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Oncology

Supplementary appendix

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

Supplement to: Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): an open-label, randomised phase 3 trial. *Lancet Oncol* 2017; published online August 4. http://dx.doi.org/10.1016/S1470-2045(17)30447-3.

A randomised trial comparing neoadjuvant cisplatin/5-FU with epirubicin/cisplatin/capecitabine followed by resection for oesophageal adenocarcinoma. Results from the UK Medical Research Council OE05 randomised clinical trial

Supplementary material

Acknowledgements

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Additional funding:

David Cunningham receives funding from The National Institute of Health Biomedical Centre at the Institute of Research and Royal Marsden Hospital.

Jane Blazeby receives funding from the Medical Research Council ConDuCT-II Hub for Trials Methodology Research at the University of Bristol.

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Heartlands Hospital	Dr	J	Thompson	43
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Royal United Hospital	Mr	R	Krysztopik	30
Guy's Hospital	Dr	P	Ross	28
Queen Elizabeth Hospital	Dr	D	Peake	28
Huddersfield Royal Infirmary	Dr	J	Dent	27
Maidstone Hospital	Dr	J	Waters	23
Western General Hospital	Dr	H	Phillips	23
Royal Surrey County Hospital	Dr	S	Cummins	21
Leicester Royal Infirmary	Dr	A	Thomas	19
Peterborough City Hospital	Dr	K	McAdam	19
Queen Alexandra Hospital	Dr	C	Archer	18
Addenbrooke's Hospital	Dr	H	Ford	17
Cheltenham General Hospital	Dr	S	Elyan	17
Queens Hospital	Mr	D	Khoo	17
St Bartholomew's Hospital	Dr	S	Slater	16
University Hospital Coventry	Dr	S	Sothi	16
Cumberland Infirmary	Dr	J	Nicoll	15
Dorset County Hospital	Dr	M	Bayne	15
Princess Alexandra Hospital	Dr	J	Bridgewater	15
Weston Park Hospital	Dr	J	Wadsley	15
Royal Cornwall Hospital (Treliske)	Dr	R	Ellis	14
Royal Bournemouth General Hospital	Dr	T	Geldart	13
Velindre Hospital	Dr	T	Crosby	13
Churchill Hospital	Dr	N	Warner	12
Royal Blackburn Hospital	Dr	W	Appel	11
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Kent and Canterbury Hospital	Dr	J	Waters	6

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Broomfield Hospital	Dr	S	Tahir	4
St Mary's Hospital (London)	Dr	D	Power	4
Weston General Hospital	Dr	S	Hilman	4
York District Hospital	Dr	K	Last	4
Burnley General Hospital	Dr	W	Appel	3
Countess of Chester Hospital	Mr	D	Monk	3
Hereford County Hospital	Dr	N	Reed	3
North Middlesex Hospital	Dr	J	Bridgewater	3
Poole General Hospital	Dr	V	Laurence	3
Royal Derby Hospital	Dr	RB	Kulkarni	3
Royal Free Hospital	Dr	T	Meyer	3
Royal Lancaster Infirmary	Dr	D	Fyfe	3
Royal Preston Hospital	Dr	E	Young	3
St George's Hospital	Dr	T	Benepal	3
Victoria Hospital	Dr	S	Susnerwala	3
Furness General Hospital	Dr	D	Fyfe	2
Whiston Hospital	Dr	E	Marshall	2
Ysbyty Gwynedd	Prof.	N	Stuart	2
Darent Valley Hospital	Dr	R	Shah	1
James Cook University Hospital	Dr	N	Wadd	1
King George Hospital	Mr	D	Khoo	1
William Harvey Hospital	Dr	J	Waters	1

