

State-of-the-Art Surgical and Radiotherapy Strategies in Endometrial Carcinoma



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Endometrium Carcinoma FIGO 2009 Classification

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

* Either G1, G2 or G3.

** Endocervical glandular involvement only should be considered as Stage I and no more as Stage II.

Positive cytology has to be reported separately without changing the stage.

Endometrioid Endometrial Cancer

Treatment paradigm shift

- **Minimize overtreatment**
 - Identify patients not requiring LND and/or RT and/or chemotherapy
- **Minimize undertreatment**
 - Identify patients benefiting from LND and/or RT and or chemotherapy

Endometrial Carcinoma

Role of Lymphadenectomy

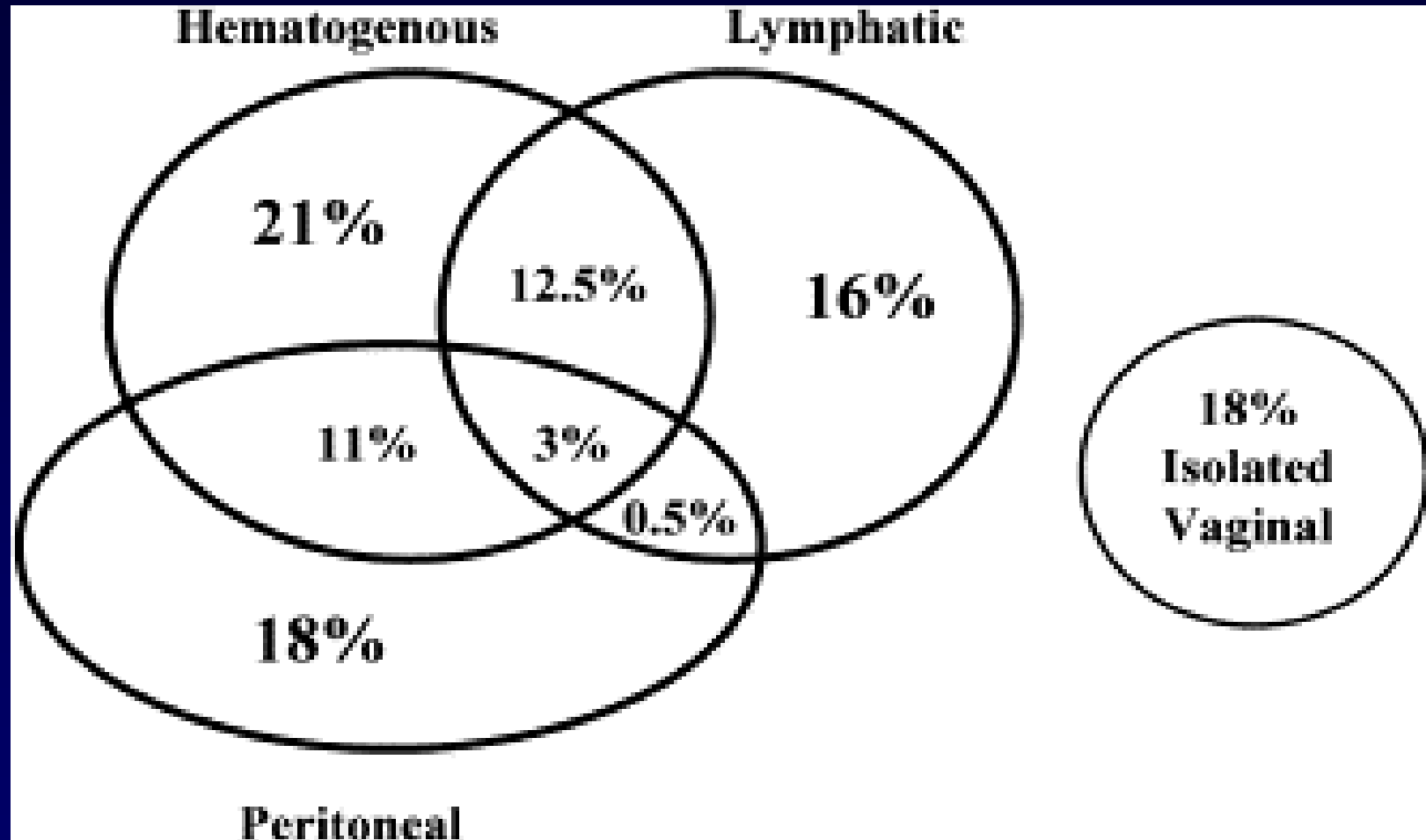
Endometrial Carcinoma

Pelvic Lymph Node Metastases

	G1	G2	G3
Endometrium	0%	3%	0%
Inner 1/3	3%	5%	9%
Middle 1/3	0%	9%	4%
Outer 1/3	11%	19%	34%

Site of Recurrence in Endometrial Cancer

*Mayo Clinic Series: n = 915 treated primarily with surgery
190 relapses (21%)*



Endometrial Carcinoma Stage I and II Paraaortic Lymphadenectomy n = 895

- **47/48 with aortic node metastases had:**
 - a. Grossly positive pelvic lymph nodes**
 - b. Grossly positive adnexal metastases**
 - c. Serosal infiltration**

Paraaortic Lymph Node Metastases in Endometrial Cancer

Approximately 27% to 40% of patients with proven paraaortic lymph node metastases are **long-term survivors** after pelvic and paraaortic RT

Potish et al. *Obstet Gynaecol.* 1985

Morrow et al. *Gynaecol Oncol.* 1991

Corn et al. *Int J Radiation Oncol Biol Phys.* 1992

Rose et al. *Int J Radiation Oncol Biol Phys.* 1992

Mariani et al. *Gynaecol Oncol.* 2000

Mariani 2005: **Adequate paraaortic lymphadenectomy AND paraaortic radiotherapy results in improved survival.**

