

PREST: Pain REduction with bone metastases STereotactic radiotherapy: A phase III randomized multicentric trial

Francesco Cellini

Fondazione Policlinico Gemelli IRCCS

Stefania Manfreda

Fondazione Policlinico Gemelli IRCCS

Francesco Deodato

Fondazione di Ricerca e Cura Giovanni Paolo II

Savino Cilla

Fondazione di Ricerca e Cura Giovanni Paolo II

Ernesto Maranzano

Azienda Ospedaliera Santa Maria di Terni

Stefano Pergolizzi

Universita degli Studi di Messina

Fabio Arcidiacono

Azienda Ospedaliera Santa Maria di Terni

Rossella Di Franco

Universita degli Studi di Napoli Federico II

Francesco Pastore

Emicenter Napoli

Matteo Muto

Azienda Ospedaliera Moscati

Valentina Borzillo

Fondazione IRCCS Istituto Nazionale dei Tumori

Costanza Donati

Azienda Ospedaliero-Universitaria di Bologna Policlinico Sant'Orsola-Malpighi

Giambattista Siepe

Azienda Ospedaliero-Universitaria di Bologna Policlinico Sant'Orsola-Malpighi

Salvatore Parisi

Ospedale Casa Sollievo della Sofferenza

Antonia Salatino

Istituto per la Ricerca e la Cura del Cancro di Candiolo

Antonino D'Agostino

Humanitas Centro Catanese di Oncologia

Giampaolo Montesi

Universita degli Studi di Perugia

Anna Santacaterina

Azienda Ospedali Riuniti Papardo Messina

Vincenzo Fusco

IRCCS CROB, Rionero in Vulture

Mario Santarelli

Ospedale San Camillo de Lellis

Maria Antonietta Gambacorta

Fondazione Policlinico Gemelli IRCCS

Renzo Corvò

Universita degli Studi di Genova

Alessio Giuseppe Morganti

Azienda Ospedaliero-Universitaria di Bologna Policlinico Sant'Orsola-Malpighi

Valeria Masiello (✉ lucvalgio@hotmail.it)

Policlinico Universitario Agostino Gemelli <https://orcid.org/0000-0001-7589-7623>

Paolo Muto

Universita degli Studi di Napoli Federico II

Vincenzo Valentini

Fondazione Policlinico Gemelli IRCCS

Study protocol

Keywords: Bone Metastases, Pain Control, Simultaneous Integrated Boost, Randomised controlled Trial

Posted Date: July 8th, 2019

DOI: <https://doi.org/10.21203/rs.2.448/v2>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on October 28th, 2019. See the published version at <https://doi.org/10.1186/s13063-019-3676-x>.

Abstract

Background Palliative analgesic treatments represent an issue for clinical management and a challenge for scientific research. Radiotherapy (RT) plays a central role. Techniques such as stereotactic body radiotherapy (SBRT) were largely investigated in several phase 2 studies with good symptom response, becoming widely adopted. Still is lacking evidence from randomized, direct comparison of RT and SBRT. Methods/Design The PREST trial was designed as an interventional study without medicinal, randomized 1:1, open-label, multicentric, phase 3. Inclusion criteria: painful spinal bone metastases presenting pain level >4 (or >1 if assuming analgesic) at numeric rating scale (NRS); expected intermediate/high prognosis (superior to 6 months) according to the Mizumoto prognostic score; low spine instability neoplastic score (SINS) scores (<7); magnetic resonance imaging (MRI) assessment of the bulky lesion. Patients will be assigned to either standard conventional radiotherapy administering 4 Gy x5 fractions (fx) to whole involved vertebra or SBRT by intensity modulated radiotherapy with simultaneous integrated boost (IMRT-SIB) administering 7 Gy x3 fx (to the whole involved vertebra) + 10 Gy x3 fx on the macroscopic disease (Gross Tumor Volume -GTV). In the experimental arm, the GTV will be contoured by registration with baseline MRI. Discussion Primary endpoint is overall pain reduction, defined in term of variation between baseline and 3-month evaluation; pain will be measured by Numeric Rating Scale (NRS) score. Secondary endpoints include: pain control duration; retreatment rates (after a minimum interval of 1 month); local control assessed with RECIST Criteria; symptom progression free survival; progression free survival; overall survival and quality of life (at 0, 30 and 90 days). Accrual of 330 lesions is planned. Experimental arm is expected to improve overall pain response rates of 15% respect to standard arm (60% according to Chow et al 2012).

