Meta-analysis Cervical Cancer

Supriya Sastri
Professor, Radia9on Oncology
ACTREC, Tata Memorial Centre

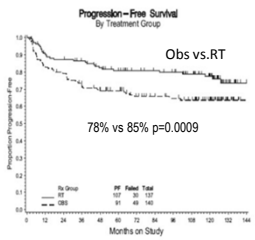
Key Metaanalysis

- Early Cervix Cancer
  - Postopera9ve Radia9on/Chemoradia9on
  - Postopera9ve adjuvant CRT + chemotherapy
- Locally Advanced Cervix cancer
  - Paraor9c lymph node dissec9on for nodal staging
  - Concurrent chemoradia9on
  - Neoadjuvant chemotherapy
  - Adjuvant chemotherapy
  - Dose Rate for brachytherapy
- Newer Radia9on Techniques

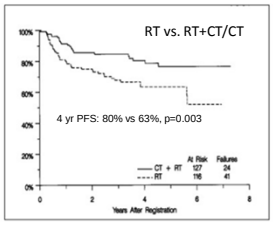
Background

•Postoperative pelvic RT improves recurrence free survival in node negative patients with adverse prognostic factors (Sedlis,1999, Rotman 2006 GOG 92)

•Chemo+RT (concurrent +adjuvant) improves PFS in patients with high risk features on histopathology. (Peeters JCO 2002, GOG 109)



GOG 92 GOG 92



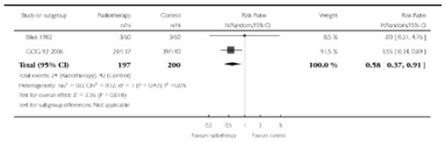
GOG 1GOG 109

Acute Sequelae Sx+PORT Phase III RCT (without brachy)

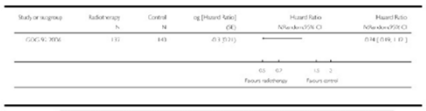
RCT	Study Design	GI Gr II	GI Gr III-IV	GU Gr I-II	GU Gr III-IV
Landoni	Sx+/-RT vs RT	28% vs. 12% (p<0.0004) Not Categorized			
Rotman	Sx vs Sx+RT	NR	0% vs 2%	NR	1.5% vs 3%
Keys	Sx vs Sx+RT	7% vs 58% P<0.001	0.4% vs 8%	8% vs 30% P<0.001	Nil
Peters	Sx+RT vs CT/RT+adj chemo	48.2% vs. 46%	5% vs. 10%	NR	NR

Peters JCO 2000. Landoni, Lancet 1997, Keys. Gynec Oncol 2004, Rotman IJROBP 2006

Postopera9ve Radia9on



Int Risk Pa9ents: Recurrence Free Survival at 5 years
Surgery vs Surgery+RT

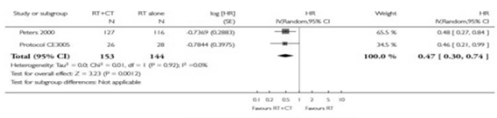


No difference in OS

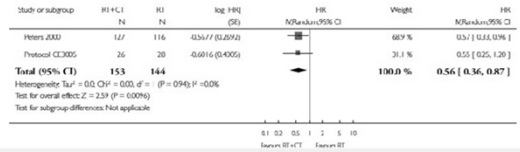
Cochrane,2014

Postopera9ve CRT vs RT

Disease Progression



Death from any cause



N=401 : 4 trials, 2 for survival endpoints. Not possible to assess by stage or chemo type

Chemoradia9on for Locally Advanced Cervical Cancer (IB2-IVA)

- Concurrent chemoradia9on
  - Lukka's MA
  - Green's MA
  - IPD Cochrane Metaanalysis
  - Others
- Neoadjuvant chemoradia9on
  - Cochrane
- Adjuvant chemotherapy
  - Only 1 trial
  - Outback awaited

Lukka's metaanalysis (2001)

- 8 randomized trials.
- Only trials that asked ques9ons of CRT vs RT (+/- hydroxyurea) were considered.
- 6 trials with LACC , others post op high risk pa9ents

