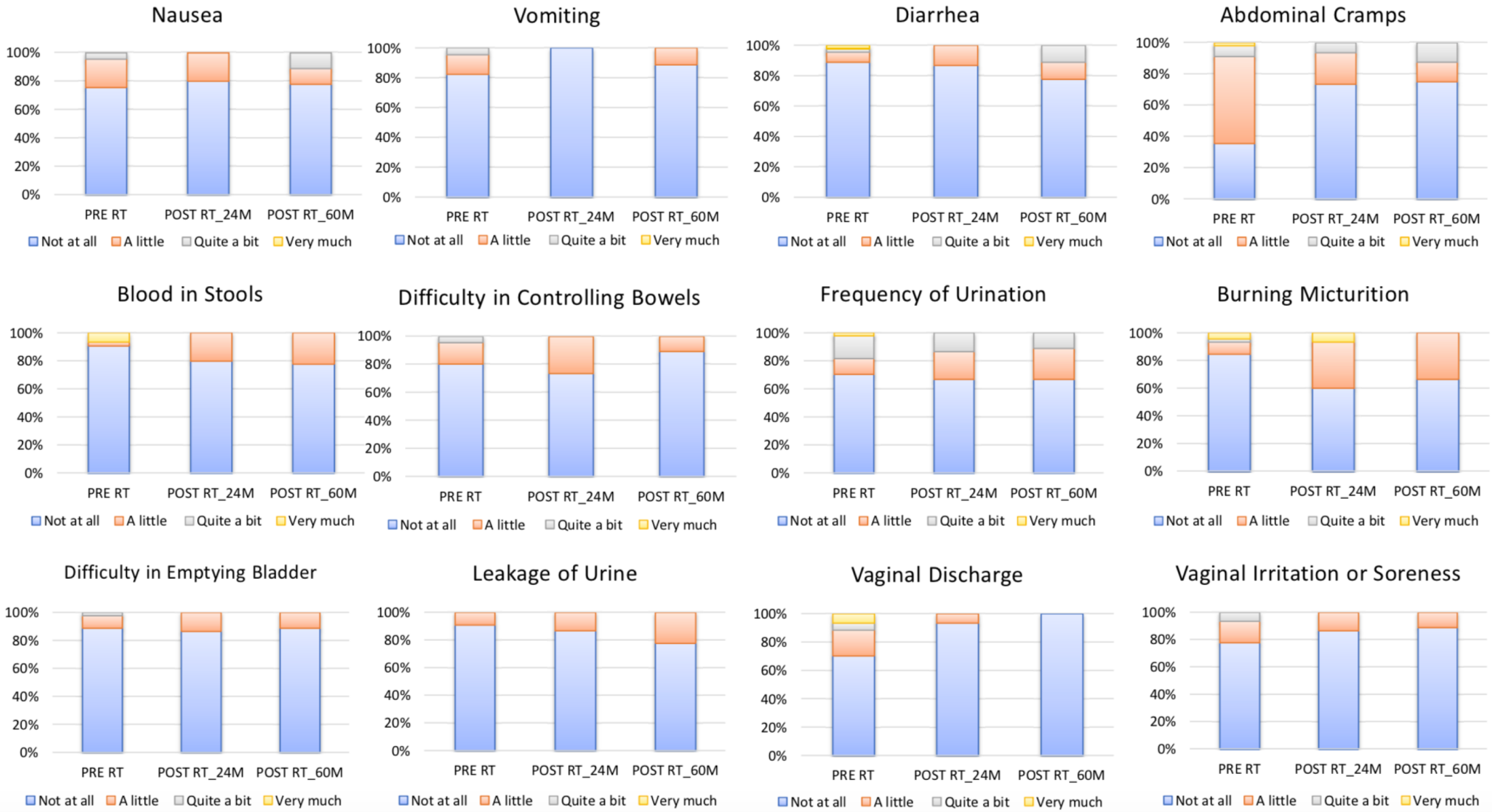
N=	50	41	29.	24.	13	0
Events	0	6	1	3	1	0

