Chemoradiation in carcinoma cervix

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Aim of concurrent chemotherapy with radiotherapy

To improve survival by

- 1. Increasing control of the ***primary cervical tumor*** (Radiosensitization)
- 2. Decreasing the rate of ***distant metastases*** (Direct anti-tumor effect for micro-metastases and indirect effect on future metastases by preventing cervical tumor recurrence)

Role of Chemotherapy

- NACT
- Adjuvant
- Concurrent

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 "

Major Trials

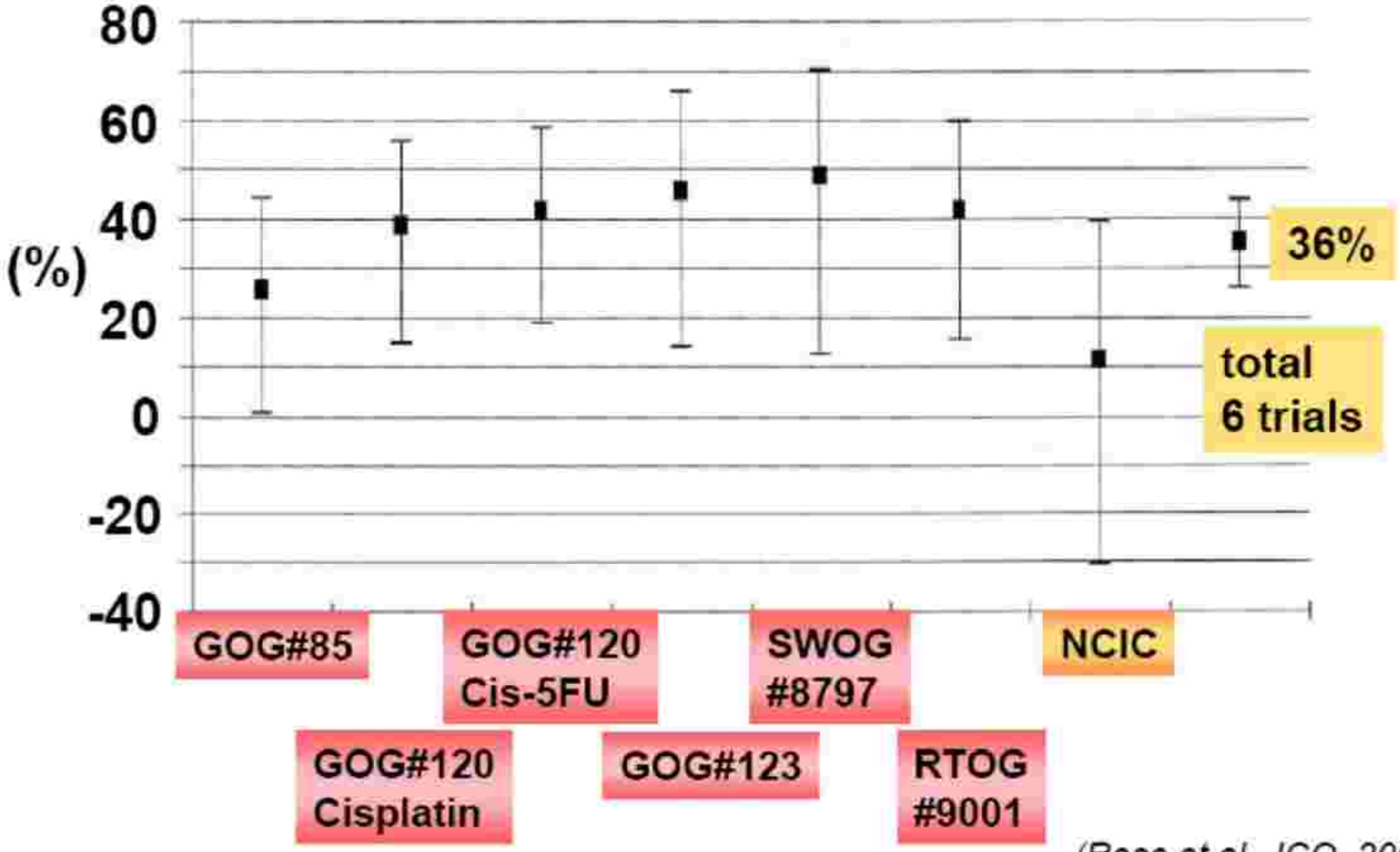
Author	Trial	No.	Investigational Arm	Control Arm	Tumor	Comment
Keys 1999	GOG 123	369	RT+ Cisplatin → Surgery	RT alone → Surgery	Stage IB (≥ 4cm)	Combined with Surgery
Peters 2000	SWOG 8797	243	Surgery → RT+Cisplatin+5FU	Surgery → RT alone	IA2, IB, IIA (with postop high risk)	Combined with Surgery
Morris & Eifel 1999 & 2004	RTOG 9001	388	RT+Cisplatin+5FU	Extended field RT	IB or IIA (≥5cmorPLN+) IIB, III, IVA	Surgical staging for PALN
Whitney 1999	GOG 85	368	RT+Cisplatin+5FU	RT+ Hydroxyurea	IIB, III, IVA	Surgical staging for PALN
Rose 1999	GOG 120	526	RT+Cisplatin RT+Cisplatin + 5FU +Hydroxyurea	RT+ Hydroxyurea	IIB, III, IVA	Surgical staging for PALN
Pearcey 2002	NCIC	253	RT+Cisplatin	RT alone	IB2, IIA(≥5cm), IIB, III, IVA	No surgical staging for PALN

Randomized controlled trials of concurrent chemotherapy

	Study group	No. of Pts	Overall survival (%) CCRT vs control	P-value	Follow-up
	GOG 85	388	65 vs 51 (5y)	0.018	104mo
	GOG 120	526	66 vs 50 (3y)	0.004	35mo
			67 vs 50 (3y)	0.002	
	GOG 123	369	83 vs 74 (3y)	0.008	36mo
	SWOG 8797	268	81 vs 71 (4y)	0.007	42mo
	RTOG 9001	388	73 vs 52 (5y)	< 0.001	43mo
	NCIC	253	62 vs 58 (5y)	0.53	82mo

(Whiteney et al, JCO, 1999. Rose et al, NEJM, 1999. Keys et al, NEJM, 1999. Peters et al, JCO, 2000. Morris et al, NEJM, 1999. Pearcy et al, JCO 2002)

Reduction in the risk of death by cisplatin-based CRT: 6 major trials



(Rose et al, JCO, 2003)

Locally advanced cervix cancer
Concurrent chemoradiation:

Results of RCTs

- Significant reduction (43-46%) in the risk of recurrence & death.
- Reduction in relative risk of recurrence & death remarkably similar in all studies.
- Compelling evidence of survival benefit (10-15%) with concurrent cisplat chemo.

