CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

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Why is there a need for chemo-radiation in carcinoma cervix ?

FIVE YEAR SURVIAL DATA FOLLOWING RADICAL RADIATION IN CARCINOMA CERVIX.

Stage	Incidence	5 Year Survival
IA		95%
IB	5.0	85%
IIA		70%
IIB	25.0	65%
III	68.0	38%
IVA	2.0	00%

Mallinckrotd Institute of Radiology, 1959-89.

FAILURE RATE FOLLOWING RADICAL RADIATION IN CARCINOMA CERVIX.

Stage	Pelvic Failure	Distant mets
IB	10%	16%
IIA	17%	30%
IIB	23%	28%
III	42%	45%
IVA	74%	65%

Mallinckrotd Institute of Radiology, 1959-89.

TUMOUR SIZE VS. 5 YEAR SURVIAL FOLLOWING RADICAL RADIATION

Tumour Size	5 year survival
≤ 3 cm	95%
3-5 cm	75%
≥ 5 cm	65%

Perez, 1992

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1. Radiation therapy is treatment of choice for all stages of carcinoma cervix except those few stage-I and IIA where surgery is also equally effective.

2. The pelvic local control decreases with advancing stage.

3. Local control is also related to size of local growth at cervix.

4. The survival also decreases with the stage in spite of radical radiation therapy.

Therefore, there is need to use some additional modality of treatment with radiation to improve results of locally advanced carcinoma cervix

METHODS TO IMPROVE RESULTS OF RADIOTHERAPY

1. Altered fractionations.
2. High LET radiation.
3. Electron affinic hypoxic cell sensitizers.
4. Hyperbaric oxygen.
5. Hyperthermia.
6. Chemo-radiation.

CHEMO-RADIATION IN CARCINOMA CERVIX

Need is :-

To improve local pelvic control of disease.

To control distant metastatic failures.

To improve survival rate, if above two can be achieved.

Sequence of chemo-radiation:-

Sequential

Neo-Adjuvant

Concurrent

Neo-adjuvant chemotherapy in carcinoma cervix

Concurrent chemoradiation in carcinoma cervix

NEO-ADJUVANT CHEMOTHERAPY IN CARCINOMA CERVIX

CONCLUSIONS:-

1. 18 trials, having 2074 patients, have been published on neo-adjuvant CT.
2. No evidence of any benefit with neoadjuvant chemotherapy
3. Cycles > 14 days & less dose intensive are detrimental
4. Tumor cells may be less sensitive to chemotherapy & conventional radiotherapy due to changed tumor kinetics
5. **Therefore, neo-adjuvant chemo-radiation has no role in the treatment of carcinoma cervix.**

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1.Additive effects:-

- Increased killing of cells.

2.Synergistic effects :-

- Inhibition of repair of radiation induced damage.
- Promoting the of synchronization of cells into a radio-sensitive phase of the cell cycle.
- Initiating proliferation in non-proliferating cells.
- Reducing fraction of hypoxic cells.

3. Independent effect:-

- Chemotherapy may independently increase the rate of death of tumour cells.

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1996 – NIH Consensus Statement on Cervical Cancer

concluded that there was no evidence that

any concomitant chemotherapy agent should be routinely combined with irradiation as standard clinical practice for women with locally advanced cervical cancer (FIGO stages IIB-IVA)

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

1999 –NCI issued a rare clinical alert

Results were based on five phase III randomized trials.

“ strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation in women who require radiation therapy for treatment of cervical cancer.”

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Study	FIGO Stage	Treatment Gr.	Control Gr.
Bulky stage IB			
Keys	**Bulky IB**	**XRT+CP+Hyst**	**XRT+Hyst**
GOG-123	**-ve pelvic & PA**	**OS - 83%**	**OS – 74%**

1. Suboptimal RT dose

2. Trial for pre op regimen IB only

Post-op. high risk			
Peters	**IA2-IIA**	**Hyst+lymad**	**Hyst+lymad**
SWOG 8797	**-ve PA**	**+XRT+CP+FU**	**+ XRT**
	+ pel,par,margin	**OS – 80%**	**OS – 63%**

1. Post op RT, no brachy

2. Early stage

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Study	FIGO Stage	Treatment Gr.	Control Gr.

