بسم الله الرحمن الرحيم

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Management of high- risk endometrial cancer: Role of radiotherapy

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Lectures Objectives:

- Evidence for the indications of EBRT and Brachytherapy(HDR)
- Review of radiotherapy's /HDR data
- Prognosis' Group Definitions
- Combined treatment for high risk group
- Update of OS and FFS
- Technical aspects of EBRT and HDR

Disclosure

I have no disclosure

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Aim and Clinical Evidence for EBRT

– To control regional disease:

- Lymph nodes
- Microscopic spread

– To optimally shrink the local disease (No surgery or local recurrence)

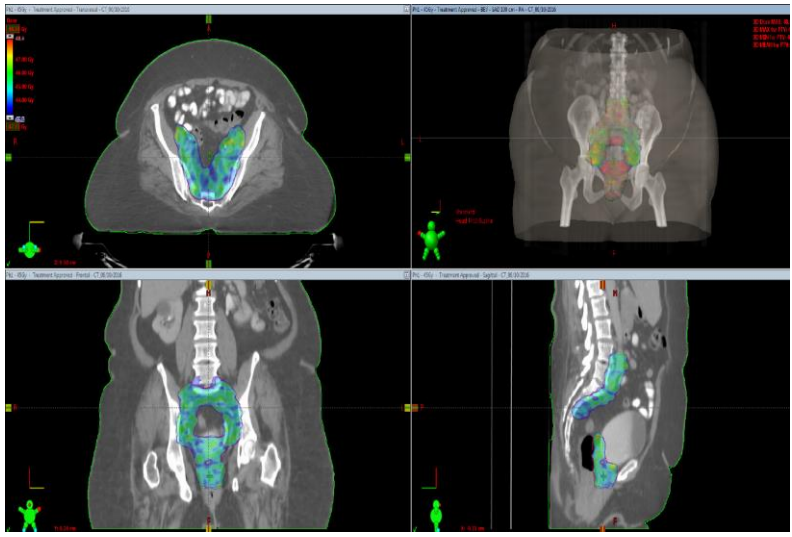
Each step in the chain of XRT planning is vital

Principle in radiotherapy treatment planning

✓Appropriate coverage of the target volume (to achieve local control)

✓As low dose as possible to the normal tissue

✓ (to avoid early and late side effects)

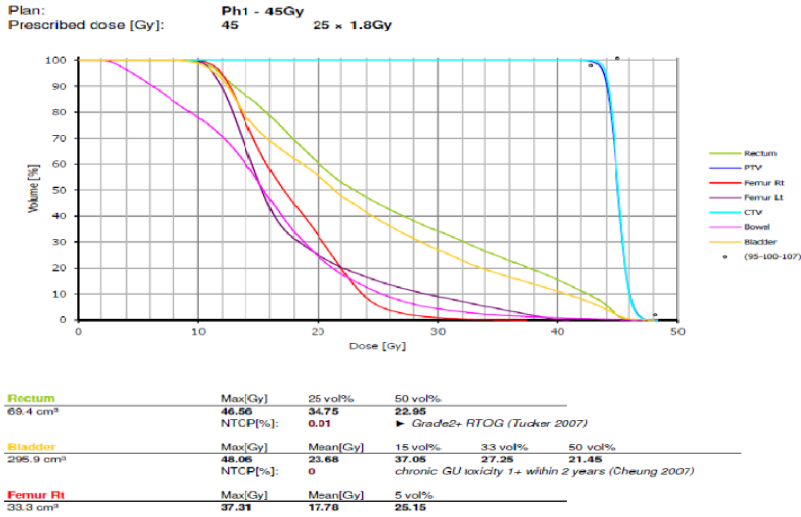


Optimal Treatment delivery

➢ Newer Delivery techniques: IMRT, VMAT, Rotational …

Optimal Target Identification & definition

➢ Newer Imaging modalities: MRI, PET-CT, SPECT CT…



Incidence

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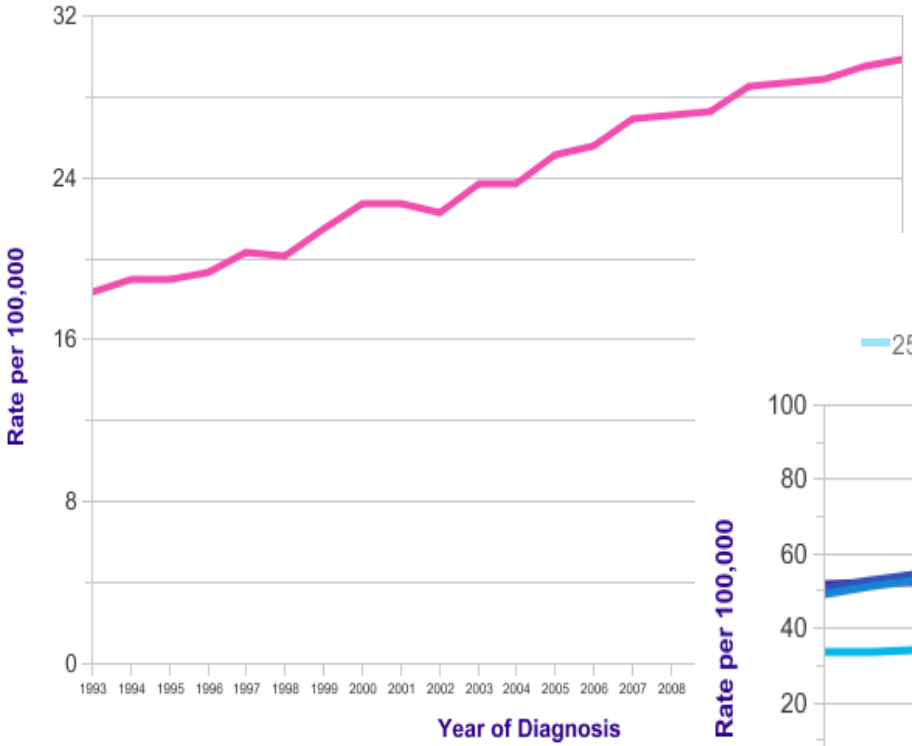
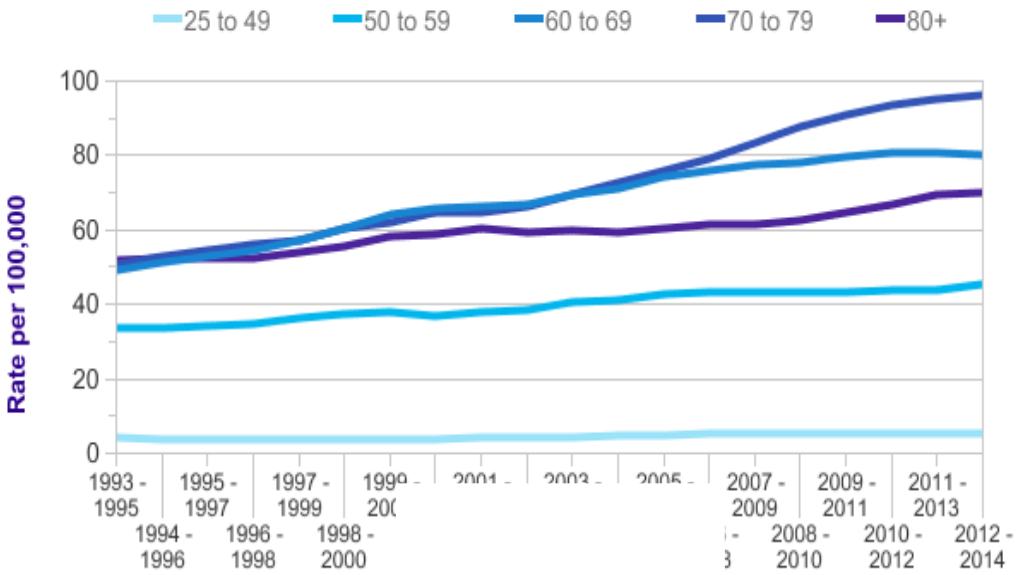
Uterine Cancer (C54-C55): 1993-2014

