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 *JAMA*. doi:10.1001/jama.2019.17913

Supplement 2. Statistical analysis plan

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

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SCORAD

STATISTICAL ANALYSIS PLAN

Date prepared	11 Oct 2012
Version number	1.0
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Reviewed by (trial statistician)	Andre Lopes
Approved by	Allan Hackshaw
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Contents

1. Summary description of the trial

Trial objectives	**To show that ambulatory status using 8Gy in 1 fraction is no worse than with 20Gy in 5 fractions for patients with metastatic spinal cord compression (SCC).**
Sample size	***700 patients***
Intervention arms (what treatments were given)	**Randomised phase III trial**
	Arm 1: Multiple fraction radiotherapy 20Gy/5f **Arm 2: Single fraction radiotherapy 8Gy/1f**
Primary outcome measure	**Ambulatory status at 8 weeks from day 1 of treatment compared to the same at randomisation.**
Secondary outcome measures	**Recovery of and time to ambulation**
	Ambulatory status at 1, 4 and 12 weeks compared to randomisation (where available)
	Maintenance of ambulatory status
	Bladder and bowel function at 1, 4, 8 and 12 weeks from day 1 of treatment compared to randomisation
	Adverse events using RTOG and CTCAE v.4.0 at 1, 4, 8 and 12 weeks from day 1 of treatment
	Quality of life measured using the EORTC QLQ-C30 questionnaire at 1, 4, 8 and 12 weeks from day 1 of treatment compared to the same at randomisation
	Further treatment
	Duration of care in hospital, hospice, nursing home or home
	Preferred place of care
	Overall survival at 12 weeks and 12 months

2. Recruitment, follow-up, and baseline characteristics

The following should be obtained:

- The month and year between which patients were recruited (eg between January 2000 and June 2006)
- The age range of patients recruited (eg 25 to 87 years)
- The number of centres that recruited patients
- The country (or countries) from which patients were recruited
- The length of follow up (patients who have died should be censored). This is obtained for all patients, and in each trial arm (to check that they are similar)
- A table of baseline characteristics, in each trial arm. This should contain age, gender, and any stratification factors used in the randomisation. Other variables could be disease stage, performance status/ECOG score, body weight, and other key biological and physiological measurements.
    - For categorical variables, each column will contain N (%)
    - For continuous variables, each column will contain the mean or median value, and in brackets, the standard deviation or 25-75th centile values
    - P-values for comparing the trial arms should not be reported (see Senn SJ (1994) Testing for baseline balance in clinical trials, Statistics in Medicine 13: 1715-1726)
- The number of patients who were ineligible in each trial arm, and the reasons why they were ineligible
- The number of patients who were recruited to the trial but withdrew later on, and the reasons (if available)
- List any possible major protocol violations or ineligibility criteria that would lead to the patient not being included in the analysis, eg patient later found not to have the cancer of interest

3. Treatment compliance

Compliance to radiotherapy

	20 Gy/5 fractions N=?	8 Gy/1 fraction N=?
Exactly as per protocol		
Reasons for non-compliance		
Died during treatment		
Too ill to complete treatment		
Withdrew from trial		
Administrative error		
Other reasons		
Reason 1		
Reason 2		
etc		
Reason not reported		

Reasons for non-compliance contd.....

	20 Gy/5 fractions N=?	8 Gy/1 fraction N=?
Reasons for delay		
reason 1		
reason 2		
etc		
Reasons for interruptions		
reason 1		
reason 2		
etc		
Reasons for dose reduction		
reason 1		
reason 2		
etc		
Reasons for stopping protocol treatment		
reason 1		
reason 2		
etc		

4. Efficacy

The following statistical analyses will be performed:

- Logrank test
- Cox regression modelling (to allow for covariates)
- Kaplan-Meier plots

Check model assumptions:

- Time-to-event data: eg use Schoenfeld residuals or a p-value to test the assumption of proportional hazards
- Continuous data: examine Normal probability plots, and look for a straight line. If very curved, take logs of the data or other transformation

Primary endpoint:

Ambulatory status at 8 weeks from day 1 of treatment compared to randomization (based on evaluable patients).

	Treatment				
	20 Gy/ 1 fraction N=?	8 Gy/ 5 fractions N=?	Risk difference (90% CI) 8 Gy-20Gy	Risk difference (95% CI) 8 Gy-20Gy	P-value
	% (n)				
Evaluable patients					
Positive response					
Maintenance of 1|2 level					
Change from 3|4 to 1|2					
Overall positive response					
Negative response					
Change from 1|2 to 3|4					
Remained at 3|4					
Died before 8 weeks' assessment#					
Withdrew from trial/consent					
Not assessed (patient too ill)					
Patient refused assessment					
Lost to follow-up					
Unknown					
Other reasons					
1					
2					
etc					

#Percentages based on the total number per treatment arm

Other endpoints

a) Survival analyses

Analyses should be intention-to-treat

	20 Gy/1 fraction N=?	8 Gy/5 fractions N=?
Overall survival (OS)		
Number of deaths		
Median OS (months), 95% CI (or IQR)		
12 weeks' survival rate (95% CI)		
1 year survival rate (95% CI)		
Time to recovery of ambulation*		
Number of events		
Median time to recovery (weeks), 95% CI		
12 weeks' rate (95% CI)		
Time to ambulation**		
Number of events		
Median time to ambulation (months), 95% CI		
12 weeks' rate (95% CI)		

*In those patients with level 3|4 ambulatory status
**In those patients with level 1|2 ambulatory status

For time-to-event data, provide Kaplan-Meier curves, with number of patients at risk in each treatment group below the x-axis.
All time points should start from the date of registration.