Chopra S, IJROBP,2019

Toxicity

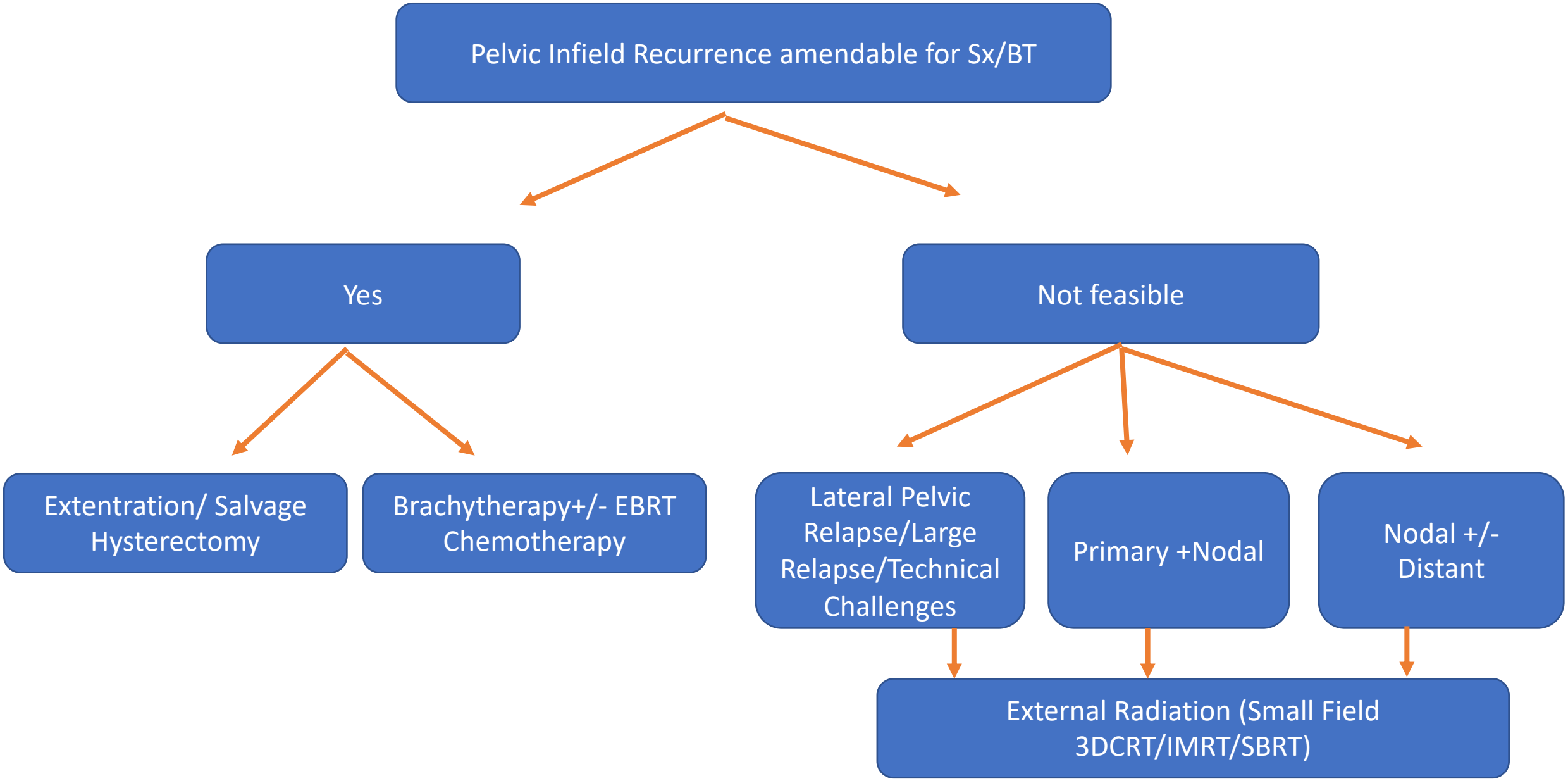
	Grade III	Grade IV	Grade V
Rectal	2 (4%)	1 (2%)	Nil
Bowel	Nil	Nil	1 (2%)
Bladder	1 (2%)	Nil	Nil
Bone	Nil	1 Avascular necrosis Head Femur and Fracture	Nil

