



8th PMH Conference on New Developments in Cancer Management 50th PMH Anniversary

**Controversies in “Early” Ca
Endometrium
Role of Radiation: EBRT/ BT or None ?**

G.Thomas MD



Sunnybrook

ODETTE CANCER CENTRE

A Cancer Care Ontario Partner

GT/08

“Early” Ca Endometrium

Past:

“Standard Therapy”

- Standard SX: BSOH (without nodal staging)
- Plus RT: EBRT/Brachy ,both. Pre or post op

Present:

Risk Based management :

- SX: BSOH +/- Lymphnode dissection (pelvic/PA)
- RT: EBRT/BT/none/chemo, where failure risk and pattern suggest indications/ benefit

Endometrial Carcinoma

Most patients have a favorable prognosis

80% stage I

Overall survival 80-85%, CSS 90-95%

Why Change Approach?

Risk based treatment

Prevent over treatment of low-risk patients

Improve outcome for high-risk patients

Improve Therapeutic Ratio

Adjuvant Treatment in Endometrial Cancer

Potential Utility depends on:

1. Risk of failure after Sx
2. Predicted sites of failure (with and without surgical staging)
3. Efficacy of interventions (currently only radiation – a loco/regional Tx and conventional chemotherapy- mainly systemic Tx)

**GOG #33, Ca Endometrium, A
Clinical/Pathological Staging Study
(Morrow et al Gyn Onc 40.'99)**

Risk and Site of Nodal Involvement: n= 621

Overall Risk Clinical Stage I and Occult II: 11%

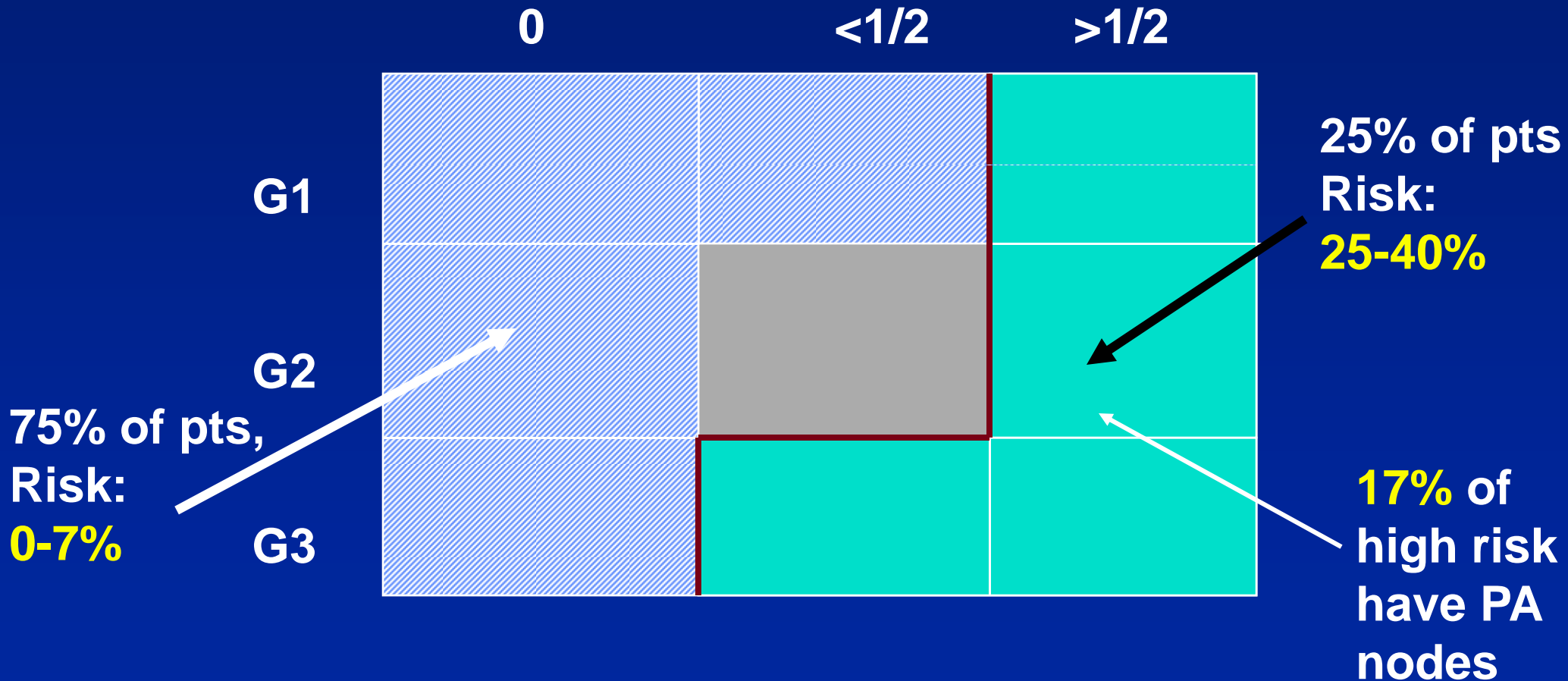
Pelvic only	36/70	Any pelvic	59/70
Pelvic and para-aortic	22/70		
Para-aortic only	12/70	Any PA	34/70

