

“Primum Non Nocere”
Above All, Do No Harm

Adjuvant Radiotherapy for Endometrial Cancer

Mansoor Raza Mirza, MD
Rigshospitalet
Copenhagen, Denmark

I Am a Medical & Radiation Oncologist

“In all affairs it’s a healthy thing now and then to hang a question mark on the things you have long taken for granted.”

Bertrand Russell

author, mathematician, & philosopher (1872–1970)

Nobel Prize Laureate

Need for level one evidence

**Adjuvant external beam
radiation therapy (EBRT) / brachytherapy**

Adjuvant EBRT + chemotherapy

Conclusions

Why Level One Evidence Is Important?

Phase II Trial in Ovarian Cancer With Gemcitabine

Results: 100% response rate

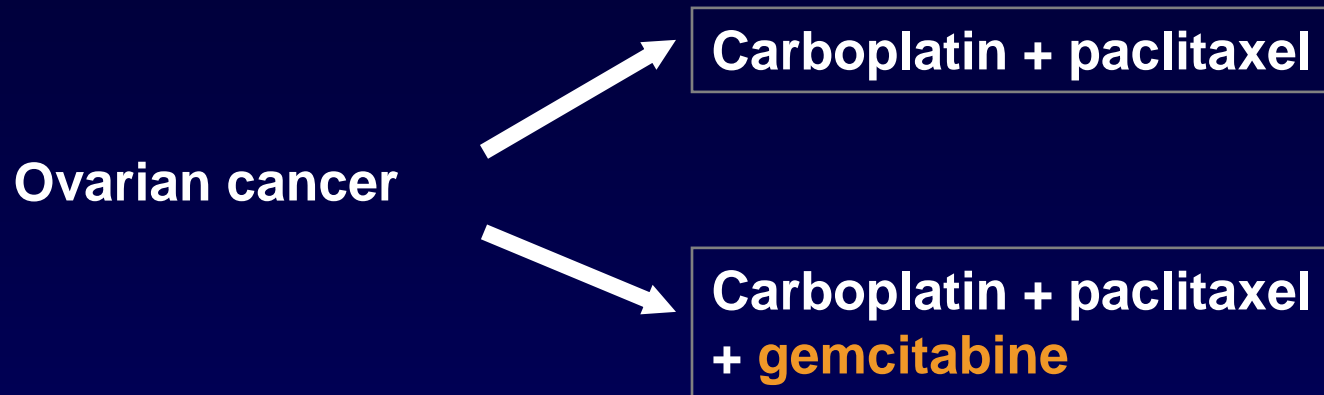
Ovarian cancer



Carboplatin + paclitaxel
+ **gemcitabine**

First-Line Phase III Trials in Ovarian Cancer

Addition of Third Drug - Gemcitabine



Agent	No. of studies	Design	Status
Gemcitabine	2	Triplet	NEGATIVE
	1	Sequential doublet	