Supplementary Table S1 CT staging information

Data		CF N=450		ECX N=446		Total N=896	
		N	**%**	**N**	**%**	**N**	**%**
CT length of tumour (cm)	**Median (IQR)**	5	(3·4-6)	5	(3·5-6)	5	(3·5-6)
	Min – Max	0–14·7		0-16		0-16	
	Missing	*119*	*26%*	*125*	*28%*	*244*	*27%*
Extent of disease	**T1-T3**	416	92%	414	93%	830	93%
	T4	11	2%	8	2%	19	2%
	Missing	*23*	*5%*	*24*	*5%*	*47*	*5%*
CT designated malignant nodes	**None**	223	50%	225	50%	448	50%
	Mediastinal	87	19%	77	17%	164	18%
	Abdominal	82	18%	78	17%	160	18%
	Mediastinal & Abdominal	49	11%	50	11%	99	11%
	Missing	*9*	*2%*	*16*	*4%*	*25*	*3%*

Note: One CF patient withdrew consent before providing any on-study staging information, and is not included in the above table.

Supplementary Table S2 EUS staging information

Data		CF N=450		ECX N=446		Total N=896	
		N	%	N	%	N	%
EUS overall length of tumour (cm)	**Median (IQR)**	5	(4-7)	5	(4-7)	5	(4-7)
	Min – Max	0·5-15		0·5-16		0·5-16	
	Missing	*52*	*12%*	*49*	*11%*	*101*	*12%*
EUS oesophageal involvement (cm)	**Median (IQR)**	5	(3-6)	5	(3-6)	5	(3-6)
	Min – Max	0-15		0·4-16		0-16	
	Missing	*90*	*21%*	*97*	*22%*	*187*	*22%*
EUS Gastric involvement (cm)	**Median (IQR)**	0	(0-0)	0	(0-0)	0	(0-0)
	Min – Max	0-6		0-6		0-6	
	Missing	*97*	*21%*	*92*	*21%*	*189*	*21%*
Extent of disease	**T1**	3	1%	5	1%	8	1%
	T2	50	11%	41	9%	91	10%
	T3	374	83%	382	86%	756	84%
	T4	13	3%	12	3%	25	3%
	Missing	10	2%	6	1%	16	2%
EUS designated malignant nodes	**None**	152	34%	158	35%	310	35%
	Mediastinal	92	20%	97	22%	189	21%
	Abdominal	116	26%	114	26%	230	26%
	Med & Abd	63	14%	55	12%	118	13%
	Missing	27	6%	22	5%	49	5%

Note: One CF patient withdrew consent before providing any on-study staging information, and is not included in the above table.

Supplementary Table S3 Other staging procedures (all patients received CT and EUS)

Data	CF N=450		ECX N=446		Total N=896	
	N	%	N	%	N	%
Laparoscopy performed	216	48%	213	48%	429	48%
PET scan performed	271	60%	270	61%	541	60%
Bone scan performed	23	5%	25	6%	48	5%
Other staging investigations performed	37	8%	33	7%	70	8%

Note: One CF patient withdrew consent before providing any on-study staging information, and is not included in the above table.

Supplementary Table S4 Grade 3/4/5 Chemotherapy toxicity

Data	CF – 2 cycles N=446		ECX – 4 cycles N=441		Total N=887		P-value for difference
	N	%	N	%	N	%	
Any grade 3/4/5 toxicity	140	31%	218	49%	358	40%	<0.0001
Neutropenia	74	17%	101	23%	175	20%	0.023
DVT/PE	19	4%	30	7%	49	6%	0.11
Vomiting	20	4%	26	6%	46	5%	0.37
Nausea	16	4%	27	6%	43	5%	0.087
Diarrhoea	6	1%	36	8%	42	5%	<0.0001
Plantar-palmar erythrodysesthesia	0	0%	38	9%	38	4%	<0.0001
Stomatitis	25	6%	7	2%	32	4%	0.0018
Infection/febrile neutropenia	3	1%	14	3%	17	2%	0.0067
Cardiac toxicity	4	1%	3	1%	7	1%	1.00
Peripheral neuropathy	1	<1%	3	1%	4	<1%	0.62
Loss of taste	2	<1%	1	<1%	3	<1%	1.00
Thrombocytopenia	2	<1%	1	<1%	3	<1%	1.00
Renal toxicity	2	<1%	1	<1%	3	<1%	1.00
Tinnitus	2	<1%	0	0%	2	<1%	0.50
Liver toxicity	0	0%	2	<1%	2	<1%	0.25
Other toxicity	39	9%	68	15%	107	12%	0.0027
Cycle of first G3/4/5 toxicity							
1	108	24%	77	17%			
2	32	7%	72	16%			
3			47	11%			
4			21	5%			
None	306	69%	224	51%			

