4TH ESO-ESMO LATIN-AMERICAN MASTERCLASS IN CLINICAL ONCOLOGY

18-22 April 2018
Mexico City, Mexico

Chairs:
A. Cervantes, ES - N. Pavlidis, GR
R.A. Stahel, CH

Scientific Co-ordinators:
M. Aapro, CH - F. Cardoso, PT

Under the auspices of

CMO Consejo Mexicano de Oncología

SMeO Sociedad Mexicana de Oncología, A.C.

LATIN-AMERICA PROGRAMME

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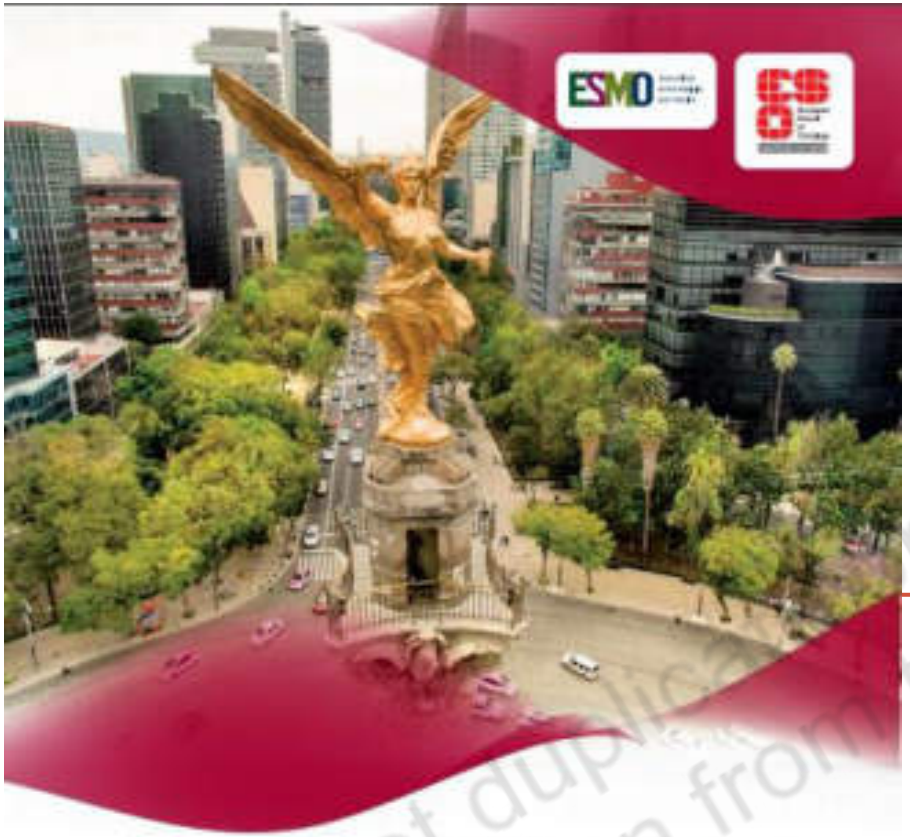

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CERVICAL CANCER SYSTEMIC TREATMENT

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Conflict of interest disclosure

- No interest conflicts for this presentation

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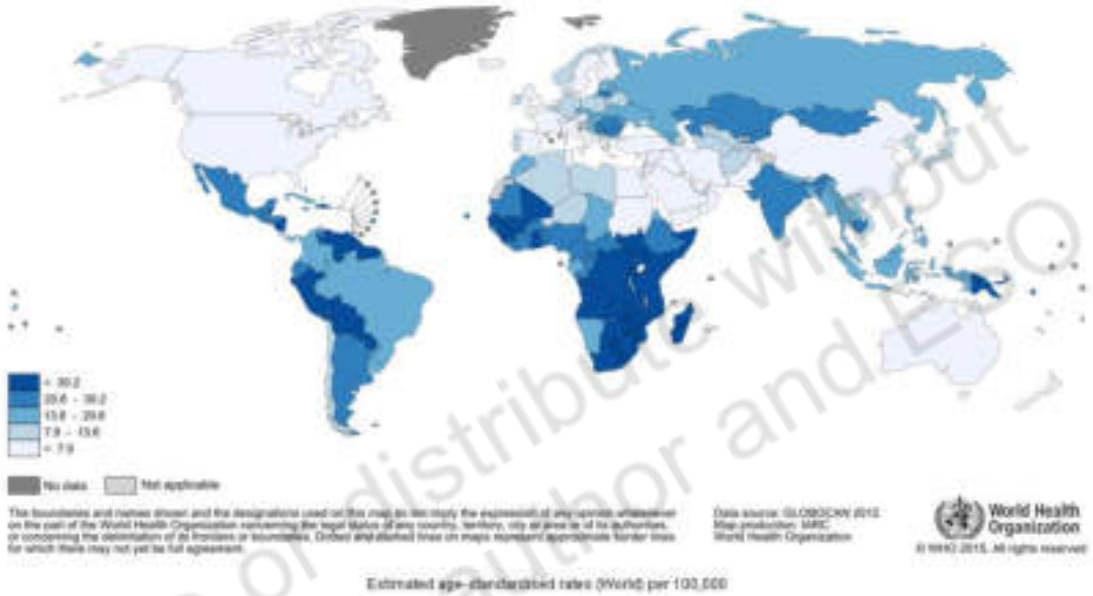
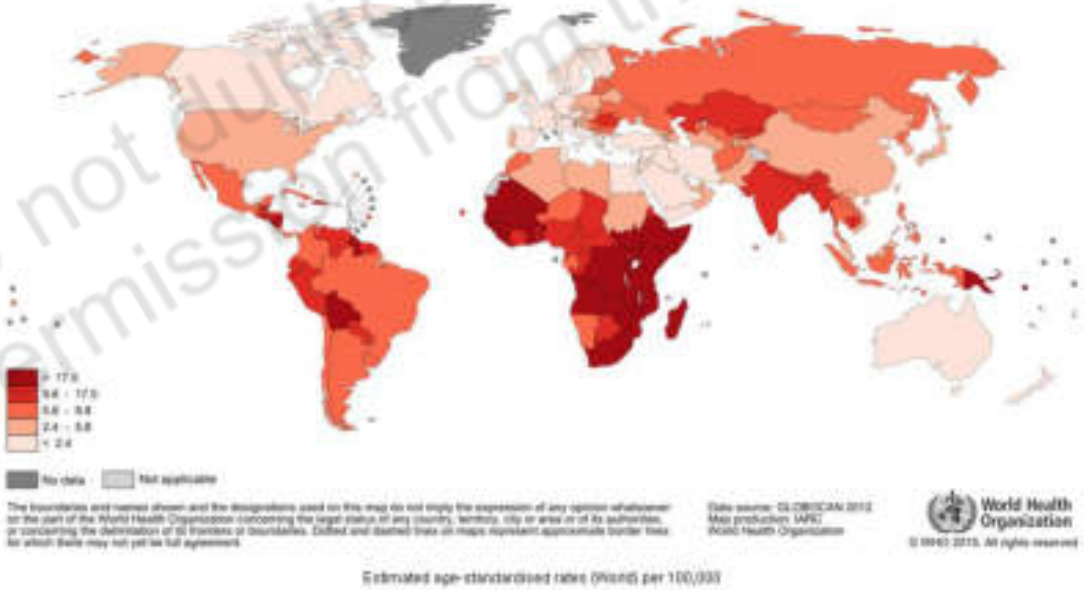
Estimated Cervical Cancer Incidence Worldwide in 2012



Estimated Cervical Cancer Mortality Worldwide in 2012



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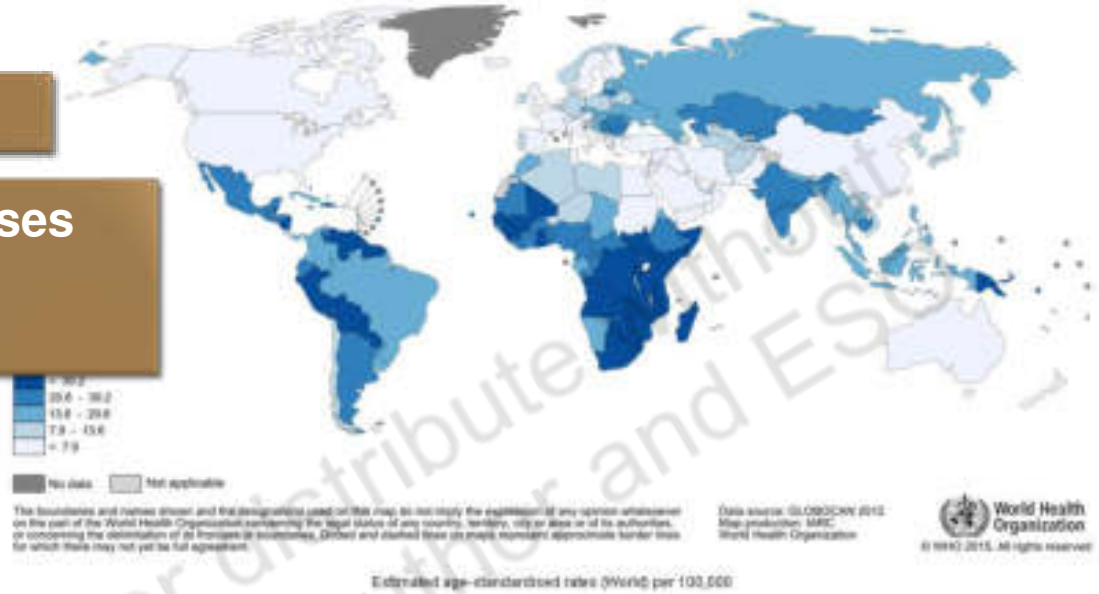
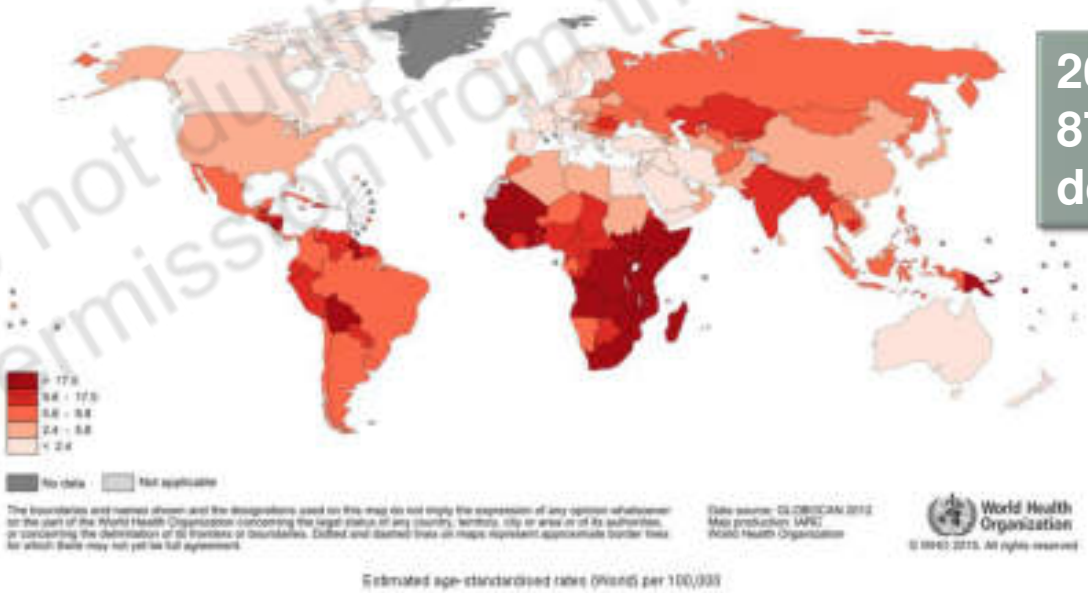
▲ Estimated Cervical Cancer Incidence Worldwide in 2012

528,000 new CC cases in 2012

LATAM: 1.1x10^6 new cancer cases
560,000 female
12% cervical cancer



▲ Estimated Cervical Cancer Mortality Worldwide in 2012



266,000 CC deaths
87% in the less developed regions

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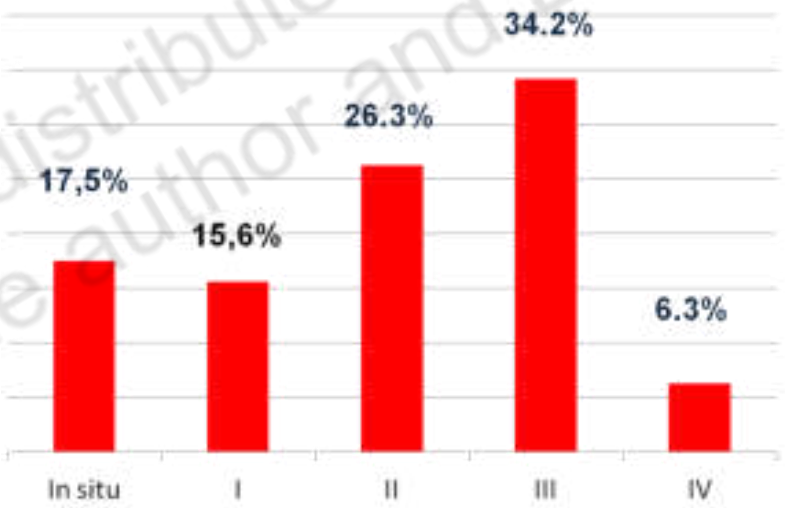
Cervical Cancer Profile In Brazil

- 600,000 new cancer cases 2016, 7.9% cervical cancer[1]
- Young age, median 49 yo[2]
- Public health system (SUS) [2]
- Poor education – 1 to 8 years of school[2]
- 52% marriage[3]
- 76.8% diagnosis in advanced stages[3]



2009-2013[1]

