"Primum Non Nocere" Above All, Do No Harm

Adjuvant Radiotherapy for Endometrial Cancer

Mansoor Raza Mirza, MD

Rigshospitalet Copenhagen, Denmark



"Primum Non Nocere"

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

"Primum Non Nocere"

Why Level One Evidence Is Important?

Phase II Trial in Ovarian Cancer With Gemcitabine

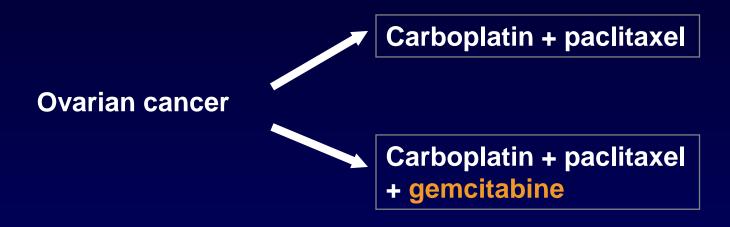
Results: 100% response rate

Ovarian cancer



Carboplatin + paclitaxel + gemcitabine

First-Line Phase III Trials in Ovarian Cancer Addition of Third Drug - Gemcitabine



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

"Primum Non Nocere"

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

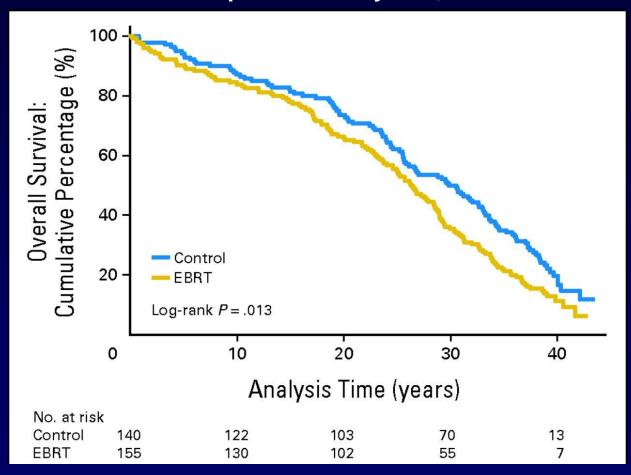
Overall Survival

			EBRT	No EBRT		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
EBRT vs no additiona	al treatment						
GOG 99 (1)	0.04	0.38	128	132	8.4%	1.04 [0.49, 2.19]	
PORTEC-1	0.2	0.2	354	360	30.4%	1.22 [0.83, 1.81]	+-
Subtotal (95% CI)			482	492	38.8%	1.18 [0.83, 1.67]	*
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.14, df =	1(P =	.71); l²	= 0%			
Test for overall effect: 2	Z = 0.93 (P = .35)						
EDDT	-14						
EBRT vs no additiona	•						
ASTEC/EN.5	0.15		358	335	25.6%	1.16 [0.76, 1.78]	
Sorbe 2011 (2)	-0.14	0.23	264	263	23.0%	0.87 [0.55, 1.36]	
Subtotal (95% CI)			622	598	48.6%	1.01 [0.74, 1.38]	—
Heterogeneity: Tau ² = 0		1 (P =	.36); I ²	= 0%			
Test for overall effect: 2	Z = 0.08 (P = .94)						
EBRT vs VBT							
PORTEC-2 (3)	-0.14	0.31	183	183	12.6%	0.87 [0.47, 1.60]	
Subtotal (95% CI)			183	183	12.6%	0.87 [0.47, 1.60]	-
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 0.45 (P = .65)						
Total (95% CI)			1287	1273	100.0%	1.05 [0.85, 1.31]	.
, ,	0.00· Chi² = 1.83 df =	4 (D =			100.070		
Heterogeneity: Tau ² = 0.00; Chi ² = 1.83, df = 4 (P = .77); I ² = 0% Test for overall effect: Z = 0.48 (P = .63) Test for overall effect: Z = 0.48 (P = .63)							
Test for overall effect: $Z = 0.48$ ($P = .03$) Test for subgroup differences: Chi ² = 0.85, df = 2 ($P = .65$), $I^2 = 0\%$							
(1) Defined by investigators as low-intermediate risk (LIR)							
(2) All women received VBT. This trial expressed HRs in terms of VBT; we have expressed the HR in terms of EBRT.							
(3) True high-intermediate risk after pathology review (N=366). HR expressed in terms of EBRT.							