Limited opportunity of further dose escalation due to rectal tolerance ? Sub-volume Dose escalation



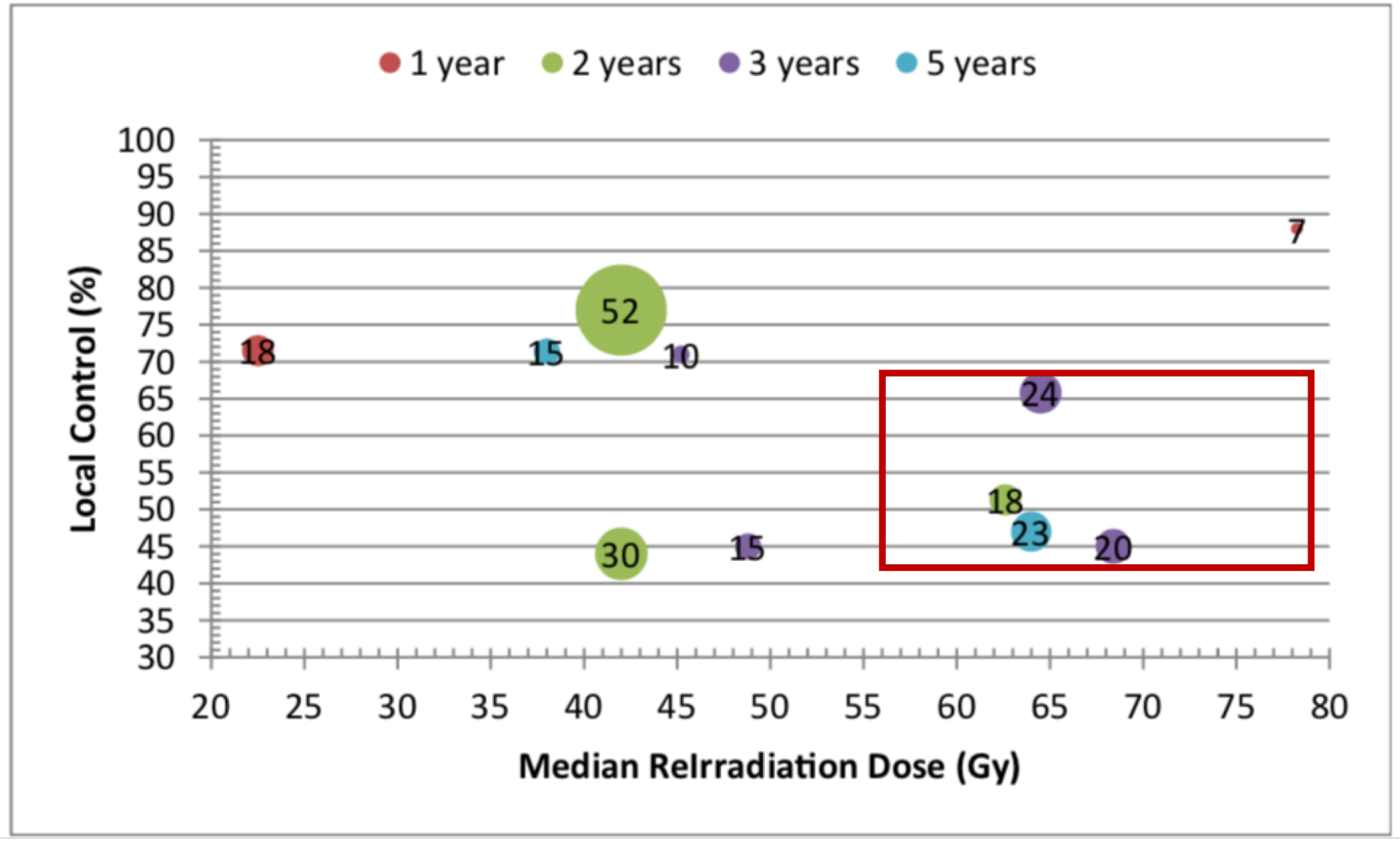
Chopra,S, IJROBP 2019

Re RT setting: DVH Evaluation



A Proportion of patients with local relapse will not be eligible for any treatment