Background

The PREST trial (NCT03597984) includes patients with spinal bone metastases from solid tumours, which present an intermediate or high level prognosis (i.e.: >6 months) according to Mizumoto score (i.e.: classes A + B) [1]. These selected cases are often debated about to receive conventional analgesic radiotherapy or higher radiotherapy (RT) dose in order to better control symptoms. Technological improvement (e.g. stereotactic body radiotherapy -SBRT-)[2], [3] and advanced treatment planning (e.g.: intensity modulated RT -IMRT-)[4] can enhance RT treatments efficacy by dose escalation to offer more effective pain (and potentially disease) control without compromising organ at risk (OAR) toxicity.

The aim of this randomized multicentre prospective trial study is to evaluate the efficacy in term of pain control of an unconventional RT fractionation (delivered by SBRT) against the standard one. Inclusion criteria will enrol patients with intermediate-to-high prognosis (i.e.: superior to 6 months) according to the Mizumoto prognostic score [1] and structural stability (according to Spine Instability Neoplastic Score - SINS-) over the threshold of 7 [5]. Highlights of this study include: the high level of treatment customization through both accurate selection and ultra-conformed RT planning; the reduced number of sessions (i.e. three instead gold standard) to which the patient will undergo, potentially limiting the discomfort.

Methods

2.1 Aims

The PREST trial aims to assess whether RT for bone metastases administered by IMRT through a simultaneous integrated boost (SIB), can better control pain symptoms than fractionated standard three-dimensional conformal radiotherapy (3D-CRT). Providing a better pain control is the crucial issue for any new technique introduced in the palliative analgic setting. Multicentre recruitment will allow an even more precise assessment of the intervention, with the aim of demonstrating that implement RT in this setting is both feasible and safe among Centres. Secondary aims are to assess potential benefit on disease control, including oncological outcomes. Moreover, prolonged response at analgic RT can avoid retreatments, thus improving quality of life in these individuals, which is an important goal.

2.2 Overview of design

The PREST trial investigates the use of advanced technique to administer 7 Gy x 3 fx (to the whole vertebra) + SIB 10 Gy x 3 fx to the macroscopic lesion (Gross Tumor Volume – GTV) mandatory defined by magnetic resonance imaging (MRI), compared to 4 Gy x 5 fx on whole vertebra (standard arm) in patients with bone metastases by solid tumour and intermediate or high level prognosis >6 months according to Mizumoto score. Further details of the rationale for this design are provided in the discussion section of this article. Figure 1 shows a summary schema for the trial.

2.3 Participants

Participants entering the PREST trial are affected by solid tumour with histologically confirmed diagnosis and associated bone metastases. The estimated prognosis is intermediate or high (i.e.: >6 months) according to the Mizumoto prognostic score. Eligibility criteria are summarized in Table 1.

2.4 Registration

The PREST trial is promoted by Fondazione Policlinico Gemelli - IRCCS in Rome (Italy), in which the local Ethical Committee approved the protocol. Every interested centre will submit the protocol to its ethical committee for approval before respective accrual. After the approval the centre will receive dedicated electronic case report form (CRF). Eligible participants who have provided consent and meet the eligibility criteria are anonymously registered on the CRF, by assigning a numerical code.

