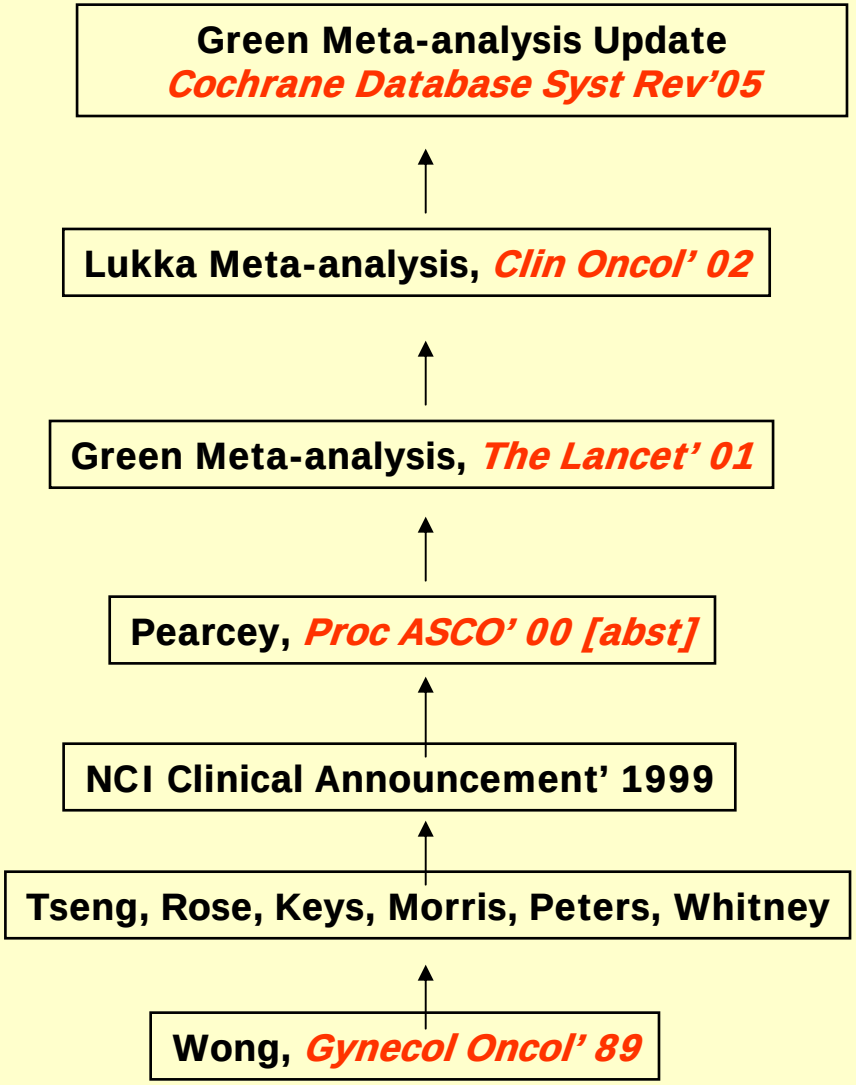
Chemo-Radiation in Advanced Stage Carcinoma Cervix



- **Cochrane Review: Green et al,** ***The Lancet' 01***
- **Canadian Meta-analysis : Lukka et al,** ***Clin Oncol' 02***
- **Green et al meta-analysis on concurrent chemoradiation:** ***Update Cochrane Database Syst Rev, 2005;Jul 20: (3)***

Critical Review of 5 trials

AUTHOR	ARMS	RESULTS	COMMENTS	CRITICISMS
Whitney et al. 1999 (GOG-85) IIB-IIIB	RT+Cisplatin / 5FU Vs. RT+HU	OS-55% Vs. 43%	Better PFS and OS than HU with manageable toxicity	1. Comparison of two CTRT regimens 2. No RT alone arm 3. Sub optimal (81Gy to pt A) 4. protracted RT (median duration 63 days)
Morris et al. 1999 (RTOG 9001) IB-IVA	RT+Cisplatin Vs. 5FU + RT	OS-73% Vs. 58%	CT had a survival advantage with decrease in both LR and distant failure	1. RT optimal, 89Gy to pt A, 58 days 2. Survival benefit in IB-IIB, not in adv stage
Keys et al. 1999 (GOG-123) Bulky IB	RT+Cisplatin+ SX Vs. RT+ SX	OS-83% Vs. 74%	Significant differences in PFS and OS favoring CTRT	1. Suboptimal RT dose 2. Trial for pre op regimen IB only

