

“Women with high risk early stage endometrial cancer should receive adjuvant chemotherapy”

Michael Friedlander

The Prince of Wales Cancer Centre and Royal Hospital for Women
Sydney Australia



Debate

- Find the common ground- where we agree
- Define high risk and what the risk of recurrence and death is without adjuvant CT
- What is evidence based medicine and how do we make decisions in the clinic
- Is adjuvant CT biologically plausible
- What evidence is there to support adjuvant chemotherapy for high risk EC

Common Ground

Pelvic radiation reduces local recurrence but no impact on survival(with some possible exceptions)

Can identify patients at high risk of distant relapse

We both attempt to practice EBM

We both want to improve the outcomes of the patients we treat

Response rates to chemotherapy in advanced disease > 40-60%

Evidence from RCT to support adjuvant chemotherapy in high risk EC

Tumor Board

Lets make this real!

- 63 year old woman
- PMH- uneventful
controlled hypertension
- Presents with post-menopausal bleeding
- Curette- grade 3 endometrioid cancer
- TAHBSO and nodal sampling
- Pathology

Pathology

- Grade 3 endometrioid cancer
- Invasion 11mm through a wall 13 mm in thickness
- Lymph vascular invasion ++
- 6 negative pelvic nodes
- Washings negative

Surgical Staging of Carcinoma of the Uterine Corpus

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 Groups

Risk	Stage
Low Risk	Stage 1 A (grade 1 ,2) Stage 1 B(grade 1 grade 2)
Intermediate Risk	Stage 1 A (grade 3) Stage 1B(grade 3) Stage 1C (grade 1,2)
High Risk	Stage 1C grade 3

Risk Group

Stage 1 B, C, 2 occult

GOG 99 subgroup of patients with "**high**" **intermediate-risk disease** was defined and accounted for one-third of the population and for two-thirds of recurrences and cancer deaths.

Cumulative risk of recurrence at 48 months was 27% for patients "high" intermediate-risk disease

defined as:

Age of at least 70 with one of the "risk factors"

- **grades 2 to 3 tumour**
- **presence of lymph vascular space involvement**
- **outer third myometrial invasion**

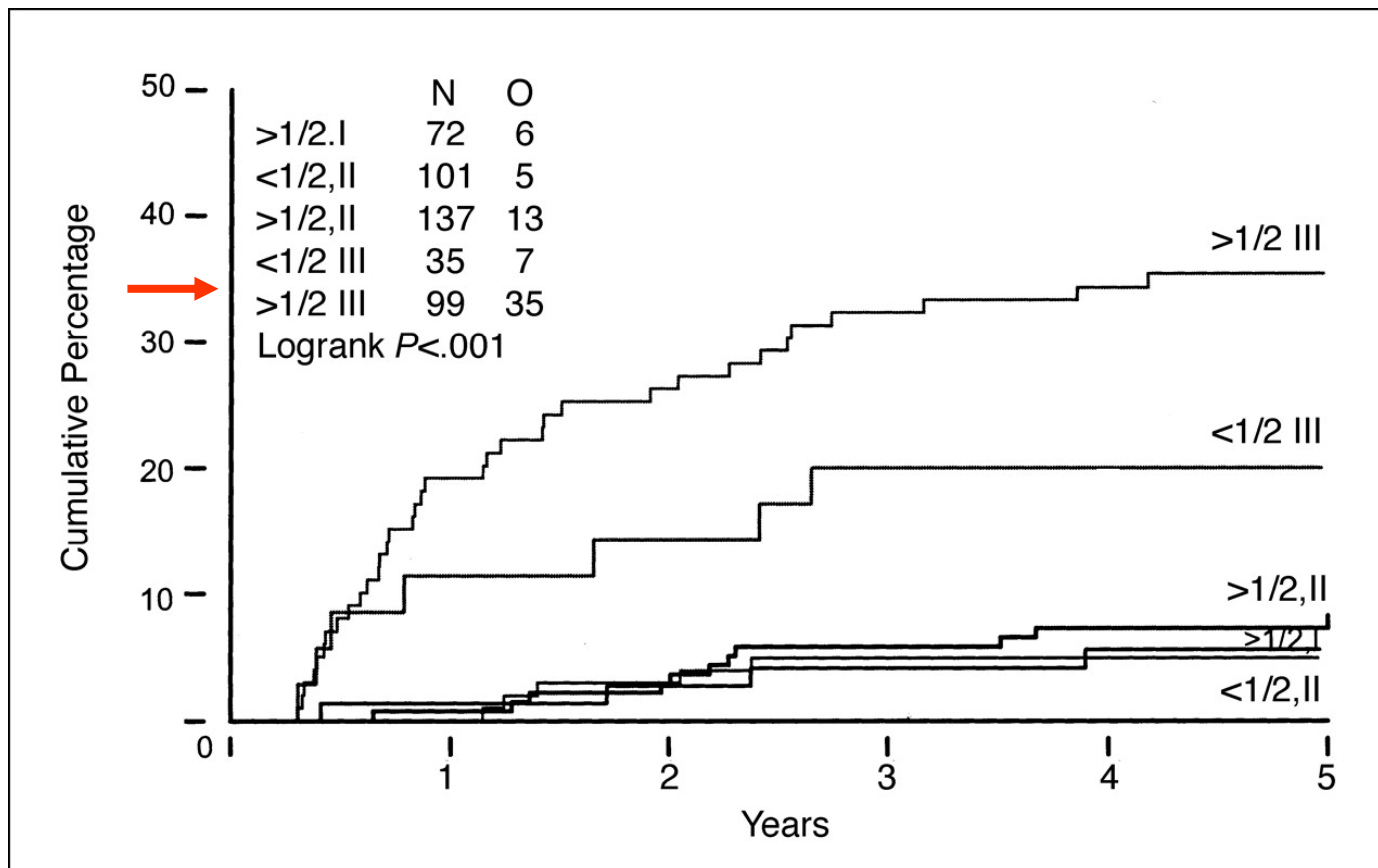
Age of at least 50 with two of the risk factors