Locally advanced-Radiotherapy +HU as a control

Whitney	**IIB-IVA**	**XRT+CP+FU**	**XRT+HU**
GOG-85	**-ve PA**	**OS – 55%**	**OS – 43%**

1. Comparison of two CTRT regimens
2. No RT alone arm
3. Protracted RT (median duration 63 days)

Rose	**IIB-IVA**	**XRT+CP;**	**XRT+CP+HU+FU;**	**XRT +HU**
GOG-120	**-ve PA**	**PFS – 67%**	**PFS – 64%**	**PFS – 47%**

1. No RT alone arm
2. Comparison of 3 CTRT regimens
3. Low total RT dose & protracted treatment time

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Study	FIGO Stage	Treatment Gr.	Control Gr.
Locally advanced-Radiotherapy as a control			
Morris	**IIB-IVA -vePA**	**XRT+CP+FU**	**XRT-PA field**
RTOG90-01	**IA,B >5cm**	**OS – 73%**	**OS – 58%**
	+ve pelvic nodes		

1. RT optimal, 89Gy to pt A, 58 days

2. Survival benefit in IB-IIB, not in adv stage

3. control arm had PA field

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

NCIC Trial : 6th RCT

Median follow-up: 82 months

Stage IB2 and IIA (5 cm in diameter), IIB, IIIB, IIIA, and IVA (< 5cm if LN + ve)			
Randomization		**CT+RT (CDDP) 127 pts**	**RT alone 126 pts**
OS	**3 yrs**	**69%**	**66%**
	5 yrs	**62%**	**58%**
	HR	**1.13 (95% CI 0.77 to 1.67)**	**P=0.42**

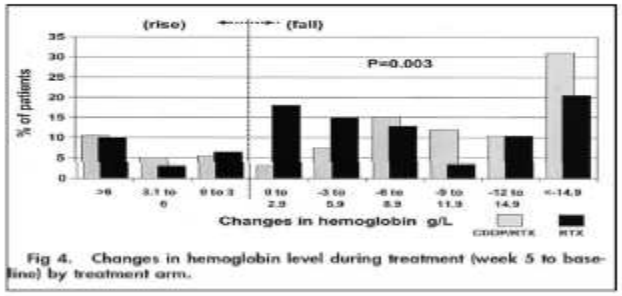


Fig 4. Changes in hemoglobin level during treatment (week 5 to baseline) by treatment arm.

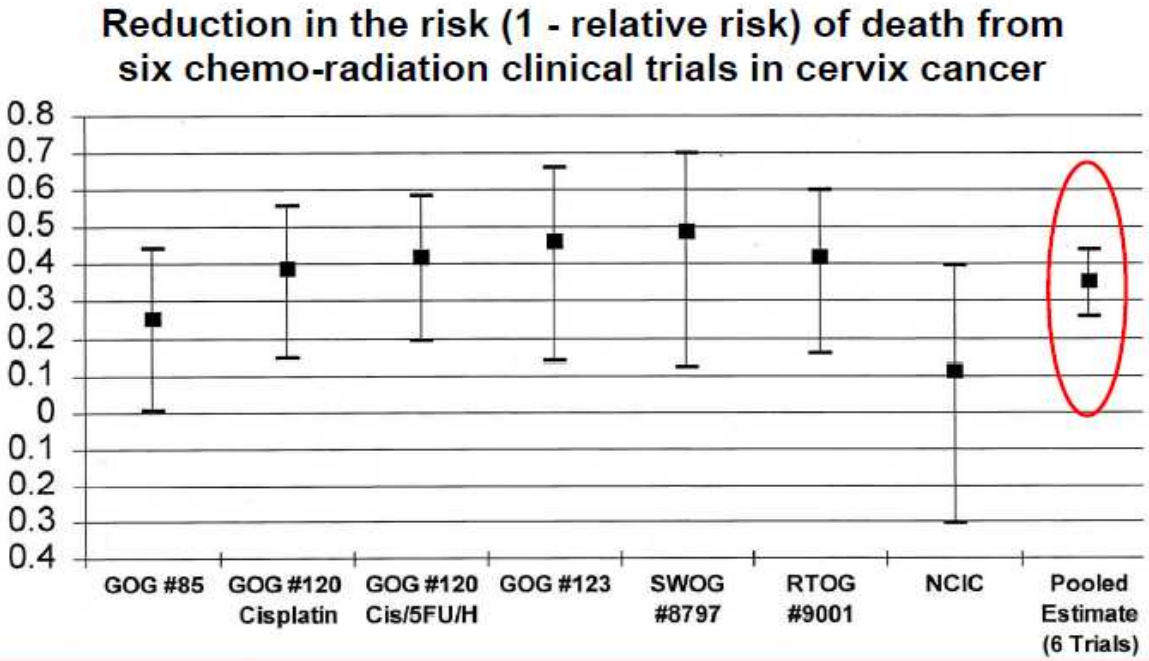
Conclusions:

The best results are certainly achieved by careful attention to RT details, including dose and overall delivery time, the use of ICBT whenever possible, and probably the addition of concurrent CDDP CRT

Approximately 53% of patients on the CRT regimen had decreases in their hemoglobin levels of 9 g/L or more.

Pearcey et al JCO 2002

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX



- Collectively, the six trials continue to support improvement in local control, progression-free survival, and survival with concurrent cisplatin-based CRT.
- Although the NCIC study alone fails to demonstrate significant differences in progression-free and overall survival, all outcomes slightly favored cisplatin CRT.

Editorial : Rose, P. G. et al. J Clin Oncol; 20:891-893 2002

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Cochrane Collaborative group

Meta-analysis – Green et all

19 (17+2)	4580	2001	*Lancet 358;781 (Sept. 2001)*
24 (21+3)	5921	2005	

Cochrane Database Syst Rev. 2005 Jul 20;(3):CD002225.

Review strongly suggests that CH-RT improves

OS with absolute benefit of 12% (10%) &

PFS with absolute benefit of 16% (13%).

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

- **There was statistical heterogeneity for these outcomes.**
- **Effect was greater in trials including a high proportion of Stage I&II patients.**
- **Acute hematological & gastrointestinal toxicity was significantly greater in CH-RT group.**
- **Late effects not well reported, hence impact on CH-RT on these effects could not be determined adequately.**

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Meta-analysis – Lukka et all

Role of concurrent Cisplatin plus radiotherapy

9 trials (-1) 6 trials for locally advanced
2 trials for early stage.

RR of death=0.74; Advanced=0.78; Early=0.56

Absolute reduction in risk of death of 11%

Lukka et al, Clinical Oncology 14;203 (June 2002)

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REVIEW ARTICLE

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

From the Meta-Analysis Group, Medical Research Council Clinical Trials Unit, London, United Kingdom.

