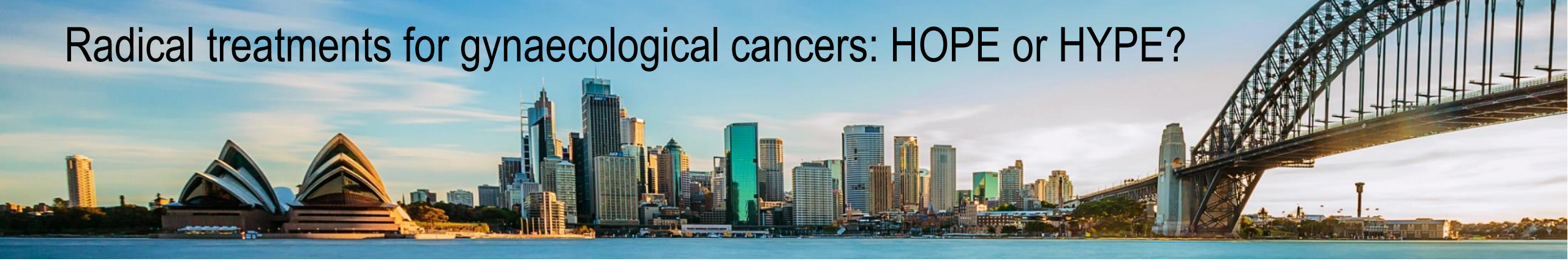


Radical treatments for gynaecological cancers: HOPE or HYPE?



Adjuvant chemotherapy in uterine cancer

Michelle Vaughan

Christchurch Hospital, Canterbury DHB
& St Georges Cancer Care Centre

Faculty Disclosure

☒	No, nothing to disclose
☐	Yes, please specify:

	<i>Honoraria/ Expenses</i>	<i>Consulting/ Advisory Board</i>	<i>Funded Research</i>	<i>Royalties/ Patent</i>	<i>Stock Options</i>	<i>Ownership / Equity Position</i>	<i>Employee</i>	<i>Other (please specify)</i>

Off-Label Product Use

Will you be presenting or referencing off-label or investigational use of a therapeutic product?	
☐	No
☐	Yes, please specify:



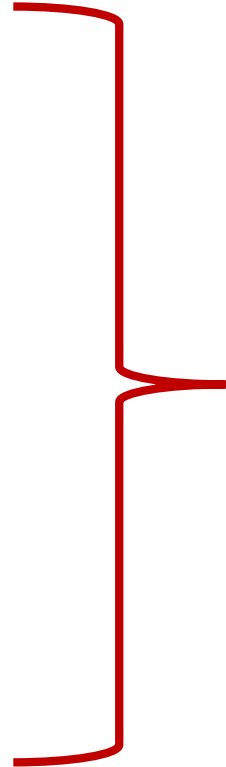
Why are we so confused?

- Heterogenous populations in RCTs
 - Are there subgroups who benefit? What are they?
- No RCT in serous and clear cell
- PFS benefit and not OS benefit
 - How do we discuss benefit?

The evidence

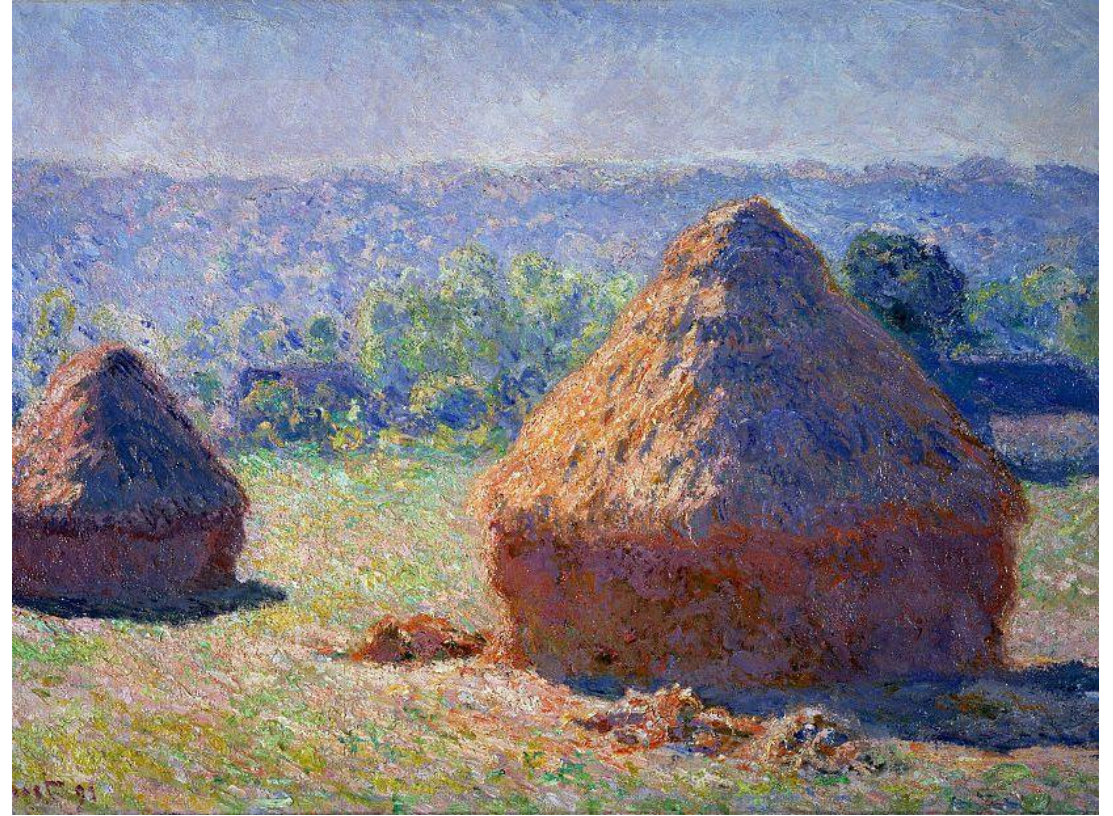
Endometrial
Serous
Clear cell

Stage I-II
Stage III



Meta-analyses
RCT
Subgroup analyses of RCT
Retrospective studies
(Database, pooled centres)

Impressionism



Adjuvant Chemo RCTs

	5 yr PFS %				5 yr OS %			
Chemo v RT	GOG 150 Wolfson 2007	206	I-IV Carcinosarc	Cis/ifos WAI	42→48	Ns	35→45	+10 p.085
	GOG 122 Randall 2006	396	III & IV opt	Cis/dox WAI	(38→50)	+12 p.007	(42→55)	+13 p.004
	GICOG Maggi 2006	340	IC-II G3 III (x CC/SC)	Cis/dox/cyclo PRT	63	ns	69→66	ns
	JGOG 2033 Susumu 2008	385	IC – IIIC >50% MI		84→82	ns	85→87	ns
Adding Chemo to RT	GOG 34 Morrow 1990	181	IA,IB, II, III	PRT + Dox PRT	?	ns	~60	ns
	MaNGO ILIADE Hogberg 2010	157	IIB-IIIC	PRT + Chemo PRT	61→74	ns	72→78	+7 p.07
	NSGO/EORTC Hogberg 2010	383	I-III hi risk	PRT (VBT) + CT PRT (VBT)	72→79	+7 p.04	76→83	
	Finnish Kuoppala 2008	156	IA-B G3, IC-IIIA	PRT + CEP PRT	82→77	ns	85	ns
	GOG 249 Randall 2017	601	I GOG HR, II I-II CC/USC	VBT + Carb/pac PRT	3-year 82→82	ns	3-year 91→88	ns
	PORTEC 3 De Boer 2018	660	IG3 inv,IBG3, II-III, any C/USC	PRT (VBT)+ C → C/P PRT (VBT)	69→76 58→69 St3	+7 p.02 +11 p.01	77→82 70→79	ns ns

ALL STAGES

Cochrane review 2011

	5 yr PFS %					5 yr OS %		
Chemo v RT	GOG 150 Wolfson 2007	206	I-IV Carcinosarc	Cis/ifos WAI	42→48	Ns	35→45	+10 p.085
	GOG 122 Randall 2006	396	III & IV opt	Cis/dox WAI	(38→50)	+12 p.007	(42→55)	+13 p.004
	GICOG Maggi 2006	340	IC-II G3 III (x CC/SC)	Cis/dox/cyclo PRT	63	ns	69→66	ns
	JGOG 2033 Susumu 2008	385	IC – IIIC >50% MI		84→82	ns	85→87	ns
Adding Chemo to RT	GOG 34 Morrow 1990	Small and poor trial						ns
	MaNGO ILIADE Hogberg 2010	157	IIB-IIIC	PRT + Chemo PRT	61→74	ns	72→78	+7 p.07
	NSGO/EORTC Hogberg 2010	383	I-III hi risk	PRT (VBT) + CT PRT (VBT)	72→79	+7 p.04	76→83	
	Finnish Kuoppala 2008	Not included						ns
	GOG 249 (Randall 2017)	Not done yet						ns
	PORTEC 3 De Boer 2018							ns ns

Cochrane review 2011

	5 yr PFS %						
Chemo v RT	GOG 150 Wolfson 2007	206	I-IV Carcinosarc	Cis/ifos WAI	42→48		+10 0.085
	GOG 122 Randall 2006	396	III & IV opt	Cis/dox WAI			+13 0.04
	GICOG Maggi 2006	340	IC-II G3				
	JGOG 2033 Susun						ns
Adding Chemo							ns
					61→74	ns	72→78
				PRT (VBT) + CT PRT (VBT)	72→79	+7 p.04	+7 p.07
Adding Chemo							ns
	GOG 249 (Randall 2017)						ns
	PORTEC 3 De Boer 2018						ns ns

Too old

Not included

Not done yet

Systematic review 2018

	5 yr PFS %					5 yr OS %		
Chemo v RT	Included all 6 trials below N= 2100, Stages I-III							
Adding Chemo to RT	GOG 34 Morrow 1990	181	IA,IB, II, III	PRT + Dox PRT	?	ns	~60	ns
	MaNGO ILIADE Hogberg 2010	157	IIB-IIIC	PRT + Chemo PRT	61→74	ns	72→78	+7 p.07
	NSGO/EORTC Hogberg 2010	383	I-III hi risk	PRT (VBT) + CT PRT (VBT)	72→79	+7 p.04	76→83	
	Finnish Kuoppala 2008	156	IA-B G3, IC-IIIA	PRT + CEP PRT	82→77	ns	85	ns
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	PORTEC 3 De Boer 2018	660	IG3 inv,IBG3, II-III, any C/USC	PRT (VBT)+ C → C/P PRT (VBT)	69→76 58→69 St3	+7 p.02 +11 p.01	77→82 70→79	ns ns

