Papel de la Radioterapia +/- Quimioterapia en el Tratamiento Adyuvante de Cancer de Endometrio. Evidencia Clínica

Higinia R. Cardenes MD PhD
Professor Radiation Oncology
Department of Radiation Oncology
Weill Cornell Medicine. New York

Definition of Risk Groups in EC

Low-risk: grade 1-2, endometrioid histology, confined to the endometrium (subset of IA)

- The overall probability of recurrence in these groups is very low following surgical treatment alone

Intermediate-risk: uterine-limited cancer that invades the myometrium (St IA or IB) or with occult cervical stromal invasion (stage II).

- Higher risk of recurrence than patients whose tumors are confined to the endometrium
- Other adverse prognostic factors used to stratify women into high and low-intermediate-risk
  - Age
  - Outer one-third myometrial invasion
  - Grade 2 or 3 differentiation
  - Presence of Lymphovascular invasion

High-risk: stage III or higher EC regardless of histology. **Any Stage UPSC, CCC**

- These women are at a high risk of relapse and death

(*) National Comprehensive Cancer Network (NCCN): involvement of the lower uterine segment is considered as part of the group with intermediate-risk endometrial cancer

PORT – St I & II (occult) EC RCTs

- Six prospective RCT's have evaluated the role of adjuvant EBRT in early stage EC
  - **Norwegian**
  - **PORTEC -1**
  - **GOG -99**
  - **ASTEC/EN 5**
  - **PORTEC -2**
  - **Swedish Trial**

Adjuvant RT decreases the risk of LRR in IR-EC, without significant impact in overall survival

The use of postoperative EBRT should be limited to patients with sufficiently high risk of LRR (≥ 10-15%)

Decision to be made based on known risk factors: Age ≥60, grade 2-3, DMI, LUS/cervical involvement and LVSI

High-Intermediate Risk Early-Stage EC

GOG definition

Based on age and any of 3 factors

- **DMI, G 2-3, (+) LVSI**

70 yo with 1 RF

50-69 yo with 2 RF

18 yo with all 3 RF

Two-thirds of all recurrences were in women who met these criteria

PORTEC definition

Based on presence of 2 of 3 factors:

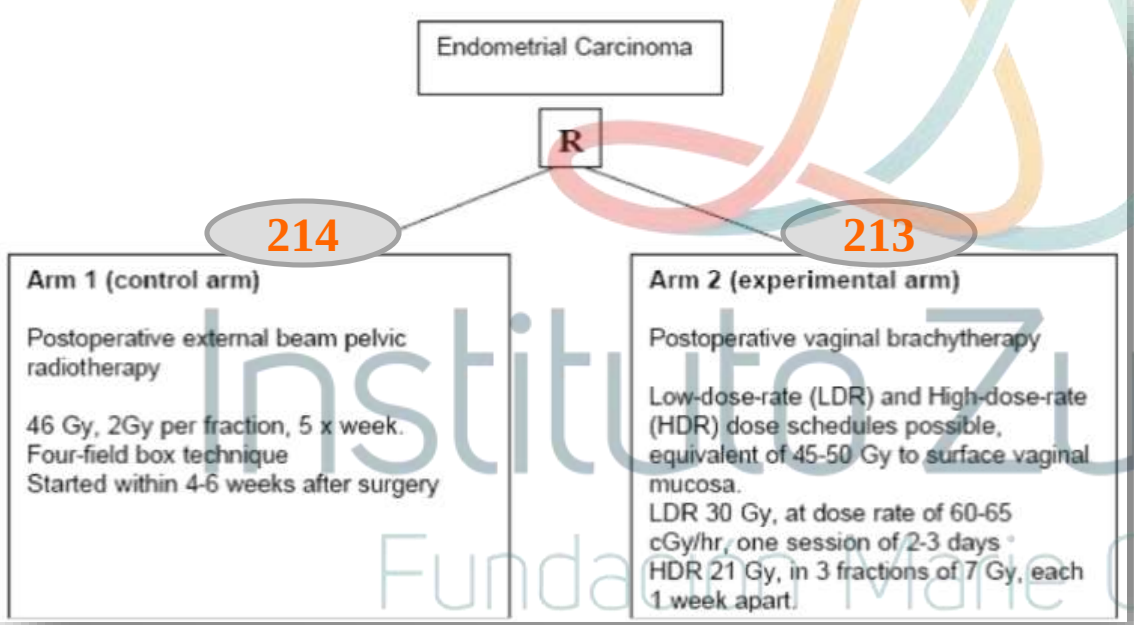
- **Age >60 years, ≥50% MI, and grade 3**

Observation associated with higher rate of relapse in the pelvis

However, the highest-risk group (G3, ≥50% MI) was not eligible for this trial

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial

RA Nout, VTH BM Smit, H Putter, IM Jürgenliemk-Schulz, JJ Jobsen, LCH W Lutgens, EM van der Steen-Banasik, JW M Mens, A Slot, MC Stenfert Kroese, BNF M van Bunningen, AC Ansink, WL J van Putten, CL Creutzberg, for the PORTEC Study Group



Primary endpoint: Vaginal Relapse Rate

Secondary: Quality of Life, Survival

Endometrial carcinoma, with one of the following combinations of postoperative FIGO stage and age:

a) Stage 1C grade 1 of 2 and age 60 or over
b) Stage 1B grade 3 and age 60 or over
c) Stage 2A, any age, grade 1 or 2
d) Stage 2A, any age, grade 3 with <1/2 myometrial invasion

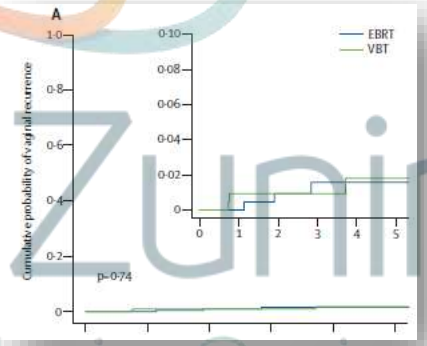
Surgery consisted of a total abdominal hysterectomy and bilateral salping-oophorectomy (TAH-BSO)

PORTEC-2 Trial . 5 year data

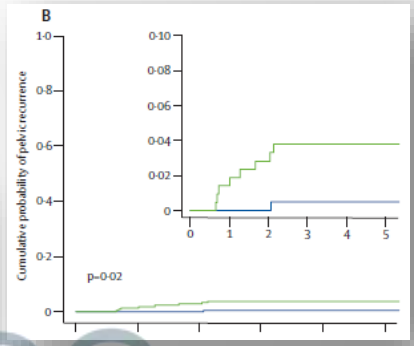
R. Nout et al. The Lancet, 2010; 375: 816-823

Outcome	EBRT	IVB	P value
Vaginal relapses	1.6%	1.8%	NS
LRR (Vagina+/- Pelvis)	2%	5%	NS
Pelvic relapses	0.5%	3.8%	P=0.02
Distant relapses	5.7%	8.3%	NS
DFS	78%	83%	NS
OS	80%	85%	NS
Grade 1-2 GI tox.	54%	13%	

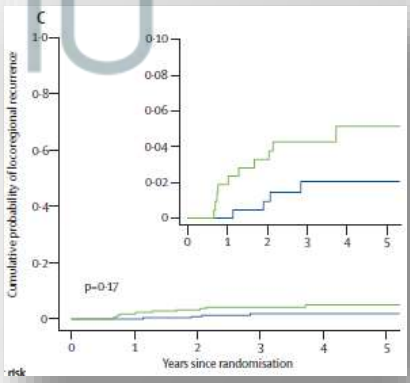
Vaginal recurrences



Pelvic recurrences



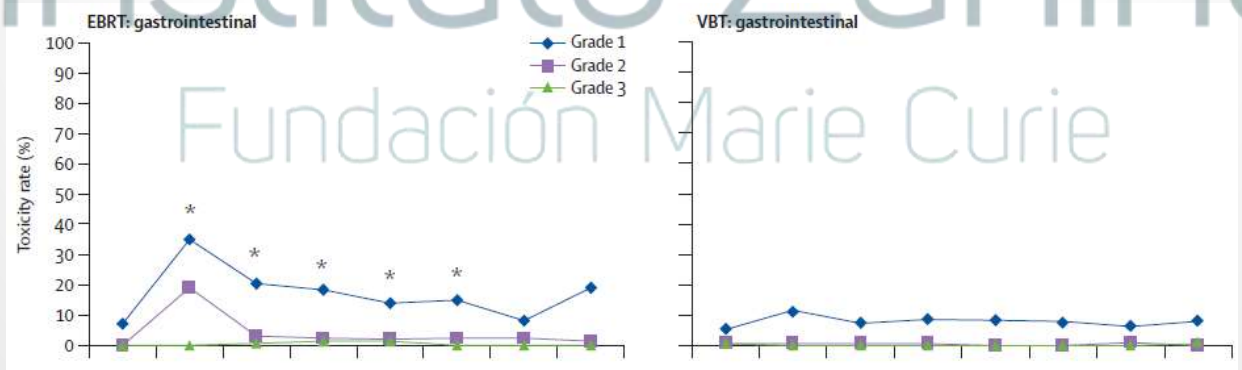
Loco-regional recurrences



PORTEC-2 Trial

R. Nout et al. The Lancet, 2010; 375: 816-823

- **Significantly decreased acute grade 1-2 GI toxicity with IVB**
  - 12.6% vs 54%
- **Overall, significant improvement in the QOL**
  - Less impairment in daily activities + Improved social functioning
- Based on the results of this trial we can only conclude that EBRT is as effective as brachytherapy in patients with intermediate high risk early stage EC as defined in this trial
- **Exclusion of IC-G3, IIA-G3->50% MI and IIB (occult)**



Ten-year results of the PORTEC-2 trial for high-intermediate risk endometrial carcinoma: improving patient selection for adjuvant therapy

British Journal of Cancer (2018) 119:1067–1074

B. G. Wortman[1], C. L. Creutzberg[1], H. Putter[2], I. M. Jürgenliemk-Schulz[3], J. J. Jobsen[4], L. C. H. W. Lutgens[5], E. M. van der Steen-Banasik[6], J. W. M. Mens[7], A. Slot[8], M. C. Stenfert Kroese[9], B. van Triest[10], H. W. Nijman[11], E. Stelloo[12], T. Bosse[12], S. M. de Boer[1], W. L. J. van Putten[13], V. T. H. B. M Smit[12] and R. A. Nout[1] for the PORTEC Study Group

Evaluate whether specific Clinico-pathologic and molecular risk factors can be used to determine optimal adjuvant treatment for subgroups at higher risk of recurrence

- IHC and DNA analysis were used to assess:
  - Polymerase-epsilon (POLE) mutations
  - Microsatellite instability (MSI)
  - P53 protein expression (scored as p53-wild type/mutant/null staining)
  - L1CAM (+) = > 10% expression
  - The presence of substantial LVSI

It was hypothesized that a small subgroup of patients with unfavorable risk features such as p53 mutation, L1CAM expression (> 10%), or substantial LVSI might have had better pelvic control if they had received EBRT

Cancer Genome Atlas (TCGA) Genomic Characterization, 2013

Mutation of the tumor suppressor gene p53 is related to

- Early tumor progression
- Grade 3 and with non-endometrial (mostly serous) histology

POLE mutation leads to only rare recurrence and excellent outcomes

MSI: intermediate risk factor, associated with Lynch syndrome; therapeutic implications

- More recently MSI detection has been replaced by analysis of mismatch repair deficiency (MMRd), and detection of MLH-1 promotor hypermethylation in those with MMRd21

Substantial LVSI (diffuse or multifocal) is associated with

- Risk of (microscopic) nodal metastases
- Higher rates of recurrence and lower CSS, both in the presence and absence of lymph node metastases

L1CAM is a cell adhesion molecule and mediates cell motility, is associated with

- Epithelial mesenchymal transition and early disease spread
- L1CAM has been shown to be an independent risk factor, frequently associated with, but independent from TP53 mutation

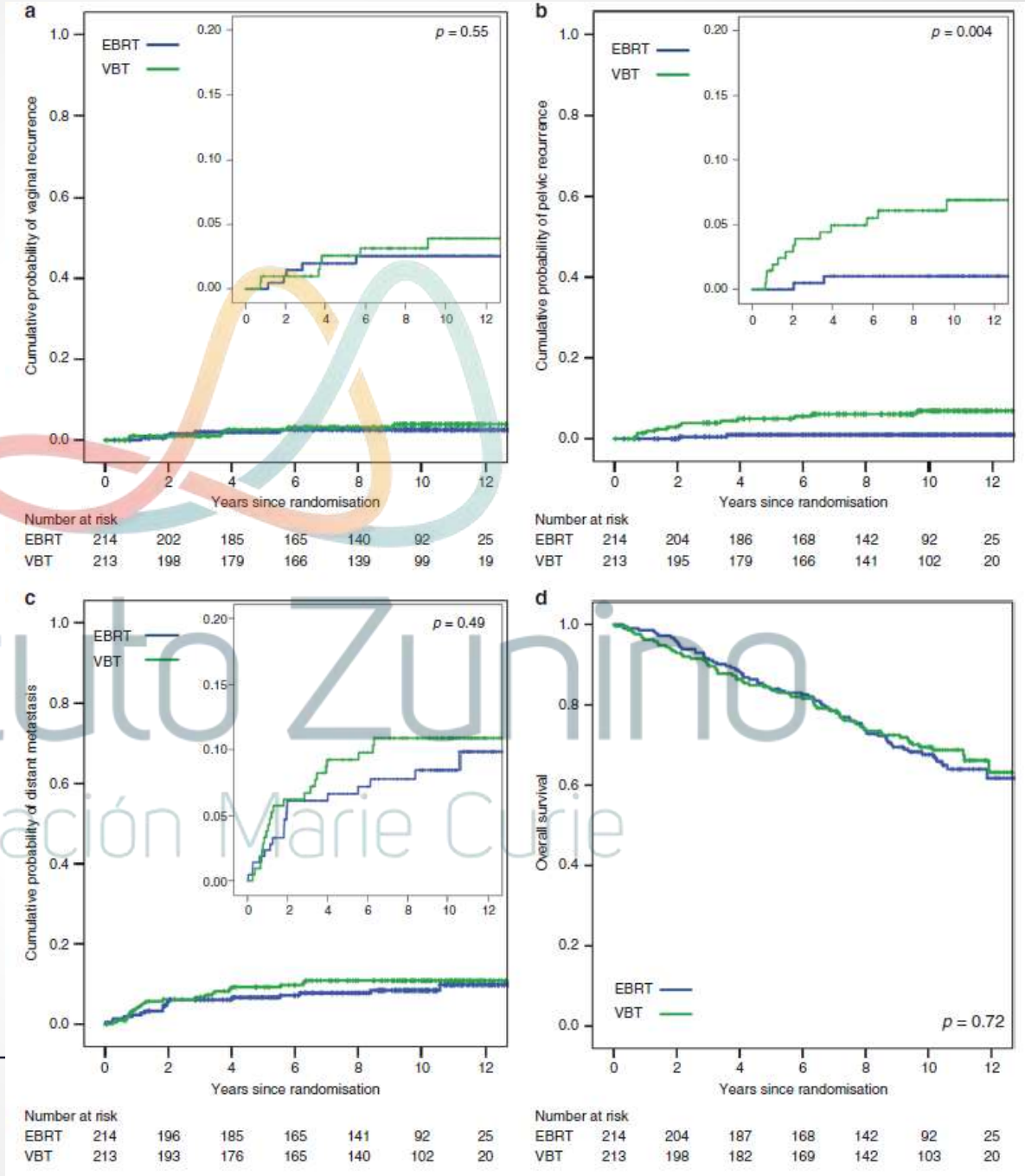
PORTEC 2

Long-Term Outcome (ITT population)

