

The Lancet Oncology

Observation versus screening spinal MRI and pre-emptive treatment for spinal cord compression in patients with castrate resistant prostate cancer and spinal metastases (PROMPTS): a randomised, controlled, phase 3 trial.

--Manuscript Draft--

Manuscript Number:	THELANCETONCOLOGY-D-21-01959R3
Article Type:	Article (Clinical Trials)
Keywords:	Randomised controlled trial Phase 3 Metastatic prostate cancer Spinal cord compression MRI Screening
Corresponding Author:	Emma Hall, PhD Institute of Cancer Research: The Institute of Cancer Research Sutton, Surrey UNITED KINGDOM
First Author:	David Dearnaley, FRCR
Order of Authors:	David Dearnaley, FRCR Victoria Hinder, B.Sc Adham Hijab, MD Gail Horan, FRCR Narayanan Srihari, FRCR Philip Rich, FRCR Graeme Houston, MD Ann M Henry, MD Stephanie Gibbs, FRCR Clare Alana Cruickshank, BSc (Hons) Ram Venkitaraman, FRCR Shama Hassan, M.Sc Alec Miners, Ph.D Malcolm Mason, MD Ian Pedley, FRCR Heather Payne, FRCR Susannah Brock, FRCR Robert Wade, FRCR Angus Robinson, FRCR Omar Din, FRCR Kathryn Lees, FRCR John Graham, FRCR Jane Worthing, FRCR Julia Murray, FRCR Chris Parker, MD

	Clare Griffin, M.Sc
	Aslam Sohaib, FRCR
	Emma Hall, Ph.D
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	<p>Background Early diagnosis of malignant spinal cord compression (SCC) is crucial as pre-treatment neurologic status is the major determinant of outcome. In metastatic castrate resistant prostate cancer (mCRPC) SCC is a significant cause of disease-related morbidity and mortality. We investigated whether screening for SCC with spinal MRI, with pre-emptive treatment if radiological SCC (rSCC) was detected, reduced the incidence of clinical SCC (cSCC) in asymptomatic mCRPC patients with spinal metastasis.</p> <p>Methods PROMPTS is a phase III parallel-group, randomised controlled superiority trial. CRPC patients aged at least 18 years with spinal metastases who did not have related back pain or neurological symptoms, no previous SCC, and no spinal MRI in previous 12 months were eligible. Participants were randomly allocated (1:1 ratio) to control (no MRI) or screening spinal MRI. Allocation was not masked. Pre-emptive treatment and 6-monthly spinal MRI were offered to patients with screen-detected rSCC. The primary endpoint was incidence of cSCC at 12 months. The study is registered: ISRCTN74112318.</p> <p>Findings Between February 26, 2013 and April 25, 2017, we randomly assigned 420 men from 45 UK centres to control (n=210) or screening MRI (n=210). Median age was 74 years (IQR: 68-79), 53% (222/420) had normal alkaline phosphatase, and median PSA was 48.0ng/ml (IQR: 17-162). rSCC was detected at screening in 61/200 (30.5%) intervention group patients with assessable scans. At 12 months, the cumulative incidence of cSCC was 6.7% (95% CI 3.8 to 10.6) in the control group and 4.3% (2.1 to 7.7) in the intervention group (difference: -2.41%; 95%CI:-4.23 to 0.11; p=0.119, HR: 0.64 (95%CI: 0.37-1.11)).</p> <p>Interpretation Despite the substantial incidence of rSCC, the development of cSCC in both groups was low. Use of screening MRI and pre-emptive treatment did not significantly reduce the incidence of cSCC in asymptomatic CRPC patients with spinal metastasis.</p> <p>Funding Cancer Research UK.</p>

TITLE: Observation versus screening spinal MRI and pre-emptive treatment for spinal cord compression in patients with castrate resistant prostate cancer and spinal metastases (PROMPTS): a randomised, controlled, phase 3 trial.

David Dearnaley, Victoria Hinder, Adham Hijab, Gail Horan, Narayanan Srihari, Philip Rich, Graeme Houston, Ann M Henry, Stephanie Gibbs, Ram Venkitaraman, Clare Cruickshank, Shama Hassan, Alec Miners, Malcolm Mason, Ian Pedley, Heather Payne, Susannah Brock, Robert Wade, Angus Robinson, Omar Din, Kathryn Lees, John Graham, Jane Worliding, Julia Murray, Chris Parker, Clare Griffin, Aslam Sohaib*, Emma Hall* on behalf of PROMPTS investigators.

* contributed equally

Affiliations

The Institute of Cancer Research, London, UK (Professor D Dearnaley FRCR, V Hinder BSc, C Cruickshank BSc, S Hassan MSc, J Murray FRCR, C Parker MD, C Griffin MSc, Professor E Hall PhD), Royal Marsden NHS Foundation Trust, London, UK (Professor D Dearnaley FRCR, A Hijab MD, J Murray FRCR, C Parker MD, A Sohaib FRCR), The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust, King's Lynn, UK (G Horan FRCR), The Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, UK (N Srihari FRCR), St George's University Hospitals NHS Foundation Trust, London, UK (P Rich FRCR), NHS Tayside, Dundee, Scotland, UK (Professor G Houston MD), University of Leeds, UK (AM Henry MD), Barking, Havering and Redbridge University Hospitals NHS Trust, London, UK (S Gibbs FRCR), East Suffolk and North Essex NHS Foundation Trust, Suffolk, UK (R Venkitaraman FRCR), London School of Hygiene and Tropical Medicine, London, UK (A Miners PhD), Cardiff University, Wales, UK (Professor M Mason MD), The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK (I Pedley FRCR), University College London Hospitals NHS Foundation Trust, London, UK (Professor H Payne FRCR), University Hospitals Dorset NHS Foundation Trust, UK (S Brock FRCR), Norfolk and Norwich University Hospitals NHS Foundation Trust, UK (R Wade FRCR), Brighton and Sussex University Hospitals NHS Trust, UK (A Robinson FRCR), Sheffield Teaching Hospitals NHS Foundation Trust, UK (O Din FRCR), Maidstone and Tunbridge Wells NHS Trust, UK (K Lees FRCR), Somerset NHS Foundation Trust, UK (J Graham FRCR), University Hospitals Coventry and Warwickshire NHS Trust, UK (J Worliding FRCR).

Corresponding Author:

Professor Emma Hall

Clinical Trials and Statistics Unit, The Institute of Cancer Research, London SM2 5NG

Tel: 020 8722 4013

Emma.Hall@icr.ac.uk

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for articles published between Jan 1, 1970 and Dec 31, 2012, before trial commencement using the terms “spinal cord compression, cancer, prostate cancer, magnetic resonance imaging, radiotherapy, spinal surgery, systematic review, guideline” and then updated results to April 1st, 2021. Systematic reviews and international guidelines have recognised the importance of early diagnosis and intervention of spinal cord compression (SCC). Spinal MRI is recommended with subsequent intervention with surgical decompression or radiotherapy. Institutional studies suggest spinal MRI can detect asymptomatic early radiological SCC (rSCC) in patients with castration resistant metastatic prostate cancer (CRPC) and early intervention with radiotherapy markedly reduces the development of clinical SCC (cSCC). National Institute of Cancer Excellence (NICE) guidance does not recommend spinal MRI and treatment intervention for asymptomatic patients with spinal metastases, but randomised trials to evaluate early diagnostic and intervention strategies were encouraged.

Added value of this study

We did the first multi-centre randomised controlled trial to study the role of screening spinal MRI to detect radiologically defined asymptomatic spinal cord compression (rSCC) in CRPC. We confirmed the reproducibility of a MR imaging epidural spinal cord compression (ESCC) scale. We showed that radiotherapy was effective at preventing progression of rSCC to symptomatic cSCC. However, although the intervention group had a lower risk of developing cSCC than the control group this did not reach statistical significance. Patients with rSCC had a high risk of progression to cSCC at other spinal sites. Although the resources needed for spinal MRI and radiotherapy were higher in the intervention group than control group, there was a decrease in the use of subsequent additional systemic treatments. We were unable to identify predictive factors for the development of rSCC or cSCC.

Implications of all available evidence

Spinal MRI can reliably detect rSCC in CRPC but early rSCC does not usually progress to cSCC in patient groups who have access to contemporary systemic treatment. We recommend that the ESCC scale be introduced into routine clinical practice as it clearly communicates the presence of early rSCC and identifies a high-risk group for subsequent development of cSCC. Close adherence to NICE Guidelines for the early investigation of spinal symptoms is important in reducing neurological disability compared with historical experience. Presently we do not recommend screening spinal MRI in unselected patients with castration resistant metastatic prostate cancer but further research to identify high risk groups is warranted.

SUMMARY (-325/300 words)

Background

Early diagnosis of malignant spinal cord compression (SCC) is crucial as pre-treatment neurologic status is the major determinant of outcome. In metastatic castrate resistant prostate cancer (mCRPC) SCC is a significant cause of disease-related morbidity and mortality. We investigated whether screening for SCC with spinal MRI, with pre-emptive treatment if radiological SCC (rSCC) was detected, reduced incidence of clinical SCC (cSCC) in asymptomatic mCRPC patients with spinal metastasis.

Methods

We did a phase III parallel-group, open-label, randomised controlled superiority trial. CRPC patients aged at least 18 years, performance status 0-2, with spinal metastases with no related back pain or neurological symptoms, no previous SCC and no spinal MRI in previous 12 months were eligible. Participants were randomly allocated (1:1) to control (no MRI) or screening spinal MRI using a minimisation algorithm with a random element (balancing factors: centre, alkaline phosphatase, number of previous systemic treatments, previous spinal treatment). Serious adverse events were monitored in the 24 hours after screening MRI. Participants with screen-detected rSCC were offered pre-emptive treatment (radiotherapy or surgical decompression was recommended) and 6-monthly spinal MRI. The primary endpoint was time to cSCC analysed by intention to treat. The study is registered: ISRCTN74112318. Trial follow-up is complete.

Findings

Between February 26, 2013 and April 25, 2017, we randomly assigned 420 men from 45 UK centres to control (n=210) or screening MRI (n=210). Median age was 74 years (IQR: 68–79); 53% (222/420) had normal alkaline phosphatase; median PSA was 48ng/ml (IQR: 17–162). Screening MRI detected rSCC in 61/200 (31%) patients with assessable scans; time to cSCC was not significantly improved (hazard ratio: 0.64 (95% CI: 0.37–1.11, gray's test p=0.12)) at a median follow-up of 22 months (IQR: 13–31). 1-year cSCC rates were 7% (95% CI 4–11) and 4% (2–8) for control and intervention respectively (difference: -2% (95% CI -4–0). No serious adverse events were reported.

Interpretation

Despite the substantial incidence of rSCC, cSCC rate in both groups was low. Routine use of screening MRI and pre-emptive treatment to prevent cSCC is not warranted in asymptomatic CRPC patients with spinal metastasis.

Funding

Cancer Research UK.

Introduction

Malignant spinal cord compression (SCC) and its complications have a profound influence on functional status and quality of life with a resulting increased burden on the health care system.¹ Early diagnosis is crucial as pre-treatment neurologic status is the major determinant influencing outcome. Almost all patients with SCC who are ambulant prior to treatment retain motor function.²⁻⁸

Metastatic castration-resistant prostate cancer (mCRPC) predominantly involves the skeleton, and a significant proportion of disease related morbidity and mortality are attributed to skeletal-related events (SRE). SCC is the most clinically significant SRE¹ and prostate cancer accounts for about 20% of all cases.^{4,8,9} Population based studies indicate that SCC occurs in about 7% of lethal PCa,⁹ although in a systematic review up to 24% of patients with metastatic prostate cancer developed SCC.⁷ In prostate cancer, studies have shown that it is possible to detect early radiological signs of impending SCC (rSCC) in 27% to 32% of asymptomatic patients using spinal MRI.^{10,11} National Institute for Health and Care Excellence (NICE) Guidance⁸ advises that serial MRI to detect SCC should only be performed as part of a randomised controlled trial (RCT) and that neither radiotherapy nor surgery should be used to treat asymptomatic spinal metastases to prevent SCC unless part of an RCT. To address these issues, we did a randomised, phase 3 study to determine the role of screening MRI to detect rSCC with subsequent pre-emptive treatment to sites of rSCC.

Methods

Study design and participants

PROMPTS is a prospective, phase 3, multicenter, parallel-group, RCT undertaken at 45 National Health Service (NHS) hospitals in the UK. The aims were to assess the value of screening spinal MRI in men with mCRPC with bone involvement to detect and treat asymptomatic SCC. The trial was approved by the London Queen Square Multi-centre Research Ethics Committee (12/LO1109), sponsored by The Institute of Cancer Research (ICR), and conducted in accordance with the principles of good clinical practice. The ICR Clinical Trials and Statistics Unit (ICR-CTSU; London, UK) coordinated the study and carried out central statistical data monitoring and all analyses. The study protocol is available (appendix p26).

Eligible patients had a confirmed pathological diagnosis of prostate adenocarcinoma or a clinical diagnosis of prostate cancer with osteoblastic bone metastases and a serum prostate specific antigen level (PSA) >100 ng/dl at diagnosis. Other inclusion criteria included the presence of asymptomatic spinal metastasis, castration-resistant state (defined as PSA > 5 ng/dl and more than 50% rise above nadir during treatment with a luteinizing hormone-releasing hormone analogue or after orchidectomy), life expectancy of 6 months or more, and

ECOG performance status 0-2. The main exclusion criteria were presence of any back pain or neurological symptoms from spinal metastasis, previous spinal MRI within 12 months from trial entry, previous external beam radiotherapy or surgery to treat SCC, and contra-indication for MRI. Patients were recruited by their clinical care teams and provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly allocated in 1:1 ratio to the control group (no MRI) or the interventional group (screening MRI). Allocation was done centrally by ICR-CTSU using a minimisation algorithm incorporating an 80% random element; balancing factors were treatment centre, alkaline phosphatase (ALP) (normal vs raised), number of previous systemic treatments (first-line vs second-line or later), previous spinal surgery or radiotherapy for metastatic disease (yes vs no) and following a protocol amendment in April 2015, CT or PET CT of thorax and abdomen within last six months (yes vs no). Allocation was not masked due to the impracticality of performing sham MRI.

Procedures

Baseline investigations included PSA measurement, full blood count and biochemistry including ALP. Neurological assessment was based on the Frankel scale,¹² which is a 5-point standardised neurological assessment tool after spinal cord injury (appendix p3). Patient reported outcomes (PROs) were with EORTC QLQ C30,¹³ EQ-5D-5L,¹⁴ Brief Pain Inventory (BPI)¹⁵ and Hospital Anxiety and Depression score (HADS).¹⁶

In the intervention group, screening spinal MRI was performed within four weeks of randomisation using a minimum field strength of 1 Tesla with a spinal coil. The whole spine was imaged from the base of skull to the coccyx with sagittal T1 and T2 weighted images. Sagittal images were supplemented with selected axial images through any suspicious areas at the discretion of the radiologist. Scans were reported by the local specialist radiologist using a modified Bilsky scoring system,^{3,6,17} which is a 6-point validated scale for epidural spinal cord compression (ESCC; appendix p4). Each vertebra was individually assessed. rSCC was defined when no neurological symptoms were present in the presence of epidural disease, whereas patients displaying neurological symptoms were deemed to have clinical SCC (cSCC).

If the baseline screening MRI was positive for rSCC, pre-emptive treatment was recommended with radiotherapy or surgical decompression. After treatment, patients had follow-up MRI every six months.

Participants in both groups were followed up at three monthly intervals for the first two years and then at 30 and 36 months, as well as at the time of any cSCC episode. Assessments included neurological status using the Frankel score,¹² PRO, and PSA, as well as new

treatments and all spinal MRI; HADS was repeated at three months only. Serious adverse events were collected for a 24 hour period after the study screening MRI scan using the National Cancer Institute's Common Terminology Criteria for Adverse events (CTCAEv4.0). In the intervention group, adverse events, EQ-5D-5L and BPI were assessed before and after (not BPI) any pre-emptive treatment. All PROs were completed on paper by the patient at their clinic visit. The main outcome of interest was EORTC QLQ-C30 physical functioning. Additional PRO scores reported were; EORTC QLQ C30: functional scales, global health and pain, BPI: Severity, Interference, HADS: anxiety and depression, EQ-5D-5L: Health state today.

If new neurological symptoms suggestive of cSCC or new onset significant back pain developed, spinal MRI was performed ideally within 24 hours in accordance with NICE and local guidelines, regardless of randomised group. All MRI scans leading to a diagnosis of rSCC or cSCC and a minimum 10% random sample of negative baseline scans were centrally reviewed (AS, PR, GH) and iterative feedback given to participating radiologists and oncologists.

The protocol recommended rSCC was treated (pre-emptively) with radiotherapy or surgery and that NICE guidelines⁸ be followed for cSCC. Short courses of high dose corticosteroids (e.g dexamethasone 8-24mgs total dose per day) were permitted. Radiotherapy was to be delivered within one week of rSCC and within 48 hours of cSCC. The recommended radiotherapy dose was 20 Gy given daily in 5 fractions prescribed to at least the mid-point of the spinal cord /cauda equina. Radiotherapy was to be planned by conventional or CT based virtual simulation using MRI information to determine the radiotherapy field level and length which should extend ≥ 1 vertebral level beyond site(s) of rSCC/cSCC.

Outcomes

The primary outcome was time to cSCC, with the time point of primary interest being one year. Participants were considered to have developed cSCC if they had a compromised Frankel score (grade A-D) with supportive radiological findings. If there was diagnostic uncertainty, cases were centrally reviewed (AH/JM) without knowledge of randomisation group using available data from MRI, clinical and PRO and radiotherapy or surgical records. Secondary outcomes were rate of detection of rSCC on screening MRI (intervention group only); one-year incidences and time (from randomisation) to functional neurological deficit (FND) (Frankel score grade A-D) and persistent FND (defined as Frankel score not returning to normal (grade E) after 3 and 6 months); incidence of any SCC (rSCC and cSCC) at one year; overall survival); cost effectiveness; pain; PROs. In light of primary results, cost effectiveness analysis have not been pursued.

Statistical analysis

We estimated a one-year cSCC incidence of 15.6% in the control group based on a baseline rSCC prevalence of 12.9% (calculated as the average rSCC rate reported in asymptomatic

patients in retrospective studies^{10,11}), median survival of 19 months¹⁸ and assuming all participants with rSCC and 3.2% of those without rSCC at screening would develop cSCC by one year if untreated.¹⁰ We targeted a hazard ratio (HR) of 0.48, equivalent to a reduction in 1 year cSCC rate to 7.8% in the intervention group. Sample size calculations were based on the log rank test with 5% two sided significance. With 90% power, the original target sample size was 541 patients. In November 2016 the statistical power was reduced to 85% to allow for timely completion of recruitment. The revised sample size of 414 (71 events) was based on uniform accrual over a four year period and a minimum of one-year follow-up for all participants. No adjustment for non-compliance with screening MRI was made.

In February 2015 a formal pre-planned interim analysis, after 54 patients in the intervention group had had their baseline MRI, confirmed the interim pre-stipulated rSCC rate was $\geq 10\%$.

Analyses were by intention to treat. To account for death as a competing risk for outcomes relating to rSCC, cSCC and FND incidence rates were estimated using the cumulative incidence function with Gray's test¹⁹ used to compare randomised groups. Estimates of the intervention effect were made using unadjusted and adjusted sub-distribution models. Baseline covariates included in all adjusted models were balancing factors and, time since development of CRPC, time since start of continuous hormone treatment, ECOG performance status (0,1&2) and PSA. HRs <1 indicate a decreased risk of the event in intervention group compared to the control group. The sub-distribution model for death (in the presence of cSCC) was also fitted to ensure results from the cSCC analysis were not due to differences seen in the numbers of deaths. Cause-specific regression models for cSCC with death as a competing risk, and for death with cSCC as a competing risk were also fitted to provide further comparisons. Patients without cSCC were censored at the date of last follow-up. Patients who died before experiencing cSCC were classified as having a competing event at the date of death.

Incidence of rSCC at screening was calculated using binomial proportions and 95% confidence intervals provided. Logistic regression was used to assess the effects of baseline covariates. To assess non-proportionality of covariates in time-to-event multivariable analysis the time dependency of all pre-specified baseline covariates was considered. Analysis of time to new additional systemic treatment was post hoc; randomised groups were compared using Gray's test. For overall survival, Kaplan-Meier methods were used to estimate rates and unadjusted and adjusted Cox regression models were fitted for intervention effect. For all non-PRO analysis p values <0.05 were considered statistically significant.

The appropriate scoring manuals were used to calculate BPI pain, EORTC QLQ C30 and HADS scores. Cross-sectional analysis was done at each time point up to 24 months using the Mann-Whitney U test, with 12 months being the primary time point of interest. Change from baseline to 12 months was assessed using ANCOVA adjusting for the baseline scores. Plots of residuals vs predicted values were used to assess the constant variance assumption. Missing

data (including deaths) were not considered to be missing at random and therefore patterns of missingness were explored. In particular completeness of data by visit period as well as baseline scores with and without paired 12 months scores were observed by randomised group for PRO to assess possible effects of missing data. To account for multiple testing of secondary PROs, only p-values below 0.01 were considered statistically significant.

Analyses were based on a database snapshot taken on April 23 2020, and were done using SAS version 9.4, except for competing risk regression models where STATA version 16 was used. The trial management group was overseen by an independent trial steering committee. Safety and efficacy data were reviewed regularly by an independent data monitoring committee (IDMC). The trial was prospectively registered (ISRCTN74112318).

Role of funding source

The funding source provided peer-reviewed approval for the trial, but had no other role in study design, collection, analysis, interpretation of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. VH, CG, and EH also had full access to the data.

Results

Between February 26, 2013, and April 25, 2017, 420 men were recruited from 45 centres in the UK (appendix p5), with 210 patients assigned to each study group (Figure 1). Demographic and clinical characteristics are presented in table 1. Clinical symptoms and signs recorded pre-randomisation were similar between randomised groups (appendix p6). Median follow-up (reverse Kaplan-Meier) was 22 months (IQR: 13-31).

Screening spinal MRI was performed in 201/210 (96%) participants in the intervention group (Figure 1) with a median time from randomisation to scan of 30 days (IQR 15-35). No serious adverse events were reported. Sixty one of 200 (31%) patients with assessable scans had rSCC and a total of 140 individual metastases associated with rSCC identified (median 1 lesion per patient, IQR 1-3). Maximum ESCC scores were 1a: 26/61 (43%); 1b: 17/61 (28%); 1c: 12/61 (20%); 2: 2/61 (3%), and 3: 4/61 (7%). Sixteen metastases (11%) were in the cervical spine, 41 (29%) in the upper thoracic spine (T1-T6), 50 (36%) in the lower thoracic spine (T7-T12), and 33 (24%) in the lumbar spine (Table 2). Central review of scans showed concordance of 92.4% with local radiology assessments (Table 2).

Radiotherapy was given to sites of rSCC in 50/61 (82%) patients (Figure 1), dose was 20 Gray in 5 fractions for 52/57 (91%) treatment sites (appendix p7). Adverse events were uncommon after spinal radiotherapy for rSCC (appendix p8). Grade 1-2 events occurring in ≥10% of patients were constipation in 8/50 (16%), back pain in 7/50 (14%). There was one grade 3 AE of chest pain. Corticosteroids were given to 28/61 (46%) of patients (median dose dexamethasone 8 mg (IQR 4-16), median duration 11 days (IQR 7-19)). Protocol defined

follow-up MRI was performed in 32/44 (73%) screen-positive patients treated with radiotherapy and alive at 6 months. In these 32 evaluable patients, out of 69 assessable and treated metastases with rSCC, 39 (57%) had improved ESCC score, 27 (39%) were stable and 3 (4%) had progressed (2 cases 1a/b to 1c, 1 case 1c to 3) (Figure 2a, appendix p9). At 12 months, out of 46 assessable and treated sites with rSCC in 21 evaluable patients (58% of 36 patients alive), 37 (80%) metastatic sites with rSCC had improved ESCC scores, 7 (15%) were stable and 2 (4%) had progressed (2 cases 1a/b to 1c) (Figure 2b). A clinical decision was made not to treat 18 sites with rSCC (all ESCC 1a/b, 1c). Of these 12 (67%) had improved ESCC score and 6 (33%) were stable, based on 6-month MRI assessment and none had progressed by 12 months (Figure 2a, 2b).

On univariable analysis, covariates associated with rSCC were raised ALP (OR 2.31, 95% CI 1.24-4.28, $p=0.008$) and lnPSA at randomisation (OR 1.50 95% CI 1.19-2.89, $p<0.001$). lnPSA at randomisation remained significant on multivariable analysis (OR 1.49 95% CI 1.15-1.92, $p=0.002$) (appendix p10)). However neither parameter appeared to usefully separate clinical groups (appendix p 11).

In the control group, cumulative incidence of cSCC at 12 and 24 months was 7% (95% CI 4-11, $n=14$) and 13% (95% CI 9-18, $n=26$) and for the intervention group was 4% (95% CI 2-8, $n=9$) and 9% (95% CI 6-14, $n=19$) respectively ($p=0.12$, Figure 3a). Unadjusted and adjusted sub-distribution models showed no statistically significant intervention effect (unadjusted HR 0.64 (95% CI: 0.37-1.11), $p=0.11$ and adjusted HR 0.62 (0.34-1.19), $p=0.10$) (appendix p13). HR for the development of cSCC calculated using a cause-specific model were similar (unadjusted HR 0.67 (0.38-1.16) $p=0.149$, adjusted HR 0.61 (0.35-1.08) $p=0.09$). Sub-distribution and cause specific models for death with cSCC as competing risk showed no intervention effect. At 12 months, the intervention rSCC screen-positive group had a higher cumulative cSCC incidence than the screen-negative group: 7 cases (12% (95% CI 5-21) vs 2 cases 1% (0-4), $p=0.13$). At 24 months, the cumulative incidence of cSCC increased to 13% (6-23) in the screen-positive group and 8% (4-13) in the screen-negative group. The incidence of cSCC was lower in the rSCC screen-negative group compared with the control group ($p=0.04$) (appendix p14). Raised ALP was the only variable found to have a significant association with the development of cSCC, but the number of events is small (appendix p 13)) and ALP groups did not adequately stratify patients for screening.

ESCC scores for the first cSCC event recorded over the duration of the trial were in similar proportion in the two randomised groups with ESCC 1a/1b, 1c and 2/3 scores in 6 (24%), 2 (8%), and 17 (68%) patients in the control group and 2 (11%), 4 (22%), and 12 (67%) patients in the intervention group (10 patients had unknown scores). Frankel scores showed most patients remained ambulant (score D) at the time of cSCC in both groups with scores of A/B, C and D in 1 (3%), 6(19%) and 19 (59%) control group patients, and in 2 (10%), 2 (10%), and 9

(43%) intervention group patients respectively (14 patients had unknown scores) (appendix p15).