Note: Two patients in each arm did not receive any chemotherapy. A further three patients in each arm did not provide any toxicity data. If some toxicity data were provided, any missing toxicity data at that cycle are assumed to indicate that toxicity did not take place.

Supplementary Table S5 Post-operative complications

Data	CF N=411		ECX N=387		Total N=798	
	N	%	N	%	N	%
Any complication	224	56%	233	62%	457	59%
Respiratory	107	27%	125	33%	232	30%
Infection	57	14%	56	15%	113	15%
Cardiac	44	11%	44	12%	88	11%
Anastomotic	45	11%	38	10%	83	11%
Surgery related	36	9%	42	11%	78	10%
Haematological	18	5%	16	4%	34	4%
Thrombo-embolic	16	4%	17	5%	33	4%
Chylothorax	12	3%	15	4%	27	4%
Other	27	7%	27	7%	54	7%
Revisional operation	34	8%	32	8%	66	8%
Died within 90 days (based on dates)	21	5%	23	6%	44	6%
Died within 30 days (based on dates)	10	2%	11	3%	21	3%

Note: Thirteen patients in each arm provided no post-operative complication data. A further ten CF and nine ECX patients did not provide follow-up data on whether a revisional operation was required, despite reporting post-operative complications.

Supplementary Table S6 Serious Adverse Events

Data	CF N=451		ECX N=446		Total N=897	
	N	%	N	%	N	%
Any serious adverse event	73	16%	108	24%	181	20%
Common body-systems						
Gastro-intestinal	23	5%	32	8%	55	6%
Infection	15	3%	18	4%	33	4%
Cardiac	12	3%	8	2%	20	2%
Common events						
Diarrhoea	0	0%	14	3%	14	2%
Dysphagia	3	1%	10	2%	13	1%
Vomiting	11	2%	6	1%	17	2%
Pulmonary Embolism	10	2%	16	4%	26	3%

Note: Only body-systems or serious adverse events reported by at least 10 patients in either arm are reported.

