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

Contents

eTable 1 - Other baseline characteristics by randomization group

Baseline characteristics	**8 Gy/1f N=345**	**20 Gy/5f 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%)

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**	**p**
	N=166	**N=176**	
Age, years			
Median (range)	71 (44 to 91)	70 (40 to 95)	0.43
Sex			
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
Extent of metastases			
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 & 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			
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			
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%)	
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

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

	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%)

a. 8 weeks' time window is from ≥ 7 weeks to <9 weeks, i.e., ≥ 49 days and <63 days

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

Sensitivity analyses	**Intention to treat population**				**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**
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 response	115 (69.3%)	128 (72.7%)	(-11.5 to 4.6)		114 (69.5%)	127 (73.4%)	(-12.0 to 4.2)
Analysis 1a (primary analysis adjusted for the randomization stratification factors: baseline 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 response	68.5%	73.3%	(-11.8 to 2.2%)		68.7%	74.0%	(-12.3% to 1.7)
Analysis 1b (primary analysis using clustered sandwich estimator) • Logistic regression was implemented with standard errors adjusted for hospital (clustered sandwich estimator which allows for intragroup correlation) and fit with the outcome being a positive response at 8 weeks and explanatory variable being treatment. • The 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	**-3.5%**		164	173	**-3.9%**
Positive response	69.3%	72.7%	(-10.3 to 3.4%)		69.5%	73.4%	(-11.5% to 3.7)
Analysis 2 (handling patients without the 8-week assessment) 40 patients were assessed between 63 and 69 days post-randomization (i.e. up to 1 week after the 62-day limit) so were not included in the main analysis above. The sensitivity analysis includes these patients. The analysis is therefore based on patients with an AS assessment between 49 and 69 days post-randomization.							
Evaluables	191	191	**-4.2**		188	188	**-4.8**
Positive response	131 (68.6%)	139 (72.8%)	(-11.8 to 3.5)		129 (68.6%)	138 (73.4%)	(-12.5 to 2.9)
Analysis 3 (handling patients without the 8-week assessment) 57 patients were assessed at 4 weeks and also after week 8 (i.e. after 62 days post-randomization). However, 51 of these had the same ambulatory response at both time points, so it was assumed that their 8-week assessment would be the same also. The other 6 patients were not included here.							
Evaluables	195	198	**-4.0**		192	195	**-4.6**
Positive response	134 (68.7%)	144 (72.7%)	(-11.6 to 3.5)		132 (68.8%)	143 (73.3%)	(-12.2 to 3.0)
Analysis 4 (imputation of missing data) This analysis assumes that the following categories of patients had a negative response (N=89): • All patients alive beyond week 9 with no ambulatory assessment at week 8 time window (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	**-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 (≥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)

Evaluables	215	216	**-3.9**		211	213	**-4.1**
Positive response	148 (68.8%)	157 (72.7%)	(-11.1 to 3.4)		146 (69.2%)	156 (73.2%)	(-11.3 to 3.2)

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:

- 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 post-randomization)
- 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

eTable 5 - Causes of death

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

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**
Skin				
Radiation reaction	40 (11.6%)	66 (19.4%)		1 (0.3%)
Other	9 (2.6%)	3 (0.9%)		2 (0.6%)
Musculoskeletal				
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				
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%)
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