Need for level one evidence

Adjuvant EBRT / brachytherapy

Adjuvant EBRT + chemotherapy

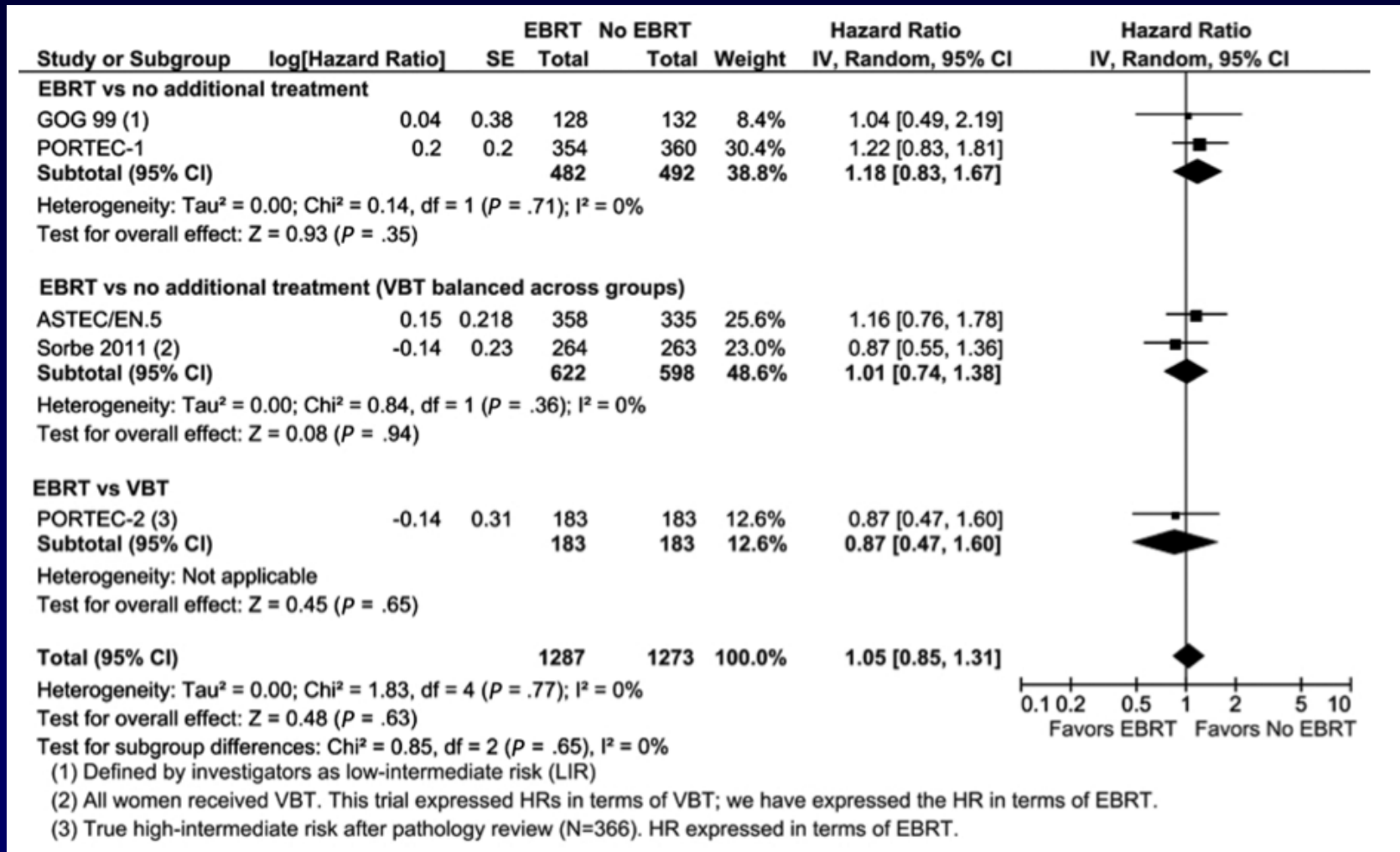
Conclusions

Level One Evidence for Adjuvant Radiotherapy in Endometrial Cancer?