OS

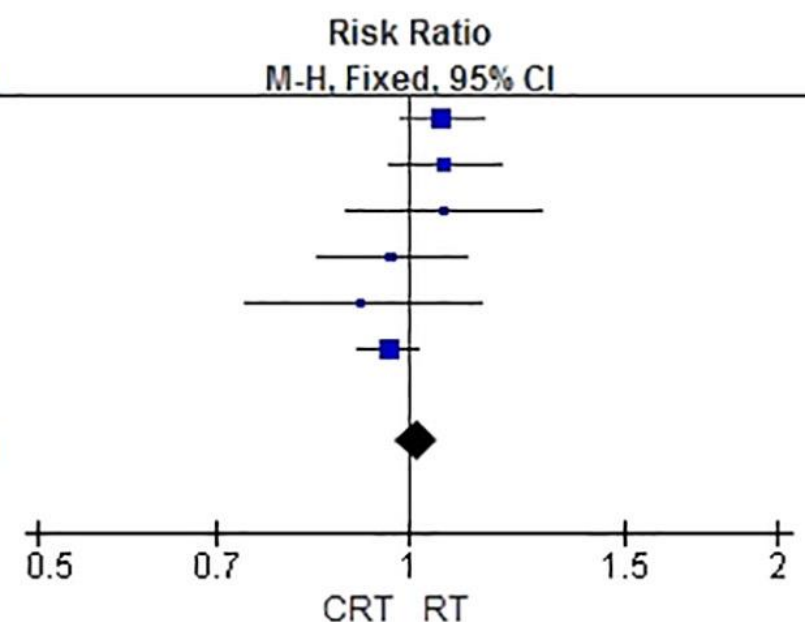
Study or Subgroup	CRT		RT		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Boer 2016	270	330	253	330	30.1%	1.07 [0.99, 1.15]
Hogberg(1) 2010	152	187	145	191	17.1%	1.07 [0.96, 1.19]
Hogberg(2) 2010	62	80	55	76	6.7%	1.07 [0.89, 1.29]
Kuoppala 2008	69	84	61	72	7.8%	0.97 [0.84, 1.12]
Morrow 1990	56	92	59	89	7.1%	0.92 [0.74, 1.15]
Randall 2017	256	291	258	283	31.1%	0.96 [0.91, 1.02]

Total (95% CI) 1064 1041 100.0% 1.02 [0.98, 1.06]

Total events 865 831

Heterogeneity: $\chi^2 = 7.40$, $df = 5$ ($P = 0.19$); $I^2 = 32\%$

Test for overall effect: $Z = 0.84$ ($P = 0.40$)



PFS (+CSS)

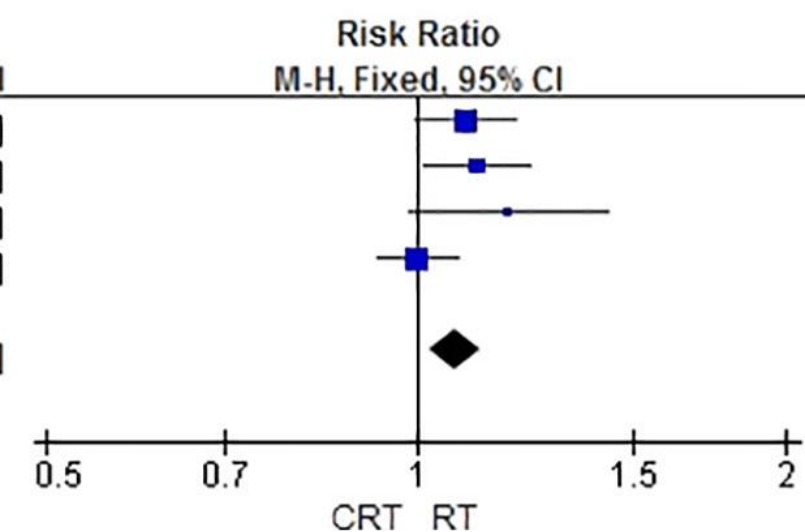
Study or Subgroup	CRT		RT		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Boer 2016	249	330	227	330	34.4%	1.10 [1.00, 1.21]
Hogberg(1) 2010	159	187	145	191	21.8%	1.12 [1.01, 1.24]
Hogberg(2) 2010	65	80	52	76	8.1%	1.19 [0.99, 1.43]
Randall 2017	239	291	232	283	35.7%	1.00 [0.93, 1.08]

Total (95% CI) 888 880 100.0% 1.08 [1.02, 1.13]

Total events 712 656

Heterogeneity: $\chi^2 = 5.19$, $df = 3$ ($P = 0.16$); $I^2 = 42\%$

Test for overall effect: $Z = 2.83$ ($P = 0.005$)



2018 systematic review/meta-ana

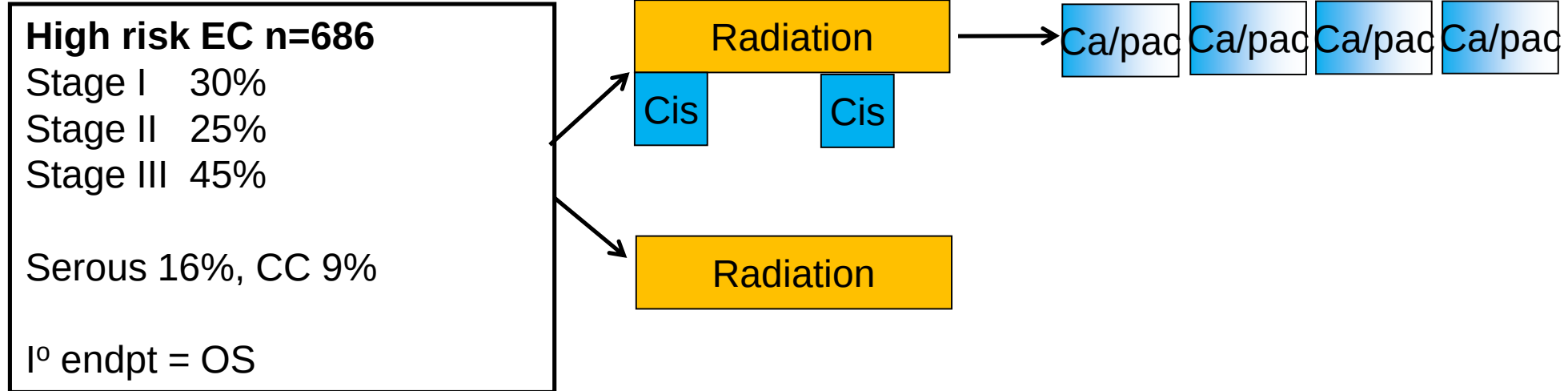
Adding chemo to RT

	5yr %	benefit	HR p
OS	80		1.02 ns
CSS	79→87	+7%	1.09 p.03
PFS	74→80	+6%	1.08 p.005
Local rec	3		0.48 ns
Distant mets	13		0.94 ns

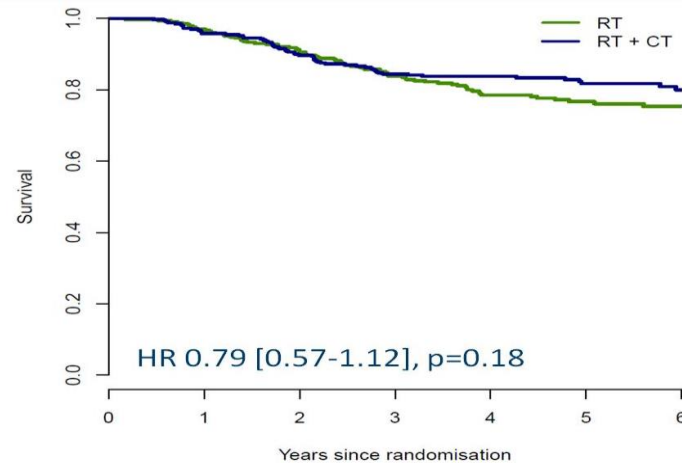
N= 2100
6 RCT

META –ANA 6x RCT:
CSS and PFS +6%
No OS diff

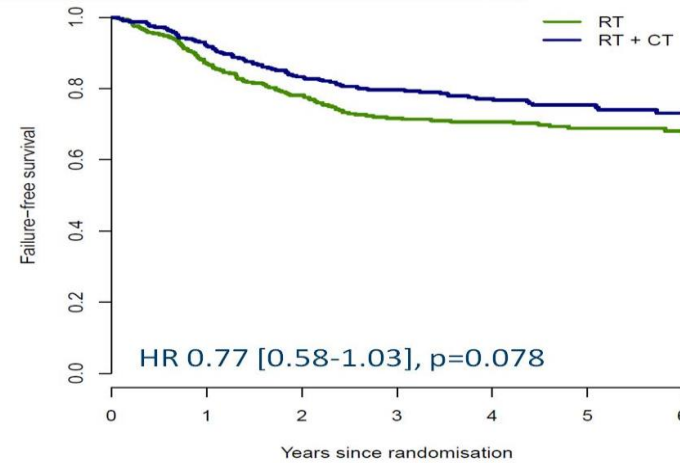
PORTEC 3



PORTEC 3 results



OS ~80% ns



FFS ITT ns
(If adj for stratification fcs
+7% 69→76
HR.71 p.02)

+7% FFS benefit
when adjust results for
stratification factors

No OS benefit

Summary table

	Type of evidence	PFS/FFS/CSS	OS	Comments
ALL patients	2018 Systematic rv	+6-7 %	ns	
	2018 RCT (PORTEC)	+7 %	ns	

STAGE I AND II

Hazard ratio of 0.66

High stage cancer



Low stage cancer



Adjuvant Chemo RCTs

	5 yr PFS %				5 yr OS %			
Chemo v RT	GOG 150 Wolfson 2007	206	I-IV Carcinosarc	Cis/ifos WAI	42→48	Ns	35→45	+10 p.085
	GOG 122 Randall 2006	396	III & IV opt	Cis/dox WAI	(38→50)	+12 p.007	(42→55)	+13 p.004
	GICOG Maggi 2006	340	IC-II G3 III (x CC/SC)	Cis/dox/cyclo PRT	63	ns	69→66	ns
	JGOG 2033 Susumu 2008	385	IC – IIIC >50% MI		84→82	ns	85→87	ns
Adding Chemo to RT	GOG 34 Morrow 1990	181	IA,IB, II, III	PRT + Dox PRT	?	ns	~60	ns
	MaNGO ILIADE Hogberg 2010	157	IIB-IIIC	PRT + Chemo PRT	61→74	ns	72→78	+7 p.07
	NSGO/EORTC Hogberg 2010	383	I-III hi risk	PRT (VBT) + CT PRT (VBT)	72→79	+7 p.04	76→83	
	Finnish Kuoppala 2008	156	IA-B G3, IC-IIIA	PRT + CEP PRT	82→77	ns	85	ns
	GOG 249 Randall 2017	601	I GOG HR, II I-II CC/USC	VBT + Carb/pac PRT	3-year 82→82	ns	3-year 91→88	ns
	PORTEC 3 De Boer 2018	660	IG3 inv,IBG3, II-III, any C/USC	PRT (VBT)+ C → C/P PRT (VBT)	69→76 58→69 St3	+7 p.02 +11 p.01	77→82 70→79	ns ns

Get rid of trials with >1/2 Stage III

	5 yr PFS %							5 yr OS %
Chemo v RT	GOG 150 Wolfson 2007	Carcinosarcoma, All stage 3-4			WAI comparator possibly harmful Old fashioned chemo			+10 p.085
	GOG 122 Randall 2006							+13 p.004
	GICOG Maggi 2006	2/3 stage III						ns
	JGOG 2033 Susumu 2008	385	IC – IIIC >50% MI	PRT	84→82	ns	85→87	ns
Adding Chemo to RT	GOG 34 Morrow 1990	Flawed, lost to follow up, protocol violations						ns
	MaNGO ILIAD Hogberg 2010	Mostly stage III						+7 p.07
	NSGO/EORTC Hogberg 2010	383	I-III hi risk	PRT (VBT) + CT PRT (VBT)	72→79	+7 p.04	76→83	
	Finnish Kuoppala 2008	156	IA-B G3, IC-IIIA	PRT + CEP PRT	82→77	ns	85	ns
	GOG 249 Randall 2017	601	I GOG HR, II I-II CC/USC	VBT + Carb/pac PRT	3-year 82→82	ns	3-year 91→88	ns
	PORTEC 3 De Boer 2018	660	IG3 inv,IBG3, II-III, any C/USC	PRT (VBT)+ C → C/P PRT (VBT)	69→76 58→69 St3	+7 p.02 +11 p.01	77→82 70→79	ns ns