Cause of death

	20 Gy/1 fraction N=?	8 Gy/5 fractions N=?
Primary cancer		
Treatment		
Combination of cancer related & treatment related		
Other		
Not known		

b) Change in ambulatory status at 4 and 12 weeks

Similar table as in the primary endpoint (see page 6)

c) Bladder, bowel function at 1, 4, 8 and 12 weeks from day 1 of treatment compared to randomisation

	Baseline		Week 1		Week 4		Week 8		Week 12	
	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?
	% (n)									
Bladder function										
Evaluable patients										
Normal										
Abnormal										
Bowel function										
Evaluable patients										
Normal										
Abnormal										

d) Place of care

	Week 1		Week 4		Week 8		Week 12	
	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?
	% (n)							
Place of care								
Evaluable patients								
Home/with relatives								
Care home								
Hospital								
Hospice								

e) Further treatment

	Week 1		Week 4		Week 8		Week 12	
	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?	20 Gy/5 fr N=?	8 Gy/1 fr N=?
	% (n)							
Supportive care for SCC								
Evaluable patients								
Corticosteroids								
Analgesics								
Anti-emetics								
Physiotherapy								
Retreatment for SCC								
Evaluable patients								
Surgery								
Chemotherapy								
Radiotherapy								
Treatment for primary or metastatic disease								
Evaluable patients								
Surgery								
Chemotherapy								
Radiotherapy								

5. Adverse events

Present results for the feasibility part and phase III trial separately because safety data are collected differently in the two parts of the trial.
For each type of event, the table will show the number (%) of patients. One patient can appear in more than one row.

a) Grade 3|4 adverse events for Phase III trial patients based on CTCAE v 4.0

Adverse event	Any time	
	20 Gy/ 5 fractions N=?	8 Gy/ 1 fraction N=?
Expected		
Anorexia or reduced appetite		
Diarrhoea		
Nausea		
Dysphagia/Oesophagitis/discomfort on swallowing		
Mucositis in oesophagus, bladder, bowel or rectum		
Erythema in the irradiated field		
Fatigue		
Other		
1		
2		
3		
etc		
Any of the above adverse events*		

***Patients counted only once**

b) Similarly list grade 1|2 adverse events.

c) Grade 3|4 adverse events for the feasibility trial patients using RTOG acute toxicity scale

Adverse event	Anytime	
	20 Gy/5 fractions N=?	8 Gy/1 fraction N=?
Skin		
Pharynx and oesophagus		
Larynx		
Lung		
Upper GI		
Lower GI including pelvis		
CNS		
Genitourinary		
Other		
1		
2		
etc		
Any of the above toxicities*		

***Patients counted only once**

d) Similarly list grade 1|2 adverse events.

e) List of Serious Adverse Events and SUSARs

6. Other analyses

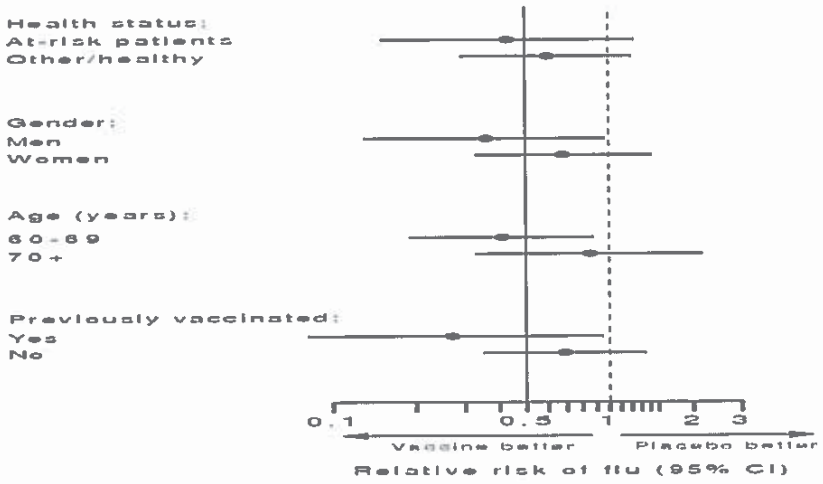
Subgroup analyses will be provided for the following factors:

Radiotherapy centre
Ambulatory status at randomisation
Primary tumour type
Extent of disease (spinal metastases or spinal and non-bony metastases)

The hazard ratio and 95% CI in each level of the factor would be obtained.

Provide a p-value from a test for interaction between the factor and the treatment allocation, in relation to the main outcome measure (eg interaction between ambulatory status and treatment group using overall survival). This could be done using multivariate Cox modelling (time-to-event data), logistic regression (binary data), or linear regression (continuous data).

If there are several subgroups, a forest plot could be provided. Add a dashed vertical line to indicate the no effect value (eg hazard ratio=1, or relative risk=1), and a solid line to indicate the overall treatment effect (eg hazard ratio from all patients), as in the following example.



Multiple primary endpoints or multiple time points

Use 99% confidence intervals in the subgroup analysis

Multiple time points: use repeated measures analyses (eg mixed modelling), repeated ANOVA

Revision Chronology:			
Version Number	**Effective date**	**Reason for change and Summary of changes**	**Author**
01	13 Oct 2012		Latha Kadalayil
02	13 Jan 2013	Added 90%CI as per design	Andre Lopes