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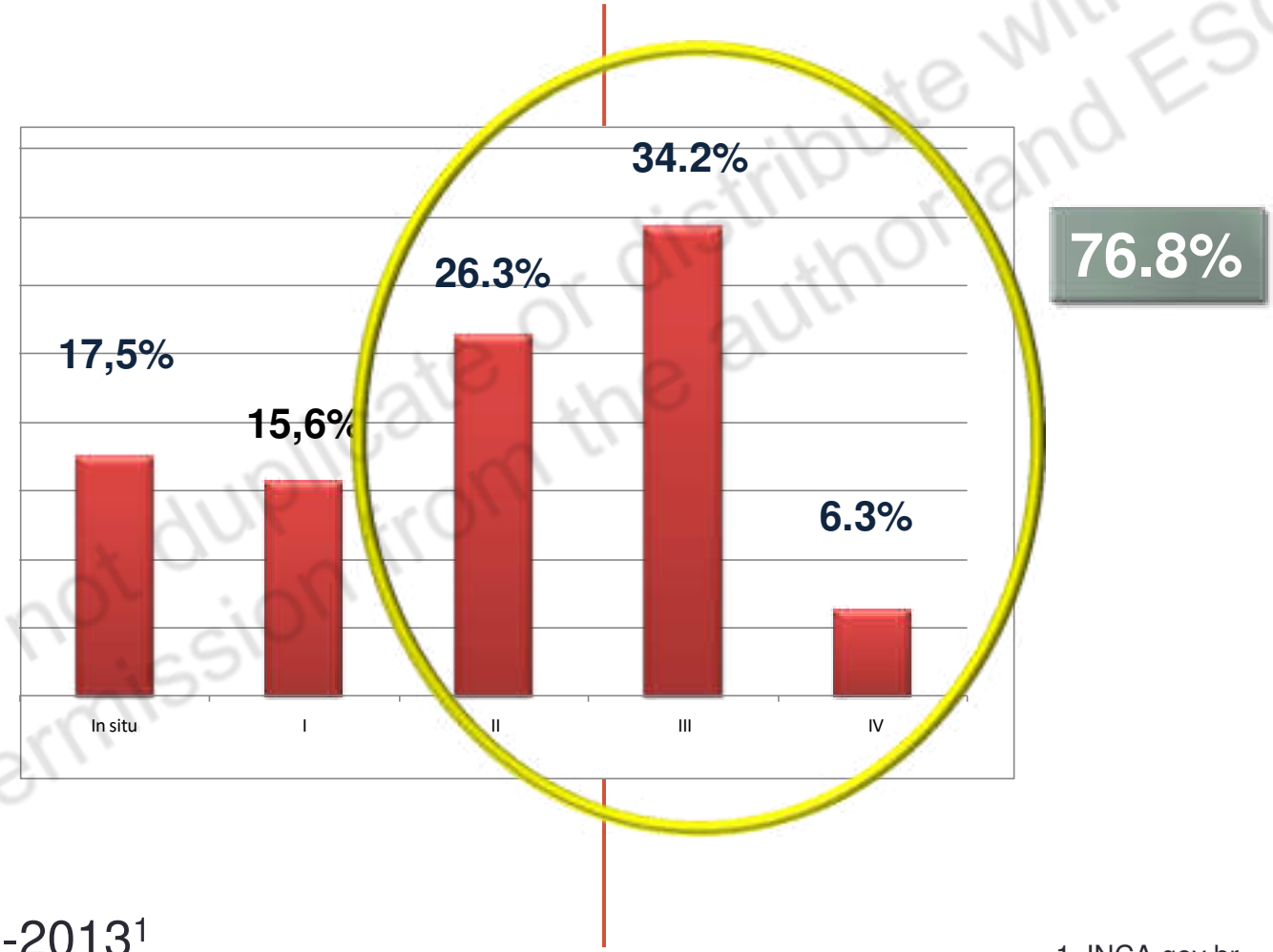
1. INCA.gov.br
2. Thuler et al. Rev Bras de Cancer 2012; 58(3): 351-357
3. Nogueira-Rodrigues et al, Gynecol Oncol. 2014

Cervical Cancer Profile In Brazil



2009-2013[1]

1. INCA.gov.br

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Cellular Classification of Cervical Cancer

- Squamous cell (epidermoid) carcinoma – up to 90%
- Adenocarcinoma – 10%
- Adenosquamous – rare

- Small cell carcinomas – rare
- Primary sarcomas of the cervix and primary and secondary malignant lymphomas – very rare

Specific treatment

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Risk factors

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Staging cervical cancer (TNM and International Federation of Gynecology and Obstetrics [FIGO])

Primary tumor (T)		
TNM categories	**FIGO stages**	**Definition**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a[1]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm in depth with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion or involvement of the lower one-third of the vagina[3,4]
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension with involvement of less than the upper two-thirds of the vagina
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

Regional lymph nodes (N)		
TNM categories	**FIGO stages**	**Definition**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis

Distant metastasis (M)		
TNM categories	**FIGO stages**	**Definition**
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

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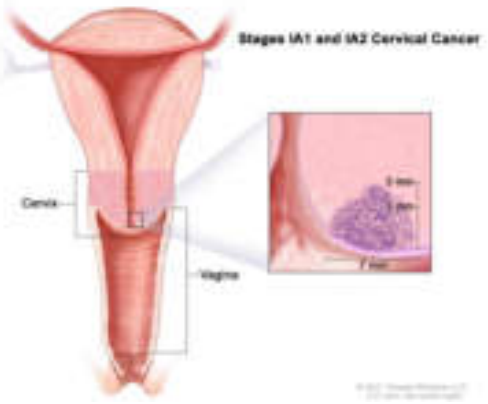
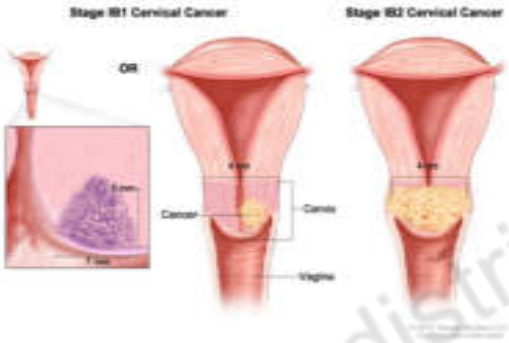
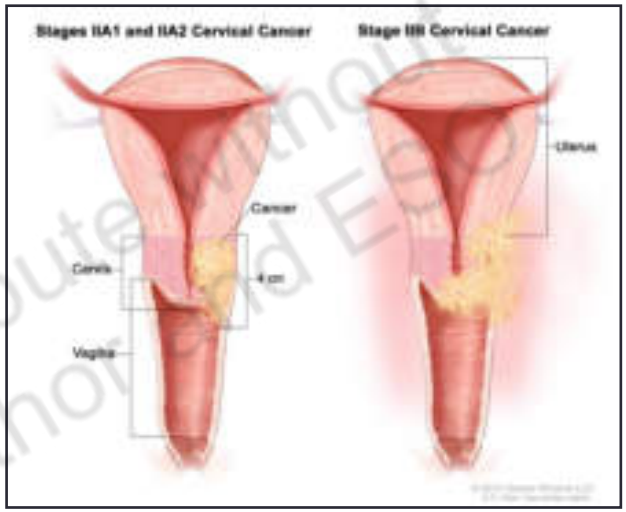
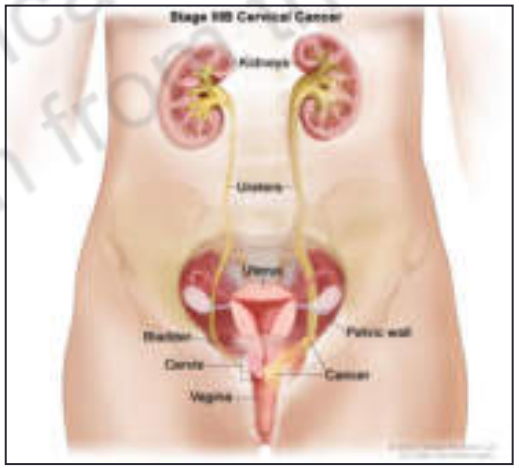
Int J Gynecol Obstet. 2009;105(2):103–104

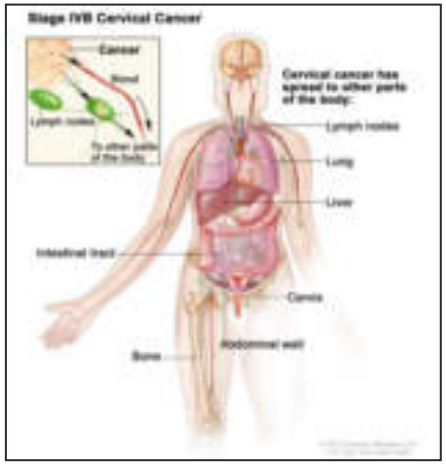
Clinical staging of invasive cervical carcinoma as defined by the International Federation of Gynecology and Obstetrics











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FIGO Committee on Gynecologic Oncology: FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet 125 (2): 97-8, 2014

FIGO staging	Overall Survival		
	One year	2 years	5 years
IA1	99.8	99.5	97.5
IA2	98.5	96.9	94.8
IB1	98.2	95.0	89,1
IB2	95.8	88.3	75.7
IIA	96.1	88.3	75.7
IIB	**91.7**	**79.8**	**65.8**
IIIA	**76.7**	**59.8**	**39.7**
IIIB	**77.9**	**59.5**	**41.5**
IVA	**51.9**	**35.1**	**22.0**
IVB	**42.2**	**22.7**	**9.3**

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Quinn MA et al. Int J Gynaecol Obstet 2006; 95:S43

Recurrence risk after surgery

Risk	Pathologic characteristics
Low	No other risk factors
Intermediate*	No high risk factors Stromal invasion ≤1/3 and LVI + and ≥ 5 cm tumor Stromal invasion >1/3 ≤ 2/3 and LVI + and ≥ 2 cm tumor Stromal invasion > 2/3 and LVI + Stromal invasion >1/3 and LVI absent and ≥ 4 cm tumor
High*	Pelvic LN + or surgical margin + or parametrial microscopic invasion

LVI: lymphatic and or vascular invasion
LN: lymph nodes

***consider concurrent chemoradiotherapy**

Int J Radiat Oncol Biol Phys 65:169, 2006
J Clin Oncol 18:1606, 2000
Cochrane Database Syst Rev Jul 8(3):CD005342, 2009
Sedlis et al. Gynecol Oncol. 1999;73(2):177
Stehman FB et al. Cancer 67:2776-2785,1991

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Concurrent chemotherapy and radiotherapy - concurrent chemoradiation

- Standard of care for advanced cervical cancer
- Better results in terms of OS and PFS

Year	Author	Paper
1999	Keys HM et al	NEJM 340:1154-1161
1999	Morris M et al	NEJM 340:1137-1143
1999	Peters WA et al	NEJM 340:1144-1153
1999	Rose PG et al	NEJM 340:1144-1153
1999	Whitney CW et al	JCO 17:1339-1348

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Standard treatment: radiotherapy concurrent with chemotherapy

- Meta analysis
- 18 randomized prospective studies
- 13 comparing CRT with the same RT

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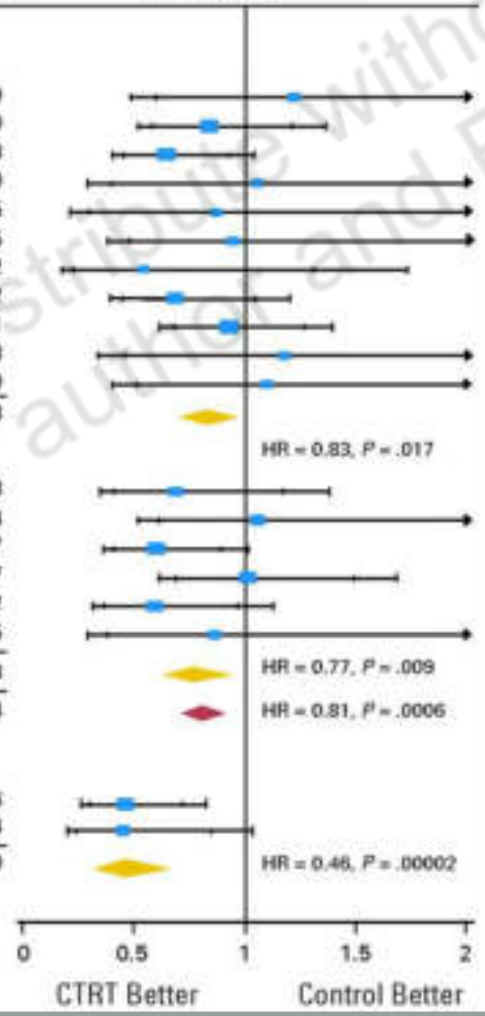
Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008;26:5802-5812

Hazard ratio (HR) plot – overall survival

A

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation v radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[4] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[24] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non-platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[24] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy v radiotherapy						
SWOG8797[5,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10



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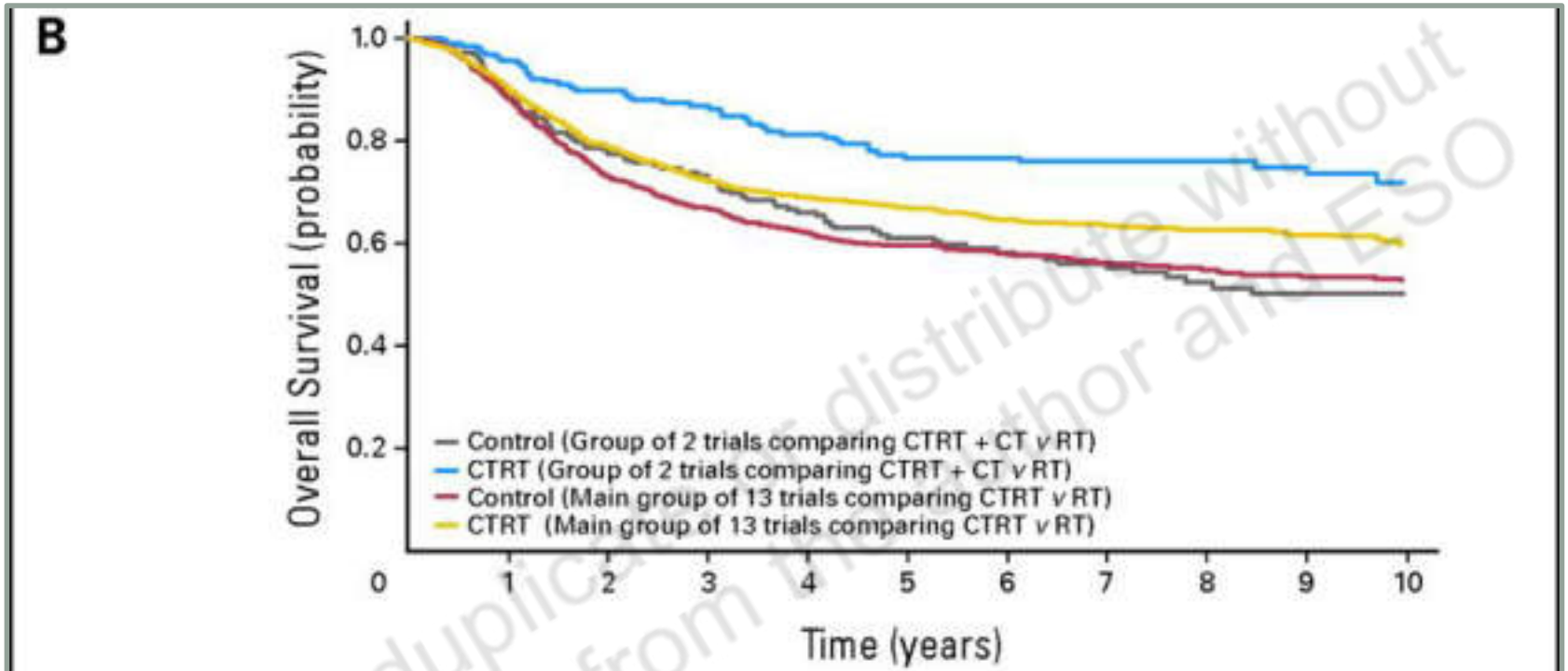
Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008;26:5802-5812

