A randomised phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer.

The GCIG INTERLACE trial

M. McCormack[1], D. Gallardo[2], G. Eminowicz[1], P. Diez[3], L. Farrelly[4], C. Kent[5], E. Hudson[6], M. Panades[7], T. Mathew[8], A. Anand[9], M. Persic[10], J. Forrest[11], R. Bhana[12], N. Reed[13], A. Drake[14], H. Stobart[15], A. Mukhopadhyay[16], A.M. Hacker[4], A. Hackshaw[4], J.A. Ledermann[4]

[1]University College Hospital NHS Trust, London, UK; [2]INCAN, Mexico; [3]RTTQA, Mount Vernon Cancer Centre, UK; [4]University College London CTC, UK; [5]University of Leicester NHS trust, UK; [6]Velindre Cancer Centre, UK; [7]United Lincolnshire Hospitals NHS Trust, UK; [8]Sheffield Teaching Hospitals NHS Trust, UK; [9]Nottingham University NHS Trust, UK; [10]University of Derby and Burton NHS Foundation Trust, UK; [11]Royal Devon and Exeter NHS Foundation Trust, UK; [12]University Hospital of North Midlands NHS Trust, UK; [13]Beatson West of Scotland Cancer Centre, UK; [14]Belfast Health and Social Care Trust, UK; [15]Independent Cancer Patients' Voice, UK; [16]Kolkata Gynaecological Oncology Trials and Translational Research Group, Kolkata India

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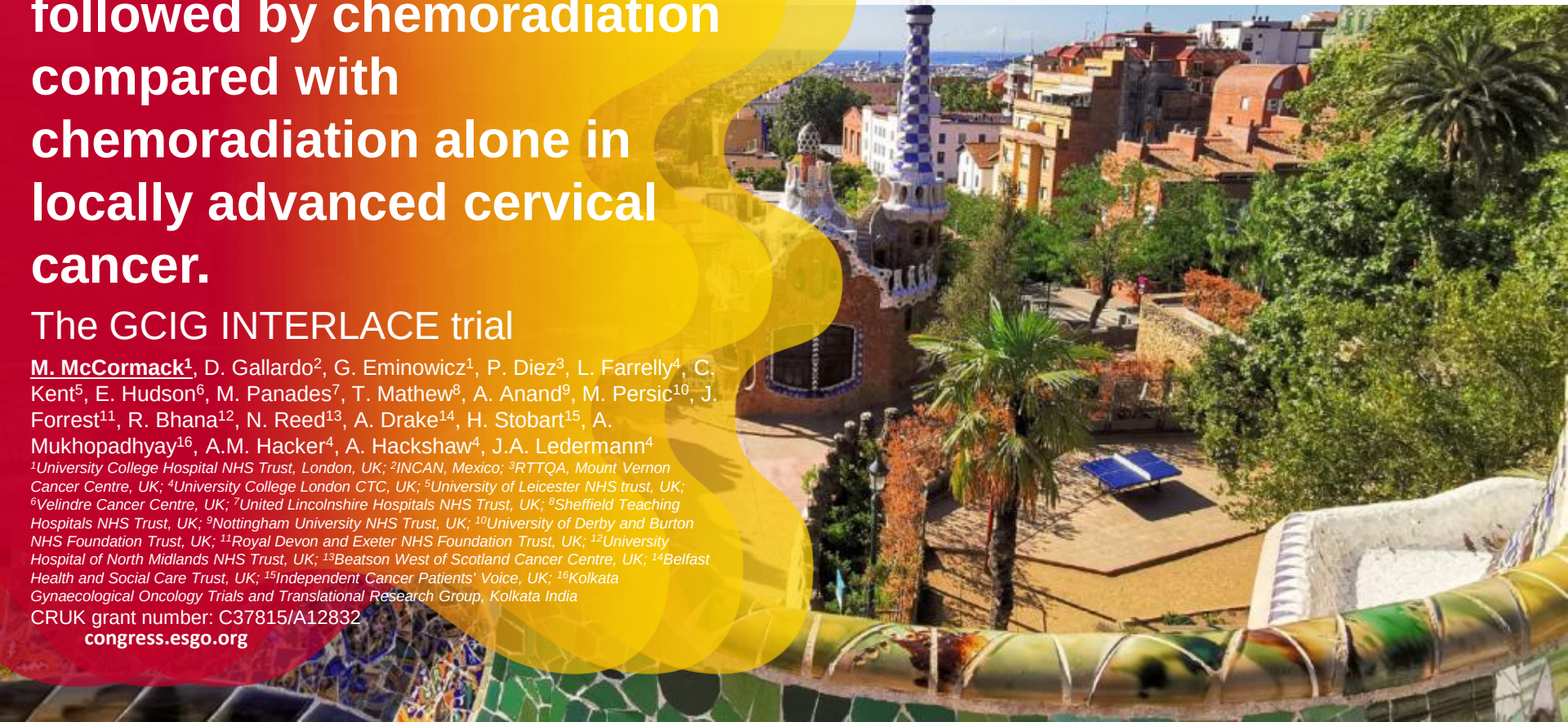