Supplementary Table S7 Quality of life

Analysis point	Time point	CF Mean (sd), N	ECX Mean (sd), N	All patients Mean (sd), N	P-value
Global Quality of Life					
Baseline	**Baseline**	76·3 (19·37), 358	75·7 (17·30), 367	76·0 (18·34), 725	
Pre-surgery	**Baseline**	76·5 (19·50), 300	75·8 (17·66), 274	76·1 (18·63), 574	
	Pre-surgery	66·5 (21·76), 300	62·8 (24·79), 274	64·7 (23·31), 574	0·0582
	Change from baseline	-10·0 (21·24), 300	-13·0 (24·20), 274	-11·4 (22·73), 574	
3 months post-op	**Baseline**	77·0 (19·60), 177	76·9 (16·57), 162	76·9 (18·19), 339	
	3 months post-op	60·1 (20·96), 177	61·7 (21·65), 162	60·9 (21·28), 339	0·4566
	Change from baseline	-16·9 (23·35), 177	-15·2 (22·79), 162	-16·1 (23·06), 339	
12 months post-op	**Baseline**	80·5 (17·80), 107	77·7 (15·77), 101	79·2 (16·89), 208	
	12 months post-op	70·0 (21·50), 107	67·3 (20·64), 101	68·7 (21·08), 208	0·6069
	Change from baseline	-10·5 (22·29), 107	-10·4 (21·03), 101	-10·5 (21·64), 208	
24 months post-op	**Baseline**	80·1 (17·22), 67	79·1 (15·64), 75	79·6 (16·36), 142	
	24 months post-op	73·8 (21·18), 67	68·3 (20·64), 75	70·9 (21·00), 142	0·1358
	Change from baseline	-6·3 (24·83), 67	-10·8 (19·70), 75	-8·7 (22·30), 142	
Appetite Loss					
Baseline	**Baseline**	38·2 (28·37), 357	36·6 (27·62), 367	37.4 (27.98), 724	
Pre-surgery	**Baseline**	38·3 (28·20), 299	35·9 (27·88), 274	37·1 (28·05), 573	
	Pre-surgery	27·6 (26·37), 299	24·4 (26·07), 274	26·1 (26·25), 573	0·2421
	Change from baseline	-10·6 (28·64), 299	-11·5 (29·42), 274	-11·1 (28·99), 573	
3 months post-op	**Baseline**	41·0 (29·20), 175	32·9 (25·84), 161	37·1 (27·90), 336	
	3 months post-op	36·1 (24·78), 175	35·7 (24·24), 161	35·9 (24·49), 336	0·6320
	Change from baseline	-4·9 (34·64), 175	2·8 (29·65), 161	-1·2 (32·53), 336	
12 months post-op	**Baseline**	33·0 (27·88), 109	33·4 (26·42), 101	33·2 (27·12), 210	
	12 months post-op	26·3 (21·67), 109	25·7 (20·72), 101	26·0 (21·17), 210	0·8226
	Change from baseline	-6·6 (30·87), 109	-7·7 (29·78), 101	-7·1 (30·28), 210	
24 months post-op	**Baseline**	35·7 (30·25), 69	30·6 (26·19), 75	33·0 (28·23), 144	

Analysis point	Time point	CF Mean (sd), N	ECX Mean (sd), N	All patients Mean (sd), N	P-value
	24 months post-op	22·1 (22·77), 69	22·9 (23·41), 75	22·5 (23·03), 144	0·6530
	Change from baseline	-13·65 (34·27), 69	-7·7 (30·50), 75	-10·5 (32·39), 144	
Reflux					
Baseline	**Baseline**	16·0 (22·15), 359	18·7 (25·74), 367	17·3 (24·05), 726	
Pre-surgery	**Baseline**	16·6 (22·67), 302	19·2 (26·01), 274	17·8 (24·33), 576	
	Pre-surgery	14·1 (21·08), 302	15·1 (22·07), 274	14·6 (21·55), 576	0·8930
	Change from baseline	-2·5 (24·47), 302	-4·0 (27·07), 274	-3·2 (25·73), 576	
3 months post-op	**Baseline**	16·0 (21·93), 177	16·5 (22·66), 159	16·2 (22·24), 336	
	3 months post-op	24·0 (27·86), 177	21·1 (24·70), 159	22·6 (26·41), 336	0·2761
	Change from baseline	8·0 (31·08), 177	4·6 (29·46), 159	6·4 (30·33), 336	
12 months post-op	**Baseline**	16·4 (21·51), 109	14·9 (22·35), 101	15·6 (21·88), 210	
	12 months post-op	25·5 (26·89), 109	27·4 (29·21), 101	26·4 (27·98), 210	0·5254
	Change from baseline	9·2 (27·92), 109	12·5 (33·20), 101	10·8 (30·54), 210	
24 months post-op	**Baseline**	13·8 (23·21), 69	17·3 (25·74), 76	15·6 (24·55), 145	
	24 months post-op	23·4 (25·46), 69	29·8 (27·26), 76	26·8 (26·52), 145	0·1930
	Change from baseline	9·7 (33·3), 69	12·5 (31·87), 76	11·1 (32·46), 145	
Pain					
Baseline	**Baseline**	19·3 (19·15), 359	21·3 (21·72), 367	20·3 (20·50), 726	
Pre-surgery	**Baseline**	19·8 (19·25), 302	21·4 (21·37), 274	20·5 (20·28), 576	
	Pre-surgery	13·1 (16·72), 302	12·0 (17·43), 274	12·6 (17·06), 576	0·2369
	Change from baseline	-6·7 (20·24), 302	-9·4 (22·23), 274	-8·0 (21·23), 576	
3 months post-op	**Baseline**	18·5 (18·72), 177	18·4 (20·30), 161	18·5 (19·46), 338	
	3 months post-op	19·7 (19·59), 177	17·56 (17·19), 161	18·7 (18·49), 338	0·2628
	Change from baseline	1·2 (23·35), 177	-0·86 (19·57), 161	0·2 (21·62), 338	
12 months post-op	**Baseline**	16·1 (16·94), 109	18·6 (19·82), 101	17·3 (18·38), 210	
	12 months post-op	15·2 (18·25), 109	16·6 (21·17), 101	15·8 (19·67), 210	0·8985

