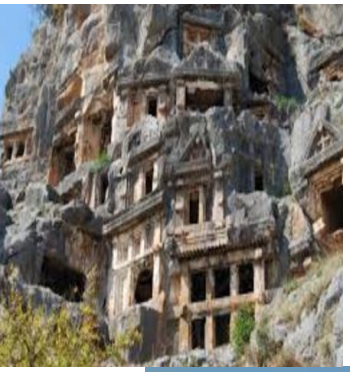
HACETTEPE UNIVERSITY

Adjuvant treatment in Cervical Cancer



FERAH YILDIZ
HACETTEPE UNI. FACULTY OF MEDICINE
DEPT OF RADIATION ONCOLOGY

Cervical Cancer

Stage Distribution and 5-year Relative Survival by Stage at Diagnosis for 1999-2006, All Races, Females

Stage at Diagnosis	Stage Distribution (%)	5-year Relative Survival (%)
Localized (confined to primary site)	49	91.2
Regional (spread to regional lymphnodes)	35	57.8
Distant (cancer has metastasized)	11	17.0
Unknown (unstaged)	5	58.1

Treatment

FIGOstage	Tretament
IA1	Conization±SLND/LND Trachelectomy+SLND/LND Histerectomy+SLND/LND
IA2, IB1, IIA	Rad. Trachelectomy+LND Rad. Histerectomy+LND Chemoradiotherapy
IB2-IVA	Chemoradiotherapy
IVB	Chemotherapy, palliative RT

IA2, IB1, IIA
Adjuvant treatment: To who?

- **Which patients show risk factors for LRR after radical surgery?**

GOG 49

GYNECOLOGIC ONCOLOGY **38,** 352–357 (1990)

Prospective Surgical–Pathological Study of Disease-Free Interval in Patients with Stage IB Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study

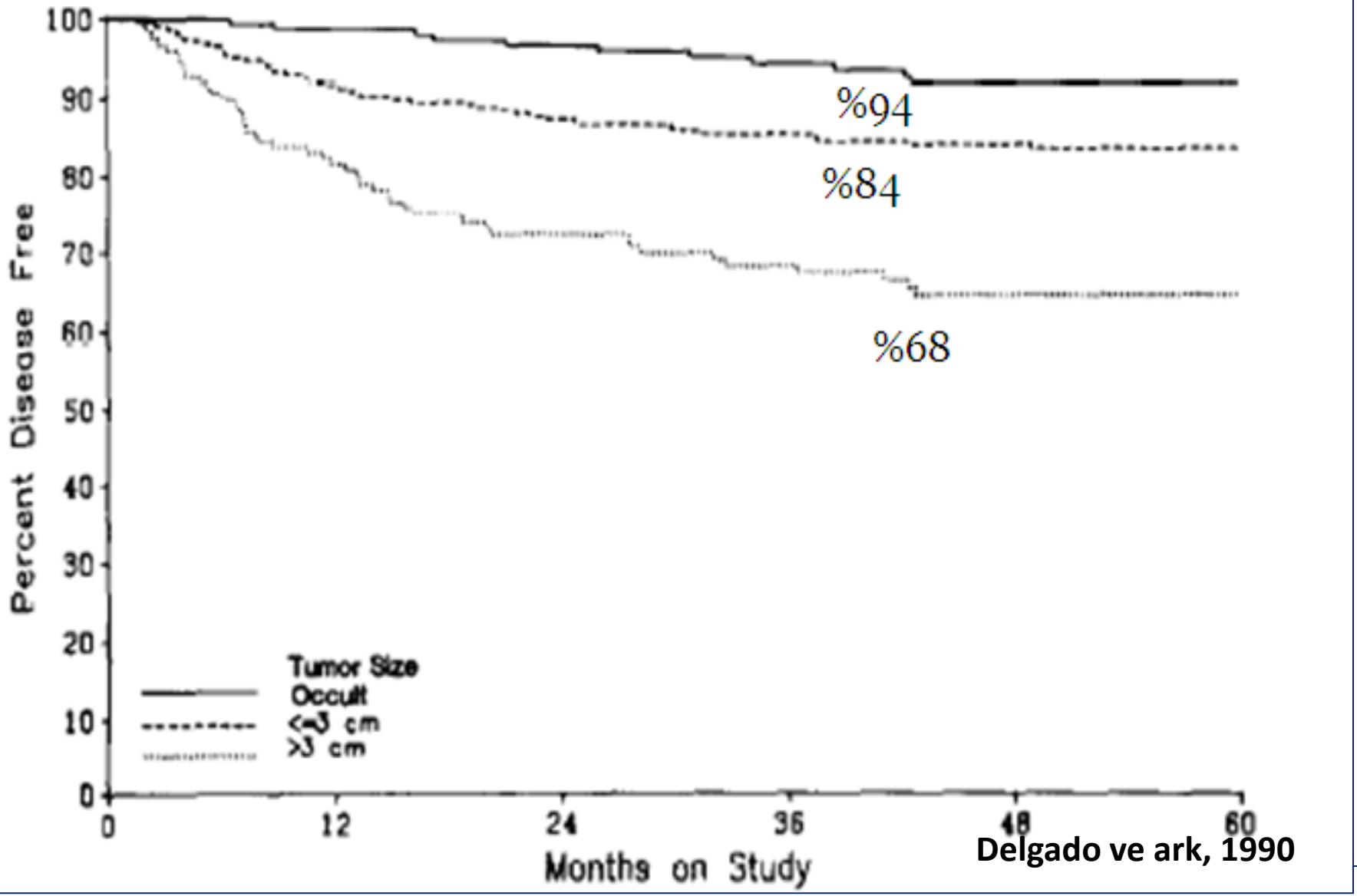
GREGORIO DELGADO, M.D.,[1] BRIAN BUNDY, PH.D.,[2] RICHARD ZAINO, M.D.,[3] BERND-UWE SEVIN, M.D.,[4] WILLIAM T. CREASMAN, M.D.,[5] AND FRANCIS MAJOR, M.D.[6]

[1]Department of Gynecologic Oncology, Georgetown University, Washington, DC 20007; [2]Gynecologic Oncology Group and Roswell Park Memorial Institute, Buffalo, New York 14263; [3]Department of Pathology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, Pennsylvania 17033; [4]Department of Obstetrics and Gynecology, University of Miami School of Medicine, Miami, Florida 33101; [5]Department of Obstetrics and Gynecology, Medical University of South Carolina, Charleston, South Carolina 29425; and [6]Department of Obstetrics and Gynecology, University of Colorado Health Sciences Center, and Gynecology Tumor Service, Denver General Hospital, Denver, Colorado 80205

Received January 22, 1990

732 pts EIB, SCC

3 yıl DFI %85.6



Delgado ve ark, 1990

Risk of Pelvic LN met

- **1125 pts, Stg IB**
- **RH+PPALND**

  Mic. pelvic LN met risk:

	p
• Stromal inv	0.0001
• PRM inv	0.0001
• LVSI	0.0001
• Grade	0.01
• Tm diameter	0.009

GOG trial, Delgado et al, 1989

Risk groups for adj RT after RH

High Risk	Intermediate Risk
• LN met	• LVSI
• PRM inv	• DSI
• Margin(+)	• Large tumor

GOG 49

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Cervical Cancer

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SEDLIS CRITERIA FOR EXTERNAL PELVIC RADIATION AFTER RADICAL HYSTERECTOMY IN NODE-NEGATIVE, MARGIN-NEGATIVE, PARAMETRIA-NEGATIVE CASES[1-4]

LVSI	Stromal Invasion	Tumor Size (cm) (determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or deep 1/3	≥4

LVSI: Lymphovascular space invasion

Stehman FB,
Gynecol Oncol 2000

Int risk pts: Do we really need adj RT

GOG 92: Postop XRT for Stage IB, intermediate risk

n = 277
FIGO IB cervical ca s/p rad hys & PLND with risk factors (see inset)