Assessment	Abnormal bladder function					Abnormal bowel function			
	8Gy/1f Events/ N (%)	20Gy/5f Events/N (%)	Odds ratios (95%CI)	p		8Gy/1f Events/ N (%)	20Gy/5f Events/N (%)	Odds ratios (95%CI)	p
Overall									
Baseline	96/342 (28%)	82/341 (24%)	1.23 (0.88 to 1.74)	0.23		177/342 (52%)	166/341 (49%)	1.13 (0.84 to 1.53)	0.42
Week 1	93/294 (32%)	76/300 (25%)	1.36 (0.95 to 1.95)	0.09		131/293 (45%)	132/300 (44%)	1.03 (0.74 to 1.42)	0.86
	Adjusted[a]		1.15 (0.67 to 1.99)	0.61					
Week 4	66/209 (32%)	53/223 (24%)	1.48 (0.97 to 2.26)	0.07		82/209 (39%)	79/223 (35%)	1.18 (0.80 to 1.74)	0.41
	Adjusted[a]		1.61 (0.92 to 2.82)	0.09					
Week 8	47/151 (31%)	34/166 (20%)	1.75 (1.05 to 2.92)	0.03		59/151 (39%)	61/166 (37%)	1.10 (0.70 to 1.74)	0.67
	Adjusted[a]		1.78 (0.93 to 3.39)	0.08					
Week 12	41/139 (30%)	35/154 (23%)	1.42 (0.84 to 2.40)	0.19		53/140 (38%)	55/155 (35%)	1.11 (0.69 to 1.78)	0.67
	Adjusted[a]		1.64 (0.86 to 3.14)	0.14					
Any time[b]	132/316 (42%)	111/322 (34%)	1.36 (0.99 to 1.88)	0.06		203/315 (64%)	204/322 (63%)	1.05 (0.76 to 1.45)	0.78
	Adjusted[a]		1.31 (0.87 to 1.97)	0.20					
Only location of SSC site within C1 to T12 (treatment exclusively to the spinal cord)									
Week 8	29/97 (30%)	29/117 (25%)	1.29 (0.70 to 2.37)	0.40		41/97 (42%)	46/117 (39%)	1.13 (0.65 to 1.95)	0.66
Any time	92/219 (42%)	85/236 (36%)	1.29 (0.88 to 1.88)	0.19		143/219 (65%)	148/236 (63%)	1.12 (0.76 to 1.64)	0.57
Only location of SSC site within L1 to S2 (treatment to the cauda equina)									
Week 8	15/44 (34%)	4/39 (10%)	4.53 (1.35 to 15.14)	0.014		14/44 (32%)	11/39 (28%)	1.19 (0.46 to 3.05)	0.72
Any time	34/81 (42%)	21/70 (30%)	1.69 (0.86 to 3.32)	0.13		51/80 (64%)	47/70 (67%)	0.86 (0.44 to 1.69)	0.66
Only location of SSC site within T6 to L5 (treatment across both the cord and cauda equina)									
Week 8	3/10 (30%)	1/8 (13%)	3.00 (0.25 to 36.32)	0.39		4/10 (40%)	3/8 (38%)	1.11 (0.16 to 7.51)	0.91
Any time	6/16 (38%)	5/14 (36%)	1.08 (0.24 to 4.79)	0.92		9/16 (56%)	7/14 (50%)	1.29 (0.30 to 5.43)	0.

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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

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

Baseline characteristics	**8 Gy/1f**	**20 Gy/5f**	**p**
	N=39	**N=38**	
Age, years			
Median (range)	68 (51 to 86)	71 (40 to 91)	0.4
Sex			
Female	10 (26%)	6 (16%)	
Male	29 (74%)	32 (84%)	0.4
Site of primary cancer			
Prostate	26 (67%)	30 (79%)	
Lung	1 (3%)	0 (0%)	
Breast	7 (18%)	3 (8%)	
GI	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			
Nonskeletal mets absence	25 (64%)	29 (76%)	
Nonskeletal mets present	14 (36%)	9 (24%)	0.32
Number of SCC sites			
Single	37 (95%)	36 (95%)	
Multiple	2 (5%)	2 (5%)	>0.99
Site of spinal cord compression (SCC)			
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

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

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

	Intention to treat population				**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 - Location 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 - Location 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 - Location 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%