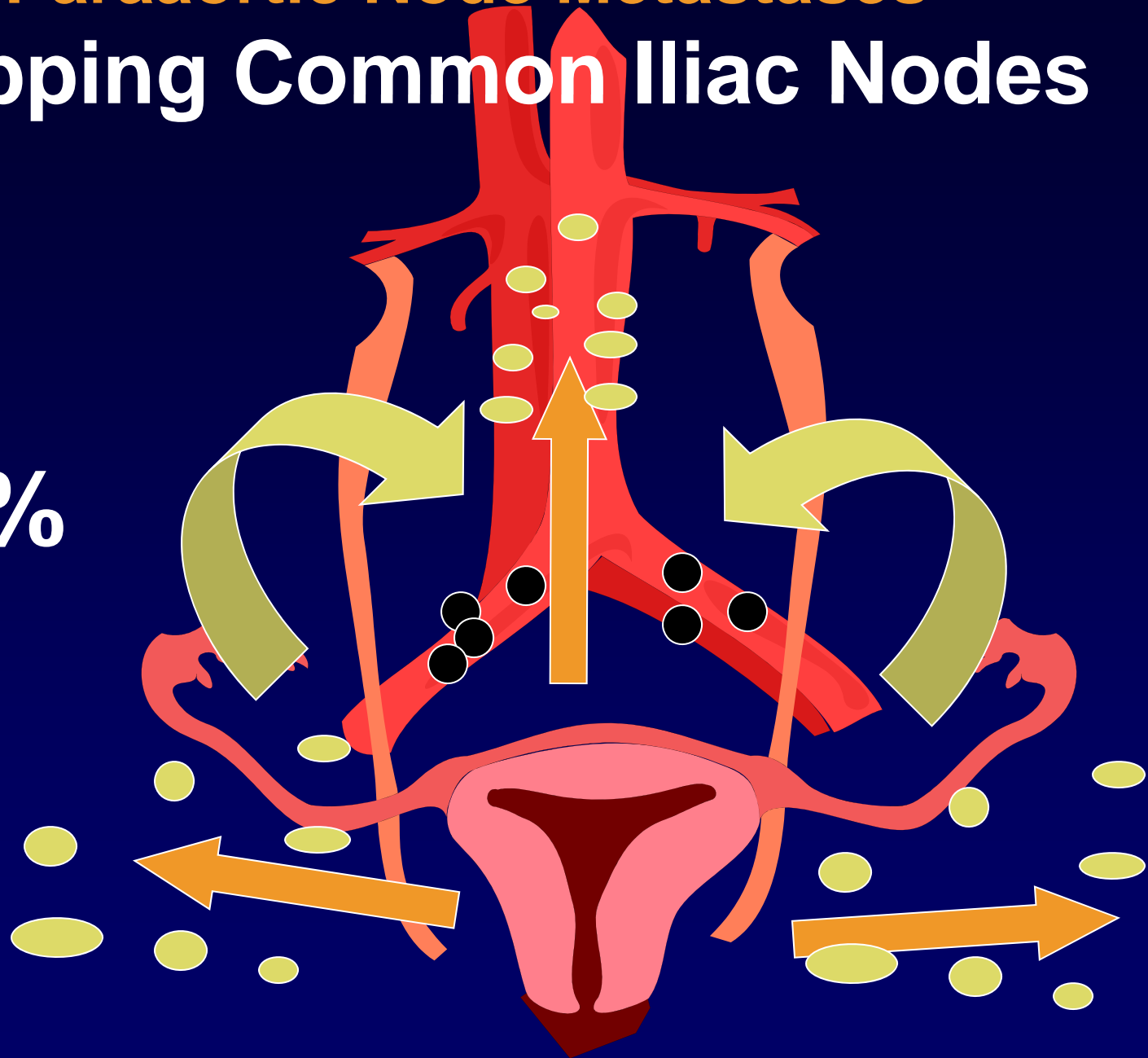
MAYO PROSPECTIVE SERIES Endometrioid Endometrial Cancer

- 32 (16%) at-risk pts Pos Nodes
 - 81% + pelvic nodes
 - 63% + paraaortic nodes
 - » 67% com Iliacs neg
 - » 73% Ipsi neg below IMA
 - » 69% pos above IMA

*Mayo prospective accrual 1/2004 to 12/2006

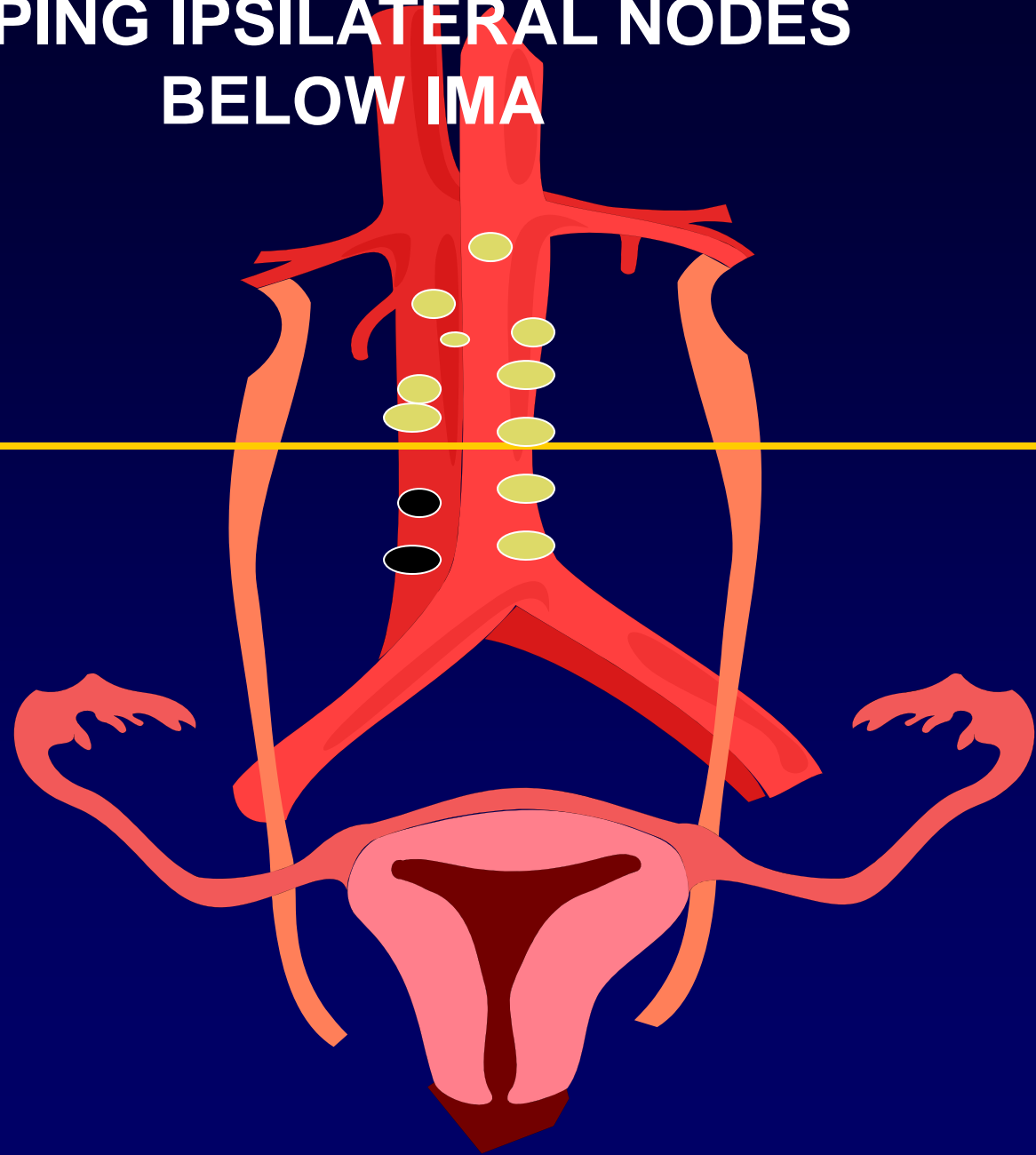
Paraaortic Node Metastases Skipping Common Iliac Nodes