All patients treated for cSCC had initial radiotherapy, one patient had subsequent salvage surgery. Dose was 20 Gray in 5 fractions for 17/36 (47%) sites treated and a further 15 sites received 8 Gray in single fraction (appendix p7). Hospitalisation for SCC was documented for 19/51 (37%) patients for a median of 5 days (IQR 4-9, n missing=1) in the control group and for 12/37 (32%) patients for a median of 15 days (IQR 4-21, n missing=1) in the intervention group.

Thirty nine patients had assessable Frankel scores at least 6 months after the initial cSCC diagnosis, 4/26 (15%) patients in the control group recovered to Frankel score E (no deficit) compared with 3/13 (23%) in the intervention group (appendix p15). Time to persistent FND (Frankel score A-D) is shown in figure 3b, with cumulative incidences of 6% (95% CI 3-10, n=12) and 11% (95% CI 7-16, n=23) in the control group compared with 3% (95% CI 1-6, n=6) and 7% (95% CI 4-11, n=15) in the intervention group at 1 and 2 years respectively ($p=0.07$). PROs revealed no significant differences between the randomised groups in any measure (appendix p16-23).

Overall survival was similar in both randomised groups with median survival of 22.2 months (IQR 12.4-32.7) and 22.0 months (IQR 12.4-34.6) for control and intervention groups respectively ($p=0.82$, figure 3c). Deaths from prostate cancer were documented in 158/174 (91%) and 150/172 (87%) of the control and intervention groups respectively (appendix p23). On multivariable analysis, covariates associated with overall survival were ALP (HR 1.9, 95% CI 1.5-2.4; $p<0.001$), ECOG status (HR 1.6, 95% CI 1.2-1.9; $p<0.001$) and lnPSA (HR 1.3, 95% CI 1.2-1.4; $p<0.001$).

Analysis of time to new additional systemic treatment was carried out post hoc. New systemic treatments were started more commonly in the control group (figure 4), significant differences were seen for chemotherapy and any new systemic treatment. At 12 months the number of patients that had received chemotherapy or any new systemic treatment was 55 (26%) and 147 (70%) in the control group and 31 (15%) and 113 (54%) in the intervention group (appendix p24). More spinal radiotherapy was used in the intervention than control group. After 12/24 months follow-up, 86/107 courses of radiotherapy had been given in the intervention group; 51 courses for rSCC on screening scans, 27/40 for subsequent r/cSCC and 8/16 for bone pain alone. In the control group 32/43 courses had been given for SCC and 17/19 for bone pain alone. By 24 months, 48 (23%) patients in the control group had received spinal radiotherapy compared with 85 (41%) patients in the intervention group (appendix p24).

Overall, 361 (201 screening, 85 protocol defined and 74 additional) and 98 spinal MRI scans were performed in the 24 months after randomisation in intervention and control groups respectively (appendix p25).

Discussion

We performed the first randomised trial to assess the role of screening²⁰ using spinal MRI to detect and treat rSCC in metastatic prostate cancer and found no statistically significant reduction in the proportion of patients with cSCC at 12 months with a difference between control and intervention groups of -2.41% (95% CI: -4.23–0.11). We chose to use a validated ESCC scale, developed by Bilsky and colleagues,^{3,6,17} for assessing rSCC on both screening and additional MRI scans. Although it is not routinely used in the UK, we found that specialist radiologists in the participating centres rapidly adapted to the scoring system with iterative feedback from the central review team. All vertebral levels were scored and levels of rSCC were reliably identified by local and central radiologists as suggested previously.¹⁷

We identified rSCC in 61/200 (31%) of the screening MRI scans. This was similar to the 27–32% reported from previous single institutional experiences although higher than the incidence in asymptomatic patients.^{10,11} Any differences are likely due to patient selection factors varying between historic and contemporary cohorts and MR reporting methods. Seventy percent of screened patients had “early” rSCC graded as ESCC 1a or b, with a further 20% graded 1c and 10% graded 2 or greater. In the screened population, 82% went on to have pre-emptive treatment. Although consideration of surgical options^{2,3,6,21} was encouraged in the protocol, treatment was uniformly with radiotherapy. The protocol standard dose of 20 Gray in 5 fractions was used most commonly which aligns with current practice for treatment of cSCC.^{8,22} The effectiveness of radiotherapy is usually judged clinically according to ambulatory status. We had the additional opportunity to assess response radiologically, and repeat MRI after 6 months showed only 3/69 (4%) of treated metastases had progressed in 2 patients. However, 23 new sites of rSCC had appeared in 8 patients.

Despite the substantial incidence of rSCC, the development of cSCC in both randomised groups was lower than anticipated. Cumulative rates of development of cSCC at 12 months, the primary endpoint of the trial, were 7% and 4% in the intervention and control groups respectively. The rSCC screen-positive subgroup were at particular risk (12% cumulative incidence at 12 months) of the subsequent development of cSCC. In the MRI screen-negative group, the rate of cSCC was very low at 1% at 12 months but then increased to 8% at 24 months which is in accordance with previous suggestions of a 12 month “protective window” of a negative spinal MRI from single centre studies.^{10,23} A population based study has suggested a prevalence of 7% of metastatic SCC in mCRPC patients⁹ although single institution estimates have been as high as 24%.^{7,24} Data from more recent trials using the new generation of life-prolonging therapies have reported slightly lower incidences of cSCC of between 3–8%.^{1,25–28} Patients enrolled in the PROMPTS trial had biochemically progressing disease and

additional systemic treatments were given as clinically appropriate. Effective systemic treatments reduce both the incidence of skeletal related events, including cSCC^{1,25,28} and are likely to have an impact on the progression of rSCC to cSCC. Assuming a similar, but undetected rate of rSCC in the control group compared with the intervention group, it is apparent that the rate of development of cSCC was considerably less than the detection of rSCC. The reduction of use of systemic treatments in the intervention group in the 12 months after randomisation was unexpected but a plausible mechanism might be through the impact of radiotherapy on progression in major sites of bone disease^{29,30}. In particular the use of radiotherapy to treat sites of oligoprogression, arising from resistant sub-clones, may allow the continuation rather than change of systemic treatments²⁹.

The majority of patients with cSCC (28/39, 72%), in the trial remained ambulant with Frankel scores \leq D, with no difference between the randomised groups. The degree of FND appears less than in past reports. Most patients with prostate cancer and SCC have previously been reported as non-ambulant,^{4,5,31}; this has improved in more recent years although the majority of patients still have motor deficits.^{3,7} We suspect the intended strict application of NICE guidelines for immediate assessment of new back pain⁸ and protocol required 3 monthly follow-up for 2 years may have had a favourable impact in both randomised groups. Early detection of cSCC may encourage use of more contemporary treatment techniques to treat spinal metastasis, such as stereotactic body irradiation,^{3,6,30,32,33} that are more effective in achieving local control. However, enthusiasm for early intervention following screening MRI should be tempered by the likelihood of over-treatment.

More imaging and radiotherapy resources were used in the intervention than control group. This can be balanced against less use of new systematic treatments and possible reduction in FND in the intervention group. Refinement in the selection of patients for MRI screening would be helpful. In common with other investigators, we found that performance status, ALP and PSA levels were related to survival.⁷ However, with the exception of ALP, we could not confirm previous observations that biochemical, clinical or pathological parameters were risk factors for the development of cSCC.^{3,7,32} This may be due to the relatively small number of patients developing cSCC as well as the intervention for rSCC. We showed that pre-screening PSA and ALP levels are related to the presence of rSCC but neither co-variate alone or in combination appeared to usefully stratify the patient population. We did not record data on extent of disease on Technetium (Tc) bone scan. Previous reports suggest that the number of spinal metastases or whole vertebral body involvement identifies high risk groups for the development of cSCC^{7,10,11,24} which might assist patient selection for screening MRI to detect clinically occult SCC.^{10,34} It would be helpful to assess the relationship of extent of spinal disease on MR and other imaging modalities with rSCC and cSCC and also whether extent of spinal disease at the time of first development of bone metastases or at the time of development of mCRPC might assist in stratification of patients for screening MRI.

Limitations of the trial include the non-blinded screening intervention allocation and the emphasis on patient and clinical staff appreciation of cSCC which although in line with NICE Guidelines⁸ may have led to earlier detection of cSCC than in usual clinical practice. With fewer than expected events the study is likely to have been underpowered for the primary endpoint. Any assessment of the impact of radiotherapy treatment intervention is confounded by the use of additional systemic treatment options but these are “standard of care” for mCRPC and included presently available life-prolonging options.^{1,14,25,27,28} A pragmatic decision was made to use the short Frankel instrument to assess FND in oncology clinics rather than more detailed neurological assessments. Data completeness reduced with duration of follow-up as might be anticipated in an increasingly frail population but was similar in the randomised groups. A full cost effectiveness analysis is outside the scope of this report. It would need linkage to Hospital Episodes Statistics data for robustness and ideally include a contemporary non-trial cohort with cSCC for comparison.

In summary, the trial demonstrated the reproducibility of the ESCC scale and we recommend its widespread adoption in oncology practice.⁶ We found no statistically significant differences in incidence of cSCC or persistent FND between the MRI screened intervention and control groups. Severity of cSCC judged by Frankel scores were similar in the randomised groups although lower than in previous reports. MRI screen-detected early rSCC does not always progress to cSCC with contemporary systemic management of CRPC and observation may be reasonable for ESCC grade 1a/b rSCC. However, particular vigilance is recommended for these patients with a low threshold for recommending spinal MRI if any new back pain manifests as they are at substantial risk of developing new sites of cSCC. Further efforts to better identify patients at high risk for rSCC and cSCC are warranted to refine selection of groups for screening spinal MR. The low rates of neurological impairment suggest that patients in both intervention and control groups may have gained benefit from trial entry and emphasise the importance of the early detection and management of cSCC in line with NICE guidelines.⁸

Total word count: 4646

Acknowledgements

PROMPTS was funded by Cancer Research UK (CRUK/11/053; A13749, C1491/A15955 C1491/A25351, C33589/A28284, A19727, C46/A10588, C33589/A19727). We acknowledge support from the National Institute for Health Research (NIHR) Cancer Research Network. This project represents independent research supported by the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. We thank the patients and all investigators and research support staff at the participating centres, and members of the Trial Management Group, Independent Data Monitoring Committee and Trial Steering Committee.

Contributors

DD was the PROMPTS Chief Investigator until August 2020 and was succeeded by AS; EH is the methodological lead. DD and EH led study design and with AHe, AM and RV acquired funding for the trial. DD, EH, VH and CG accessed and verified the data. EH and CG oversaw statistical analysis performed by VH. CC contributed to study design and provided senior trial management oversight. SH conducted central study management at ICR-CTSU. DD, GHor, NS, GHou, SG, AHe, IP, HP, SB, RW, AR, OD, KL, JG and JW were involved in recruitment and treatment of participants. DD, VH, GHou, NS, PR, GHor, AHe, SG, RV, CC, SH, AM, MM, CG, AS and EH are members of the PROMPTS Trial Management Group which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation. AHi also contributed to data interpretation. DD, VH, AHi, AS and EH led manuscript writing; all other authors contributed to and reviewed the manuscript. All authors had access to data reported in this study.

Declaration of interests

EH reports grants from Cancer Research UK, during the conduct of the study and outside the submitted work reports: grants and non-financial support from Astra Zeneca and Bayer, and grants from Accuray Inc, Varian Medical Systems Inc., Janssen-Cilag, Roche Products Ltd, Merck Sharp & Dohme and Pharma Limited (Sanofi). VH reports grants from Cancer Research UK, during the conduct of the study. GHor reports speaker fees from Janssen outside the submitted work. CP reports speaker fees from Bayer and Janssen; advisory board fees from AAA , Clarity Pharmaceuticals, Myovant, ITM Radiopharma and Janssen advisory board membership and Bayer education steering committee membership, outside the submitted work. DD reports grants from Cancer Research UK, during the conduct of the study and National Institute for Health Research Biomedical Research Centre grants and he has a patent (EP1933709B1), outside the submitted work. AS reports NIHR BRC funding to The Royal Marsden Hospital, speaker fees from Pfizer and past president and on executive board for International Cancer Imaging Society without payment, outside the submitted work. MM reports participation on Data Monitoring Board/Advisory Board for Endocyte and Clovis, outside the submitted work. AHi, GH, NS, PR, GHou, AHe, SG, RV, CC, SH, AM, IP, HP, SB, RW, AR, OD, KL, JG, JW, JM and CG declare no competing interests.

Data sharing

De-identified data will be made available to other researchers on request, subject to approval of a formal data access request in accordance with the ICR-CTSU data and sample access policy. Trial documentation including the protocol are available on request by contacting prompts-icrctsu@icr.ac.uk. The ICR-CTSU supports the wider dissemination of information from the research it does, and increased cooperation between investigators. Trial data is collected, managed, stored, shared, and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity, and utility of the data. Formal

requests for data sharing are considered in line with the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and intellectual property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is allowed if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Trial Steering Committee as required. Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymising identifiable patient data. Additionally all indirect identifiers that might lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines. Additional documents might be shared if approved by the TMG and Trial Steering Committee (e.g. statistical analysis plan and informed consent form).

References

1. Saad F, Ivanescu C, Phung D, Loria Y, Abhyankar S, Beer TM, et al. Skeletal-related events significantly impact health-related quality of life in metastatic castration-resistant prostate cancer: data from PREVAIL and AFFIRM trials. *Prostate Cancer and Prostatic diseases*. 2017;20(1):110-6.
2. Al-Qurainy R, Collis E. Metastatic spinal cord compression: diagnosis and management. *BMJ*. 2016;353.
3. Lawton AJ, Lee KA, Cheville AL, Ferrone ML, Rades D, Balboni TA, et al. Assessment and management of patients with metastatic spinal cord compression: a multidisciplinary review. *Journal of Clinical Oncology*. 2019;37(1):61-71.
4. Levack P, Graham J, Collie D, Grant R, Kidd J, Kunkler I, et al. Don't wait for a sensory level—listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clinical Oncology*. 2002;14(6):472-80.
5. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *The Journal of Urology*. 2006;175(2):480-.
6. Spratt DE, Beeler WH, de Moraes FY, Rhines LD, Gemmete JJ, Chaudhary N, et al. An integrated multidisciplinary algorithm for the management of spinal metastases: an International Spine Oncology Consortium report. *The Lancet Oncology*. 2017;18(12):e720-e30.
7. Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala N, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. *Health Technology Assessment (Winchester, England)*. 2013;17(42):1.
8. NICE. Metastatic spinal cord compression in adults: risk assessment, diagnosis and management 2008 [Available from: <https://www.nice.org.uk/guidance/cg75>].
9. Loblaw D, Laperriere N, Mackillop W. A population-based study of malignant spinal cord compression in Ontario. *Clinical Oncology*. 2003;15(4):211-7.
10. Bayley A, Milosevic M, Blend R, Logue J, Gospodarowicz M, Boxen I, et al. A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2001;92(2):303-10.
11. Venkitaraman R, Sohaib S, Barbachano Y, Parker C, Khoo V, Huddart R, et al. Detection of occult spinal cord compression with magnetic resonance imaging of the spine. *Clinical Oncology*. 2007;19(7):528-31.
12. Frankel H, Hancock D, Hyslop G, Melzak J, Michaelis L, Ungar G, et al. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. *Spinal Cord*. 1969;7(3):179-92.
13. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, Kaasa S. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *JNCI: Journal of the National Cancer Institute*. 1993 Mar 3;85(5):365-76.
14. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. *Health policy*. 1990 Dec 1;16(3):199-208.

15. BPI: Poquet N, Lin C. The brief pain inventory (BPI). *Journal of physiotherapy*. 2015 Aug 21;62(1):52.
16. HADS: Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica scandinavica*. 1983 Jun;67(6):361-70.
17. Bilsky MH, Laufer I, Fourny DR, Groff M, Schmidt MH, Varga PP, et al. Reliability analysis of the epidural spinal cord compression scale. *Journal of Neurosurgery: Spine*. 2010;13(3):324-8.
18. Tannock IF, De Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *New England Journal of Medicine*. 2004 Oct 7;351(15):1502-12.
19. 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.
20. Institute NC. PDQ® Screening and Prevention Editorial Board. PDQ Cancer Screening Overview. Bethesda, MD 2021 [Available from: <https://www.cancer.gov/about-cancer/screening/hp-screening-overview-pdq>].
21. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *The Lancet*. 2005;366(9486):643-8.
22. Hoskin PJ, Hopkins K, Misra V, Holt T, McMenemin R, Dubois D, et al. Effect of single-fraction vs multifraction radiotherapy on ambulatory status among patients with spinal canal compression from metastatic cancer: the SCORAD randomized clinical trial. *JAMA*. 2019;322(21):2084-94.
23. Venkitaraman R, Sohaib S, Barbachano Y, Parker C, Huddart R, Horwich A, et al. Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer. *Clinical Oncology*. 2010;22(2):147-52.
24. Soerdjbalie-Maikoe V, Pelger RC, à Nijeholt GAL, Arndt J-W, Zwinderman AH, Bril H, et al. Bone scintigraphy predicts the risk of spinal cord compression in hormone-refractory prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging*. 2004;31(7):958-63.
25. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *New England Journal of Medicine*. 2019;381(26):2506-18.
26. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *The Lancet*. 2011;377(9768):813-22.
27. Logothetis CJ, Basch E, Molina A, Fizazi K, North SA, Chi KN, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *The Lancet Oncology*. 2012;13(12):1210-7.
28. Parker C, Nilsson S, Heinrich D, Helle SI, O'sullivan J, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine*. 2013;369(3):213-23.

29. Patel P, Palma D, McDonald F, Tree A. The dandelion dilemma revisited for oligoprogression: Treat the whole lawn or weed selectively? *Clinical Oncology*. 2019;31(12):824-33.
30. van der Velden JM, van der Linden YM. Spinal stereotactic radiotherapy for painful spinal metastasis. *The Lancet Oncology*. 2021;22(7):901-3.
31. Husband D. Malignant spinal cord compression: prospective study of delays in referral and treatment. *Bmj*. 1998;317(7150):18-21.
32. Ropper AE, Ropper AH. Acute spinal cord compression. *New England Journal of Medicine*. 2017;376(14):1358-69.
33. Sahgal A, Myrehaug SD, Siva S, Masucci GL, Maralani PJ, Brundage M, Butler J, Chow E, Fehlings MG, Foote M, Gabos Z. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. *The Lancet Oncology*. 2021 Jun 11.
34. Gillessen S, Omlin A, Attard G, De Bono JS, Efstathiou E, Fizazi K, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Annals of Oncology*. 2015;26(8):1589-604.

FIGURE legends

Figure 1: Trial profile

Figure 2: Epidural Spinal Cord Compression (ESCC) vertebra levels scores at screening and follow-up spinal MRI scans at 6 months (panel A) and 12 months (panel B) in patients in the intervention group with rSCC on screening MRI managed with or without spinal radiotherapy.

Legend

Number of patients in circles; white circles indicate radiotherapy given; grey circles indicate radiotherapy not given.

Points on diagonal line represent no change in ESCC score; points above diagonal line represent improvement in maximum ESCC score. Radiotherapy was given to vertebra adjacent to sites of rSCC so that ESCC scores 0 and 9 could increase to $\geq 1a$ on follow-up.

Figure 3. Cumulative incidence and Kaplan-Meier plots

Legend

Cumulative incidence of clinical spinal cord compression (cSCC, panel A), persistent neurological functional deficit (panel B) and, Kaplan-Meier plot of overall survival (panel C).

Figure 4. Time to first additional post randomisation systemic anti-cancer treatment

Legend: Death treated as a competing risk; A) new hormone therapy, B) new chemotherapy, C) new radioisotope therapy, D) any new systemic treatment.

TITLE: Observation versus screening spinal MRI and pre-emptive treatment for spinal cord compression in patients with castrate resistant prostate cancer and spinal metastases (PROMPTS): a randomised, controlled, phase 3 trial.

David Dearnaley, Victoria Hinder, Adham Hijab, Gail Horan, Narayanan Srihari, Philip Rich, Graeme Houston, Ann M Henry, Stephanie Gibbs, Ram Venkitaraman, Clare Cruickshank, Shama Hassan, Alec Miners, Malcolm Mason, Ian Pedley, Heather Payne, Susannah Brock, Robert Wade, Angus Robinson, Omar Din, Kathryn Lees, John Graham, Jane Worliding, Julia Murray, Chris Parker, Clare Griffin, Aslam Sohaib*, Emma Hall* on behalf of PROMPTS investigators.

* contributed equally

Affiliations

The Institute of Cancer Research, London, UK (Professor D Dearnaley FRCR, V Hinder BSc, C Cruickshank BSc, S Hassan MSc, J Murray FRCR, C Parker MD, C Griffin MSc, Professor E Hall PhD), Royal Marsden NHS Foundation Trust, London, UK (Professor D Dearnaley FRCR, A Hijab MD, J Murray FRCR, C Parker MD, A Sohaib FRCR), The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust, King's Lynn, UK (G Horan FRCR), The Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, UK (N Srihari FRCR), St George's University Hospitals NHS Foundation Trust, London, UK (P Rich FRCR), NHS Tayside, Dundee, Scotland, UK (Professor G Houston MD), University of Leeds, UK (AM Henry MD), Barking, Havering and Redbridge University Hospitals NHS Trust, London, UK (S Gibbs FRCR), East Suffolk and North Essex NHS Foundation Trust, Suffolk, UK (R Venkitaraman FRCR), London School of Hygiene and Tropical Medicine, London, UK (A Miners PhD), Cardiff University, Wales, UK (Professor M Mason MD), The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK (I Pedley FRCR), University College London Hospitals NHS Foundation Trust, London, UK (Professor H Payne FRCR), University Hospitals Dorset NHS Foundation Trust, UK (S Brock FRCR), Norfolk and Norwich University Hospitals NHS Foundation Trust, UK (R Wade FRCR), Brighton and Sussex University Hospitals NHS Trust, UK (A Robinson FRCR), Sheffield Teaching Hospitals NHS Foundation Trust, UK (O Din FRCR), Maidstone and Tunbridge Wells NHS Trust, UK (K Lees FRCR), Somerset NHS Foundation Trust, UK (J Graham FRCR), University Hospitals Coventry and Warwickshire NHS Trust, UK (J Worliding FRCR).

Corresponding Author:

Professor Emma Hall

Clinical Trials and Statistics Unit, The Institute of Cancer Research, London SM2 5NG

Tel: 020 8722 4013

Emma.Hall@icr.ac.uk

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for articles published between Jan 1, 1970 and Dec 31, 2012, before trial commencement using the terms “spinal cord compression, cancer, prostate cancer, magnetic resonance imaging, radiotherapy, spinal surgery, systematic review, guideline” and then updated results to April 1st, 2021. Systematic reviews and international guidelines have recognised the importance of early diagnosis and intervention of spinal cord compression (SCC). Spinal MRI is recommended with subsequent intervention with surgical decompression or radiotherapy. Institutional studies suggest spinal MRI can detect asymptomatic early radiological SCC (rSCC) in patients with castration resistant metastatic prostate cancer (CRPC) and early intervention with radiotherapy markedly reduces the development of clinical SCC (cSCC). National Institute of Cancer Excellence (NICE) guidance does not recommend spinal MRI and treatment intervention for asymptomatic patients with spinal metastases, but randomised trials to evaluate early diagnostic and intervention strategies were encouraged.

Added value of this study

We did the first multi-centre randomised controlled trial to study the role of screening spinal MRI to detect radiologically defined asymptomatic spinal cord compression (rSCC) in CRPC. We confirmed the reproducibility of a MR imaging epidural spinal cord compression (ESCC) scale. We showed that radiotherapy was effective at preventing progression of rSCC to symptomatic cSCC. However, although the intervention group had a lower risk of developing cSCC than the control group this did not reach statistical significance. Patients with rSCC had a high risk of progression to cSCC at other spinal sites. Although the resources needed for spinal MRI and radiotherapy were higher in the intervention group than control group, there was a decrease in the use of subsequent additional systemic treatments. We were unable to identify predictive factors for the development of rSCC or cSCC.

Implications of all available evidence

Spinal MRI can reliably detect rSCC in CRPC but early rSCC does not usually progress to cSCC in patient groups who have access to contemporary systemic treatment. We recommend that the ESCC scale be introduced into routine clinical practice as it clearly communicates the presence of early rSCC and identifies a high-risk group for subsequent development of cSCC. Close adherence to NICE Guidelines for the early investigation of spinal symptoms is important in reducing neurological disability compared with historical experience. Presently we do not recommend screening spinal MRI in unselected patients with castration resistant metastatic prostate cancer but further research to identify high risk groups is warranted.

SUMMARY (-325/300 words)

Background

Early diagnosis of malignant spinal cord compression (SCC) is crucial as pre-treatment neurologic status is the major determinant of outcome. In metastatic castrate resistant prostate cancer (mCRPC) SCC is a significant cause of disease-related morbidity and mortality. We investigated whether screening for SCC with spinal MRI, with pre-emptive treatment if radiological SCC (rSCC) was detected, reduced incidence of clinical SCC (cSCC) in asymptomatic mCRPC patients with spinal metastasis.

Methods

We did a phase III parallel-group, open-label, randomised controlled superiority trial. CRPC patients aged at least 18 years, performance status 0-2, with spinal metastases with no related back pain or neurological symptoms, no previous SCC and no spinal MRI in previous 12 months were eligible. Participants were randomly allocated (1:1) to control (no MRI) or screening spinal MRI using a minimisation algorithm with a random element (balancing factors: centre, alkaline phosphatase, number of previous systemic treatments, previous spinal treatment). Serious adverse events were monitored in the 24 hours after screening MRI. Participants with screen-detected rSCC were offered pre-emptive treatment (radiotherapy or surgical decompression was recommended) and 6-monthly spinal MRI. The primary endpoint was time to cSCC analysed by intention to treat. The study is registered: ISRCTN74112318. Trial follow-up is complete.

Findings

Between February 26, 2013 and April 25, 2017, we randomly assigned 420 men from 45 UK centres to control (n=210) or screening MRI (n=210). Median age was 74 years (IQR: 68–79); 53% (222/420) had normal alkaline phosphatase; median PSA was 48-0ng/ml (IQR: 17–162). Screening MRI detected rSCC in 61/200 (~~30-531~~) patients with assessable scans; time to cSCC was not significantly improved (hazard ratio: 0.64 (95% CI: 0.37–1.11, gray's test p=0.1492)) at a median follow-up of 22 months (IQR: 13–31). 1-year cSCC rates were ~~6-77~~% (95% CI ~~3-84-10-611~~) and 4-3% (~~2-1-7-78~~) for control and intervention respectively (difference: ~~-2-412%-; % (95% CI -4-23-0-44)~~). No serious adverse events were reported.

