Primary Chemo-radiotherapy in Loco-regionally Advanced Cervical Cancer

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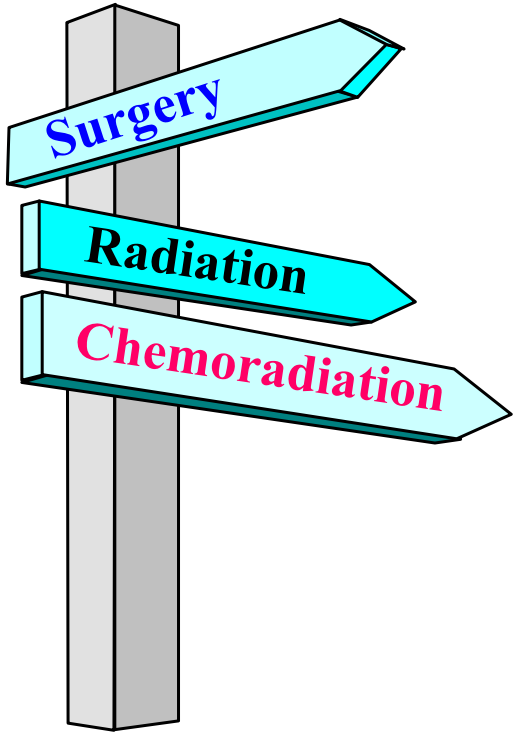
Primary CCRT in Loco-regionally Advanced Cervical Cancer

1. Introduction
2. Clinical trials of primary CCRT
   for loco-regionally advanced
   cancer (IB ~ VIA), and
   for locally advanced cancer (IB2)
3. Chemoradiation, What's next?
4. Ajou university experiences



CCRT : Concurrent Chemo-Radiotherapy

Curies : Radium 1896

- Discovery
  - Radioactivity (Thorium)
  - Polonium & Radium
- Marie Curie
  - won Nobel Prize
  - died of Leukemia
- Radium was subsequently found to cure cervix cancer

5-year Survival rate for stage IB cervical cancer

Reference	No. pts	% with tumor diameter <4cm	% overall 5-Yr survival
Radical hysterectomy			
Piver & Chung 1975	157	65	80
Alvarez 1991	200	88	85
Brewster et al. 2001	784	73.5	86/72
Radiotherapy			
Homesley 1980	45	49	80
Mendenhall 1984	101	32	81
Perez 1992	384	64	85
Eifel 1990	1494	46	81

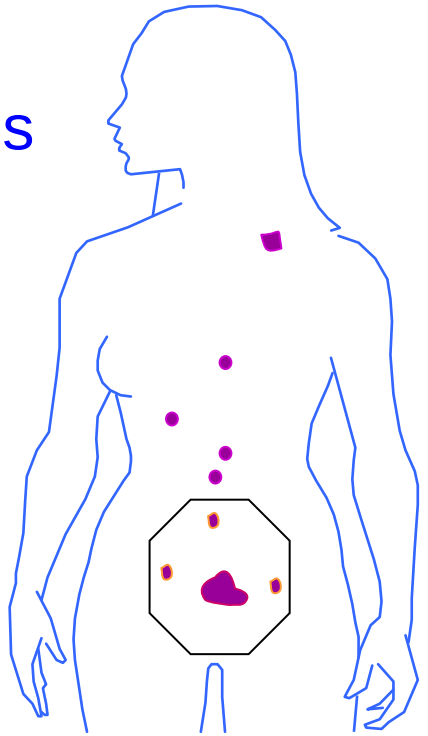
Tumor size & outcome in patients with tumors ≥ 5cm of cervical cancer treated with RT alone*

Size (cm)	No. pts	CTC %	PTC %	DSS %
5-5.9	200	93	85	69
6-6.9	99	92	79	69
7-7.9	55	90	81	58
≥ 8	48	69	57	40

CTC=Central tumor control; PTC=Pelvic tumor control; DSS=Disease specific survival, * Exclude patients who underwent adjuvant hysterectomy.

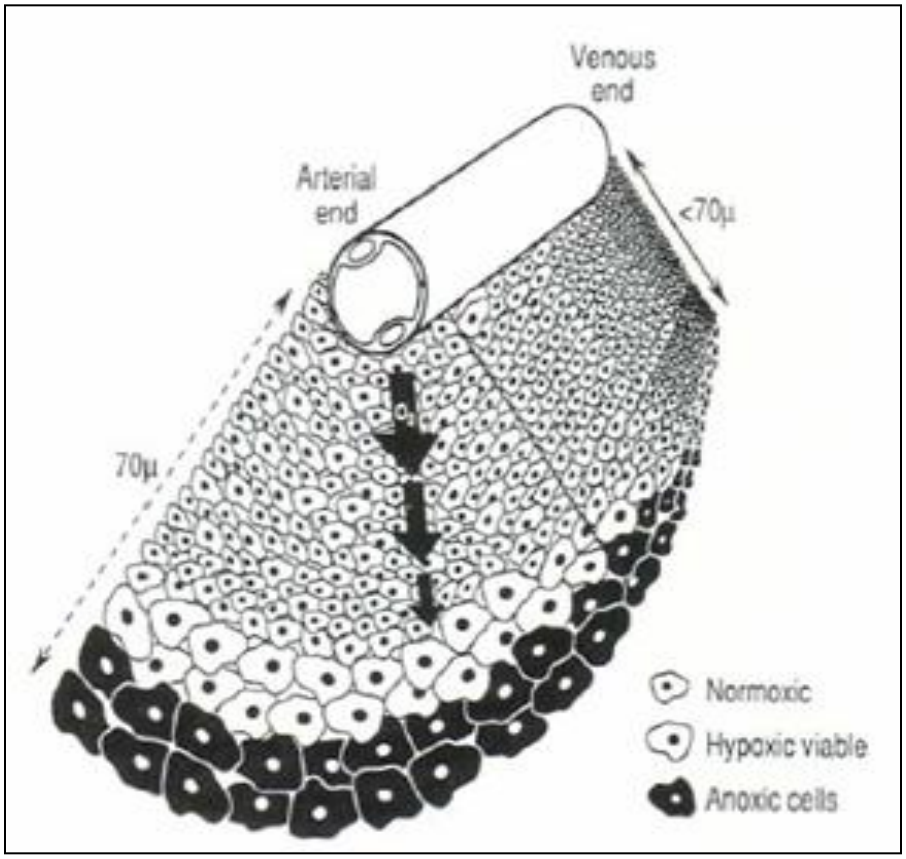
Role of chemotherapy for radiotherapy failure

- Central failure & Regional failure
  - ➥CT agent acts as a radiosensitizer, thus producing a synergistic effect between RT & CT.
- Geographic failure
  - ➥CT agent acts systemic therapy.
- Drugs : cisplatin, 5-FU, paclitaxel etc.

