Supplementary Online Content

Hoskin PJ, Hopkins K, Misra V, et al. Effect of single-fraction vs multifraction radiotherapy on ambulatory status among patients with spinal canal compression from metastatic cancer

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This supplementary material has been provided by the authors to give readers additional information about their work.

Online Only Supplements

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Baseline characteristics	8 Gy/1f	20 Gy/5f
	N=345	N=341
Bladder function ^a		
Normal	246 (71%)	259 (76%)
Abnormal	96 (28%)	82 (24%)
Not reported	3 (1%)	0 (0%)
Bowel function		
Normal	165 (48%)	175 (51%)
Abnormal	177 (51%)	166 (49%)
Constipation	141 (41%)	148 (43%)
Diarrhoea/incontinence	29 (8%)	17 (5%)
Constipation & Diarrhoea/incontinence	7 (2%)	1 (<1%)
Not reported	3 (1%)	0 (0%)
Duration of symptoms before SCC diagnosis ^b		
<1 day	13 (4%)	7 (2%)
<1 week	134 (39%)	126 (37%)
<1 month	102 (30%)	104 (31%)
<3 months	37 (11%)	41 (12%)
>3 months	18 (5%)	22 (6%)
Not reported	41 (12%)	41 (12%)

eTable 1 - Other baseline characteristics by randomization group

a. Abnormal bladder function is defined as significant urinary incontinence or urinary retention requiring catheterisation

b. Time between onset of symptoms and SCC diagnosis. This data was not collected in the feasibility part of the study.

eTable 2 - Baseline characteristics by randomization group amongst patients evaluable for the primary endpoint

Baseline characteristics	8 Gy/1f	20 Gy/5f	р	
	N=166	N=176		
Ano 110010				
Age, years	74 (44 to 04)	70 (40 to 05)	0.40	
Median (range)	71 (44 to 91)	70 (40 to 95)	0.43	
Sex		400 (700()	0.00	
Male	125 (75%)	123 (70%)	0.26	
Site of primary cancer				
Prostate	91 (55%)	91 (52%)		
Lung	15 (9%)	25 (14%)		
Breast	22 (13%)	24 (14%)		
GI	14 (8%)	15 (9%)		
Renal	4 (2%)	6 (3%)		
Skin	4 (2%)	3 (2%)		
Bladder	3 (2%)	1 (1%)		
Gynae, head & neck, sarcoma, unspecified	13 (8%)	11 (6%)	0.83	
Friday to family to a to a to				
Extent of metastases			0.40	
Nonskeletal mets present	74 (45%)	66 (38%)	0.18	
Number of SCC sites				
Single	151 (91%)	165 (94%)		
Multiple	15 (9%)	11 (6%)	0.33	
Site of spinal cord compression (SCC)				
Cervical vertebrae	5 (3%)	7 (4%)		
Cervical and thoracic	2 (1%)	4 (2%)		
Thoracic	101 (61%)	113 (64%)		
Thoracic and lumbar	11 (7%)	9 (5%)		
Lumbar	41 (25%)	34 (19%)		
Lumbar and sacrum	1 (1%)	2 (1%)		
Sacrum (S1 and S2)	5 (3%)	5 (3%)		
Not reported	0 (0%)	2 (1%)	0.71	
WHO performance status	0 (078)	2 (170)	0.71	
0&1	65 (39%)	65 (37%)		
2	47 (28%)	46 (26%)		
3	40 (24%)	51 (29%)		
4	13 (8%)	12 (7%)		
Not reported	1 (1%)	2 (1%)	0.85	
Ambulatory status	1 (170)	2 (170)	0.00	
Grade 1: Ambulatory without walking aids	49 (30%)	49 (28%)		
Grade 2: Ambulatory with walking aids	83 (50%)	83 (47%)		
Grade 3: Unable to ambulate	26 (16%)	33 (19%)		
Grade 4: No motor power	8 (5%)	11 (6%)	0.80	
Treatment at baseline	0 (0 %)		0.00	
Chemotherapy only (≤ 4 weeks prior randomization)	6 (4%)	17 (10%)		
Hormone therapy only (≤ 4 weeks prior randomization)	53 (32%)	59 (34%)		
Radiotherapy only (≤ 6 months prior randomization)	13 (8%)	13 (7%)		
Combination of the above	22 (13%)	14 (8%)	0.40	
None/Not reported	72 (43%)	73 (41%)	0.19	

Note: P value for age derived from quantile regression which compares medians; all the other p-values are derived from chi-square test

	Treatment	
	8 Gy/1F	20 Gy/5F
	N=345	N=341
	N (%)	·
Unknown outcome at 8 weeks' timeframe ^a	179 (51.88%)	165 (48.4%)
Died before week 7	119 (66.5%)	106 (64.2%)
Died between week 7 and week 8	8 (4.5%)	17 (10.3%)
Died between week 8 and week 9	3 (1.7%)	2 (1.2%)
Lost to follow-up before week 7	3 (1.7%)	5 (3.0%)
Lost to follow-up between week 7 and week 8	0 (0%)	0 (0%)
Lost to follow-up between week 8 and week 9	0 (0%)	1 (0.6%)
Alive beyond week 9 (all with baseline assessment):		
Baseline only	4 (2.2%)	0 (0%)
Assessment(s) only before 8 week target ^b	9 (5.0%)	9 (5.5%)
Assessment(s) only after 8 weeks' target ^b	1 (0.6%)	0 (0%)
Assessments only before and only after the 8 weeks' target ^b	32 (17.9%)	25 (15.2%)

eTable 3 - Patients with unknown outcome at 8 weeks' time frame

^b. These patients had assessments outside the protocol specified time window for the 8 weeks assessment

eTable 4 – Sensitivity analyses for the primary endpoint: ambulatory status (AS) at week 8