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Background

- In 2024 cervical cancer remains a global health issue[1]
  - 604,000 new cases diagnosed in 2020 with 324,000 deaths
  - 90% of new cases and deaths occurred in low and middle income countries.

- For more than 2 decades chemoradiation (CRT) has been the standard of care in locally advanced disease.

- Advances in radiotherapy techniques coupled with attention to radiation dose and overall treatment time have led to enhanced local control yet up to 30% relapse and die from metastatic disease.

1. Who cervical cancer statistics 2020

Induction Chemotherapy (IC)

- Clinical trials of IC have shown conflicting results.
- A meta-analysis failed to demonstrate a clear improvement in overall survival (OS) with IC but did show an association between outcome and short course IC (OS improved by 7% at 5 years).[1]
- An IC protocol was developed using weekly paclitaxel and carboplatin followed within 7 days by chemoradiotherapy (CRT).
- The single arm CX2 trial (46 patients) demonstrated that this approach was feasible with an objective response rate of 70% to IC.[2]

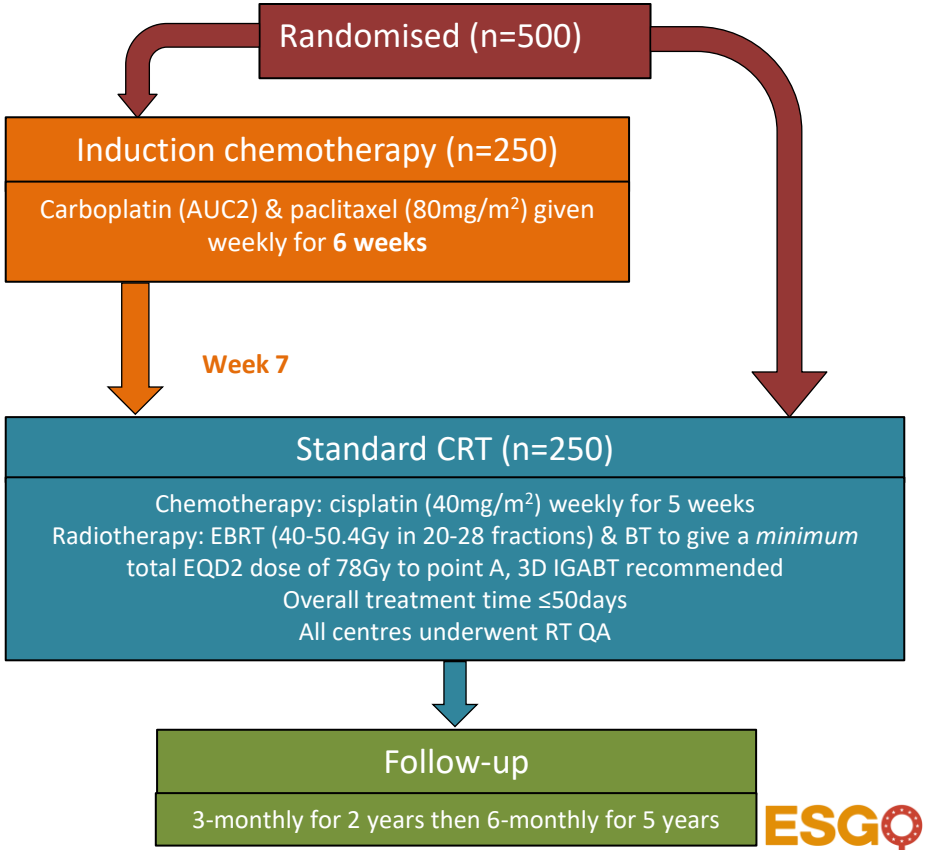
1.Neoadjuvant chemotherapy for locally advanced cervical cancer meta-analysis collaboration .EJC 2003
2. McCormack et al ;A phase II study of weekly NACT followed by CRT. BJC 2013

