Supplemental Online Content

eMethods.

eResults.

eTable 1. Baseline characteristics of 1939 patients by treatment included in this study.

eTable 2. Baseline characteristics of patients randomized in the STAMPEDE M1|RT comparison and the patients included in this study, by treatment.

eTable 3. Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) for models evaluating interaction of treatment with linear, FP1 and FP2 functions of bone metastasis count.

eTable 4. Summary of estimated treatment effects for overall and failure-free survival, for all 1939 patients in subgroups based on ≤3, 4 to 7 and >7 bone metastases.

eTable 5. Baseline characteristics of 1587 patients with bone metastases (±NRLN) and without visceral metastasis stratified by ≤3 and ≥4 bone metastasis, by treatment.

eTable 6. Summary of estimated treatment effects for each outcome measure, for all 1272 patients with only bone metastasis and in subgroups based on ≤3 and ≥4 bone metastases.

eTable 7. Baseline characteristics of 181 patients with only non-regional lymph node metastasis (M1a), by treatment.

eTable 8. Baseline characteristics of 171 patients with any visceral or other metastasis, by treatment arms.

eTable 9. Summary of treatment effects for each outcome measure by the newly devised metastatic burden criteria.

eFigure 1. Hazard ratios and 95% confidence intervals for overall and failure-free survival in non-overlapping sub-populations based on bone metastases count for 1939 patients.

eFigure 2. Kaplan-Meier estimated 3-year (A) overall and (B) failure free survival in non-overlapping sub-populations based on bone metastases count for 1939 patients.

eFigure 3. Kaplan-Meier curves for overall and failure-free survival by treatment in 1272 patients with only bone metastasis and no non-regional lymph node/visceral/other metastasis stratified by (A,B) ≤3 and (C,D) ≥4 bone metastases.

eFigure 4. Kaplan-Meier curves for overall and failure-free survival in the newly devised (A,B) low and (C,D) high metastatic burden subgroups.

eFigure 5. Effect of prostate radiotherapy on overall survival across baseline factors in low and high metastatic burden subgroups.

eFigure 6. Effect of prostate radiotherapy on failure-free survival across baseline factors in low and high metastatic burden subgroups.

eReferences.

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

eMethods.

Secondary outcome measures

Secondary outcome measures evaluated included progression-free survival (PFS) defined as FFS without biochemical events, metastatic progression-free survival (mPFS) defined as time from randomisation to new metastases or progression of existing metastases or death and prostate cancer-specific survival (PCSS). Patients without the event of interest were censored at the time last known to be event-free. The outcomes dataset frozen for the published STAMPEDE "M1|RT comparison" was used for survival analyses.[1]

Statistical analyses

To evaluate treatment and bone metastasis interaction on a continuous scale, the multivariable fractional polynomial interaction (MFPI) approach was utilized. The MFPI algorithm is an extension of the MFP algorithm based on fractional polynomial analysis of continuous predictors.[2, 3] This approach for detecting interactions between treatment and a continuous variable avoids the assumption of linearity and arbitrary categorization.[4, 5] It aims to use all information from a continuous variable while allowing for possible non-linearity using first (FP1) and second degree (FP2) fractional polynomial transformations of the continuous variable. Interaction of treatment with linear, FP1 and FP2 functions of bone metastasis counts were evaluated using nested Cox models adjusted for minimisation factors used at randomisation: age (<70 or ≥70), N stage (N0, N+ or NX), WHO PS (0 or 1-2), NSAID or aspirin use (uses either or no) and planned docetaxel use (yes or no) along with metastatic site (only NRLN metastasis, bone±NRLN metastasis or any visceral/other metastasis). Despite the benefits of the fractional polynomial approach, overfitting of interaction terms with FP2 transformations is a real concern.[6] Such overfitting can be avoided by selecting a simplified model based on Bayesian Information Criteria (BIC) and Akaike Information Criteria (AIC).[6-8] To guard against such overfitting, model with the lowest BIC was preferred. Model comparison was performed using the BIC adapted for censored data which corrects for number of events rather than sample size.[9] Differences between BIC (ΔBIC) values for two models were interpreted as per the BIC evidence grades presented by Raftery.[10] Selection based on BIC was verified using the Akaike information criteria (AIC).[8] A p-value from a likelihood ratio test of the interaction between treatment group and bone metastasis count is presented. The MFPI model-estimated treatment effect as a function of bone metastasis count was plotted graphically on the HR scale with 95%CI. Further details regarding the MFPI have been published previously.[2, 6]

In the newly devised low and high metastatic burden subgroups, we evaluated treatment effects for primary and secondary outcome measures. Adjusted Cox proportional hazards regression models were used to estimate relative treatment effects. Flexible parametric models fitted using (5,5) degrees of freedom with adjustment variables as specified above were used to generate 3-year survival estimates. Restricted mean survival time (RMST) were evaluated using a t-star of 59 months as determined by the Royston and Parmar method.[11] Fine and Gray regression models were used for competing risk analysis of prostate cancer-specific survival.[12] Consistency of treatment effect within the low and high burden subgroups was explored across selected baseline characteristics of clinical relevance: patient age (<70 or ≥70), pre-ADT PSA (quartiles), WHO performance status (0 or 1–2), Gleason sum score (≤7, 8–10 or unknown), tumour stage (≤T2, T3 or T4), regional nodal status (N0, N1 or NX), nominated RT schedule (36 Gy/6f/6 weeks or 55 Gy/20f/4 weeks) and planned docetaxel use (No or Yes). A HR below 1 favoured the prostate radiotherapy group. Statistical analyses were performed using Stata v15.1 (StataCorp, College Station, TX, USA).

eResults.

