Non-inferiority randomised phase 3 trial comparing two radiation schedules (single vs. five fractions) in malignant spinal cord compression

Pierre G. Thirion, Mary T. Dunne, Paul J. Kelly, Aileen Flavin, Joe M. O'Sullivan, Dayle Hacking, Wojciech Sasiadek, Cormac Small, Maeve M. Pomeroy, Joseph Martin, Orla McArdle, Imelda Parker, Lydia S. O'Sullivan, Aoife M. Shannon, Angela Clayton-Lea, Conor D. Collins, Michael R. Stevenson, Alberto Alvarez-Iglesias, John G. Armstrong and Michael Moriarty

BACKGROUND: The optimal EBRT schedule for MSCC is undetermined. Our aim was to determine whether a single fraction (SF) was non-inferior to five daily fractions (5Fx), for functional motor outcome.

METHODS: Patients not proceeding with surgical decompression in this multicentre non-inferiority, Phase 3 trial were randomised to 10 Gy/SF or 20 Gy/5Fx. A change in mobility from baseline to 5 weeks for each patient, was evaluated by a Modified Tomita score: 1 = 'Walk unaided', 2 = 'With walking aid' and 3 = 'Bed-bound'. The margin used to establish non-inferiority was a detrimental change of −0.4 in the mean difference between arms.

RESULTS: One-hundred and twelve eligible patients were enrolled. Seventy-three patients aged 30–87 were evaluated for the primary analysis. The 95% CI for the difference in the mean change in mobility scores between arms was −0.12 to 0.6. Since −0.4 is not included in the interval, there is evidence that 10 Gy/SF is non-inferior to 20 Gy/5Fx. One grade 3 AE was reported in the 5Fx arm. Twelve (26%) patients in the 5Fx arm had a Grade 2–3 AE compared with six (11%) patients in the SF arm (p = 0.093).

CONCLUSION: For mobility preservation, one 10-Gy fraction is non-inferior to 20 Gy in five fractions, in patients with MSCC not proceeding with surgical decompression.

CLINICAL TRIAL REGISTRATION: Cancer Trials Ireland ICORG 05-03; NCT00968643; EU-20952.
estimated life expectancy of less than 6 months.\textsuperscript{17,18} Despite multiple studies reporting similar outcomes with SF RT,\textsuperscript{9,10,14,16–18} worldwide surveys of patterns of practice show consistent underuse of SF for bone metastases.\textsuperscript{5}

Purpose/objective

The aim of the Cancer Trials Ireland (formerly All Ireland Cooperative Oncology Research Group) ICORG 05-03 study was to determine if a 10 Gy/SF of EBRT is not inferior to the commonly used radiation schedule of 20 Gy/SFx, in terms of functional motor outcome, for the treatment of MSCC patients not proceeding with surgical decompression. The results were presented at the American Society for Radiation Oncology 2014 meeting.\textsuperscript{20} This paper presents the full report of the study based on the analysis of eligible patients with available data at baseline and at the 5-week follow-up.

METHODS

Study design

The trial was conducted across five Irish sites (Belfast, Cork, Dublin, Galway and Waterford). Patients were randomly assigned to one of two treatment arms in a 1:1 ratio, to receive EBRT delivering either an experimental 10 Gy/SF, or a 20 Gy/SFx standard fractionated radiation schedule. An Independent Data Monitoring Committee (IDMC) reviewed unblinded data for patient safety, and found no safety concerns with the trial intervention. There were no interim analyses for efficacy or futility. The primary outcome was the change in mobility status between baseline and the 5-week follow-up, evaluated by an in-house modified Tomita mobility scale that had three possible scores: 1 = ‘Unaided’, 2 = ‘With walking aid’ and 3 = ‘Bed-bound’. The scale was modified to allow for telephone follow-up. A detrimental difference of 0.4 between the two arms in the mobility-scale change between the baseline and 5-week assessment, was deemed unacceptable. An interim analysis in March 2011 of 47 evaluable patients found a residual standard deviation of 0.7, which was used in the sample size calculation. For this non-inferiority study to have a power of 80% for a test using a one-sided 95% confidence limit, that the mean difference in the mobility change between the arms would not include −0.4, required 38 evaluable patients in each arm, 76 evaluable patients overall. Evaluable patients were those with a documented mobility status at 5 weeks. A sample size of 126 patients was estimated as being necessary, given an anticipated early death-related attrition of 40%.

Participants

Eligibility criteria. The inclusion criteria were (1) age ≥18 years, (2) magnetic resonance imaging (MRI)-documented symptomatic MSCC/cauda equina syndrome (whole-spine MRI required), (3) histologically proven malignancy (excluding leukaemia, myeloma, lymphoma, germ cell tumours and primary spinal bone tumours), (4) Karnofsky Performance Status (KPS) ≥30% and (5) written informed consent. Patients with ≤2 compression levels were eligible. For the purpose of the trial, the diagnosis of symptomatic MSCC or cauda equina syndrome was based on a combination of clinical symptoms and MRI-based radiological criteria. The symptoms could be MSCC-level-related pain and/or neurological symptoms. MRI-based definition of MSCC was an epidural mass, touching, displacing, indenting the spinal cord or leading to complete loss of definition of the spinal cord or cauda equina. The exclusion criteria were (1) previous irradiation of any spinal segment to be included within the RT volume for the treatment of the MSCC, (2) isolated bone metastasis with controlled primary site, (3) patients deemed suitable for neurosurgical intervention or (4) those with a medical or psychiatric condition, which in the opinion of the investigator, contraindicates participation.

