PORTEC trials – Evolution in management of EC

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Senior Director
Radiation Oncology
Max Superspeciality Hospital, Saket. Delhi

31 august – 9.30 – 10.00 a.m

- PORTEC - acronym for Post-Operative Radiation Therapy in Endometrial Carcinoma.

- A series of clinical trials - investigate various aspects of adjuvant treatment for EC primarily focusing on the role of RT, often with or without chemotherapy, to reduce recurrence and improve outcomes for patients

PORTEC 1	Surgery and post operative radiotherapy versus surgery alone in Duration : 1990-1997 Sample size: 715
PORTEC 2	Vaginal BT versus pelvic EBRT in HIR EC Duration : 2002 - 2006 Sample size: 427
PORTEC 3	Adjuvant CT RT versus RT alone in high risk EC Duration : 2006- 2013 Sample size: 686
PORTEC 4a	Molecular profile based adjuvant treatment for high intermediate risk EC Duration : 2016 – 2021 Sample size: 500

MAX Healthcare

PORTEC 1

1990-1997

PORTEC-1 Study

ELSEVIER

The Lancet

Volume 355, Issue 9213, 22 April 2000, Pages 1404-1411

Articles

Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial *

Carien L Creutzberg MD [a], Wim LJ van Putten MSc [b], Peter CM Koper MD [a], Marnix LM Lybeert MD [e], Jan J Jobsen MD [f], Carla C Wárlám-Rodenhuis MD [g], Karin AJ De Winter MD [h], Ludy CHW Lutgens MD [i], Alfons CM van den Bergh MD [j], Elzbieta van de Steen-Banasik MD [k], Henk Beerman MD [d], Mat van Lent MD [c], for the PORTEC Study Group

1990-1997

Creutzberg et al, The Lancet, Volume 355, April 2000

PORTEC-1

- Multicentric, prospective, randomized trial
- FIGO 1988 staging
- n= 714 - 354 in RT and 361 – no further treatment
- All (but one) of the 20 RO centres in the Netherlands took part

Creutzberg et al, The Lancet, Volume 355, April 2000

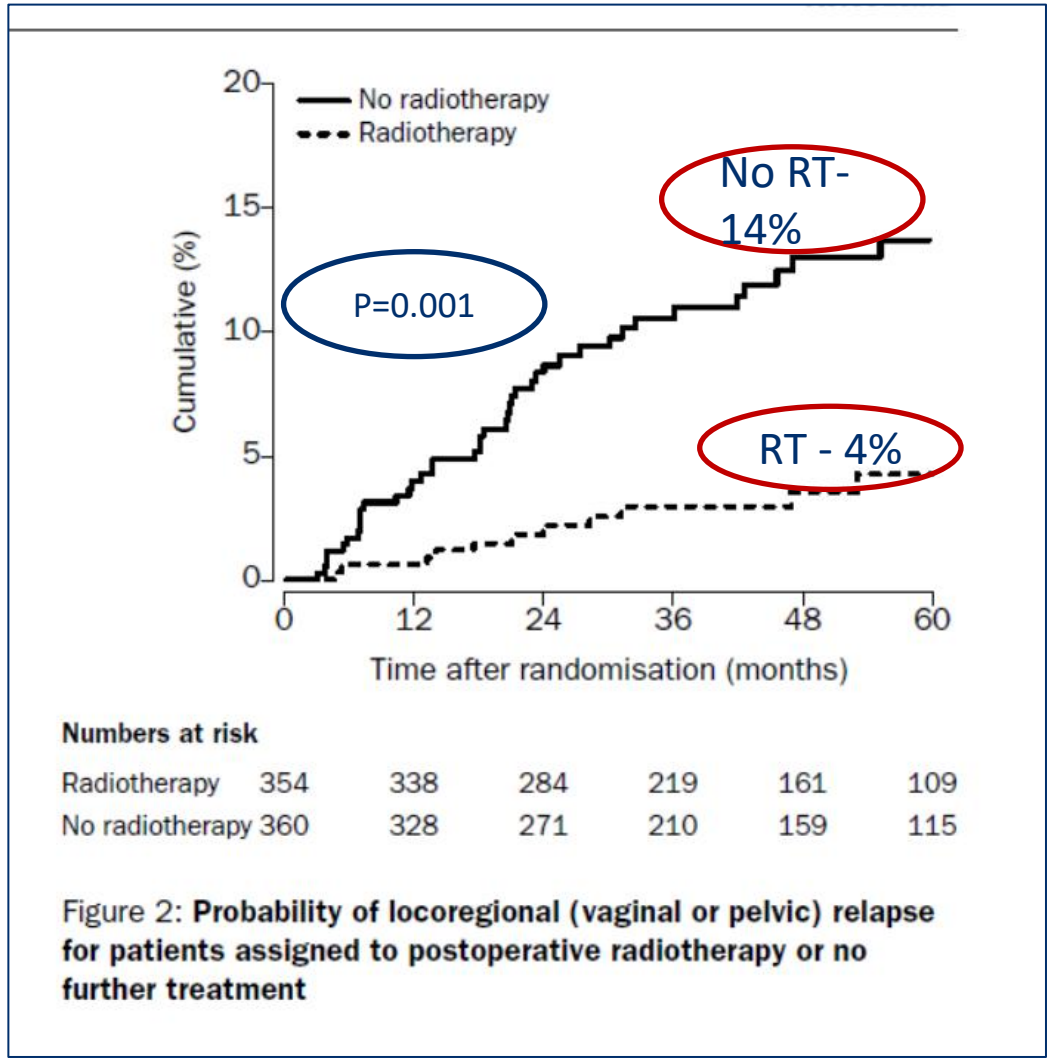
PORTEC-1

- Inclusion criteria
  - endometrial adenocarcinoma stage I, grade 1 with deep (50%) myometrial invasion
  - grade 2 with any invasion
  - grade 3 with superficial (50%) invasion were eligible.

- Objectives
  - Primary outcomes – Locoregional recurrence and OS
  - Secondary objective – Morbidity and survival after relapse

Creutzberg et al, The Lancet, Volume 355, April 2000

5 yr LOCOREGIONAL RELAPSE



Numbers at risk

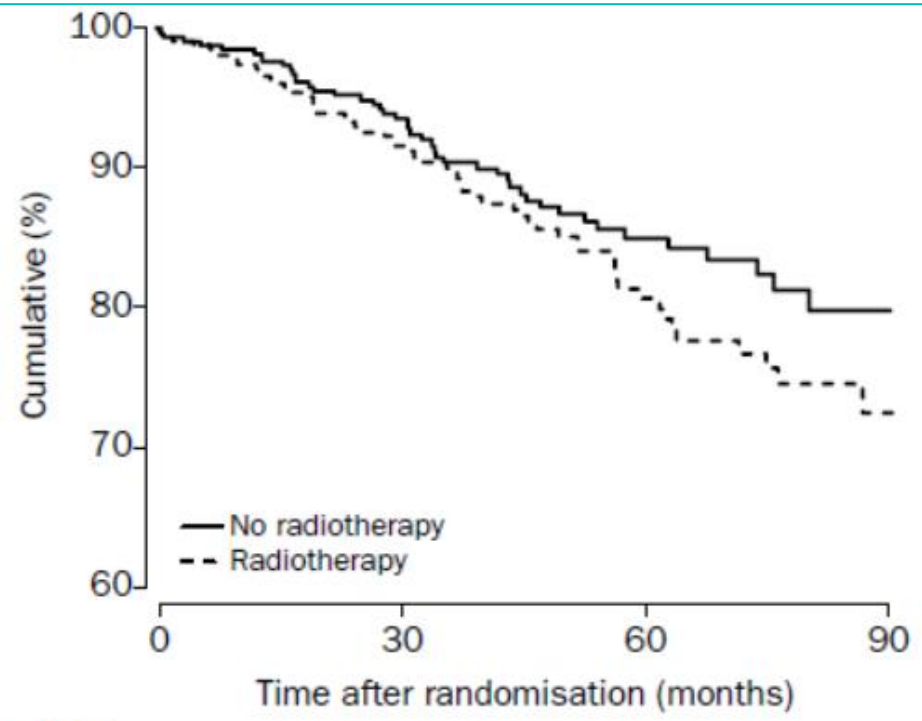
Radiotherapy	354	338	284	219	161	109
No radiotherapy	360	328	271	210	159	115

Figure 2: **Probability of locoregional (vaginal or pelvic) relapse for patients assigned to postoperative radiotherapy or no further treatment**

- 5 year LRR
  - 4% in the radiotherapy group
  - 14% in the control group
    (p = 0·001)
- Most of the recurrences were restricted to vagina (73%)
- Distant mets were similar in both arms

Creutzberg et al, The Lancet, Volume 355, April 2000

OVERALL SURVIVAL



Numbers at risk

Radiotherapy	354	260	111	24
No radiotherapy	360	257	125	23

Figure 3: **Probability of survival for patients assigned to postoperative radiotherapy or no further treatment**

Overall survival at 5 years was

- 81% in the RT group
- 85% in the control group
- (log-rank test, p= 0·31)

Creutzberg et al, The Lancet, Volume 355, April 2000

Multivariate Analysis

	Locoregional relapse		Death due to endometrial cancer	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age ⩾60	3·2 (1·3–7·5)	0·003	3·1 (1·2–8·0)	0·02
Invasion ⩾50%	1·8 (0·9–3·8)	0·11	1·9 (0·8–4·4)	0·16
Grade 1	0·77 (0·4–1·6)	0·50	0·45 (0·2–1·3)	0·15
Grade 3	2·2 (0·8–5·8)	0·11	4·9 (1·9–12·5)	0·0008
No radiotherapy	3·9 (2·0–7·6)	<0·0001	0·76 (0·4–1·4)	0·37

Hazard ratio describes relative hazard of failure per unit time, for age ⩾60 years compared with <60 years; for myometrial invasion ⩾50% compared with <50%; for grade 1 and 3 compared with grade 2; for no radiotherapy compared with postoperative radiotherapy.

Table 3: **Cox-regression analysis**

The risk of endometrial-cancer-related death was significantly higher for patients aged 60 and over (HR 3·1, p=0·02) and for patients with grade-3 tumours (HR 4·9, p=0·0008).

Multivariate analyses showed the LRR rate to be
- 3 fold higher for pts aged 60 and over

compared with those below this age (p=0·003)
- almost 4 fold higher for pts in the control group compared with the RT group (p<0·0001).

Creutzberg et al, The Lancet, Volume 355, April 2000

CONCLUSION

In PORTEC-1, major risk factors for recurrence were

- invasion in the outer half of the myometrium
- grade 3 histology
- age greater than 60 years

For patients at high-intermediate risk with two of these three major risk factors, locoregional recurrence at 5 years was reduced from 23% to 5% after EBRT

Creutzberg et al, The Lancet, Volume 355, April 2000

VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

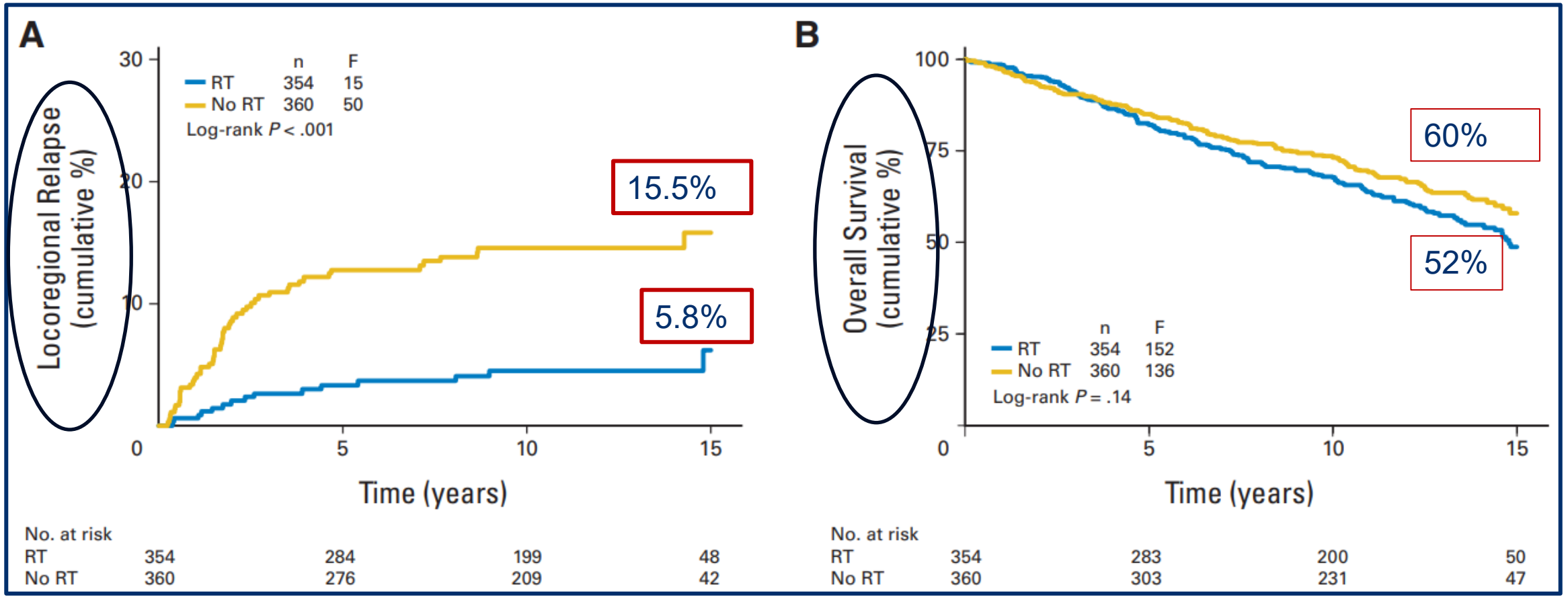
ORIGINAL REPORT

Long-Term Outcome and Quality of Life of Patients With Endometrial Carcinoma Treated With or Without Pelvic Radiotherapy in the Post Operative Radiation Therapy in Endometrial Carcinoma 1 (PORTEC-1) Trial

Remi A. Nout, Lonneke V. van de Poll-Franse, Marnix L.M. Lybeert, Carla C. Wárlám-Rodenhuis, Jan J. Jobsen, Jan Willem M. Mens, Ludy C.H.W. Lutgens, Betty Pras, Wim L.J. van Putten, and Carien L. Creutzberg

Nout RA et al, Journal of Clinical Oncol., vol 29, May 2011

LRR and OS at 15 yrs



Probability of locoregional (vaginal and/or pelvic) relapse (A) and overall survival (B) for patients assigned to postoperative radiotherapy (RT) or no additional treatment (no RT). F, total number of events.

Nout RA et al, Journal of Clinical Oncol., vol 29, May 2011

QOL

Results

- Median follow-up -13.3 years.
- Patients treated with EBRT reported significant (p=.01) and clinically relevant higher rates of urinary incontinence, diarrhea, and fecal leakage leading to more limitations in daily activities.

Conclusion

- EBRT is associated with long-term toxicities even 15 years after treatment.
- Despite its efficacy in reducing LRR, EBRT should be avoided in patients with low- and intermediate-risk EC.

