Stereotactic body radiotherapy followed by surgical stabilization for patients with painful unstable spinal metastases: First-in-man study according to the IDEAL recommendations

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Primary Objective To assess the feasibility and safety of combining stereotactic body radiotherapy and pedicle screw fixation in a 48-hour window for the treatment of painful unstable metastases of the thoracic and/or lumbar spine.Secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Interventional

Summary

ID

NL-OMON42087

Source
ToetsingOnline

Brief title
BLEND study

Condition

- Bone disorders (excl congenital and fractures)
- Metastases
- Bone and joint therapeutic procedures

Synonym
metastatic spine tumor, spinal metastases

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Palliative, Spinal metastases, Stereotactic Body Radiotherapy, Surgical stabilization

Outcome measures

Primary outcome

The main outcome of this study is safety of the combined procedure, defined as

grade 3 or higher treatment-induced toxicity according to CTC-AE 4.0 as a

result of the procedure within 60 days after the surgery.

Secondary outcome

The secondary study endpoints of this study are:

* Pain response to combined therapy according to the International Bone

Metastases Consensus Endpoints for Clinical Trials (Chow 2002; Chow 2012b)

* Duration of pain relief, as measured by the Brief Pain Inventory (BPI)

(Cleeland 1994)

* Length of stay in the hospital

* 30-days mortality

* Neurological detoriation, defined as detoriation of more than one ASIA scale

* Evaluation of quality of life, as measured by the

o EQ-5D

o EORTC QLQ-C15-PAL

o EORTC QLQ-BM22

o Spine Oncology Questionnaire

* Overall survival

Study description

Background summary

Bone metastases are a frequent distant manifestation from different types of malignant tumors, especially in patients with breast or prostate cancer. Bone metastases affect 60-75% of these patients, and 30-40% of patients with lung or kidney cancer (Coleman 2006, Hage 2000, Nguyen 2011). The spinal column is the most common location among osseous sites for metastatic deposits: between 30 to 70% of the patients with cancer have evidence of spinal metastases at autopsy (Falicov 2006). The exact incidence of bone metastases is unknown, but is has been estimated that 16,000 to 22,000 people in the Netherlands die from bone metastases each year (Nguyen 2011).

Pain is a common and devastating consequence of bone metastases. It strongly interferes with quality of life and daily functioning and often requires hospitalization. While similar to other bone metastases in terms of bone involvement and pain relief after external beam radiation therapy (Howell 2013), spinal metastases have a unique clinical consideration. Spinal metastases can present with epidural compression caused by a soft tissue mass at the paraspinal area, a compression or a burst fracture. Therefore, patients with spinal metastases can have severe back pain with (impending) associated neurological problems. When neurological problems occur, the performance status of these patients can further compromise.

Survival prospects vary greatly and range from several months in patients with multiple organs involved, to more than 5 years for patients with exclusively skeletal metastases. The survival of patients with bone metastases has substantially improved as a result of effective systemic chemotherapy, immunotherapy and radiotherapy (Fisher 2010, Nguyen 2011). With prolongation in survival, the main challenge is to maintain the quality of the patient*s remaining life.

Spinal instability

The concept of spinal instability is critical in the management of spinal metastases. Spinal instability as the result of a neoplastic process differs considerably from high-energy traumatic injuries in the pattern of bony and

ligamentous involvement, potential for healing, and bone quality. Therefore, spinal metastases require a specific and different set of criteria for stability assessment. The Spinal Oncology Study Group (SOSG), which consists of spine oncology experts, defined spinal instability due to metastatic disease as **loss of spinal integrity as a result of a neo-plastic process that is associated with movement-related pain, symptomatic or progressive deformity and/or neural compromise under physiological loads* (Fisher 2010).