Randomisation. Patients were randomly assigned, using simple randomisation procedures (computerised random numbers), to one of two arms. The allocation sequence was concealed from the investigator in sequentially numbered, opaque sealed envelopes, opened only after the enrolled participants completed all baseline assessments. The sealed randomisation envelopes were prepared centrally for each participating centre prior to enrolling patients, each of the participating hospitals having their own series of sequential envelopes, and the randomisation arms being statistically pre-determined from a randomisation master list. The study could not be blinded, as this is not practical in the case of a radiation study addressing a fractionation question.

Treatment. The steroids, dose schedule and the EBRT technique (field arrangement, beam type and energy) were left to institutional practice and physician preferences. Regarding EBRT volume, the field included the compression level with a suitable margin, typically one to two vertebrae above and below the compression level. If a direct posterior field was indicated, the protocol stipulated that the prescription should be at cord depth (depth of the posterior border of the vertebral body calculated from the diagnostic MRI images). IMRT and stereotactic radiation therapy technique were not allowed. The emergency context made the implementation of central QA impossible.

After provision of informed consent and completion of EBRT simulation, patients were randomised to one of the two arms. In the control arm, patients received a total dose of 20 Gy/SFx (4 Gy/Fx) starting on the day of simulation. In the experimental arm, patients received 10 Gy/SF, delivered on the day of simulation.

Assessment. Identical follow-up schedules applied to both study groups. All patients were followed up until death. The initial assessment included history and physical examination, recording of symptoms (type, duration and graduation according to trial’s related scales), documentation of the underlying malignancy and previously received treatment (including radiotherapy) and completion of the Quality of life (QoL) questionnaire. Following treatment, patients were assessed at 1, 5 and 12 weeks, and then every 3 months until death, with a window of 5 working days allowed for the first follow-up and 7 working days thereafter. Post-treatment evaluation included survival status, documentation of ongoing medication and requirement of further EBRT, recording of symptoms and radio-induced side effects and completion of the QoL questionnaire. The evaluation scales were (1) an in-house modified Tomita 3-point scale for mobility (1 = ‘Unaided’, 2 = ‘With walking aid’ and 3 = ‘Bed-bound’), (2) an in-house 3-point scale for bladder function (1 = ‘Continent’, 2 = ‘Incontinent’ and 3 = ‘Catheterised’), (3) the Acute and long-term radio-induced toxicity RTOG scale, (4) VAS and (5) the EORTC QLQ–C30 questionnaire.

Outcomes

The primary outcome was the change in mobility status between baseline and 5 weeks, as evaluated by the in-house modified Tomita mobility scale.

The secondary objectives were to analyse QoL (evaluated by EORTC QLQ–C30 questionnaire, addressed in another paper\textsuperscript{21}), radiation-induced toxicity (RTOG toxicity scale), pain control (evaluated by a visual analogue scale, addressed in another paper\textsuperscript{21}), bladder function (evaluated by an ‘in-house’ bladder function scale) and overall survival (OS).

Statistical analysis

Individual patient changes in mobility and bladder function scores were determined by calculating the difference between the baseline score and the score at the time of follow-up. Mean
differences with 95% confidence interval (CI) in change between the groups were computed. A paired-sample t test was used to compare differences, from baseline to the 5-week follow-up. One-way between-group analyses of covariance (ANCOVA) were conducted to compare the effectiveness of the two different radiation schedules. For these analyses, the independent variable was the radiation schedule, the dependent variable was the score at 5 weeks post treatment and the covariate was the baseline score. Preliminary checks were conducted to ensure that there was no violation of the associated assumptions of normality, linearity, homogeneity of variances and homogeneity of regression slopes. All available data from eligible patients were included in the analyses.

Safety analyses included all eligible patients. The maximum toxicity occurring within 5 weeks of completing treatment and late toxicity—defined as events occurring or persistent 90 days or later post EBRT, were tabulated.

OS was calculated from the date of randomisation until death. Time to neurological deterioration was calculated from the date of randomisation to the date of the first worsening of either mobility or bladder function or the last follow-up. The following pre-determined potential prognostic factors for OS were evaluated: preserved baseline mobility, baseline KPS, young age, primary other than lung and dose fractionation. The Kaplan–Meier method was used to estimate OS. The log-rank test was used to compare differences in survival. The Cox proportional hazard model was used to assess potential prognostic factors on survival times.

Other continuous variables were analysed using the Mann–Whitney U test, and categorical variables were compared between arms using Fisher’s exact test. Statistical tests were two-sided, except for the primary endpoint, and assessed for significance at the 0.05 level. Statistical analyses were carried out using IBM® SPSS® statistical software version 23. All analyses were performed according to the intention-to-treat principle. The protocol did not allow the imputation of missing values.

RESULTS
Patient accrual and follow-up
From January 2006 to April 2014, five Irish institutions accrued 117 patients. Five patients were found to be ineligible (one because of previous irradiation of the relevant spinal segment not documented at the time of initial assessment and inclusion, two because of a change in the pathological diagnosis at the time of post-radiotherapy review and two because of non-completion of whole-spine MRI).

Seventy-six percent of the 1466 patients screened did not meet the inclusion criteria. The main reasons were MRI-documented MSCC not fulfilling the radiological definition (45%), no MR and/or no whole-spine MR performed (9%), no available documented histological proof of malignancy at the time of initial evaluation (18%) and previous irradiation of the relevant spinal segment (8%).