Interpretation

Despite the substantial incidence of rSCC, cSCC rate in both groups was low. Routine use of screening MRI and pre-emptive treatment to prevent cSCC is not warranted in asymptomatic CRPC patients with spinal metastasis.

Funding

Cancer Research UK.

Introduction

Malignant spinal cord compression (SCC) and its complications have a profound influence on functional status and quality of life with a resulting increased burden on the health care system.¹ Early diagnosis is crucial as pre-treatment neurologic status is the major determinant influencing outcome. Almost all patients with SCC who are ambulant prior to treatment retain motor function.²⁻⁸

Metastatic castration-resistant prostate cancer (mCRPC) predominantly involves the skeleton, and a significant proportion of disease related morbidity and mortality are attributed to skeletal-related events (SRE). SCC is the most clinically significant SRE¹ and prostate cancer accounts for about 20% of all cases.^{4,8,9} Population based studies indicate that SCC occurs in about 7% of lethal PCa,⁹ although in a systematic review up to 24% of patients with metastatic prostate cancer developed SCC.⁷ In prostate cancer, studies have shown that it is possible to detect early radiological signs of impending SCC (rSCC) in 27% to 32% of asymptomatic patients using spinal MRI.^{10,11} National Institute for Health and Care Excellence (NICE) Guidance⁸ advises that serial MRI to detect SCC should only be performed as part of a randomised controlled trial (RCT) and that neither radiotherapy nor surgery should be used to treat asymptomatic spinal metastases to prevent SCC unless part of an RCT. To address these issues, we did a randomised, phase 3 study to determine the role of screening MRI to detect rSCC with subsequent pre-emptive treatment to sites of rSCC.

Methods

Study design and participants

PROMPTS is a prospective, phase 3, multicenter, parallel-group, RCT undertaken at 45 National Health Service (NHS) hospitals in the UK. The aims were to assess the value of screening spinal MRI in men with mCRPC with bone involvement to detect and treat asymptomatic SCC. The trial was approved by the London Queen Square Multi-centre Research Ethics Committee (12/LO1109), sponsored by The Institute of Cancer Research (ICR), and conducted in accordance with the principles of good clinical practice. The ICR Clinical Trials and Statistics Unit (ICR-CTSU; London, UK) coordinated the study and carried out central statistical data monitoring and all analyses. The study protocol is available (appendix p26).

Eligible patients had a confirmed pathological diagnosis of prostate adenocarcinoma or a clinical diagnosis of prostate cancer with osteoblastic bone metastases and a serum prostate specific antigen level (PSA) >100 ng/dl at diagnosis. Other inclusion criteria included the presence of asymptomatic spinal metastasis, castration-resistant state (defined as PSA > 5 ng/dl and more than 50% rise above nadir during treatment with a luteinizing hormone-releasing hormone analogue or after orchidectomy), life expectancy of 6 months or more, and

ECOG performance status 0-2. The main exclusion criteria were presence of any back pain or neurological symptoms from spinal metastasis, previous spinal MRI within 12 months from trial entry, previous external beam radiotherapy or surgery to treat SCC, and contra-indication for MRI. Patients were recruited by their clinical care teams and provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly allocated in 1:1 ratio to the control group (no MRI) or the interventional group (screening MRI). Allocation was done centrally by ICR-CTSU using a minimisation algorithm incorporating an 80% random element; balancing factors were treatment centre, alkaline phosphatase (ALP) (normal vs raised), number of previous systemic treatments (first-line vs second-line or later), previous spinal surgery or radiotherapy for metastatic disease (yes vs no) and following a protocol amendment in April 2015, CT or PET CT of thorax and abdomen within last six months (yes vs no). Allocation was not masked due to the impracticality of performing sham MRI.

Procedures

Baseline investigations included PSA measurement, full blood count and biochemistry including ALP. Neurological assessment was based on the Frankel scale,¹² which is a 5-point standardised neurological assessment tool after spinal cord injury (appendix p3). Patient reported outcomes (PROs) were with EORTC QLQ C30,¹³ EQ-5D-5L,¹⁴ Brief Pain Inventory (BPI)¹⁵ and Hospital Anxiety and Depression score (HADS).¹⁶

In the intervention group, screening spinal MRI was performed within four weeks of randomisation using a minimum field strength of 1 Tesla with a spinal coil. The whole spine was imaged from the base of skull to the coccyx with sagittal T1 and T2 weighted images. Sagittal images were supplemented with selected axial images through any suspicious areas at the discretion of the radiologist. Scans were reported by the local specialist radiologist using a modified Bilsky scoring system,^{3,6,17} which is a 6-point validated scale for epidural spinal cord compression (ESCC; appendix p4). Each vertebra was individually assessed. rSCC was defined when no neurological symptoms were present in the presence of epidural disease, whereas patients displaying neurological symptoms were deemed to have clinical SCC (cSCC).

If the baseline screening MRI was positive for rSCC, pre-emptive treatment was recommended with radiotherapy or surgical decompression. After treatment, patients had follow-up MRI every six months.

Participants in both groups were followed up at three monthly intervals for the first two years and then at 30 and 36 months, as well as at the time of any cSCC episode. Assessments included neurological status using the Frankel score,¹² PRO, and PSA, as well as new

treatments and all spinal MRI; HADS was repeated at three months only. Serious adverse events were collected for a 24 hour period after the study screening MRI scan using the National Cancer Institute's Common Terminology Criteria for Adverse events (CTCAEv4.0). In the intervention group, adverse events, EQ-5D-5L and BPI were assessed before and after (not BPI) any pre-emptive treatment. All PROs were ~~paper and~~ completed on paper by the patient at their clinic visit. The main outcome of interest was EORTC QLQ-C30 physical functioning. Additional PRO scores reported were; EORTC QLQ C30: functional scales, global health and pain, BPI: Severity, Interference, HADS: anxiety and depression, EQ-5D-5L: Health state today.

If new neurological symptoms suggestive of cSCC or new onset significant back pain developed, spinal MRI was performed ideally within 24 hours in accordance with NICE and local guidelines, regardless of randomised group. All MRI scans leading to a diagnosis of rSCC or cSCC and a minimum 10% random sample of negative baseline scans were centrally reviewed (AS, PR, GH) and iterative feedback given to participating radiologists and oncologists.

The protocol recommended rSCC was treated (pre-emptively) with radiotherapy or surgery and that NICE guidelines⁸ be followed for cSCC. Short courses of high dose corticosteroids (e.g dexamethasone 8-24mgs total dose per day) were permitted. Radiotherapy was to be delivered within one week of rSCC and within 48 hours of cSCC. The recommended radiotherapy dose was 20 Gy given daily in 5 fractions prescribed to at least the mid-point of the spinal cord /cauda equina. Radiotherapy was to be planned by conventional or CT based virtual simulation using MRI information to determine the radiotherapy field level and length which should extend ≥ 1 vertebral level beyond site(s) of rSCC/cSCC.

Outcomes

The primary outcome was time to cSCC, with the time point of primary interest being one year. Participants were considered to have developed cSCC if they had a compromised Frankel score (grade A-D) with supportive radiological findings. If there was diagnostic uncertainty, cases were centrally reviewed (AH/JM) without knowledge of randomisation group using available data from MRI, clinical and PRO and radiotherapy or surgical records. Secondary outcomes were rate of detection of rSCC on screening MRI (intervention group only); one-year incidences and time (from randomisation) to functional neurological deficit (FND) (Frankel score grade A-D) and persistent FND (defined as Frankel score not returning to normal (grade E) after 3 and 6 months); incidence of any SCC (rSCC and cSCC) at one year; overall survival); cost effectiveness; pain; PROs ~~with EORTC QLQ-C30 physical functioning the main outcome of interest. Additional PRO scores reported are; EORTC QLQ C30: functional scales, global health and pain, BPI: Severity, Interference, HADS: anxiety and depression, EQ-5D-5L: Health state today.~~ In light of primary results, cost effectiveness analysis have not been pursued.

Statistical analysis

We estimated a one-year cSCC incidence of 15.6% in the control group based on a baseline rSCC prevalence of 12.9% (calculated as the average rSCC rate reported in asymptomatic patients in retrospective studies^{10,11}), median survival of 19 months¹⁸ and assuming all participants with rSCC and 3.2% of those without rSCC at screening would develop cSCC by one year if untreated.¹⁰ We targeted a hazard ratio (HR) of 0.48, equivalent to a reduction in 1 year cSCC rate to 7.8% in the intervention group. Sample size calculations were based on the log rank test with 5% two sided significance. With 90% power, the original target sample size was 541 patients. In November 2016 the statistical power was reduced to 85% to allow for timely completion of recruitment. The revised sample size of 414 (71 events) was based on uniform accrual over a four year period and a minimum of one-year follow-up for all participants. No adjustment for non-compliance with screening MRI was made.

In February 2015 a formal pre-planned interim analysis, after 54 patients in the intervention group had had their baseline MRI, confirmed the interim pre-stipulated rSCC rate was $\geq 10\%$.

Analyses were by intention to treat. To account for death as a competing risk for outcomes relating to rSCC, cSCC and FND incidence rates were estimated using the cumulative incidence function with Gray's test¹⁹ used to compare randomised groups. Estimates of the intervention effect were made using unadjusted and adjusted sub-distribution models. Baseline covariates included in all adjusted models were balancing factors and, time since development of CRPC, time since start of continuous hormone treatment, ECOG performance status (0,1&2) and PSA. HRs<1 indicate a decreased risk of the event in intervention group compared to the control group. The sub-distribution model for death (in the presence of cSCC) was also fitted to ensure results from the cSCC analysis were not due to differences seen in the numbers of deaths. Cause-specific regression models for cSCC with death as a competing risk, and for death with cSCC as a competing risk were also fitted to provide further comparisons. Patients without cSCC were censored at the date of last follow-up. Patients who died before experiencing cSCC were classified as having a competing event at the date of death.

Incidence of rSCC at screening was calculated using binomial proportions and 95% confidence intervals provided. Logistic regression was used to assess the effects of baseline covariates. To assess non-proportionality of covariates in time-to-event multivariable analysis the time dependency of all pre-specified baseline covariates was considered. Analysis of time to new additional systemic treatment was post hoc; randomised groups were compared using Gray's test. For overall survival, Kaplan-Meier methods were used to estimate rates and unadjusted and adjusted Cox regression models were fitted for intervention effect. For all non-PRO analysis p values <0.05 were considered statistically significant.

The appropriate scoring manuals were used to calculate BPI pain, EORTC QLQ C30 and HADS scores. Cross-sectional analysis was done at each time point up to 24 months using the Mann-Whitney U test, with 12 months being the primary time point of interest. Change from baseline to 12 months was assessed using ANCOVA adjusting for the baseline scores. Plots of residuals vs predicted values were used to assess the constant variance assumption. Missing data (including deaths) were not considered to be missing at random and therefore patterns of missingness were explored. In particular completeness of data by visit period as well as baseline scores with and without paired 12 months scores were observed by randomised group for PRO to assess possible effects of missing data. To account for multiple testing of secondary PROs, only p-values below 0.01 were considered statistically significant.

Analyses were based on a database snapshot taken on April 23 2020, and were done using SAS version 9.4, except for competing risk regression models where STATA version 16 was used. The trial management group was overseen by an independent trial steering committee. Safety and efficacy data were reviewed regularly by an independent data monitoring committee (IDMC). The trial was prospectively registered (ISRCTN74112318).

Role of funding source

The funding source provided peer-reviewed approval for the trial, but had no other role in study design, collection, analysis, interpretation of data, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. VH, CG, and EH also had full access to the data.

Results

Between February 26, 2013, and April 25, 2017, 420 men were recruited from 45 centres in the UK (appendix p5), with 210 patients assigned to each study group (Figure 1). Demographic and clinical characteristics are presented in table 1. Clinical symptoms and signs recorded pre-randomisation were similar between randomised groups (appendix p6). Median follow-up (reverse Kaplan-Meier) was 22 months (IQR: 13-31).

Screening spinal MRI was performed in 201/210 (96%) participants in the intervention group (Figure 1) with a median time from randomisation to scan of 30 days (IQR 15-35). No serious adverse events were reported. Sixty one of 200 (31%) patients with assessable scans had rSCC and a total of 140 individual metastases associated with rSCC identified (median 1 lesion per patient, IQR 1-3). Maximum ESCC scores were 1a: 26/61 (42-63%); 1b: 17/61 (27-928%); 1c: 12/61 (19-720%); 2: 2/61 (3-3%), and 3: 4/61 (6-67%). Sixteen metastases (11-4%) were in the cervical spine, 41 (29-3%) in the upper thoracic spine (T1-T6), 50 (35-736%) in the lower thoracic spine (T7-T12), and 33 (23-624%) in the lumbar spine (Table 2). Central review of scans showed concordance of 92.4% with local radiology assessments (Table 2).

Radiotherapy was given to sites of rSCC in 50/61 (82%) patients (Figure 1), dose was 20 Gray in 5 fractions for 52/57 (91%) treatment sites (appendix p7). Adverse events were uncommon after spinal radiotherapy for rSCC (appendix p8). Grade 1-2 events occurring in $\geq 10\%$ of patients were constipation in 8/50 (16%), back pain in 7/50 (14%). There was one grade 3 AE of chest pain. Corticosteroids were given to 28/61 (46%) of patients (median dose dexamethasone 8 mg (IQR 4-16), median duration 11 days (IQR 7-19)). Protocol defined follow-up MRI was performed in 32/44 (73%) screen-positive patients treated with radiotherapy and alive at 6 months. In these 32 evaluable patients, out of 69 assessable and treated metastases with rSCC, 39 (~~56-55~~57%) had improved ESCC score, 27 (39-~~4~~1%) were stable and 3 (4-~~3~~3%) had progressed (2 cases 1a/b to 1c, 1 case 1c to 3) (Figure 2a, appendix p9). At 12 months, out of 46 assessable and treated sites with rSCC in 21 evaluable patients (58% of 36 patients alive), 37 (80-~~4~~4%) metastatic sites with rSCC had improved ESCC scores, 7 (15-~~2~~2%) were stable and 2 (4-~~3~~3%) had progressed (2 cases 1a/b to 1c) (Figure 2b). A clinical decision was made not to treat 18 sites with rSCC (all ESCC 1a/b, 1c). Of these 12 (~~66-76~~67%) had improved ESCC score and 6 (33-~~3~~3%) were stable, based on 6-month MRI assessment and none had progressed by 12 months (Figure 2a, 2b).

On univariable analysis, covariates associated with rSCC were raised ALP (OR 2.31, 95% CI 1.24-4.28, $p=0.008$) and lnPSA at randomisation (OR 1.50 95% CI 1.19-2.89, $p<0.001$). lnPSA at randomisation remained significant on multivariable analysis (OR 1.49 95% CI 1.15-1.92, $p=0.002$) (appendix p10)). However neither parameter appeared to usefully separate clinical groups (appendix p 11).

In the control group, cumulative incidence of cSCC at 12 and 24 months was ~~6-7~~7% (95% CI ~~3-8~~4-~~10-6~~11, $n=14$) and ~~12-6~~13% (95% CI ~~8-5~~9-~~17-5~~18, $n=26$) and for the intervention group was 4-~~3~~3% (95% CI 2-~~1~~7-~~7~~8, $n=9$) and 9-~~2~~2% (95% CI ~~5-8~~6-~~13-7~~14, $n=19$) respectively ($p=0.12$, Figure 3a). Unadjusted and adjusted sub-distribution models showed no statistically significant intervention effect (unadjusted HR 0.64 (95% CI: 0.37-1.11), $p=0.11$ and adjusted HR 0.62 (0.34-1.19), $p=0.10$) (appendix p13). HR for the development of cSCC calculated using a cause-specific model were similar (unadjusted HR 0.67 (0.38-1.16) $p=0.149$, adjusted HR 0.61 (0.35-1.08) $p=0.09$). Sub-distribution and cause specific models for death with cSCC as competing risk showed no intervention effect. At 12 months, the intervention rSCC screen-positive group had a higher cumulative cSCC incidence than the screen-negative group: 7 cases (~~11-5~~12%) (95% CI 5-~~0~~21-~~0~~0) vs 2 cases 1-~~3~~3% (0-~~2~~4-~~4~~4), $p=0.13$). At 24 months, the cumulative incidence of cSCC increased to 13-~~2~~2% (~~6-1~~23-~~1~~1) in the screen-positive group and ~~7-6~~8% (~~4-0~~12-~~6~~13) in the screen-negative group. The incidence of cSCC was lower in the rSCC screen-negative group compared with the control group ($p=0.04$) (appendix p14). Raised ALP was the only variable found to have a significant association with the development of cSCC, but the number of events is small (appendix p 13)) and ALP groups did not adequately stratify patients for screening.

ESCC scores for the first cSCC event recorded over the duration of the trial were in similar proportion in the two randomised groups with ESCC 1a/1b, 1c and 2/3 scores in 6 (24.0%), 2 (8.0%), and 17 (68.0%) patients in the control group and 2 (11.4%), 4 (22.2%), and 12 (66.7%) patients in the intervention group (10 patients had unknown scores). Frankel scores showed most patients remained ambulant (score D) at the time of cSCC in both groups with scores of A/B, C and D in 1 (3.4%), 6 (18.8%) and 19 (59.4%) control group patients, and in 2 (9.5%), 2 (9.5%), and 9 (42.9%) intervention group patients respectively (14 patients had unknown scores) (appendix p15).

All patients treated for cSCC had initial radiotherapy, one patient had subsequent salvage surgery. Dose was 20 Gray in 5 fractions for 17/36 (47%) sites treated and a further 15 sites received 8 Gray in single fraction (appendix p7). Hospitalisation for SCC was documented for 19/51 (37.3%) patients for a median of 5 days (IQR 4-9, n missing=1) in the control group and for 12/37 (32.4%) patients for a median of 15 days (IQR 4-21, n missing=1) in the intervention group.

Thirty nine patients had assessable Frankel scores at least 6 months after the initial cSCC diagnosis, 4/26 (15.4%) patients in the control group recovered to Frankel score E (no deficit) compared with 3/13 (23.1%) in the intervention group (appendix p15). Time to persistent FND (Frankel score A-D) is shown in figure 3b, with cumulative incidences of 5.7% (95% CI 3.1-9.5%, n=12) and 11.2% (95% CI 7.3-16.0, n=23) in the control group compared with 2.9% (95% CI 1.2-5.8%, n=6) and 7.3% (95% CI 4.3-11.4, n=15) in the intervention group at 1 and 2 years respectively (p=0.07). PROs revealed no significant differences between the randomised groups in any measure (appendix p16-23).

Overall survival was similar in both randomised groups with median survival of 22.2 months (IQR 12.4-32.7) and 22.0 months (IQR 12.4-34.6) for control and intervention groups respectively (p=0.82, figure 3c). Deaths from prostate cancer were documented in 158/174 (90.8%) and 150/172 (87.2%) of the control and intervention groups respectively (appendix p23). On multivariable analysis, covariates associated with overall survival were ALP (HR 1.9, 95% CI 1.5-2.4; p<0.001), ECOG status (HR 1.6, 95% CI 1.2-1.9; p<0.001) and lnPSA (HR 1.3, 95% CI 1.2-1.4; p<0.001).

Analysis of time to new additional systemic treatment was carried out post hoc. New systemic treatments were started more commonly in the control group (figure 4), significant differences were seen for chemotherapy and any new systemic treatment. At 12 months the number of patients that had received chemotherapy or any new systemic treatment was 55 (26%) and 147 (70%) in the control group and 31 (15%) and 113 (54%) in the intervention group (appendix p24). More spinal radiotherapy was used in the intervention than control group. After 12/24 months follow-up, 86/107 courses of radiotherapy had been given in the intervention group; 51 courses for rSCC on screening scans, 27/40 for subsequent r/cSCC and

8/16 for bone pain alone. In the control group 32/43 courses had been given for SCC and 17/19 for bone pain alone. By 24 months, 48 (~~22-923~~%) patients in the control group had received spinal radiotherapy compared with 85 (~~40-541~~%) patients in the intervention group (appendix p24).

Overall, 361 (201 screening, 85 protocol defined and 74 additional) and 98 spinal MRI scans were performed in the 24 months after randomisation in intervention and control groups respectively (appendix p25).

Discussion

We performed the first randomised trial to assess the role of screening²⁰ using spinal MRI to detect and treat rSCC in metastatic prostate cancer and found no statistically significant reduction in the proportion of patients with cSCC at 12 months with a difference between control and intervention groups of -2.41% (95% CI: -4.23-0.11).~~To have clinical value, a screening intervention must be reproducible, adequately sensitive and lead to an effective intervention which is likely to improve patient outcome.~~²⁰ We chose to use a validated ESCC scale, developed by Bilsky and colleagues,^{3,6,17} for assessing rSCC on both screening and additional MRI scans. Although it is not routinely used in the UK, we found that specialist radiologists in the participating centres rapidly adapted to the scoring system with iterative feedback from the central review team. All vertebral levels were scored and levels of rSCC were reliably identified by local and central radiologists as suggested previously.¹⁷

We identified rSCC in 61/200 (31%) of the screening MRI scans. This was similar to the 27-32% reported from previous single institutional experiences although higher than the incidence in asymptomatic patients.^{10,11} Any differences are likely due to patient selection factors varying between historic and contemporary cohorts and MR reporting methods. Seventy percent of screened patients had “early” rSCC graded as ESCC 1a or b, with a further 20% graded 1c and 10% graded 2 or greater. In the screened population, 82% went on to have pre-emptive treatment. Although consideration of surgical options^{2,3,6,21} was encouraged in the protocol, treatment was uniformly with radiotherapy. The protocol standard dose of 20 Gray in 5 fractions was used most commonly which aligns with current practice for treatment of cSCC.^{8,22} The effectiveness of radiotherapy is usually judged clinically according to ambulatory status. We had the additional opportunity to assess response radiologically, and repeat MRI after 6 months showed only 3/69 (~~4-3~~%) of treated metastases had progressed in 2 patients. However, 23 new sites of rSCC had appeared in 8 patients.

Despite the substantial incidence of rSCC, the development of cSCC in both randomised groups was lower than anticipated. Cumulative rates of development of cSCC at 12 months, the primary endpoint of the trial, were ~~6-77~~% and ~~4-3~~% in the intervention and control groups respectively. The rSCC screen-positive subgroup were at particular risk (~~11-512~~% cumulative incidence at 12 months) of the subsequent development of cSCC. In the MRI screen-negative

group, the rate of cSCC was very low at 1-3% at 12 months but then increased to 7-68% at 24 months which is in accordance with previous suggestions of a 12 month “protective window” of a negative spinal MRI from single centre studies.^{10,23} A population based study has suggested a prevalence of 7% of metastatic SCC in mCRPC patients⁹ although single institution estimates have been as high as 24%.^{7,24} Data from more recent trials using the new generation of life-prolonging therapies have reported slightly lower incidences of cSCC of between 3-8%.^{1,25-28} Patients enrolled in the PROMPTS trial had biochemically progressing disease and additional systemic treatments were given as clinically appropriate. Effective systemic treatments reduce both the incidence of skeletal related events, including cSCC^{1,25,28} and are likely to have an impact on the progression of rSCC to cSCC. ~~We noted that in the 7 patients with rSCC and repeat MRI who did not receive pre-emptive treatment, only 2 had progression of rSCC after 6 months and assuming~~ Assuming a similar, but undetected rate of rSCC in the control group compared with the intervention group, it is apparent that the rate of development of cSCC was considerably less than the detection of rSCC. The reduction of use of systemic treatments in the intervention group in the 12 months after randomisation was unexpected but a plausible mechanism might be through the impact of radiotherapy on progression in major sites of bone disease^{29,30}. In particular the use of radiotherapy to treat sites of oligoprogression, arising from resistant sub-clones, may allow the continuation rather than change of systemic treatments²⁹.

The majority of patients with cSCC (28/39, 72%), in the trial remained ambulant with Frankel scores \leq D, with no difference between the randomised groups. The degree of FND appears less than in past reports. Most patients with prostate cancer and SCC have previously been reported as non-ambulant,^{4,5,31}; this has improved in more recent years although the majority of patients still have motor deficits.^{3,7} We suspect the intended strict application of NICE guidelines for immediate assessment of new back pain⁸ and protocol required 3 monthly follow-up for 2 years may have had a favourable impact in both randomised groups. Early detection of cSCC may encourage use of more contemporary treatment techniques to treat spinal metastasis, such as stereotactic body irradiation,^{3,6,30,32,33} that are more effective in achieving local control. However, enthusiasm for early intervention following screening MRI should be tempered by the likelihood of over-treatment.

More imaging and radiotherapy resources were used in the intervention than control group. This can be balanced against less use of new systematic treatments and possible reduction in FND in the intervention group. Refinement in the selection of patients for MRI screening would be helpful. In common with other investigators, we found that performance status, ALP and PSA levels were related to survival.⁷ However, with the exception of ALP, we could not confirm previous observations that biochemical, clinical or pathological parameters were risk factors for the development of cSCC.^{3,7,32} This may be due to the relatively small number of patients developing cSCC as well as the intervention for rSCC. We showed that pre-screening PSA and ALP levels are related to the presence of rSCC but neither co-variate alone

or in combination appeared to usefully stratify the patient population. We did not record data on extent of disease on Technetium (Tc) bone scan. Previous reports suggest that the number of spinal metastases or whole vertebral body involvement identifies high risk groups for the development of cSCC^{7,10,11,24} which might assist patient selection for screening MRI to detect clinically occult SCC.^{10,34} It would be helpful to assess the relationship of extent of spinal disease on MR and other imaging modalities with rSCC and cSCC and also whether extent of spinal disease at the time of first development of bone metastases or at the time of development of mCRPC might assist in stratification of patients for screening MRI.

Limitations of the trial include the non-blinded screening intervention allocation and the emphasis on patient and clinical staff appreciation of cSCC which although in line with NICE Guidelines⁸ may have led to earlier detection of cSCC than in usual clinical practice. With fewer than expected events the study is likely to have been underpowered for the primary endpoint. Any assessment of the impact of radiotherapy treatment intervention is confounded by the use of additional systemic treatment options but these are “standard of care” for mCRPC and included presently available life-prolonging options.^{1,14,25,27,28} A pragmatic decision was made to use the short Frankel instrument to assess FND in oncology clinics rather than more detailed neurological assessments. Data completeness reduced with duration of follow-up as might be anticipated in an increasingly frail population but was similar in the randomised groups. A full cost effectiveness analysis is outside the scope of this report. It would need linkage to Hospital Episodes Statistics data for robustness and ideally include a contemporary non-trial cohort with cSCC for comparison.