Median FU = 116 months

	EBRT ($n = 214$)			VBT ($n = 213$)			HR (95% CI)	
	Events	5-year %	10-year %	Events	5-year %	10-year %	VBT:EBRT	*p* value
First failure type								
Vaginal recurrence	3	1.1%	1.5%	5	0.9%	3.0%	1.68 (0.40 - 7.03)	0.47
Pelvic recurrence	1	0.5%	0.5%	5	1.4%	2.5%	5.07 (0.59 - 43.41)	0.10
Distant recurrence	18	6.6%	8.9%	22	8.9%	10.4%	1.25 (0.67 - 2.33)	0.49
Distant alone	15	5.7%	7.0%	13	5.5%	6.6%	0.88 (0.42 - 1.86)	0.75
Distant and pelvic	1	0.5%	0.5%	7	3.0%	3.6%	7.16 (0.88 - 58.23)	0.03
Distant and vaginal	2	0.5%	1.1%	1	0.5%	0.5%	0.51 (0.05 - 5.65)	0.58
Total failure								
Vaginal recurrence	5	1.9%	2.4%	7	2.4%	3.4%	1.42 (0.45 - 4.46)	0.55
Pelvic recurrence	2	0.9%	0.9%	13	4.6%	6.3%	6.65 (1.50 - 29.48)	0.004
Distant recurrence	18	6.6%	8.9%	22	8.9%	10.4%	1.25 (0.67 - 2.33)	0.49
Endometrial cancer-related survival	18	93.2%	90.9%	23	91.7%	88.2%	1.29 (0.70 - 2.39)	0.42
Disease-free survival	71	82.1%	68.0%	72	81.2%	66.7%	1.03 (0.74 - 1.43)	0.87
Overall survival	70	84.0%	67.6%	66	84.0%	69.5%	0.94 (0.67 - 1.32)	0.72

PORTEC 2 Long-Term Outcome (ITT population)

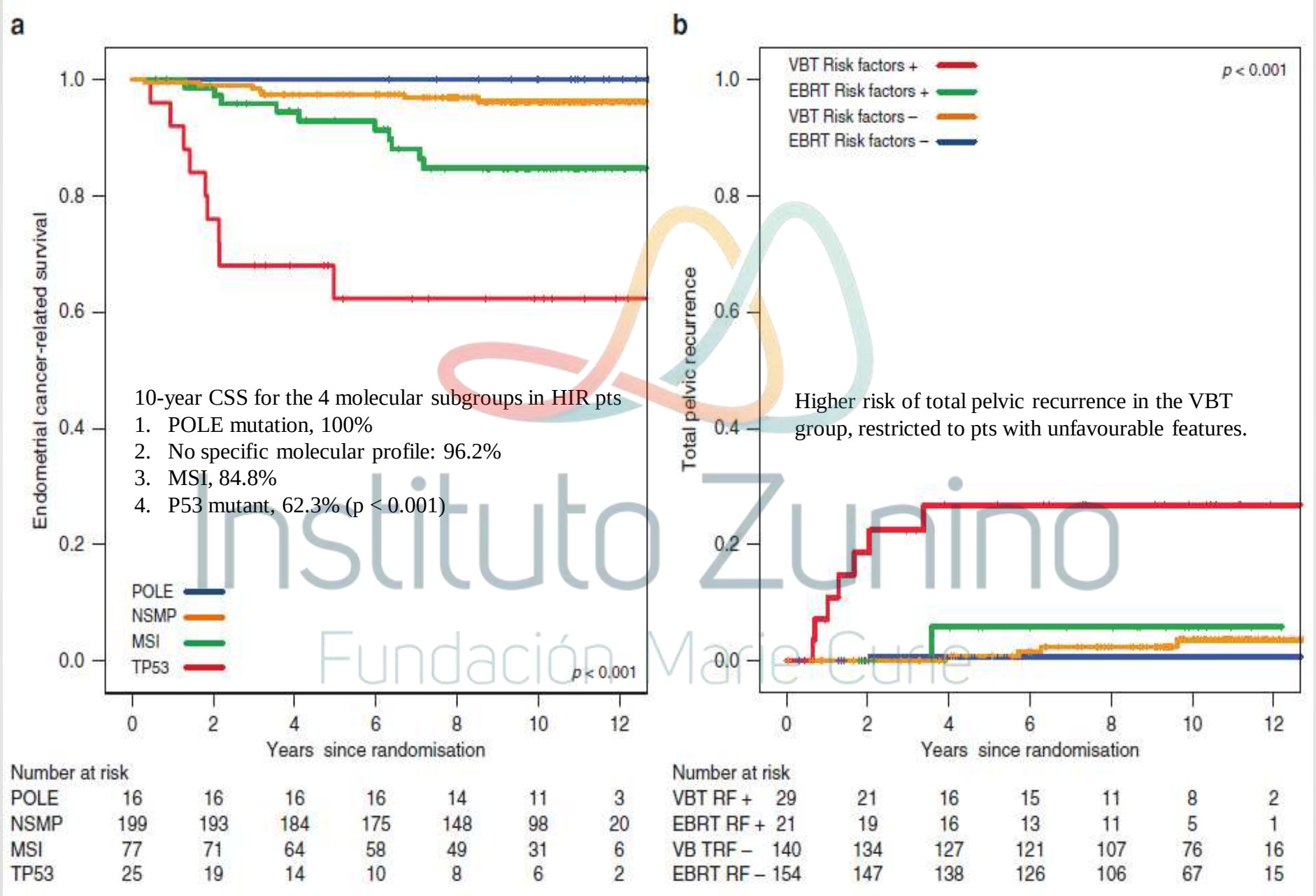


MVA of Prognostic Factors for Recurrence in Confirmed-HIR Patients

- Substantial LVSI: pelvic and distant recurrence, as well as for CSS
- L1CAM and p53-mutant expression: distant recurrence and CSS

		Pelvic recurrence (total)		Distant recurrence		Endometrial cancer-related survival	
	No. [a]	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Treatment group							
EBRT	163	1	0.054	1	0.805	1	0.740
VBT	154	4.58 (0.97 - 21.52)		0.91 (0.41 - 2.00)		0.87 (0.40 - 1.94)	
LVSI							
no/mild	301	1	0.005	1	0.001	1	< 0.001
substantial	16	8.73 (1.95 - 39.22)		5.36 (1.91 - 15.07)		7.16 (2.71 - 18.91)	
TP53 [b]							
wild type	288	1	0.065	1	0.015	1	0.015
mutation	29	3.82 (0.92 - 15.83)		3.35 (1.27 - 8.84)		3.30 (1.26 - 8.64)	
L1CAM							
< 10%	300	1	0.126	1	0.016	1	0.006
> 10%	17	3.79 (0.69 - 20.93)		4.18 (1.31 - 13.33)		5.05 (1.59 - 16.06)	

[a] Total no. 317; 27 cases had insufficient material for analysis of all factors
[b] As assessed by p53 protein expression



10-year CSS for the 4 molecular subgroups in HIR pts

1. POLE mutation, 100%
2. No specific molecular profile: 96.2%
3. MSI, 84.8%
4. P53 mutant, 62.3% ($p < 0.001$)

Higher risk of total pelvic recurrence in the VBT group, restricted to pts with unfavourable features.

PORTEC 2 - Conclusions

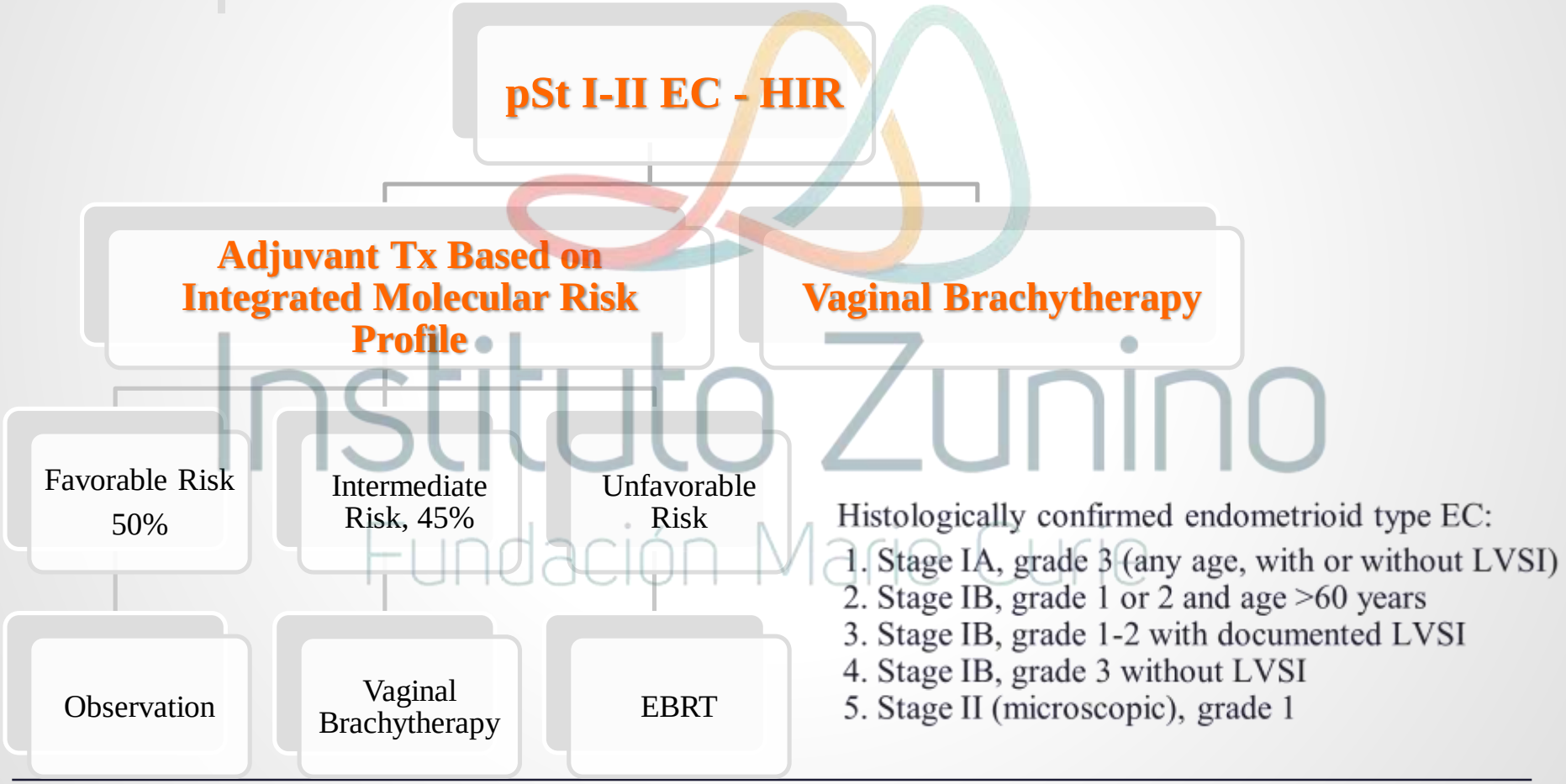
The combination of clinicopathologic and molecular factors allow to select the small percentage of women with HIR-EC who might benefit from EBRT or more intensive treatment.

This is supported by the fact that more pelvic recurrences occurred in the VBT group, in which more pts with p53-mutant expression and with L1CAM expression were found compared to the EBRT group.

These long-term results of PORTEC-2 confirmed VBT as the adjuvant treatment of choice for women with HIR-EC.

EBRT might provide better pelvic control in the small subgroup of women with unfavorable risk factors (substantial LVSI, L1CAM expression or p53-mutant expression).

PORTEC-4a trial: Randomized trial of standard or molecular profile-based recommendation for radiotherapy after surgery for women with early stage endometrial cancer



Is adding Chemotherapy warranted in Early stage EC?

Intermediate - High-Risk Group. PORTEC

C. Creutzberg et al, JCO 2004; 22: 1234-1241

- N= 99 evaluable pts with pSt IC, G3 (all histologies)
- Results
  - Median FU = 83 m
  - 5 y LRR: 1-3 % PORTEC-1, RT group vs **14% IC G3** (all got RT!)
  - **5y Distant mets: 3-8% G1-2; 20% IB G3; 31% IC G3**
  - 5 y OS: 83-85% G1-2; 74% IB G3; **58% IC G3**
- G3 and DMI most significant prognostic factors for relapse and depth from EC

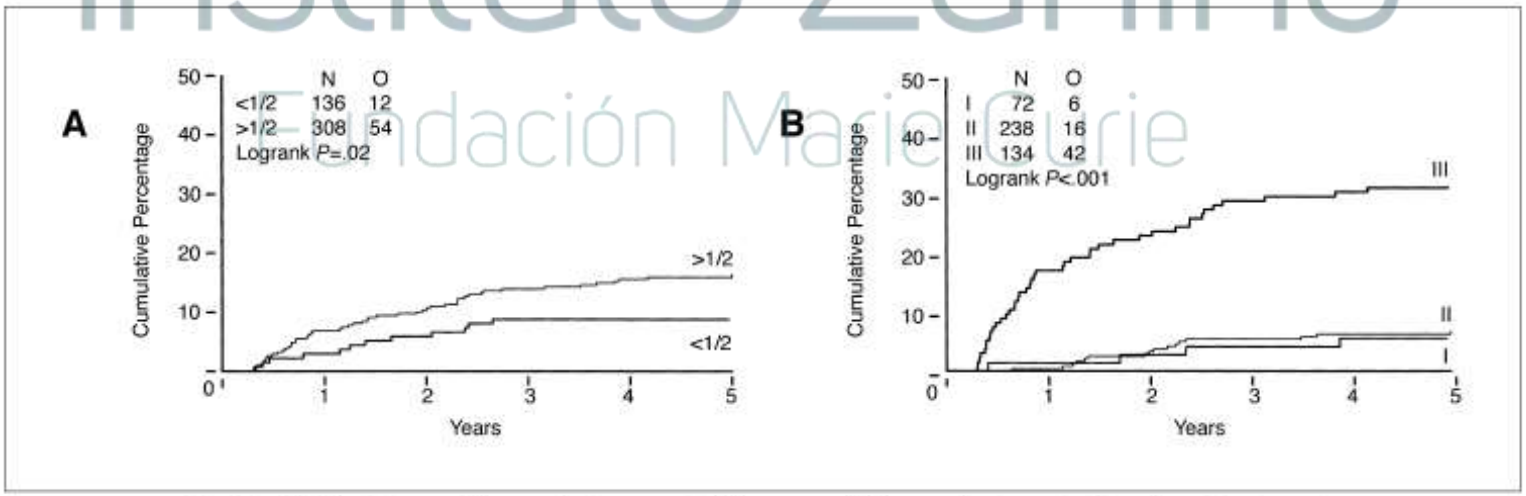


Fig 2. Probability of relapse (A) according to myometrial invasion and (B) according to grade. N, number; O, observed.

