Early-Stage Endometrial Cancer

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A National Cancer Institute Designated Cancer Center

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Outline

- Epidemiology
- Staging/Evaluation
- Prognostic Factors
  - Clinicopathologic
  - Molecular
- Clinical Trials
  - PORTEC 1
  - GOG 99
  - PORTEC 2
  - GOG 249

Epidemiology

- 2018, 65,950 new cases of uterine cancer, 4th
  - 12,550 deaths
  - 1% increase/year, non-endometrioid
- Pathology
  - Endometrioid carcinoma: adenocarcinoma and adenocarcinoma-variants (with squamous differentiation; secretory variant; villoglandular variant; and ciliated cell variant)
  - Mucinous adenocarcinoma
  - Serous adenocarcinoma
  - Clear cell adenocarcinoma
  - Undifferentiated carcinoma
  - Neuroendocrinetumors
  - Mixed carcinoma (carcinoma composed of more than one type, with at least 10% of each component)
  - Carcinosarcoma

Estimated New Cases

Females

Breast	287,850	31%
Lung & bronchus	118,830	13%
Colon & rectum	70,340	8%
Uterine corpus	65,950	7%
Melanoma of the skin	42,600	5%
Non-Hodgkin lymphoma	36,350	4%
Thyroid	31,940	3%
Pancreas	29,240	3%
Kidney & renal pelvis	28,710	3%
Leukemia	24,840	3%

Estimated Deaths

Females

Lung & bronchus	61,360	21%
Breast	43,250	15%
Colon & rectum	24,180	8%
Pancreas	23,860	8%
Ovary	12,810	4%
Uterine corpus	12,550	4%
Liver & intrahepatic bile duct	10,100	4%
Leukemia	9,980	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	7,570	3%
All Sites	**287,270**	**100%**

Siegel, CA Cancer J Clin 2022

Racial Disparity

- Among black women, high incidence of non-endometrioid histologies
  - Poorer survival
- Compared to white patients, black patients are less likely to receive:
  - Hysterectomy
  - Chemotherapy
  - Radiotherapy

Genetics

- Germline Mutations
  - Lynch Syndrome: mutation in mismatch repair genes
    - 3% of endometrial cancers are related to Lynch Syndrome
    - Lifetime risk of endometrial cancers by age 70 years
      - 46-54% for MLH1 mutations
      - 21-51% for MSH2 mutations
      - 16-49% for MSH6 mutations
      - 13-24% for PMS2 mutations
  - Cowden Syndrome: breast, thyroid and endometrial cancer
    - PTEN mutation
    - 28% lifetime risk of endometrial cancer

Staging

FIGO Stage	
I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
II[a]	Tumor invades cervical stroma, but does not extend beyond the uterus[b]
III[a]	Local and/or regional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/or adnexae[c]
IIIB[a]	Vaginal involvement and/or parametrial involvement[c]
IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodes[c]
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladder and/or bowel mucosa
IVB[a]	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes)

Amant, IJGO 2018

Traditional Classification

	Type I	Type II
Age	Younger	Older
Grade	1-2	3
Smoking	No	Yes
Estrogen	Yes	No
Atypical Hyperplasia	Yes	No
Early Stage	Yes	No
Non-endometrioid	No	Yes

Amant, IJGO 2018

Prognostic Factors

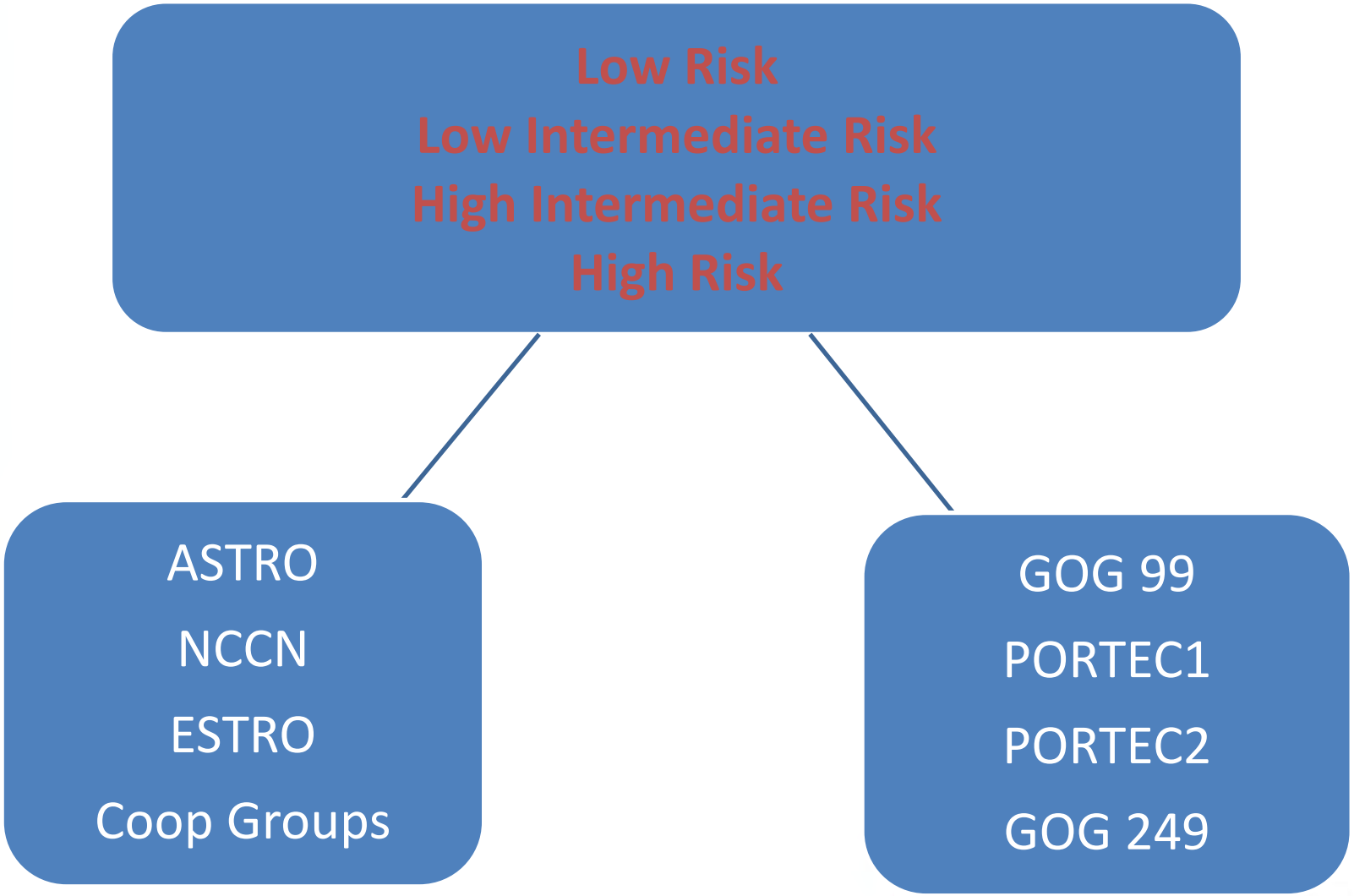
Clinical Factors

- Grade
- Pathologic subtype
- Age
- Lymphovascular space invasion
- Depth of myometrial invasion
- Stage
- Size
- Microcystic elongated and fragmented pattern (MELF)

Molecular Factors

- TP53 mutation
- P13/AKT/mTOR pathway defects
- L1CAM Expression
- HER2 mutation
- Loss of function PTEN
- MSI
- KRAS mutation

Risk Stratification



Risk Stratification: GOG

Clinicopathologic Risk Factors

GOG 99 HIR

- > 70 years old with one factor
  - Grade 2-3
  - Outer 1/3 MI
  - LVSI
- ≥ 50 years old with two risk factors
- Any age with three risk factors

GOG 249 HIR

- > 70 years old with one factor
  - Grade 2-3
  - Outer ½ MI
  - LVSI
- ≥ 50 years old with two risk factors
- Any age with three risk factors
- Stage II endometrioid carcinoma