For models evaluating the interaction between treatment and bone metastasis counts, **eTable 3** shows the BIC and AIC statistics for linear, FP1 and FP2 models. For both OS and FFS, the linear model had the lowest BIC. Also, the BIC criteria suggest that both FP1 and FP2 models were overfit (ΔBIC >6) compared to the linear model. Since both the AIC and the BIC are smallest for the linear model, each criterion would select this model for OS and FFS.

The effect of treatment was heterogeneous across the newly devised metastatic burden subgroups for secondary outcome measures (interaction p-values: PFS=0.004; mPFS=0.009; PCSS=0.005) with good evidence of benefit noted for all outcome measures in patients with low metastatic burden **(eTable 9 in supplement)**. In the low metastatic burden subgroup, there was good evidence that prostate RT improved PFS (HR=0.72, 95%CI 0.57 – 0.92), mPFS (HR=0.74, 95%CI 0.58 – 0.94) and PCSS (sub-HR=0.60, 95%CI 0.43 – 0.86). The absolute improvement in 3-year PFS, mPFS and PCSS was 9%, 7% and 9% respectively in patients with low metastatic burden.

eTable 1. Baseline characteristics of 1939 patients by treatment included in this study.

	SOC (n=976)		SOC+RT (n=963)	
	n	%	n	%
Age at randomisation				
Median	68		68	
IQR	63-73		63-73	
PSA (ng/mL) before ADT				
Median	98		98	
IQR	31-315		33-312	
WHO performance status				
0	695	71	689	72
1 to 2	281	29	274	29
Primary tumour stage				
≤T2	89	9	94	10
T3	555	57	563	59
T4	246	25	232	24
TX	86	9	74	8
Gleason score				
≤7	161	17	165	17
8 to 10	781	80	757	79
Unknown	34	4	41	4
Regional node status				
N0	332	34	329	34
N1	582	60	569	59
NX	62	6	65	7
Nominated RT schedule				
36Gy in 6f over 6 weeks	447	46	459	48
55Gy in 20f over 4 weeks	529	54	504	52
Planned Docetaxel use				
No	804	82	792	82
Yes	172	18	171	18
Sites of metastases				
Bone	872	89	860	89
NRLN	276	28	277	29
Lung	36	4	41	4
Liver	22	2	18	2
Other	34	3	32	3
Number of bone metastases				
≤3	417	43	409	42
4 to 9	204	21	203	21
≥10	355	36	351	36
Abbreviations: SOC – standard-of-care, RT – radiotherapy, IQR- inter-quartile range, PSA – prostate specific antigen, ADT – androgen deprivation therapy, NRLN- Non-regional lymph nodes.				

eTable 2. Baseline characteristics of patients randomized in the STAMPEDE M1|RT comparison and the patients included in this study, by treatment.

	M1|RT comparison (n=2061)				Included (n=1939)			
	SOC (n=1029)		SOC+RT (n=1032)		SOC (n=976)		SOC+RT (n=963)	
	n	%	n	%	n	%	n	%
Age at randomisation								
Median	68		68		68		68	
IQR	63 - 73		63-73		63-73		63-73	
PSA (ng/ml) before ADT								
Median	98		97		98		98	
IQR	30 - 316		33 - 313		31-315		33-312	
WHO performance status								
0	732	71	734	71	695	71	689	72
1 to 2	297	29	298	29	281	29	274	29
Primary tumour stage								
≤T2	96	9	103	10	89	9	94	10
T3	585	57	603	58	555	57	563	59
T4	260	25	246	24	246	25	232	24
TX	88	9	80	8	86	9	74	8
Gleason score								
≤7	173	17	172	17	161	17	165	17
8 to 10	820	80	810	78	781	80	757	79
Unknown	36	3	50	5	34	4	41	4
Regional node status								
N0	345	34	344	33	332	34	329	34
N1	620	60	620	60	582	60	569	59
NX	64	6	68	7	62	6	65	7
Nominated RT schedule								
36Gy in 6f over 6 weeks	482	47	497	48	447	46	459	48
55Gy in 20f over 4 weeks	547	53	535	52	529	54	504	52
Planned Docetaxel use								
No	845	82	849	82	804	82	792	82
Yes	184	18	183	18	172	18	171	18
Sites of metastases								
Bone	919	89	917	89	872	89	860	89
NRLN	294	29	304	29	276	28	277	29
Lung	42	4	48	5	36	4	41	4
Liver	23	2	19	2	22	2	18	2
Other	35	3	33	3	34	3	32	3

Abbreviations: SOC – standard of care, RT – radiotherapy, IQR- inter-quartile range, PSA – prostate specific antigen, ADT – androgen deprivation therapy, NRLN- Non-regional lymph nodes.

eTable 3. Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) for models evaluating interaction of treatment with linear, FP1 and FP2 functions of bone metastasis count.

Outcome evaluated	Model class	BIC	AIC
Overall survival			
	Linear	9782.17	9768.46
	FP1	9788.88	9770.59
	FP2	9801.80	9769.79
Failure-free survival			
	Linear	17810.99	17795.45
	FP1	17818.17	17797.45
	FP2	17838.25	17801.99

eTable 4. Summary of estimated treatment effects for overall and failure-free survival, for all 1939 patients in subgroups based on ≤3, 4 to 7 and >7 bone metastases.

	Events/patients		HR (95%CI) [a]	3-year KM survival %	
	SOC	SOC+RT		SOC	SOC+RT
Overall survival					
≤3 bone metastases	123/417	89/409	0.65 (0.49-0.85)	73%	83%
≥4 and ≤7 bone metastases	53/180	63/168	1.39 (0.96-2.00)	69%	62%
>7 bone metastases	192/379	195/386	1.03 (0.84-1.25)	46%	47%
Failure-free survival					
≤3 bone metastases	266/417	199/409	0.60 (0.50-0.72)	31%	51%
≥4 and ≤7 bone metastases	121/180	121/168	0.89 (0.68-1.15)	25%	23%
>7 bone metastases	333/379	322/386	0.85 (0.73-1.00)	11%	13%

[a] **Hazard ratios and 95%CI are from Cox proportional hazards models adjusted for age (<70 or ≥70), N stage (N0, N+ or NX), WHO performance status (0 or 1-2), NSAID or aspirin use (uses either or no), docetaxel use (yes or no) and metastatic site (only NRLN, bone±NRLN or any visceral/other).**

Abbreviations: SOC – standard of care, RT – radiotherapy, HR – hazard ratio, CI – confidence interval, KM – Kaplan-Meier.

eTable 5. Baseline characteristics of 1587 patients with bone metastases (±NRLN) and without visceral metastasis stratified by ≤3 and ≥4 bone metastases, by treatment.

