THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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CHORUS Paper Supplementary Appendix

Contents

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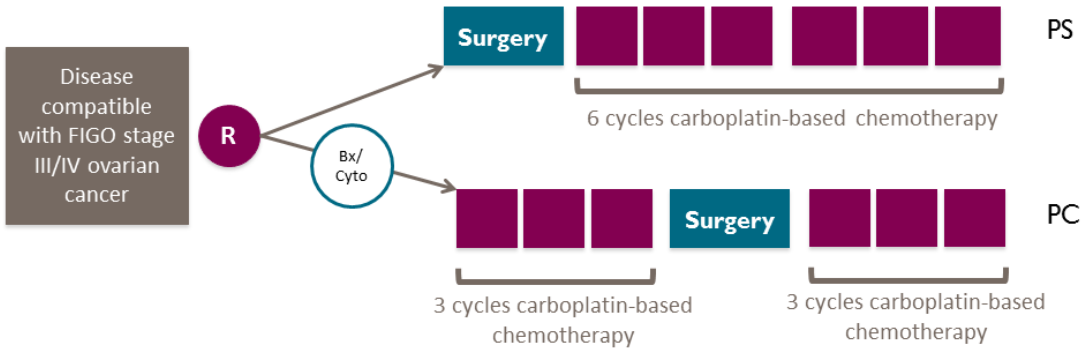
2. Supplementary figures and tables

Supplementary figure 1. Trial Design



PS = primary surgery, PC = primary chemotherapy, R = randomised, Bx= biopsy, Cyto = cytology

Supplementary table 1. Duration of therapy in each arm

		Primary surgery	Primary chemotherapy
Time from randomisation to first allocated treatment (days)[1]	Median	13	14
	Range	1 – 69	0 – 55
	IQR	7 – 18	9 – 20
	n	251	253
Time from randomisation to surgery in neoadjuvant chemotherapy group (days)[2]	Median		87
	Range		20 – 216
	IQR		80 – 97
	n		219
Time from surgery to first post-operative chemotherapy (days)[3]	Median	32	29
	Range	5 – 82	7 – 113
	IQR	26 – 41	22 – 35
	n	214	199
	>= 8 weeks	11 (5%)	3 (1%)
Time from randomisation to completion of protocol treatment (days)[4]	Median	153	156
	Range	1 – 376	7 – 235
	IQR	120 – 166	137 – 170
	n	266	255

n = number of women included in each summary. Exclusions from summaries are:

[1]Primary surgery (PS): 15 women had chemotherapy as first trial treatment; 10 had no trial treatment. Primary chemotherapy (PC): 2 women had surgery as first trial treatment: 19 had no trial treatment.

[2]PC: 19 had no trial treatment; 36 had no surgery following chemotherapy.

[3]PS: 10 had no treatment; 11 had chemotherapy first with no surgery afterwards; 39 had no post-op chemotherapy (1 of whom had pre-op chemo); 1 with unknown post-op treatment status; 1 had post-op chemotherapy, but dates not reported.

PC: 19 had no treatment; 36 had no surgery following chemotherapy; 17 had no post-op chemotherapy (1 of whom had primary surgery); 3 had post-op chemotherapy, but dates not reported.

[4]PS: 10 had no treatment. PC: 19 had no treatment.

Supplementary table 2. Grade 3/4 adverse events occurring during chemotherapy administration

Symptom	Primary surgery (n=228)	Primary chemotherapy (n=254)
Any grade 3/4 toxicity	110 (49%)	102 (40%)
Nausea	13 (6%)	10 (4%)
Vomiting	19 (8%)	14 (6%)
Neurotoxicity	9 (4%)	6 (2%)
Neutropenia	45 (20%)	40 (16%)
Thrombocytopenia	19 (8%)	9 (4%)
Anaemia	21 (9%)	12 (5%)
Febrile neutropenia	4 (2%)	3 (1%)
Renal toxicity	2 (1%)	0 (0%)
Other*	60 (27%)	66 (26%)
Missing	*3*	*1*

* Others including: Fatigue (13 vs 12); Constipation (7 vs 7); Allergic Reaction (3 vs 5); Diarrhoea (4 vs 4); Pain, abdominal (4 vs 4); Thrombosis/Embolism (2 vs 7); Leucopenia (5 vs 3); Grade 5 neutropenic sepsis (1, PC).