Risk Stratification: NCCN

Clinicopathologic Risk Factors

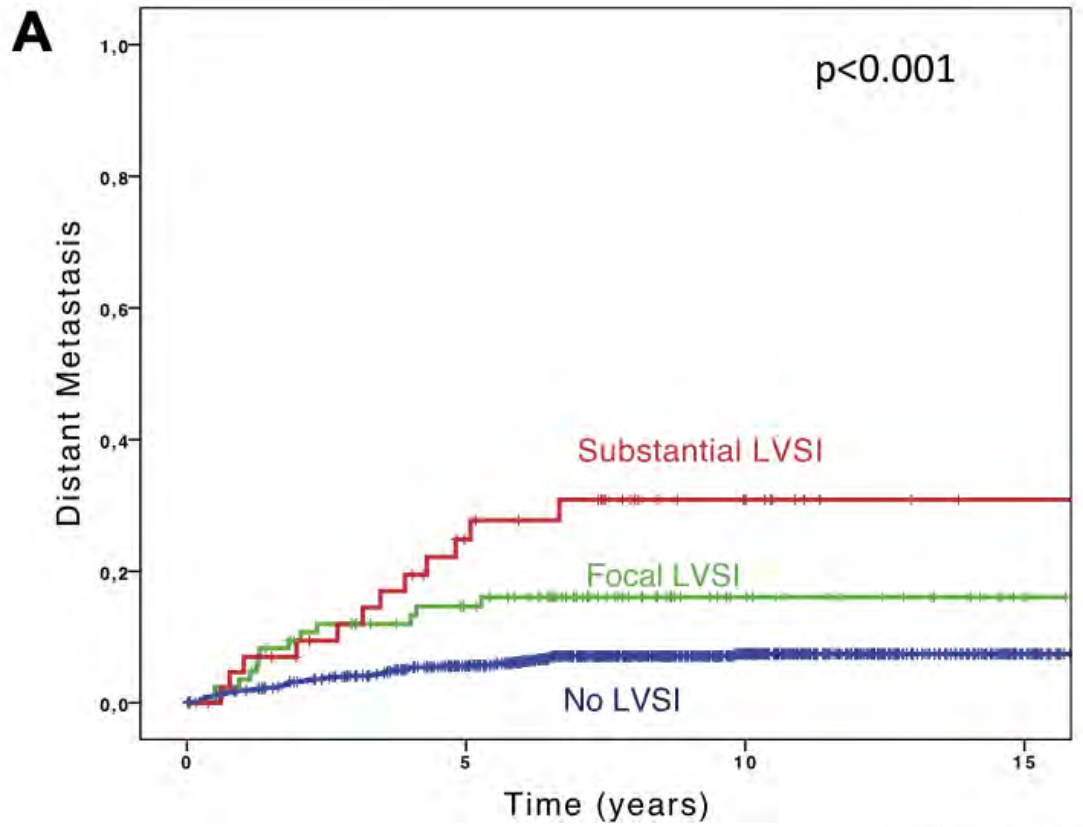
- Risk Factors
  - Age ≥ 60
  - Depth of invasion
  - LVSI
- Consider vaginal brachytherapy if 1 factor present, strongly consider if two risk factors present

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if ≥60 y and/or LVSI or Consider observation if age <60 y and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

LVSI in PORTEC 1 and 2

- N=954, three-tiered scoring for LVSI

Risk of Distant Metastasis



Bosse, Eur J Ca 2015

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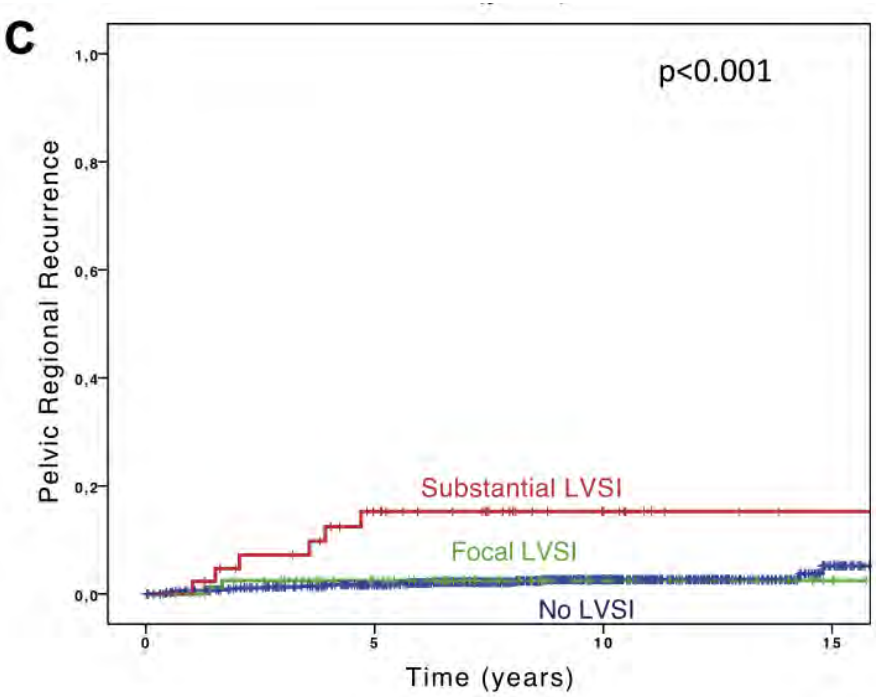
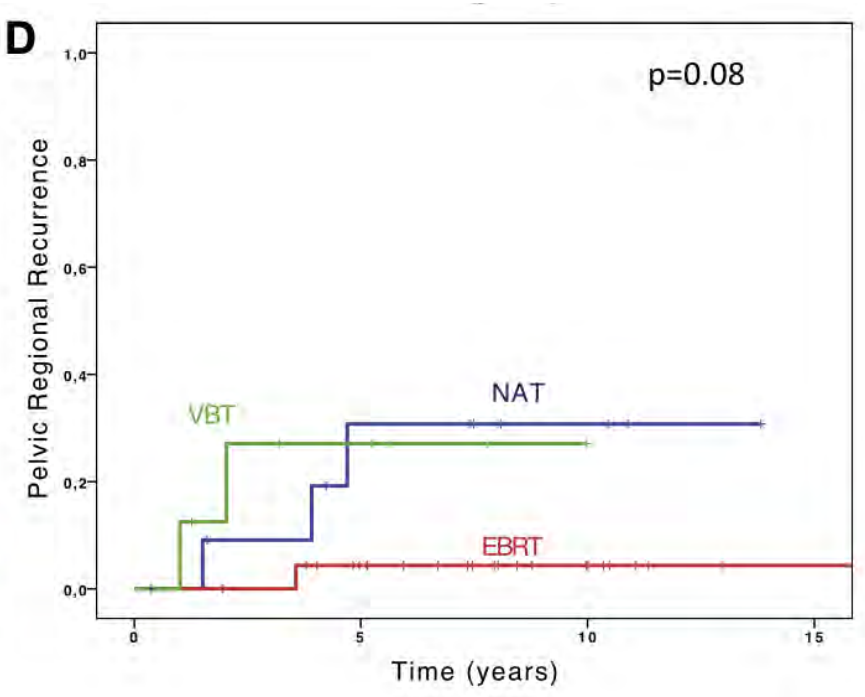
LVSI in PORTEC 1 and 2

- N=954, three-tiered scoring for LVSI

Risk of Pelvic Recurrence



Recurrence by Treatment



Bosse, Eur J Ca 2015

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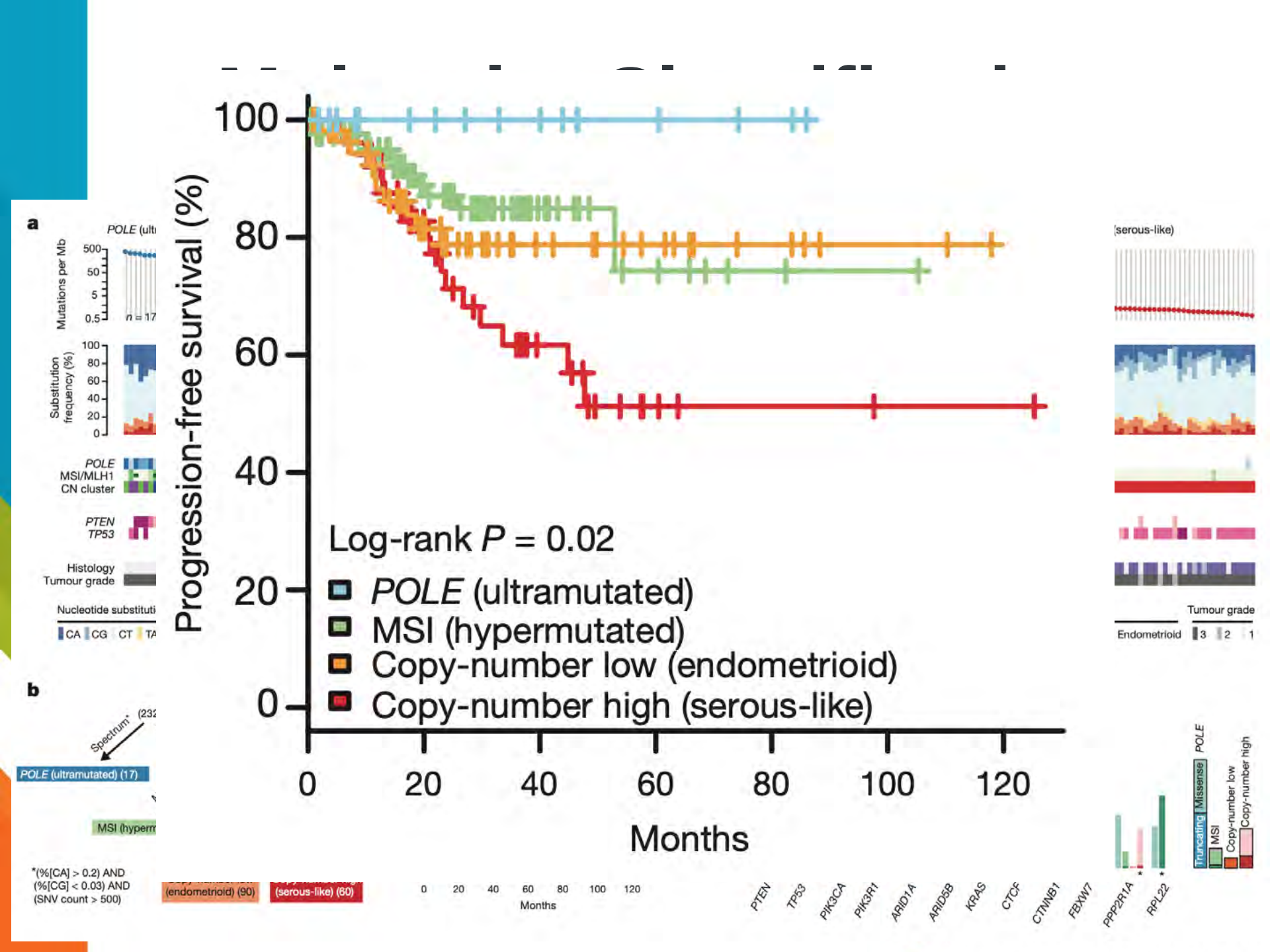