	≤3 Bone metastases (± NRLN) (n=577)				≥ 4 Bone metastases (± NRLN) (n=1010)			
	SOC (n=290)		SOC+RT (n=287)		SOC (n=512)		SOC+RT (n=498)	
	n	%	n	%	n	%	n	%
Age at randomisation								
Median	68		69		68		68	
IQR	64-73		63-73		63-73		63-73	
PSA (ng/ml) before ADT								
Median	44		46		183		182	
IQR	15-100		20-98		58-581		53-638	
WHO performance status								
0	212	73	223	78	348	68	341	69
1 to 2	78	27	64	22	164	32	157	32
Primary tumour stage								
≤T2	39	13	26	9	40	8	50	10
T3	182	63	177	62	273	53	277	56
T4	55	19	71	25	135	26	120	24
TX	14	5	13	5	64	13	51	10
Gleason score								
≤7	65	22	63	22	78	15	74	15
8 to 10	218	75	216	75	418	82	405	81
Unknown	7	2	8	3	16	3	19	4
Regional node status								
N0	136	47	127	44	175	34	177	36
N1	141	49	151	53	293	57	271	54
NX	13	5	9	3	44	9	50	10
Nominated RT schedule								
36Gy in 6f over 6 weeks	126	43	119	42	235	46	270	54
55Gy in 20f over 4 weeks	164	57	168	59	277	54	228	46
Planned Docetaxel use								
No	246	85	243	85	417	81	407	82
Yes	44	15	44	15	95	19	91	18
Sites of metastases								
Bone	290	100	287	100	512	100	498	100
NRLN	44	15	46	16	120	53	105	47
Lung	0	0	0	0	0	0	0	0
Liver	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Number of bone metastases								
≤3	290	100	287	100	0	0	0	0
4 to 9	0	0	0	0	185	36	183	37
≥10	0	0	0	0	327	64	315	63
Abbreviations: NRLN- Non-regional lymph nodes., SOC – standard of care, RT – radiotherapy, IQR-inter-quartile range, PSA – prostate specific antigen, ADT – androgen deprivation therapy.								

eTable 6. Summary of estimated treatment effects for each outcome measure, for all 1272 patients with only bone metastasis and in subgroups based on ≤3 and ≥4 bone metastases.

	Events/patients		HR (95% CI)[a]	3 year KM survival %		Interaction p value
	SOC	SOC+ RT		SOC	SOC+ RT	
Overall survival						
Only bone metastasis	230/638	229/634	0.94 (0.79 - 1.13)	63%	67%	0.044
≤3 bone metastases	63/246	48/241	0.67 (0.46 - 0.97)	77%	86%	
≥4 bone metastases	167/392	181/393	1.07 (0.87 - 1.32)	54%	56%	
Failure-free survival						
Only bone metastasis	463/638	420/634	0.75 (0.65 - 0.85)	24%	33%	0.013
≤3 bone metastases	150/246	108/241	0.56 (0.44 -0.72)	36%	56%	
≥4 bone metastases	313/392	312/393	0.85 (0.72 - 0.99)	16%	17%	

[a] **Hazard ratios and 95%CI are from Cox proportional hazards models adjusted for minimisation factors used at randomisation: age (<70 or ≥70), WHO performance status (0 or 1-2), N stage (N0, N+ or NX), NSAID or aspirin use (uses either or no) and docetaxel use (yes or no).**

Abbreviations: SOC – standard of care, RT – radiotherapy, HR – hazard ratio, CI – confidence interval, KM – Kaplan-Meier, NRLN – non-regional lymph node.

eTable 7. Baseline characteristics of 181 patients with only non-regional lymph node metastasis (M1a), by treatment.

	Only NRLN (n=181)			
	SOC (n=89)		SOC+RT (n=92)	
	n	%	n	%
Age at randomisation				
Median	66		68	
IQR	63-72		63-72	
PSA (ng/ml) before ADT				
Median	64		92	
IQR	27-151		33-197	
WHO performance status				
0	73	82	68	74
1 to 2	16	18	24	26
Primary tumour stage				
≤T2	6	7	9	10
T3	56	63	65	71
T4	26	29	15	16
TX	1	1	3	3
Gleason score				
≤7	6	7	16	17
8 to 10	80	90	69	75
Unknown	3	3	7	8
Regional node status				
N0	4	4	5	5
N1	83	93	87	95
NX	2	2	0	0
Nominated RT schedule				
36Gy in 6f over 6 weeks	45	51	34	37
55Gy in 20f over 4 weeks	44	49	58	63
Planned Docetaxel use				
No	72	81	75	82
Yes	17	19	17	18
Sites of metastases				
NRLN	89	100	92	100
Bone	0	0	0	0
Lung	0	0	0	0
Liver	0	0	0	0
Other	0	0	0	0
Abbreviations: NRLN- Non-regional lymph node, SOC – Standard of care, RT – radiotherapy, IQR- inter-quartile range, PSA – prostate specific antigen, ADT – androgen deprivation therapy.				

eTable 8. Baseline characteristics of 171 patients with any visceral or other metastasis, by treatment arms.