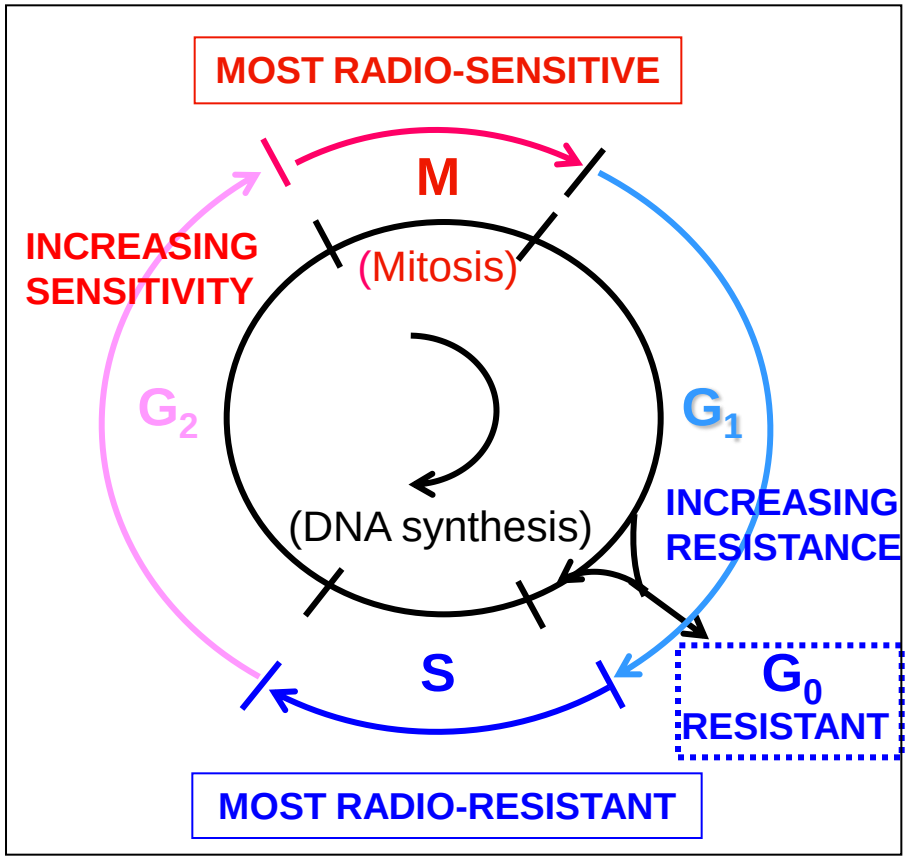


RT : Radiotherapy
CT : Chemotherapy

Reduction of radio-resistant hypoxic fraction by CT

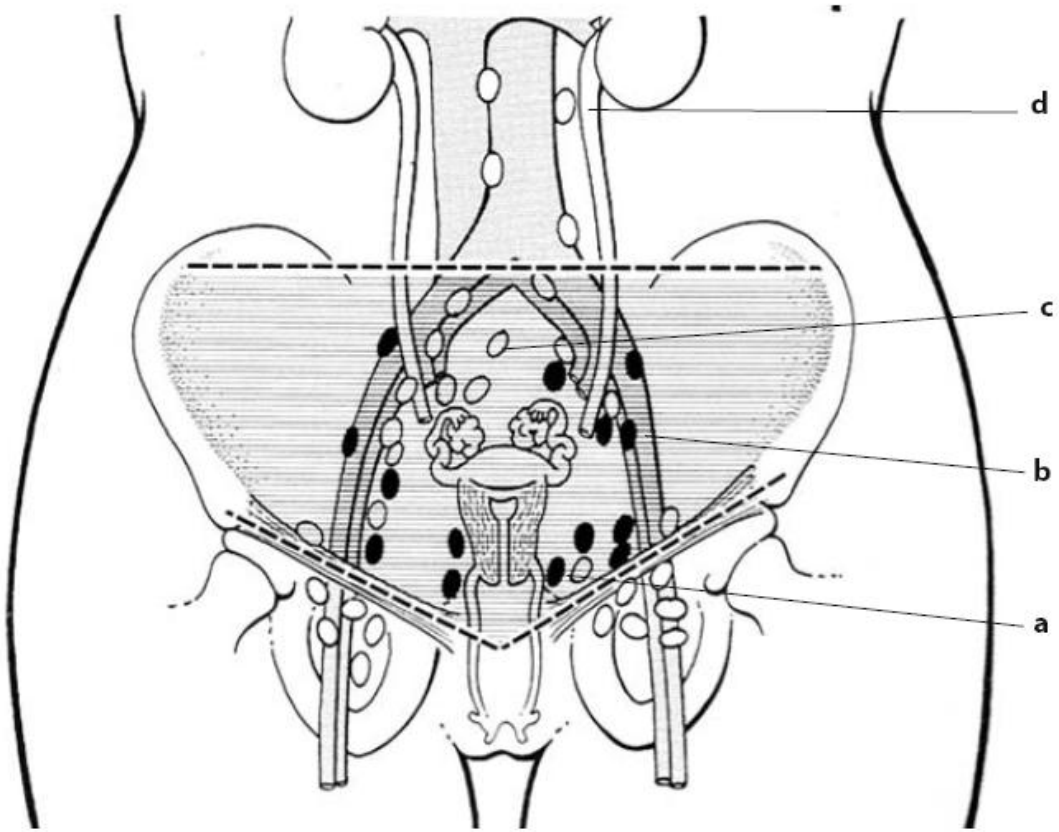


Inhibition of radiation damage repair in cell cycle by CT

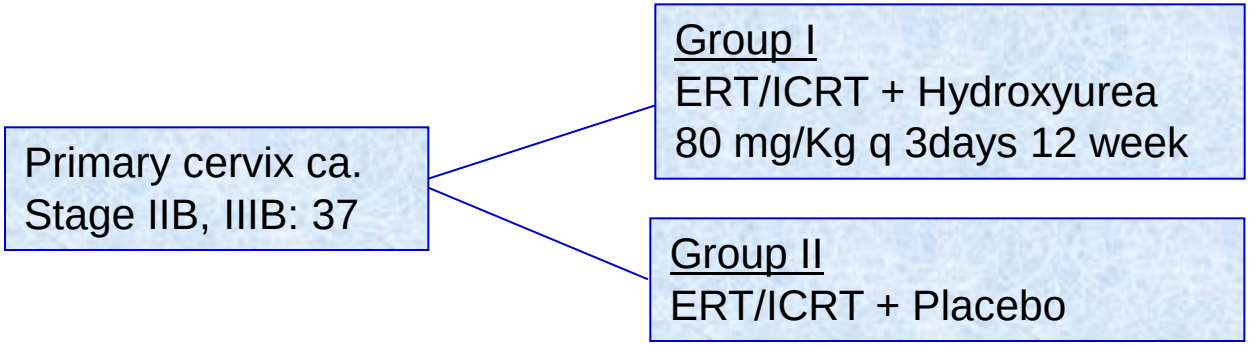


CT : Chemotherapy

Clinical trials of primary CCRT for loco-regionally advanced cancer (stage IB ~ VIA)



Hydroxyurea & RT

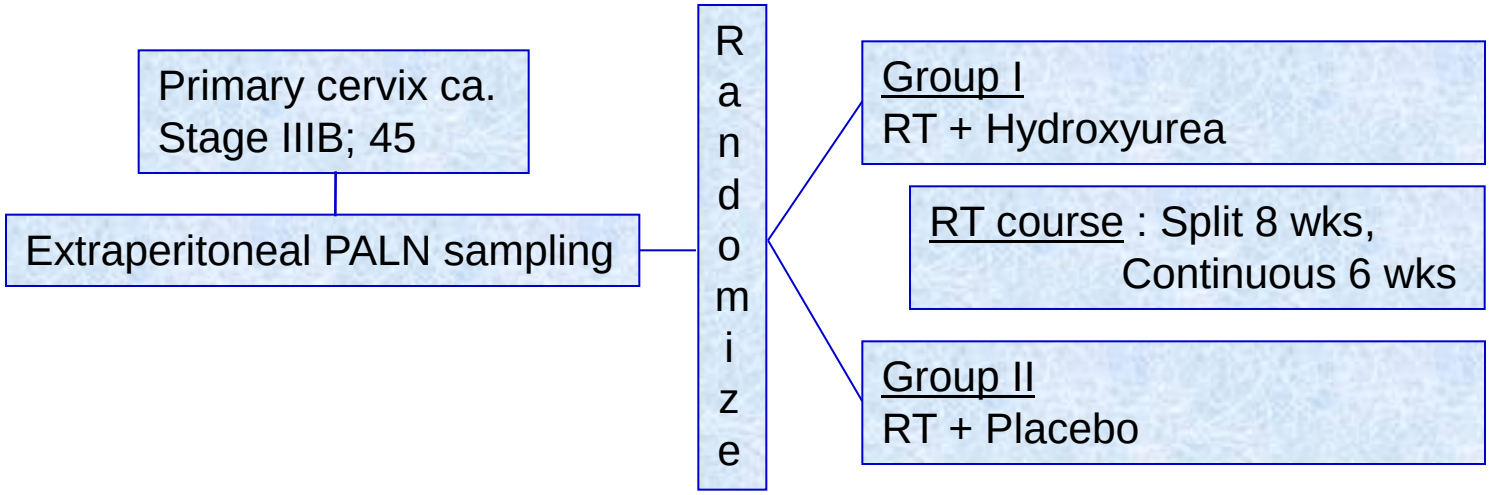


Tumor status at 2 Years (NED %)

Stage	Hydroxyurea	Placebo	*P*
IIB	7/9 (77.7 %)	6/13 (46.1 %)	*0.03*
IIIB	3/6 (50.0 %)	1/9 (11.1 %)	*0.13*
Total	10/15 (66.6 %)	7/22 (31.8 %)	*0.0014*

2 years PFS benefit with hydroxyurea, but failed overall survival benefit

Hydroxyurea & RT

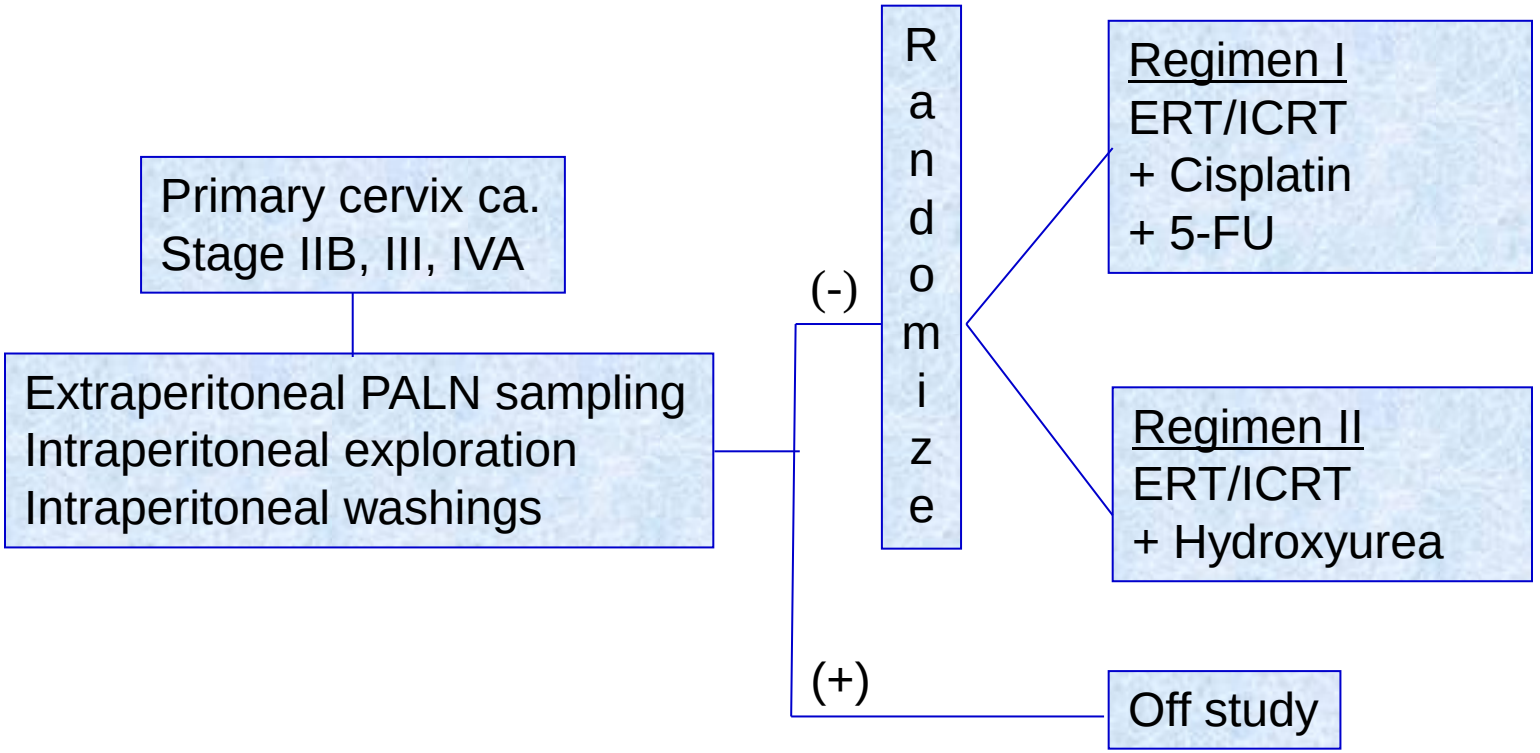


5 Years Progression-free Survival

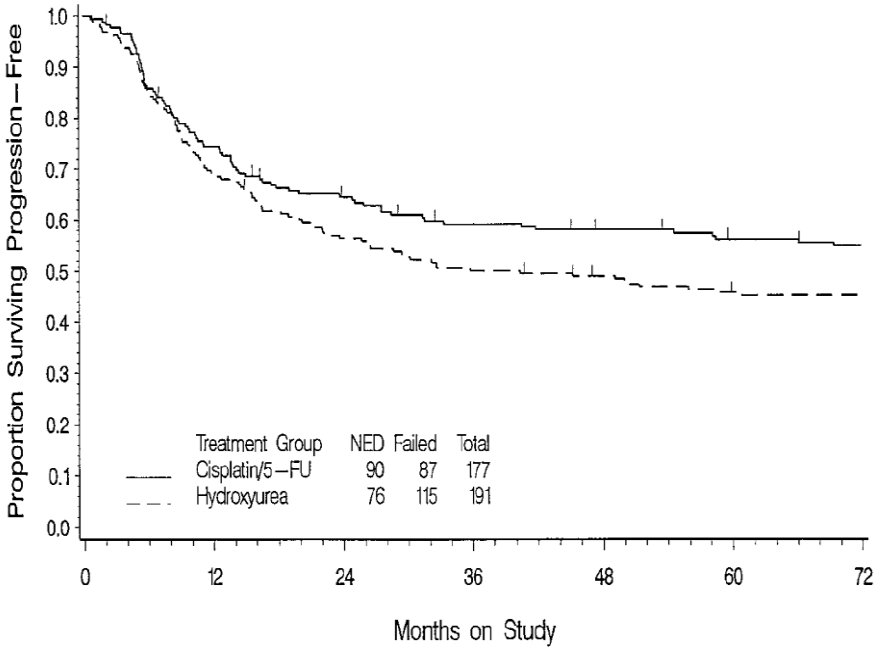
RT course	Hydroxyurea	Placebo	*P*
All	60 %	52 %	*0.49*
Continuous RT	91 %	60 %	*0.06*

Continuous RT w/ Hydroxyurea improved local control rate & survival.