European Age-Standardised Incidence Rates per 100,000 Population, Females, UK

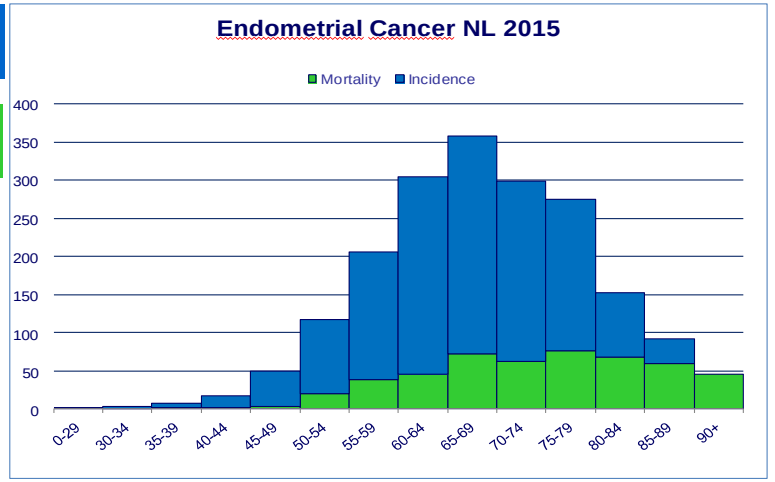




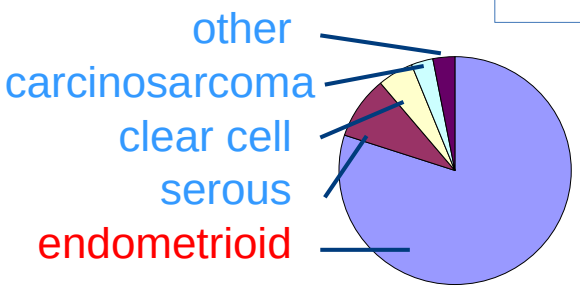
Endometrial Carcinoma

Incidence
22 / 100.000

Mortality
5.5 / 100.000

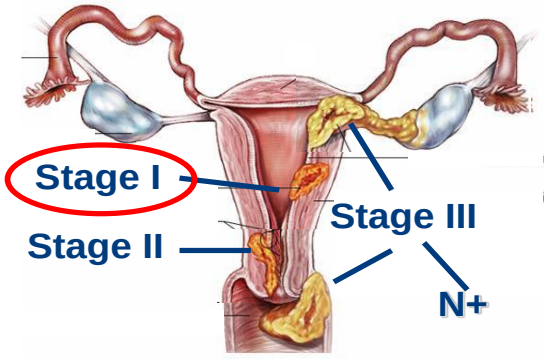


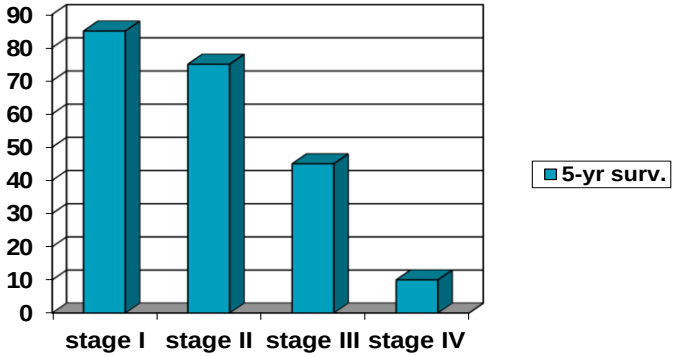
Histology



VIKC, cijfers over kanker 2016

Stage and histologic subtype





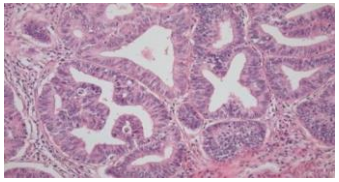
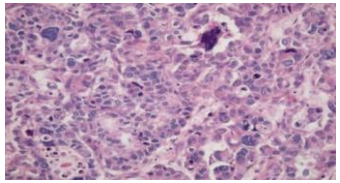
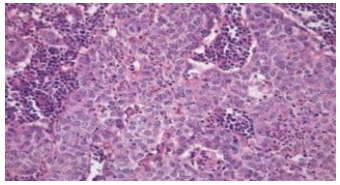
Histological type (5 yr OS)

endometrioid carcinoma: 80-85%
serous carcinoma: 50-55%
clear cell carcinoma: 60-65%

Alektiar, IJROBP, 2002; Scholten, IJROBP, 2002

Major prognostic factors

- Age
- Stage
  - Depth of myometrial invasion
- Histology
  - Histological type
  - Grade
  - Lymph-vascular space invasion

High-risk endometrial cancer is defined as:

- **Endometrioid endometrial cancer stage I, grade 3 with deep invasion,**
- **Stage II or III endometrioid endometrial cancer**
- **Non-endometrioid (serous or clear cell) histology**

Intermediate Risk – Randomised trials

Trial	No. patients eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian 1968-1974	540 Stage I	TAH-BSO	Brachytherapy vs. brachy and pelvic RT	7% vs. 2% at 5 years p<0.01	89% vs. 91% at 5 years p=NS	NA
PORTEC 1990-1997	714 IB grade 2-3 IC grade 1-2	TAH-BSO	NAT vs. pelvic RT	14% vs. 4% at 5 years p<0.001	85% vs. 81% at 5 years p=0.31	3% GI at 5 years (actuarial)
GOG-99 1987-1995	392 St IB, IC St II (occult)	TAH-BSO and lymph-adenectomy	NAT vs. pelvic RT	12% vs. 3% at 2 years p<0.01	86% vs.92% at 4 years p=0.56	8% GI at 2 years (crude)
ASTEC/EN5 1996-2005	905 St IAB g3, IC, St II, serous/cc	TAH-BSO +/- lymph-adenectomy	NAT vs. pelvic RT	7% vs. 4% at 5 years p=0.038	84% vs.84% at 5 years p=0.98	3 vs 7% gr 3/4

Aalders et al 1980, Creutzberg et al 2000, Keys et al 2004, ASTEC/EN.5 Study Group 2009

High intermediate risk

	PORTEC-1	GOG #99
	NAT vs. RT	NAT vs. RT
PORTEC risk groups		
- 10 yr LR relapse	23% vs. 5% (RR 0.22)	
GOG risk groups		
- 10 yr LR relapse	22% vs. 8% (RR 0.36)	
- 4 yr any relapse		27% vs. 13% (RR 0.48)
- 4 yr local relapse		13% vs. 5% (RR 0.38)

Scholten et al. 2005; Keys et al 2004

Summary – intermediate risk

15 year PORTEC-1 results

- LRR risk reduction with EBRT 67%
- no survival advantage

EBRT has long-term impact on quality of life

- higher levels of bladder & bowel symptoms
- lower physical functioning, more role limitation