Any age with all three risk factors

5 year survival by Stage and Grade

Stage IB, grade 1	88
Stage IB, grade 2	93
Stage IB, grade 3	82
Stage IC, grade 1	87
Stage IC, grade 2	84
Stage IC, grade 3	66
Stage IIIA, grade 1	77
Stage IIIA, grade 2	69
Stage IIIA, grade 3	38
Stage IIIC, grade 1	62
Stage IIIC, grade 2	59
Stage IIIC, grade 3	47

Fig 3. Probability of relapse according to prognostic group (grade and myometrial invasion combined)



Creutzberg, C. L. et al. J Clin Oncol; 22:1234-1241 2004

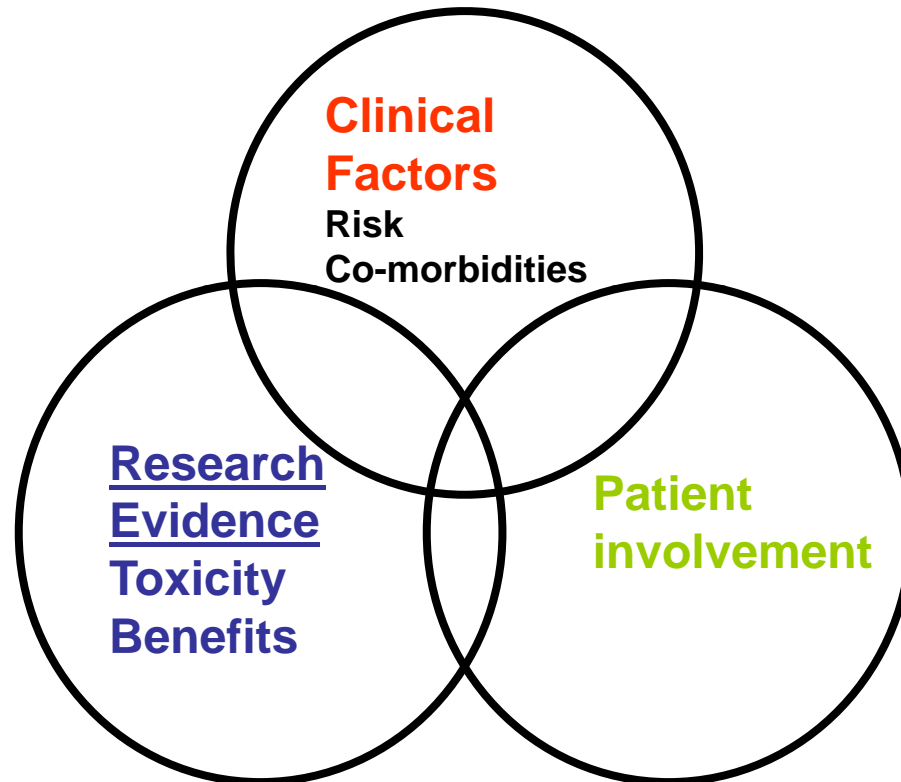
Agree

- Risk of relapse high- 30%+
- 65-70% 5 year survival
- Pelvic RT RCT – reduces local recurrence but ? Impact on survival
- Discuss options with patient

Evidence Based Medicine (EBM)

*The "conscientious, explicit and judicious use of **current best evidence** in making decisions about the care of individual patients."*

Decision making



Discuss diagnosis ,implications ,available data and treatment options

What my opponent said !

“Women who have a poorer prognosis are those with: poor prognosis stage 1 disease (i.e. high-grade disease, deep myometrial invasion or certain histological types...)

Women with poor prognosis stage 1 disease or more advanced disease are candidates for clinical trials addressing the role of adjuvant or ancillary treatment”.

What is the evidence to support
Adjuvant Chemotherapy ?