In summary, the trial demonstrated the reproducibility of the ESCC scale and we recommend its widespread adoption in oncology practice.⁶ We found no statistically significant differences in incidence of cSCC or persistent FND between the MRI screened intervention and control groups. Severity of cSCC judged by Frankel scores were similar in the randomised groups although lower than in previous reports. MRI screen-detected early rSCC does not always progress to cSCC with contemporary systemic management of CRPC and observation may be reasonable for ESCC grade 1a/b rSCC. However, particular vigilance is recommended for these patients with a low threshold for recommending spinal MRI if any new back pain manifests as they are at substantial risk of developing new sites of cSCC. Further efforts to better identify patients at high risk for rSCC and cSCC are warranted to refine selection of groups for screening spinal MR. The low rates of neurological impairment suggest that patients in both intervention and control groups may have gained benefit from trial entry and emphasise the importance of the early detection and management of cSCC in line with NICE guidelines.⁸

Total word count: ~~4619~~4646

Acknowledgements

PROMPTS was funded by Cancer Research UK (CRUK/11/053; A13749, C1491/A15955 C1491/A25351, C33589/A28284, A19727, C46/A10588, C33589/A19727). We acknowledge support from the National Institute for Health Research (NIHR) Cancer Research Network. This project represents independent research supported by the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. We thank the patients and all investigators and research support staff at the participating centres, and members of the Trial Management Group, Independent Data Monitoring Committee and Trial Steering Committee.

Contributors

DD was the PROMPTS Chief Investigator until August 2020 and was succeeded by AS; EH is the methodological lead. DD and EH led study design and with AHe, AM and RV acquired funding for the trial. DD, EH, VH and CG ~~had access~~[accessed](#) and verified the data. EH and CG oversaw statistical analysis performed by VH. CC contributed to study design and provided senior trial management oversight. SH conducted central study management at ICR-CTSU. DD, GHor, NS, GHou, SG, AHe, IP, HP, SB, RW, AR, OD, KL, JG and JW were involved in recruitment and treatment of participants. DD, VH, GHou, NS, PR, GHor, AHe, SG, RV, CC, SH, AM, MM, CG, AS and EH are members of the PROMPTS Trial Management Group which contributed to study design, was responsible for oversight throughout the trial and contributed to data interpretation. AHi also contributed to data interpretation. DD, VH, AHi, AS and EH led manuscript writing; all other authors contributed to and reviewed the manuscript. [All authors had access to data reported in this study.](#)

Declaration of interests

EH reports grants from Cancer Research UK, during the conduct of the study and outside the submitted work reports: grants and non-financial support from Astra Zeneca and Bayer, and grants from Accuray Inc, Varian Medical Systems Inc., Janssen-Cilag, Roche Products Ltd, Merck Sharp & Dohme and Pharma Limited (Sanofi). VH reports grants from Cancer Research UK, during the conduct of the study. GHor reports speaker fees from Janssen outside the submitted work. CP reports speaker fees from Bayer and Janssen; advisory board fees from AAA , Clarity Pharmaceuticals, Myovant, ITM Radiopharma and Janssen advisory board membership and Bayer education steering committee membership, outside the submitted work. DD reports grants from Cancer Research UK, during the conduct of the study and National Institute for Health Research Biomedical Research Centre grants and he has a patent (EP1933709B1), outside the submitted work. AS reports NIHR BRC funding to The Royal Marsden Hospital, speaker fees from Pfizer and past president and on executive board for International Cancer Imaging Society without payment, outside the submitted work. MM reports participation on Data Monitoring Board/Advisory Board for Endocyte and Clovis, outside the submitted work. AHi, GH, NS, PR, GHou, AHe, SG, RV, CC, SH, AM, IP, HP, SB, RW, AR, OD, KL, JG, JW, JM and CG declare no competing interests.

Data sharing

De-identified data will be made available to other researchers on request, subject to approval of a formal data access request in accordance with the ICR-CTSU data and sample access policy. Trial documentation including the protocol are available on request by contacting prompts-icrctsu@icr.ac.uk. The ICR-CTSU supports the wider dissemination of information from the research it does, and increased cooperation between investigators. Trial data is collected, managed, stored, shared, and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity, and utility of the data. Formal requests for data sharing are considered in line with the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and intellectual property. Requests are reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is allowed if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Trial Steering Committee as required. Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymising identifiable patient data. Additionally all indirect identifiers that might lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines. Additional documents might be shared if approved by the TMG and Trial Steering Committee (e.g., statistical analysis plan and informed consent form).

References

1. Saad F, Ivanescu C, Phung D, Loria Y, Abhyankar S, Beer TM, et al. Skeletal-related events significantly impact health-related quality of life in metastatic castration-resistant prostate cancer: data from PREVAIL and AFFIRM trials. *Prostate Cancer and Prostatic diseases*. 2017;20(1):110-6.
2. Al-Qurainy R, Collis E. Metastatic spinal cord compression: diagnosis and management. *BMJ*. 2016;353.
3. Lawton AJ, Lee KA, Cheville AL, Ferrone ML, Rades D, Balboni TA, et al. Assessment and management of patients with metastatic spinal cord compression: a multidisciplinary review. *Journal of Clinical Oncology*. 2019;37(1):61-71.
4. Levack P, Graham J, Collie D, Grant R, Kidd J, Kunkler I, et al. Don't wait for a sensory level—listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clinical Oncology*. 2002;14(6):472-80.
5. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *The Journal of Urology*. 2006;175(2):480-.
6. Spratt DE, Beeler WH, de Moraes FY, Rhines LD, Gemmete JJ, Chaudhary N, et al. An integrated multidisciplinary algorithm for the management of spinal metastases: an International Spine Oncology Consortium report. *The Lancet Oncology*. 2017;18(12):e720-e30.
7. Sutcliffe P, Connock M, Shyangdan D, Court R, Kandala N, Clarke A. A systematic review of evidence on malignant spinal metastases: natural history and technologies for identifying patients at high risk of vertebral fracture and spinal cord compression. *Health Technology Assessment (Winchester, England)*. 2013;17(42):1.
8. NICE. Metastatic spinal cord compression in adults: risk assessment, diagnosis and management 2008 [Available from: <https://www.nice.org.uk/guidance/cg75>].
9. Loblaw D, Laperriere N, Mackillop W. A population-based study of malignant spinal cord compression in Ontario. *Clinical Oncology*. 2003;15(4):211-7.
10. Bayley A, Milosevic M, Blend R, Logue J, Gospodarowicz M, Boxen I, et al. A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 2001;92(2):303-10.
11. Venkitaraman R, Sohaib S, Barbachano Y, Parker C, Khoo V, Huddart R, et al. Detection of occult spinal cord compression with magnetic resonance imaging of the spine. *Clinical Oncology*. 2007;19(7):528-31.
12. Frankel H, Hancock D, Hyslop G, Melzak J, Michaelis L, Ungar G, et al. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. *Spinal Cord*. 1969;7(3):179-92.
13. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, Kaasa S. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *JNCI: Journal of the National Cancer Institute*. 1993 Mar 3;85(5):365-76. (2021). "The EORTC QLQ-C30." 2021, from <https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf>.

14. ~~Group TE. EuroQol-a new facility for the measurement of health-related quality of life. Health policy. 1990 Dec 1;16(3):199-208. Reenen MV, Janssen B. EQ 5D-5L User Guide. Basic information on how to use the EQ 5D-5L instrument. EuroQol Res Found. 2015;1:1-20.~~
15. ~~BPI: Poquet N, Lin C. The brief pain inventory (BPI). Journal of physiotherapy. 2015 Aug 21;62(1):52. (1991). "The Brief Pain Inventory." Retrieved 12 Aug 2021, 2021, from https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.~~
16. ~~HADS: Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica. 1983 Jun;67(6):361-70. Montgomery SA, Åsberg MA. A new depression scale designed to be sensitive to change. The British Journal of Psychiatry. 1979 Apr;134(4):382-9~~
17. Bilsky MH, Laufer I, Fournay DR, Groff M, Schmidt MH, Varga PP, et al. Reliability analysis of the epidural spinal cord compression scale. Journal of Neurosurgery: Spine. 2010;13(3):324-8.
18. Tannock IF, De Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. New England Journal of Medicine. 2004 Oct 7;351(15):1502-12.
19. 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.
20. Institute NC. PDQ® Screening and Prevention Editorial Board. PDQ Cancer Screening Overview. Bethesda, MD 2021 [Available from: <https://www.cancer.gov/about-cancer/screening/hp-screening-overview-pdq>].
21. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. The Lancet. 2005;366(9486):643-8.
22. Hoskin PJ, Hopkins K, Misra V, Holt T, McMenemin R, Dubois D, et al. Effect of single-fraction vs multifraction radiotherapy on ambulatory status among patients with spinal canal compression from metastatic cancer: the SCORAD randomized clinical trial. JAMA. 2019;322(21):2084-94.
23. Venkitaraman R, Sohaib S, Barbachano Y, Parker C, Huddart R, Horwich A, et al. Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer. Clinical Oncology. 2010;22(2):147-52.
24. Soerdjbalie-Maikoe V, Pelger RC, à Nijeholt GAL, Arndt J-W, Zwinderman AH, Bril H, et al. Bone scintigraphy predicts the risk of spinal cord compression in hormone-refractory prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2004;31(7):958-63.
25. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. New England Journal of Medicine. 2019;381(26):2506-18.
26. Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. The Lancet. 2011;377(9768):813-22.
27. Logothetis CJ, Basch E, Molina A, Fizazi K, North SA, Chi KN, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and

- skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *The Lancet Oncology*. 2012;13(12):1210-7.
28. Parker C, Nilsson S, Heinrich D, Helle SI, O'sullivan J, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *New England Journal of Medicine*. 2013;369(3):213-23.
 29. Patel P, Palma D, McDonald F, Tree A. The dandelion dilemma revisited for oligoprogression: Treat the whole lawn or weed selectively? *Clinical Oncology*. 2019;31(12):824-33.
 30. van der Velden JM, van der Linden YM. Spinal stereotactic radiotherapy for painful spinal metastasis. *The Lancet Oncology*. 2021;22(7):901-3.
 31. Husband D. Malignant spinal cord compression: prospective study of delays in referral and treatment. *Bmj*. 1998;317(7150):18-21.
 32. Ropper AE, Ropper AH. Acute spinal cord compression. *New England Journal of Medicine*. 2017;376(14):1358-69.
 33. Sahgal A, Myrehaug SD, Siva S, Masucci GL, Maralani PJ, Brundage M, Butler J, Chow E, Fehlings MG, Foote M, Gabos Z. Stereotactic body radiotherapy versus conventional external beam radiotherapy in patients with painful spinal metastases: an open-label, multicentre, randomised, controlled, phase 2/3 trial. *The Lancet Oncology*. 2021 Jun 11.
 34. Gillessen S, Omlin A, Attard G, De Bono JS, Efstathiou E, Fizazi K, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. *Annals of Oncology*. 2015;26(8):1589-604.

FIGURE legends

Figure 1: Trial profile

Figure 2: Epidural Spinal Cord Compression (ESCC) vertebra levels scores at screening and follow-up spinal MRI scans at 6 months (panel A) and 12 months (panel B) in patients in the intervention group with rSCC on screening MRI managed with or without spinal radiotherapy.

Legend

Number of patients in circles; white circles indicate radiotherapy given; grey circles indicate radiotherapy not given.

Points on diagonal line represent no change in ESCC score; points above diagonal line represent improvement in maximum ESCC score. Radiotherapy was given to vertebra adjacent to sites of rSCC so that ESCC scores 0 and 9 could increase to $\geq 1a$ on follow-up.

Figure 3. Cumulative incidence and Kaplan-Meier plots

Legend

Cumulative incidence of clinical spinal cord compression (cSCC, panel A), persistent neurological functional deficit (panel B) and, Kaplan-Meier plot of overall survival (panel C).

Figure 4. Time to first additional post randomisation systemic anti-cancer treatment

Legend: Death treated as a competing risk; A) new hormone therapy, B) new chemotherapy, C) new radioisotope therapy, D) any new systemic treatment.

<u>Editor's comments:</u>	author response	changes made (additional text is underlined)	page (para)
1. Editorial comment 4d: thank you for adding symbols to denote agreement/disagreement. As do not allow shading or bolding in tables, please remove the grey shading and change the bold values to normal.	Bold and shading has been removed		table 2
2. Collaborators list: Would you like to list the names of the PROMPTS investigators on PubMed? If so, please upload with your revision a separate Word document with a list of names of the study group members presented as a two-column table. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to appear on PubMed. The table will not be included in the paper itself – it's simply used to make sure that PubMed adds the names correctly. **We will not make changes to the collaborator list after publication, so please ensure names are spelled correctly and first names and surnames are in the correct columns**.	A separate document with PROMPTS investigators has been uploaded.		
3. Summary – Methods: please briefly describe what pre-emptive treatment patients were given.	Added. And the word pre-emptively has been added to description of rSCC/cSCC treatment to emphasis this refers to treatment for rSCC found after screening MRI as well as subsequent rSCC diagnosis.	Participants with screen-detected rSCC were offered pre-emptive treatment (<u>radiotherapy or surgical decompression was recommended</u>) and 6-monthly spinal MRI.	P3 (2)
4. Summary – Methods: please add a sentence to describe that serious adverse events were monitored in the 24 hours after MRI.	added	<u>Serious adverse events were monitored in the 24 hours after screening MRI.</u>	P3 (2)
5. Summary – Findings: thank you for clarifying that no serious adverse events were reported within 24 hours of MRI. Please add a statement to that effect in the Summary – Findings section.	added	<u>No serious adverse events were reported.</u>	P3 (3)
6. Methods – Procedures: for the PRO questionnaires, please cite references here in the Methods to show their validity.	PRO citations have been update to ones showing their validity		P5 (3)
7. Methods – Procedures: please move the information on the specific PRO domains assessed from the Outcomes section to the Procedures section.	This has been moved		P6 (1)
8. Methods – Statistical analysis: please ensure that you have included a statement to say that for all non-PRO analysis, you used p<0.05 as a significance threshold.	added	<u>For all non-PRO analysis p values <0.05 were were considered statistically significant.</u>	P7 (4)

<u>Editor's comments:</u>	author response	changes made (additional text is underlined)	page (para)
9. Methods – Statistical analysis: thank you for clarifying that analysis of time to new additional systemic treatment was done post hoc. Please also state in the Results section that this was analysed post hoc.		<u>Analysis of time to new additional systemic treatment was carried out post hoc.</u>	P10 (5)
10. Results: where the denominator is less than 1000, please round percentages to the nearest whole number (throughout text, tables, and figures).	The manuscript text, the tables and figures have been update, including the supplementary material. Note table 2 presents the central review of MRI were the denominator is >1000 therefore % associated with this have been left as 1 decimal place and corresponding data in text.		
11. Figures 3 and 4: thank you for providing numbers at risk (censored).			
a. Please remove the cumulative and incident number of events from the graphs.	These have been removed for all time to event graphs.		Fig3, fig4 and appendix fig
b. Please add HR (95% CIs) to each graph as appropriate.	Sub-distribution unadjusted HR (95% CI and p-values) have been added to cSCC (fig3a) and Cox regression unadjusted HR (95% CI and p-values) to fig 3c. Gray's test has been kept in fig 3a and the log rank test in fig3c as these are the primary test statistics for these analysis. Parametric model fitting was not carried out for persistent neurological deficit (fig 3b) and time to new systemic treatment (fig4 a,b,c and d) and therefore no hazard ratio's are included in these graphs and just the the relevant Gray's test statistic are included		Fig3a and fig3c
12. Discussion: The Discussion should start with a summary of the main findings of this study. Please revise.	We have replaced the first sentence in the discussion with a sentence that summarises the main findings at the start. In addition some other wording has been removed/changed to improve clarity.	To have clinical value, a screening intervention must be reproducible, adequately sensitive and lead to an effective intervention which is likely to improve patient outcome.20 We performed the first randomised trial to assess the role of screening 20 using spinal MRI to detect and treat rSCC in metastatic prostate cancer and found no statistically significant reduction in the proportion of patients with cSCC at 12 months with a difference between	P11(3)

<u>Editor's comments:</u>	author response	changes made (additional text is underlined)	page (para)
		<p><u>control and intervention groups of -2.41% (95% CI: -4.23–0.11).</u></p> <p>We noted that in the 7 patients with rSCC and repeat MRI who did not receive pre-emptive treatment, only 2 had progression of rSCC after 6 months and Assuming a similar, but undetected rate of rSCC in the control group <u>as compared with</u> the intervention group, it is apparent that the rate of development of cSCC was considerably less than the detection of rSCC</p>	P12(1)
13. Author statement forms: The forms for Graeme Houston and Philip Rich were not signed. Please provide completed, signed forms for these two authors with your revision.	We have been unable to contact Graeme Houston, we will continue to pursue this outstanding signed author's statement. We have include one signed by Philip Rich.		
14. Contributors: As of Sept 21, 2020, all authors must have access to all the data reported in the study – please confirm this in the Contributors section.	This has been added to the contributors section	<u>All authors had access to data reported in this study</u>	P14 (20

TITLE: Results of a phase III randomised trial of observation versus screening spinal MRI and pre-emptive treatment for spinal cord compression in castrate resistant prostate cancer patients with spinal metastases: the PROMPTS trial.

Table 1. Baseline characteristics

	Control (n=210)	Intervention (n=210)
Age at randomisation, years (median (IQR))	74.3 (68.0, 79.3)	74.2 (68.5, 79.3)
Time from initial diagnosis to randomisation ¹ , years (median (IQR))	4.4 (2.4, 8)	4.2 (2.4, 7.5)
Time from CRPC diagnosis to randomisation, years (median (IQR))	1.1 (0.3, 2.7)	0.81 (0.3, 1.7)
Primary tumour stage at diagnosis		
T1 - T2	45 (21%)	40 (19%)
T3 - T4	126 (60%)	134 (64%)
TX	35 (17%)	30 (14%)
Unknown	4 (2%)	6 (3%)
Metastatic disease at diagnosis	130 (62%)	124 (59%)
Biopsy at initial diagnosis	161 (77%)	170 (81%)
Gleason score at diagnosis ²		
≤6	15 (9%)	11 (6%)
7	51 (32%)	50 (29%)
≥8	86 (54%)	96 (56%)
Unknown	9 (6%)	13 (8%)
Serum PSA, ng/ml:within 3 weeks of randomisation ³ (median (IQR))	62 (20, 187)	40 (15, 120)
Alkaline phosphatase, U/L (median (IQR))	132 (93, 248)	132 (88, 226)
Alkaline phosphatase, U/L ³ (median (IQR))		
Normal	111 (53%)	111 (53%)
Raised	99 (47%)	99 (47%)
ECOG performance status		
0	116 (55%)	116 (55%)
1	85 (41%)	83 (40%)
2	9 (4%)	11 (5%)
Sites of metastatic disease at randomisation		
Bone	210 (100%)	209 ⁴ (99.5%)
Lymph nodes	45 (21%)	39 (19%)
Other	6 (3%)	6 (3%)
Treatments pre-randomisation		
Prostatectomy	13 (6%)	17 (8%)
Prostate radiotherapy	59 (28%)	55 (26%)
Initial first line hormone treatment		
LHRH analogues	174 (83%)	179 (85%)
Anti androgen monotherapy	18 (9%)	11 (5%)
Maximal androgen blockade	14 (7%)	19 (9%)
Orchidectomy	1 (<1%)	0 (0%)
Unknown	3 (1%)	1 (<1%)
Number of second line systemic treatments ³		

0	7 (3%)	8 (4%)
1	50 (24%)	38 (18%)
2-3	83 (40%)	101 (48%)
4 or more	70 (33%)	63 (30%)
Treatments before randomisation		
Second-generation endocrine therapy ⁵	93 (44%)	87 (41%)
Chemotherapy	66 (31%)	57 (27%)
Bone-protecting agent	13 (6%)	20 (10%)
Radioisotope therapy	7 (3%)	6 (3%)
Previous spinal radiotherapy and/or surgical procedure for metastatic disease ³	16 (8%)	14 (7%)
Symptoms (CTCAE) at randomisation ⁶		
Back pain (all grade 1 or 2)	31 (15%)	42 (20%)
Urinary incontinence (grade 1 to 3)	9 (4%)	16 (8%)
Urinary retention (grade 1 to 3)	8 (4%)	11 (5%)
Ataxia (all grade 1)	1 (<1%)	2 (1%)
Parasthesia (all grade 1 or 2)	10 (5%)	8 (4%)
Degenerative spinal and neuro-muscular disorders	20 (10%)	20 (10%)
Previous spinal surgery for non-malignant disease	3 (1%)	1 (<1%)
CT or PET CT scan of trunk within 6 months of randomisation ^{3,7}	64 (30%)	62 (30%)
<p>Data are n (%) or median (IQR). CRPC=castrate resistant prostate cancer. PSA=prostate specific antigen. LHRH=luteinizing hormone-releasing hormone analogue. ECOG=Eastern Cooperative Oncology Group. CTCAE=Common toxicity criteria for adverse events.</p> <p>1. One control group patient has data missing</p> <p>2. Denominator is number with biopsy at diagnosis</p> <p>3. Balancing factor at randomisation</p> <p>4. One patient had no demonstrable bone metastases.</p> <p>5. Abiraterone, Enzalutamide</p> <p>6. Detailed tabulation by grade in Supplementary material Table 2</p> <p>7. Permitted by protocol amendment (approved 08/04/2015)</p>		

Table 2. Sites of radiological spinal cord compression (rSCC) and local and centrally reviewed epidural spinal cord compression (ESCC) scores

	Local centre ESCC score						
	0/9 (n (%))	1a n (%)	1b n (%)	1c n (%)	2 n (%)	3 n (%)	Total n (%)
Site(s) of rSCC for screen positive patients							
Any ESCC^a score 1a-3							
Cervical spine C1-C7	411	4 (3%)	9 (6%)	2 (1%)	1 (1%)	0 (0%)	16 (11%)
Thoracic Spine Upper T1-6	325	24 (17%)	7 (5%)	5 (4%)	3 (2%)	2 (1%)	41 (29%)
Thoracic Spine Lower T7-12	316	30 (21%)	15 (11%)	3 (2%)	0 (0%)	2 (1%)	50 (36%)
Lumbar Spine L1-5	272	10 (7%)	16 (11%)	6 (4%)	0 (0%)	1 (1%)	33 (24%)
Total	1324	68 (49%)	47 (34%)	16 (11%)	4 (3%)	5 (4%)	140 (100%)
Site(s) of maximum ESCC score^b							
Cervical spine C1-C7	0 (0%)	0 (0%)	4 (6%)	2 (3%)	1 (2%)	0 (0%)	7 (11%)
Thoracic Spine Upper T1-6	0 (0%)	11 (16%)	2 (3%)	4 (6%)	1 (2%)	2 (30%)	20 (30%)
Thoracic Spine Lower T7-12	0 (0%)	14 (21%)	7 (11%)	3 (5%)	0 (0%)	1 (2%)	25 (37%)
Lumbar Spine L1-5	0 (0%)	6 (9%)	5 (8%)	3 (5%)	0 (00%)	1 (2%)	15 (22%)
Total	0 (0%)	31 (46%)	18 (27%)	12 (18%)	2 (3%)	4 (6%)	67 (100%)
Central review							
ESCC score for individual vertebra							
9	924 (44.9%)*	1 (0.0%) [†]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	925 (44.9%)
0	991 (48.1%)*	17 (0.8%) [†]	5 (0.2%) [†]	2 (0.1%) [†]	0 (0.0%)	0 (0.0%)	1015 (49.3%)
1a	6 (0.3%) [†]	48 (2.3%)*	5 (0.2%) [†]	0 (0.0%)	1 (0.0%) [†]	0 (0.0%)	60 (2.9%)
1b	2 (0.1%) [†]	1 (0.0%) [†]	32 (1.6%)*	4 (0.2%) [†]	0 (0.0%)	0 (0.0%)	39 (1.9%)
1c	4 (0.2%) [†]	0 (0.0%)	4 (0.2%) [†]	4 (0.2%)*	0 (0.0%)	0 (0.0%)	12 (0.6%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%) [†]	3 (0.1%)*	2 (0.1%) [†]	6 (0.3%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.1%)*	3 (0.1%)
Total	1927 (93.5%)	67 (3.3%)	46 (2.2%)	11 (0.5%)	4 (0.2%)	5 (0.2%)	2060 ^c (100.0%)
a: ESCC scoring system (Bilsky score). 9= No bone metastasis (additional score for PROMPTS trial), 0= Metastatic bone disease without epidural impingement, 1a= Epidural impingement without deformation of the thecal sac, 1b= Deformation of the thecal sac, 1c= Deformation of the thecal sac with spinal cord abutment, but without cord compression, 2= Spinal cord compression but with cerebrospinal fluid (CSF) visible around the cord, 3= Spinal cord compression, no CSF visible around the cord.							
b: 5 patients had multiple sites of rSCC with their maximum ESCC score in more than 1 spinal region							
c: Total number patients reviewed was 87, for local review 1 patient had no score for 23 out of 24 vertebra, for central review 1 patient had no score for 5 out of 24 vertebra							
*show agreement and [†] disparities between interpretation of MRI scans comparing central review and local assessments							