Overall survival



No. at risk

Main group of 13 trials (Additional numbers at risk on control arm due to double counting of control arm from one three-arm trial[24])

Control	1,558	1,244	921	760	610	499	350	274	192	131	81
CTRT	1,570	1,285	1,019	836	694	582	401	309	223	158	101

Group of two trials comparing CTRT + CT v RT

Control	173	155	133	121	106	95	82	67	51	35	21
CTRT	175	165	155	144	129	115	106	89	74	58	37

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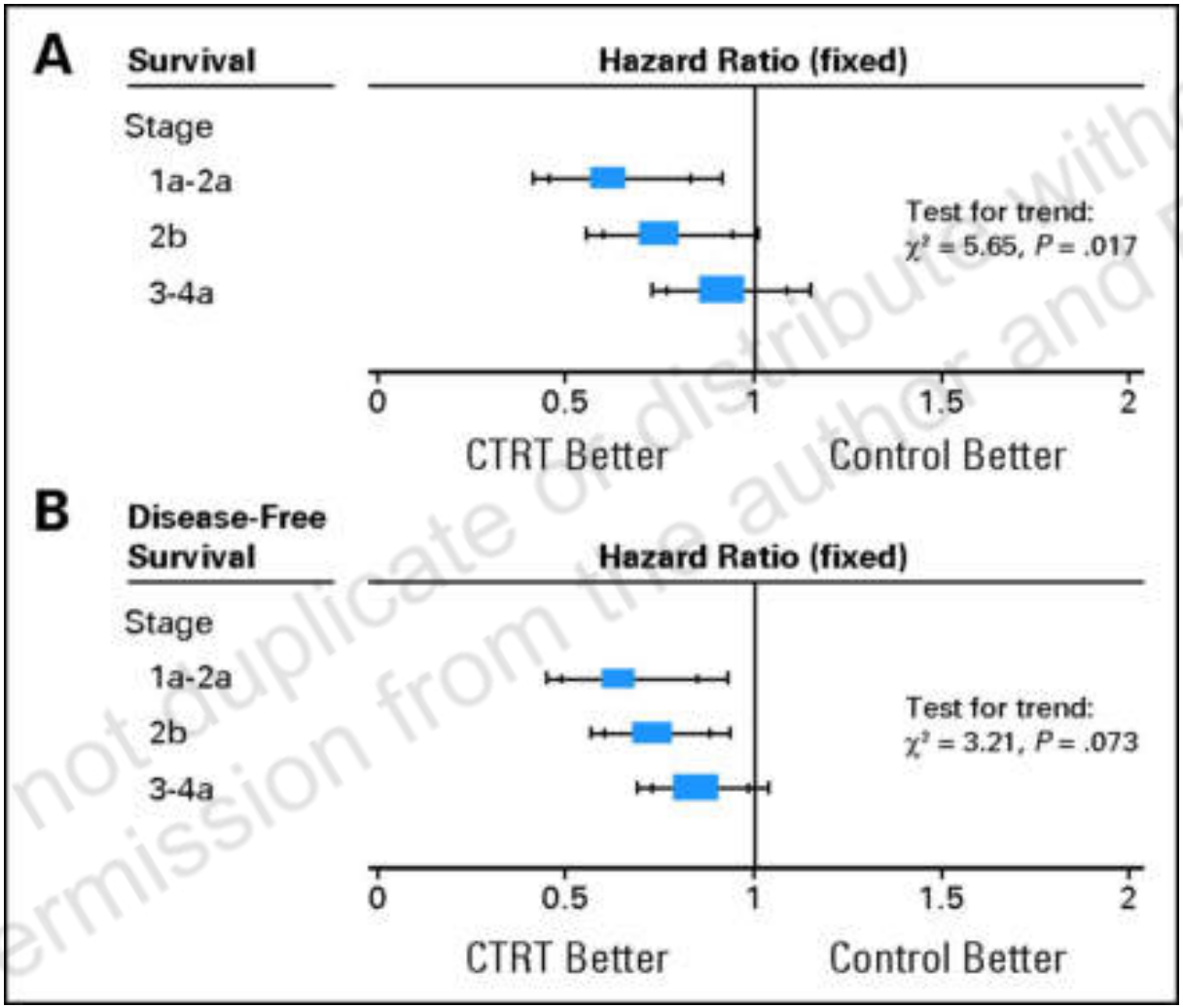
Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008;26:5802-5812

(A) Overall survival and (B) progression free survival (13 main studies)



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Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008;26:5802-5812

	Main analysis – 13 studies			
Survival	**HR**	**CI 95%**	**p**	**Absolute benefit 5 year survival (%)**
Progression free survival	0.78	0.70-0.87	0.000005	8
Disease free survival Locoregional disease	0.76	0.68-0.86	0.000003	9
Metastasis free survival	0.81	0.72-0.91	0.0004	7
Disease free interval Locoregional disease	0.74	0.64-0.86	0.00009	6
Metastasis free interval	0.83	0.71-0.99	0.37	4

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- **Survival benefit** for **both the group of trials** that used platinum-based (HR 0.83, P .017) and non–platinum-based (HR 0.77, P .009) CRT, no difference in different schedules of CT/RT
- **CRT**
  - Improved PFS (local and distant recurrence)
  - Increased acute hematologic and GI toxicity

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration JCO 2008;26:5802-5812

concurrent chemoradiation

Risk of death from cervical cancer reduction by 30% to 50% in advanced stages.

Concurrent cisplatin 40mg/m^2/w should be considered the standard treatment

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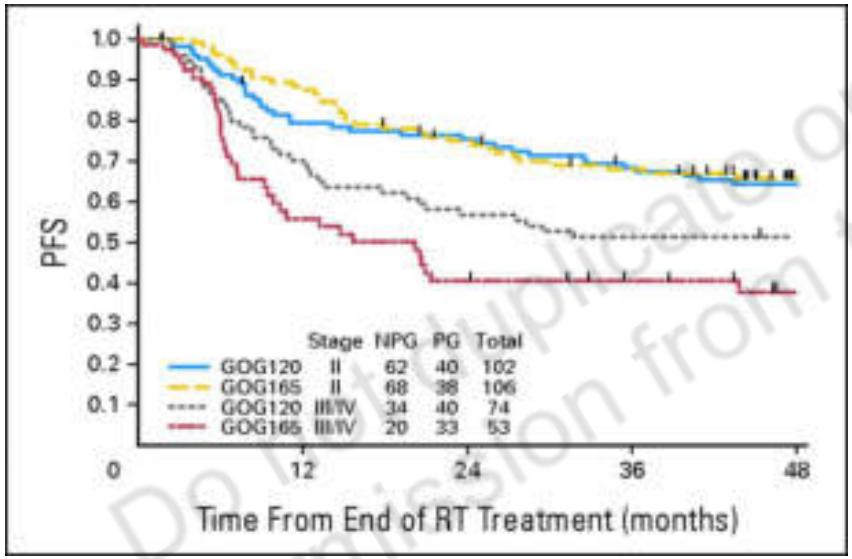
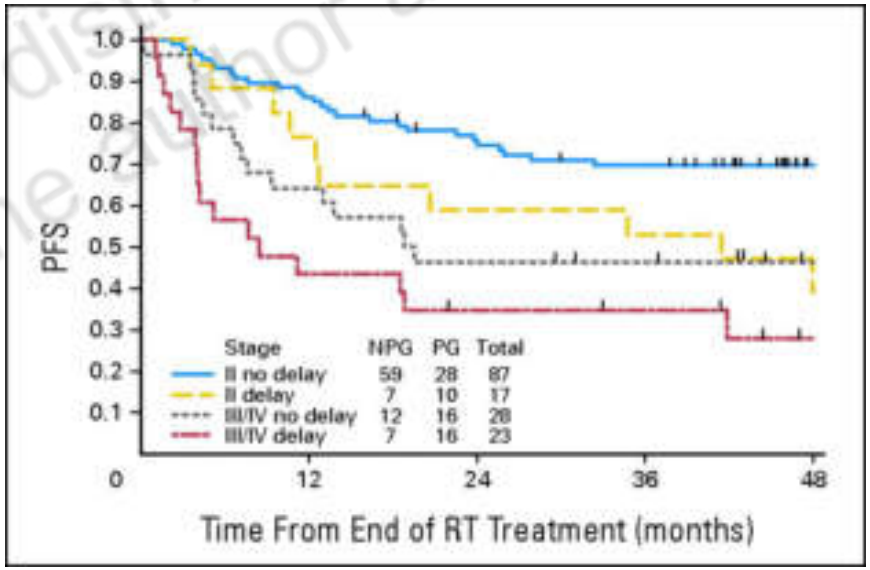
Prognostic factors – concurrent CRT

- Retrospective analysis
- GOG 120 and 165
- 365 women, PFS/OS
- Multivariate analysis :
  - stage, tumor grade, race and age were independently predictive of PFS and OS (for all, p<.05)





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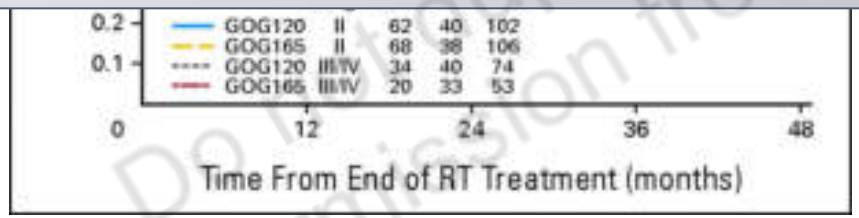
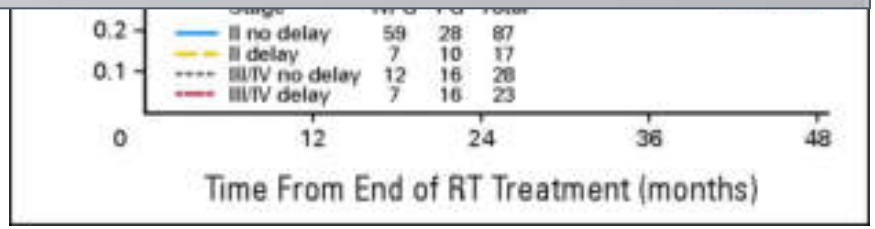
Monk JB et al. Gynecol Oncol 2007;105:427–433

Prognostic factors – concurrent CRT

- Retrospective analysis
- GOG 120 and 165
- 365 women, PFS/OS
- Multivariate analysis :
  - stage, tumor grade, race and age were independently predictive of PFS and OS (for all, p<.05)

Prolonged (delayed for any cause) radiation was associated with poorer PFS (hazard ratio [HR], 1.98; 95% confidence interval [CI], 1.16–3.38; p=0.012) and OS (HR, 1.88; 95% CI, 1.08–3.26; p=0.024) in GOG 165 but not GOG 120





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Monk JB et al. Gynecol Oncol 2007;105:427–433

Neoadjuvant Chemotherapy

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Neoadjuvant Chemotherapy

- 40% recurrence after CRT
- Few radiotherapy equipments, later begining of the treatment
- Adjuvant chemotheray: high toxicity rate

Is there a role to neoadjuvant chemotherapy to chemoradiation?

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Neoadjuvant chemotherapy

A Randomized Trial of Chemotherapy Followed by Pelvic Radiation Therapy in Stage IIIB Carcinoma of the Cervix

By Luis Souhami, Roberto A. Gil, Sergio E. Allen, Paulo Cezar V. Canary, Carlos Manoel M. Araújo, Luiz Henrique J. Pinto, and Telma Ruth P. Silveira

N: 107
SCC cervical cancer
IIIB
3 cycles BOMP folowed by RT
VS
Radiotherapy

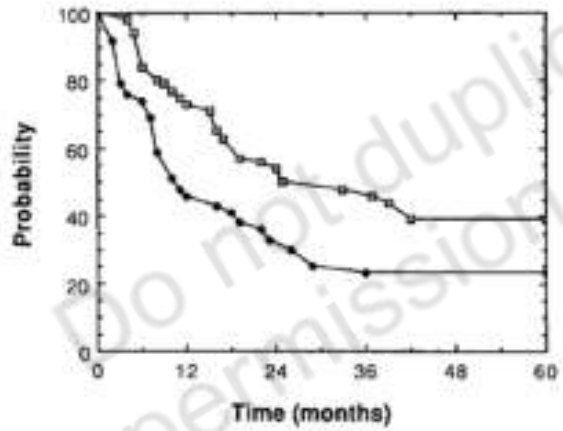

Fig 1. Overall survival rates. (□) RT, (●) CT + RT; P = .02.

J Clin Oncol. 1991;9:970-977

Chemotherapy Followed by Radiotherapy versus Radiotherapy Alone in Locally Advanced Cervical Cancer: A Randomized Study

Lalit Kumar, R. Kaushal, M. Nandy, B. M. Bansal, S. Kumar, A. Khullar, Rajveer Singh, G. K. Rath, and V. Kochupillai

Department of Medical Oncology, Radiotherapy, Gynaecology and Obstetrics and Biostatistics, Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

Received September 1, 1994

N: 184
Cervical cancer - SCC
IIB-IVA
2 cycles of cisplatin + bleomycin+ ifosfamide → RT
VS
Radiotherapy

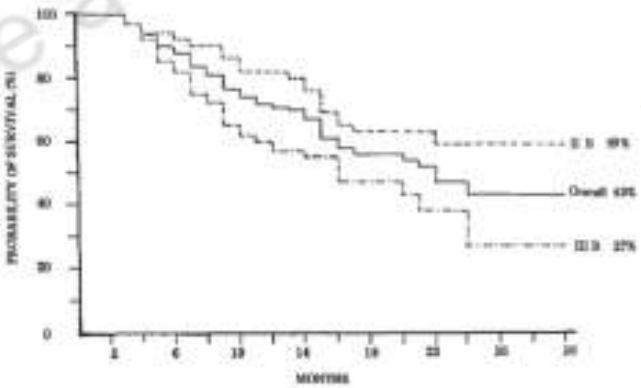

FIG. 3. Survival in radiotherapy group (n = 90).

all 43%

Overall Survival RT

There was no difference in overall survival between both groups
38% *vs* 43% p= 0.54

Gynecol Oncol. 1994;54:307-3015

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The role of neoadjuvant chemotherapy in the management of locally advanced cervix cancer: a systematic review

- 1,760 pacientes that recieved neoadjuvant chemotherapy
- 90% surgical treatment

RR 84%
PFS 5 years 61.9%
OS 5 years 72.8%

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Oncology Reviews. 2014;8:250

Neoadjuvant chemotherapy

- **No randomized study CT→ CRT *vs* CRT**

- studies CT→ RT *vs* RT

  - Higher toxicity
  - No OS benefit
  - but...