EBRT to be avoided in intermediate risk cases

- HIR criteria for treatment selection
- vaginal brachytherapy

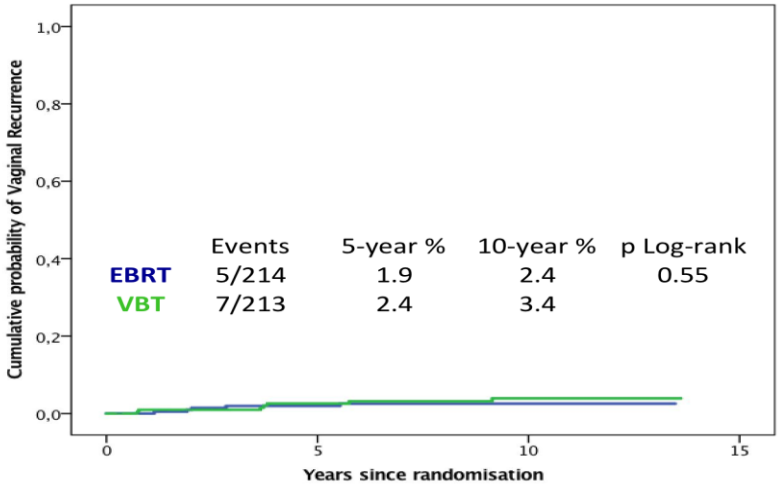
Creutzberg et al IJROBP 2011, Nout et al JCO 2011

Vaginal Recurrence & Overall Survival

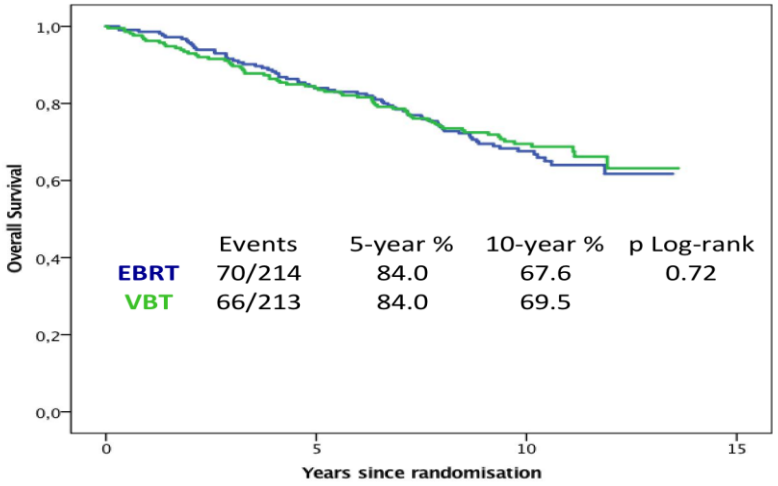
PORTEC II

- Median follow-up 10.5 years

Vaginal Recurrence



Overall Survival



Nout et al, IGCS 2016

Summary high-intermediate risk

- Brachytherapy effective in preventing vaginal recurrence: 2.9% at 8 years
- More pelvic recurrences after brachytherapy, most with simultaneous distant metastases (isolated pelvic failure 1.5% vs 0.5%)
- No difference in distant metastases and survival
- VBT better QoL/functioning
- Substantial LVSI: consider IMRT
- No increased risk of second cancers

ESMO-ESGO-ESTRO consensus: risk groups

Risk Group	Description (FIGO 2009)
Low	• Stage IA Endometrioid + grade 1-2 + LVSI negative
Intermediate	• Stage IB Endometrioid + grade 1-2 + LVSI negative
High Intermediate	• Stage IA Endometrioid + grade 3, regardless of LVSI status • Stage I Endometrioid + grade 1-2 + LVSI unequivocally positive, regardless of depth of invasion
High 15%	• Stage IB Endometrioid + grade 3, regardless of LVSI status • Stage II & stage III with no residual disease • Non endometrioid (serous, clear cell, undifferentiated carcin carcinosarcoma, mixed >10%)
Advanced Metastatic	• Stage III with residual disease & IVA • Stage IVB

No RT

VBT

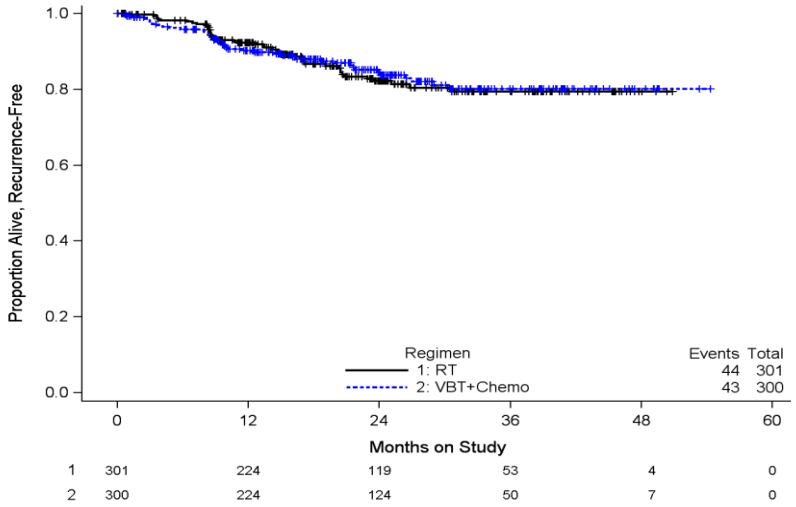
Pelvic IMRT

- Radiotherapy?
- Chemotherapy?
- Both?