71%



Paraaortic Node Metastases SKIPPING IPSILATERAL NODES BELOW IMA

IMA
60%

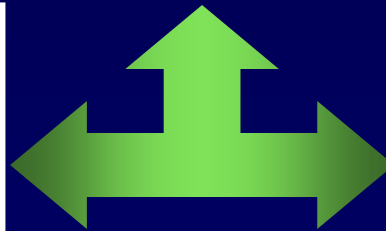


Italian Study (n = 514)

Clinical stage I endometrial carcinoma

HT + BSO
Peritoneal cytology

ARM A
PELVIC SYSTEMATIC
LYMPHADENECTOMY



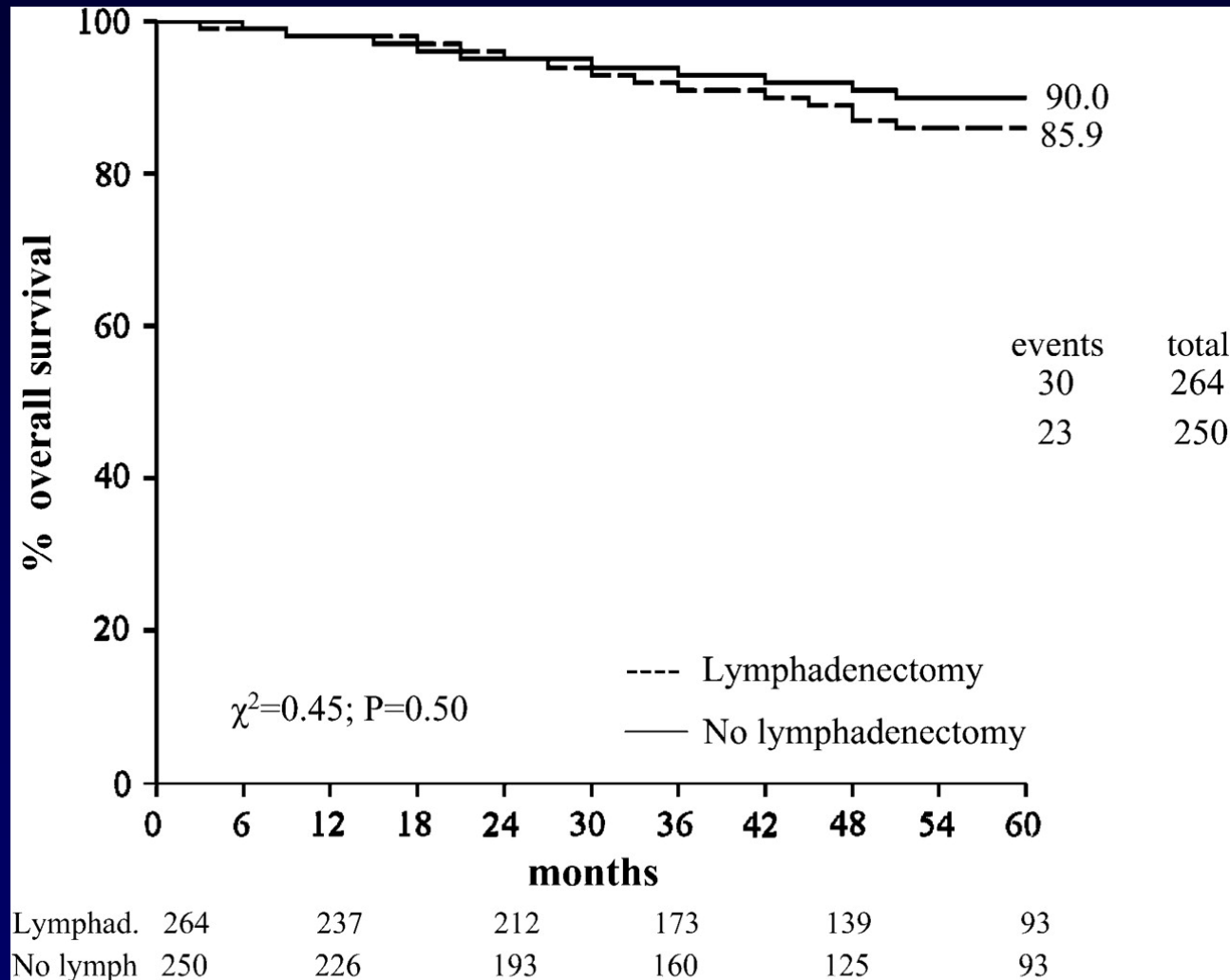
ARM B
BULKY NODES RESECTION
Or
NO LYMPHADENECTOMY

Italian Study (n = 514)

	Pelvic LNE (n = 264)	No Pelvic LNE (n = 250)
Stage (old FIGO)		
Ia	0%	3%
Ib	33%	43%
Ic	39%	32%
IIc	13%	3%
Grade		
I	7%	7%
II	57%	59%
III	35%	31%
Serous/clear cell	0.8%	0.8%
Median number of LN	26	0
Also paraaortic LN	26%	2%
Postop RT	22%	30%
Postop chemo	14%	10%