Five patients in the 20 Gy/SFx arm could not complete the allocated treatment because of early death or significant alteration of their general condition, but not because of toxicity. One-hundred patients were assessed at the 1-week follow-up. Thirty-three patients died before the 5-week follow-up, confirming that the protocol predicted a high attrition rate—estimated at 40%. On the other hand, only one patient in the 20 Gy/SFx arm was lost to follow-up, confirming the feasibility of the trial follow-up protocol. Consequently, 73 patients were evaluable for the primary-efficacy endpoint analysis (Fig. 1). One of the 73 (control arm) did not have an assessment at the 1-week follow-up assessment. Only 52 patients were available for the 12-week follow-up (20 had died and 1 was not contactable at the time). Twenty-two percent of the 73 patients (10 in the control arm and 6 in the experimental arm) had cauda equina.

Patient characteristics
The baseline characteristics of evaluable patients were balanced between arms (Table 1). There was no significant association between baseline mobility and arm (p = 0.544). The median baseline KPS was 70% (range: 30–100). Twenty percent of eligible patients had primary lung cancer compared with 10% of evaluable patients. Forty-two percent of eligible patients could walk unaided at baseline compared with 53% of evaluable patients. At baseline, all patients were on dexamethasone with a median dose of 8 mg (range: 2–16 mg).

Primary-efficacy endpoint
The median follow-up for neurological assessment was 5.6 months (range: 1–100 months) from consent, for evaluable patients. Only evaluable patients were included in the 5-week mobility analysis. Overall, EBRT—whatever the radiation schedule—led to a mobility improvement or stabilisation at 5 weeks in 11 and 63% of patients, respectively, but did not prevent a worsening in 26% of them (Table 2). The mobility score improved for eight patients: two patients improved from score 3 to score 1, five patients improved from score 3 to score 2 and one patient improved from score 2 to score 1. Table 3 shows the mobility status at 5 weeks, and 12 weeks post EBRT compared with baseline (Supplementary Table 1 shows the mobility status at 1 week post EBRT compared with baseline). The average change, in this case, a deterioration, in the Modified Tomita score from baseline to the 5-week assessment, was −0.3 (SD 0.78) in the Control group and −0.06 (SD 0.75) in the Trial group. The estimated difference between the two arms is therefore 0.24 in favour of the Trial group (differences calculated as Trial-Control with positive values indicating better improvement for the Trial group), with a 95% CI for the differences in means of −0.12 to 0.6. The lower bound of the two-sided 95% CI is equivalent to the lower bound of a one-sided 97.5% CI. Since −0.4 is not included in the interval, there is evidence that 10 Gy/SF is non-inferior to 20 Gy/SFx (Table 4).

The mean change in the mobility score was compared across the arms using ANCOVA where the response variable was the mobility score at 5 weeks, and the covariate was the score at baseline. There was a small-to-moderate statistically significant relationship between the pre-treatment and post-treatment mobility scores, as indicated by a partial eta-squared value of 0.33. After adjusting for pre-intervention mobility, the estimated difference in mean mobility score between the Control and Trial groups is 0.28 (95% CI −0.03 to 0.6). These estimates and confidence intervals are consistent with the hypothesis that the Trial arm is not inferior to the Control arm (lower bound of the confidence interval excludes the non-inferiority limit −0.4).

However, as the analysis of the mobility score as described in the protocol, treating this ordinal variable (with levels 1, 2 and 3) as continuous, might be considered flawed, the effect of the treatment group was explored further with the fitting of an ordinal logistic model where mobility was treated as an ordinal variable. The results were similar to those obtained from the ANCOVA analysis, with no significant differences between the two arms. The model showed that patients in the Trial arm had twice (2.16) the odds of a higher (vs. a lower) level of mobility than patients in the control arm, which supports the conclusion of non-inferiority of the Trial arm when treating the mobility score as numeric.

When categories were collapsed, the 5-week (n = 73) and 12-week (n = 52) ambulatory rates (unaided + aided) were 65% in the 20 Gy/SFx arm and 78% in the 10 Gy/SF arm (p = 0.337), and 68 and 85% (p = 0.254), respectively.

Secondary endpoints
Secondary-efficacy endpoint: bladder function preservation. Overall, EBRT—whatever the radiation schedule—led to a bladder
function improvement or stabilisation in 7 and 71% of patients, respectively, but bladder function worsened in 19% of them (Table 2). Information on 5-week bladder function was missing in two patients, one in each study arm.

After adjusting for pre-intervention scores, there was no significant difference between the two radiation schedules on post-treatment bladder function scores $F(1, 68) = 0.49, p = 0.487$, partial eta squared $= 0.007$ (Table 4). There was a small-to-moderate statistically significant relationship between pre-treatment and post-treatment bladder function scores, as indicated by a partial eta-squared value of 0.27.

Secondary-efficacy endpoint: overall survival. For eligible patients ($n = 112$), the median OS was 3 months ($95\% CI = 1.5–4.5$), with 1- and 2-year survival of 18 and 8%, respectively. Median OS was 3.0 months in each arm. On multivariate analysis, with age, mobility at baseline, mobility at week 5, preserved baseline mobility, KPS and lung primary cancer (Y/N) in the model, diagnosis of other than lung cancer was the strongest predictor of longer OS (HR: 3.0, 95% CI: 1.3–6.7, $p = 0.011$). Better mobility at week 5 (HR: 2.7, 95% CI: 1.3–5.6, $p = 0.006$), and younger age (HR: 1.03, 95% CI: 1.01–1.05, $p = 0.006$) were also predictive for longer OS.