2.5 Randomisation

Following the assessment for eligibility, after informed consent signing, eligible participants are randomised by phone to the promoting Centre. Participants undergo a blind randomisation. Randomisation uses minimization algorithms based on key prognostic factors, incorporating a random element. Patients are allocated in a 1:1 ratio to either gold standard radiotherapy treatment or interventional SIB radiotherapy treatment.

2.6 Radiotherapy

CT simulation will be carried out with custom immobilization support for single patient (Aquaplast® head mask and/or vacuum mattresses). Regarding target delineation, a co-registration with MRI will be performed on Velocity® application. The gross tumor volume (GTV) is defined as the visible lesion at MRI imaging. In the experimental arm, two volume will be defined: PTV1, including GTV + 2 mm isotropic margin; PTV2 including total vertebra + 2 mm isotropic margin. In the standard arm, a single volume will be contoured: PTV1 (total vertebra + 1 cm isotropic margin).

In the experimental arm, both spinal canal and spinal cord will be defined on MRI imaging, and their cranial and caudal margin will respectively be cranial margin of superior vertebra and caudal margin of inferior vertebra. Dose constraint limit for spinal canal will be $D_{max} < 15$ Gy, while for spinal cord will be considered both $D_{max} < 10$ Gy [6] and $D_{0.035}$. For cauda, dose constraints considered will be $D_{max} < 24$ Gy and Threshold Dose of 21.9 Gy to less < 5 cc [6]. Moreover, in the SIB cohort, PTVs coverage should be of 95% of prescribed dose at 95% defined volume. Major deviation for PTV2 will be $< 77\%$ of dose prescribed at 95% of volume, while minor deviation will be $< 84\%$ of prescribed dose at 95% of volume. For PTV1, major deviation will be defined as $< 79\%$ of prescribed dose at 95% of volume, while minor deviation will be $< 84\%$ of prescribed dose at 95% of volume.

Reporting of dose prescription will be according to ICRU 83 for experimental arm, while it will be according to ICRU 62 for standard arm. Furthermore, as security criteria, all the treatment plans validation will rely on QUANTEC and AAPM reports for organ at risk (OAR) constraints [7] [6].

2.7 Follow-up

Patients are assessed according to International Bone Metastases Consensus Working Party [8] Criteria. Pain control will be assessed at every visit according to IBMC criteria (Appendix 1). IBMC criteria are based on pain level and analgic opioid therapies on going. Pain level will be defined on 11-points Numeric Rating Scale (NRS) score. Moreover, NRS score subscales evaluated will be the sequent:

0: no pain [better outcome]

1-3: mild pain

4-6: moderate pain

7-10 severe pain [worse outcome]

Opioid therapies will be quantified according to Oral Morphine Equivalent Dose (OMED). Visit schedule is: 15 days, 30 days, 3 months, 6 months and 12 months after end of radiotherapy at every visit, patients underwent also Quality of Life measurement by QLQ-C15-PAL questionnaire [9]. Other outcomes that will be tested during follow up visits are rate of retreatment for non-responding patients; pain control duration; local control; symptom progression free survival; progression free survival; overall survival. Long-term passive follow-up data will be obtained from routinely-collected healthcare databases for at least ten further years.

For participants that are registered but do not go on to be randomised, active participation in the trial will end at that time. However, passive follow-up will continue via routinely collected healthcare datasets where consent for this has been obtained. The trial assessment schedule for each arm is aligned with standard practice where possible to ensure they can be implemented easily. This is balanced with the need to ensure appropriate monitoring of patients on trial treatment and assessment of outcome measures. The trial follow-up schedules are available in Appendix 2.

2.8 Toxicity management

Participants that experienced every radiotherapy-related severe toxicity, defined as Grade 3 Common Terminology Criteria for Adverse Events (CTCAE v4)[10], will be signalled in the study final report. For grade 1 and 2 toxicity, they are considered as normal in clinical practice, but they will be at the same reported.

Discussion

3.1 Outcomes

One-month pain control analysis will take place at 90 days from the end of RT of last patient. Primary and secondary outcome measures are available in Table 2.