Study	FIGO stage	Treatment group	Control group	No. of patients	Median follow-up (months)
Locally advanced cervical cancer, radiotherapy alone as a control					
Wong, 1989 [3]	IIB-IIIB	XRT[a]+weekly CP	XRT[a]	47[c]	range: 42 to 72
Tseng, 1997 [4]	IIB-IIIB	XRT[a]+CP/bleo/VCR	XRT[a]	122	47
Morris, 1999 [1] (RTOG 90-01)	IB-IVA	XRT[a]+CP/5FU	XRT[b]	386	43
Pearcey, 2000 [7] (NCIC)	IB-IVA	XRT[a] + CP	XRT[a]	253	65
Locally advanced cervical cancer, radiotherapy plus hydroxyurea as a control					
Rose, 1999 [5] (GOG-120)	IIB-IIIB	XRT[a]+CP	XRT[a]+HU	353[d]	35
Whitney, 1999 [6] (GOG-85)	IIB-IIIB	XRT[a]+CP/5FU	XRT[a]+HU	368	104 (among survivors)
Bulky stage IB cervical cancer					
Keys, 1999 [10] (GOG-123)	bulky IB	XRT[a]+CP+hysterectomy	XRT[a]+hysterectomy	369	36
Postoperative high-risk cervical cancer					
Peters, 2000 [11] (SWOG 8797)	IA2-IIA	Hysterectomy +pelvic lymphadenectomy +XRT[a]+CP/5FU	Hysterectom +pelvic lymphadenectomy +XRT[a]	243	42

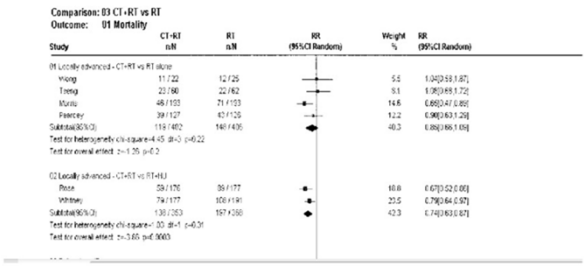
Clinical Oncology 2002

Pa9ent Characteris9cs

Study	No. randomized/ No. eligible/ No. analysed	Histology	Method of staging	Stage of disease – number of patients (%) IB/IIA	IIB	IIIA	IIIB	IVA
Locally advanced cervical cancer								
Wong, 1989 [3]	64/64/64	63 squamous cell (98%) 1 adenocarcinoma	clinical	–				
Tseng, 1997 [4]	122/122/122	122 squamous cell (100%)	clinical & surgical, FIGO (1991)	–				
Morris, 1999 [1] (RTOG 90-01)	403/388/386*	350 squamous cell (90%) 14 adenosquamous 24 adenocarcinoma	clinical & surgical, FIGO (1995)	130 (34%)				
Pearcey, 2000 [7] (NCIC)	259/253/253	253 squamous cell (100%)	clinical, FIGO	stages IB, IIA, IIB >5 cm, III or IVA; number of patients with each stage not reported				
Rose, 1999 [5] (GOG-120)	575/526/526	472 squamous cell (90%) 30 adenosquamous 18 adenocarcinoma 6 other	clinical & surgical, FIGO	–				
Whitney, 1999 [6] (GOG-85)	388/374/368**	335 squamous cell (91%) 19 adenosquamous 14 adenocarcinoma	clinical & surgical, FIGO	–				
Bulky stage IB cervical cancer								
Keys, 1999 [10] (GOG-123)	374/369/369	299 squamous cell (81%) 27 adenosquamous 23 adenocarcinoma 20 other	clinical & surgical	stage IB (>4 cm)	–	–	–	–
Postoperative high-risk cervical cancer								
Peters, 2000 [11] (SWOG 8797)	268/243/243	193 squamous cell (79%) 19 adenosquamous 31 adenocarcinoma	surgical	Ia2, IB, IIA	–	–	–	–

*, no follow-up data for two patients; **, no follow-up data for six patients; FIGO, International Federation of Obstetrics and Gynecology.

