

Chemotherapy for
Early Stage High-Risk
Endometrial Cancer:
Opposed

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The Emperor's New Clothing



The Emperor's New Chemotherapy



Outline

- Staging of Endometrial Cancer
- Risk Factors for Recurrence
- Results of Randomized Studies
- Unanswered Questions
- Summary and Conclusions

FIGO Staging of Endometrial Cancer

Stage	Feature
IA	Absence of myometrial invasion
IB	Less than 50% myometrial invasion
IC	At least 50% myometrial invasion
IIA	Extension to the cervical glands only
IIB	Extension to the cervical stroma
IIIA	Malignant peritoneal washings, adnexal involvement, or uterine serosal involvement
IIIB	Extension to the vagina
IIIC	Pelvic or para-aortic lymphatic dissemination
IVA	Extension to bowel or bladder serosa
IVB	Distant metastases, including peritoneal or inguinal lymph nodes

Risk Factors For Recurrence

■ Uterine

- Histologic grade
- Depth of myometrial invasion
- Vascular space invasion
- Cervical extension

■ Extrauterine

- Pelvic node metastases
- Aortic node metastases
- Adnexal metastases
- Positive peritoneal cytology
- Gross tumour breakthrough of the uterine serosa

Histologic Grade and Depth of Invasion

TABLE 2. Histologic Grade and Depth of Invasion

Depth	Grade			Total
	G1	G2	G3	
Endometrium only	44 (24%)	31 (11%)	11 (7%)	86 (14%)
Superficial	96 (53%)	131 (45%)	54 (35%)	281 (45%)
Middle	22 (12%)	69 (24%)	24 (16%)	115 (19%)
Deep	18 (10%)	57 (20%)	64 (42%)	139 (22%)
Total	180 (100%)	288 (100%)	153 (100%)	621 (100%)

Grade, Depth of Invasion and Node Metastasis

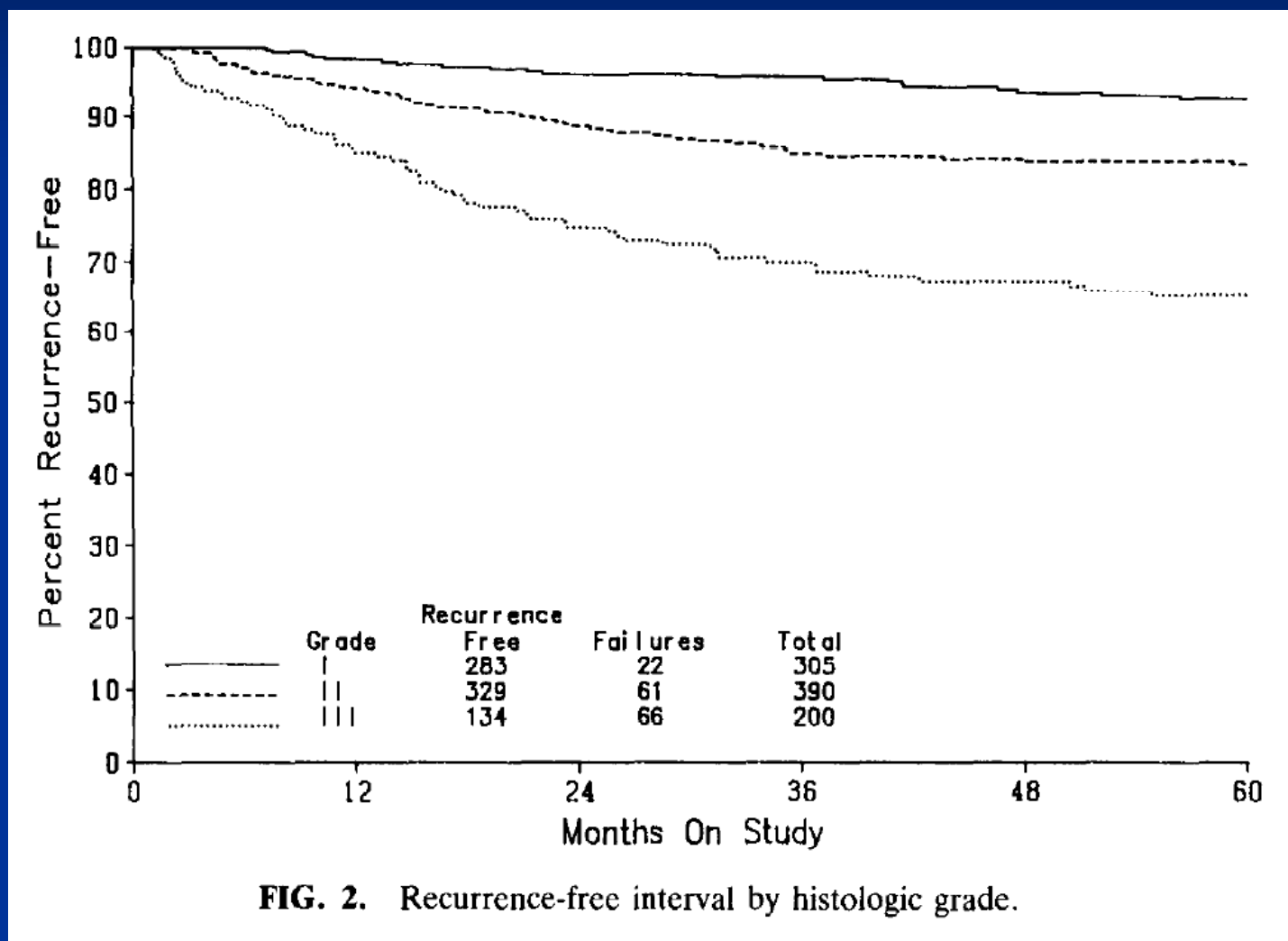
TABLE 5. Grade, Depth of Invasion and Pelvic Node Metastasis