    → Should the results be different with third generation platinun schedules and modern radiotherapy?

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Current studies

- **CIRCE**
  - One institution (ICESP)
  - Fase II
  - IIB-IVA

Chemoradiation with cisplatin

X

Cisplatin+gemcitabine x 3 → Chemoradiation with cisplatin

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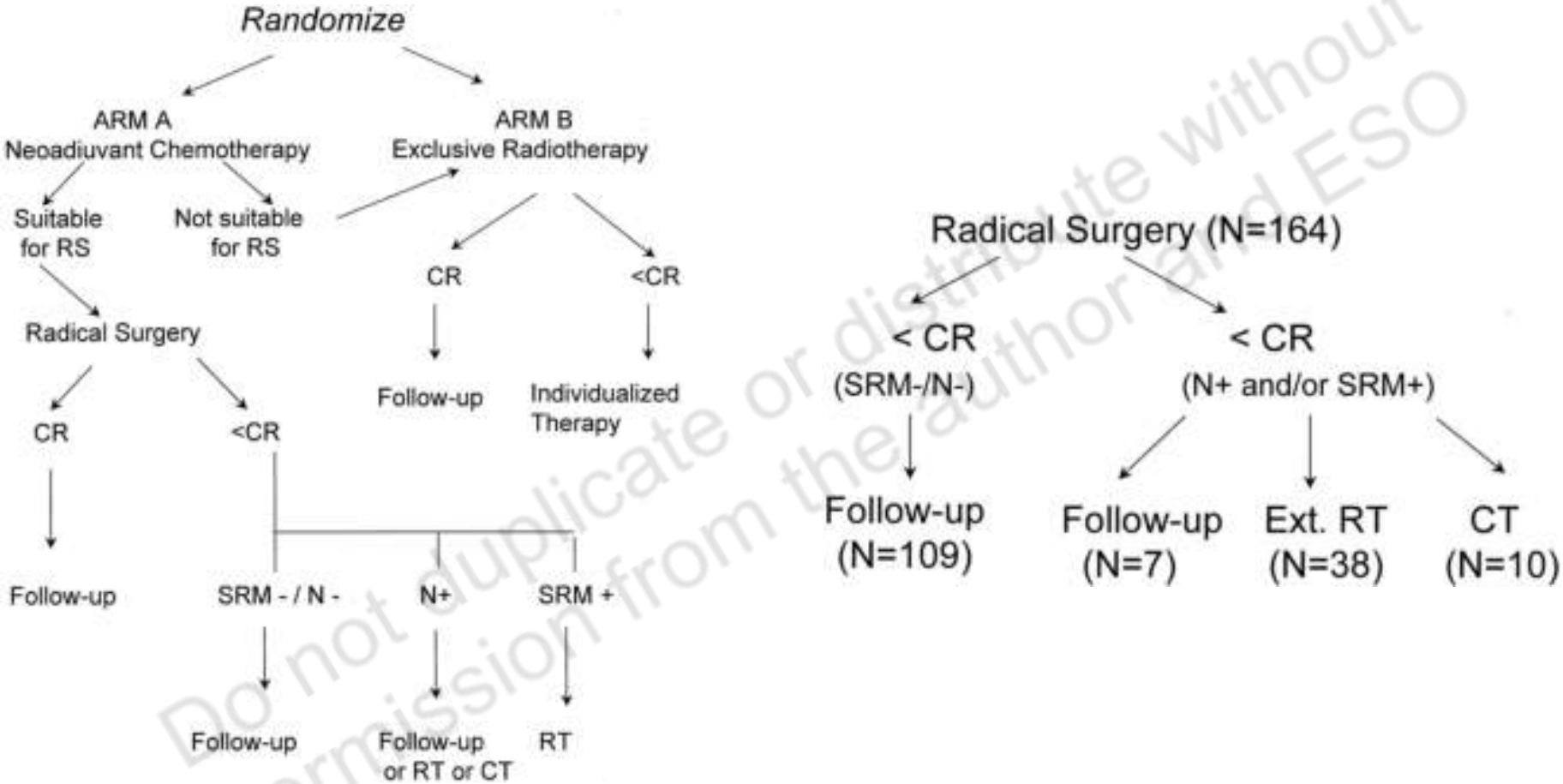
Neoadjuvant Chemotherapy and Radical Surgery Versus Exclusive Radiotherapy in Locally Advanced Squamous Cell Cervical Cancer: Results From the Italian Multicenter Randomized Study



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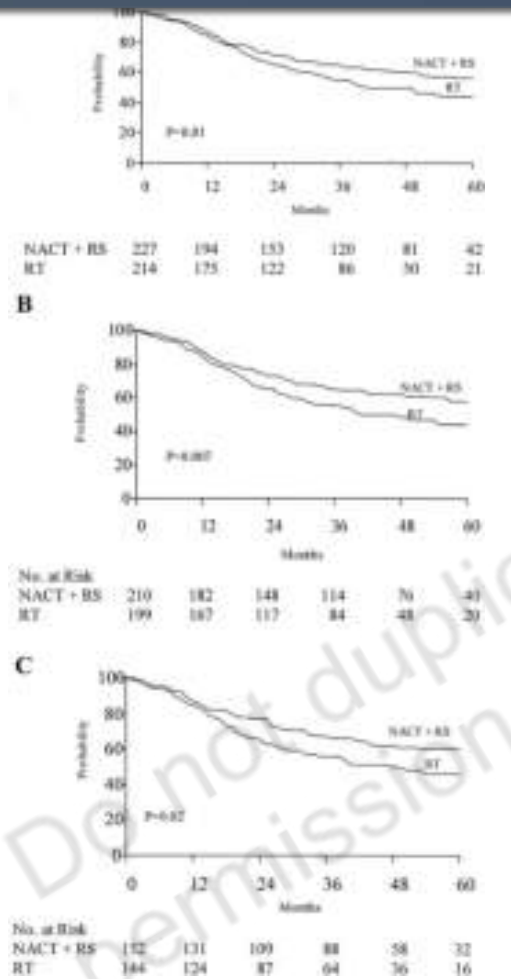
441 patients randomly assigned to NACT+RS or RT
eligibility was confirmed in 210 and 199 patients, respectively

Pierluigi Benedetti-Panici et al. JCO 2002;20:179-188

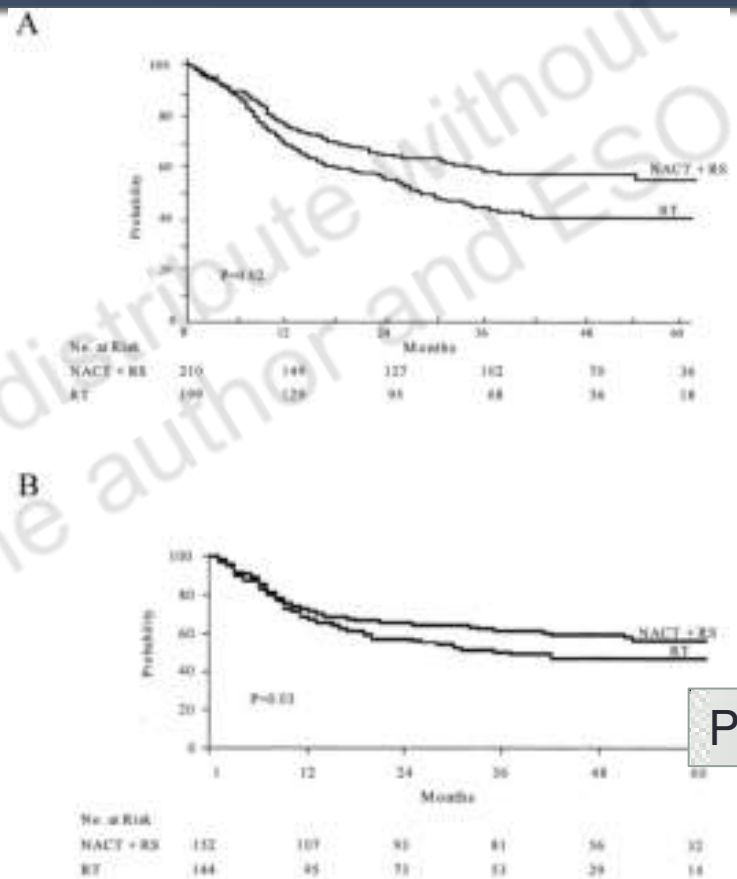
Neoadjuvant Chemotherapy and Radical Surgery Versus Exclusive Radiotherapy in Locally Advanced Squamous Cell Cervical Cancer: Results From the Italian Multicenter Randomized Study



P= 0.007

Overall survival

(A) all randomized patients, (B) eligible patients, and (C) patients treated according to the protocol



P= 0.02

Progression free survival

(A) eligible patients and (B) patients treated according to the protocol.

Pierluigi Benedetti-Panici et al. JCO 2002;20:179-188

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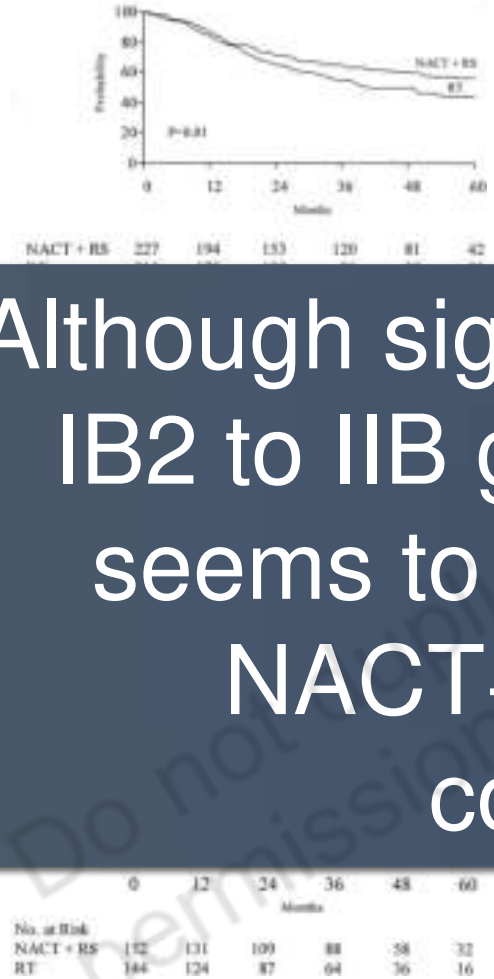
Neoadjuvant Chemotherapy and Radical Surgery Versus Exclusive Radiotherapy in Locally Advanced Squamous Cell Cervical Cancer: Results From the Italian Multicenter Randomized Study



Although significant only for the stage IB2 to IIB group, a survival benefit seems to be associated with the NACT+RS compared with conventional RT

Overall survival
(A) all randomized patients, (B) eligible patients, and (C) patients treated according to the protocol

Progression free survival
(A) eligible patients and (B) patients treated according to the protocol.

Pierluigi Benedetti-Panici et al. JCO 2002;20:179-188

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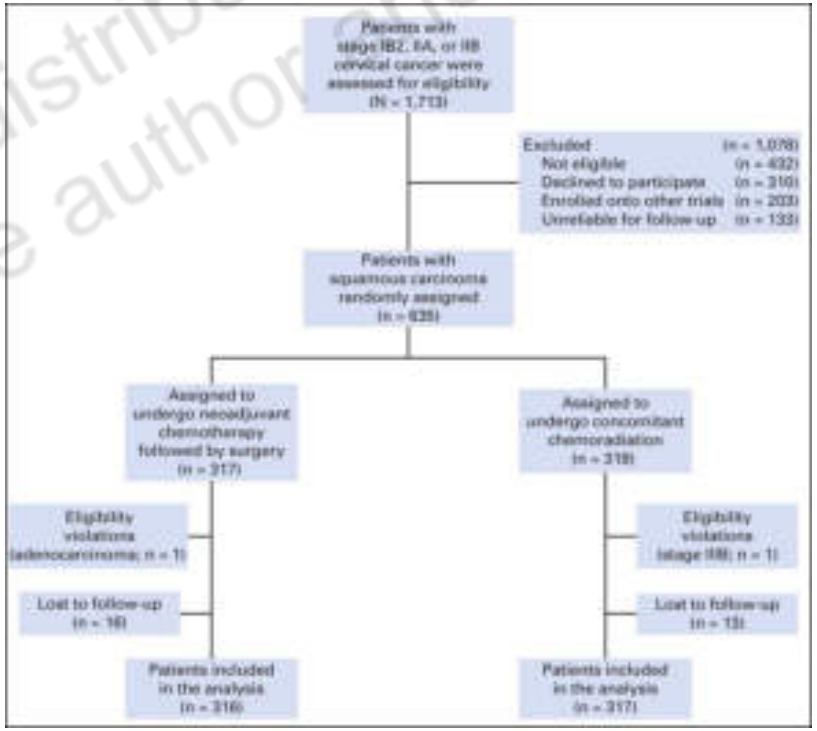
Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Pts and methods

- Single center
- Phase III
- IB2, IIA, IIB SCC
- Carboplatin+paclitaxel q3w/3 cycles
- Radical hysterectomy vs CRT (CDDP)
- ± CRT
- DFS, OS, AE

Sep 2003-Feb 2015
635 pts



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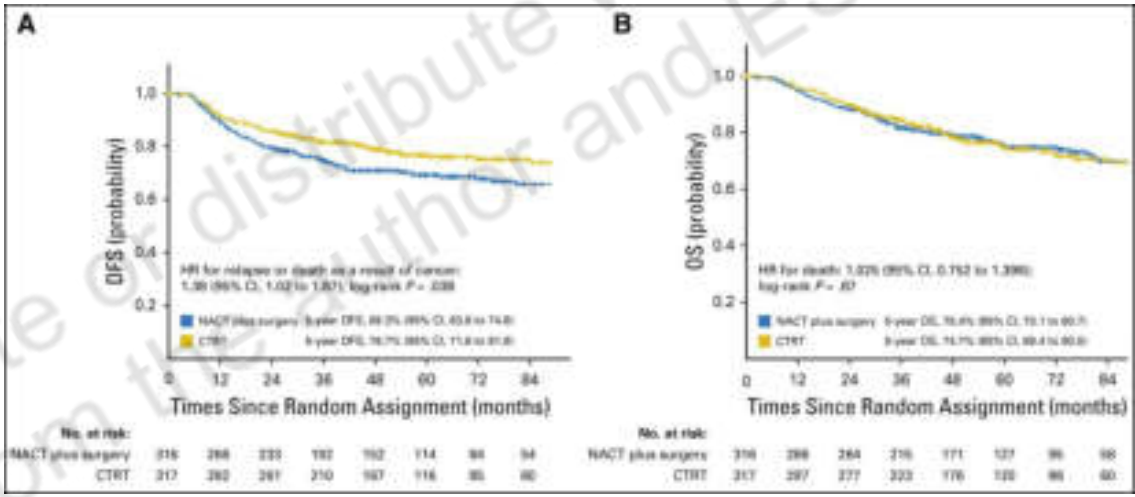
Gupta S et al. J Clin Oncol 36, 2018

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Table 1. Baseline Patients Characteristics

Characteristic	NACT Plus Surgery (n = 316)	CTRT (n = 317)
Median age, years (range)	50 (27-65)	48 (26-65)
Median hemoglobin, g/dL (range)	11.5 (7.6-15.6)	11.5 (7.4-15.5)
Median body mass index, kg/m^2 (range)	22.6 (12.8-44.2)	22.5 (14.5-38.4)
Comorbidities		
Yes	67 (21.2)	61 (19.2)
No	249 (78.8)	256 (80.8)
Eastern Cooperative Oncology Group performance status		
0	290 (91.8)	293 (92.4)
1	26 (8.2)	24 (7.6)
FIGO stage		
IB2	57 (18.0)	56 (17.7)
IIA	80 (25.3)	78 (24.6)
IIB	179 (56.7)	183 (57.7)
Radiologic pelvic lymph node status		
Positive	46 (14.6)	45 (14.2)
Negative	270 (85.4)	272 (85.8)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: CTRT, concomitant chemotherapy and radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; NACT, neoadjuvant chemotherapy.