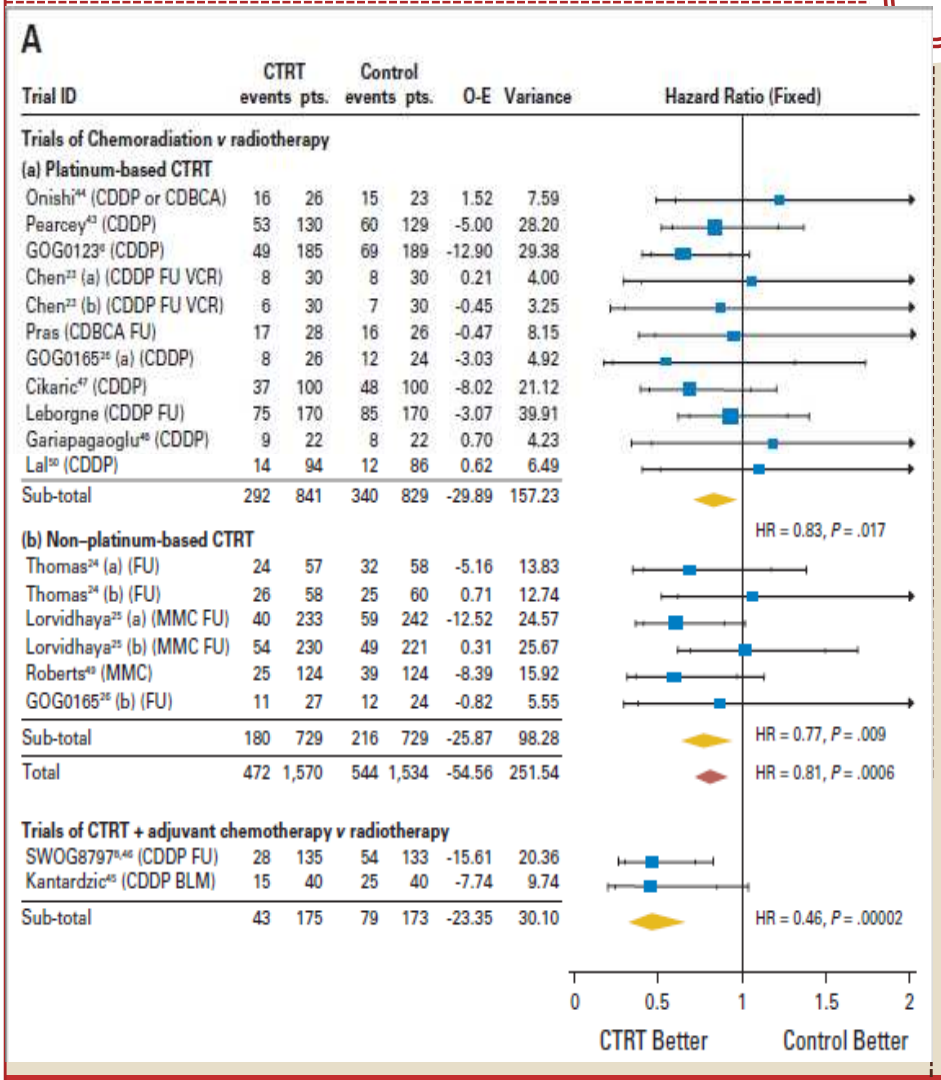
A B S T R A C T

15 trials evaluated

3452 women

1138deaths

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX



A

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[8] (CDDP)	49	185	69	189	-12.90	29.38
Chen[22] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[22] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[46] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[8,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10

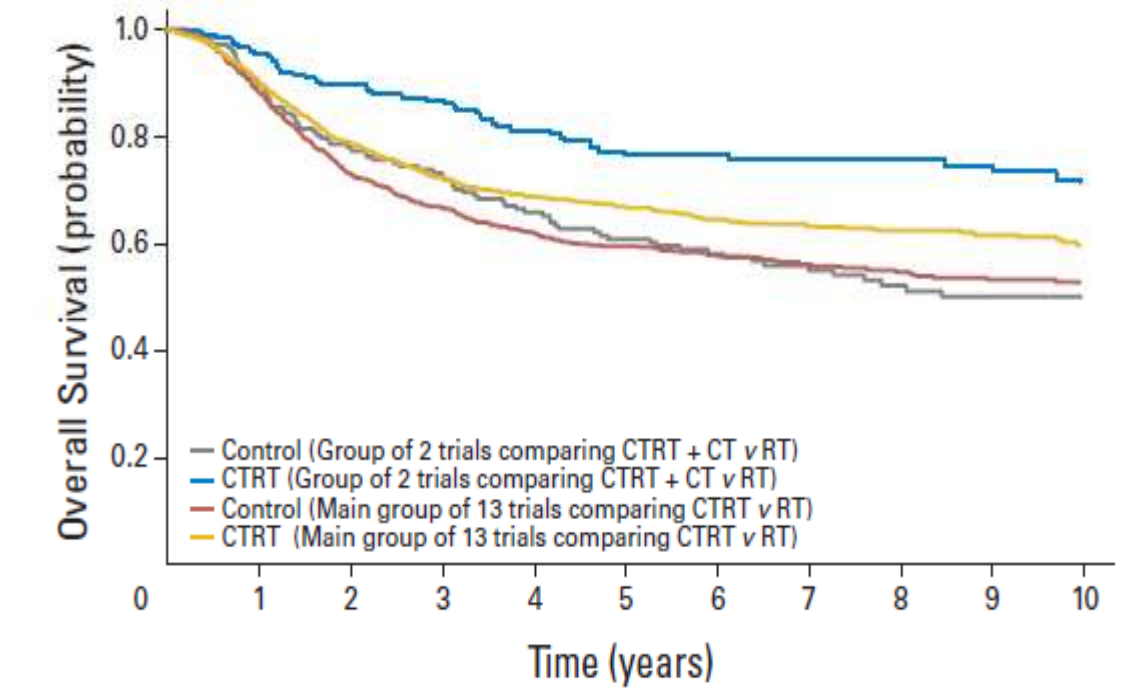
- 13 trials with no adjuvant
  - HR of 0.81-