Years: 1988-1995

Exclusion criteria:
- +LN

RANDOMIZE

No further tx

Intermediate Risk

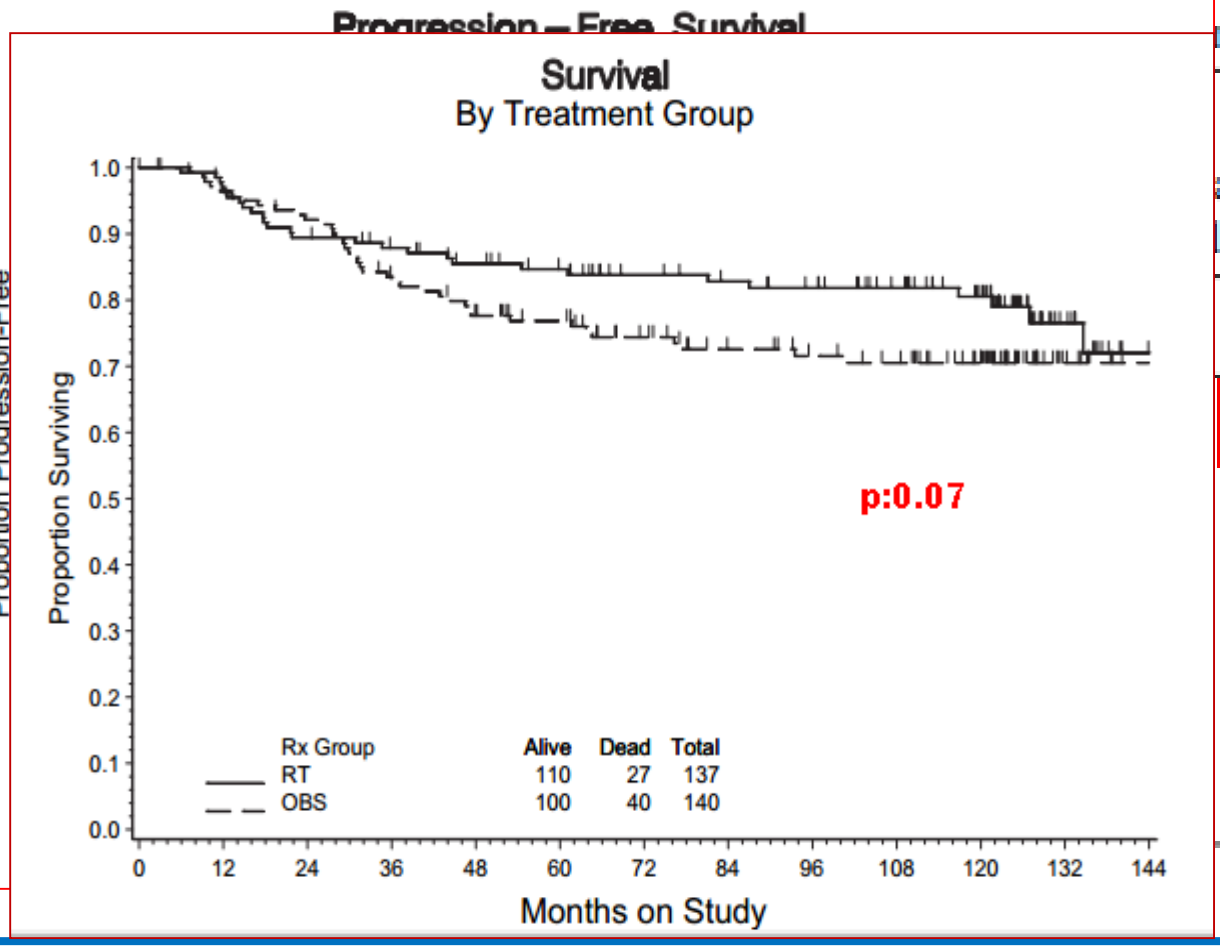
CLS	Stromal invasion	Tumor size
+CLS	Deep 1/3	Any
+CLS	Middle 1/3	≥2 cm
−CLS	Deep or middle 1/3	≥4 cm
+CLS	Superficial 1/3	≥5 cm

WPRT (46 Gy/23 fx or 50.8 Gy/28 fx)

- Primary outcome: Recurrence risk/recurrence-free interval
- Secondary outcomes: OS
- Median f/u: 5 years for surviving patients

Sedlis et al, *Gyn Onc* 1999
Rotman, et al. IJROBP 2006 May 1;65(1):169-76

GOG 92: 12y follow-up



Rotman et al, 2006

GOG 92

Recurrence by cell type and treatment regimen

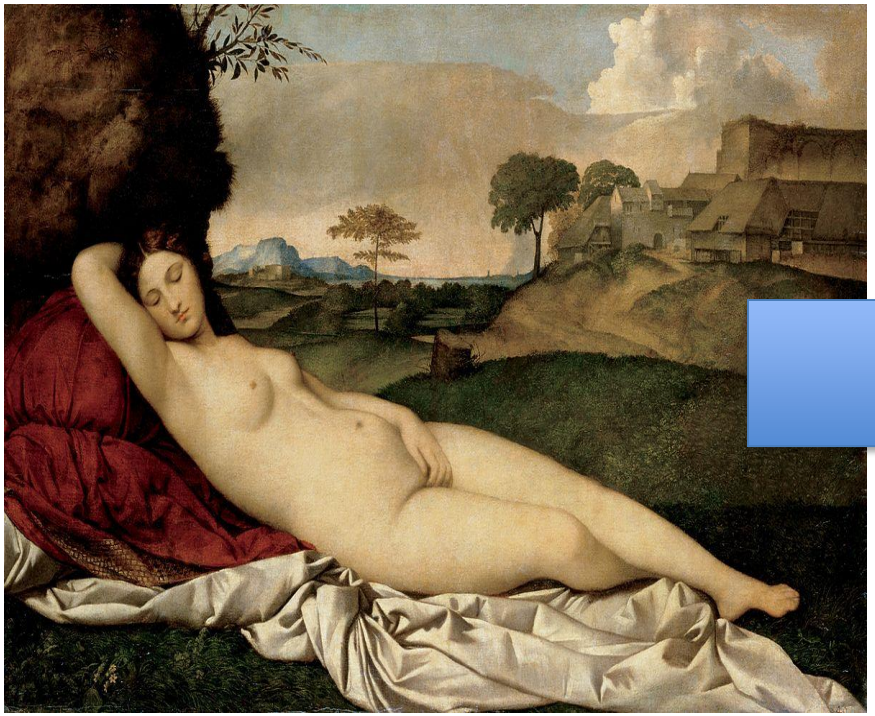
	Radiation therapy (n = 137)			Observation (n = 140)		
Cell type	NED	Recurred (%)	Total	NED	Recurred (%)	Total
Adenocarcinoma	16	0 (0)	16	7	4 (36.4)	11
Adenosquamous	15	3 (16.7)	18	7	7 (50.0)	14
Squamous	82	21 (20.4)	103	83	32 (27.8)	115

Rotman et al, 2006

GOG 92/LOE-1

- ***Adj EBRT in pts with intermediate risk:***
  - **significantly increases PFS**
  - **produces a trend for OS**
  - **This beneficial effect seems to be more pronounciated in AC and ASC**
  - **Produced higher grade 3-4 acute toxicity (6.6 %vs 2.1%)**

Rotman et al, 2006



Is it time to change the classical treatment policy?

Questions?