Progression-free survival (%)
100
80
60
40
20
0
Log-rank P = 0.02
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
0
20
40
60
80
100
120
Months
a
b
Mutations per Mb
Substitution frequency (%)
POLE MSI/MLH1 CN cluster
PTEN TP53
Histology Tumour grade
Nucleotide substituti
CA CG CT TA
(serous-like)
Tumour grade
Endometrioid 3 2 1
Spectrum*
POLE (ultramutated) (17)
MSI (hyperm
*(%[CA] > 0.2) AND (%[CG] < 0.03) AND (SNV count > 500)
(endometrioid) (90)
(serous-like) (60)
Months
PTEN
TP53
PIK3CA
PIK3R1
ARID1A
ARID5B
KRAS
CTCF
CTNNB1
FBXW7
PPP2R1A
RPL22
Truncating
Missense
POLE
MSI
Copy-number low
Copy-number high

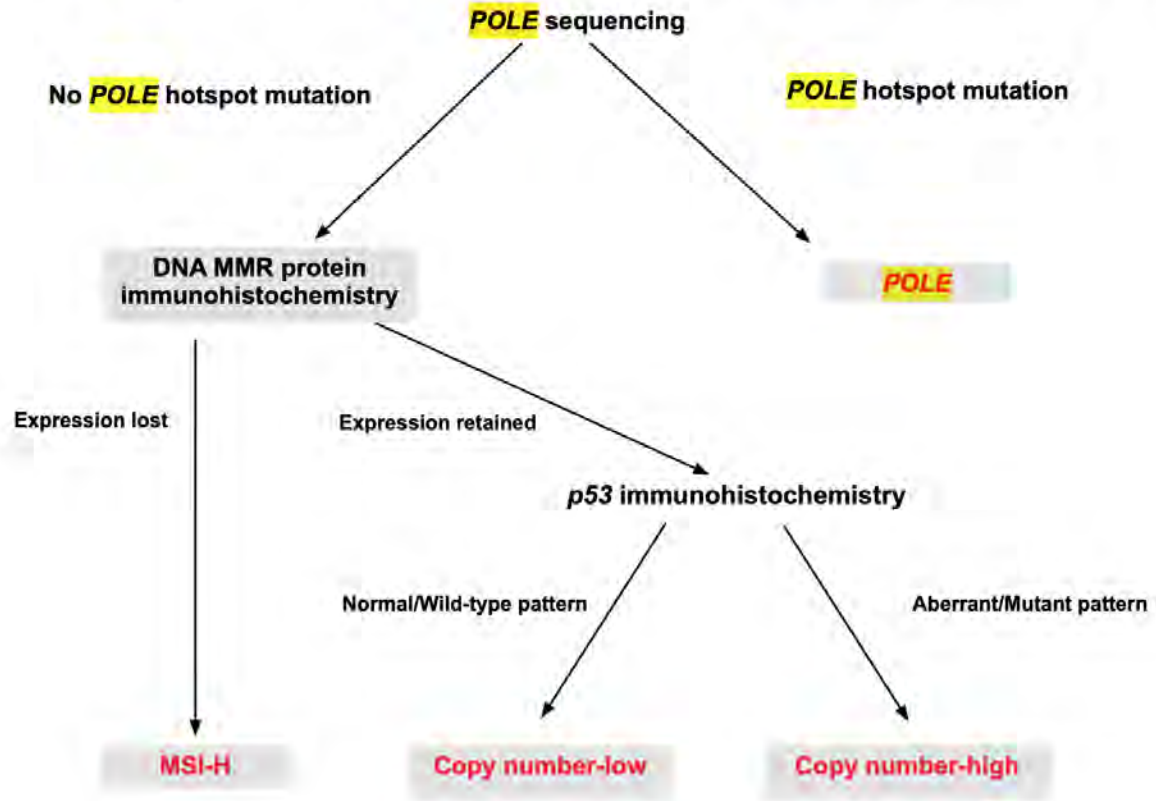
Molecular Classification

- POLE (DNA Polymerase epsilon) ultramutated
  - Best prognosis
  - Frequent mutations in POLE domain
  - 4% of endometrioid carcinoma
- MSI hypermutate (MMRd)
  - High mutation rates
  - High methylation rate, low PTEN expression
  - 39% of endometrioid carcinomas
- Copy number low (NSMP)
  - SOX17 and KRAS frequently mutated
  - High PR rate, RAD50 expressed
  - 49% of endometrioid carcinomas
- Copy number high (p53mut)
  - Worst prognosis
  - Frequent p53 mutations, unique PTEN mutation
  - 8% of endometrioid carcinoma

NCCN Guidelines

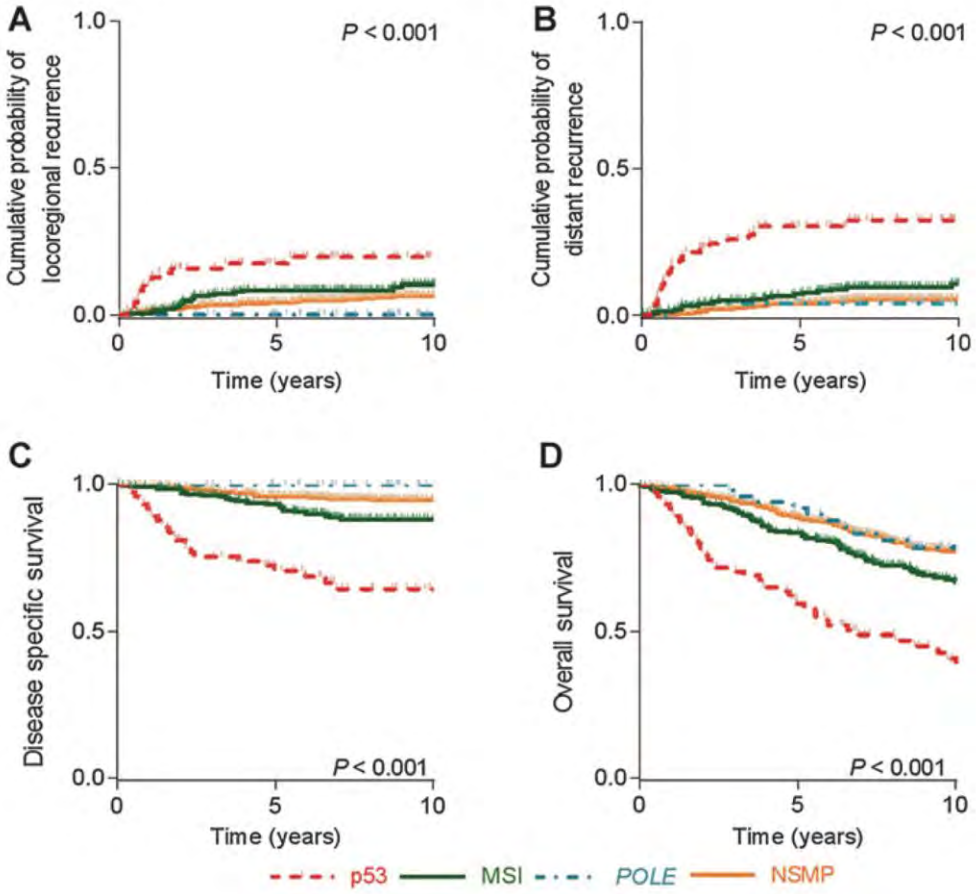
PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center)[f,g]