INTERLACE Trial Design

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stages IB1 node+,IB2, II, IIIB, IVA squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation on imaging
- Adequate renal, liver & bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

RT = Radiotherapy
3D-Conformal = 3D conformal radiotherapy
IMRT = Intensity modulated radiotherapy
EBRT = External beam radiotherapy
BT = Brachytherapy
IGABT = Image-guided adaptive brachytherapy
RT QA = Radiotherapy quality assurance



Stratified by

- Site
- Stage
- Nodal status
- 3D-Conformal v IMRT EBRT
- Tumour size
- SCC v other

Primary endpoints

- PFS
- OS

Secondary endpoints

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment

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Statistical Analysis

- Primary endpoints:
  - Progression-free survival (PFS)
  - Overall survival (OS)

- Target efficacy:
  - PFS: HR 0.65 (132-168 events for 70-80% power)
  - OS: HR 0.65-0.70 (70-84% power)

To maintain an overall error rate of 5%, a hierarchical sequential testing approach based on PFS first will be used and PFS must be statistically significant first ($p<0.05$) to allow a formal statistical analysis of OS afterwards.

- Sample size: 500 patients

Demographics at Baseline

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
Age, years median (range)	46 (24-78)	46 (26-78)
ECOG status	No. of patients (%)	
0	221 (88)	214 (86)
1	29 (12)	36 (14)
Country		
UK	190 (76)	190 (76)
Mexico	51 (20)	49 (20)
Italy	3 (1)	5 (2)
India	5 (2)	5 (2)
Brazil	1 (<1)	1 (<1)

Disease Characteristics at Baseline

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
FIGO stage (2008)	No. of patients (%)	
IB1	2 (<1)	2 (<1)
IB2	23 (9)	19 (8)
IIA	14 (6)	17 (7)
IIB	176 (70)	178 (71)
IIIB	30 (12)	26 (10)
IVA	5 (2)	8 (3)
Cell type		
Non-squamous	45 (18)	44 (18)
Squamous	205 (82)	206 (82)
Nodal status		
Negative	142 (57)	146 (58)
Positive	108 (43)	104 (42)
Longest tumour diameter, cm median (range)	4.9 (1.8-12.8)	4.8 (1.3-13.5)

Adherence to Induction Chemotherapy

	Paclitaxel / Carboplatin No. of patients (%)
Completed 6 weekly cycles	211 (84)
Completed at least 5 cycles	230 (92)
Main reasons for <6 cycles:	
Adverse events:	29 (11)
Haematological	9
Non-haematological	17
Both	3
Withdrawal/other	10 (4)
Median Interval from IC to RT days (range)	7 (5-53)