Results: Lukka's Metaanalysis



95% CI demonstrate benefit of CRT however 99% CI straddle unity.
25-52% pa9ents with locally advanced stage.
Largest cleanest trial by Pearcey was nega9ve

Green's Metaanalysis (Cochrane)

- Ques9ons addressed
  - OAS
  - PFS
  - Local and Distant Control
  - Acute and Late Toxicity

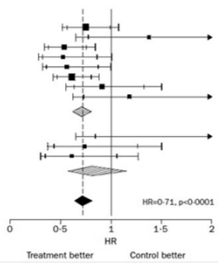
  - NCI Alert based on only 5 trials
  - Lukka's metaanalysis included 8 trials
  - 4580 randomized pa9ents 19 trials
  - 62-78% pa9ents available for analysis

Trials	Accrual period (year)	Median follow up (months)	Patients randomised (excluded)	Drugs	Stage I & II included (%)	Affected para-aortic nodes not eligible	Sequential chemotherapy	RT opt%
Platinum								
Wong (1989)[16]	1982–83	NS	64 (0)	CDDP	70	Yes	No	Yes
Whitney[10]	1986–90	NS	388 (20)	CDDP 5FU	64	Yes	No	Yes
Thomas[9]	1987–95	59	234 (13)	5FU	NS	No	No	Yes
Lorvidhaya[26]	1988–92	25	873 (0)†	MMC 5FU	44	No	Yes	No
Wong (1999)[11]	1989–92	66/96	??? (?)	Epi	80	No	Yes	Yes
Ferrandez[28]	1990–92	25	82 (0)	MMC 5FU	0	NS	No	No
Roberts[14]	1994–97	NS	212 (52)	MMC	62	No	No	Yes

- Ø 70% pa9ents had stage I and II Cervix Cancer
- Ø Both Pla9num and Non Pla9num Regimens tested
- Ø 4/19 included trials had sequen9al chemotherapy
- Ø 3/19 trials did not have op9mal RT dose delivery
- Ø Median follow up < 3 years for 4/19 trials
- Ø Median follow up not known in 7/19 trials

Green's Metaanalysis

	Treatment*	Control*	O–E	Variance
Platinum				
Whitney[10]	79/177	108/191	−13·69	45·45
Tseng[20]	23/60	22/62	3·69	11·25
Morris[8]	48/195	71/193	−19·13	29·41
Peters[13]	21/127	36/116	−9·60	14·25
Keys[7]	27/183	49/186	−10·84	17·86
Rose[9]	116/349	89/177	−23·38	45·77
Pearcey[12]	49/127	52/126	−2·38	25·26
Leborgne[†]	42/75	39/78	2·61	15·02
Subtotal	405/1293	466/1129	−72·72	204·27
Non-platinum				
Hernandez[27]	21/36	6/18	3·56	5·30
Wong (1999)[11]	21/110	34/110	−3·93	12·41
Roberts[14]	20/82	30/78	−5·93	11·45
Subtotal	62/228	70/206	−6·30	29·16
Total	467/1521	536/1335	−79·02	233·43



Approximately 12% survival benefit (5 year OS: 40% to 52%)

PFS (-11% to+28%) Overall 13% benefit

Impact of chemoradia9on in advanced stage not clear

Results

- Effect of chemoradia9on much higher when trials included> 70% early stage benefit
- 5 year DFS benefit essen9ally in Stage IB-IIB pa9ents
- Cau9on against extrapola9on of results to advanced stage disease

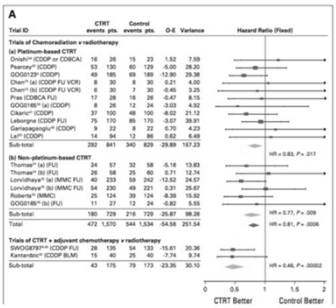
Treatment related Toxicity

	Number of trials	Treatment (events/patients)	Control (events/patients)	Odds ratio (95% CI)	p
Site of toxicity					
Haemoglobin	6[9-11,13,26,28]	64/1141	30/796	1·49 (0·98–2·27)	0·06
White cell count*	9[9-14,24-26]	216/1328	74/979	2·21 (1·72–2·93)	<0·0001
Platelets	8[9-14,24,25]	18/1223	2/874	3·73 (1·53–9·10)	0·004
Haematological not otherwise specified	3[7,8,21]	112/390	5/391	8·60 (5·81–12·74)	<0·0001
Genitourinary*	6[7-9,13,28]	9/1106	18/941	0·43 (0·20–0·92)	0·03
Gastrointestinal*	6[7-9,13,15,28]	105/1106	40/941	2·22 (1·58–3·11)	<0·0001
Neurological	3[9,10,13]	3/653	2/484	1·11 (0·19–6·56)	0·90
Dermatological	4[7-9,13]	15/836	11/670	1·09 (0·50–2·39)	0·80