- **Pts with intermediate risk factors**
  - ***Do we really need adjuvant tx in the modern era***
  - ***Can we use concomittant CT***

Contemporary Series

- **Favors EPRT**

  SD in RFS with RT

  even better OS rates when ≥2 risk factors

  Ryu et al, 2011

  Tuipae et al,2012

  Pieterse et al, 2006

  Rushdan et al, 2004

- **NSD with RT**

  EPRT did not produce survival and local control benefit

  LRR after radical surgery ↓↓

  Cibula et al, 2018

  Nakamura et al, 2016

  Schorge et al, 1997

Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest
DOI: 10.1159/000501683

Received: March 6, 2019
Accepted after revision: June 22, 2019
Published online: July 25, 2019

Cervical Cancer with Intermediate Risk Factors: Is there a Role for Adjuvant Radiotherapy? A Systematic Review and a Meta-Analysis

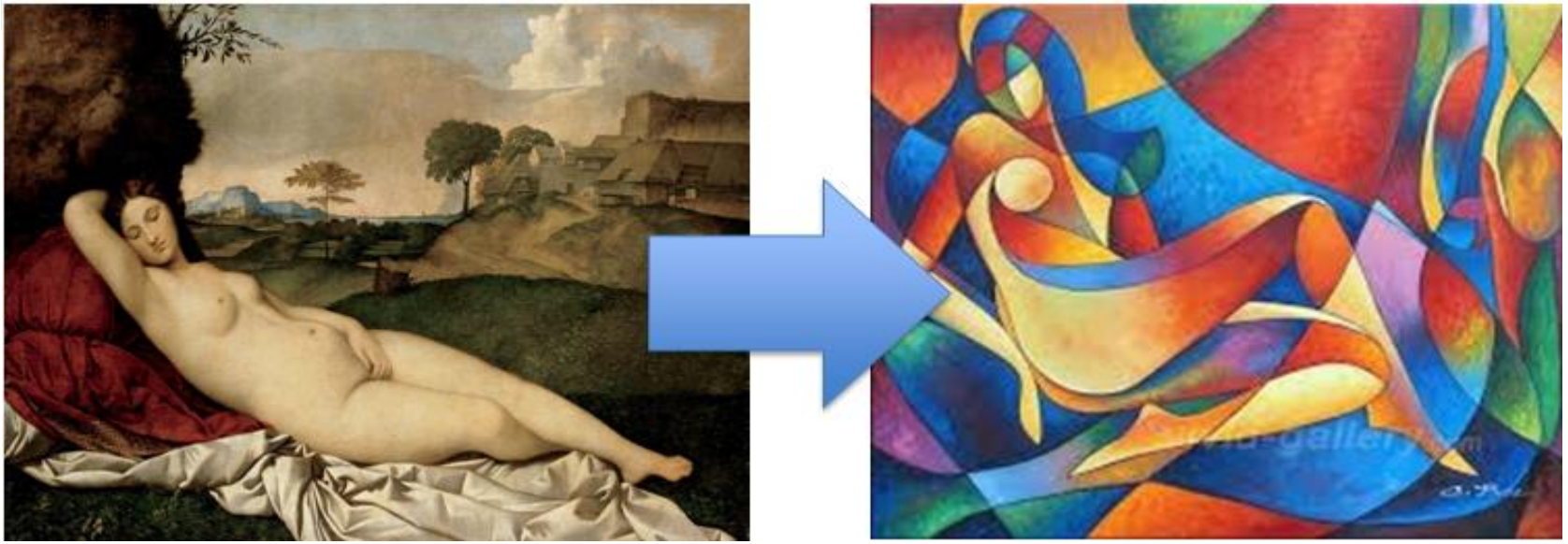
Lena Sagi-Dain[a] Sereen Abol-Fol[a] Ofer Lavie[a, b] Shlomi Sagi[c] Alon Ben Arie[d] Yakir Segev[a, b]

- **591 pts with IR**
- **RT is beneficial RR when ≥2 risk factors**

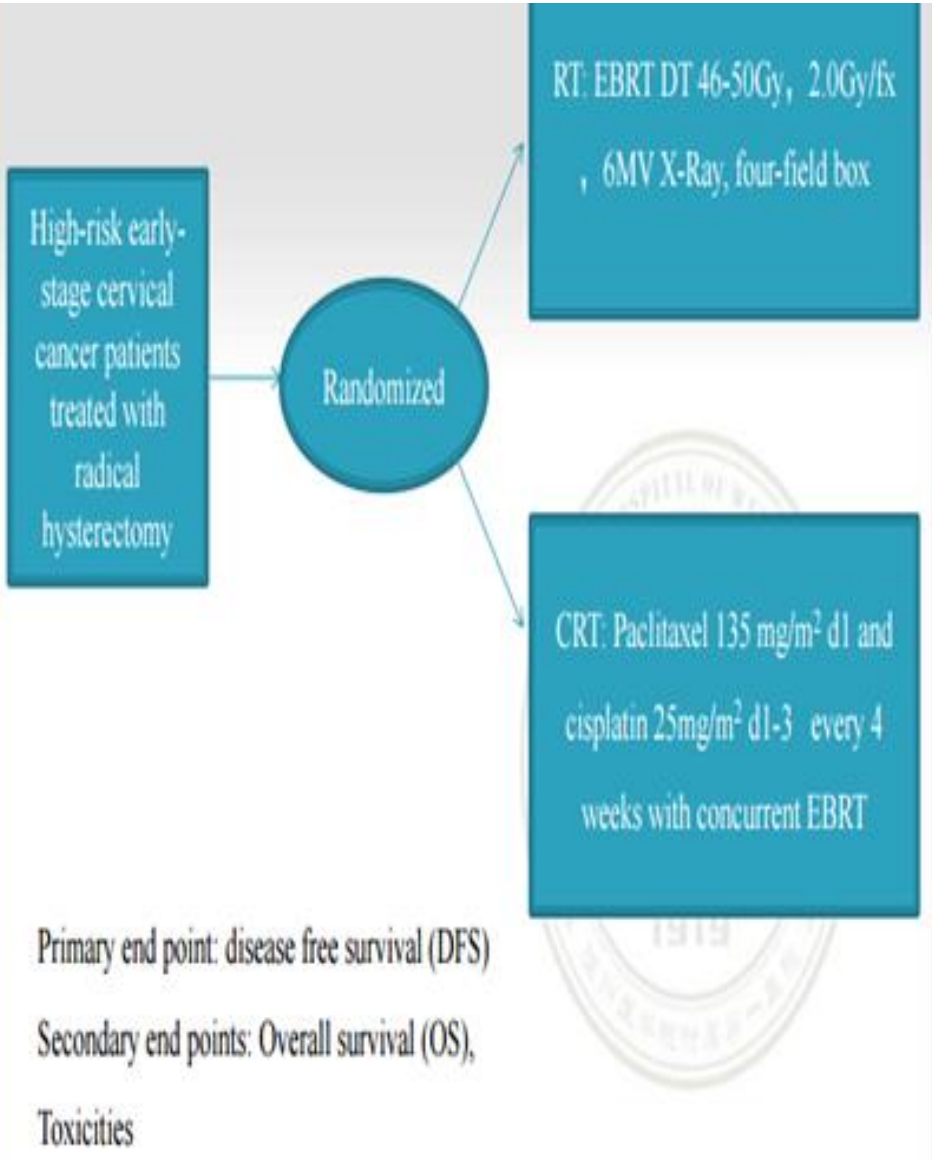
	HR with RT	p value
RR	0.46	0.001
OS	1.86	0.04

Questions?