Concurrent Chemoradiation Results of Meta-analyses

"Grade A"

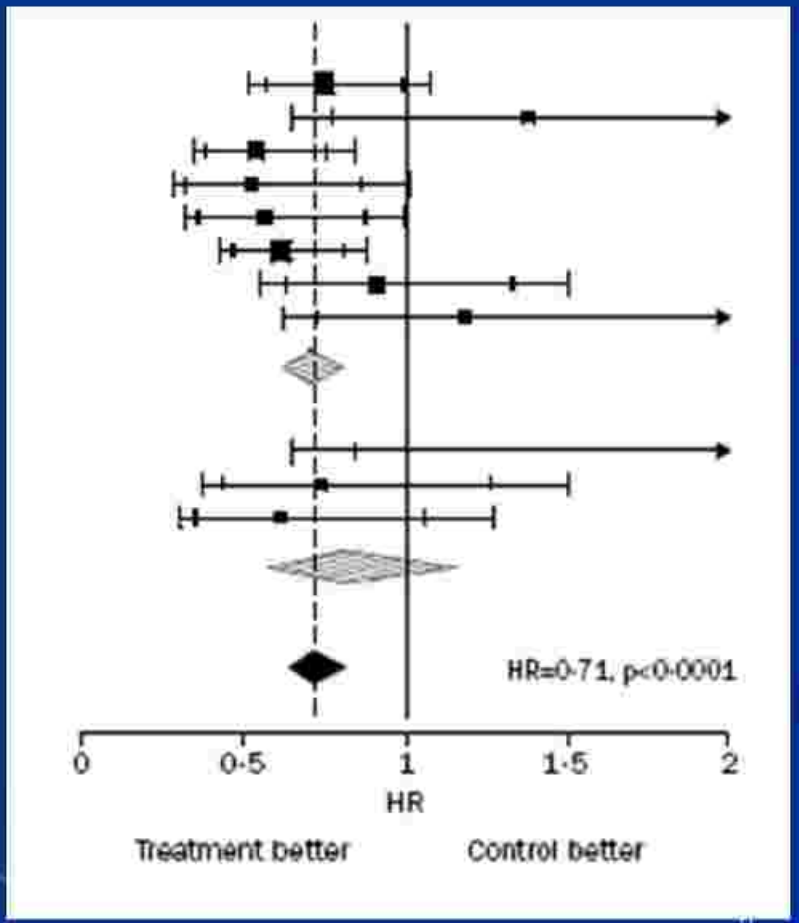
Cochrane Collaborative Group (19 Trials) (4580 patients)

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

- 19 RCTs between 1981 and 2000 : 4580 randomized patients
- 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

Concurrent Chemoradiation Results of Meta-analyses

"Grade A"

Canadian Group(9 Trials) - 4 year survival data

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

- Cisplatin based Concomitant Chemo-radiation
- Significant improvement in Overall Survival
  - Advanced Stages
  - Bulky IB tumors (prior to surgery)
  - High risk early disease (post-surgery)
- Toxicites
  - Acute Grade 3/4 Hematological and G.I significantly higher : all short lived
  - 2 deaths due to the toxicities
  - No significant late toxicities seen (small data)

Comparability of Outcomes, CT/RT Advanced Cervix Trials

	Control	CT/RT
Positive trials:		
(Morris, Whitney, Rose)	40- 47	57 – 64
Negative trials:	53- 58	58 - 62
(Thomas, Pearcey)		

Difference is in the "control arms".

RT dose, use of IC similar .

But Overall TIME :Positive trials 58-64 dys

Negative trials 44-59 dys

Loss of LC is □1% per day; prolongation over □50 days .

Critics

- Large study(Pearcey et al.) –no survival benefit

  (30% patients in CTRT arm had a drop in Hb >15gm/dl vs 20% in RT alone)
- Heterogeneous groups
- Protracted (suboptimal) radiation - Poor local control
- Decrease in distant metastasis –improved local control or direct cytotoxic effect

Major Trials

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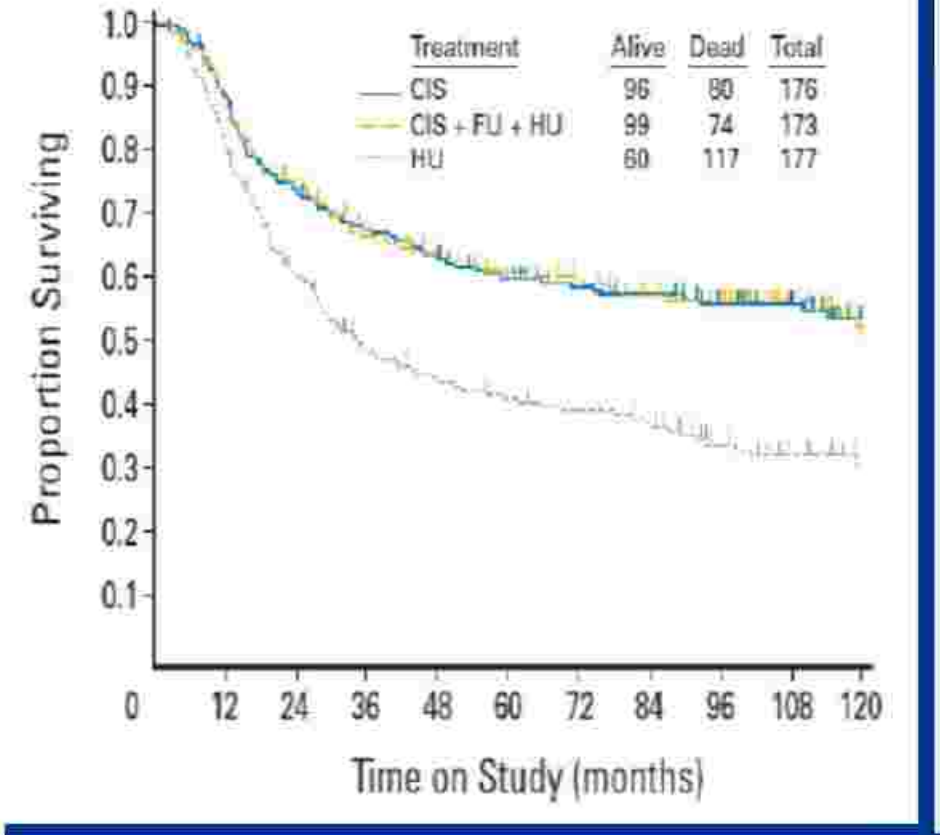
Issues of concurrent chemoradiotherapy (CCRT) in the US trials

1. Long-term efficacy of CCRT
2. Benefit for patients with stage III or IVA
3. Late toxicities after treatment
4. Impact of surgical staging on survival
5. Patient selection
6. Standard regimen of chemotherapy
7. Control arm (Radiotherapy)

Long-term efficacy of CCRT(1)