Cochrane Meta-Analysis of 8 Clinical Trials (n = 3628)

Aalders; ASTEC; GOG99; PORTEC1; PORTEC2; Soderini2003; Sorbe2009; Sorbe 2011

Overall Survival



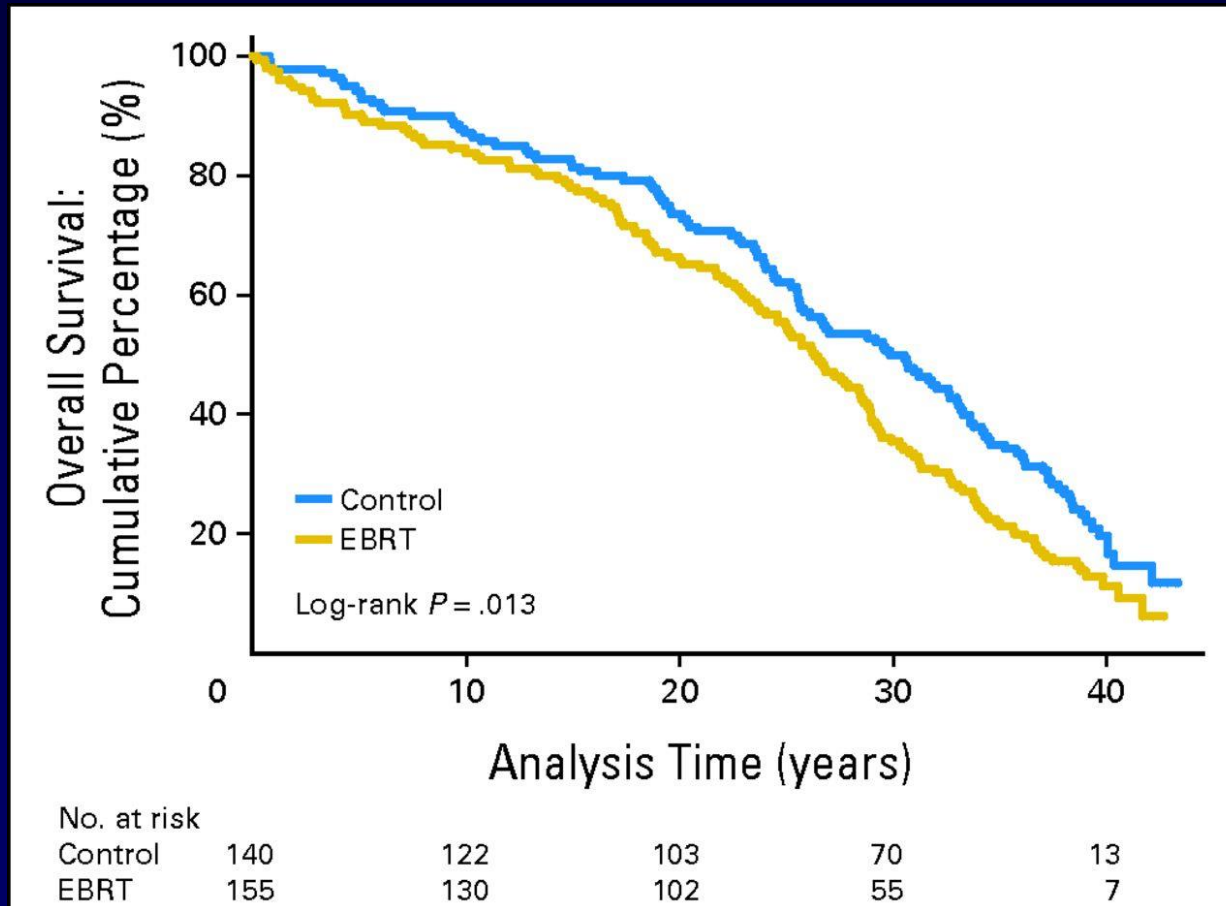
Kong A, et al. *J Natl Cancer Inst.* 2012;104(21):1625-1634.