For evaluable patients ($n = 73$), the median OS was 6.0 and 6.6 months, respectively, in the five and SF arms ($p = 0.392$).

Unplanned secondary-efficacy endpoint: time to neurological deterioration (death not an event). For evaluable patients ($n = 73$), the median time to neurological deterioration was 3 ($95\% CI = 2.5–3.4$), 1.7 and 3.1 months, respectively, in the 20 Gy/5Fx and 10 Gy/SF arm ($p = 0.332$).

Secondary endpoint: toxicity. For toxicity, the analysis included all eligible patients, having received at least one dose of RT and completed at least one post-baseline assessment. Eleven percent of patients ($11/100$) had grade 2 acute lower intestinal toxicity, five (11%) in the 20 Gy/5Fx arm and six (11%) in the 10 Gy/SF arm. Six percent of patients (6/100) had grade 2 acute upper intestinal toxicity, five (11%) in the 20 Gy/5Fx arm and one (2%) in the 10 Gy/SF arm. Four patients had grade 2 acute fatigue (three in the 20 Gy/5Fx arm and one in the 10 Gy/SF arm). Three patients had grade 2 acute oesophageal toxicity (two in the 20 Gy/5Fx arm and one in the 10 Gy/SF arm). Three patients had grade 2 acute upper intestinal toxicity, five (11%) in the 20 Gy/5Fx arm and one (2%) in the 10 Gy/SF arm. Four patients had grade 2 acute fatigue (three in the 20 Gy/5Fx arm and one in the 10 Gy/SF arm). Three patients had grade 2 acute oesophageal toxicity (two in the 20 Gy/5Fx arm and one in the 10 Gy/SF arm). Two patients had grade 2 acute skin toxicity (one in each arm). One patient (in the 10 Gy/SF arm) had grade 2 acute salivary gland toxicity.

Ten percent of patients ($5/52$) had grade 2 late intestinal toxicity, four (16%) in the 20 Gy/5Fx arm and one (4%) in the
10 Gy/SF arm. Two patients had grade 2 late fatigue (one in each arm). There was one grade 3 late adverse event (pain-upper thigh-hip) in the 20 Gy/5Fx arm, and no higher-grade toxicity was reported at any time point.

When baseline AEs were discounted, 12 (26%) patients in the 20 Gy/5Fx arm had a Grade 2–3 AE at any time compared with six (11%) patients in the 10 Gy/SF arm (p = 0.069).

Re-treatment. Of the 101 eligible patients who had at least one post-RT assessment, 11 (11%) received further radiotherapy for MSCC at the same site, and two of the 11 received treatment to more than one site (these two had initially been treated at one site). Nine patients (17%) in the 10 Gy/SF arm received re-treatment compared with two patients (4%) in the 20 Gy/5Fx arm (p = 0.058). However, the median follow-up for neurological assessment was 3.0 months for those not receiving re-treatment and 6.6 months for those receiving re-treatment.

Of the 73 evaluable patients, 11 patients (15%) received further radiotherapy at the same site, with a statistically significant association between re-treatment and arm (p = 0.024) with 9 patients (25%) in the 10 Gy/SF arm receiving re-treatment compared with 2 patients (5.4%) in the 20 Gy/5Fx arm. The median follow-up for neurological assessment was 6.3 months for those not receiving re-treatment and 6.6 months for those receiving re-treatment.

**DISCUSSION**

ICORG 05-03 is one of six published or presented prospective randomised trials trying to identify the optimal radiation schedule for patients diagnosed with MSCC treated by primary radiotherapy.

| Table 1. Baseline patient demographic and clinical characteristics. | Eligible | Evaluable | 20 Gy/5Fx | 10 Gy/SF |
|---|---|---|---|---|
| Patients, No. (%) | 112 | 73 | 37 (51) | 36 (49) |
| Age, Median (range) | 68.8 (30–87) | 68.5 (30–87) | 68.5 (33–87) | 67.7 (30–85) |
| Sex, No. (%) | | | | |
| Men | 72 (64) | 44 (60) | 20 (54) | 24 (67) |
| Women | 40 (36) | 79 (40) | 17 (46) | 12 (33) |
| Primary, No. (%) | | | | |
| Breast | 22 (20) | 19 (26) | 10 (27) | 9 (25) |
| Lung | 22 (20) | 7 (10) | 2 (5) | 5 (14) |
| Prostate | 27 (24) | 22 (30) | 11 (30) | 11 (31) |
| Other | 41 (37) | 25 (34) | 14 (38) | 11 (31) |
| Compression level | | | | |
| Cervical | 4 (4) | 1 (1) | 0 (0) | 1 (3) |
| Cervical–thoracic | 2 (2) | 2 (3) | 2 (5) | 0 (0) |
| Thoracic | 75 (67) | 52 (71) | 25 (68) | 27 (75) |
| Lumbar | 27 (24) | 15 (20) | 8 (22) | 7 (19) |
| Lumbar–sacral | 1 (1) | 0 | 0 | 0 |
| Sacral | 3 (3) | 3 (4) | 2 (5) | 1 (3) |
| Mobility | | | | |
| Unaided | 47 (42) | 39 (53) | 18 (49) | 21 (58) |
| With walking aid | 28 (25) | 16 (22) | 10 (27) | 6 (17) |
| Bed-bound | 37 (33) | 18 (25) | 9 (24) | 9 (25) |
| Bladder function | | | | |
| Continent | 82 (74) | 53 (74) | 25 (68) | 28 (80) |
| Incontinent | 7 (6) | 6 (8) | 4 (11) | 2 (6) |
| Catheterised | 22 (20) | 13 (18) | 8 (22) | 5 (14) |
| Missing | 1 | 1 | 0 | 1 |
| KPS | | | | |
| 30 | 3 (3) | 2 (3) | 0 (0) | 2 (6) |
| 40 | 7 (6) | 3 (4) | 2 (5) | 1 (3) |
| 50 | 34 (30) | 16 (22) | 10 (27) | 6 (17) |
| 60–80 | 52 (46) | 40 (55) | 20 (53) | 20 (56) |
| 90–100 | 16 (14) | 12 (16) | 5 (14) | 7 (20) |
| Dexamethasone dose | | | | |
| Median | 8 mg | 8 mg | 8 mg | 8 mg |
| Range | 2–16 mg | 2–16 mg | 2–16 mg | 4–16 mg |