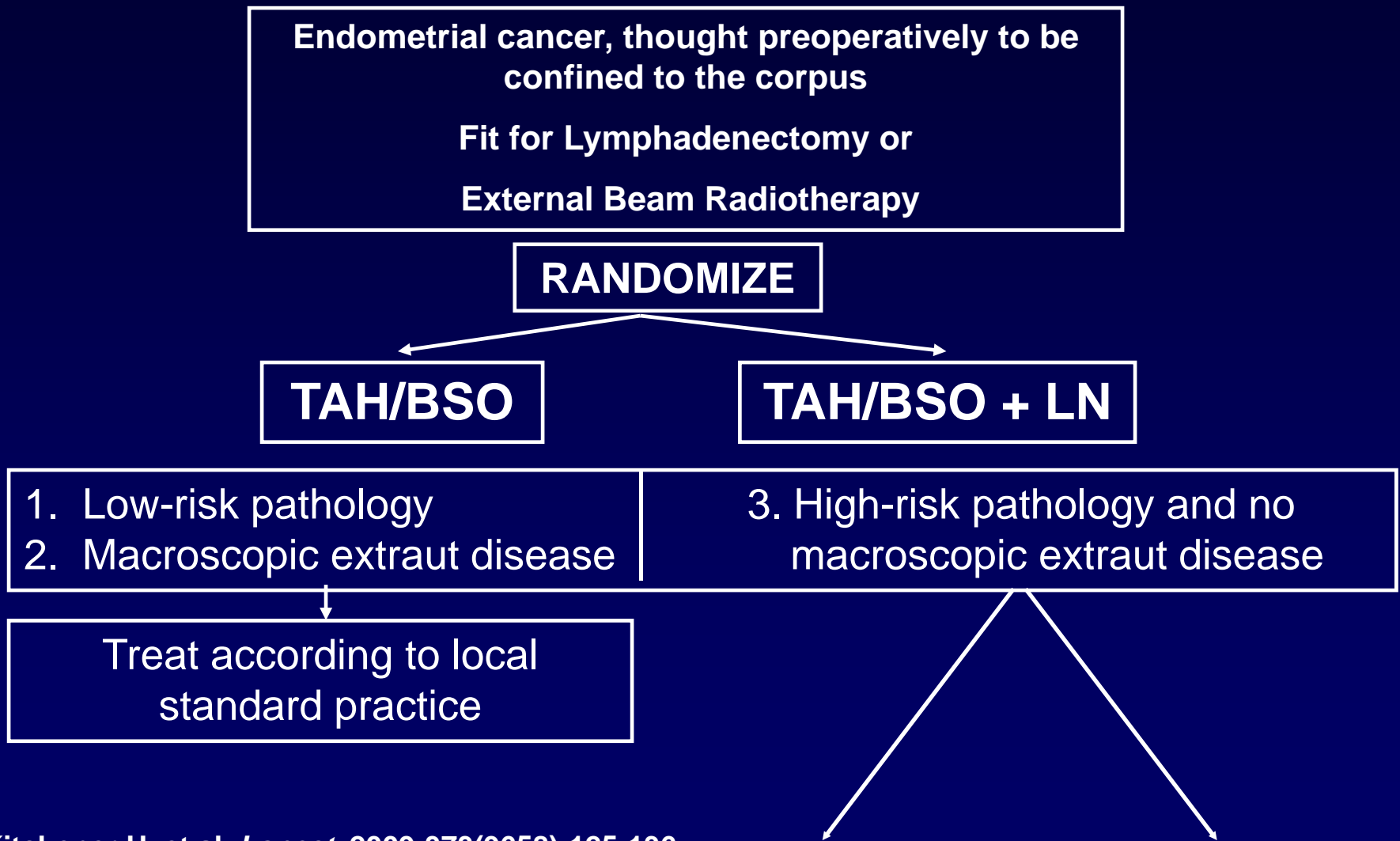
Benedetti-Panici PL, et al. *J Natl Cancer Inst.* 2008;100(23):1707-1716.

Overall Survival



Benedetti-Panici PL, et al. *J Natl Cancer Inst.* 2008;100(23):1707-1716.

ASTECC Trial Design: Surgery (n = 1408)



ASTECC Trial Design: Surgery (n = 1408)

Trial was designed to look at an
**increase in 5-year overall
survival of 10%** from 80% to 90%
with a significance level of 5%
and a power of 90%