	Any visceral/other metastasis (n=171)			
	SOC (n=85)		SOC+RT (n=86)	
	n	%	n	%
Age at randomisation				
Median	68		69	
IQR	63-72		62-74	
PSA (ng/ml) before ADT				
Median	131		124	
IQR	48-421		36-373	
WHO performance status				
0	62	73	57	66
1 to 2	23	27	29	34
Primary tumour stage				
≤T2	4	5	9	10
T3	44	52	44	51
T4	30	35	26	30
TX	7	8	7	8
Gleason score				
≤7	12	14	12	14
8 to 10	65	76	67	78
Unknown	8	9	7	8
Regional node status				
N0	17	20	20	23
N1	65	76	60	70
NX	3	4	6	7
Nominated RT schedule				
36Gy in 6f over 6 weeks	41	48	36	42
55Gy in 20f over 4 weeks	44	52	50	58
Planned Docetaxel use				
No	69	81	67	78
Yes	16	19	19	22
Sites of metastases				
Bone	70	82	75	87
NRLN	23	27	34	40
Lung	36	42	41	48
Liver	22	26	18	20
Other	34	40	32	37
Number of bone metastases				
≤3	38	45	30	35
4 to 9	19	22	20	23
≥10	28	33	36	42

Abbreviations: SOC – Standard of care, RT – radiotherapy, IQR- inter-quartile range, PSA – prostate specific antigen, ADT – androgen deprivation therapy, NRLN- Non-regional lymph nodes.

eTable 9. Summary of treatment effects for each outcome measure by the newly devised metastatic burden criteria. Low metastatic burden is defined as patients with only NRLN metastasis or ≤3 bone metastases (±NRLN) and without any visceral or other metastasis.

	Events/Patients		HR (95%CI) [a]	Interaction by metastatic burden p-value	Restricted mean survival time (months)[b]			3-year survival[b]	
	SOC	SOC+RT			SOC	SOC+RT	Difference (95% CI)	SOC	SOC+RT
Overall survival									
Low burden	109/379	79/379	0.62 (0.46 - 0.83)	0.003	45.1	49.6	4.5 (1.9 - 7.0)	74%	82%
High burden	259/597	268/584	1.08 (0.91 - 1.28)		39.2	37.9	-1.3 (-3.8 - 1.2)	55%	54%
Failure-free survival									
Low burden	238/379	181/379	0.57 (0.47 - 0.70)	0.002	27.9	37.1	9.2 (5.9 - 12.4)	34%	52%
High burden	482/597	461/584	0.87 (0.76 - 0.99)		17.4	19.1	1.7 (-0.3 - 3.6)	17%	19%
Progression-free survival									
Low burden	157/379	129/379	0.72 (0.57 - 0.92)	0.004	39.3	43.7	4.4 (1.3 - 7.5)	57%	66%
High burden	366/597	385/584	1.10 (0.95 - 1.27)		28.6	26.6	-2.0 (-4.6 - 0.6)	36%	31%
Metastatic progression-free survival									
Low burden	144/379	120/379	0.74 (0.58 - 0.94)	0.009	40.9	44.8	3.9 (1.1 - 6.7)	61%	68%
High burden	351/597	370/584	1.11 (0.96 - 1.28)		29.9	27.8	-2.1 (-4.7 - 0.5)	38%	33%
Prostate cancer-specific survival[b]									
Low burden	81/379	56/379	0.60 (0.43 - 0.86)	0.005	48.5	52.3	3.8 (1.4 - 6.2)	79%	88%
High burden	229/597	240/584	1.10 (0.92 - 1.32)		40.9	39.4	-1.6 (-3.9 - 0.7)	58%	57%

Hazard ratios and restricted means survival time differences are for prostate radiotherapy relative to control.

Low burden is defined as patients with only NRLN metastasis or ≤3 bone metastases (+/-NRLN) and no visceral or other metastasis.
[a] Hazard ratios and 95%CI are from Cox proportional hazards models adjusted for age (<70 or ≥70), N stage (N0, N+ or NX), WHO performance status (0 or 1-2), NSAID or aspirin use (uses either or no), docetaxel use (yes or no) and stratified by time period.
[b] Survival probabilities and restricted mean survival time estimates are taken from flexible parametric models (t-star, 59 months).
[c] Sub-distribution hazard ratios and 95%CI are from Fine and Grey Competing risk regression adjusted for variables as stated above.
Abbreviations: SOC – standard of care, RT – radiotherapy, HR – hazard ratio, CI – confidence interval, NRLN-non-regional lymph node metastasis.