Kaplan-Meier plots for (A) disease-free survival (DFS) and (B) overall survival (OS) in the intent-to-treat population by study group. CTRT, concomitant chemoradiation; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NACT, neoadjuvant chemotherapy.

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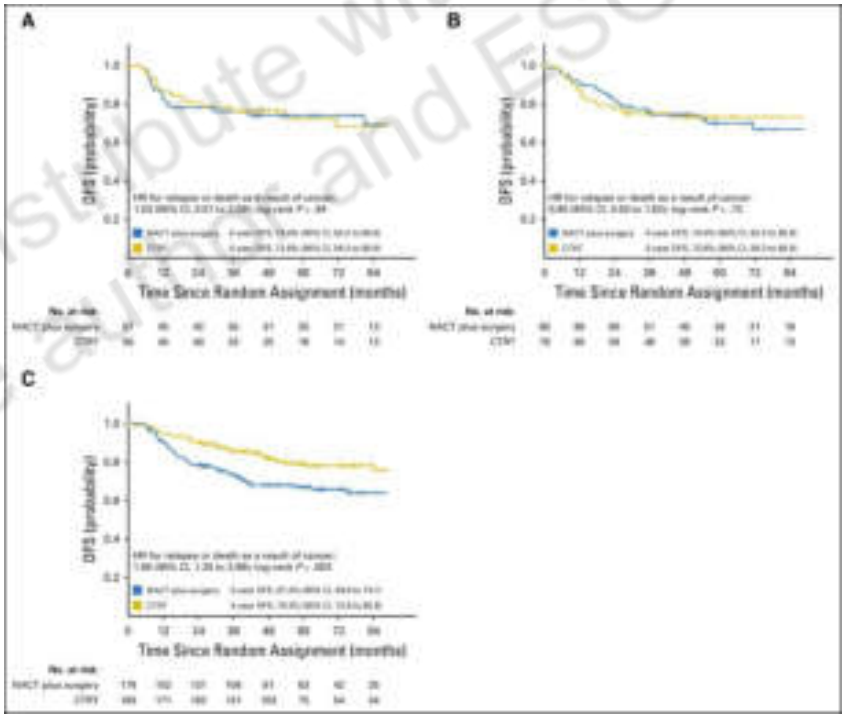
Gupta S et al. J Clin Oncol 36, 2018

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

	No. of Events/No. of Patients			P for Interaction
	NACT Plus Surgery	CTRT	HR (95% CI)	
Stage				
IB2	16/57	15/56		.14
IIA	22/80	23/78		.04
IIB	57/179	36/183		
Hemoglobin				.78
> 11 g/dL	60/206	44/203		
≤ 11 g/dL	35/110	30/114		
Pelvic lymph node status				.15
Negative	82/270	58/272		
Positive	13/48	16/45		
ECOG performance status				.79
0	90/290	71/293		
1	5/26	3/24		
All patients	95/316	74/317		

Disease-free survival (DFS) of subgroups. P values are for the interaction term from a model with study arm, the subgroup variable, and arm × subgroup interaction term. DFS hazard ratios are indicated by diamonds, and 95% CIs are indicated by the crossing horizontal lines. Diamond size is proportional to each patient subgroup population size. All hazard ratios (HR) are unadjusted. CTRT, concomitant chemoradiation; NACT, neoadjuvant chemotherapy.



A. Kaplan-Meier plots for disease-free survival (DFS) in patients with (A) stage IB2, (B) stage IIA, and (C) stage IIB disease by study group. CTRT, concomitant chemoradiation; HR, hazard ratio; NACT, neoadjuvant chemotherapy.

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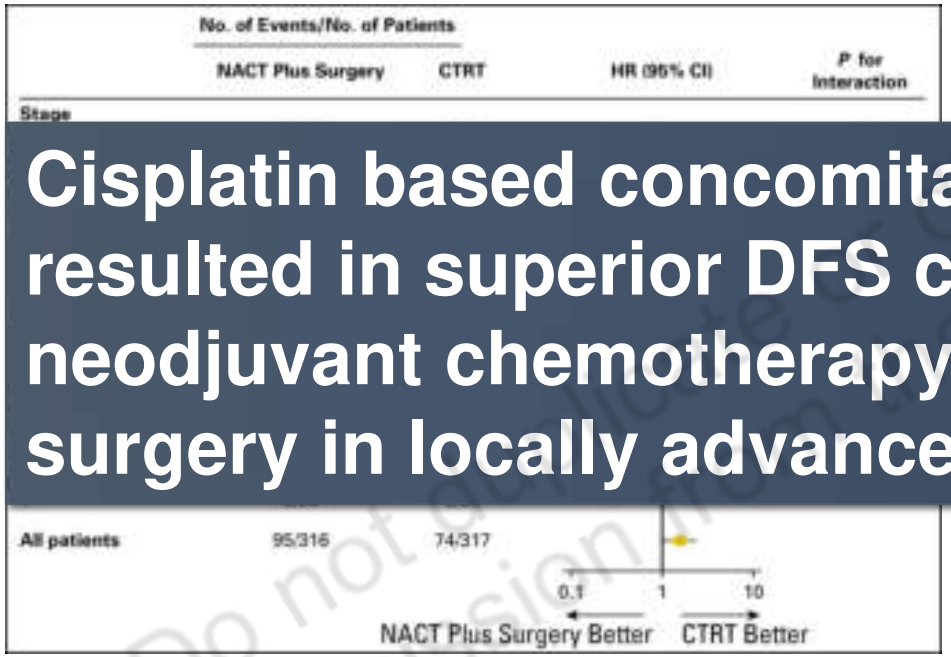
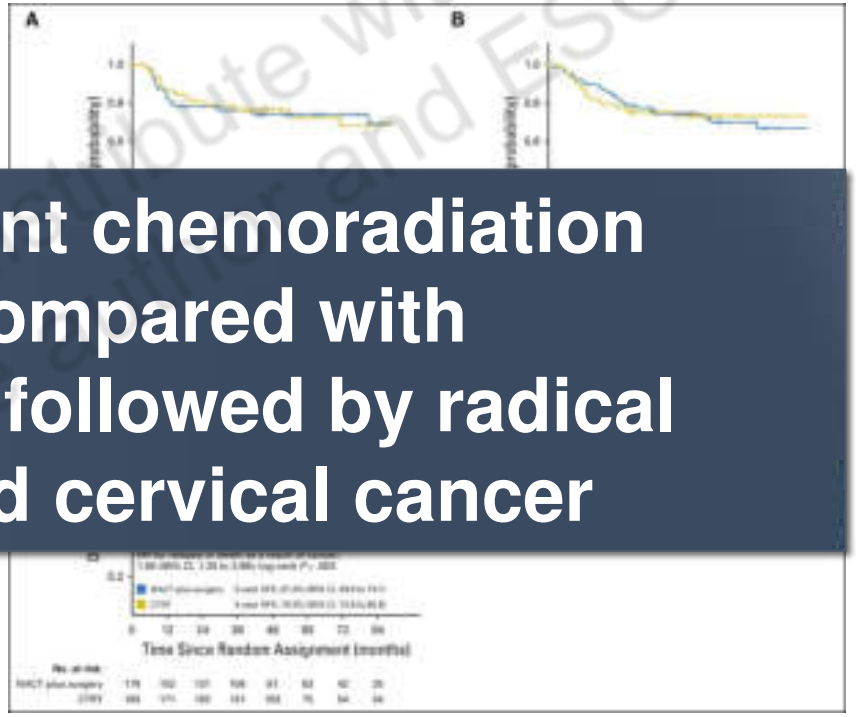
Gupta S et al. J Clin Oncol 36, 2018

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial



Disease-free survival (DFS) of subgroups. P values are for the interaction term from a model with study arm, the subgroup variable, and arm × subgroup interaction term. DFS hazard ratios are indicated by diamonds, and 95% CIs are indicated by the crossing horizontal lines. Diamond size is proportional to each patient subgroup population size. All hazard ratios (HR) are unadjusted. CTRT, concomitant chemoradiation; NACT, neoadjuvant chemotherapy.



A. Kaplan-Meier plots for disease-free survival (DFS) in patients with (A) stage IB2, (B) stage IIA, and (C) stage IIB disease by study group. CTRT, concomitant chemoradiation; HR, hazard ratio; NACT, neoadjuvant chemotherapy.

Cisplatin based concomitant chemoradiation resulted in superior DFS compared with neodjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer

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Gupta S et al. J Clin Oncol 36, 2018

But, in the era of CRT…

- EORTC-55994 (NCT00039338)
- Randomized, multicenter study
- Stages IB2, IIA2, and IIB cervical cancer
- Standard chemoradiation vs neoadjuvant chemotherapy (with a cisplatin backbone for three cycles) followed by evaluation for surgery
- Primary endpoint: OS

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Adjuvant chemotherapy

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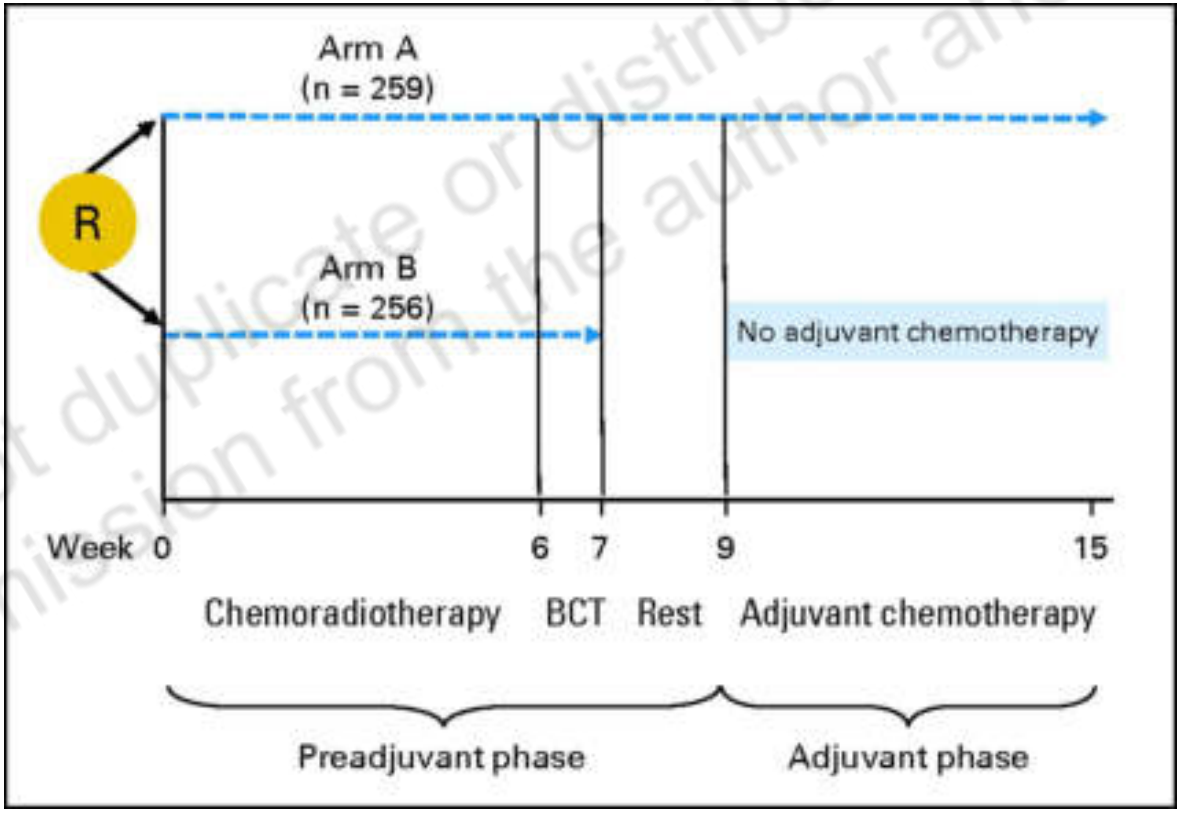
VOLUME 29 · NUMBER 13 · MAY 1 2011
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix



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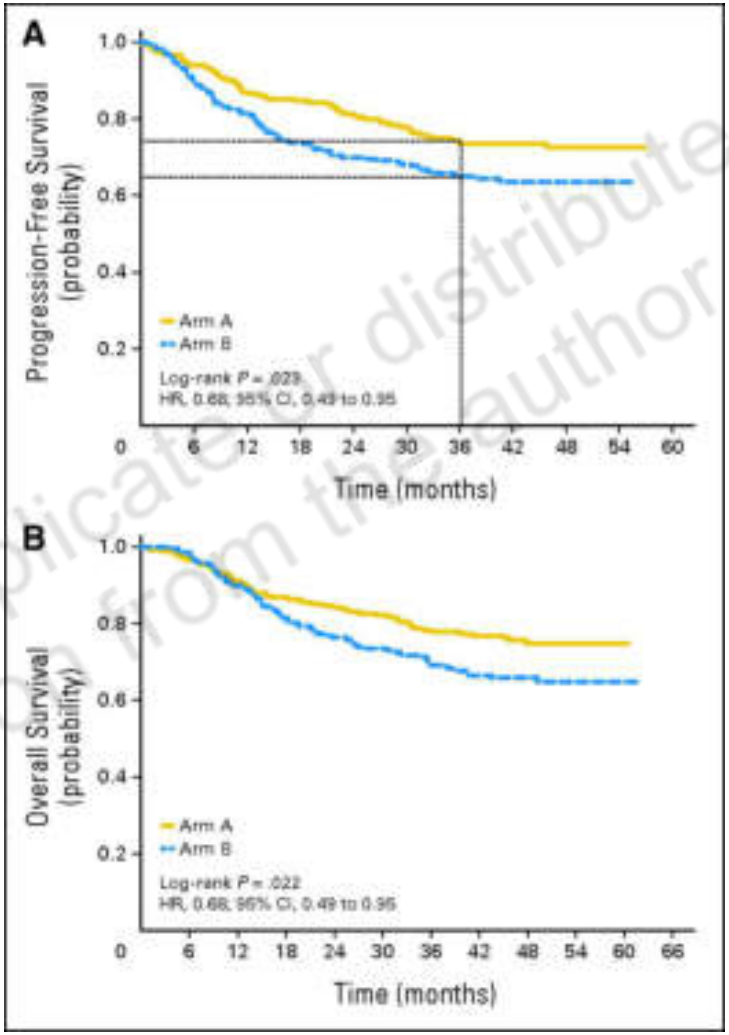
Alfonso Dueñas-González et al. JCO 2011;29:1678-1685

Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival for patients who were randomly assigned to arm A or arm B. PFS at 3 years is shown by the dotted black lines and was 74.4% for arm A and 65.0% for arm B (P = .029).