- **Pts with ≥2 intermediaterisk factors**
  - ***Do we really need adjuvant tx in the modern era:***
    YES
  - ***–Can we use concomittant CT***

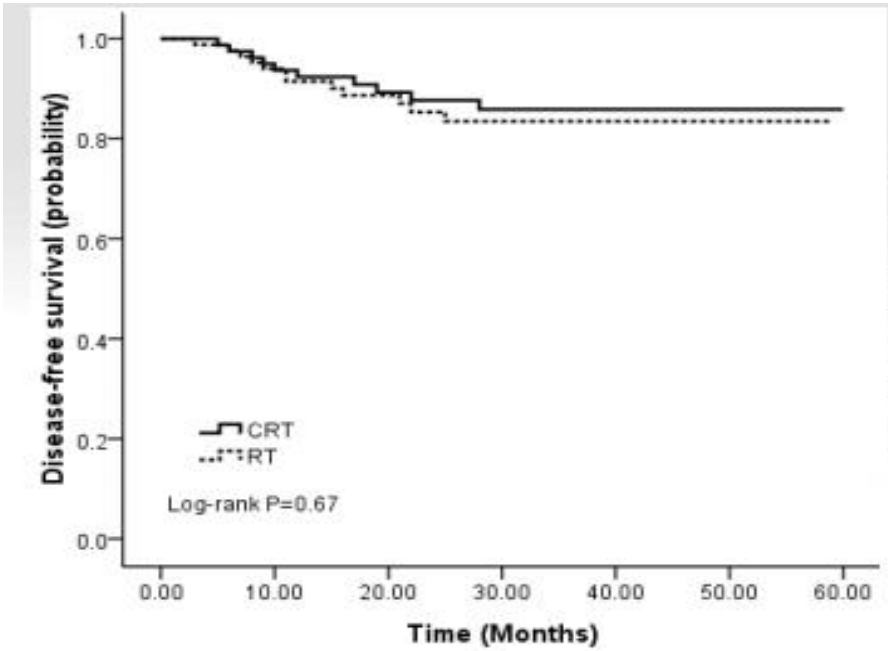


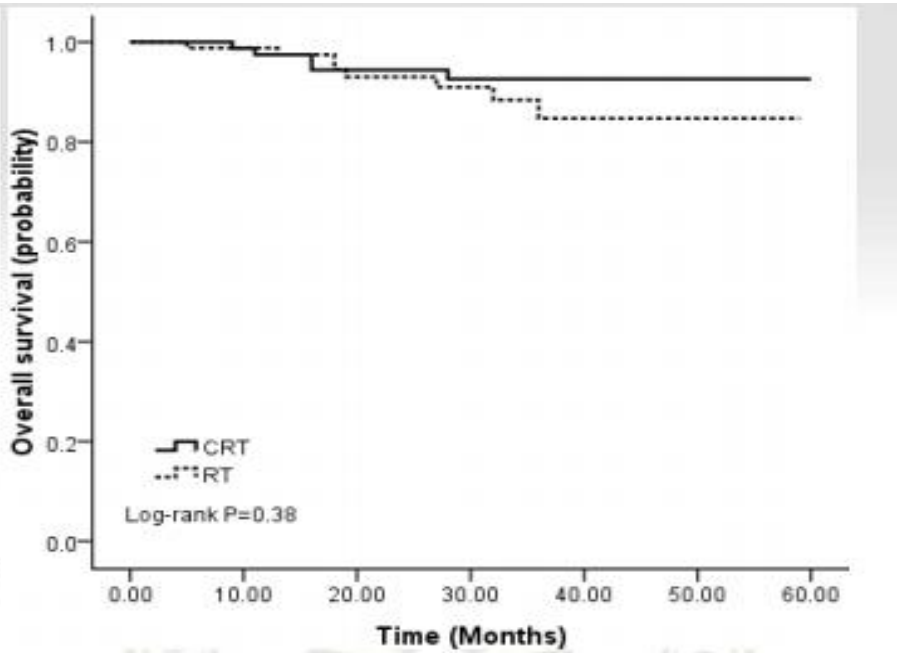
- 165 pts
- LN(-)
- 2 risk factors:
  - ≥1/3 Stromal inv
  - LVSI
  - >4 cm
  - Nerve inv
- 7-8% with non SCC histology



Chin X et al, ASTRO 2016
September 25-28, 2016. Boston Convention Center
Boston, Massachusetts

NSD in LRR, DM or recurrence pattern





Median follow-up time: 29 months.

5y-DFS: CRT 85.9% vs RT 83.5% , HR 0.84 (95% CI = 0.36–1.93, p = 0.67) , P=0.67

5y-OS: CRT 92.6% vs RT 88.4% , HR 0.61 (95% CI = 0.20–1.86, p = 0.38), P=0.38

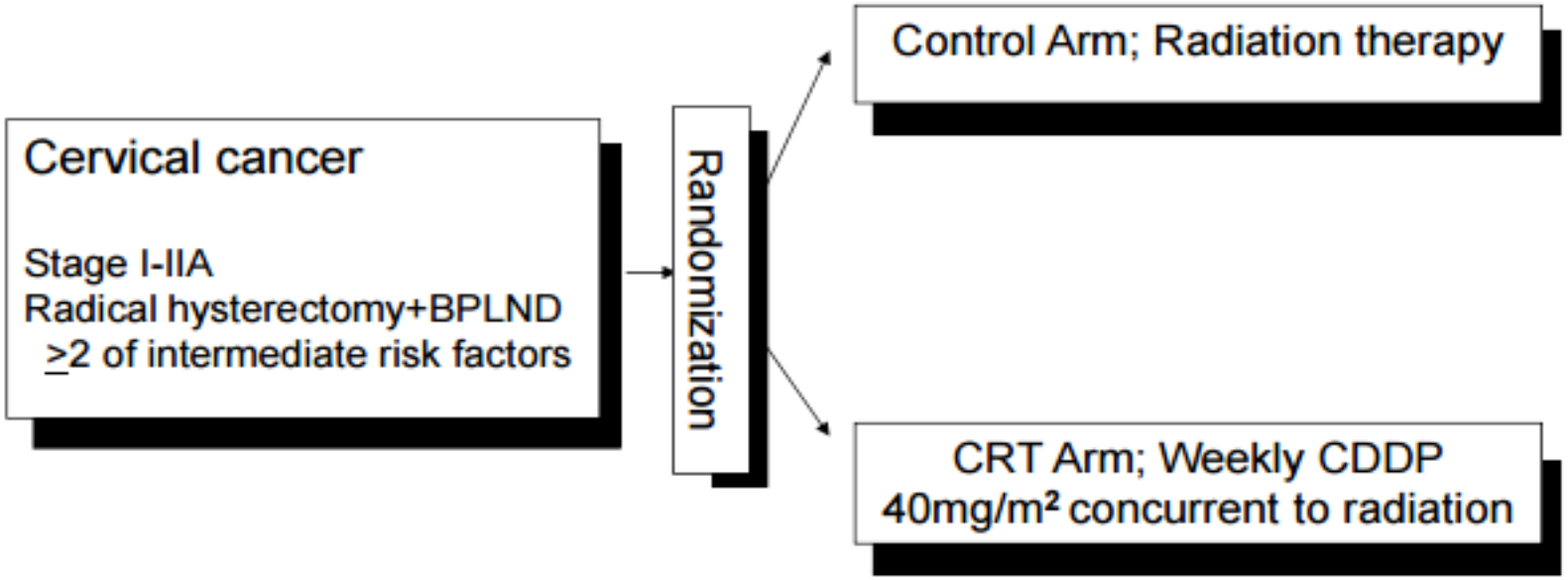
Chin X et al, ASTRO 2016
September 25-28, 2016. Boston Convention Center
Boston, Massachusetts

Ongoing Trial

GOG 263/KGOG 1008

PI; Sang Young Ryu, MD

Randomized Phase III Clinical Trial of Adjuvant Radiation vs Chemoradiation In Intermediate Risk, Stage I/IIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy



High Risk

- LN met
- PRM inv
- margin(+)

with only RH+LND

RR>%45

5y OS: %50-60

Recurrence Rate when pelvic LN met(+)

RH+LND

	pt number	recurrence ;(%)	pelvic rec(%)	DM (%)
Morrow, 1980	146	57 (39)	48 (33)	30 (21)
Fuller, 1982	39	15 (38)	13 (33)	5 (13)
Larson, 1987	10	5 (50)	2 (20)	3 (30)
Kinney, 1989	60	21 (35)	15 (25)	7 (12)
Berman, 1990	26	17 (65)	NA	NA
Remy, 1990	13	6 (46)	6 (46)	2 (15)
Stock, 1995	35	21 (59)	19 (55)	NA
Total	329	142 (43)	103 (34)*	47 (17)†

Radiotherapy and Oncology 114 (2015) 389–394

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Population benefit of RT

The population benefit of radiotherapy for cervical cancer: Local control and survival estimates for optimally utilized radiotherapy and chemoradiation

T.P. Hanna *, J. Shafiq, G.P. Delaney, M.B. Barton

Collaboration for Cancer Outcomes Research and Evaluation (CCORE), Ingham Institute, University of New South Wales, Liverpool, Australia

Cervical cancer overall survival and local control indication benefit (absolute).