eFigure 1. Hazard ratios and 95% confidence intervals for overall and failure-free survival in non-overlapping sub-populations based on bone metastases counts for 1939 patients.
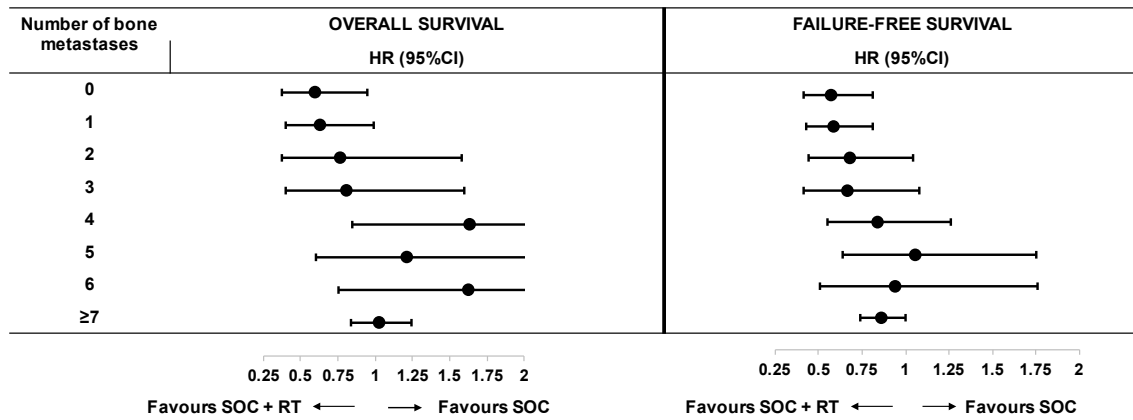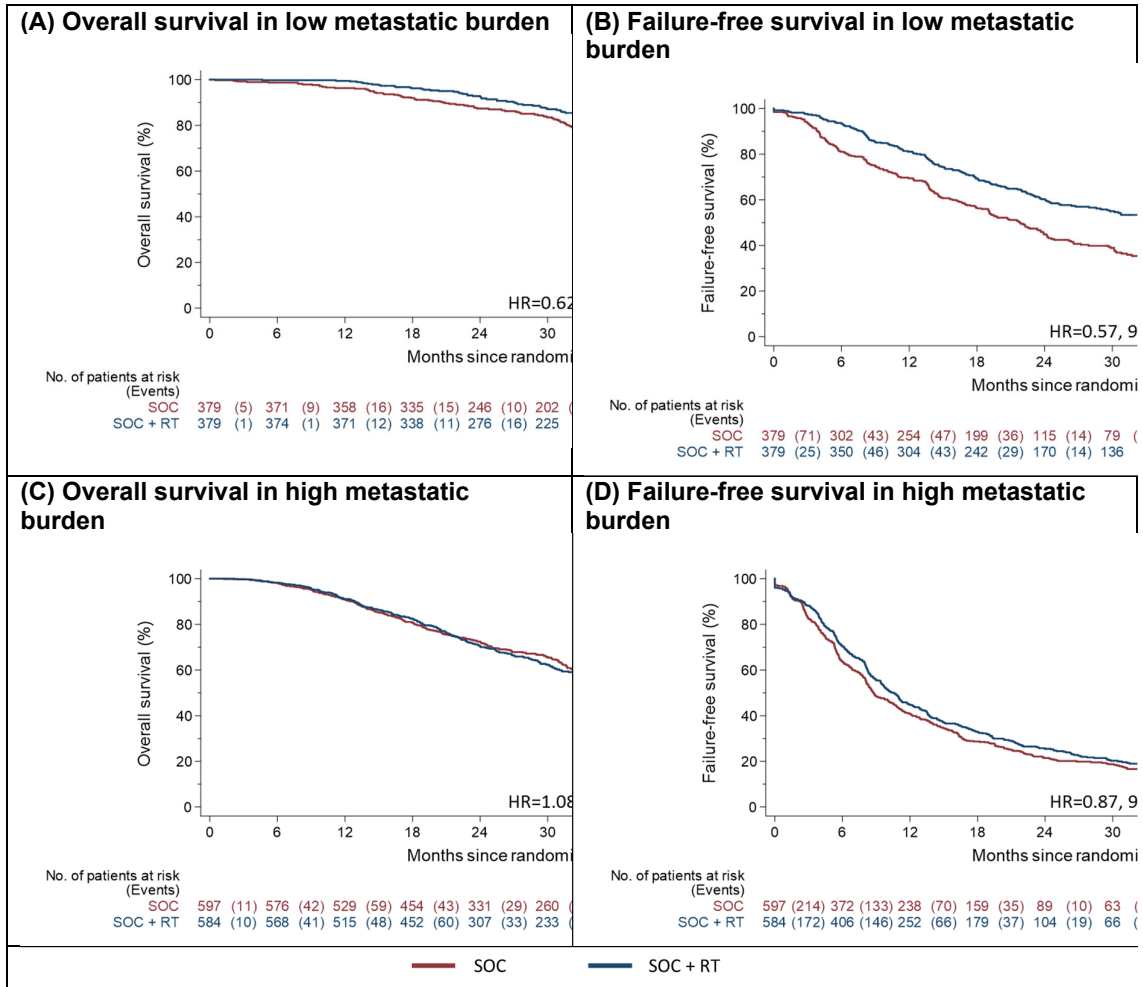
eFigure 2. Kaplan-Meier estimated 3-year (A) overall and (B) failure free survival in non-overlapping sub-populations based on bone metastasis counts for 1939 patients.
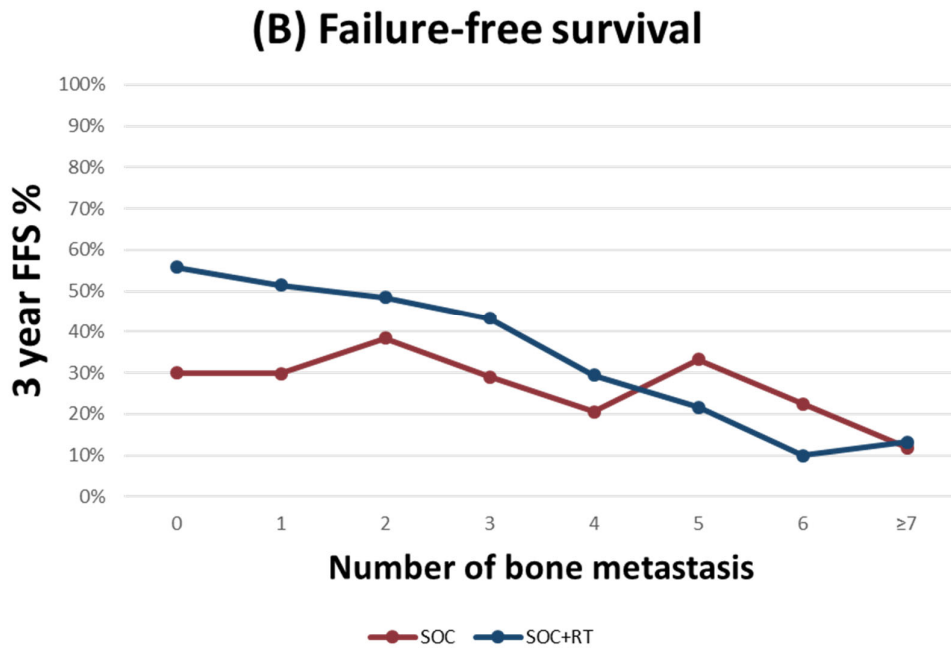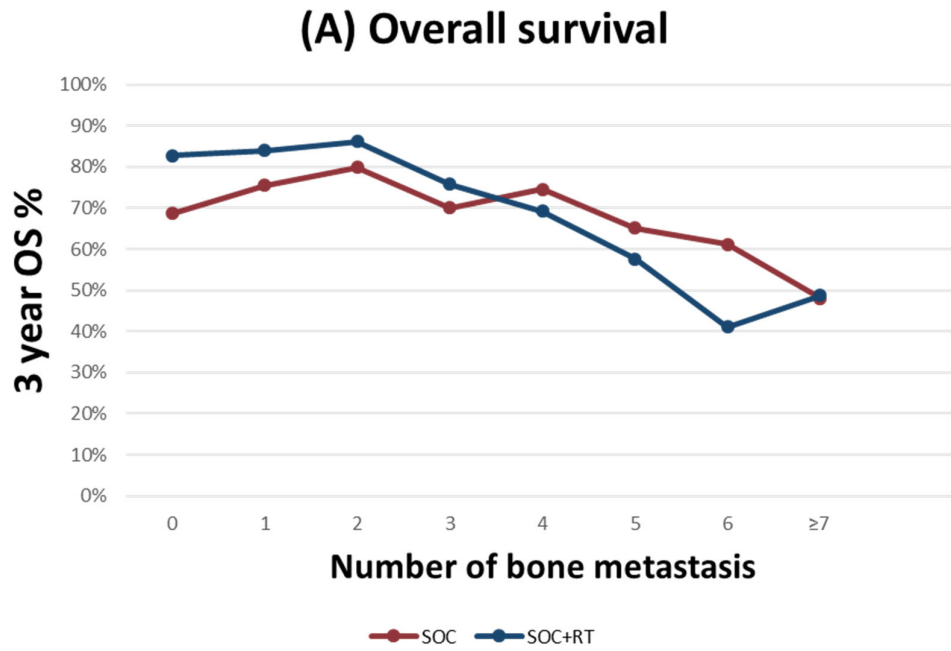
(A) Overall survival