You be the judge

Are the benefits of adjuvant CT
biologically plausible?

YES

Breast cancer

Colon cancer

Ovarian cancer

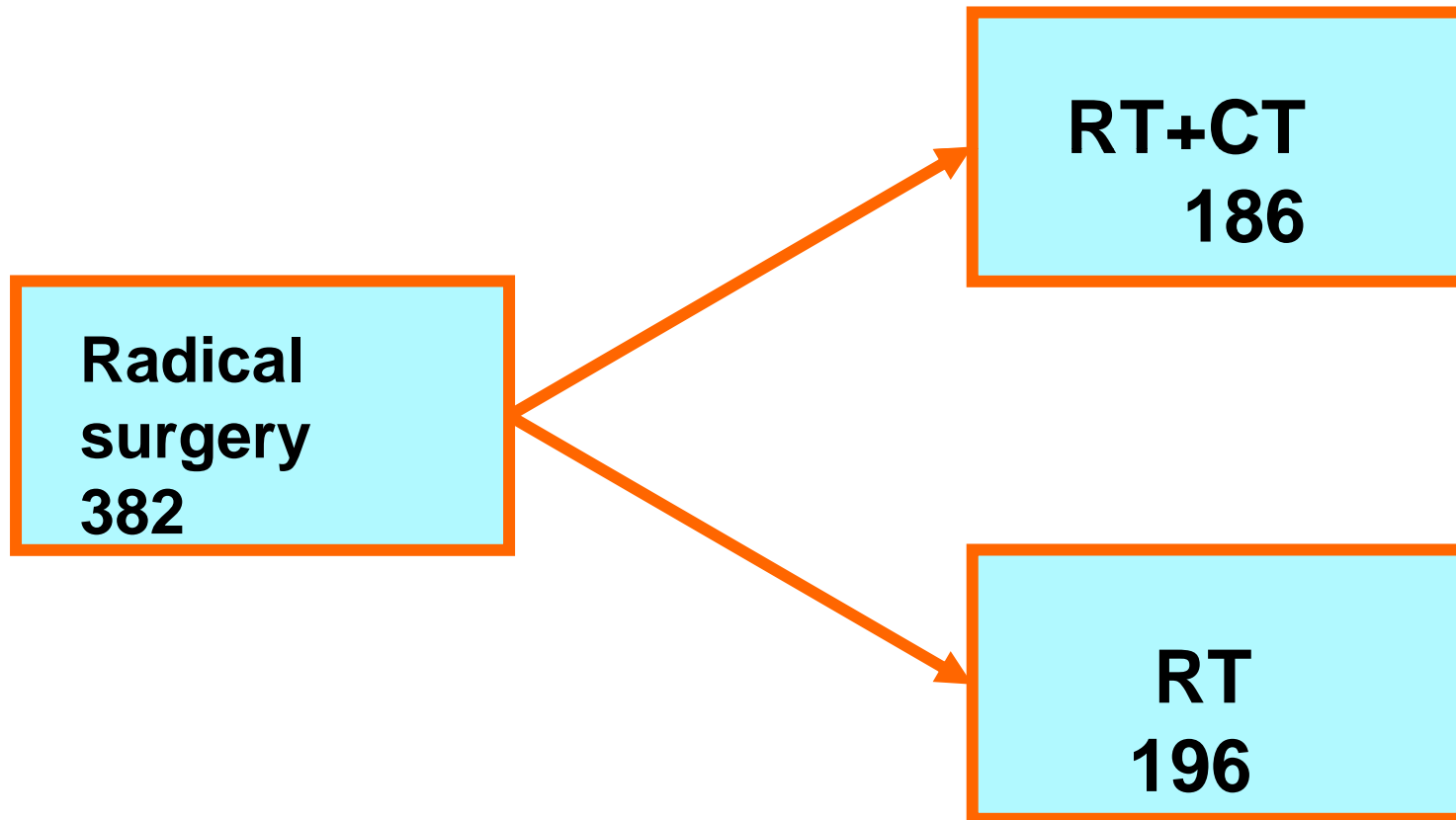
Gastric cancer

Lung cancer

Pancreatic cancer

NSGO EC-9501/EORTC-55991

Randomization



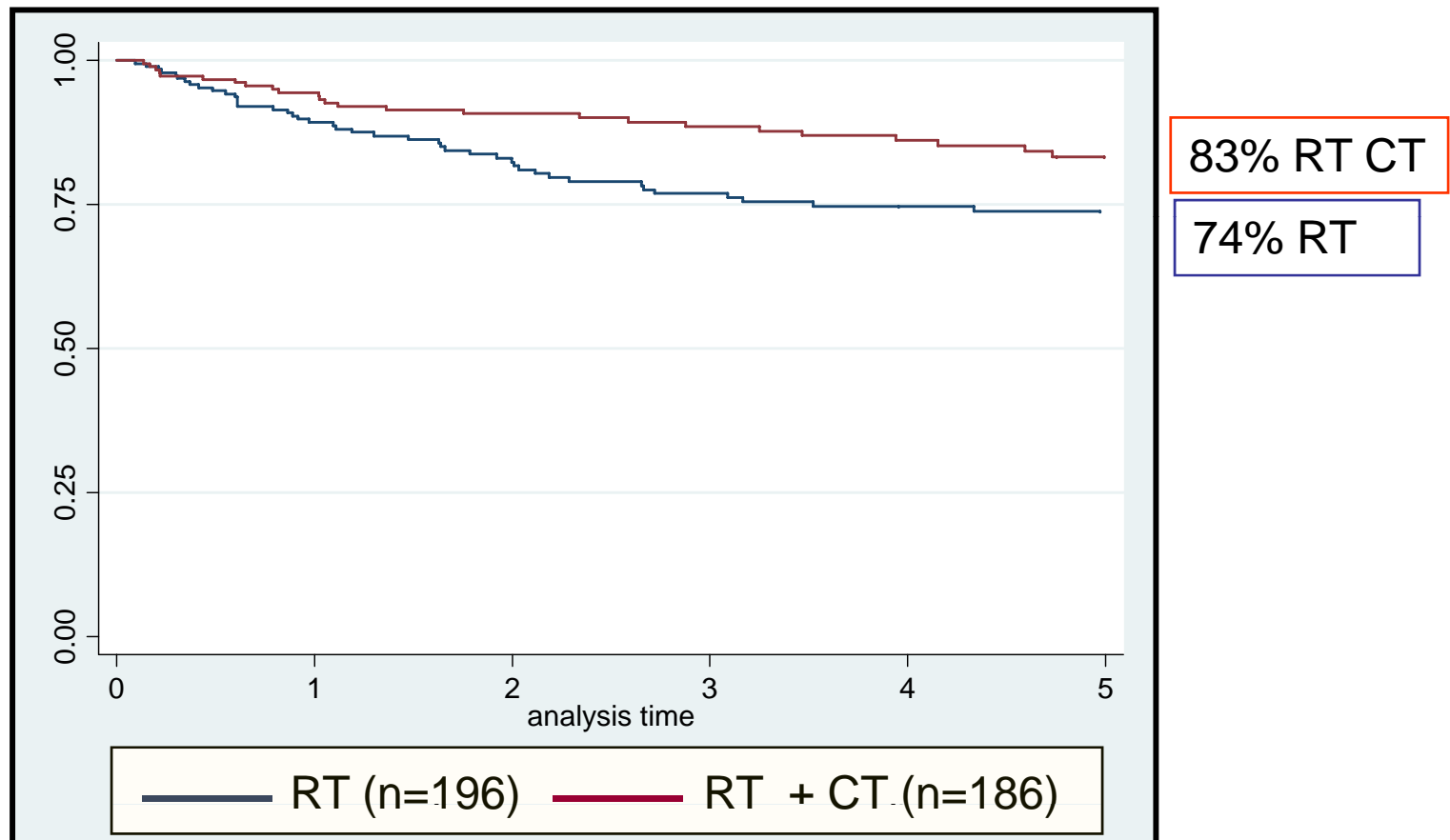
NSGO EC-9501/EORTC-55991

Stage	Randomization				Total	
	RT		RT+CT			
	n	(%)	n	(%)	n	(%)
IA	27	(14)	18	(10)	45	(12)
IB	48	(24)	62	(33)	110	(29)
IC	99	(51)	90	(48)	189	(49)
II	13	(6.6)	9	(4.8)	22	(5.8)
III	4	(2.0)	2	(1.1)	6	(1.6)
Unknown	5	(2.6)	5	(2.7)	10	(2.6)
Total	196	(100)	186	(100)	382	(100)

Pearson chi2 p=0.39

NSGO EC-9501/EORTC-55991

Progression-free survival (deaths from intercurrent causes censored)