This table includes only women who had chemotherapy. Exclusions are, PS: 10 had no treatment; 38 had no post-operative chemotherapy. PC: 19 had no treatment; 1 had primary surgery with no post-op chemotherapy.

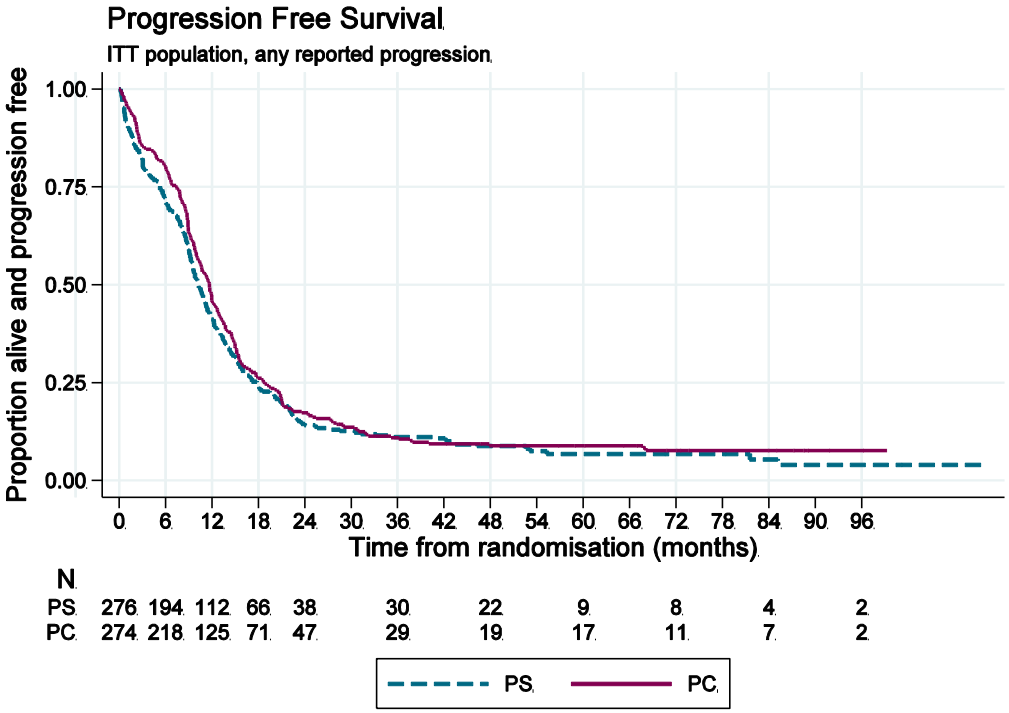
Supplementary table 3. Types of event

		Primary surgery (n=276)	Primary chemotherapy (n=274)
Current status	Alive without progression	28	26
	Alive with progression	17	28
	Dead	231	220
Cause of death	Disease	205	194
	Treatment	3	1
	Other/unknown	23 Ischaemic bowel; Pulmonary oedema; Pneumonia post surgery; Post-op complications; Pulmonary embolism (3); Unknown (10); Cervical cancer; Unspecified; multiple organ failure; septic pneumonia; Cardiac disease; Femoral embolism.	25 Cardiac failure; Acute GI bleeding; Bronchial pneumonia; Cardiac dysfunction; Heart attack (2); Ovarian cancer or heart failure; Small bowel obstruction (2); Colorectal cancer; Post-operative; Stroke with complications; Pulmonary embolism (2); Pelvic vein thrombosis; Unknown (9)