(B) Failure-free survival

eFigure 3. Kaplan-Meier curves for overall and failure-free survival by treatment in 1272 patients with only bone metastasis and no non-regional lymph node/visceral/other metastasis stratified by (A,B) ≤3 and (C,D) ≥4 bone metastases. SOC- standard of care, RT-radiotherapy.
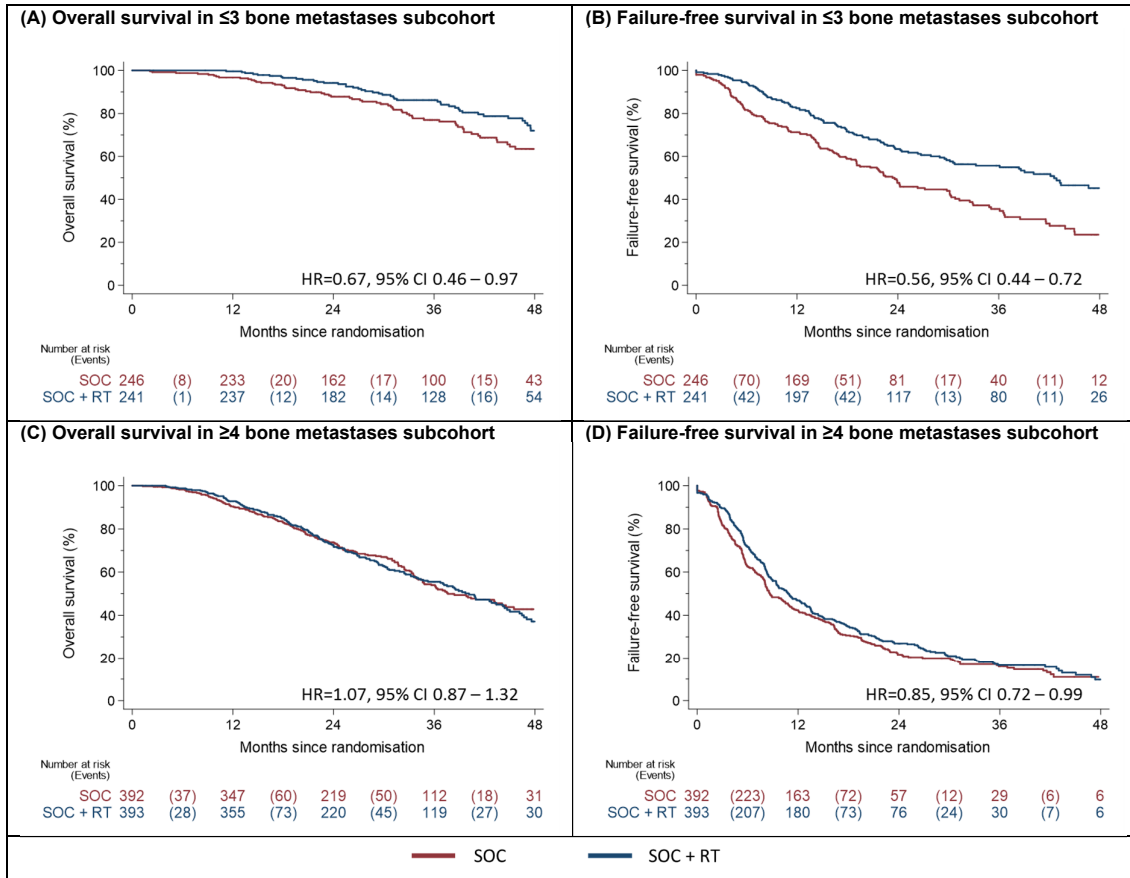
eFigure 4. Kaplan-Meier curves for overall and failure-free survival in the newly devised (A,B) low and (C,D) high metastatic burden subgroups. Low metastatic burden is defined as patients with only NRLN metastasis or ≤3 bone metastases (±NRLN) and without any visceral or other metastasis. SOC- standard of care, RT-radiotherapy.