Dose Response Relationship with Brachytherapy+/-EBRT

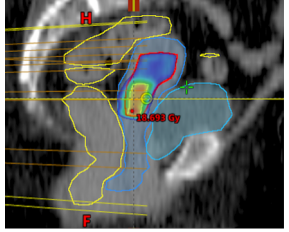


Key Findings

- 45-77% 2 yr local control
- Ability to deliver > 50 Gy equivalent better control (often dependent on previous RT)
- 51-68% 2 yr overall survival
- 15-25% patients will develop Grade III Toxicity
- Very Low Incidence of Grade IV/V Toxicity

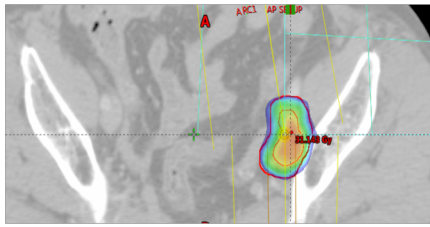
N= 417 patients from 18 different publications (23-25/institute)

Sturdza, IJROBP2020



Outcomes following Stereotactic Re RT

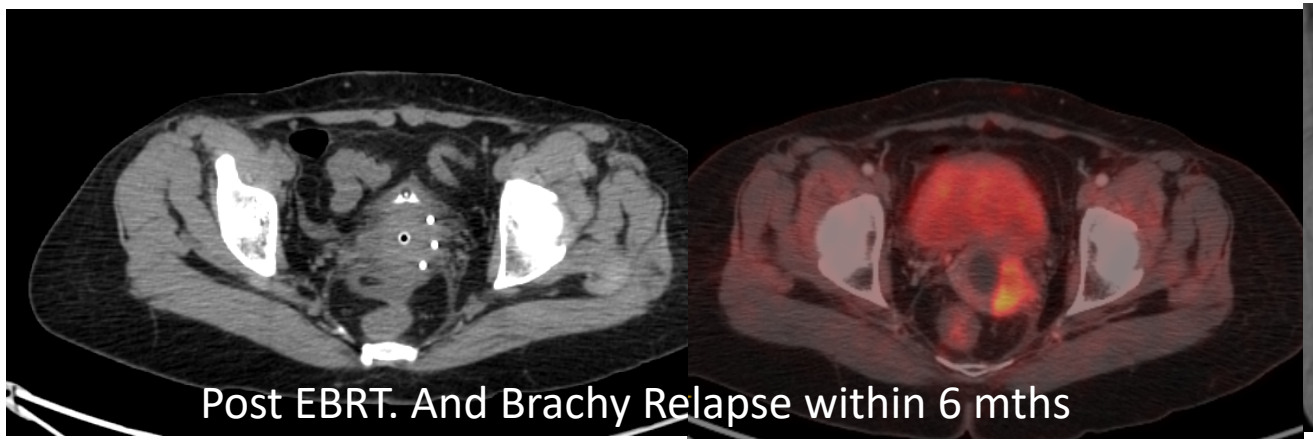
(Nodal/ Local)