Potential Benefit of CT in HIR-EC

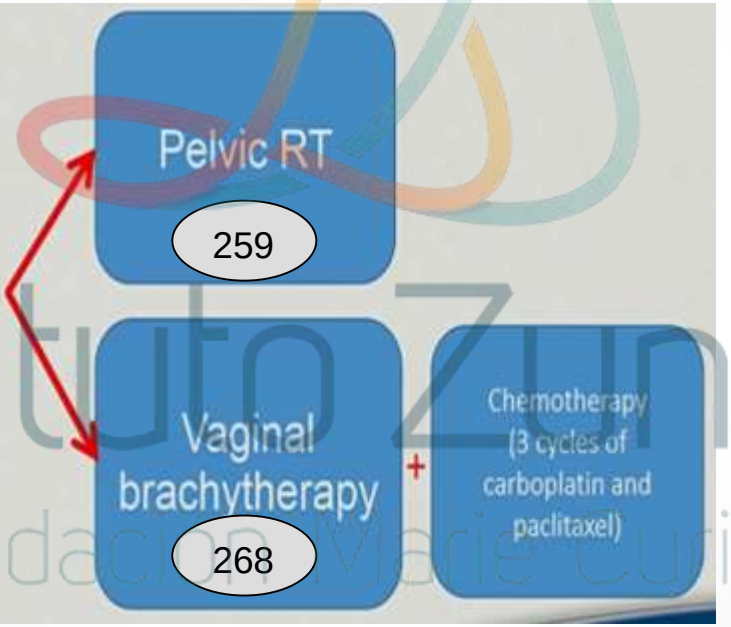
- The potential benefit of adjuvant chemotherapy to decrease disease recurrence in women with early stage, high-intermediate or high-risk endometrial cancer has been subject of several trials, which did not show differences in overall and relapse-free survival compared to EBRT

Phase III trials using CT in HIR-ESEC

Author	# Pts	Randomization	PFS	OS	Comments
Maggi, 2006	345 65% St III	PRT vs CAP	5y 63% vs 63% NSS	5y 69% vs 66% NSS	Pelvic RT represents the standard Tx
Susumu, 2008	385 25% St III	PRT vs CAP	5y 83.5% vs 82% NSS	5y 85% vs 87% NSS	31% HR pts [IC, >70 yo, G3; St II-IIIA ≥50% MI] Benefit of CT over RT in PFS and OS
Kuoppala 2008	156 St I-IIIA	PRT vs RT+CAP	5y 85% vs 82% NSS	5y 85% vs 83% NSS	Survival better for the RT group Severe complications higher in the RT+CT [10% severe GI toxicity]

GOG-0249
A PHASE III TRIAL OF PELVIC RT vs VAGINAL CUFF BRACHYTHERAPY FOLLOWED BY PACLITAXEL/CARBOPLATIN IN PATIENTS WITH HIGH RISK, EARLY STAGE EC
PI: Scott McMeekin, MD

- Endometrioid Carcinoma
  - Stage I (with risk factors: grade 2-3, deep myometrial invasion and LVSI);
    - age ≥70 years with 1 risk factor
    - age ≥50 years with 2 risk factors
    - Any age >18 years with 3 risk factors
  - Any patients with stage II
- Non-endometrioid carcinoma
  - Stage I-II with negative peritoneal cytology



"This trial compared a **STANDARD** treatment (PRT) to a **PROMISING** experimental one (VBT + CT X 3)"

Complete surgical staging WAS not required!

In fact, Vaginal hysterectomy without oophorectomy was allowed!

Primary Endpoint: RFS

GOG – 249. Toxicity

Treatment Toxicity: Acute

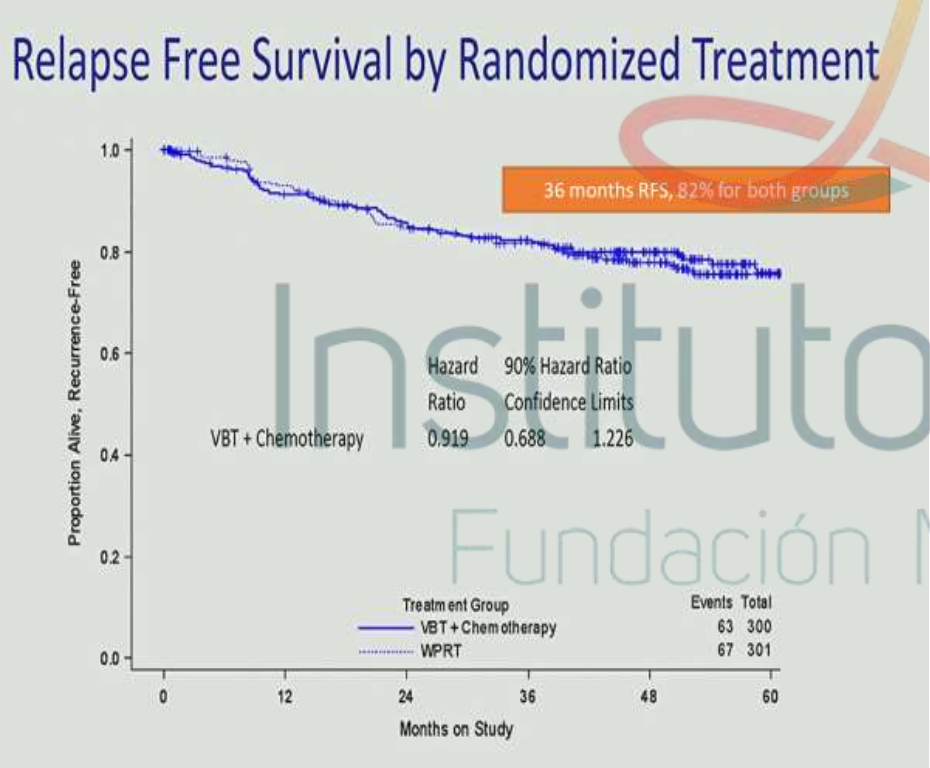
- Acute toxicity was more common and more severe with VCB/C
  - **Grade 3 or higher adverse events**
    - **PXRT – 32 patients (11%), VCB/C – 187 patients (64%)**
    - Differences most pronounced in Constitutional Symptoms, Dermatologic, Blood/Bone Marrow, Infection, Metabolic, Neurologic and Pain
- 1 Grade 5 Adverse Event (death) on VCB/C arm
  - Related to disease progression, not study treatment

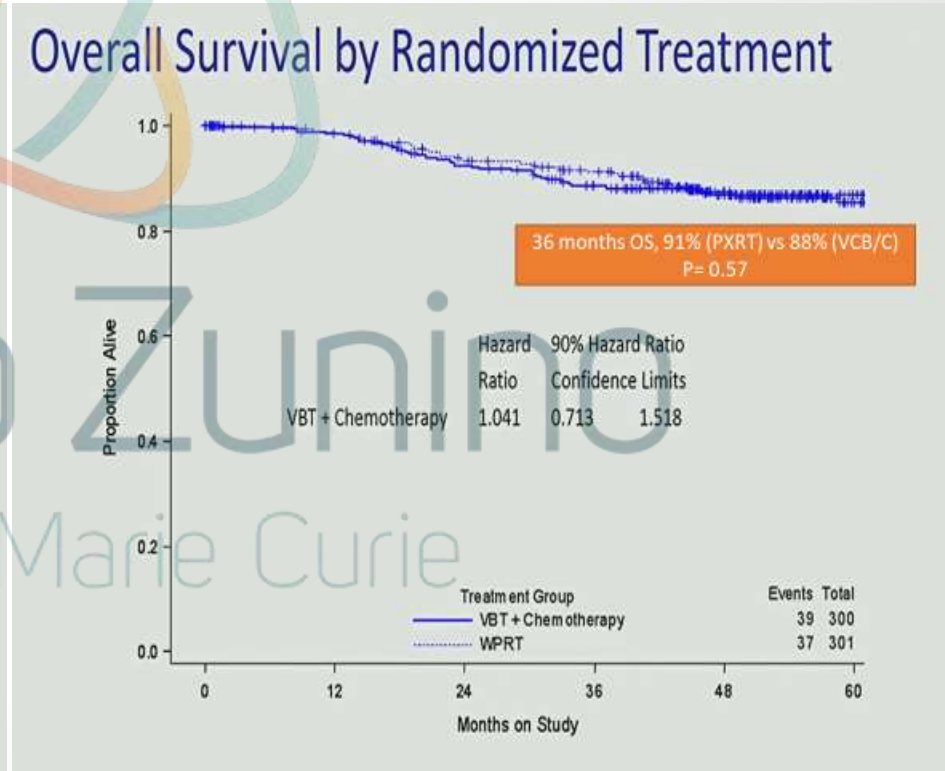
Treatment Toxicity: Late

- Late toxicity was comparable in the 2 arms
  - **Grade 3 or higher late adverse events**
    - PXRT - 37 patients (13%), VCB/C - 35 patients (12%)
  - Grade 3 GI Adverse Events: PXRT – 2% vs 1% in VCB/C
- Two grade 5 Adverse events (death), 1 in each arm.
  - Renal failure and thrombotic event following sepsis, ? intercurrent disease
  - Disease progression
  - Neither thought due to study treatment

No difference in ≥ grade 3 acute of late toxicities between 3DCRT and IMRT

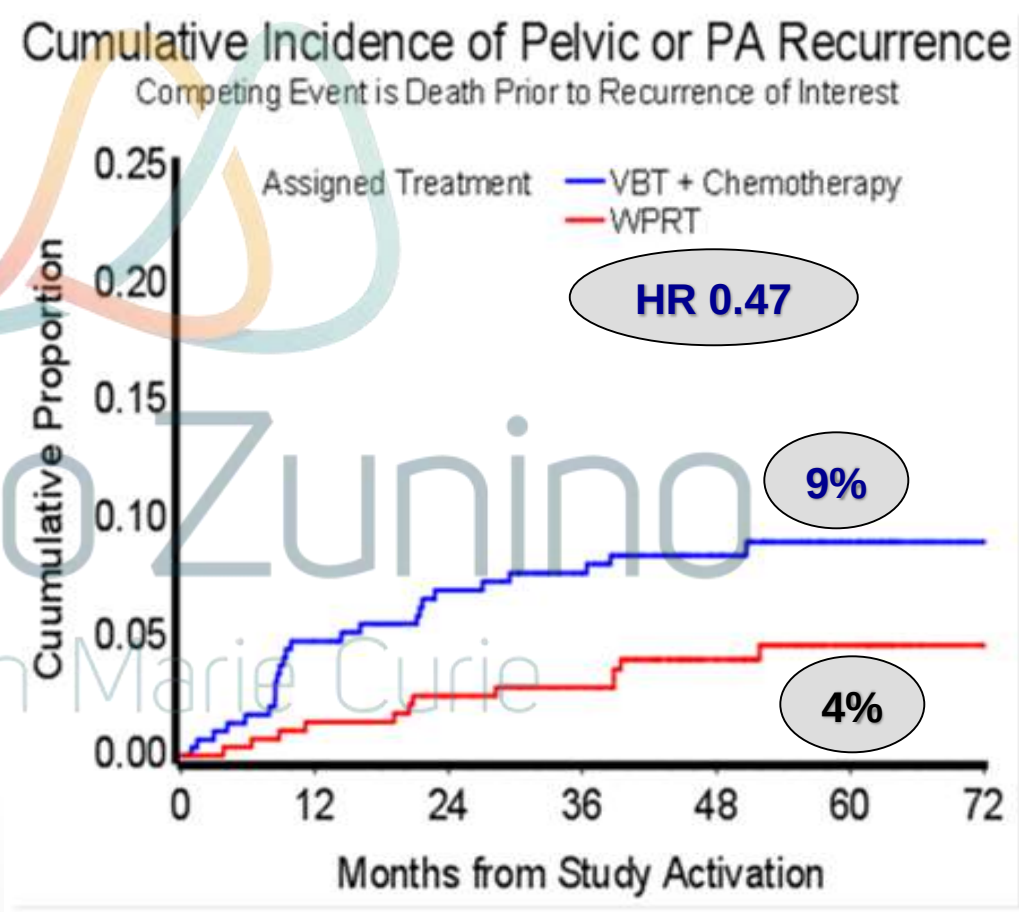
GOG – 249. Outcome





GOG – 249. Comparative Outcomes

- No heterogeneity between the two arms with respect to RFS and OS
- Recurrences
  - Vaginal recurrence : 2.5%
  - Distant recurrences:18%
    - No diff. between the two arms
  - 5-year Pelvic and Peri-Aortic nodal failures:
    - VBT-CT 9% vs WPRT 4%, HR 0.47



GOG – 249. Conclusions

- This Phase III study did not demonstrate superiority of VCB/C over PXRT
- RFS and OS were not improved with VCB/C compared to PXRT
- Significantly lower nodal failure rate in the PXRT arm. Distant failure is the predominant failure pattern in this patient population (18% in both arms).
- Acute toxicity greater in VCB/C arm; late toxicity was similar in the 2 arms
- Pelvic RT remains an appropriate (and preferable) treatment for HR-ES-EC
- Better treatment strategies to systemic disease are necessary