Analysis point	Time point	CF Mean (sd), N	ECX Mean (sd), N	All patients Mean (sd), N	P-value
	Change from baseline	-0·9 (21·81), 109	-2·0 (20·12), 101	-1·5 (20·97), 210	
24 months post-op	**Baseline**	15·6 (19·09), 69	17·8 (20·05), 76	16·8 (19·56), 145	
	24 months post-op	14·0 (17·64), 69	14·3 (22·06), 76	14·2 (20·01), 145	0·8187
	Change from baseline	-1·6 (19·46), 69	-3·5 (22·16), 76	-2·6 (20·87), 145	
Dysphagia					
Baseline	**Baseline**	73·7 (25·83), 359	74·1 (25·55), 367	73·9 (25·67), 726	
Pre-surgery	**Baseline**	73·7 (25·75), 301	75·1 (25·01), 274	74·4 (25·39), 575	
	Pre-surgery	79·4 (23·73), 301	84·4 (24·25), 274	81·8 (24·08), 575	0·0173
	Change from baseline	5·7 (28·40), 301	9·2 (28·00), 274	7·4 (28·24), 575	
3 months post-op	**Baseline**	73·0 (26·47), 177	79·4 (22·68), 161	76·1 (24·91), 338	
	3 months post-op	81·6 (23·06), 177	82·1 (23·27), 161	81·8 (23·12), 338	0·8142
	Change from baseline	8·6 (32·25), 177	2·6 (29·22), 161	5·8 (30·94), 338	
12 months post-op	**Baseline**	79·3 (25·19), 109	77·6 (22·78), 100	78·5 (24·02), 209	
	12 months post-op	88·4 (17·70), 109	85·3 (24·76), 100	86·9 (21·38), 209	0·3176
	Change from baseline	9·1 (27·48), 109	7·7 (32·54), 100	8·5 (29·94), 209	
24 months post-op	**Baseline**	79·4 (25·16), 69	78·8 (23·53), 76	79·1 (24·23), 145	
	24 months post-op	87·1 (23·77), 69	89·3 (19·41), 76	88·3 (21·55), 145	0·5183
	Change from baseline	7·7 (33·46), 69	10·5 (25·65), 76	9·2 (29·55), 145	

Note: Quality of life data are collected using the EORTC QLQ-C30 and OES-18 questionnaires.
Note: Treatment groups are compared using analysis of variance, with adjustment for baseline values.

Supplementary Table S8 Survival times from planned sub-group analyses.