Depth of invasion	Grade		
	G1	G2	G3
	(N = 180)	(N = 288)	(N = 153)
Endometrium only (N = 86)	0 (0%)	1 (3%)	0 (0%)
Inner (N = 281)	3 (3%)	7 (5%)	5 (9%)
Middle (N = 115)	0 (0%)	6 (9%)	1 (4%)
Deep (N = 139)	2 (11%)	11 (19%)	22 (34%)

TABLE 6. Grade, Depth of Invasion, and Aortic Node Metastasis

Depth of invasion	Grade		
	G1	G2	G3
	(N = 180)	(N = 288)	(N = 153)
Endometrium only (N = 86)	0 (0%)	1 (3%)	0 (0%)
Inner (N = 281)	1 (1%)	5 (4%)	2 (4%)
Middle (N = 115)	1 (5%)	0 (0%)	0 (0%)
Deep (N = 139)	1 (6%)	8 (14%)	15 (23%)

Recurrence-Free Interval and Grade



Recurrence-Free Interval and Depth of Invasion

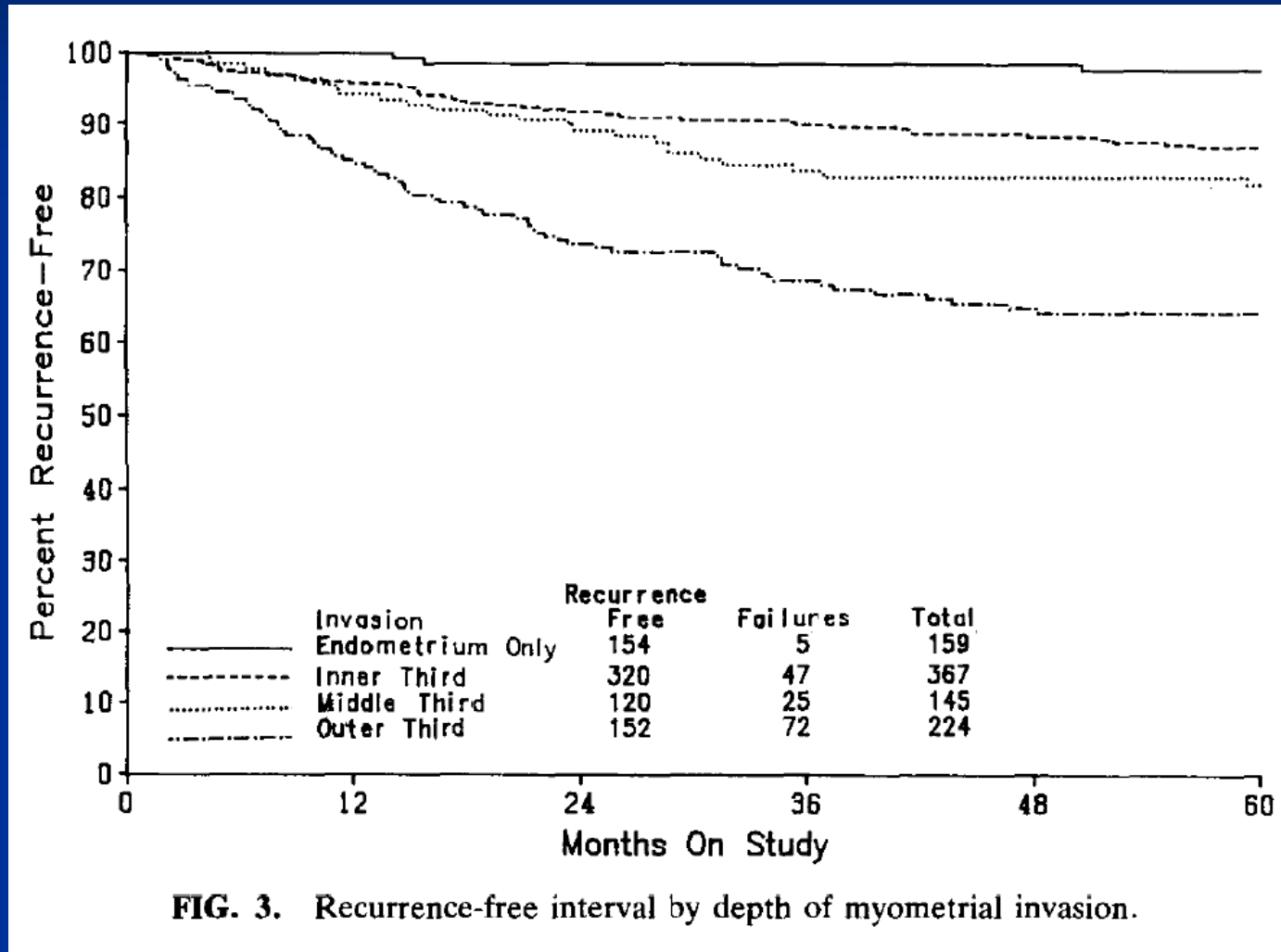


FIG. 3. Recurrence-free interval by depth of myometrial invasion.

Risk of Recurrence Within Stage I Endometrial Cancer

	Grade 1	Grade 2	Grade 3
Stage IA (limited to endometrium)			
Stage IB (<50% myometrial invasion)			
Stage IC (>50% myometrial invasion)			
	Low-risk, risk of recurrence		
	Intermediate-risk		
	High-risk, risk of recurrence		

Results of 4 Randomized Studies Reported to Date

- Radiotherapy \pm chemotherapy (2)
- Radiotherapy versus chemotherapy (2)

Morrow et al (GOG-34)

GYNECOLOGIC ONCOLOGY 36, 166-171 (1990)

Doxorubicin as an Adjuvant following Surgery and Radiation Therapy in Patients with High-Risk Endometrial Carcinoma, Stage I and Occult Stage II: A Gynecologic Oncology Group Study*

C. PAUL MORROW, M.D.,¹ BRIAN N. BUNDY, PH.D.,² HOWARD D. HOMESLEY, M.D.,³ WILLIAM T. CREASMAN, M.D.,⁴ NED B. HORNBACK, M.D.,⁵ ROBERT KURMAN, M.D.,⁶ AND J. TATE THIGPEN, M.D.⁷

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Morrow et al (GOG-34)