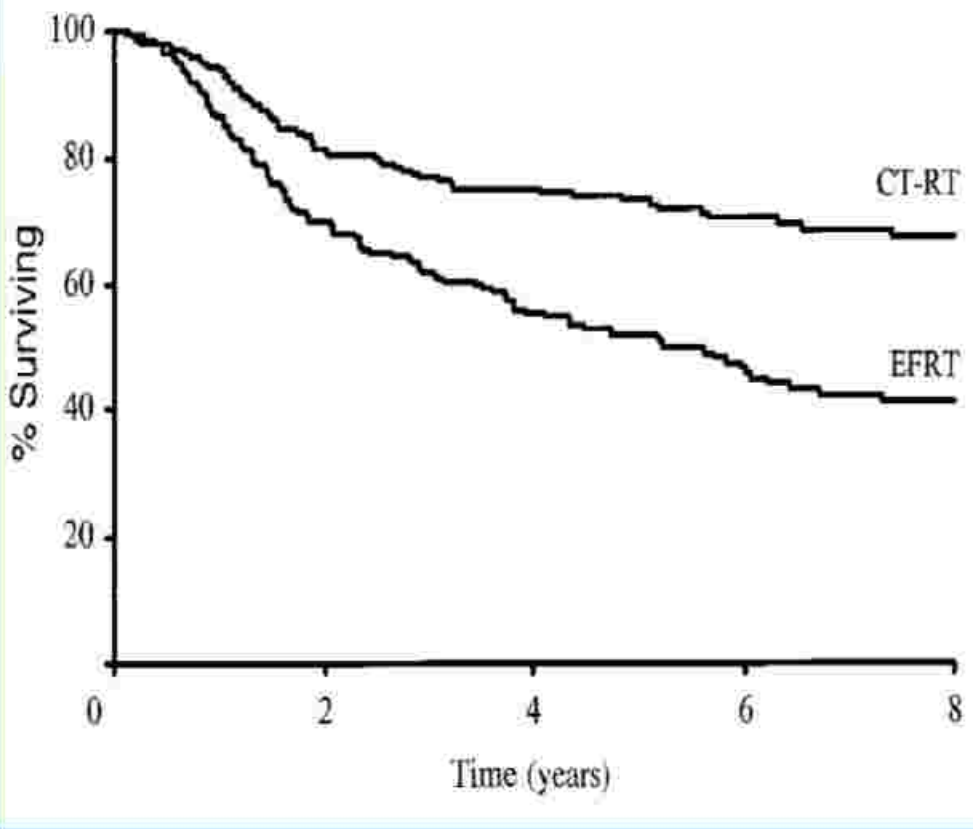
GOG 120

Median follow-up time: 106 months
(extended from 35 months)



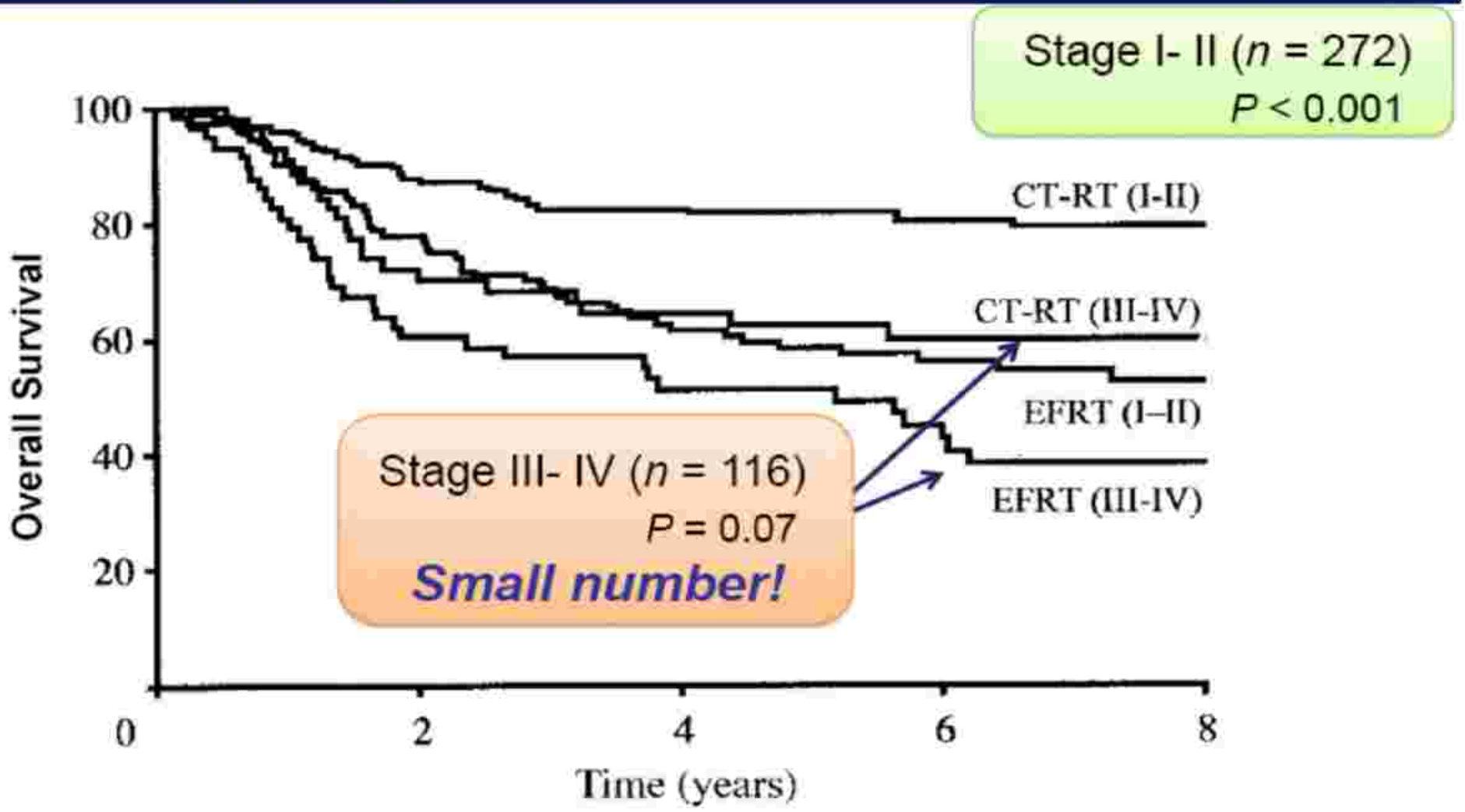
RTOG9001

Median follow-up time: 79 months
(extended from 43 months)



(Rose PG et al: J Clin Oncol 2007, Eifel PJ et al: J Clin Oncol 2004)

Subgroup analysis in RTOG9001 (2)



(Eifel PJ et al: J Clin Oncol 2004)