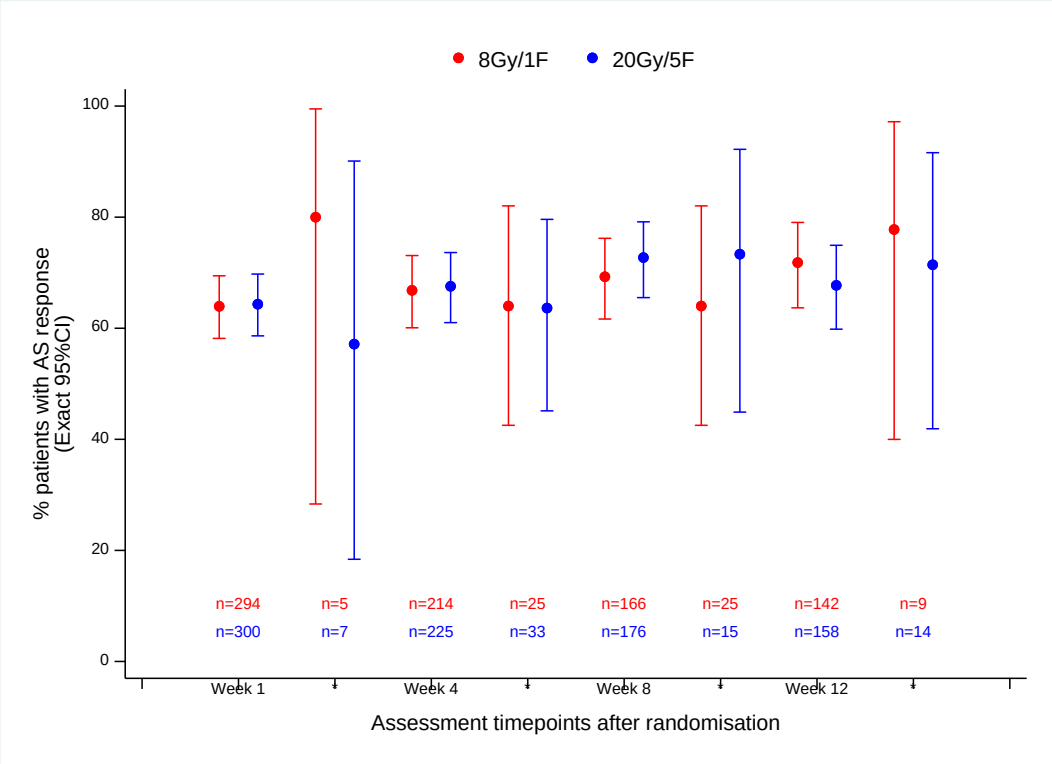
Note: The total is 340 instead of 342 because two patients had unknown location of SSC site (it was not reported at baseline)

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

Quality of Life scales by ambulation status	Ambulatory response (Grade 1-2)		(Grade 3-4)		Mean difference adjusted for QoL baseline scores	
	N	Mean	N	Mean	(1-2) vs (3-4) (95%CI)	p