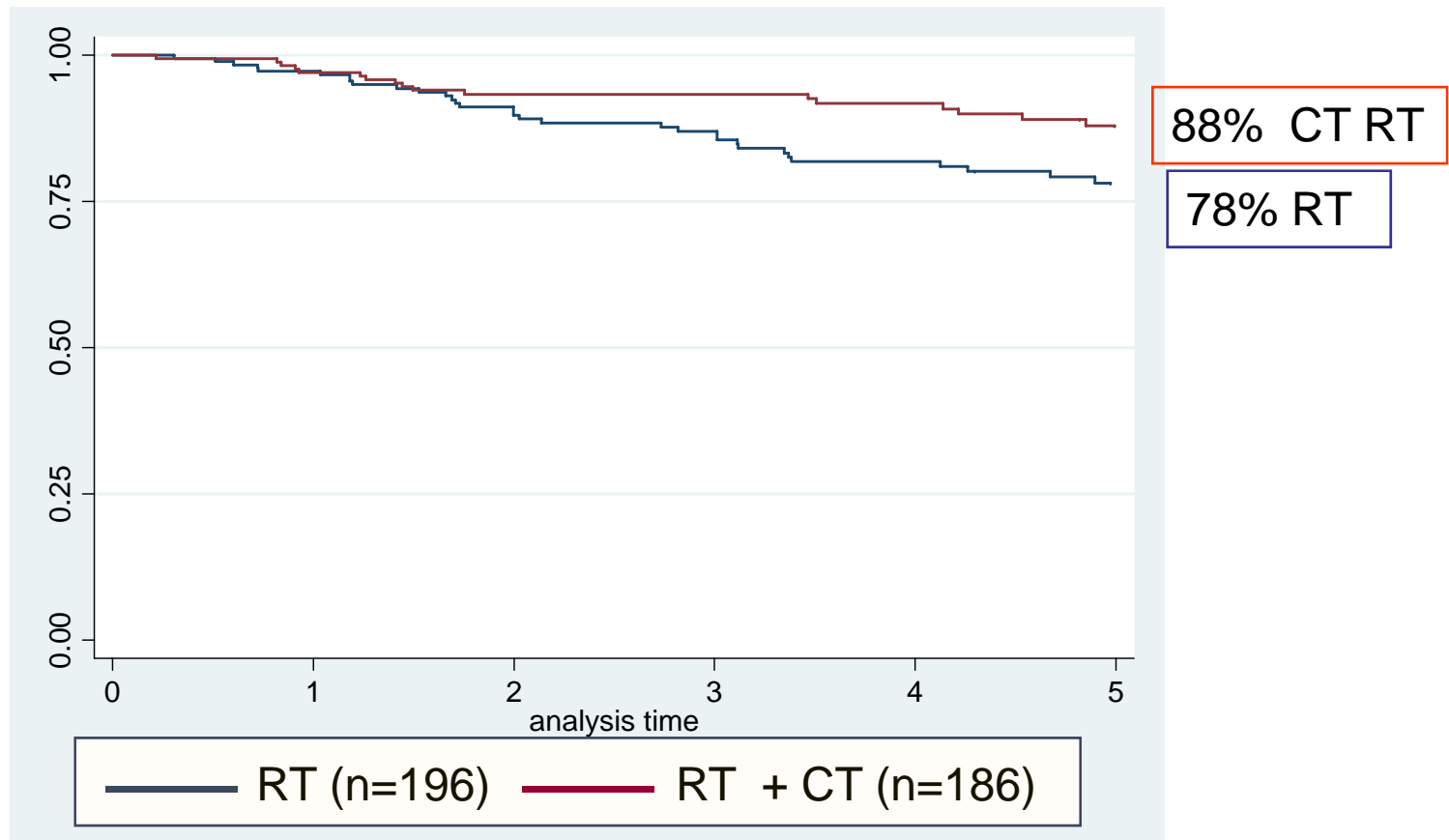


HR 0.53 (CI 0.33-0.87) p=0.01; 9 % INCREASE in PFS 74 % to 83 %

Thomas Hogberg, NSGO

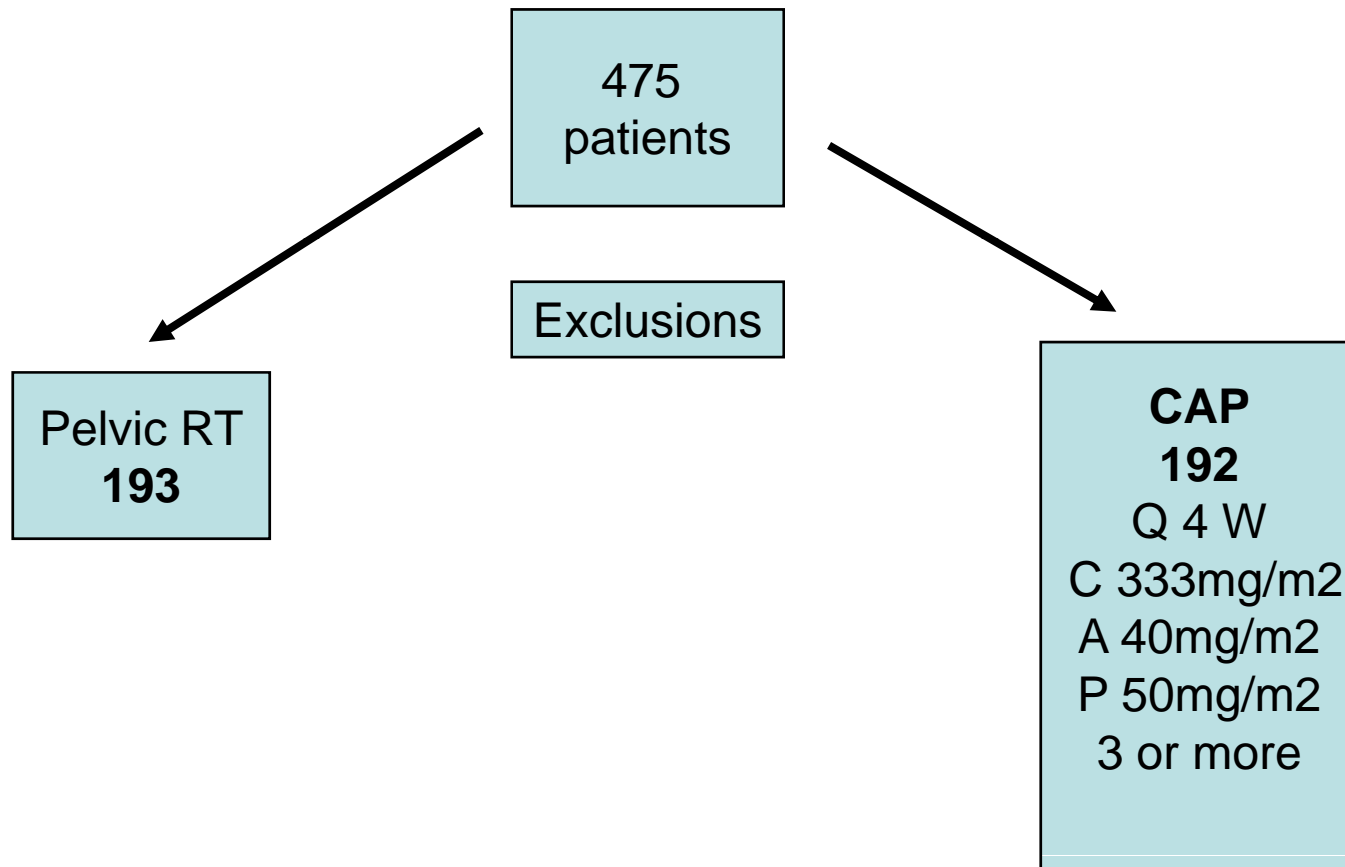
NSGO EC-9501/EORTC-55991

Cancer-specific survival



HR 0.51 (CI 0.29-0.91) p=0.02; Increase in CSS by 10 % from 78 % to 88 %

Randomized phase 3 trial of Pelvic RT vs. CT in intermediate –high risk EC