Figure 1 Trial profile

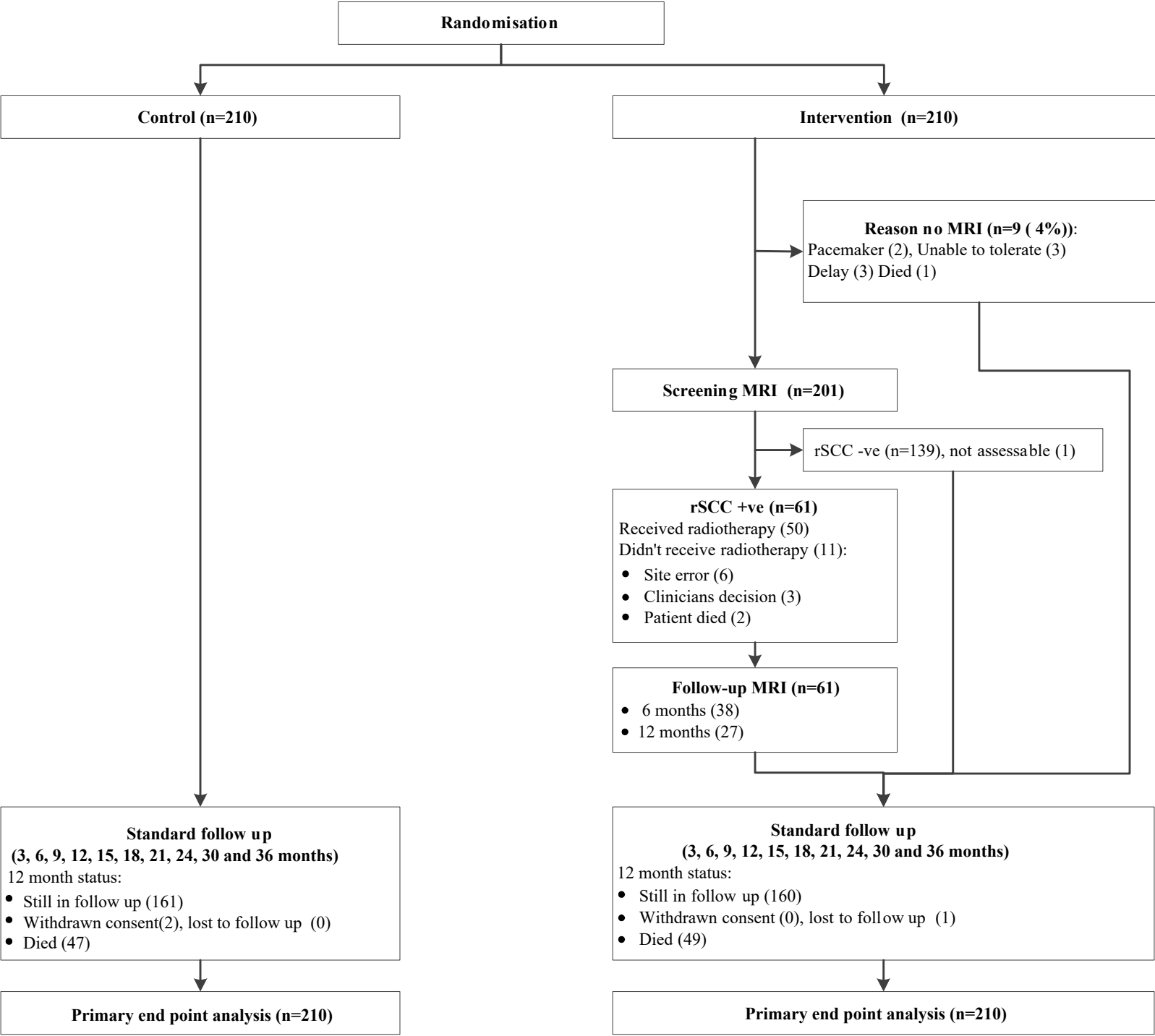


Figure 2. ESCC bubble plot

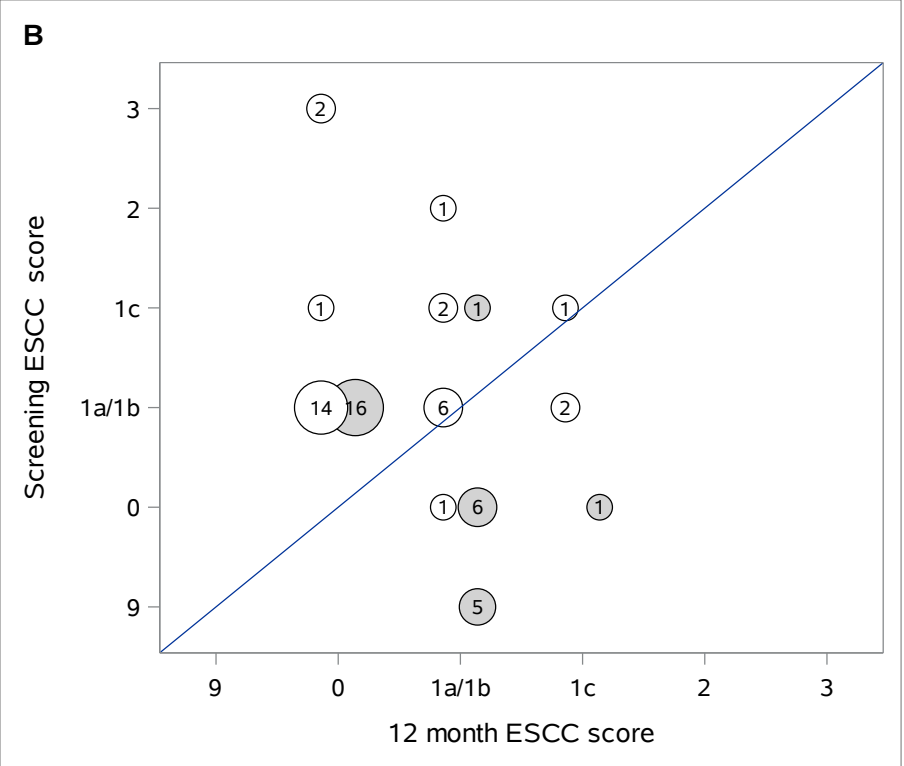
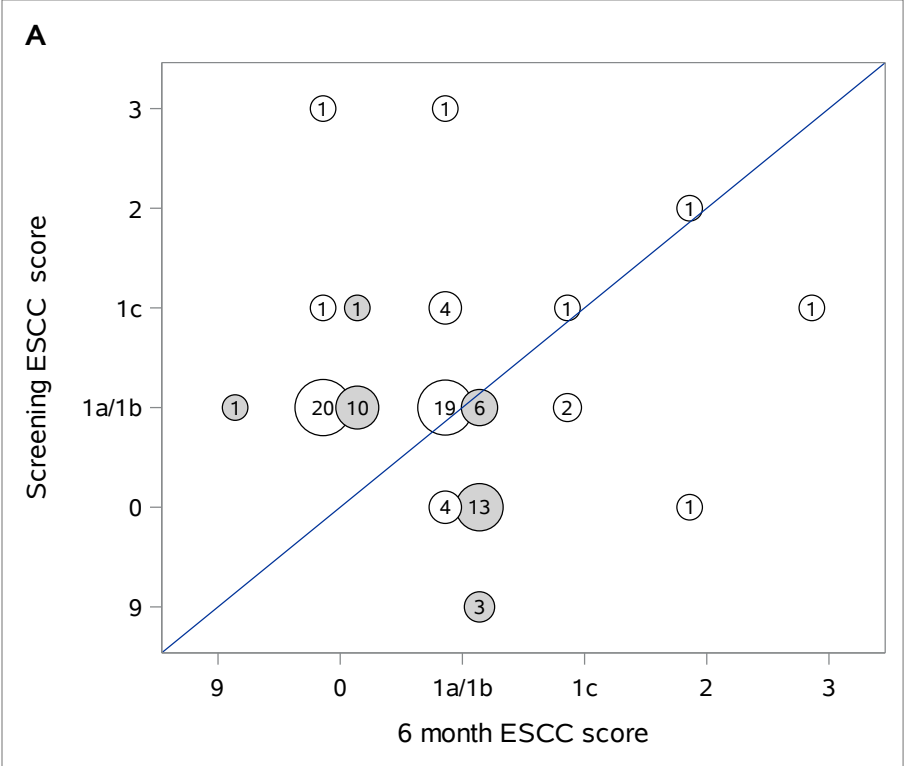


Figure 3 SCC pNFD OS

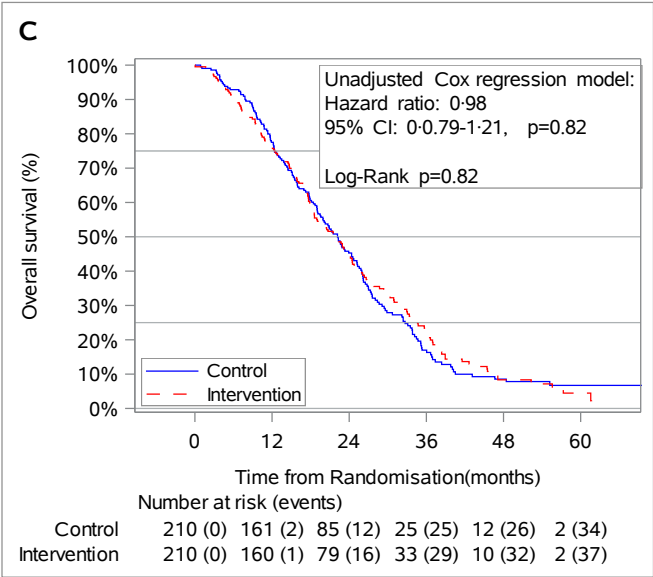
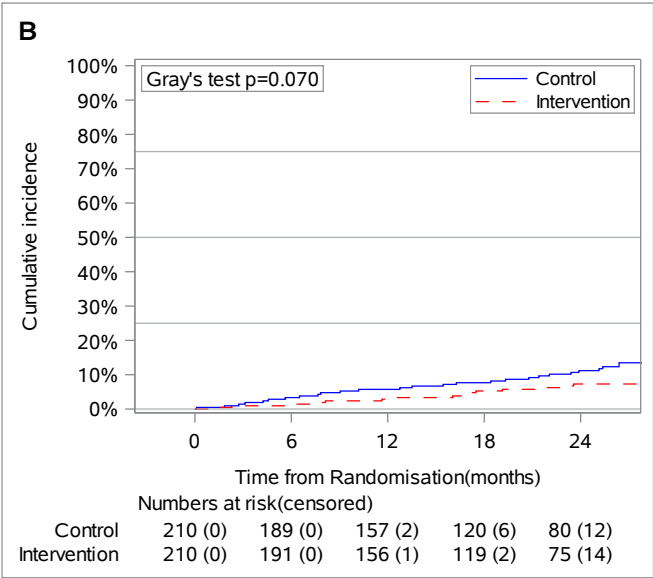
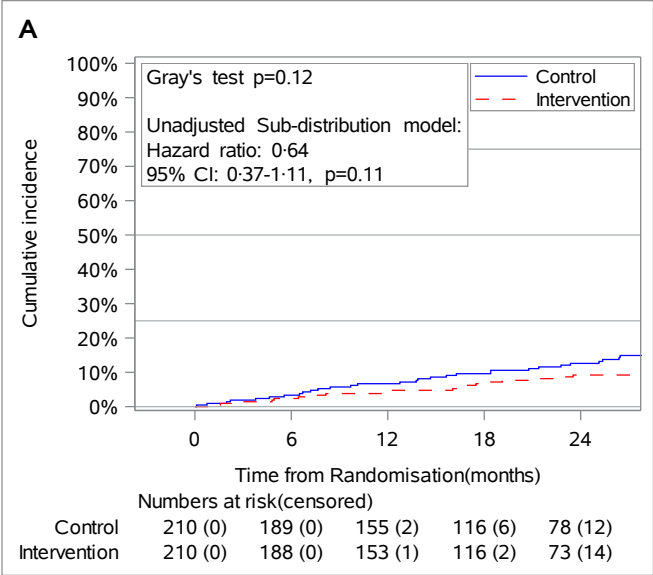
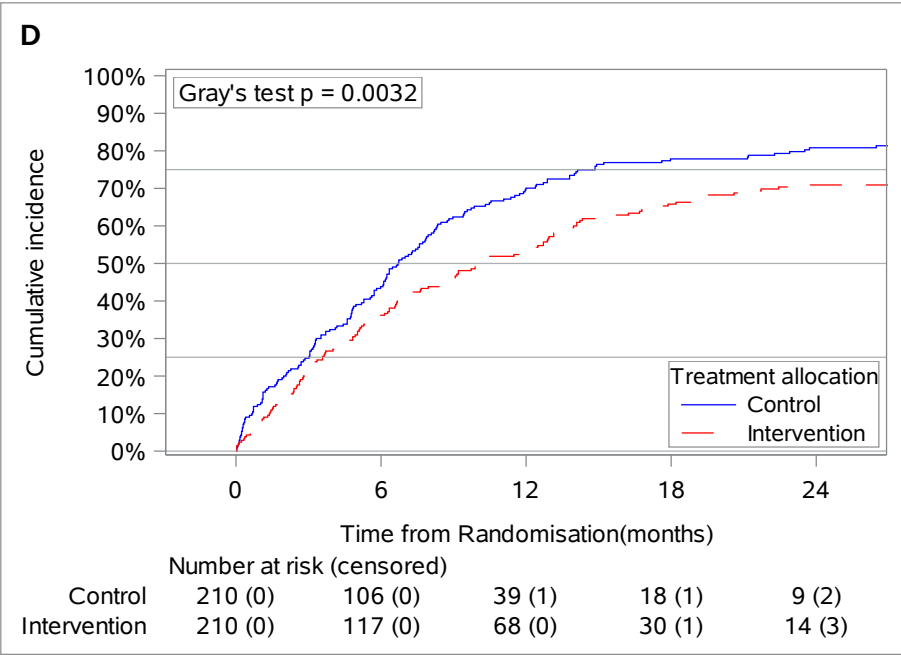
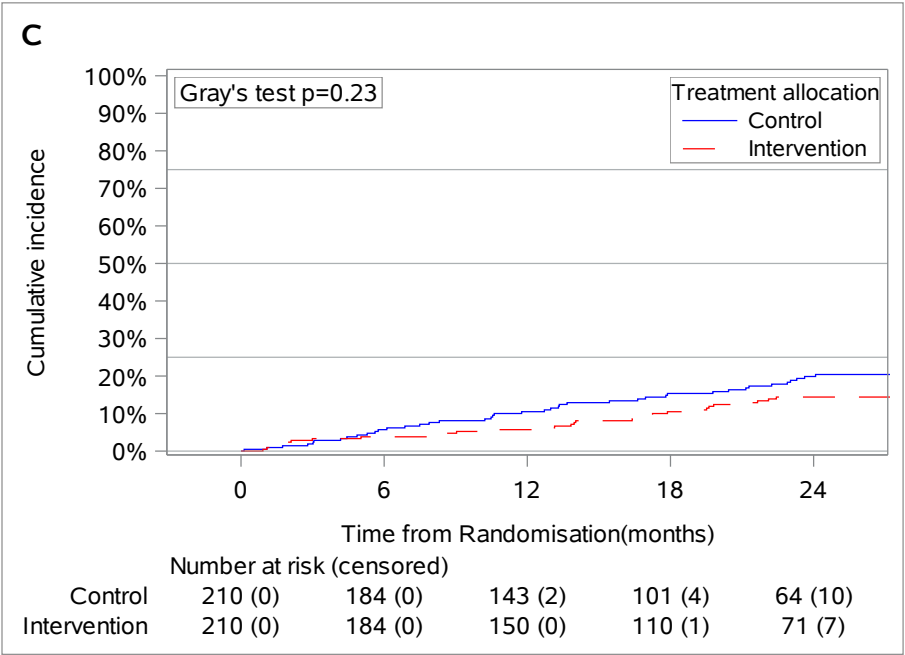
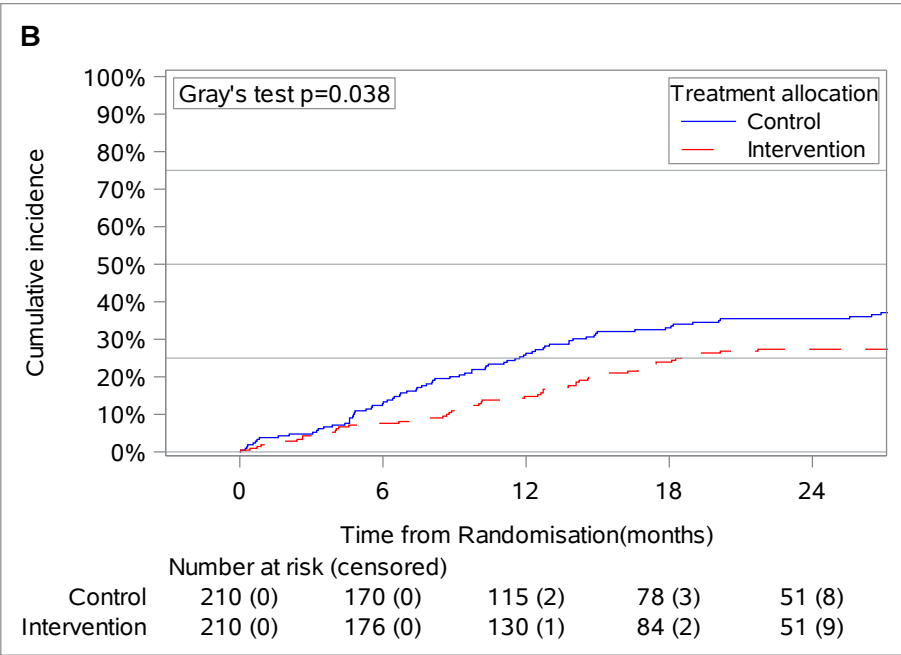
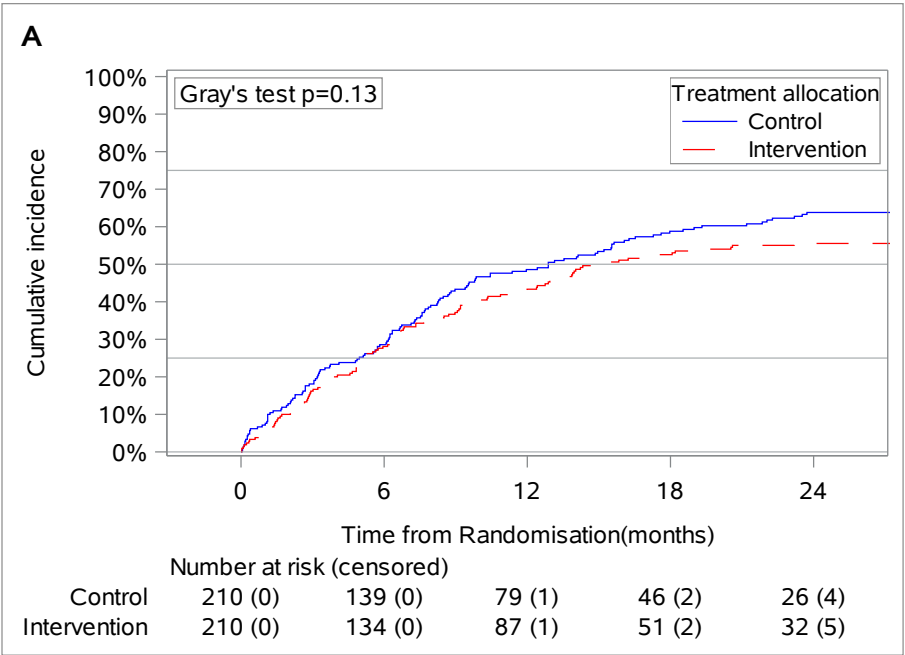
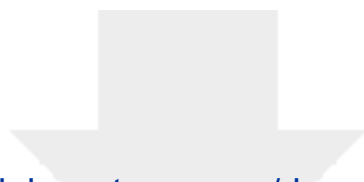


Figure 4 Time to trt

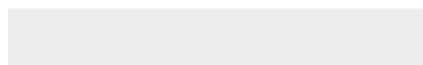




[Click here to access/download](#)

Necessary Additional Data

PROMPTS investigators v1.0 09Feb2022.docx





[Click here to access/download](#)

Necessary Additional Data

PROMPTS Suppl material with protocol revised v3.1
08Feb2022.pdf



A Prospective Randomised Phase III Study of Observation Versus Screening MRI And Pre-Emptive Treatment in Castrate Resistant Prostate Cancer Patients With Spinal Metastasis

PROMPTS

Chief Investigator:	Professor David Dearnaley
Sponsor:	The Institute of Cancer Research
Approval:	Clinical Trials Advisory & Awards Committee (CTAAC)
Funders:	Cancer Research UK
Coordinating Trials Unit:	ICR Clinical Trials and Statistics Unit (ICR-CTSU) The Institute of Cancer Research

PROTOCOL VERSION 7.0 29 November 2016

ICR-CTSU Protocol Number:	ICR-CTSU/2012/10035
Main REC Reference Number:	12/LO/1109
ISRCTN:	ISRCTN74112318
Funder's Reference Number:	CRUK/11/053

The PROMPTS trial has been scientifically approved by
Cancer Research UK's Clinical Trials Advisory & Awards Committee (CTAAC)

The PROMPTS trial is part of the National Institute for
Health Research Clinical Research Network Trial Portfolio



<p>This protocol is a controlled document and should not be copied, distributed or reproduced without the written permission of the ICR-CTSU</p>
--

ADMINISTRATION

Clinical Co-ordination

Professor David Dearnaley (Chief Investigator)
Consultant Clinical Oncologist
ICR – Academic Radiotherapy
The Institute of Cancer Research
London

Tel: 0208 661 3271

E-mail: David.Dearnaley@icr.ac.uk

Trial Coordination

ICR-CTSU (a UKCRC registered and NCRI accredited clinical trials unit) is responsible for the day to day conduct of the trial.

**ICR Clinical Trials & Statistics Unit (ICR-CTSU),
Division of Clinical Studies,
The Institute of Cancer Research,
Sir Richard Doll Building,
Cotswold Road,
Sutton, Surrey SM2 5NG**

ICR-CTSU Scientific Lead: Emma Hall

Tel: 020 8722 4292

Emma.Hall@icr.ac.uk

Statistician: Helen Mossop

Tel: 020 8722 4008

Helen.Mossop@icr.ac.uk

Senior Trial Manager: Clare Cruickshank

Tel: 020 8722 4058

Clare.Cruickshank@icr.ac.uk

PROMPTS Trial Manager:

Shama Hassan

Tel: 020 8722 4183

prompts-icrctsu@icr.ac.uk

Any questions relating to this protocol should be addressed in the first instance to the PROMPTS Trial Manager within ICR-CTSU:

Email: prompts-icrctsu@icr.ac.uk

General enquiries: 020 8722 4183

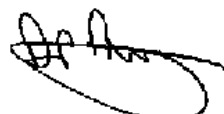
Fax: 020 8770 7876

Protocol Development Group

David Dearnaley	Chief Investigator	ICR-Academic Radiotherapy, The Institute of Cancer Research, London.
Emma Hall	Deputy Director	ICR-CTSU, The Institute of Cancer Research, London.
Ann Henry	Co-investigator	St. James's University Hospital
Pamela Levack	Co-investigator	Ninewells Hospital, Dundee
Malcolm Mason	Co-investigator	Cardiff University
Alec Miners	Co-investigator	London School of Hygiene and Tropical Medicine
Philip Rich	Co-investigator	St. George's Healthcare NHS Trust
Aslam Sohaib	Collaborator	The Royal Marsden NHS Trust
Ramachandran Venkitaraman	Co-investigator	The Ipswich Hospital NHS Trust
Clare Cruickshank	Senior Trial Manager	ICR-CTSU, The Institute of Cancer Research, London.
Clare Griffin	Statistician	ICR-CTSU, The Institute of Cancer Research, London

The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group and Principal Investigators from a subset of participating centres. A copy of the current membership of the TMG can be obtained from the PROMPTS Trial Manager at ICR-CTSU.

Protocol Authorised by:

Name & Role	Signature	Date
Professor David Dearnaley (Chief Investigator)		29/11/2016

This protocol describes the PROMPTS trial and provides information about procedures for entering patients. The protocol should not be used as a guide for the treatment of other patients. Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but centres entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version. Protocol amendments will be circulated to participating centres as they occur.

This trial will be conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care. It will be conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.

CONTENTS

List of Abbreviations	v
Practical definitions for the purpose of the protocol	v
TRIAL SUMMARY	vi
1. Introduction	1
1.1. Malignant Spinal Cord Compression	1
1.2. MRI spine to detect spinal cord compression	1
1.3. Frequency of screening MRI Spine	2
1.4. Treatments for early spinal cord compression	3
1.5. DEFINITION OF TERMS	4
1.6. Rationale for Study	5
2. Trial objectives	5
2.1. Primary Objective	5
2.2. Secondary Objectives	5
3. Trial design	5
3.1. Figure 1: STUDY FLOW CHART	6
4. Patient selection & eligibility	6
4.1. Source of Patients	6
4.2. Number of Patients	6
4.3. Inclusion Criteria	6
4.4. Exclusion Criteria	7
5. RANDOMISATION AND TREATMENT ALLOCATION	7
5.1. Randomisation procedure	7
6. Trial assessments	8
6.1. Baseline Assessments	8
6.2. On-study Assessments	8
Assessments for intervention group patients	8
Assessments at each neurologic event	8
6.3. Table 1 SCHEDULE OF ASSESSMENTS	10
7. Trial intervention	11
7.1. Group 1 (control):	11
7.2. Group 2 (INTERVENTION GROUP):	11
8. Management of patients in the study who develop rSCC or cSCC	11
8.1. MRI protocol	11
8.2. TREATMENT protocol	12
Dose and Fractionation	12
Planning technique	12
8.3. Assessments during each episode of SCC.	13
8.4. Systemic treatment	13
9. EVALUATION OF OUTCOME	13
9.1. DEFINITIONS of CLINICAL and RADIOLOGICAL SCC	13
9.2. Definition of findings on MRI spine	14
Practical definitions for the purpose of the protocol	14
9.3. Definition of Functional Neurologic Deficit due to SCC.	14
10. CONCURRENT MEDICATIONS	15
11. SAFETY REPORTING	15
11.1. Definition Of An Adverse Event (AE)	15
11.2. Definition Of Related Adverse Event	15
11.3. Reporting Of Adverse Events	15
11.4. Definition Of Serious Adverse Events (SAEs)	15
11.5. Events Not Subject To Expedited Reporting:	16
11.6. SAE Causality	16
Definitions for SAE causality	16
11.7. Reporting Serious Adverse Events	17
11.8. Review Of Serious Adverse Events (SAEs)	17
11.9. Expedited Reporting Of Related Unexpected SAEs	17
11.10. Follow Up Of Serious Adverse Events	17

11.11.	Annual Reporting Of Serious Adverse Events	18
12.	Statistical considerations	18
12.1.	Sample size calculation	18
12.2.	ENDPOINT DEFINITIONS	18
12.3.	Statistical ANALYSIS	19
13.	TRIAL MANAGEMENT	21
13.1.	Trial Management Group (TMG)	21
13.2.	Trial Steering Committee (TSC)	21
13.3.	Independent Data Monitoring Committee (IDMC).....	21
14.	RESEARCH GOVERNANCE	21
14.1.	Sponsor Responsibilities	21
14.2.	Responsibilities Of Chief Investigator	21
14.3.	Responsibilities Of ICR-CTSU	22
14.4.	Responsibilities Of Participating Centres.....	22
15.	TRIAL ADMINISTRATION AND LOGISTICS.....	22
15.1.	Protocol Compliance.....	22
15.2.	Investigator Training	22
15.3.	Data Acquisition	23
15.4.	Central Data Monitoring.....	23
15.5.	On Site Monitoring	23
15.6.	Protocol Amendments	24
15.7.	End Of Study	24
15.8.	Archiving	24
16.	PATIENT PROTECTION AND ETHICAL CONSIDERATIONS.....	24
16.1.	Risk Assessment	24
16.2.	Patient Confidentiality	24
16.3.	Ethical Considerations	24
16.4.	Patient Information.....	25
16.5.	Data Sharing.....	25
16.6.	Data Protection Act (DPA)	25
16.7.	Liability/Indemnity/Insurance	25
17.	FINANCIAL MATTERS.....	25
18.	PUBLICATION POLICY	25
19.	Associated studies.....	26
19.1.	Quality of Life	26
19.2.	Health Economics.....	26
	References.....	26
	Appendix A - ECOG Scale.....	28
	Appendix B – Frankel Spinal Cord Injury Assessment Tool.....	29
	Appendix C – Bilsky Spinal Cord Compression Scale^{53 (modified)}	31

List of Abbreviations

AE	Adverse event
BPI	Brief Pain Inventory
CRAG	Clinical Resource Audit Group
CRF	Case report form
CRPC	Castrate Resistant Prostate Cancer
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol-5 dimensions
FND	Functional neurologic deficit
GCP	Good clinical practice
ICR	The Institute of Cancer Research
ICR-CTSU	The Institute of Cancer Research Clinical Trials and Statistics Unit
LHRH	Leutinisising hormone releasing hormone
MRI	Magnetic resonance imaging
NICE	National Institute for Clinical Excellence
PSA	Prostate specific antigen
QALYS	Quality adjusted life years
QL	Quality of Life
RT	Radiotherapy
SAE	Serious adverse event
SCC	Spinal cord compression
	cSCC Clinical spinal cord compromise or compression (see below)
	rSCC Radiological spinal canal/cord compromise or compression (see below)
WBC	White blood cell count

Practical definitions for the purpose of the protocol

This section outlines the cSCC and rSCC definitions in terms of Bilsky scoring (Appendix C). The terms cSCC and rSCC will be used throughout the protocol.

cSCC – Clinical spinal cord compromise or compression – patients are symptomatic

Clinical spinal cord compromise –Bilsky score 1a-c (Bilsky 1a-b would be exceptional)

Clinical spinal cord compression – Bilsky score 2 or 3

rSCC – Radiological spinal canal/cord compromise or compression – patients are asymptomatic

Radiological spinal canal compromise – Bilsky score 1a or 1b

Radiological spinal cord compromise – Bilsky score 1c

Radiological spinal cord compression – Bilsky score 2 or 3

TRIAL SUMMARY

TITLE A **P**rospective **R**andomised Phase III Study of **O**bservation Versus Screening **M**RI And Pre-Emptive **T**reatment in Castrate Resistant Prostate Cancer Patients With **S**pinal Metastasis

STUDY OBJECTIVES:

Primary: Does detection of radiological spinal cord/canal compression (rSCC) by screening MRI of the spine and pre-emptive treatment reduce the incidence of clinical spinal cord/canal compromise or compression (cSCC) in asymptomatic castrate resistant prostate cancer (CRPC) patients with spinal metastasis?