First GOG#249 results

- Stage I-II HIR factors
- Stage I-II serous / cc

R
- Pelvic RT
- 3x carboplatin + paclitaxel + VBT



Completed accrual 2012

N=601, primary endpoint PFS

89% underwent lymphadenectomy

15% serous, 5% clear cell, 74% stage I

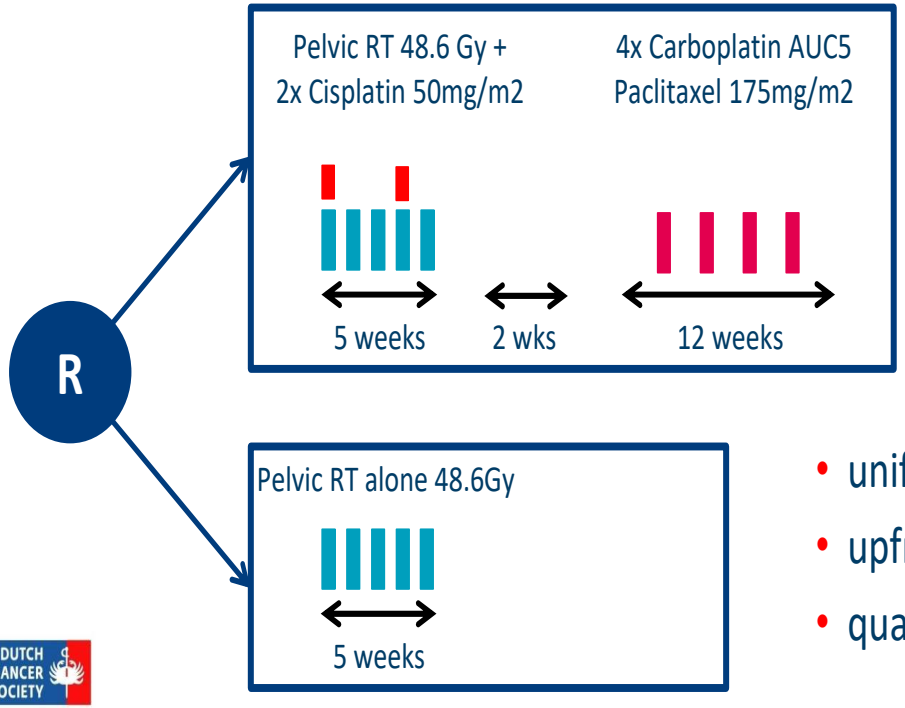
Update, median FU 53 months

No difference RFS and Overall Survival

McMeekin, SGO 2014, Fleming, IGCS 2014; Randall ASTRO 2017

PORTEC-3 trial design

- 686 stage I High risk, stage II/III Endometrial Cancer



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

Survival, median follow-up 60.2 months

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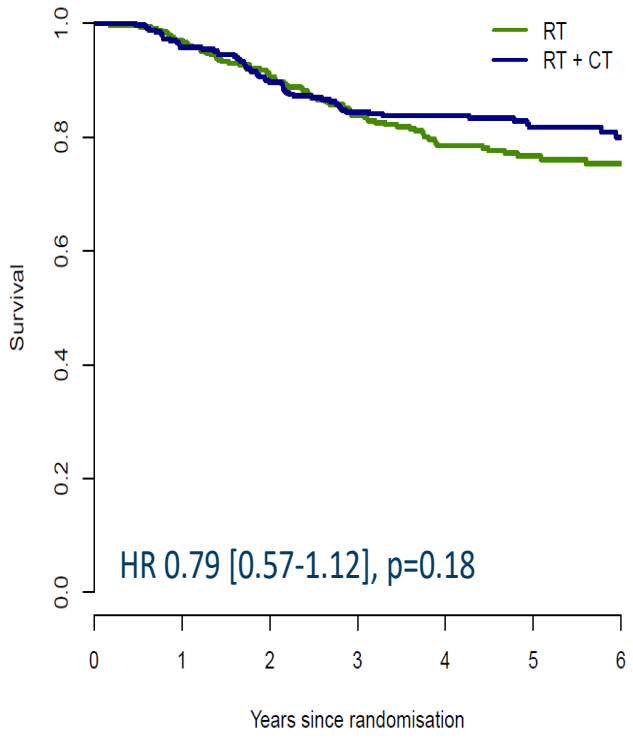

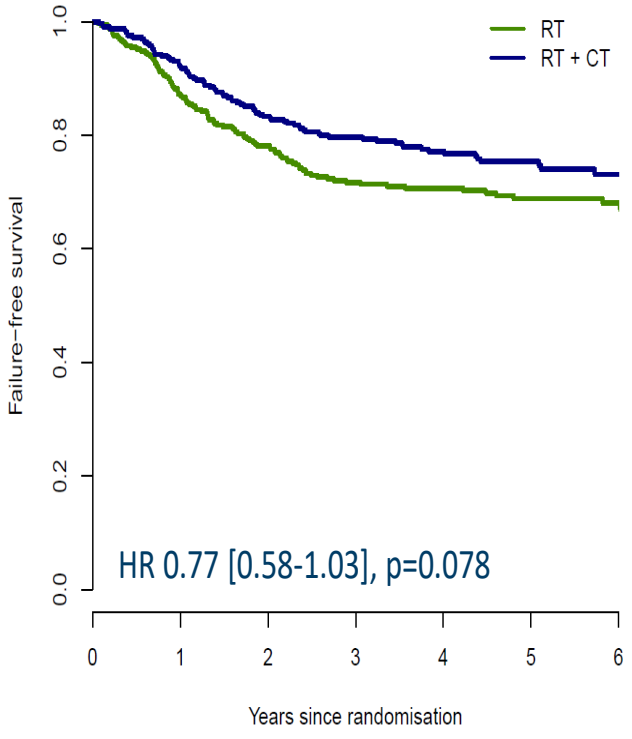

5 yr OS: 82% (CTRT) versus 77% (RT)

5 yr FFS: 76% (CTRT) versus 69% (RT)

First sites of recurrence

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5 years	CTRT		RT		HR	P-value
	N	%	N	%		
Vaginal recurrence	1	0.30%	1	0.30%	1	1
Pelvic recurrence	3	0.95%	5	1.5%	0.60	0.478
Distant recurrence	76	22.4%	93	28.3%	0.78	0.108
- Distant + vaginal	4	1.2%	4	1.2%	-	-
- Distant + pelvic	11	3.2%	20	6.1%	-	-
- Distant only	61	18.0%	69	21.0%	-	-

Conclusion High Risk: CT+RT vs RT

- NSGO-EORTC/Iliade: significant PFS benefit (9%); trend for OS (7%)
- PORTEC-3: trend for improved FFS (7%) with CT+RT
- Does benefit outweigh the added toxicity, without OS benefit?
- Good pelvic control with RT alone (PORTEC-3 and GOG-249)

 CT+RT schedule cannot be recommended as standard for stage I-II

- Translational studies will hopefully identify those who benefit

 Stage III disease largest FFS improvement with both CT+RT and CT

- PORTEC-3 significant 11% FFS benefit for stage III with CT+RT
- GOG-258 better local control with CT+RT

Any recent update on OS?

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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, Melanie E Powell, Linda Mileshkin, Dionyssios Katsaros, Paul Bessette, Christine Haie-Meder, Petronella B Ottevanger, Jonathan A Ledermann, Pearly Khaw, Romerai D'Amico, Anthony Fyles, Marie-Helene Baron, Ina M Jürgenliemk-Schulz, Henry C Kitchener, Hans W Nijman, Godfrey Wilson, Susan Brooks, Sergio Gribaudo, Diane Provencher, Chantal Hanzen, Roy F Kruitwagen, Vincent T H B M Smit, Naveena Singh, Viet Do, Andrea Lissoni, Remi A Nout, Amanda Feeney, Karen W Verhoeven-Adema, Hein Putter, Carien L Creutzberg, on behalf of the PORTEC Study Group**

Summary

Background The PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy and radiotherapy versus pelvic radiotherapy alone for women with high-risk endometrial cancer. We updated the analysis to investigate patterns of recurrence and did a post-hoc survival analysis.

Lancet Oncol 2019; 20: 1273–85
Published Online
July 22, 2019
http://dx.doi.org/10.1016/

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- **This updated analysis shows significantly improved OS and FFS with CRT vs 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.**
- **Follow-up is ongoing to evaluate long-term survival**

www.thelancet.com/oncology Vol 20 September 2019

***Lancet Oncol* 2019; 20: 1273–85**

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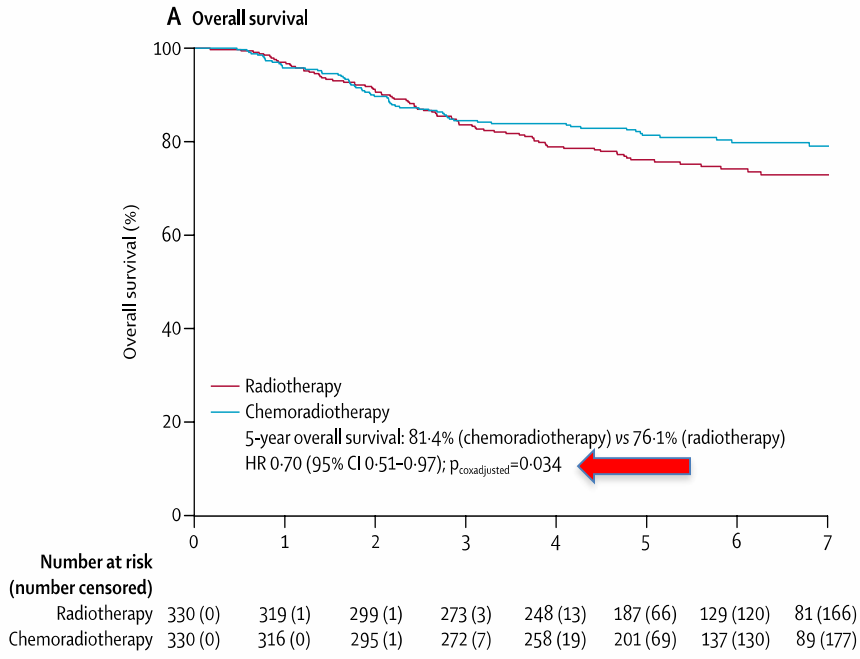