Molecular Prognosis Confirmation Studies

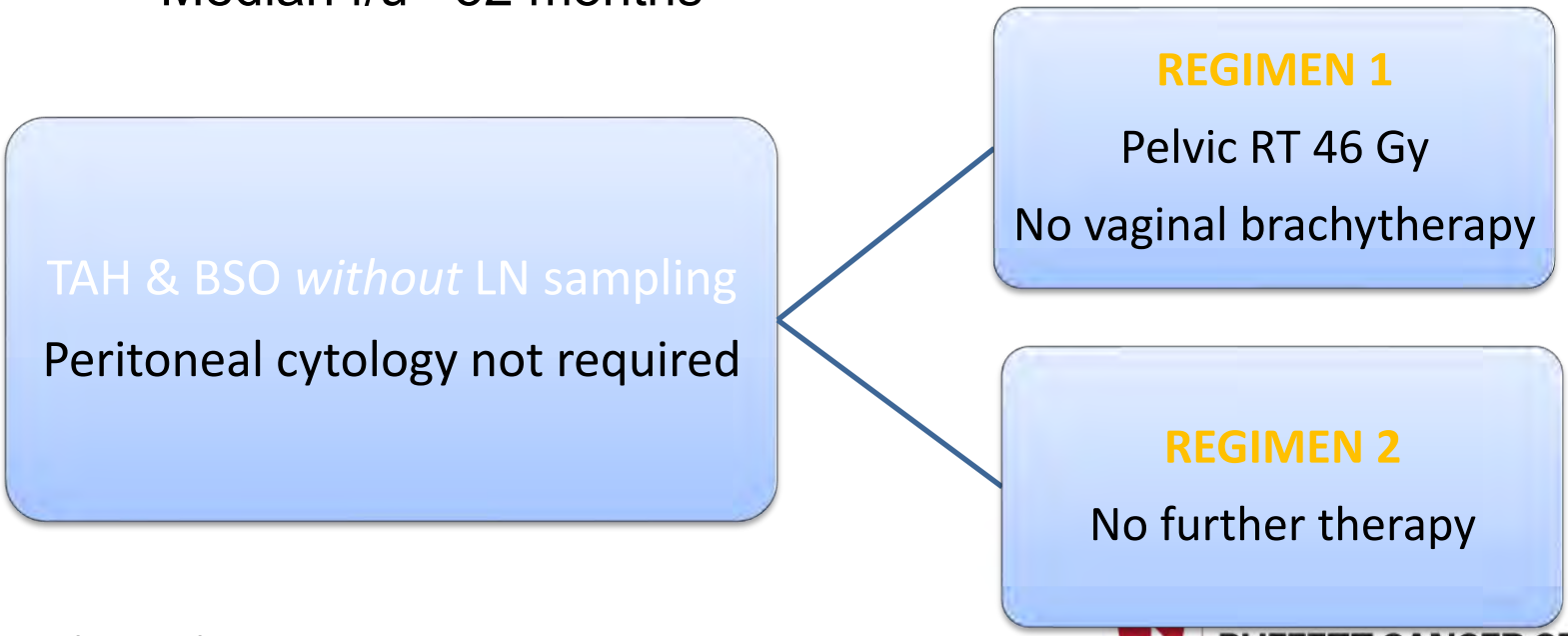
- N=947, PORTEC-1 and 2 patients



Stelloo, CCR 2016

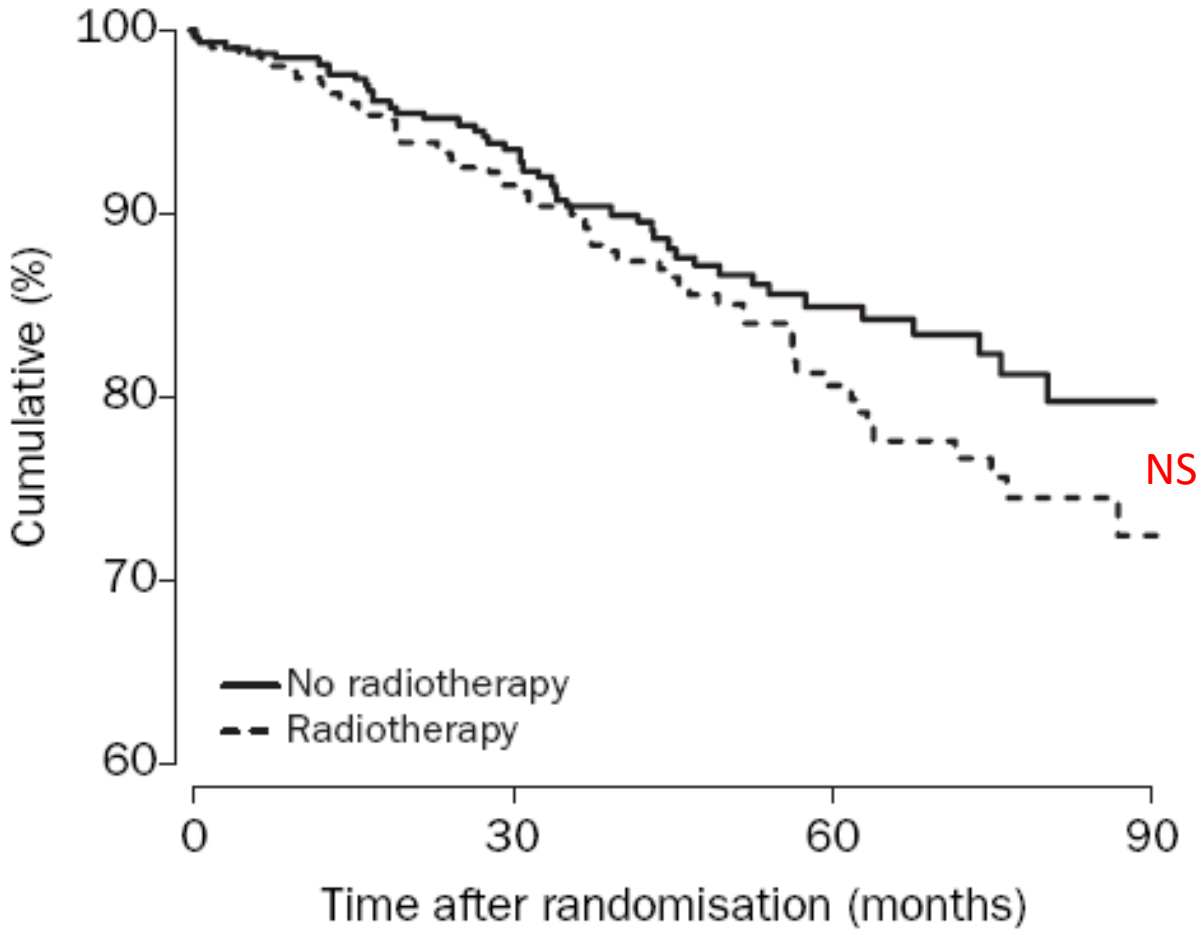
PORTEC

- Post-operative stage I, n=715
  - Grade 1, > 0.5 MI
  - Grade 2, any MI
  - Grade 3, < 0.5 MI
- Primary endpoint: OS and LR
  - Median f/u= 52 months