(A) Overall survival in low metastatic burden

No. of patients at risk (Events)
SOC   379 (5) 371 (9) 358 (16) 335 (15) 246 (10) 202
SOC + RT 379 (1) 374 (1) 371 (12) 338 (11) 276 (16) 225

HR=0.62

(B) Failure-free survival in low metastatic burden

No. of patients at risk (Events)
SOC   379 (71) 302 (43) 254 (47) 199 (36) 115 (14) 79
SOC + RT 379 (25) 350 (46) 304 (43) 242 (29) 170 (14) 136

HR=0.57, 9

(C) Overall survival in high metastatic burden

No. of patients at risk (Events)
SOC   597 (11) 576 (42) 529 (59) 454 (43) 331 (29) 260
SOC + RT 584 (10) 568 (41) 515 (48) 452 (60) 307 (33) 233

HR=1.08

(D) Failure-free survival in high metastatic burden

No. of patients at risk (Events)
SOC   597 (214) 372 (133) 238 (70) 159 (35) 89 (10) 63
SOC + RT 584 (172) 406 (146) 252 (66) 179 (37) 104 (19) 66

HR=0.87, 9

SOC   SOC + RT

eFigure 5. Effect of prostate radiotherapy on overall survival across baseline factors in low and high metastatic burden subgroups. Low burden is defined as patients with only NRLN metastasis or ≤3 bone metastases (±NRLN) and without any visceral or other metastasis. Solid vertical line indicates a hazard ratio of 1, dotted line indicates the hazard ratios for overall survival within low and high metastatic burden subgroups.
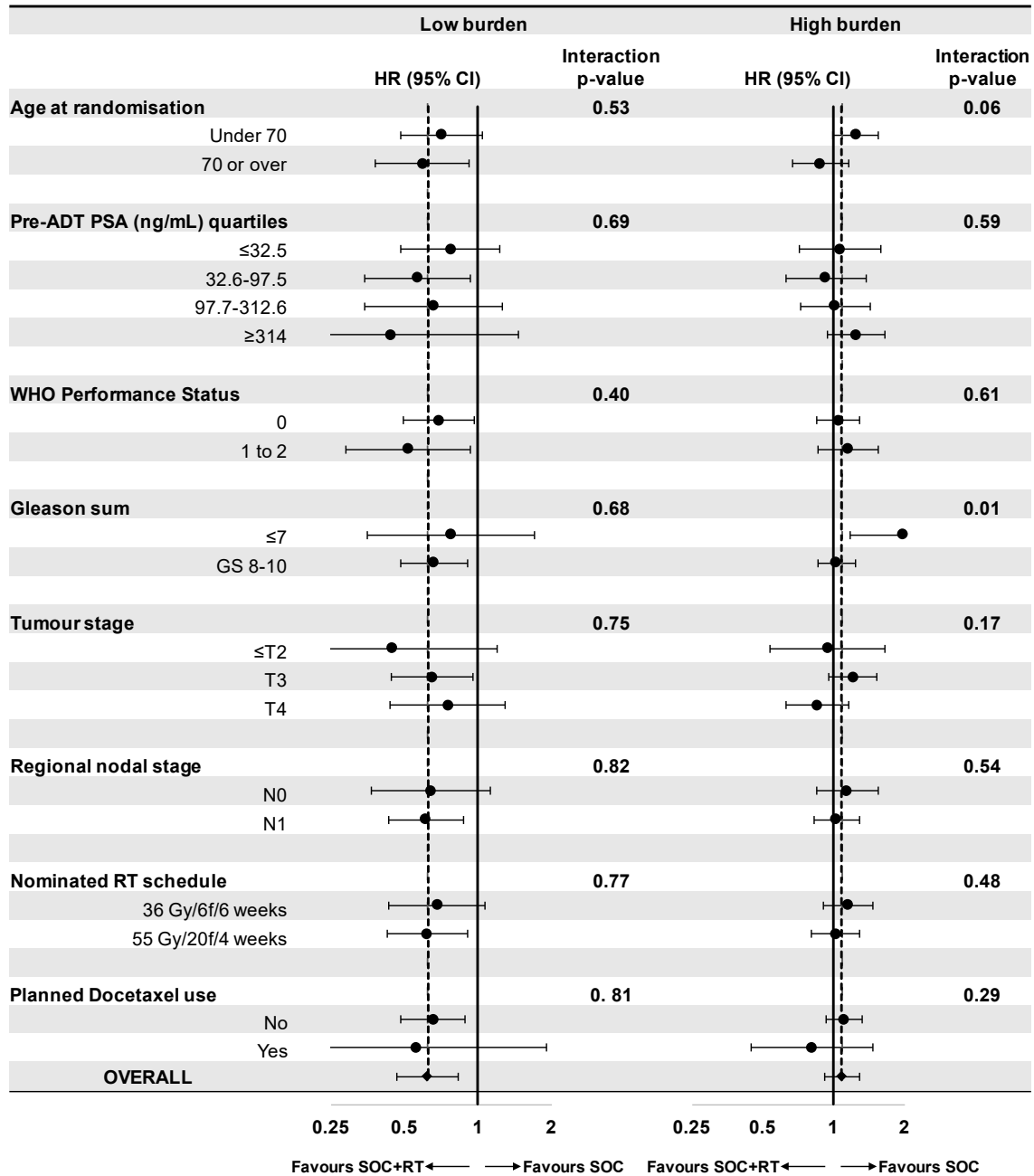
eFigure 6. Effect of prostate radiotherapy on failure-free survival across baseline factors in low and high metastatic burden subgroups. Low burden is defined as patients with only NRLN metastasis or ≤3 bone metastases (±NRLN) and no visceral or other metastasis. Solid vertical line indicates a hazard ratio of 1, dotted line indicates the hazard ratios for failure-free survival within low and high metastatic burden subgroups.