To assess spinal instability due to metastatic disease the SOSG developed the Spinal Instability Neoplastic Score (SINS) (Fisher 2010, Fourney 2011), to provide a tool to guideline referrals to appropriate oncology specialists (e.g. surgeons or radiation oncologists). The SINS is the sum of six easily assigned radiographical and clinical parameters, resulting in a score ranging from 0 to 18 (Fisher 2010). The total score is divided in three categories of stability; stable (0 to 6 points), potentially unstable (7 to 12 points), and unstable (13 to 18 points). Surgical consultation is recommended for patients with a score of * 7.

The cervical spine is unique from other regions of the spine because of the generous mobility in all planes, stability role for the head, neighboring anatomy and a spectrum of anatomic and biomechanical variability throughout the region (specifically O-C1, C1-C2, C3 *C7 and finally C7-T1) compared to the thoracic, lumbar and sacral spine. In the current study, we therefore focus on thoracic and lumbar metastases only.

Current treatment of thoracic and lumbar metastases

A major goal in the treatment of metastatic disease is the preservation or restoration of spinal stability, since spinal instability increases the risk on neurological compromise (Falicov 2006, Weber 2011). When patients are closely evaluated, loss of neurological function and ambulatory status due to spinal instability is preventable. This is important since loss of neurological function and ambulatory status before treatment is correlated with a poor prognosis (Rades 2008, Harel 2010). Early identification of these lesions is necessary, as prompt referral and early surgical intervention can improve outcomes and survival for patients with spinal metastases (Weber 2011). Surgical decompression and stabilization in patients with spinal metastatic disease is now feasible and is supported by strong evidence, due to advances in biomaterials, imaging and surgical techniques (Weber 2011, Falicov 2006, Thomas 2006).

Another major goal in the treatment of spinal metastases is to achieve pain relief. Regardless of localization, primary loco-regional treatment for most patients is low dose single-fraction external beam radiation therapy (EBRT) (Gerszten 2000, Lutz 2011). Although radiotherapy is effective in achieving pain relief in most patients, 30-40% of patients do not obtain any pain relief and complete response even occurs in only 30% of responders (Sze 2004, Chow

2012). It is not completely understood why some patients respond well to radiotherapy and others do not. We hypothesize that metastatic bone pain, if predominantly caused by mechanical instability of the spine, responds less well to radiotherapy than metastatic bone pain caused by local tumor activity. Local tumor activity may consist of direct invasion of tumor cells, periosteal stretching, or the release of inflammatory mediators (Coleman 2006, Mercadante 1997; Nguyen 2011) On the other hand, disruption of the homeostasis between osteoclasts and osteoblasts can cause loss of mechanical integrity leading to painful (micro-) motion within the vertebrae. As affected vertebrae weaken and become compressed, adjacent muscles may spasm attempting to maintain stability (Nguyen 2011; Tomita 2001; Vakaet 2004). Besides these compression fractures, metastases may also cause burst fractures. Tumors are more likely to cause burst fractures if they are located in the posterior portion of the centrum, the region most sensitive to changes in centrum pressurization, due to the *bean* shape of the vertebra (Weber 2011). Probably, both generators of pain (local tumor-related and mechanical) are present simultaneously in spinal metastases although their relative contribution to pain may vary.

Therefore, painful unstable spinal metastases may benefit from surgical stabilization prior to EBRT. Ghogawala et al (2001) demonstrated a relation between pre-operative conventional radiotherapy and the rate of wound complications. Therefore, a minimum two-week interval between surgery and irradiation is currently considered necessary to avoid wound complications in the postoperative phase. Yet, this study was a retrospective chart review involving patients from 1970 till 1996 who underwent surgery for spinal cord compression. The systematic review of Itshayek et al (2010) reported a range of 11% to 50% for major wound complications in patients who had radiotherapy before surgical intervention. Yet, this included three retrospective studies and two very small prospective studies. In a recently conducted prospective study on adverse events in patients who underwent emergent spinal surgery for spinal metastatic disease, did not show a significant relation between conventional radiation therapy and wound complication rate (Dea 2013). Advancements in radiation treatments, surgical techniques and post-operative care may account for these differences in influence on wound complications.