Supplementary table 4. Event table

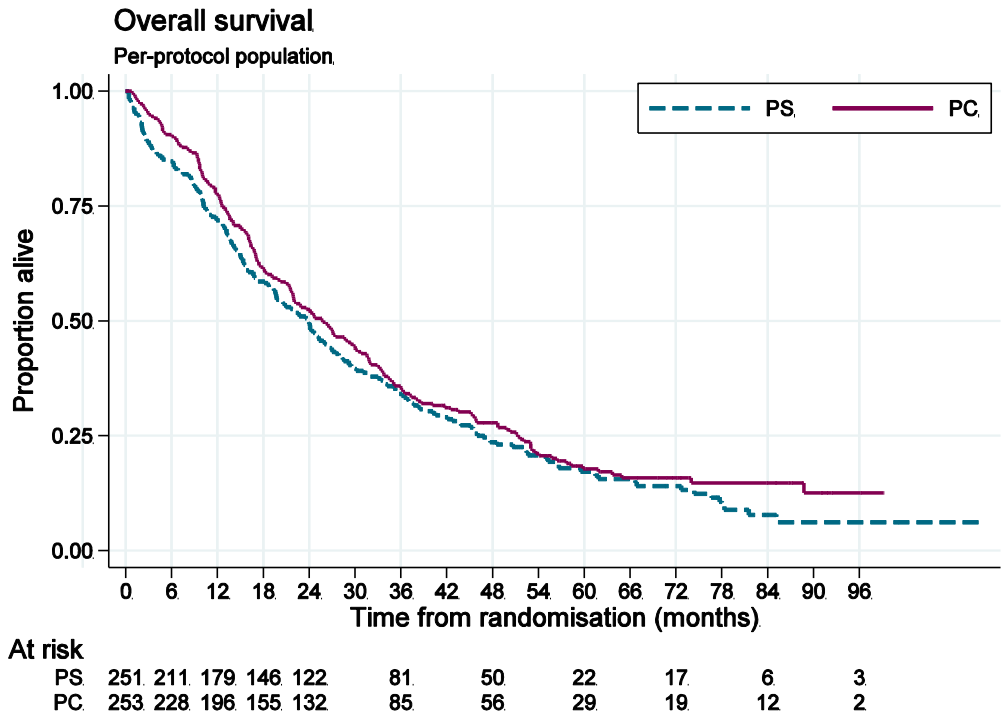
A. Intention-to-treat population			
		Primary surgery (N=276)	**Primary chemotherapy (N=274)**
Overall survival	**Events**	231	220
	Median (months) (95% CI)	22.6 (18.6, 25.9)	24.1 (21.0, 28.7)
	1-year	69%	75%
	3-year	32%	34%
	HR		0.87
	95% CI		(0.72, 1.05)
	One-sided 90% CI		(NA, 0.99)
Progression-free survival (confirmed events only)	**Events**	248	248
	Median (months) (95% CI)	10.7 (9.7, 11.9)	12.0 (10.6, 13.1)
	HR (95% CI)		0.90 (0.76, 1.08)
Progression-free survival (including unconfirmed and CA125 only events)	**Events**	252	249
	Median (months) (95% CI)	10.3 (9.3, 11.3)	11.7 (10.4, 12.5)
	HR (95% CI)		0.90 (0.75, 1.07)
B. Per protocol population			
Overall survival	**Patients**	251	253
	Events	209	203
	Median (months) (95% CI)	23.7 (19.5, 26.9)	25.8 (21.7, 30.1)
	1-year	72%	77%
	3-year	34%	35%
	HR (95% CI)		0.89 (0.78, 1.01)

Supplementary figure 2. Kaplan-Meier Curve for secondary analysis of progression-free survival, intention-to-treat population