FIGO clinical Stage I or II (occult):

- greater than 50% myometrial invasion
- pelvic or aortic node metastasis
- cervical involvement
- adnexal involvement



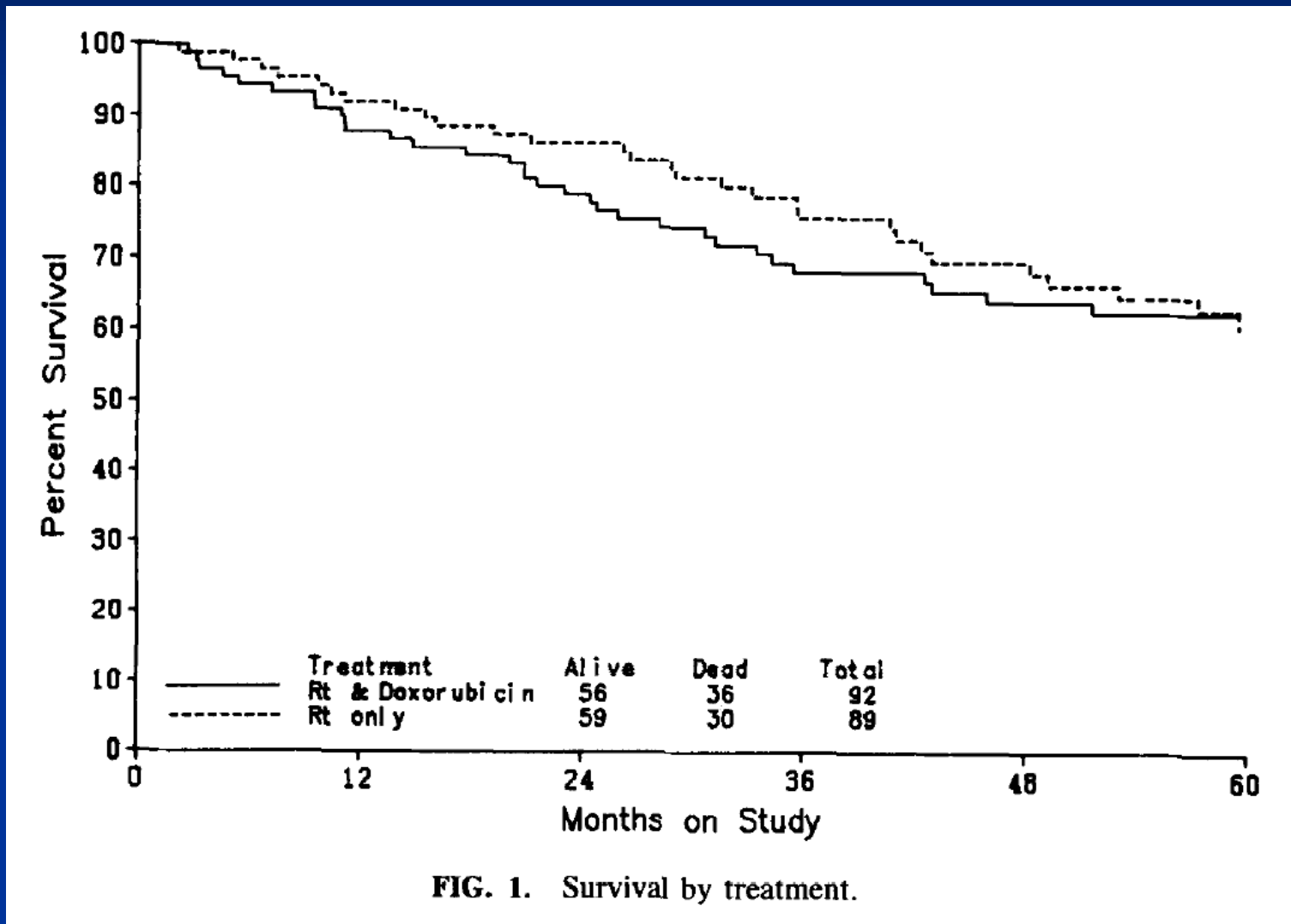
Radiation – 5000 cGy to
whole pelvis at 160-180 cGy/day