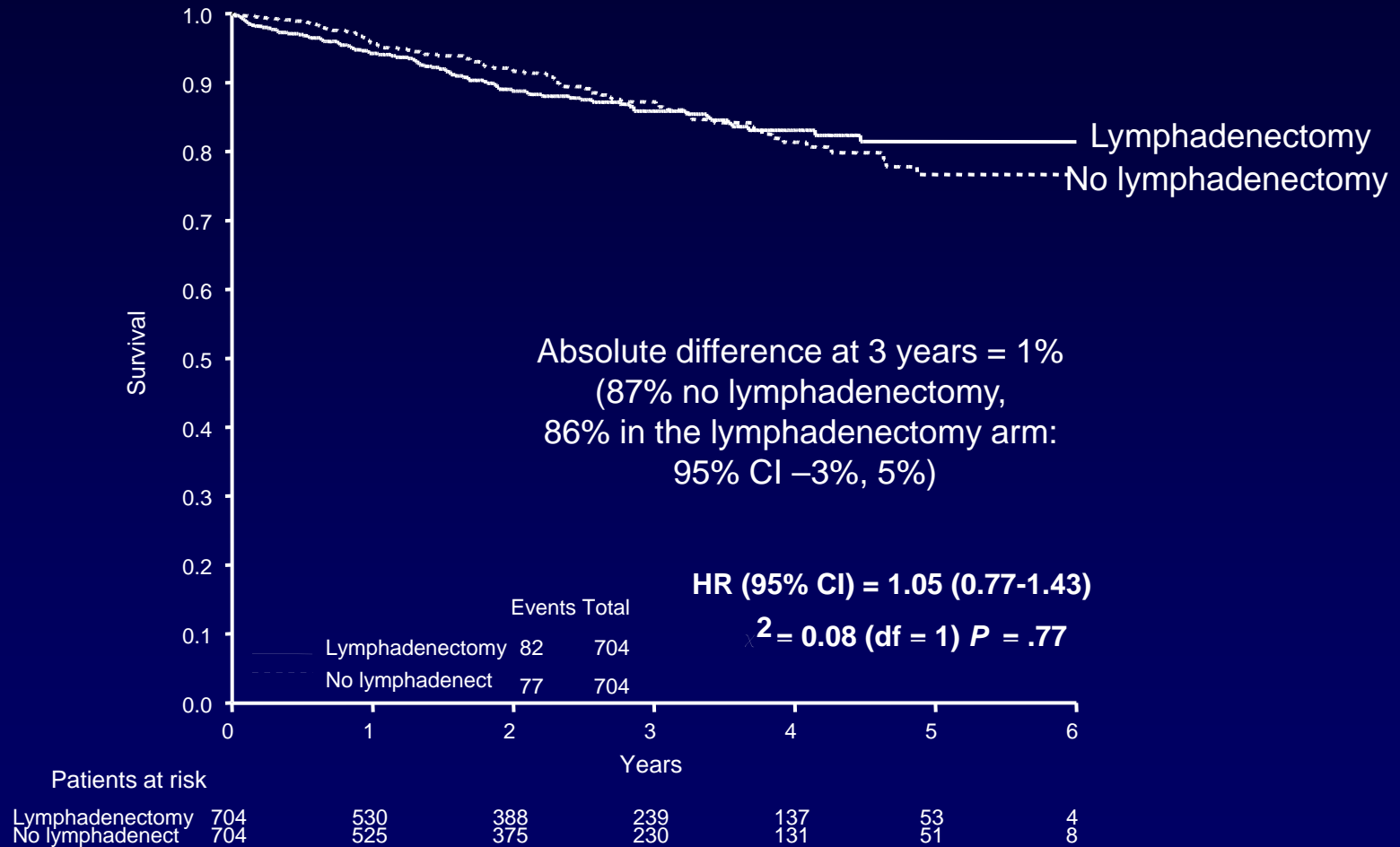
ASTECC Trial: Surgery

	TAH/BSO (n = 704)	TAH/BSO + LN (n = 704)	Total
Age			
Median (range)	63 (36-89)	63 (34-93)	63 (34-93)
Technique used:			
Laparotomy	94%	94%	94%
Laparoscopic	6%	6%	6%
FIGO stage (excluding LN pos pat)			
IA	13%	13%	13%
IB	48%	42%	45%
IC	21%	27%	24%
IIA	5%	4%	5%
IIB	8%	8%	8%
III/IV	5%	6%	6%

ASTECS Surgery

	TAH/BSO (n = 704)	TAH/BSO + LN (n = 704)	Total
Differentiation or Grade			
Well or Grade 1	34%	34%	34%
Moderate or Grade 2	48%	46%	47%
Poor or Grade 3	18%	20%	19%
Lymphovascular Permeation			
	21%	23%	22%
Number nodes			
1-4		10%	
5-9		23%	
10-14		25%	
>14		41%	
Nodal Involvement			
		9%	

Overall Survival—ASTECC Trial

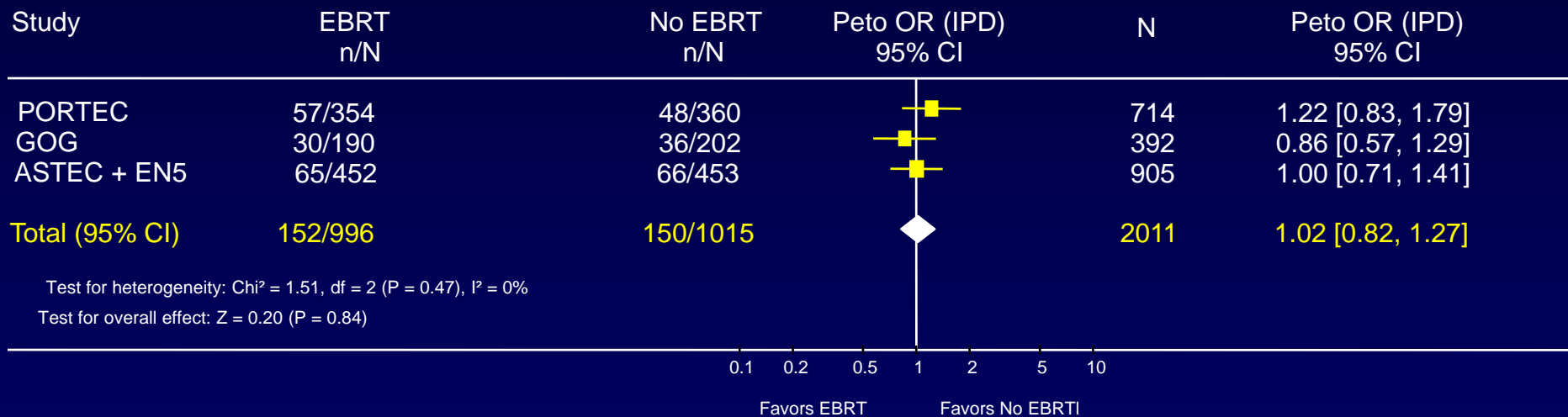


Kitchener H, et al. *Lancet*. 2009;373(9658):125-136.

Endometrial Carcinoma

Role of Adjuvant Radiotherapy

Endometrial Carcinoma and Adjuvant External Radiotherapy: Meta-Analysis



0.2% difference in 5-year OS (87.8% in EBRT and 88% in no EBRT)
 95% CI of difference = -2.0% to 3.0%

Overall survival – Blake P, et al. *Lancet*. 2009;373(9658):137-146.

Design PORTEC-2

Endometrial carcinoma (High Intermediate Risk):

- *Age ≥ 60 years and IC grade 1-2, or IB grade 3*
- *Stage 2A (except grade 3 $>1/2$)*
- *Surgery: TAH-BSO, no lymphadenectomy*