Randomized phase 3 trial of Pelvic RT vs. CT in intermediate –high risk EC

- 1C 61%; 2 13%;3A 13%;3C 11.9%
- Median no. of cycles CT 3(1-7)
- PFS **83% RT vs. 82% CT** (NS)

But what about high risk

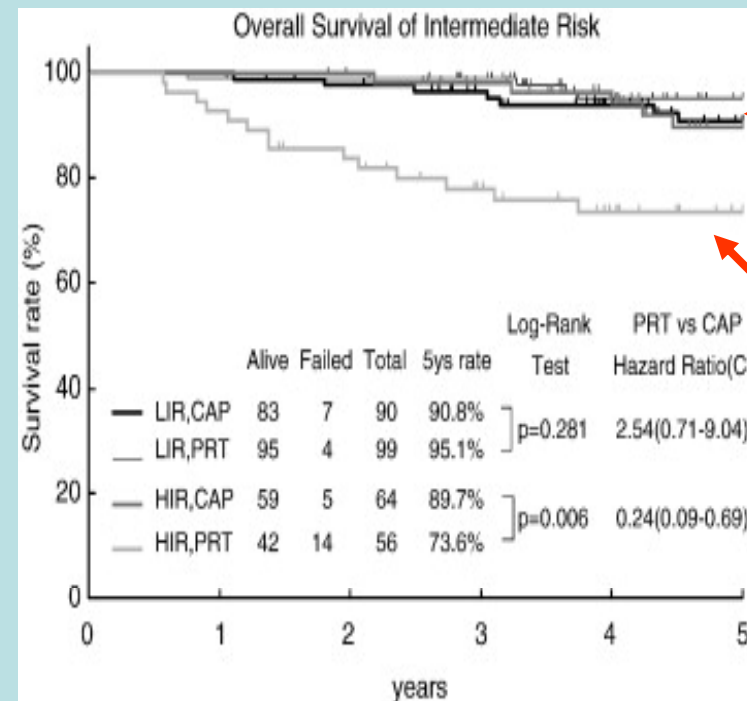
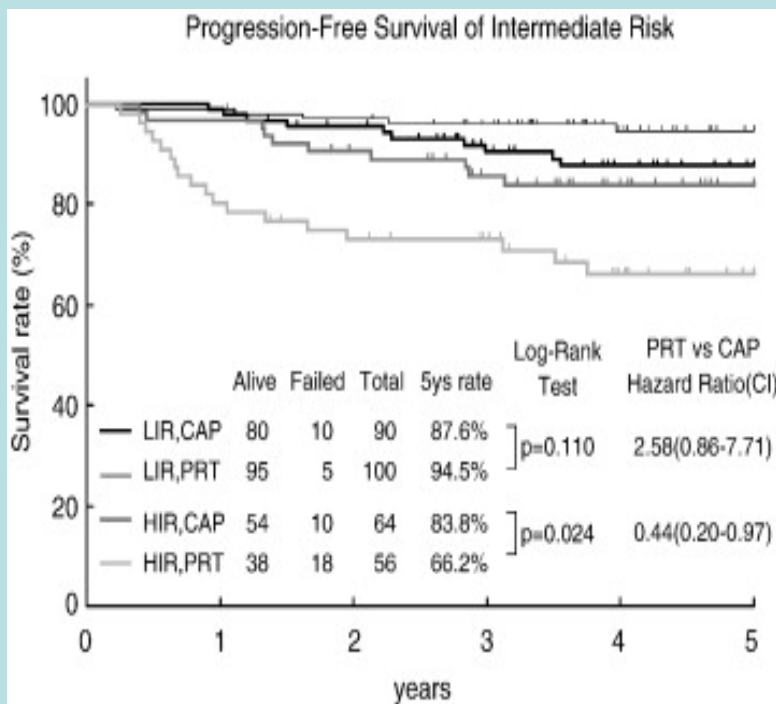
CT 89% 5 yr survival RT 73% (p=.006 HR0.24 (0.09-0.69))