Nout RA et al, Journal of Clinical Oncol., vol 29, May 2011

PORTEC -2

2002-2006

PORTEC-2 Study

THE LANCET

ARTICLES · Volume 375, Issue 9717, P816-823, March 06, 2010

Download Full Issue

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

Dr RA Nout, MD [a] · VTHBM Smit, MD [b] · H Putter, PhD [c] · IM Jürgenliemk-Schulz, MD [d] · JJ Jobsen, MD [e] · LCHW Lutgens, MD [f] · et al. Show more

PORTEC 2

- N= 427.
- randomly allocated to either VBT or pelvic radiotherapy (EBRT).
- HIR was defined as either (FIGO 1988)
  - stage 1C (≥50% myometrial invasion) with age > 60 and grade 1 or 2
  - stage 1B (<50% myometrial invasion) with age > 60 and grade 3
  - stage 2A (endocervical glandular involvement), with any age, grade 1,2 or 3 with less than half myometrium invasion.

Exclusion criteria were: serous or clear cell carcinoma

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

DOSES

EBRT

- A dose of 46 Gy, with 2 Gy fractions
- For all patients, computerised treatment planning with 3 D CRT or multiple field techniques, with individual shielding in all fields.

VBT

- 21 Gy in three fractions of 7 Gy, 1 week apart for the high-dose rate;
- 30 Gy at 50–70 cGy/h for the low dose rate
- 28 Gy at 100 cGy/h in one session for the medium-dose rate.

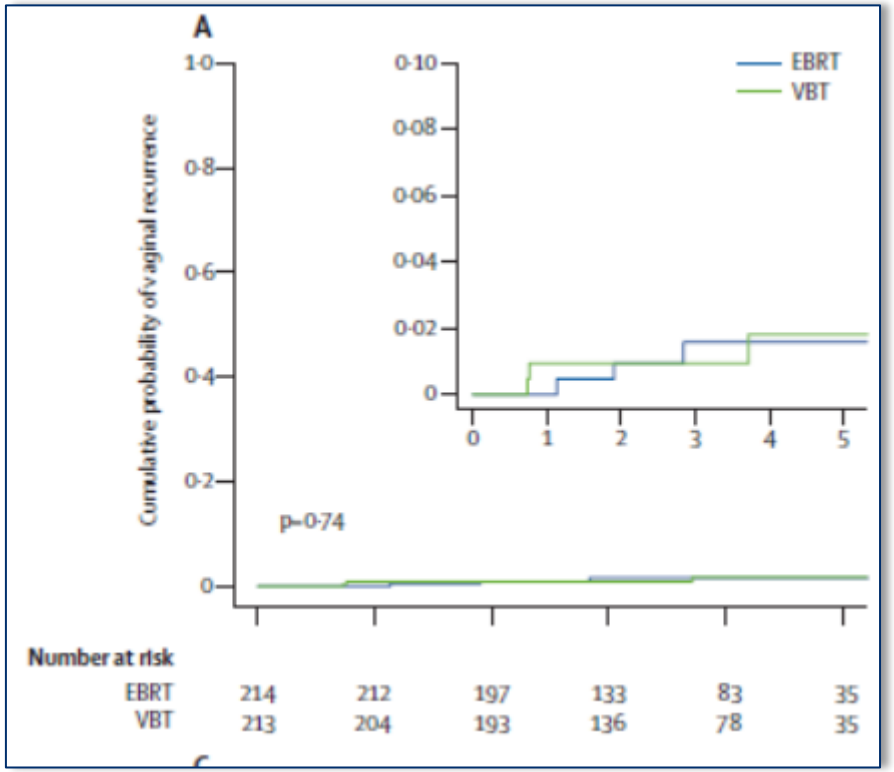
Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

PORTEC 2

Primary outcome measure	5-year actuarial vaginal relapse
Secondary outcome measures	1. 5-year overall survival and cancer-specific survival 2. Quality of life and treatment related morbidity 3. 5-year rates of pelvic and distant relapse 4. Local control and survival after relapse

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

VAGINAL RECURRENCE

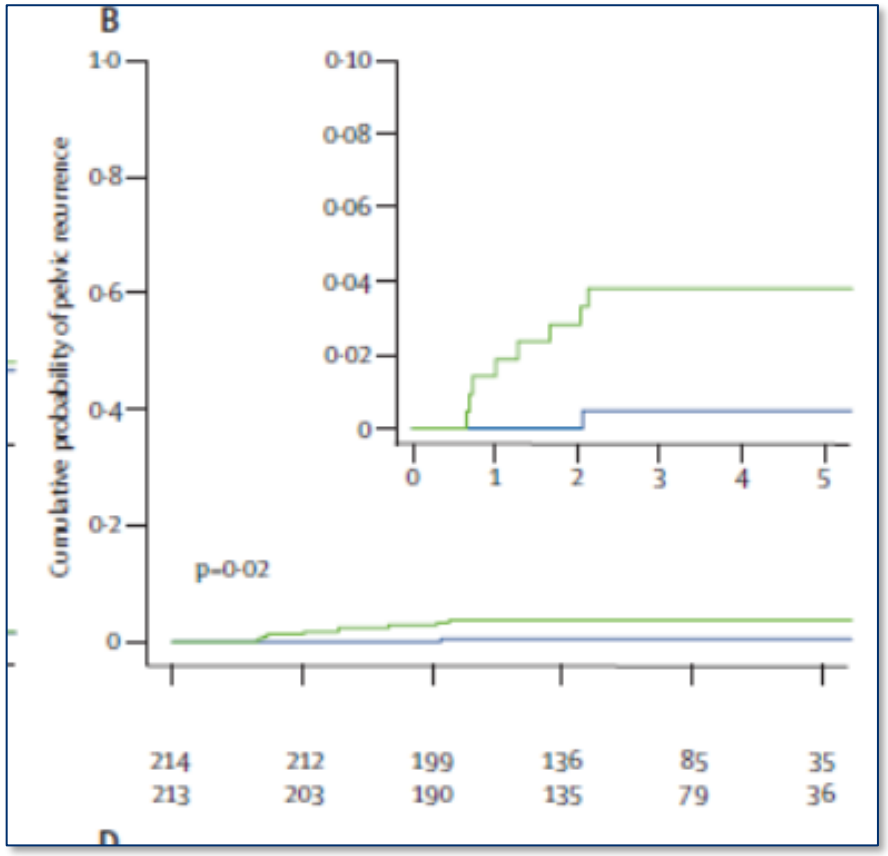


Estimated 5-year vaginal recurrence rates

- 1.8% after VBT
- 1.6% after EBRT
- log-rank p= 0.74

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

PELVIC RECURRENCE

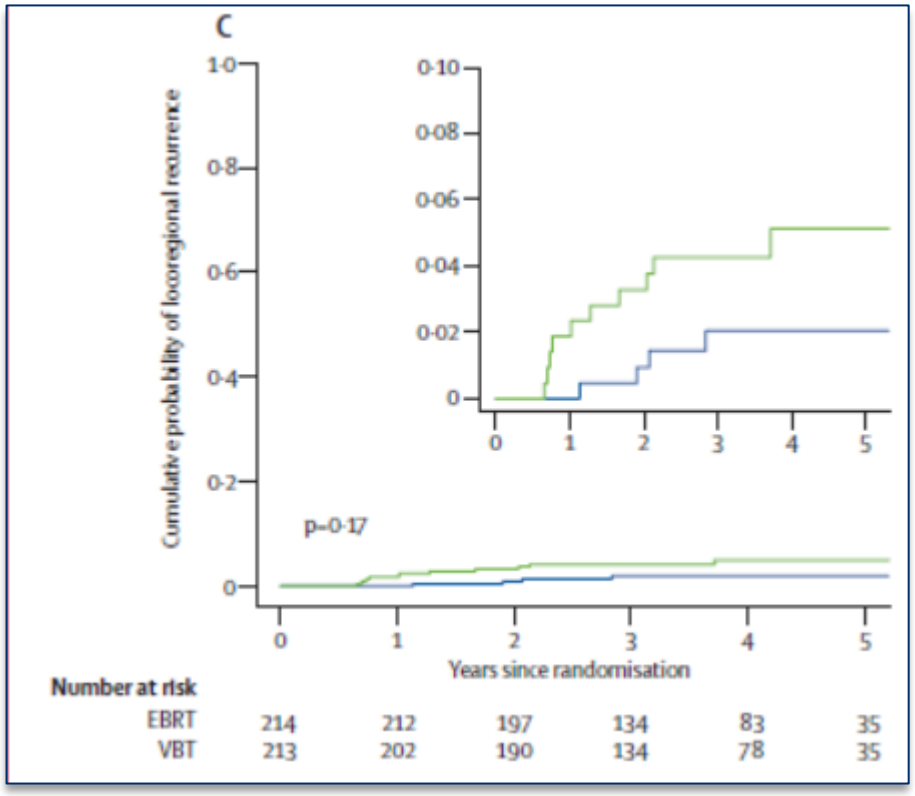


Estimated 5-year pelvic recurrence rates

- 3.8% after VBT
- 0.5% after EBRT
- log-rank p= 0.02

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

LOCOREGIONAL RELAPSE

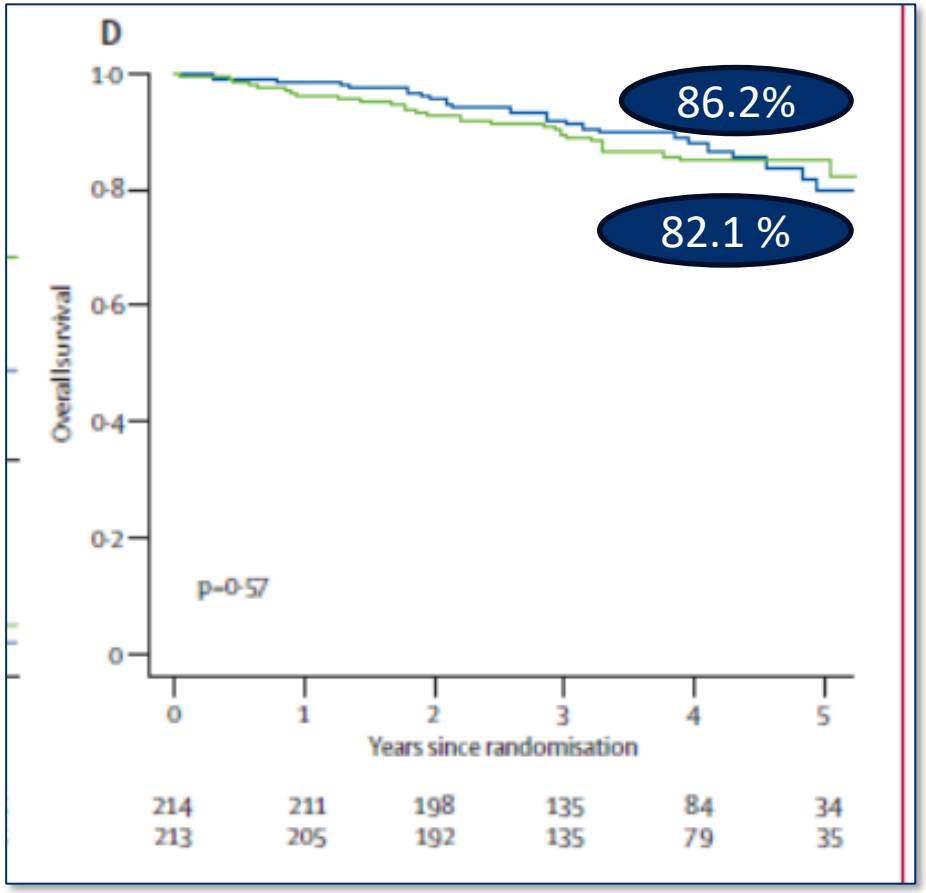


5-year rates of locoregional relapse (vaginal or pelvic recurrence, or both)
5·1% (2·8–9·6) for VBT
2·1% (0·8–5·8) for EBRT
HR 2·08; p=0·17

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

DFS and OS

DFS at 5 yrs similar
EBRT- 80.2%
VBT – 84.5%
P=0.89



No difference in OS
EBRT – 82.1%
VBT- 86.2%,
p= 0.66

TOXICITY

At median follow-up of 45 months

- Rates of acute grade 1–2 GI toxicity were significantly lower in the VBT -12·6% group than in the EBRT group - 53·8%. This difference decreased and lost statistical significance after 24 mths
- Late grade 3 GI toxic effects - four (2%) pts receiving EBRT and in one (<1%) receiving VBT
- Vaginal atrophy grade 2 more in VBT
- Sexual activity - no difference in both the groups

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

CONCLUSIONS

- VBT achieves excellent vaginal control and rates of locoregional recurrence, overall survival, and disease-free survival that are similar to EBRT
- quality of life and gastrointestinal toxic effects are significantly better with VBT.
- VBT should be the adjuvant treatment of choice for patients with endometrial carcinoma of high-intermediate risk.