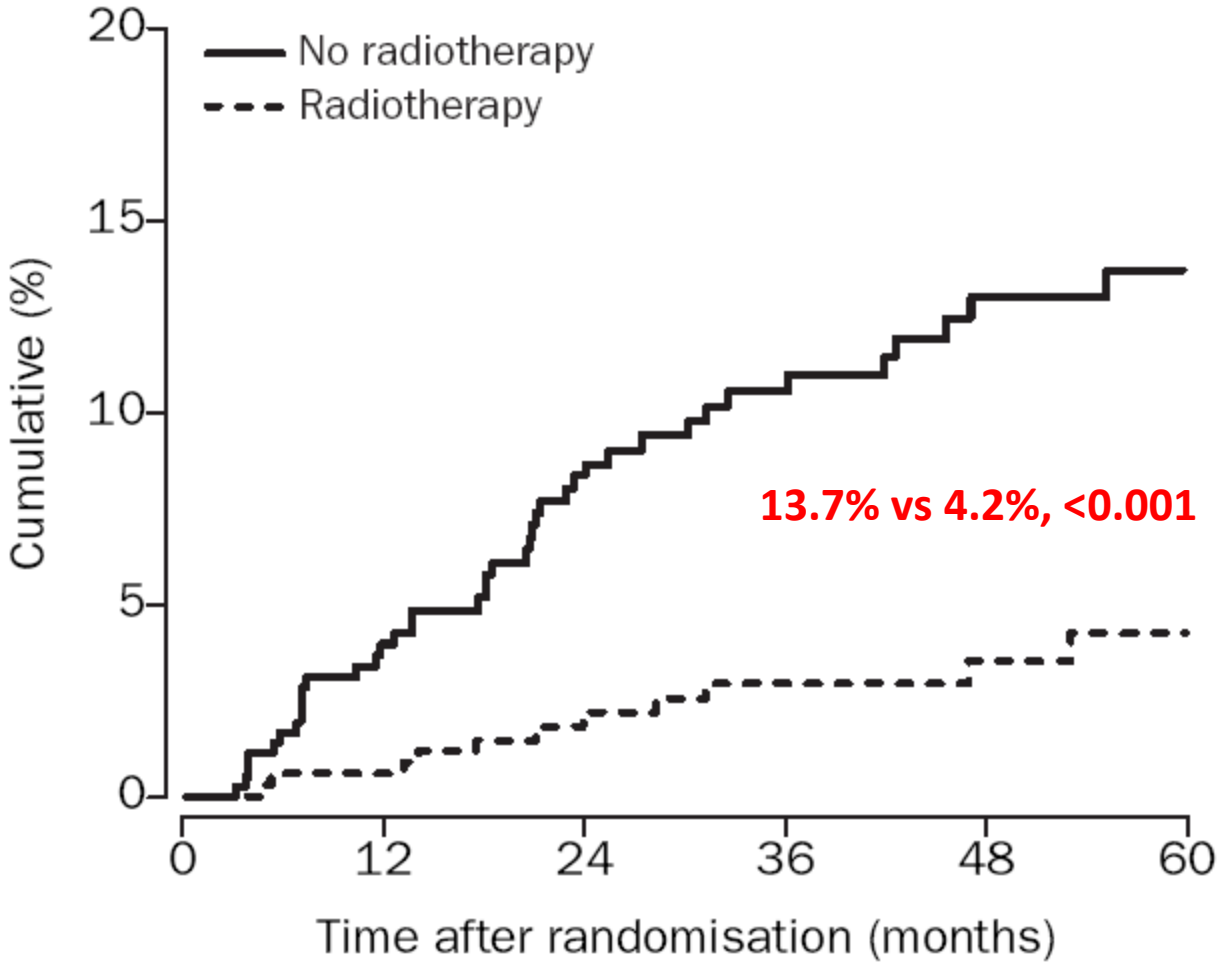
Creutzberg al., Lancet, 2000

PORTEC- Overall Survival



Creutzberg al., Lancet, 2000

PORTEC- Local Recurrence



Creutzberg al., Lancet, 2000

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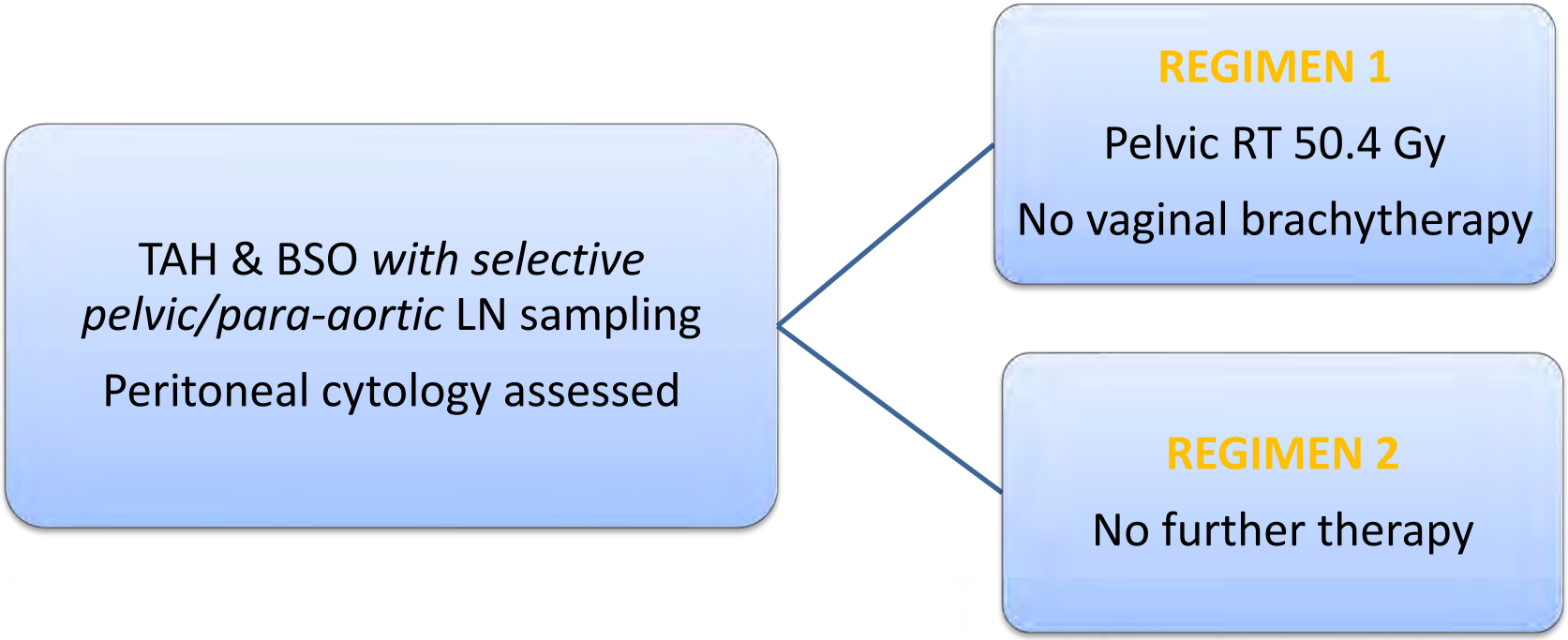
PORTEC- Toxicity

	Observation	Pelvic RT
5-year LR	14%	4%
5-year OS	85%	81%
Any treatment complications	6%	25%
Grade 3-4 complications	0%	2%

Creutzberg al., Lancet, 2000

GOG 99

- Post-operative stage IB-occult II, n=392
- Primary endpoint: Recurrence free survival