AUTHOR	ARMS	RESULTS	COMMENTS	CRITICISMS
Peters et al. 2000 **IA2-IIA**	**SX+RT+Cisplatin/5 FU** **Vs.** **SX+RT**	**OS-80%** **Vs.** **63%**	**Survival favored the chemoradiotherapy arm**	**1. Post op RT, no brachy** **2. Early stage**
Rose et al. 1999 **(GOG 120)** **IIB-III-IVA**	**RT+Cisplatin** **Vs.** **RT+Cisplatin/5FU/HU** **Vs.** **RT+HU**	**PFS–67%** **Vs.** **64%** **Vs.** **47%**	**Superiority of concomitant CTRT regimen with cis alone was less toxic then 3 drug regimen**	**1. No RT alone arm** **2. Comparison of 3 ctrt regimens** **3. Low total RT dose & protracted Rx time**

BACKGROUND AND RATIONALE

NATIONAL CANCER INSTITUTE CLINICAL ANNOUNCEMENT

'CONCURRENT CHEMORADIATION FOR CERVICAL CANCER'

in February 1999

"Five major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery "

Cochrane Collaborative Group (19 Trials)

Meta - analysis

Green JA et al Lancet 358;781 (Sept. 2001)

- **19 RCTs between 1981 and 2000 : 4580 pts**
- **Increase in OAS by 12% & RFS by 16% (absolute benefit) (p=0.0001)**
- **Greater benefit in patients in stages IB2 and IIB**
- **Decrease in local and systemic recurrence (p=0.0001)**

- Update in July 2005: 21 trials and 4921 pts
- Similar findings (absolute benefit: 10%)
- Test for Heterogeneity : Positive
- No data on late toxicities

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

Canadian Group (9 Trials) - 4 year survival data

Meta-analysis

- **Cisplatin based Concomitant Chemo-radiation**
- **Significant improvement in Overall Survival**

  - Advanced Stages (Only 30% tumors)
  - Bulky IB tumors (prior to surgery)
  - High risk early disease (post-surgery)

- **Toxicities**

  Acute Grade 3/4 Hematological and G.I significantly higher : all short lived

  2 deaths due to the toxicities

  No significant late toxicities seen

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

Critical Review of Trials
Chemo-radiation in Carcinoma Cervix

- **Heterogenous patient data**
- **Suboptimal Radiotherapy Schedules Used**
- **Non-uniform use of CT drugs and Sequencing**
- **QOL issues : Unknown**
- **Cost effectiveness ?**
- **Hence Concomitant chemo-radiation needs to be tested optimally in our setting**
- **Sparse literature form Developing Countries**

Chemo-Radiation in Advanced Stage Carcinoma Cervix

(FIGO IIIB): A Phase III Randomized Trial *(CRACx Trial)*

HSRC / HEC Project No: 114/2003

Clinicaltrials.gov ID : NCT00193791

Protocol ID : TMH/114/2003/CRACx TRIAL

TMC Cervix Working Group

Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial): 2003

Carcinoma Cervix Stage FIGO IIIB

425 patients

Radical Radiotherapy Ext RT+ICA

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

LDR: 30Gy or HDR: 7Gyx3#

425 patients

Concomitant chemotherapy

weekly Cisplatin and

Radiotherapy

- **Hypothesis: Improvement in OAS by 10% (35% to 45%)**
- **Power of detection: 80% (alpha error: 0.05)**
- **Intent to treat basis**
- **Accrual Period: 5-6 years**
- **Interim analysis : Twice One at 50 % and another at 75 % event rates**

Aims & Objectives

Primary

1. To compare the overall and disease free survivals
2. To compare acute toxicities
3. To evaluate single agent chemotherapy ‘Cisplatin’

Secondary

1. To compare distant metastasis rate.
2. To compare late toxicities in both groups.

Pre-treatment Evaluation

- Pelvic Examination / EUA (sos) / Gynae Joint Clinic
- Complete Blood Profile
- Serum Biochemistry (Liver+Renal functions+ Electrolytes)
- Chest X-Ray
- USG (A + P) / CT Scan (A+P) : Optional
- ECG
- Cystoscopy: if indicated.

Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

Inclusion Criteria

- **Squamous carcinoma**
- **Performance index WHO Grade 0 or 1**
- **Age < 65 years**
- **FIGO stage IIIB**
- **Normal ECG and Cardiovascular systems**
- **Normal hematological parameters.**
- **Normal renal & liver function test.**