Acute Toxicity reported by only 8/19 trials
Late toxicity reported only by 3/19 trials
Odd's ra9o 1.5-8 9mes for GI and Hematological Toxicity

Green, Lancet 2001

IPD Metaanalysis



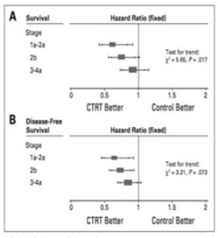
Denonstrated benefit of Pla9num and Non Pla9num
Also in adjuvant sejng on basis of 2 small adjuvant trials

Cochrane JCO 2008 2010

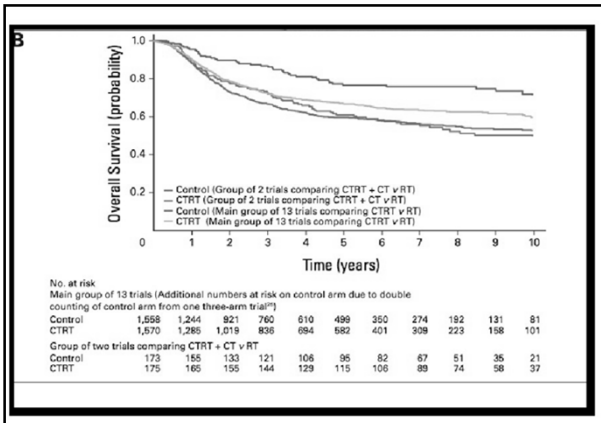
Table 2. Results of Trial Group Analyses for Survival

Variable	Main Analysis (13 trials) HR	95% CI	Interaction P
Planned chemotherapy type			
Platinum based	0.84	0.72 to 0.98	
Nonplatinum based	0.76	0.62 to 0.94	.48
Planned radiotherapy dose			
≥ 45 Gy + BRT	0.78	0.68 to 0.89	
< 45 Gy + BRT	0.93	0.70 to 1.24	.26
Planned radiotherapy duration, weeks			
≤ 8	0.83	0.72 to 0.96	
> 8	0.73	0.57 to 0.93	.35
Planned chemotherapy cycle length, weeks*			
≤ 1	0.74	0.60 to 0.92	
> 1	0.95	0.72 to 1.25	.16
Planned cisplatin dose-intensity, mg/m²/wk*			
≤ 25	0.93	0.70 to 1.24	
> 25	0.76	0.62 to 0.96	.25
Cisplatin regimen*			
Single agent	0.76	0.62 to 0.93	
Combination	0.93	0.70 to 1.24	.25
Chemotherapy regimen			
Single agent	0.75	0.63 to 0.88	
Combination	0.86	0.71 to 1.04	.29

NOTE. Two trials in which additional adjuvant chemotherapy was administered on the treatment arm are excluded.
*Results are based only on trials in which cisplatin-based chemoradiation was administered.



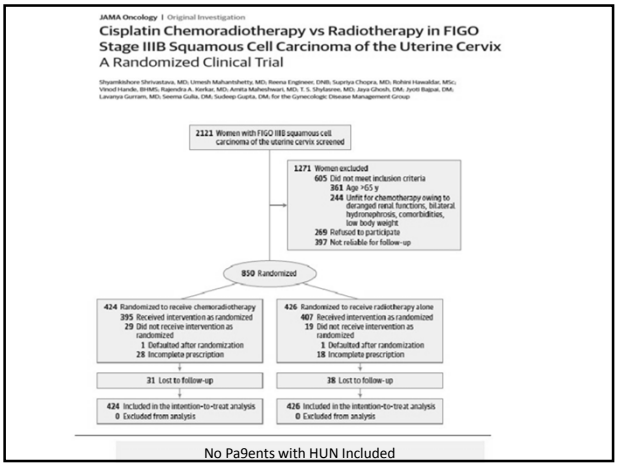
JCO, 2008



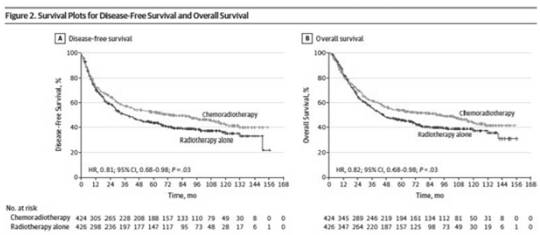
Metaanalysis on Chemoradia1on in Cervical Cancer