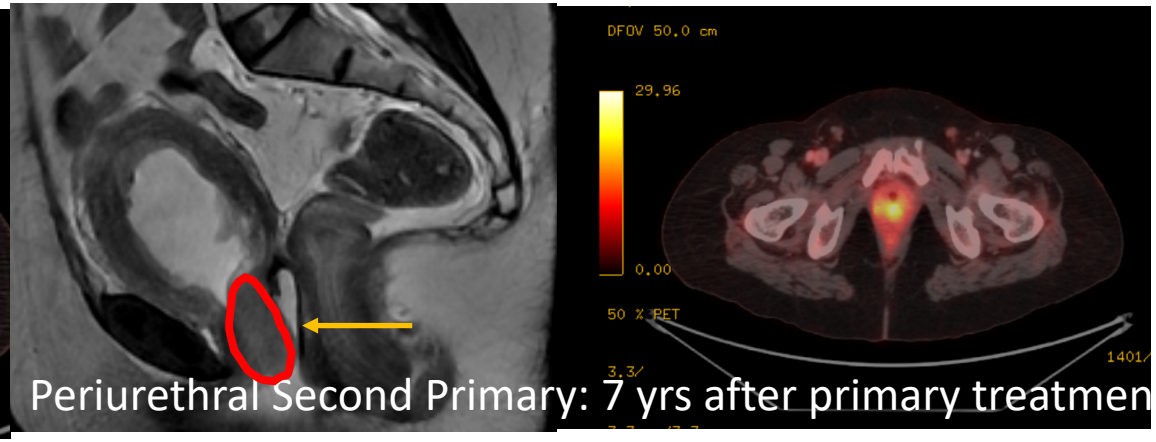
Author	Number of Cases (Re RT)	Prior RT	Sites	Dose	Follow up	Local Control	Toxicity
Ling	20	100%	Nodal	44.5 Gy/5#	31 mths	62%	Grade III:14.3%
Iftode	26	NK	Nodal/Distant	45 Gy/6#	28.5mths	93%	Grade II:11%
Mesko	28	46%	62% Nodal	40 Gy/5#	12.8 mths	No failures	Grade >/=II: 10.7%
Laliscia	45	40%	61% Nodal	27 Gy/3#	40 mths	NR	No Late toxicity
Park	85	68%	89% nodal 3% local	39 Gy/3#	20. mths	82.5%	Late Grade>III:5%
Kunos	50	44%	68% Nodal	24 Gy/3#	21mths	NR	NR
Deodato	11	55%	45% Nodal	30 Gy/6#	19 mths	81.8%	Late Grade II=10%

Ling,2019

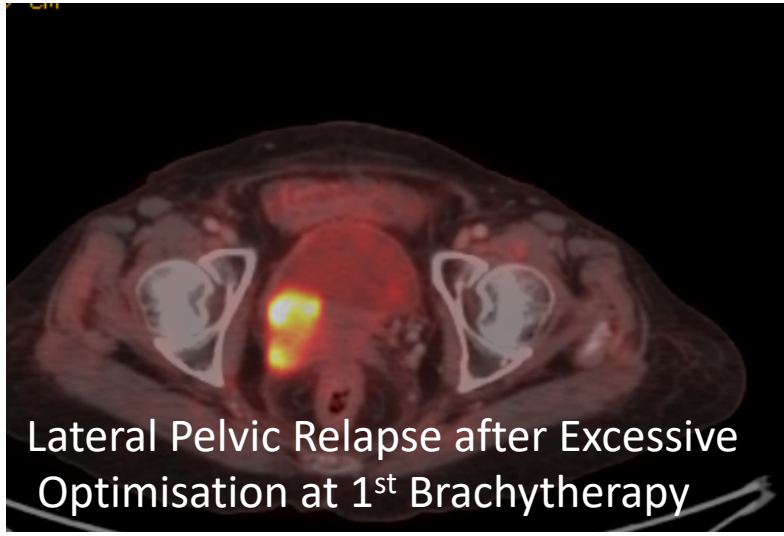
Spectrum of In field Relapses after Gyn Radiation