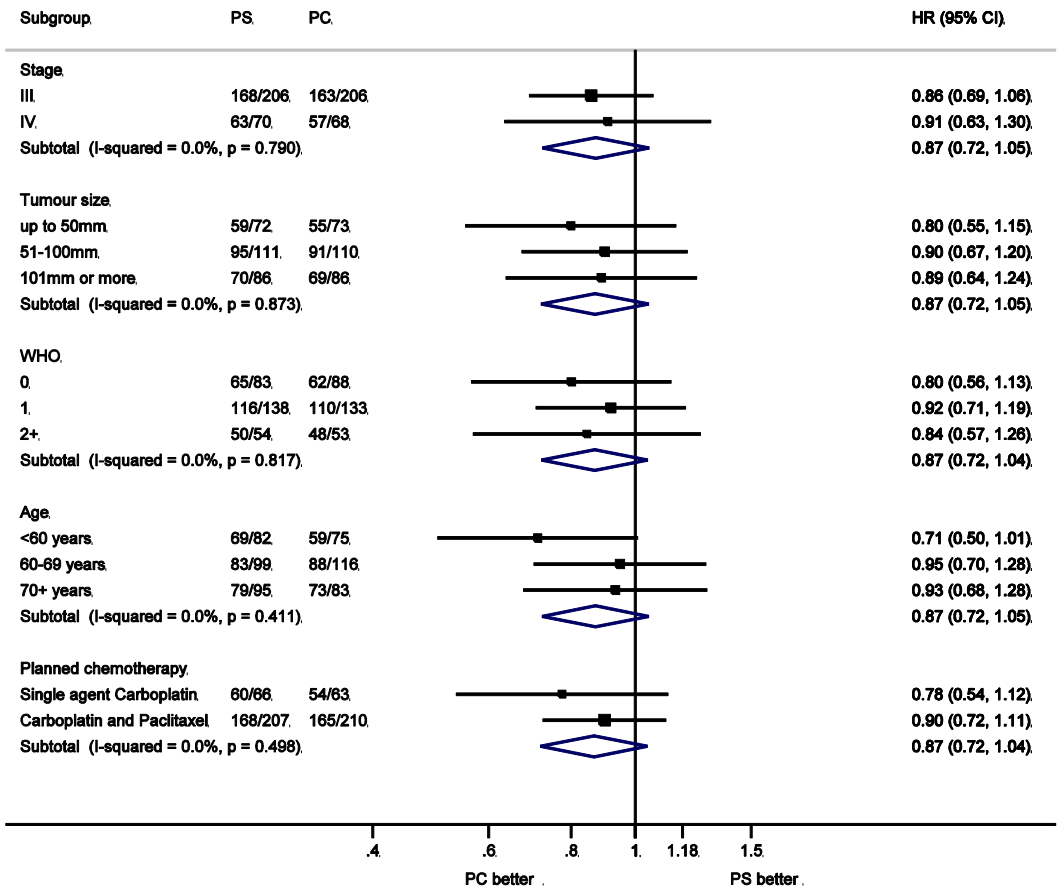
This analysis includes all reported progression events, including confirmed radiological or clinical progression plus CA125-only progression and unconfirmed events.

Supplementary figure 3. Kaplan-Meier Curve for overall survival, per-protocol population



The per-protocol population comprises women who commenced their allocated treatment: 251 in the PS group and 253 in the PC group.