Secondary:

- What is the utility of screening magnetic resonance imaging (MRI) in detecting rSCC in patients with asymptomatic spinal metastases?
- How does early intervention and prophylactic treatment of rSCC affect the development of cSCC?
- What is the effect of screening MRI and prophylactic treatment on;
 - preservation of neurological function;
 - rates of subsequent spinal radiotherapy and surgery;
 - subsequent mobility, pain and health related quality of life;
 - survival;
 - cost effectiveness?

TRIAL DESIGN: Prospective, randomised, two-group, non-blinded, phase III, interventional study

PATIENT TYPE: The target population is patients with CRPC with proven spinal metastasis, and with no neurologic symptoms.

SAMPLE SIZE 414 patients

TRIAL TREATMENT: Patients will be randomised in a 1:1 ratio to one of the following two treatment groups:

- Control group: patients followed up as per standard practice i.e., in accordance with National Institute of Clinical Excellence (NICE) guidelines, MRI spine performed if patient develops clinical neurological deficit or significant spinal pain with treatment given if there is clinical (c)SCC on MRI;
- Intervention group: Baseline screening MRI and pre-emptive treatment to sites of radiological (r) SCC; following detection of rSCC and pre-emptive treatment patients will receive an MRI scan every 6 months. rSCC is defined according to the Bilsky scoring system (see page v of this protocol).

ENDPOINTS: **Primary:** Incidence of cSCC at one year and time to development of confirmed cSCC.

Secondary:

- Rate of detection of rSCC (Bilsky 1a -3) on the baseline screening MRI (in the intervention group only).
- Incidence of and time to functional neurological deficit due to cSCC.
- Incidence of and time to irreversible functional neurological deficit due to cSCC.
- Incidence of SCC (Bilsky 1-3) in both the control and intervention groups during follow-up.
- Pain, quality of life, overall survival, cost effectiveness.

1. INTRODUCTION

1.1. MALIGNANT SPINAL CORD COMPRESSION

Spinal cord compression (SCC), the most clinically significant complication due to spinal skeletal metastasis, is reported to occur in 3 - 10 % of cancer patients resulting in significant debility and impact on quality of life¹⁻³. Patients with breast, lung and prostate cancer account for about 60% of metastatic SCC cases but it can be caused by any malignancy⁴. The risk of SCC is also proportionally related to the duration of disease and therefore, as cancer survival times increase, so too does the incidence of SCC. SCC occurs when there is pathological vertebral body collapse or direct tumour growth causing compression of the spinal cord or cauda equina. The development of SCC in patients with metastatic cancer is a clinical disaster, resulting in neurological deficit causing paraplegia which may be irreversible⁵.

SCC and its complications have a profound influence on the functional, social, emotional and physical quality of life of the patient with a resulting increased burden on the health care system. SCC is reported to be associated with a doubling of the time spent in hospital in the last year of life⁶. Complications of motor deficit from SCC such as pneumonia and thrombotic events are known to adversely impact on survival, and it could be postulated that the prevention of functional neurologic deficit by early diagnosis and treatment, might reduce the adverse influence of SCC on survival. In addition to the poor quality of life, the high cost of emergency hospital admissions, palliative care and rehabilitation may be more demanding on resources than the prevention of SCC with early imaging and prophylactic treatment⁷⁻⁹.

Incidence of SCC and its clinical outcome has an important effect on overall survival in patients with metastatic cancer, though the outcome is also influenced by the aggressiveness of the underlying primary malignancy. In patients with SCC, primary tumours like breast and prostate have a favourable outcome ranging from 12-18 months, compared to tumours like lung where the median survival would be approximately 6 months¹⁰⁻¹².

Early diagnosis of SCC is essential, as pre-treatment neurologic status is the major determinant influencing outcome^{2,5,11,13}. In the study by Husband et al of 301 patients with SCC, lack of symptom recognition by the patient and diagnostic delay by the physician resulted in preventable loss of neurologic function in approximately 70 % of patients, the median delay being 14 days¹⁴. In a prospective observational study of 319 patients with SCC by Levack et al, 82% of whom were non-ambulant, weakness and sensory abnormalities were reported late, despite 94% of patients reporting pain for approximately 3 months. The delay in detection of SCC was due to delay in referral and investigation of a median of 66 days, suggesting that patients with cancer who describe severe back pain or spinal nerve root pain need urgent assessment by MRI spine on the basis of their symptoms, as signs may occur too late⁴.

Studies have suggested that approximately 80% of patients who were ambulant pre-treatment, would remain ambulant after treatment, while only 15 – 30 % of patients who were non-ambulant would be expected to regain ambulant status following treatment, the rate of recovery very much dependent on the level of neurologic deficit¹⁵⁻²⁰. The results of several studies including the Clinical Resource Audit Group (CRAG audit) study, suggests that the patients who were ambulant prior to treatment for SCC and patients who remained ambulant after treatment, had a statistically significant longer survival, with systemic relapse being the commonest cause of death^{4,16,21}.

1.2. MRI SPINE TO DETECT SPINAL CORD COMPRESSION

Clinical signs are unreliable indicators of the presence or the level of suspected SCC and MRI of the spine is considered a mandatory investigation for detecting SCC and for planning management^{2,3,7-9}.

Abnormal neurologic examination, back pain, metastatic disease at diagnosis and extensive skeletal metastasis were found to be independent clinical predictors of SCC in 134 cancer patients evaluated with MRI spine by Lu et al²³. In this study 100 patients had a normal neurologic

examination, of whom 30 had thecal sac compression on MRI spine, with back pain and metastatic disease at presentation being the significant predictors. In the study by Talcott in patients with various malignancies where CT scans were utilized to detect SCC, inability to walk, increased deep tendon reflexes, compression fractures on radiographs of spine, bone metastases present, bone metastases diagnosed more than 1 year earlier, and age less than 60 years were risk factors for developing SCC²⁴. In the study by Venkitaraman et al in metastatic prostate cancer patients, back pain was an independent predictor of future adverse neurological outcome²⁵.

The NICE clinical guideline 75 suggests that cancer patients with symptoms or signs suggestive of spinal metastasis and neurologic symptoms or signs suggestive of SCC including radicular pain, any limb weakness, difficulty in walking sensory loss or bowel or bladder dysfunction or any neurological signs of spinal cord or cauda equina compression should be considered as an oncologic emergency and should have an urgent MRI spine to detect SCC¹.

Once a diagnosis of SCC has been made on MRI, the treatment goals include pain relief, restoration of neurological status, prevention of further neurological damage and stabilisation of the spine²⁶. MRI spine is also essential for planning surgery or radiotherapy for SCC because of the better delineation of extent of disease²⁶.

In prostate cancer, investigations have shown that it is possible to detect early radiological signs of impending SCC (radiological spinal canal/cord compromise or compression (rSCC)) in asymptomatic patients with or without bone pain. The definitions used for SCC on MRI scan have varied in different studies. Bayley et al, had used a definition for rSCC of 'impingement of the subarachnoid space by metastatic tumour involving the vertebrae or bone fragments, or frank compression of cord or cauda equina'⁸. Similarly, Venkitaraman et al, had used the definition of 'involvement or compression of either the spinal cord or the cauda equina by an epidural or an intramedullary mass lesion metastatic disease causing impingement, indentation or loss of definition of the thecal sac'²². Lu et al, had used a definition of 'thecal sac compression' in their study²³.

Detection of rSCC before clinical manifestations such as neurologic deficit or intractable pain by MRI spine may provide an important lead time for early treatment and thus may minimize the likelihood of irreversible functional neurologic deterioration²⁶. Bayley et al, detected rSCC in 22 of 68 patients (32%) with metastatic prostate cancer with no functional neurologic deficit (FND), the extent of disease on bone scan and the duration of continuous hormonal therapy being independent predictive factors⁸. In the study by Venkitaraman et al, 41 of 150 patients (27.33 %) with no FND were detected to have rSCC by MRI spine with the presence of back pain and extensive bone metastasis being the most important predictors²². Godersky et al, detected rSCC in 5 out of 22 patients (23 %) with back pain and without neurologic deficit²⁷. As there is clinical evidence that patients with neurologic back pain do benefit from investigations to rule out SCC, further research to evaluate the benefits of screening MRI and pre-emptive treatment may need to target the subgroup of asymptomatic patients with spinal metastasis. This is one of the key research recommendations of the NICE guideline CG75 committee¹.

1.3. FREQUENCY OF SCREENING MRI SPINE

No prospective information is available regarding the proportion of patients with rSCC who would go on to develop neurologic symptoms, as it would be unethical not to treat them. The risk of SCC may be expected to increase with longer survival. In the study by Bayley et al, the risk of developing cSCC within 1 year of a negative screening MRI was 3.2% and the risk of developing cSCC within 2 years of a negative screening MRI was 13.7%⁸. If serial screening MRI spine are planned to detect SCC in 90 % of patients prior to development of neurologic signs, the optimum frequency could range from approximately every three months to every twelve months, considering the wide variation in patient criteria and results reported in various studies and also the metastatic potential and aggressiveness of the underlying primary malignancy. As the expected median survival for patients with spinal metastasis could range from 12-36 months depending on the

primary malignancy, a prospective screening study would involve an average of approximately 2-5 MRI scans, depending on the characteristics of the study group⁵⁴. In PROMPTS a single screening MRI scan will be performed and we shall follow patients to determine what the appropriate repeat screening frequency might be. In patients who have rSCC found on screening, 6 monthly repeat scans are mandated as previous studies have demonstrated a high rate of progression^{6,25,54}.

1.4. TREATMENTS FOR EARLY SPINAL CORD COMPRESSION

It has been suggested that high-risk patients should undergo MRI screening with the aim of diagnosing and treating incipient SCC before development of FND^{1,8}. Detection of rSCC by MRI spine before the development of cSCC and early institution of treatment might preserve neurologic function in the majority of patients. Complications of motor deficit from SCC such as pneumonia and thrombotic events are known to adversely impact on survival, and it could be postulated that the prevention of functional neurologic deficit by early detection and treatment of SCC would reduce the adverse influence of the occurrence of such an event on survival.

The treatment options for SCC include high dose corticosteroids, surgery and radiotherapy. High dose corticosteroids, especially Dexamethasone, has been shown to improve ambulation when given in combination with radiotherapy in patients who had SCC^{2,28,29}. The role of maintenance steroids and their role in patients who already have a good motor function is controversial^{30,31}.

Radiotherapy is proven to be an effective treatment for cSCC from metastatic disease, especially in ambulatory patients without bony instability^{5,11,13,32,33}. Almost all patients with SCC who are ambulant prior to treatment would retain motor function and are expected to be ambulant after radiotherapy². Radiotherapy causes tumour decompression, may reduce venous congestion and prevent arterial infarction, which have been postulated to be responsible for neurologic injury in SCC^{3,32,34}. Tumours with favorable histology like breast, myeloma and prostate have been reported to be associated with a longer median response to radiotherapy¹². Kaplan et al have shown a reduction in spinal metastasis after pre-emptive radiation in prostate cancer³⁵. Whether the same would hold true for SCC from spinal metastasis requires investigation. Helweg-Larsen and colleagues irradiated symptomatic synchronous compressions with a two vertebral body margin. At a median follow-up of 3.5 years, none of the 14 patients who had lesions within the irradiated volume relapsed in the same area as the previous lesion³⁶. In a retrospective study by Soerdjbalie-Maikoe et al, none of the patients who received local radiotherapy for spinal metastasis developed SCC³⁷. In the prospective study by Maranzano et al, 20 patients with no signs of neurologic spinal compression received 30 Gy in 10 fractions with no steroids to sites of subclinical SCC. All patients (100%) responded to radiotherapy because the 16 patients able to walk without support at diagnosis did not deteriorate and the other 4, who needed support, became ambulatory without motor impairment³⁰. The findings from the retrospective study by Venkitaraman et al, also suggest that radiotherapy may prevent neurologic deficit in case of rSCC²⁵. This hypothesis is also supported by the tumour response and resolution of cord compression evident on post radiotherapy MRI scans.

The dose of radiotherapy has varied in different studies. Rades et al, in three different studies comparing different radiotherapy regimes did not find a significant difference in neurologic outcome between doses ranging from 8Gy x 1, 4Gy x 5, 3Gy x 10, 2.5Gy x 15 and 2Gy x 20³⁸⁻⁴⁰. The infield recurrences at two years though were lower for longer courses of treatment. However, in another prospective study by the same group short course radiotherapy was found to be similar to long course radiotherapy (≥ 30 Gy) for functional outcome and overall survival, but resulted in inferior progression free survival and local control⁴¹. Similarly Maranzano et al, did not detect any difference in two split course regimes of 5 Gy x3 followed by 3 Gy x5 or 8 Gy x2⁴². In patients with prostate cancer who had SCC, overall response to radiotherapy has been reported to be 86% (33% improvement of motor function, 53% no further progression), with 33% of the non-ambulatory patients regaining the ability to walk. In this study the 2 year local control of SCC was 84% , with better results after long course radiotherapy⁵. Results of the meta-analysis of patients in randomized trials of single versus multiple fractions of radiotherapy for painful bone metastasis,

suggest no significant difference in the incidence of SCC for either regimes, though there was a trend for lower SCCs in patients who received fractionated radiotherapy⁴³. The local practice in the UK has been to offer 20 Gy in 5 daily fractions over a week for patients with SCC.

Surgical decompression and stabilisation has been found to result in better neurologic outcome than radiotherapy in patients with bony compression or unstable spine. In the meta-analysis by Klimo et al the percentage of patients remaining ambulant after radiotherapy or surgery for SCC were found to be 64 % and 85 % respectively, with surgical patients twice as likely to regain ambulatory function⁴⁴. In retrospective studies decompressive laminectomy followed by radiotherapy has been reported to have a better functional response than patients treated with either surgery or radiotherapy alone^{20,45}. In the prospective randomised study by Patchell et al direct decompressive surgery and postoperative radiotherapy was found to be superior to radiotherapy alone for patients with metastatic SCC, with the percentage of patients ambulant being 84 % and 54 % respectively in the two groups⁴⁶. In a study of 81 patients, emergency surgical spinal decompression (61.5 %) led to better outcomes compared to elective surgery (25 %), despite initial delays in referral and even if the patient were incontinent and immobile⁴⁷. Surgery in patients with vertebral metastasis without neural deficit has been reported to result in substantial functional improvement, but with no improvement in survival⁴⁸.

Systemic treatments like chemotherapy and hormonal treatment for individual primary tumours have been shown to reduce disease progression and may reduce complications like metastatic SCC. Patients with bone metastasis disease receiving bisphosphonates have been shown to have significantly reduced incidence of skeletal related complications, and may have a reduction in the incidence of SCC³⁷. There is a suggestion that bisphosphonate use in patients with SCC may improve functional outcome and even overall survival⁴¹.

An economic evaluation as part of the NICE guidelines has shown the cost-effectiveness of the main treatment options available for SCC i.e. surgery and radiotherapy compared to no treatment¹.

In spite of all these treatments, the prognosis of CRPC patients with malignant SCC is bleak and further research is warranted aiming to prevent the onset of this complication. CRPC patients with spinal metastasis would be an ideal patient group for studies of early imaging to detect spinal cord compromise and prophylactic treatment to prevent neurologic deficit, and such research would be a priority area for the NHS¹.

1.5. DEFINITION OF TERMS

The validated **Bilsky** epidural SCC scoring system⁵³ evaluates metastatic disease causing impingement, indentation or loss of definition of the thecal sac or frank compression of spinal cord or cauda equina using a 6 point scale (0,1a-c,2,3) (Appendix C).

Clinical (or overt) SCC is defined in the NICE metastatic SCC guidelines as. “spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability”. For the purposes of the PROMPTS protocol patients with cSCC will be symptomatic with imaging confirming cSCC according to the NICE definition. Imaging will be scored according to the Bilsky system (appendix C). Patients with cSCC will usually have Bilsky scores of 2 or 3.

Radiologic (or occult) SCC (rSCC) will be defined by MRI in asymptomatic patients: MRI findings will usually give a Bilsky 1a- 1c score but exceptionally Bilsky 2-3 scores may be found in asymptomatic patients.

1.6. RATIONALE FOR STUDY

To determine whether the early detection of rSCC by screening MRI spine and pre-emptive treatment with radiotherapy facilitates preservation of neurologic function in CRPC patients with spinal metastasis.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVE

Does detection of rSCC by screening MRI of the spine and pre-emptive treatment reduce the incidence of cSCC in asymptomatic CRPC patients with spinal metastasis?

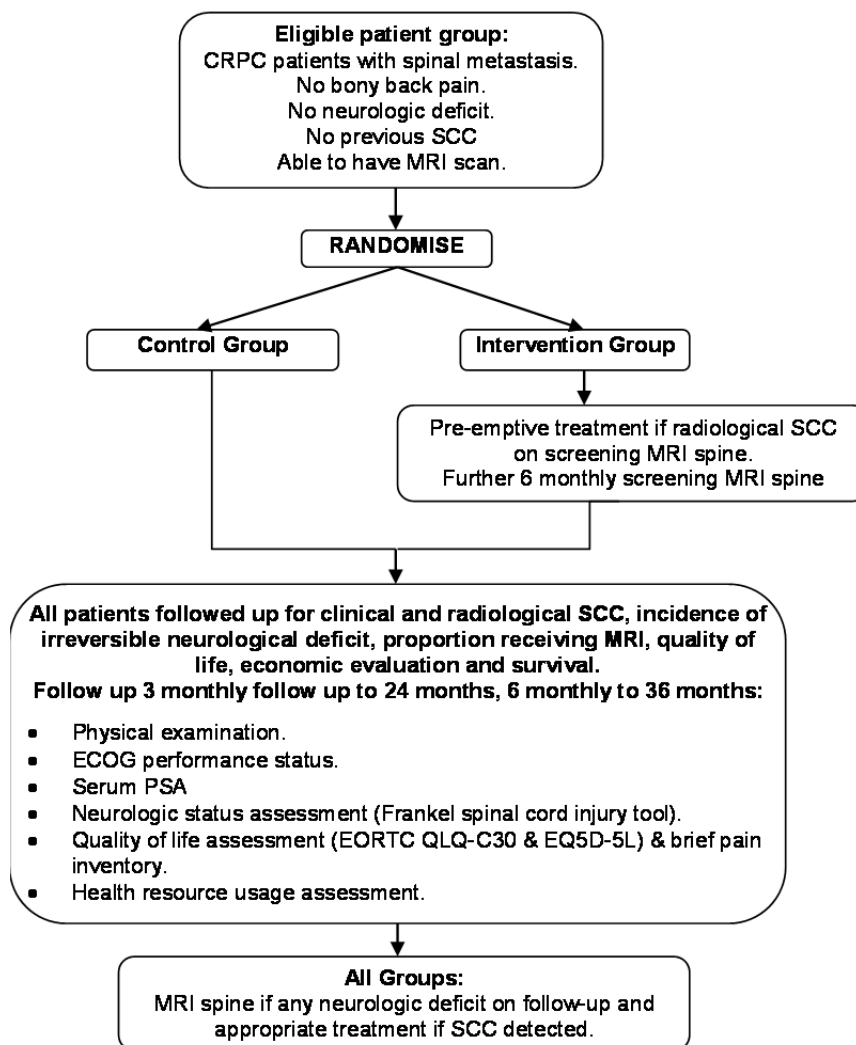
2.2. SECONDARY OBJECTIVES

- What is the utility of screening MRI in detecting rSCC in patients with asymptomatic spinal metastases?
- How does early intervention and prophylactic treatment of rSCC affect the development of cSCC? What is the effect of screening MRI and prophylactic treatment on:
 - preservation of neurological function;
 - rates of subsequent spinal radiotherapy and surgery;
 - subsequent mobility, pain and health related quality of life;
 - survival;
 - cost effectiveness?

3. TRIAL DESIGN

A multicentre prospective, randomised, two group, non-blinded, phase III interventional study in CRPC patients with spinal metastasis:

3.1. FIGURE 1: STUDY FLOW CHART



4. PATIENT SELECTION & ELIGIBILITY

4.1. SOURCE OF PATIENTS

The target population is patients with CRPC with proven spinal metastasis, and with no neurologic symptoms.

4.2. NUMBER OF PATIENTS

424 patients will be randomised in a 1:1 ratio to the control and intervention groups.

4.3. INCLUSION CRITERIA

- Either histologically/cytologically confirmed adenocarcinoma of the prostate **or** clinical diagnosis of prostate cancer with osteoblastic bone metastases and PSA \geq 100ng/ml at **any** time between diagnosis and randomisation;
- Castrate resistant disease;*
- PSA $>$ 5ng/ml within 21 days prior to randomisation
- One or more spinal* metastasis on imaging (by technetium bone scan with confirmatory x-ray as appropriate clinically, or by CT, PET-CT or MRI scan) undertaken at any time during the patient's illness.
- Life expectancy of 6 months or more;

- ECOG performance status 0-2;
- Written, informed consent.

rising PSA (>5 ng /ml **and >50% rise from nadir) after LHRHa therapy or orchidectomy with or without anti-androgen.*

** metastases in cervical, thoracic or lumbar spine*

4.4. EXCLUSION CRITERIA

- Back pain related to metastatic cancer, requiring regular (daily) analgesics which requires an immediate MRI as per NICE guidelines
- Previous malignancy that, in the opinion of the local investigator, makes it difficult to confirm that spinal metastases are secondary to prostate cancer or otherwise make the patient unsuitable for inclusion in the study.
- Current or previous SCC or neurologic deficit;
- Spinal MRI within last 12 months;
- Planned MRI of spine or thorax AND abdomen
- Previous external beam radiotherapy to the vertebra or spinal surgery with the primary aim to prevent or treat SCC;
- Serious or uncontrolled co-existent non-malignant diseases;
- Any contra indications for MRI;
- Inability to comply with neurologic and Quality of Life (QoL) assessments.

+ (previous palliative radiotherapy to painful spinal metastases in now asymptomatic patients is permissible).

5. RANDOMISATION AND TREATMENT ALLOCATION

5.1. RANDOMISATION PROCEDURE

Central randomisation will be performed by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU).

Treatment allocation will be 1:1 and will use a minimization algorithm incorporating a random element. The following balancing factors will be used : centre, alkaline phosphatase (normal vs. raised), number of previous systemic treatments, excluding neo/adjuvant hormone therapy unless failed during treatment (i.e. whether the patient has had a first line treatment failure vs. second line or later), previous spinal radiotherapy and/or surgical procedure for metastatic disease and previous CT or PET CT scan of both thorax and abdomen within the last 6 months.

Once written informed consent has been obtained, an eligibility and randomisation checklist must be completed prior to randomisation. The clinician / research nurse should contact ICR-CTSU to confirm eligibility and obtain a unique trial number and treatment allocation.

The following information will be required at randomisation:

- Name of Hospital, consultant and person randomising patient;
- Confirmation that patient is eligible for the trial by completion of the checklist;
- Confirmation that patient has given written informed consent;
- Patient's full name, hospital number, date of birth, postcode and NHS/CHI number;
- Confirmation of alkaline phosphatase (normal vs raised), number of previous treatments (first failure vs second or later), details of any previous spinal radiotherapy and/or surgical procedure for metastatic disease (yes vs no) and detail of any CT or PET CT scan of both thorax AND abdomen within the last 6 months (yes vs no).
- PSA within 21 days prior to randomisation.

The caller will be given the patient's unique randomisation number (Trial ID). The Trial ID together with the patient's initials, date of birth and hospital number should be used on all Case Report

Forms (CRFs) and correspondence relating to the patient. To randomise a patient telephone:

ICR Clinical Trials and Statistics Unit (ICR-CTSU)
The Institute of Cancer Research
020 8643 7150
09.00-17.00 Monday to Friday

6. TRIAL ASSESSMENTS

6.1. BASELINE ASSESSMENTS

The following should be done not more than 21 days prior to randomisation:

- Medical history.
- Physical examination (including neurologic assessment using Frankel spinal cord injury assessment tool (see appendix B) and evaluation of pain).
- ECOG performance status
- Haematology tests: Haemoglobin, white blood cell (WBC) count and platelet count.
- Clinical biochemistry tests: serum creatinine, alkaline phosphatase and serum albumin.
- Pre-trial clinical signs and symptoms using Common Toxicity Criteria for Adverse Event Reporting (CTCAEv4.0) grading.
- Serum prostate specific antigen (PSA).