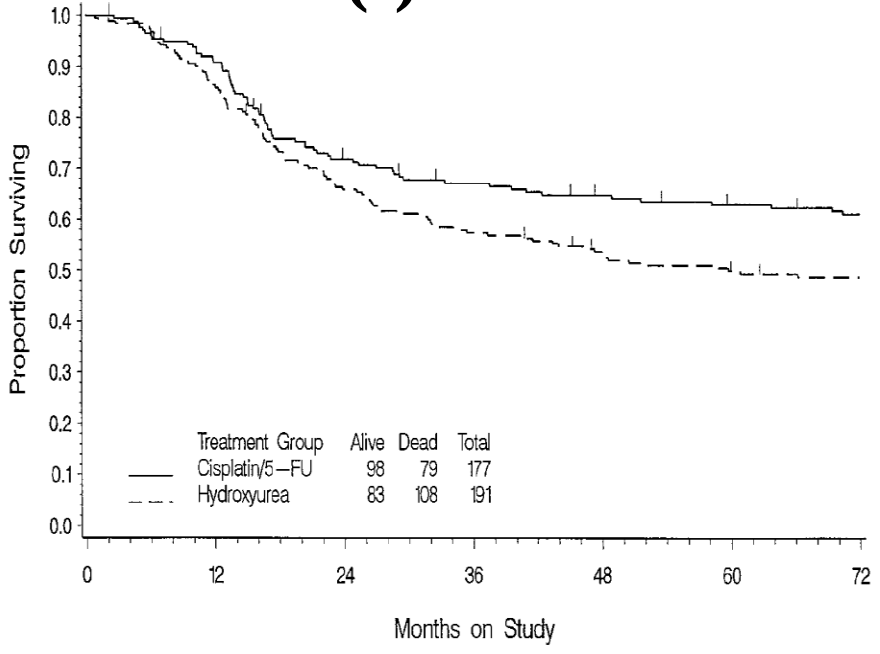
GOG #85 (SWOG #8695)



Cisplatin + 5-FU / Hydoxyurea as CCRT in IIB-IVA Cervical Cancer w/ (-) PALN



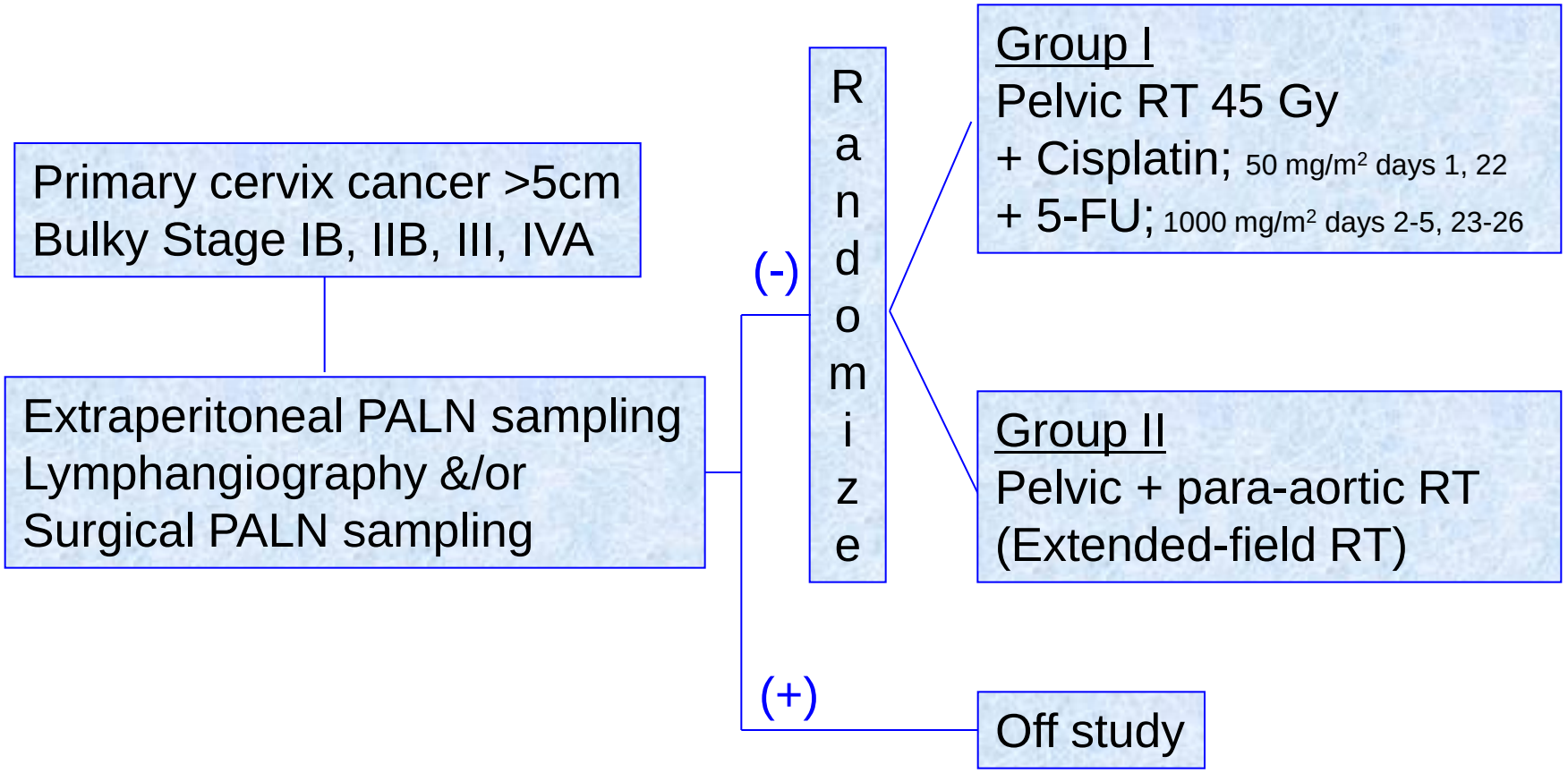
PFS : 60% vs. 48% (*P*=0.033)



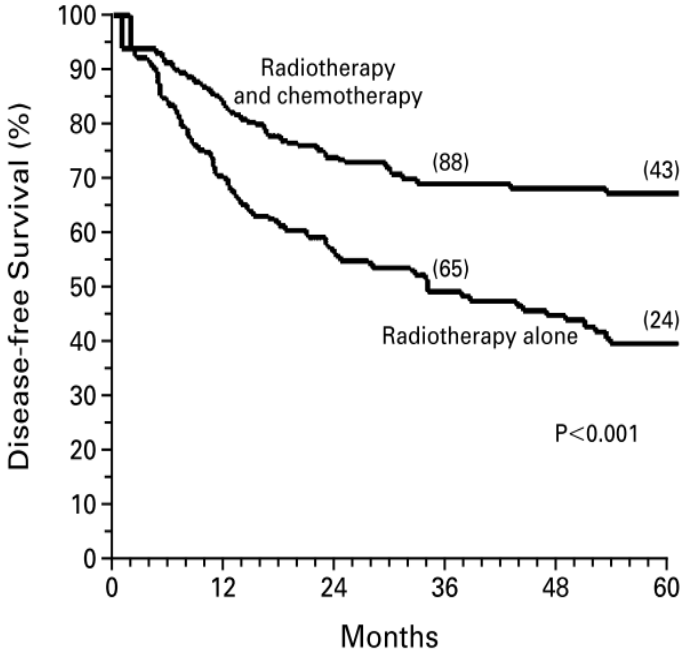
OS : 65 % 50% (*P*=0.018)

RT w/ Cisplatin+5-FU offers patients better progression-free & overall survival than HU, and manageable toxicity

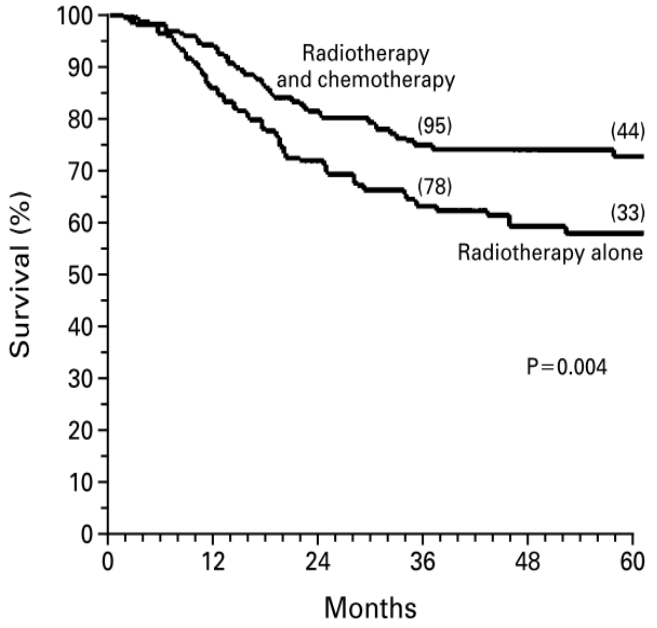
RTOG # 9001


Primary cervix cancer >5cm
Bulky Stage IB, IIB, III, IVA
Extraperitoneal PALN sampling
Lymphangiography &/or
Surgical PALN sampling
(-)
(+)
Randomize
Group I
Pelvic RT 45 Gy
+ Cisplatin; 50 mg/m2 days 1, 22
+ 5-FU; 1000 mg/m2 days 2-5, 23-26
Group II
Pelvic + para-aortic RT
(Extended-field RT)
Off study