Population of interest	Clinical attribute	Proportion of all cases	Indication type	Local control (SE)		2-year overall survival (SE)		5-year overall survival (SE)		Level of evidence** XRT/CRT	References XRT/CRT
				XRT	CRT	XRT	CRT	XRT	CRT		
Stage IB–IIA											
	Adjuvant RT: Nonbulky, Node Positive	.05	IA	33% (9.5)	13% (5.5)	13% (8.8)	9% (4.7)	12% (9.9)	14% (6.8)	III–2/II	[31]/[32,33]
	Adjuvant RT: Nonbulky, Node Negative, Positive Margins	.01	IA	0%	13% (5.5)	0%	9% (4.7)	0%	14% (6.8)	NA/II	NA/[32,33]
	Adjuvant RT: Nonbulky, Node Negative, High Risk of LF	.02	IA	13% (5.3)	0%	−3% (3.4)	0%	8% (4.9)	0%	II/NA	[34]/NA
	Radical RT for Recurrence: Vault	<.01	IC	52% (10.4)	0%	64% (8.6)	0%	53% (10.0)	0%	IV/NA	[35]/NA
	Radical RT for Recurrence: Sidewall involvement	<.01	IC	53% (8.5)	0%	46% (8.1)	0%	40% (8.4)	0%	IV/NA	[36]/NA
	Radical RT: bulky disease	.09	RC/IC	76% (3.4)	13% (4.2)	78% (2.7)	8% (2.1)	61% (3.2)	10% (2.6)	IV/I	[37,38]/[37–3
Stage IIB–IVA											
	Radical RT: Stage IIB	.12	IC	70%* (2.3)	7%* (1.5)	72% (1.4)	6% (2.1)	50% (1.6)	7% (2.4)	IV/I	[38,40–44]/[3
	Radical RT: Stage III–IVA	.23	IC	70%* (2.3)	7%* (1.5)	41% (1.5)	3% (3.3)	24% (1.3)	3% (3.3)	IV/I	[38,40–44]/[3

Concomittant CRT in high risk

- ***can enhance local and systemic control***
- ***radiosensitizing effect***
- ***different toxicity profile***

GOG 109, SWOG 8797, RTOG 9112: Postop RT vs. RT+CDDP/5-FU for high-risk

n = 243
FIGO IA_2 – IIA high-risk cervical cancer s/p hys & PLND
- +LN &/or
- +margin &/or
- +parametria

Years: 1991-1996

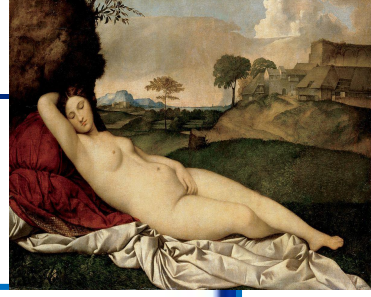
RANDOMIZE

WPRT
- 49.3 Gy/29 fractions (EBRT)
- 45 Gy to PA field (1.5 Gy/fx) if high common iliac LN+

WPRT + CDDP/5-FU (4 cycles)
- Bolus CDDP (70 mg/m²) & 5-FU (4000 mg/m² in 4 days) Q3 weeks
- Cycles 1 & 2 with XRT

- Primary outcomes: PFS, OS
- Secondary outcomes: Toxicity
- Median f/u: 3.5 years