Aalders J, et al. *Obstet Gynecol.* 1980;56(4):419-427. Soderini A, et al. *Int J Gynecol Cancer.* 2003;13(suppl 1): Abstract P0147:78.

Sorbe B, et al. *Int J Gynecol Cancer.* 2009;19(5):873-878. Sorbe B, et al. *Int J Radiat Oncol Biol Phys.* 2012 82(3):1249-1255.

Long Term Outcomes After EBRT for Early Stage Endometrial Cancer, Oslo Trial – Revisited!

Overall survival in patients <60 years, intent-to-treat

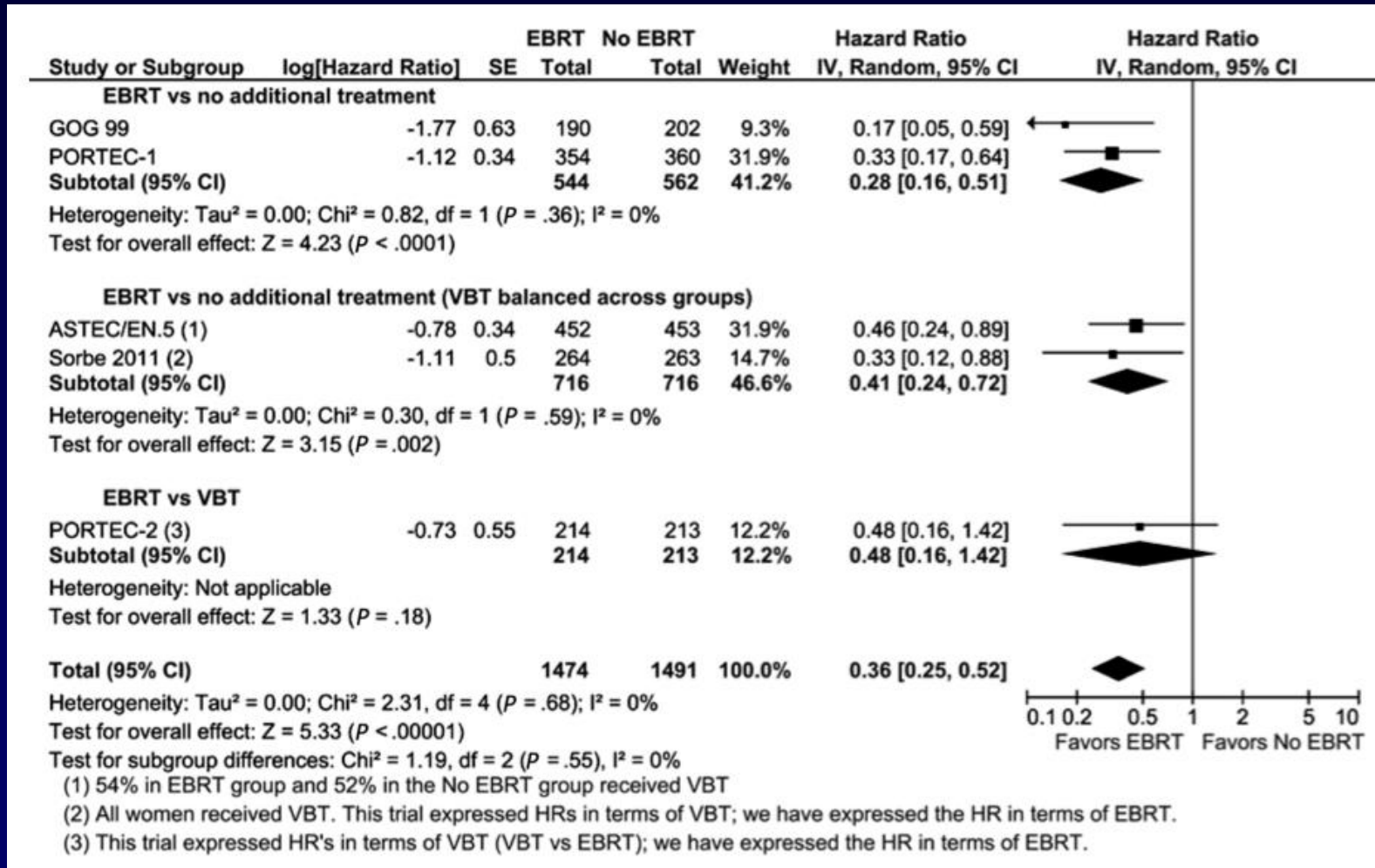


Cochrane Meta-Analysis **Long-Term Follow-Up**

- Radiotherapy deteriorates overall survival
 - PORTEC 1 & Aalders
 - HR = 1.26; CI = 1.03-1.54