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

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

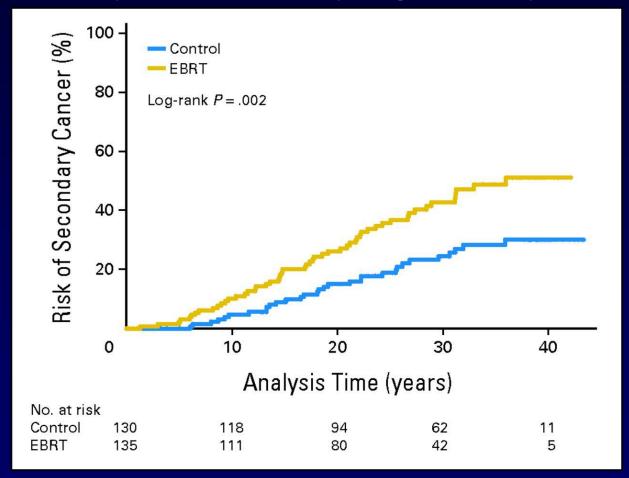
				No EBRT		Hazard Ratio	Hazard Ratio
Study or Subgroup EBRT vs no addit	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
		0.00	400	200	0.00/	0.47 (0.05. 0.50)	
GOG 99	-1.77		190		9.3%	0.17 [0.05, 0.59]	` <u> </u>
PORTEC-1 Subtotal (95% CI)	-1.12	0.34	354 544	360 562	31.9% 41.2 %	0.33 [0.17, 0.64] 0.28 [0.16, 0.51]	•
Heterogeneity: Tau ² = 0.	00; Chi ² = 0.82, df =	= 1 (P	= .36);	$ ^2 = 0\%$			
Test for overall effect: Z		•					
EBRT vs no addit	ional treatment (VI	BT ba	lanced	across gro	ups)		
ASTEC/EN.5 (1)	-0.78	0.34	452	453	31.9%	0.46 [0.24, 0.89]	
Sorbe 2011 (2)	-1.11	0.5	264	263	14.7%	0.33 [0.12, 0.88]	-
Subtotal (95% CI)			716	716	46.6%	0.41 [0.24, 0.72]	•
Heterogeneity: Tau ² = 0. Test for overall effect: Z EBRT vs VBT	일일이 뭐하는데 있다는 그렇게 되었다면 되었다면 되었다.	- 1 (P	59);	F = 0%			
PORTEC-2 (3)	-0.73	0.55	214	213 213	12.2%	0.48 [0.16, 1.42]	
Subtotal (95% CI)			214	213	12.2%	0.48 [0.16, 1.42]	
Heterogeneity: Not appli Test for overall effect: Z							
Total (95% CI)			1474	1491	100.0%	0.36 [0.25, 0.52]	•
Heterogeneity: Tau ² = 0.	00; Chi2 = 2.31, df =	= 4 (P	= .68); 1	2 = 0%			0.10.2 0.5 1 2 5 10
Test for overall effect: Z							0.1 0.2 0.5 1 2 5 10 Favors EBRT Favors No EBRT
Test for subgroup differe (1) 54% in EBRT group	[2017] [11] [12] [12] [12] [12] [12] [13] [14] [14] [15] [15] [15]				зт		PAVOIS EDICI PAVOIS NO EDICI
(2) All women received							
(3) This trial expressed	HR's in terms of VE	BT (VE	BT vs E	BRT); we ha	ive expres	ssed the HR in terms of	EBRT.

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; Cl = 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)

Onsrud M, et al. *J Clin Oncol*. 2013;31(31):3951-3956.