Meta-analysis

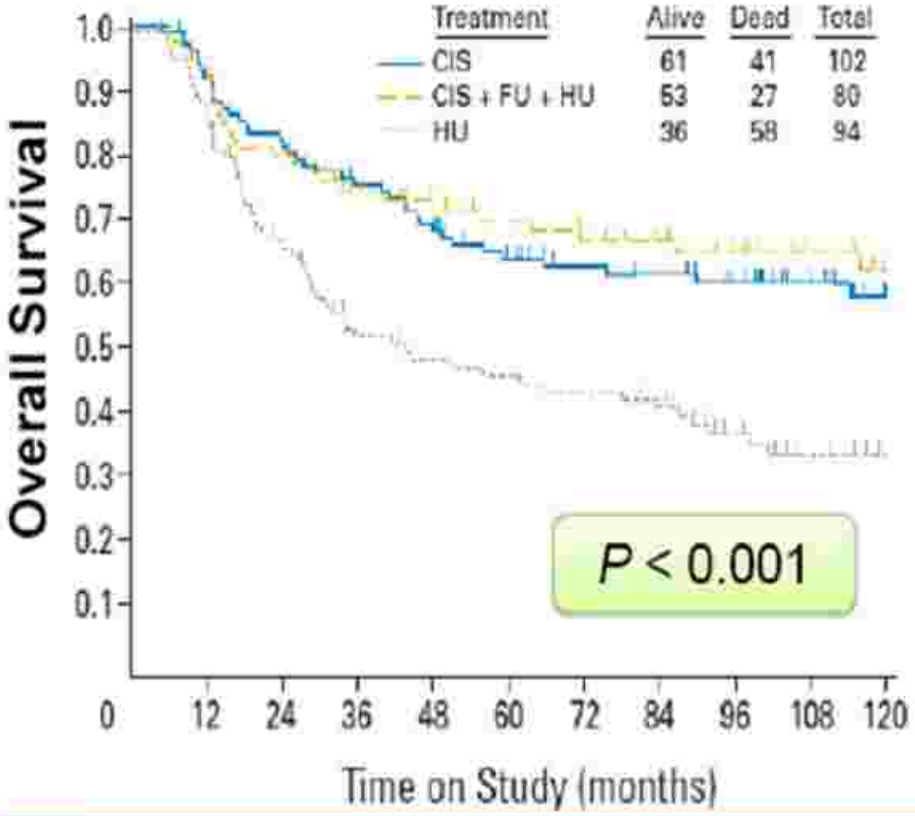
- The effect of CCRT was greater in trials randomizing a high proportion of stage I and II patients (p= 0.009).

Proportion of stage I&II	Hazard ratio 95% CI	Interaction p value
≥70%	0.56(0.44-0.70)	
<70%	0.80 (0.69-0.93)	
All Trials	71 (0.63-0.81)	0.009

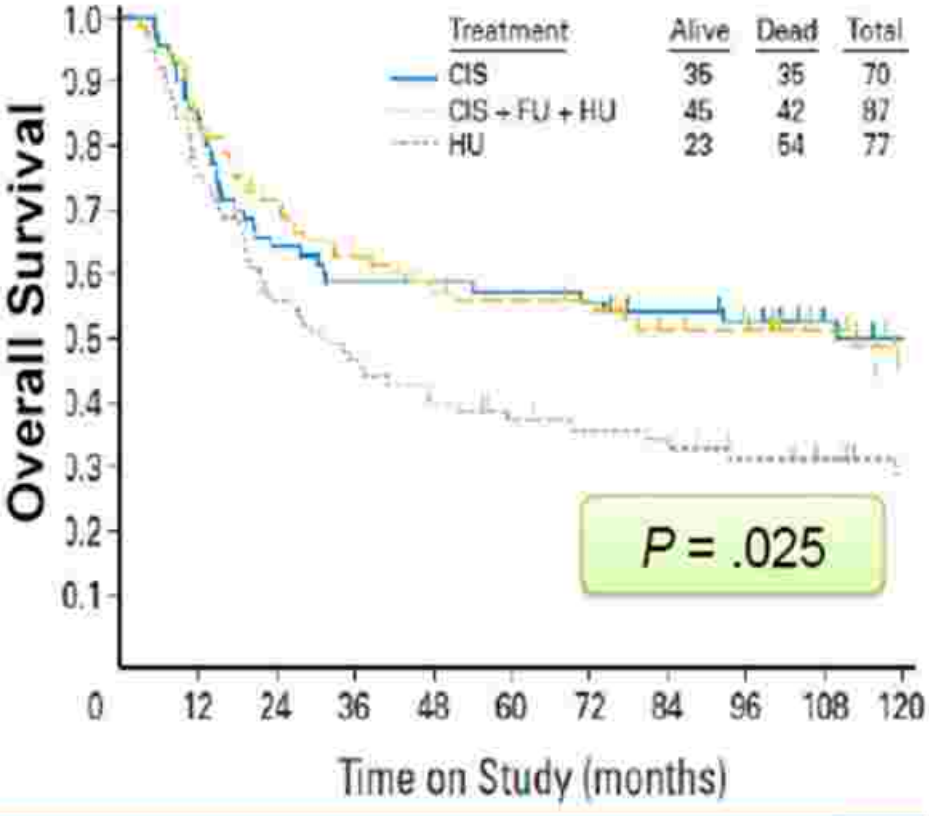
(Green et al: Lancet 2001)

Benefit for stage III in GOG120

Stage IIB (*n* = 276)



Stage III (*n* = 234)



(Rose PG et al: J Clin Oncol 2007)

Late toxicities in grade 3-5 (3)

Trial	CcRT ARM	Control Arm
RTOG 9001	14%	14%
GOG 120	3%	3%

Overall incidence of late toxicities was similar or both arms, although the absolute number of events seems to be different.

(Rose PG et al: J Clin Oncol 2007, Eifel PJ et al: J Clin Oncol 2004)

Impact of surgical staging (4)

Trial	Eligibility	Surgical staging
RTOG 9001	IB or IIA (>5cm or PLN)	Yes
GOG 85	IIB, III, IVA	Yes
GOG 120	IIB, III, IVA	Yes