Cochrane Meta-Analysis

Locoregional Control

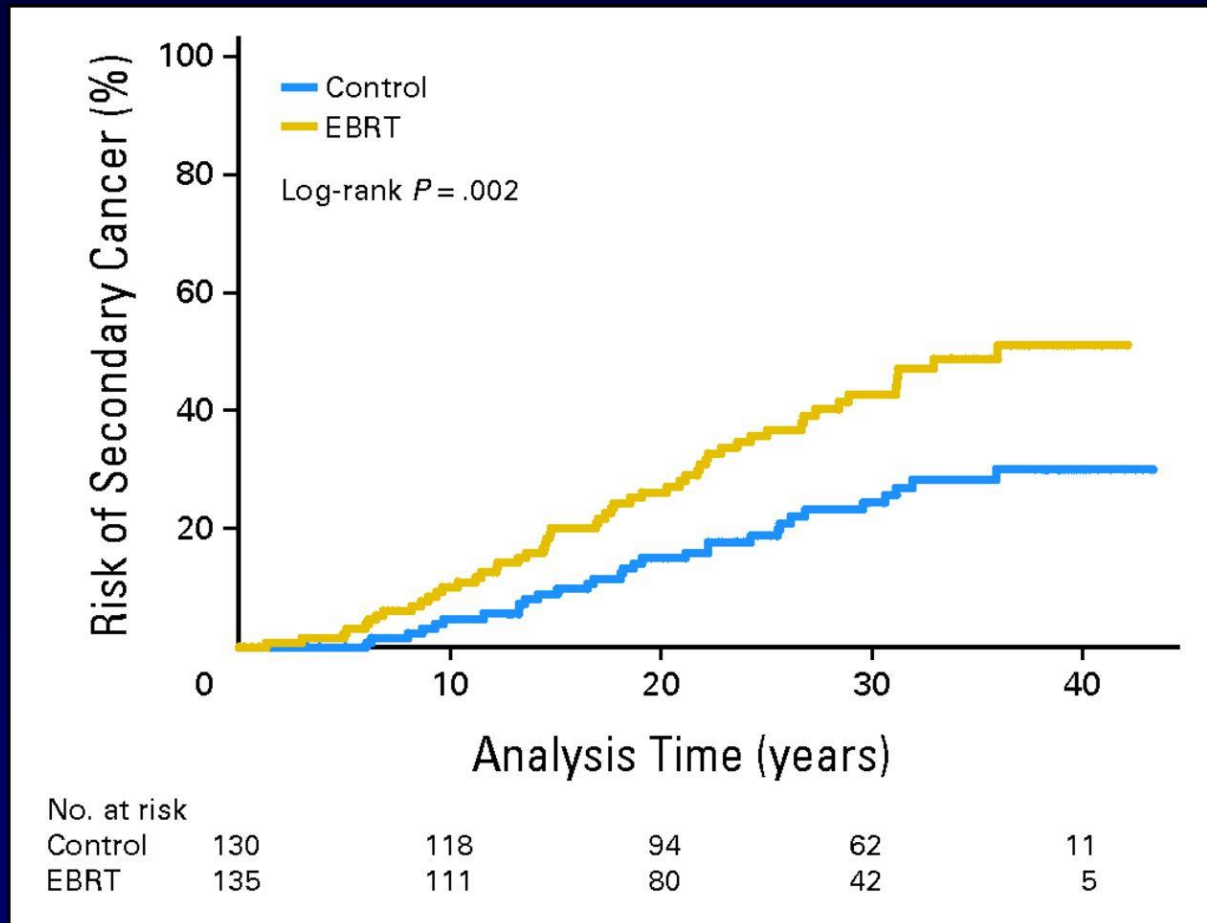


Cochrane Meta-Analysis **Toxicity & QoL**

- **Acute grade 3-4 (5) toxicity**
 - 2 trials; n = 1328; HR = 4.68; CI = 1.35-16.16
 - Fatal complications: 4
- **Late grade 3-4 toxicity**
 - 6 trials; n = 3501; HR = 2.58; CI = 1.61-4.11
- **Deteriorated quality of life**
 - Urinary incontinence, diarrhea, fecal leakage, limited daily activities
 - Worsened physical functioning
 - Bodily pain

Risk of Secondary Cancer

Risk of secondary cancer in women younger than 60 years at treatment



Univariate Cox regression HR: 1.99 (95% CI: 1.27-3.10)

Stage I: Low-Risk Women Increase Risk of Endometrial Cancer-Related Death

	Grade I	Grade II	Grade III	Serous/ clear cell
IA	-	-	+	+
IB	-	-	+	+
IC	+	+	+	+
IIA	+	+	+	+
HR: 2.64 (95% CI: 1.05 – 6.66)				

Stage I: Intermediate-Risk Women No Benefit in Survival

	Grade I	Grade II	Grade III	Serous/ clear cell
IA	-	-	-	+
IB	-	-	-	+
IC	-	-	+	+
IIA	+	+	+	+

HR: 1.05 (95% CI: 0.85 – 1.31)

Stage I: High-Risk Women

No Benefit in Survival

	Grade I	Grade II	Grade III	Serous/ clear cell
IA	—	—	—	—
IB	—	—	—	—
IC	—	—	—	—
IIA	—	—	—	—
HR: 0.91 (95% CI: 0.60 – 1.39)				

Interpretation of a Radiotherapist

- “If a **man** radiotherapist is offered a fact which goes against his instincts, he will scrutinize it closely, and unless the evidence is overwhelming, he will refuse to believe it.
- If, on the other hand, he is offered something which affords a reason for acting in accordance to his instincts, he will accept it even on the slightest evidence. The origin of myths is explained in this way.”

Bertrand Russell

author, mathematician, & philosopher (1872–1970)

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PORTEC-2

FIGO stage I

Medium risk patients
(n = 715)

Hysterectomy

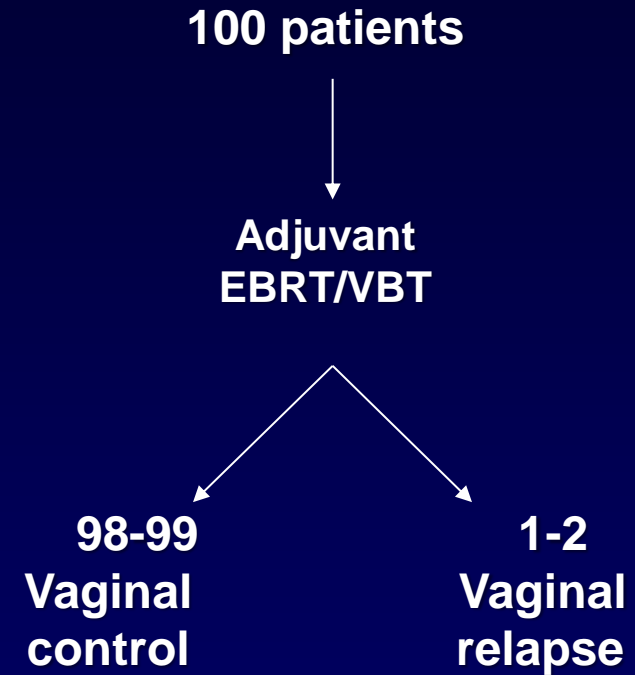
EBRT
(n = 354)

Vaginal brachytherapy (VBT)
(n = 361)