R └── Pelvic external beam radiotherapy
└── Vaginal brachytherapy

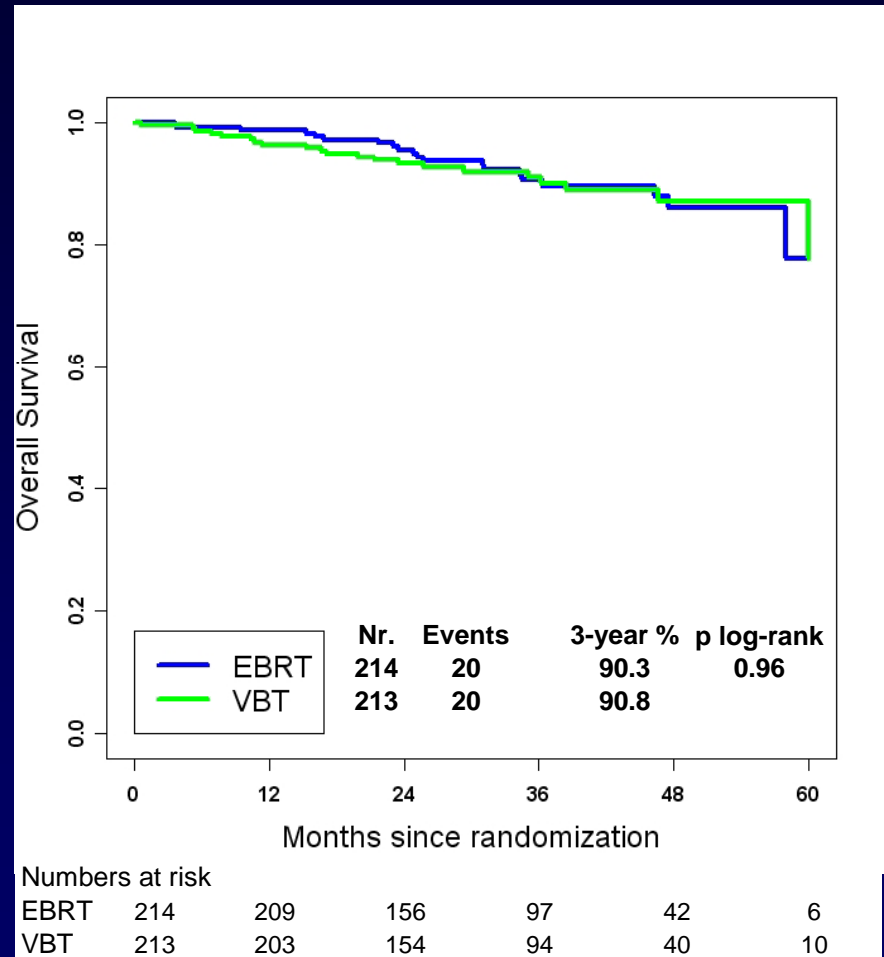
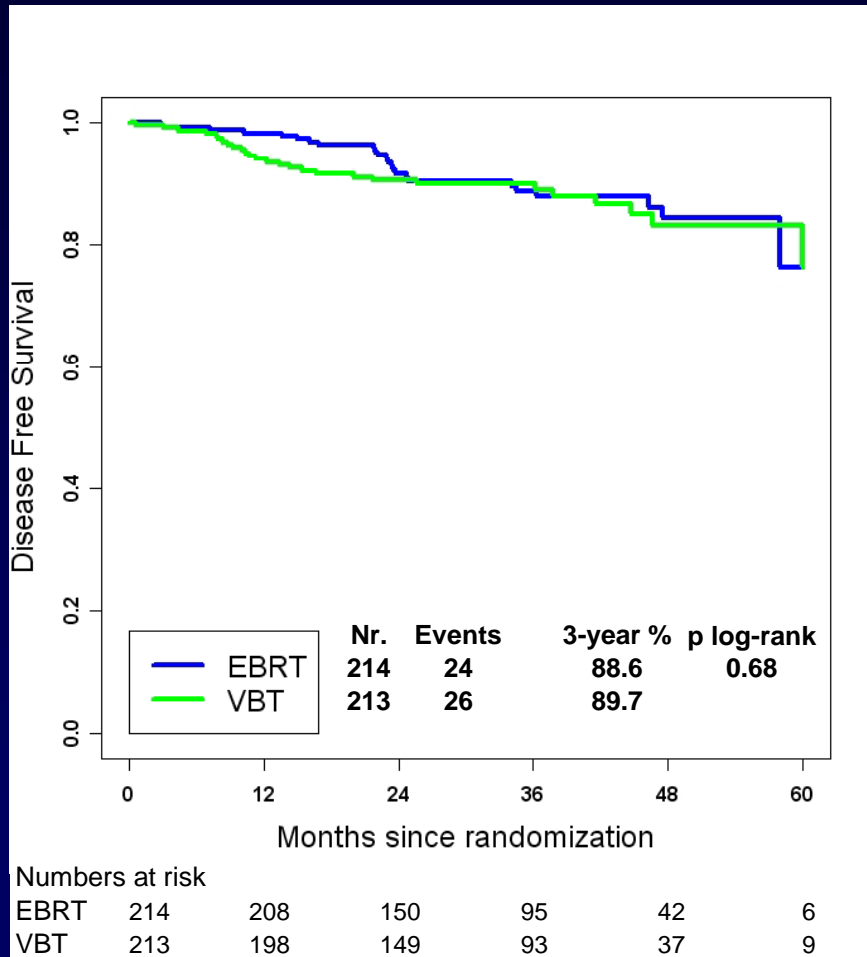
Primary endpoint: Vaginal relapse rate

Secondary : Quality of life, survival

Nout RA, et al. *J Clin Oncol.* 2008;26(May 20 Suppl): Abstract LBA5503.