		CF (N=451)		ECX (N=446)	
		N	**Med OS (95% CI)**	**N**	**Med OS (95% CI)**
Sex	**Male**	412	2·00 (1·70, 2·28)	398	2·11 (1·93, 2·36)
	Female	39	4·03 (1·50, Undef)	48	2·63 (1·55, Undef)
Age	**<60**	171	2·42 (1·71, 3·67)	172	2·17 (1·85, 2·64)
	60-69	212	1·80 (1·52, 2·11)	192	2·33 (1·93, 3·27)
	70+	68	2·07 (1·70, 2·68)	82	1·80 (1·59, 2·25)
WHO PS	**0**	311	2·28 (2·00, 2·94)	292	2·28 (1·98, 3·03)
	1	140	1·50 (1·23, 1·90)	154	1·80 (1·59, 2·33)
T-stage	**T2**	47	2·00 (1·50, 4·48)	40	2·36 (1·64, 4·56)
	T3	386	2·11 (1·75, 2·42)	389	2·10 (1·85, 2·33)
	T4	15	1·65 (0·58, 2·06)	12	3·14 (0·80, Undef)
N-stage	**N0**	97	1·75 (1·28, 2·66)	97	2·89 (2·22, Undef)
	N1	350	2·05 (1·80, 2·40)	345	2·02 (1·82, 2·31)

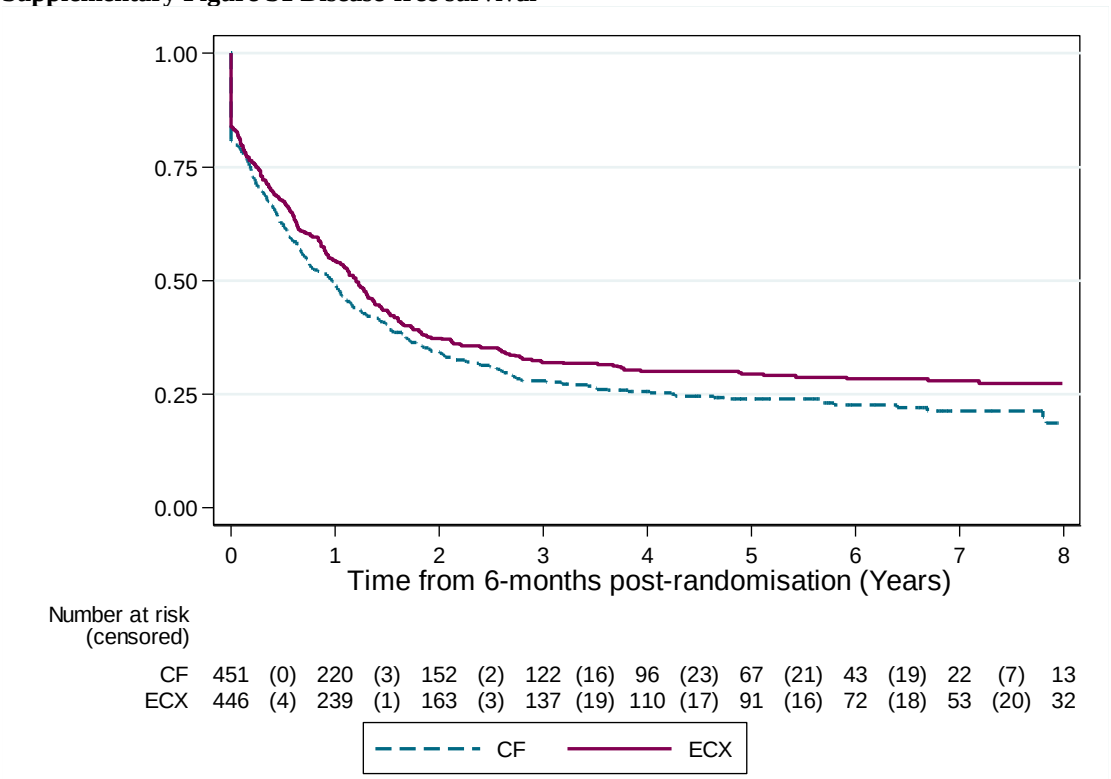
Note: WHO PS = World Health Organisation Performance Status.
Note: T-stage and N-stage are as reported at time of randomisation.
Note: Undef = upper or lower limit of confidence interval is not defined.
Note: P-values for heterogeneity of treatment effect are 0·69 for sex; 0·05 for age; 0·46 for WHO PS; 0·11 for T-stage; and 0·05 for N-stage.