1.IC > 70 or G3

2.2 or 3A with > 50% myometrial invasion

120 of whole group

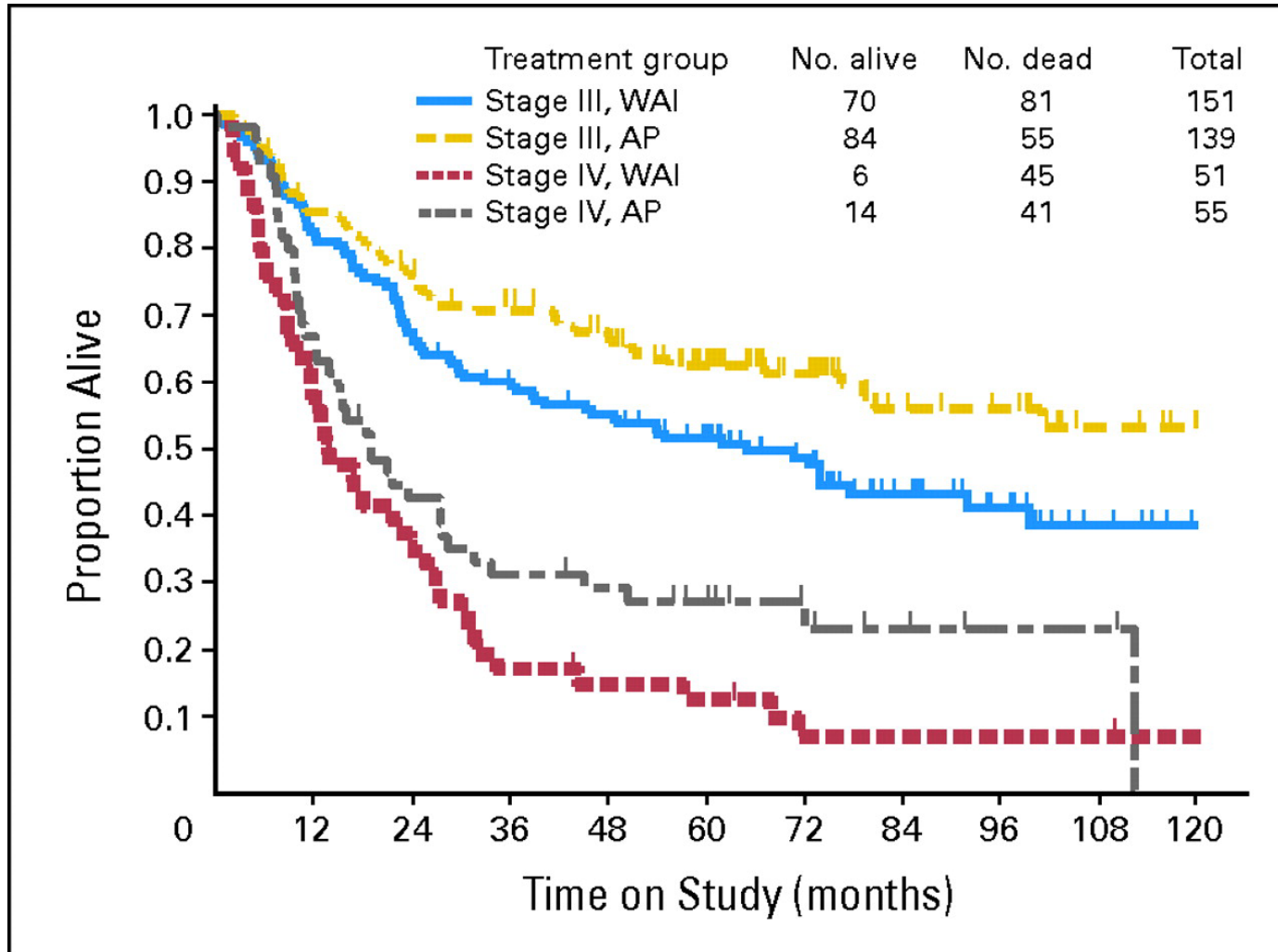
Randomized phase 3 trial of Pelvic RT vs. CT in intermediate –high risk EC