QoL at 4 weeks according to ambulatory response 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 according to ambulatory response 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
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: 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.

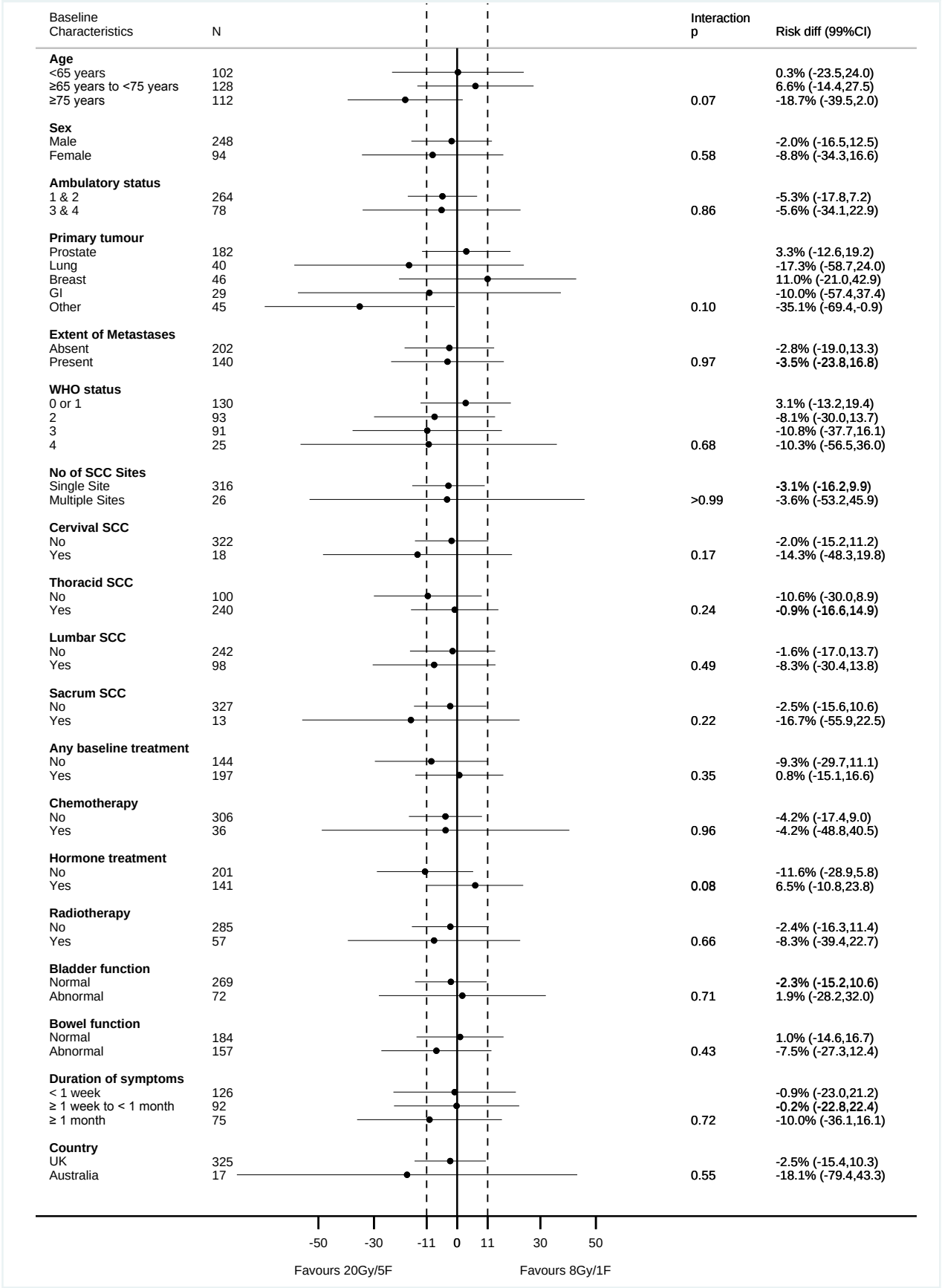
eFigure 1 - Ambulatory status by randomization group