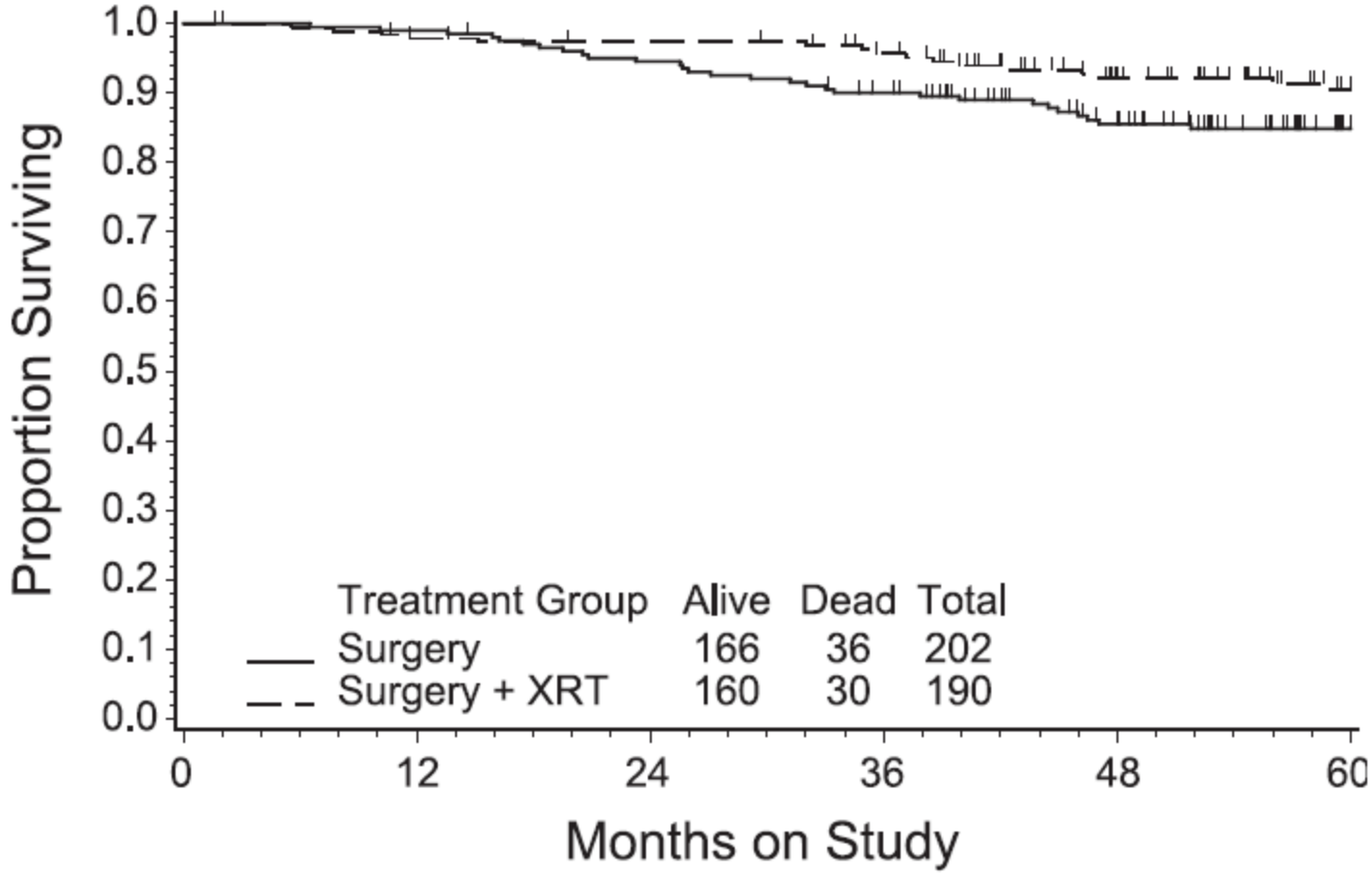
Keys et al., Gyne Oncol, 2004

GOG 99

- A non-significant improvement in survival was noted in RT group
  - 92% versus 86%, p=0.55
  - ½ of deaths not due to endometrial cancer
- RT group had superior pelvic control at 2 years
  - 12% versus 3%, p<0.01
  - Of the 3 recurrence in RT arm, 2 did not receive RT
- Recurrence rate at 5.5 years without RT was 15%
- 15% complication rate in RT arm, 6% in Obs arm

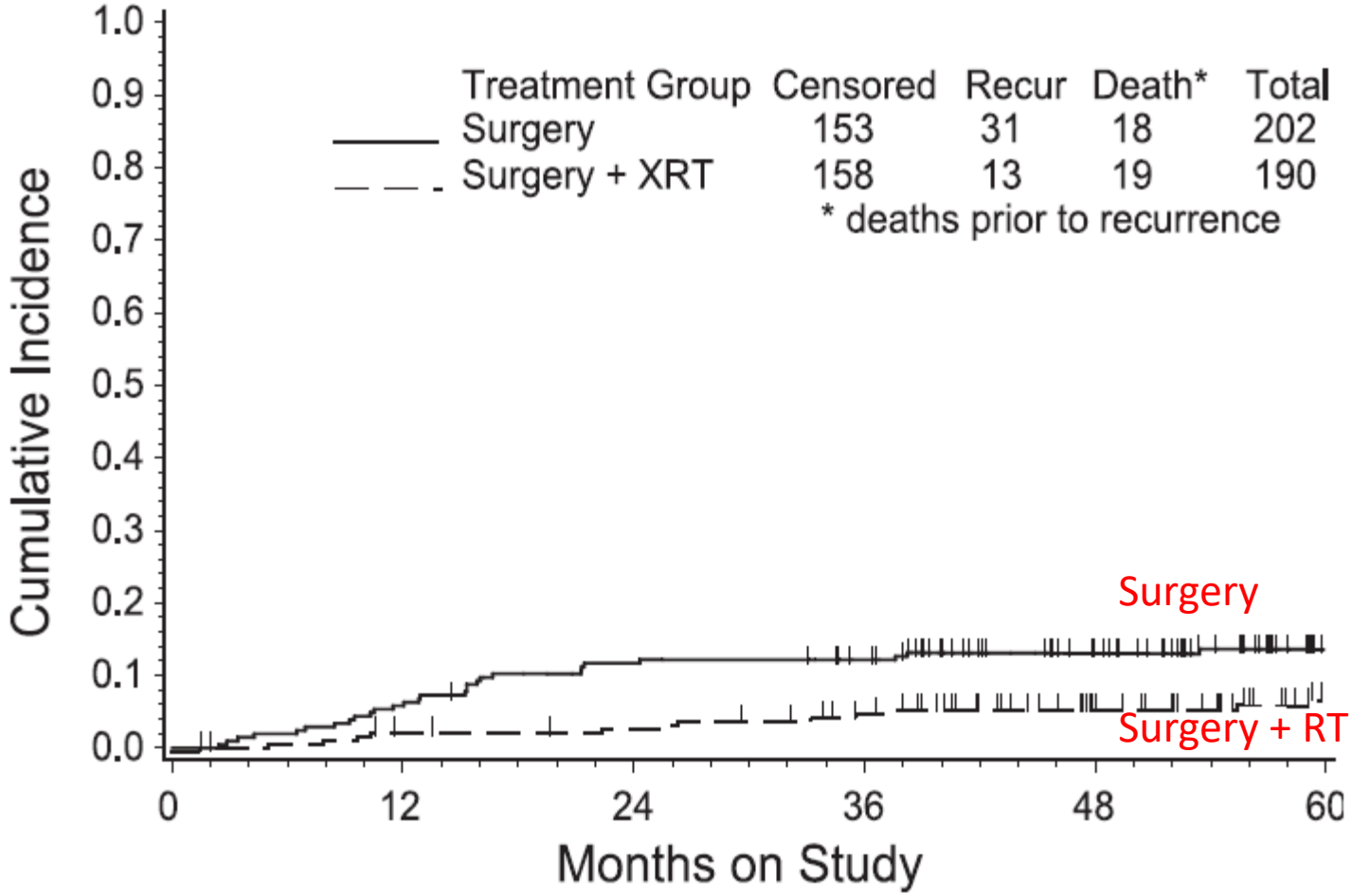
Keys et al., Gyne Oncol, 2004

GOG 99- Survival



Keys et al., Gyne Oncol, 2004

GOG 99- Local Recurrence



Keys et al., Gyne Oncol, 2004

GOG 99- Subgroup Analysis

- Target population had lower risk of recurrence than expected
- HIR (high intermediate risk) patient classification developed
  - Age ≥ 70 with 1 factor: grade 2-3, +LVI, outer 1/3 MI
  - Age ≥ 50 with 2 factors: grade 2-3, +LVI, outer 1/3 MI
  - Any age with all 3 factors

	4-yr OS	4-yr LR
Pelvic RT	88%	27%
No RT	74%, p=NS	13%

Keys et al., Gyne Oncol, 2004

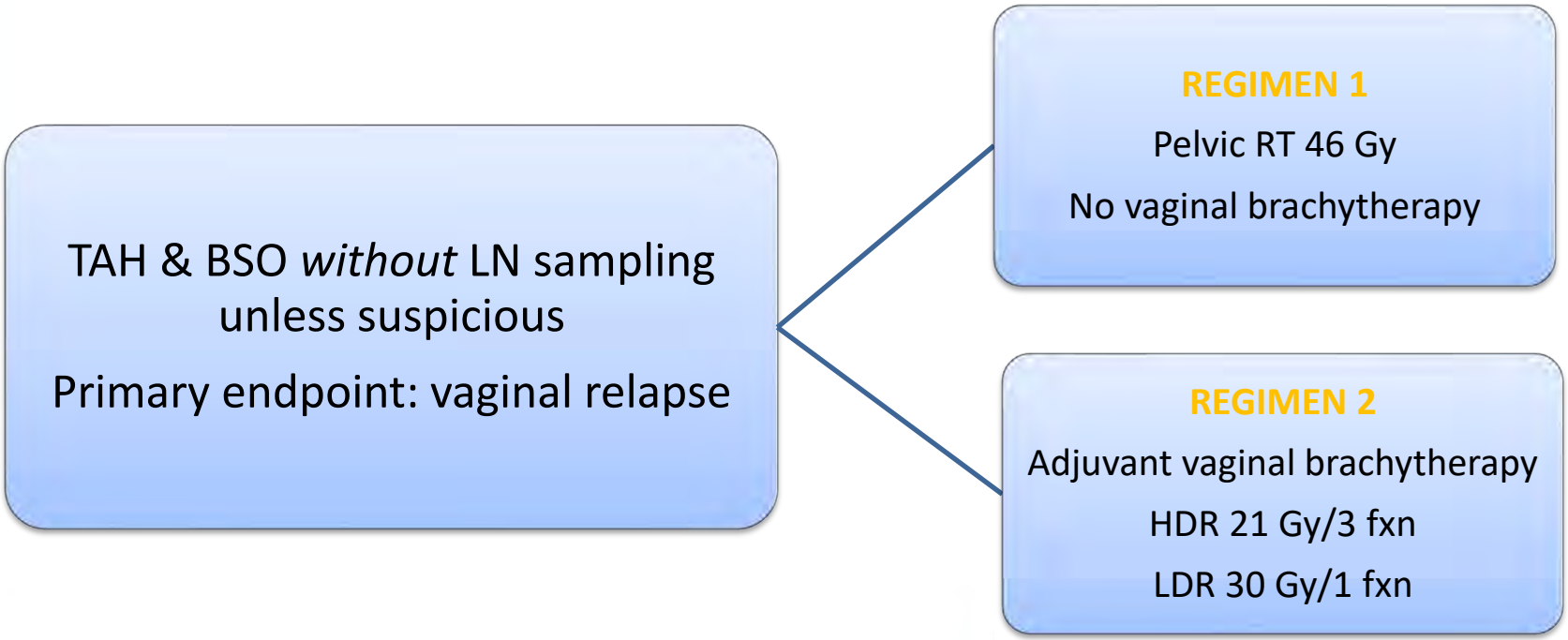
Comparison of Risk Groups: GOG & PORTEC

Risk Levels	PORTEC	GOG 99
Risk Factors Age Grade Deep Invasion LVI	 <60 vs. >60 Grade 1-2 vs. 3 <50% vs. >50% ---	 <50 vs. <70 vs. >70 Grade 1 vs. 2-3 <66% vs. >66% Absent vs. present
High-risk definition	At least 2 of 3 factors	Any age and 3 factors Age ≥ 50 and 2 factors Age ≥ 70 and 1 factor
Results in high risk group	10-yr locoregional relapse RT: 5% No RT: 23% With GOG high-risk criteria RT: 8% No RT: 22%	4-year relapse (any): RT: 14% No RT: 27% 4-yr isolated local relapse: RT: 5% No RT: 13%