Exclusion Criteria

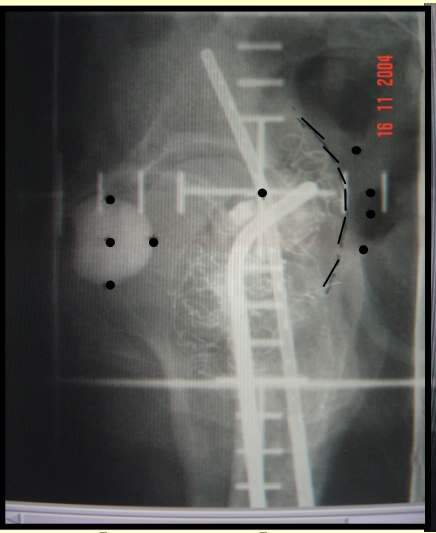
- **Co-morbid conditions like medical renal disease.**
- **Medical or psychological condition that would preclude Rx.**
- **History of previous treatment.**
- **Patient unreliable for treatment completion & follow-up.**

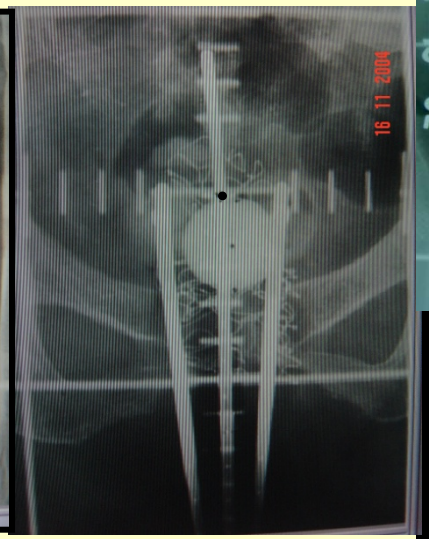
Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

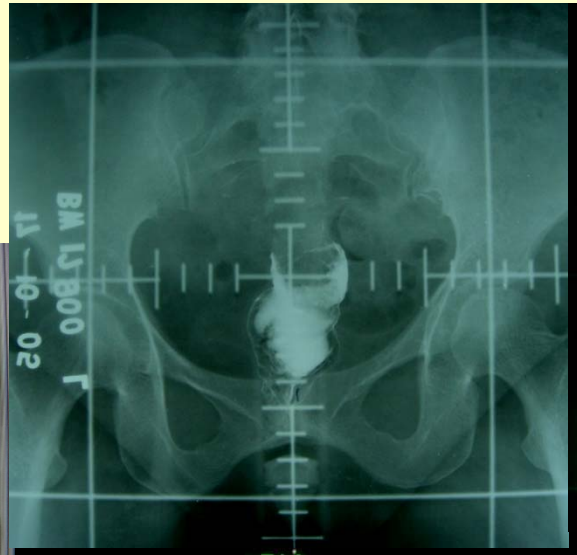
Treatment Protocol

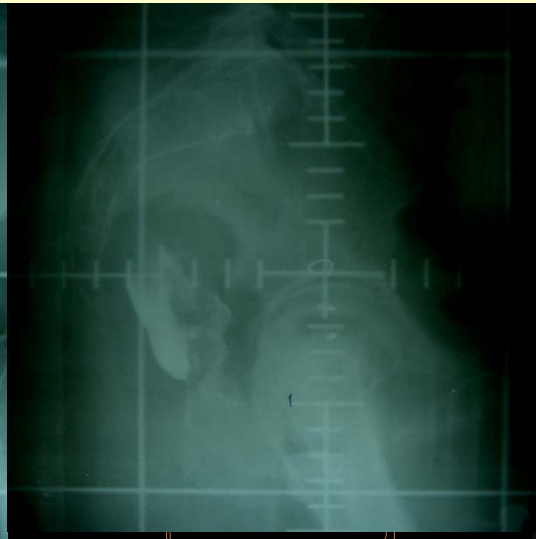
- **External RT :** Whole Pelvis with AP/PA or four field box technique
- **Dose :** 50 Gy / 25 # / 5 Weeks (40 Gy open + 10 Gy with MLB)
- **Brachytherapy :**

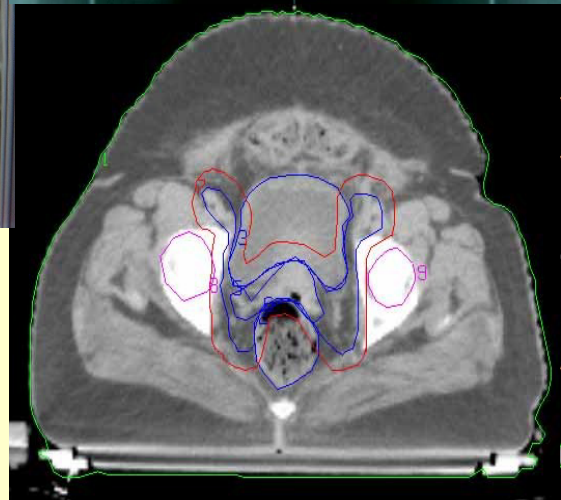
LDR : 30 Gy X 1 # to pt A
Or
HDR : 7 Gy X 3 # to pt A