Chemotherapy – doxorubicin 60 mg/m² iv
q3weekly to maximum dose of 500 mg/m²
(N=92)

Control – observation
(N=89)

Results



Conclusions

- Study was terminated prematurely because of slow recruitment
- 27% of patients randomized to doxorubicin did not receive it
- No significant difference in OS or PFS
- Study unable to determine effect of doxorubicin on recurrence due to protocol violations, small sample size and number of patients lost to follow-up

Maggi et al

British Journal of Cancer (2006) 95, 266–271

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www.bjcancer.com

Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial

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Maggi et al

FIGO stage IC gr 3, stage IIA-B gr 3
with $\geq 50\%$ myometrial invasion,
stage III



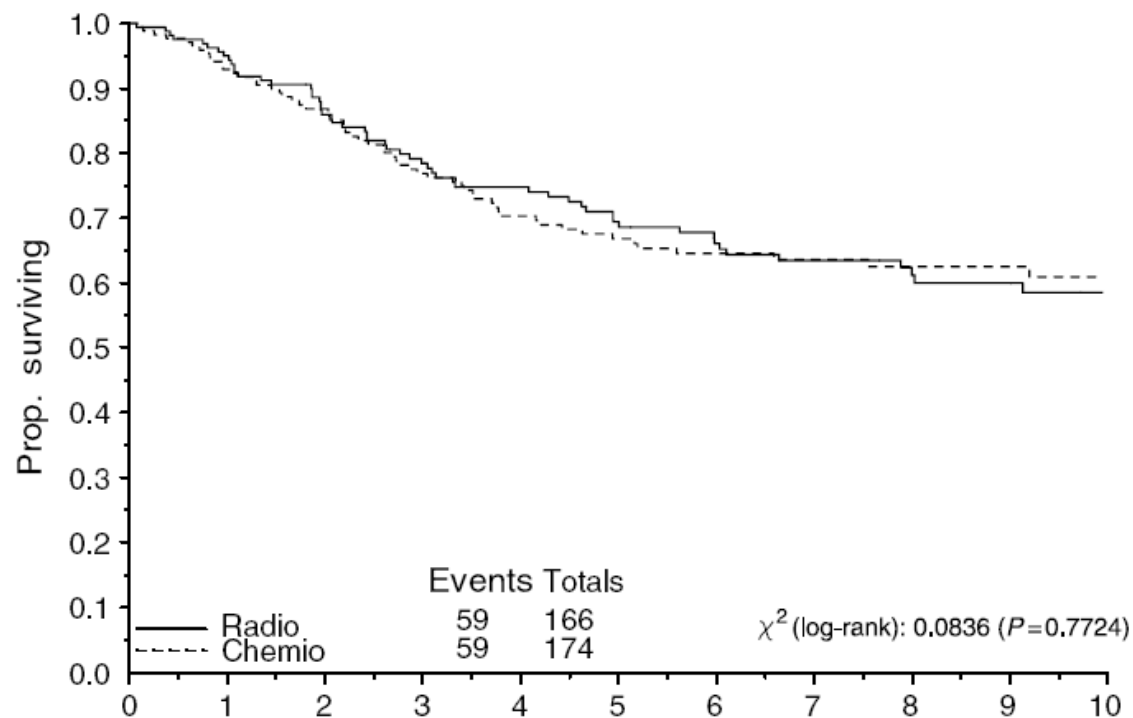
Randomize



Chemotherapy:
cyclophosphamide 600 mg/m²
doxorubicin 45 mg/m²
cisplatin 50 mg/m²
q4weeks X 5 cycles
(n=174)

Pelvic XRT:
45-50 Gy in 5-7 weeks
+ para-aortics if involved
(n=166)

Results



	Patients at risk										
	Years from randomisation										
	0	1	2	3	4	5	6	7	8	9	10
Radio	166	151	129	109	100	88	77	68	51	42	27
Chemio	174	156	141	119	105	91	79	65	54	39	30

Figure 2 Overall survival of patients with high-risk endometrial carcinoma (stage IcG3, IIg3 with myometrial invasion >50%, and III) receiving adjuvant radiotherapy (Radio) or chemotherapy (Chemio). Five-year overall survival was 69% and 66% respectively for adjuvant radiotherapy and chemotherapy.