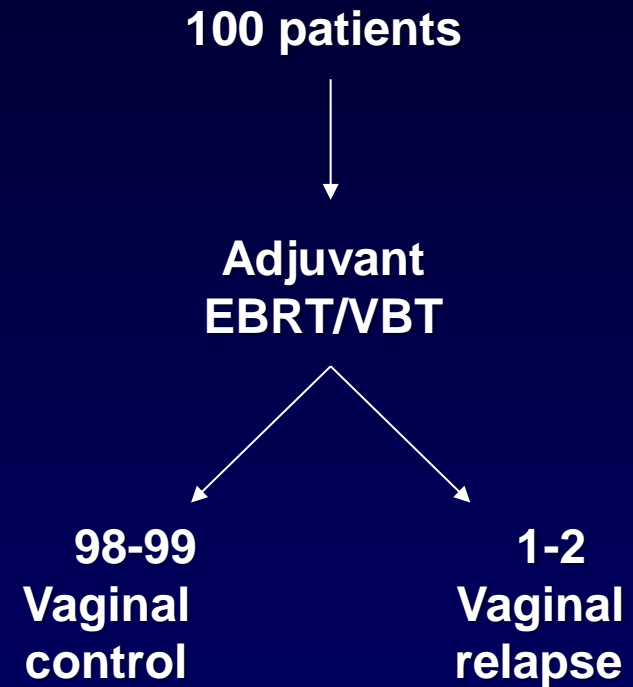
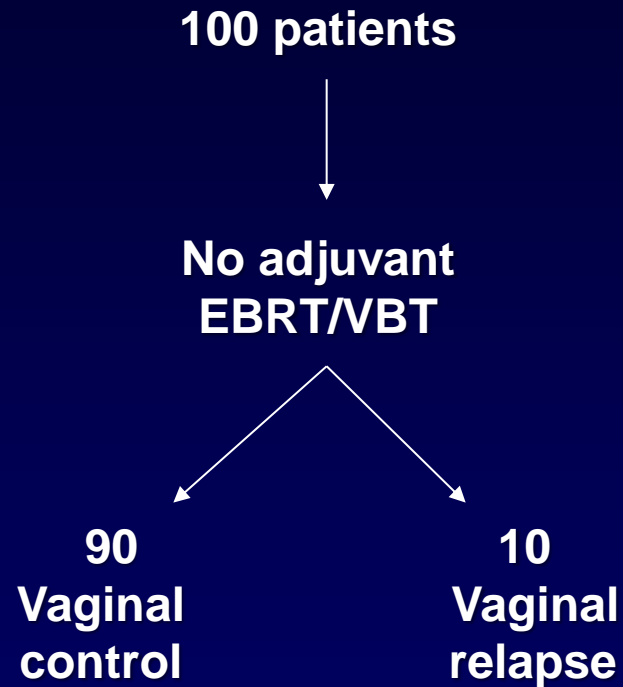
5-year actuarial percentages