Local control and overall survival will also be assessed as secondary outcomes in all participants for 10 years. The longer follow-up and large sample size associated with this analysis will enable any long-term benefits of a RT with IMRT-SIB to be realised, including number of retreatments. Consideration of rates of serious toxicity (and particularly serious myelotoxicities), as well as other secondary health outcomes, alongside the efficacy results will be particularly important in these analyses in order to provide a holistic assessment of the potential risks and benefits associated with different schedule of radiotherapy administration.

3.2 Statistical Considerations and Sample Size

Primary analysis will compare the response in terms of reduction of pain symptomatology from bone metastases, comparing the conformational radiotherapy (3D-CRT) administered in conventional fractionation versus IMRT-SIB. The study involves the enrolment of 330 patients divided into two groups of 165 patients for each of the two study arms. Arm A - standard: 4 Gy x 5 fx; arm B - sperimental: SIB 7 Gy x 3 fx (whole vertebra) + 10 Gy x 3 fx on the GTV (defined by MRI). The expected difference between the two treatments one-month pain control in terms of overall response rates is 15% more in the experimental arm compared to the standard arm (60%). The calculation of the sample size considered a 95% CI with a coefficient α of 0.05 and a drop-out rate of 10%.

3.3 Ethical Consideration

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2008, the principles of Good Clinical Practice (GCP) and Italian National Normative for clinical experimentation. At

the moment of the sign of the protocol, every investigator gives consent to procedure and instructions present into the Protocol and run the study according to GCP, Declaration of Helsinki and National Normative. Every amendment of the study will be registered and submitted to Ethical Commission. The PREST trial protocol and its material attached have been approved by Ethical Commission of Fondazione Policlinico Gemelli IRCCS of Rome (Italy). Every participant centre needs to submit PREST trial protocol to its Ethical commission, before enrolling patients.

3.4 Quality Assurance (QA)

Dose escalating in radiotherapy needs quality assurance procedure. In our study protocol we guarantee this procedure defining sequent key points:

Diagnostic imaging: MRI imaging before treatment for GTV contouring. A follow-up MRI imaging at three months is recommended but not mandatory;

Personalized set-up system: the use of personalized set-up systems is considered mandatory;

Planning verification: every single treatment plan needs to respect coverage and constraints indicated in the protocol; before enrolling, every single centre should participate to dummy studies to confirm its treatment planning possibilities;

Image-guided Radiotherapy (IGRT): Cone-beam daily acquisition before treatment is mandatory for assure a good IGRT. A 6-degree-of-freedom couch is recommended but not mandatory for set-up errors correction.

3.5 Final considerations

Palliative antalgic oncological treatments represent a serious problem for both clinical management and scientific research. However, they are involving an ever-increasing volume of patients due to the increased incidence of cancer in all its phases and the potential chronicity of illness linked to new therapies. The use of palliative RT treatments potentially involves up to 40% of patients in a radiation oncology Centre. RT is commonly used in palliative treatment for symptomatic bone metastases[11] being an effective treatment to improve symptoms and, consequently, quality of life (QoL) of these patients.

Ideally, this treatment should be as short as possible to re-direct them either to systemic therapies, or to home care or long-term care systems (e.g.: Hospice). In order to deliver a clinically effective dose in a short period, hypofractionated regimens must be used. SBRT is a technique of RT allowing to deliver a high equivalent biological dose in a highly conformed manner, with a favourable toxicity profile [3], generally in a few fractions (fx). The possibility of using special techniques such as SBRT in palliative antalgic setting for bone metastases has been investigated in several phase 2 studies, with good results in terms of symptom response[12] [13] [14] [15] [16] [17]. In order to better manage the toxicity profile of such hypofractionated regimens (mainly related to risk of vertebral fracture[18]) further studies [19] [20] have suggested the possibility of using a hypofractionated regimen over the entire bone compartment and going to over-dose with a stereotactic regimen only the macroscopically visible disease to the

instrumental examinations. In patients with more favourable prognosis, this regimen could improve the possible onset of acute and late complications, while increasing the RT dose to the bulky lesion.