    Absolute survival benefit of 6% at 5 yrs (60-66%)

- 2 trials with CRT + adjuvant chemotherapy
  - HR of 0.46 –

    Absolute survival benefit of 19% at 5 yrs (60-79%)

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX



CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

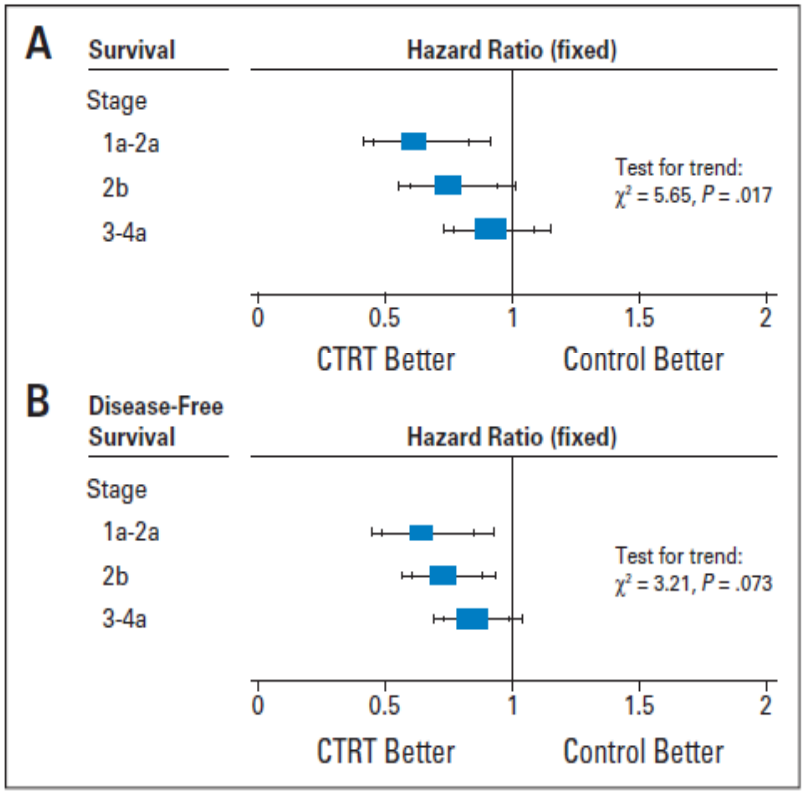


Fig 2. (A) Survival and (B) disease-free survival by tumor stage (main group of 13 trials only). CTRT, chemoradiotherapy.