Author	Trials/Pts	PFS	OAS	Early Stage	Stage Wise Benefit
Green,2001 Lancet	19 trials 4580 pts	16%	12%	68% pts	Not Reported
Lukka,2002 Clin Onco	8trials, 2141 pts	NR	11%	28%	Greatest in postop high risk, lowest in advanced stage
Cochrane, 2005	24 trials	13%	10%	70%	Higher benefit in early stage
CACC-MAC, 2008 JCO (IPD)	18 trials, 4818 pts	DFS: 8%	6%*	66%	3% OAS beefit for advanced stage
Cochrane, 2010	24 trials,4921	13%	10%	70%	Higher benefit in early stage
Cochrane IPD, 2010 CACC-MAC	18 trials,	DFS: 8%	6%*	66%	3% benefit in IIIB 7% in IIb 10% in IB1-IIA

*= 19% benefit in trials using concurrent CTRT and adjuvant chemotherapy



No Pa9ents with HUN Included



46% vs 54% OS in Stage IIIB, p=0.03

43.8% vs 52.3% DFS in Stage IIIB, p=0.04

Shrivastava et al, 2018

Meta-analysis:Summary

- Results of large Phase III trial yet to be included.
- Benefit from CRT with OTT < 50 days (EMBRACE Data)
- Chemo dose intensity important (> 160-200 mg/m2)
- Strategies such as chemotherapy dose intensity and 9ming (weekly vs. three weekly need to be further inves9gated)

Hyperthermia in LACC

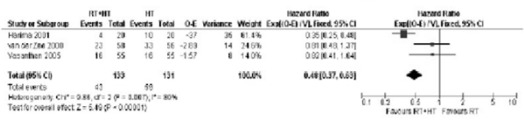
Chemoradia9on+Hyperthermia Network Meta-analysis

- 217 abstracts
- 6 RCT HTRT/CT (n=215) vs RT/CT (n=212)
- Non significant survival advantage of HTRT over RT.
- HTCRTvs RT (complete response 83% vs.46%)
- HTCTRT best therapeu9c op9on for OS.
- Need for prospec9ve randomized trial.