Supplementary Table S9 Survival times from unplanned sub-group analyses.

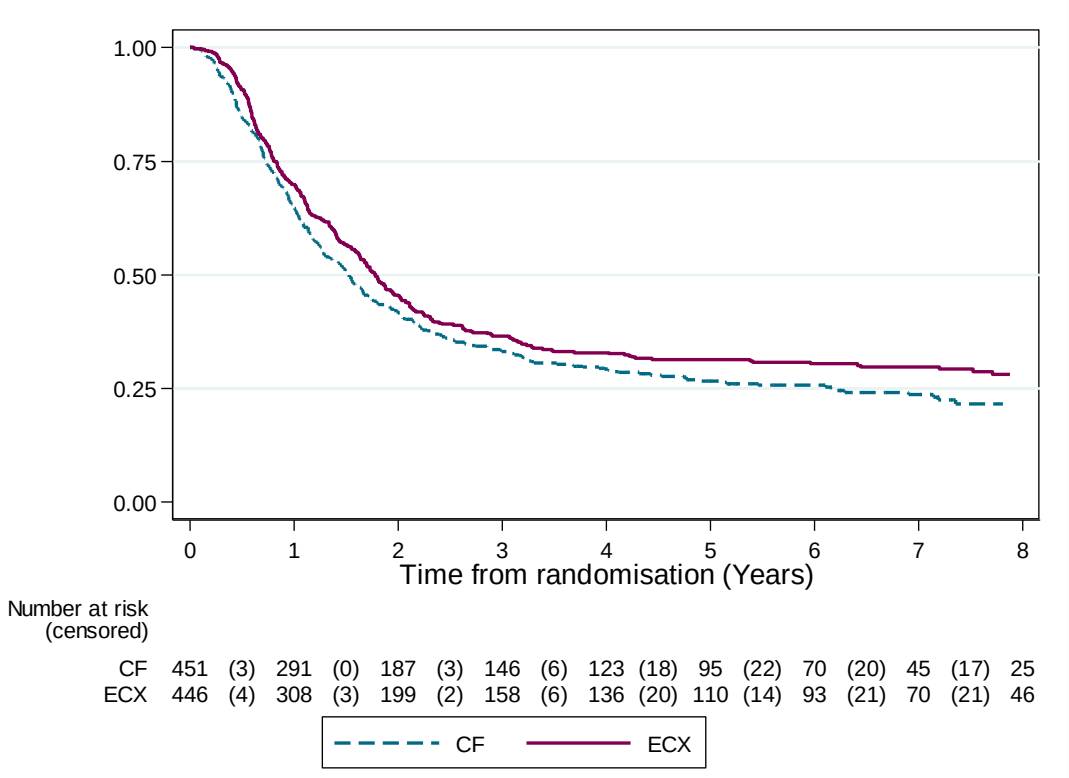
		CF (N=451)		ECX (N=446)	
		N	**Med OS (95% CI)**	**N**	**Med OS (95% CI)**
Year of randomisation	**2005**	42	1·67 (1·30, 2·42)	44	2·78 (1·34, 4·54)
	2006	74	1·44 (1·03, 2·09)	73	2·23 (1·63, Undef)
	2007	66	1·59 (1·33, 2·02)	63	2·64 (1·74, 4·28)
	2008	81	2·51 (1·51, 4·55)	82	2·03 (1·64, 3·42)
	2009	67	3·02 (1·61, 4·96)	67	1·73 (1·34, 2·23)
	2010	82	2·26 (1·80, 4·03)	81	2·00 (1·63, 2·62)
	2011	39	1·88 (1·21, 3·33)	36	3·14 (1·62, Undef)
PET scan	**Yes**	271	2·28 (2·00, 2·68)	270	1·88 (1·70, 2·18)
	No	179	1·64 (1·31, 2·06)	175	2·64 (2·23, 3·47)