Image: Second	Sensitivity	Intention	to treat pop	ulation	Per protoc	ol population	1
Image: Second	analyses	8 Gy/1f		difference	8 Gy/1f		difference
Main analysis (Table 2 of the paper) Main analysis (Table 2 of the paper) Main analysis by intention to treat and per protocol, where the 8-week assessment is defined as any occurring between 49 and 62 days inclusive post-randomization (i.e. at weeks 7 or 8) Evaluables 166 176 -3.5% 164 173 -3.9% Positive 115 128 (-11.5 to 4.6) 114 127 (-12.0 to 4.1) Response (69.3%) (72.7%) (11.5 to 4.6) 114 127 (-12.0 to 4.1) Analysis 1a (primary analysis adjusted for the randomization stratification factors: baselin ambulatory status, primary tumour and extension of metastases) • Logistic regression was implemented with the outcome being a positive response at 8 weeks, and explanatory variables being treatment and minimisation stratification factors. • The adjusted probabilities of positive response by treatment, the difference in these probabilities and estimated 90%CI for the difference were derived from the logistic regression Evaluables 166 176 -4.8% 164 173 -5.3% Positive 68.5% 73.3% (-11.8 to 6.8,7% 74.0% (-12.3% to 1.2,7%) • Logistic regression was implemented with standard errors adjusted for hospital (clustered sandwich est		N (%)	N (%)	(90% CI)	N (%)	N (%)	· · ·
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• All patients lost to follow-up before week 9 and therefore with no ambulatory assessment at week 8 time window

Evaluables	215	216	-5.8	211	213	-5.6
Positive response	115 (53.5%)	128 (59.3%)	(-13.6 to 2.1)	114 (54.0%)	127 (59.6%)	(-13.5 to 2.3)

Analysis 5 (imputation of missing data)

This analysis assumes that the following categories of patients had a positive response (N=89): • All patients alive beyond week 9 with no ambulatory assessment at week 8 (49-62 days post-randomization)

• All patients lost to follow-up before week 9 and therefore with no ambulatory assessment at week 8 time window

Evaluables	215	216	-1.5	211	213	-2.1
Positive response	164 (76.3%)	168 (77.8%)	(-8.2 to 5.2)	161 (76.3%)	167 (78.4%)	(-8.8 to 4.6)

Analysis 6 (imputation of missing data)

This analysis assumes that the following categories of patients had the same positive response rate at week 8 as the rate observed in the intention-to-treat analysis in the 8Gy/1f group (N=89): • All patients alive beyond week 9 (\geq 63 days post-randomization) with no ambulatory assessment at week 8

• All patients lost to follow-up before week 9 with no ambulatory assessment at week 8 time window

Evaluables	215	216	-2.9	211	213	-3.6
Positive response	149 (69.3%)	156 (72.2%)	(-10.1 to 4.3)	146 (69.2%)	155 (72.8%)	(-10.8 to 3.7)

Analysis 7 (imputation of missing data)

This analysis assumes that the following categories of patients had the same positive response rate at week 8 as the rate observed in the intention-to-treat analysis in the **20Gy/5f** group (N=89):

• All patients alive beyond week 9 with no ambulatory assessment at week 8

• All patients lost to follow-up before week 9 with no ambulatory assessment at week 8

Evaluables	215	216	-2.5	211	213	-3.0
Positive response	151 (70.2%)	157 (72.7%)	(-9.6 to 4.7)	148 (70.1	156 %) (73.2%)	(-10.3 to 4.1)

Analysis 8 (imputation of missing data)

This analysis considers the following:

• If a patient has the same ambulatory assessment before and after the week 8 time period and the patient does not have an assessment done during week 8 (as defined), it is assumed that the week 8 assessment is the same as the response the patient obtained before and after the week 8 time period (N=51).

• All the patients with no ambulatory assessment at week 8 (a) alive beyond week 9 and (b) lost to follow-up before week 9 are assumed to have the same rate of positive response as the ones with known ambulatory status at the week 8 time period (N=38)

Internet and a	latery status			00	·)		
Evaluables	215	216	-3.9		211	213	-4.1
Positive	148	157	(-11.1 to 3.4)		146	156	(-11.3 to 3.2)
response	(68.8%)	(72.7%)			(69.2%)	(73.2%)	

Analysis 9 (Multiple imputation using chained equations - outcome imputed as a binary variable)

The data for the following category of patients were imputed using multiple imputation (N=89 for ITT and N=87 for PP):

- All patients alive beyond week 9 with no ambulatory assessment at week 8 (49-62 days post-randomization)
- All patients lost to follow-up before week 9 and therefore had no ambulatory assessment at week 8.

The multiple imputation was done considering the following:

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- The auxiliary variables used were: age, sex, primary tumour, ambulatory status at randomization, the extent of metastases, number of SSC sites, site of spinal cord compression, recruiting country, hospital site and treatment group.
- 50 imputations were used in the procedure using a random seed.
- A direct multiple imputation of the binary outcome response at 8 weeks (AS response at 8 weeks as positive or negative) was done using logistic regression.
- An unadjusted logistic regression model was estimated using multiple imputations in order to evaluate the association between treatment group and response at 8 weeks.
- The predicted odds ratios and 90%CI from logistic regression using multiple imputations were converted into the difference in predicted probabilities and estimated 90%CI.

Evaluables	215	216	-4.4%	211	213	-5.0%
Positive response	65.3%	69.7%	(-12.5% to 3.6%)	65.1%	70.2%	(-13.4% to 3.3%)

Analysis 10 (Multiple imputation using chained equations - outcome imputed directly as an ordinal variable)

- The data for the following categories of patients were imputed using multiple imputation (N=89 for ITT and N=87 for PP):
- All patients alive beyond week 9 with no ambulatory assessment at week 8 (49-62 days postrandomization)
- All patients lost to follow-up before week 9 and therefore had no ambulatory assessment at week 8 time window
- The multiple imputation was done considering the following:
- The auxiliary variables used were: age, sex, primary tumour, ambulatory status at randomization, the extent of metastases, number of SSC sites, site of spinal cord compression, recruiting country, hospital site and treatment group.
- 50 imputations were used in the procedure using a random seed.
- Multiple imputation of the ordinal outcome at 8 weeks (AS 1,2,3,4) was carried out using an ordered logistic regression imputation method. Once the ordinal outcome was imputed, it was then transformed into a binary variable (positive/negative response) defined in the protocol.
- An unadjusted logistic regression model was estimated using multiple imputations to evaluate the association between treatment group and response at 8 weeks.
- The predicted odds ratios and 90%CI from logistic regression using multiple imputations were converted into difference in predicted probabilities and estimated 90%CI to be in line with the primary analysis results.

Evaluables	215	216	-3.4%	211	213	-4.4%
Positive response	65.5%	68.9%	(-11.7% to 4.9%)	65.9%	70.3%	(-12.5% to 3.7%)

Analyses 4 to 10 are based on the 8 week assessment defined as between 49 and 62 days inclusive post-randomization.