Mobility: assessed by an in-house modified Tomita scale. Bladder function: assessed by an in-house scale. Gy, gray; Fx, fractions; SF, single fraction; SD, standard deviation; VAS, visual analogue scale.
In the present era of evidence-based medicine, randomised trials remain essential to provide clinicians with the necessary evidence to guide their daily practice. Interestingly, the rationale of all these randomised trials was based on the recognition of the burden of protracted radiation schedules for patients treated with MSCC, and they all compared a prolonged schedule with an accelerated one. The trials were designed to demonstrate either equivalence or non-inferiority (design information unavailable for one trial). All trials excluded patients eligible for surgery, recognising the superiority of the multimodality treatment for the very small fraction of patients eligible for surgery.8

Three trials included only patients with a predicted limited life expectancy (≤6 months), estimated using various algorithms. This trial did not select patients for their predicted life expectancy.

The challenge of conducting trials in the studied population is the high attrition rate related to early death reported in other trials from 7% to 24% at 4 weeks, 51% at 8 weeks post treatment and 35% at 5 weeks in this trial.

The other randomised trials compared various radiation schedules, e.g. 30 Gy delivered in 3–10 fractions, 20 Gy in 5 fractions, 16 Gy in 2 fractions, 8 or 10 Gy in 1 fraction and 20 × 2 Gy illustrating the current absence of standard of care. The primary endpoints were functional outcome/mobility, assessed by various mobility scales, comparing for each individual patient the early post-treatment score achieved at 4–8 weeks with the pre-radiotherapy baseline one. All trials concluded that there was no statistically significant difference in the short-term efficacy of the short-radiation schedule when compared with the more protracted higher-dose one, with similar toxicity.

Like other trials, the present one has several limitations. The rationale and form of the non-inferiority power calculation used for the sample size estimation assumed that the outcome variable (modified Tomita score) was a continuously distributed variable that can be analysed by ANCOVA. Strictly speaking, this is not true because the outcome variable is actually a 3-point ordinal variable. So, we have to assume that the outcome is effectively continuous but is ‘rounded’ to one of only three possible values.
(1) Practice and physician preferences, partly due to the context of arrangement, beam type and energy) were left to institutional − interval for the differences between the groups is clearly above the after the closure of the study, had minimal effect, as the con − difference of 10 Gy/SF minus 20 Gy/5Fx; a positive difference favours SF. a: signi −ance level resulting from the ANCOVA model, including terms for treatment, and baseline covariate. * Two-sided; ** one-sided.

**Table 4.** Baseline and 5-week mobility and bladder function scores.

|                      | Baseline | 5-week | Between arms |
|----------------------|----------|--------|--------------|
|                      | n        | Mean   | SD | Mean   | SD | Difference | 95% CI  | p      |
| Mobility score       |          |        |    |        |    |            |        |        |
| 20 Gy/5Fx            | 37       | 1.76   | 0.83 | 2.05   | 0.81 | 0.24       | -0.12 to 0.6 | 0.077**/0.038** |
| 10 Gy/SF             | 36       | 1.67   | 0.86 | 1.72   | 0.81 |            |        |        |
| Bladder function score |        |        |    |        |    |            |        |        |
| 20 Gy/5Fx            | 36       | 1.54   | 0.84 | 1.78   | 0.96 | 0.05       | -0.35 to 0.45 | 0.487*   |
| 10 Gy/SF             | 35       | 1.34   | 0.72 | 1.51   | 0.89 |            |        |        |

SD: standard deviation, CI: confidence interval, Gy: gray, Fx: fractions, SF: single fraction.

(1) Higher score indicates worse mobility or bladder function.

(2) An administrative error whereby three patients were identified as non-eligible.

**Table 5.** Phase III randomised controlled trials comparing radiation schedules for MSCC.

| Series [reference] | Randomised (n) | Design | Arms* | Primary outcome | Ambulatory rates | OS (months) | Grade 3–4 toxicity |
|-------------------|---------------|--------|-------|-----------------|------------------|-------------|-------------------|
| Maranzano et al.19| 300 (92% evaluable at 4 wks) | Equivalence | 16 Gy/2Fx vs. split: 15 Gy/3Fx + 15 Gy/5Fx | Response rate at 4 wks | 68% | 4 | 6% (NS) |
| Maranzano et al.21| 327 (93% evaluable at 4 wks) | Equivalence | 8 Gy/1Fx vs. 16 Gy/2Fx | Symptom control at 4 wks | 62% | 4 | 0% (NS) |
| Abu-Hegazy and Wahba22 | 285 | Unavailable | 8 Gy/1Fx, 30 Gy/10Fx vs. 40 Gy/20Fx | Functional outcome at 4 wks | 65.8% | n/a | 0% (NS) |
| SCORE-2 Trial23 | 203 (76% evaluable at 4 wks) | Non-inferiority | 20 Gy/5Fx vs. 30 Gy/10Fx | Motor function at 4 wks | 71.8% | 3.2 | 0% (NS) |
| SCORAD III Trial24 | 688 (49% evaluable at 8 wks) | Non-inferiority | 8 Gy/1Fx vs. 20 Gy/5Fx | Ambulatory at 8 wks | 69.5% | 2.9 | 20.6% (NS) |
| This trial | 112 (65% assessable at 5 wks) | Non-inferiority | 10 Gy/1Fx vs. 20 Gy/5Fx | Change in mobility at 5 wks | 78% | 6.6* | 0% (NS) |