RCT mainly early stages

	n	Stage				Type II path %		5yr PFS %		5yr OS %	
		I	II	III	IV	Serous	Clear cell	Control	benefit	Control	benefit
JGOG ¹	385	60	15	25	-	-	-	84	0	85	0
NSGO/EORTC ²	383	90	10	-	-	20	17	72	+7 p.04	76	
Finnish ³	156	70	20	10	-	-	4	82	-5	85	0
GOG 249 ⁴	575	75	25	-	-	15	5	82	0	91 (3yr)	-3
PORTEC 3 ⁵	661	←53→ 45 -				25		77	+4	?	?
								Stage 2 data			

¹Susumu 2008 *Gyn Oncol* 108:226, ²Hogberg 2010 *EurJ Cancer* 46:2422, ³Kuoppala 2008 *Gyn Oncol* 110:190, ⁴Randall 2017 *ASTRO LBA* 1, ⁵de Boer 2018 *Lancet Oncol* 19:295

RCT mainly early stages

	n	Stage				Type II path %		5yr PFS %		5yr OS %	
		I	II	III	IV	Serous	Clear cell	Control	benefit	Control	benefit
JGOG ¹	385	60	15	25	-	-	-	84	0	85	0
NSGO/EORTC ²	383	90	10	-	-	20	17	72	+7 p.04	← BUT: Nodal staging o so ?high occult And high % sero	
Finnish ³	156	70	20	10	-	-	4	82	-5		
GOG 249 ⁴	575	75	25	-	-	15	5	82	0		
PORTEC 3 ⁵	661	←53→ 45 -				>25		77	+4		
								Stage			



BUT:

Nodal staging optional,
so ?high occult stage III

And high % serous

¹Susumu 2008 *Gyn Oncol* 108:226, ²Hogberg 2010 *EurJ Cancer* 46:2422,
³Kuoppala 2008 *Gyn Oncol* 110:190, ⁴Randall 2017 *ASTRO LBA* 1, ⁵de Boer
2018 *Lancet Oncol* 19:295

Summary table

	Type of evidence	PFS/FFS/CSS	OS	Comments
ALL patients	2018 Systematic rv	+6-7 %	ns	
	2018 RCT (PORTEC)	+7 %	ns	
Stage I-II	1 of 5 RCT (Hogberg)	7%	ns	But 37% serous or CC & may be stage III contamination
	2018 RCT (PORTEC)	ns	ns	

Database analysis: Stage IB and II HREC

NCDB n= 11,750

74% Stage IB

25% serous/CC

Pts given chemo had worse prog fcs

Pts given chemo more healthy

Multivariate analysis, chemo:

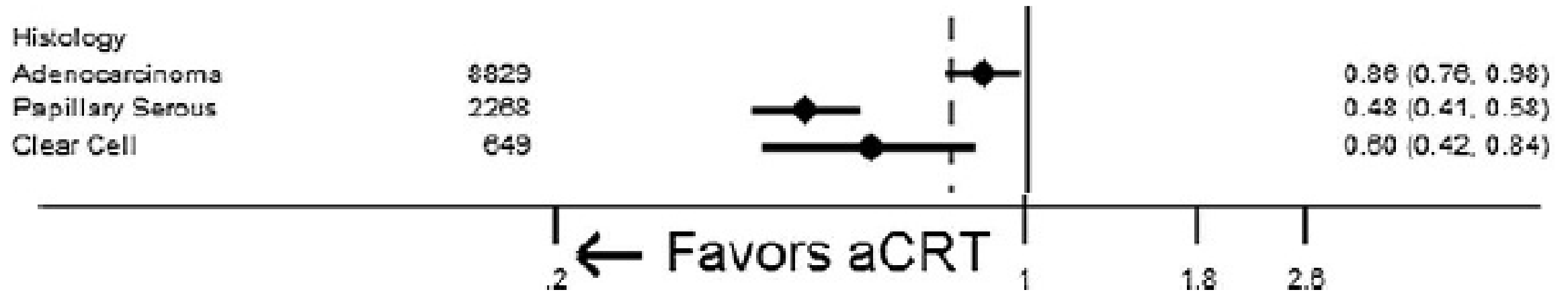
- **+4% 5yOS (79→83%)**

HR death 0.61 p.04

(HR 0.74 p<.01 propensity score matched)

**Hypothesis generating
+4% OS chemo advantage**

Subgroup by pathology



Is survival benefit driven by the 25% with serous and clear cell??

Database analysis: Stage II EEC

NCDB n= 6100

Stage II EEC

No Rx	54%
RT	31%
Chemo	6%
ChemoRT	9%

Multivariable analysis:

- 3y OS RT=CRT (~92%)
- Propensity score matching of 757 pts RT v CRT , also no sig diff in OS

So Stage II EEC, Chemo doesn't add to RT in this retrospective database analysis

Summary table

	Type of evidence	PFS/FFS/CSS	OS	Comments
ALL patients	2018 Systematic rv	+6-7 %	ns	
	2018 RCT (PORTEC)	+7 %	ns	
Stage I-II	1 of 5 RCT (Hogberg)	7%	ns	But 37% serous or CC & may be stage III contamination
	2018 RCT (PORTEC)	ns	ns	
	US NCDB St I-II	?	+4%	But 25% serous or CC
	US NCDB St II EEC only	?	ns	

STAGES III & IV

Omit trials with early stage

	5 yr PFS %						5 yr OS %	
Chemo v RT	GOG 150 Wolfson 2007	Carcinosarcoma						+10 p.085
	GOG 122 Randall 2006	396	III & IV opt	Cis/dox WAI	(38→50)	+12 p.007	(42→55)	+13 p.004
	GICOG Maggi 2006	340	IC-II G3 III (x CC/SC)	Cis/dox/cyclo	63	ns	69→66	ns
	JGOG 2033 Susumu 2008	Stage I-II						ns
Adding Chemo to RT	GOG 34 Morrow 1990	Flawed, lost to follow up, protocol violations						ns
	MaNGO ILIADE Hogberg 2010	157	IIB-IIIC	PRT + Chemo PRT	61→74	ns	72→78	+7 p.07
	NSGO/EORTC Hogberg 2010	Stage I-II						ns
	Finnish Kuoppala 2008							
	GOG 249 Randall 2017							
	PORTEC 3 De Boer 2018	660	IG3 inv,IBG3, II-III, any C/USC	PRT (VBT)+ C → C/P PRT (VBT)	69→76 58→69 St3	+7 p.02 +11 p.01	77→82 70→79	ns ns

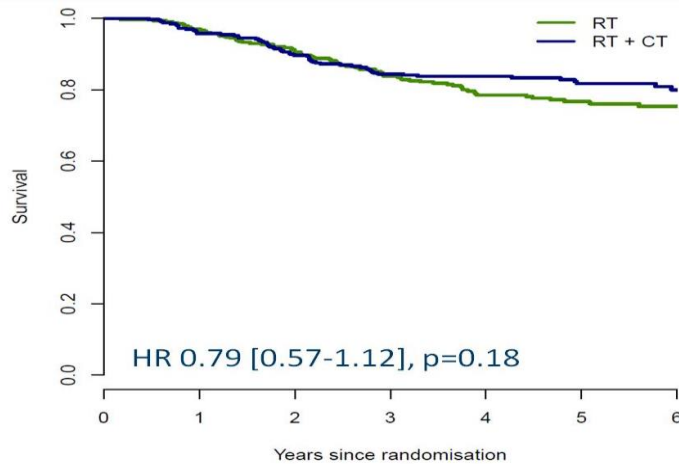
RCT

		n	Stage				Type II path %		5yr PFS %		5yr OS %	
			I	II	III	IV	Serous	Clear	Control	benefit	Control	benefit
RT v CT	GOG 122 ¹	396	0	0	50	50	20	5	38	+12 p.007	42	+13 p.004
	GICOG ²	340	25	10	65	-	-	-	63	0	69	-3
RT +/- CT	MaNGO ILIADE ³	157	0	30	70	-	-	-	61	+13	72	
	PORTEC 3 ⁴	661	←53→		45	-	? <25%		58	+11 p.03	70	+9
									Stage III data			

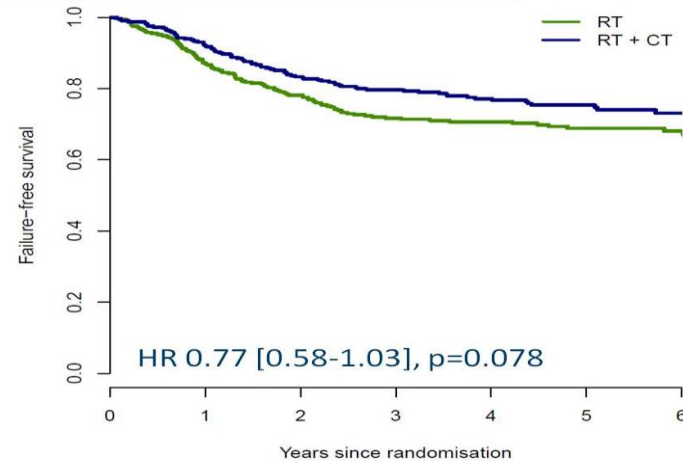
¹Randall 2006 *JCO* 24:36, ²Maggi 2006 *BJC* 95:266

³Hogberg 2010 *EurJ Cancer* 46:2422, ⁴de Boer 2018 *Lancet Oncol* 19:295

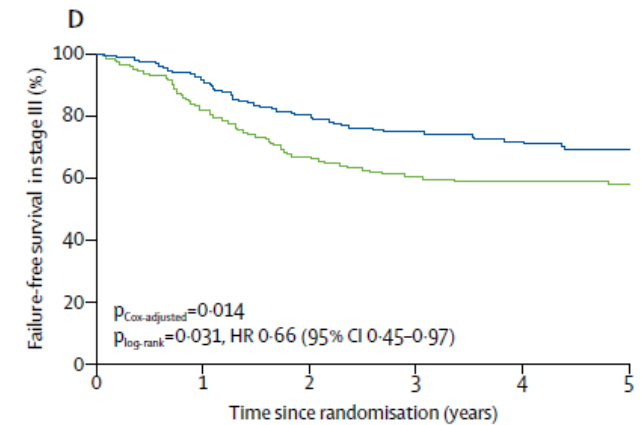
PORTEC 3 results



OS ~80% ns



FFS ITT ns
(If adj for stratification fcs
+7% 69→76
HR.71 p.02)



Stage III subgroup

FFS +11%

58→69%

HR0.66 p.014

Summary table

	Type of evidence	PFS/FFS/CSS	OS	Comments
ALL patients	2018 Systematic rv	+6-7 %	ns	
	2018 RCT (PORTEC)	+7 %	ns	
Stage I-II	1 of 5 RCT (Hogberg)	7%	ns	But 37% serous or CC & may be stage III contamination
	2018 RCT (PORTEC)	ns	ns	
	US NCDB St I-II	?	+4%	But 25% serous or CC OS a flawed endpoint?
	US NCDB St II EEC only	?	ns	
Stage III (IV)	2 of 4 RCT (PORTEC, Randall GOG122)	+ 11-12%	+13 GOG122	But GOG 122 50% stage IV
	2018 RCT (PORTEC)	+11%	ns	

Summary of summary table

- **Stage I-II EC:** No convincing evidence of benefit from chemo
 - 4/5 trials with mostly early stage are –ve,
 - PORTEC subgroup ns
 - Database evidence unimpressive
- **Stage III EEC:** ~10% benefit in FFS from chemo
 - 2/4 RCT trials both ~10% benefit
 - PORTEC subgroup +ve

The downside – Toxicity and QOL

TOXICITY At 2 years:

- **PRO: 25% (vs 6%) 'Quite a bit/very much N&T' $p < .0001$**
- **10% (v 1%) Grade 2+ neuropathy**
= limiting shopping, housework, food prep, transport

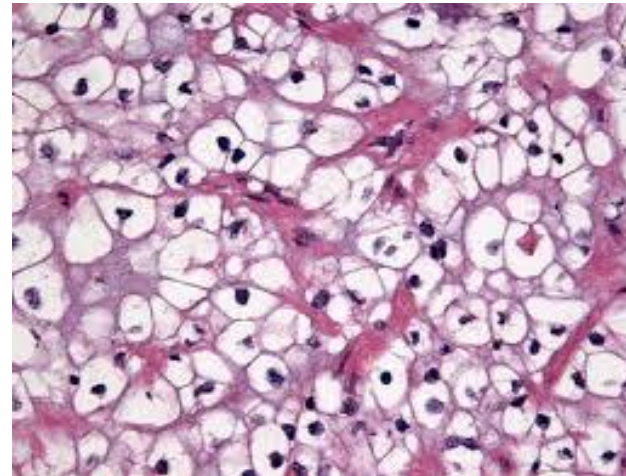
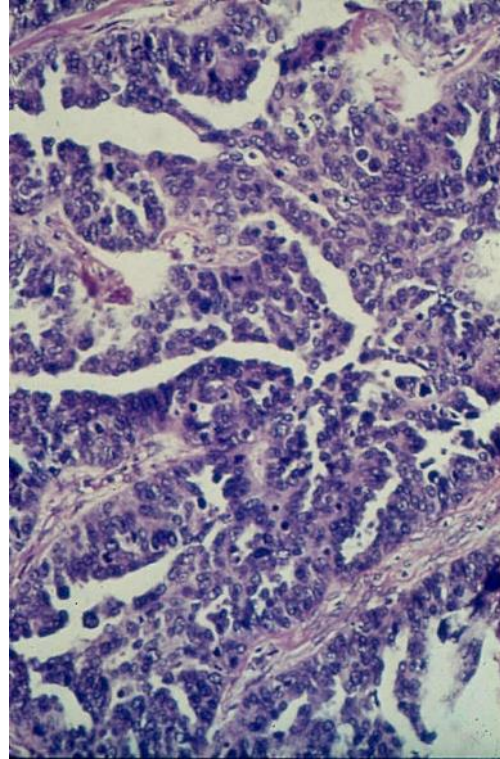
QOL at 1 and 2 years:

No diff >12m (worse at 6m as patients just finished chemo)

Opinions

De Boer review Oct 2018

- Chemo ...should be considered for stage III to optimise outcome
- Stage I-II with high risk features – EBRT remains the standard
- Higher rates AE and ↓QOL with chemo
- **Counselling each Pt important**
- Translational Rx is needed (TransPORTEC)

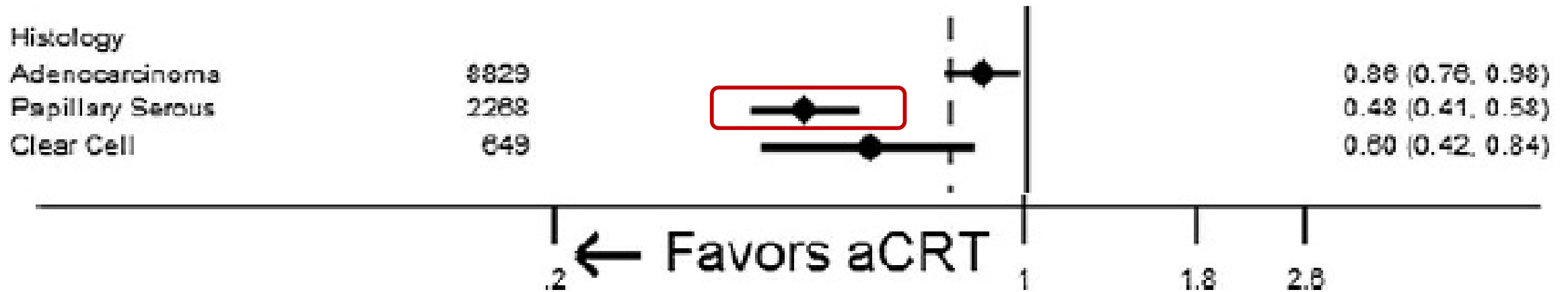


SEROUS (AND CLEAR CELL)

Serous and clear cell

- Only comprises small minority of EC
 - USC ~10% (higher with lower stages)
 - Clear cell 1-5%
- Most serous and CC EC is EARLY stage
- There is **no randomised data** (best is retrospective database)
- The numbers of patients in the RCTs are **too small to allow effective subgroup analysis** (but see Hogberg and PORTEC)

Does chemo benefit Serous (and CC) more?



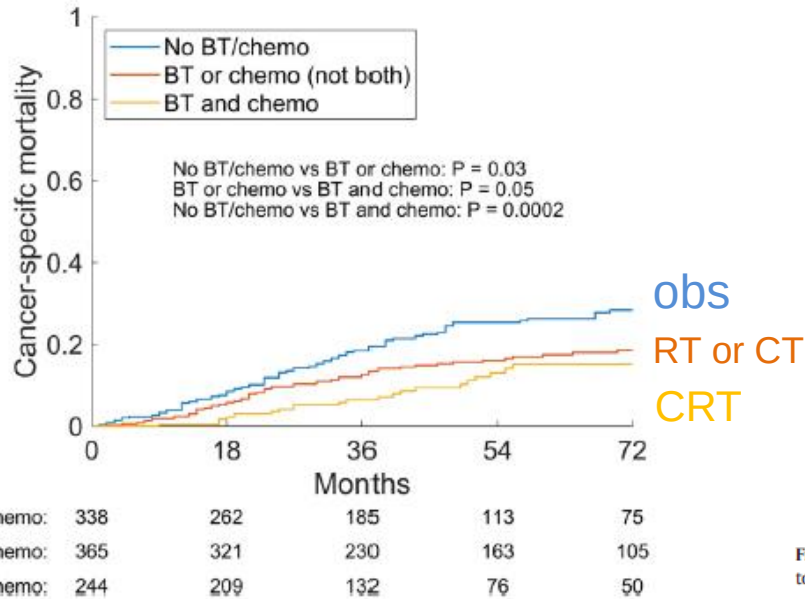
2016 NCDB registry review

n=11,000

Chemo in Stage I-II serous/CC

	n	USC:CC:mix	Stage	5 yr outcome		HR
Xiang 2018 US Seer-Medicare database	1789	80:20:0	I-II	~70→80 CSS	~10%	0.7 p.05
			III	45→55 CSS	+10%	.66 p.006
Qu 2018 Canadian pooled data	190 224	64:9:27	IA M- IA M+	69→84 DFS	+15%	0.47 p.009
Boothe 2016 US NCDB	1021	70:30:0	I-II	? OS	?	0.48

US Database Serous & clear cell



Stage I-II

Multivariable analysis:

Serous only:

~10% CSM benefit

HR 0.71 p=0.05

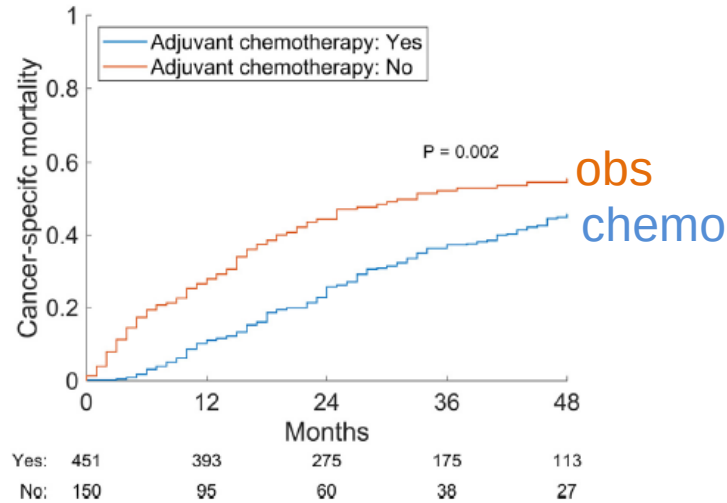


Fig. 3. Cancer-specific mortality (CSM) for stage III serous and clear cell cancers according to receipt of adjuvant chemotherapy.

Stage III

Multivariable analysis:

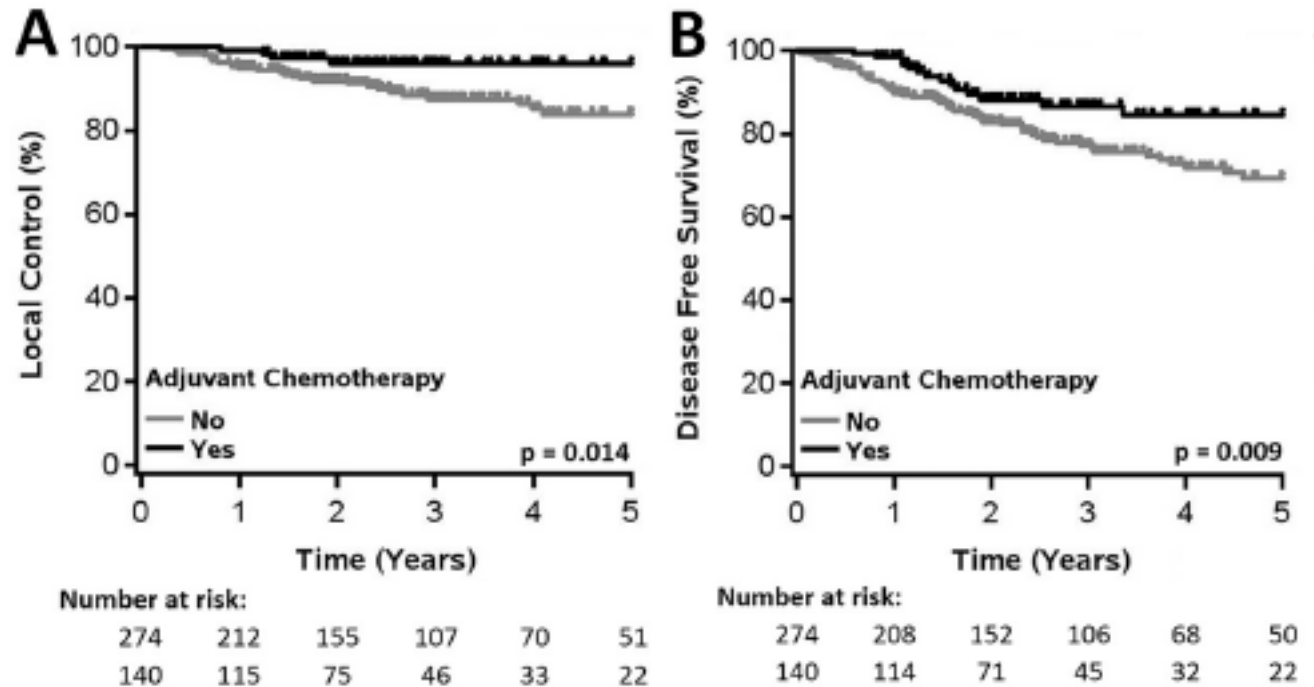
10% CSM benefit

55% → 45%

HR 0.66 p.002

Seer-Medicare data
N=1789 (80% serous)

Canadian pooled series IA serous



Local control

DFS

N=414 Pts 6 centres

Multivariable analysis:

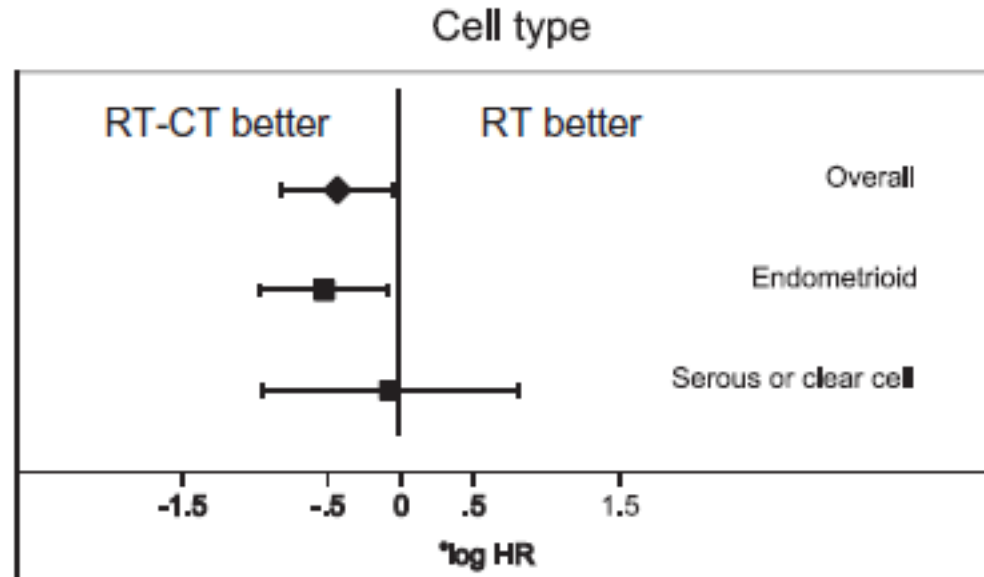
DFS + 15%,

69→84%

HR 0.50 p.009

CSS and OS ns

Hogberg RCT subgroup: Serous & clear cell



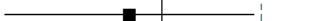
n=75 serous, 67 clear cell

**No convincing impression
chemo works better in
serous/clear cell**

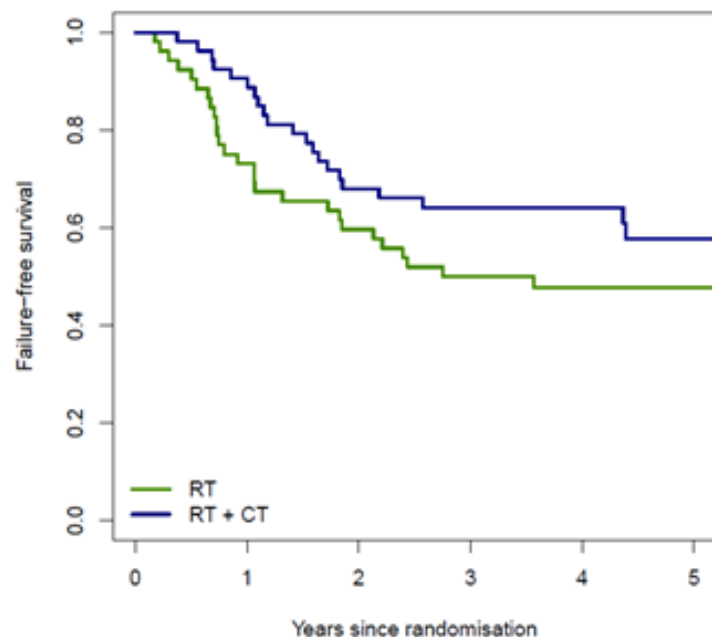
in this otherwise positive trial of
adj chemo (but small nos)

PORTEC 3 subgroup: Serous cancers

B

Histology and grade	Radiotherapy		Chemoradiotherapy			Chemoradiotherapy vs radiotherapy		
	Events/ patients	5-year failure-free survival (95% CI)	Events/ patients	5-year failure-free survival (95% CI)		HR (95% CI)	p value	p _{interaction}
Endometrioid grade 1-2	32/131	75% (66-82)	26/127	82% (74-88)		0.74 (0.44-1.26)	0.27	0.79
Endometrioid grade 3	32/106	69% (59-77)	28/106	74% (64-81)		0.73 (0.44-1.22)	0.23	
Serous, clear cell, other	39/93	59% (48-68)	29/93	69% (58-77)		0.60 (0.37-0.97)	0.036	

C. Failure-free survival for serous cancers



Multivariable analysis: n=186

+10% FFS

59 → 69%

CI 0.37-0.97, p 0.036

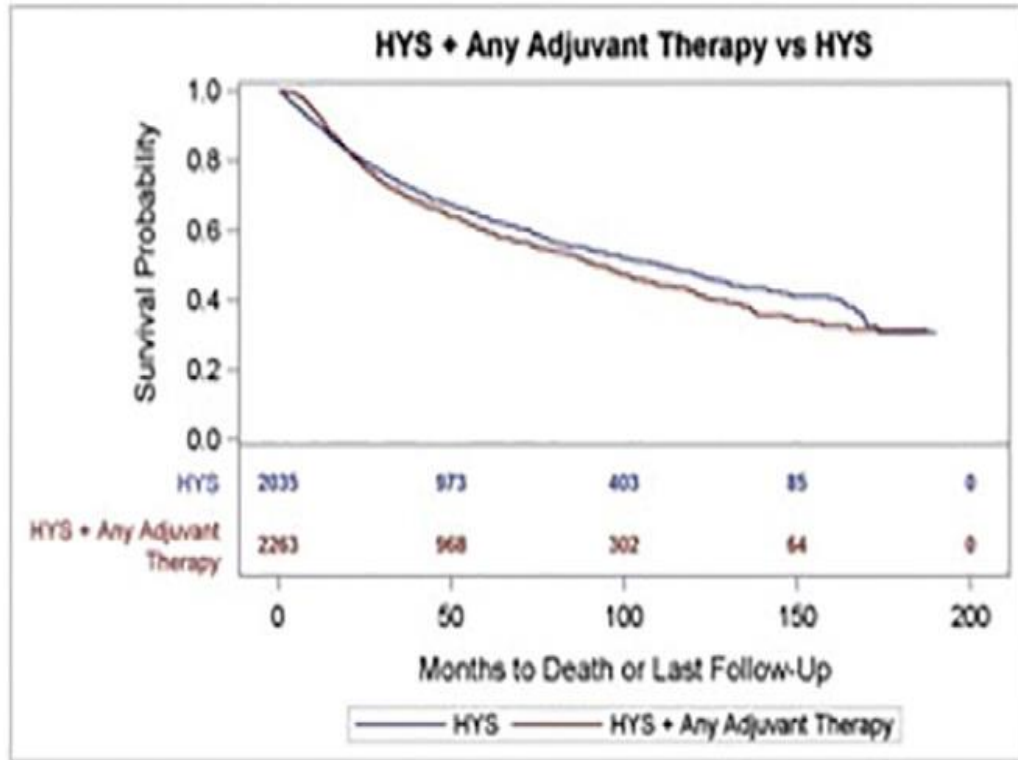
Summary table - serous

	Type of evidence		Stage I-II	Stage III	Comments
Serous /mix	Database	1800	+10% CSS	+10% CSS	
	Database	400	+15% DFS	-	
	Database	1000	+? OS	-	
	RCT subgroup (Hogberg)	140	ns	ns	
	(PORTEC)	186	+10%		

Summary table - serous

	Type of evidence		Stage I-II	Stage III	Comments
Serous /mix	Database	1800	+10% CSS	+10% CSS	
	Database	400	+15% DFS	-	
	Database	1000	+? OS	-	
	RCT subgroup (Hogberg)	140	ns	ns	
	(PORTEC)	186	+10%		

US NCDB Clear cell #1



N= 4298 Clear cell ca uterus

Multivariable analysis

No difference in any Rx vs surgery alone

US NCDB Clear cell #2

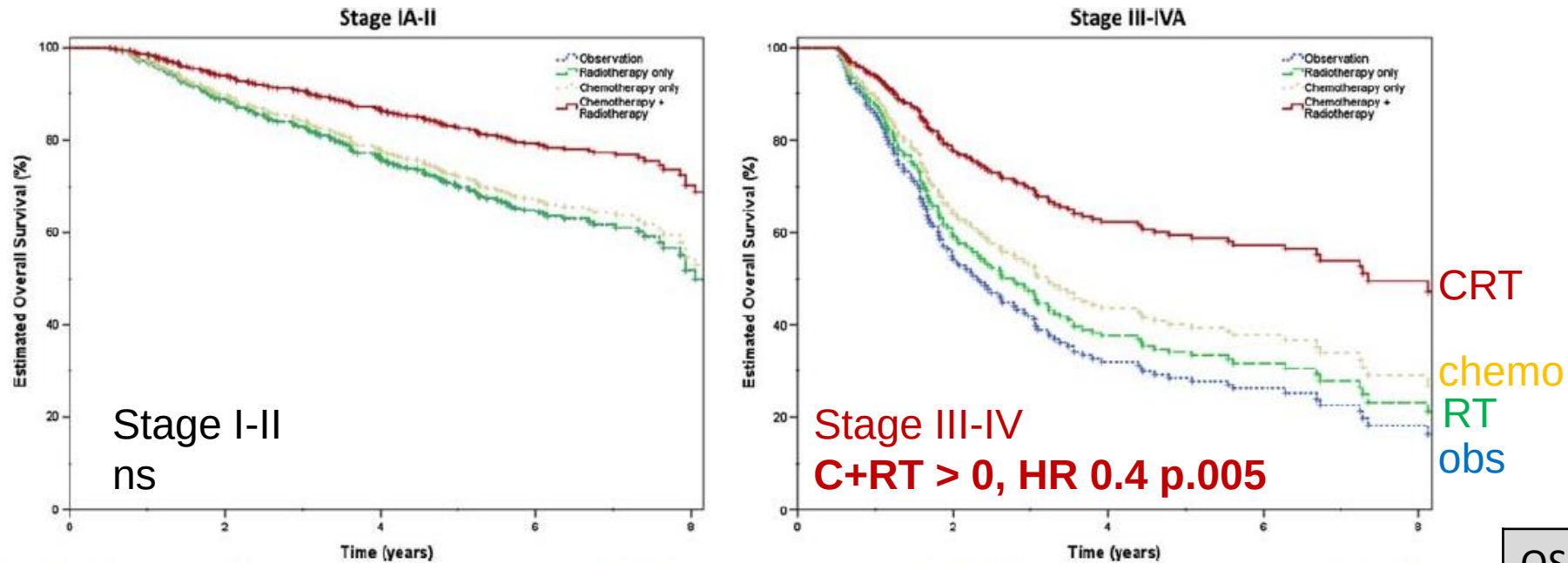


FIGURE 2. Overall survival estimates based on treatment approaches after IPTW adjustment among stage IA to II (left) and stage III to IVA patients (right).

N= 2504

Multivariable analysis with propensity score matching (IPTW)

OS	St I	St III-IV
Raw data	+10%	+17%
Multivar	ns	ns
PSM	ns	HR 0.4 p.005

Summary table – serous and clear cell

	Type of evidence		Stage I-II	Stage III	Comments
Serous /mix	Database	1800	+10% CSS	+10% CSS	
	Database	400	+15% DFS	-	
	Database	1000	+? OS	-	
	RCT subgroup (Hogberg)	140	ns	ns	
	(PORTEC)	186	+10%		
Clear cell	Database	4300	ns	ns	
	Database	2500	Ns	+ OS St III & IV	But includes stage IV

Serous discussion

- We don't really know what the right thing to do is in your rare cancer, as there are no good studies to help us
- Chemotherapy MAY reduce the chances of your cancer recurring, by around 10%, maybe even more
- But there might be no benefit at all, in which case you will only get the toxicity of chemotherapy
- To go ahead with Rx I need to know that you want this for the *possibility* of benefit, not for a *proven* benefit

SUMMARY SUMMARY

Nothing is mandatory

Stage I-II endometroid - Meh

Stage III endometiod – recoMmend

All stages serous – Mull over (recommend)

Stage I-II clear cell – Meh

Stage III clear cell – Mull over



thank you

AWAITED RCTs of Chemo

	n	Inclusion	Chemo	Comments
Does Chemo add to RT?				
GOG 249	560	I + HIR, II CC/serous and –ve cyto	VBT + carbo/pac x3 PRT	Early stage PRT vs VCBT +chemo
ENGOT-EN2- DGCG EORTC 55102	680	I G3 and II I-II serous/CC/Sq/undiff	(VBT) + carbo/pac (VBT)	Early stage Does chemo add to VBT
Does RT add to chemo?				
GOG 258	800	III-IVA (1998) I-II serous/CC +cyto	Carbo/pac + PRT/cis Carbo/pac	Late stage Does RT add to chemo??