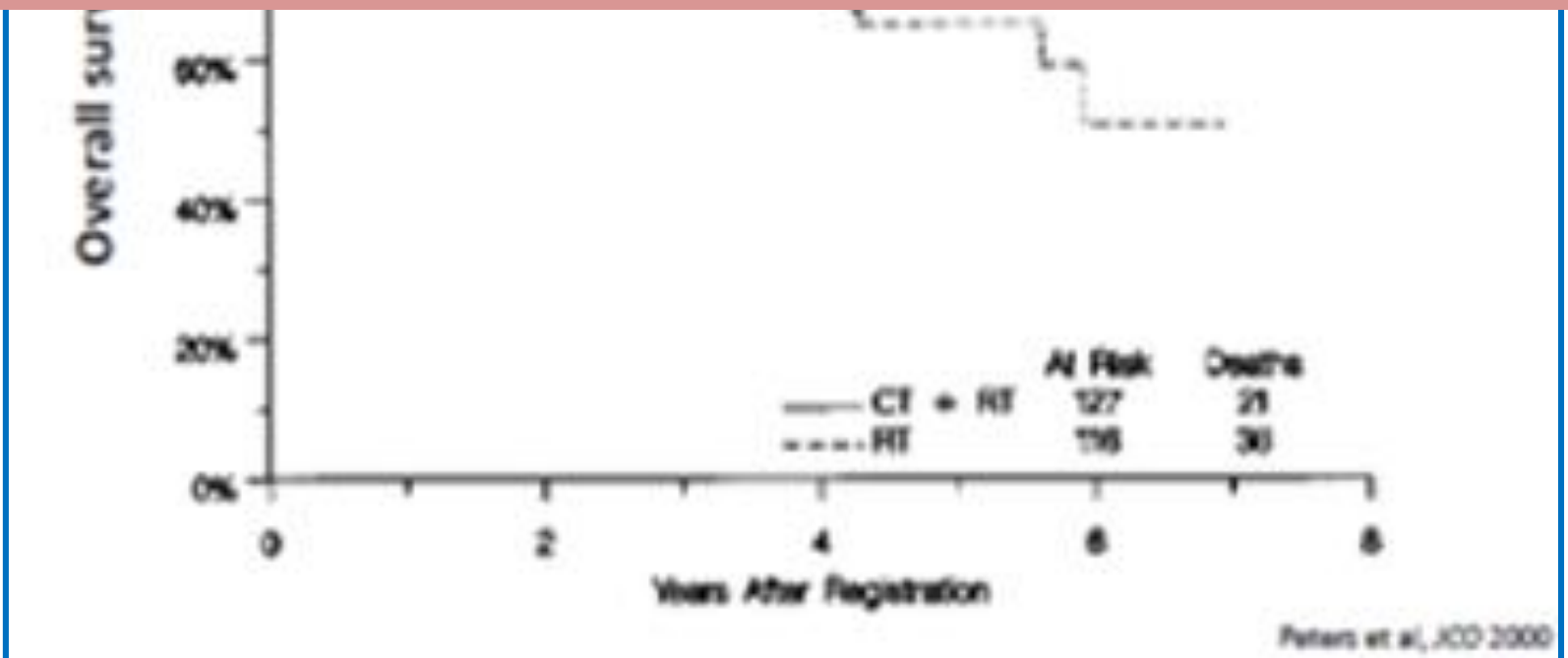
Peters et al, *JCO* 2000



PFS: %80 vs %63,
HR 2.01 , p: 0.003

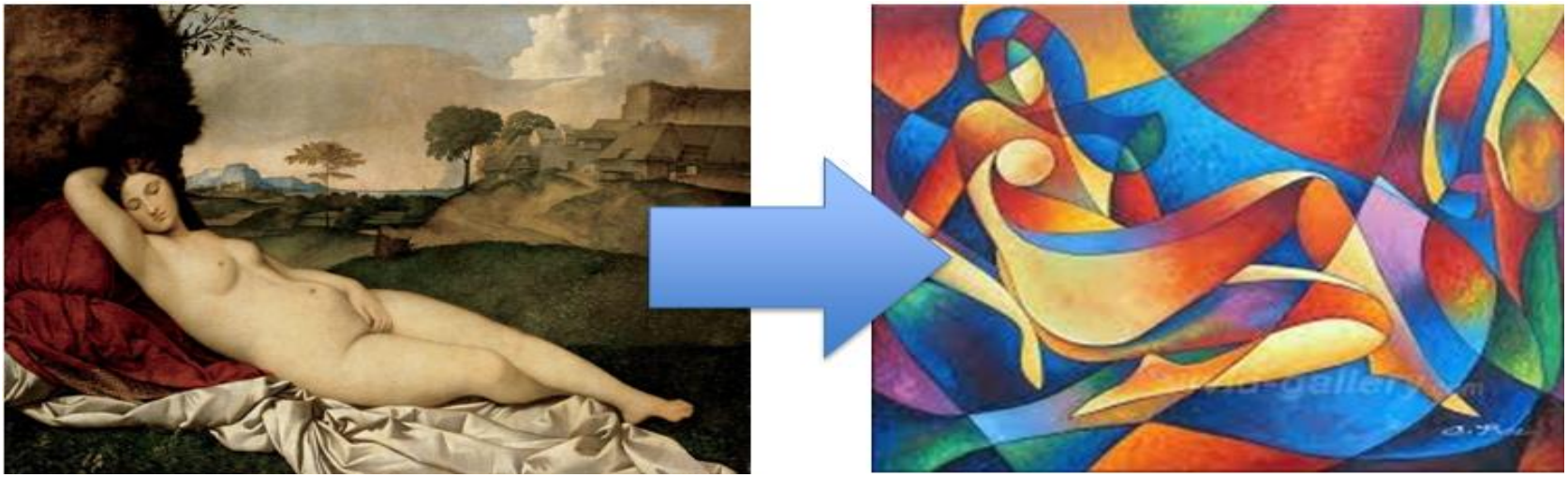
OS: %81 vs %71
HR: 1.96, p:0.007

LOE: CCRT is mandatory in pts with high risk criteria



Questions?

- **Pts with high risk factors**
  - **Do we have to give CCRT always?**
  - ***Can CT replace RT?***
  - ***Can BRT replace EBRT in pts with vaginal margin*(+) *only?***



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Gynecologic Oncology 96 (2005) 721–728

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical–pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial

	RT alone		RT + CT	
Age (years) [median (range)]	38 [20–64]		40 [19–74]	
Characteristic	No.[a]	%	No.[a]	%
Race				
White	62	53	70	55
Black	18	16	18	14
Hispanic	18	16	18	14
Other	6	5	2	2
Histology				
Squamous	95	82	98	77
Nonsquamous	21	18	29	23
Grade				
1	14	12	12	9
2	52	45	67	53
3	47	41	45	35
Size (cm)[b]				
Median (range)	2.1	[0.2–4.0]	2.2	[0.6–5.2]
Depth of invasion				
Inner 1/3	3	3	4	3
Middle 1/3	10	19	14	11
Outer 1/3	71	61	79	62
Margin status				
Negative	108	93	119	94
Positive	8	7	8	6
Parametrial extension				
Negative	69	60	77	61
Positive	47	40	50	39
Node status[c]				
Negative	19	16	17	13
1 Positive node	44	38	55	43
≥2 Positive nodes	53	46	56	44
Lymph vascular space				
Negative	32	28	35	28

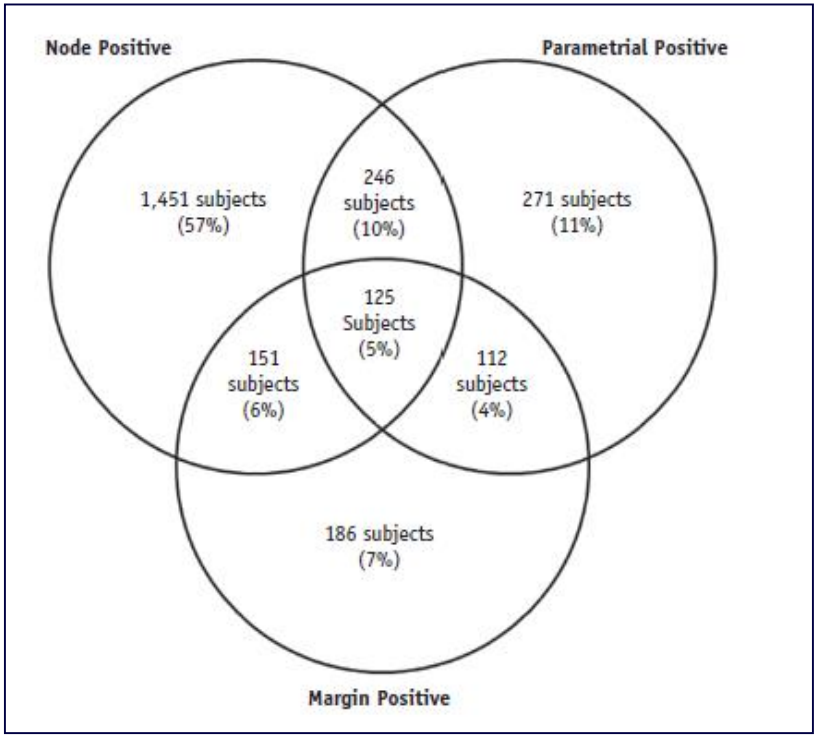
The majority of patients were with LN met.