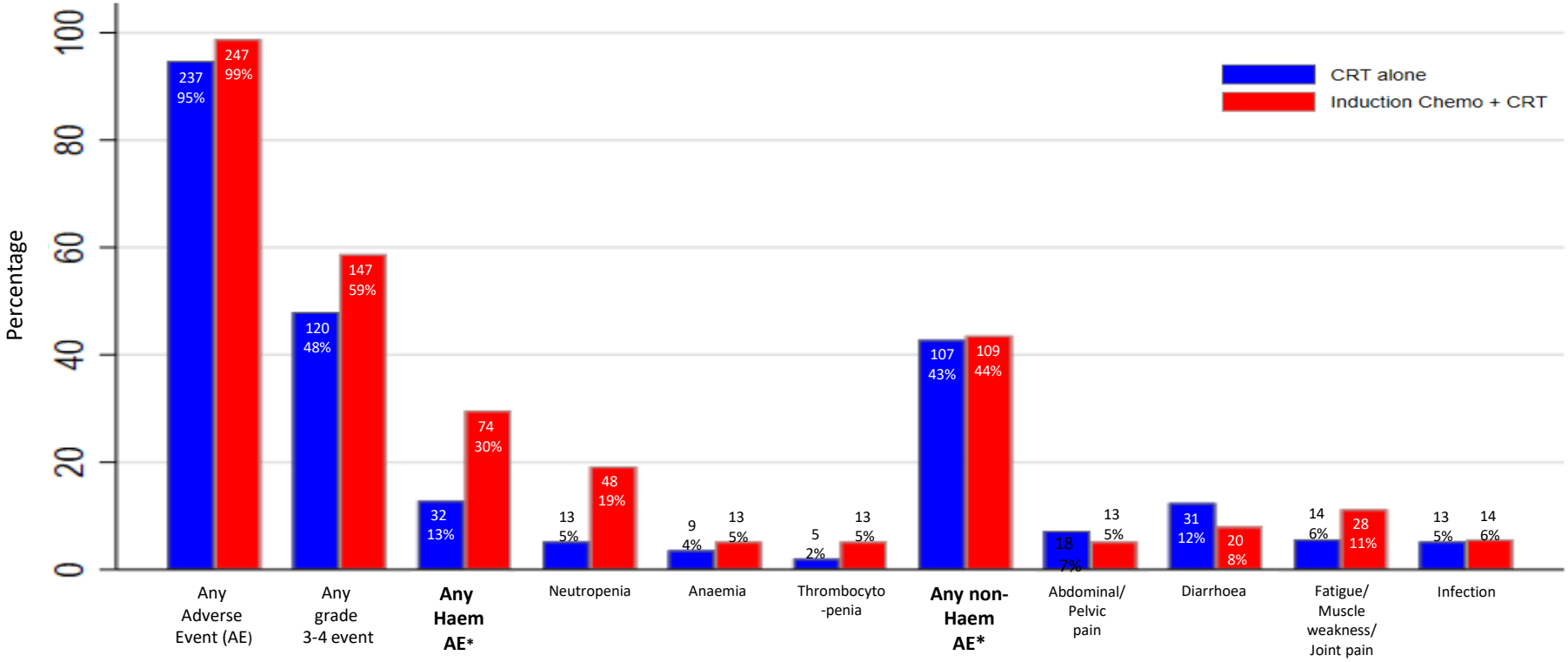
Adherence to Cisplatin

	CRT alone (n=250)	IC + CRT (n=250)
	No. of patients (%)	
Completed 5 weekly cycles	197 (79)	169 (68)
Completed at least 4 cycles	224 (90)	212 (85)
Main reasons for <5 cycles:		
Adverse events leading to discontinuation:	33 (13)	68 (27)
Haematological	4	34
Non-haematological	25	20
Both	4	14
Other	20 (8)	13 (5)