The population used for the intention to treat analysis includes all eligibible randomised patients who did not die by the week 8 timepoint. The population used for the per protocol analysis includes all eligible randomised patients who received treatment as per protocol who did not die by the week 8 timepoint

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eTable 5 - Ca	auses of	death
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Cause of death	Deaths						
	N=529						
	8Gy/1f	20Gy/5f					
	N (%)	N (%)					
	N=266	N=263					
Progressive Cancer	226 (85%)	220 (83%)					
Other:							
Infections and infestations	4 (2%)	4 (2%)					
Cardiovascular disorders	1 (<1%)	5 (2%)					
Other ^a	5 (2%)	6 (2%)					
Uncertain/Not Known	30 (11%)	28 (11%)					

a. Other:

8Gy1f: (1) disease progression; (2) Injury, poisoning and procedural complications; (1) metabolism and nutrition disorder; (1) nervous system disorder 20Gy5f: (3) disease progression; (1) Injury, poisoning and procedural complications; (1) General disorders and administration site conditions; (1) Secondary Cancer

	eTable	6 -	Adverse	events
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Adverse events	Grade 1 & 2	Grade 3 & 4 ^a			
	N=686		N=686		
	8Gy/1f	20Gy/5f	8Gy/1f	20Gy/5f	
	N=345	N=341	N=345	N=341	
Olvin					
Skin	40 (44 00()	00 (40 40()		4 (0.00()	
Radiation reaction	40 (11.6%)	66 (19.4%)		1 (0.3%)	
Other	9 (2.6%)	3 (0.9%)		2 (0.6%)	
Musculoskeletal			10 (5 00()		
Pain	35 (10.1%)	33 (9.7%)	18 (5.2%)	9 (2.6%)	
Edema	7 (2.0%)	6 (1.8%)			
Muscle weakness	5 (1.4%)	5 (1.5%)	3 (0.9%)	4 (1.2%)	
Other	2 (0.6%)			1 (0.3%)	
Gastrointestinal					
Anorexia	101 (29.3%)	101 (29.6%)	6 (1.7%)	4 (1.2%)	
Nausea	65 (18.8%)	63 (18.5%)	4 (1.2%)	1 (0.3%)	
Diarrhoea	49 (14.2%)	36 (10.6%)	2 (0.6%)	6 (1.8%)	
Dysphagia	23 (6.7%)	32 (9.4%)	3 (0.9%)		
Constipation	22 (6.4%)	12 (3.5%)	1 (0.3%)		
Sore throat	13 (3.8%)	33 (9.7%)			
Vomiting	3 (0.9%)	8 (2.3%)	2 (0.6%)		
Abdominal pain		4 (1.2%)	2 (0.6%)	1 (0.3%)	
Abdominal distension	1 (0.3%)		2 (0.6%)		
Oral pain	3 (0.9%)	2 (0.6%)			
Other	19 (5.5%)	25 (7.3%)		1 (0.3%)	
CNS				, <i>i</i>	
Fatigue	168 (48.7%)	189 (55.4%)	28 (8.1%)	33 (9.7%)	
Headache	3 (0.9%)	, , , , , , , , , , , , , , , , , , ,		, ,	
Other	12 (3.5%)	14 (4.1%)	9 (2.6%)	5 (1.5%)	
Blood and lymphatic	()			- (,	
Anaemia	1 (0.3%)	1 (0.3%)		2 (0.6%)	
Febrile neutropenia	()	()		1 (0.3%)	
Other	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	
Other					
Respiratory	11 (3.2%)	16 (4.7%)	12 (3.5%)	13 (3.8%)	
Urinary	10 (2.9%)	10 (2.9%)	4 (1.2%)	1 (0.3%)	
Infective	6 (1.7%)	9 (2.6%)	3 (0.9%)	2 (0.6%)	
Psychiatric	9 (2.6%)	5 (1.5%)	1 (0.3%)	4 (1.2%)	
Metabolic	1 (0.3%)		1 (0.3%)	3 (0.9%)	
Renal	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	
Thromboembolic and other vascular	1 (0.3%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	
Other	4 (1.2%)	4 (1.2%)	7 (2.0%)	3 (0.9%)	
		1 ` ´	, í	1	
Any adverse event	179 (51.9%)	194 (56.9%)	71 (20.6%)	70 (20.5%	

^{a.} Three patients had grade 5 adverse event in 8Gy/1f Group: (1) Intracranial haemorrhage (Nervous system disorders); (1) Supraventricular tachycardia (Cardiac disorders) and Thromboembolic event (Vascular disorders); (1) Sudden death NOS (General disorders and administration site conditions)

Five patients had grade 5 adverse event in 20Gy/5f Group: (1) Myocardial infarction (Cardiac disorders); (1) Upper respiratory infection (Infections and infestations) and Other injury, poisoning and procedural complications: Hospital-acquired upper respiratory tract infection (Injury, poisoning and procedural complications); (1) Stridor (Respiratory, thoracic and mediastinal disorders); (1) Cardiac arrest (Cardiac disorders); (1) Respiratory failure (Respiratory, thoracic and mediastinal disorders) All of the above 8 deaths were unrelated to radiotherapy

Note: Each row represents the number of patients that experienced a particular type of adverse event. On each row patients are counted only once based on the worst grade experienced for each adverse event.