Survivals among patients assigned to CCRT & RT alone



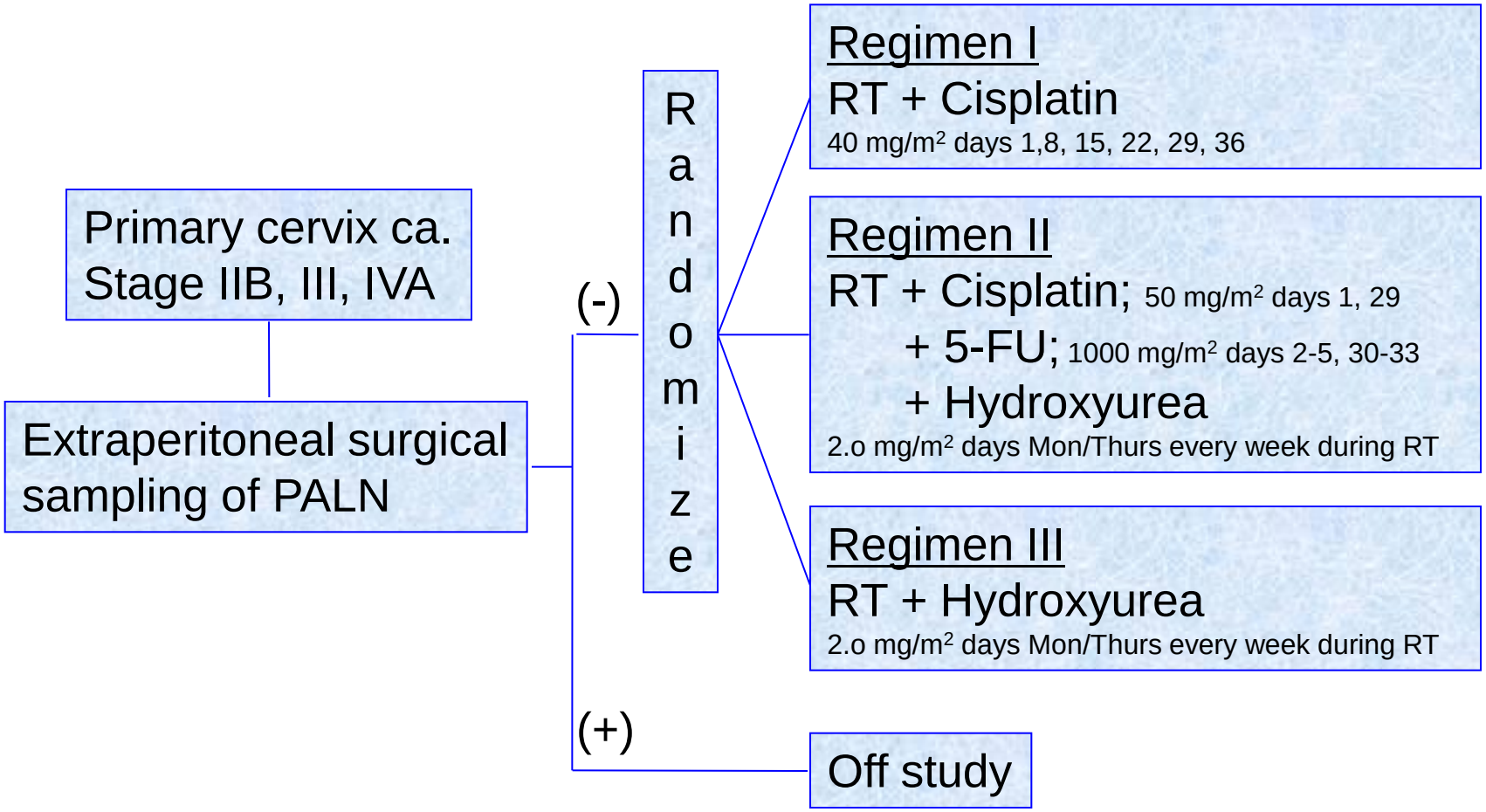
PFS : 67% vs. 40% (*P*<0.001)



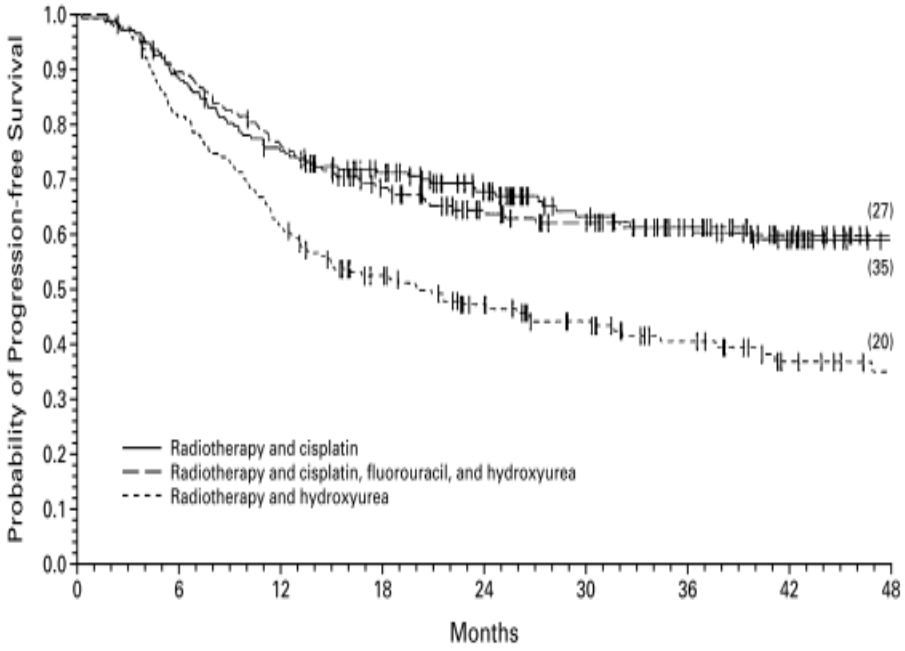
OS : 73 % 58% (*P*=0.004)

DFS & OS were significantly better among patients with CCRT compared to the radiotherapy alone group.

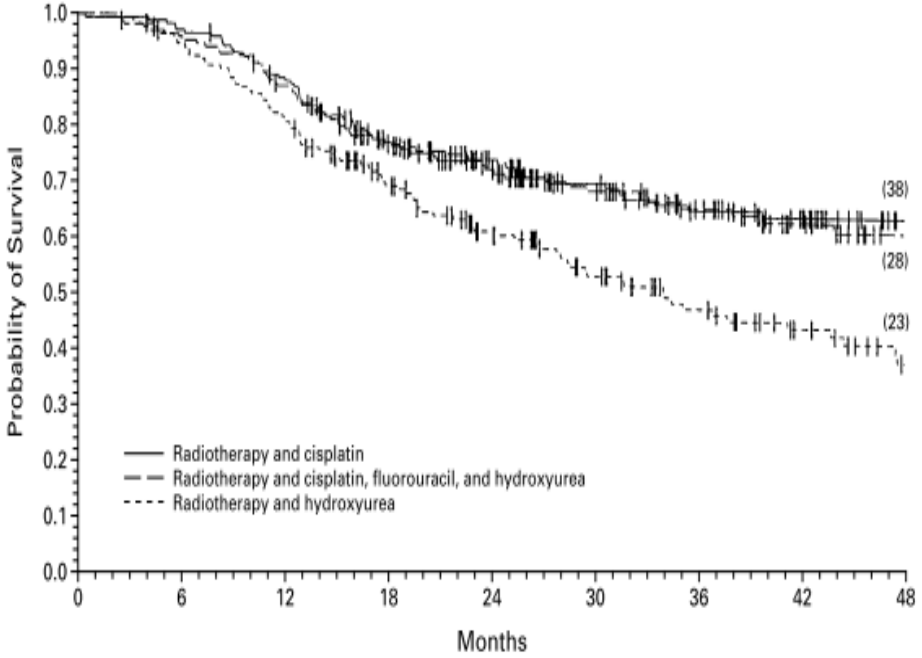
GOG #120


Primary cervix ca.
Stage IIB, III, IVA
Extraperitoneal surgical sampling of PALN
(-)
(+)
Randomize
Regimen I
RT + Cisplatin
40 mg/m2 days 1,8, 15, 22, 29, 36
Regimen II
RT + Cisplatin; 50 mg/m2 days 1, 29
+ 5-FU; 1000 mg/m2 days 2-5, 30-33
+ Hydroxyurea
2.o mg/m2 days Mon/Thurs every week during RT
Regimen III
RT + Hydroxyurea
2.o mg/m2 days Mon/Thurs every week during RT
Off study

PFS and overall survivals of cisplatin based CCRT for IIB ~ IVA cervical cancer



PFS : 60% vs. 60% vs. 45% (*P*<0.001)



OS : 60% vs. 58% vs. 34% (*P*=0.002)

CCRTs containing cisplatin improved PFS & OS, and weekly cisplatin group showed less toxicity than monthly cisplatin+5FU group

Two-year survival among patients assigned to receive RT alone, monthly & weekly CCRT

Stage	N	**RT Alone (%)**	**M-CCRT (%)**	**W-CCRT (%)**	***p***
IB	19	10/13 (76.9)	3/3 (100)	3/3 (100)	<0.05
IIB	74	29/36 (80.6)	16/18 (88.9)	18/20 (90)	0.05
III	9	0/3 (0)	1/3 (33.3)	2/3 (66.7)	<0.05
Total	102	39/52 (75)	20/24 (83.3)	23/26 (88.5)	<0.05

RT: radiation therapy, MCCRT: monthly chemoradiotherapy, WCCRT: weekly chemoradiotherapy

Survivals in CCRT groups, whether monthly or weekly than RT alone were improved in loco-regionally advanced cervical cancers.

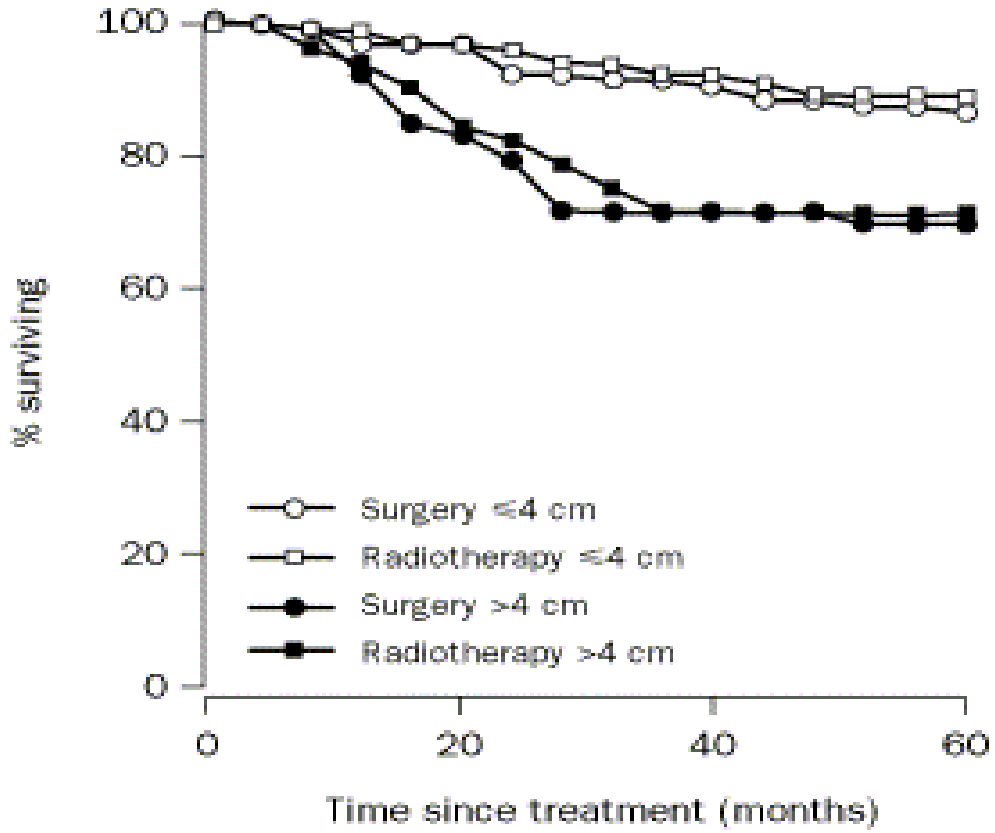
Patients having at least one episode of grade 3/4 toxicity during CCRT