Adherence to Radiation

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
Received external beam radiotherapy	**231 (92)**	**242 (97)**
IMRT	93 (40)	102 (42)
3D conformal	138 (60)	140 (58)
Received brachytherapy	**223 (97)**	**238 (98)**
2D point A	49(22)	46 (19)
3D point A	106 (48)	120 (51)
3D HRCTV D90	68 (30)	72 (30)
Median overall treatment time days (range)	**45 (37-88)**	**45 (36-70)**
% completing treatment within 56 days	**95%**	**96%**

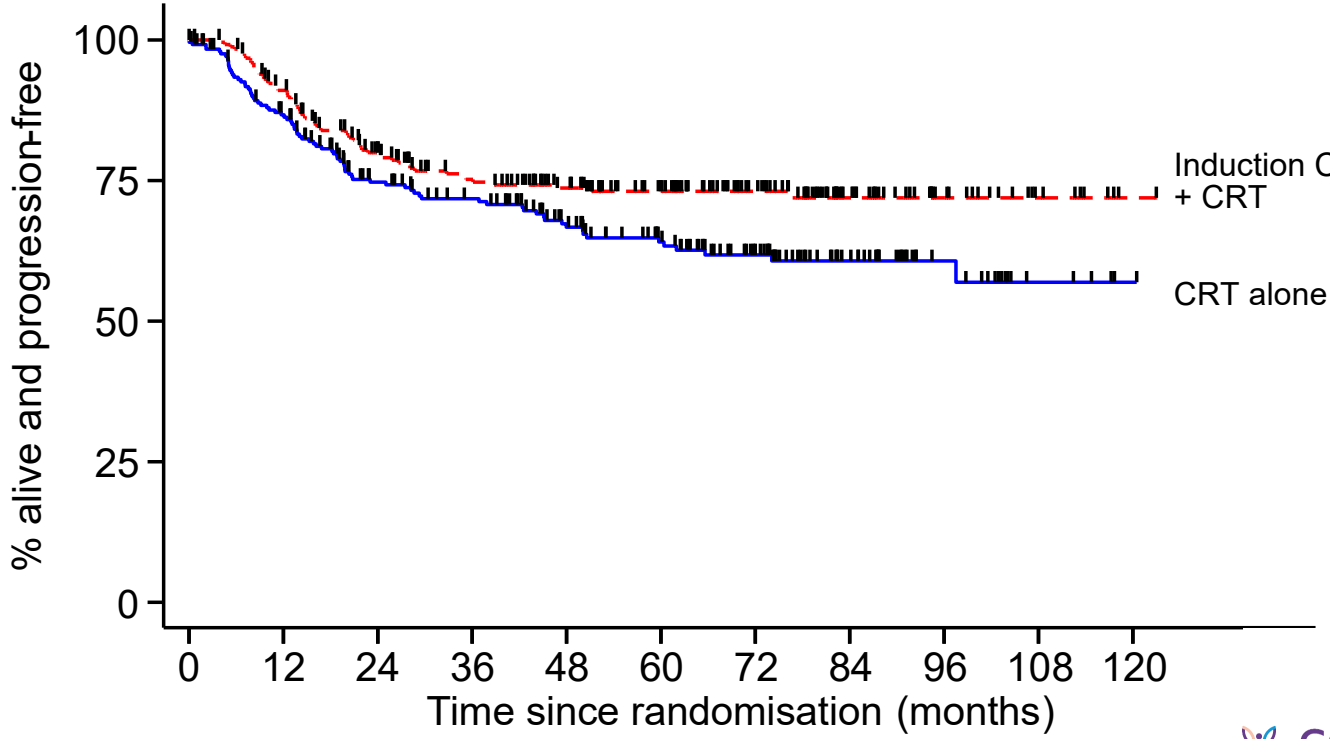
Adverse Events at any time



G5 AE in 3 patients- 2 CRT and 1 IC/CRT arm

*Grade 3-4 only . *106 people (42%) reported grade 2 alopecia in the IC/CRT*

INTERLACE Progression-Free Survival (median FU 64m)



146 PFS events
HR 0.65; 95% CI: 0.46-0.91
P=0.013

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

Number at risk											
CRT alone	250	205	157	140	110	88	63	36	16	5	1
Induction Chemo + CRT	250	220	178	152	132	105	72	40	19	8	1