PFS Stage III uterine ca varies A LOT

H.D. Homesley et al. / Gynecologic Oncology 112 (2009) 543–552

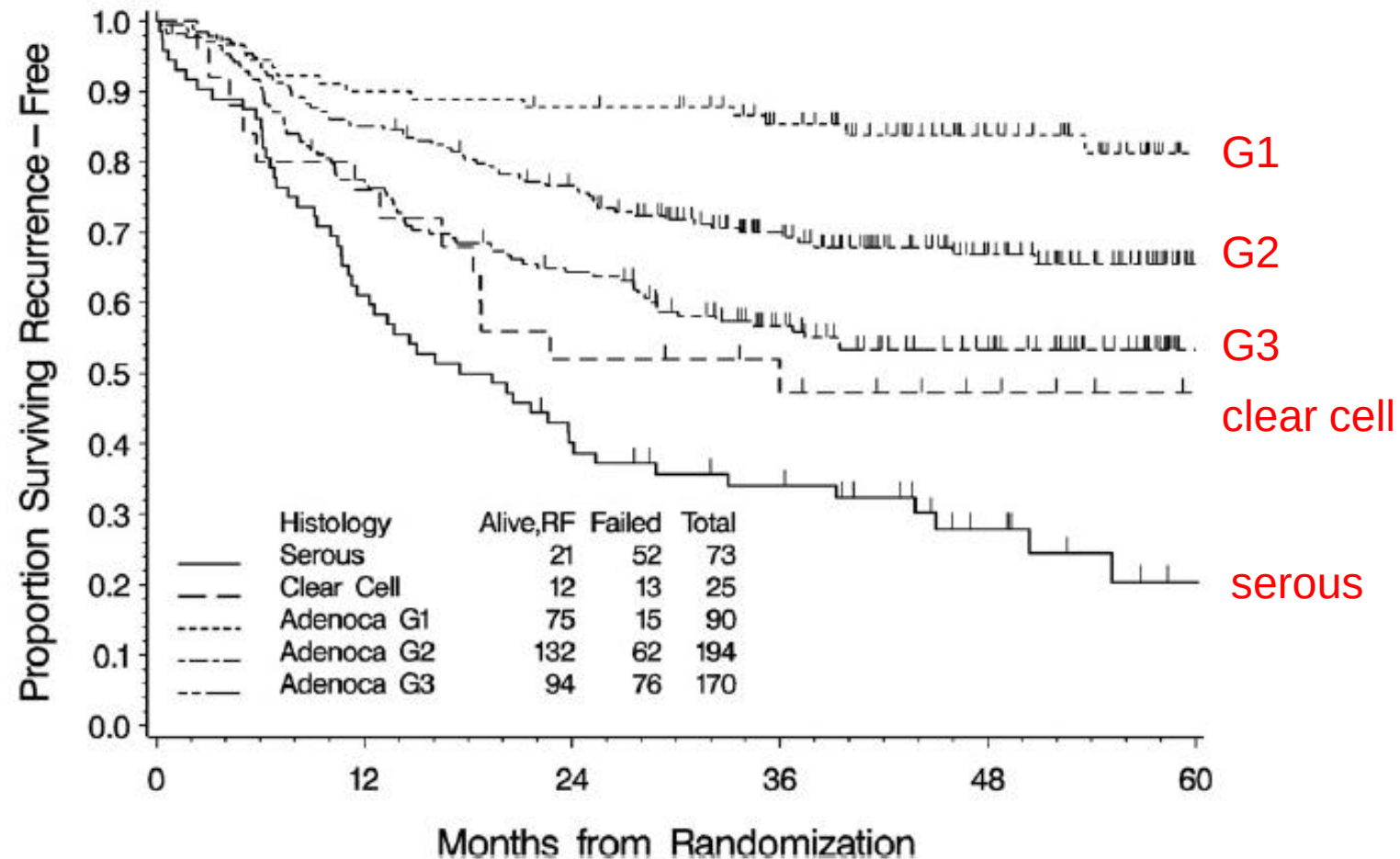
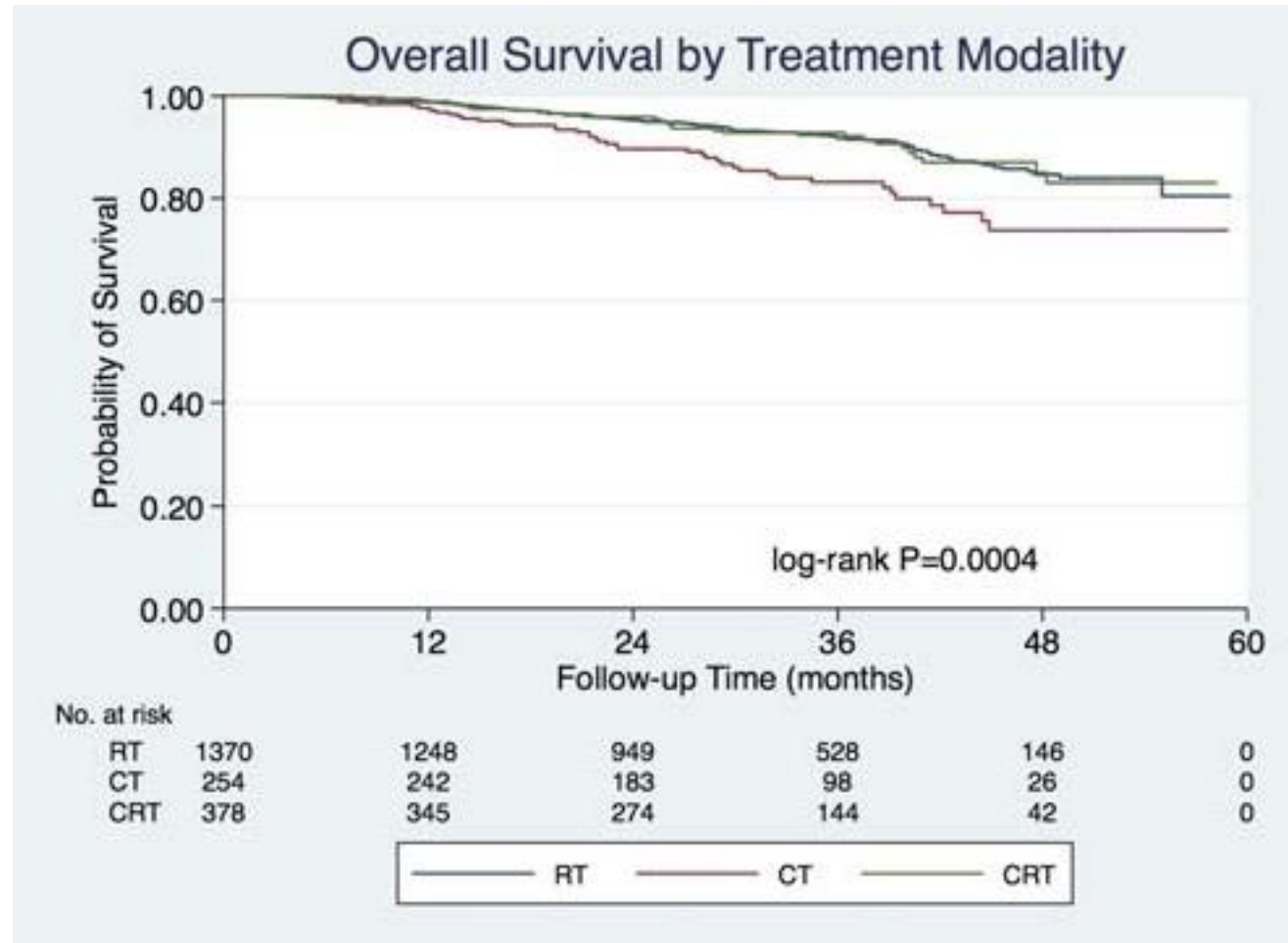
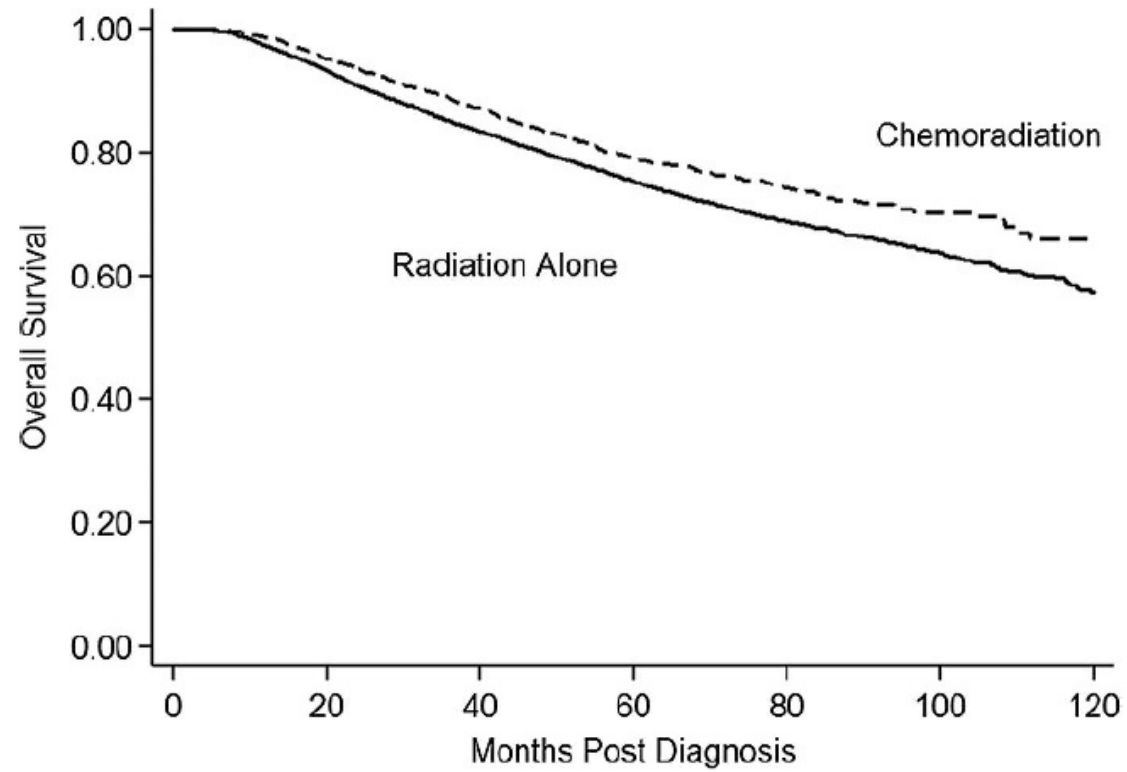


Fig. 6. Recurrence-free survival by tumor histology and grade.