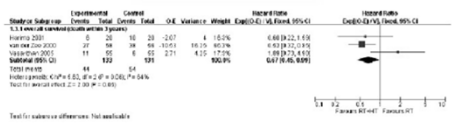
Dana NR, Int J

Cochrane Metaanalysis:Hyperthermia

Local Recurrence

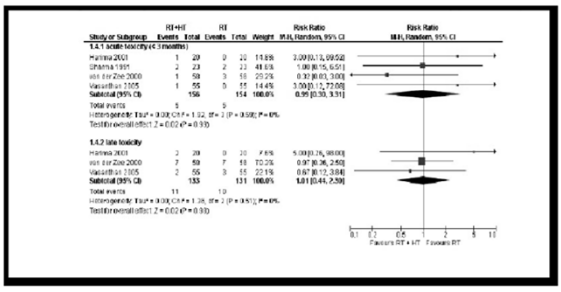


Overall Survival



Lutgens, Cochrane Library 2010

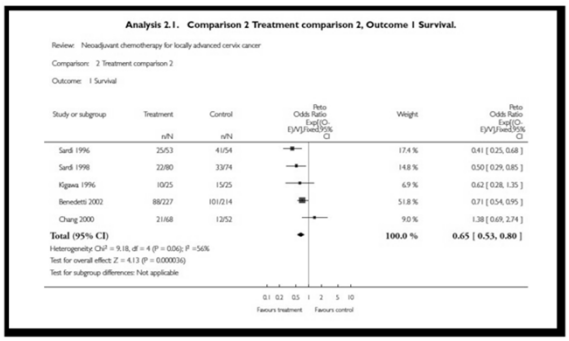
Toxicity: Hyperthermia(C) RT



Lutgens, Cochrane Library 2010

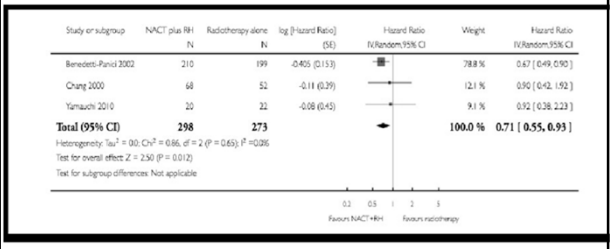
Neoadjuvant chemotherapy for LACC

Neoadjuvant Chemotherapy for LACC



High Heterogeneity in Included Trials, Time between chemo and Dose

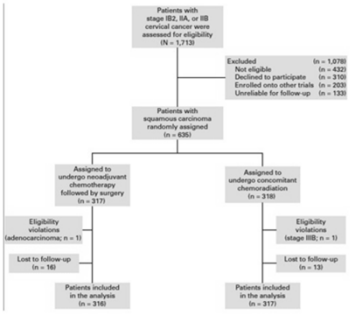
Neoadjuvant chemo+Sx vs RT alone



Cochrane Library

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Sudeep Gupta, Amita Maheshwari, Pallavi Parab, Umesh Mahantshetty, Rohini Hawaldar, Supriya Sastri (Chopra), Rajendra Kerkar, Reena Engineer, Hemant Tongaonkar, Jaya Ghosh, Seema Gulia, Neha Kumar, T. Surappa Shylasree, Renuka Gawade, Yogesh Kembhavi, Madhuri Gaikar, Santosh Menon, Meenakshi Thakur, Shyam Shrivastava, and Rajendra Badwe



NACT-Sx(CTRT) vs. CTRT

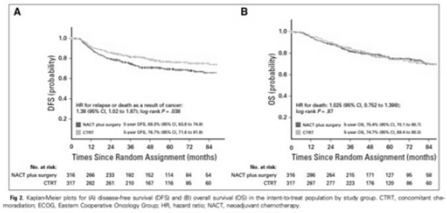
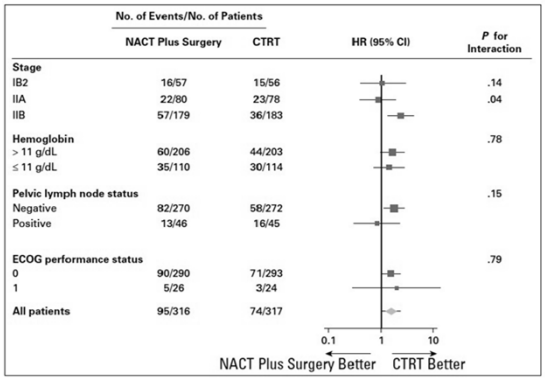


Fig 2. Kaplan-Meier plots for (A) disease-free survival (DFS) and (B) overall survival (OS) in the intent-to-treat population by study group. CTRT, concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NACT, neoadjuvant chemotherapy.

Upto 40% u9lisa9on of CTRT in NACT-Sx group either due to cross over or adjuvant RT or salvage RT

Pa9ents those who were crossed over did worse than pa9ents who were considered for upfront CRT

Gupta S, et al. JCO 2018



Gupta S, et al. JCO 2018

Dose Rate in Cervical Brachytherapy

Pooled Analysis

		Overall survival (%)*		Disease-free survival (%)*		Toxicity (%)†	
	FIGO stage	HDR	LDR	HDR	LDR	HDR	LDR
Patel et al.[38]	Stage I <3 cm	100	100	85	81	0.4	2.4
	Stage II <3 cm	82	82	71	66		
	Stage I >3 cm	87	88	75	70		
	Stage II >3 cm	74	78	63	60		
	Stage III	71	76	43	50		
Teshima et al.[37]	Stage I	66	89‡	85	93	9	4
	Stage II	61	73	73	78		
	Stage III	47	45	53	47		
Hareyama et al.[40]	Stage II	89	100	69	87	10	13
	Stage III	69	70	51	60		
Lertsanguansinchai et al.[39§]	Stage IIB	65	74	65	76	9	4
	Stage IIIB	71	63	74	59		

* 5-year results unless otherwise stated.
† Combined bowel and bladder grades 3-5 late complications, reported for all stages.
‡ Statistically significant difference.
§ 3-year results.