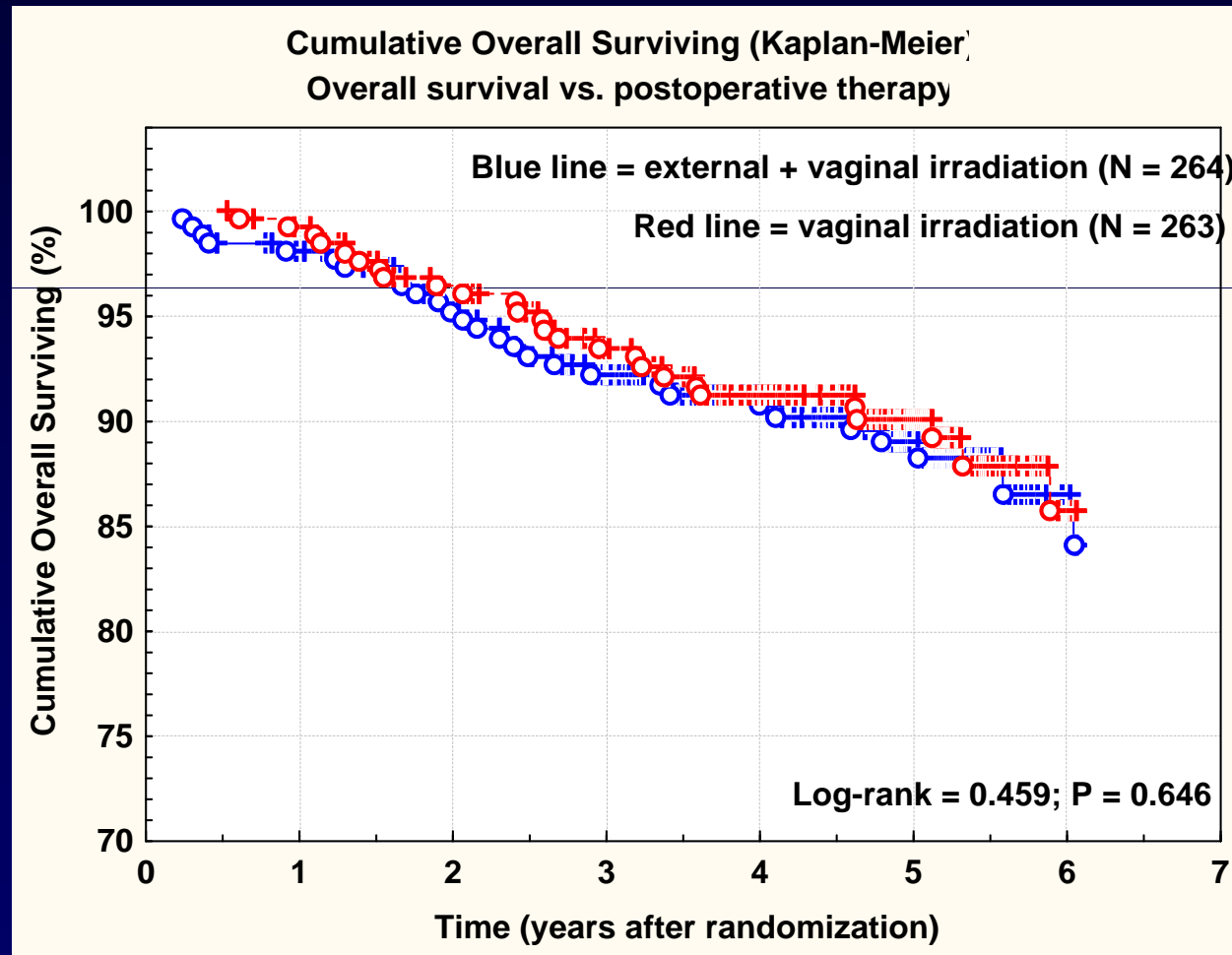


Disease-Free Survival and Overall Survival



Nout RA, et al. *J Clin Oncol*. 2008;26(May 20 Suppl): Abstract LBA5503.

Overall Survival—Medium Risk Swedish Study



Sorbe B, et al. *Int J Gynecol Cancer*. 2009;19(5):873-878.

Endometrium G1/2 Stage Ia (FIGO 2009) No RT: Vaginal Recurrences

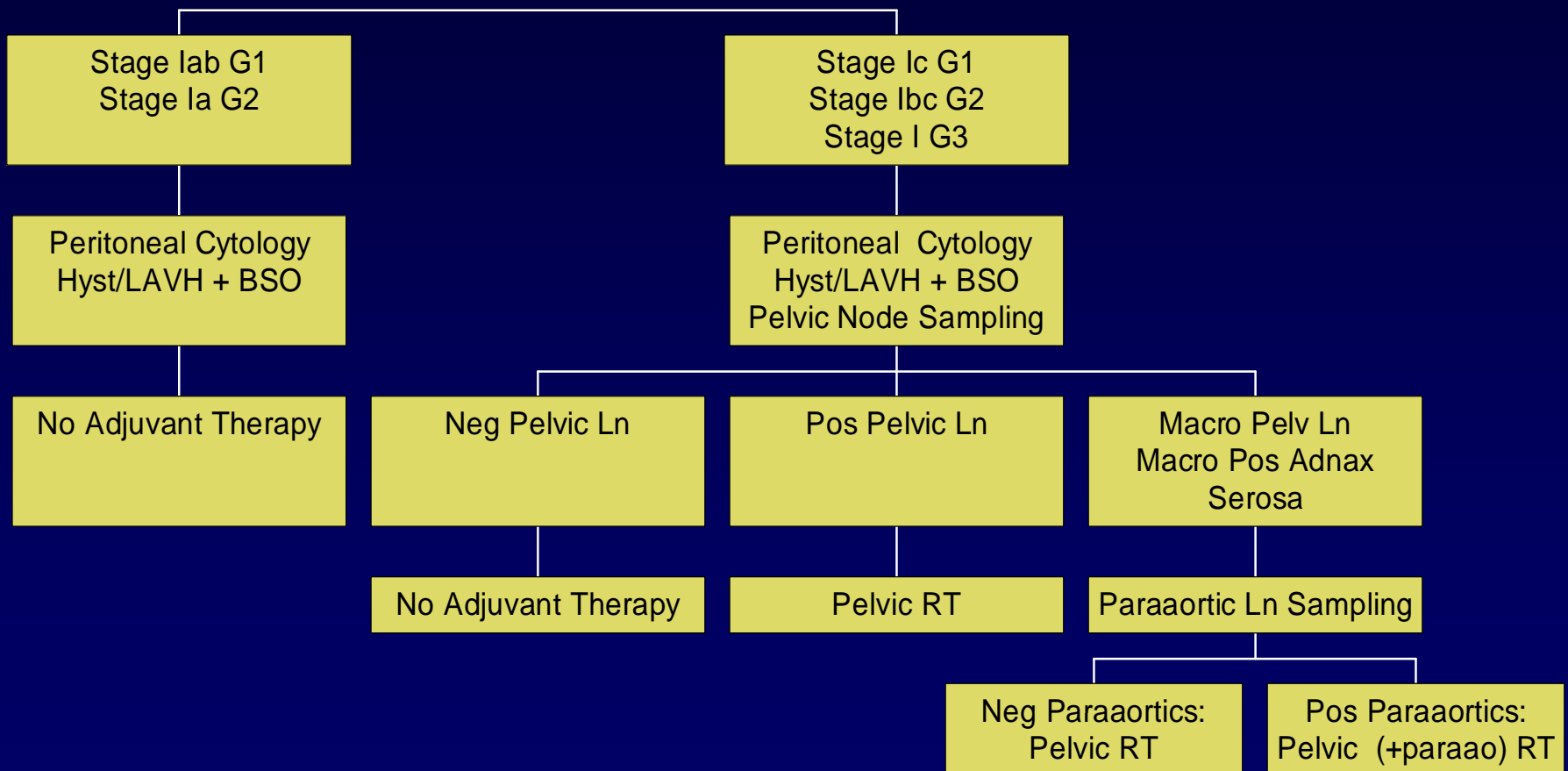
	n	Median FU	Isolated Vaginal Relapse, %	Died CA, %
Lim 1999	315	45	3	0
Carey 1995	227	54	1	0.9
Poulsen 1996	641	68-92	3	0.3
Leijon 1997	248	42	2	0.4
Larson 1998	102	40-46	1	0
Mariani 2000	263	88	2	0.4
Hogberg 2004	283	60	4	0.7
TOTAL	2079		3%	0.4%

Radiotherapy of Vaginal Relapse in Patients Not Treated Primarily with Adjuvant Radiotherapy

- *Mandall 1985: 95% (n =20) (vagina)*
- *Curran 1988: 100% (n = 15) (vagina)*
- *Ackerman 1996: 79% (n = 32), vagina*
- *Poulsen 1997: 88% (n = 17) (vagina, FU 61 months, low risk)*
- *Roberts 1998: 61% (n = 16)*
- *Nag 2002: 77% 8-yr disease specific survival (vagina, n = 13)*
- *Creutzberg 2003: 65% 5y OS in vaginal relapses (n = 35, intermediate risk)*
- *Jingran 2003: 86% 5-yr local control in vaginal relapses (n = 52)*
- *Hogberg 2004: 83% survival 39 months after relapse (n =12)*
- *Leuven 2006: 100% local control in 9 vaginal relapses treated at relapse with RT*
- *Huh WK 2007: 81% local control and 75% 5-yr OS and in 69 relapses (mean FU 63 months)*
- ...