eTable 7 - Bladder and bowel function endpoints

ment				n				
	8Gy/1f Events/ N (%)	20Gy/5f Events/N (%)	Odds ratios (95%Cl)	p	8Gy/1f Events/ N (%)	20Gy/5f Events/N (%)	Odds ratios (95%Cl)	р
Overall								
Baseline	96/342 (28%)	82/341 (24%)	1.23 (0.88 to	0.2	177/342	166/341 (49%)	1.13 (0.84 to	0.4
Week 1	93/294	76/300	1.36 (0.95 to	0.0	131/293	132/300	1.03 (0.74 to	0.8
	(32%)	(25%)	1.95)	9	(45%)	(44%)	1.42)	6
	Aujusieu		1.99)	1				
Week 4	66/209 (32%)	53/223 (24%)	1.48 (0.97 to 2.26)	0.0 7	82/209 (39%)	79/223 (35%)	1.18 (0.80 to 1.74)	0.4 1
	Adjusted ^a		1.61 (0.92 to	0.0				
Week 8	47/151	34/166			59/151	61/166	1.10 (0.70 to	0.6
	(31%)	(20%)	2.92)	3	(39%)	(37%)	1.74)	7
	Adjusted ^a							
Week	41/139	35/154	1.42 (0.84 to	0.1	53/140	55/155	1.11 (0.69 to	0.6
Events/ N (%) Events/ (%) Events/ N (%) Events/ (%) (95%Cl) Overall	7							
	Aujusteu	r						
Anv	132/316	111/322	1.36 (0.99 to	0.0	203/315	204/322	1.05 (0.76 to	0.7
	(42%)		1.88)	6				8
	Adjusted ^a							
			1.07)					
Only loca	tion of SSC	site within	C1 to T12 (treat	ment ex	clusively to t	the spinal co	rd)	
Wester								
VVEEK X	29/97 (30%	() 29/117	1 29 (0 70	04	41/97 (42)	%) 46/117	1 13 (0 65 to	0 0
Week 8	29/97 (30%				41/97 (42			
WEEK 8	29/97 (30%				41/97 (42)			6
Week 8	29/97 (30%				41/97 (42			6
Any	92/219	85/236	to 2.37)	0	143/219	(39%)	1.95) 1.12 (0.76 to	6 6
Any	92/219	85/236	to 2.37)	0	143/219	(39%)	1.95) 1.12 (0.76 to	6 6 0 0 0
Any	92/219	85/236	to 2.37)	0	143/219	(39%)	1.95) 1.12 (0.76 to	6 6 0 0 5
Any time	92/219 (42%)	(25%) 85/236 (36%)	to 2.37)	0 0.1 9	143/219 (65%)	(39%)	1.95) 1.12 (0.76 to	6 6 0 0 5
Any time	92/219 (42%)	(25%) 85/236 (36%)	to 2.37)	0 0.1 9	143/219 (65%)	(39%)	1.95) 1.12 (0.76 to	6 6 0 0 5
Any time Only loca	92/219 (42%) tion of SSC	(25%) 85/236 (36%) site within	to 2.37)	0 0.1 9 ent to t	143/219 (65%) he cauda equ	(39%) 148/236 (63%) Jina)	1.95) 1.12 (0.76 to 1.64)	6 6 7 0 0 5 7
Any time Only loca	92/219 (42%) tion of SSC	(25%) 85/236 (36%) site within	to 2.37)	0 0.1 9 ent to t	143/219 (65%) he cauda equ	(39%) 148/236 (63%) uina) %) 11/39	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to	6 6 7 5 7 7 0 0 0
Any time Only loca	92/219 (42%) tion of SSC	(25%) 85/236 (36%) site within	to 2.37)	0 0.1 9 ent to t	143/219 (65%) he cauda equ	(39%) 148/236 (63%) uina) %) 11/39	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to	6 6 7 7 7 0 0 0 7
Any time Only loca	92/219 (42%) tion of SSC	(25%) 85/236 (36%) site within 1 6) 4/39 (10%)	to 2.37) 1.29 (0.88 to 1.88) L1 to S2 (treatm 4.53 (1.35 to 15.14)	0 0.1 9 0.1 9 0.0 14	143/219 (65%) he cauda equ 14/44 (32)	(39%) 148/236 (63%) Jina) %) 11/39 (28%)	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05)	6 6 7 5 7 7 0 0 0 0 0 7 2
Any time Only loca Week 8 Any	92/219 (42%) tion of SSC	 (25%) 85/236 (36%) site within 4/39 (10%) 21/70 	to 2.37)	0 0.1 9 0.1 9 0.0 14 0.1	143/219 (65%) he cauda equ 14/44 (32)	(39%) 148/236 (63%) Jina) %) 11/39 (28%) %) 47/70	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to	6 6 7 5 7 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Any time Only loca Week 8 Any	92/219 (42%) tion of SSC	 (25%) 85/236 (36%) site within 4/39 (10%) 21/70 	to 2.37)	0 0.1 9 0.1 9 0.0 14 0.1	143/219 (65%) he cauda equ 14/44 (32)	(39%) 148/236 (63%) Jina) %) 11/39 (28%) %) 47/70	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to	6 6 7 5 7 7 0 0 0 0 0 0 0 0 0 0 0 0
Any time Only loca Week 8 Any	92/219 (42%) tion of SSC	 (25%) 85/236 (36%) site within 4/39 (10%) 21/70 	to 2.37)	0 0.1 9 0.1 9 0.0 14 0.1	143/219 (65%) he cauda equ 14/44 (32)	(39%) 148/236 (63%) Jina) %) 11/39 (28%) %) 47/70	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to	66 67 77 77 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Any time Only loca Week 8 Any time	92/219 (42%) tion of SSC 15/44 (34% 34/81 (42%	(25%) 85/236 (36%) site within 1 4/39 (10%) 21/70 (30%)	to 2.37)	0 0.1 9 eent to ti 0.0 14 0.1 3	143/219 (65%) he cauda equ 14/44 (32) 51/80 (64)	(39%) (39%) (39%) (63%) (63%) (63%) (28%) (28%) (28%) (28%) (67%)	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to 1.69)	66 67 77 77 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Any time Only loca Week 8 Any time	92/219 (42%) tion of SSC 15/44 (34% 34/81 (42%	byth 20Gy/ff Odds ratios (95%Cl) p Beyntf 20Gy/ff Odds ratios (95%Cl) p 1/32 Events/N (95%Cl) 1.73 0.88 to 0.2 1.77/342 166/341 1.13 (0.84 to 0.4 1/34 82/341 1.23 (0.88 to 0.2 1.77/342 166/341 1.13 (0.84 to 0.4 27%0 (25%) 1.951 9 (45%) 1.49% 1.23 (0.74 to 0.8 1/32 52/23 1.48 (0.97 to 0.6 1.49% 1.42) 6 1/209 53/223 1.48 (0.97 to 0.0 83/209 79/223 1.18 (0.80 to 0.4 1/151 34/166 1.75 (1.05 to 0.0 59/151 61/166 1.10 (0.70 to 0.6 1/33 35/154 1.42 (0.84 to 0.1 53/140 55/155 1.11 (0.69 to 0.7 1/34 1.64 (0.86 to 0.1 53/140 56/165 1.11 (0.69 to 0.7 1/351 1.11 (0.270 to 0.1 1.42 1						
Any time Only loca Week 8 Any time	92/219 (42%) tion of SSC 15/44 (34% 34/81 (42%	 (25%) 85/236 (36%) site within 4/39 (10%) 4/39 (10%) 21/70 (30%) site within 	to 2.37) 1.29 (0.88 to 1.88) L1 to S2 (treatm 4.53 (1.35 to 15.14) 1.69 (0.86 to 3.32) T6 to L5 (treatm 3.00 (0.25)	0 0.1 9 0.1 9 0.1 14 0.0 14 0.1 3 0.1 3 0.1 3	143/219 (65%) he cauda equ 14/44 (32' 51/80 (64' 551/80 (64'	(39%) 148/236 (63%) Jina) (28%) (28%) (28%) (28%) (67%) Cord and cau	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to 1.69) Uda equina) 5) 1.11 (0.16 to	6 6 7 7 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Any time Only loca Week 8 Any time	92/219 (42%) tion of SSC 15/44 (34% 34/81 (42%	 (25%) 85/236 (36%) site within 4/39 (10%) 4/39 (10%) 21/70 (30%) site within 	to 2.37) 1.29 (0.88 to 1.88) L1 to S2 (treatm 4.53 (1.35 to 15.14) 1.69 (0.86 to 3.32) T6 to L5 (treatm 3.00 (0.25)	0 0.1 9 0.1 9 0.1 14 0.0 14 0.1 3 0.1 3 0.1 3	143/219 (65%) he cauda equ 14/44 (32' 51/80 (64' 551/80 (64'	(39%) 148/236 (63%) Jina) (28%) (28%) (28%) (28%) (67%) Cord and cau	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to 1.69) Uda equina) 5) 1.11 (0.16 to	6 6 7 7 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Any time Only loca Week 8 Any time	92/219 (42%) tion of SSC 15/44 (34% 34/81 (42%	 (25%) 85/236 (36%) site within 4/39 (10%) 4/39 (10%) 21/70 (30%) site within 	to 2.37) 1.29 (0.88 to 1.88) L1 to S2 (treatm 4.53 (1.35 to 15.14) 1.69 (0.86 to 3.32) T6 to L5 (treatm 3.00 (0.25)	0 0.1 9 0.1 9 0.1 14 0.0 14 0.1 3 0.1 3 0.1 3	143/219 (65%) he cauda equ 14/44 (32' 51/80 (64' 551/80 (64'	(39%) 148/236 (63%) Jina) (28%) (28%) (28%) (28%) (67%) Cord and cau	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to 1.69) Uda equina) 5) 1.11 (0.16 to	6 6 7 7 7 0 0 0 0 6 6 6 6 6 0 0 0 9
Any time Only loca Week 8 Any time	92/219 (42%) tion of SSC 15/44 (34% 34/81 (42% 34/81 (42% 34/81 (42%)	 (25%) 85/236 (36%) site within 4/39 (10%) 21/70 (30%) 21/70 (30%) 1/8 (13%) 	to 2.37)	0 0.1 9 0.0 14 0.0 14 0.1 3 ent acro	143/219 (65%) he cauda equ 14/44 (32) 51/80 (64) 551/80 (64) 055 both the 4/10 (40%	(39%) 148/236 (63%) Jina) (28%) %) 11/39 (28%) %) 47/70 (67%) Cord and cau 5) 3/8 (38%)	1.95) 1.12 (0.76 to 1.64) 1.19 (0.46 to 3.05) 0.86 (0.44 to 1.69) 1.69) 1.11 (0.16 to 7.51)	6 6 7 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0