The following should be done not more than 7 days prior to randomisation:

- Quality of life and neurologic assessment forms:
 - Brief Pain Inventory
 - EORTC QLQ-C30, EQ-5D-5L and HADS.

6.2. ON-STUDY ASSESSMENTS

Follow-up will take the following format:

Year 1: 3, 6, 9, 12 months

Year 2: 15, 18, 21, 24 months

Year 3: 30, 36 months

Year 4 onwards: annual Long Term Follow Up (LTFU)

At each of these time-points (except the annual LTFU) the following assessments will take place:

- Physical examination including neurologic assessment using Frankel spinal cord injury assessment tool (see appendix B).
- ECOG performance status
- Serum PSA
- EORTC QLQ-C30, EQ-5D-5L, Brief Pain Inventory, HADS to be completed by the patient at their clinic visit (HADS at 3 months only).

Assessments for intervention group patients

- Screening MRI (the screening MRI should be performed within 8 weeks following randomisation).
- MRI (every 6 months) for patients where rSCC has been seen on the screening scan.
- Health Economics questionnaire for patients with rSCC (once only approximately three months after treatment)

Assessments at each neurologic event

For any patient who has suffered a neurological event* the following assessments will take place:

- Physical examination including neurologic assessment using Frankel spinal cord injury assessment tool (see appendix B) (pre and post treatment)
- ECOG performance status (pre and post treatment)
- Pre and post treatment serum PSA
- Brief Pain Inventory (pre-treatment only) and EQ-5D-5L (pre and posttreatment) questionnaire to be completed by the patient at their clinic visit.
- Pre and post treatment toxicity assessments using CTCAEv4.0 grading (both radiotherapy and surgery) and Clavian Scale (surgery only).
- Health Economics questionnaire (approximately three months after treatment)

*(*detection of rSCC or cSCC)*

Once a patient has suffered a neurological event follow up remains the same as for patients who have not, as per protocol.

Discontinuation from follow-up

If a patient withdraws from further follow-up a trial deviation form should be submitted to ICR-CTSU stating whether the patient has withdrawn consent for information to be sent to the ICR-CTSU or whether they simply no longer wish to attend trial follow up visits. In the very rare event that a patient requests that their data is removed from the study entirely, the implications of this should be discussed with the patient first to ensure that this is their intent and, if confirmed, ICR-CTSU should be notified in writing. If this request is received after results have been published the course of action will be agreed between the Sponsor and independent Trial Steering Committee/Independent Data Monitoring and Steering Committee.

6.3. TABLE 1 SCHEDULE OF ASSESSMENTS

				Follow up month / year											
	Screening (within 21 days prior to randomisation)	Baseline (within 7 days prior to randomisation)	After randomisation	3	6	9	12	15	18	21	24	30	36	4 year onwards	At each neurologic event
Inclusion/Exclusion criteria	X														
Informed consent	X														
Demography	X														
Medical history	X														
ECOG	X			X	X	X	X	X	X	X	X	X	X		X
Physical examination ¹	X			X	X	X	X	X	X	X	X	X	X		X
Haematology & Biochemistry ²	X ²														
PSA	X			X	X	X	X	X	X	X	X	X	X		X
Quality of Life ³		X		X	X	X	X	X	X	X	X	X	X		X
Control group															MRI ⁴
Intervention group			MRI ⁴		MRI ⁵		MRI ⁵		MRI ⁵		MRI ⁵	MRI ⁵	MRI ⁵		MRI ⁴
Toxicity assessment ⁶	X														X
Annual Long term follow up forms (LTFU)														X	

1. Including neurologic examination according Frankel spinal cord injury assessment tool (see appendix B).

2. This should include: haemoglobin, white blood cell (WBC) count, platelet count, serum creatinine, alkaline phosphatase and serum albumin.

3. Quality of Life assessment with EORTC QLQ C30, EQ-5D-5L, Brief Pain Inventory and HADS*.

4. MRI denotes MRI of the spine

5. MRI (only for patients who have evidence of rSCC at screening (baseline) scan. *(If a patient cannot attend a scheduled scan appointment, the replacement appointment should be made as close to the original appointment as possible. The next scan after this, should keep at its original time.)*

6. Post treatment toxicity assessments using CTC AE grading (both radiotherapy and surgery) and Clavian Scale (surgery only).

* HADS will only be completed at baseline and 3 months follow up. EORTC QLQ C30 not required at each neurologic event.

7. TRIAL INTERVENTION

7.1. GROUP 1 (CONTROL):

Control group: Patients will be followed up at three monthly intervals (from randomisation) for 2 years and then at 30 and 36 months with clinical examination patients. MRI spine performed if patient develops clinical neurological deficit or significant spinal pain with treatment given if there is cSCC on MRI, annual LTFU forms will be completed from year 4 onwards;

7.2. GROUP 2 (INTERVENTION GROUP):

Intervention group: If baseline screening is negative, follow up is as for the control group. If baseline screening MRI is positive pre-emptive treatment will be given to sites of rSCC. Following pre-emptive treatment patients will receive an MRI scan every 6 months. Patients will be followed up at three monthly intervals (from randomisation) for 2 years and then at 30 and 36 months, annual LTFU forms will be completed from year 4 onwards;

8. MANAGEMENT OF PATIENTS IN THE STUDY WHO DEVELOP rSCC OR cSCC

All patients who develop rSCC (Bilsky $\geq 1a$) or cSCC (usually with Bilsky 2 or 3) should have their management reviewed in the specialist SCC MDT (if available) and the recommendations of the MDT should be followed. Alternatively the patient pathway should follow expert local practice. Most commonly, we expect radiotherapy to be the treatment of choice for both rSCC and cSCC. The recommended treatment for rSCC for patients in the study is with external beam radiotherapy which should be instituted within one week of confirmation of rSCC. Patients who develop cSCC or established neurological deficit should be treated according to the MDT recommendations with radiotherapy, spinal decompression or vertebro/kyphoplasty. For patients with rSCC or cSCC treated by radiotherapy, the recommended dose is 20Gy in 4Gy fractions daily over one week delivered with external beam photons and prescribed at an adequate depth.

Physicians may consider concurrent high dose steroids, preferably Dexamethasone 4 to 8 mg, 2 to 3 times a day during radiotherapy, under cover of proton pump inhibitors according to local protocols.

All patients in the study would receive systemic treatment for metastatic disease according to the local protocols for their primary malignancy, including hormonal treatment, chemotherapy, biological therapy, bisphosphonates, radionuclides or palliative radiotherapy to non-spinal sites. These treatments may be within other clinical trials. The use of other investigational agents is allowed during the study period. Palliative radiotherapy to the spine for pain relief is permitted but patients should be adequately assessed for SCC according to NICE guidelines.

8.1. MRI PROTOCOL

MRI of the spine should be performed on a MRI system with minimum field strength of ≥ 1 Tesla and with a spinal coil. The whole spine should be imaged from the base of skull to the coccyx with sagittal T1 and T2 weighted images. Sagittal images may be supplemented with selected axial images through any suspicious areas at the discretion of the radiologist.

For patients reporting to the physician with symptoms or signs suggestive of neurologic deficit, MRI spine should ideally be performed within 24 hours in accordance with NICE and local guidelines.

All MRIs leading to a diagnosis of rSCC or SCC and a 10% random sample of negative baseline MRIs will be subject to central review. An instruction manual depicting examples of rSCC will be distributed to participating centres.

Additionally, a validated epidural SCC scoring system⁵³ (Bilsky Spinal Cord Compression Scale (Appendix C)) will be used in all centres. This is well suited for defining rSCC using MRI. This scale showed excellent reproducibility when assessed for inter and intra observer reliability.

Non-trial imaging including isotope scans (CT and MRI) and their impact on detection of SCC will be monitored. The CRF's will be designed to capture non-trial imaging.

8.2. TREATMENT PROTOCOL

Most commonly, we expect radiotherapy to be the treatment of choice for both rSCC and cSCC but the recommendation of the specialist SCC MDT (if available) or expert local practice should be followed. Details of treatment received for any SCC detected on any MRI will be collected on the relevant CRF.

8.2.1 High dose corticosteroids

Following the diagnosis of rSCC or cSCC, high dose corticosteroids may be prescribed (commonly dexamethasone 8-24mgs total dose per day in divided doses with gastric protection) at the investigators discretion. If used, the maximum dose and duration of high dose corticosteroid usage will be recorded. The duration will be from the start of high dose treatment to the time when corticosteroid dose is <3mgs/day of dexamethasone or equivalent.

8.2.2 Radiotherapy

Radiotherapy should be delivered as soon as reasonable after detection of rSCC on screening MRI. For Bilsky 1a-1c graded rSCC treatment should be within one week (maximum 2 weeks) following confirmation of rSCC after review at relevant MDT or other local process.

Patients with Bilsky 2 - 3 rSCC or with clinical symptoms of SCC should be treated within 48 hours of diagnosis in line with NICE Guidance.

Dose and Fractionation

The recommended radiotherapy dose is 20 Gy given daily in 5 fractions prescribed at an adequate depth and at least to the mid-point of the spinal cord /cauda equina for patients who have asymptomatic rSCC.

Planning technique

Radiotherapy may be planned by conventional simulation or by CT based virtual simulation. The findings of the MRI scans should be taken into account while deciding the PTV. Field size will be at least 1 vertebral level above / below site of rSCC and include the pedicles of the vertebrae laterally and should cover the whole of the soft tissue disease with an adequate margin. If at the time of radiotherapy planning there is any doubt of the accuracy of localisation this should be increased to +/- 2 vertebra. If there is additional bony involvement of adjacent vertebra clinical judgement should be used to increase field length. The treatment technique will most commonly be with a single under couch direct posterior field treating with the patient in the supine position. Other techniques may be used as clinically indicated (for example, lateral fields for cervical spine metastases). The prescription point (or depth) should give a dose of at least 20Gy in five fractions to the mid-point of the spinal cord or cauda equina but may be modified to adequately treat soft tissue or bony involvement.

Similar guidelines would be used for clinically established SCC treated with radiotherapy.

8.2.3 Surgery

Additionally the role of spinal surgery should be assessed with the specialist cancer network SCC MDT team (if available) or expert local practice. Any surgical treatment should follow the recommendations of the specialist MDT (if available) or expert local practice and all such treatment details will be recorded. If surgery is performed, most patients will then receive post-operative radiotherapy as above.

Surgery may be considered in the following situations:

1. Patients with spinal instability or pathological spine fractures or evidence of bone in the spinal canal.
2. Patients who have progressed neurologically on radiotherapy.
3. Patients who have relapsed at previously radiated sites.
4. Instances where the treating doctor feels the patient may be benefited by surgical decompression or stabilisation.

The aim of surgery is to provide immediate decompression of the spinal cord. Surgery should be tailored for each patient depending on the level of the spine involved and the patient's circumstances.

Post-operative radiotherapy to sites where decompression or stabilisation surgery has been done should be considered. The radiotherapy dose and plan would be similar to that stated previously.

8.3. ASSESSMENTS DURING EACH EPISODE OF SCC.

The radiologic level of SCC (Bilsky 1a-3), days of inpatient admissions, details of radiotherapy treatment, pre and post treatment neurologic scores, pre and post treatment level of analgesia scores and quality of life scores, neurologic improvement after treatment and concurrent systemic treatments will be collected during each episode of cord compression or treatment for rSCC or cSCC (Bilsky 1a-3).

The incidence of repeat episodes of SCC in treated patients, and the details of any follow up MRI spine will be collected.

8.4. SYSTEMIC TREATMENT

Patients should be managed according to standard local practice and treatments should be similar for patients in both groups of the study. Alternative treatment strategies may be prescribed at the discretion of the responsible physician in accordance with standard local practice. Entry to other clinical trials which do not mandate MRI spine and the use of investigational agents are permitted. Systemic treatments will be recorded on the CRF.

9. EVALUATION OF OUTCOME

9.1. DEFINITIONS OF CLINICAL AND RADIOLOGICAL SCC

Clinical SCC (cSCC) is defined in the NICE metastatic SCC guidelines as “spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability”. For the purposes of the PROMPTS protocol patients with clinical SCC will be symptomatic with imaging confirming SCC according to the NICE definition. Imaging will be scored according to the Bilsky system (appendix C). Patients with clinical SCC will usually have Bilsky scores of 2 or 3.

Radiologic SCC (rSCC) will be defined by MRI in asymptomatic patients: MRI findings will usually give a Bilsky 1a- 1c score but exceptionally Bilsky 2-3 scores may be found in asymptomatic patients.

Please also refer to page v of the protocol ‘Practical definitions for the purposes of the protocol’.

9.2. DEFINITION OF FINDINGS ON MRI SPINE.

MRI findings in the spine will be classified as either:

- i. SCC (radiological or clinical) defined as metastatic disease causing impingement, indentation or loss of definition of the thecal sac or frank compression of spinal cord or cauda equina (Bilsky score 1a – 3)
- ii. no SCC.

A validated epidural SCC scoring system⁵³ (the modified Bilsky Spinal Cord Compression Scale below and in appendix C) will be used by radiologists in participating centres. This scale is well suited for defining rSCC using MRI and showed excellent reproducibility when assessed for inter and intra observer reliability.

0	Metastatic bone disease without epidural impingement
1a	Epidural impingement without deformation of the thecal sac
1b	Deformation of the thecal sac
1c	Deformation of the thecal sac with spinal cord abutment, but without cord compression
2	Spinal cord compression but with cerebrospinal fluid (CSF) visible around the cord
3	Spinal cord compression, no CSF visible around the cord
9	No bone metastasis (additional score for PROMPTS trial)

Practical definitions for the purpose of the protocol

cSCC – Clinical spinal cord compromise or compression – patients are symptomatic

Clinical spinal cord compromise – Bilsky score 1a-c (Bilsky 1a-b would be exceptional)

Clinical spinal cord compression – Bilsky score 2 or 3

rSCC – Radiological spinal canal/cord compromise or compression – patients are asymptomatic

Radiological spinal canal compromise – Bilsky score 1a or 1b

Radiological spinal cord compromise – Bilsky score 1c

Radiological spinal cord compression – Bilsky score 2 or 3

9.3. DEFINITION OF FUNCTIONAL NEUROLOGIC DEFICIT DUE TO SCC.

Functional neurologic deficit is defined as detection of one or more of the following on clinical examination:

1. Objective motor power loss due to involvement of the spinal cord or nerve roots.
2. Objective sensory loss due to involvement of the spinal cord or nerve roots.
3. Urinary incontinence or retention due to involvement of the spinal cord or nerve roots.
4. Bowel incontinence due to involvement of the spinal cord or nerve roots.

Functional neurologic deficit will be assessed and scored according to the Frankel System (see appendix B).

Neurologic deficit due to base of skull involvement or peripheral nerve involvement should be ruled out clinically and would not be considered as an endpoint for the study.

10. CONCURRENT MEDICATIONS

All medication considered necessary for the patients' welfare and which is not expected to interfere with the evaluation of the study intervention may be given at the discretion of the investigator. Only treatment related to the patient's prostate cancer should be recorded on the appropriate pages of the CRF.

11. SAFETY REPORTING

11.1. DEFINITION OF AN ADVERSE EVENT (AE)

An 'adverse event' is any untoward medical occurrence in a patient administered a research procedure; where the events do not necessarily have a causal relationship with the procedure. For the purpose of this trial, any detrimental change in the patient's condition subsequent to the start of the trial (i.e. randomisation) and during any treatment given for rSCC or cSCC, which is not unequivocally due to progression of disease (prostate cancer), should be considered as an adverse event.

Whenever one or more signs and/or symptoms correspond to a disease or well-defined syndrome only the main disease/syndrome should be reported. For each sign/symptom the highest grade observed since the last visit should be reported.

We expect adverse events to be rare in the context of this trial, with the intervention being MRI scanning and therefore, there is no expected list of event occurrences relating to MRI in this protocol. Events such as disease progression, disease relapse or admissions due to these causes, and death as a result of disease relapse are not considered to be SAE's and should be reported on the appropriate CRF. Events related to co-morbid conditions should not be reported or considered as SAEs.

11.2. DEFINITION OF RELATED ADVERSE EVENT

An adverse event assessed by the Principal Investigator (PI) or Chief Investigator (CI) as having a reasonable causal relationship to the administration of the research procedure (MR scan) i.e. is possibly, probably, or definitely related to the research procedure. Any such events are expected to have occurred within 24 hours of the MR scan.

11.3. REPORTING OF ADVERSE EVENTS

Adverse events will be reported during the trial at the time points detailed in section 6 of the protocol. Adverse events should be recorded in the appropriate section of the CRF.

11.4. DEFINITION OF SERIOUS ADVERSE EVENTS (SAES)

Serious Adverse Events will be collected for a 24 hour period only after the study related screening MRI scan. A serious adverse event is one which falls in one of the following categories:

1. **Results in death;** the patient's death is suspected as being a direct outcome of the adverse event.
2. **Is life-threatening;** refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that would result which hypothetically might have caused death if it were more severe.
3. **Requires hospitalisation, or prolongation of existing inpatient hospitalisation:** admission to hospital overnight or prolongation of a stay in hospital was necessary as a result of the AE.

Outpatient treatment in an accident and emergency department is not itself an SAE, although the reasons for it may be. Hospital admissions/surgical procedures planned for a pre-existing condition before a patient is randomised to the study are not considered SAEs, unless the illness/disease deteriorates in an unexpected way during the study.

4. **Results in persistent or significant disability or incapacity:** The AE results in a significant or persistent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
5. **Consists of a congenital anomaly or birth defect.**

Whenever one or more signs and/or symptoms correspond to a disease or well-defined syndrome, only the main disease/syndrome should be reported. For each sign/symptom the highest grade observed should be reported.

11.5. EVENTS NOT SUBJECT TO EXPEDITED REPORTING:

The following are anticipated treatment, disease or co-morbidity related adverse events which are not subject to expedited reporting. All such events should be reported in the appropriate sections of the CRF.

- a) Any radiotherapy treatment related events will be collected on a post radiotherapy complications form.
- b) Any surgical treatment related events will be collected on a post-surgery complications form.
- c) *Disease related events:*
 - Progressive disease
 - Symptoms related to progressive disease
 - Death due to disease

11.6. SAE CAUSALITY

The Principal Investigator is responsible for the assessment of causality of serious adverse events as defined in the table below:

Definitions for SAE causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial procedure
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after the trial procedure. There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after the trial procedure. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out

Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.
-----------------------	---

11.7. REPORTING SERIOUS ADVERSE EVENTS

SAEs subject to expedited reporting from date of randomisation and up to 24 hours post screening MRI scan must be reported.

All SAEs should be reported within 24 hours of the investigator becoming aware of the event, by completing the PROMPTS SAE form and faxing it to:

PROMPTS Trial Manager
The Safety Desk
Clinical Trials and Statistics Unit (ICR-CTSU)
FAX: 0208 722 4369
(Monday – Friday 09.00 – 17.00)

The SAE form must be completed, signed and dated by the Principal Investigator or nominated person identified on the site delegation log, although initial notification should not be delayed for signature, but should be followed by a report signed and dated by the Principal Investigator or nominated representative as soon as possible. A hard copy must also be sent by post to the trials office using the address on the SAE form. ICR-CTSU office will send a fax to the Site to acknowledge receipt of the SAE.

Any relevant follow up information, including final resolution of the event, should be completed on the relevant part of the original SAE form and faxed to the ICR-CTSU within 15 days of the local investigator becoming aware of this information. The Chief Investigator (or a nominated representative) will review all SAEs to assess relatedness and expectedness. The Site SAE log should be completed and the SAE form filed in the Site Investigator File.

11.8. REVIEW OF SERIOUS ADVERSE EVENTS (SAES)

Reported SAES will be assessed by the Chief Investigator (or designated representative) for causality and expectedness.

NB. The Chief Investigator cannot down grade the Principal Investigator's assessment of causality. SAES assessed as having a causal relationship to the study procedure and as being unexpected (related unexpected SAES) will undergo expedited reporting to the main REC by ICR-CTSU.

Centres should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of the SAE.

11.9. EXPEDITED REPORTING OF RELATED UNEXPECTED SAES

If an SAE is defined as related and unexpected by the Chief Investigator, ICR-CTSU will report the SAE to the main REC within 15 days from the date the Chief Investigator or designated Co-Investigator became aware of the event. Any subsequent reporting will be carried out as appropriate.

11.10. FOLLOW UP OF SERIOUS ADVERSE EVENTS

Centres should continue to follow up SAES until the event is resolved e.g. recovered, recovered with sequelae, or died. Information on outcome of the SAE should be completed on the relevant PROMPTS trial protocol version 7.0 – 29 November 2016

part of the original SAE and faxed to ICR-CTSU as soon as the Principal Investigator becomes aware.

11.11. ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS

An annual report of related unexpected SAEs will be provided to the Main REC, by ICR-CTSU, in the annual progress report at the end of the reporting year. This will be defined as the anniversary of the date when the study received a favourable opinion from the Main REC.

12. STATISTICAL CONSIDERATIONS

The study is aimed at comparing how the experimental intervention (screening MRI and pre-emptive radiotherapy) compares to what we consider to be standard practice which is observation with MRI spine if there is clinically evident neurologic deficit.

For screening MRI to be deemed a better schedule than observation, the proportion of patients who develop neurologic deficit should be significantly less.

12.1. SAMPLE SIZE CALCULATION

414 patients will be randomised in a 1:1 ratio to the control and intervention groups.

The sample size is based on a superiority design using the log-rank comparison of the proportion of patients with cSCC at one year. The incidence of cSCC at one year in the control arm is estimated to be 15.6%. This is based on the following assumptions:

- the baseline prevalence of rSCC is 12.9%. This figure is the average rSCC rate detected by MRI in metastatic CRPC patients with no back pain and no analgesics (i.e. the eligible population for PROMPTS) reported in the non-randomised studies of Bayley⁸ (5/29 patients) and Venkitaraman²² (3/33 patients).
- all patients with rSCC will develop cSCC by one year if untreated
- 3.2% of rSCC “negative” patients will develop cSCC by one year⁸ (also untreated).

With 414 patients (71 events) there is 85% power to detect a 50% relative reduction in one year incidence of cSCC (from 15.6% control to 7.8% intervention). This corresponds to a hazard ratio (HR) of 0.48 (with a 5% two-sided alpha).

The sample size assumes uniform accrual over a 4 year period and a minimum of one year of follow-up for all patients. Death is treated as a censoring event assuming a median overall survival of 19 months⁴⁹. No adjustment for non-compliance has been made as eligible patients are not anticipated to withdraw from trial intervention.

It should be noted that the sample size calculations are sensitive to the assumptions made about the prevalence rSCC and the effectiveness of the intervention. The figure of 12.9% comes from two studies in which the subgroup of CRPC patients without back pain and not on analgesics is small and it may be that in the multi-centre phase III trial setting the estimates of SCC rates in both arms are lower than predicted from these studies. With 414 patients, there will be adequate statistical power if observed rSCC rates are lower than those estimated above. As an example, there would be 80% power to detect a 50% relative reduction from 11.5% to 5.7% in 1 year incidence of cSCC.

12.2. ENDPOINT DEFINITIONS

Primary endpoint

Incidence of and time to development of confirmed cSCC. One year incidence is of primary interest. Time will be measured from randomisation.

Confirmed cSCC is defined as per NICE metastatic SCC guidelines i.e. “spinal cord or cauda equina compression by direct pressure and/or induction of vertebral collapse or instability by metastatic spread or direct extension of malignancy that threatens or causes neurological disability”. See section (9.1).

Episodes of SCC suspected clinically will be confirmed by MRI (usually Bilsky score 2 or 3); or rarely by other clinically appropriate imaging when MRI is contraindicated.

Secondary Endpoints

- Rate of detection of rSCC (Bilsky 1a-3) on the baseline screening MRI (in the intervention group only);
- Incidence of and time to functional neurological deficit due to clinical SCC - Neurological deficit will be assessed using the Frankel spinal cord injury assessment tool. This indicates the grade of neurological and ambulatory compromise on a 5 point scale and has been used in other studies of metastatic spinal disease (appendix B). Functional neurological deficit will be defined as Frankel Score A-D.
- Incidence of and time to irreversible functional neurological deficit (irreversible defined as no improvement after 3 and 6 months following first incidence).
- Incidence of SCC (Bilsky 1-3) in both the control and intervention groups during follow-up.
- Pain - this will be measured using the Brief Pain Inventory (short form).
- Quality of life – this will be measured using the standard EORTC QLQ C30, EQ5D-5L and HADS questionnaires
- Overall survival – will include deaths from any cause
- Cost effectiveness.

12.3. STATISTICAL ANALYSIS

Primary analysis set

Analyses of outcome data will be on the basis of intention to treat and therefore include all patients who deviate from trial protocol for the following reasons: ineligibility for trial intervention, unwillingness to continue with follow-up visits, withdrawal of consent after randomisation, deviation from allocated intervention and loss to follow-up.

Analysis methods

The primary analysis will be based a log-rank intention to treat comparison of cSCC incidence in the intervention and control group. Time to cSCC, time to neurological deficit, and overall survival will be analysed using Kaplan-Meier estimates and the log-rank test, with event rates at 1 and 2 years reported for each group. A Cox model will be used to adjust for important prognostic factors including alkaline phosphatase (normal vs. raised), number of previous treatments (first line failure vs. 2nd or later), use of previous spinal radiotherapy and/or surgical procedure for metastatic disease (yes/no), number of spinal metastases on bone scan, time since development of CRPC, time since start of continuous hormone treatment, performance status and PSA or PSA doubling time. Alternatives such as a piecewise-constant HR will be considered if the proportional hazards assumption is not appropriate. The use of cumulative incidence curves, Gray's test and a Fine & Gray model for time to cSCC treating death as a competing risk will also be explored.

The proportion of patients having MR and total number of MR scans performed will be reported for both groups. The observed baseline rate of rSCC will be presented for the intervention group with a 95% confidence interval; subsequent rates of rSCC detected by the 6-month screening schedule in patients with rSCC identified and treated at baseline will be reported separately. A multiple logistic regression model will be used to identify clinical predictors of rSCC in the baseline MRI.

The primary analysis will be event driven and will be conducted once all patients have been followed up for at least one year. A formal interim analysis will be conducted after 54 patients have been recruited to the intervention group (estimated to be approximately 6 months after start of PROMPTS trial protocol version 7.0 – 29 November 2016

recruitment). The timing of subsequent analyses for the Independent Data Monitoring Committee (IDMC) review will be at the discretion of the IDMC but meetings are planned at least annually.

There are no pre-planned subgroup analyses.

Quality of life (QL) assessment will be conducted by questionnaire (EORTC QLQ C30, HADS and EQ-5D-5L) and will be assessed at baseline and 3, 6, 12, 15, 18, 21, 24, 30 and 36 months.