	EBRT	VBT	
Vaginal relapse	2%	1%	$P < .001$
Overall survival	81%	85%	$P = .31$

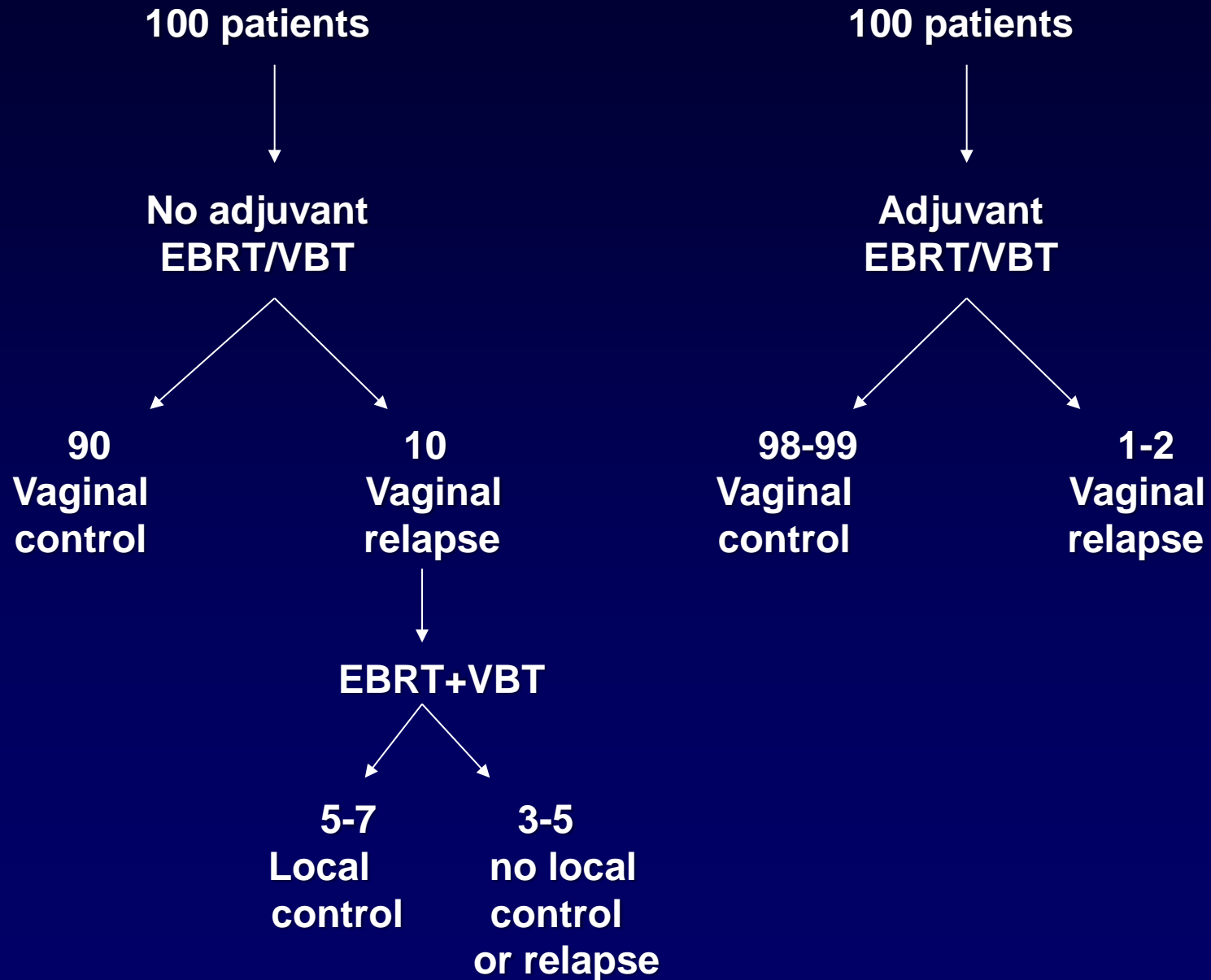
Local Control



Local Control



Local Control



Radiotherapy of Vaginal Relapse in Patients Not Treated Primarily With Adjuvant Radiotherapy

- **Mandall 1985:** 95% (*n* =20) (vagina)
- **Curran 1988:** 100% (*n* = 15) (vagina)
- **Ackerman 1996:** 79% (*n* = 32) (vagina)
- **Poulsen 1997:** 88% (*n* = 17) (vagina, FU 61 months, low risk)
- **Roberts 1998:** 61% (*n* = 16)
- **Nag 2002:** 77% 8-yr disease-specific survival (vagina, *n* = 13)
- **Creutzberg 2003:** 65% 5-yr OS in vaginal relapses (*n* = 35, intermed risk)
- **Jingran 2003:** 86% 5-yr local control in vaginal relapses (*n* = 52)
- **Hogberg 2004:** 83% survival 39 months after relapse (*n* =12)
- **Leuven 2006:** 100% local control in 9 vaginal relapses treated at relapse with radiotherapy
- **Huh WK 2007:** 81% local control and 75% 5-yr OS and in 69 relapses (mean FU 63 months)
- ...

CURE RATE IS HIGH IN CENTRAL PELVIC RELAPSES

Need for level one evidence

Adjuvant EBRT / brachytherapy

Adjuvant EBRT + chemotherapy

Conclusions

5-Year Survival - FIGO

<u>Stage</u>		<u>G1</u>	<u>G2</u>	<u>G3</u>
Ia	1a	93	91	80
Ib	1a	92	93	82
Ic	1b	91	86	75
IIa	1b	90	84	68
IIb	2	81	77	65

Phase III Trials of Adjuvant Radiotherapy With Chemotherapy

	GOG 34 Morrow, et al	Finnish Study Kuoppala, et al	GOG184 Homeslay, et al	NSGO9501/ILAIDE Hogberg, et al
Population (stage)	1-3	1A-B, G3 1C-3A	3-4	1-3
n	181	157	586	534
Regimen	RT RT-Doxo8	RT (split) CEP/RT/CEP/RT/CEP	RT-AP6 RT-TAP6	RT RT+CT
PFS	-	NS	NS	69 78 HR 0.63*
OS	NS	NS	-	HR 0.69 NS
Cancer specific survival	-	-	-	HR 0.55* <i>Ad hoc</i>

Morrow CP, et al. *Gynecol Oncol.* 1991;40(1):55-65. Kuoppala T, et al. *Gynecol Oncol.* 2008;110(2):190-195. Homesley HD, et al. *Gynecol Oncol.* 2009;112(3):543-552. Hogberg T, et al. *Eur J Cancer.* 2010;46(13):2422-2431.