GOG – 249. Questions

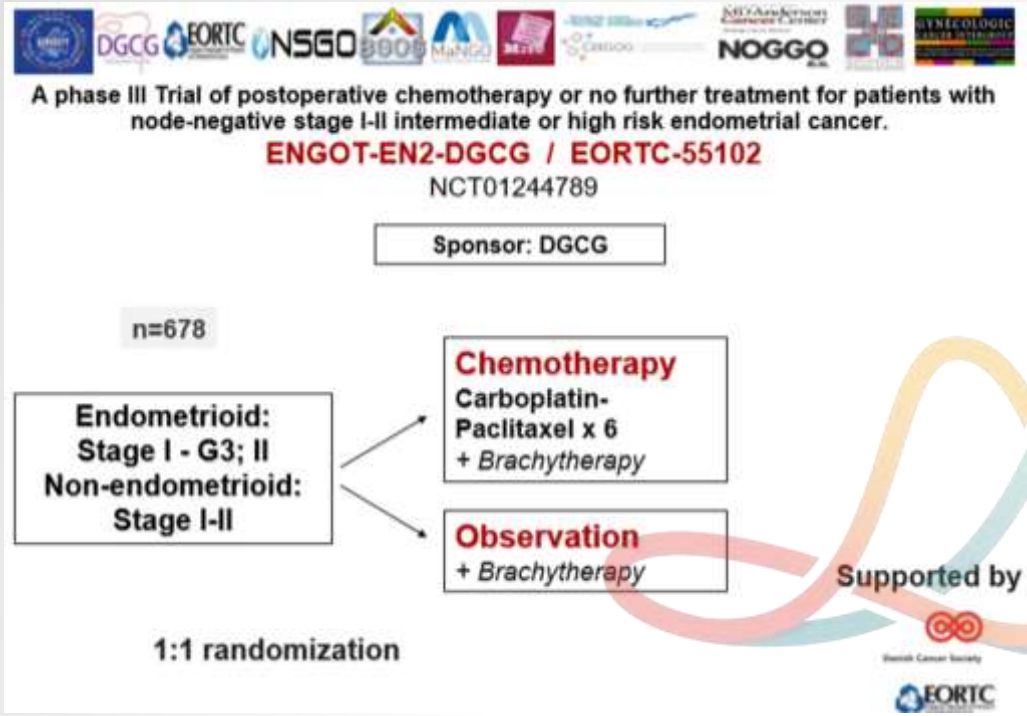
Twice as many Pelvic + PA failures in the VCB +CT without impact in the rate of Distant metastasis failures even though the RT arm treated the pelvis only

Was Pelvic RT able to minimize the risk of PA and Distant failures ?

Why the CT arm did not have impact on the % of Distant failures?

What if we had combined Pelvic RT + CT?

Do we need more CT?



Question: Does RT add anything to CT? OPEN

Stratifications:

1: Histological type (endometrioid versus non-endometrioid)

2: stage (1a vs. 1b vs. 2 disease)

3: para-aortic (≥10)and pelvic (≥20) LNE versus lesser LNE

4: Brachytherapy (planned yes/no)

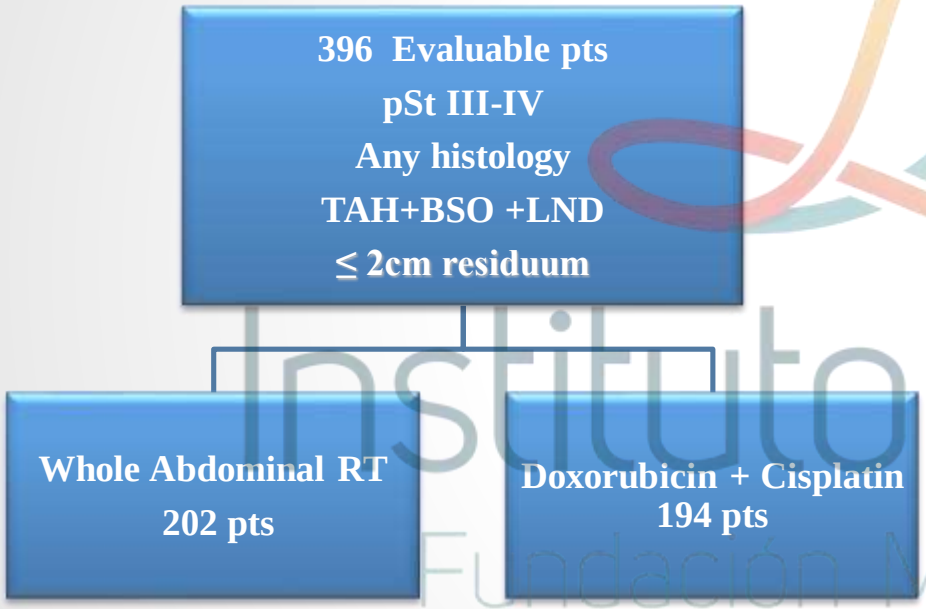
Patients are randomized to one of the two treatment arms (1:1 randomization): Arm I: Postoperative adjuvant paclitaxel (175mg/m2) and carboplatin (AUC5), q 3 wks. X 6 Arm II: Postoperative follow-up without any further treatment

Brachytherapy is permitted in both arms.


High-Risk, St III-IVA
Endometrial Cancer
Instituto Zunino
Fundación Marie Curie

Phase III: WAR versus Doxorubicin-Cisplatin Chemotherapy in Advanced Endometrial Carcinoma: GOG 122

Randall et al, JCO 2006; 24: 36-44



	WAR	*AP ChemoTx*
Completed Tx	84%	**63%**
Stopped Tx due to toxicity	3%	**17%**
Median duration of Tx	1.3 m	**5.1 m**
Did not receive Tx as per Protocol	12%	**27%**

No Stratification
Primary Endpoint: PFS
Reporting of Relapse: First Site of Relapse
Median FU = 74 months

GOG 122: DFS

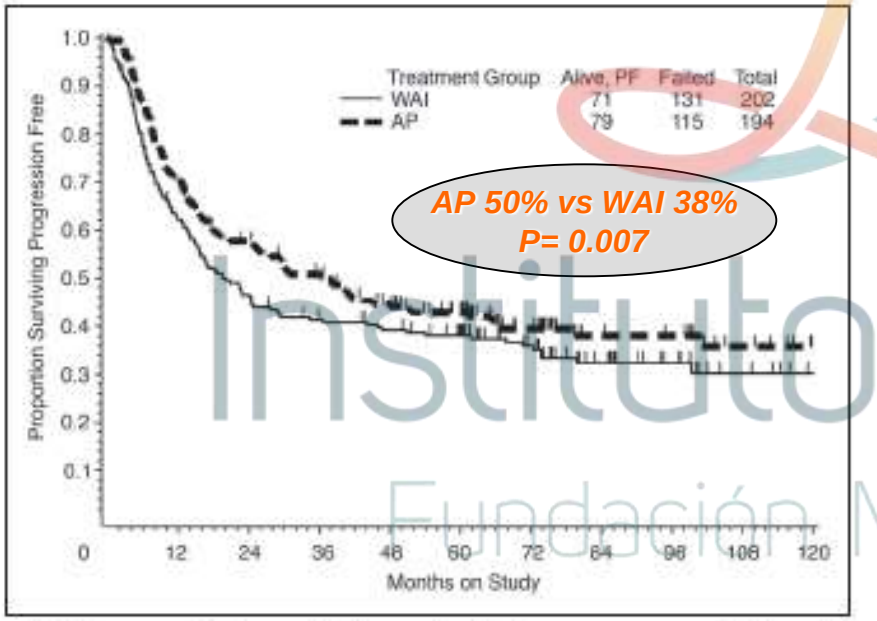


Fig 1. Progression-free survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

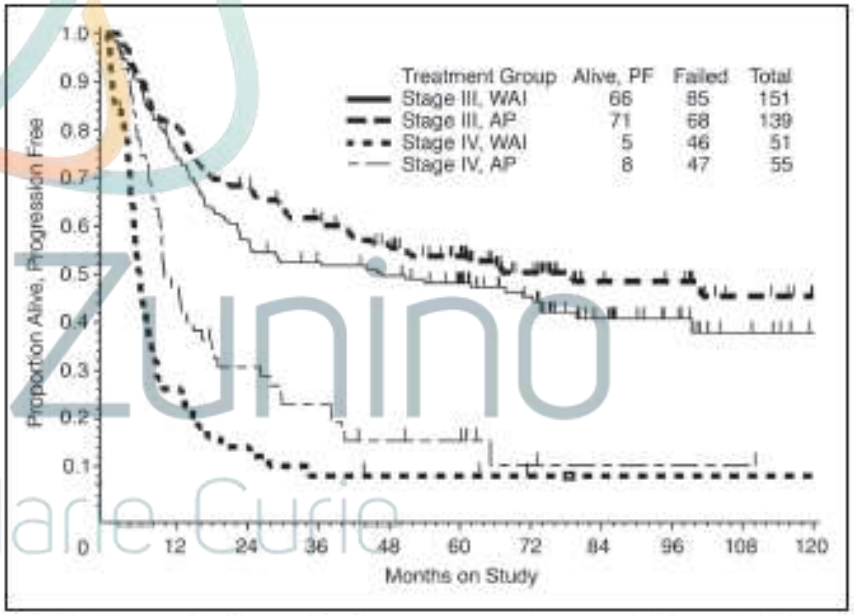


Fig 3. Progression-free survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

GOG 122: Survival

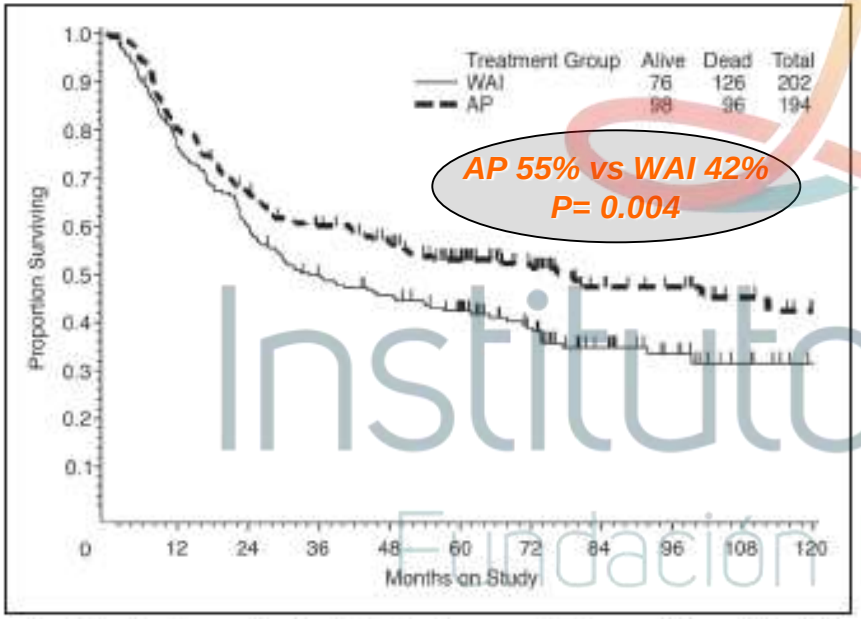


Fig 2. Survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

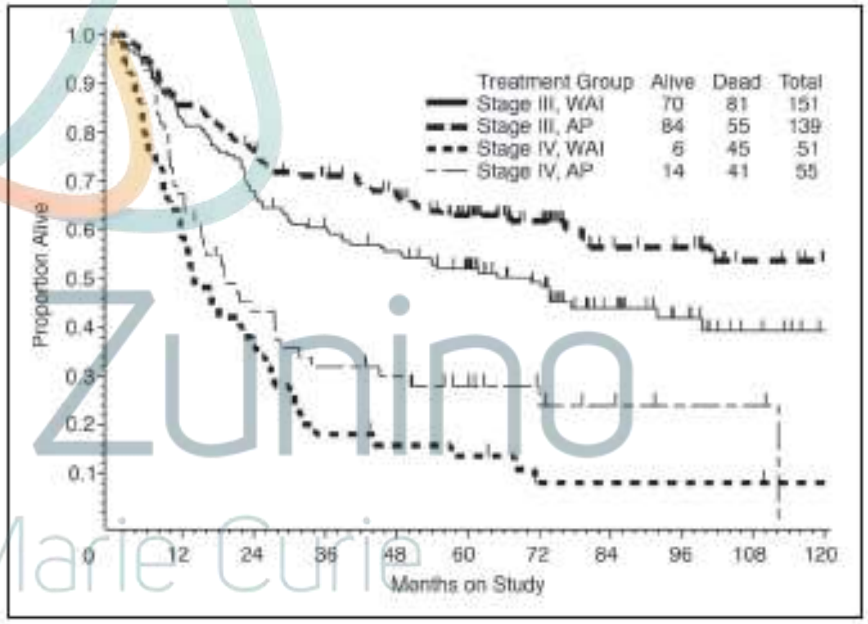


Fig 4. Survival by treatment and stage. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

GOG 122: Conclusions

AP significantly improves PFS and OS compared with WAI

Risk of progression or death reduced by 29%, and risk of death reduced by 32% with AP

Toxicity is significantly increased with AP compared to WAI

Recurrence rates are still significant - approximately 40-50% in Stage III patients and 80-90% in Stage IV patients

Chemotherapy with Cisplatin + Adriamycin as sole adjuvant treatment leaves much to be desired but does contribute to the treatment of advanced endometrial cancer


How to combine
ChTx and RT?

Sequential Adjuvant chemotherapy and radiotherapy in EC: Results of two Randomized Trials

Hogberg T et. al. Europ J of Cancer, 2010; 46: 2422-2431

- In the NSGO/EORTC study and the MaNGO ILIADE – III a total of 534 evaluable pts , St I-III, were randomized to adjuvant RT +/- sequential CT

The CMT was associated with a 37% reduction in the risk of relapse or death

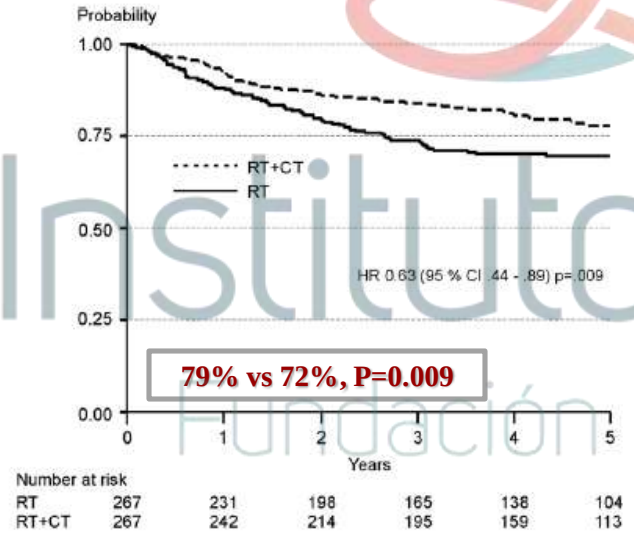


Fig. 2 – Progression-free survival in the pooled NSGO-EC-9501/EORTC-5591 and MaNGO studies (CI: confidence interval, HR: hazard ratio, RT: radiotherapy and RT–CT: sequential radiotherapy and chemotherapy).