- Benefit of Chemo-RT
- 5 yrs survival benefit of
  - 10% for Stage IB-IIA
  - 7% for Stage IIB
  - 3% for Stage III-IVA

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journal homepage: www.elsevier.com/locate/clon

Original Article

Substantial Improvement in UK Cervical Cancer Survival with Chemoradiotherapy: Results of a Royal College of Radiologists' Audit

C.L. Vale *, J.F. Tierney *, S.E. Davidson †, K.J. Drinkwater ‡, P. Symonds §

OS at 5 yrs with any radical treatment – 56%

Radical RT	44%
Radical CRT	55%
Surg + post-op RT	71%

	Radiotherapy	Chemotherapy
IB	59%	65%
IIB	44%	61%
IIIB	24%	44%
Gr 3-4 Toxicity	8%	10%

Articles

Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis

John A Green, John M Kirwan, Jayne F Tierney, Paul Symonds, Lydia Fresco, Mandy Collingwood, Christopher J Williams

- **In the review 68% of all patients were of Stage I & II**
- **Although an overall reduction in risk of death with CTRT was shown Gillian Thomas advised " caution in extrapolation of the results to advanced stages"**
- **This analysis shows less benefit & more heterogeneity in studies with a high proportion of advanced stage disease than in those with a low proportion of such patients**

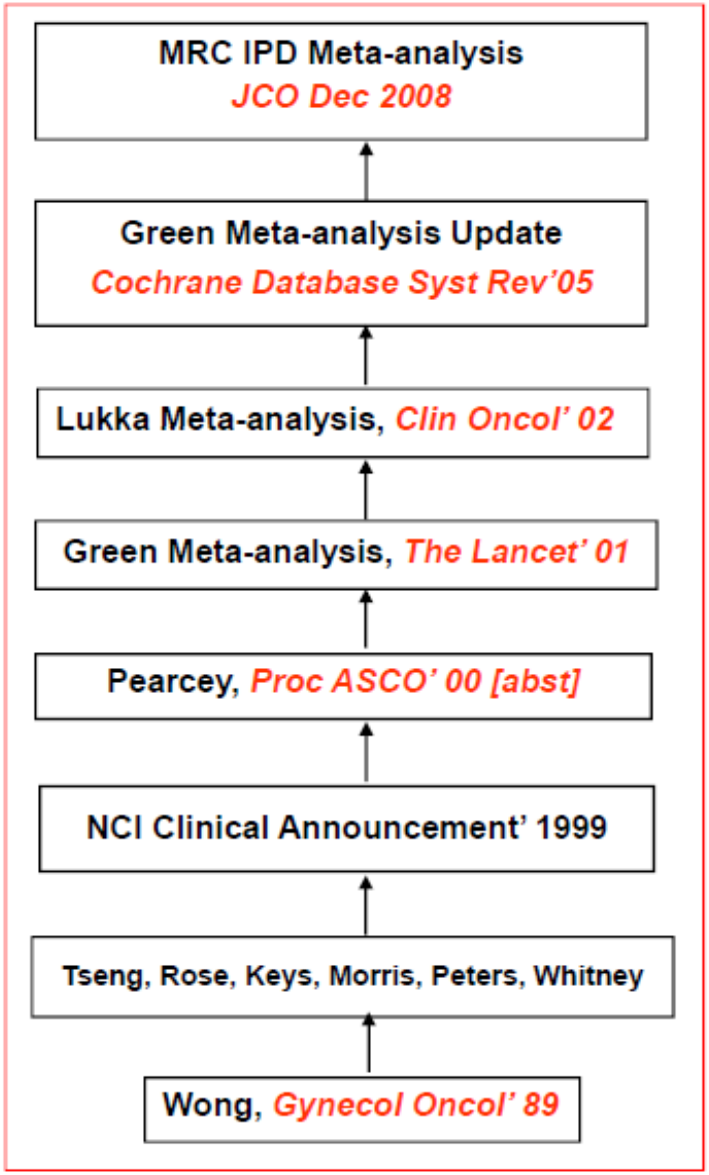
CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

- **Large well conducted RCT has merit over a meta-analysis.**
- **Publication bias.**
- **Difference in stage, CT regimen & dose, RT treatment, protraction of treatment, hemoglobin levels etc.**
- **Investigations to assess PA nodes.**

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Conclusion

- Selected group of trial patients
- 70% had Stage I&II Disease
- PA Nodes negative
- Better results in early stage patients
- More early complications in CT-RT group
- Late effects??