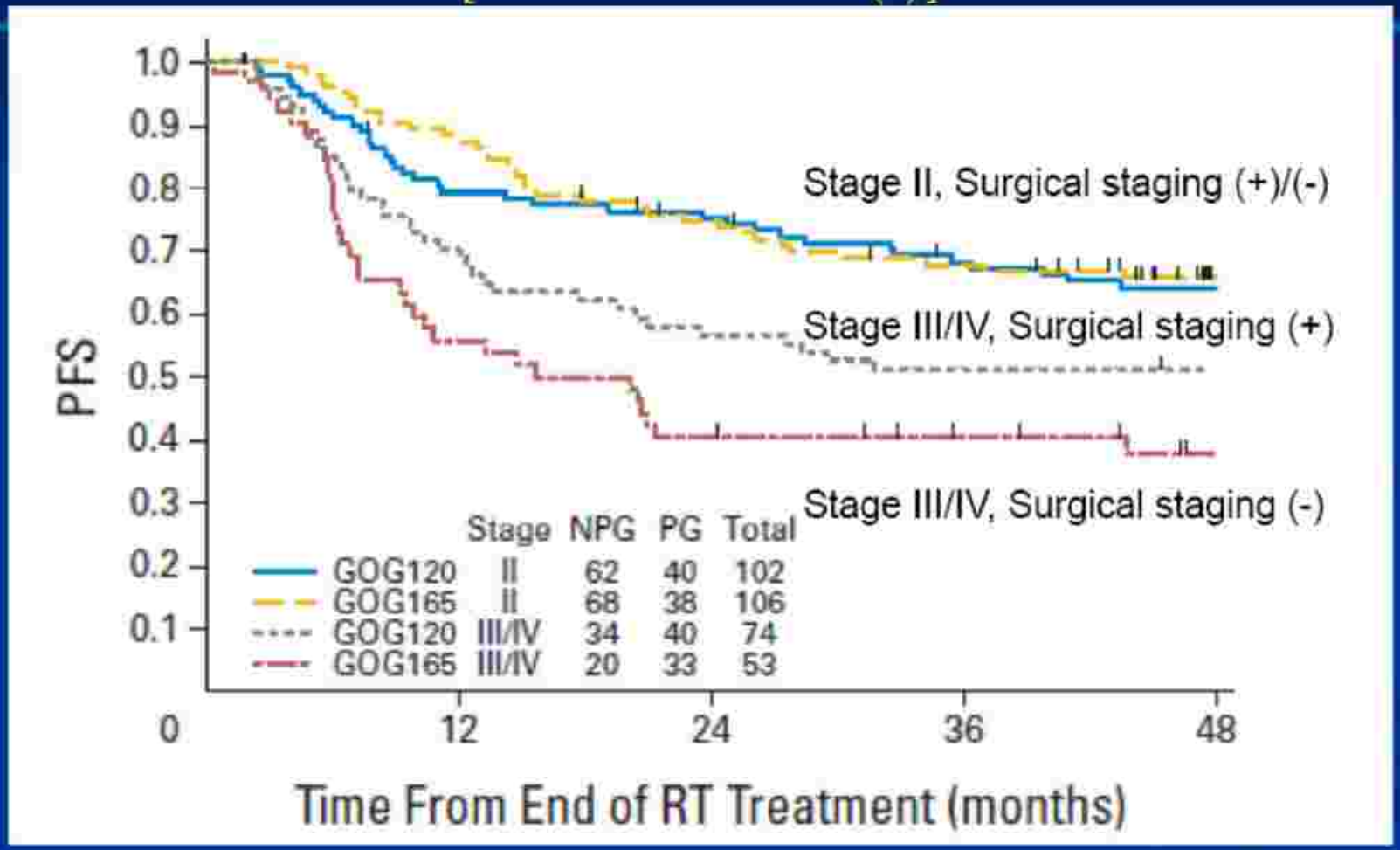
* This population has locally advanced tumor, but low incidence of distant metastasis. Improved pelvic control rate could result in improved survival.

Pelvis as site of first recurrence

Trial0	CRT	Control
RTOG 9001	19%	35%
GOG 85	25%	30%
GOG 120		
(weekly Cis)	19%	30%
(Cis+5FU+HU)	20%	30%
NCIC	27%	33%

Impact of surgical staging on survival

[Patient selection(5)]



(Monk BJ,*et al: J Clin Oncol 2007*)

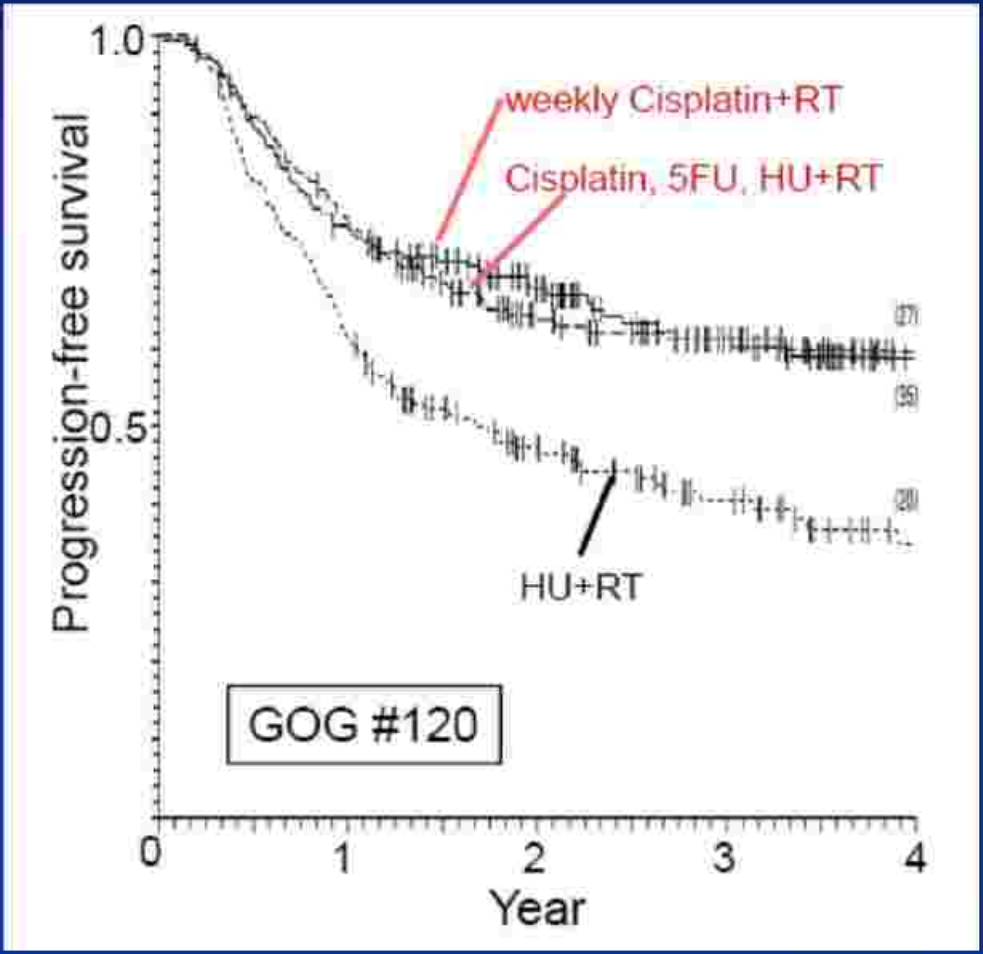
Chemotherapy of investigational arm (6)