There was no difference in OS, although there was a 31% reduction in the risk of death

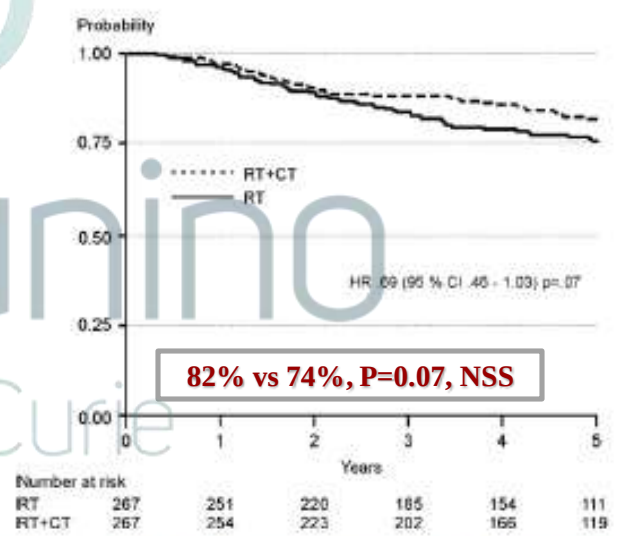


Fig. 3 – Overall survival in the pooled NSGO-EC-9501/EORTC-5591 and MaNGO studies (CI: confidence interval, HR: hazard ratio, RT: radiotherapy and RT–CT: sequential radiotherapy and chemotherapy).

Phase III: Volume directed RT followed by Cisplatin + Doxorubicin vs Cisplatin + Doxorubicin + Paclitaxel in Advanced EC: GOG 184

Homesley, H et al, Gynecol Oncol, 2009; 112: 543

552 pts

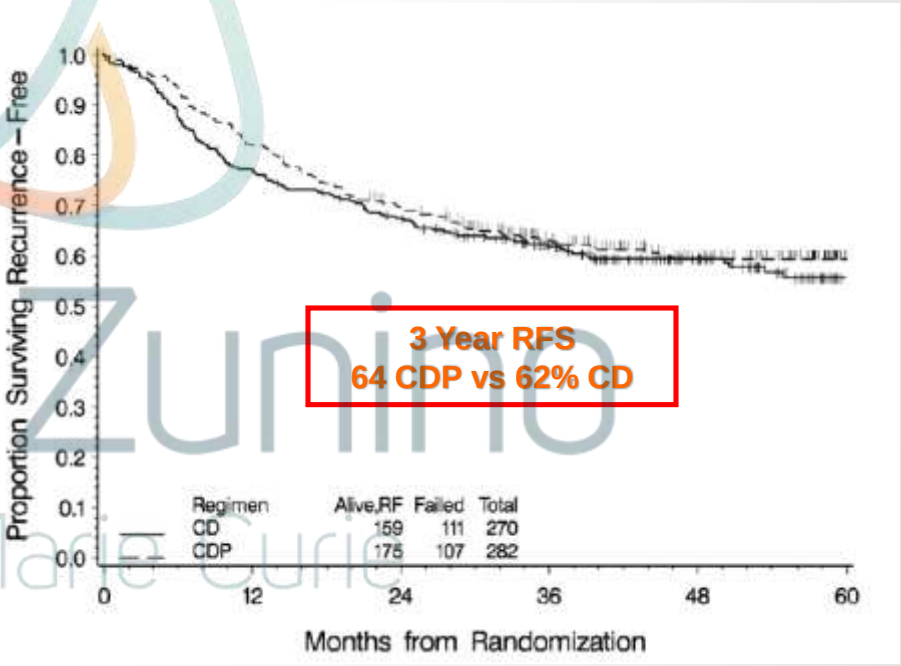
TAH+BSO+Pelvic and PA-LND

pSt III EC, ≤ 2 cm residual

Adjuvant RT Pelvic +/- PA +/- Vaginal brachytherapy

AP x 6 cycles, 270 pts

TAP x 6 cycles, 282 pts



3 Year RFS
64 CDP vs 62% CD

Conclusions of the Role of CT in HR - EC

No definitive conclusions can be drawn given the differences in the inclusion criteria in the available RCT's

Benefit of chemotherapy only in the subset analysis but not in the overall series

Recurrence rates are similar with EBRT and chemotherapy (~ 15-20%) and 50% of them are LRR-pelvic confined recurrences

Adequately designed trials based on defined risk-groups are needed in order to improve outcome in this patient population


What about CONCURRENT
ChTx and RT?

Phase II Chemo-Radiation Therapy in High-Risk EC: RTOG 97-08. Final analysis

Greven K et al, Gynecol Oncol 2006; 103: 155-159

Incidence of distant metastasis in HR-EC

- G2-3 with > 50% MI,
- St II, St III (pelvic confined disease): 15-25%

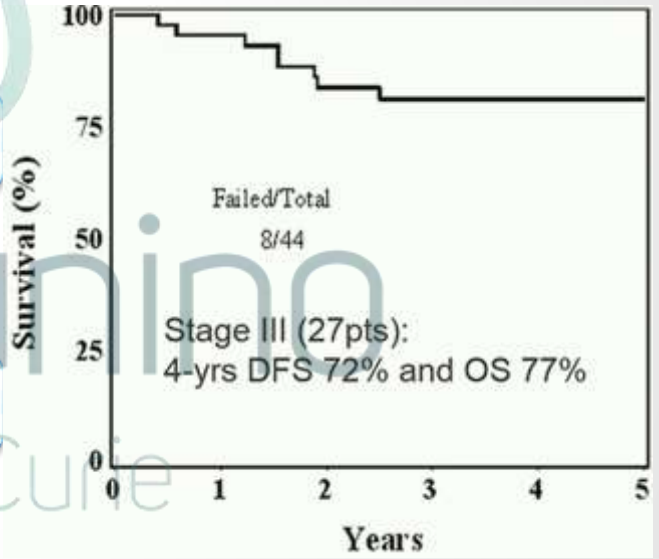
10/97 – 4/99: 44 evaluable patients

- St I-II: 34%; **St III 66%**
- [Pelvic RT 45 Gy] + [CDDP 50 mg/m2 dys 1 & 28] + [IVB]
- Adjuvant [CDDP + Taxol] x 4 cycles

Results: Median FU 4.3 years

- Toxicity
  - Grade 3: 16%
  - Grade 4: 5%
- RR: none in pts with St IC-IIB

Phase III: RT vs RT+CT closed due to lack of accrual



Leiden University Medical Center

2017 ASCO ANNUAL MEETING

Final results of the PORTEC-3 trial

ASCO Annual meeting 2017

PORTEC-3 international collaborators

Stephanie de Boer
Department of Radiation Oncology
Leiden University Medical Center, the Netherlands

Presented By Stephanie de Boer at 2017 ASCO Annual Meeting

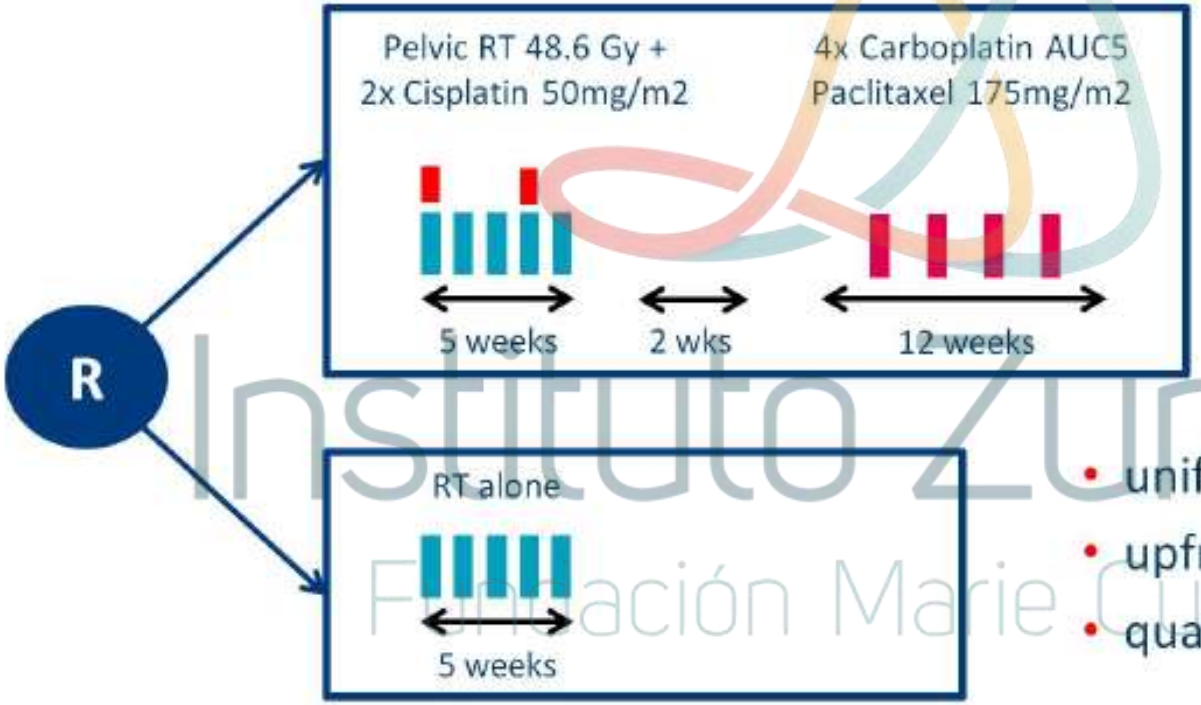
Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial

*Stephanie M de Boer, Melanie E Powell, Linda Mileshkin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Alessandro Colombo, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Silvestro Carinelli, Diane Provencher, Chantal Hanzen, Ludy C H W Lutgens, Vincent T H B M Smit, Naveena Singh, Viet Do, Romerai D'Amico, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC study group**

www.thelancet.com/oncology **Published online February 12, 2018 http://dx.doi.org/10.1016/S1470-2045(18)30079-2**

PORTEC-3 trial design

- High risk Endometrial Cancer (HREC)



- Endometrial carcinoma
  - stage I grade 3, with deep invasion or LVSI+
  - stage II - III
  - stage I-III serous or clear cell cancers (>25%)
- WHO PS 0-2
- No residual macroscopic tumor after surgery
- Pathology review before randomisation

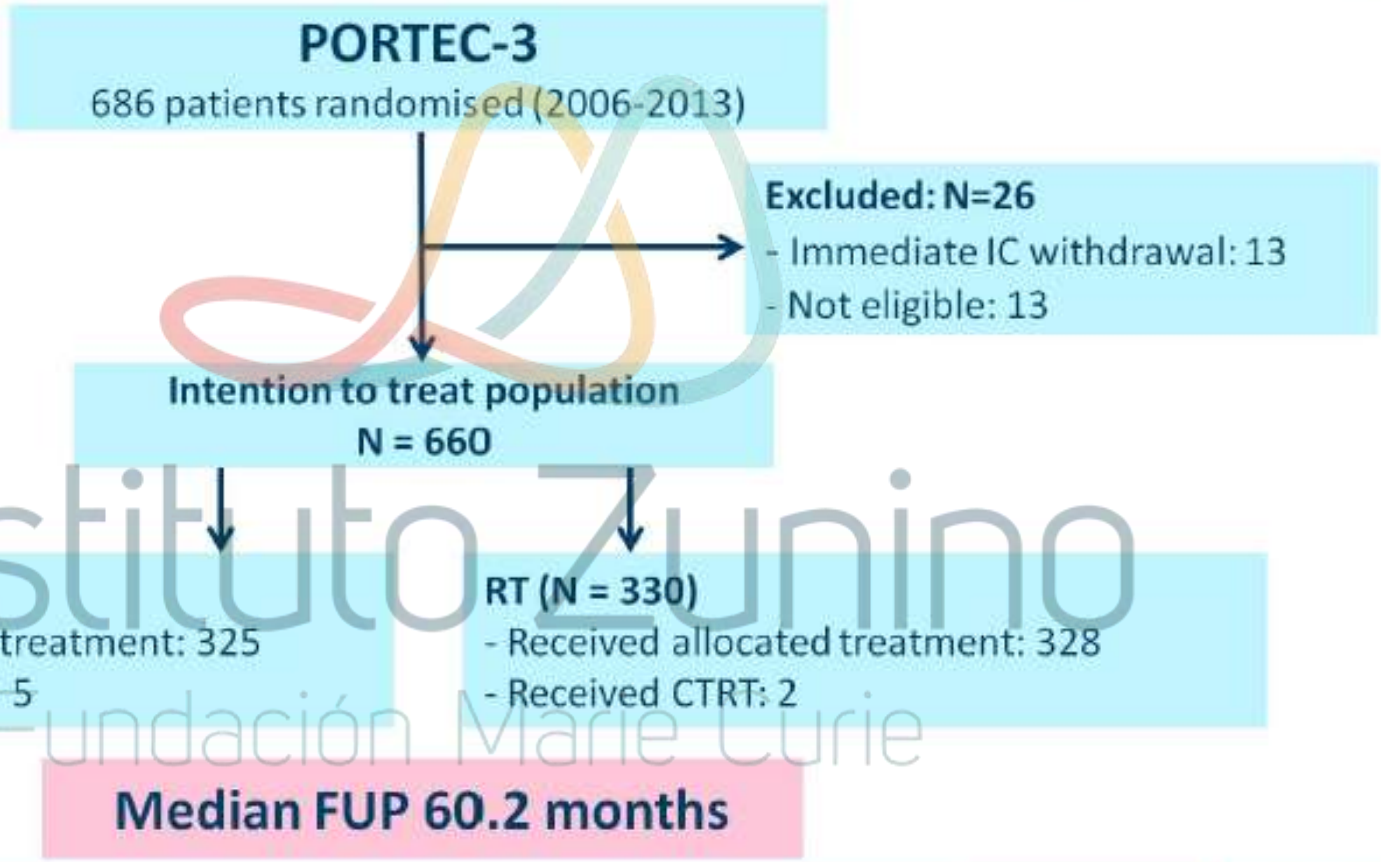
- uniform treatment schedule
- upfront pathology review
- quality of life analysis

Presented By Stephanie de Boer at 2017 ASCO Annual Meeting

Endpoints

- Primary endpoints:
  - 5 yr overall survival (OS)
  - 5 yr failure free survival (FFS)
    - FFS: relapse or endometrial cancer-related death
- Secondary endpoints:
  - Vaginal, pelvic and distant recurrence
  - Toxicity and quality of life