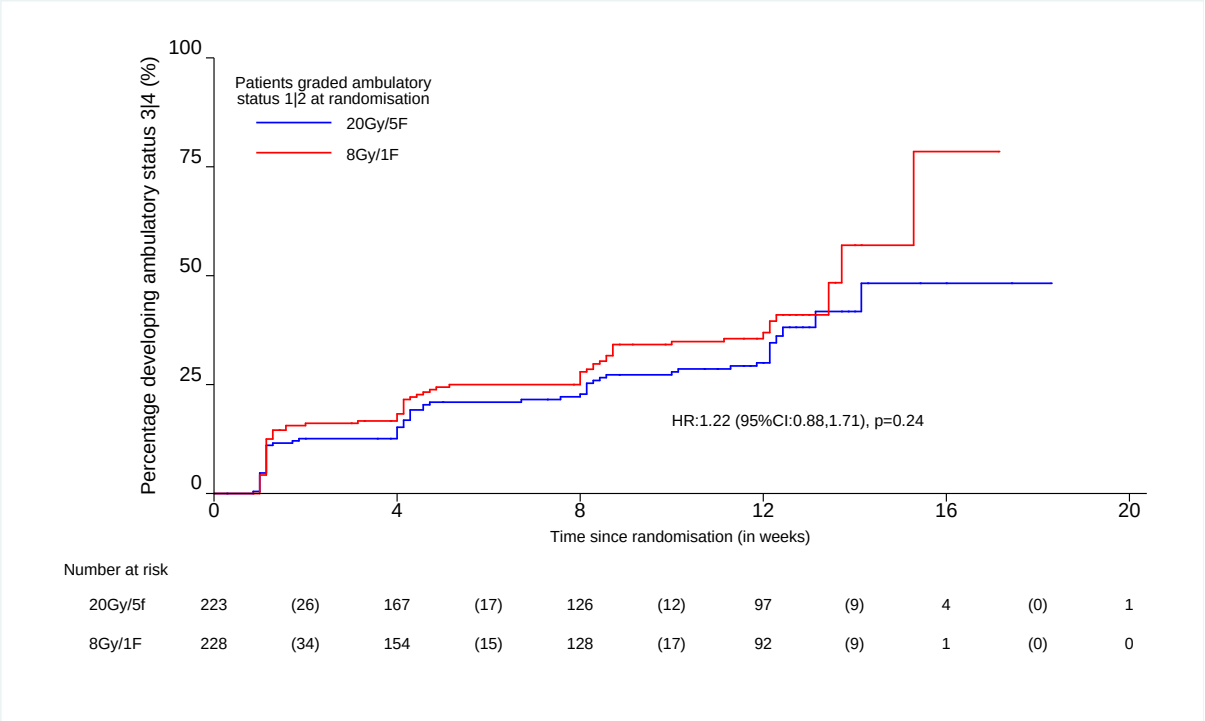
Note: Week 1 is between day 7 and 13 inclusive after randomization. Week 4 is between day 21 to 34 inclusive after randomization. Week 8 is between day 49 to 62 inclusive after randomization. Week 12 is between day 70 to 97 inclusive after randomization.