Conclusions

- No improvement in PFS or OS for patients treated with chemotherapy
- Trend for radiotherapy to delay local relapses and chemotherapy to delay distant relapses

Susumu et al (JGOG-2033)



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Available online at www.sciencedirect.com



Gynecologic Oncology 108 (2008) 226–233

Gynecologic
Oncology

www.elsevier.com/locate/ygyno

Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study[☆]

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Susumu et al (JGOG-2033)

FIGO stage IC to III
with $\geq 50\%$ myometrial invasion



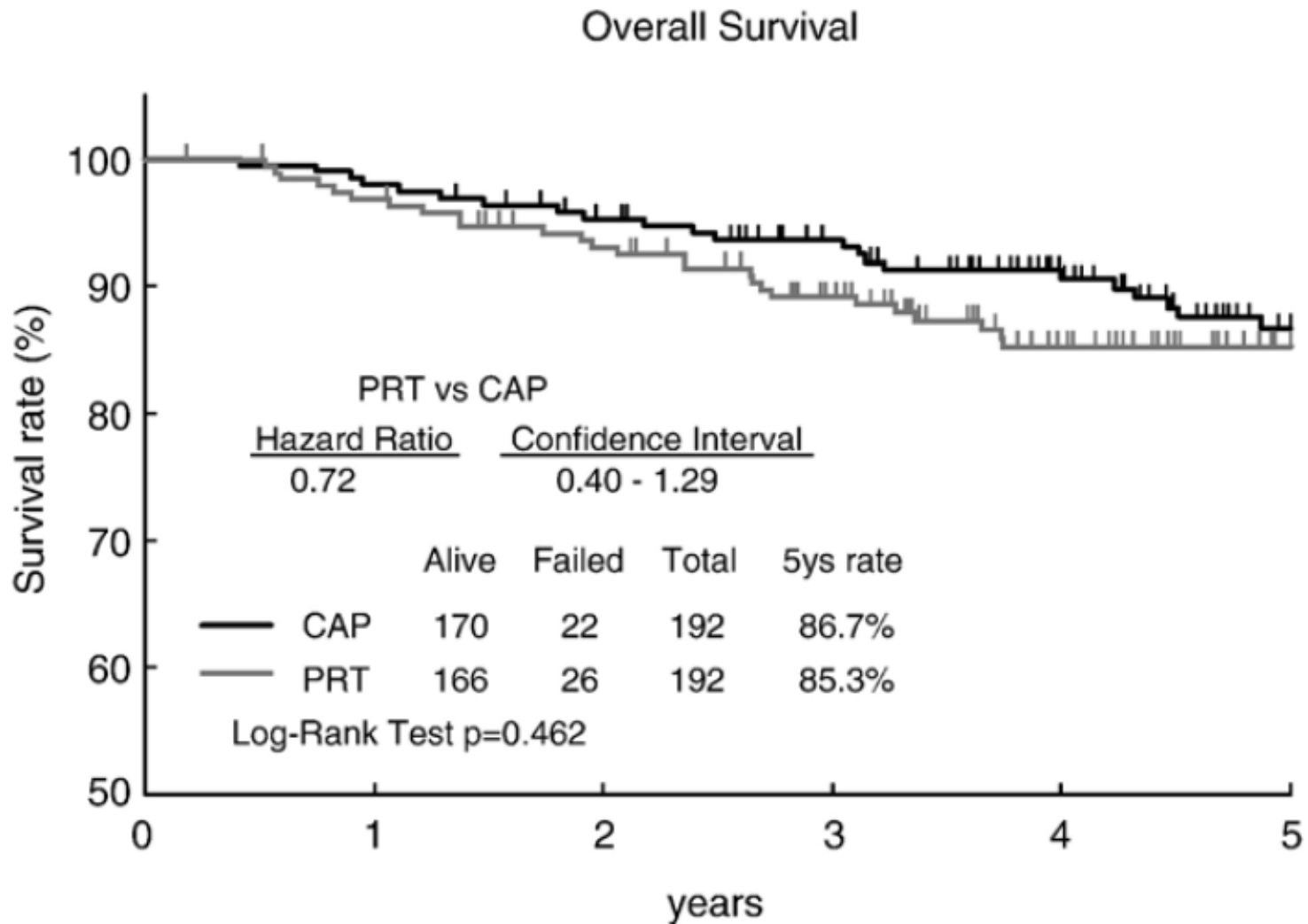
Randomize



Chemotherapy:
cyclophosphamide 333 mg/m²
doxorubicin 40 mg/m²
cisplatin 50 mg/m²
q4weeks X 3 or more cycles
(N=188)

Pelvic XRT:
45-50 Gy in 4-6 weeks
+ para-aortics if involved
(N=186)

Results



Conclusions

- No improvement in PFS or OS for patients treated with chemotherapy
- Retrospective subgroup analysis of “high to intermediate risk” group (stage IC > 70 years, IC grade 3, stage II or IIIA n=120) found that chemotherapy significantly improved PFS and OS, however no PFS or OS difference found in “high risk” group (stage IIIA-IIIC n=75)

Hogberg et al (NSGO/EORTC)

A randomized phase-III study on adjuvant treatment with radiation (RT) \pm chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991).

T. Hogberg, P. Rosenberg, G. Kristensen, C. F. de Oliveira, R. de Pont Christensen, B. Sorbe, C. Lundgren, T. Salmi, H. Andersson, N. S. Reed

Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 5503

Hogberg et al (NSGO/EORTC)

FIGO stage I, II, IIIA (cytology), or IIIC
with high risk for recurrence:

One or more of

- grade 3 tumour
- deep myometrial invasion
- non-diploid DNA
- serous or clear cell or anaplastic histology



Pelvic radiotherapy \pm vaginal brachytherapy
Given to dose of ≥ 44 Gy



Chemotherapy given before OR after XRT:

- doxorubicin 40 mg/m², cisplatin \pm 50 mg/m² X 4 cycles
- epirubicin 75 mg/m², cisplatin \pm 50 mg/m² X 4 cycles
- paclitaxel 175 mg/m², epirubicin 60 mg/m², carboplatin AUC5
- paclitaxel 175 mg/m², carboplatin AUC5-6

(n=177)

No chemotherapy
(n=190)

Results

- Improved PFS on the chemotherapy arm
 - 7% improvement at 5 years, $p=0.03$
- Survival data too early to draw conclusions

Conclusions

- Not clear if this was truly a randomized study since a variety of chemotherapy regimens could be given either before or after radiation, thus casting doubt about PFS benefits attributed to chemotherapy
- Study terminated before target of 400 patients reached due to slow recruitment and thus underpowered
- 27% of patients received no or only part of prescribed chemotherapy

Unanswered Questions in Adjuvant Therapy of High Risk Early Stage Endometrial Carcinoma

- Would adjuvant chemotherapy be efficacious if optimal chemotherapy were used?
- What is optimal sequencing of combined therapy?