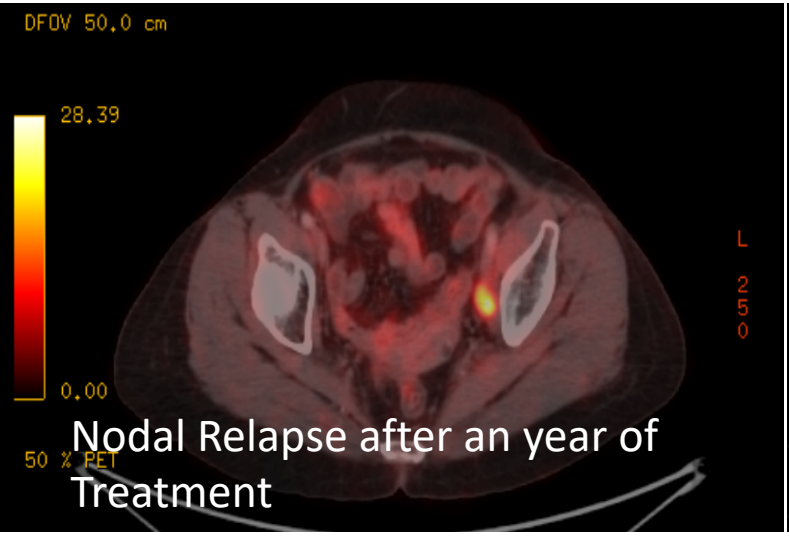
Post EBRT. And Brachy Relapse within 6 mths



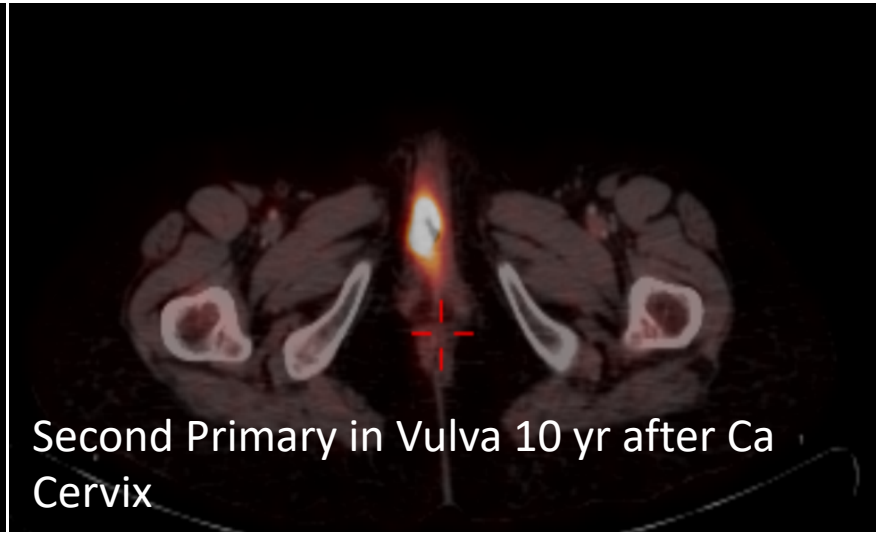
Periurethral Second Primary: 7 yrs after primary treatmen