Study	Cisplatin	5FU	Schedule	Cycles
GOG 123 Keys HM	40mg/mt2	-	weekly	Six
SWOG 8797 Peters WA	70mg/mt2	1 Gm/mt2 x 4 days	3 weekly	Four
RTOG 9001 Morris M	50mg/mt2	1 Gm/mt2 x 4 days	3 weekly	Three
GOG 85 Whitney et al	75mg/mt2	1 Gm/mt2 x 4 days	3 weekly	Two
GOG 120 Rose PG	40mg/mt2	-	3 weekly	Six
	50mg/mt2	1g/m2X4 day +Hydroxiurea	4 weekly	Two
NCIC Pearcey	40mg/mt2	-	1 weekly	Five

Weekly Cisplatin vs Cisplatin+5FU

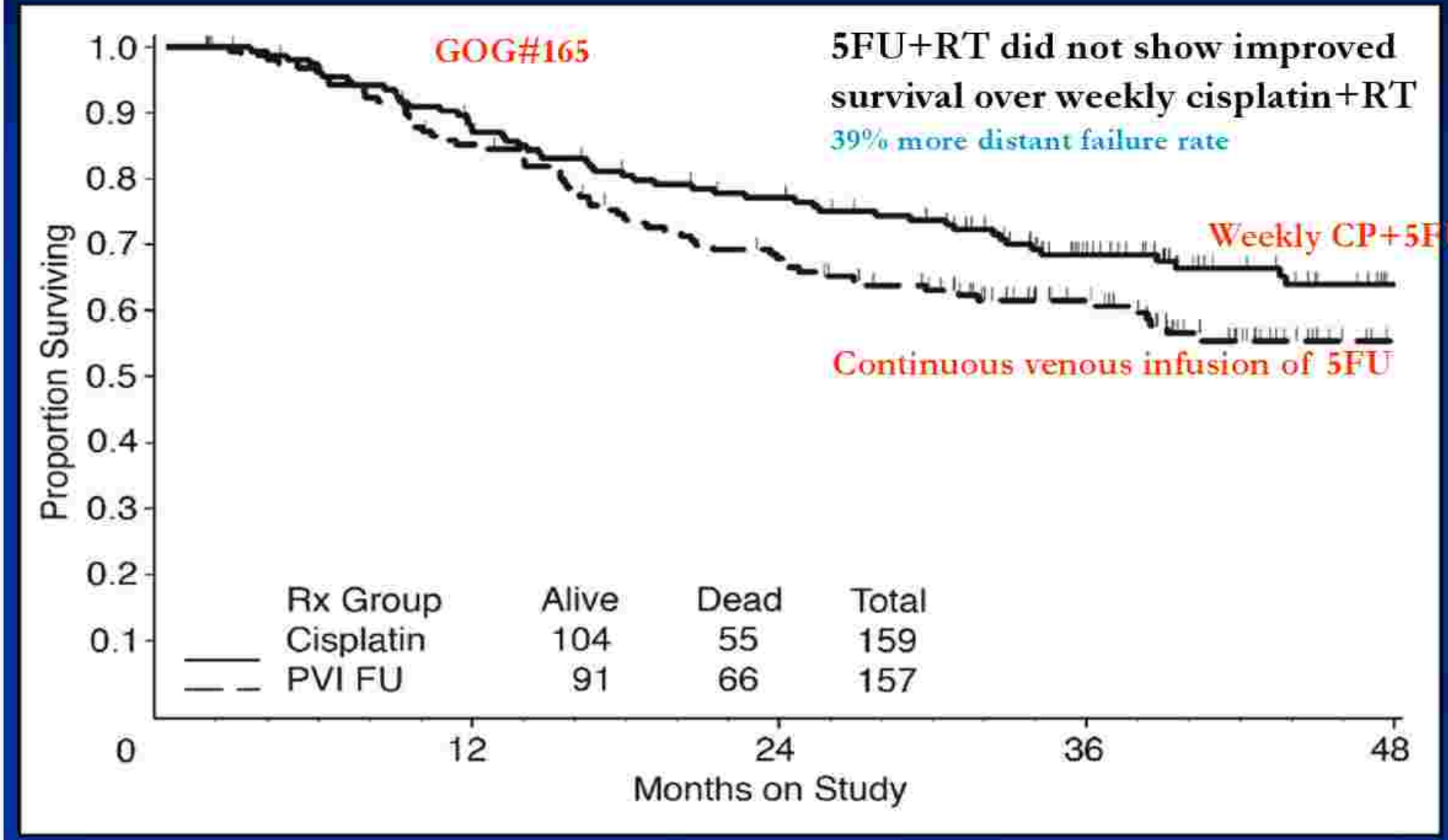
Efficacy

Weekly Cisplatin = Cis/5FU/HU



- Continuous infusion of 5FU
  expensive and inconvenient
- Acute Toxicity
  Weekly Cisplatin<Cis/5FU/HU
- Late Toxicity
  no comparative data
- Recommendation

Weekly Cisplatin vs 5FU



Lanciano, R. et al. J Clin Oncol; 23:8289-8295 2005

Control arm in the US trials (7)

Trial	EBRT	Brachy	TD (Gy)	OTT (days)
RTOG 9001	Extended field RT	LDR	89	58
GOG 85	RT+ Hydroxyurea	LDR	81	63
GOG 120	RT+ Hydroxyurea	LDR	81	63

- Standard RT is different between the US and Asian countries.
  (RT alone for the pelvis and HDR brachytherapy)
- The total dose and overall treatment time of the US trials were not appropriate in light of the American Brachytherapy Society's recommendation *(Nag S, et al. IJROBP, 2002).*