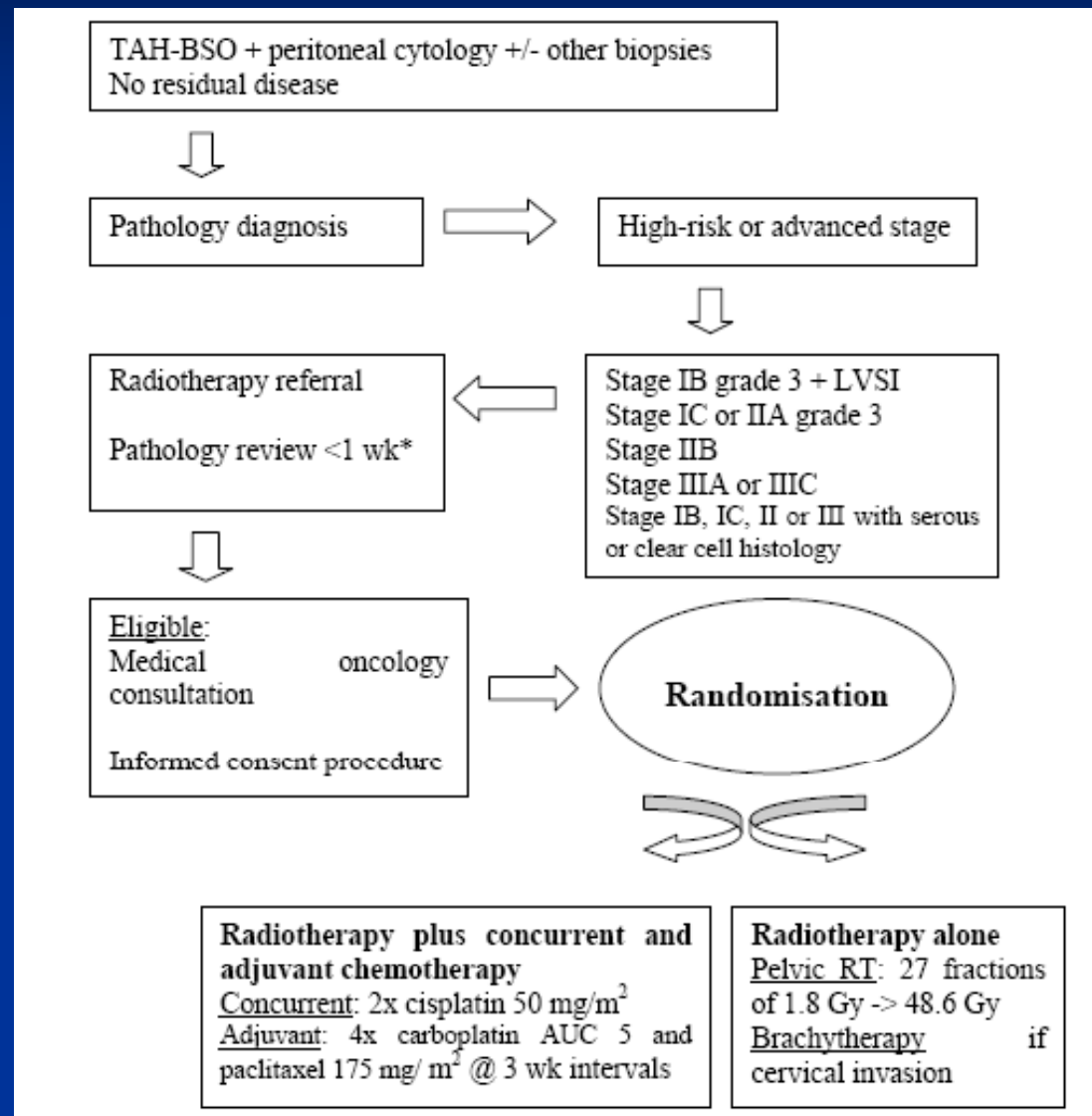
Chemotherapeutic Agents

- In advanced disease, chemotherapeutic agents with activity (response rates of over 20%) demonstrated in phase II studies include:
 - doxorubicin
 - cisplatin/carboplatin
 - paclitaxel
 - cyclophosphamide
 - ifosfamide
- Role of combinations such as carboplatin/paclitaxel

Optimal Sequencing of Chemotherapy and Radiation

- Concurrent with radiation?
- Following radiation?
- Both concurrent and sequential?
- Chemotherapy can be safely combined with radiation and the outcomes of such treatment compared to radiation alone are being tested

PORTEC-3 (NCIC EN.7) Study



Final Conclusions

- No evidence exists to support the routine use of adjuvant chemotherapy in patients with high risk early stage endometrial carcinoma from the 4 randomized studies reported to date
- Strategies to evaluate potentially more effective combination chemotherapy together with radiation remain to be tested
- Patients with high risk early stage disease should be encouraged to participate in clinical trials addressing these questions

The Emperor has no new clothes!