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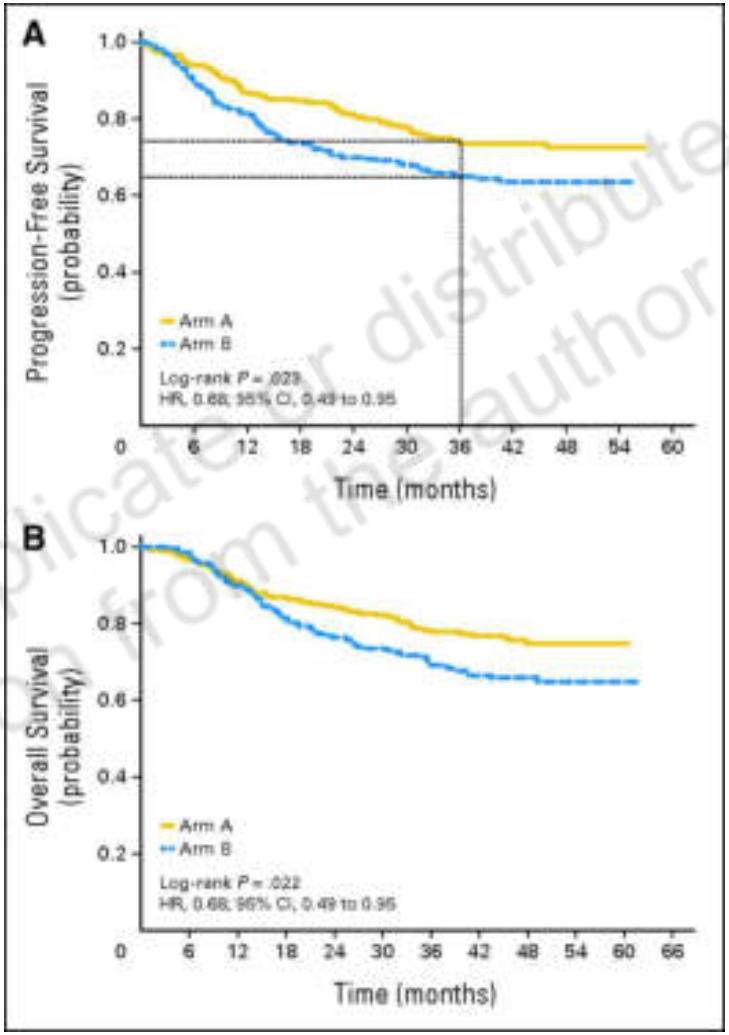

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Alfonso Dueñas-González et al. JCO 2011;29:1678-1685

Acute toxicity	A: grade 3 (%)	B: grade 3 (%)	A: grade 4 (%)	B: grade 4 (%)
Neutropenia	45	5.1	6.2	0.8
Diarreia	17.7	4.7	0	0
Anemia	7.7	1.6	1.5	0.4
Vomiting	7.7	2.4	0	0.4
Dermatitis	11.2	10.6	0	0
Abdominal pain	2.7	0.4	0	0
Proctitis	2.7	0.4	0.8	0
Febril neutropenia	1.5	0.4	0.8	0
Late toxicity				
All	0.5	0.5	3.6	0.9
Intestinal	0	0.5	2.3	0
Bladder	0	0	1.4	0.5

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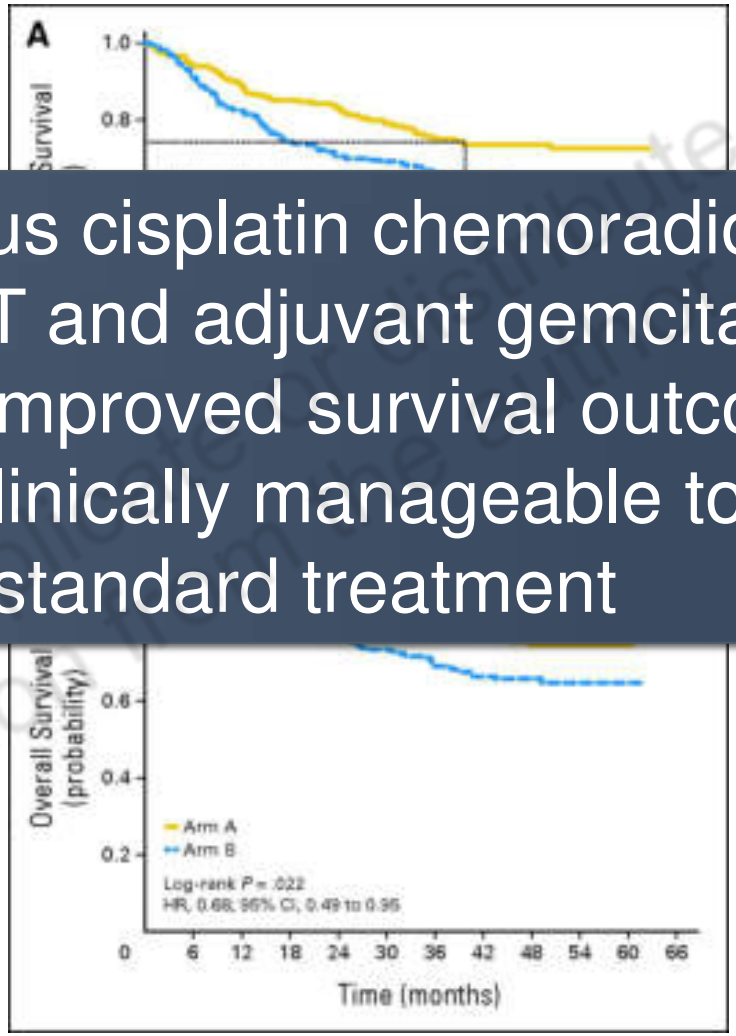
RT leght (days): arm A 49 > arm B 45, p<0.001

J Clin Oncol. 2011;29:1678-1685

Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival for patients who were randomly assigned to arm A or arm B. PFS at 3 years is shown by the dotted black lines and was 74.4% for arm A and 65.0% for arm B (P = .029).



Gemcitabine plus cisplatin chemoradiotherapy followed by BCT and adjuvant gemcitabine/cisplatin chemotherapy improved survival outcomes with increased but clinically manageable toxicity when compared with standard treatment

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Alfonso Dueñas-González et al. JCO 2011;29:1678-1685

Ongoing study

- IB1 LN + to IVA
- CRT with cisplatin

Follow up

X

Chemotherapy carboplatin + paclitaxel x 4 cycles

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Concurrent chemoradiotherapy with carboplatin

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Carboplatin-based chemoradiotherapy in advanced cervical cancer: an alternative to cisplatin-based regimen?

Ana Morais Sebastião, Lucila Soares da Silva Rocha, Rodrigo Darouche Giménez, Laryssa Almeida Borges de Barros, Julia Tizuko Fukushima, Samantha Cabral Severino da Silva, Vanessa da Costa Miranda, Inacelli Queiros de Souza Caires, Daniela de Freitas, Elias Abdo Filho, Maria Del Pilar Estevez Diz

- Retrospective analysis
- Cervical cancer IIB – IVA, CDDP+RT or carboplatin +RT
- 184 pts from May 2008 to December 2012
- 159 CDDP 40mg/m2/w/6 weeks
- 25 carboplatin AUC2/w/6 weeks

Significant #:
Older
Co morbidities

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European Journal of Obstetrics and Gynecology and Reproductive Biology. 2016,201:161

Concurrent chemoradiotherapy with carboplatin

Progression free survival

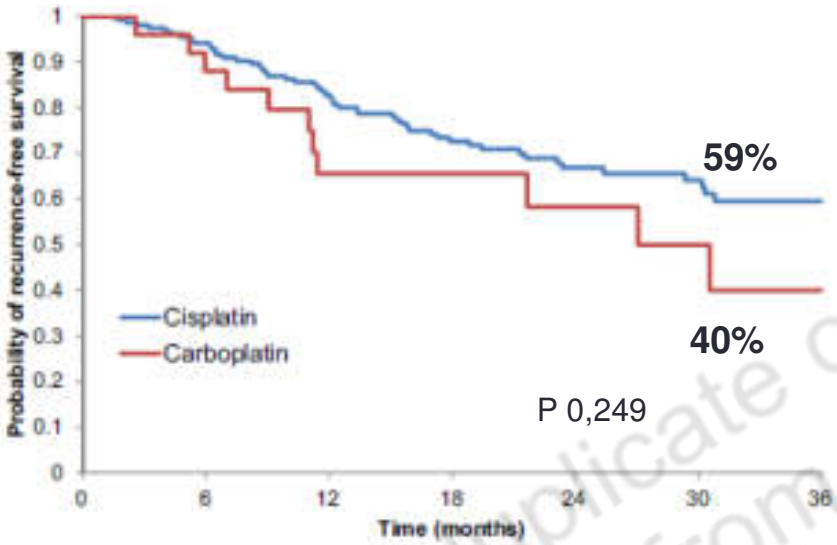

Fig. 1. Progression-free survival curves.

Overall survival

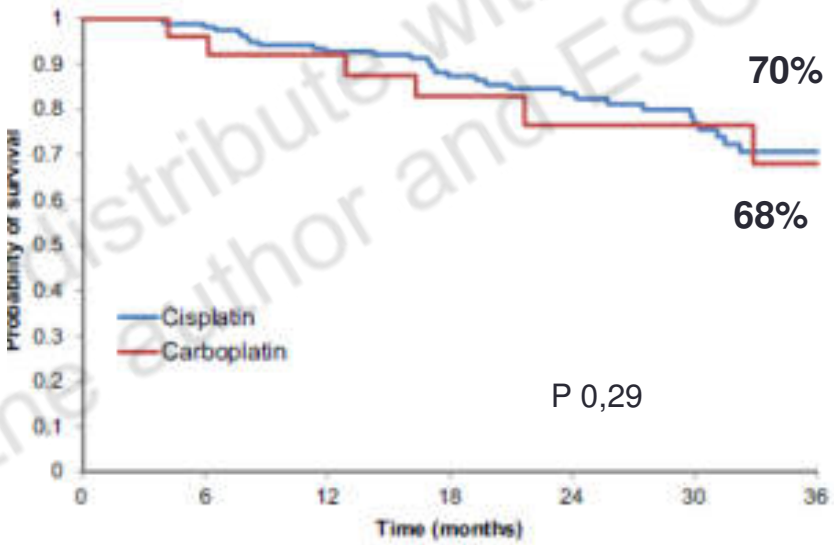

Fig. 2. Overall survival curves.

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RR 95.3%
X
95.4%

European Journal of Obstetrics and Gynecology and Reproductive Biology. 2016,201:161

Palliative chemotherapy

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What is the best platinum combination?

Primary Stage IVB or recurrent/persistent carcinoma of the cervix
- measurable disease
- PS= 0 or 1
- creat. clairance >50 ml/mn
- no prior chemotherapy (unless concurrent with radiation)
- bilateral stent or percutaneous nephrostomy allowed

RANDOMIZE

Regimen 1
PACLITAXEL 135 mg/m2 over 24 hours + Cisplatin 50mg/m2 q 3 wks X 6 cycles

Regimen 2
VINORELBINE 30 mg/m2 IV day1 and 8 and Cisplatin 50 mg/m2 IV d1 q 3 wks X 6 cycles

Regimen 3
GEMCITABINE 1000mg/m2 IV d1 and 8 and Cisplatin 50 mg/m2 IV d1 q 3 wks X 6 cycles

Regimen 4
TOPOTECAN 0.75 mg/m2 d1, 2, & 3 Cisplatin 50 mg/m2 IV day 1, q 3 wks for 6 cycles

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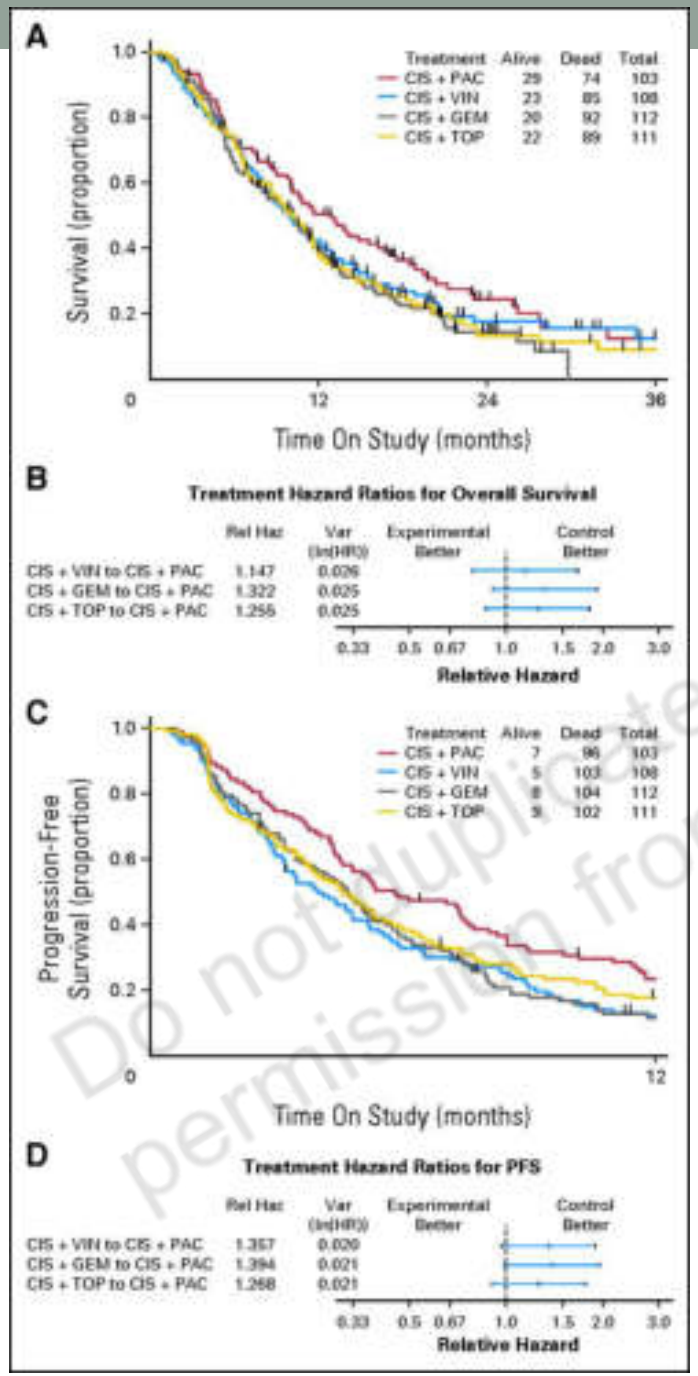
Bradley J. Monk et al. JCO 2009;27:4649-4655



(A) Overall survival Kaplan-Meier plots for the 434 patients in the study sample and
(B) Hazard ratios with 95% CIs adjusted for multiplicity, using Dunnett's procedure.
(C) Progression-free survival Kaplan-Meier plots for the 434 patients in the study sample and
(D) hazard ratios with 95% CIs adjusted for multiplicity, using Dunnett's procedure.