Literature indications about the RT schedules to be preferred are available, although there is no globally coded and unique clinically applied therapeutic standard for prescription [21] [22]. The most commonly applied conventional radiation treatment schedules include: i) 8 Gy in 1 fx; ii) 20 Gy in 5 fx; iii) 30 Gy in 10 fx[23].

Although achieving similar rates of overall pain control, multiple fractionation schedules have been reported to provide better symptom control over time, lower rate of need for retreatment and improved bone stability profiles over the single fx approach, in case of patient's longer life expectation. Single fraction (8Gy) RT should be preferred for patients at inferior prognosis. Fractionated schedules are therefore often preferred for patients with better prognosis (i.e.: >6 months): the most widely adopted and supported by expert consensus is represented by 20Gy delivered in 5 fx of 4 Gy [24]. Routine use of prognostic scores to characterize life expectancy and define the most appropriate treatment regimen is very rarely applied in everyday clinical practice. To date, some randomized trials [12] [22] are underway investigating the role of SBRT compared to conventional approaches for these patients, not all of them through patient selection by validated prognostic scores. At the present time, a study by Guckenberger M. et al. (NCT02800551 – DOSIS RCT) is comparing directly compare the schedule administering 20 Gy in 5 fxs to SBRT-SIB given with 5 or 10 fr.

The Ethical Commission approval for PREST trial was reached on May 2018. Registration on [ClinicalTrial.gov](https://clinicaltrials.gov) was approved on July 2018. The PREST trial was granted for insurance costs by Fondazione Policlinico Gemelli IRCCS. The first patient is expected to be recruited on January 2019.

Conclusions

The PREST trial will provide insight on efficacy of an hypofractionated SBRT IMRT-SIB in pain control respect to gold standard fractionation. Highlights of this study include personalization by prognostic score's stratification, selection based on imaging-driven stability scores, ultra-conformed RT planning and lower number of RT sessions. To our knowledge, this is the first study design in its kind. Attended results will clarified if this high level of personalized approach would be practice-changing in the setting of metastatic bone patients.

Trial status

Patient recruitment not completed.

Declarations

Ethics approval and consent to participate. This trial design was definitively approved by Fondazione Polilclinico Gemelli IRCCS Ethical Committee on June 2018. The number of protocol was Prot. 8440/18

(20360/18) ID:1911.

Consent for publication: All the author gave their consent for publication of study protocol. No patients' consent is needed for this publication.

Availability of data and material: Not applicable.

Competing interests: The authors declare that they have no competing interests.

Funding: This trial will be conducted with no external funding. Patients' assurance would be financed by our Institute "Fondazione Policlinico Gemelli IRCSS".

Authors' contributions: FC analyzed literature and choice study design. VM provided protocol and paper elaboration and submission. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

Authors' information (optional)

Bibliography

- [1] M. Mizumoto *et al.*, «Prognostic factors and a scoring system for survival after radiotherapy for metastases to the spinal column: A review of 544 patients at Shizuoka Cancer Center Hospital», *Cancer*, vol. 113, n. 10, pagg. 2816–2822, nov. 2008.
- [2] H. Blomgren, I. Lax, I. Naslund, e R. Svanstrom, «Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients.», *Acta Oncologica*, vol. 34, n. 6, pagg. 861–70, 1995.
- [3] R. Correa, J. Salama, M. Milano, e D. Palma, «Stereotactic Body Radiotherapy for Oligometastasis: Opportunities for Biology to Guide Clinical Management.», *Cancer J*, vol. 22, n. 4, pagg. 247–56, ago. 2016.
- [4] C. Xu, «Intensity-modulated arc therapy with dynamic multileaf collimation: an alternative to tomotherapy.», *Phys Med Biol*, vol. 40, n. 9, pagg. 1435–49, set. 1995.
- [5] C. Fisher *et al.*, «A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group.», *Spine (Phila Pa 1976)*, vol. 35, n. 22, pagg. E1221-9, ott. 2010.
- [6] S. H. Benedict *et al.*, «Stereotactic body radiation therapy: The report of AAPM Task Group 101: Stereotactic body radiation therapy: The report of TG101», *Medical Physics*, vol. 37, n. 8, pagg. 4078–4101, lug. 2010.