Supplementary figure 4. Exploratory sub-group analyses

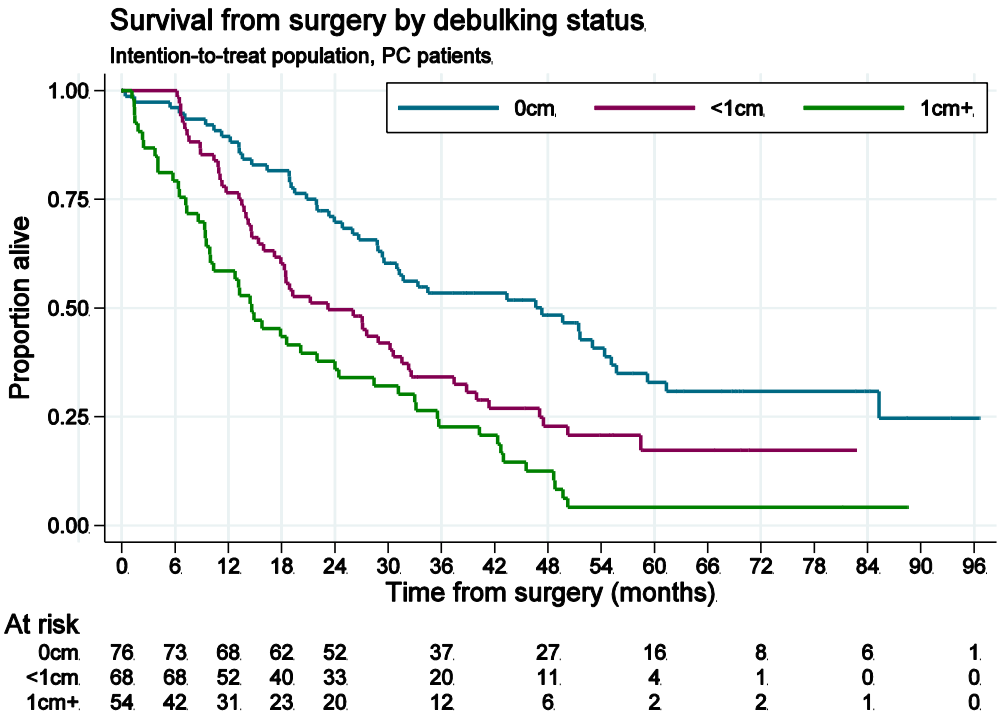


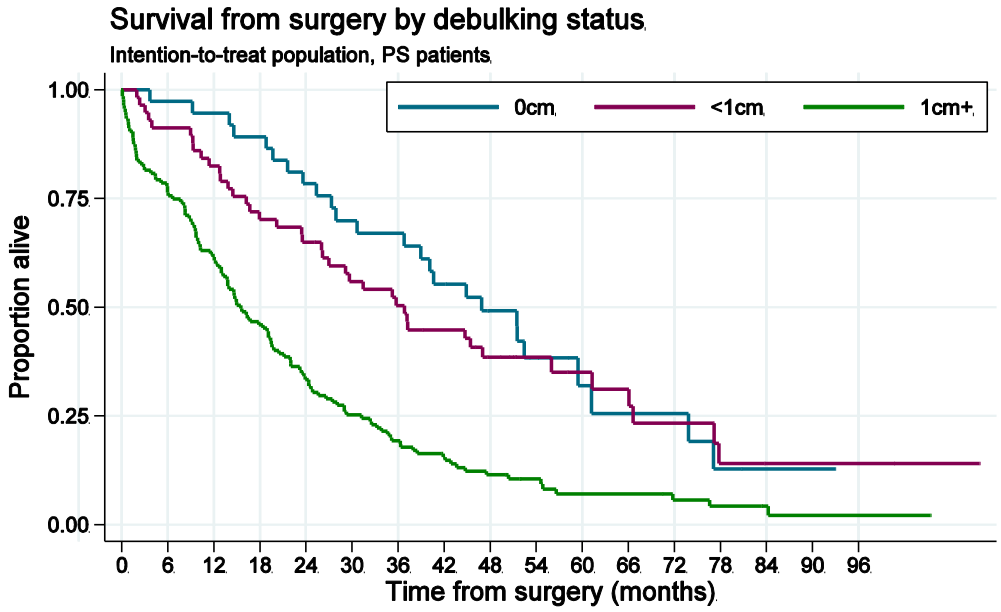
Supplementary table 5. Baseline characteristics of patients enrolled in CHORUS and EORTC 55971

		CHORUS (n=550)	EORTC 55971 (n=670)
Age	Median	65	62(PS group) 63 (PC group)
	Range	26 – 88	25-86
WHO PS	0	171 (31%)	300 (45%)
	1	271 (49%)	284 (43%)
	2	102 (19%)	84 (13%)
	3	5 (<1%)	-
	Missing	1	2
Clinical FIGO Stage	III	412 (75%)	510 (76%)
	IV	138 (25%)	158 (24%)
	Other	-	2 (<1%)
Tumour size (cm)	0cm	-	3 (<1%)
	>0-2cm	26 (5%)	11 (2%)
	>2-5cm	119 (22%)	175 (28%)
	>5-10cm	221 (40%)	178 (28%)
	>10-20cm	158 (29%)	218 (34%)
	>20cm	14 (3%)	50 (8%)
	Unmeasurable disease	12 (2%)	-
	Missing		35
Histologic type*	Serous	390 (85%)	414 (62%)
	Mucinous	6 (1%)	19 (3%)
	Endometrioid	16 (3%)	16 (2%)
	Clear cell	17 (4%)	10 (1%)
	Undifferentiated	14 (3%)	159 (24%)
	Mixed	2 (<1%)	3 (<1%)
	Other or unknown	15 (3%)	-
	Other or unknown	-	49 (7%)
	Missing	14	-
Histologic grade*	Poorly differentiated	314 (77%)	275 (69%)
	Moderately differentiated	70 (14%)	98 (25%)
	Well differentiated	25 (6%)	24 (6%)
	Unknown/missing	65	273