90% have no nodes, staging Sx unnecessary in 90%

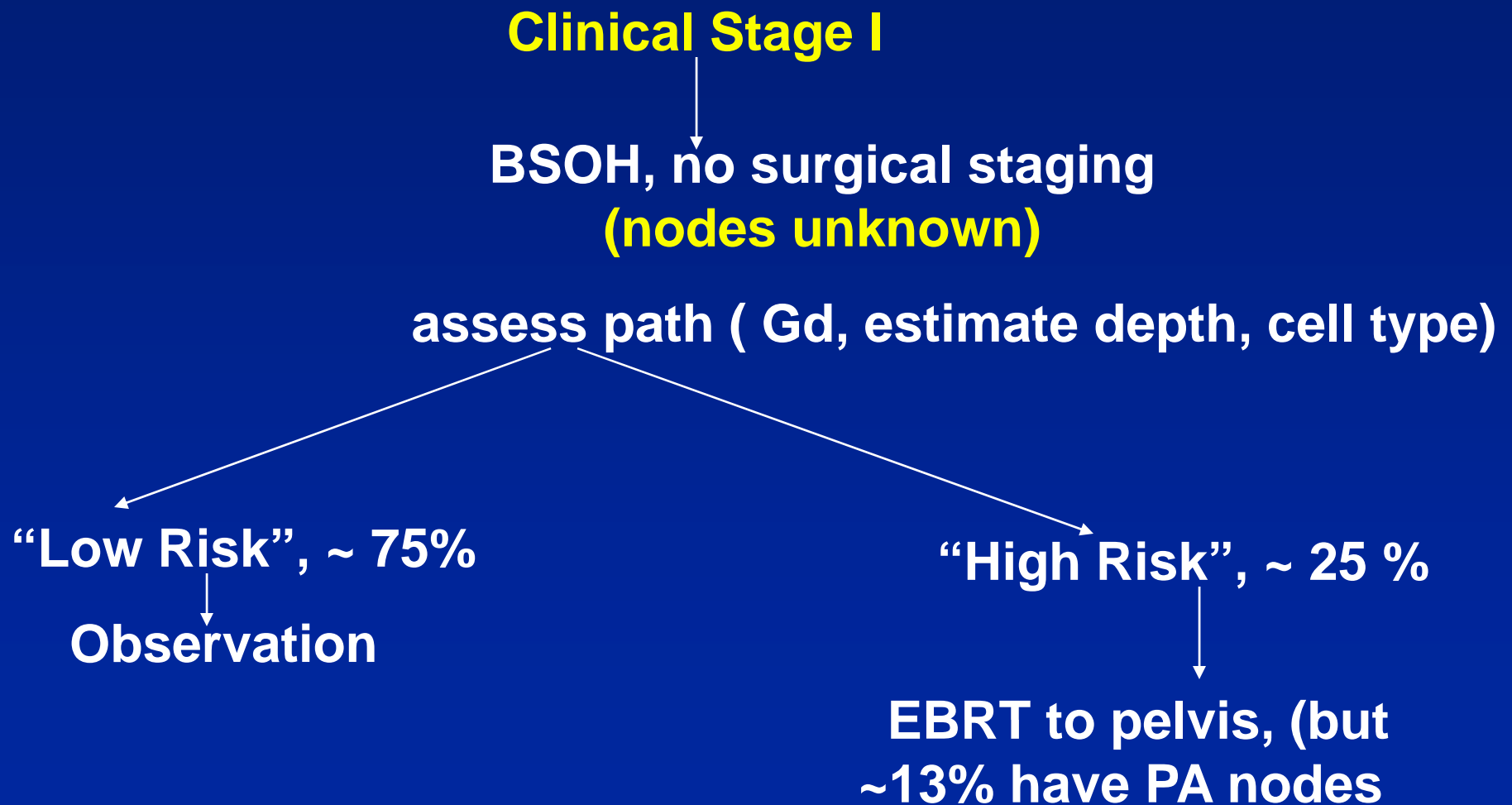
Orr et al. Am J Obstet Gynecol 1997:incidence : 10.8%

