

# Ovarian clear cell cancer- proposal to evaluate RT in early stage disease

on behalf of NCRI Gynae CSG

UK

# Background

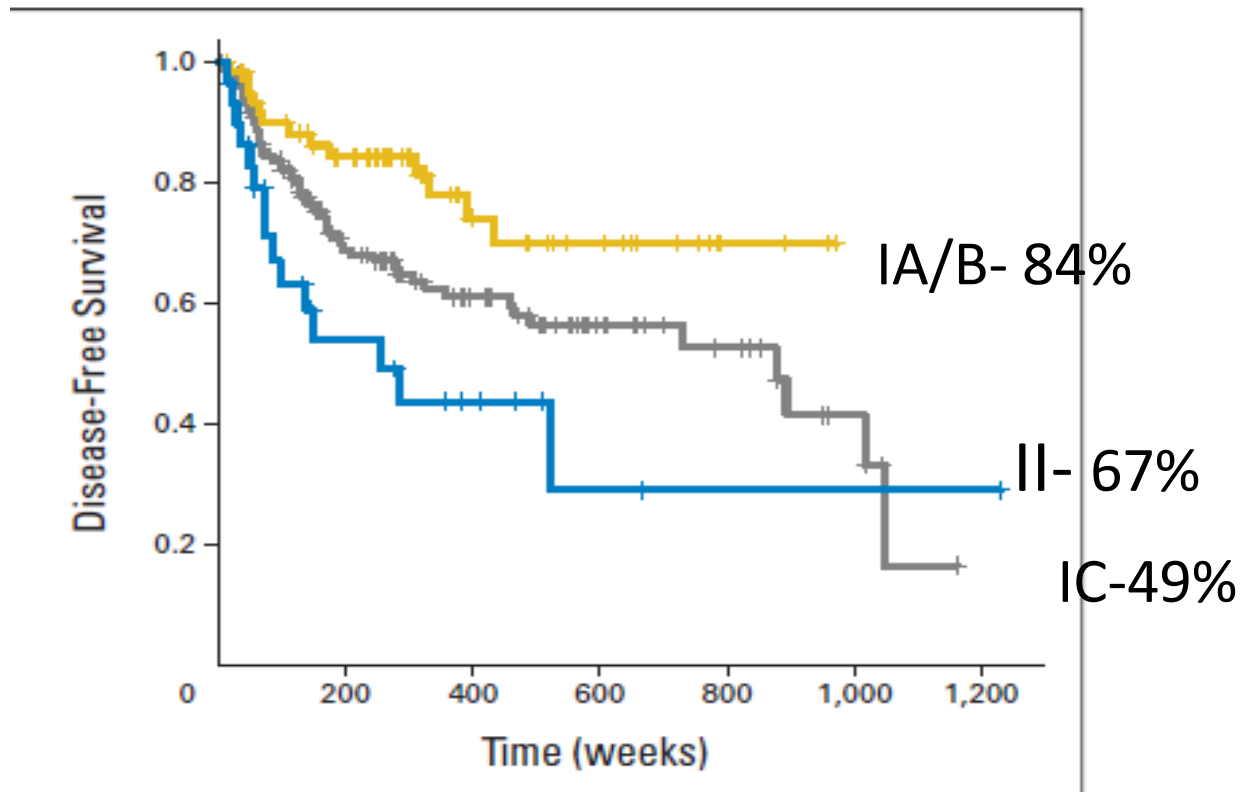
- Rare & distinct subtype of EOC 5-25% of all cases
- 47-80% stage I/II at diagnosis cf other EOC
- Most OCCC studies are retrospective /single institution and from Japan
- Lack of consensus on adjuvant treatment
- Relapsed disease refractory to chemo
- Some reports suggesting RT reduces relapse



# Hoskins et al JCO May10, 2012

- Patients with stage I/II OCCC treated in BC 2000-2008
- Retrospective review of charts- 241pts
- All underwent Surgery- TAH/BSO/oment/removal suspicious nodes and washings
- Protocol treatment 3xCarbo/taxol followed by WART, default was 6xC/P
- Treating oncologists were consistent in their approach to RT