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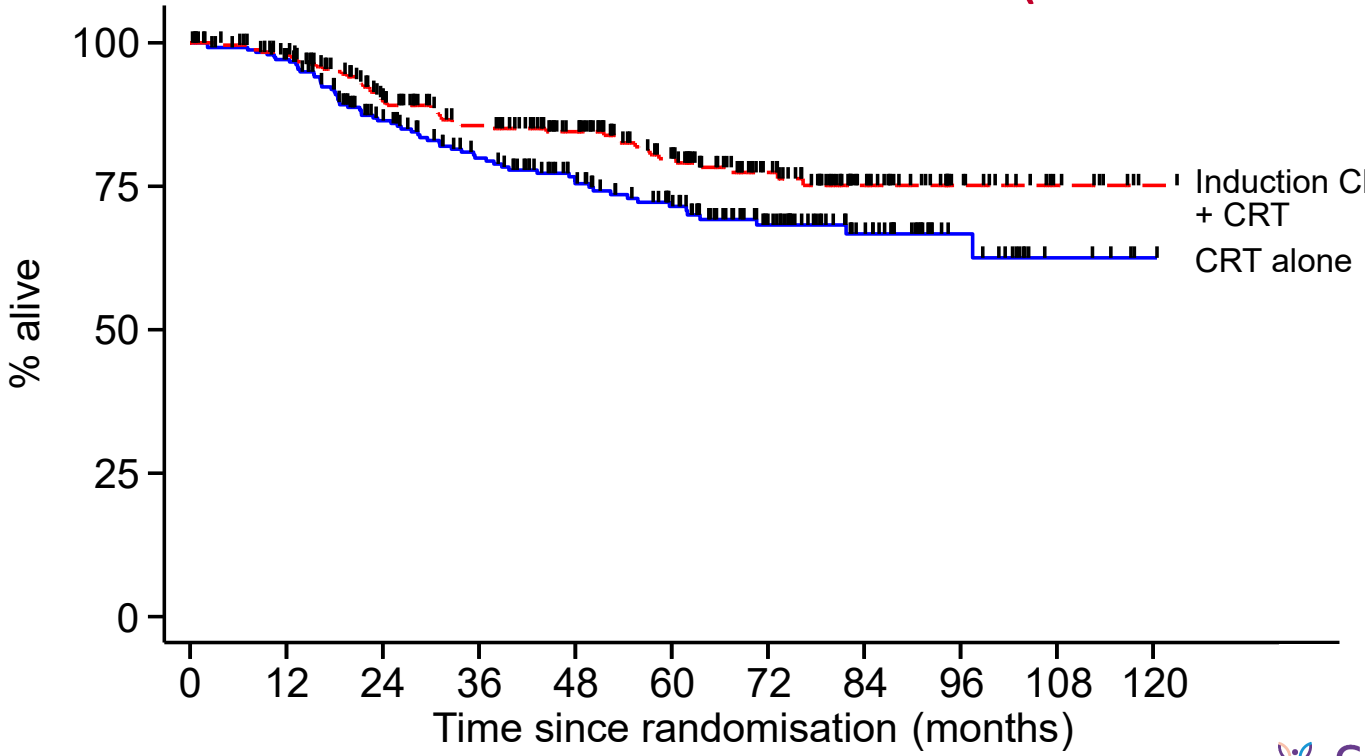
INTERLACE Overall Survival (median FU 64m)



109 deaths
HR 0.61; 95% CI: 0.40-0.91
P=0.04

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

Number at risk											
CRT alone	250	229	181	154	124	99	67	39	16	5	1
Induction Chemo + CRT	250	236	195	168	146	111	75	42	19	8	1