**CURE RATE IS HIGH IN RELAPSES
CONFINED TO THE VAGINA,
especially in low-risk disease.**

Endometrioid Endometrial Carcinoma Clinical Stage I—Old FIGO Classification Leuven Algorithm 1995-2007



Endometrial Carcinoma (Clinical Stage I) Univ Hospitals Leuven Series: n = 208

- 5-year disease-specific survival **94%**
- All patients with only **vaginal** relapse (n = 9) were cured locally with salvage radiotherapy
- The **pelvic relapse** rate in the high risk group with negative nodes was very low, as only one patient recurred in the pelvis only

Adjuvant Therapy of Endometrioid Endometrial Carcinoma: Conclusions (1)

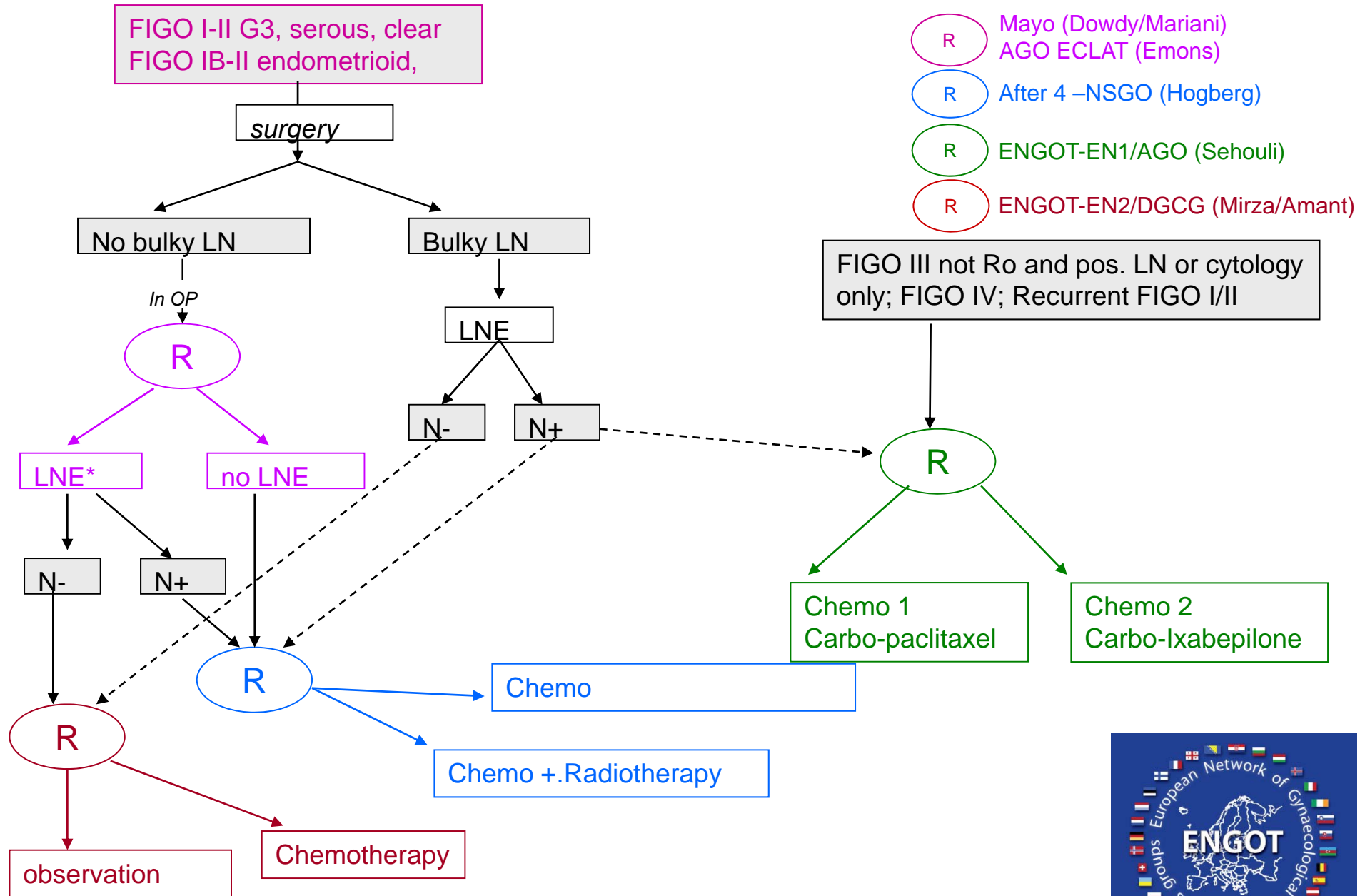
1. The combination of radiotherapy and lymphadenectomy results in the highest number of **complications**
2. There is no proven overall survival benefit of **adjuvant radiotherapy nor lymphadenectomy**. However, all randomized trials are **too small** to detect a survival difference of about **2.5% to 3.5%**, ie, the incidence of isolated lymphatic relapses. Hence, ...

Adjuvant Therapy of Endometrioid Endometrial Carcinoma: Conclusions (2)

3. Hence, we will have to continue **TAILORING** our therapy. The rationale for lymphadenectomy is mainly to **better select patients** for further adjuvant therapy
4. Based on subgroup analyses, adjuvant **chemotherapy** seems to improve survival in patients with medium-risk or high-risk endometrial endometrioid carcinoma, but this needs to be confirmed in prospective randomized studies

Where Are We Going?

ENGOT - NESTEC: Network Study in Endometrial Cancer in cooperation with Mayo



*LNE = Pelvic + para-aortic; Definitions according to LION or Definitions according to Mayo (No.)



Endometrial Carcinoma Clinical Stage I—FIGO 2009 Leuven Algorithm 2009