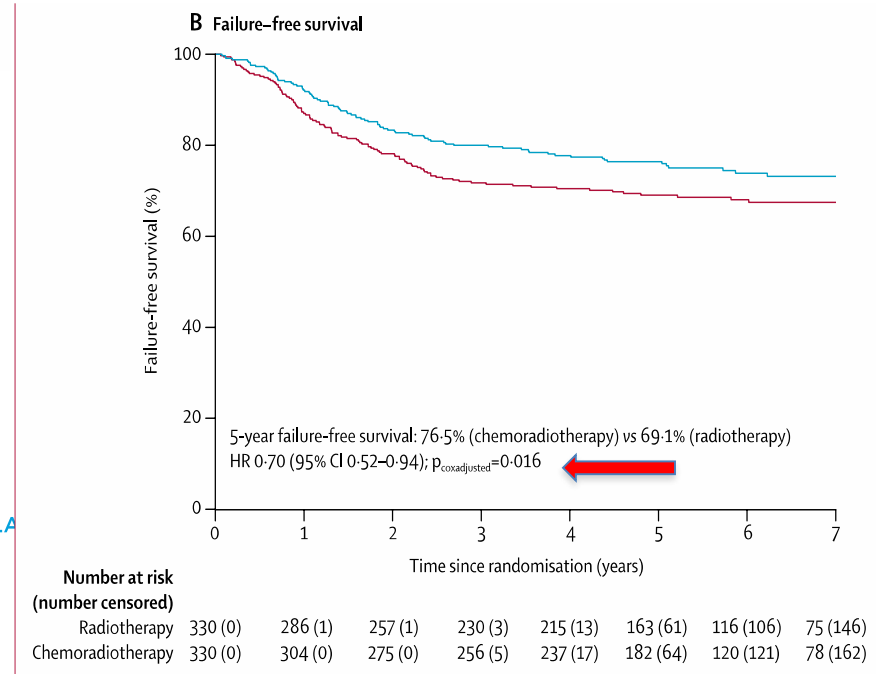
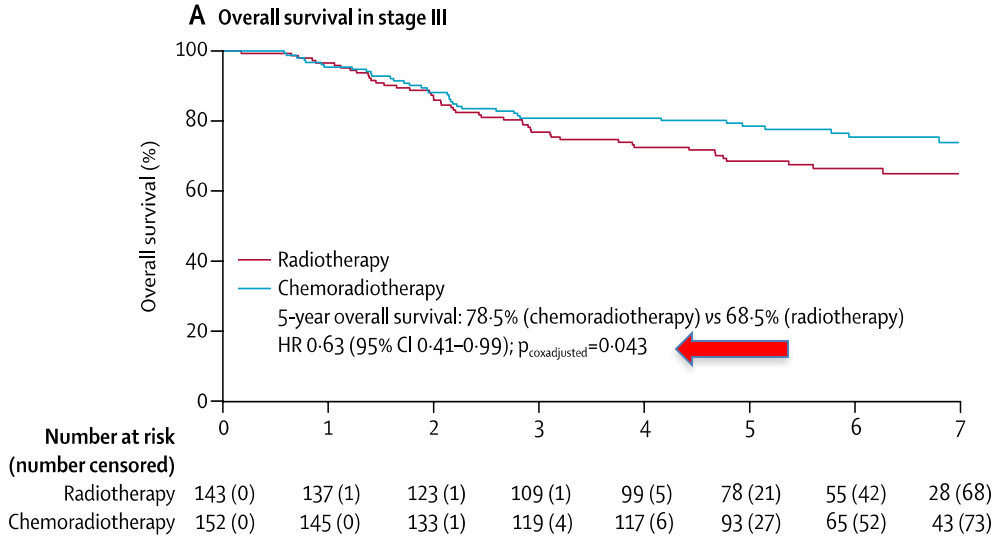
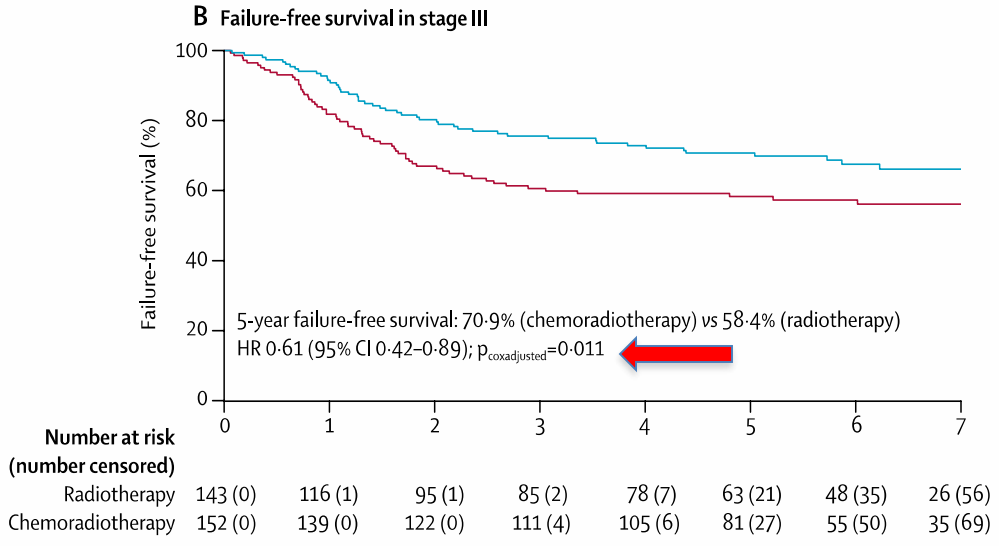


Figure 2: **Kaplan-Meier survival curves for overall survival (A) and failure-free survival (B) in all patients**
HR=hazard ratio.