CRITICAL REVIEW OF EVIDENCE

- Heterogenous patient data
- Suboptimal Radiotherapy Schedules Used
- Non-uniform use of CT drugs and Sequencing
- QOL issues : Unknown
- Cost effectiveness in India including developing countries ? due to
  - Advance Disease at presentation
  - Poor nutritional status (anemia) & low compliance rates
  - inadequate supportive therapy & financial constraints
- Sparse literature from developing countries
- Hence Concomitant chemo-radiation needs to be tested optimally in Indian setting

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

In India:

- **Present in late stages.**
- **Compromised renal functions.**
- **Poor nutritional status.**
- **Poor patients, unable to afford costly investigations, chemotherapy & supportive care for reactions.**

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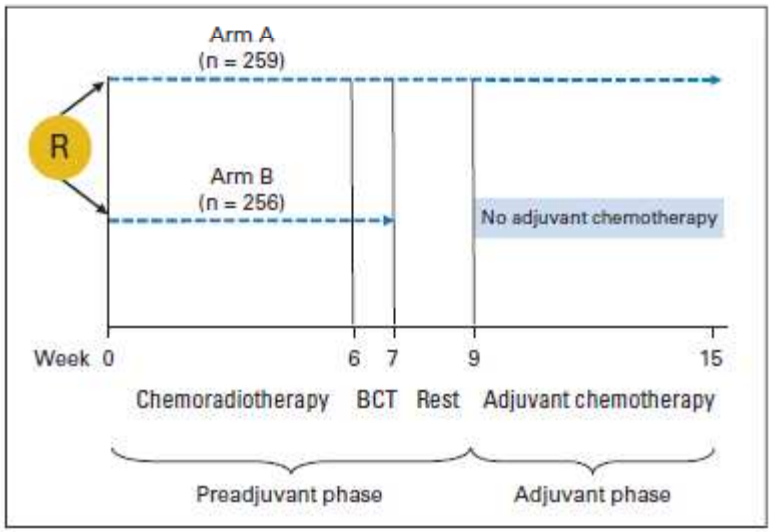
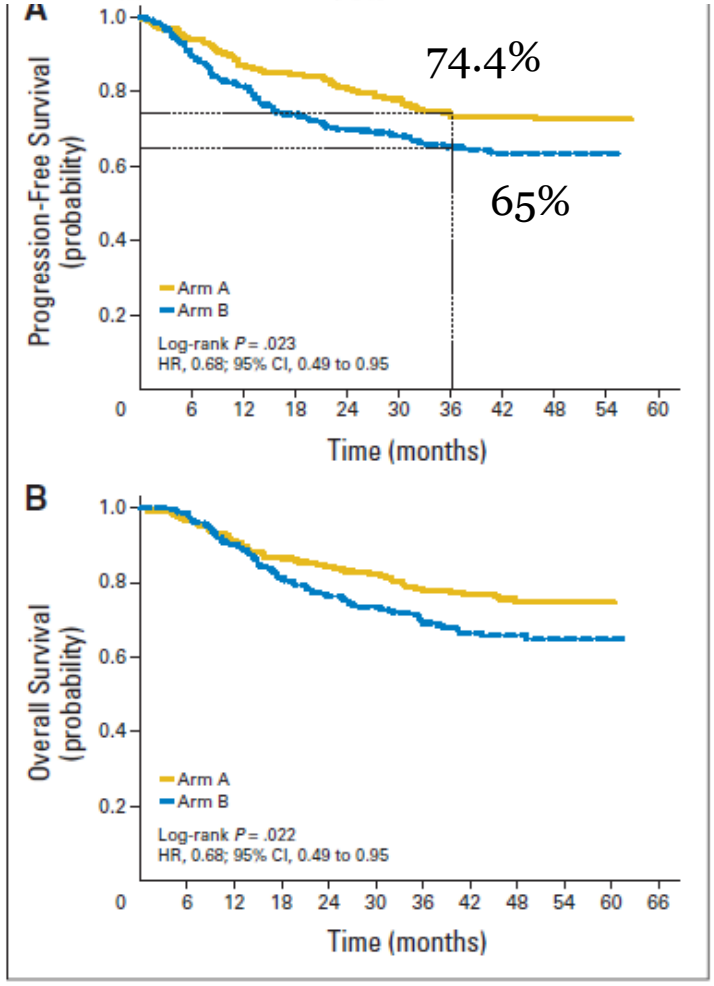
ORIGINAL REPORT

Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix

Alfonso Dueñas-González, Juan J. Zarbá, Firuza Patel, Juan C. Alcedo, Semir Beslija, Luis Casanova, Pittayapoom Pattaranutaporn, Shahid Hameed, Julie M. Blair, Helen Barraclough, and Mauro Orlando



AEs : Arm A 71.9%, Arm B 23.9%



Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix:

A Phase III Randomized Trial *(CRACx Study - NCT00193791)*

Carcinoma Cervix Stage FIGO IIIB (SQ CA)

- 10%(35 to 45%) improvement in Overall Survival with CRT
- Two tailed test
- Power of detection: 80% (alpha error: 0.05)
- 10% lost to follow-up and Protocol violations

425 patients

Radical Radiotherapy (Ext RT+ICA)

50 Gy (MLB at 40) /5wks + LDR / HDR

LDR: 30Gy or HDR: 7Gy x 3#

425 patients

Concomitant chemotherapy

weekly Cisplatin (40 mg/m2 x 4 - 5 #) &

Radical Radiotherapy

Objectives:

Overall Survival

Disease free Survival

Acute toxicities

Late Toxicities

Initiated in August 2003

Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix (CRACx)

August 2003 to Dec. 2008 = 631 pts Randomized

Accrual Details

- Study Started : Aug. 2003
- Randomized till March 2010 : 727 pts
- Audit of pts till Dec. 2008 : 631 pts
- Planned Accrual Completion : Dec 2010

Concomitant Cisplatin CT Compliance

No of Cycles	No of pts (%)
5 - 6#	217 (68.8%)
4#	45 (14.2%)
3#	18 (5.5%)
<2#	33 (10.5 %) (1pt had single kidney)

Acute Toxicities

		RT Alone 316 pts	CT + RT* 315 pts
GI	Gr II	88 (28%)	102 (32%)
	Gr III	44 (14%)	53 (17%)
GU	Gr II	19 (6%)	30 (10%)
	Gr III	9 (3%)	16 (5%)
Anemia	Gr II	68 (21.5%)	110 (40%)
	Gr III	11 (1.9%)	22 (7%)
Neutropenia	Gr II	02 (0.5%)	39 (12.8%)
	Gr III	-	9 (3%)
Thrombocytopenia			
	Gr II	-	23 (7.6%)
	Gr III	03 (1%)	07 (2.4%)

* 2 pts dyselectrolytemia and death

* 2 pts Gr IV Oto-toxicity (Irreversible)

Concomitant Chemo-Radiation in Advanced Stage Carcinoma Cervix (CRACx)

August 2003 to Dec. 2008 = 631 pts Randomized

Follow-up: Median: 36 months (mean : 39 range : 12 - 76)

December 2008	RT ALONE (316 pts)	CT + RT (315 pts)
NED	187	205
Recurrences	129	110
Loco - regional Recurrence	66	64
Distant Mets	42	34
LR - Distant	21	12
Died due to Disease	126	105
Died due to Rx Complications	01 (Unknown)	02
Died of other causes / UK	12	08
Lost to follow-up	36	26
Late sequelae		
Rectal Gr 2	10 (2%)	15 (3%)
Rectal Gr 3	8 (1.5%)	4 (0.8%)

- *Acute Haematological and GI toxicities : Higher with concomitant CRT*
- *Disease outcome and late Sequelae : Comparable so far*
- *Completion of accrual and final outcome analysis : Awaited*

CHEMO-RADIOTHERAPY IN CARCINOMA CERVIX

Conclusion

- **Use CT-RT judiciously in Indian population:**
- **70% advanced stage**
- **12% hydronephrosis**
- **Increased toxicity – prolong treatment**
- **Aim for good quality radiotherapy planning & brachytherapy.**

Thank you