Lester coll



boothe



aRT	8206	7197	5256	3658	2034	904	152
aCRT	3540	3089	1924	1082	517	180	24

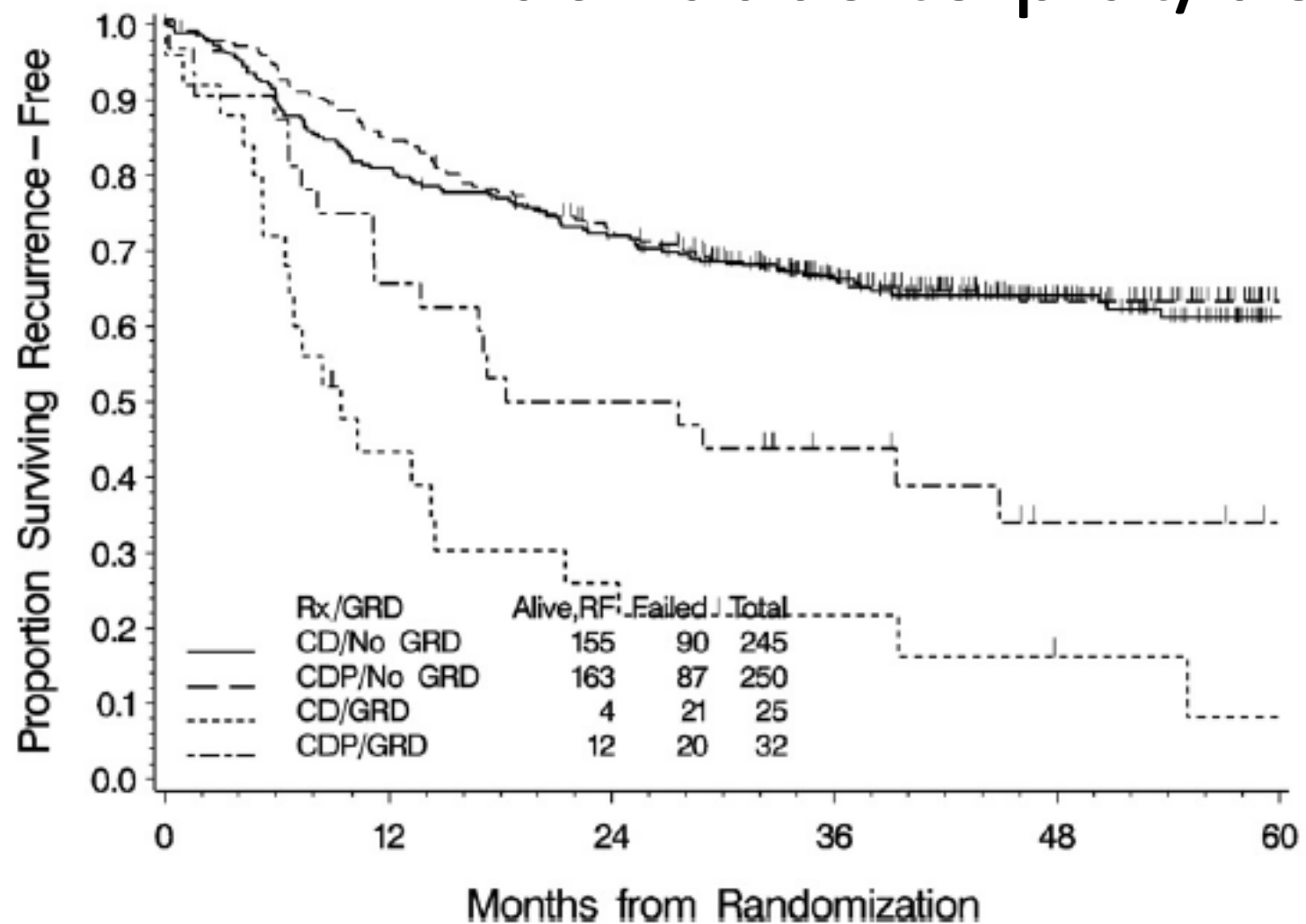
3. Survival analysis.

How to define risk?

	STAGE	Type II path	Myo invasion	Grade	LVSI	Risk +ve nodes (%)	CHEAT FOR MO
LOW (50%)	I	-	<50	1-2	-	<5	NONE
INT	I	-	>50	1-2	-	5-10	ONE
High INT	I	-	<50	3		10-20	
	I	-		1-2	+		
HIGH (15-20%)	I	-	>50	3		30-40	TWO Stage II+ Type II
	II or III	-					
			+				

Blank = doesn't matter what's in this box

Paclic adds to plat/dox if R2



R0/1 Either chemo

R2 cis/dox/paclic

R2 cis/dox

Fig. 5. Recurrence-free survival by residual tumor status.

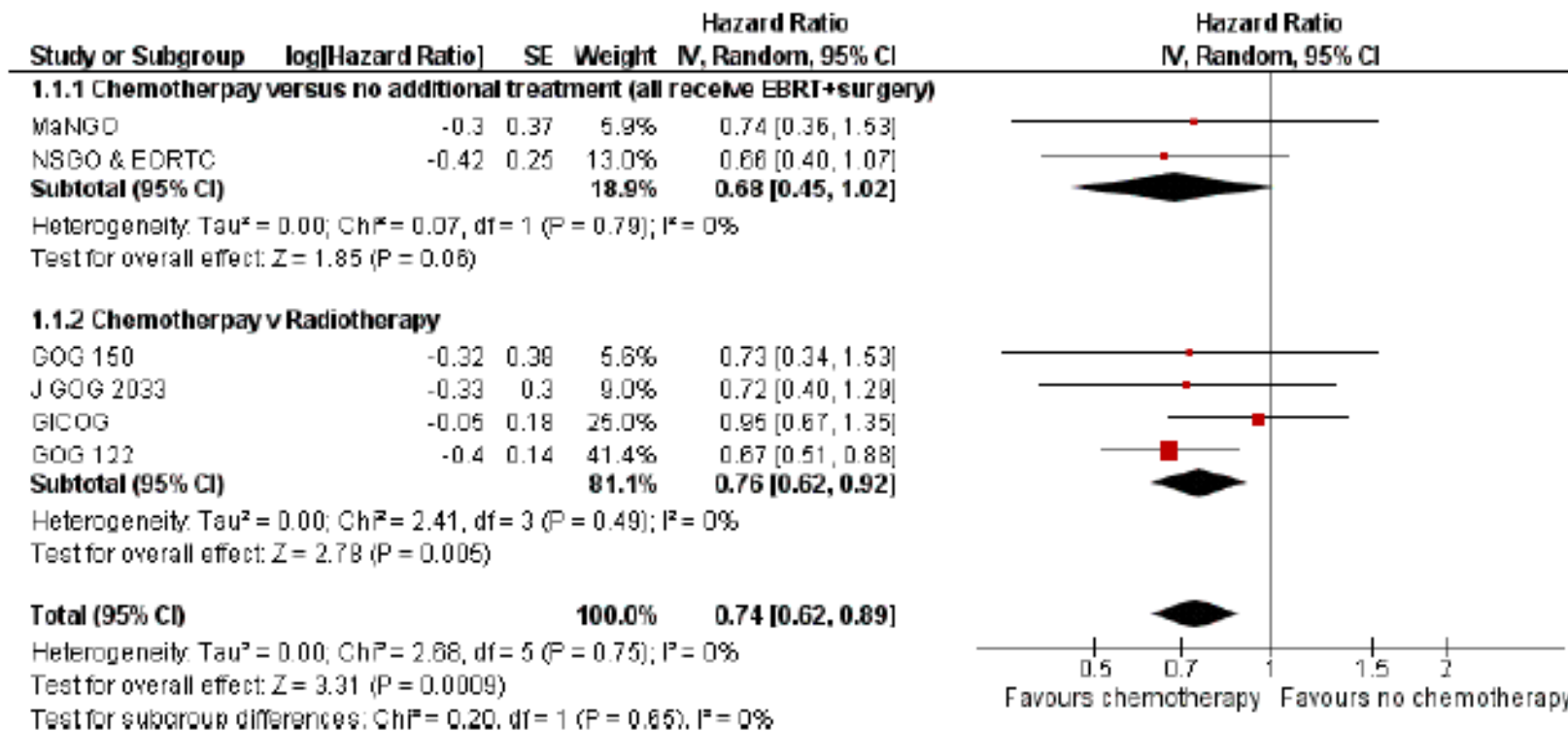
Chemo in Stage I-II serous/CC case series

(post 2009, n>50)

	n	USC:CC: mix	Stage	Recurrence % : no chemo→ chemo		5 yr OS % (CSS) [DFS]	
Xiang 2018 US database	1789	80:20:0	I-II			ns	ns
			III			(45→55)	+10%
Qu 2018 Canadian pooled data	190 224	64:9:27	IA M- IA M+	16→4	-12*	[69→84]	+15%
Vogel 2016	95 38	50:27:22	IA IB-II			80 →80 20 → 83	0
Velker 2016	77	70:22:8	IA M+/-	22 → 0	-22	-	
Liang 2016	85	66:14:15	Ia M-	10 →9	-1	97→100	
Van der Putten 2014	41 56 30	100:0:0	IA M- IA M+ II	10 →18 18 → 3 17 →30	+8 -15 +13	-	
Barney 2013	103	72:20:8	IAM-, M+,B	14 →6	-8	83 → 86	+3
Growdon 2011	84	69:0:31	IA-B	12 → 7	- 5	85 → 91	+6
TOTAL	1024	65:15:20	IAM+ most		-5-8		

All stages: Cochrane (PRE PORTEC & 249)

Figure 2. Forest plot from all trials of the hazard ratio for death from any cause (representing overall survival).