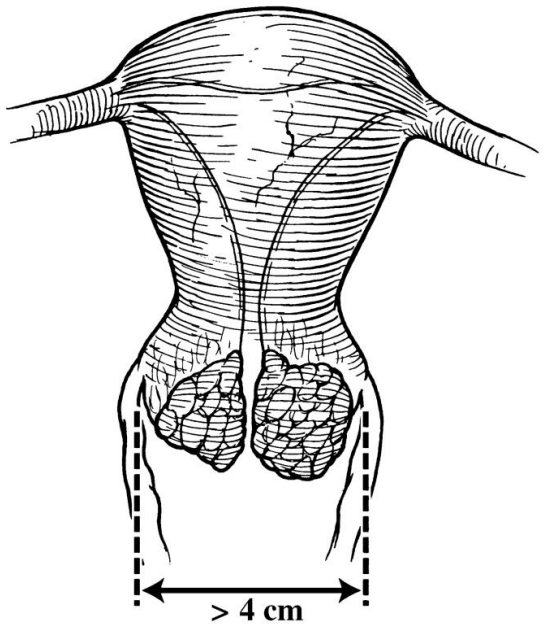
	M-CCRT(%)	WCCRT(%)	*P*
Nausea/Vomiting	5 (20.8)	1 (3.8)	*P<0.05*
Enteritis	3 (12.5)	2 (7.7)	NS
Leukopenia	7 (29.1)	4 (15.4)	*P<0.05*
Anemia	3 (12.5)	2 (7.7)	NS
Neurosensory	0 (0.0)	0 (0.0)	NS
Nephrotoxicity	0 (0.0)	0 (0.0)	NS

CCRT: concurrent chemoradiotherapy, WCCRT : weekly CCRT
N (%), G: grade, chi-square test. NS: not significant

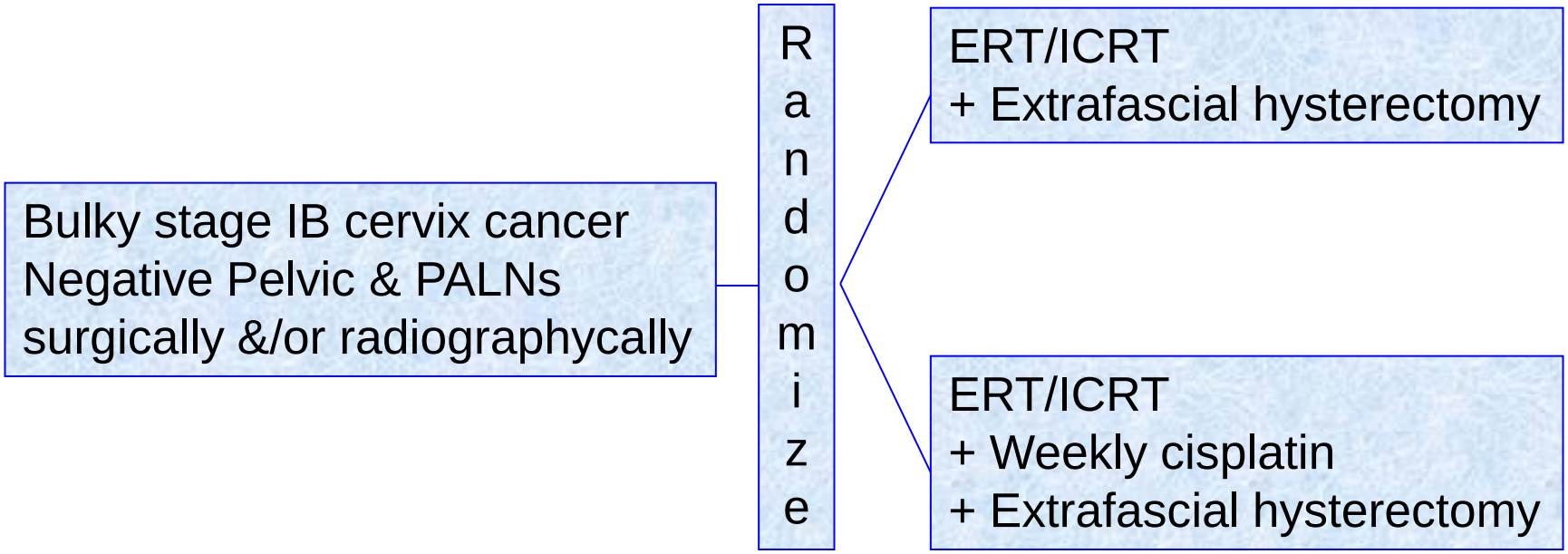
Toxicity was slightly increased especially M-CCRT group but manageable

Concurrent chemoradiation for bulky stage IB (IB2)

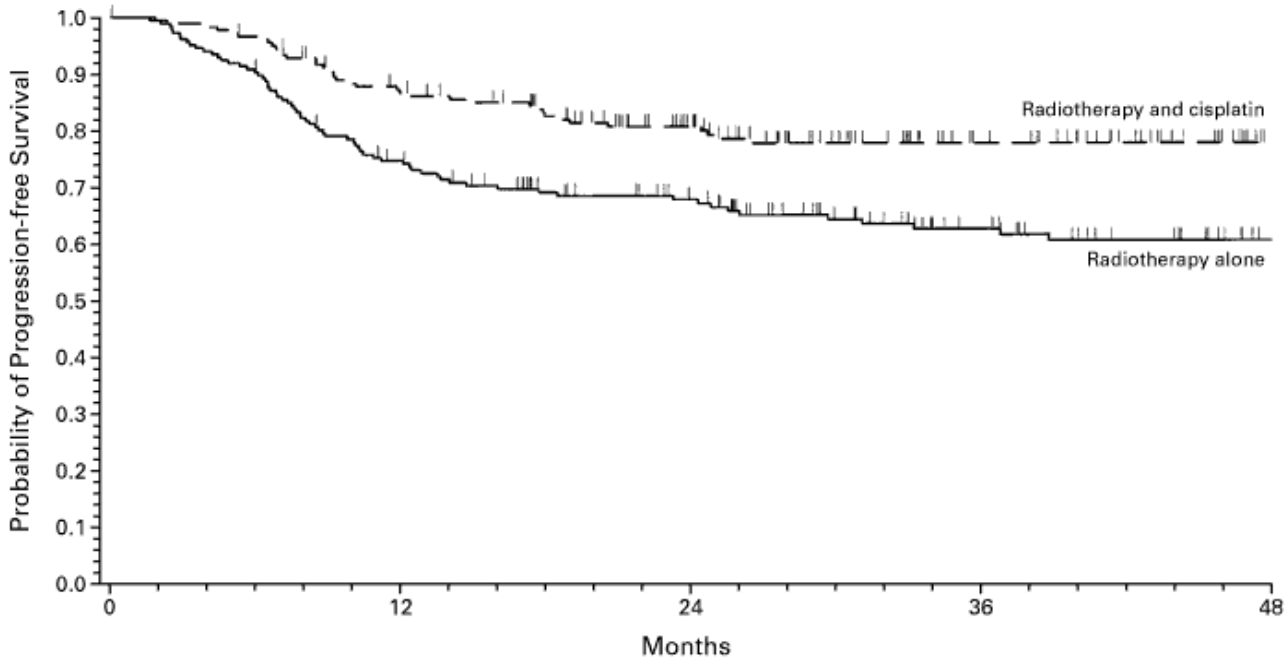




GOG #123


Bulky stage IB cervix cancer
Negative Pelvic & PALNs
surgically &/or radiographycally
Randomize
ERT/ICRT
+ Extrafascial hysterectomy
ERT/ICRT
+ Weekly cisplatin
+ Extrafascial hysterectomy

CCRT w/ Adj. EAH and RT w/ Adj. EAH For Stage IB2 Cervical Cancer



Adding weekly cisplatin to pelvic RT followed by hysterectomy significantly reduced risk of recur & death.

A multi-center retrospective study of CCRT for stage IB2 cancer in Korea

Management Strategies grouped by primary modality

Group 1
- Radical Hysterectomy only
- Radical Hysterectomy + adjuvant RT / CCRT

Group 2
- NAC + Radical Hysterectomy
- NAC + Radical Hysterectomy + Radiation
- NAC + Radical Hysterectomy + Chemotherapy

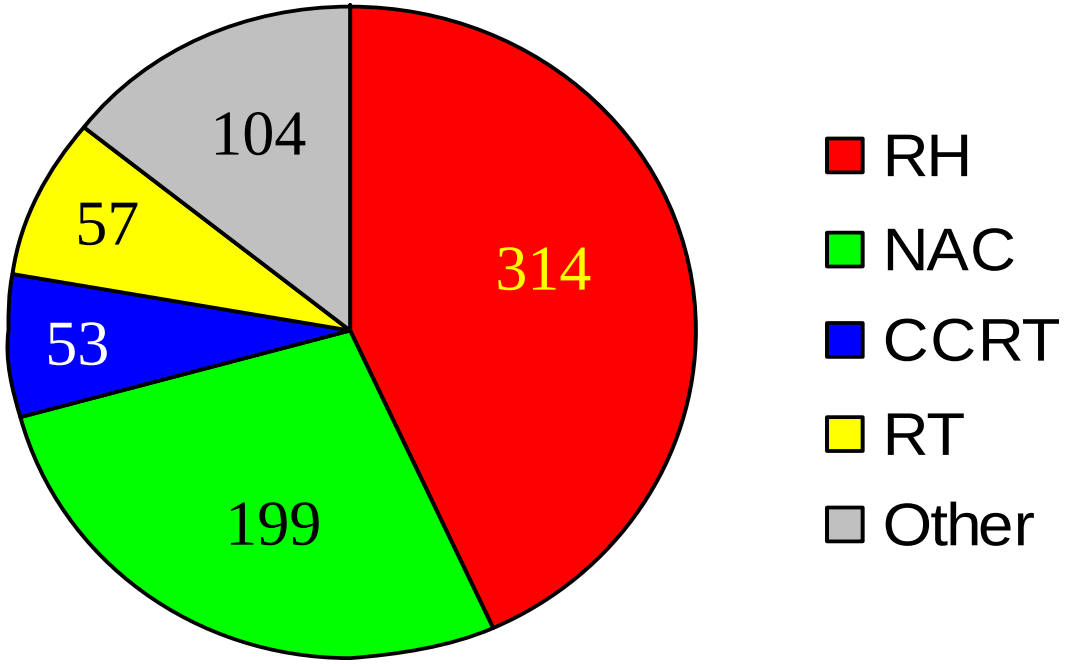
Group 3
- CCRT
- CCRT + Extrafascial Hysterectomy