Lateral Pelvic Relapse after Excessive Optimisation at 1st Brachytherapy

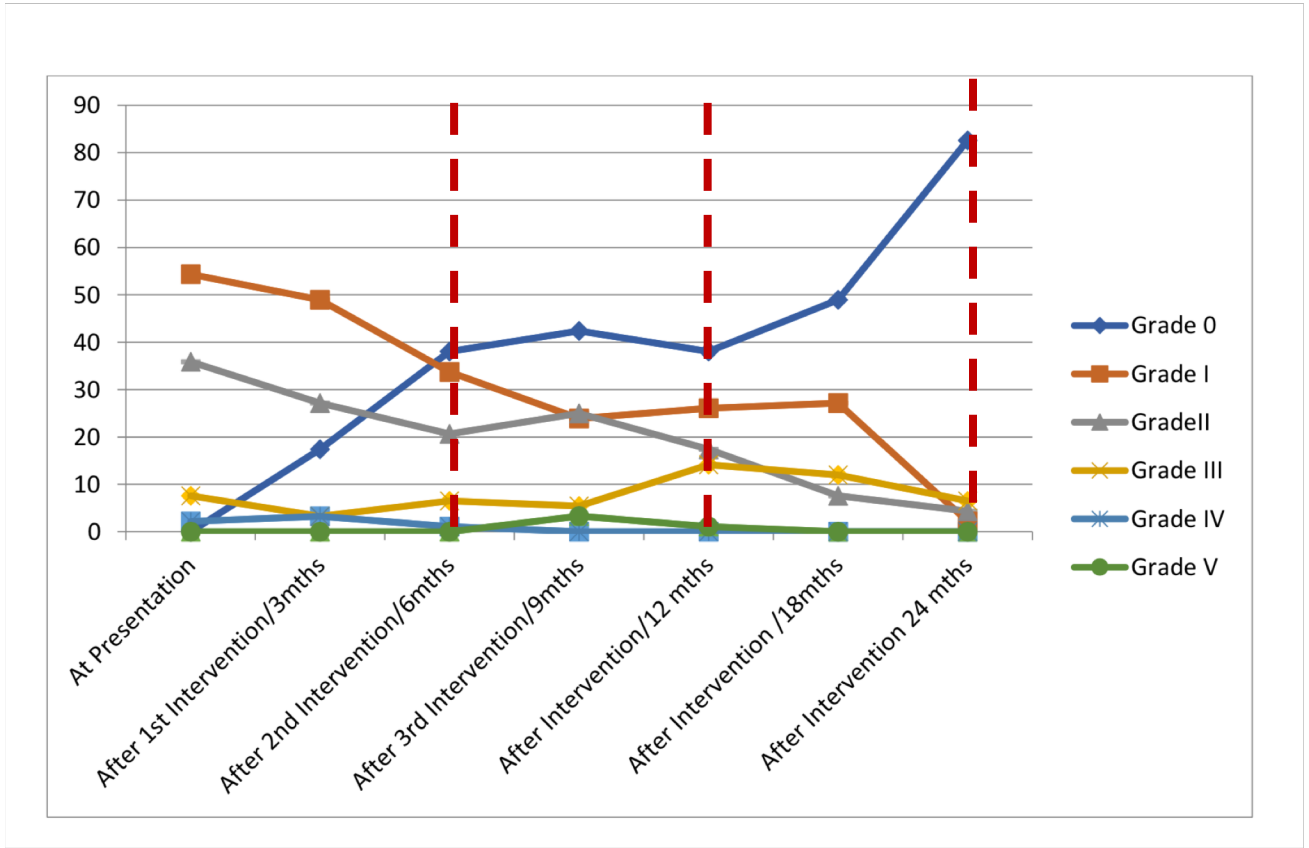


Nodal Relapse after an year of Treatment



Second Primary in Vulva 10 yr after Ca Cervix

Toxicity : Temporal Course after 1st Course of RT



Shejul, Chopra, Advances in Rad Onc, In review 2020

Tissue Recovery after First Course of RT

- 25% Radiation Dose Recovery for Pelvic OARs in 6-12 months, 50% Dose Recovery in 6-12 months.
- Bladder may have less dependency on Fraction size (alpha/beta =6)
- 15-25% Grade III toxicity expected (Bladder/Rectum/Sigmoid)
- 10-12% Fractures
- 5-7% for Vascular Blow outs :Nodal Re RT data

Abusaris, TCRT,2012, Radiotherapy and Oncology,2012
Sesikeran, Journal of Current Oncology 2020

Third course Radiation: Pelvic Structures

Median Overlapping Volume =204 cc

16 month follow up after 3rd course of Radiation and no Grade IV toxicity

Table 4a

Dose (EQD_2) and cumulative dose (EQD_2) given to the organs at risk after three radiation courses.

Uncorrected Doses

Organs at risk	Median dose of 1st course	Median dose of 2nd course	Median dose of 3th course	Median	Min	Max	No. of patients
Bladder	50	31	34	114	86	151	13
Bowel	50	30	21	108	80	148	10
Rectum	52	28	36	127	99	189	8
Sacral nerves/cauda equina	38	54	29	106	80	149	9
Plexus brachialis	53	24	23	92	79	142	3
Myelum	43	14	16	72	66	79	2

Time Corrected Doses for Repair

Table 4b

Cumulative dose (EQD_2) given to the organs at risk after three radiation courses with dose reduction due to tissue repair.