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					7 3

Note: Logistic regression was done comparing 8Gy/1f versus 20Gy/5f. The analysis was based only on the number of patients with assessment (evaluable patients)

- a. Adjusted for bladder function at baseline, sex, age, baseline AS, primary tumour, number of SSC sites, the extent of metastases at baseline and extent of metastases
- b. Includes assessments at all time points except baseline assessment

Baseline characteristics	8 Gy/1f N=39	20 Gy/5f N=38	р
	11-55	11=50	
Age, years			
Median (range)	68 (51 to 86)	71 (40 to 91)	0.4
Sex		71 (40 10 01)	0.4
Female	10 (26%)	6 (16%)	
Male	29 (74%)	32 (84%)	0.4
Site of primary cancer	20 (11/0)		0.1
Prostate	26 (67%)	30 (79%)	
Lung	1 (3%)	0 (0%)	
Breast	7 (18%)	3 (8%)	
Gl	1 (3%)	1 (3%)	
Renal	1 (3%)	0 (0%)	
Skin	0 (0%)	1 (3%)	
Bladder	0 (0%)	1 (3%)	
Gynae, head & neck, sarcoma, unspecified	3 (8%)	2 (5%)	0.59
Extent of metastases	\/	()	0.00
Nonskeletal mets absence	25 (64%)	29 (76%)	
Nonskeletal mets present	14 (36%)	9 (24%)	0.32
Number of SCC sites	11(00/0)	0 (2170)	0.02
Single	37 (95%)	36 (95%)	
Multiple	2 (5%)	2 (5%)	>0.99
Site of spinal cord compression (SCC)	_ (0,0)	_ (0,0)	
Cervical vertebrae	1 (3%)	1 (3%)	
Cervical and thoracic	1 (3%)	0 (0%)	
Thoracic	22 (56%)	23 (61%)	
Thoracic and lumbar	3 (8%)	4 (11%)	
Lumbar	10 (26%)	8 (21%)	
Lumbar and sacrum	1 (3%)	1 (3%)	
Sacrum (S1 and S2)	1 (3%)	1 (3%)	0.98
WHO performance status			
0&1	19 (49%)	18 (47%)	
2	11 (28%)	8 (21%)	
3	9 (23%)	9 (24%)	
4	0 (0%)	2 (5%)	
Not reported	0 (0%)	1 (3%)	0.59
Ambulatory status			
Grade 1: Ambulatory without walking aids	13 (33%)	13 (34%)	
Grade 2: Ambulatory with walking aids	21 (54%)	15 (39%)	
Grade 3: Unable to ambulate	4 (10%)	8 (21%)	
Grade 4: No motor power	1 (3%)	2 (5%)	0.48
Treatment at baseline			
Chemotherapy only (≤ 4 weeks prior randomization)	1 (3%)	1 (3%)	
Hormone therapy only (≤ 4 weeks prior randomization)	16 (41%)	19 (50%)	
Radiotherapy only (≤ 6 months prior randomization)	0 (0%)	4 (11%)	
Combination of the above	6 (15%)	2 (5%)	
None	16 (41%)	12 (32%)	0.06