Group 4
- Radiation only
- Radiation + Extrafascial Hysterectomy

Group 5
- Other

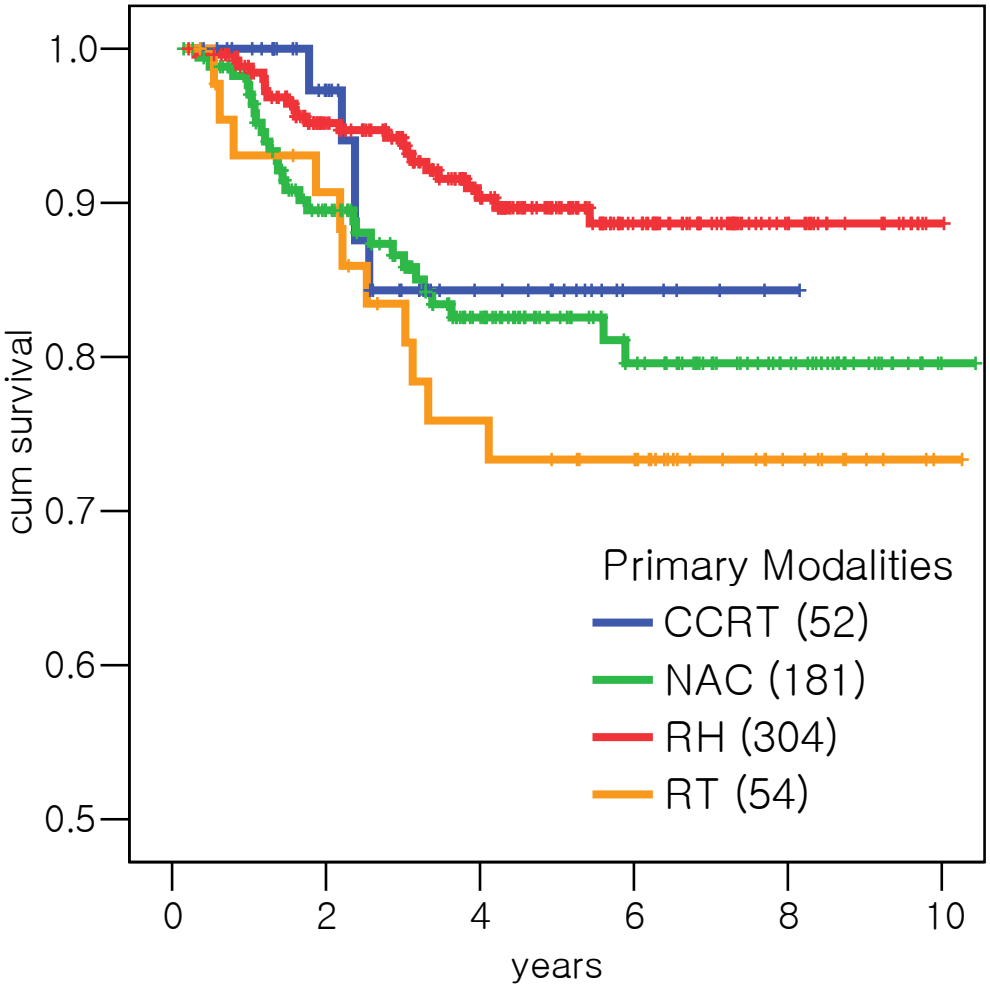
RT : Radiotherapy, NAC : Neoadjuvant chemoradiotherapy
CCRT : Concurrent chemoradiotherapy

Patients by Strategies for Stage IB2, Recruited (N)



RH : Radical hysterectomy, NAC : Neoadjuvant chemoradiotherapy
CCRT : Concurrent chemoradiotherapy, RT : Radiotherapy

10-Year Survival According to Primary Modality



5 Prospective randomized trials for the role of CCRT

Authors (1999)	Eligibility	Chemotherapy in Investigational arm	Chemotherapy in Control arm	RR of Recur (90% CI)	*P*
Rose et al.	FIGO IIB-IVA	Cisplatin 40mg/m^2/wk Cisplatin 75mg/m^2 5-FU 4g/m^2/96h (3cycles)	HU 3g/m^2 (2X/wk) HU 3g/m^2 (2X/wk)	0.57 (0.42-0.78) 0.55 (0.40-0.75)	*<0.001* *<0.001*
Morris et al.	FIGO IB-IIA ($\geq$5cm) IIB-IVA	Cisplatin 50mg/m^2/wk 5-FU 4g/m^2/96h HU 2g/m^2 (2X/wk)(2cycles)	None	0.48 (0.35-0.66)	*<0.001*
Keys et al.	FIGO IB ($\geq$4cm)	Cisplatin 40mg/m^2/wk	None	0.51 (0.34-0.75)	*0.001*
Whitney et al.	FIGO IIB-IVA	Cisplatin 50mg/m^2 5-FU 4g/m^2/96h (2cycles)	HU 3g/m^2 (2X/wk)	0.79 (0.62-0.99)	*0.03*
Peters III et al.	FIGO I-IIA after RAH w/ parametria, nodes, margins+	Cisplatin 70mg/m^2 5-FU 4g/m^2/96h (2cycles)	None	0.50 (0.29-0.84)	*0.01*

CCRTs which contains cisplatin significantly improved survival rates of cervical cancer from 30 to 50% by local & distant disease control.

Cervical cancer treatment option overview

"The risk of death from cervical cancer was decreased by 30% to 50% by concurrent chemoradiation. Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer."

Chemoradiation for stage IB ~ IVA - What next?

Trials	**Upfront (NACT) Trial**	**OUTBACK Trial**
Cycles	short course 6 weeks	4 cycles q 3weeks
Toxicity	minimal	likely significant (Haem/GI)
Compliance	no disruption to CCRT	likely to be poor
Overall Tx time	13 weeks	20 weeks

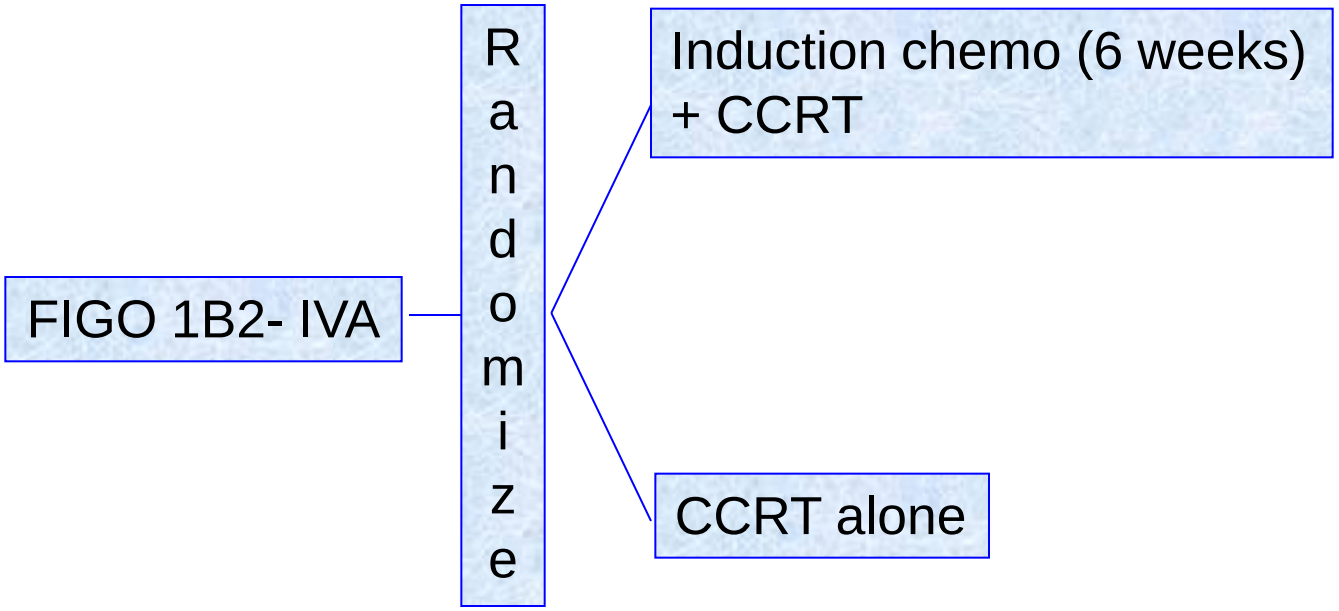
NACT : Neoadjuvant chemotherapy

NACT + CCRT in stage IB2 ~ IVA cervix cancer

- Wkly Paclitaxel (80mg/m^2) + Carboplatin (AUC2) x 6 Weeks
  followed by CCRT (cisplatin 40 mg/m^2) x Weeks 7-13
- 44 pts assessable for response
- CR/PR
  - Post NACT : 68% [95% CI 52-81%]
  - 12 Weeks post CCRT : 82% [95% CI 67-92%]
- Positive PALN 6 pts- 5 completed all treatment (4/5 NED)

NACT : Neoadjuvant chemotherapy
CCRT : Concurrent Chemoradiation

Upfront trial

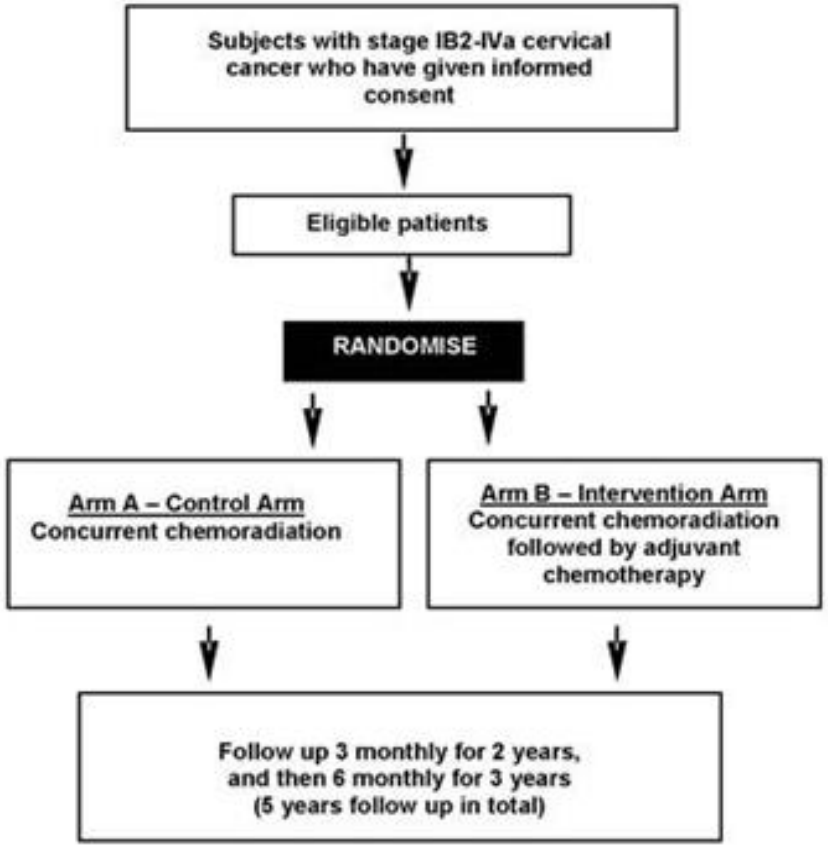


A randomized phase 3 trial in loco-regionally advanced cervix cancer

THE OUTBACK TRIAL

A Phase III trial of adjuvant chemotherapy following CCRT as primary treatment for LACC compared to CCRT alone