Metaanalysis 1265 pa9ents, 4 RCT's

Toxicity Results

Grade 3 or 4 rectal complication

Number of studies	Total patients	Patients/events HDR	Patients/events LDR	OR	CI95%	P value
5	2065	27/1068	27/997	0.9	0.52–1.56	0.7

Grade 3 or 4 bladder complication

Number of studies	Total patients	Patients/events HDR	Patients/events LDR	OR	CI95%	P value
5	2065	17/1068	16/997	0.98	0.49–1.96	0.95

Grade 3 or 4 small intestine complication

Number of studies	Total patients	Patients/events HDR	Patients/events LDR	OR	CI95%	P value
3	783	13/432	3/351	3.15	0.9–10.37	0.06

Cochrane Metaanalysis

Year	Study	Patients	Fraction of LDR (Gy/fraction)	Fraction of HDR (Gy/Fraction)	Pelvic RT Dose (Gy)	Clinical stage	
						LDR	HDR
2004	Lertsanguansinchai	237	25–35/2	15–16.6/2	40–50	IB-5 IIA-2 IIB-61 IIIB-41	IB-7 IIA-1 IIB-64 IIIB-40
2002	Hareyama	132	IIA-50/4 IIB-40/3 III-30/3	IIA-29.5/4 IIB-23.3/3 or 4 III-17.3/3 or 2	30–40	II-26 III-39	II-22 III-45
1993	Teshima	430	I-56/2 II-57/2 III-58/2	I-28/4 II-30/4 III-29/3	16–20	I-28 II-61 III-82	I-32 II-80 III-147
1994	Patel	482	I-II>3 cm-75/2 I-II<3 cm-35/1 III-35/1	I-II>3 cm-38/2 I-II<3 cm-18/2 III-18/2	35–40	I-39 II-93 III-114	I-35 II-90 III-111
2006	Shrivastava	800	I and II-60/2 III-30/1	I and II-35/5 III-21/3	40/20	I II-200 III-200	I II-200 III-200

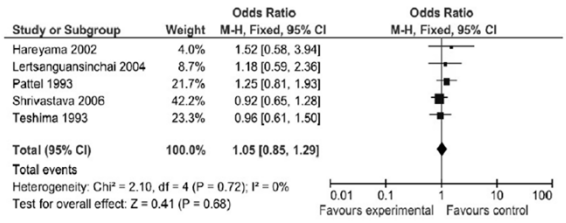
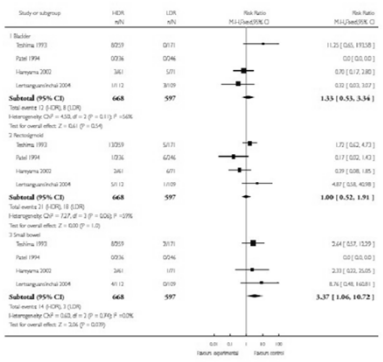


Figure 5
Local recurrence for all clinical stages in cervix cancer.

Late Effects



Hysterectomy aoer CRT

- RCT by French Group
- No advantage of adjuvant hysterectomy aoer CRT.