* 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.

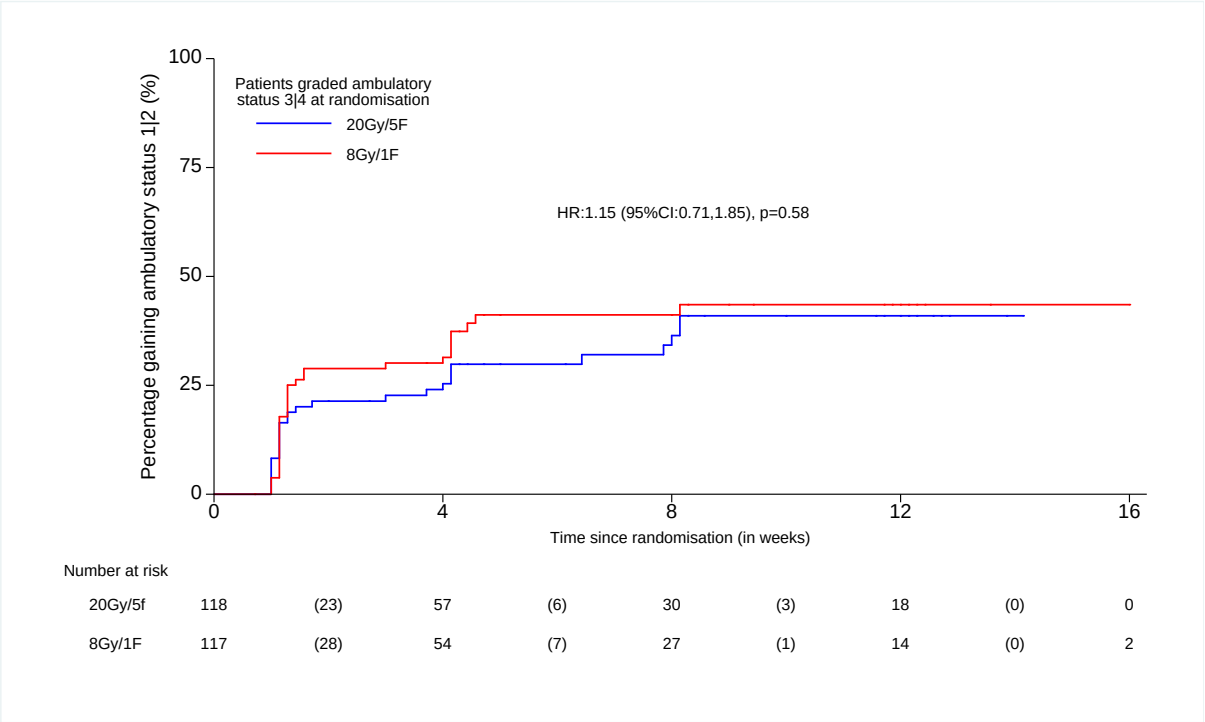


eFigure 3 – Time to loss of ambulation



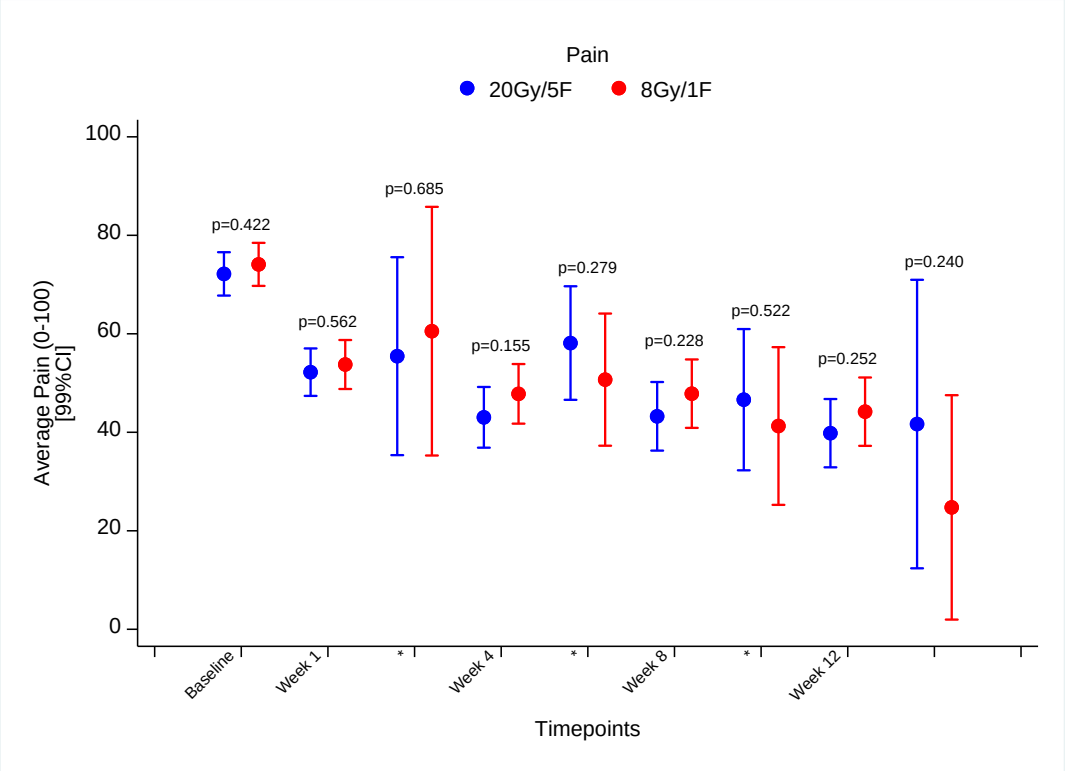
Note: Proportionality assumption test p=0.96