eTable 8 - Baseline characteristics by randomization group amongst patients evaluable for the primary endpoint who lived beyond 48 weeks

values are derived from Fishers' exact test

	Intention to	treat popula	tion	Per protocol population			
	8 Gy/1f	20 Gy/5f	Risk difference	8 Gy/1f	20 Gy/5f	Risk difference	
	N (%)	N (%)	(90% CI)	N (%)	N (%)	(90% CI)	
			8 Gy-20Gy			8 Gy-20Gy	
Group 1 - Locatio	n of SSC site	within C1 to	T12				
Evaluables	108	124	-1.0%	108	122	-1.3%	
Positive response	73 (67.6%)	85 (68.6)	-11.1% to 9.1%	73 (67.6%)	84 (68.9%)	-11.4% to 8.9%	
Group 2 - Locatio	n of SSC site	within L1 to	S2				
Evaluables	47	41	-8.8%	46	40	-9.2%	
Positive response	36 (76.6%)	35 (85.4%)	-22.4% to 4.9%	36 (78.3%)	35 (87.5%)	-22.4% to 4.0%	
Group 3 - Locatio	n of SSC site	within T6 to	L5				
Evaluables	11	9	-12.1%	10	9	-16.7%	
Positive response	6 (54.6%)	6 (66.7%)	-47.9% to 23.6%	5 (50.0%)	6 (66.7%)	-53.3% to 20.0%	

eTable 9 - Ambulatory response at 8 weeks by location of SSC site

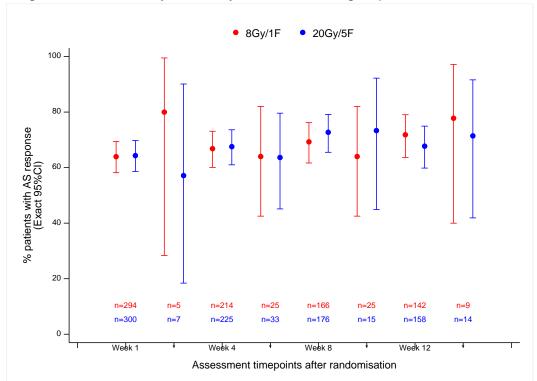
Note: The total is 340 instead of 342 because two patients had unknown location of SSC site (it was not reported at baseline)

eTable 10 – Quality of life at 4 and 8 weeks by ambulatory response in 20Gy/5f and 8Gy/1f

Quality of Life scales	Ambu	latory respo			Mean difference ad	justed for	
by ambulation status	(Grade	e 1-2)	(Gra	de 3-4)	QoL baseline scores		
	N	Mean	N	Mean	(1-2) vs (3-4)	р	
					(95%CI)		
QoL at 4 weeks accord	ling to a	mbulatory r	esponse	at 4 weeks			
20Gy/5f							
Global health status	99	45.3	37	27.0	13.4(5.3 to 21.5)	0.001	
Physical functioning	98	44.4	37	6.9	21.9(13.6 to 30.1)	p<0.0001	
Role functioning	98	34.4	37	2.7	23.2(13.1 to 33.3)	p<0.0001	
Emotional functioning	99	74.4	37	69.1	2.0(-7.2 to 11.1)	0.67	
Cognitive functioning	99	75.6	37	64.9	7.4(-1.9 to 16.7)	0.12	
Social functioning	98	49.5	37	14.4	23.0(11.0 to 35.0)	p<0.0001	
8Gy/1f							
Global health status	105	46.8	39	28.0	15.2(7.5 to 22.9)	p<0.0001	
Physical functioning	105	43.4	39	3.2	29.6(20.9 to 38.4)	p<0.0001	
Role functioning	103	33.5	38	4.0	25.6(15.2 to 36.0)	p<0.0001	
Emotional functioning	105	74.0	39	66.3	7.5(-0.8 to 15.7)	0.08	
Cognitive functioning	105	79.0	39	66.7	8.6(-0.01 to 17.1)	0.05	
Social functioning	105	40.3	39	18.6	16.0(5.3 to 26.7)	0.004	
QoL at 8 weeks accord	ling to a	mbulatory r	esponse	at 8 weeks			
		,					
20Gy/5f							
Global health status	81	48.6	26	33.0	14.0(4.3 to 23.7)	0.005	
Physical functioning	82	43.7	26	6.9	27.6(17.2 to 38.0)	p<0.0001	
Role functioning	81	34.6	27	8.0	24.0(11.7 to 36.3)	p<0.0001	
Emotional functioning	82	74.2	26	69.6	0.8(-8.7 to 10.1)	0.88	
Cognitive functioning	82	77.0	26	75.6	1.3(-8.7 to 11.2)	0.80	
Social functioning	81	50.0	26	11.5	32.1(18.8 to 45.6)	p<0.0001	
90v/46							
8Gy/1f							
Global health status	83	45.9	22	31.8	11.0(-1.0 to 23.0)	0.07	
Physical functioning	83	45.5	22	3.2	34.5(21.4 to 47.7)	p<0.0001	
Role functioning	82	35.9	22	5.3	27.2(12.8 to 41.7)	p<0.0001	
Emotional functioning	82	70.0	22	61.0	5.3(-7.5 to 18.1)	0.41	
Cognitive functioning	82	74.3	22	69.7	1.8(-11.0 to 14.6)	0.78	
Social functioning	82	45.7	22	18.2	18.1(2.2 to 34.0)	0.03	
Ambulatory status - Grade 1-2							

Ambulatory status - Grade 1-2: able to walk/mobile. Grade 3-4: unable to walk easily/not mobile.