Cragun et al. JCO 2005: 5% pelvic, 3% PA node +

Ca Endometrium :GOG #33 "Risk Groups" in Clinical Stage I



Ca Endometrium , Treatment Algorithms



Ca Endometrium *Clinical* Stage I: Pelvic Recurrences without RT in Low Risk

First Author	n	Risk Factors	% Recurrent
Podczaski	152	all	6.5
Elliot	511	<1/3,G1-2	3.0
Carey	227	IB,G1-2	4.0
Larson	102	IB,G1-2	3.0

No.who had **pelvic nodes positive: 5%**

No. who **recur in pelvis alone: 3/5**

No. **salvaged at recurrence :2/3**

Negligible gains from knowing nodal status.

Neither nodal dissection nor adjuvant RT are justified in “low risk” disease.

Consequences of Routine Adjuvant Pelvic RT in “High Risk Early” EC (Nodal Status Unknown)

25 “high risk” patients:

60-70% **16/100** “early” patients

no node metastases;

no need for pelvic RT ??

19-34% **5-6** patients

only pelvic node metastases;

may have **S benefit from pelvic RT**

14-23% **5** patients

para-aortic node metastases/other;

no survival benefit from pelvic RT

Randomized Trials: Adjuvant RT vs None

Trial	No. patients eligibility	Surgery	Randomization	Locoregional recurrence	Survival	Severe complications
Norwegian[5] 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[2] 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[1] 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)
ASTECC	1208		†NAT vs EBRT	7% vs 4%	89% vs 89%	

Adjuvant RT ↓ local recurrence but no ↑ Survival.

Sx vs Sx + EBRT in *Clinical Stage I* Ca Endometrium (PORTEC 1)

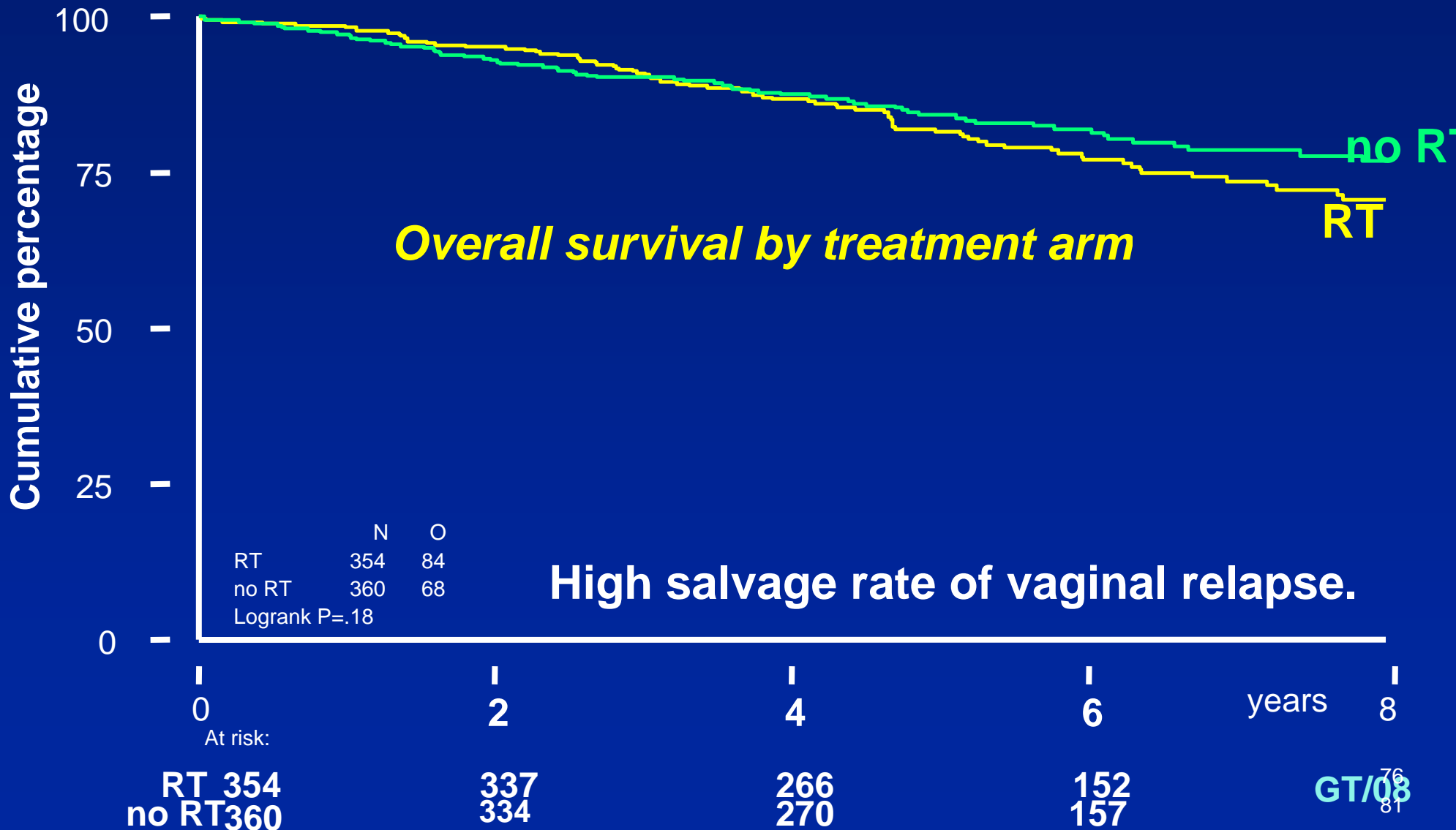
Creutzberg et al, Lancet 35, '00, Gyn Onc '03; Scholten IJORBP '05