Adapted from Creutzberg, 2007

PORTEC 2 Trial

- Eligibility
  - Age>60 and stage IC, grade 1 or 2
  - Age>60 and stage IB, grade 3
  - Any age, stage IIA, any grade



Nout et al., *Lancet* 26: 2010

PORTEC 2 Trial

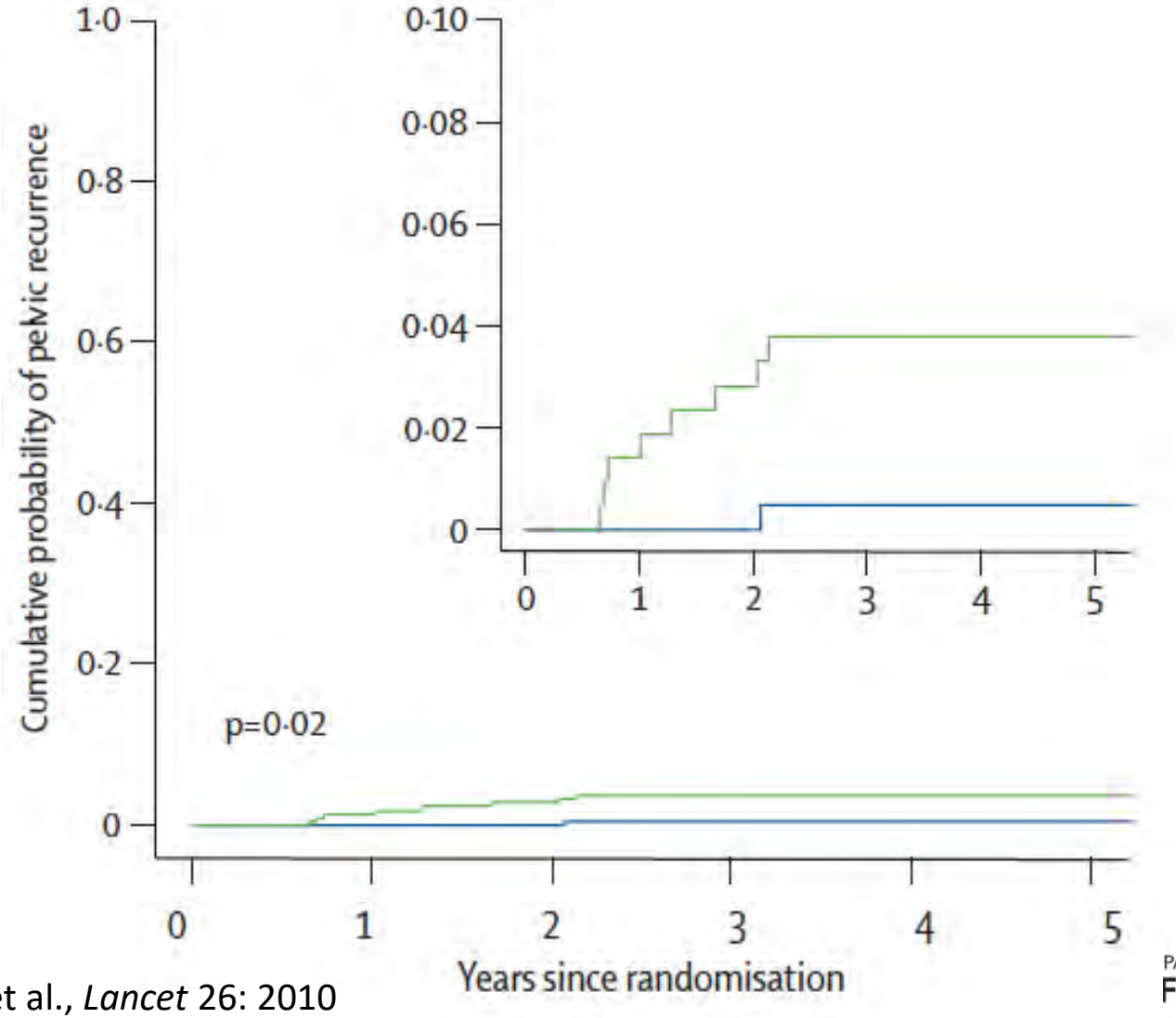
	EBRT (n=214)	VBT (n=213)
Time between surgery and radiotherapy (days)	43·4 (0·8)	42·5 (0·8)
Duration of radiotherapy (days)	30·9 (0·2)	12·9 (0·4)
Dose (Gy)		
EBRT	46·0 (0·9)	..
VBT: HDR*	..	21·1 (0·1)
VBT: MDR*	..	28·5 (0·5)
VBT: LDR*	..	29·0 (0·3)
Median VBT cylinder diameter (mm [range])	..	30 (20–40)
VBT length of 100% isodose (mm)	..	46·5 (0·7)

Data are mean (SE) unless otherwise indicated. EBRT=external beam radiotherapy. VBT=vaginal brachytherapy. HDR=high-dose rate. MDR=medium-dose rate. LDR=low-dose rate. *VBT was delivered with HDR in 182 (85·4%) patients, with LDR in 19 (8·9%) patients, and with MDR in eight (3·8%) patients.

Table 2: **Treatment characteristics**

Nout et al., *Lancet* 26: 2010

PORTEC 2 Trial



Nout et al., *Lancet* 26: 2010

PORTEC 2 Trial

	Events/total	Estimated 5-year (%; 95% CI)	Hazard ratio (95% CI)*	Log-rank p value*
Vaginal recurrence				
EBRT	4/183	1·9% (0·6–5·8)	1·00	0·39
VBT	2/183	1·5% (0·4–6·5)	0·48 (0·09–2·64)	
Pelvic recurrence				
EBRT	1/183	0·6% (0·1–4·0)	1·00	0·06
VBT	6/183	3·3% (1·5–7·3)	6·10 (0·73–50·7)	
Locoregional recurrence				
EBRT	5/183	2·4% (0·9–6·5)	1·00	0·42
VBT	8/183	4·8% (2·4–9·7)	1·58 (0·52–4·86)	
Distant metastases				
EBRT	10/183	5·0% (2·6–9·4)	1·00	0·79
VBT	11/183	6·4% (3·6–11·5)	1·12 (0·48–2·64)	
Disease-free survival				
EBRT	24/183	80·2% (71·4–89·0)	1·00	0·89
VBT	25/183	84·5% (78·6–90·4)	1·04 (0·59–1·82)	
Overall survival				
EBRT	19/183	82·1% (73·5–90·7)	1·00	0·66
VBT	22/183	86·2% (80·5–91·9)	1·15 (0·62–2·13)	

EBRT=external beam radiotherapy. VBT=vaginal brachytherapy. *Both log-rank tests and Cox proportional hazards models are stratified for FIGO (International Federation of Gynecology and Obstetrics) stage.

