

Green Meta-analysis: Role of Chemo RT in Cervical cancer

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- Published in Lancet in Sept 8, 2001
- Update available . Cochrane database 2005

Methods

- RCT Ca Cx. FIGO Stage 1B-IV A
- All trials comparing Concurrent Chemotherapy +RT(\pm Surgery) vs RT (\pm Surgery) including those used adjuvant chemotherapy.
- Hydroxyurea considered inactive and acceptable in control group.
- Primary outcome. OS and PFS
- Secondary outcome . LR + DR and A/c + C/c toxicity

Results :Overall Survival

	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

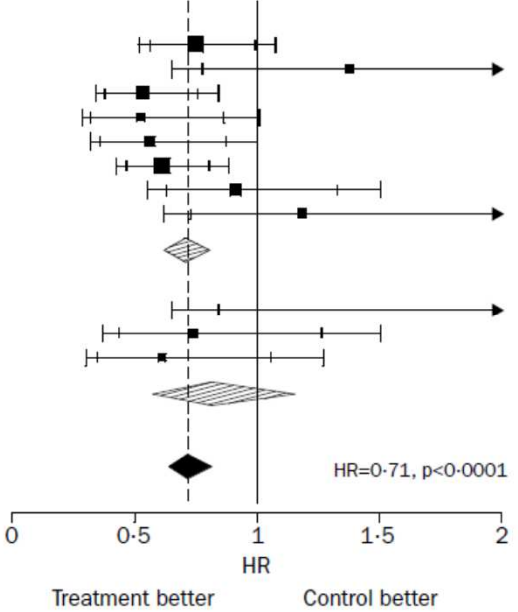


Figure 1: Results for overall survival
 O-E=observed minus expected; HR=hazard ratio.*Number of events/number entered. †Unpublished data.

Results : Overall Survival

- 11 trials. 3656 randomized patients
- Overall survival . HR 0.71(0.63-0.81) p = <.0001
- 29% reduction of risk of death
- 12% absolute improvement in survival(95%CI 8-16)
- Effect was more in trials with $\geq 70\%$ stage 1 or 2 disease.

Results

- PFS .Absolute Improvement 13% (95% CI 13-19)
- LR . Reduced by Chemo RT . OR = 0.61 (95% CI 0.51-0.73)
- DR. Reduced by ChemoRT. OR =0.57 (95% CI 0.46- 0.77)

Toxicity

Acute .

- Haematological (WBC 16% Vs 8%, Platelet 1.5% Vs 0.2% , others 29% vs 1%)
- Gastrointestinal (9% Vs 4%)

Late .

- Good long term data lacking.
- 7 deaths. 1 control Vs. 4 related to chemo .

Discussion

- Different trials have different control arms
- Different inclusion criteria

Summary of individual trials

Keys et al, NEJM 1999

- 374 patients with 1B2 No.
 - Pelvic RT 45 Gy/25 # → 30 Gy to Point A
Brachytherapy → Hysterectomy
 - Pelvic RT 45 Gy/25 # + concurrent cis-platin → 30 Gy to
Point A Brachytherapy → Hysterectomy
- 3 year survival rates were 74 % RT alone and 83 % with
CCRT (P=0.008 by the log-rank test)

Peters WA et al, JCO 2000

- 268 high risk post op patients
 - Pelvic RT .49.3Gy /29#
 - DDP+ FFU q 3w X 4 cycles + Pelvic RT
- Median FU 42 months
- 4 year survival 81% vs 71% favoring CCRT.

Morris M et al. NEJM .1999

- 403 patients 2B-4A, 1B/2A if >5cm or Pelvic LN+ve
 - Extended field RT 45Gy/25# → Brachytherapy
 - Pelvic RT 45 Gy/25# + DDP&FFU infusion Q3W
→ Brachytherapy
- 5 year survival 58% Vs 73% (for RT alone Vs CCRT)

Ross PG et al ,NEJM 1999

526 patients . 2B-4A PALN -Ve

- Weekly Cis platin + Pelvic RT+ Brachytherapy
- 2 cycles of Cisplatin+ FFU + Hydroxyurea+ Pelvic RT+ Brachytherapy
- Hydroxyurea + Pelvic RT+ Brachytherapy
- Median FU 35 months
- RR of death 0.61 (95% CI 0.44-0.85) in Group1 and 0.58 (95% CI 0.41-0.81) in group 2 compared to group 3.