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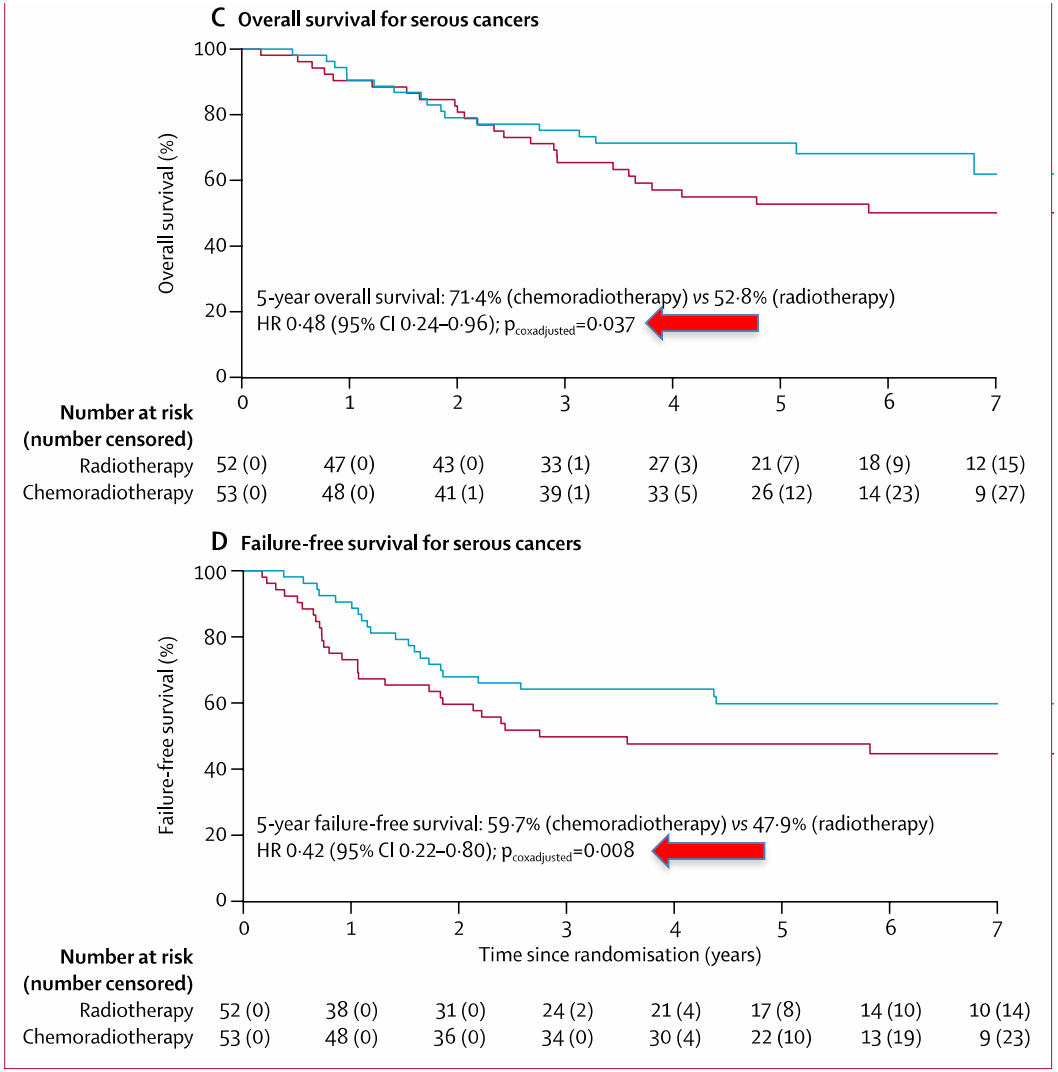

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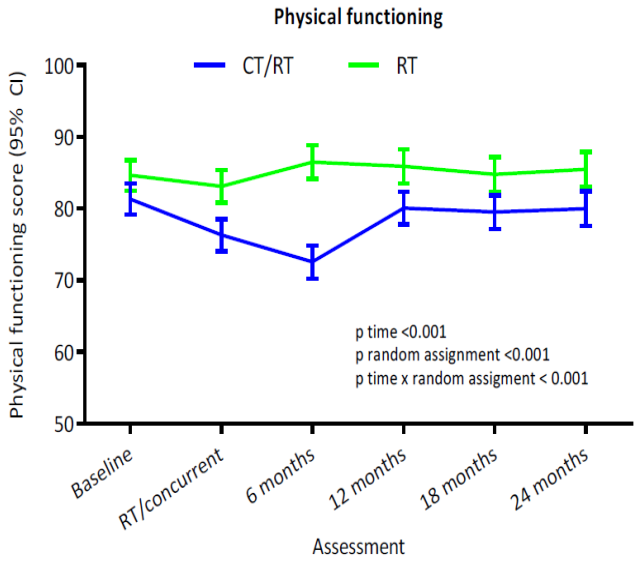
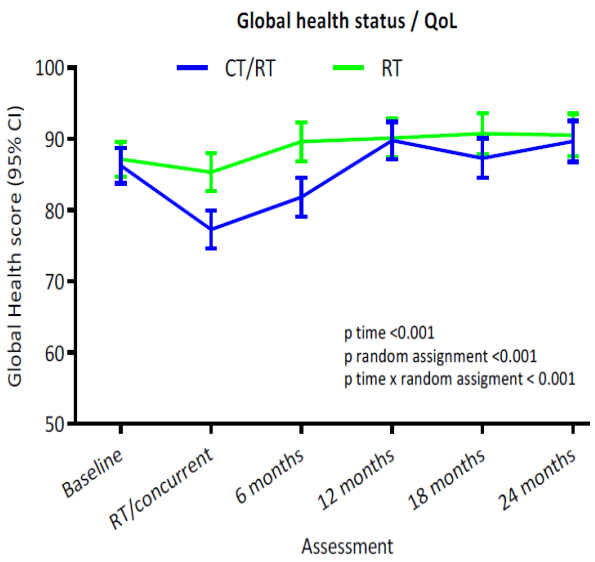
Quality of life





Toxicity and quality of life after adjuvant chemo radiotherapy vs radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): An open-label, multicenter, randomized, phase 3 trial

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Despite the increased physician and patient-reported toxicities, this schedule of adjuvant chemotherapy given during and after radiotherapy in patients with high-risk endometrial cancer is feasible, with rapid recovery after treatment, but with persistence of patient-reported sensory neurological symptoms in 25% of patients. We await the analysis of primary endpoints before final conclusions are made.