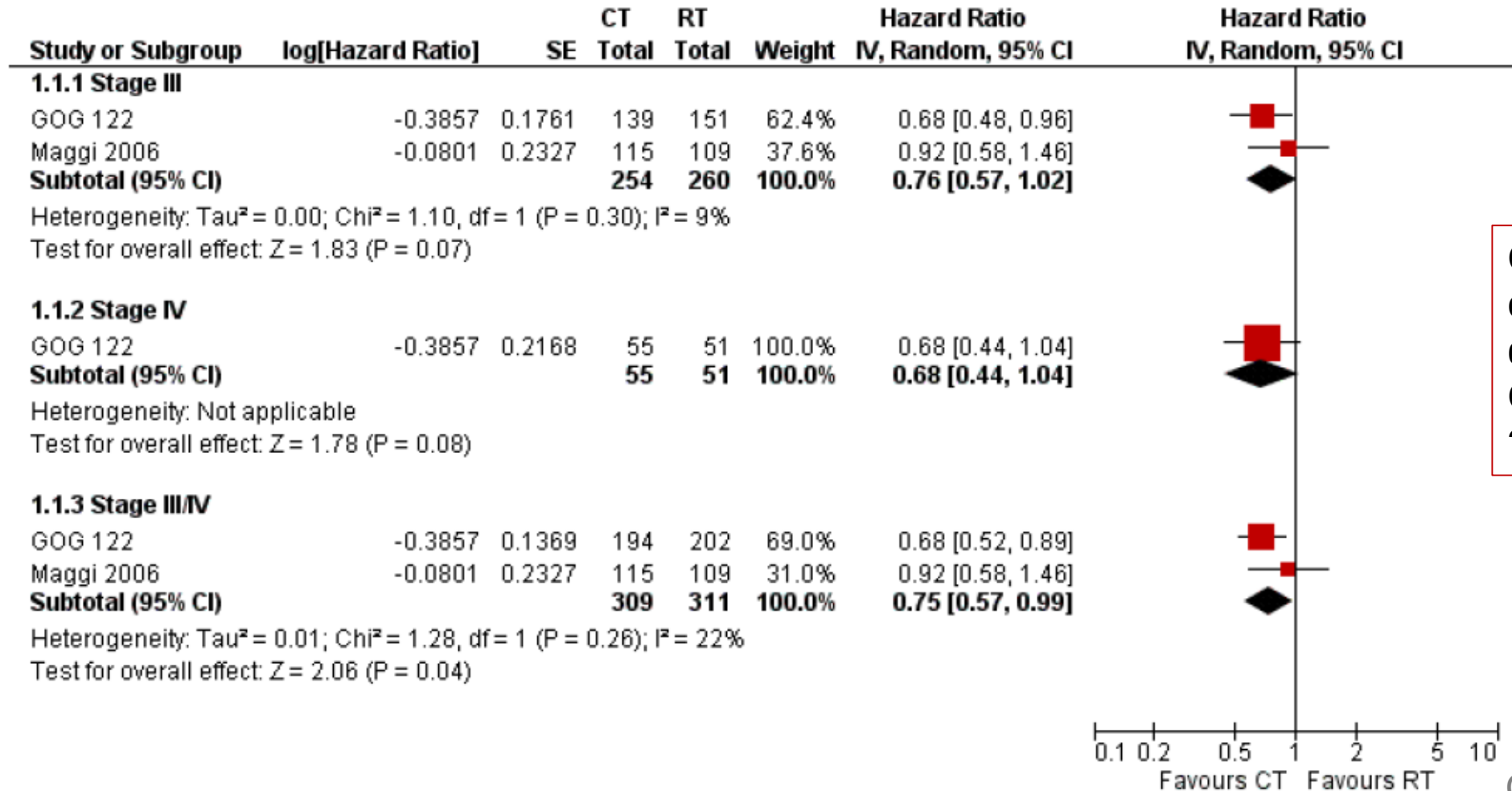
+4% OS
HR.74 p.0009

BUT:
Heavily influenced by
GOG 122 (stage III –IV)
Not GOG 249 (big, -ve)
Not PORTEC

TOO OLD - disregard

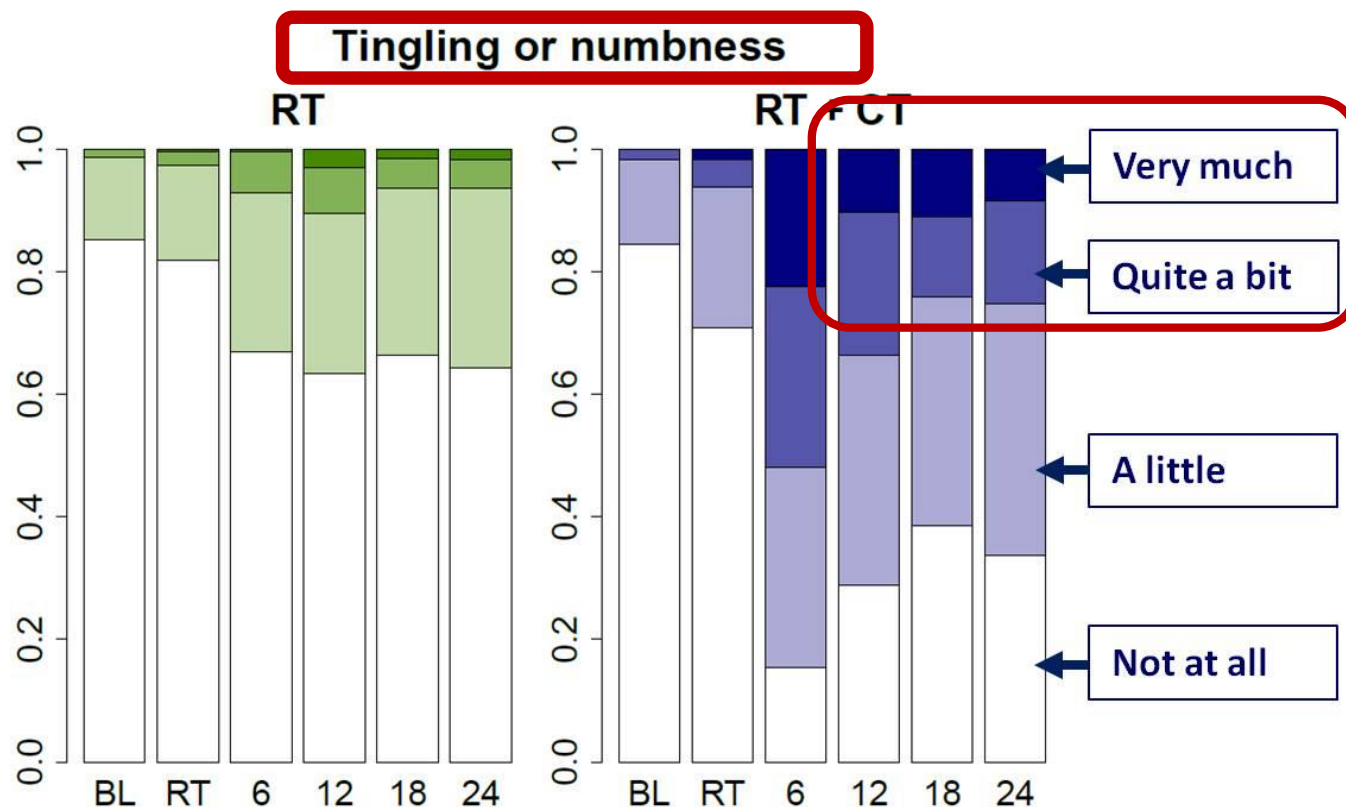
Cochrane Stage III and IV

Figure 3. Forest plot of comparison: I Chemotherapy vs radiotherapy, outcome: I.1 OS (Stage III/IV).



Concluded chemo
effective – but ALL
data essentially from
GOG122
???? JGOG trial

Quality of life

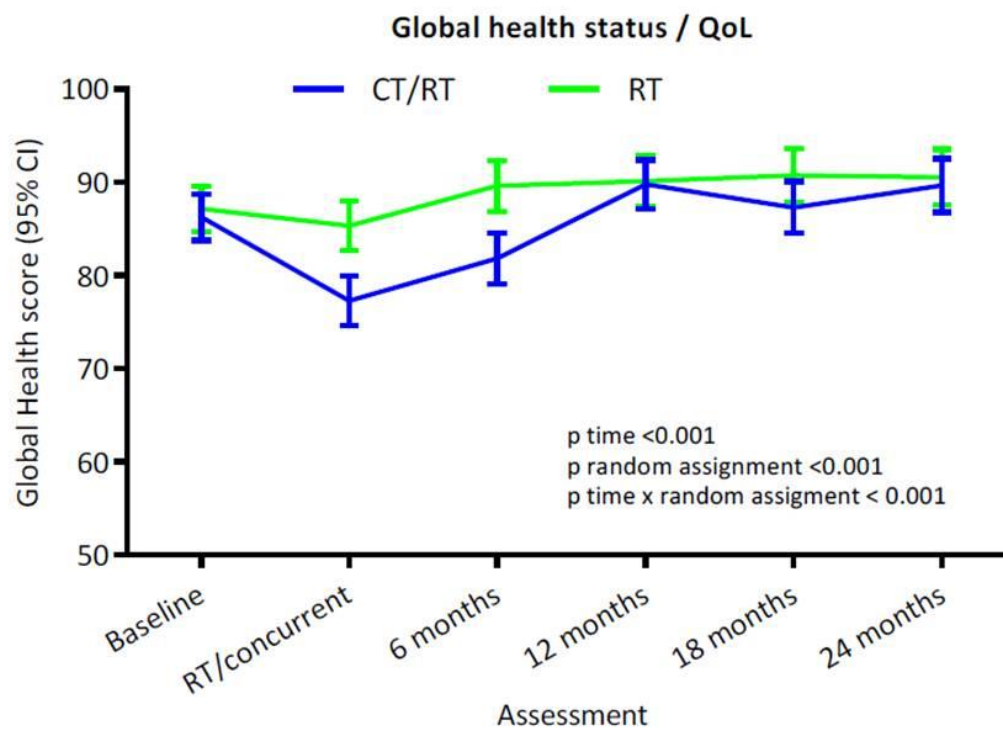
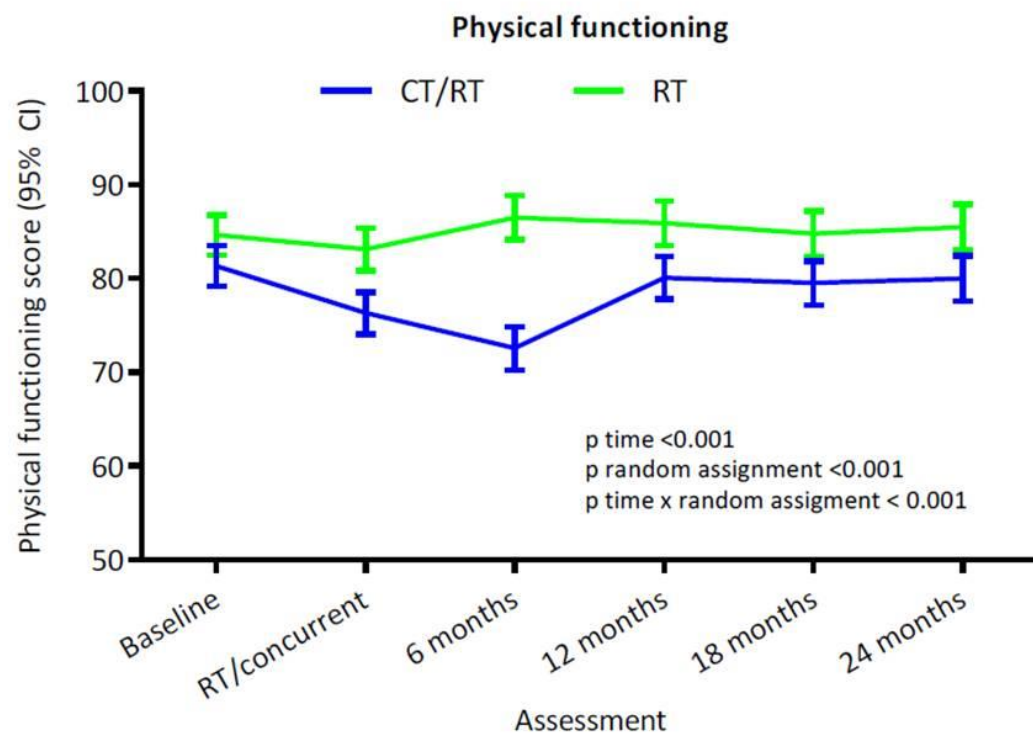


2 years later:

25% 'quite a bit' or 'very much' tingling/numbness

Sensory neuropathy ("quite a bit" or "very much"): 25% vs 6%

Quality of life



Chemo in Stage I-II serous/CC

	n	USC:CC:mix	Stage	5 yr survival		HR
Xiang 2018 US Seer-Medicare database	1789	80:20:0	I-II	ns	ns	ns
			III	45 → 55 CSS	+10%	.66 p.006
Qu 2018 Canadian pooled data	190 224	64:9:27	IA M- IA M+	69 → 84 DFS	+15%	0.47 p.009
Boothe 2016 US NCDB	1021	70:30:0	I-II	? OS	?	0.48
Vogel 2016	95 38	50:27:22	IA IB-II	80 → 80 20 → 83	0	
Velker 2016	77	70:22:8	IA M+/-	-		
Liang 2016	85	66:14:15	Ia M-	97 → 100		
Van der Putten 2014	41 56	100:0:0	IA M- IA M+	-		
Barney 2013	103	72:20:8	IAM-, M+,B	83 → 86	+3	
Growdon 2011	84	69:0:31	IA-B	85 → 91	+6	