OS: overall survival, Fx: fractions, S: significant, NS: non-significant, wk: week.

and (2) the middle option lies approximately midway between the other two options. Further analysis, fitting an ordinal logistic model where the primary outcome mobility was treated as an ordinal variable, showed results similar to those from the ANCOVA analysis, with no significant differences between the two treatment arms. The model showed that patients in the Trial arm had twice the odds of a higher level of mobility than patients in the control arm, which supports the conclusion of non-inferiority of the Trial arm when treating the mobility score as numeric.

Our study was powered to find an unacceptable a detrimental difference of −0.4 between the two arms in the mobility-scale change between the baseline and 5-week assessment. The administrative error whereby three patients were identified as non-eligible after the closure of the study, had minimal effect, as the confidence interval for the differences between the groups is clearly above the −0.4 non-inferiority limit, so there is evidence of non-inferiority.

In addition, the steroids and the EBRT technique (field arrangement, beam type and energy) were left to institutional practice and physician preferences, partly due to the context of emergency. The applied radiotherapy technique therefore varied, with the sole restriction being the exclusion of IMRT and stereotactic-ablative radiotherapy.

Finally, the evaluation of the long-term local efficacy of the compared radiation schedules is made difficult because of the limited life expectancy of patients diagnosed with MSCC. In this trial, there was a significant difference in the KPS between those eligible and evaluable at the 5-week follow-up, suggesting that the KPS eligibility criterion was perhaps too low. Eligible patients had a median KPS of 50% compared with a median of 70% for evaluable patients (p = 0.001).

The potential limitation of short-course radiotherapy is a higher risk of in-field recurrence. Such a risk has been suggested in various publications. In a prospective non-randomised study, Rades et al. found that long-course RT resulted in significantly better 1-year in-field local control; however, the same authors did not find any difference for patients with limited life expectancy.

Three of the randomised trials also reported the in-field recurrence rate. Abu-Hegazy et al. reported a statistically non-significant difference for patients with limited life expectancy.
significantly higher cumulative rate of in-field recurrence at 2 years in patients treated with a SF of 8 Gy, when compared with those treated with protracted schedules [2-year in-field recurrence rate: 22.2% (8 Gy/1) vs. 16.1% (30 Gy/10) and 13.5% (40 Gy/20), p = 0.01]. Using MRI-based diagnosis, Maranzano et al. reported a higher in-field recurrence with lower dose short schedules in both their trials (3.5% (16 Gy/2) vs. 0% (30 Gy/8) and 6% (8 Gy/1) vs. 4% (16 Gy/2)) with a median time to occurrence of 5–8 months. In the present trial, the same was observed, with an increased rate of re-irradiation in patients on the SF arm, and median time to occurrence of less than 3 months.

The six randomised trials confirm the conclusions of the George et al. Cochrane review,29 which recommended a short-radiation schedule for ambulant adults with metastatic extradural MSCC with stable spines, and predicted survival of less than 6 months. When this trial was designed, the predicted survival score, generated by Rades et al. based on data from 1852 spinal cord compression patients, was not available.29

However, more research is warranted to improve the outcome of patients with MSCC treated with primary radiotherapy. As demonstrated by the published evidence, patient selection is crucial, and refinement of currently available individualised prognosis prediction tools is necessary to allow personalised management plans. The observed high early death rate—within the first 2 months after completion of radiotherapy—supports the hypothesis that some patients will not benefit from primary radiotherapy. However, the higher rate of in-field recurrence associated with short-course radiotherapy in patients surviving beyond 6 months provides a rationale for more aggressive therapy to improve local control. Re-treatment was addressed by Rades et al. in a retrospective investigation of 124 patients with rather favourable results.30 Radiation myelopathy was not observed after re-treatment. Thus, re-treatment appears feasible and helpful.

It should be noted that the response rate calculation method can be misleading, as it usually includes both ambulatory patients maintaining mobility and non-ambulatory patients recovering mobility. Unfortunately, the reported ambulatory recovery rate remains largely below 50%. Beyond demonstrating the importance of early diagnosis and treatment, this also highlights the limitation of EBRT.

One potential avenue of improvement is the use of a radiation- ablative schedule as this has demonstrated benefit in other clinical scenarios. The results of this trial indirectly support the rationale of such an approach, as an unplanned analysis showed a trend in favour of the SF schedule when the results are reported by preserved ambulatory rate-collapsed categories. Promising results coming from limited institutional experience and small phase II trials of Stereotactic Body Radiation Therapy or Radiosurgery in patients with MSCC have been reported. Ryu reported a 52% recovery rate and a 11% improvement rate in patients (n = 27) with symptomatic MSCC treated with radiosurgery delivering a SF of 16 Gy (12–20 Gy).31 Other authors reported similar promising outcomes with low toxicity,32–34 indicating that spine radiosurgery has the potential to change clinical practice in the management of MSCC.