Note: Undef = upper or lower limit of confidence interval is not defined.
Note: P-values for heterogeneity of treatment effect are 0·0004 for year of randomisation; and 0·0008 for use of PET scan.
Note: Use of PET scan by year of randomisation: 12% (2005), 18% (2006), 40% (2007), 77% (2008), 84% (2009), 90% (2010), 89% (2011).

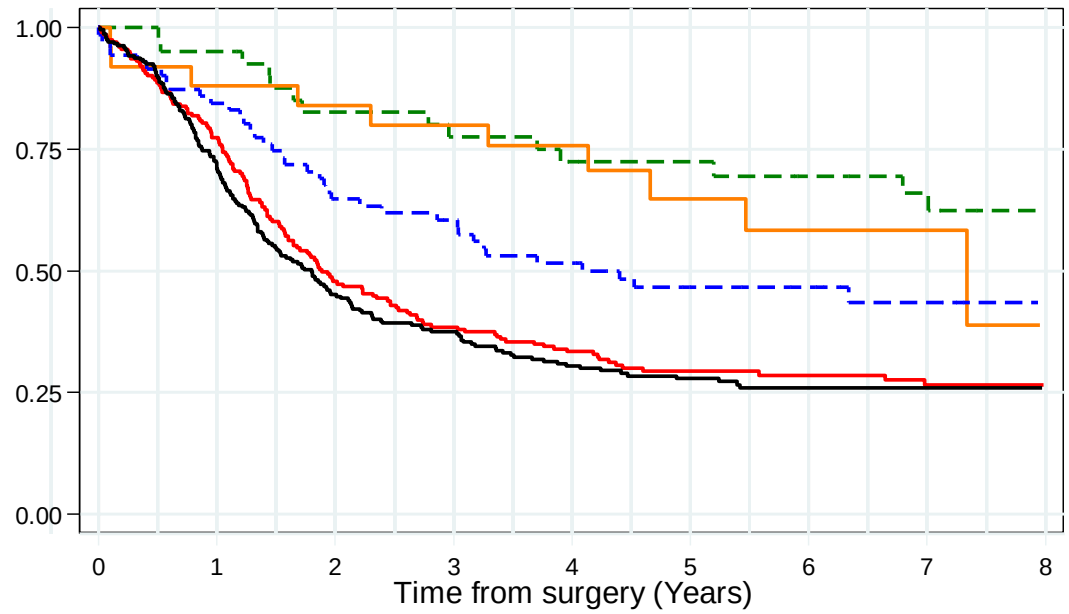
Supplementary Figure S1 Disease-free survival



Supplementary Figure S2 Progression-free survival



Supplementary Figure S3 Post-operative survival according to local Mandard TRG assessment.



At risk (censored)

Grade 1	41	(0)	39	(1)	33	(0)	31	(2)	27	(2)	25	(2)	22	(3)	18	(8)	9
Grade 2	25	(0)	22	(0)	21	(1)	19	(2)	16	(3)	11	(1)	9	(3)	6	(5)	1
Grade 3	71	(0)	60	(1)	45	(1)	41	(1)	34	(6)	25	(7)	18	(3)	14	(6)	8
Grade 4	204	(1)	157	(0)	97	(0)	78	(6)	62	(12)	43	(9)	33	(8)	23	(7)	16
Grade 5	243	(2)	173	(2)	107	(2)	87	(8)	63	(9)	49	(12)	34	(12)	22	(6)	16

Note: HR (95% CI), p-value for comparison with grade 1 or 2 is 1.77 (1.06, 2.96), p=0.028 for grade 3, and 3.04 (2.01, 4.61), p<0.0001 for grade 4 or 5.