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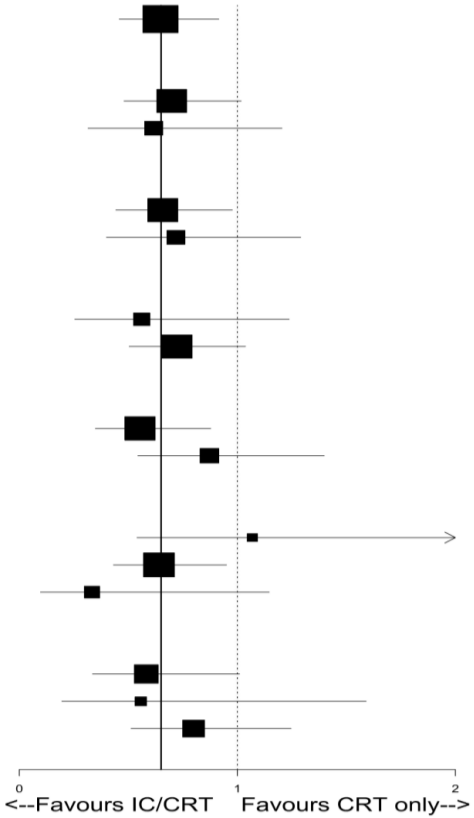
Patterns of Relapse

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
Local/pelvic	21 (8)	26 (10)
Local/pelvic & distant	20 (8)	14 (6)
Distant	30 (12)	16 (6)
Total local/pelvic relapses	41 (16)	40 (16)
Total distant relapses	50 (20)	30 (12)

Subgroup analysis

Subgroup	IC/CRT	Events	CRT alone	Events	HR (95% CI)	P Value
All	250	63	250	83	0.65 (0.46,0.91)	
FIGO stage						**0.33**
I/II	216	48	215	63	0.70 (0.48,1.02)	
III/IV	34	15	35	20	0.62 (0.32,1.20)	
Lesion size						**0.78**
Less than 6cm	196	42	196	59	0.66 (0.44,0.98)	
More than 6cm	54	21	54	24	0.72 (0.40,1.29)	
Cell type						**0.54**
Non-Squamous	44	10	45	16	0.56 (0.25,1.24)	
Squamous	206	53	205	67	0.72 (0.50,1.04)	
Radiotherapy						**0.17**
3D CRT	146	29	151	48	0.55 (0.35,0.88)	
IMRT	104	34	99	35	0.87 (0.54,1.40)	
Age						**0.21**
Less than 35	53	17	54	16	1.07 (0.54,2.12)	
36-65	180	42	182	60	0.64 (0.43,0.95)	
66+	17	4	14	7	0.33 (0.10,1.15)	
FIGO 2018 stage						**0.30**
I/II	130	21	127	32	0.58 (0.34,1.01)	
IIIB/IVA	22	7	16	7	0.56 (0.20,1.59)	
IIIC	98	35	107	44	0.80 (0.51,1.25)	



CONCLUSIONS

- **Induction chemotherapy prior to chemoradiation led to a 9% improvement in PFS rate and an 8% improvement in OS rate at 5 years.**
  PFS : HR 0.65 (95%CI: 0.46-0.91) p=0.013
  OS : HR 0.61 (95%CI: 0.40-0.91) p=0.04 Follow up continues

- Adherence to standard chemoradiation was high in both arms and reflected best clinical practice.

- OS in the standard CRT arm is similar to that in the recent published literature.

- As anticipated haematological toxicity was greater in the IC/CRT arm but this did not compromise the delivery of radiotherapy.

- **Induction chemotherapy with weekly paclitaxel and carboplatin before CRT should be considered the new standard in locally advanced cervical cancer and is feasible across diverse healthcare settings.**

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TMG members

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Independent Data Monitoring Committee (IDMC) and Trial Steering Committee (TSC)

UCL CTC Trial Staff

Jonathan Ledermann
Allan Hackshaw
Mandy Feeney
Jaymi Patel
Lee Webber
Lindsay James
Laura Farrelly
Nicola McGowan
Abby Sharp
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