***** In CHORUS confirmation of histological diagnosis was not required prior to study entry. The histologic type and grade reported here were obtained at surgery.

Supplementary Figure 5. Kaplan-Meier Curves for survival post-surgery, by level of debulking achieved.





At risk

0cm	37	36	35	33	28	23	14	5	4	1	0
<1cm	57	52	47	40	37	27	16	9	6	2	2
1cm+	137	103	83	62	45	26	14	6	4	2	1

Supplementary Table 6. Survival from surgery, by level of debulking achieved.

		Primary surgery	Primary chemotherapy
0cm	Patients	37	76
	Events	25	48
	Median (months) (95% CI)	46.9 (30.7, 59.5)	47.3 (29.3, 55.1)
>0cm, <=1cm	Patients	57	68
	Events	40	52
	Median (months) (95% CI)	36.8 (26.0, 56.0)	23.2 (17.2, 31.5)
>1cm	Patients	137	54
	Events	126	50
	Median (months) (95% CI)	15.5 (13.0, 19.5)	14.7 (9.5, 24.0)

Note: P-value for interaction between treatment arm and debulking level is 0.976.

Supplementary Table 7. Type of surgical procedure.

		Primary surgery	Primary chemotherapy
Incision	Vertical midline	245 (98%)	200 (95%)
	Pfannenstiel / transverse	1 (<1%)	1 (<1%)
	Other	5 (2%)	9 (4%)
Hysterectomy	Not performed	67 (27%)	25 (12%)
	Previously performed	36 (14%)	33 (15%)
	Total hysterectomy	131 (52%)	146 (68%)
	Sub-total hysterectomy	16 (6%)	10 (5%)
Bilateral salpingo-oophorectomy	Not performed	61 (24%)	22 (10%)
	Previously performed	2 (1%)	1 (<1%)
	Performed	188 (75%)	190 (89%)
LUSO	Not performed	213 (88%)	164 (83%)
	Previously performed	1 (<1%)	1 (1%)
	Performed	28 (12%)	33 (17%)
RUSO	Not performed	204 (84%)	160 (81%)
	Previously performed	4 (2%)	1 (1%)
	Performed	34 (14%)	37 (19%)
Omentectomy	Not performed	36 (14%)	11 (5%)
	Supra and infracolic	120 (48%)	123 (58%)
	Infracolic omentectomy	63 (25%)	67 (32%)
	Omental biopsy	31 (12%)	11 (5%)
Pelvic nodes	Not performed	228 (91%)	193 (91%)
	Sampled	15 (6%)	16 (8%)
	Total lymphadenectomy	7 (3%)	2 (1%)
Para-aortic nodes	Not performed	231 (92%)	204 (97%)
	Sampled	16 (6%)	6 (3%)
	Total lymphadenectomy	3 (1%)	1 (<1%)
Stoma formation	Not performed	226 (90%)	202 (95%)
	Colostomy	11 (4%)	7 (3%)
	Ileostomy	14 (6%)	3 (1%)
Bowel resection	Not performed	224 (89%)	195 (92%)
	Small bowel resection	7 (3%)	1 (<1%)
	Large bowel resection	19 (8%)	15 (7%)
	Small and large bowel	1 (<1%)	2 (1%)
Other procedure	No	176 (70%)	148 (70%)
	Yes	75 (30%)	63 (30%)