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

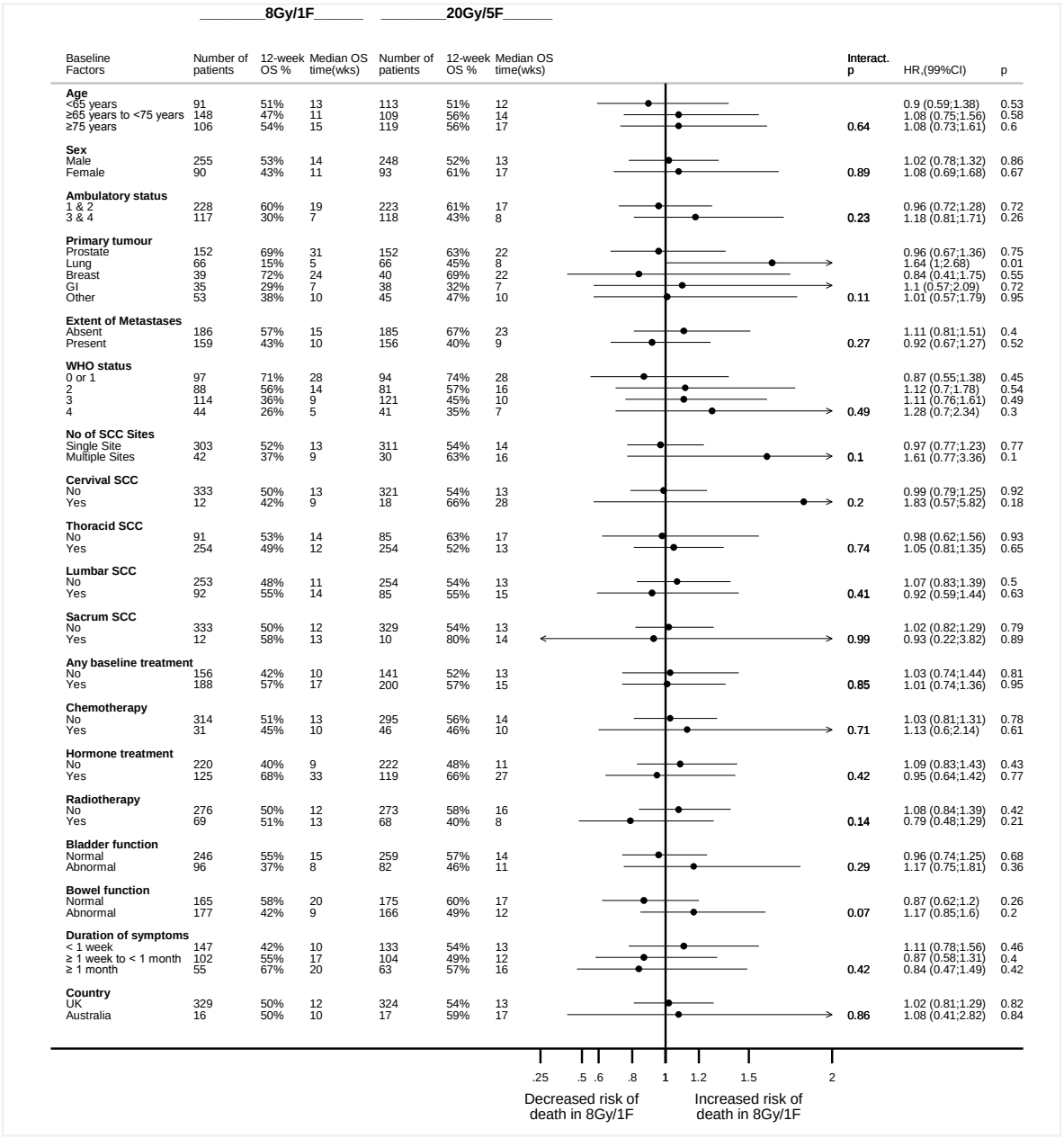


Note: Week 1 is between day 7 and 13 inclusive after randomization. Week 4 is between day 21 to 34 inclusive after randomization. Week 8 is between day 49 to 62 inclusive after randomization. Week 12 is between day 70 to 97 inclusive after randomization.

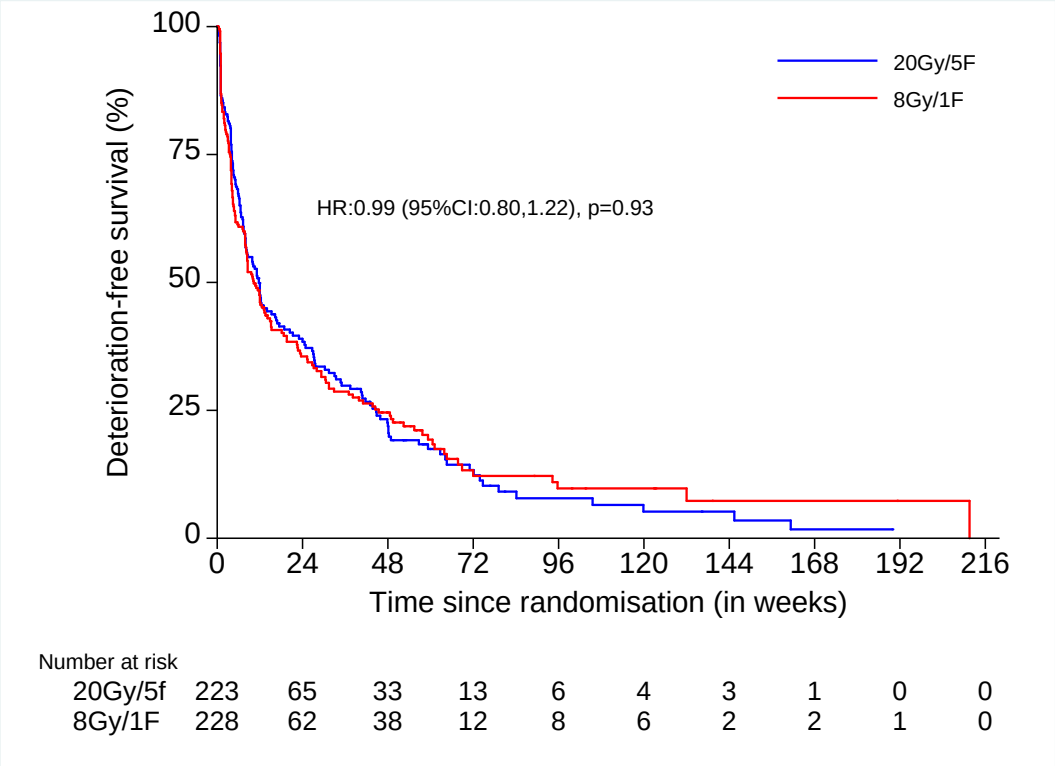
* These time points were outside the protocol specified time frames for the assessments and are shown here for completeness.

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.

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).