Whitney CW et al , JCO 1999

- 388 patients with 2B-4A , PALN-ve
 - 2 cycles of DDP+ FFU infusion (4 W)+ Pelvic RT
→ Brachytherapy
 - Pelvic RT + HU → Brachytherapy
- Median FU 8.7 years
- RR of death for DDP+FFU was 0.75 (90% CI 0.58-0.95).

Pearcey R et al, JCO 2002

- 259 patients, 2B-4A, 1B-2B if > 5 cm or Pelvic LN+
 - Weekly DDP +Pelvic RT 45Gy/25# → Brachy 8GyX 3 or similar
 - Pelvic RT 45Gy/25# → Brachy 8GyX 3 or similar
- Median FU 82 months.
- 5 year Survival 62% Vs 58% . Not significant
- 62% v 58% (arm 1 v arm 2), respectively

MRC (UK) Meta-analysis , JCO 2008

Survival advantage

- 19% Relative risk reduction (of death)
- 6% absolute survival benefit at 5 years
- The benefit is more for earlier stages.

Benefit and disease stage.

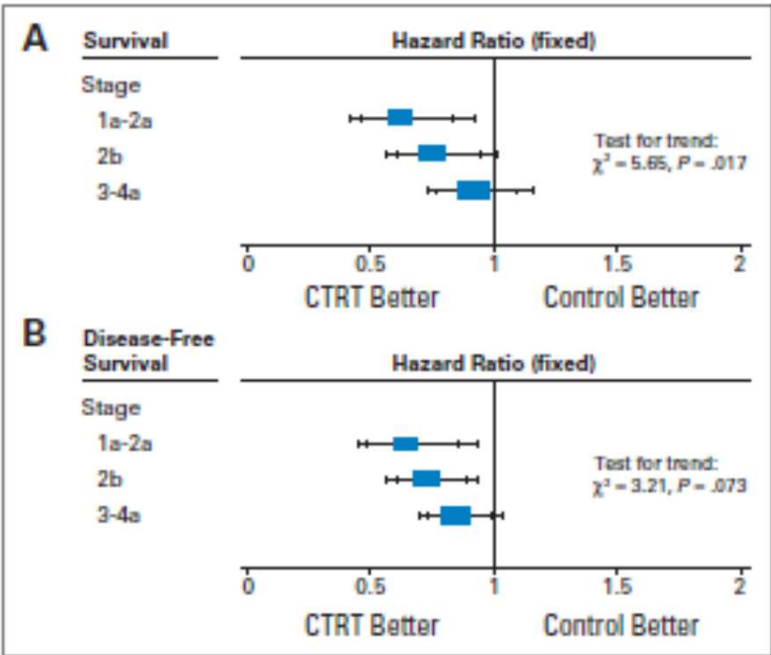
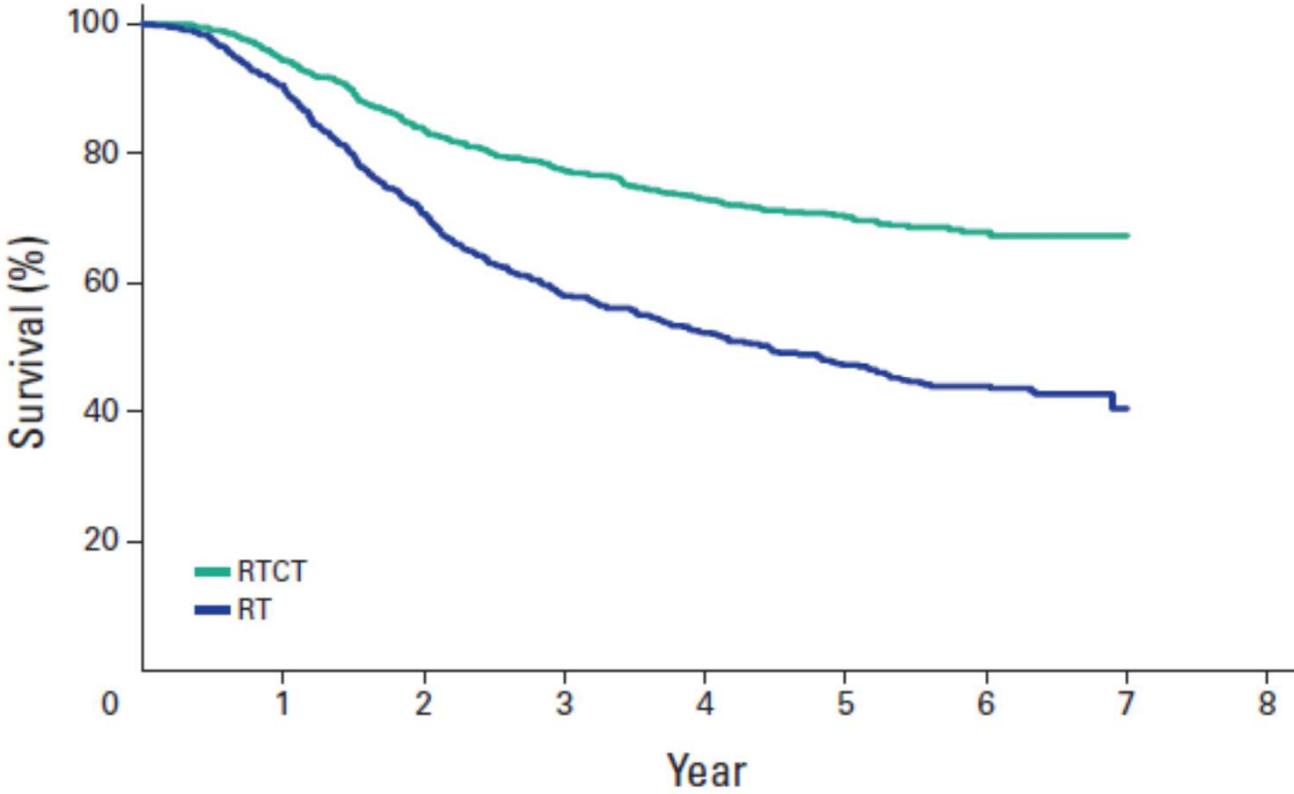