FIGO guideline in 2000

- **Advanced cervical cancer**
  - **(stage IIb, III and IVa)**

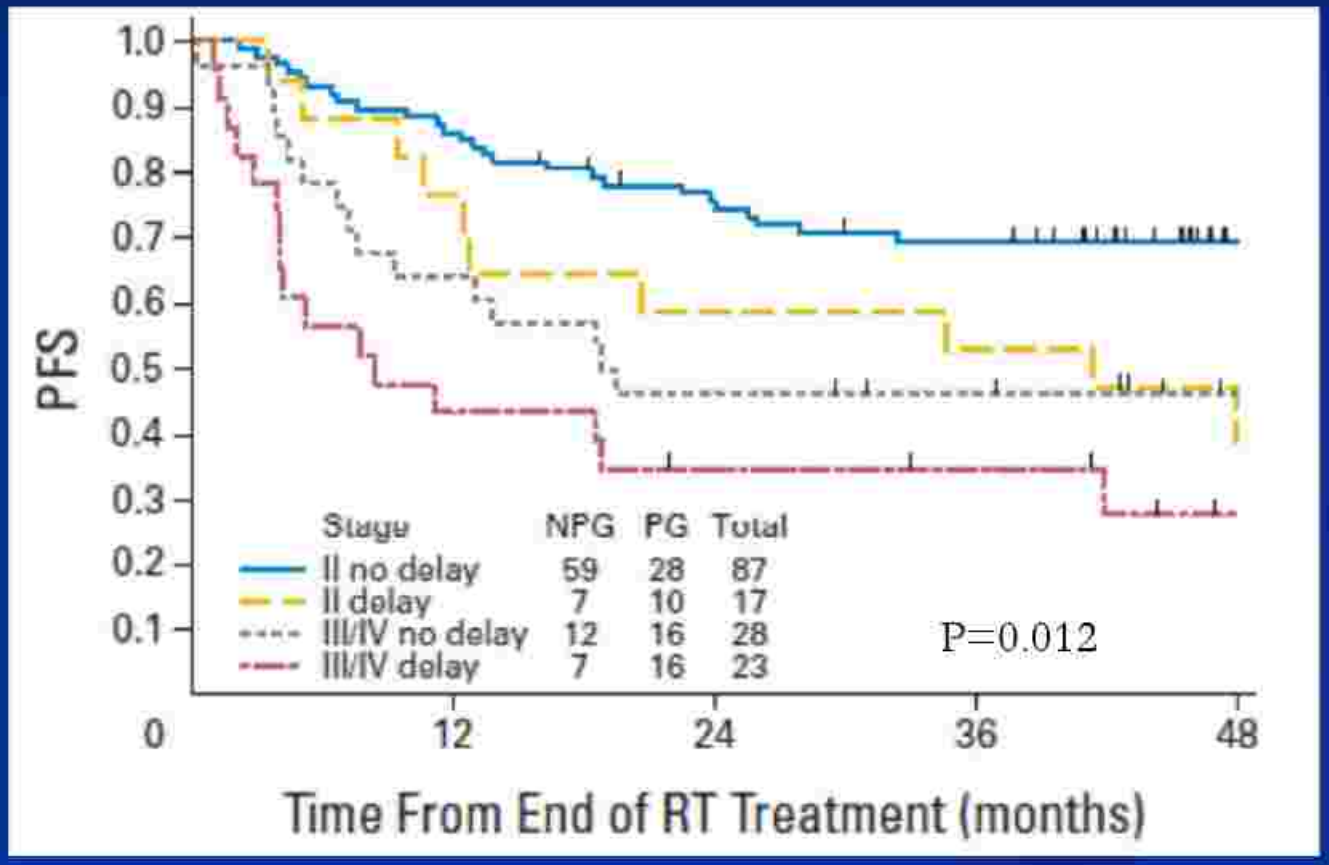
Standard primary treatment is concurrent chemoradiation.

Cisplatin is given in a dose of 40mg/m2 weekly during external beam therapy.

(Level of Evidence A)

Benedet et al Int J of Gynecol Oncol 2000

Impact of RT delay on survival
(GOG 120&165)

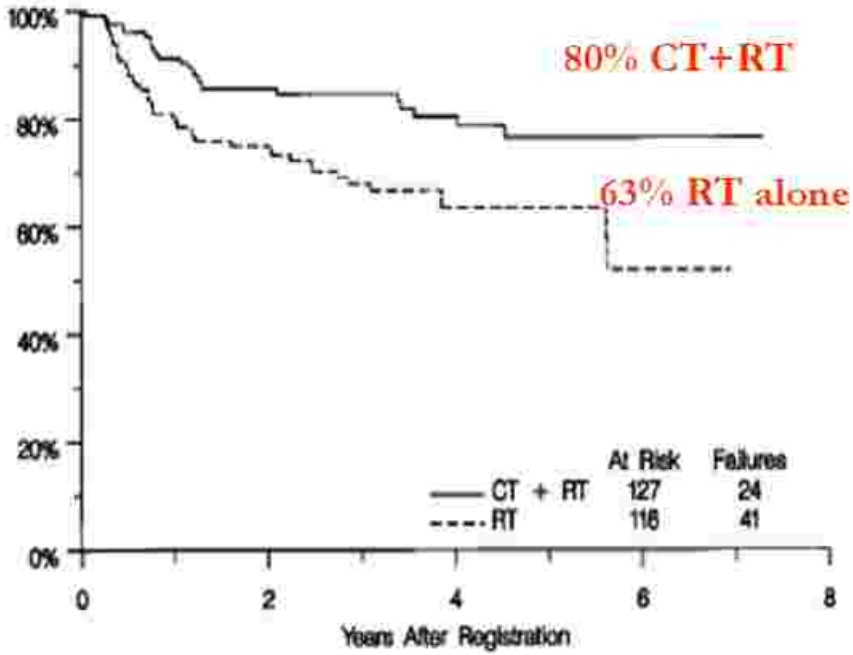


(Monk BJ,*et al: J Clin Oncol 2007)*

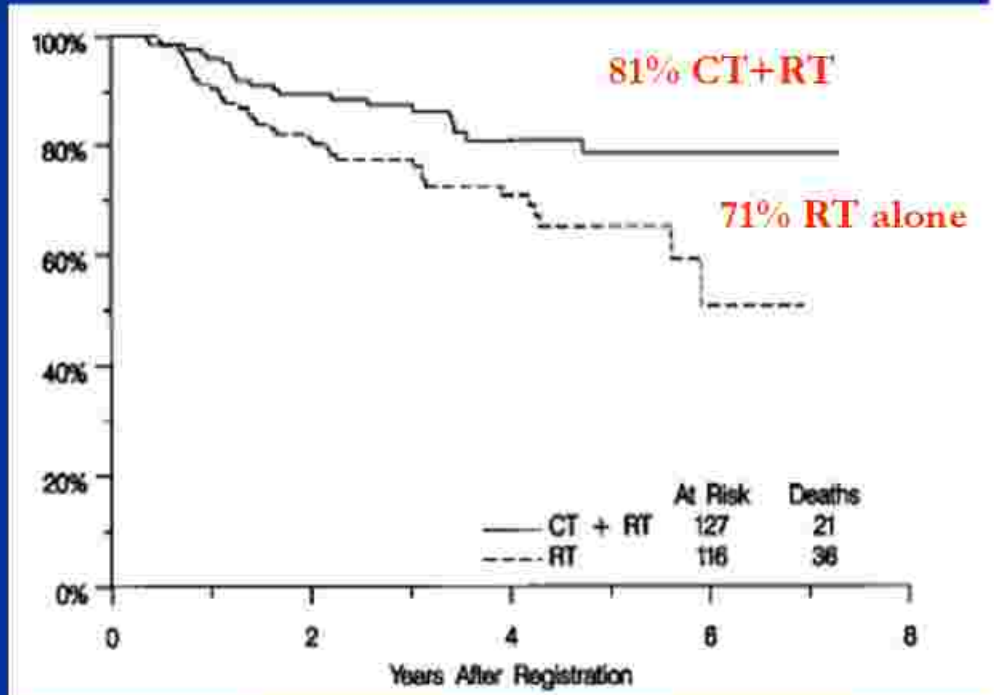
Adjuvant Treatment
RT alone vs CT+RT

(As post surgical adjuvant for IB/IIA node, parametrial inv, margin positive)