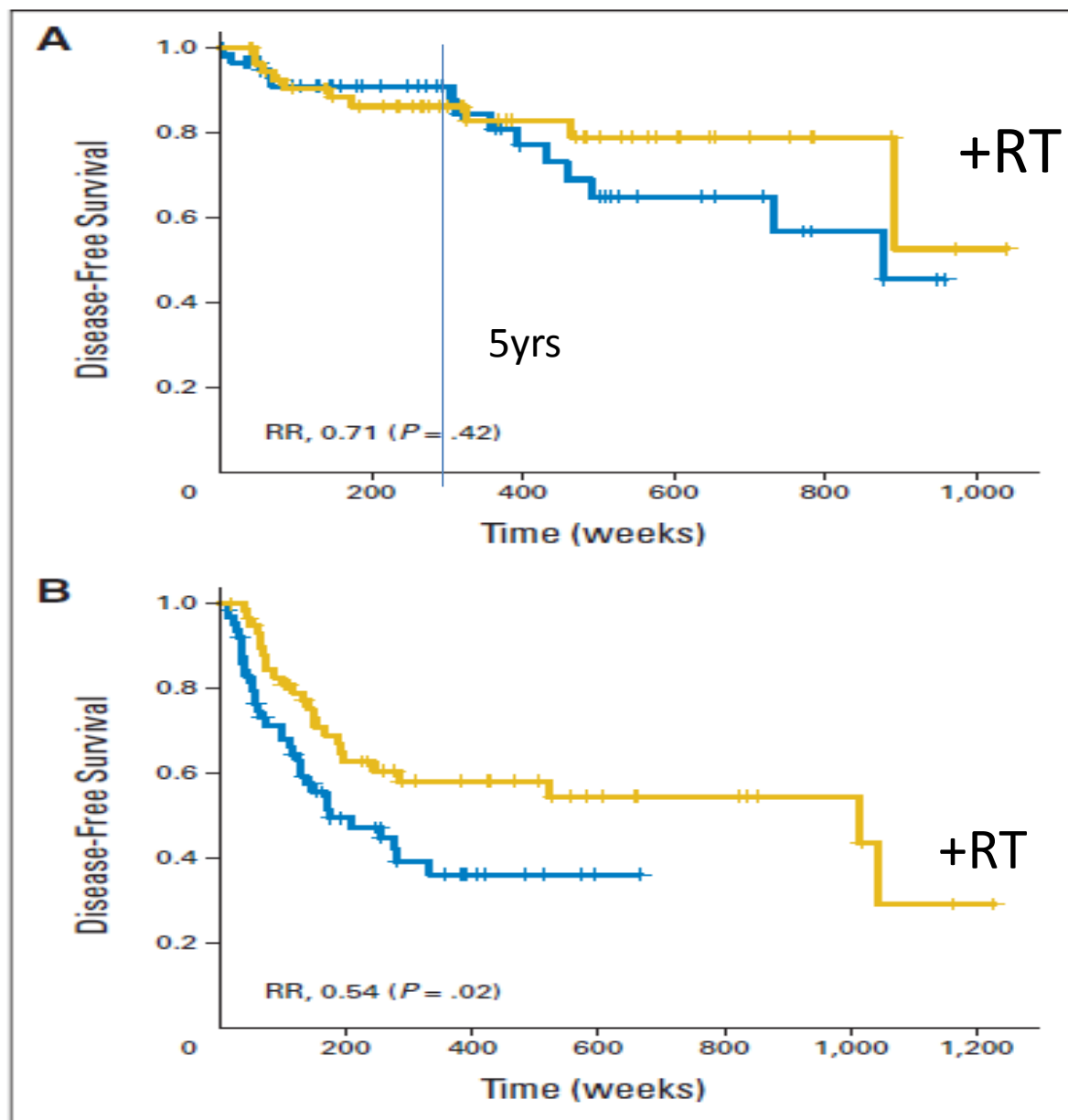
# Hoskins- DFS stage



**Fig 1.** Disease-free survival by stage/substage (gold, stage IA/IB, n = 64; gray, stage IC, n = 147; and blue, stage II, n = 30).

# Impact of Radiation

Hoskins et al JCO 2012



IA/B,  
IC rupture

IC other /II

**Fig 4.** Impact of irradiation. (A) Stage IA/B and IC defined by rupture alone (gold, with irradiation, n = 57; blue, no irradiation, n = 63). (B) All other stage IC and stage II (gold, with irradiation, n = 59; blue, no irradiation, n = 62). RR, relative risk.