This randomised trial demonstrates that 5-week mobility in the experimental arm, 10 Gy/SF, was non-inferior when compared with the multi-fraction standard arm, 20 Gy/SFx. Given the convenience of the single-fraction radiation schedule, both for patients and health facilities, the SF schedule should be considered in patients diagnosed with MSCC with a predicted short life expectancy.

ACKNOWLEDGEMENTS
Cancer Trials Ireland (formerly ICORG), as the study sponsor, was involved in protocol development and approval, study conduct and audit, data collection, management, analysis and interpretation, and in the decision to submit the paper for publication. The abstract of this study was presented at ASTRO in September 2014. ICORG 05-03: Prospective Randomised Non-Inferiority Phase 3 Trial Comparing Two Radiation Schedules in Malignant Spinal Cord Compression not proceeding with Surgical Decompression’.

AUTHOR CONTRIBUTIONS
Conception and design: M.M., O.Mc.A., C.S. and J.M.O. Acquisition, collection and assembly of data: A.F., J.M.O.S., D.H., W.S., C.S., M.M.P., J.M., O.Mc.A., L.S.O’S., A.M.S., A.C.-L., C.D.C., M.R.S., A.A.-I., J.G.A. and M.M. Data analysis and interpretation: M.T.D., P.G.T., I.P. and A.A.-I. Drafting of the work, revising it critically for important intellectual content and paper writing: P.G.T., M.T.D., J.G.A., P.J.K. and C.S. Final approval of the paper: all authors. Integrity of the work as a whole, from inception to published article: P.G.T. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: M.T.D. and P.G.T.

ADDITIONAL INFORMATION
Ethics approval and consent to participate Subjects provided their informed consent to participate. ICORG 05-03 was a ICH—Good Clinical Practice (GCP) compliant prospective non-inferiority Phase 3 trial, performed in accordance with the Declaration of Helsinki and with the approval of St. Luke’s Hospital Ethics and Medical Research Committee, the Clinical REC of The Cork Teaching Hospitals, Office for RECs Northern Ireland, REC HSE South Eastern Area and Clinical REC Merlin Park Hospital Galway.

Consent to publish Not applicable.

Data availability Data supporting the results reported in this article can be requested from Cancer Trials Ireland.

Competing interests The authors declare no competing interests.

Funding information Funding was received from St. Luke’s Institute of Cancer Research, under Grant S056, and the Health Research Board, under Grant CCT/06/10. The funding sources had no involvement in study design or conduct; in the collection, management, analysis and interpretation of data; preparation, review or approval of the paper; in the decision to submit the paper for publication.

Supplementary information is available for this paper at https://doi.org/10.1038/s41416-020-0768-z.

Note This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution 4.0 International (CC BY 4.0).

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES
1. Loblaw, D. A. & Lapierre, N. J. Emergency treatment of malignant extradural spinal cord compression: an evidence-based guideline. J. Clin. Oncol. 16, 1613–1624. (1998).
2. Prasad, D. & Shiff, D. Malignant spinal-cord compression. Lancet Oncol. 6, 15–24 (2005).
3. Oster, G., Lamerato, L., Glass, A. G., Richert-Boe, K. E., Lopez, A., Chung, K. et al. Natural history of skeletal-related events in patients with breast, lung, or prostate cancer and metastases to bone: a 15-year study in two large US health systems. Support Care Cancer 21, 3279–3286 (2013).
4. Schiff, D. Spinal cord compression. Neurol. Clin. 21, 67–86 (2003).
5. Chow, E. Palliative radiotherapy trials for bone metastases: a systematic review. J. Clin. Oncol. 25, 1423–36. (2007).
6. Loblaw, D. A., Lapierre, N. J. & Mackillop, W. J. A population based study of malignant spinal cord compression in Ontario. Clin. Oncol. 15, 211–217 (2003).
7. Sjoutos, P. J., Arbit, E., Meshulam, C. F. & Galichic, J. H. Spinal metastases from solid tumours. Anal. factors affecting survival. Cancer 76, 1453–1459 (1995).
8. Patchell, R. A., Tibbs, P. A., Regine, W. F., Payne, R., Saris, S., Kryscio, R. J. et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. Lancet 366, 643–648 (2005).
9. Makin W. P. Management of surgical cord compression due to metastatic cancer. Proceedings of the first International Consensus Workshop on Radiation Therapy in the treatment of metastatic and locally advanced cancer, Abstract 3A-7 (1990).
10. Jeremic B. Role of radiotherapy in metastatic spinal cord compression. Proceed- ings of the first International Consensus Workshop on Radiation Therapy in the treatment of metastatic and locally advanced cancer, Abstract 3A-8 (1990).

11. Jeremic, B., Grujicic, D., Cirovic, V., Djuric, L. & Mijatovic, L. Radiotherapy of metastatic spinal cord compression. Acta Oncologica 30, 985–986 (1991).

12. Maranzano, E., Latini, P., Perrucci, E., Beneventi, S., Lupattelli, M. & Corina, E. Short-course radiotherapy (8 Gy x 2) in metastatic spinal cord compression: an effective and feasible treatment. Int J. Radiat. Oncol. Biol. Phys. 38, 1037–1044 (1997).

13. Rades, D. 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, 1160–1164 (2002).

14. Hoskin, P. J., Grover, A. & Bhana, R. Metastatic spinal cord compression: radiotherapy outcome and dose fractionation. Radiother. Oncol. 68, 175–180 (2003).