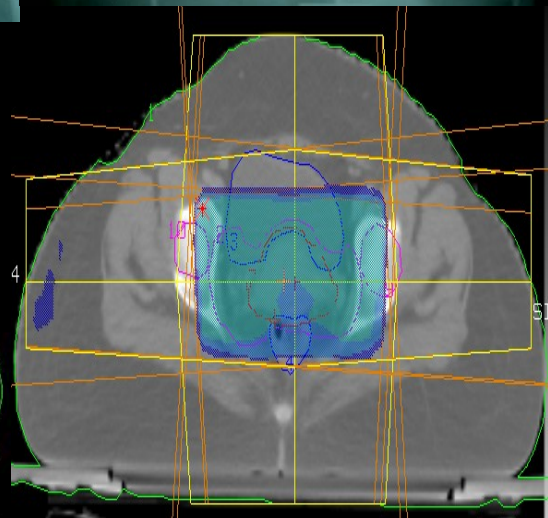












- **Chemotherapy**

Patient randomised to CT+ RT

receive Inj. Cisplatin 40 mg/m2 wkly

Evaluation of Response & Toxicity

- **Response :** WHO Criteria
- **Toxicity Scoring**
  - Acute toxicities : CTC version 2.0
  - Late toxicities : RTOG / LENT-SOMA scoring criteria.
- **Follow Up :**

  Clinical examination, Assessment of tumor response, late complications & relevant investigations / Rx will be done accordingly
  - 1st follow-up: 6 -10 weeks
  - Subsequently every 3 - 4 mths for the first 2 years.
  - 6 monthly thereafter

__C__hemo-__R__adiation in __A__dvanced __C__arcinoma Cervi__x__ (CRACx Trial)

ACCRUAL DETAILS

- **Study Started : August 2003**
- **Pts randomised till Nov. 2008 : 627 pts**
- **Audit of pts till Dec. 2007 : 528 pts**
- **Planned Accrual Completion : Dec 2009**
- **Interim Analysis : Jan 2010**
- **Final Analysis : Dec 2011**

Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

AUDIT

- **Audit of pts till Dec. 2007 : 528 pts**
- **RT Alone : 255 pts**
- **CT + RT : 263 pts**
- **Randomization : Computerized (open label)**
- **Analysis : ITT**

Cisplatin Chemotherapy Compliance

No of Cycles	No of pts (263 pts)
6#	03
4-5#	226 (4#: 43 pts)
3#	17
2#	7 (1pt had single kidney)
0-1#	10 (Incomplete Rx)

Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

RESPONSE RATES (6-10 weeks Post Rx)

	RT Alone 255 pts	CT + RT 263 pts
CR	229	227
PR	08	14
Prog. Disease	05	06
Not assessed*	13	16

** 6-10 weeks Post Rx not completed*

Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

ACUTE TOXICITIES

		RT Alone 255 pts	CT + RT* 263 pts
GI	Gr II	68	78
	Gr III	12 (4.7%)	17 (7%)
GU	Gr II	15	23
	Gr III	10 (4%)	15 (5.7%)
Skin	Gr II	63	63
	Gr III	29	26
Anemia	Gr II	24	101
	Gr III	5 (2%)	15 (5.7%)
Neutropenia	Gr II	06	39
	Gr III	02 (0.7%)	09 (3.5%)
Thrombocytopenia	Gr II	01	16
	Gr III	02 (0.7%)	09 (3.5%)

**** 1 pt Dyselectrolytemia and death & 2 pt Gr IV Oto-toxicity (Irreversible)***

Chemo-Radiation in Advanced Carcinoma Cervix (FIGO IIIB) (CRACx Trial)

N= 486 pts: Follow-up: Median: 24 months (3 - 48 months)

	RT ALONE (255 pts)	**CT + RT (263 pts)**
Recurrences	47	38
Progressive Disease Loco-regional Recurrence LR + Distant Recurrence Distant Mets	04 13 07 23	04 11 04 19
Died due to Rx Complications	01 (Unknown)	01
Lost to follow-up (after 1- 2 FU)	16	12

**** Acute Gr II/III Genitourinary/hematological toxicities higher in CT+ RT arm***

**** Grade II / III Procitiits seen in 7 pts in each arm so far***

Ongoing

Chemo-Radiation in Advanced Carcinoma Cervix (CRACx Trial)

AUDIT SUMMARY

- *Acute Grade III GI and Hematological toxicities : Higher with CT+ RT*
- *Recurrence event rates comparable so far*
- *Late toxicities yet to evaluated*
- *Cost benefit analysis – most critical in our setting*
- *Completion of accrual and outcome analysis*
- *Report on 1st Interim Analysis : Jan 2010*

Thank You