Study Schema



Primary CCRT in loco-regionally advanced cervical cancer

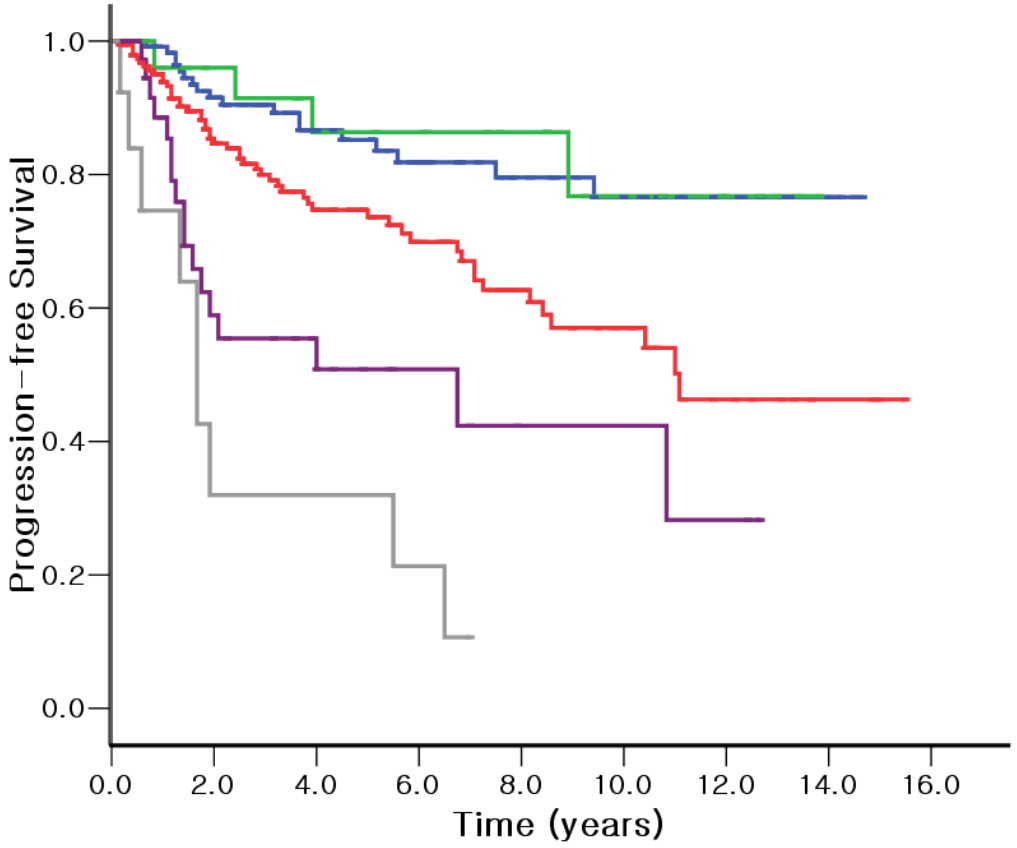
in Ajou University Hospital experience in16-year (1994.06-2010.05)

Ajou University Hospital data, unpublished

Clinico-pathological characteristics of 415 cervical cancer patients treated by primary CCRT

Mean age at diagnosis, yr	59 (26-87)	
Mean gravidity	5 (0-16)	
Mean parity	3 (0-12)	
Mean SCC Ag, ng/mL	3.9 (0.1-330)	
FIGO stage		
IB1	**102 (24.6)**	**154 (37.1)**
IB2	**24 (5.8)**	
IIA	**28 (6.7)**	
IIB	**204 (49.2)**	**254 (61.5)**
IIIA	**6 (1.4)**	
IIIB	**36 (8.7)**	
IVA	**9 (2.2)**	
IVB	6 (1.4)	
Histologic type		
Squamous cell carcinoma	386 (93.0)	
Adenocarcinoma	22 (5.3)	
Adenosquamous carcinoma	7 (1.7)	

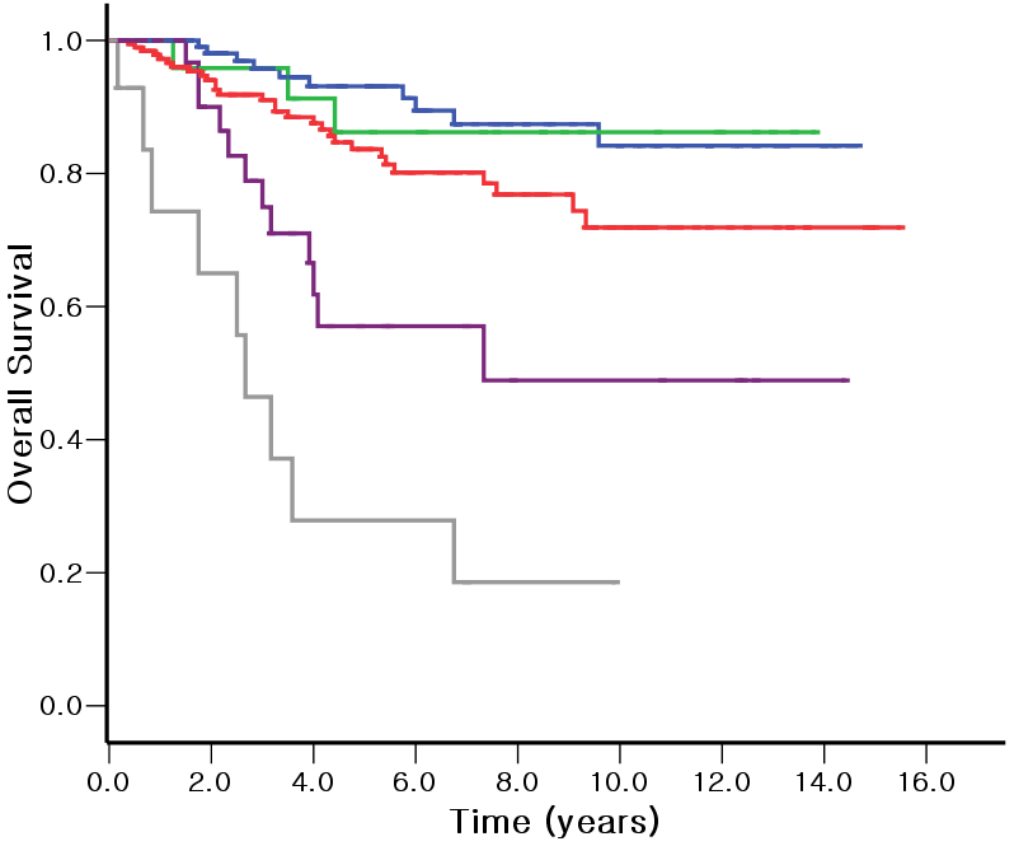
Progression-free survival according to the FIGO stage in 415 patients treated by primary CCRT



P =0.798 (IB vs. IIA)
P =0.003 (IB vs. IIB)
P <0.001 (IB vs. III)
P <0.001 (IB vs. IV)
P =0.045 (IIA vs. IIB)
P =0.002 (IIA vs. III)
P <0.001 (IIA vs. IV)
P =0.006 (IIB vs. III)
P <0.001 (IIB vs. IV)
P =0.055 (III vs. IV)

Ajou University Hospital data, unpublished

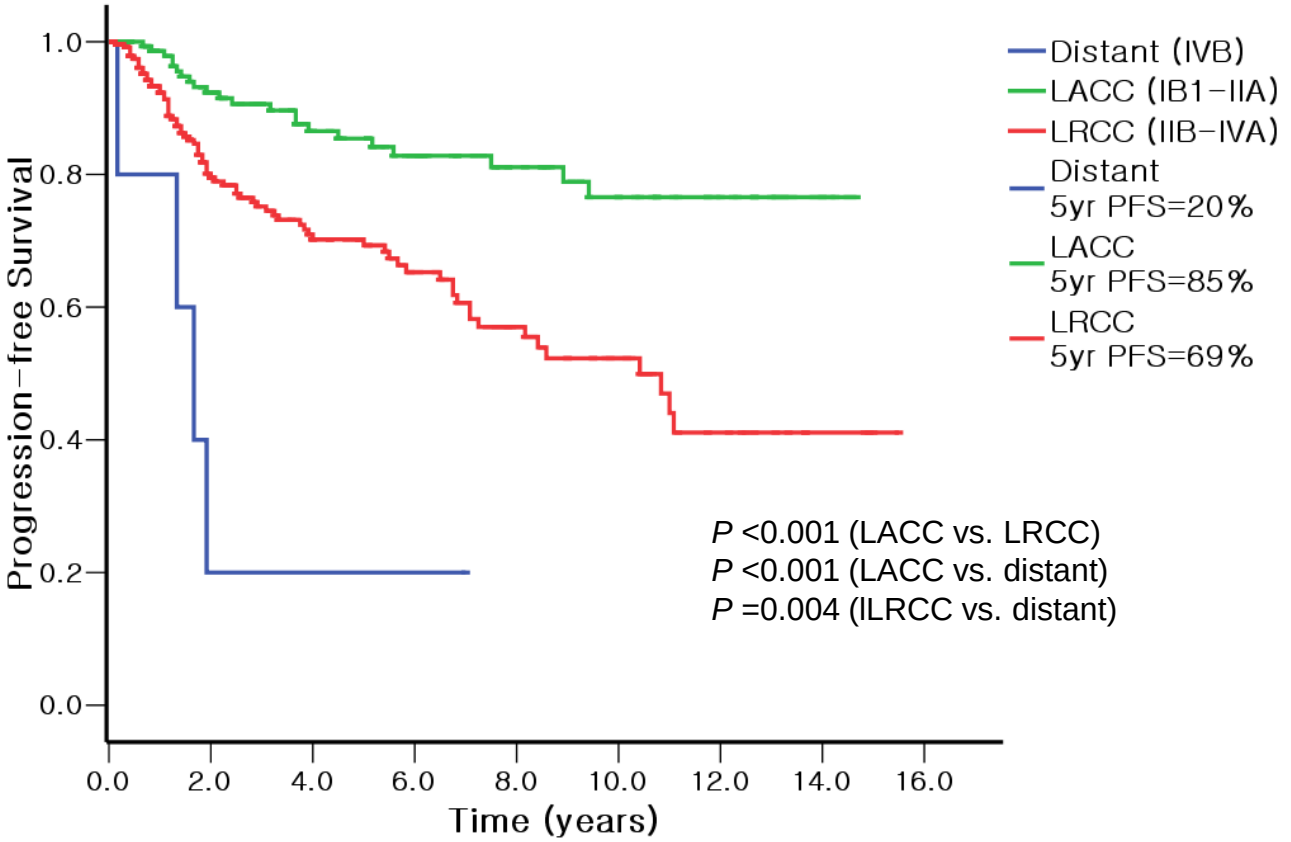
Overall survival according to the FIGO stage in 415 patients treated by primary CCRT.