PORTEC I: n=714, (only 10% Gd3, 40% <50% depth

	<u>Sx</u>	<u>Sx+EBRT</u>	
<i>n</i>	361	354	
Recurred % (vag)	14 (10)	4 (2)	p<0.001
Deaths	36 %	28 %	
Endometrial ca (%)	10	8	
Second Cancer	5	11	RR 1.57 p=0.0004
Intercurrent (%)	15	15	
5/10 yr Survival	85/66%	86/73%	p= 0.15
Serious Complications	<1%	3%	

Sx vs Sx + RT in Stage I Ca Endometrium

(Creutzberg et al, Lancet 355'00. Update.Pers.Comm.2003)



**Sx vs Sx + RT in “Intermediate Risk” (IB,IC,II)
Node Negative Ca Endometrium (GOG #99)
(Keys et al.Gyn Onc, 2004)**

	Observat'n	EBRT(50.4Gy)	
<i>n</i>	202	190	
Recurrence (#)	12% (31)	3% (13)	
Recur ,high risk group[†]	27%	13% [‡]	Rel HR death with RT: 0.73
LR (vag/total)	9 % (14/18)	2% (3/3)	
4yr S	86%	92%	ns
Deaths			
Tx	0	2/30	
Disease	17/36	13/30	
Other	19/36	15/30 (44%)	

GOG High Risk Group, Node Negative

Keys et al. Gyn Oncol. 2004)

Risk Factors

Age

Grade 2 or 3

Outer third invasion

LVI

High Risk Definition

➤ 70 and 1 risk factor

50-70 and 2 risk factors

Any age and 3 risk factors

Similar definition of HR from PORTEC trial:

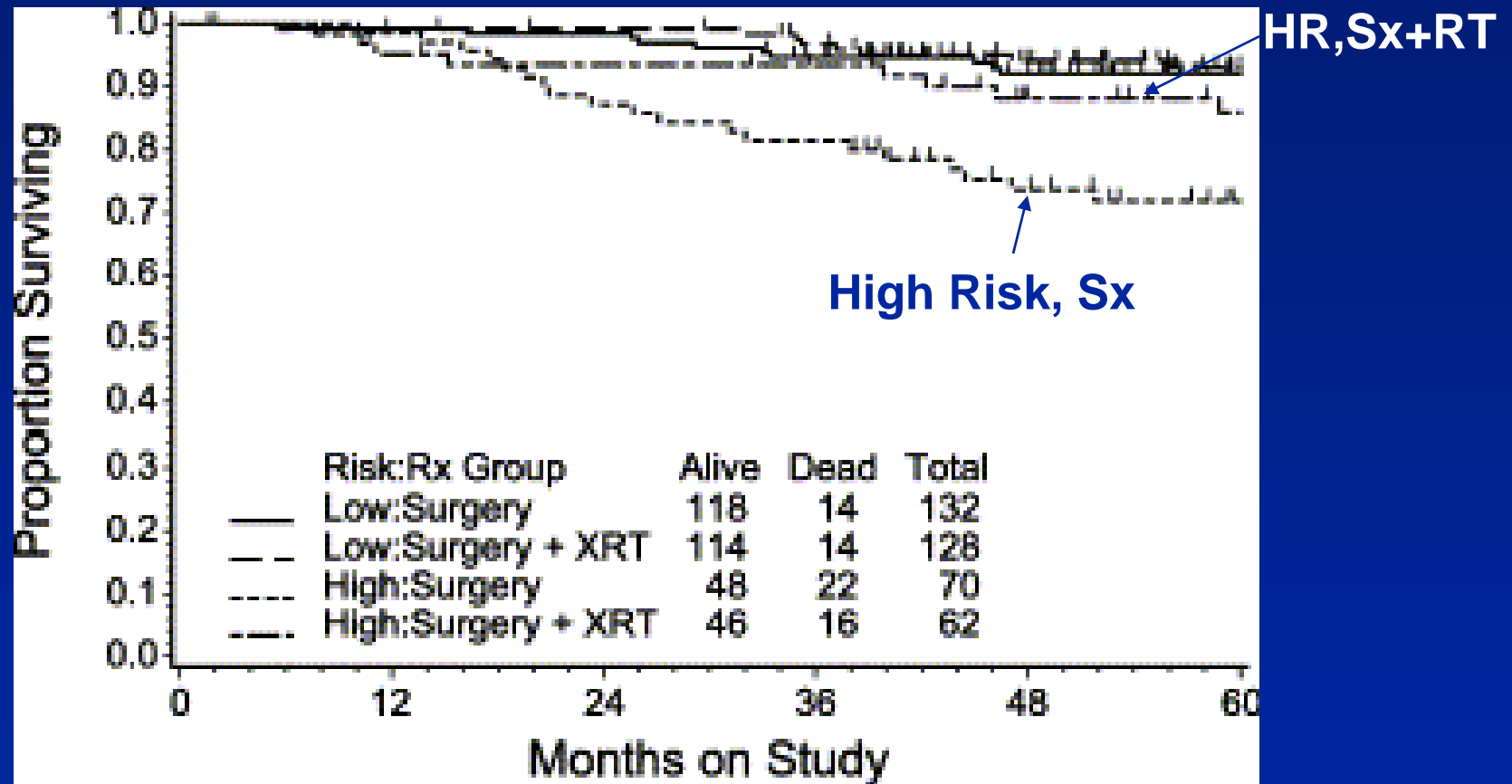
Gd 3, >50% depth, age \geq 60yrs:

\geq 2 factors, 20% local/regional recurrence

RT vs NAT in Node Negative Endometrial Ca

Keys et al Gyn Onc 92, 2004

Survival by Treatment and Risk group:



GOG Study: **EBRT 45-50 gy (BT allowed for St II) vs BT + Carbo/Taxol X3**

ASTECC

Kitchener et al. ESGO 2005/ASCO 2006.

Surgery:	BSOH	BSOH + LND
n	704	704
Alive %	89	88

High risk path (IC/IIA Gd1.2, all Gd 3, UPSC no macro. resid disease)