PFS at 4 years



Overall Survival



Peters et al JCO 18, 2000

TREATMENT OF THE PARA-AORTIC REGION

Role of prophylactic para-aortic nodal RT

Randomized trials:

EORTC - no significant improvement in survival

RTOG (OAS at 10 years):

Prophylactic para-aortic RT : 55%
Pelvic RT alone : 44%
Improvement attributed to decreased systemic failure

TREATMENT OF THE PARA-AORTIC REGION

Role of Chemotherapy

GOG 125: Concomitant CDDP+ 5FU & RT
(para-aortic + pelvic)
(biopsy proven lymph node mets+)

Results (DFS at 3 years):
Stage I: 52%
Stage II: 36%
Stage III & IV: 22%

TREATMENT OF THE PARA-AORTIC REGION

Role of Chemotherapy

RTOG randomized trial:

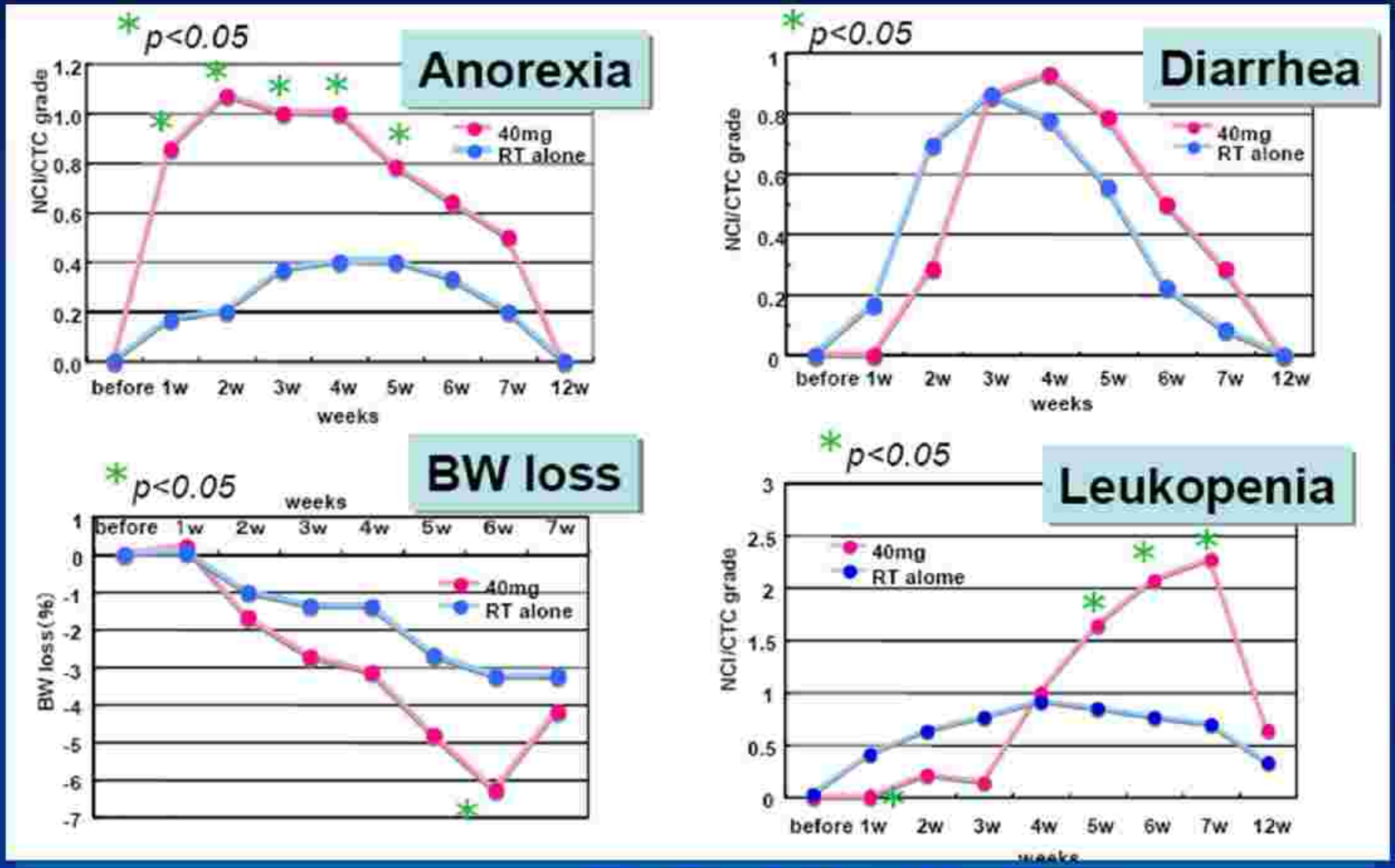
Stage IIB - IVA, IB - IIA with tumor > 5 cm, pelvic lymph nodes

Arm A: Pelvic RT + Concurrent CT
Arm B: Pelvic + Para-aortic RT

Results (At 5 years):
OAS: Arm A: 73%
Arm B: 58%

Morris at al.,NEJM, 1999

Optimal timing of intervention for acute toxicity



(Ohno T. et al, Gynecol. Oncol. 2006)

Criteria for modification of chemotherapy

- Cisplatin is suspended in
  - -Grade 2 hematological toxicities
  - (WBC < 3000, Plt < 75000)
  - -Fever > 38°C
  - -PS 3-4
  - -Grade >3 non-hematological toxicities
  - (e.g. diarrhea, loss of appetite, fatigue)
  - -Serum creatinine > 2.0 mg/dl
  - -Cases that are judged to be difficult to administer cisplatin by responsible physician.
- Cisplatin is resumed when the hematological and nonhematological toxicities are recovered to grade 1.

Chemotherapy Trials in Cervical Cancer

StudyDesign	Population	N	Regimen	Results
Moore and colleagues	Phase 3* Recurrent/IVB	264	C vs C/P	RR = 36% vs 19% Median survival = 9.7 vs 8.8 months
Mickiewicz and colleagues	Phase 2 IVB	32	Cb/P	RR = 72% PFI = 7 months
Garin and colleagues	Phase 2* IVB†	97	1) I 2) I + C 3) C	1) RR = 13% 2) RR = 37% 3) RR = 19%
Zarba and colleagues	Phase 1/2 IIB-IVA	29	Gem/C + RT	91% CR 9% PR
Mahfouf and colleagues	Phase 2 IIB-IVB/recurrent	40	Gem/C	RR = 90% (no prior RT) RR = 53% (prior RT)

*Chemo-**R**adiation in **A**dvanced **C**arcinoma Cervi**x** (CRACx Trial)*

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: July 2003 - 2007**
- **Interim analysis : Twice One at 50 % and another at 75 % event rates**