# Five year DFS by stage

**Table 2.** Five-Year DFS in the Modern Era

Study Characteristic and DFS	Study					
	Chan et al <sup>4</sup>	Takano et al <sup>16</sup>	Suzuki et al <sup>25</sup>	Sugiyama et al <sup>10</sup>	Mizuno et al <sup>19</sup>	Current Study
No. of patients	1,411	254	143	49	82	241
Country	United States	Japan	Japan	Japan	Japan	Canada
Study period	1988-2001	1992-2003	1986-2006	1998-1998	1988-1996	2000-2008
Disease-free survival by stage, %						
IA	92	96		100	96	84
IC	77		77	63	76	64
IC (rupture alone)		89			86	88
IC (other)*		66			59	41
II	66	57			62	44

Abbreviation: DFS, disease-free survival.

\*Stage IC (other): cytologic positivity and/or surface involvement.



# Macrie et al 2014

- 56 pts ,
- 40 pts stage I/II , med FU 39m
- All pts receive chemo and 6/40 also had pelvic RT
- Overall 8/40 pts relapsed, med time 33m
  - 5 P only / 2 P +EP /1 EP
- 1/6 pts who had pelvic RT relapsed--PEP remaining 5/6 NED at last FU

# Recurrence by site

**TABLE 2.** Details of recurrence

**Time to Recurrence (Months)**

	Early Stage	Advanced Stage	
Median (range)	33.4 (4.6–91)	6.3 (1–38.3)	
Recurrence by initial stage			
IA		2	
IC		4	
IIA		1	
IIIB		1	
IIIA		1	
IIIB		1	
IIIC		10	
Sites of first recurrence, n (%)			
	Early Stage	Advanced Stage	Total
Pelvic	5 (8.1)	3 (4.8)	8 (12.9)
Pelvic + extrapelvic	2 (3.2)	4 (6.5)	6 (9.7)
Extrapelvic	1 (1.6)	5 (8.1)	6 (9.7)

Early stage  
8/40= 20%

5/8=62% P



# Recurrence rates in early OCCC

**TABLE 4. Recurrence in early-stage ovarian CCA studies**

Author	Stage (n)	Adjuvant Therapy	Recurrence Rate, %
Sugiyama et al <sup>7</sup>	IA–C (49)	CT	29
	II (10)	CT	30
	III (31)	CT	62
Timmers et al <sup>24</sup>	IA–IIA (63)	Observation or CT	25.4
Hoskins et al <sup>20</sup>	IA–IIC (125)	CT	39.2
	IA–IIC (116)	CT and WART	30.2
Takano et al <sup>25</sup>	I (195)	CT	18.0
	I (24)	Observation	4
Present study	IA–IIC (40)	CT and PRT*	17.5
	III (16)	CT	43.8

\*Only 6 patients treated with RT.  
CT, platinum chemotherapy; PRT, pelvic RT.

# Pelvic recurrence

**TABLE 1.** Recurrence sites

	<b>IA /Rupture-IC Group (n = 134)</b>	<b>Other-IC Group (n = 50)</b>	<b><i>P</i></b>
Patients with recurrence	8.2% (11/134)	32% (16/50)	<0.001
Recurrence sites			
Pelvic	27.2% (3/11)	10.1% (3/16)	0.22
Distant*	36.3% (4/11)	12.5% (2/16)	
Peritoneal dissemination	36.3% (4/11)	68.7% (11/16)	

\*Distant sites included metastasis of lung, liver, or lymph nodes in the mediastinum.

22%



# Radiotherapy- other retrospective reports

- Swenerton et al 2010
  - >300 pts C / E/ M stage I/II -40% reduction in DSM with chemo + WART
  - 20 % decrease in initial pelvic relapse with C &RT
- Nagai et al 2007
  - 28 pts CAP or WART sequential cohorts
  - 5yr DFS 25% v 81% with RT

# Rationale

- Almost 25% pts who relapse do so in pelvis
- Low doses of RT given to whole abdomen unlikely to contribute to control
- Unlikely that 3 cycles chemo sufficient to improve outcome
- Role of chemo in this disease is unknown- OCCC has been treated like HG serous



# Proposal

- Randomised phase III trial of post op pelvic RT alone vs Chemo in early stage OCCC
- Full surgical staging
- Inclusion-all stage I/II except stage Ia, fit to receive Chemo / RT
- Chemo- Carbo/ Taxol std doses q21days x6
- RT- 45Gy /25# / 5 weeks / pelvis /IMRT
- International collaboration required

# Stats

- Consider HR 0.65 & outcome in control/  
chemo arm
- 5 yr DFS in control 50%----require 408pts  
60%-----516pts  
70%----- 690pts
- 80% power at 5%level