Meta-analysis : Dosimetric Impact of IMRT

13 ar9cles 222 IMRT treated and 233 3DCRT treated pa9ents included

First author, [Reference]	Country	Prescribed dose, Gy	Sample size		Organs at risk	Level of the dose, Gy
			IMRT*	3D-CRT*		
Heron DE [26]	USA	45	10	10	Rectum, Small bowel, Bladder	10, 20, 30, 40, 45
Chen MF [36]	Taiwan	50.4	33	35	Rectum, Small bowel, Bladder, Bone marrow	5, 10, 15, 20, 25, 30, 35, 40, 45
Mell LK [30]	USA	45	7	7	Rectum, Small bowel, Bladder, Bone marrow	5, 10, 20, 30, 40, 45
Igdem S [31]	Turkey	45 or 50.4	10	10	Rectum, Small bowel, Bladder, Bone marrow	5, 10, 15, 20, 25, 30, 40, 45
Roeske JC [17]	USA	45	10	10	Rectum, Small bowel, Bladder	5, 10, 15, 20, 25, 30, 35, 40, 45
Portelance L [17]	USA	45	10	10	Rectum, Small bowel, Bladder	45
Lujan AE [38]	USA	45	10	10	Bone marrow	5, 10, 15, 20, 25, 30, 35, 40, 45
Briey CJ [39]	USA	45	36	88	Iliac crest, Lumbar spine, Sacrum	5, 10, 15, 20, 25, 30, 35, 40, 45
Ahmed RS [27]	USA	45	5	5	Bone marrow	5, 10, 15, 20, 25, 30, 35, 40, 45
Mell LK [37]	USA	45	37	0	Bone marrow	10, 20, 30, 40
Mundt AJ [38]	USA	45	36	30	Small bowel	5, 10, 15, 20, 25, 30, 35, 40, 45
Salama JK [40]	USA	45	13	13	Rectum, Small bowel	5, 10, 15, 20, 25, 30, 35, 40, 45
Georg D [41]	Austria	50.4	5	5	Rectum, Small bowel, Bladder	5, 10, 15, 20, 25, 30, 35, 40, 45

•Rectum : One Third reduc1on in volumes receiving >30 Gy; p=0.002)

•Small Bowel : Reduc1on in V40 and V45 Small Bowel by 17%; p=0.04)

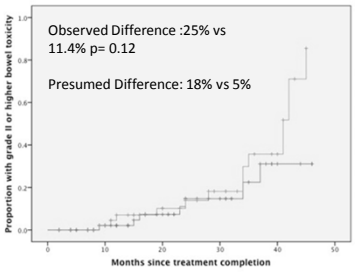
•No difference in Bone Marrow Doses

Yang, Radia9on Oncology,2012

Phase III Randomized Controlled Trials Postoperative Gynecological IMRT

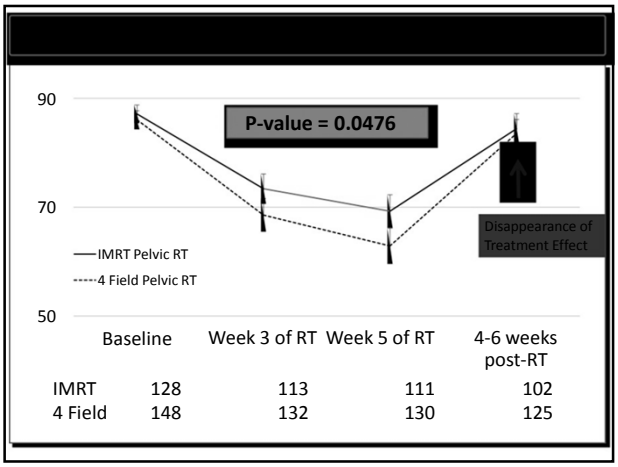
Trial	Ini1ated/ Pa1ent Popula1o n	Endpoints	Sample Size
PARCER Study (NCT01279135) ACTREC, Tata Memorial Centre, India	2011 Post Op Cervix	**Primary Endpoint** Late Grade ≥ II GI Toxicity (13 GI subscales of CTCAE)	**N= 240**
TIME-C (NCT01672892) NRG/RTOG1203 MD Anderson Cancer Centre, USA	2012 Postop Cervix Endometri um	**Primary Endpoint** Acute (Wk5) GI Toxicity (EPIC Bowel Domain 14 func9onal and bother scales)	**N= 289**

Phase III RCT of Postoperative 3DCRT Vs. IG-IMRT for reducing Late Bowel Toxicity in Cervical Cancer (PARCER): Interim Analysis



Number at Risk (Number of Events)					
3DCRT (n=56)	42(1)	28 (3)	17(2)	8(2)	7(3)
IMRT (n=61)	46 (1)	29 (2)	15(2)	3(2)	3(0)

Chopra, S ASTRO



	Baseline	Week 3 of RT	Week 5 of RT	4-6 weeks post-RT
IMRT	128	113	111	102
4 Field	148	132	130	125

Summary

- Difference in week 5 EPIC scores in IMRT cohort in endometrial cancer pa9ents (86% RT alone)
- 14% difference in late effects (p=ns) phase III trial from India
- Further data and pooling data for clinical endpoint awaited