The main scales of interest are functional QL, global health QL and pain. According to the EORTC reference manual⁵⁰, for the physical functioning subscale a difference of 8 points is considered clinically relevant and standard deviation for metastatic prostate cancer is 21.9 points. Using a two-sided 5% significance level there is 90% power to detect an 8-point difference in this subscale with 159 patients per group (this requires only 59% participation in QL study). The primary endpoint will be physical functioning from the EORTC QLQ C30.

Analysis of QL will include between group comparisons at individual time points. Methods to model changes over time, such as generalised estimating equations, will be explored. Scales of interest will be analysed using total scale score (e.g. ANCOVA of change from baseline); dichotomisation of scales or individual items of relevance will also be considered where clinically relevant, analysed by chi-square-based or Fisher's exact test as appropriate. To account for multiple testing, only p-values 0.01 will be considered statistically significant on endpoints other than the primary QL endpoint.

Pain will be measured using the Brief Pain Inventory (BPI) Short form assessed at the same timepoints as QL. The BPI will be analysed according to standard methods⁵¹ Pain severity will be presented as mean scores for each of the individual scales of "worst", "least", "average" and "now" at each time point. A mean pain severity score (a composite of all 4 pain severity scores) will also be presented comparisons made between randomised groups at each time point. Pain interference will be presented as mean scores for the 7 individual daily activities (general activity, mood, walking ability, normal work, relations, sleep and enjoyment of life) at each time point. A mean pain interference score (a composite of the 7 daily activities) will also be presented and compared between randomised groups at each time point. If at least 4/7 individual pain severity scores have been given then a mean score will be calculated. To account for multiple testing, only p-values below 0.01 will be considered statistically significant.

Stopping Rules and Interim Analysis

An early stopping rule based on detecting a minimum level of rSCC is proposed.

For there to be an opportunity to prevent cSCC with pre-emptive treatment, rSCC needs to be detected. If the "pick-up" rate is very low, the opportunity to prevent SCC is small and the intervention is unlikely to be cost-effective (at a population level). The rSCC pick up rate will be continuously monitored throughout the course of the trial by the Independent Data Monitoring Committee and the Trial Steering Committee It will ultimately be for the TSC to agree the lowest acceptable rate of detecting rSCC which would warrant continuing with the study. As an example, it would be considered worthwhile screening patients with MRI if the rSCC pick-up rate is 1 in 10 (10%) but not if it is as low as 1 in 40 (2.5%). Under these assumptions, an interim analysis would be carried out to assess the detection rate of rSCC after 54 patients had been recruited to the intervention group. If less than 4 cases of rSCC had been identified (ruling out a lower limit of the confidence interval of 2.5% with 80% power and a one-sided alpha of 5% if the true rate is 10%), then the TSC would be asked to advise on continuing recruitment to the study having considered all internal and external evidence.

No early stopping rules for toxicity are proposed.

Recruitment milestones will be set in discussion with the TSC. It is proposed that recruitment rates are closely monitored and subject to formal review by the TSC at 12 and 18 months after five centres have opened and have recruited at least one patient with subsequent recruitment conditional on demonstrating that the target sample size is achievable within agreed timelines. An IDMC will review recruitment rates, safety and emerging efficacy data in confidence at least annually.

13. TRIAL MANAGEMENT

13.1. TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be set up and will include the Chief Investigator, Co-investigators and identified collaborators, the Trial Statistician and the Trial Manager. Principal Investigators and key study personnel will be invited to join the TMG as appropriate to ensure representation from a range of centres and professional groups. Notwithstanding the legal obligations of the Co-Sponsors and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. Where possible, membership will include a lay/consumer representative. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSUS.

13.2. TRIAL STEERING COMMITTEE (TSC)

This study will fall under the governance of the ICR-CTSUS Prostate Radiotherapy Trial Steering Committee. This group will include an independent Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members, the Chief Investigator and the ICR-CTSUS Scientific Lead. It is the role of the TSC to monitor progress of the trial and to ensure there is adherence to the protocol and the principles of Good Clinical Practice. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSUS.

13.3. INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An IDMC will be instigated to monitor the progress of the trial. Membership of the IDMC will be proposed by the TMG and approved by the TSC. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSUS. The IDMC should meet in confidence at regular intervals, and at least annually. A report of the findings and recommendations will be produced following each meeting. This report will be submitted to the TMG and TSC, and if required, the main REC.

The IDMC reserve the right to release any data on outcome or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

14. RESEARCH GOVERNANCE

The Institute of Cancer Research (ICR) is the sponsor of this trial in accordance with the Research Governance Framework for Health and Social Care and the principals of Good Clinical Practice (GCP).

14.1. SPONSOR RESPONSIBILITIES

The Institute of Cancer Research has sponsorship responsibility for obtaining authorisation and appropriate ethics committee opinion.

14.2. RESPONSIBILITIES OF CHIEF INVESTIGATOR

The Chief Investigator is responsible for:

- Selection of investigators

- Prompt decision as to which serious adverse events are related and unexpected; and
- Prompt reporting of that decision to the ICR-CTSU, for onward reporting to the main REC.

14.3. RESPONSIBILITIES OF ICR-CTSU

ICR-CTSU has overall responsibility for facilitating and co-ordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting interim and final analyses.

The responsibilities of ICR-CTSU for the day-to-day management of the trial will include the following:

- Ensuring an appropriate ethics opinion has been sought, and any amendments have been approved.
- Giving notice of amendments to protocol, making representations about amendments to the main REC.
- Giving notice that the trial has ended.
- Randomising patients.
- Collating QL questionnaires returned by post.
- Raising and resolving queries with local investigators.
- Logging clinical and QL data received; raising queries.
- Keeping records of all serious adverse events (SAEs) reported by investigators.
- Notifying the main REC and Investigators of related unexpected Serious Adverse Events.

14.4. RESPONSIBILITIES OF PARTICIPATING CENTRES

Centres wishing to recruit to this study will be asked to provide evidence that they can deliver protocol treatment. This will include:

- Putting and keeping in place arrangements to adhere to the principles of GCP.
- Keeping a copy of all 'essential documents' (as defined under the principles of GCP) and ensuring appropriate archiving of documentation once the trial has ended.
- Providing evidence that local practice conforms to the standards set in the NICE Improving Outcomes Guidance;

Responsibilities are defined in an agreement between an individual participating centre and The Institute of Cancer Research.

15. TRIAL ADMINISTRATION AND LOGISTICS

15.1. PROTOCOL COMPLIANCE

The PROMPTS trial is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the Research Governance Framework for Health and Social Care and the principles of GCP. Before activating the trial, participating centres are required to sign an agreement accepting responsibility for all trial activity which takes place within their centre. Sites may only commence recruitment once centre agreements have been signed by both parties, trial documentation is in place and a site initiation (visit or teleconference) has taken place. Site initiation visits will be conducted at sites where the Principal Investigator has requested one or where ICR-CTSU deems it is appropriate.

15.2. INVESTIGATOR TRAINING

Prior to commencing trial recruitment, training and advice will be provided by members of the Trial Management Group via a trial launch meeting, training workshops, and QA feedback to identified key individuals in each participating centre. Training will include discussion on the background to

the study and discussion on the issues of clinical equipoise. Participating centres will be asked to maintain a screening log to monitor randomisation acceptance rates, and additional support/training will be offered when lower than anticipated rates are encountered.

15.3. DATA ACQUISITION

The clinical data should be recorded on the PROMPTS case report forms (CRFs) and the relevant pages forwarded to ICR-CTSU in a timely manner. The Trial Management Group reserves the right to amend or add to the CRFs as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres in accordance with the guidelines provided by ICR-CTSU. Where appropriate, data may need to be collected retrospectively if an additional question has been added to the CRF.

By participating in the PROMPTS trial, the Principal Investigators at each centre are confirming agreement with his/her local NHS Trust to ensure that:

- Sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
- Source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- Original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- All essential documents are retained for five years after the trial ends to comply with current legislation.
- Staff will comply with the protocol and Trial Guidance Notes for PROMPTS.

On receipt at ICR-CTSU, CRFs will be recorded as received and any missing forms will be reported to the originating site. Illegible forms may be returned to site for clarification.

15.4. CENTRAL DATA MONITORING

ICR-CTSU will review incoming CRFs for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found, queries will be sent to the relevant centre for resolution. Following initial review, the CRF data items will be entered into the clinical study database held at ICR-CTSU.

Data will be further reviewed for data anomalies / missing data, by central statistical monitoring. Any systematic inconsistencies identified may trigger monitoring visits to centres.

15.5. ON SITE MONITORING

If a monitoring visit is required, ICR-CTSU will contact the centre to discuss dates of proposed visit. Once a date has been confirmed, the centre should ensure that the relevant patient notes are available for monitoring.

If any problems are detected in the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator to resolve issues and, if necessary, to determine the centre's future participation in the study.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the site agreement and trial protocol to ensure the protection of patients' rights as detailed in the Declaration of Helsinki 1964 as amended October 1996.

15.6. PROTOCOL AMENDMENTS

Proposed major protocol amendments will be submitted to the TMG by the Chief Investigator. The TMG will agree protocol amendments prior to submission to the Main REC. Once approved the Principal Investigator at each centre will be informed of the change and sent all the associated documentation. It is the Principal Investigator's responsibility to submit amendments to their R&D department for approval. Confirmation that this has been done must be provided to ICR-CTSU.

15.7. END OF STUDY

For the purposes of ethics approval, the study end date is deemed to be the date of the last data capture.

15.8. ARCHIVING

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and substantiate the quality of the data collected. Essential documents will be maintained at ICR-CTSU in a way that will facilitate the management of the trial, audit and inspection. They should be retained for a sufficient period (at least 15 years) for possible audit. Documents should be securely stored and access restricted to authorised personnel.

16. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

16.1. RISK ASSESSMENT

This study has been formally assessed for clinical risk using a generic risk assessment.

16.2. PATIENT CONFIDENTIALITY

Patients will be asked to consent to their full name being collected at randomisation in addition to their date of birth, hospital number, postcode and NHS number (CHI in Scotland) to allow tracing through their GP and national records to assist with long term follow up. The personal data recorded on all documents will be regarded as confidential, and any information which would allow individual patients to be identified will not be released into the public domain.

The Principal Investigator must maintain in strict confidence trial documents, which are to be held in the local centre (e.g. patients' written consent forms). The Principal Investigator must ensure the patient's confidentiality is maintained.

ICR-CTSU will maintain the confidentiality of all patients and will not reproduce or disclose any information by which patients could be identified. Representatives of ICR-CTSU and the regulatory authorities will be required to have access to patients notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems it is also necessary to have access to the complete study records provided that patient confidentiality is protected.

16.3. ETHICAL CONSIDERATIONS

It is the responsibility of the Chief Investigator to obtain a favourable ethical opinion (main REC approval). It is the responsibility of the Principal Investigator at each participating centre to obtain site-specific approval of the trial protocol and any subsequent amendments. All correspondence with the local REC should be filed by the Principal Investigator in the Site Investigator File.

Patients will be approached about participation in PROMPTS by a member of their clinical care or research team. They will receive a verbal explanation of the trial, together with a Patient Information Sheet which they will take home with them. It is the responsibility of the Principal Investigator to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved.

Sufficient time (a minimum of 24 hours) should be allowed for the patient to decide on trial entry. Patients must be informed about their right to withdraw from the trial at any time. Written patient information must be given to each patient before enrolment. They will be given at least 24 hours to make a decision about whether they would like to participate, during which time they will be able to discuss their options with friends, family or their GP. They will have the opportunity to raise any questions about PROMPTS with their clinical care or research team and these will be addressed prior to their decision about whether to participate. The written patient information is an approved patient information sheet according to national guidelines. This also outlines the QL study. Patients will be encouraged to participate in this associated study but if they subsequently decline, this will not exclude them from the main trial.

It is the responsibility of the Principal Investigator or designated representative, to obtain signed informed consent from all patients prior to inclusion in the trial.

16.4. PATIENT INFORMATION

The importance of providing a high level of information to patients is recognised. Local leaflets on radiotherapy should be provided by each centre, but these must be approved by the appropriate local research committees before distribution.

16.5. DATA SHARING

Data arising from this research will be managed and made available to maximise public benefit. Data sharing will be in a timely and responsible manner. Appropriate regulatory permissions relating to the ethical use of data must be in place before the data can be shared. Requests to use trial data must be submitted in writing to the ICR-CTSU for approval by the TMG and TSC.

16.6. DATA PROTECTION ACT (DPA)

ICR-CTSU will comply with all aspects of the DPA 1998. Any requests from patients for access to data about them held at ICR-CTSU should be directed to the Trial Manager in the first instance who will refer the request to the Data Protection Officer at The Institute of Cancer Research.

16.7. LIABILITY/INDEMNITY/INSURANCE

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

17. FINANCIAL MATTERS

The trial is investigator designed and led and has been approved by the Clinical Trials Advisory & Awards Committee (CTAAC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

The trial has received funding from Cancer Research UK. If further funding is received from any other source this will be made apparent in the patient information sheet and to the approving Main REC and CTAAC.

National RTQA and NCRN (or regional equivalent) network resources should be made available for PROMPTS, as the trial is part of the NIHR portfolio by virtue of its approval by CTAAC.

18. PUBLICATION POLICY

The main trial results will be published in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the Trial Management Group, and participating clinicians. All participating centres and clinicians will be acknowledged in this publication together with staff from the ICR-CTSU. All presentations and publications relating to the trial must be authorised by the Trial Management Group, on whose behalf publications should usually be made. Authorship of any secondary publications will reflect the intellectual and

PROMPTS trial protocol version 7.0 – 29 November 2016

time input into these, and will not necessarily be the same as on the primary publication. No investigator may present or attempt to publish data relating to the PROMPTS trial without prior permission from the Trial Management Group.

19. ASSOCIATED STUDIES

19.1. QUALITY OF LIFE

Quality of life (QL) assessment will be conducted by questionnaire (EORTC QLQ C30, EQ-5D-5L and HADS) and will be assessed at baseline and 3, 6, 12, 15, 18, 21, 24, 30 and 36 months. Participation in the QL study is not optional. Due to the relatively poor health of participants and the potential for rapid decline, questionnaires will be handed out in clinic (so as to avoid the situation where a questionnaire is sent centrally from the CTU to a patient with very short life expectancy or recently deceased). Pain will be measured using the Brief Pain Inventory (BPI) Short form assessed at the same timepoints as QL.

19.2. HEALTH ECONOMICS

An economic evaluation will be integrated into the design of the trial, and supplemented with decision modelling as the benefits of intervention are likely extend beyond the duration of the trial. The specific aim of the evaluation will be to compare the cost-effectiveness of screening MRI & pre-emptive treatment against standard practice i.e. MRI spine performed if patients develop clinical neurological deficit or significant spinal pain and subsequent treatment if there is overt SCC. The type of economic evaluation will be a cost-utility analysis, estimated using quality-adjusted life-years (QALYs). The analysis will be performed from a NHS and personal social services cost perspective. Resource use data to be collected alongside the RCT will include those relating to the screen, treatment and all aspects of health care in and outside of the treating centre. Resources directly attributable to the trial protocol will be excluded from the analysis. Health resources will be valued using nationally available NHS cost data. Regression methods will be used to account for missing trial data and censoring, and costs and QALYs occurring after 1 year will be discounted at 3.5% per annum. Results will be presented as mean costs, mean QALYs along with 95% confidence intervals, and the probability that the intervention is cost-effective at different levels of willingness to pay for a QALY gained. Utilities will be calculated using the EQ-5D-5L. Sensitivity analysis will test whether the results are robust to methodological assumptions. The PROMPTS Resource Use Questionnaire will be given to all patients who have developed spinal cord compression (radiological and clinical). This questionnaire will look at the changes that have been made or are planned to the house in which the patient lives. The questionnaire will be optional and if the patient does not wish to take part in the sub-study then they can still take part in the main PROMPTS trial.

References

1. NICE guideline: Metastatic spinal cord compression: Diagnosis and management of patients at risk of or with metastatic spinal cord compression. National Institute of Health and Clinical Excellence CG75, 2008

2. Loblaw DA, Perry J, Chambers A, et al: Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. *J Clin Oncol* 23:2028-37., 2005
3. Maranzano E, Trippa F, Chirico L, et al: Management of metastatic spinal cord compression. *Tumori* 89:469-75, 2003
4. Levack P, Graham J, Collie D, et al: Don't wait for a sensory level--listen to the symptoms: a prospective audit of the delays in diagnosis of malignant cord compression. *Clin Oncol (R Coll Radiol)* 14:472-80, 2002
5. Rades D, Stalpers LJ, Veninga T, et al: Evaluation of functional outcome and local control after radiotherapy for metastatic spinal cord compression in patients with prostate cancer. *J Urol* 175:552-6, 2006
6. Loblaw DA, Laperriere NJ, Mackillop WJ: A population-based study of malignant spinal cord compression in Ontario. *Clin Oncol (R Coll Radiol)* 15:211-7, 2003
7. Tazi H, Manunta A, Rodriguez A, et al: Spinal cord compression in metastatic prostate cancer. *Eur Urol* 44:527-32., 2003
8. Bayley A, Milosevic M, Blend R, et al: A prospective study of factors predicting clinically occult spinal cord compression in patients with metastatic prostate carcinoma. *Cancer* 92:303-10., 2001
9. Cook AM, Lau TN, Tomlinson MJ, et al: Magnetic resonance imaging of the whole spine in suspected malignant spinal cord compression: impact on management. *Clin Oncol* 10:39-43, 1998
10. Rades D, Dunst J, Schild SE: The first score predicting overall survival in patients with metastatic spinal cord compression. *Cancer* 112:157-61, 2008
11. Rades D, Fehlauer F, Schulte R, et al: Prognostic factors for local control and survival after radiotherapy of metastatic spinal cord compression. *J Clin Oncol* 24:3388-93, 2006
12. Maranzano E, Latini P: Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial. *Int J Radiat Oncol Biol Phys* 32:959-67, 1995
13. Osborn JL, Getzenberg RH, Trump DL: Spinal cord compression in prostate cancer. *J Neurooncol* 23:135-47, 1995
14. Husband DJ: Malignant spinal cord compression: prospective study of delays in referral and treatment. *Bmj* 317:18-21, 1998
15. Turner S, Marosszeky B, Timms I, et al: Malignant spinal cord compression: a prospective evaluation. *Int J Radiat Oncol Biol Phys* 26:141-6, 1993
16. Helweg-Larsen S, Sorensen PS, Kreiner S: Prognostic factors in metastatic spinal cord compression: a prospective study using multivariate analysis of variables influencing survival and gait function in 153 patients. *Int J Radiat Oncol Biol Phys* 46:1163-9, 2000
17. Helweg-Larsen S: Clinical outcome in metastatic spinal cord compression. A prospective study of 153 patients. *Acta Neurol Scand* 94:269-75, 1996
18. Solberg A, Bremnes RM: Metastatic spinal cord compression: diagnostic delay, treatment, and outcome. *Anticancer Res* 19:677-84, 1999
19. Leviov M, Dale J, Stein M, et al: The management of metastatic spinal cord compression: a radiotherapeutic success ceiling. *Int J Radiat Oncol Biol Phys* 27:231-4, 1993
20. Bach F, Larsen BH, Rohde K, et al: Metastatic spinal cord compression. Occurrence, symptoms, clinical presentations and prognosis in 398 patients with spinal cord compression. *Acta Neurochir (Wien)* 107:37-43, 1990
21. Rades D, Veninga T, Stalpers LJ, et al: Improved Posttreatment Functional Outcome is Associated with Better Survival in Patients Irradiated for Metastatic Spinal Cord Compression. *Int J Radiat Oncol Biol Phys* 67:1506-9, 2007
22. Venkitaraman R, Sohaib SA, Barbachano Y, et al: Detection of occult spinal cord compression with magnetic resonance imaging of the spine. *Clin Oncol (R Coll Radiol)* 19:528-31, 2007
23. Lu C, Gonzalez RG, Jolesz FA, et al: Suspected spinal cord compression in cancer patients: a multidisciplinary risk assessment. *J Support Oncol* 3:305-12., 2005
24. Talcott JA, Stomper PC, Drislane FW, et al: Assessing suspected spinal cord compression: a multidisciplinary outcomes analysis of 342 episodes. *Support Care Cancer* 7:31-8., 1999
25. Venkitaraman R, Barbachano Y, Dearnaley DP, et al: Outcome of early detection and radiotherapy for occult spinal cord compression. *Radiother Oncol* 85:469-72, 2007
26. Husband DJ, Grant KA, Romaniuk CS: MRI in the diagnosis and treatment of suspected malignant spinal cord compression. *Br J Radiol* 74:15-23., 2001
27. Godersky JC, Smoker WR, Knutson R: Use of magnetic resonance imaging in the evaluation of metastatic spinal disease. *Neurosurgery* 21:676-80., 1987
28. Sorensen S, Helweg-Larsen S, Mouridsen H, et al: Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. *Eur J Cancer* 30A:22-7, 1994
29. Vecht CJ, Haaxma-Reiche H, van Putten WL, et al: Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology* 39:1255-7, 1989
30. Maranzano E, Latini P, Beneventi S, et al: Radiotherapy without steroids in selected metastatic spinal cord compression patients. A phase II trial. *Am J Clin Oncol* 19:179-83, 1996

31. Heimdal K, Hirschberg H, Slettebo H, et al: High incidence of serious side effects of high-dose dexamethasone treatment in patients with epidural spinal cord compression. *J Neurooncol* 12:141-4, 1992
32. Loblaw DA, Laperriere NJ: Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. *J Clin Oncol* 16:1613-24, 1998
33. Rades D, Veninga T, Stalpers LJ, et al: Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. *Int J Radiat Oncol Biol Phys* 64:182-8, 2006
34. Pigott KH, Baddeley H, Maher EJ: Pattern of disease in spinal cord compression on MRI scan and implications for treatment. *Clin Oncol (R Coll Radiol)* 6:7-10, 1994
35. Kaplan ID, Valdagni R, Cox RS, et al: Reduction of spinal metastases after preemptive irradiation in prostatic cancer. *Int J Radiat Oncol Biol Phys* 18:1019-25, 1990
36. Helweg-Larsen S, Hansen SW, Sorensen PS: Second occurrence of symptomatic metastatic spinal cord compression and findings of multiple spinal epidural metastases. *Int J Radiat Oncol Biol Phys* 33:595-8, 1995
37. Soerdjbalie-Maikoe V, Pelger RC, Lycklama a Nijeholt GA, et al: Strontium-89 (Metastron) and the bisphosphonate olpadronate reduce the incidence of spinal cord compression in patients with hormone-refractory prostate cancer metastatic to the skeleton. *Eur J Nucl Med Mol Imaging* 29:494-8, 2002
38. Rades D, Stalpers LJ, Hulshof MC, et al: Comparison of 1 x 8 Gy and 10 x 3 Gy for functional outcome in patients with metastatic spinal cord compression. *Int J Radiat Oncol Biol Phys* 62:514-8, 2005
39. Rades D, Fehlauer F, Stalpers LJ, et al: A prospective evaluation of two radiotherapy schedules with 10 versus 20 fractions for the treatment of metastatic spinal cord compression: final results of a multicenter study. *Cancer* 101:2687-92, 2004
40. Rades D, Karstens JH, Alberti W: Role of radiotherapy in the treatment of motor dysfunction due to metastatic spinal cord compression: comparison of three different fractionation schedules. *Int J Radiat Oncol Biol Phys* 54:1160-4, 2002
41. Rades D, Lange M, Veninga T, et al: Preliminary results of spinal cord compression recurrence evaluation (score-1) study comparing short-course versus long-course radiotherapy for local control of malignant epidural spinal cord compression. *Int J Radiat Oncol Biol Phys* 73:228-34, 2009
42. Maranzano E, Latini P, Beneventi S, et al: Comparison of two different radiotherapy schedules for spinal cord compression in prostate cancer. *Tumori* 84:472-7, 1998
43. Chow E, Harris K, Fan G, et al: Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 25:1423-36, 2007
44. Klimo P, Jr., Thompson CJ, Kestle JR, et al: A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol* 7:64-76, 2005
45. Milross CG, Davies MA, Fisher R, et al: The efficacy of treatment for malignant epidural spinal cord compression. *Australas Radiol* 41:137-42, 1997
46. Patchell RA, Tibbs PA, Regine WF, et al: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet* 366:643-8, 2005
47. Harris JK, Sutcliffe JC, Robinson NE: The role of emergency surgery in malignant spinal extradural compression: assessment of functional outcome. *Br J Neurosurg* 10:27-33, 1996
48. Chataigner H, Onimus M: Surgery in spinal metastasis without spinal cord compression: indications and strategy related to the risk of recurrence. *Eur Spine J* 9:523-7, 2000
49. Tannock I.F. et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advance prostate cancer. *NEJM* 351(15): 1502-12, 2004
50. Scott et al. EORTC QLQ-C30 Reference Values. EORTC Quality of Life Group, July 2008.
51. http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/BPI_UserGuide.pdf
52. <http://info.cancerresearchuk.org/cancerstats/incidence/commoncancers/>
53. Bilsky et al: Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine* 13:324-328, 2010
54. Venkitaraman R et al. Frequency of screening magnetic resonance imaging to detect occult spinal cord compromise and to prevent neurological deficit in metastatic castration-resistant prostate cancer. *Clin Oncol (R Coll Radiol)*. Mar;22(2):147-52.) 2010

Appendix A - ECOG Scale

- 0 Fully active, able to carry out all pre-disease performance without restriction.

- 1 Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (e.g. light housework, office work).
- 2 Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
- 5 Dead.

Appendix B – Frankel Spinal Cord Injury Assessment Tool

Grade A	Complete neurological injury - no motor or sensory function clinically detected below the level of the injury.
---------	--

Grade B	Preserved sensation only - no motor function clinically detected below the level of the injury; sensory function remains below the level of the injury but may include only partial function (sacral sparing qualifies as preserved sensation).
Grade C	Preserved motor non-functional - some motor function observed below the level of the injury, but is of no practical use to the patient.
Grade D	Preserved motor function - useful motor function below the level of the injury; patient can move lower limbs and walk with or without aid, but does not have a normal gait or strength in all motor groups.
Grade E	Normal motor - no clinically detected abnormality in motor or sensory function with normal sphincter function; abnormal reflexes and subjective sensory abnormalities may be present.

Appendix C – Bilsky Spinal Cord Compression Scale⁵³ (modified)

0	Metastatic bone disease without epidural impingement
1a	Epidural impingement without deformation of the thecal sac
1b	Deformation of the thecal sac
1c	Deformation of the thecal sac with spinal cord abutment, but without cord compression
2	Spinal cord compression but with cerebrospinal fluid (CSF) visible around the cord
3	Spinal cord compression, no CSF visible around the cord
9	No bone metastasis (additional score for PROMPTS trial)