- [7] S. M. Bentzen *et al.*, «Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An Introduction to the Scientific Issues», *International Journal of Radiation Oncology*Biological*Physics*, vol. 76, n. 3, pagg. S3–S9, mar. 2010.
- [8] E. Chow *et al.*, «Update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases», *International Journal of Radiation Oncology*Biological*Physics*, vol. 82, n. 5, pagg. 1730–1737, apr. 2012.
- [9] K. Lam *et al.*, «Predictive factors of overall well-being using the EORTC QLQ-C15-PAL extracted from the EORTC QLQ-C30.», *J Palliat Med*, vol. 16, n. 4, pagg. 402–8, apr. 2013.
- [10] «Common Terminology Criteria for Adverse Events (CTCAE)», pag. 147, 2017.
- [11] A. Furfari *et al.*, «Genetic biomarkers associated with pain flare and dexamethasone response following palliative radiotherapy in patients with painful bone metastases», *Annals of Palliative Medicine*, vol. 6, n. S2, pagg. S240–S247, dic. 2017.
- [12] J. M. van der Velden *et al.*, «Comparing conventional RadioTherapy with stereotactic body radiotherapy in patients with spinal metastases: study protocol for a randomized controlled trial following the cohort multiple randomized controlled trial design», *BMC Cancer*, vol. 16, n. 1, dic. 2016.
- [13] T. Murai *et al.*, «Intensity modulated stereotactic body radiation therapy for single or multiple vertebral metastases with spinal cord compression.», *Pract Radiat Oncol*, vol. 4, n. 6, pagg. e231-7, dic. 2014.
- [14] P. Braam, P. Lambin, e J. Bussink, «Stereotactic versus conventional radiotherapy for pain reduction and quality of life in spinal metastases: study protocol for a randomized controlled trial», *Trials*, vol. 17, n. 1, dic. 2016.
- [15] F. Deodato *et al.*, «Stereotactic radiosurgery (SRS) with volumetric modulated arc therapy (VMAT): interim results of a multi-arm phase I trial (DESTROY-2).», *Clin Oncol (R Coll Radiol)*, vol. 26, n. 12, pagg. 748–56, dic. 2014.
- [16] S. Ryu *et al.*, «RTOG 0631 Phase II/III Study of Image-guided Stereotactic Radiosurgery for Localized Spine Metastases: Phase II Results», *International Journal of Radiation Oncology*Biological*Physics*, vol. 81, n. 2, pagg. S131–S132, ott. 2011.
- [17] T. Sprave *et al.*, «Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy», *Radiotherapy and Oncology*, vol. 128, n. 2, pagg. 274–282, ago. 2018.
- [18] S. Faruqi *et al.*, «Vertebral Compression Fracture After Spine Stereotactic Body Radiation Therapy: A Review of the Pathophysiology and Risk Factors», *Neurosurgery*, vol. 83, n. 3, pagg. 314–322, set. 2018.