The lancet oncology Vol 17 August 2016

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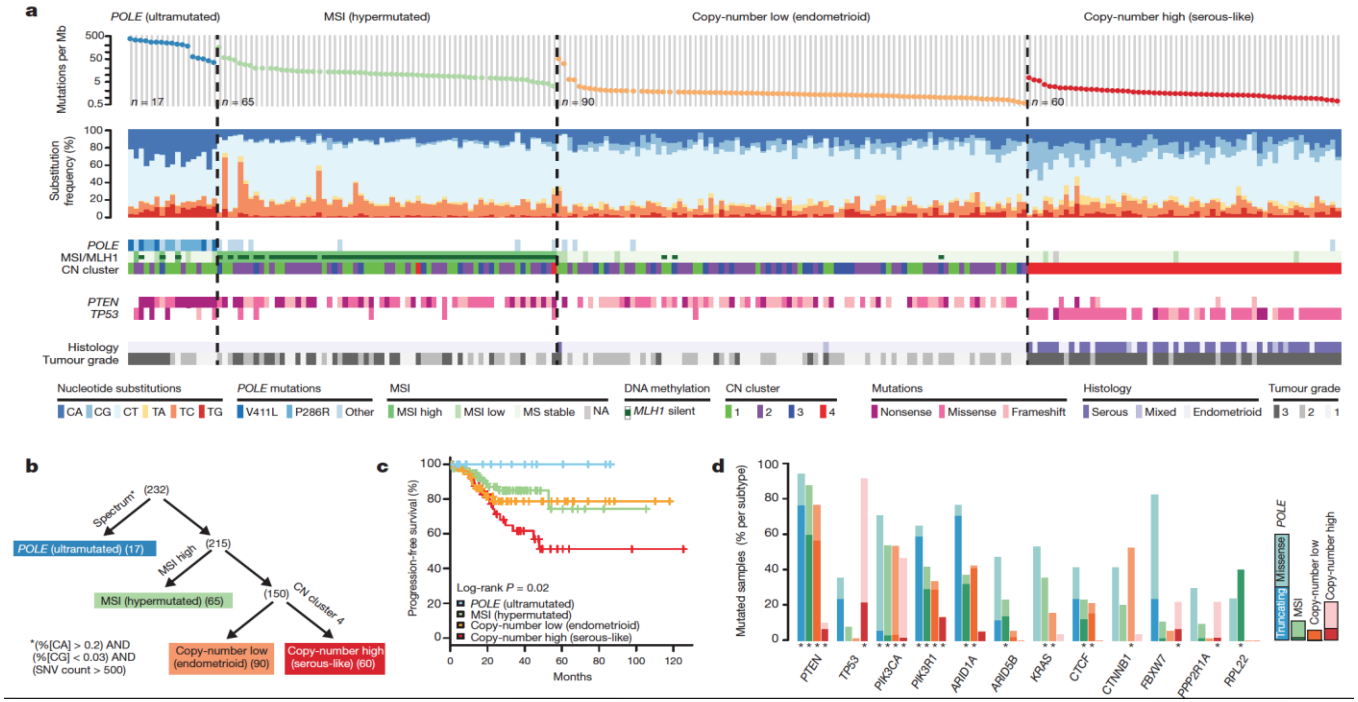
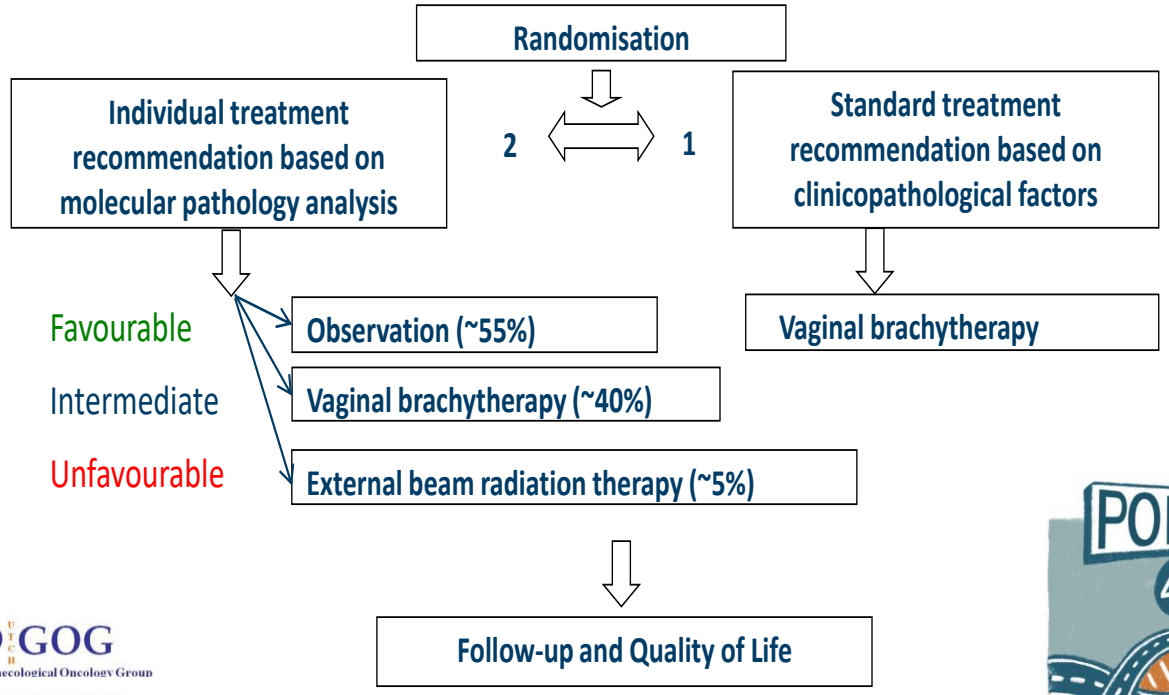
Molecular characteristics of endometrial cancer



TGCA, Kandoth et al, Nature 2013

PORTEC-4a trial design

- **Molecular integrated vs standard indications for adjuvant treatment:**



DUTCH GYNAECOLOGICAL ONCOLOGY GROUP
Dutch Gynaecological Oncology Group
DUTCH CANCER SOCIETY

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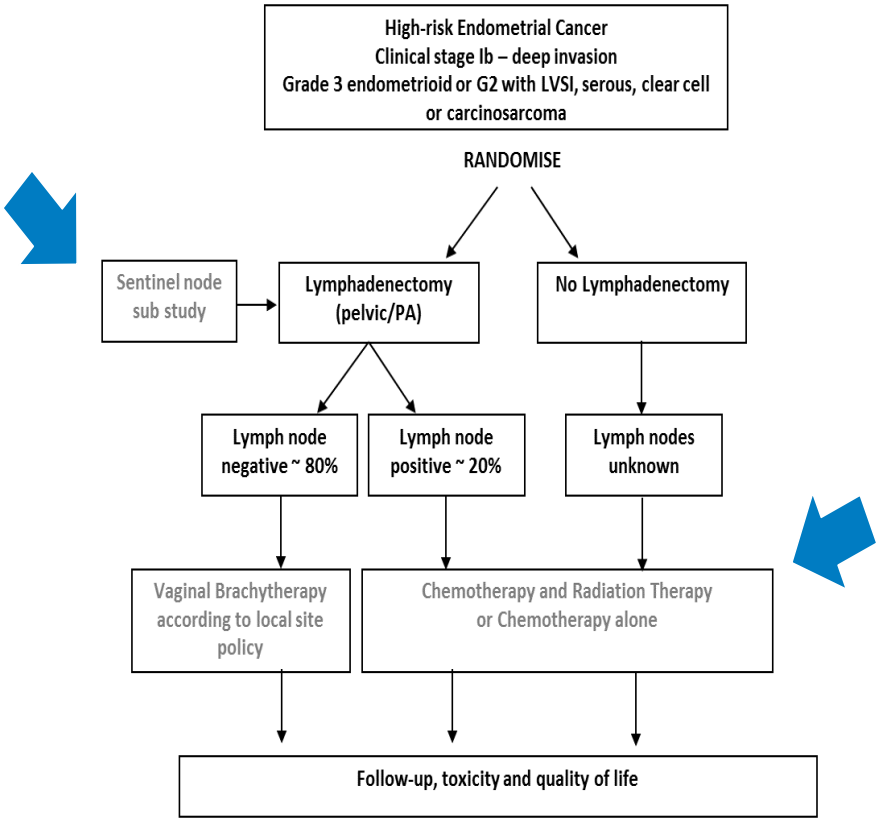
STATEC trial in high risk endometrial cancer



GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Brachytherapy as postoperative treatment