Nout RA et al, et alwww.thelancet.com ***Vol 375 March 6, 2010***

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

Clinical Study

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

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

Wortman BG et al,British Journal of Cancer (2018

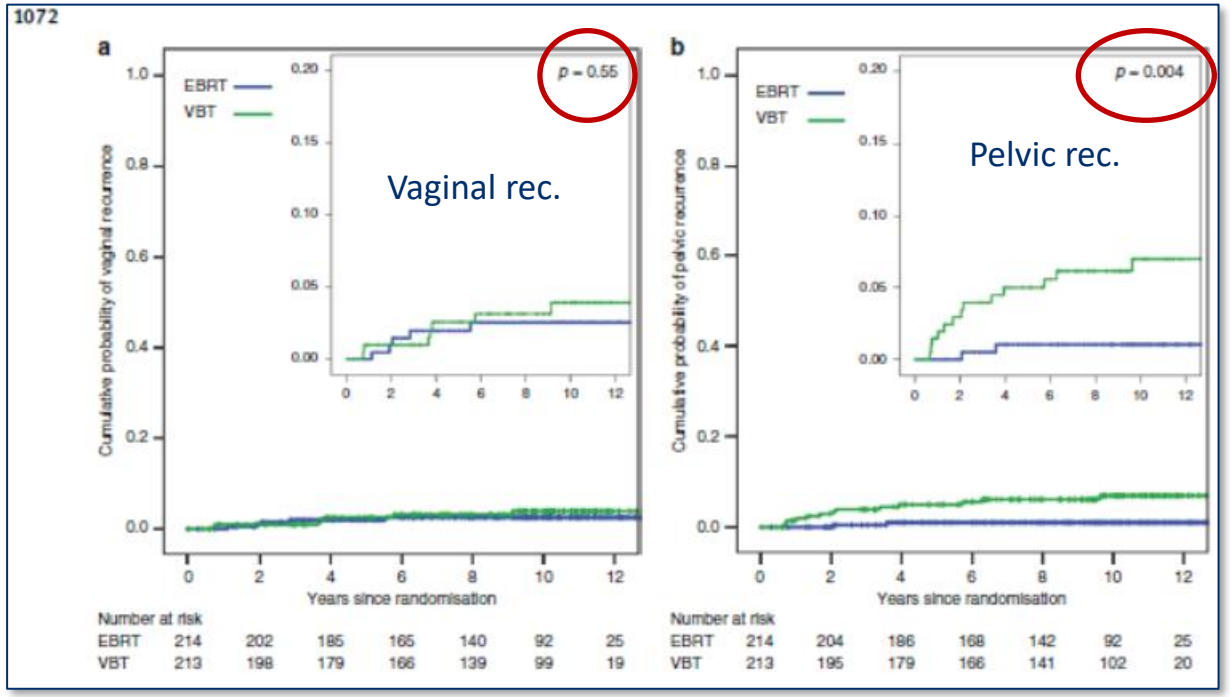
Table 3. Multivariable analysis of recurrence in confirmed-HIR patients

		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

Wortman BG et al,British Journal of Cancer (2018

10 yr results of PORTEC 2



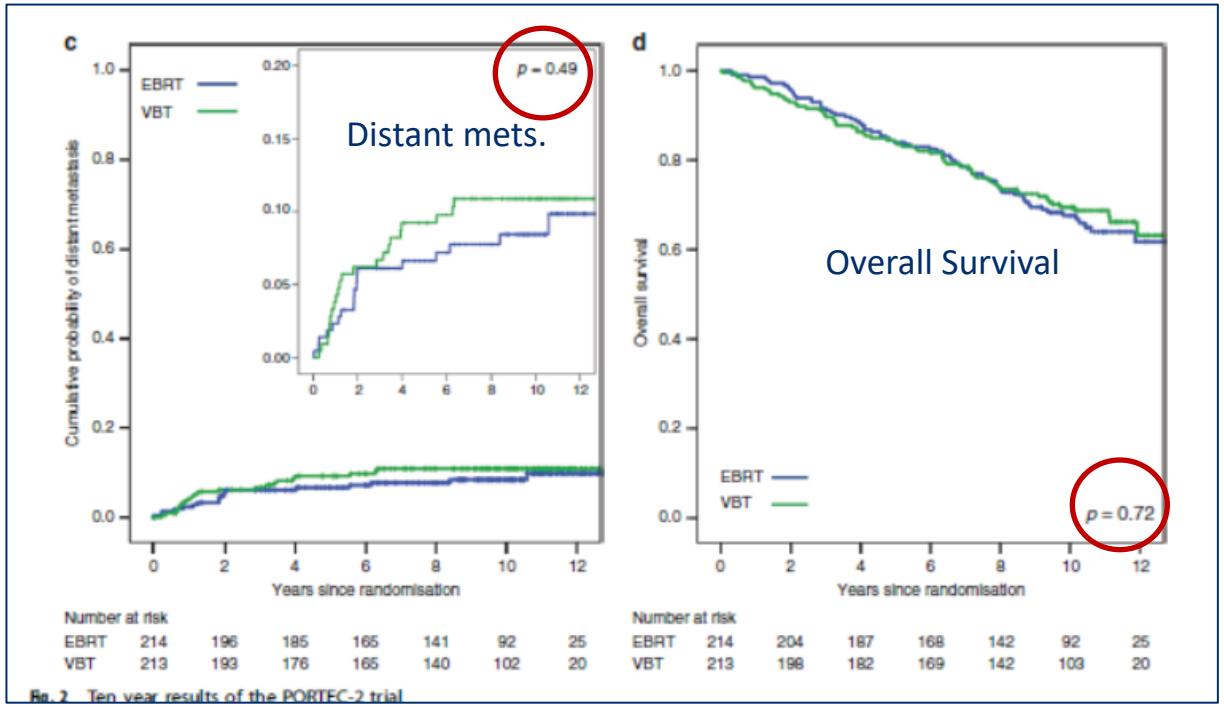


Fig. 2 Ten year results of the PORTEC-2 trial

Wortman BG et al,British Journal of Cancer (2018

Outcomes in relation to molecular markers

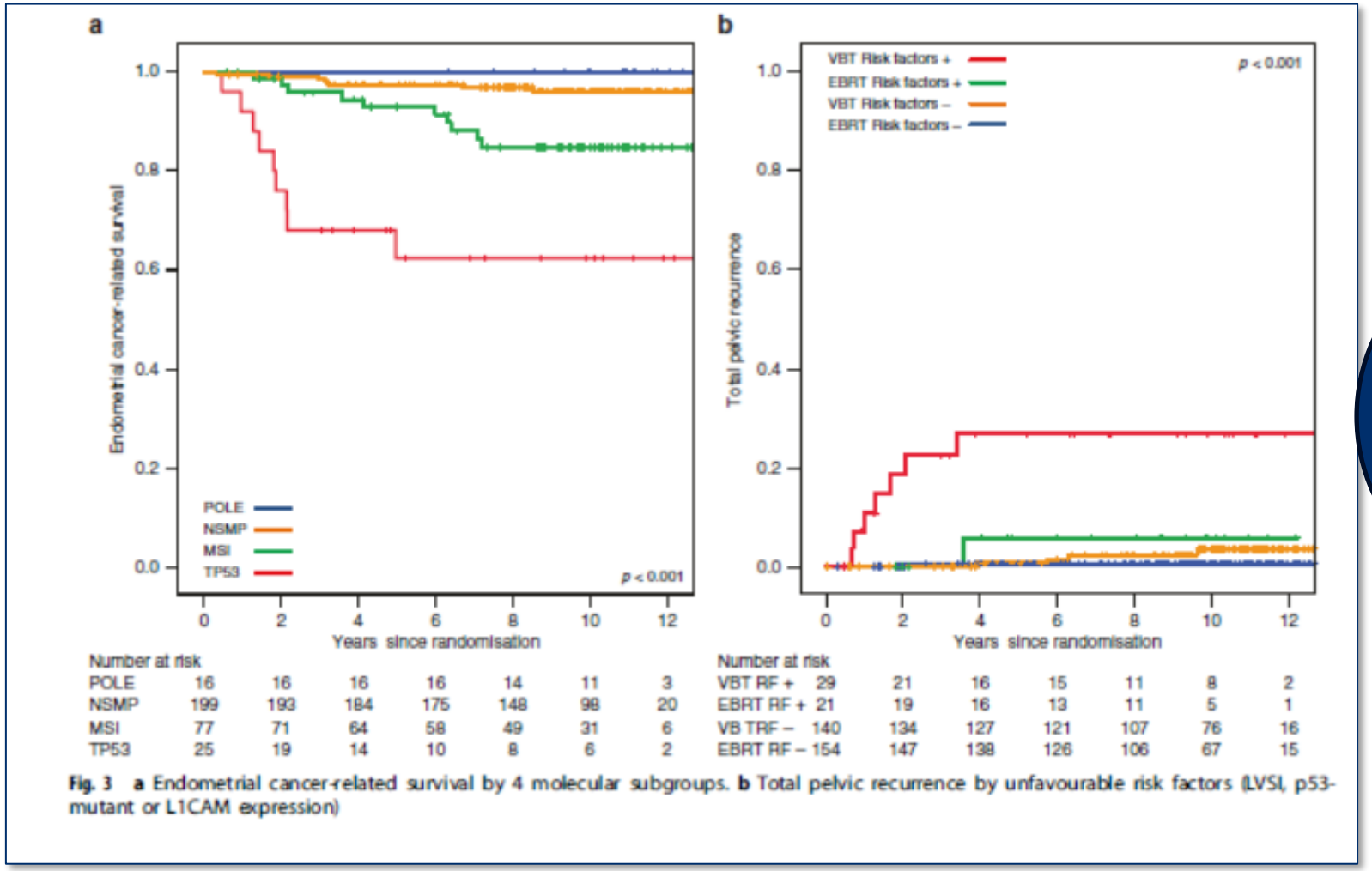


Fig. 3 **a** Endometrial cancer-related survival by 4 molecular subgroups. **b** Total pelvic recurrence by unfavourable risk factors (LVSI, p53-mutant or L1CAM expression)

Risk Factors-
LVSI
P53 mutant
L1CAM

Wortman BG et al,British Journal of Cancer (2018

10 yr results of PORTEC 2

- Confirmed VBT as the adjuvant treatment of choice for women with HIR EC

- EBRT might provide better pelvic control in pts with unfavourable risk factors
  - substantial LVSI
  - L1CAM expression
  - p53-mutant expression

Wortman BG et al,British Journal of Cancer (2018

Original Reports | Gynecologic Cancer

Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer

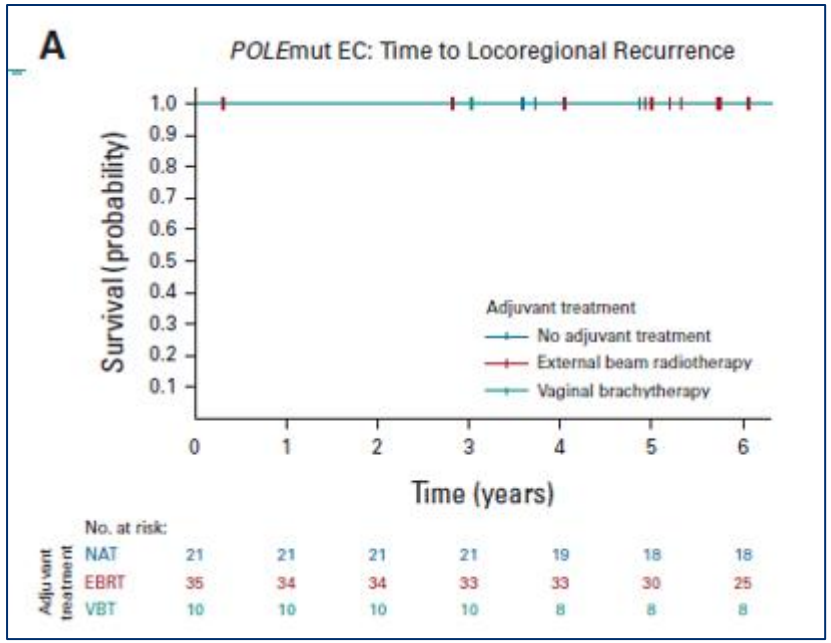
Nanda Horeweg, MD, PhD[1]; Remi A. Nout, MD, PhD[1,2]; Ina M. Jürgenliemk-Schulz, MD, PhD[3]; Ludy C.H.W. Lutgens, MD, PhD[4]; Jan J. Jobsen, MD, PhD[5]; Marie A.D. Haverkort, MD[6]; Jan Willem M. Mens, MD[2]; Annerie Slot, MD[7]; Bastiaan G. Wortman, MD, PhD[1,8]; Stephanie M. de Boer, MD, PhD[1]; Ellen Stelloo, PhD, MSc[9]; Karen W. Verhoeven-Adema, PhD[10]; Hein Putter, PhD[11]; Vincent T.H.B.M. Smit, MD, PhD[9]; Tjalling Bosse, MD, PhD[9]; and Carien L. Creutzberg, MD, PhD[1]; for the PORTEC Study Group

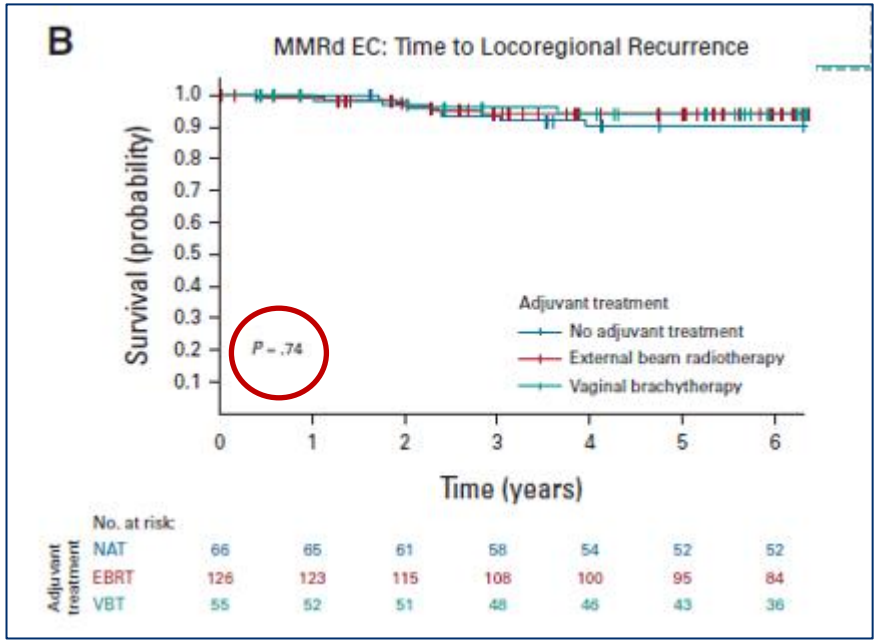
DOI https://doi.org/10.1200/JCO.23.00062

- A total of 880 molecularly classified ECs, 484 from PORTEC-1 and 396 from PORTEC-2, were included.
- The majority were FIGO-2009 stage I EEC (97.2%).
- The median follow-up was 11.3 years.

Horewag N et al. July 24, 2023; J Clin Oncol 41:4369-4380

Molecular markers and RT – LRR free survival



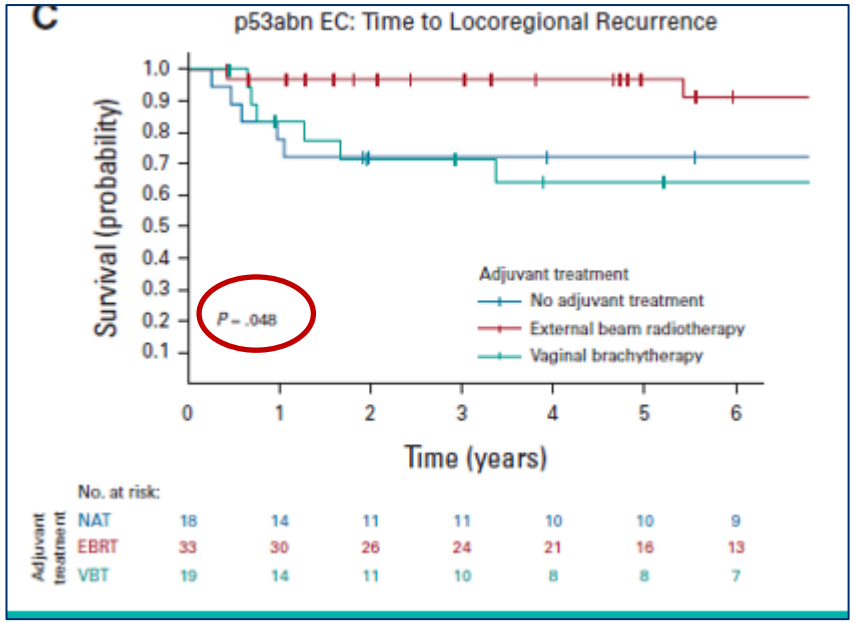


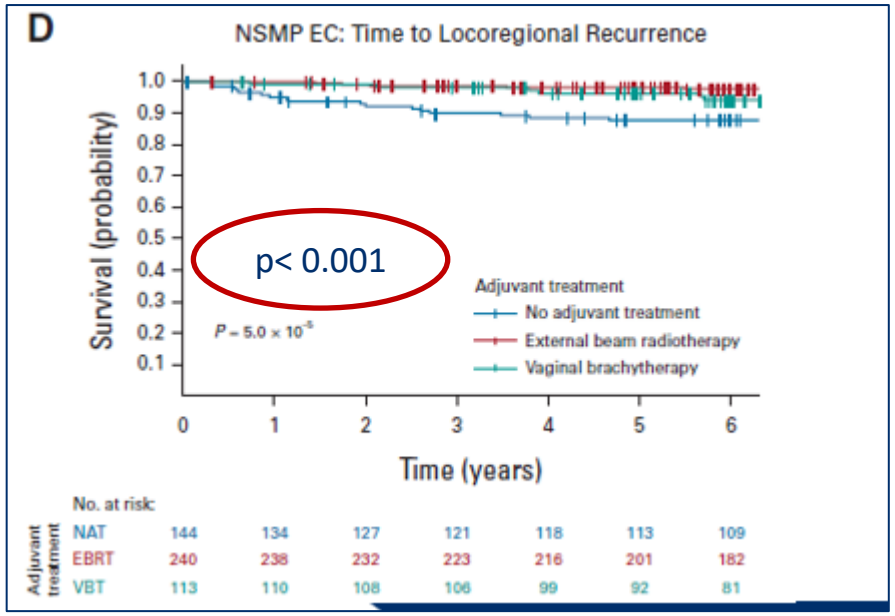
- No locoregional recurrences - with a pathogenic mutation of DNA polymerase-e (POLE mut EC).