All QoL scores are on a scale 0-100, where a high score indicates good health. Hence a positive mean difference indicates that QoL is better among patients with ambulatory grades 1-2.



eFigure 1 - Ambulatory status by randomization group

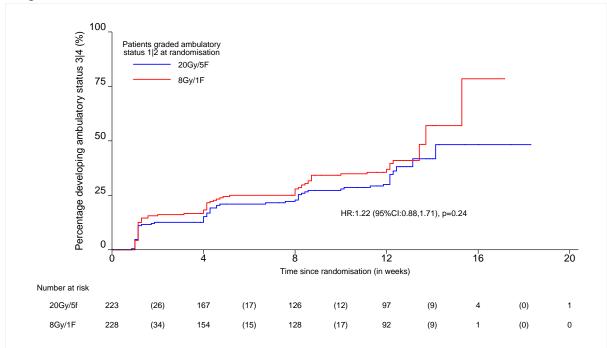
Note: Week 1 is between day 7 and 13 inclusive after randomization. Week 4 is between day 21 to 34 inclusive after randomization. Week 8 is between day 49 to 62 inclusive after randomization. Week 12 is between day 70 to 97 inclusive after randomization.

* These time points were outside the protocol specified time frames for the assessments and are shown here for completeness

eFigure 2 – Difference in ambulatory status at 8 weeks according to baseline characteristics (99% CIs are shown due to multiple analyses). The protocol pre-specified factors were ambulatory status, primary tumor type and extent of metastases.

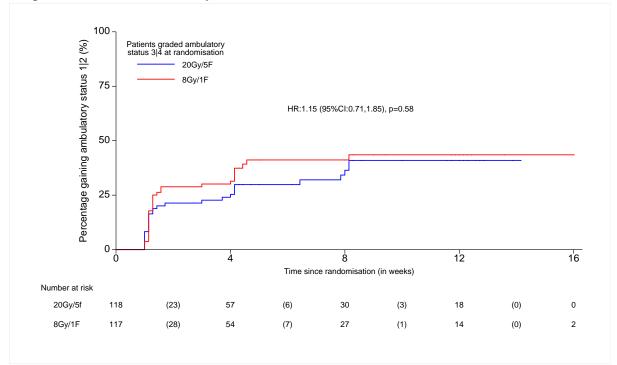
Baseline Characteristics	N		Interaction p	Risk diff (99%CI)
Age :65 years :65 years to <75 years :75 years	102 128 112		0.07	0.3% (-23.5,24.0) 6.6% (-14.4,27.5)
iex Male	248			-18.7% (-39.5,2.0) -2.0% (-16.5,12.5)
emale mbulatory status	94		0.58	-8.8% (-34.3,16.6)
& 2 & 4	264 78		0.86	-5.3% (-17.8,7.2) -5.6% (-34.1,22.9)
P rimary tumour Prostate ung	182 40			3.3% (-12.6,19.2) -17.3% (-58.7,24.0)
reast	46 29			11.0% (-21.0,42.9) -10.0% (-57.4,37.4)
Other	45 —		0.10	-35.1% (-69.4,-0.9)
xtent of Metastases bsent resent	202 140		0.97	-2.8% (-19.0,13.3) -3.5% (-23.8,16.8)
VHO status				
) or 1	130 93			3.1% (-13.2,19.4) -8.1% (-30.0,13.7)
	91 25		0.68	-10.8% (-37.7,16.1) -10.3% (-56.5,36.0)
lo of SCC Sites	316			-3.1% (-16.2,9.9)
Aultiple Sites	26		>0.99	-3.6% (-53.2,45.9)
lo Yes	322 18		0.17	-2.0% (-15.2,11.2) -14.3% (-48.3,19.8)
horacid SCC	100			-10.6% (-30.0,8.9)
'es	240		0.24	-0.9% (-16.6,14.9)
umbar SCC lo ′es	242 98		0.49	-1.6% (-17.0,13.7) -8.3% (-30.4,13.8)
acrum SCC lo	327	- <u>i</u>		-2.5% (-15.6,10.6)
'es	13		0.22	-16.7% (-55.9,22.5)
i ny baseline treatment lo res	144 197		0.35	-9.3% (-29.7,11.1) 0.8% (-15.1,16.6)
Chemotherapy	306			-4.2% (-17.4,9.0)
es	36		0.96	-4.2% (-48.8,40.5)
lormone treatment	201			-11.6% (-28.9,5.8)
íes	141		0.08	6.5% (-10.8,23.8)
t adiotherapy lo Yes	285 57		0.66	-2.4% (-16.3,11.4) -8.3% (-39.4,22.7)
es Bladder function	57		0.00	-0.3% (-39.4,22.7)
lormal Ibnormal	269 72		0.71	-2.3% (-15.2,10.6) 1.9% (-28.2,32.0)
Sowel function Normal	184			1.0% (-14.6,16.7)
bnormal	157		0.43	-7.5% (-27.3,12.4)
Duration of symptoms	126			-0.9% (-23.0,21.2)
: 1 week to < 1 month : 1 month	92 75		0.72	-0.2% (-22.8,22.4) -10.0% (-36.1,16.1)
Country JK	305			-2 50/ / 45 / 40 2)
Australia	325 17		0.55	-2.5% (-15.4,10.3) -18.1% (-79.4,43.3)
		-50 -30 -11 0 11 30 50		

eFigure 3 – Time to loss of ambulation



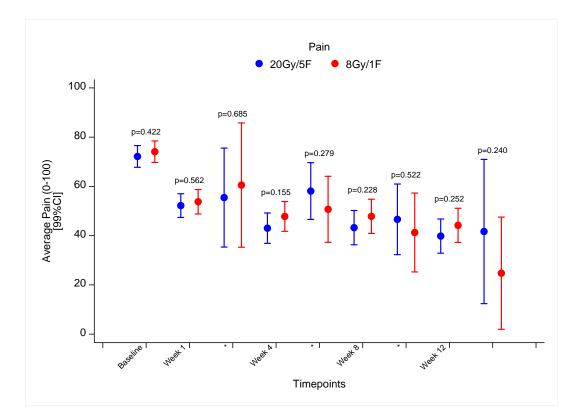
Note: Proportionality assumption test p=0.96

eFigure 4 – Time to recovery of ambulation



Note: Proportionality assumption test p=0.55

eFigure 5 - Pain scores in 8Gy/1f and in 20Gy/5f



Note: Week 1 is between day 7 and 13 inclusive after randomization. Week 4 is between day 21 to 34 inclusive after randomization. Week 8 is between day 49 to 62 inclusive after randomization. Week 12 is between day 70 to 97 inclusive after randomization.