CONSORT diagram



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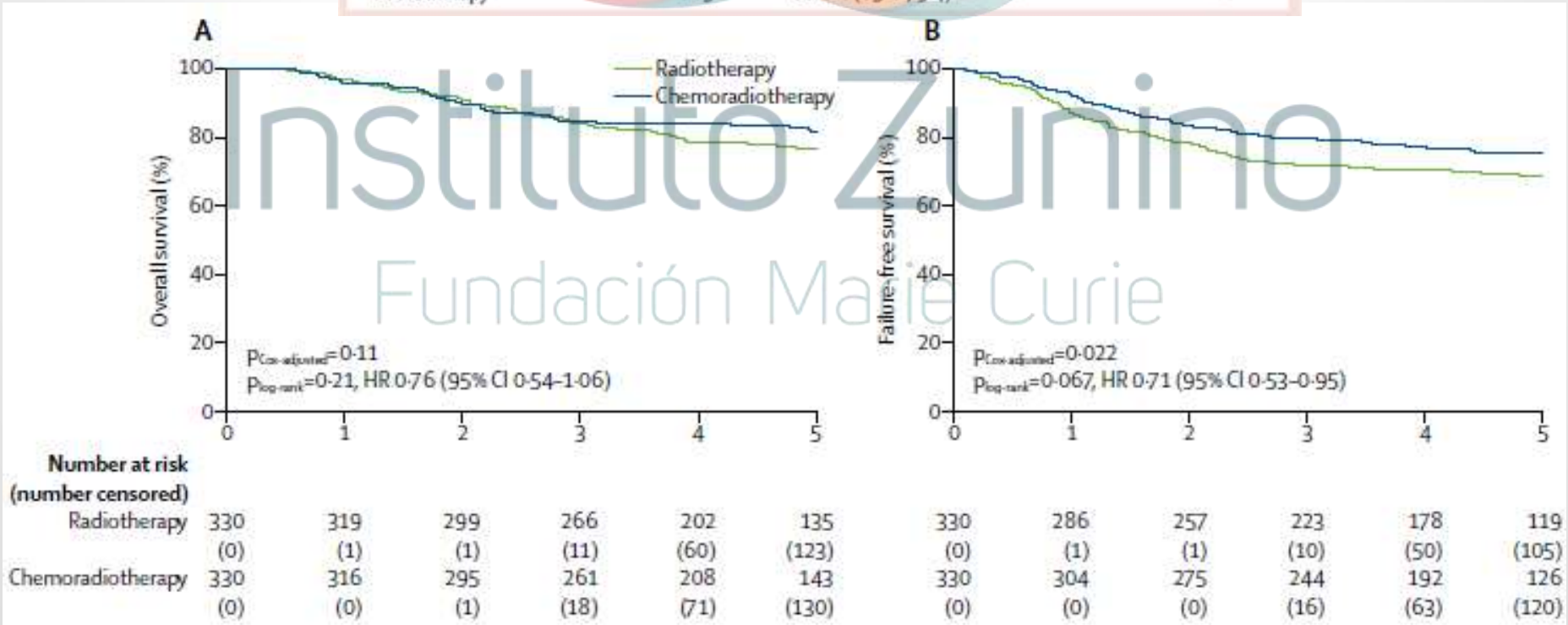
PORTEC 3 – OS and FFS - Entire Series

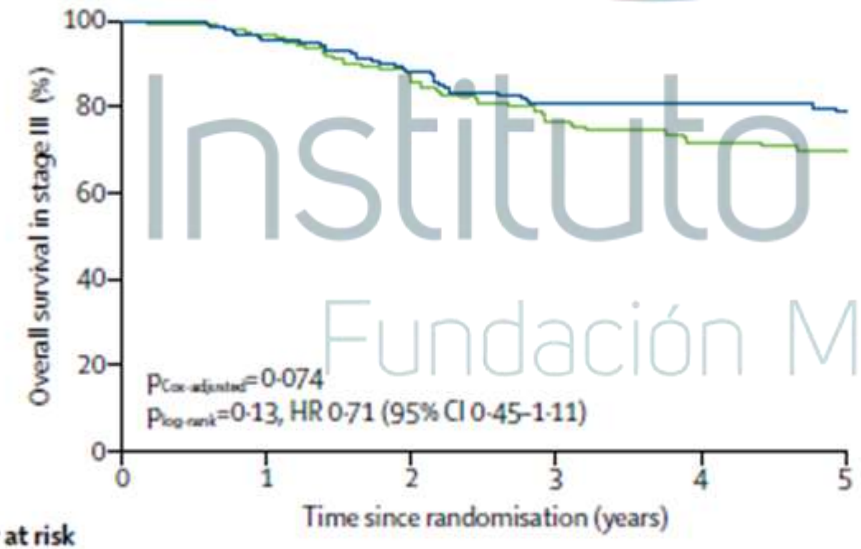
	Events	5-year estimate, % (95% CI)	Hazard ratio (95% CI)	p value
Overall survival*	..	..	0·76 (0·54–1·06)	0·109
Failure-free survival*	..	..	0·71 (0·53–0·95)	0·022
Overall survival†				
Chemoradiotherapy	61	81·8% (77·5–86·2)	0·81 (0·58–1·13)	0·213
Radiotherapy	75	76·7% (72·1–81·6)	..	..
Failure-free survival†				
Chemoradiotherapy	83	75·5% (70·3–79·9)	0·76 (0·57–1·02)	0·067
Radiotherapy	103	68·6% (63·1–73·4)	..	..

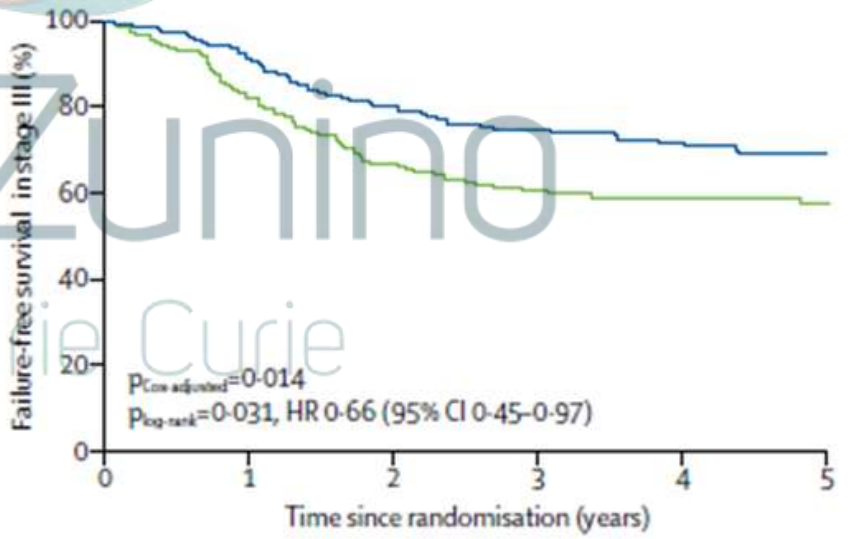


Number at risk (number censored)												
Radiotherapy	330	319	299	266	202	135	330	286	257	223	178	119
	(0)	(1)	(1)	(11)	(60)	(123)	(0)	(1)	(1)	(10)	(50)	(105)
Chemoradiotherapy	330	316	295	261	208	143	330	304	275	244	192	126
	(0)	(0)	(1)	(18)	(71)	(130)	(0)	(0)	(0)	(16)	(63)	(120)

PORTEC 3 – OS and FFS, Stage III

- 5-year FFS 69% for CTRT vs 58% for RT
  [HR 0.66, 95% CI 0.45-0.97, **p=0.032**]
- 5-year OS 79% vs 70%
  [HR 0.69, 0.44-1.09, p=0.114]





Number at risk (number censored)												
Radiotherapy	143	137	123	106	81	49	143	116	95	82	67	40
	(0)	(1)	(1)	(4)	(23)	(53)	(0)	(1)	(1)	(5)	(18)	(44)
Chemoradiotherapy	152	145	133	115	98	69	152	139	122	106	88	57
	(0)	(0)	(1)	(8)	(26)	(52)	(0)	(0)	(0)	(8)	(23)	(50)

Sites of Failure

	Events	5-year estimate, % (95% CI)	Hazard ratio (95% CI)	p value
Vaginal recurrence (first recurrence)†				
Chemoradiotherapy	1	0·3% (0·0–2·1)	0·99 (0·06–15·90)	0·999
Radiotherapy	1	0·3% (0·0–2·1)	..	..
Pelvic recurrence (first recurrence)†				
Chemoradiotherapy	3	1·0% (0·3–2·9)	0·60 (0·14–2·49)	0·473
Radiotherapy	5	1·5% (0·6–3·6)	..	..
Distant metastases (first recurrence)†				
Chemoradiotherapy	76	22·4% (18·1–27·4)	0·78 (0·58–1·06)	0·108
Radiotherapy	93	28·3% (23·7–33·7)	..	..
Vaginal recurrence (total)†				
Chemoradiotherapy	8	2·1% (1·0–4·4)	0·99 (0·37–2·65)	0·995
Radiotherapy	8	2·1% (1·0–4·4)	..	..
Pelvic recurrence (total)†				
Chemoradiotherapy	16	4·9% (3·0–7·9)	0·51 (0·28–0·92)	0·026
Radiotherapy	31	9·2% (6·5–12·9)	..	..
Distant metastases (total)†				
Chemoradiotherapy	79	23·1% (18·8–28·3)	0·77 (0·57–1·03)	0·077
Radiotherapy	97	29·7% (24·9–35·1)	..	..

MVA Prognostic Factors OS

	Patients (n)	Events (n)	5-year overall survival (95% CI)	Hazard ratio (95% CI)	p value
Total	660	136	79% (74·8–83·9)	..	..
Treatment group	..	..	..	..	0·075
Radiotherapy	330	75	77% (72·1–81·6)	..	..
Chemoradiotherapy	330	61	82% (77·5–86·2)	0·73 (0·52–1·03)	..
Age (years)	..	..	..	..	<0·0001
<60	268	31	89% (85·0–92·9)	..	..
60–69	272	66	75% (69·6–80·6)	2·31 (1·48–3·59)	..
≥70	120	39	67% (58·7–76·3)	3·29 (1·99–5·44)	..
Stage	..	..	..	..	<0·0001
Stage I and II	365	59	83% (79·1–87·3)	..	..
Stage III	295	77	74% (69·3–79·7)	2·41 (1·66–3·51)	..
Histology and grade	..	..	..	..	<0·0001
Endometrioid grade 1 and 2	258	36	86% (81·9–90·9)	..	..
Endometrioid grade 3	213	45	79% (73·0–85·7)	1·76 (1·10–2·81)	..
Serous/clear cell	189	55	71% (65·2–77·4)	2·35 (1·48–3·72)	..
LVSI	..	..	..	..	0·11
No	271	43	85% (80·5–89·4)	..	..
Yes	389	93	75% (70·9–79·9)	1·36 (0·93–1·98)	..
Lymphadenectomy	..	..	..	..	0·33
No	278	61	77% (71·4–82·1)	..	..
Yes	382	75	81% (77·1–85·2)	0·82 (0·55–1·22)	..

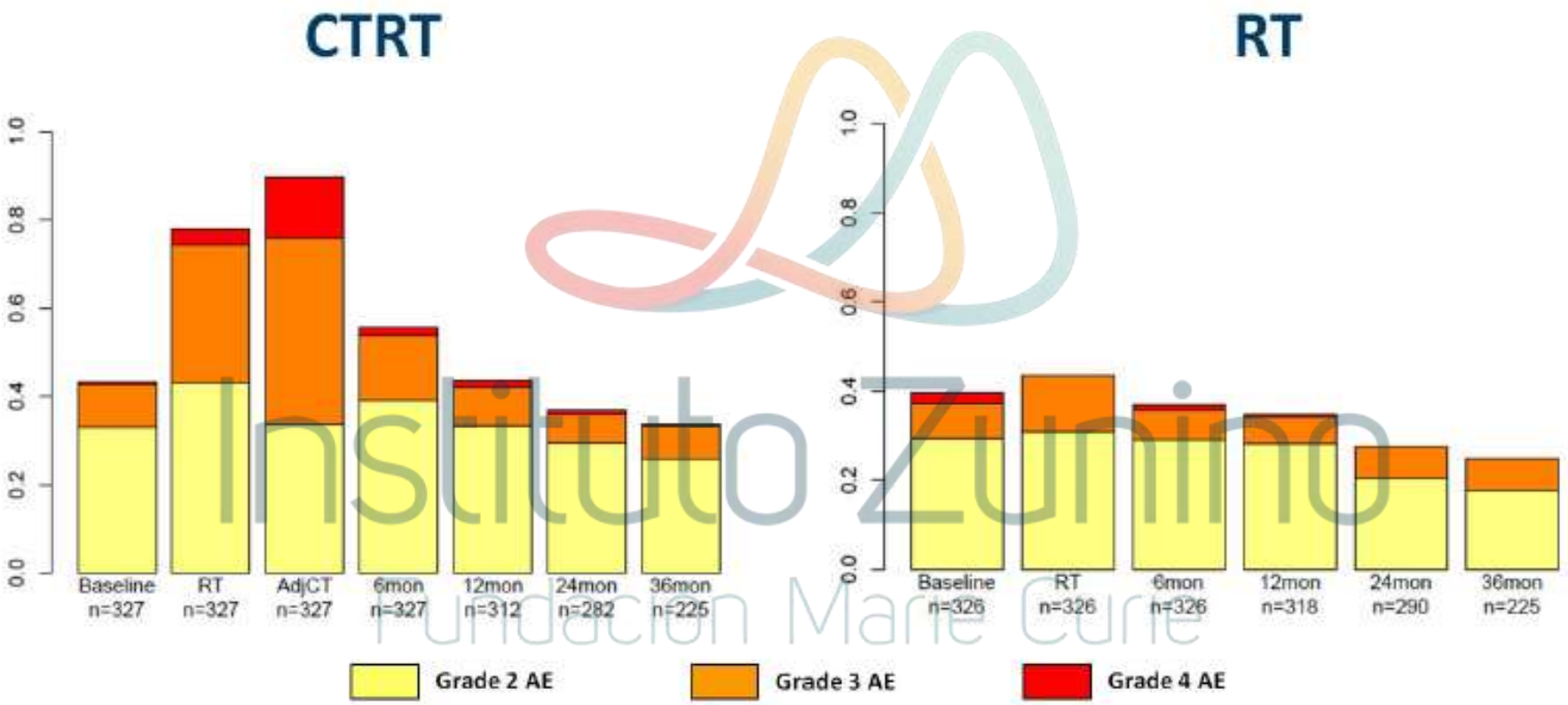
Adjusted for participating groups. LVSI=lymph-vascular space invasion.