- In MMRd EC, locoregional recurrence-free survival was similar after EBRT (94.2%), VBT (94.2%), and no adjuvant therapy (90.3%; p=0.74).

Horewag N et al. July 24, 2023; J Clin Oncol 41:4369-4380

Molecular markers and RT – LRR free survival





- In p53abn EC, EBRT (96.9%) had a substantial benefit over VBT (64.3%) and no adjuvant therapy (72.2%).

- In NSMP EC, both EBRT (98.3%) and VBT (96.2%) yielded better LRC than no adjuvant therapy (87.7%).

Horewag N et al. July 24, 2023; J Clin Oncol 41:4369-4380

- RT in the form of EBRT or VBT - helped in control of LRR but not in DM and OS.
- Also the evolving molecular markers started dictating the risk categorisation and the outcomes, hence the role of CT RT needed to be explored

MAX Healthcare

PORTEC 3

2006-2013

MAX Healthcare

THE LANCET
Oncology

ARTICLES · Volume 19, Issue 3, P295-309, March 2018 · *Open Access* Download Full Issue

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, MD [a] · Melanie E Powell, MD [d] · Linda Mileshkin, MD [f,g] · Prof Dionyssios Katsaros, MD [h] · Prof Paul Bessette, MD [i] · Christine Haie-Meder, MD [j] · et al. Show more

- PORTEC-3 - phase 3 trial enrolled 686 pts (103 centres)

Primary objectives:

- overall survival
- failure-free survival

Secondary objectives:

- pelvic and distant recurrence
- severe treatment-related toxicity
- quality of life

Staging - FIGO 2009, High Risk

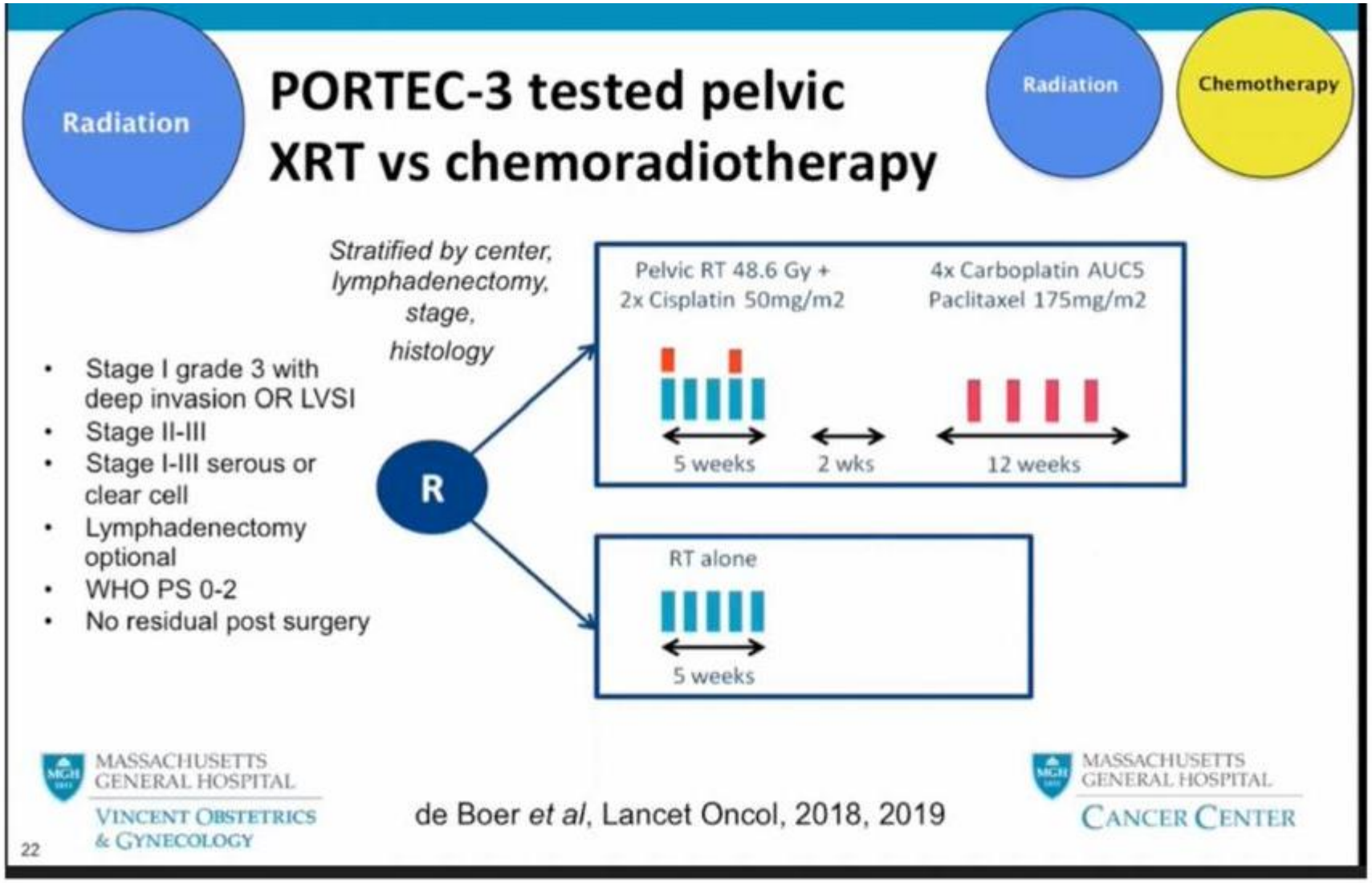
- Endometroid type Endometrial cancer with either
  - stage 1A grade 3 with documented LVSI
  - stage IB, grade 3
  - stage II, IIIA, IIIB (parametrial invasion), or IIIC

- Serous or clear-cell histology endometrial cancer with stages
  - IA (with invasion)
  - IB, II, or III

Exclusion:

- uterine carcinosarcoma

PROTOCOL



Whitfield Growdon GYOEDU lecture

Patient, tumour and Treatment characeristics

	Chemoradiotherapy (n=330)	Radiotherapy alone (n=330)
Age at randomisation (years)		
Median	62·4 (56·5–67·9)	62·0 (55·8–68·2)
<60	128 (39%)	140 (42%)
60–69	144 (44%)	128 (39%)
≥70	58 (18%)	62 (19%)
Participating groups		
NCRI (UK)	82 (25%)	95 (29%)
DGOG (Netherlands)	72 (22%)	66 (20%)
ANZGOG (Australia and New Zealand)	60 (18%)	58 (18%)
MaNGO (Italy)	52 (16%)	46 (14%)
CCTG (Canada)	36 (11%)	29 (9%)
Fedegyn (France)	28 (9%)	36 (11%)
FIGO 2009 stage		
Stage IA	39 (12%)	38 (12%)
Stage IB	59 (18%)	59 (18%)
Stage II	80 (24%)	90 (27%)
Stage III	152 (46%)	143 (43%)
Histological grade and type		
EEC grade 1	68 (21%)	56 (17%)
EEC grade 2	59 (18%)	73 (22%)
EEC grade 3	90 (27%)	95 (29%)
Serous	53 (16%)	52 (16%)
Clear cell	29 (9%)	33 (10%)
Mixed	17 (5%)	13 (4%)
Other	14 (4%)	8 (2%)
Myometrial invasion		
<50%	116 (35%)	123 (37%)
≥50%	212 (65%)	206 (63%)
Missing	2 (<1%)	1 (<1%)
LVSI		
Yes	197 (60%)	192 (58%)
No	133 (40%)	138 (42%)
WHO performance score		
0–1	323 (99%)	324 (99%)
≥2	5 (2%)	5 (2%)
Missing	2 (<1%)	1 (<1%)

	Chemoradiotherapy (n=330)	Radiotherapy alone (n=330)
(Continued from previous column)		
Type of surgery		
TAH/BSO	95 (29%)	97 (29%)
TAH/BSO + LND/full staging	143 (43%)	131 (40%)
TLH/BSO	45 (14%)	41 (12%)
TLH/BSO + LND/full staging	47 (14%)	61 (18%)
Number of nodes removed		
TAH/BSO or TLH/BSO	0 (0–0)	0 (0–0)
TAH/BSO or TLH/BSO +LND/full staging	15 (9–25)	14 (8–22)
Missing	9	16
Radiotherapy		
EBRT completion	329 (100%)	325 (99%)
Dose at prescription point		
Dose <45 Gy	1 (<1%)	4 (1%)
Dose 45·0–50·4 Gy	329 (100%)	322 (98%)
Dose >50·4 Gy	0	4 (1%)
Vaginal brachytherapy boost	151 (46%)	158 (48%)
Chemotherapy completed		
1 cycle cisplatin	326 (99%)	–
2 cycles cisplatin	304 (92%)	–
1 cycle carboplatin and paclitaxel*	302 (91%) and 302 (91%)	–
2 cycles carboplatin and paclitaxel*	294 (89%) and 291 (88%)	–
3 cycles carboplatin and paclitaxel*	279 (85%) and 263 (80%)	–
4 cycles carboplatin and paclitaxel*	262 (79%) and 233 (71%)	–

Data are median (IQR) or n (%). NCRI=National Cancer Research Institute. DGOG=Dutch Gynaecological Oncology Group. ANZGOG=Australia and New Zealand Gynaecologic Oncology Group. MaNGO=Mario Negri Gynaecologic Oncology Group. CCTG=Canadian Cancer Trials Group. FIGO=International Federation of Gynecology and Obstetrics. EEC=endometrioid endometrial cancer. LVSI=lymphovascular space invasion. TAH/BSO=total abdominal hysterectomy with bilateral salpingo-oophorectomy. LND=lymph node dissection. TLH=total laparoscopic hysterectomy. EBRT=external beam radiotherapy. *In some cases, both drugs were not given because of toxicities.

Table 1: Patient, tumour, and treatment characteristics

Radiotherapy details

- **EBRT**: total dose of 45 - 48·6 Gy in 1·8 Gy fractions, 5 days a week.
- **CTV**: extended to include
  - the aortic bifurcation in case of iliac lymph node involvement
  - to include the lower peri-aortic region for common iliac node involvement
  - to include the higher para-aortic region in case of para-aortic involvement (with a margin of ≥2 cm above the highest involved lymph node).
- Most pts. treated with a four-field technique; use of intensity-modulated radiotherapy was allowed
- In case of cervical involvement (glandular, stromal, or both), a brachytherapy boost was given to the vaginal vault.
- **Brachytherapy** dose was equivalent to 14 Gy in 2 Gy fractions (with recommended scheme of 10 Gy high-dose rate [HDR] in fractions of 5 Gy), specified at 5 mm from the vaginal vault surface.
- Treatment - to start within 4–6 weeks of surgery, but no later than 8 weeks.
- Overall radiotherapy treatment time was not to exceed 50 days.

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ARTICLES · Volume 20, Issue 9, P1273-1285, September 2019 · *Open Access*

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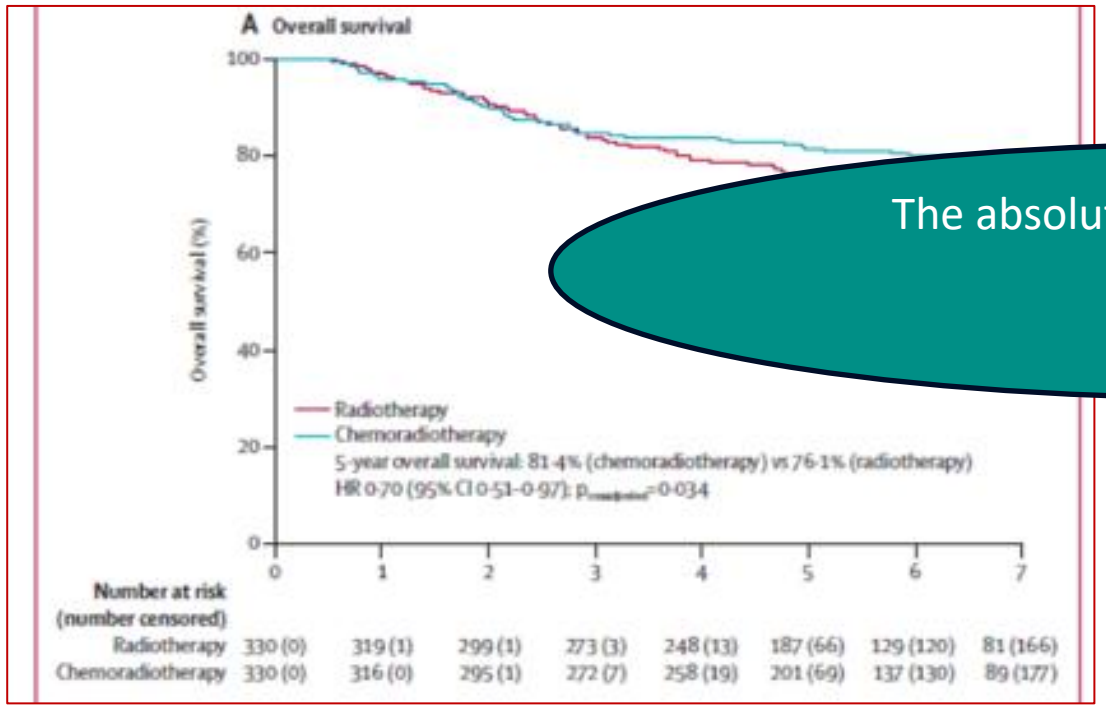
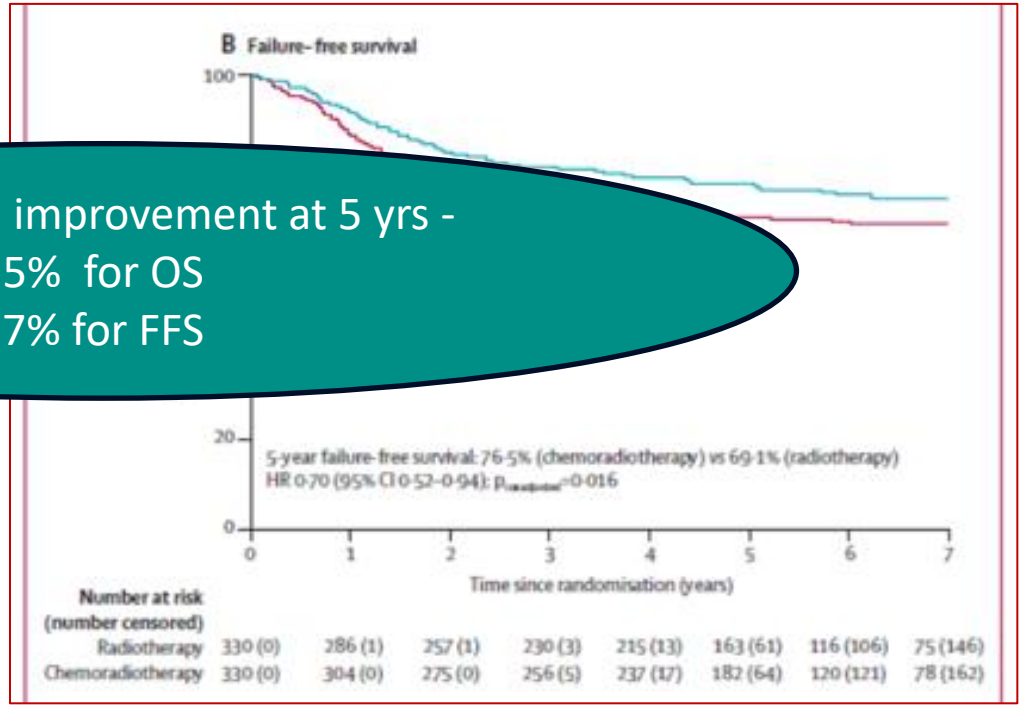
Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial

Stephanie M de Boer, MD [a] · Melanie E Powell, MD [d] · Linda Mileshkin, MD [f] · Prof Dionyssios Katsaros, MD [h] · Prof Paul Bessette, MD [i] · Christine Haie-Meder, MD [j] · et al. Show more

OS and FFS





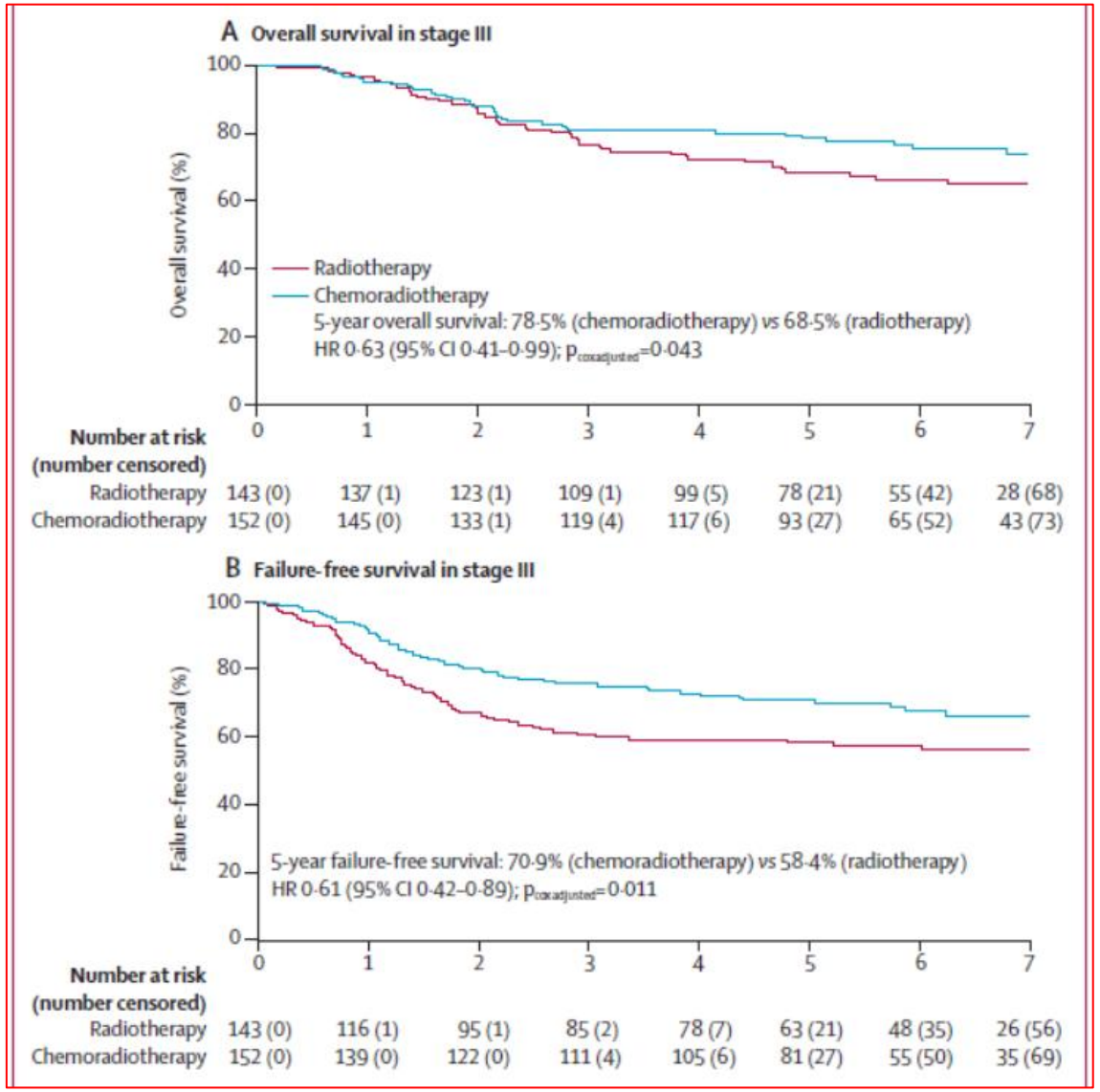
The absolute improvement at 5 yrs -
5% for OS
7% for FFS

Estimated 5-year OS a
- 81 · 4% with CT RT
- 76 · 1% with RT alone
- HR - 0.70 , p= 0.034

Estimated 5-year failure-free survival
- 76 · 5% with CT RT
- 69 · 1% with RT alone
- HR 0.70, p=0 · 016

***Boer S et al, Lancet Oncol* 2019; 20: 1273–85**

Stage III



5-year overall survival was
- 78.5% with CT RT
- 68.5% with RT alone
- P = 0.043

5-year failure-free survival –
- 70.9% with CT RT
- 58.4% with RT alone
- P = 0.011

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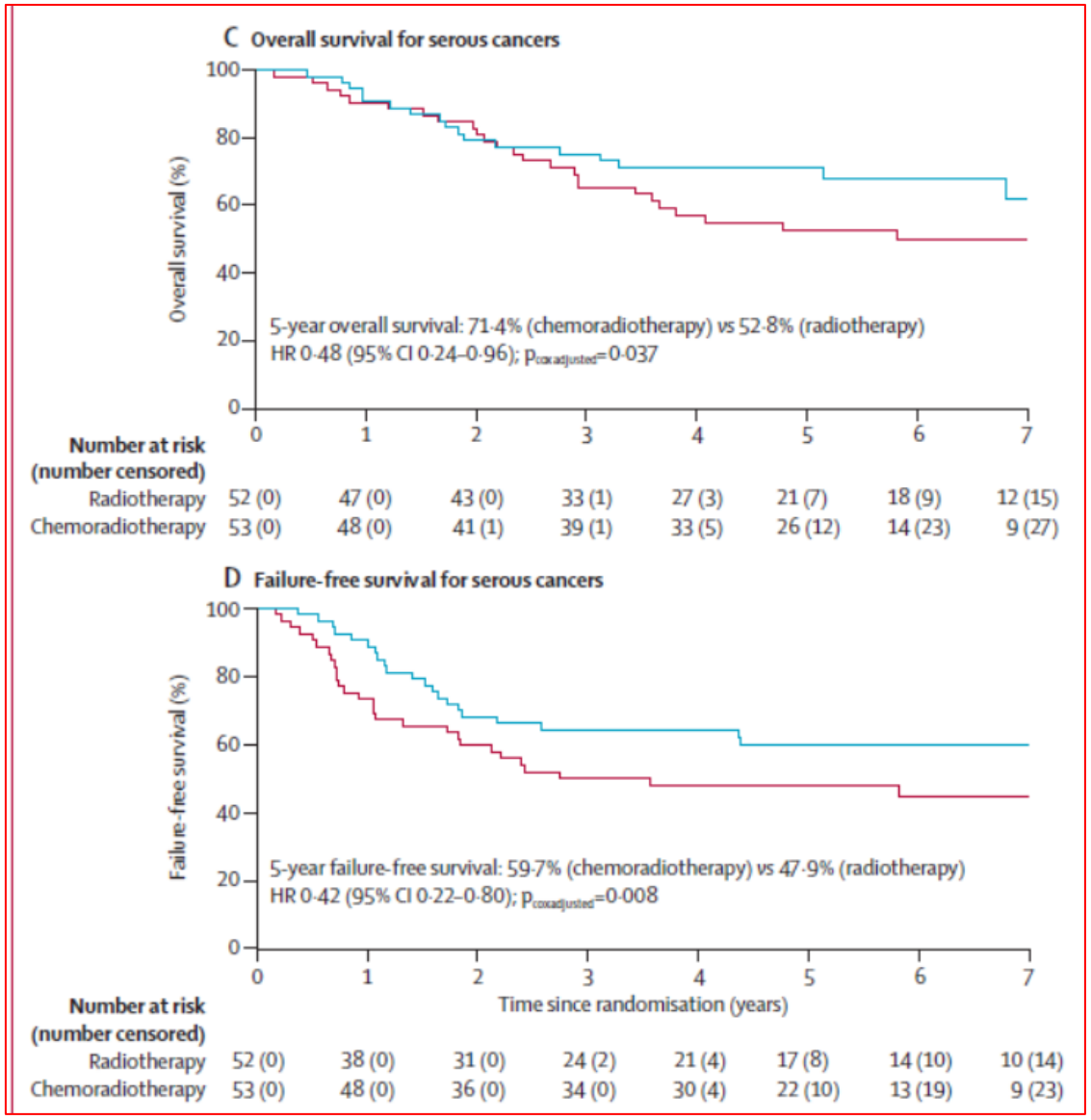
Serous carcinoma



5-year overall survival was
- 71.4% with CT RT
- 52.8% with RT alone
- p=0.037

5-year failure-free survival was
- 59.7% with CT RT
- 47.9% with RT alone
- p=0.008

Boer S et al, Lancet Oncol 2019; 20: 1273–85

Stage I and II

5-year overall survival was
- 83.8% with CT RT
- 82.0% with radiotherapy alone
- HR 0.84 , p = 0.50

5-year FFS was
- 81.3% with CT RT
- 77.3% with radiotherapy alone
- HR 0.87; p=0.54

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ADVERSE EVENTS

At 60 months, grade 2 or worse adverse events were reported for (38%) women in the CT RT group versus 23% of 187 women in the RT group
P = 0.002

At 5 years Sensory neuropathy grade 2 or worse was the major difference,, seen in 6% patients after CT RT versus no patients in the RT

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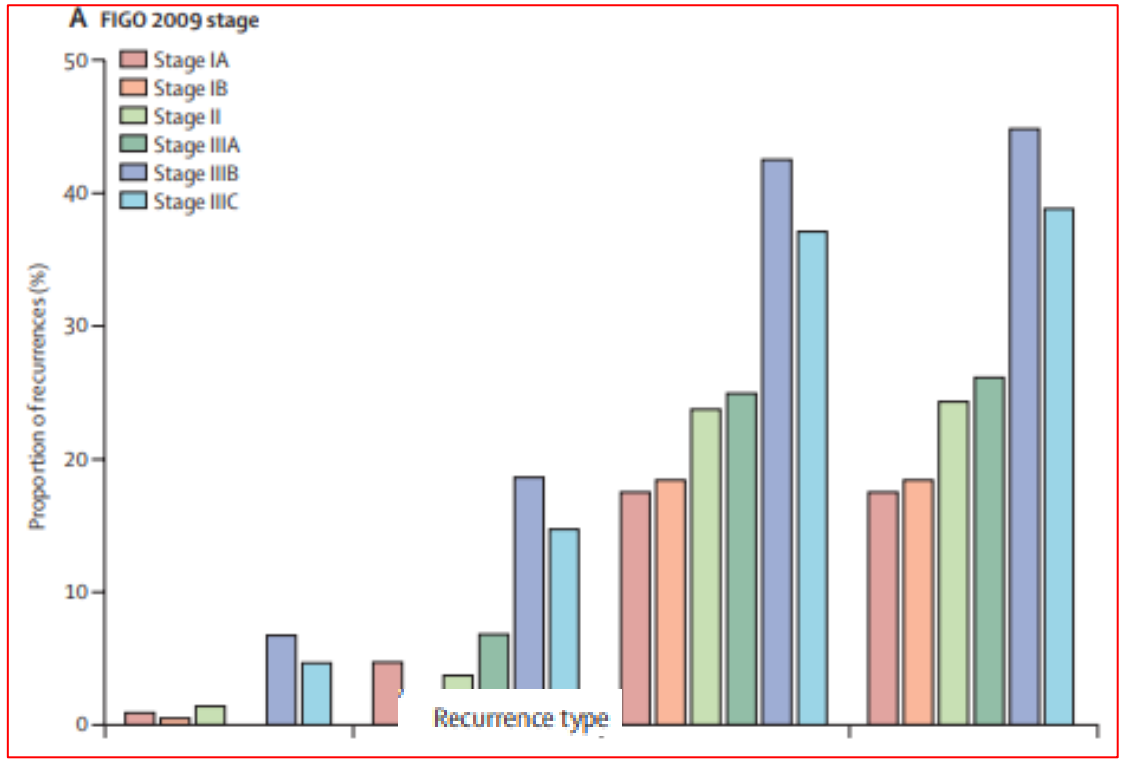
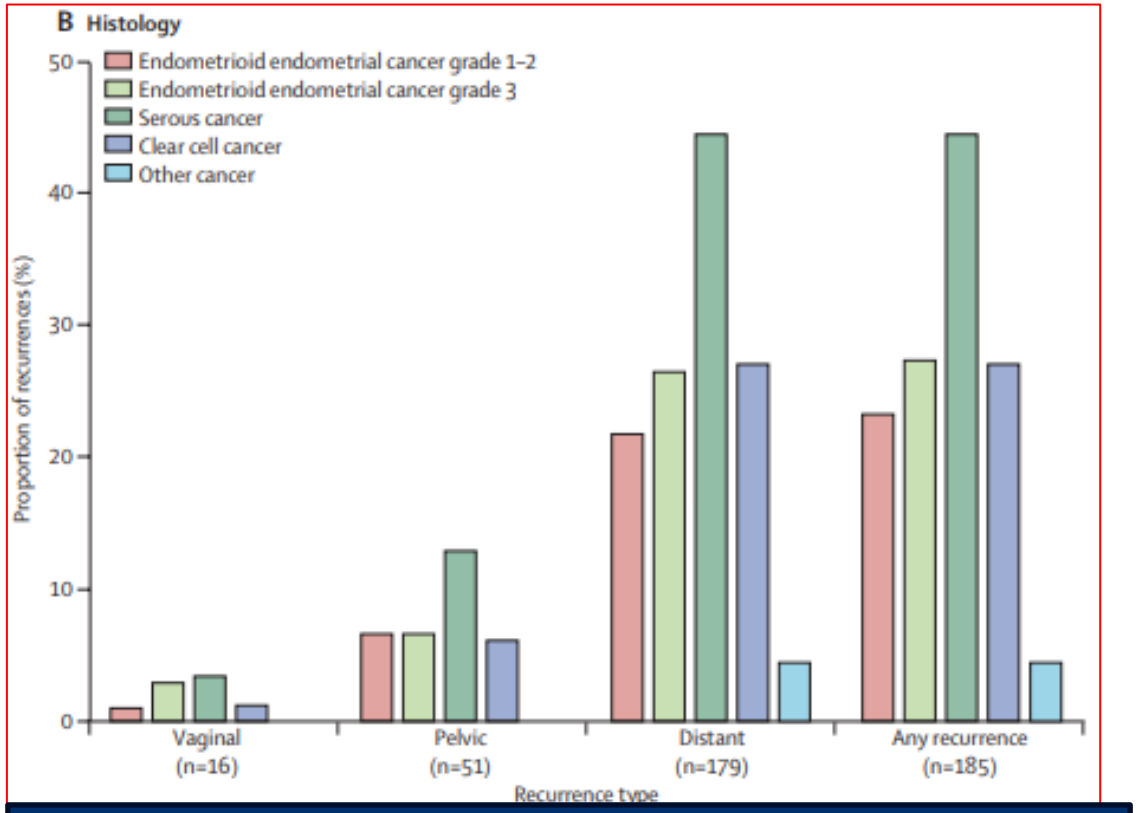
RECURRENCES