- [19] Y. K. Lee, J. L. Bedford, H. A. McNair, e M. A. Hawkins, «Comparison of deliverable IMRT and VMAT for spine metastases using a simultaneous integrated boost», *The British Journal of Radiology*, vol. 86, n. 1022, pag. 20120466, feb. 2013.
- [20] Q. Wu, S. Yoo, J. Kirkpatrick, D. Thongphiew, e F. Yin, «Volumetric arc intensity-modulated therapy for spine body radiotherapy: comparison with static intensity-modulated treatment.», *Int J Radiat Oncol Biol Phys*, vol. 75, n. 5, pagg. 1596–604, dic. 2009.
- [21] E. Chow, J. Wu, P. Hoskin, L. Coia, S. Bentzen, e P. Blitzer, «International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases.», *Radiotherapy and Oncology*, vol. 64, n. 3, pagg. 275–80, 2002.
- [22] E. Chow *et al.*, «Update of the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases», *International Journal of Radiation Oncology*Biology*Physics*, vol. 82, n. 5, pagg. 1730–1737, apr. 2012.
- [23] S. Rich *et al.*, «Update of the systematic review of palliative radiation therapy fractionation for bone metastases.», *Radiotherapy and Oncology*, vol. 126, n. 3, pagg. 547–557, mar. 2018.
- [24] R. Chow *et al.*, «Efficacy of multiple fraction conventional radiation therapy for painful uncomplicated bone metastases: A systematic review», *Radiotherapy and Oncology*, vol. 122, n. 3, pagg. 323–331, mar. 2017.

Tables

Table 1 - PREST Trial Eligibility Criteria

INCLUSION CRITERIA:

- Patients diagnosed with spinal bone metastases from solid, uncomplicated tumor
- Primary or secondary tumor histology related to the treatment lesion
- Patients aged >18 Years
- Obtained informed consent
- ECOG 0-2
- Symptomatic patients at the treatment site (NRS \geq 4)
- Symptomatic patients at the treatment site (NRS 1-3) assuming opioid therapy ongoing since more than 3 days
- Spine Instability Neoplastic Score (SINS) <7
- Prognosis >6 months according to Mizumoto Prognostic Score (i.e. Class A and B)
- Spinal metastases verified at MRI including the sites to be enrolled
- No more than 3 non-contiguous spinal segments (e.g. Separated by at least two metamers) involved in the study

EXCLUSION CRITERIA:

- Impossibility to assign specific NRS for each CTV to be enrolled
- Impossibility to express autonomous consent to therapies
- Pregnancy
- Patient in Hospice or with prognosis <6 months
- Unavailability forecast for follow-up
- Absence of MRI pre-treatment study
- Impossibility to maintain the treatment position for SBRT
- Previous radiotherapy at the same site or at the level of adjoining metameres (higher or lower than the one to be enrolled)
- Previous radiometabolic therapy
- Previous enrolment of the same patient for 3 irradiated lesions
- Epidural compression of the spinal cord or of the cauda equina
- Injuries affecting >25% of the medullary canal and/or a distance <5 mm from the medulla or from the cauda
- Injuries with indication of surgical stabilization
- Chemotherapy or target therapy within the previous 7 days and 7 days after SBRT

Table 2 – Endpoint definitions and measurement

PRIMARY OUTCOME MEASURE

Pain control [EFFICACY and PAIN] [Time Frame: 3 month]

Overall Pain control measured according to IBMC (Complete response + partial response events)

SECONDARY OUTCOMES MEASURES

· Pain control duration [EFFICACY and PAIN] [Time Frame: 12 months after end of radiotherapy]

Interval from the end of the RT to the relapse of the symptom

· Rate of retreatments [EFFICACY] [Time Frame: Time Frame: 12 months after end of radiotherapy]

Interval from the end of the RT to the start of retreatment

· Local control [EFFICACY] [Time Frame: At 3, 6 and 12 months from the end of radiotherapy]

Control of local disease with diagnostic exams according to RECIST 1.1 Criteria

· Symptom Progression Free Survival (SPFS) [EFFICACY and PAIN] [Time Frame: 12 months after end of radiotherapy]

Interval from the end of radiotherapy and progressive disease with symptoms according to the criteria of Chow et al. in 2012

· Progression-free survival - PFS [EFFICACY] [Time Frame: 12 months]

Interval from the end of radiotherapy and new disease progression

· Overall survival [EFFICACY] [Time Frame: 12 months]

Interval between the end of radiotherapy and death

· Quality of Life (QoL) [EFFICACY and QUALITY OF LIFE] [Time Frame: At first visit, 1 month and 3 months after the end of radiotherapy]