Fig 2. (A) Survival and (B) disease-free survival by tumor stage (main group of 13 trials only). CTRT, chemoradiotherapy.

Meta-analysis. NR Datta et al ,Gyn Oncol 2017

- Survival advantage of 7.5% with CCRT in carcinoma cervix
- 10.4% excess acute toxicities -grade 3 or 4.

Indian Data. Nandakumar et al JGO 2015



JGO 2015. cont'd

Table 5 – Comparison of Survival Rates With Relevant Publications

Reference	Study Type	FIGO Stage	Treatment	No. of Patients	5-Year OS (months)
Morris et al ²²	Randomized clinical trial	IB-IVA	RT	195	58
			RTCT	195	73
Eifel et al ²³	Randomized clinical trial	IB-IVA	RT	195	52
			RTCT	195	73
Fujiwara et al ²⁴	Retrospective	IB2-IVA	RTCT*	52	78
Robert et al ²⁵	Randomized clinical trial	IB2-IVA	RT	82	56†
			RTCT‡	78	72†
		IB-IVA	RT	1,061	54
This study	Observational		RTCT	1,183	72
		IB2-IVA	RT	971	52
			RTCT	1,145	72

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- For the 790 patients who had radical treatment, the five year survival probability is 70.3%. (2006-2008).
- The patients who had concurrent chemotherapy (two third of patients) did better (74.2% compared to 62.3%)

Summary

- There is sufficient evidence for benefit of concurrent chemotherapy with radiotherapy for carcinoma cervix
- The benefit is more for earlier stages than stage 3 or 4
- There is more acute toxicity.
- Data on long term toxicity inadequate.
- Value of adjuvant chemotherapy to be identified.

Thank you.