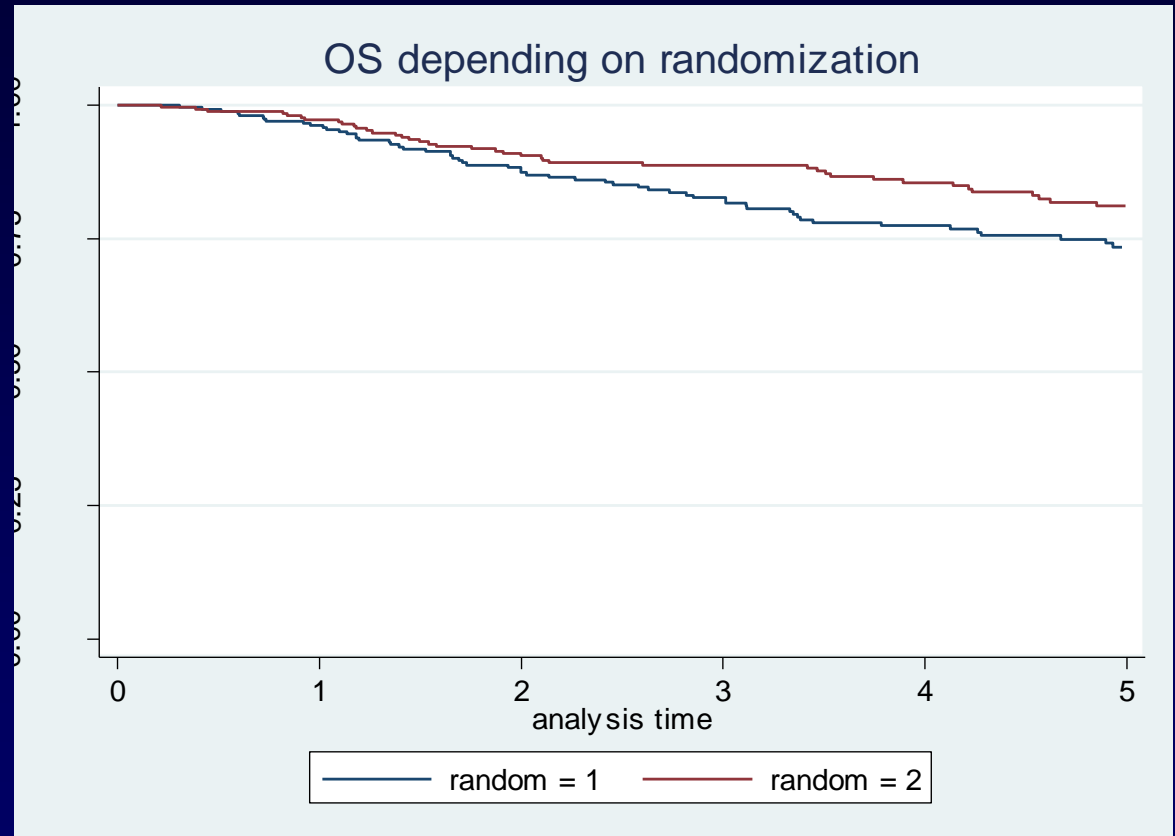
NSGO EC-9501/EORTC-55991/ILIADE

Inclusion

RT → CT

Stage
Ic-G3
II, IIIa,
IIIc

RT



PFS: HR 0.63 (CI 0.44-0.89);

OS: HR 0.69 (CI 0.46-1.03);

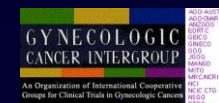
CSS adhoc : HR 0.55 (CI 0.35-0.88)

Pelvic Lymphnode Metastases (%)

<u>Depth of invasion</u>	<u>G1</u>	<u>G2</u>	<u>G3</u>
No invasion	0	3-4	0
<50%	0-3	5-10	7-9
>50%	0-11	17-19	28-34

LNE not performed in NSGO-EC-9501

Is the difference in survival due to effect on node-positive patients only (stage IIIc)?



“Primum Non Nocere”

A Phase III Trial of Postoperative Chemotherapy or No Further Treatment for Patients With Node-Negative Stage I-II Intermediate or High Risk Endometrial Cancer

ENGOT-EN2-DGCG / EORTC-55102

Chief Investigators: Mirza (DGCG); Amant (EORTC)

N = 678

**Endometrioid:
Stage I-G3; II
Non-endometrioid:
Stage I-II**

**Chemotherapy
carboplatin-paclitaxel x 6
+ *brachytherapy***

**Observation
+ *brachytherapy***

Supported by



Conclusions

“Primum Non Nocere”

Above All, Do No Harm

- No improvement in survival by adjuvant radiotherapy
- Decreased survival after EBRT in women <60 years of age at treatment
- Increased incidence of secondary cancer after EBRT, especially in women <60 years of age at treatment
- Improvement in survival from adjuvant chemotherapy + radiation may come from chemotherapy alone
- Trials are needed to establish role of adjuvant chemotherapy

2015

Progress and
Controversies
in Gynecologic
Oncology
Conference