QoL score according to European Organization for Research and Treatment of Cancer (EORTC): QLQ-C15-PAL

Figures

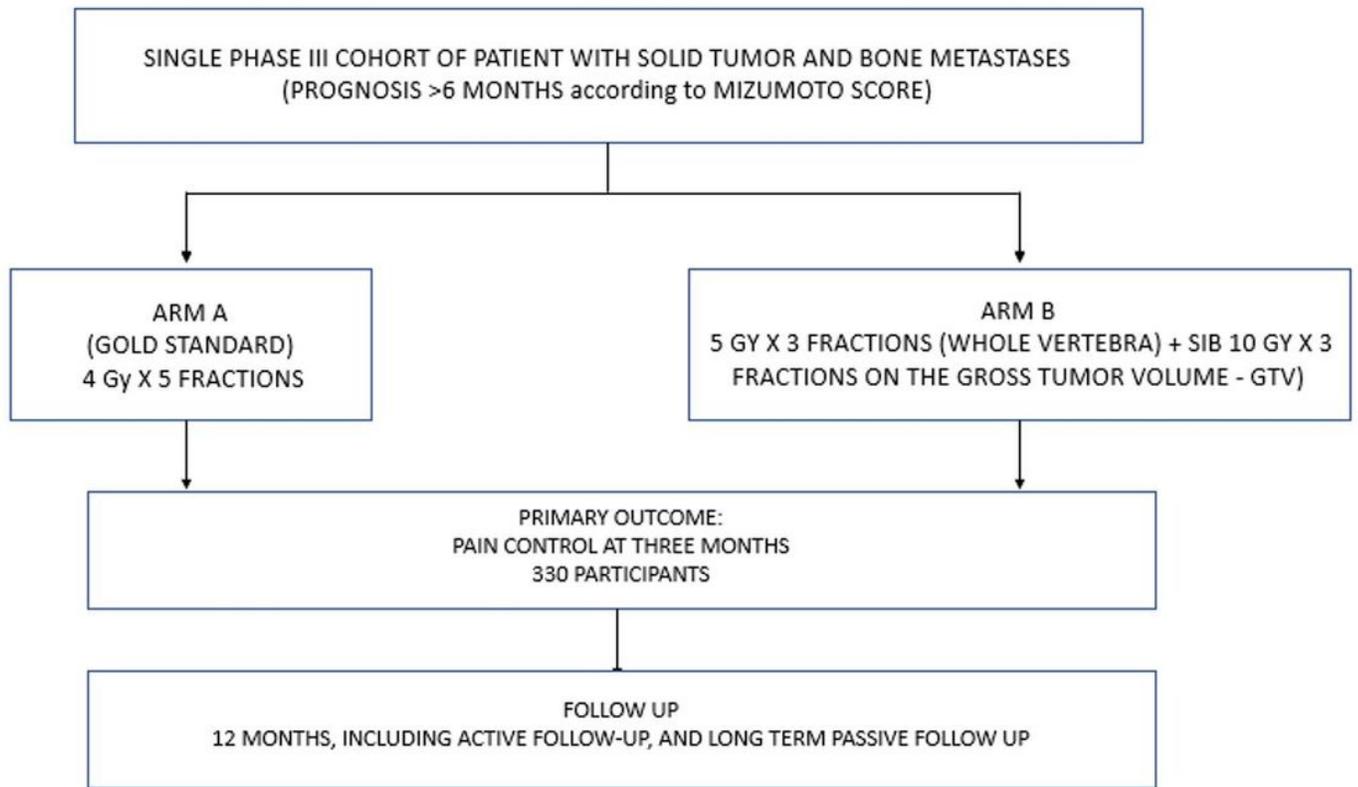


Figure 1

PREST Trial (NCT03597984) schema

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.docx](#)
- [supplement2.pdf](#)
- [supplement3.doc](#)