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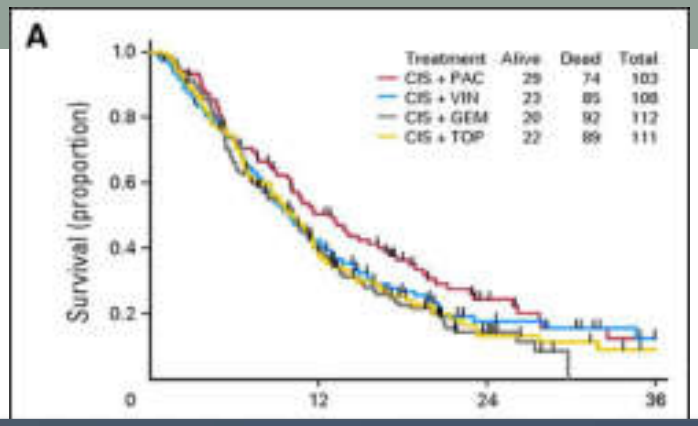
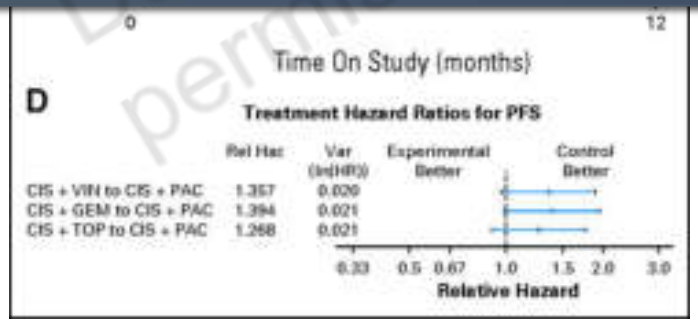
Bradley J. Monk et al. JCO 2009;27:4649-4655



(A) Overall survival Kaplan-Meier plots for the 434 patients in the

VC, GC, and TC are not superior to PC in terms of overall survival (OS). However, the trend in RR, PFS, and OS favors PC. Differences in chemotherapy scheduling, pre-existing morbidity, and toxicity are important in individualizing therapy.



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Bradley J. Monk et al. JCO 2009;27:4649-4655

Improved Survival with Bevacizumab in Advanced Cervical Cancer

Krishnansu S. Tewari, M.D., Michael W. Sill, Ph.D., Harry J. Long, III, M.D., Richard T. Penson, M.D., Helen Huang, M.S., Lois M. Ramondetta, M.D., Lisa M. Landrum, M.D., Ana Oaknin, M.D., Thomas J. Reid, M.D., Mario M. Leitao, M.D., Helen E. Michael, M.D., and Bradley J. Monk, M.D.

In this large randomized clinical trial, the median survival among women with recurrent cervical cancer was 17 months when bevacizumab was added to their chemotherapy regimen, as compared with 13 months with chemotherapy alone.

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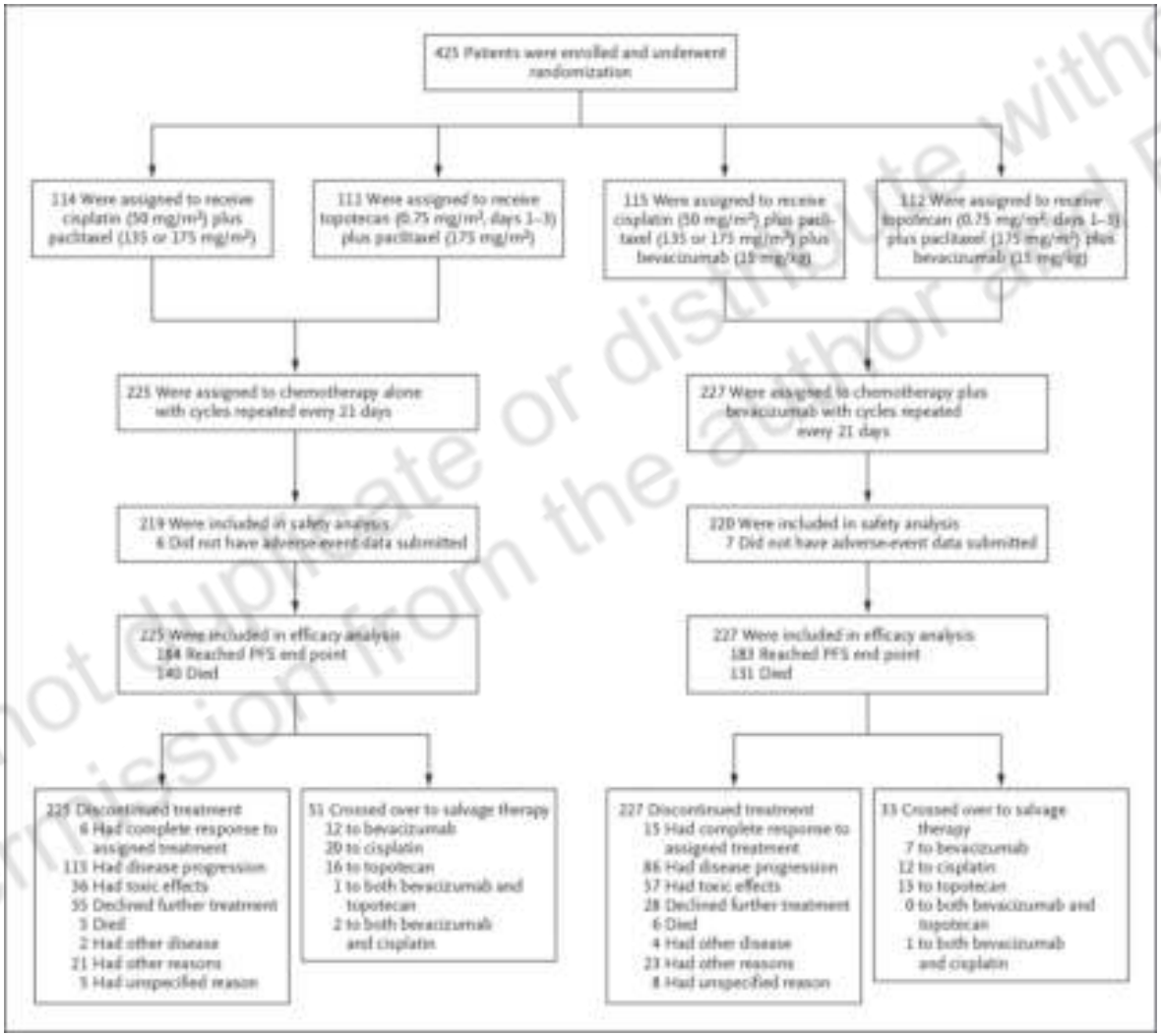
N Engl J Med
Volume 370(8):734-743
February 20, 2014

Enrollment, Randomization, and Follow-up of the Study Patients.



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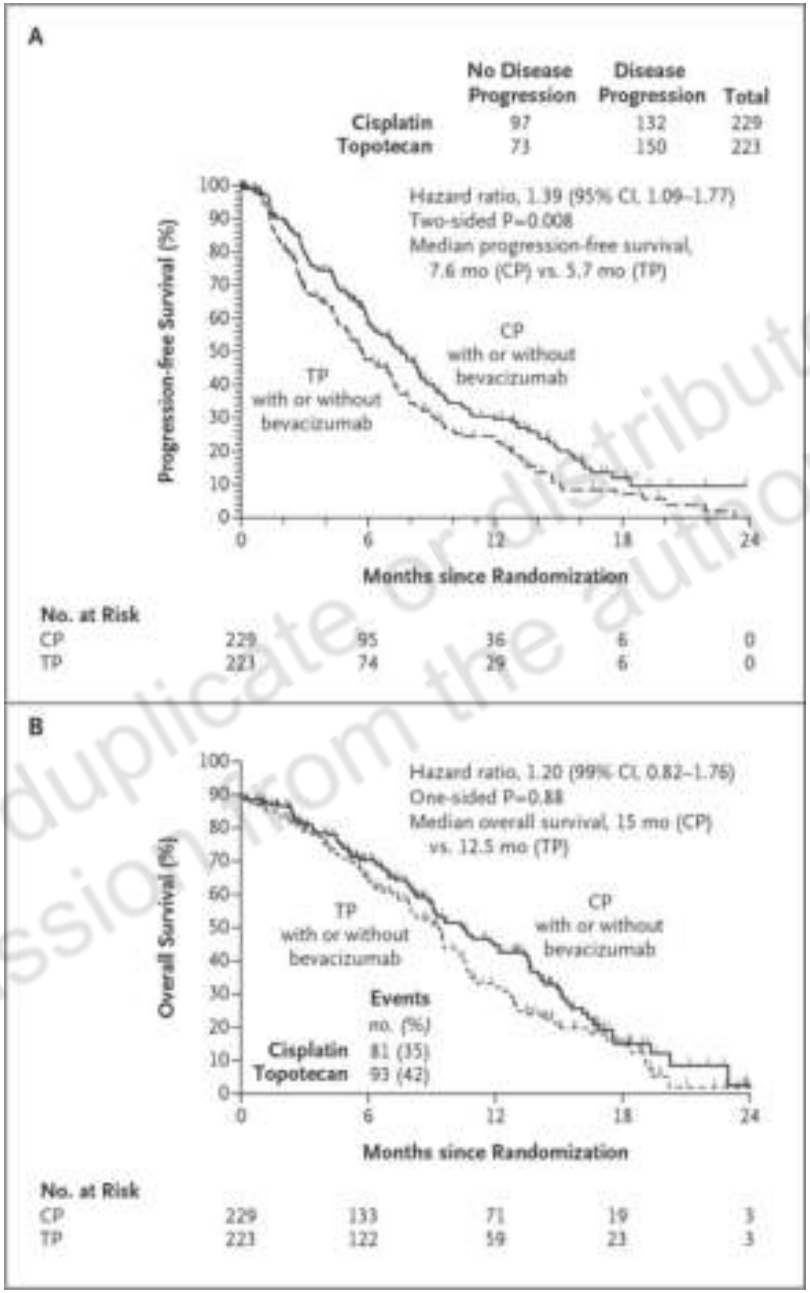
Tewari KS et al. N Engl J Med 2014;370:734-743

Progression-free and Overall Survival, According to the Chemotherapy Regimen.



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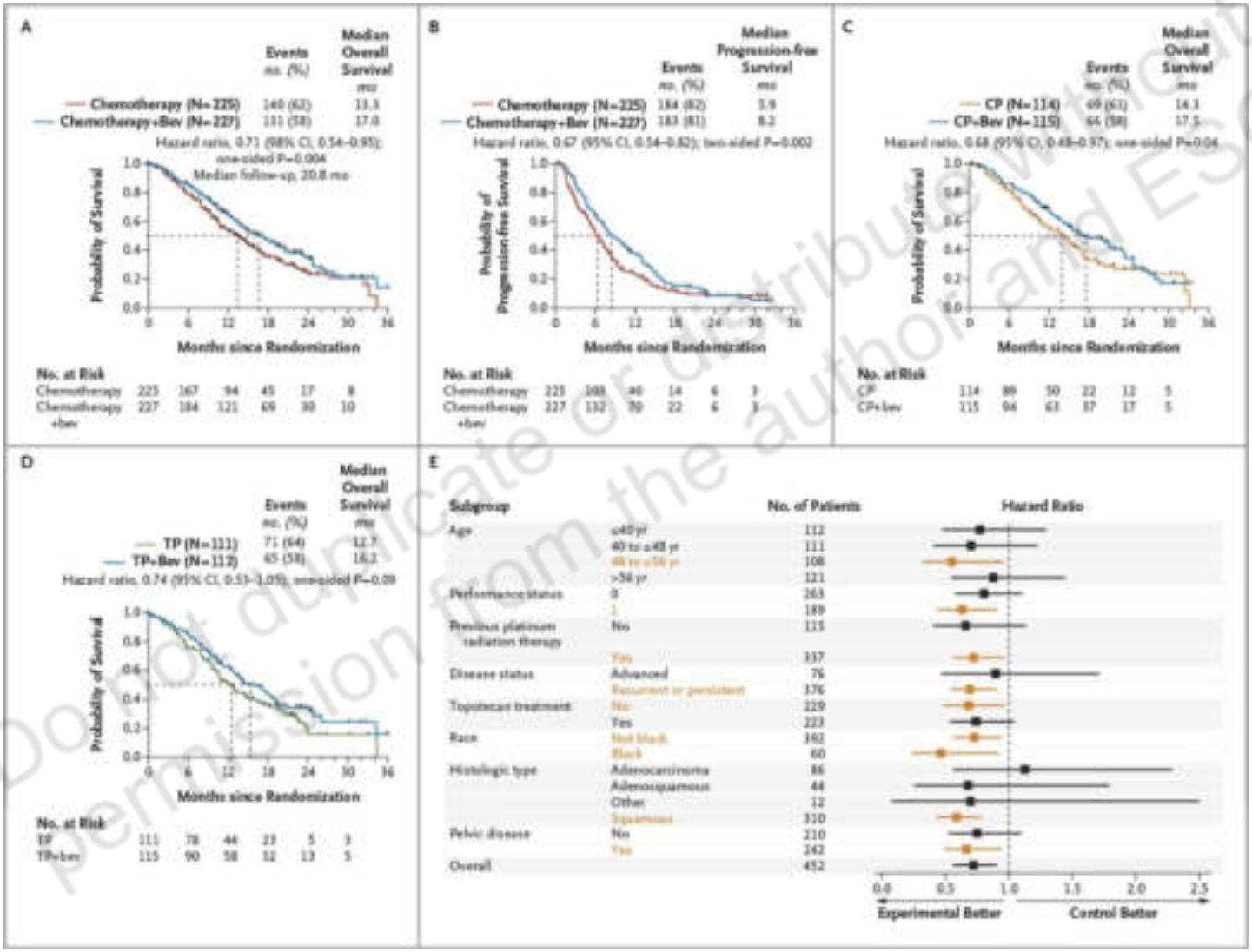
Tewari KS et al. N Engl J Med 2014;370:734-743

Effect of Incorporation of Bevacizumab on Survival



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Tewari KS et al. N Engl J Med 2014;370:734-743

Selected Adverse Events among the Study Patients, According to Treatment Group.