Recurrences were highest in women with stage IIIB [45·2%] and stage IIIC [38·8%]

Greatest risk of recurrence - serous cancers [44·8%], f/b clear cell cancers [27·4%]and grade 3 ECC [27·7%]

***Boer S et al, Lancet Oncol* 2019; 20: 1273–85**

Interpretation – PORTEC 3

- The updated analysis shows significantly improved OSl and FFS with CT RT versus RT alone.
- This treatment schedule should be discussed and recommended, especially for women with stage III or serous cancers, or both, as part of shared decision making between doctors and patients.

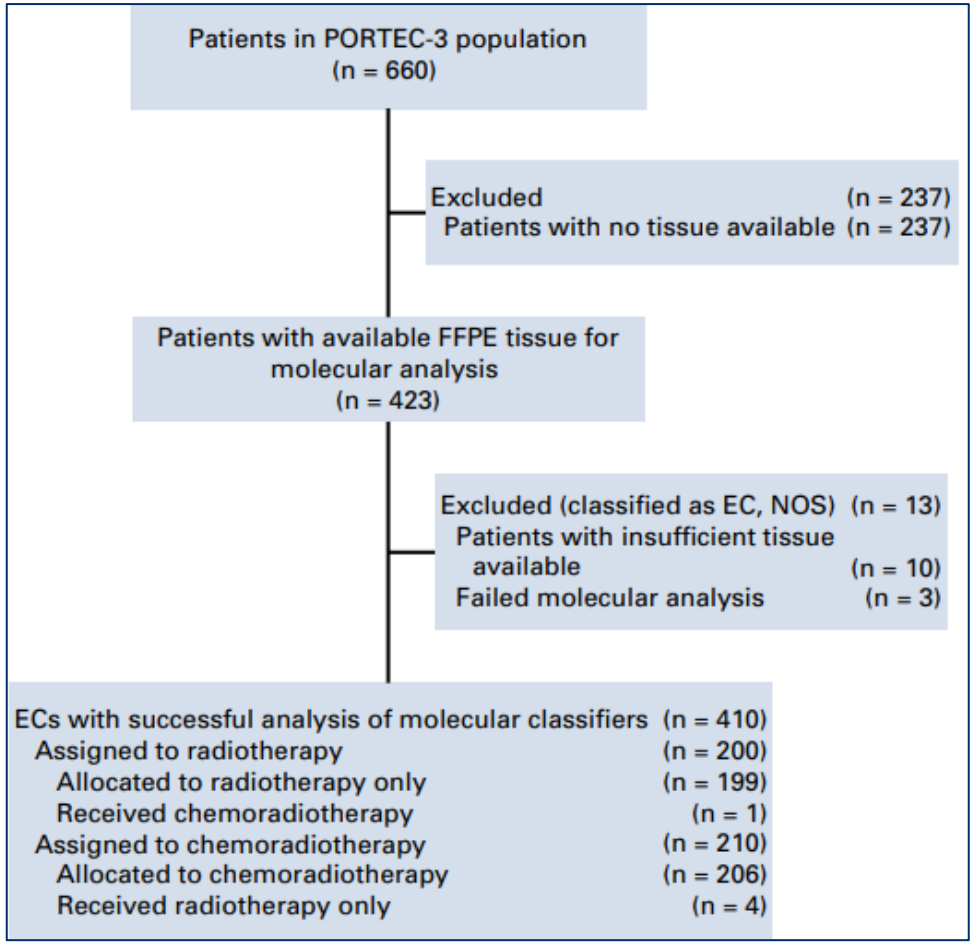
Boer S et al, Lancet Oncol 2019; 20: 1273–85

original reports

Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy

Alicia León-Castillo, MD[1]; Stephanie M. de Boer, MD[2]; Melanie E. Powell, MD[3]; Linda R. Mileshkin, MBBS[4]; Helen J. Mackay, MD[5]; Alexandra Leary, MD, PhD[6]; Hans W. Nijman, MD, PhD[6,7]; Naveena Singh, MD, MBBS[8]; Pamela M. Pollock, PhD[9]; Paul Bessette, MD[10]; Anthony Fyles, MD[11]; Christine Haie-Meder, MD[12]; Vincent T. H. B. M. Smit, MD, PhD[1]; Richard J. Edmondson, MD[13]; Hein Putter, MD[14]; Henry C. Kitchener, MD[13]; Emma J. Crosbie, MD, PhD[13]; Marco de Bruyn, PhD[7]; Remi A. Nout, MD[2]; Nanda Horeweg, MD, PhD[2]; Carien L. Creutzberg, MD, PhD[2]; and Tjalling Bosse, MD, PhD[1] on behalf of the TransPORTEC consortium

Accepted on June 25, 2020 and published at ascopubs.org/journal/ jco on August 4, 2020:



Molecular Subtypes

The 410 ECs were classified in 1 of the 4 molecular subgroups:

1. p53abn - 22.7%
2. POLEmut - 12.4%
3. MMRd - 33.4%
4. NSMP - 31.5%

- 7.3% (30 pts) - multiple-classifier
  - 1.7% - POLEmut-p53abn
  - 2.2% - POLEmut-MMRd
  - 2.7% MMRd-p53abn
  - 0.7% - POLEmut-MMRd-p53

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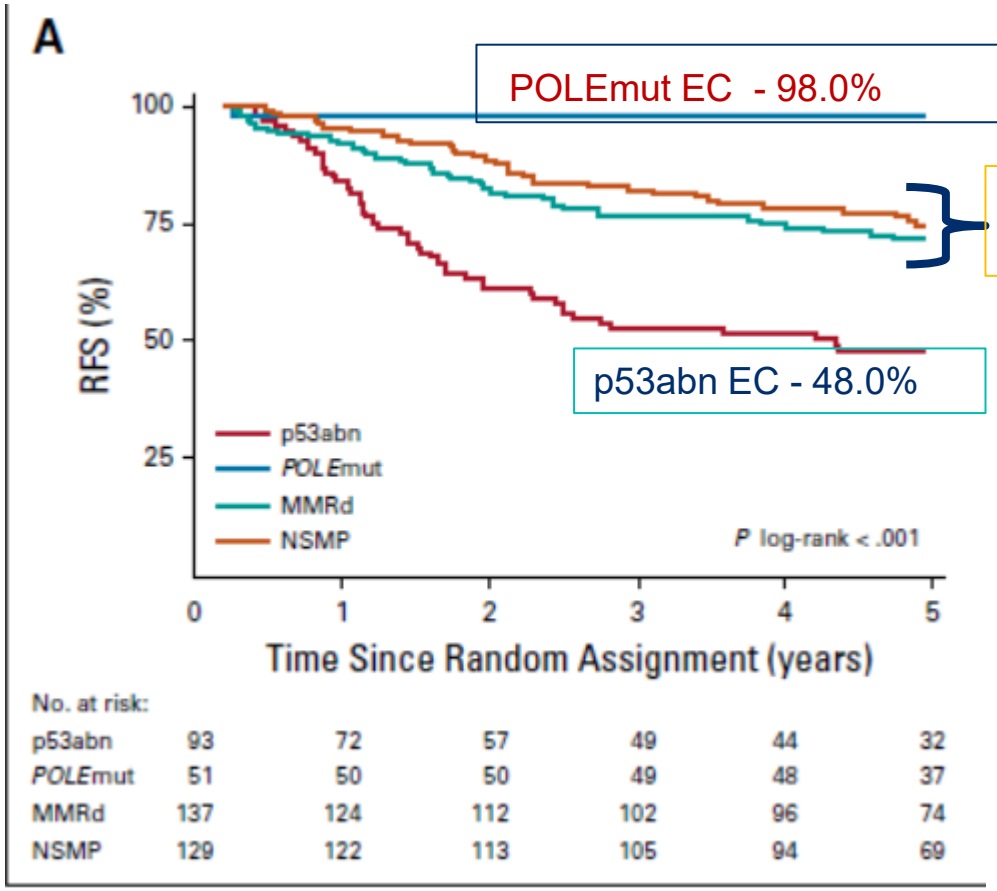
5-year **recurrence-free survival (RFS)**



POLEmut EC - 98.0%

MMRd - 71.7%
NSMP - 74.4%

p53abn EC - 48.0%

	CT RT	RT	
P53 abn	59%	36%	P=0.019
POLE mut	100%	97%	P=0.637
MMRd	68%	76%	P=0.428
NSMP	80%	68%	P=0.243

Kaplan-Meier survival curves

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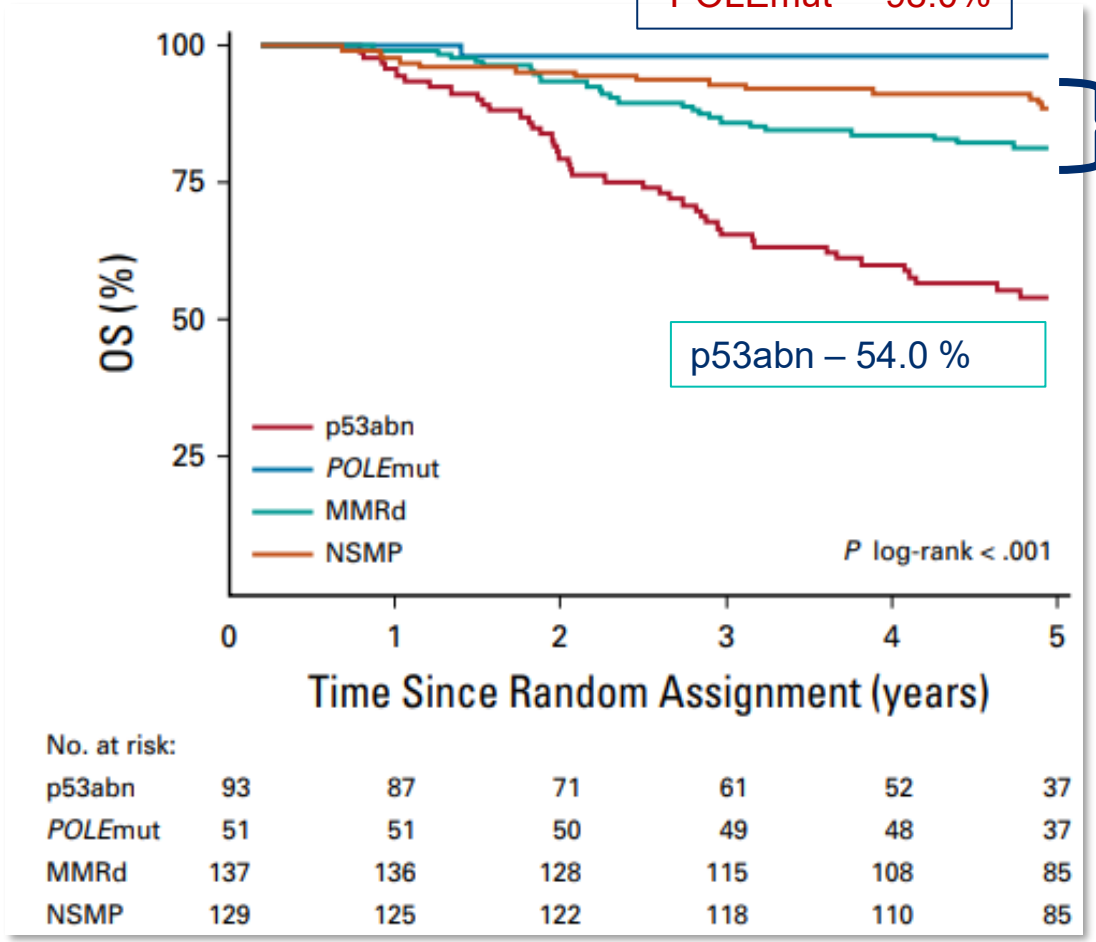
5 year Overall Survival

POLEmut - 98.0%



NSMP – 88.5%
MMRd - 81.3%

p53abn – 54.0 %

Kaplan-Meier survival curves for 5-year **OS**

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KEY TAKEAWAYS

- Pts with p53abn EC had poor prognosis, in contrast to the excellent survival outcomes of pts with POLEmut EC, even among high-grade and advanced-stage cancers.
- Pts with MMRd or NSMP EC - intermediate clinical outcome.

- **p53abn** EC pts - had a highly significant benefit from CTRT with an absolute benefit of 22.4% and 23.1% for 5-year RFS and OS, respectively
- Pts with **POLEmut** EC - excellent survival in both treatment arms.
- Pts with ***MMRd*** - No benefit was observed from CTRT versus RT alone
- **NSMP** EC pts had a trend toward benefit from CTRT, similar to the overall trial outcomes, but additional studies will be needed to elucidate the role of CT in this subgroup.