CT High Risk **89%**

RT High Risk **73%**

Overall survival by treatment and stage on the Gynecologic Oncology Group 122 trial



Fleming, G. F. J Clin Oncol; 25:2983-2990 2007

Randall, M. E. et al. J Clin Oncol; 24:36-44 2006

Are there negative studies

- GOG 34 Morrow 1991- adjuvant doxorubicin- flawed study- “ authors said utility of chemotherapy unknown”
- Maggi et al- 2006 adjuvant chemotherapy vs. RT- 345 patients- no difference in Survival
only 26% 1C –predominantly stages 3 A,B,C
- Kuoppala et al 2008 RT vs. Sequential CT
156 (128 Stages 1C-3A G 1-3)- no difference but
powered to detect a 20% absolute difference in
survival!

Chemotherapy for Advanced Disease

- Cochrane Review and Systematic Review from Cancer Care Ontario
- Chemo-sensitive disease
- Active agents- **RR 43-57%**
platinum, doxorubicin, paclitaxel
- Higher responses with combination- increased DFS and modest effect on OS
- Carboplatin and paclitaxel active and require further study

Carboplatin and Paclitaxel

Phase 2 studies

Hoskins et al JCO 2001

Akram et al Am J Obstet Gynecol 2005

Michener et al J Cancer Res Clin Oncol 2005

Sorbe et al Gynecol Oncol 2008



67% RESPONSE RATE CR 29%

Median duration 14 months

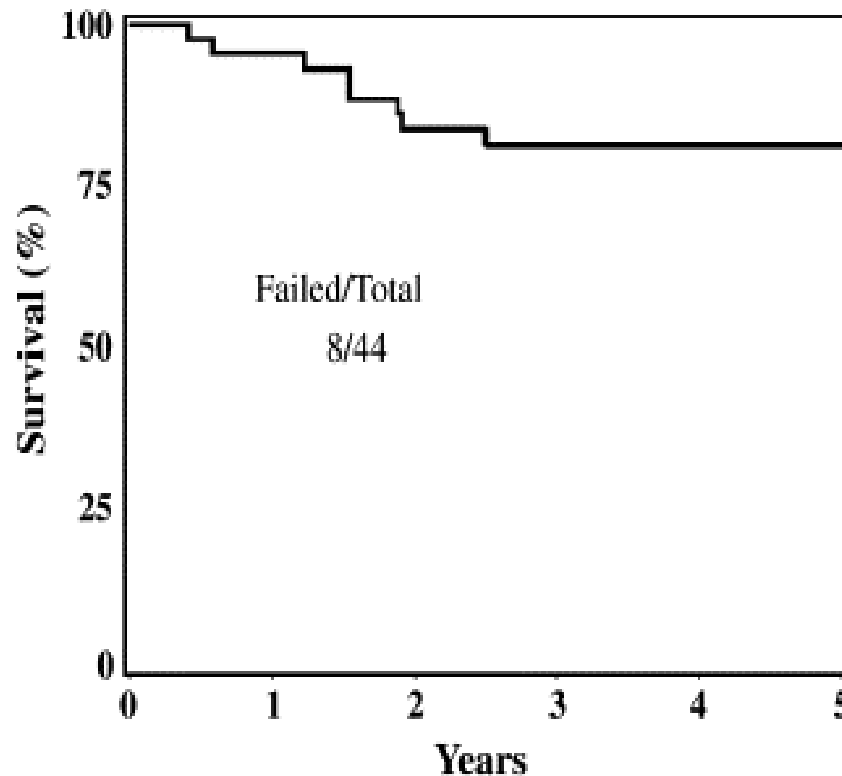
Primary advanced – RR 89% CR 50%

94% completed 3 cycles and 82% 6 cycles

Well tolerated 14% grade 3 sensory neuropathy

RTOG 9708: Adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer

Greven et al Gynecol Oncol 2006



Concurrent cisplatin day 1 and 28 with RT 4 Cycles Cisplatin and paclitaxel

Phase 2 46 patients
No recurrences in 1C,2A,2B
Stage 3 77% Survival

What I would offer the patient

And the potential winner is

THE PATIENT

Open and full discussion regarding potential benefits and side effects and providing no serious medical co-morbidities

“Women with high risk early stage endometrial cancer should receive adjuvant chemotherapy”