RANDOMIZE
ASTECC+EN5

No external beam RT
453, 51% Brachy

External beam RT
452, 52% Brachy

HDR VBT:Phase III Comparison of Two Dose Schemes

Sorbe et al. IJORBP 2005

Vag cylinder 2-3cm diam

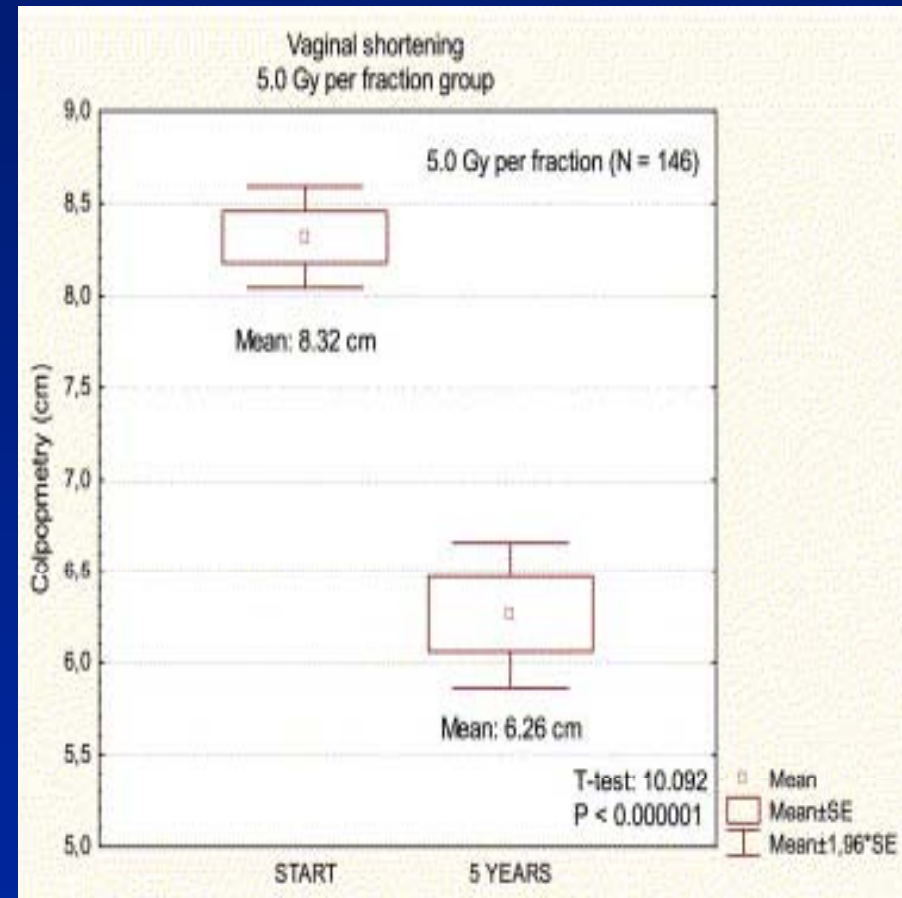
2.5 vs 5Gy /fraction

6 fractions/8dys

(15Gy vs 30Gy at 0.5cm depth)

	15Gy	30Gy
#	144	146
†Vag Recur	.7%(1)	.7%(1)
L-R	.7%	.7%
CSS	99%	95%

† Power: detect > 10% difference.
60% Ia, 30% Ib. Gd 1/2



No shortening in 15 Gy group.

Clinical Stage I, G3 Results

Creutzberg JCO 2004

1 >1/2 2 <1/2 2 >1/2 3 <1/2 3 >1/2

actuarial 5-year percentages

	1 >1/2	2 <1/2	2 >1/2	3 <1/2	3 >1/2
<i>Number</i>	72	101	137	35	99
<i>Death EC</i>	6%	3%	6%	20%	30%
<i>Locoreg</i>	1%	2%	2%	3%	12%
<i>Metast.</i>	4%	3%	7%	17%	23%
<i>Alive</i>	83%	86%	85%	74%	58%

High Risk and Advanced Stage Ca Endometrium

Decreased survival mainly due to distant metastases

Future:

Role of adjuvant chemotherapy

Adjuvant chemotherapy versus RT?

Combined treatment?

Role of targeted therapies

Quality of life issues

Ca Endometrium

Evidence that Radiotherapy is still an effective modality:

1. **Curative** in a proportion of **inoperable** patients
2. Significantly **reduces pelvic failure** in “high risk” Stage I disease
3. **Curative** in some patients with **proven PA nodal involvement**
4. **Curative** in some patients with isolated **pelvic recurrence** following BSOH

Is there still a role for RT in high risk and advanced disease?

Portec-3: Creutzberg et al.

Intergroup trial (includes NCIC , planned accrual 500 pts
power >0.8 for 5-yr OS difference 12.5% (HR 0.68

Concurrent chemoradiation: Cisplatin 50 mg/m² day 1 & 21
("sensitizing" effect during RT + Chemo starts immediately)

PLUS

Adjuvant Chemotherapy: Carboplatin AUC 5 and paclitaxel 175
mg/m² 4x # 3 wk

(phase II trials: 70% RR; ongoing GOG trial TAP vs.Carbo/taxol)

Adjuvant Treatments in Endometrial Cancer

Clinical Stage I

Risk based therapy: Prevent over treatment, preserve QoL

Low risk: **TAH-BSO alone**

† “Intermediate risk”: **vaginal brachytherapy or observe?**

Higher intermediate risk: **? EBRT**

High Risk (Gd 3,outer 1/2), serous/clear cell and Stage III:

-challenge for research - **roles of pelvic RT and chemotherapy, targeted therapy, strategies to ↓ morbidity**

† as defined by those actually included in PORTEC 2