Isolated smargin (+) or PRM inv: rare

Clinical Investigation

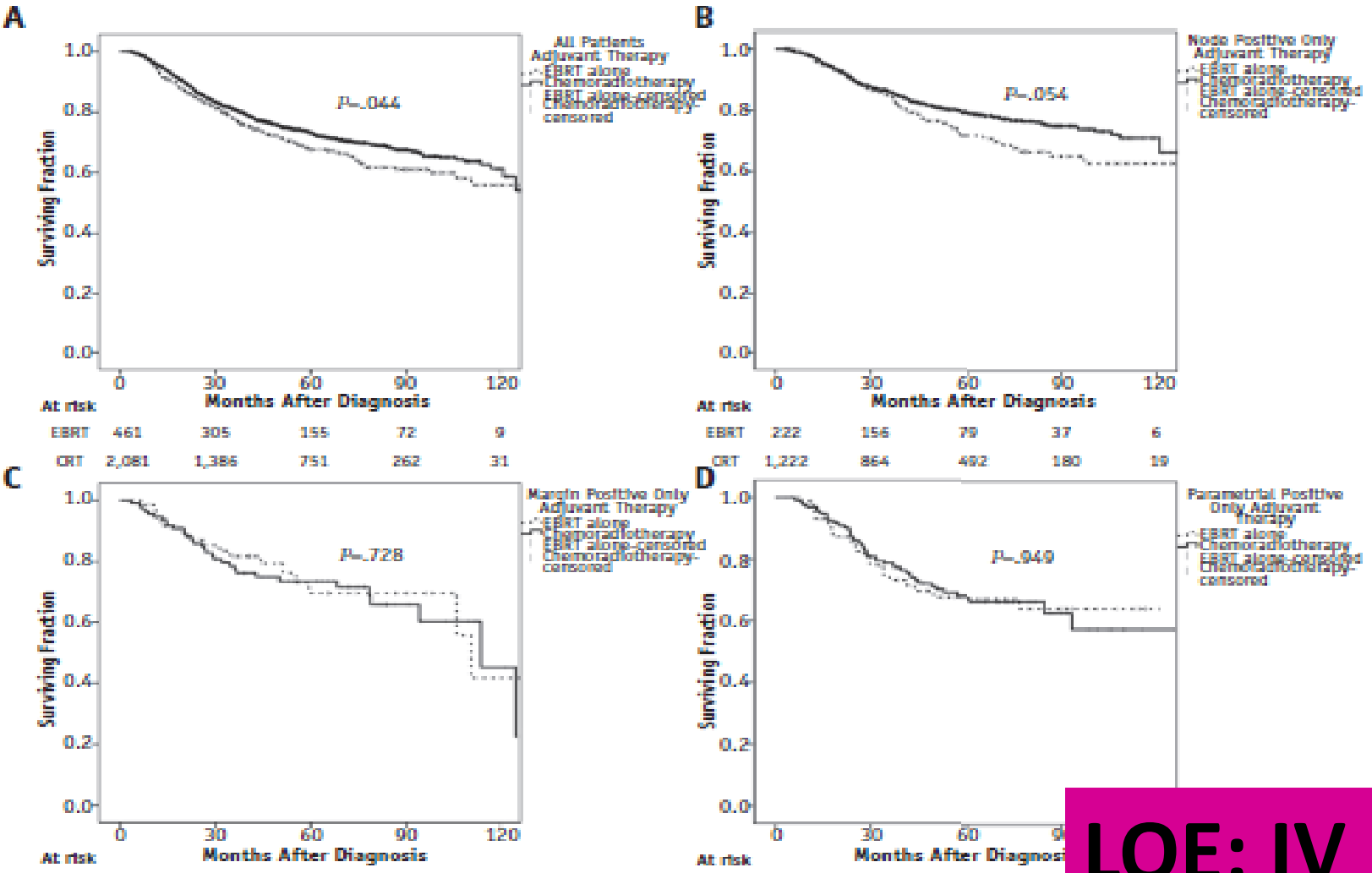
Postoperative Chemoradiation Therapy in High-Risk Cervical Cancer: Re-evaluating the Findings of Gynecologic Oncology Group Study 109 in a Large, Population-Based Cohort

- **USA,National Cancer Data Base**
- **2002-2012, 3053 pts**
- **High risk after RH**



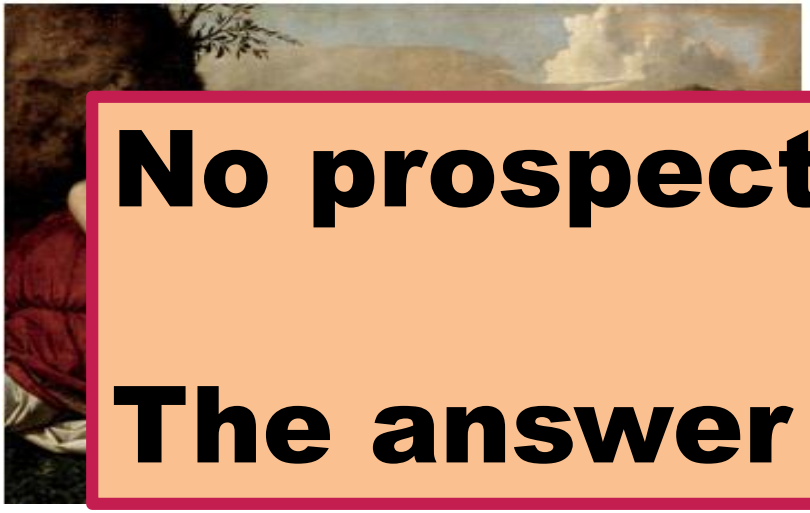
Trifiletti DM et al, Int J Radiat Oncol Biol Phys 2015

Postoperative Chemoradiation Therapy in High-Risk Cervical Cancer: Re-evaluating the Findings of Gynecologic Oncology Group Study 109 in a Large, Population-Based Cohort



LOE: IV

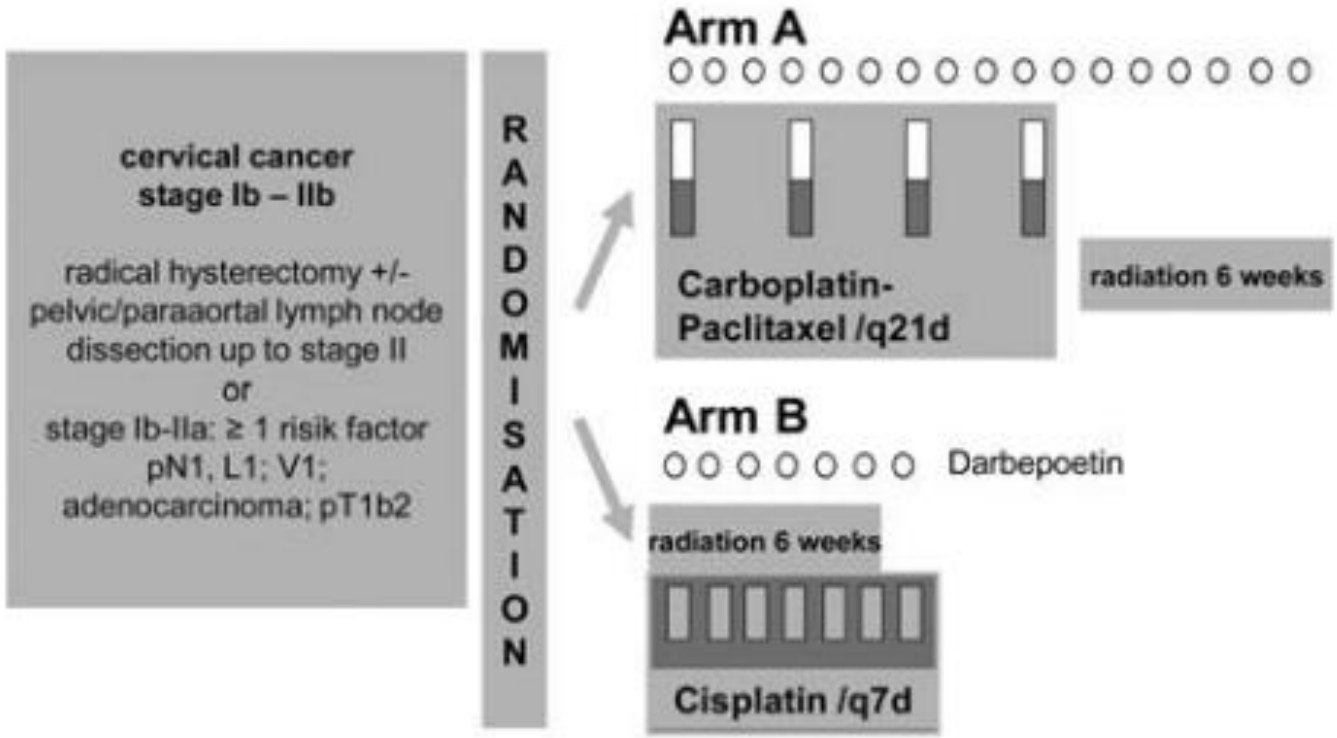
Are we ready to change our tx policy in pts with margin(+) or PRM inv only?



No prospective data.

The answer is NO

A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO Intergroup Study FREE



RT: 50.4 Gy/1.8 Gy EPRT

Sehouli J et al, Ann Oncol 2012;23: 2259-2264

A randomized phase III adjuvant study in high-risk cervical cancer: simultaneous radiochemotherapy with cisplatin (S-RC) versus systemic paclitaxel and carboplatin followed by percutaneous radiation (PC-R): a NOGGO-AGO Intergroup Study FREE

- **217 pts, RH+LND**

	4 CP-T EPRT	vs	EPRT+40 mg/m2CDDP	
2y OS	87%		82%	NSD
2y PFS	86%		79%	NSD

To

Conclusions: Sequential chemotherapy and radiation in high-risk CC could not show any significant survival benefit; however, a different toxicity profile appeared. This sequential regime may constitute an alternative option when contraindications for immediate postoperative radiation are present.