15. Rades, D. A prospective evaluation of two radiotherapy schedules with 10 versus 20 fractions for the treatment of metastatic spinal cord compression. Cancer 101, 2687–2692 (2004).

16. Rades, D., Stalpers, L. J. A., Hulshof, M., Zschenker, O., Alberti, W. & Koning, C. Effectiveness and toxicity of single-fraction radiotherapy with 1x8 Gy for Metastatic spinal cord compression. Radiother. Oncol. 75, 70–73 (2005).

17. Rades, D., Stalpers, L. J., Hulshof, M. C., Borgmann, K., Karstens, J. H., Koning, C. C. et al. Comparison of 1 × 8 Gy and 10 × 3 Gy for Functional Outcome in patients with metastatic spinal cord compression Int. J. Radiat. Oncol. Biol. Phys. 62, 514–518 (2005).

18. Rades, D., Stalpers, L. J., Veninga, T., Schulte, R., Hoskin, P. J., Obralic, N. et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression in a series of 1304 patients. J. Clin. Oncol. 23, 3366–3375 (2005).

19. Maranzano, E., Bellavita, R., Rossi, R., De Angelis, V., Frattegiani, A., Bagnoli, R. et al. Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial. J. Clin. Oncol. 23, 3358–3365 (2005).

20. Thirion, P., O’Sullivan, L., Clayton-Lea, A., Small, C., McArdle, O., Kelly, P. et al. ICORG 05-03: Prospective randomized non-inferiority phase 3 trial comparing two radiation schedules in malignant spinal cord compression not proceeding with surgical decompression [abstract]. Int J. Radiat. Oncol. Biol. Phys. 90, 1263–1264 (2014).

21. Lee, K. A., Dunne, M., Small, C., Kelly, P., McArdle, O., O’Sullivan, L. et al. (ICORG 05-03): prospective randomized non-inferiority phase III trial comparing two radiation schedules in malignant spinal cord compression (not proceeding with surgical decompression); the quality of life analysis. Acta Oncol. 57, 965–972 (2018).

22. Maranzano, E., Trippa, F., Casale, M., Costantini, S., Lupattelli, M., Bellavita, R. et al. 8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase II randomized multicentre Italian trial. Radiother. Oncol. 93, 174–179 (2009).

23. Rades, D., Šegedin, B., Conde-Moreno, A. J., Garcia, R., Perpar, A., Metz, M. et al. Radiotherapy with 4 Gy × 5 versus 3 Gy × 10 for metastatic epidural spinal cord compression: final results of the SCORE-2 Trial (ARO 2009/01). J. Clin. Oncol. 30, 597–602 (2012).

24. Hoskin, P., Misra, V., Hopkins, K., Holt, T., Brown, G., Arnott, S. et al. SCORAD III: Randomized noninferiority phase III trial of single-dose radiotherapy (RT) compared to multifraction RT in patients with metastatic spinal canal compression (SCC). J. Clin. Oncol. 35 (suppl; abstr LBA10004) (2017).

25. Abu-Hegazy, M. & Wahba, H. A. Single-versus multi-fraction radiation treatment for metastatic spinal cord compression: functional outcome study. Chinese-German. J. Clin. Oncol. 10, 535–540 (2011).

26. Rades, D., Lange, M., Veninga, T., Stalpers, L. J. A., Bajrovic, A., Adamietz, I. A. et al. Final results of a prospective study comparing the local control of short-course and long-course radiotherapy for metastatic spinal cord compression. Int J. Radiat. Oncol. Biol. Phys. 79, 524–530 (2011).

27. Rades, D., Huttonlocher, S., Šegedin, B., Perpar, A., Conde, A. J., Garcia, R. et al. Single-fraction versus 5-fraction radiation therapy for metastatic epidural spinal cord compression in patients with limited survival prognoses: results of a matched-pair analysis. Int J. Radiat. Oncol. Biol. Phys. 93, 368–372 (2015).

28. George, R., Jeba, J., Ramkumar, G., Chacko, A. G. & Tharyan, P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst. Rev. 9, CD006716 (2015).

29. Rades, D., Dunst, J. & Schild, S. E. The first score predicting overall survival in patients with metastatic spinal cord compression. Cancer 112, 157–161 (2008).

30. Rades, D., Rudat, V., Veniga, T., Stalpers, L. J. A., Hoskin, P. J. & Schild, S. E. Prognostic factors for functional outcome and survival after reirradiation for in-field recurrences of metastatic spinal cord compression. Cancer 113, 1090–1096 (2008).

31. Ryu, S., Rock, J., Jain, R., Lu, M., Anderson, J., Jin, J. Y. et al. Radiosurgical decompression of metastatic epidural compression. Cancer 116, 2250–2257 (2010).

32. Lee, I., Omodon, M., Rock, J., Schultz, I. & Ryu, S. Stereotactic radio-surgery for high-grade metastatic epidural cord compression. J. Radiosurg SRT 3, 51–58 (2014).

33. Yang, K., Balagamwala, E. H., Tariq, M. B., Suh, J. H., Angelov, L., Reddy, C. A. et al. Spine stereotactic body radiation therapy for management of spinal cord compression. Int J. Radiat. Oncol. Biol. Phys. 93, E64–E65 (2015).

34. Anand, A. K., Venkadamanickam, G., Punnakal, A. U., Walia, B. S., Kumar, A., Bansal, A. K. et al. Hypofractionated stereotactic body radiotherapy in spinal metastasis - with or without epidural extension. Clin. Oncol. (R. Coll. Radiol.) 27, 345–352 (2015).