Organs at risk	Median	Min	Max	No. of patients
Bladder	79	50	118	13
Bowel	73	49	108	10
Rectum	91	68	156	8
Sacral nerves/cauda equina	65	47	117	9
Plexus brachialis	85	66	106	3
Myelum	62	55	68	2

Abusaris, Radiotherapy and Oncology,2011

Dose recommendations for pelvic organs

	Alpha/Beta=3 (2cc volume)’	Re RT (10 cc volume)
Rectum-Sigmoid	75 Gy EQD2	100 -110Gy3
Bowel	75 Gy EQD2	90-100 Gy 3
Bladder	90 Gy EQD2	110-120 Gy3
Cauda Equina	45-50 Gy EQD2	105 Gy3
Urethra	0.1 cc 85 Gy EQD2	120 Gy EQD3

Temporal (Time Based) Recovery of 25 and 50 % may be presumed of no persisting late toxicity

Abusaris, TCRT,2012, Radiotherapy and Oncology,2012
Sesikeran, Journal of Current Oncology 2020

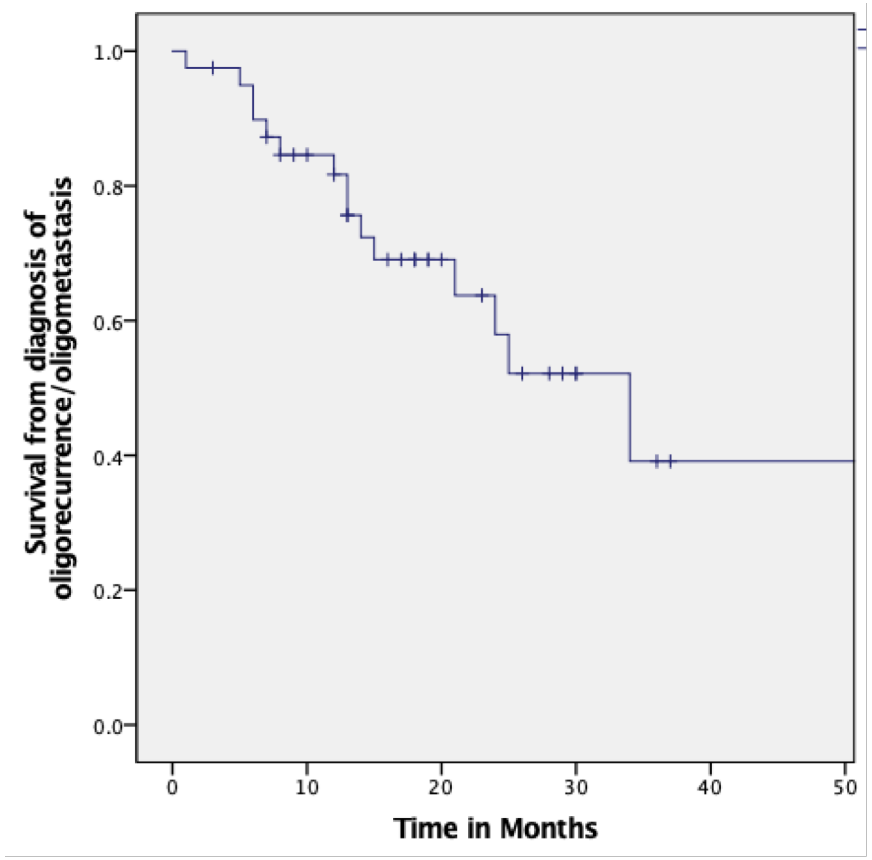
Outcomes of Oligoprogression/Oligorecurrence treated with IMRT/SBRT: Tata Cohort

N=40
Median time to first relapse=14 months (6-22)
Median ReRT/RT dose=30-42 Gy/5-6#
Those with denovo metastastasis recd

Oligorecurrence (N=26)
Infield=46%
Out of field=19%
In and out of field= 35%

Oligometastasis (N=14)
50% received salvage chemotherapy (others did not due to poor performance status)
Median OS from relapse =17 mths (9-26)
Only 37% patients have died
Likely to improve further.

Grade III toxicity:12.5%



Tata Memorial Centre, Work in Progress

Deformable dose accumulation : 2020+2019+2018
EQD2 & BED