Table 4: Recurrence and survival for patients at true high-intermediate risk after pathology review (n=366)

Nout et al., *Lancet* 26: 2010

PORTEC 2 Results

	N	5 yr Vaginal Rel.	5 yr Pelvic Rel.	5 yr DM	5 yr OS
Vaginal Brachy	214	1.8%	3.8%	8.9%	84.8%
Pelvic RT	213	1.6%	4.6%	5.7%	79.6%
		p=0.74	*p*=0.02	*p*=0.46	*p*=0.57
	N	**10 yr Vag Rel.**	**10 yr Pelv Rel.**	**10 yr DM**	**10 yr OS**
Vaginal Brachy	214	3.4%	6.3%	10.4%	69.5%
Pelvic RT	213	2.4%	0.9%	8.9%	67.6%
		p=0.55	*p*=0.004	*p*=0.49	*p*=0.72

Conclusion: vaginal brachytherapy should be treatment of choice for high-intermediate risk endometrial cancer

Wortman et al., *BJC* 2018
Nout et al., *Lancet* 26: 2010

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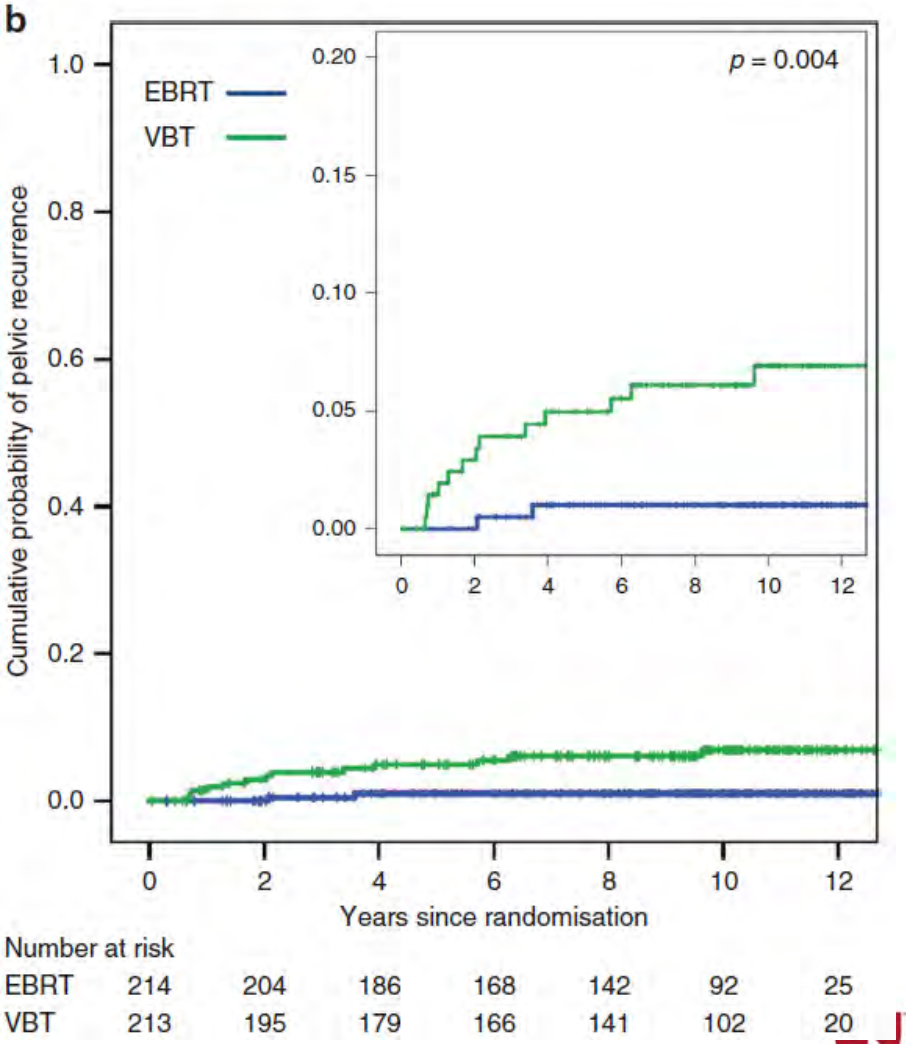
PORTEC 2 10-year Update

Pelvic Recurrence



Wortman et al., *BJC* 2018

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GOG 249

- N=601
- Primary outcome was RFS

Stage I-II
≥70 yo with 1 Risk Factor
≥50 yo or older with 2 Risk Factors
≥18 yo with 3 Risk Factors

Risk Factors: grade 2-3,
Outer 1⁄2 depth invasion, LVSI

Clear cell and pap serous included

Pelvic RT

45-50.4 Gy in 25-28 fx 3D or IMRT
VBT boost allowed for cervix + or clear cell

VBT + 3c Carbo/Taxol

6-7 Gy @ 0.5 cm depth x 3 fractions
10-10.5 Gy @ surface x 3 6 Gy @ surface x 5
3-5 cm length

Randall et al., *JCO* 2019

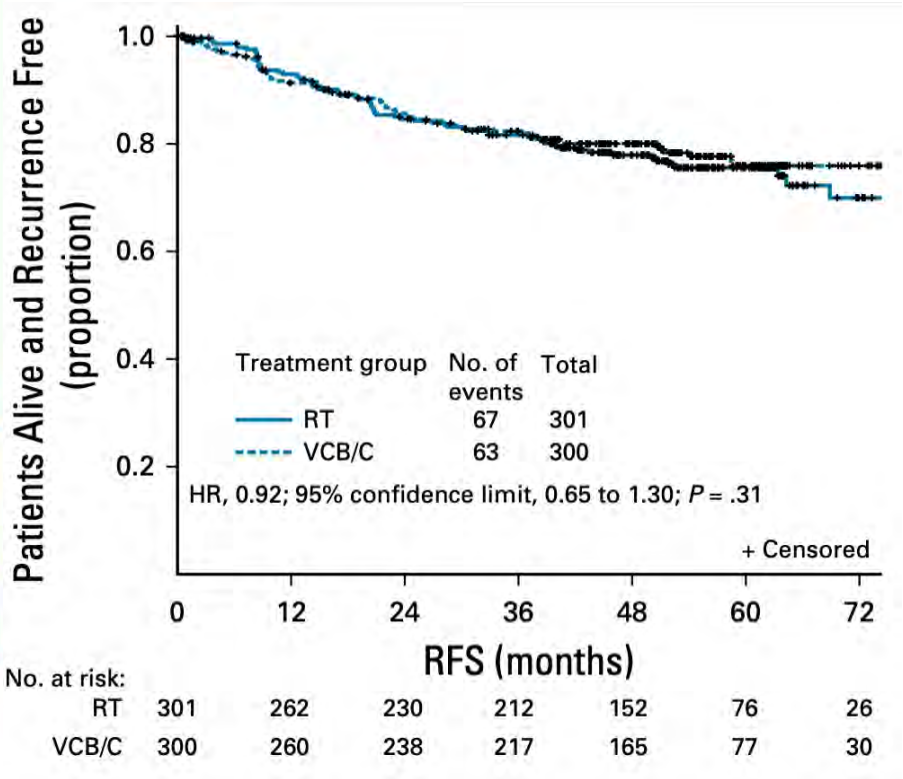
GOG 249

- Median FU was 53 months
- 5-year RFS: 76% (RT) vs 76% (VBT + CT), p=NS
- 5-year OS: 87% (RT) vs 85% (VBT + CT), p=NS
- 5-year pelvic and PALN recurrence
  - 4% (RT) vs 9% (VBT + CT)
- No differences in
  - Vaginal cuff recurrence: 2.5%
  - Distant recurrence: 18%
- Increased fatigue and neurotoxicity in VBT and chemotherapy arm

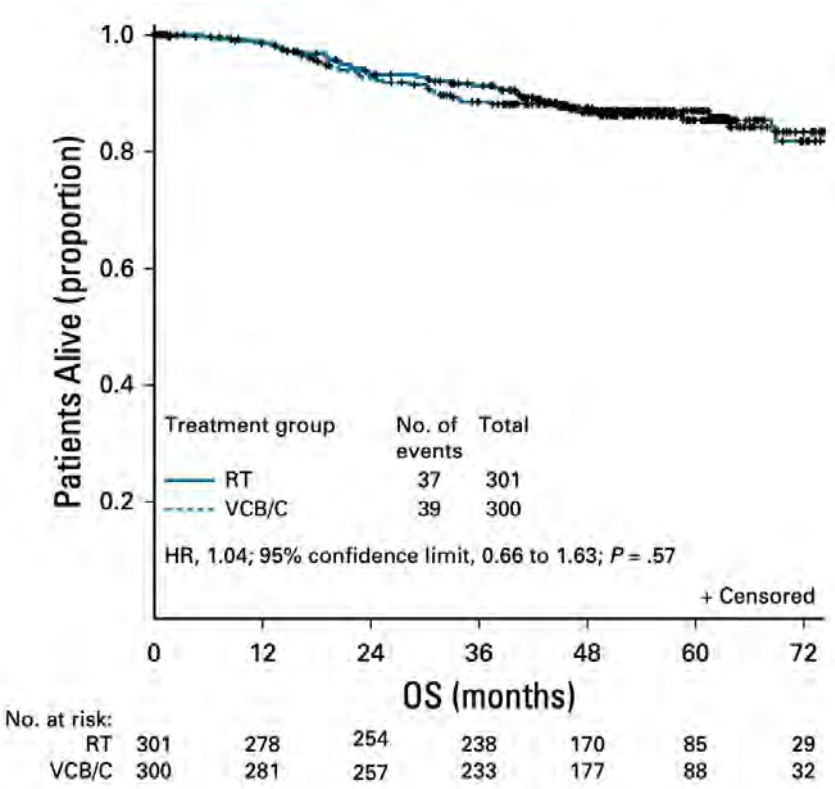
Randall et al., *JCO* 2019

GOG 249

Relapse Free Survival



Overall Survival



Randall et al., *JCO* 2019

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