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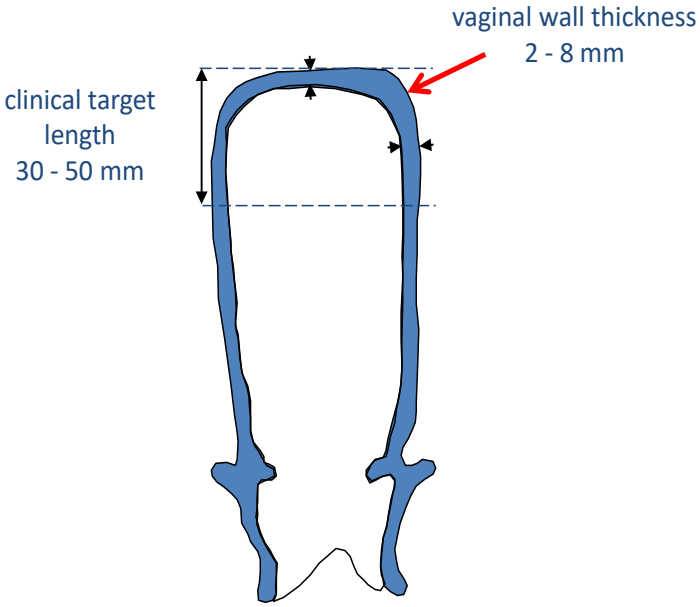
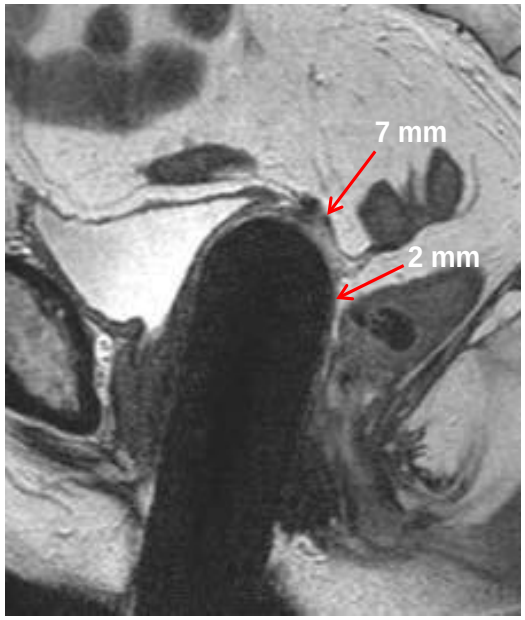
After hysterectomy for endometrial and cervical cancer

- Mucosa of the vaginal cuff including scar
- Recurrences
  - 90 % in cuff
  - 10 % distal part





Applicators

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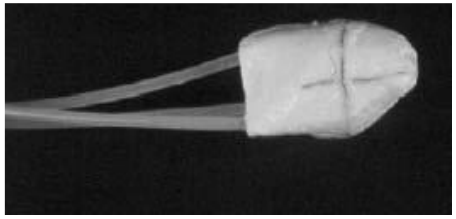
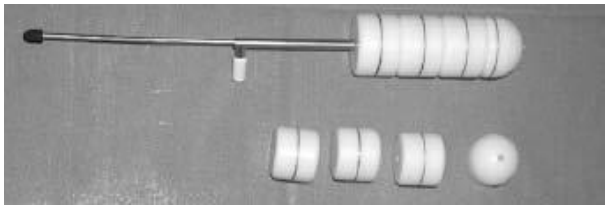
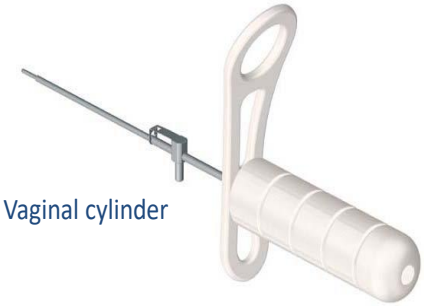
- Size according to the dimensions of the vaginal cuff and of the vagina
- Close contact between the applicator surface and the vaginal mucosa

Vaginal mould

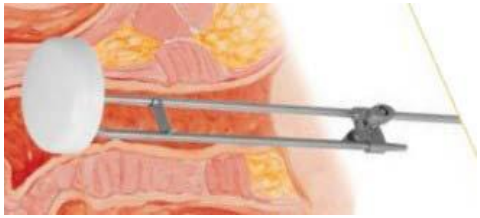




Vaginal cylinder



Ring



Ovoids

Ongoing developments

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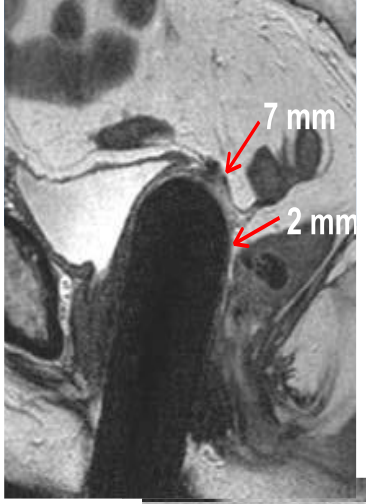
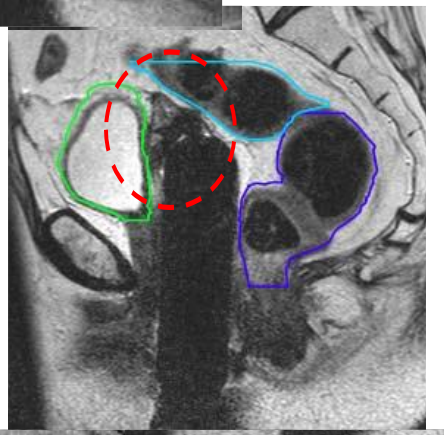
Image guidance

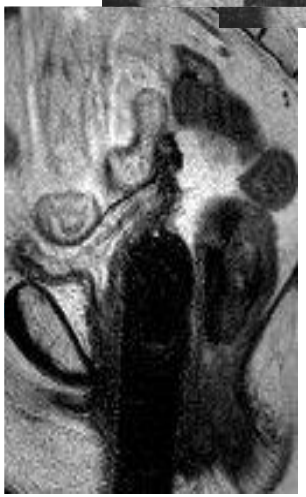
- Sagittal MRI with vaginal applicator in place Detailed information on vaginal wall thickness

Additional anatomical information

- Post-operative cervical rest
- Misplacement of the applicator







MRI after initial insertion

MRI after replacement

Ongoing developments

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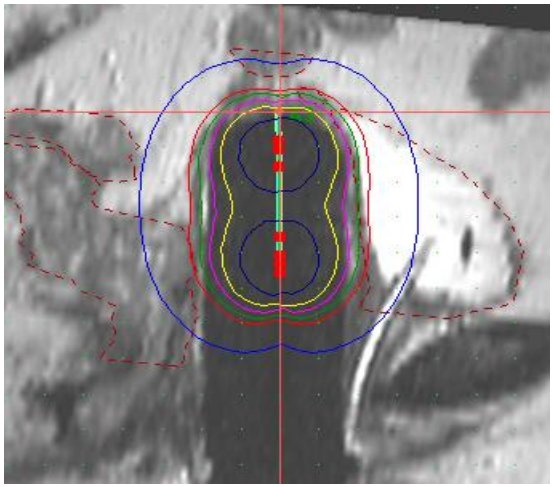
Impact on treatment planning

- Development of volume based treatment planning approach
- Optimization of dose distribution
- Development of vaginal applicators
- Especially interesting in case of vaginal recurrences



Conclusions for vaginal vault BT

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- Target volume post-op
  - upper 1/3 of the vagina (3- 5cm)
- Size of applicator
  - According to the dimensions of the vaginal cuff and of the vagina
- Contact
  - Close contact between the applicator surface and the vaginal mucosa
- Technique

➢3D individualized technique preferable(non favorable anatomy or if high doses needed)

- New developments to come

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شكراً!

THANK YOU!

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