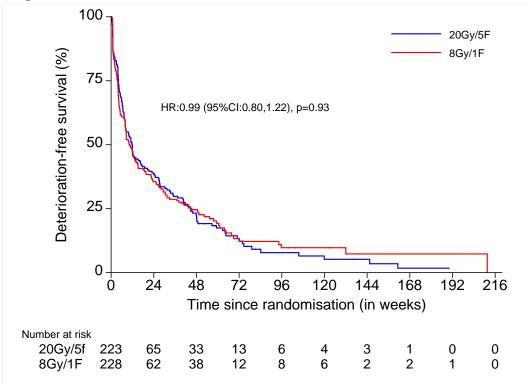
* These time points were outside the protocol specified time frames for the assessments and are shown here for completeness.

The figure shows the mean pain score at each time point, adjusted for the baseline score, from a repeated measures mixed model that included an interaction term between time and treatment group.

Factors pi Age <65 years 9 >65 years to <75 years 1 >75 years 11 Sex Male 22 Female 9 Ambulatory status 9	Aumber of patients	OS %	Median OS time(wks)	Number of patients	12-week OS %	Median OS				Interact.		
≥75 years 11 Sex Male 24 Female 94	48				03 /8	time(wks)				р	HR,(99%CI)	р
Male 29 Female 9 Ambulatory status		51% 47% 54%	13 11 15	113 109 119	51% 56% 56%	12 14 17		-	•	0.64	0.9 (0.59;1.38) 1.08 (0.75;1.56) 1.08 (0.73;1.61)	0.53 0.58 0.6
Ambulatory status	255 10	53% 43%	14 11	248 93	52% 61%	13 17			•	0.89	1.02 (0.78;1.32) 1.08 (0.69;1.68)	0.8 0.6
1 & 2 2 3 & 4 1	28 17	60% 30%	19 7	223 118	61% 43%	17 8		•	•	0.23	0.96 (0.72;1.28) 1.18 (0.81;1.71)	0.7 0.2
Primary tumour Prostate 11 Lung 66 Breast 33 GI 33 Other 55	19 15	69% 15% 72% 29% 38%	31 5 24 7 10	152 66 40 38 45	63% 45% 69% 32% 47%	22 8 22 7 10		•	 	→ → 0.11	0.96 (0.67;1.36) 1.64 (1;2.68) 0.84 (0.41;1.75) 1.1 (0.57;2.09) 1.01 (0.57;1.79)	0.7 0.0 0.5 0.7
Extent of Metastases Absent 11 Present 11	86 59	57% 43%	15 10	185 156	67% 40%	23 9	-	•	_	0.27	1.11 (0.81;1.51) 0.92 (0.67;1.27)	0.4 0.5
WHO status 0 or 1 9' 2 8' 3 1' 4 4'	18 14	71% 56% 36% 26%	28 14 9 5	94 81 121 41	74% 57% 45% 35%	28 16 10 7		•	• • •	→ 0.49	0.87 (0.55;1.38) 1.12 (0.7;1.78) 1.11 (0.76;1.61) 1.28 (0.7;2.34)	0.4 0.5 0.4 0.3
No of SCC Sites Single Site 34 Multiple Sites 42	103 12	52% 37%	13 9	311 30	54% 63%	14 16		_•	•	→ 0.1	0.97 (0.77;1.23) 1.61 (0.77;3.36)	0.7 0.1
	133 2	50% 42%	13 9	321 18	54% 66%	13 28			•	→ 0.2	0.99 (0.79;1.25) 1.83 (0.57;5.82)	0.9 0.1
Thoracid SCC No 9 Yes 25)1 254	53% 49%	14 12	85 254	63% 52%	17 13	_	•	•	0.74	0.98 (0.62;1.56) 1.05 (0.81;1.35)	0.9 0.6
Lumbar SCC No 24 Yes 92	253 12	48% 55%	11 14	254 85	54% 55%	13 15			•	0.41	1.07 (0.83;1.39) 0.92 (0.59;1.44)	0.5 0.6
	133 2	50% 58%	12 13	329 10	54% 80%	13 14 ←		•	•	→ 0.99	1.02 (0.82;1.29) 0.93 (0.22;3.82)	0.7 0.8
Any baseline treatment No 11 Yes 11	56 88	42% 57%	10 17	141 200	52% 57%	13 15			•	0.85	1.03 (0.74;1.44) 1.01 (0.74;1.36)	0.8 0.9
Chemotherapy No 3 Yes 3	314 31	51% 45%	13 10	295 46	56% 46%	14 10	_		•	→ 0.71	1.03 (0.81;1.31) 1.13 (0.6;2.14)	0.7 0.6
Hormone treatment No 22 Yes 12	20 25	40% 68%	9 33	222 119	48% 66%	11 27	_		•	0.42	1.09 (0.83;1.43) 0.95 (0.64;1.42)	0.4 0.7
Radiotherapy No 2 Yes 6	276 19	50% 51%	12 13	273 68	58% 40%	16 8		•	•	0.14	1.08 (0.84;1.39) 0.79 (0.48;1.29)	0.4 0.2
Bladder function Normal 24 Abnormal 9	246 16	55% 37%	15 8	259 82	57% 46%	14 11				0.29	0.96 (0.74;1.25) 1.17 (0.75;1.81)	0.6 0.3
Bowel function Normal 10 Abnormal 17	65 77	58% 42%	20 9	175 166	60% 49%	17 12	_	•		0.07	0.87 (0.62;1.2) 1.17 (0.85;1.6)	0.2 0.2
	47 02 5	42% 55% 67%	10 17 20	133 104 63	54% 49% 57%	13 12 16		•	• <u> </u>	0.42	1.11 (0.78;1.56) 0.87 (0.58;1.31) 0.84 (0.47;1.49)	0.4 0.4 0.4
Country UK 33 Australia 10	29 6	50% 50%	12 10	324 17	54% 59%	13 17			•	→ 0.86	1.02 (0.81;1.29) 1.08 (0.41;2.82)	0.8 0.8

eFigure 6 - Overall survival (hazard ratio) according to baseline characteristics

eFigure 7 - Deterioration-free survival



An event is any patient who had ambulatory status grade 1 or 2 at baseline who then deteriorated to grade 3-4 during the trial (mostly within the 12-week time frame, but some assessments went beyond this), or had died at any time, whichever came first. Patients whose ambulatory status did not progress to grade 3 or 4 (mostly within 12 weeks) and did not die were censored at the date last seen alive (acknowledging that some of these patients may have progressed to grade 3-4 after their last ambulatory assessment but we do not have this information).