Event	Chemotherapy Alone (N=219)	Chemotherapy plus Bevacizumab (N=220)	Odds Ratio (95% CI)	P Value
	no. of patients (%)			
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12
Total†	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002
Hypertension (grade ≥2)‡	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001
CNS bleeding (grade ≥3)	0	0	NA	
Gastrointestinal bleeding (grade ≥3)§	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37
Genitourinary bleeding (grade ≥3)§	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12

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Tewari KS et al. N Engl J Med 2014;370:734-743

Selected Adverse Events among the Study Patients, According to Treatment Group.

Table 1. Selected Adverse Events among the Study Patients, According to Treatment Group.*

	Chemotherapy	Chemotherapy plus

The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median overall survival.

‡ Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 24 hours or a symptomatic increase in blood pressure by more than 20 mm Hg diastolic or to more than 150/100 mm Hg if the blood pressure was previously within the normal range.

§ Bleeding was managed primarily with supportive therapy and transfusions of packed red cells, most commonly in the outpatient setting.

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Tewari KS et al. N Engl J Med 2014;370:734-743

Single agent chemotherapy

Drug Name	Response Rate
Cisplatin	15%–25%
Ifosfamide	31%
Paclitaxel	17%
Vinorelbine	18%
Irinotecan	17%
Topotecan	16%
Docetaxel	13%
Gencitabine	8%

Alberts DS 1987; Thigpen JT 1989; Coleman RE 1986; Kudelka AP 1996; Verschraegen CF 1997

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Stage (FIGO Staging Criteria)	Standard Treatment Options
Stages IIB, III, and IVA cervical cancer	Radiation therapy with concomitant **chemotherapy**
	Interstitial brachytherapy
	Neoadjuvant **chemotherapy**
Stage IVB cervical cancer	Palliative radiation therapy
	Palliative **chemotherapy***
Recurrent cervical cancer	Radiation therapy and **chemotherapy**
	Palliative **chemotherapy***
	Pelvic exenteration

***+/- bevacizumab**

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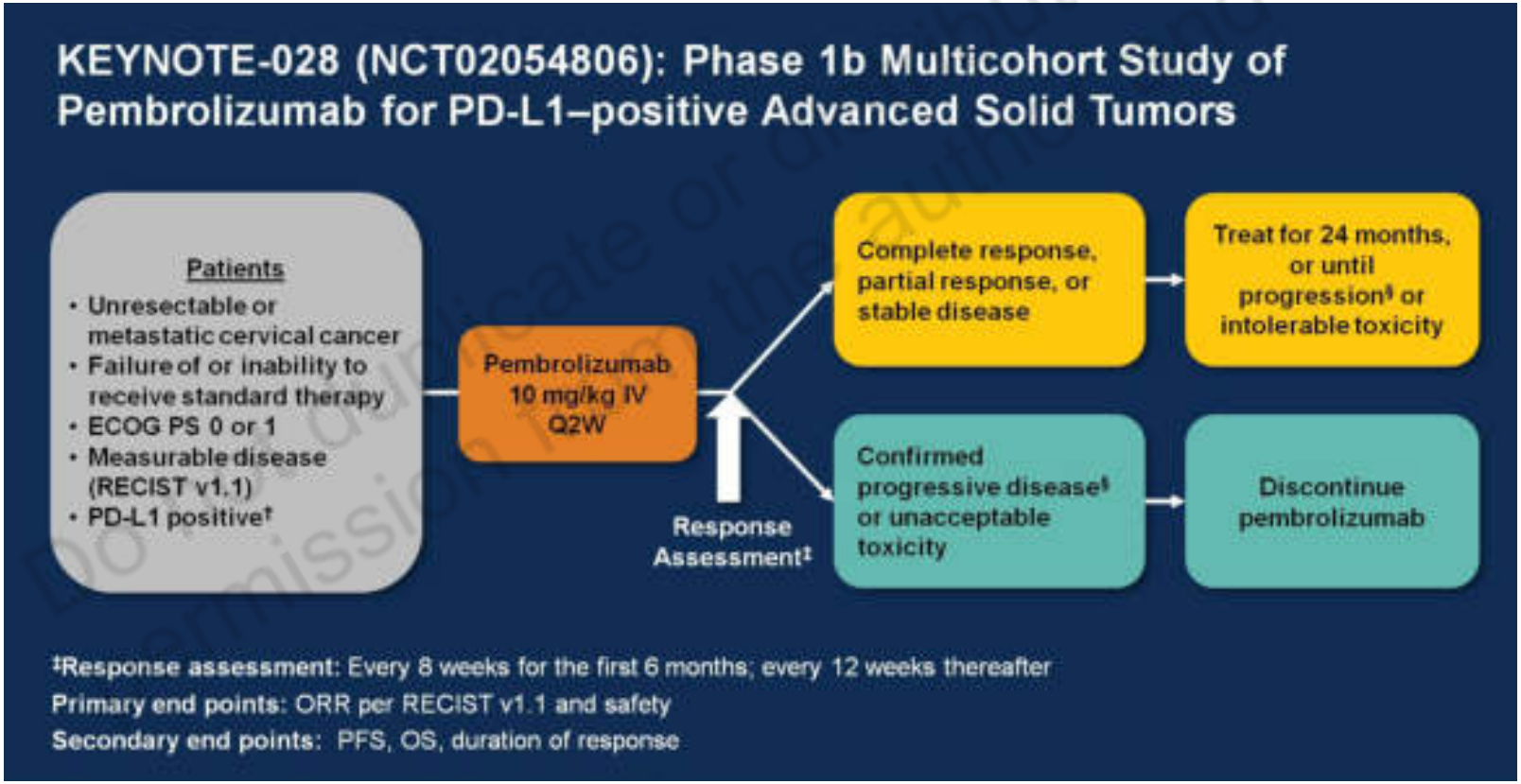
Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1–Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial



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Frenel JS et al. J Clin Oncol 2015, 35: 4035

Anti tumor activity- RECIST

Table 3. Best Overall Response as Assessed by Investigator Review According to RECIST v1.1 (N = 24)

Best Overall Response	No.	% (95% CI)
Partial response*	4	17 (5 to 37)
Stable disease	3	13 (3 to 32)
Progressive disease	16	67 (45 to 84)
No assessment†	1	4 (< 1 to 21)

NOTE. Only confirmed responses were included. Patients who received one or more doses of pembrolizumab and had measurable disease at baseline as per RECIST v1.1 were included.

Abbreviation: RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

*There were no complete responses.

†Patient was treated but had no postbaseline response evaluation because that patient discontinued the treatment as a result of an adverse event before the scan.

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Best Overall Response as Assessed by Investigator Review According to RECIST v1.1 (N = 24)

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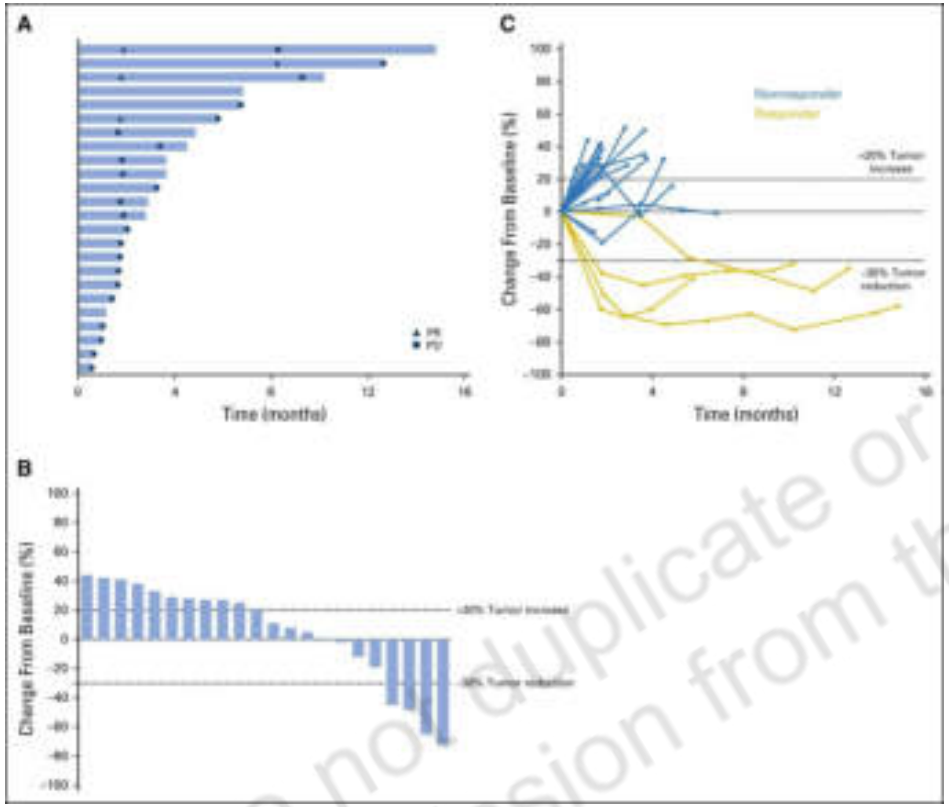

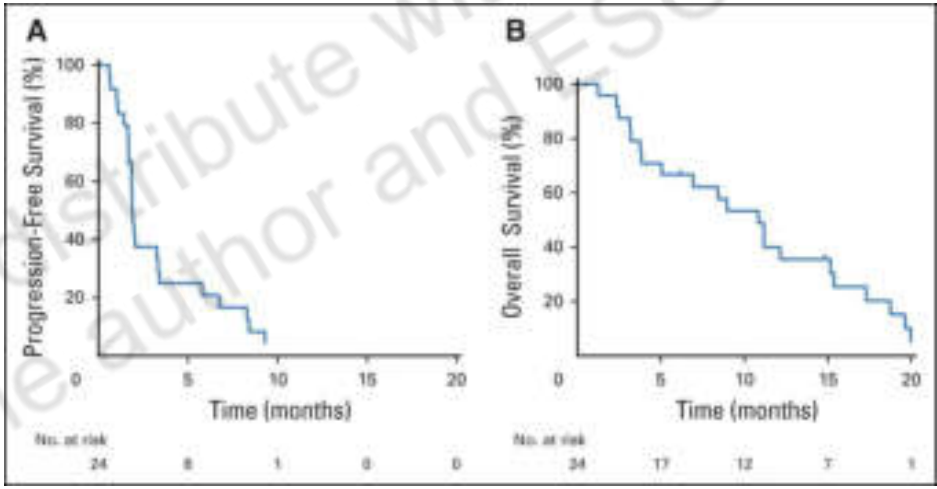

Fig 3. Kaplan-Meier estimates. (A) Progression-free survival. (B) Overall survival.

(A) Treatment exposure and duration of response (n = 24). The length of the bars corresponds with time to the last tumor assessment. (B) Best change from baseline in tumor size (n = 22). Dotted lines at 20% and −30% indicate the percentage change from baseline and represent progressive disease and partial response, respectively, per RECIST v1.1. (C) Longitudinal change from baseline in tumor size (n = 24). Dotted lines at 20% and −30% indicate the percentage change from baseline and represent progressive disease and partial response, respectively, per RECIST v1.1 PD, progressive disease; PR, partial response.

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Safety and Efficacy of Pembrolizumab in Advanced, Programmed Death Ligand 1–Positive Cervical Cancer: Results From the Phase Ib KEYNOTE-028 Trial

- Overall response: 17% (95% CI, 5% to 37%)
  - 4 pts (17%) PR
  - 3 pts (13%) SD
- Median duration of response (PR): 5.4 months (4.1 to 7.5 months)
- AEs: 18 pts (75%)
  - rash (n = 5; 21%) and pyrexia (n = 4; 17%) and occurred in ≥ 10% of patients.
  - 5 pts G3 AEs
  - No G4 AEs or deaths were observed.
- **Conclusion**
- In patients with programmed death ligand 1–positive advanced cervical cancer, pembrolizumab demonstrated antitumor activity and exhibited a safety profile consistent with that seen in other tumor types.

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ADXS11-001 immunotherapy in squamous or non-squamous persistent/recurrent metastatic cervical cancer: Results from stage 1 [and stage 2] of the phase II GOG/NRG-0265 study

NCT01266460

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ASCO 2016
Monday, June 6, 2016

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ADX11-001 immunotherapy
Attenuated *Listeria monocytogenes* (Lm), alive,
Secretion of E7 HPV-16 protein + truncated fragment of listeriolisina O (tLLO)
Randomized Phase II study of ADXS11-001 +/- cisplatin: 12m OS = 32%
Active in all HPV (16, 18, 45, others)

Take home messages

- Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality in women worldwide.
- Standard treatment for locally advanced disease is concomitant chemotherapy with weekly cisplatin and radiotherapy followed by brachytherapy
- Platinun doublets are indicated for recurrence or IVB disease
- Bevacizumab may be used in the palliative scenario in selected patients
- Carboplatin may be used in patients with impaired renal function replacing for cisplatin.

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Take home messages

- Immunotherapy is under investigation, with promising results
- A number of ongoing clinical trials are examining the role of adjuvant chemotherapy in addition to the standard-of-care treatment, low-dose chemotherapy (cisplatin) concurrent with pelvic radiotherapy for locally advanced cervical cancer.
- Women undergoing treatment for locally advanced cervical cancer experience significant psychosocial distress. Multidisciplinary supportive care may reduce the magnitude of long-term sequelae and improve quality of life.

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