Sehouli J et al, Ann Oncol 2012;23: 2259-2264

SGO Annual Meeting on Women's Cancer

NEW ORLEANS

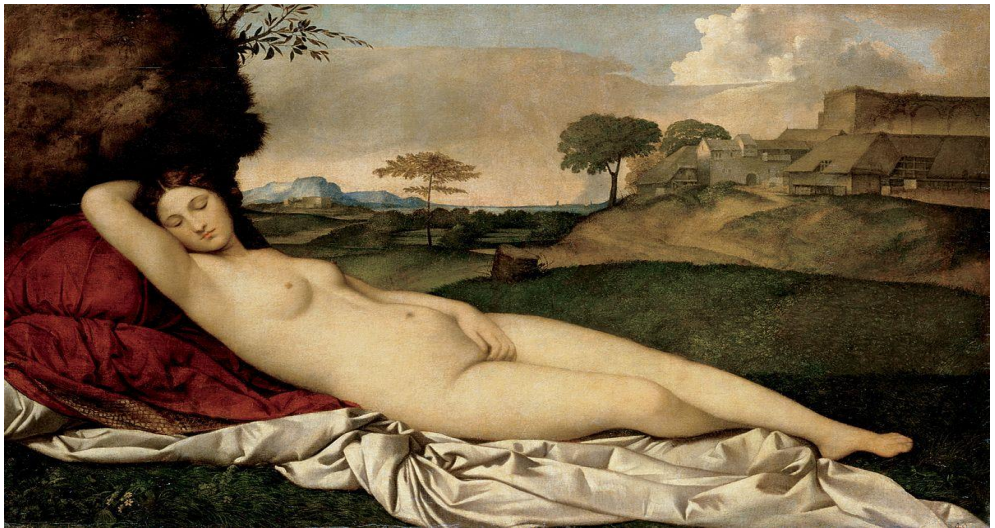
March 24 – 27, 2018

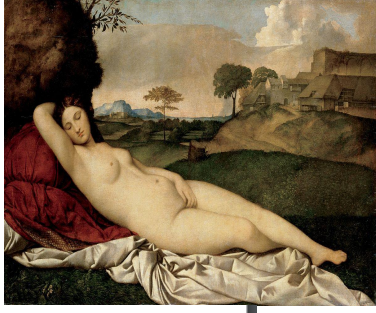
59: Randomized trial of adjuvant chemotherapy versus concurrent chemoradiotherapy in early-stage cervical cancer after radical surgery: A Chinese Gynecologic Oncology Group study (CSEM-002)

- **324 pts, SCC with 1 risk factor:**
- **Lnmet,PRM inv, gr 2-3, DSI, LVSI, T>4 cm**
- ***3-6 course Paclitaxel-CDDP vs CCRT***
- **2y PFS, OS: similar**
- **Trend for ↑ DM in CCRT arm**

Are we ready to change our policy in HR patients in the adjuvant setting?

- ***Definitively No***
  - **CCRT and 2 courses of adjuvant CT …YES in pts with high risk criteria according to Intergroup trial**
  - **CT instead of CCRT in high risk…..still needs time**





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Cervical Cancer

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SURGICAL FINDINGS → **ADJUVANT TREATMENT**

Negative nodes, negative margins, negative parametrium →
- Observe
  or
- Pelvic EBRT[n] if combination of risk factors (ie, primary tumor size, stromal invasion, and/or LVSI that meet Sedlis criteria[t] [category 1])
  ± concurrent platinum-containing chemotherapy[q]
  (category 2B for chemotherapy)

→ See Surveillance (CERV-10)

Positive pelvic nodes and/or Positive surgical margin and/or Positive parametrium →
- EBRT[n] + concurrent platinum-containing chemotherapy[q] (category 1)
  ± vaginal brachytherapy[n]

Para-aortic lymph node positive by surgical staging → **Imaging workup for metastatic disease[c]**
- Negative for distant metastasis → Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] ± brachytherapy[n]
- Positive for distant metastasis → Biopsy suspicious areas as indicated
  - Negative → Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] ± brachytherapy[n]
  - Positive → Systemic therapy[u] ± individualized EBRT[n]

[c]See Principles of Imaging (CERV-B)

Annals of Oncology 28 (Supplement 4): iv72–iv83, 2017
doi:10.1093/annonc/mdx220

CLINICAL PRACTICE GUIDELINES

Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

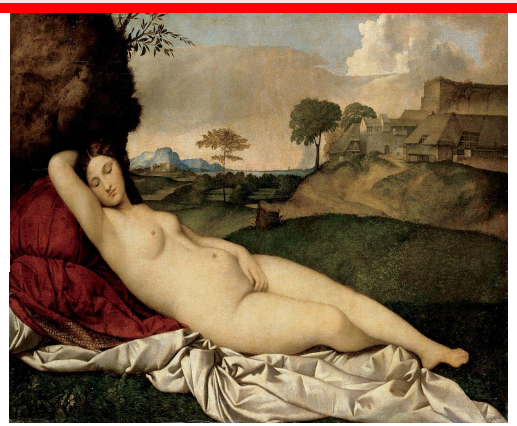
[I, A].

djuvant treatment

Women with intermediate- and high-risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy (see Table 3).

Cervical cancer patients with intermediate-risk disease do not need further adjuvant therapy [II, B], whereas adjuvant CRT is recommended in high-risk patients [I, A].

recurrence rate alone but, when combined, the risk of recurrence is increased to 15%–20%, similar to that of high-risk factors.



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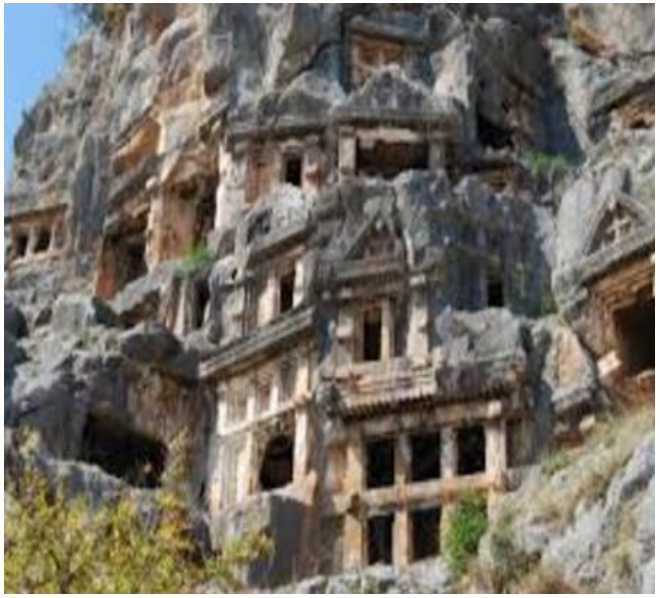
Special Issue: FIGO Cancer Report 2018
Pages: i-iv, 1-158
October 2018

Cancer of the cervix uteri

tive pelvic nodes, parametrial infiltration, positive margins, deep stromal invasion, etc. According to various prognostic factors, patients may be categorized into high-risk, intermediate-risk, or low-risk disease. High-risk disease includes patients with either positive surgical margins or lymph node metastases or parametrial spread, and such patients should be offered PORT with chemotherapy since the GOG 109 trial has shown overall survival advantage.[67] Intermediate-risk patients with any two of three factors (tumor size more than 4 cm, lymphovascular invasion, deep stromal invasion) require PORT[64,81] and no chemotherapy should be offered to these patients. All other patients following radical hysterectomy are termed as low-risk disease patients and do not need any adjuvant therapy.



Thank You.....