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PORTEC – 4a

2016 - 2021

PORTEC-4a Study

Clinical trial

OPEN ACCESS

PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer

Anne Sophie V M van den Heerik [1], Nanda Horeweg [1], Remi A Nout,[2] Ludy C H W Lutgens,[3] Elzbieta M van der Steen-Banasik,[4] G Henrike Westerveld,[5] Hetty A van den Berg,[6] Annerie Slot,[7] Friederike L A Koppe,[8] Stefan Kommoss,[9] Jan Willem M Mens,[2] Marlies E Nowee,[10] Stefan Bijmolt,[11] David Cibula,[12] Tanja C Stam,[13] Ina M Jurgenliemk-Schulz,[14] An Snyers,[15] Moritz Hamann,[16] Aleida G Zwanenburg,[17] Veronique L M A Coen,[18] Katrien Vandecasteele,[19] Charles Gillham,[20] Cyrus Chargari,[21] Karen W Verhoeven-Adema,[22] Hein Putter,[23] Wilbert B van den Hout,[24] Bastiaan G Wortman,[1] Hans W Nijman,[25] Tjalling Bosse,[26] Carien L Creutzberg[1]

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Correspondence to
Anne Sophie V M van den

HIGHLIGHTS

- PORTEC-4a is the first trial to introduce molecular factors in the adjuvant treatment of endometrial cancer.
- Randomization between standard or individualized treatment based on the molecular risk profile.
- PORTEC-4a will show if omitting treatment in cases of favorable molecular profiles is safe and cost-effective.

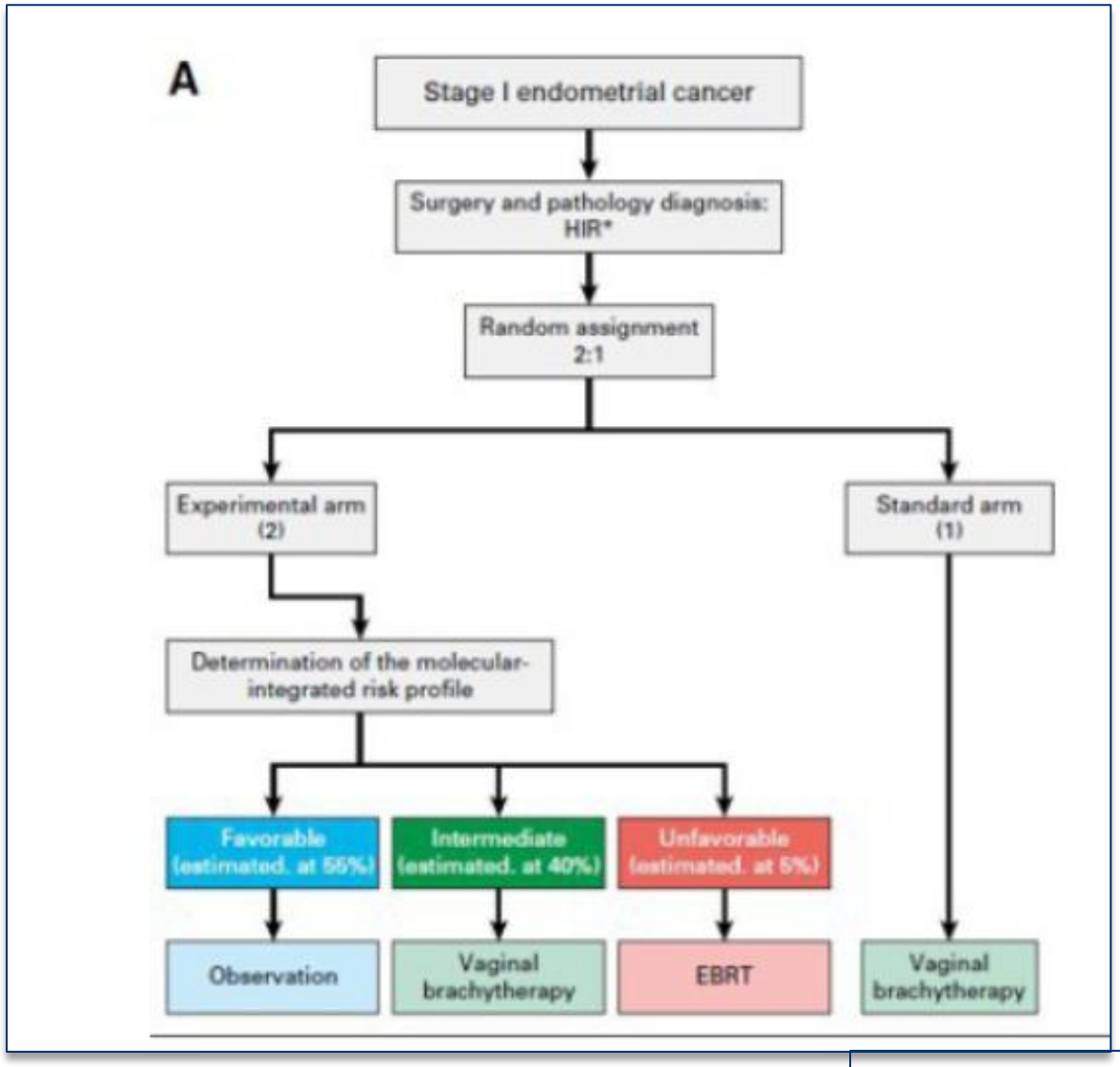
van den Heerik ASVM, et al. Int J Gynecol Cancer 2020;30:2002–2007

Inclusion criteria

- Endometroid endometrial cancer with high-intermediate risk features:
  - Stage IA (with invasion), grade 3 (any age, with or without LVSI)
  - Stage IB, grade 1 or 2 and age >60 years
  - Stage IB, grade 1 or 2 with LVSI
  - Stage IB, grade 3 without LVSI
  - Stage II (microscopic), grade 1

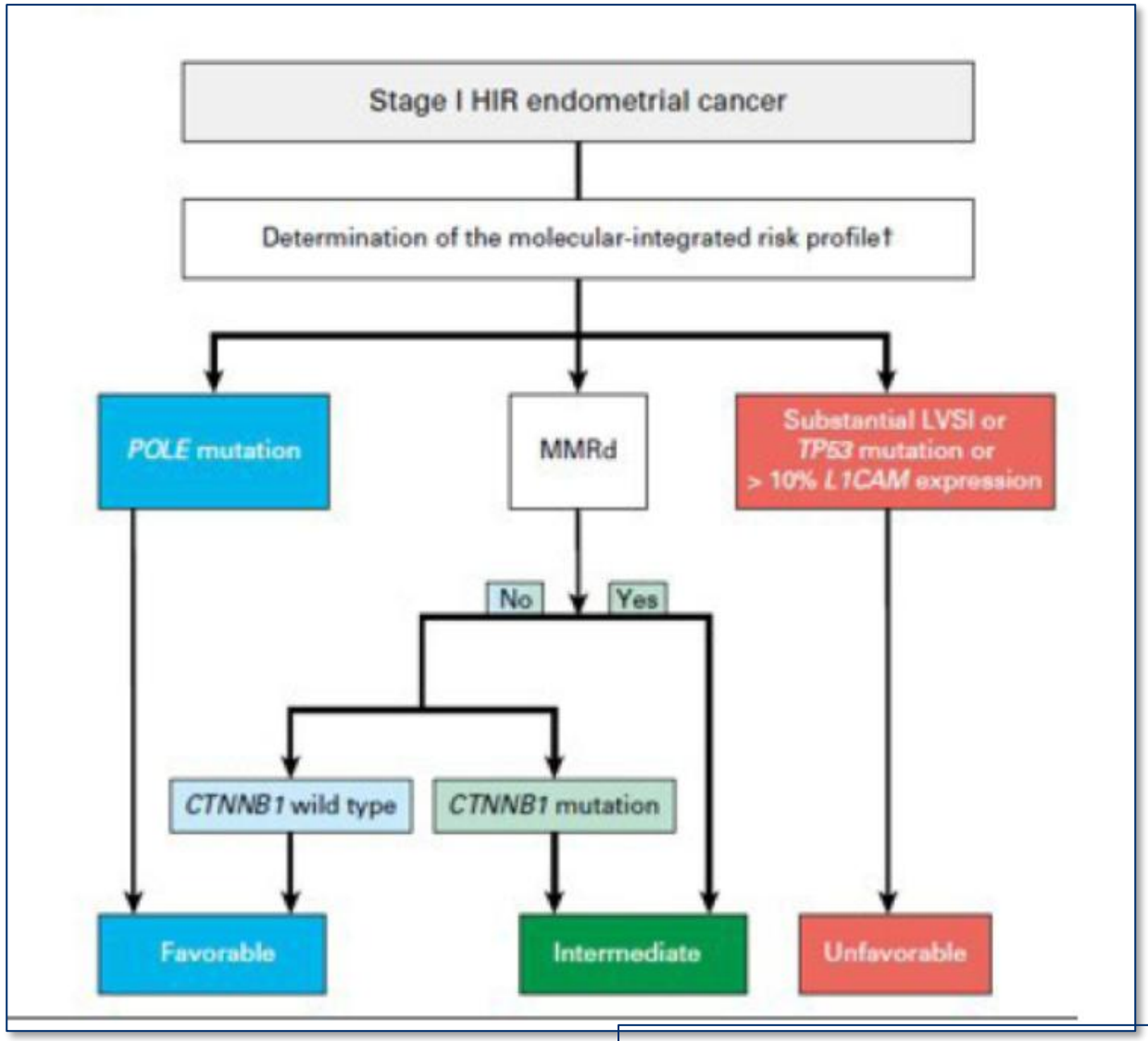
van den Heerik ASVM, et al. Int J Gynecol Cancer 2020;30:2002–2007

Trial design of the PORTEC-4a



van den Heerik ASVM, et al. Int J Gynecol Cancer 2020;30:2002–2007

Decision tree for the molecular-integrated profile



van den Heerik ASVM, et al. Int J Gynecol Cancer 2020;30:2002–2007

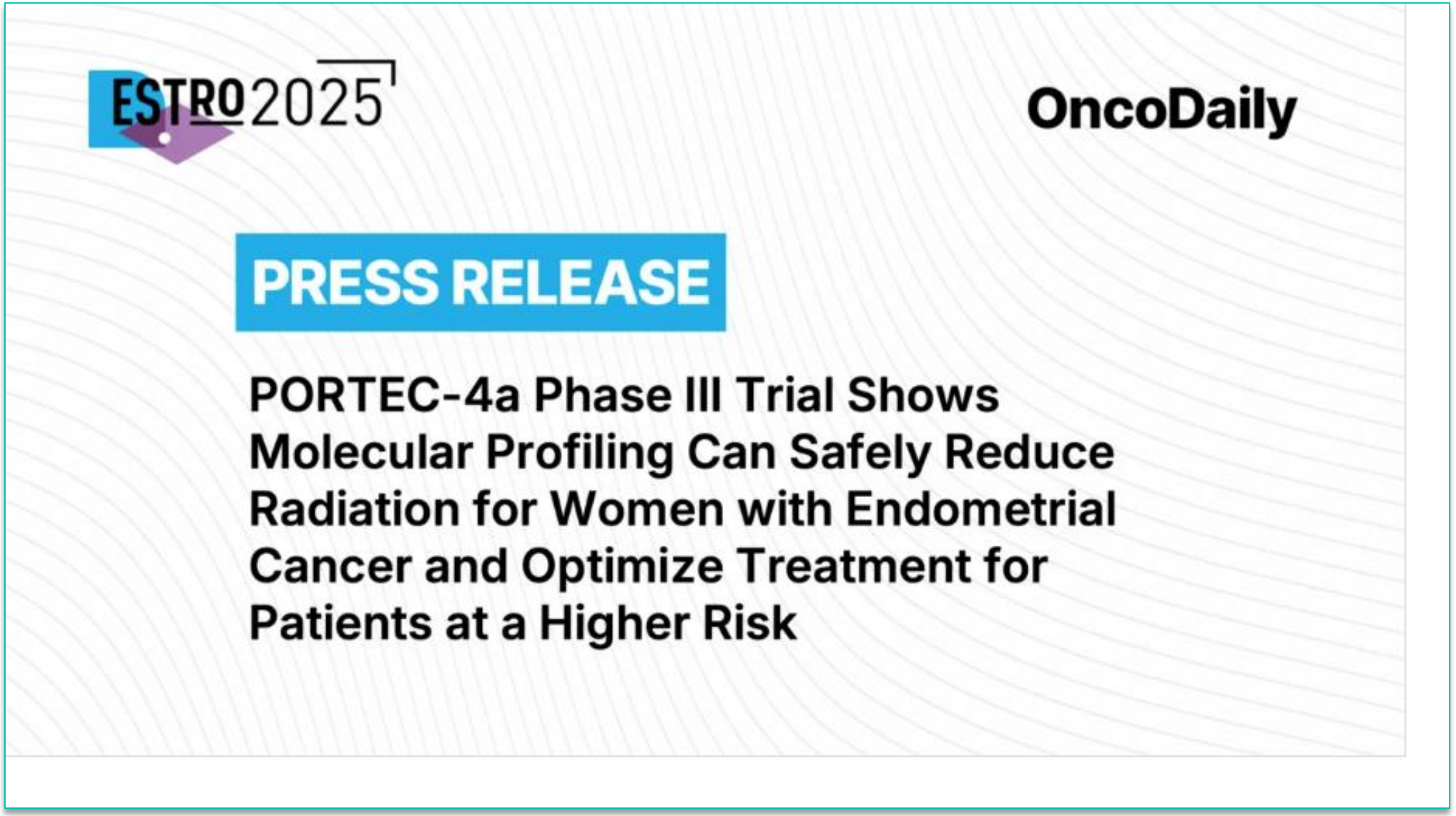
PORTEC -4a

Primary Endpoint
vaginal recurrence.