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)
Nobel Prize Laureate

PORTEC-2

FIGO stage I

Medium risk patients (n = 715)

5-year actuarial percentages

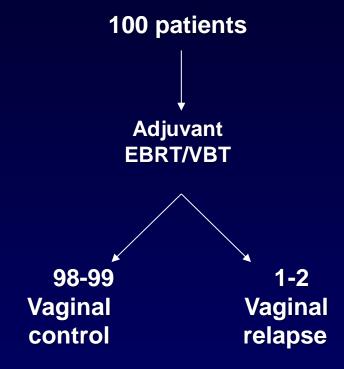
EBRT (n = 354)

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

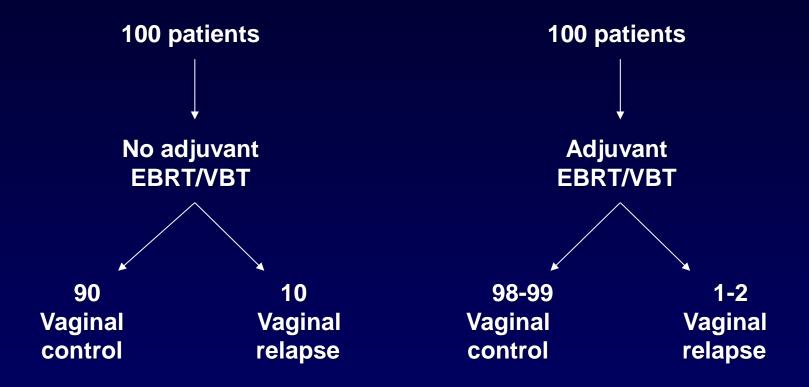
Hysterectomy

Vaginal brachytherapy (VBT)

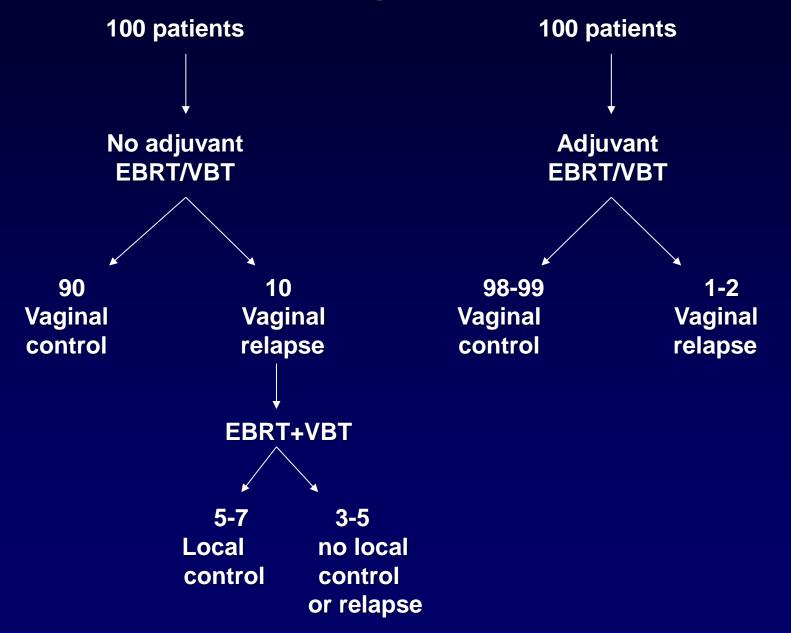
Local Control



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>e</u>	G1	G2	<u>G3</u>
la	1a	93	91	80
lb	1a	92	93	82
lc	1b	91	86	75
lla	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* Ad hoc

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.



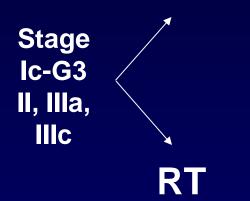


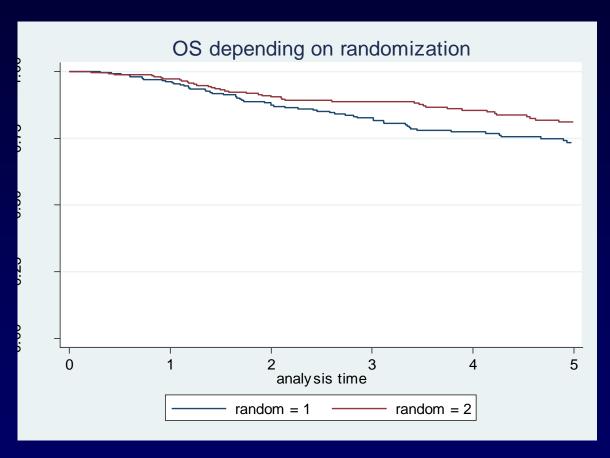


NSGO EC-9501/EORTC-55991/ILIADE

Inclusion

RT→ CT





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 (%)

Depth of invasion	G1	G2	<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)?





















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