P =0.831 (IB vs. IIA)
P =0.034 (IB vs. IIB)
P <0.001 (IB vs. III)
P <0.001 (IB vs. IV)
P =0.332 (IIA vs. IIB)
P =0.015 (IIA vs. III)
P <0.001 (IIA vs. IV)
P =0.007 (IIB vs. III)
P <0.001 (IIB vs. IV)
P =0.012 (III vs. IV)

Ajou University Hospital data, unpublished

Progression-free survival according to stage groups in 415 patients treated by primary CCRT

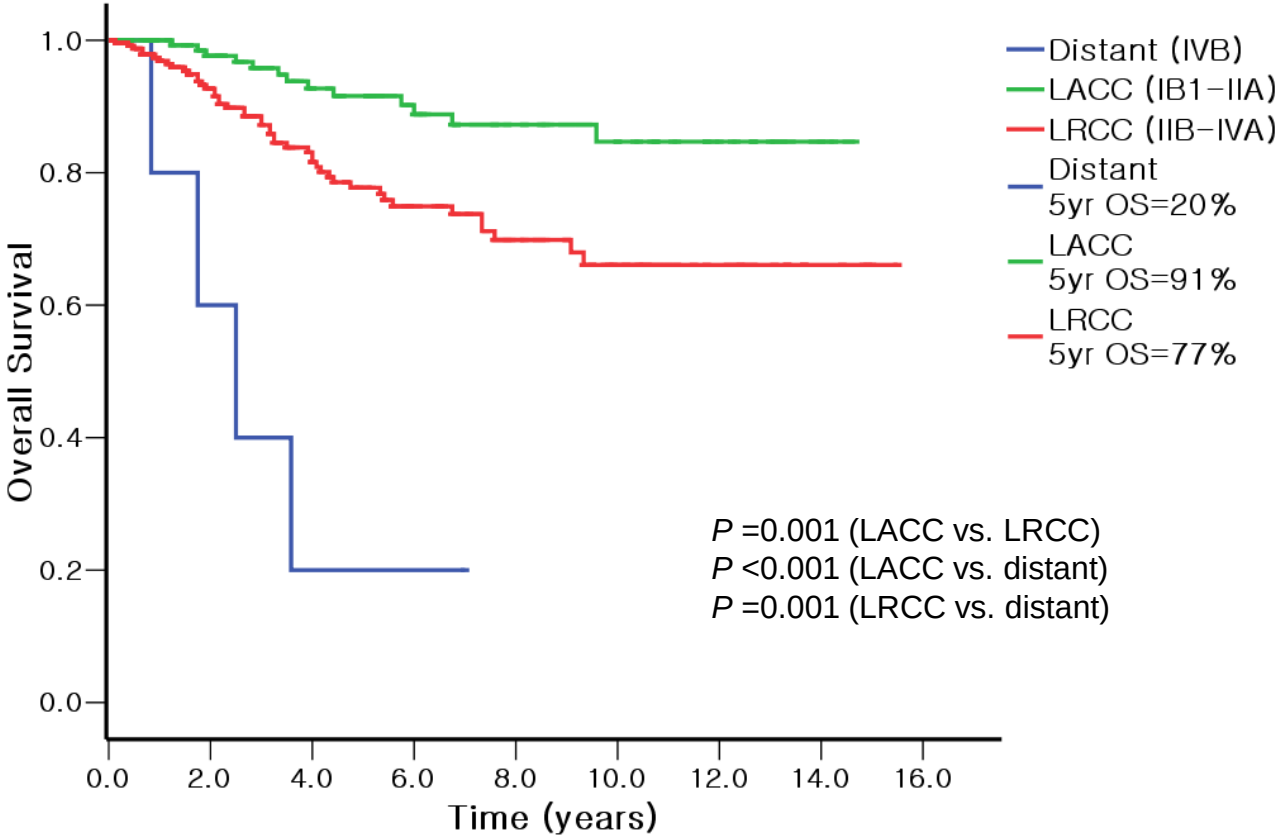


P <0.001 (LACC vs. LRCC)
P <0.001 (LACC vs. distant)
P =0.004 (ILRCC vs. distant)

LACC : Locally advanced cervix cancer
LRCC: Loco-regionally advanced cervix cancer

Ajou University Hospital data, unpublished

Overall survival according to stage groups in 415 patients treated by primary CCRT



P =0.001 (LACC vs. LRCC)
P <0.001 (LACC vs. distant)
P =0.001 (LRCC vs. distant)

LACC : Locally advanced cervix cancer
LRCC: Loco-reginally advanced cervix cancer

Concurrent Chemoradiotherapy for Loco-regionally Advanced Cervical Cancer

Pros

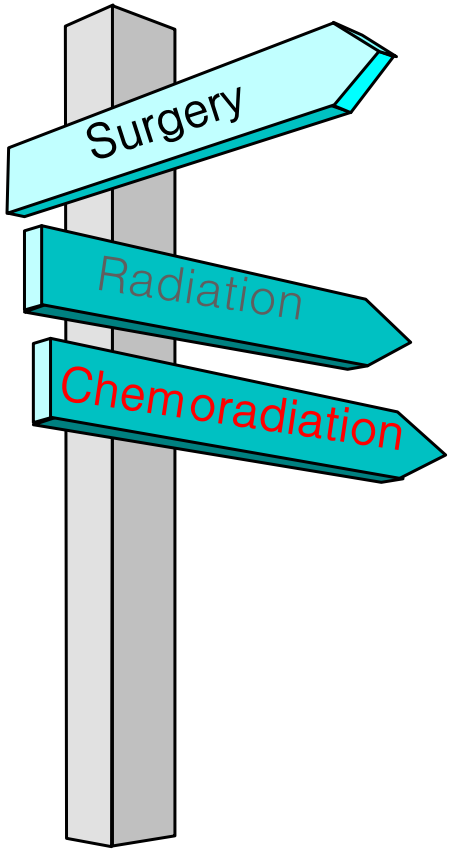
Improvement in survival

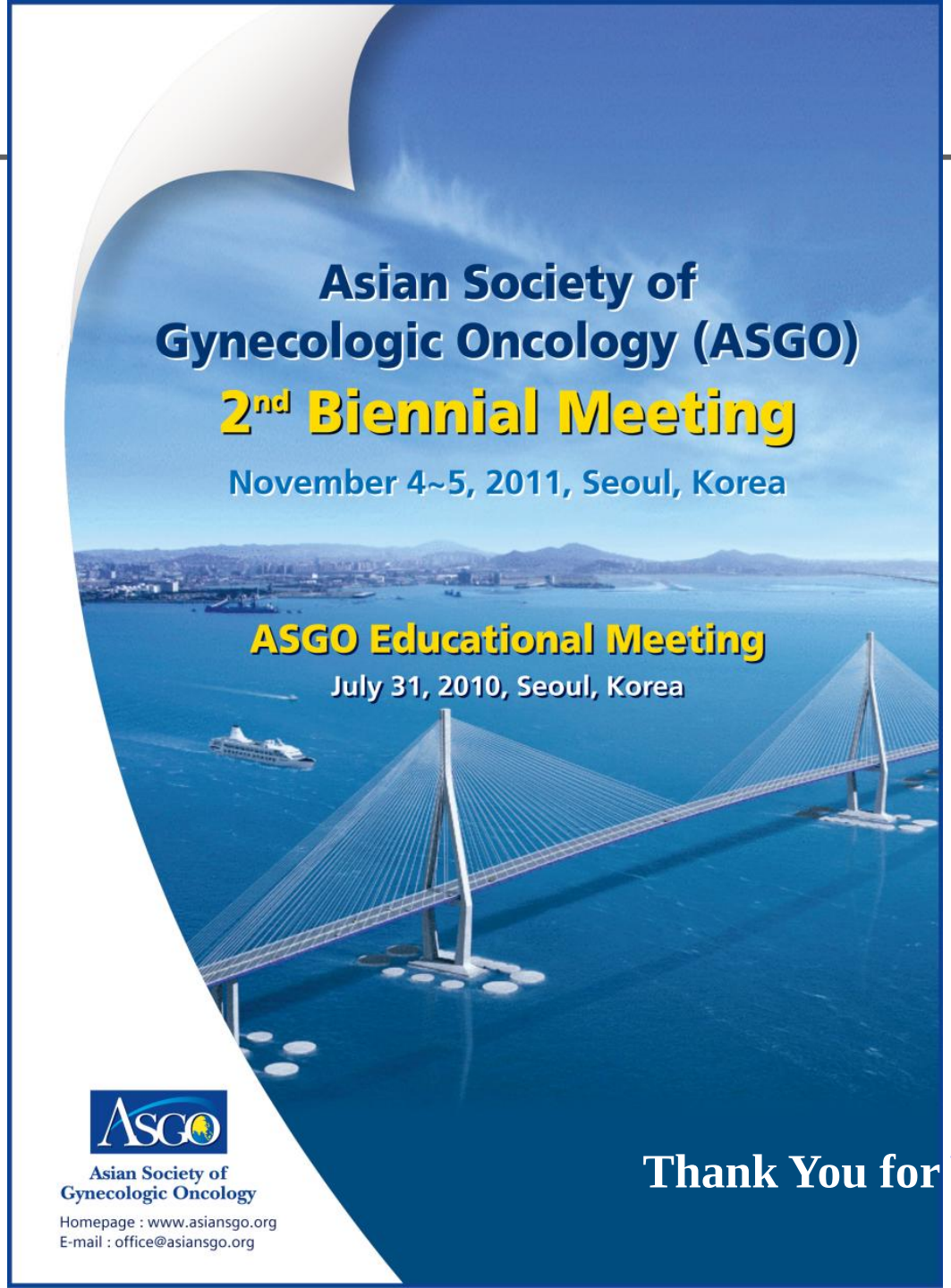
- Tumor volume reduction
- Radiosensitizer
- Sterilize micrometastasis

Cons

Increase in

- Morbidity
- Cost effectiveness





Thank You for Your Attention