Secondary endpoints

- recurrence-free and overall survival
- pelvic and distant recurrence
- 5-year vaginal control (including treatment for relapse)
- adverse events and patient-reported symptoms and quality of life
- endometrial cancer-related healthcare costs.

van den Heerik ASVM, et al. Int J Gynecol Cancer 2020;30:2002–2007

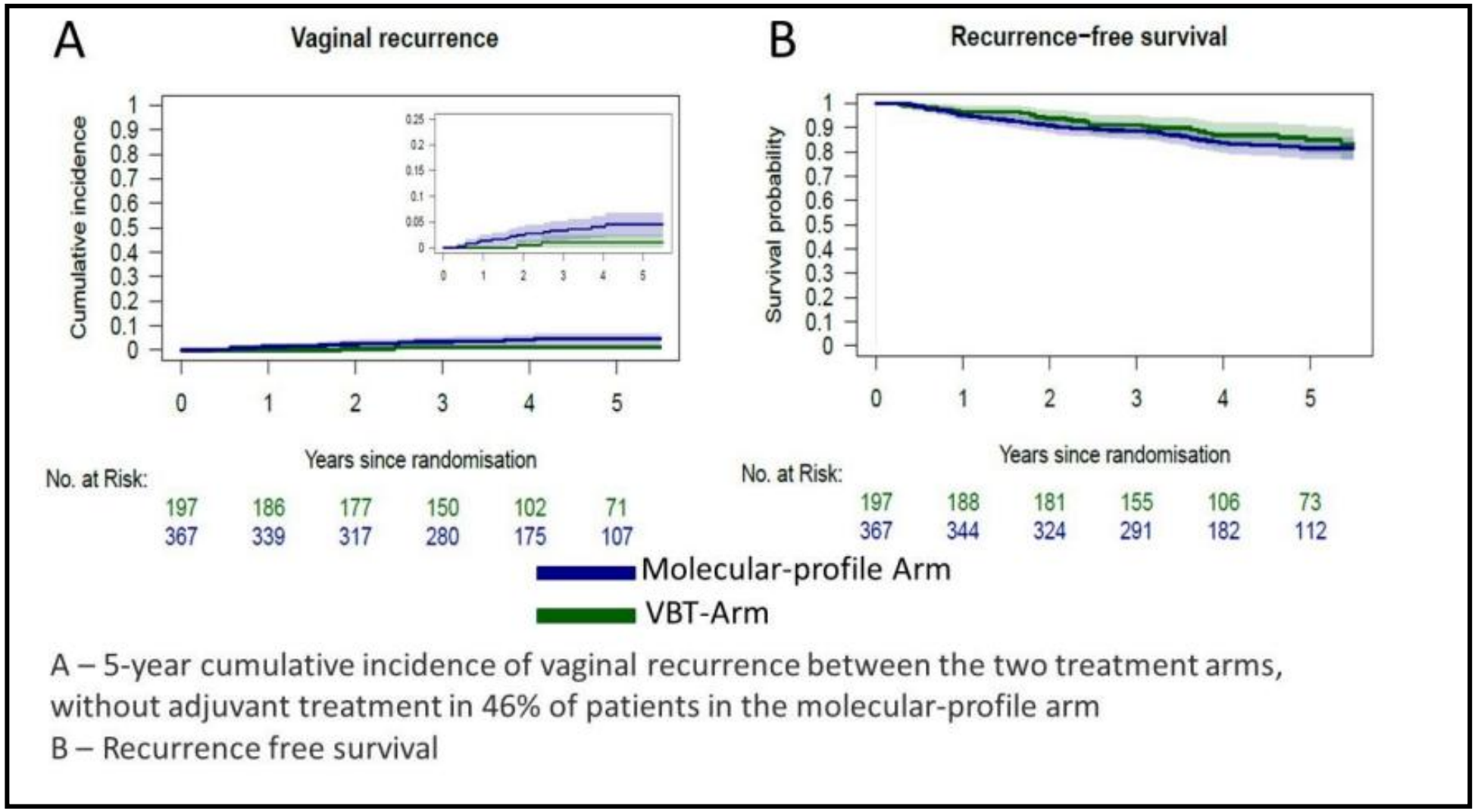

ESTRO 2025
OncoDaily
PRESS RELEASE
PORTEC-4a Phase III Trial Shows Molecular Profiling Can Safely Reduce Radiation for Women with Endometrial Cancer and Optimize Treatment for Patients at a Higher Risk

The PORTEC-4a trial is a game-changer

- The trial enrolled 592 women across eight European countries
  - 397 pts in molecular profile arm and 197 pts in std arm - VBT
- Median age – 69 years
- Median Follow up – 58.1 mths
- Experimental Arm
  - Adjuvant RT was omitted in 46 % of the pts
  - 40 % received VBT
  - 14 % received EBRT
- Std arm - 100 % pts received VBT

RESULTS

	Molecular profile	VBT	
VR	4.5%	1.6%	HR=2.72
PR	3.2%	5.2%	P=0.32
LRR	8.8%	7.5%	P=0.62
RFS	81.7 %	85.1%	P=0.36
OS	88%%	90.9%%	P=0.34



A – 5-year cumulative incidence of vaginal recurrence between the two treatment arms, without adjuvant treatment in 46% of patients in the molecular-profile arm

B – Recurrence free survival

Key Findings:

- In the molecular-profile-guided treatment arm:
  - 46% of patients safely avoided radiotherapy altogether.
  - Patients with unfavourable molecular profiles were offered pelvic radiotherapy instead of standard vaginal brachytherapy.
  - These subgroup showed a 5-year cumulative incidence of LRR of 8.4% vs. 30.5% (p=0.05) and DM of 22.3% vs 41.8%(p=0.47)

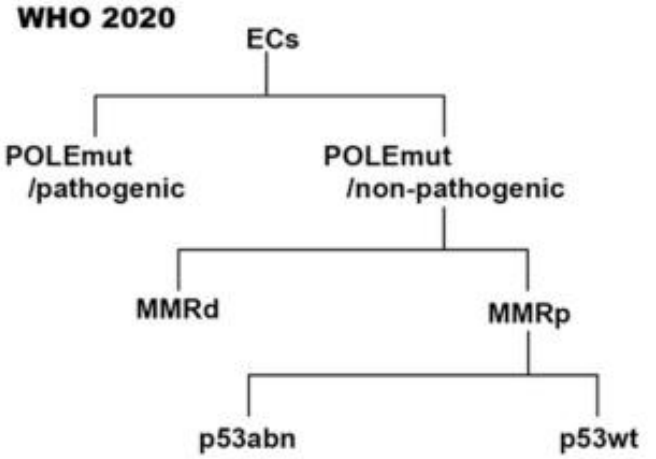
Conclusion

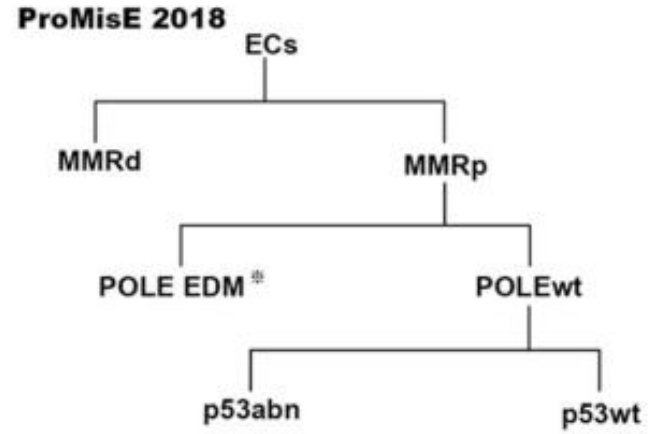
- PORTEC-4a trial - first to incorporate a molecular-integrated classification into decisions for adjuvant therapy in EC.
- Individualised treatment was shown to achieve similar high local control, while sparing almost half of the patients adjuvant treatment, and suggesting better locoregional control with EBRT for those with unfavourable profile.


Thank You!

Histomolecular classification/subgroups of ECs. The 2020 WHO classification is a “hybrid” of TCGA and ProMisE.

WHO 2020 / TCGA 2013 / ProMisE 2018	Mutational load	Surrogate marker	Histological type	Prognosis (Stage)	Diagnostic algorism
POLEmut (Ultramutated / EDM)	Ultramutated ＞100mut/Mb (232×10^{-6}) MSS	POLE exonuclease domain Hotspot :Ex9-14 (p.Pro286Arg,p.Val411Leu, p.Ser297Phe,p.Ala456Pro, p.Ser459Phe)	Endometrioid High-grade (EAC G3, Giant cells, TIL)	Excellent (I >> II-IV)	WHO 2020
MMRd (MSI-H / MMRd)	High-mutated 10 ～ 100mut/Mb (18×10^{-6}) MSI	MMR protain loss (MLH1, PMS2, MSH2, MSH6)	Enometrioid Low-grade (TIL)	Intermediate (I > II-IV)	
NSMP (CNL (Endometrioid) / NSMP)	Low ＜ 10mut/Mb	Abscent	Enometrioid Low-grade	Intermediate to excellent (I > II-IV)	ProMisE 2018
p53mut (CNH (Serous-like) / p53abn)	Low ＜ 10mut/Mb	Abnormal p53 expression	Non-endometrioid Serous	Poor (I=II-IV)	

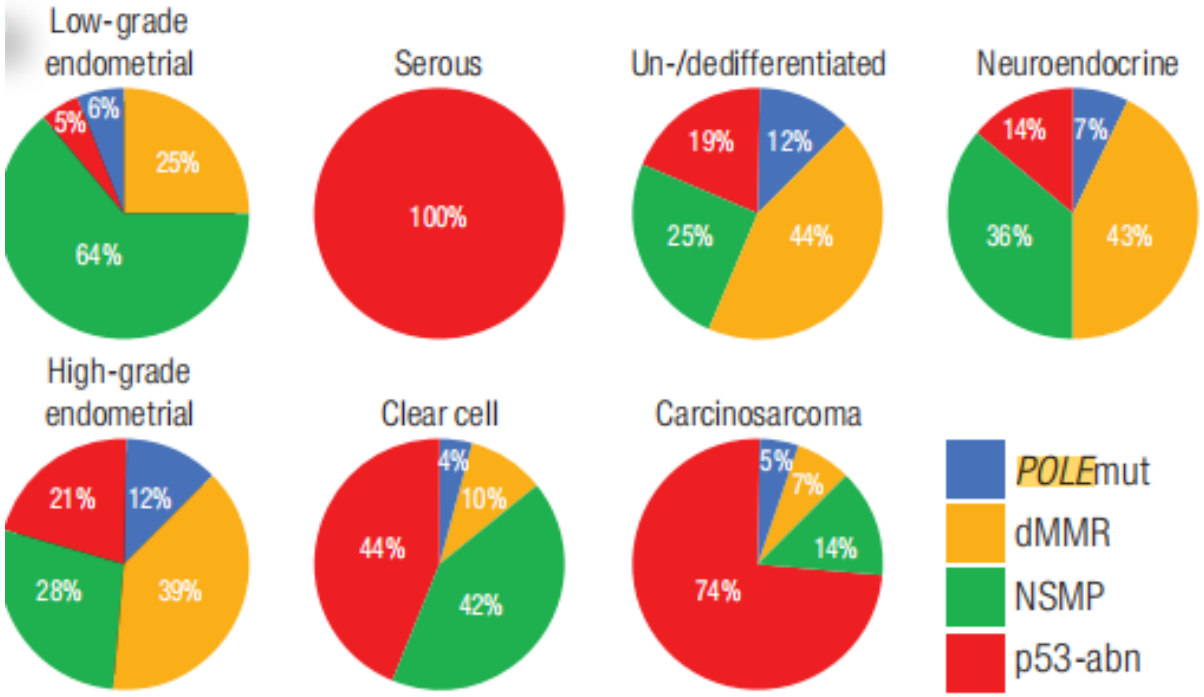




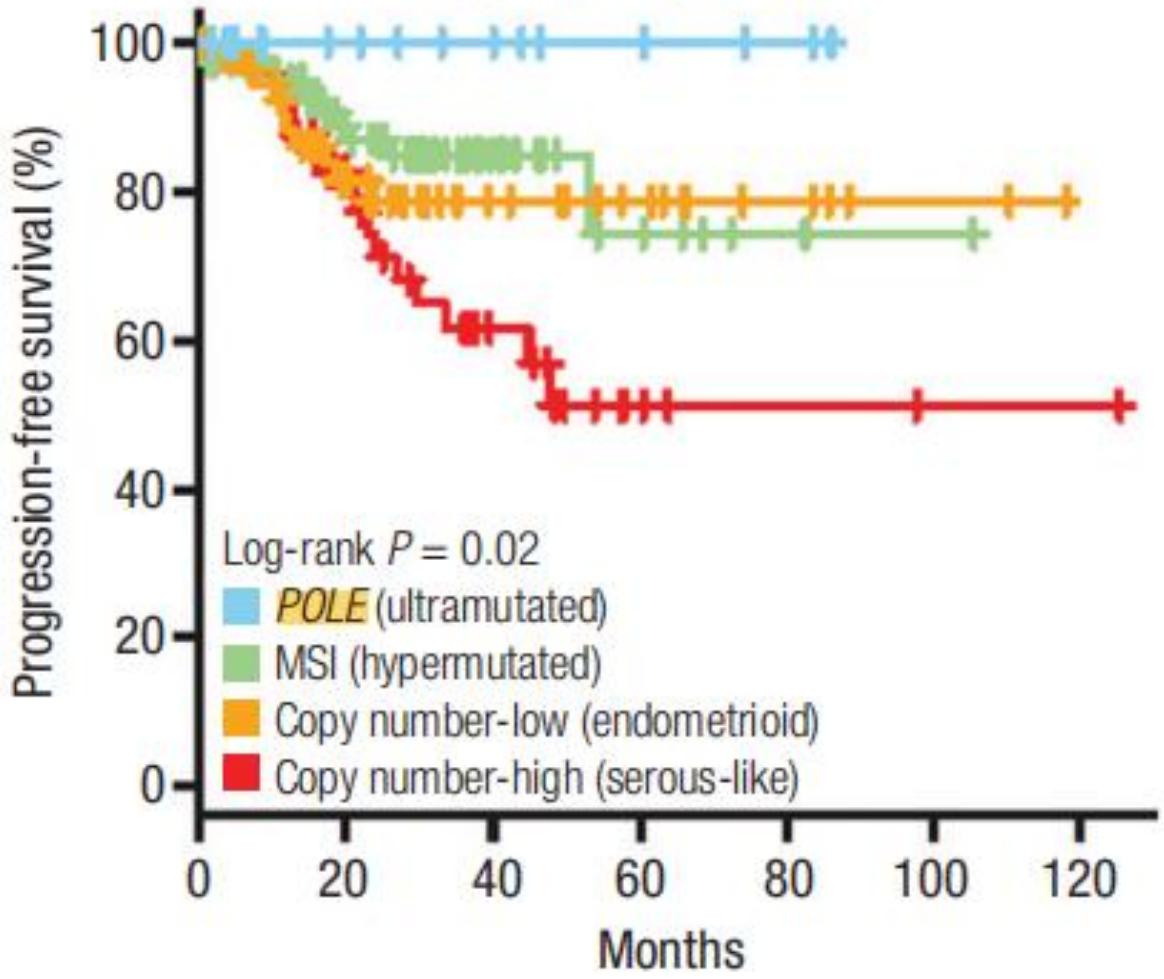
※ Exonuclease domain mutation

Yasuda M. New clinicopathological concept of endometrial carcinoma with integration of histological features and molecular profiles. Pathol Int. 2024;74:557–73.

Distribution of TCGA molecular groups according to histological types



Prognostic implications



FIGO endometrial cancer stage with molecular classification

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

- Molecular classification testing (POLEmut, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions.
- In case the molecular classification reveals POLEmut or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of “m” for molecular classification, and a subscript is added to denote POLEmut or p53abn status.
- FIGO Stages III and IV are based on surgical/anatomical findings. The stage category is not modified by molecular classification; however, the molecular classification should be recorded if known.