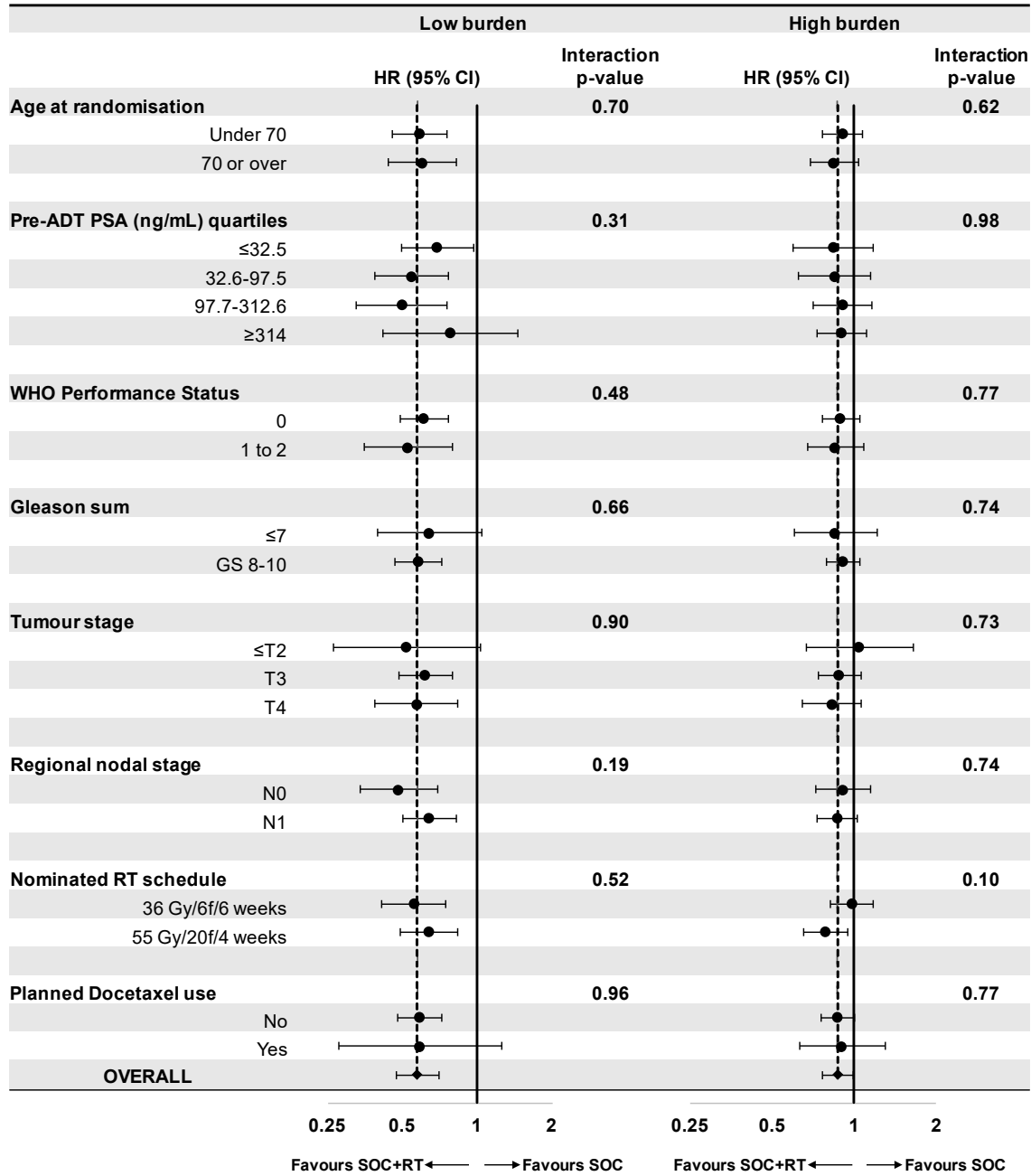
eReferences.

1.   Parker CC, James ND, Brawley CD, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392(10162):2353-2366.

2.   Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med*. 2004;23(16):2509-25.

3.   Royston P, Altman DG. Regression Using Fractional Polynomials of Continuous Covariates: Parsimonious Parametric Modelling. *Journal of the Royal Statistical Society Series C (Applied Statistics)*. 1994;43(3):429-467.

4.   Farewell VT, Tom BDM, Royston P. The Impact of Dichotomization on the Efficiency of Testing for an Interaction Effect in Exponential Family Models. *Journal of the American Statistical Association*. 2004;99(467):822-831.

5.   Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst*. 1994;86(11):829-35.

6.   Royston P, Sauerbrei W. *Multivariable model-building : a pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables*. New York: John Wiley; 2008.

7.   Schwarz G. Estimating the Dimension of a Model. *Ann Statist*. 1978;6(2):461-464.

8.   Akaike H. A new look at the statistical model identification. *IEEE transactions on automatic control*. 1974;19(6):716-723.

9.   Volinsky CT, Raftery AE. Bayesian information criterion for censored survival models. *Biometrics*. 2000;56(1):256-62.

10.   Raftery AE. Bayesian Model Selection in Social Research. *Sociological Methodology*. 1995;25:111-163.

11.   Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med*. 2011;30(19):2409-21.

12.   Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-509.