MVA Prognostic Factors FFS

	Patients (n)	Events (n)	5-year failure-free survival (95% CI)	Hazard ratio (95% CI)	p value
Total	660	186	72% (66·7–76·7)	..	..
Treatment group	..	..	..	..	0·010
Radiotherapy	330	103	68% (63·1–73·4)	..	..
Chemoradiotherapy	330	83	75% (70·3–79·9)	0·68 (0·51–0·91)	..
Age (years)	..	..	..	..	<0·0001
<60	268	54	81% (75·3–85·0)	..	..
60–69	272	87	67% (60·7–72·4)	1·74 (1·23–2·46)	..
≥70	120	45	64% (54·4–71·7)	2·14 (1·41–3·25)	..
Stage	..	..	..	..	<0·0001
Stage I and II	365	78	79% (73·9–82·6)	..	..
Stage III	295	108	64% (58·0–69·2)	2·62 (1·90–3·61)	..
Histology and grade	..	..	..	..	<0·0001
Endometrioid grade 1 and 2	258	58	78% (72·7–83·1)	..	..
Endometrioid grade 3	213	60	71% (64·5–77·1)	1·56 (1·06–2·30)	..
Serous or clear cell	189	68	64% (56·6–70·4)	2·15 (1·46–3·16)	..
LVSI	..	..	..	..	0·054
No	271	62	77% (71·4–81·8)	..	..
Yes	389	124	68% (63·4–72·9)	1·36 (0·99–1·87)	..
Lymphadenectomy	..	..	..	..	0·41
No	278	81	72% (65·7–76·6)	..	..
Yes	382	105	72% (67·4–76·7)	0·87 (0·61–1·22)	..

Adjusted for participating groups. LVSI=lymph-vascular space invasion.

Adverse events (CTCAE v3.0)



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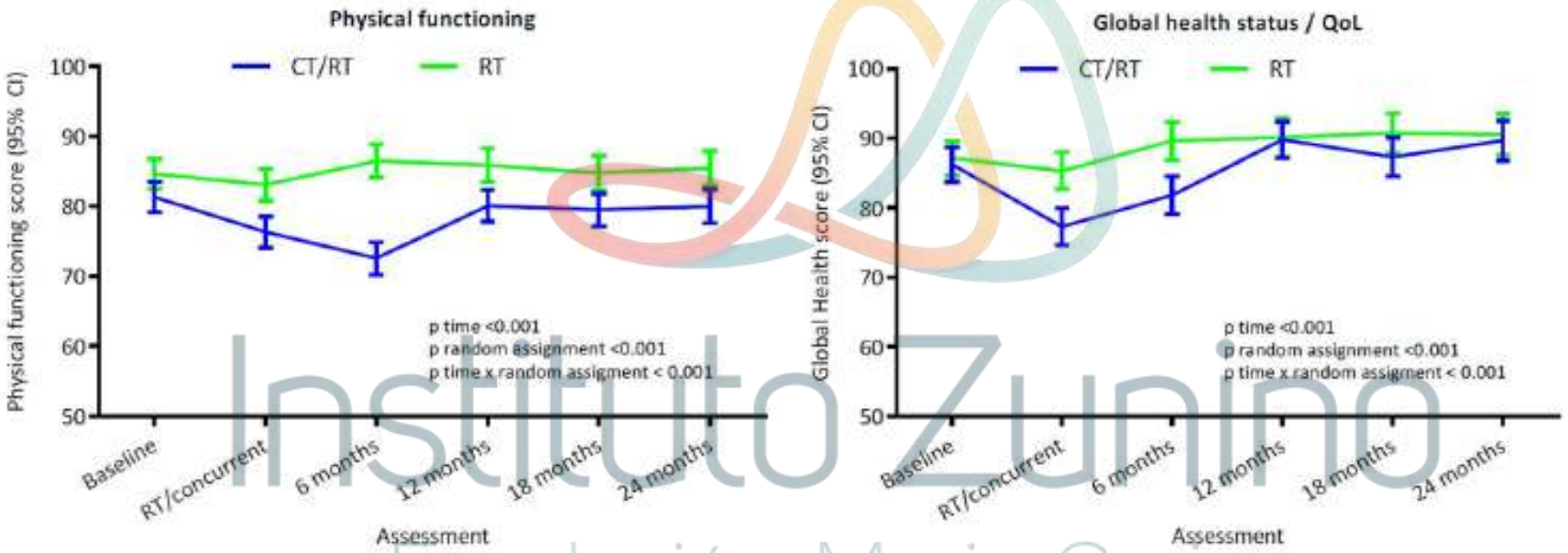
Quality of life



PORTEC-3 results De Boer et al, Lancet Oncology 2016

Presented By Stephanie de Boer at 2017 ASCO Annual Meeting

Conclusions

Although treatment with CRT significantly improved 5-year FFS for pts with HR-EC compared with RT alone, there was no significant difference in OS.

For women with stage III EC, a significant improvement in FFS was found. For each pt, the cost in terms of increased toxicity and longer treatment duration should be weighed against the benefit in terms of improvement in FFS.

Because pelvic control was high with RT alone, this CRT schedule cannot be recommended as a new standard for pts with stage I–II EC.

However, in view of the higher risk of recurrence among women with stage III disease, this CRT schedule should be considered to maximize FFS, and benefits and risks should be individually discussed.

A Randomized Phase III Trial of Cisplatin and Tumor Volume Directed Irradiation Followed by Carboplatin and Paclitaxel vs. Carboplatin and Paclitaxel for Optimally Debulked, Locally Advanced Endometrial Carcinoma

A Gynecology Oncology Group/NRG Oncology Study

Daniela Matei, Virginia Filiaci, Marcus Randall, David Mutch, Margaret Steinhoff, Paul DiSilvestro, Katherine M. Moxley, Byoung Kim, Matthew A. Powell, David M. O'Malley, Nicola M. Spirtos, Krishnanu S. Tewari, Edward Richards, John Nakayama, David Miller

Northwestern University; NRG Oncology SDMC, Buffalo, NY; University of Kentucky, Women and Infants Hospital in Rhode Island, University of Oklahoma Health Sciences Center, Samsung Medical Center, Sungkyunkwan University School of Medicine,; Washington University School of Medicine in St. Louis,; The Ohio State University College of Medicine; Womens' Cancer Center; University of California Irvine Medical Center, Lewis Cancer and Research Pavilion at St. Joseph's/Candler, University Hospital; The University of Texas Southwestern Medical Center

Presented by: Daniela Matei, MD

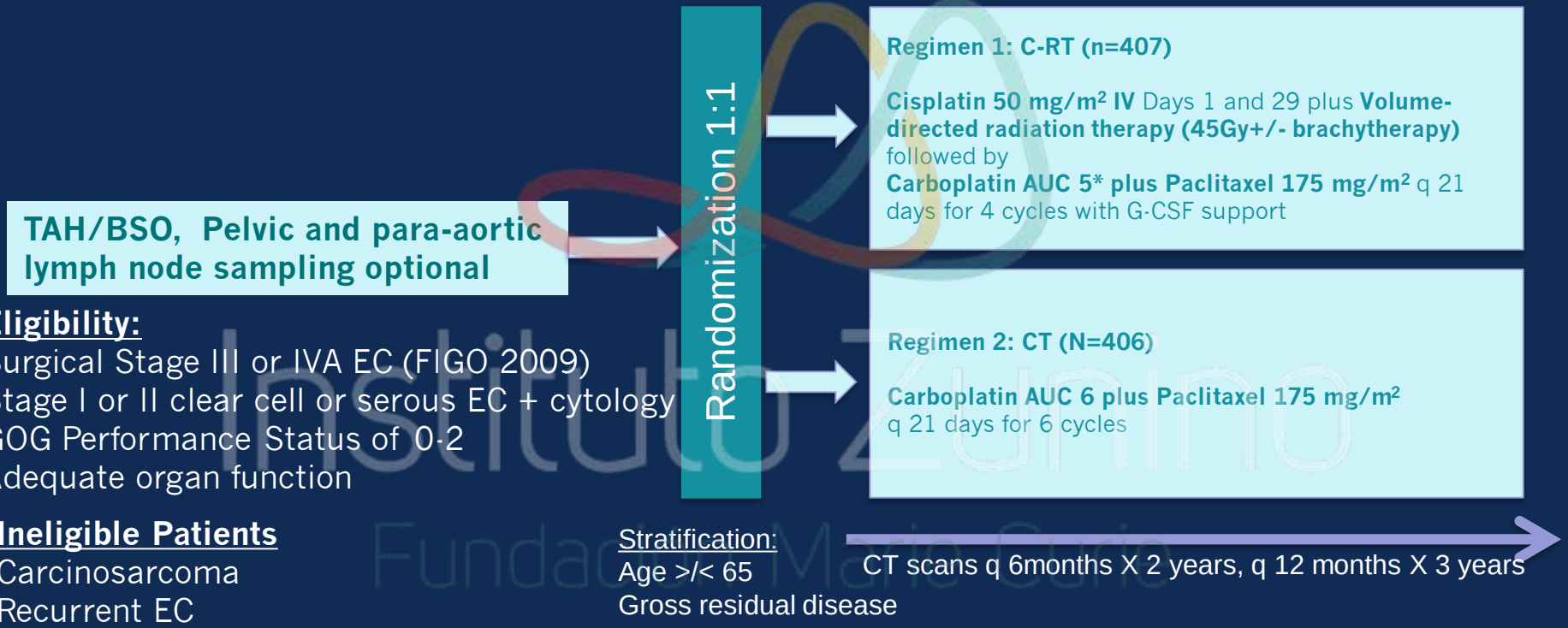
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

Research Hypothesis

Combined systemic chemotherapy and tumor volume directed radiotherapy (C-RT) improves recurrence-free survival and overall survival compared to systemic chemotherapy alone (CT) in patients with optimally debulked stage III/IVA EC.

Presented by: Daniela Matei, MD

Study Schema



Eligibility:
Surgical Stage III or IVA EC (FIGO 2009)
Stage I or II clear cell or serous EC + cytology
GOG Performance Status of 0-2
Adequate organ function

Ineligible Patients
Carcinosarcoma
Recurrent EC
Residual tumor after surgery > 2 cm

Presented by: Daniela Matei, MD

Study Objectives

Primary Objective:

- To determine if C-RT increases recurrence-free survival (RFS) vs. CT.

Secondary Objectives:

- To determine if C-RT reduces the rate of death (i.e., increases survival) when compared to CT.
- To compare acute and late adverse effects of C-RT and CT.
- To determine patient-reported quality of life during and following treatment.

Presented by: Daniela Matei, MD

Patient Characteristics

Characteristic	C-RT (N=370)		CT (N=366)	
	N	%	N	%
Age (mean, range)	60.5	(31-88)	60	(31-85)
Race				
White	291	78.6	279	76.2
Black/African American	37	10.0	42	11.5
Asian/other/not specified	42	11.3	45	12.2
Performance Status				
0	278	75.1	268	73.2
1	88	23.8	96	26.2
2	4	1.1	2	0.5
FIGO Stage (2009)				
Stage 1 or 2	6	1.6	11	3.0
Stage 3A	69	18.6	78	21.3
Stage 3B	15	4.1	13	3.6
Stage 3C	277	74.9	261	71.3
Stage 4A	3	0.8	3	0.8
Histology/Grade				
Endometrioid, grade 1	87	23.5	79	21.6
Endometrioid, grade 2	103	27.8	118	32.2
Endometrioid, grade 3	64	17.3	61	16.7
Serous	66	17.8	65	17.8
Clear Cell	10	2.7	12	3.3
Mixed Epithelial/Other	40	7.7	30	6.3
BMI Category				
Median (range)	32.9	(11.2-65.3)	32.9	(18-60.2)
Normal or underweight	72	19.5	71	19.4
Overweight	84	22.7	81	22.1
Obese Class I-III	214	57.8	214	58.4

Presented by: Daniela Matei, MD

Acute Toxicity

Adverse Events	Grd 1-2		Grd 3-5	
	C-RT (n=346) %	CT (n=361) %	C-RT (n=346) %	CT (n=361) %
Constitutional*	81	78	6	2
Fatigue*	79	73	5	2
Cardiac	12	16	3	4
Endocrine	11	11	1	0
Gastrointestinal**	77	75	13	4
Renal/Genitourinary*	31	10	2	1
Blood/Bone Marrow**	55	38	40	52
Infection	19	15	4	5
Lymphatics	17	15	<1	<1
Musculoskeletal**	16	12	3	1
Metabolic/Laboratory*	33	35	15	9
Neurology	69	74	7	5
Pulmonary	29	26	2	1
Pain	62	63	8	5

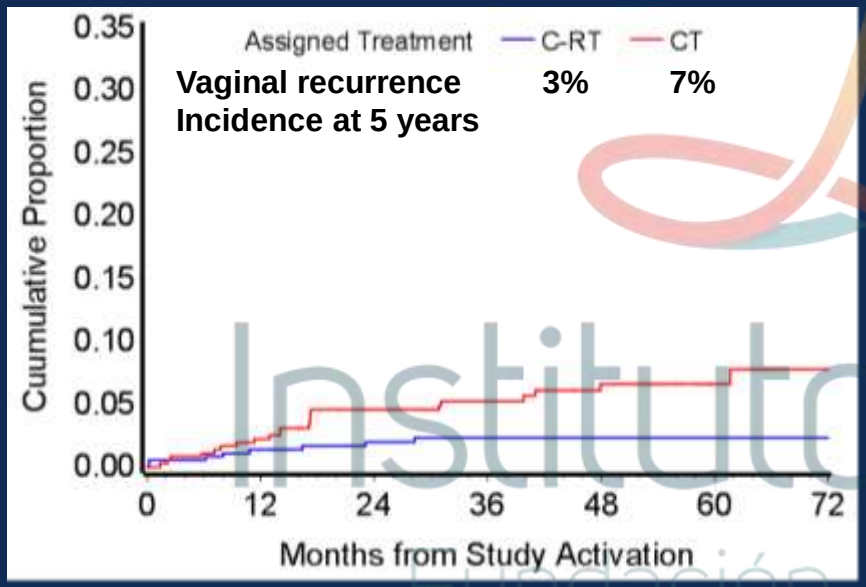
* p<0.05
** p<0.01

Grd. 5 events: 3 in CT arm, none in C-RT:

Presented by: Daniela Matei, MD

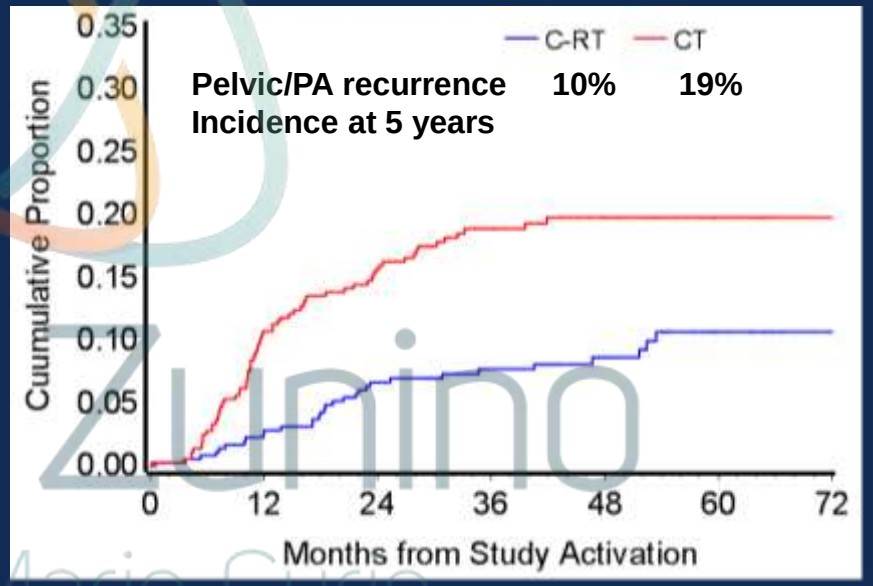
Cumulative Incidence of Recurrence

Vaginal Recurrence



C-RT vs. CT : HR=0.36 (CI: 0.16-0.82)

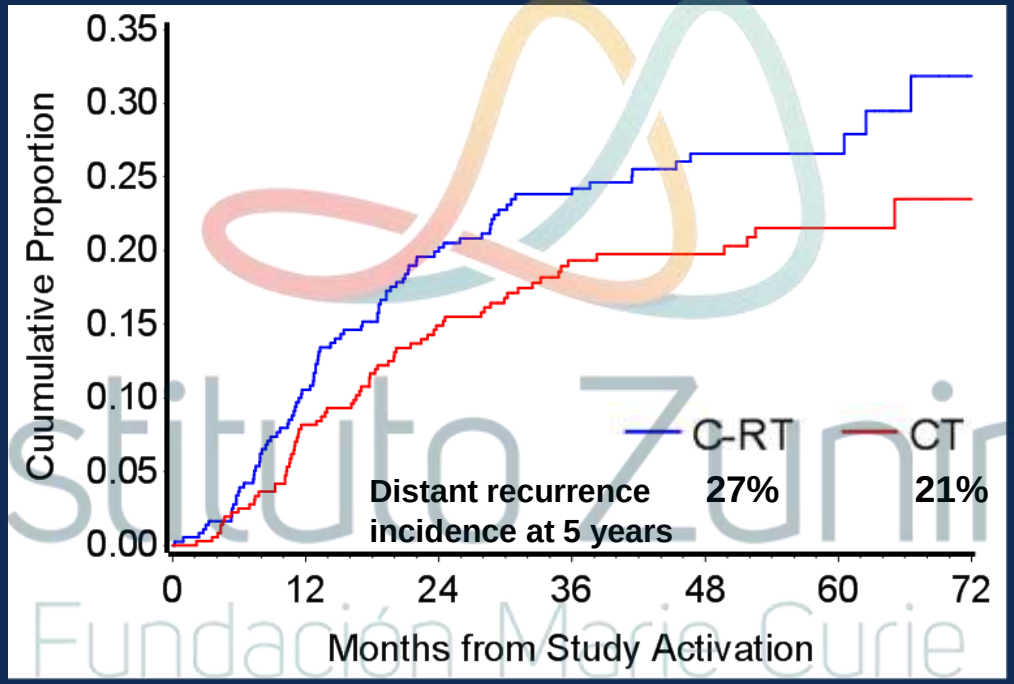
Pelvic and PA Recurrence



C-RT vs. CT : HR=0.43 (CI: 0.28-0.66)

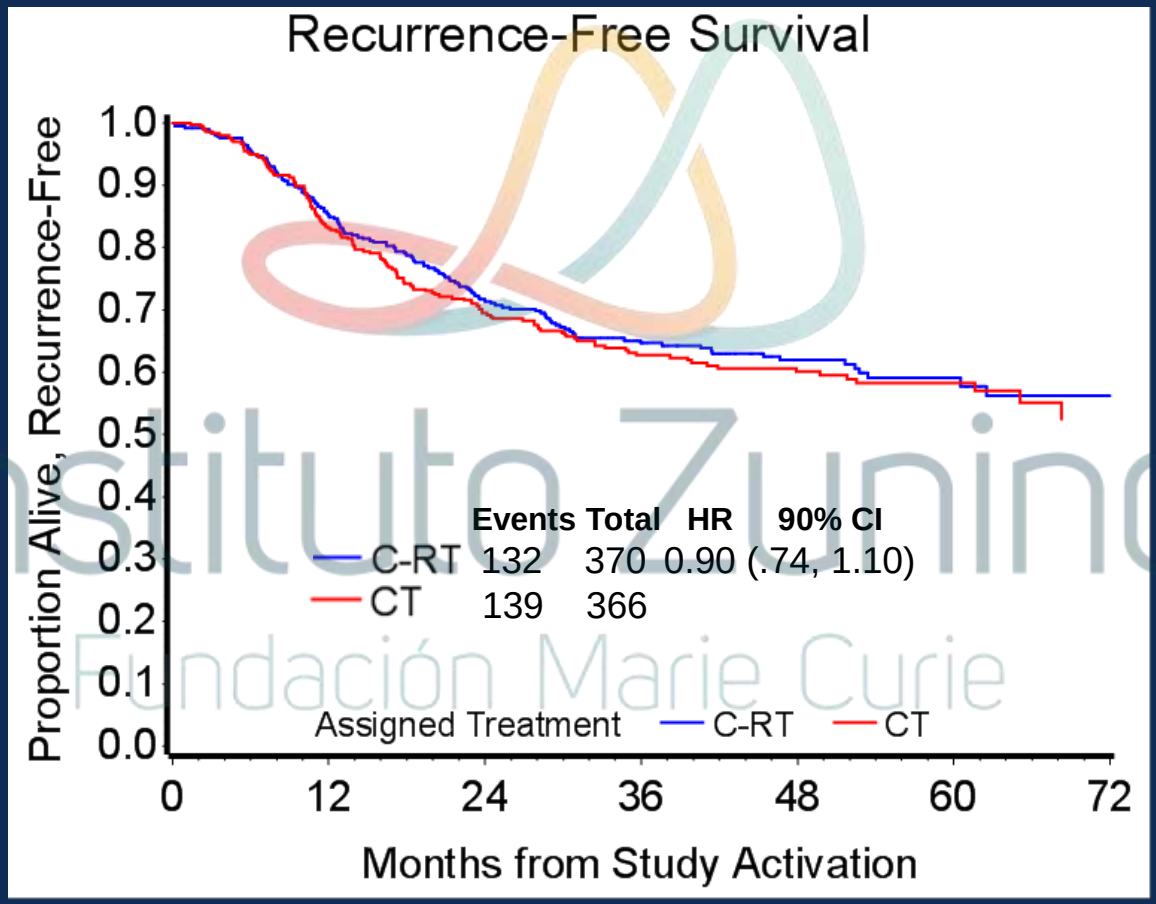
Cumulative Incidence of Recurrence

Distant Recurrence

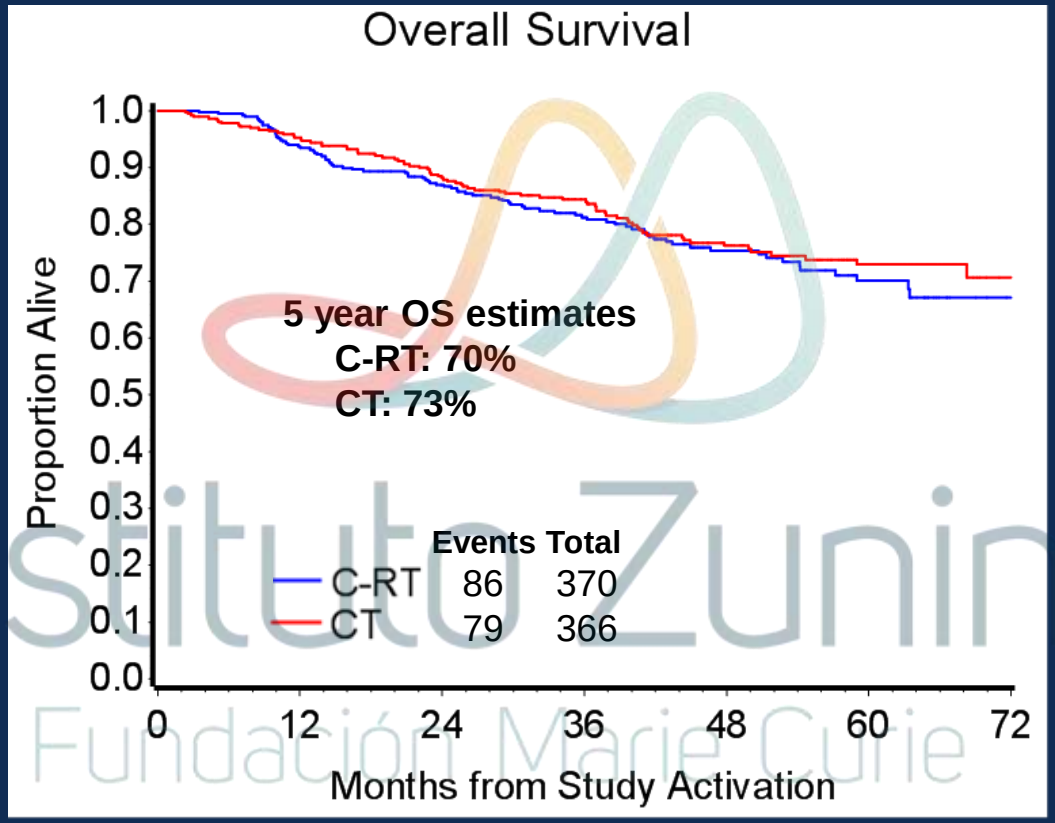


C-RT vs. CT : HR=1.36 (CI: 1.00-1.86)

Recurrence-Free Survival



Overall Survival



Data cut-off 03/09/2017 Data not mature for final analysis

Conclusions

- Chemo-RT did not improve RFS compared to CT
- Acute mid/moderate toxicities increased for chemo-RT vs. CT
- 75% patients completed therapy in C-RT arm compared to 85% in CT arm
- Chemo-RT reduced the incidence of vaginal, pelvic and para-aortic recurrences compared to CT
- Distant recurrences were more common with C-RT vs. CT.
- Survival and QOL endpoints will be reported in the future.

NCCN Guidelines. 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS | **ADJUVANT TREATMENT[f,g,m]**

Surgically staged:[d] Stage III, IV[t]

- Surgically staged:[d] Stage IIIA-IVA → EBRT ± vaginal brachytherapy ± systemic therapy or Systemic therapy ± vaginal brachytherapy
- Stage IVB → Systemic therapy ± EBRT ± vaginal brachytherapy

NRG ONCOLOGY/RTOG 0921

A PHASE II STUDY OF POSTOPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT) WITH CONCURRENT CISPLATIN AND BEVACIZUMAB FOLLOWED BY CARBOPLATIN AND PACLITAXEL FOR PATIENTS WITH ENDOMETRIAL CANCER

A. N. Viswanathan et al. *Cancer*. 2015 July 1; 121(13): 2156–2163

NRG ONCOLOGY - RTOG 0921

To assess acute and late AEs, OS, pelvic failure (PF), regional failure, distant failure and DFS in a Phase II trial of bevacizumab (Bev) + Pelvic IMRT + CT in HR-EC.

Primary endpoint: Grade ≥3 AEs in the first 90 days.

34 pts accrued, 30 eligible – TAH+BSO+LND – 60% Endometrioid; 40% UPSC , CCC

HR-EC: ≥1 of the following High-risk factors: Grade 3 with >50% MI; Grade 2 or 3 disease with any cervical stromal invasion; Known extrauterine extension confined to the pelvis

Pelvic IMRT + CDDP [dys 1&29] + Bev (5 mg/kg, dys 1, 15 & 29], followed by Carbo+Taxol x 4

23% Grade ≥3 treatment-related non-hematologic toxicities within 90 days2-year

OS, 97%; 2-year DFS, 79%.

No pelvic recurrences. No pts with St I-IIIA relapsed after a median FU of 26 m

Conclusion—Postoperative Bev added to CT and Pelvic IMRT is well tolerated and results in high overall survival rates at 2 years for patients with HR-EC

RTOG 0921

A. N. Viswanathan et al. Cancer. 2015 July 1; 121(13): 2156–2163

Summary of Worst Adverse Event per Patient (definitely, probably, or possibly related to treatment) comparing RTOG 9708 with RTOG 0921

	AEs ≤90 days from the start of all RX[1]	AEs >90 days from the start of all RX[2]		AEs occurring during concurrent RX[3]		AEs occurring during adjuvant chemo[4]	
Grade	*RTOG 0921*	*RTOG 0921*	*RTOG 9708*	*RTOG 0921*	*RTOG 9708*	*RTOG 0921*	*RTOG 9708*
1	0 (0%)	3 (10%)	9 (20%)	1 (3%)	12 (27%)	0 (0%)	3 (7%)
2	10 (33%)	10 (33%)	17 (39%)	9 (30%)	19 (43%)	6 (20%)	3 (7%)
3	11 (37%)	9 (30%)	7 (16%)	7 (23%)	12 (27%)	12 (40%)	9 (21%)
4	5 (17%)	6 (20%)	1 (2%)	2 (7%)	1 (2%)	6 (20%)	26 (62%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	4-Year Estimate (%)	
OUTCOME	RTOG 0921 (n=30)	RTOG 9708 (n=44)
Pelvic Failure	0	2
Para-aortic Failure	7	2
Distant Failure	24	19
DFS	73	81
OS	87	85
≥ Grade 3 Toxicity	17%	19%

- The addition of bevacizumab did not increase long-term toxicities
- High overall survival rates with no pelvic recurrences at 4 years
- **BUT.... [HRC Comments]**
  - More PA failures
  - More distant failures
  - Worse DFS
  - Almost Identical OS

Conclusions

- EC is a major issue for the health-care system because of its increasing incidence in high-income countries.
- Trials are ongoing in patients at high risk of recurrence (including CT, CRT, and MTT) to assess the modalities that best balance optimization of survival with the lowest adverse effects on quality of life.
- Pathways that have been targeted in clinical trials in EC are those that inhibit EGFR, VEGFR, and PI3K/PTEN/AKT/mTOR.
- The role of Immunotherapy is still to be defined


GRACIAS