Advantages of combining two effective treatments

When more advanced radiotherapy planning and delivering techniques are employed (for example, stereotactic body radiotherapy (SBRT)), exposure of the vulnerable surgical site to radiation can largely be avoided. Therefore, the interval between surgical stabilization and radiotherapy may be shortened or even eliminated. As a result, the patient may experience the analgesic effect from irradiation two weeks earlier and both interventions can be planned and performed in a single, shorter hospital admission period. Both irradiation and surgical techniques have been proven to be safe and effective in isolation and are commonly practiced in our hospital. To date, no information on feasibility or safety is available when the two modalities are combined in a 48-hour window.

In 2009, the IDEAL recommendations were introduced (McCulloch 2009). These recommendations provide direction for reporting and evaluation of innovative surgical procedures which are being undertaken for the first time, and for adoption of new procedures in other centers and by other teams. IDEAL is an acronym for the five stages that complex interventions go through, namely Innovation, Development, Evaluation, Assessment and Long term evaluation.
In stage 1 (Innovation or Idea), the new procedure is used in humans for the first time. The initial patients are usually highly selected on an individual basis. Feasibility, duration and complication are reported for a small number of patients. These reports should contain clear anonymous details of the patient, their condition, the rationale and background for use of the procedure, exactly what was done, and adequate details of relevant outcomes.
Progression to stage 2a (Development) is justified by successful implementation of the new procedure in several consecutive patients without serious adverse events. With practitioners maintaining confidence, the new approach becomes a practical alternative to the standard procedure. Reporting during this stage needs to include: selection criteria and proportion of eligible patients selected; a clear description of the procedure and each modification, with timing; and relevant outcomes, with recognized standard definitions of important categories, such as specific complications.
Transition to stage 2b (Evaluation or Exploration) is justified by improvements in procedure times and the avoidance of adverse events, with major refinements of the method completed. This stage consists of a larger series of consecutive patients. Stage 3 (Assessment) aims to answer the essential question: Is the clinical efficacy of this intervention better than the standard treatment? Comparative studies, preferably with a randomized component, are favored. Stage 4 (Long term evaluation) starts when the effectiveness of new intervention has been demonstrated and the intervention is implemented in daily clinical practice. The current study is a combination of stage 1 (Idea) and stage 2a (Development).

Study objective

Primary Objective

To assess the feasibility and safety of combining stereotactic body radiotherapy and pedicle screw fixation in a 48-hour window for the treatment of painful unstable metastases of the thoracic and/or lumbar spine.

Secondary Objectives

The secondary objectives of this study are:

* Measurement of pain response to combined therapy
* Measurement of duration of pain relief
* Measurement of rapidity of pain relief
* Length of stay in the hospital

* 30-days mortality
* Neurological detoriation
* Evaluation of quality of life
* Overall survival

Study design

This study will be a prospective development study (IDEAL stage 1 and 2a) (McCulloh 2009) performed at the University Medical Center Utrecht (UMCU). A group of 13 patients with (impending) spinal instability requiring radiation therapy and surgical intervention will be studied to assess the safety and feasibility of combining stereotactic body radiotherapy ensued by surgical stabilization within a 48-hours window. Patients will be recruited from the outpatient clinics of Oncology; Radiation Oncology; Neurology; Neurosurgery and Orthopedic Surgery. Adverse events will be scored using the SAVES [Street 2012] form (appendix) and according to CTC-AE 4.0

Intervention

Shortened time window
Stereotactic body radiotherapy and surgical stabilization will be performed within a 48-hour time window instead of today*s standard of care of two weeks between surgical stabilization and external beam radiotherapy.

Stereotactic Body Radiotherapy
Stereotactic body radiotherapy will be used to irradiate the spinal metastases instead of today*s standard of care of external beam radiotherapy. Stereotactic body radiotherapy (SBRT) is a radiation technique that delivers high-dose radiation precisely to the spinal metastases in a single or a few fractions. It does so using a combination of image-guidance, to remediate the inter- and intra-fraction motion, and advanced inverse treatment planning algorithms to achieve highly conformal dose distributions (Sahgal 2008, Sahgal 2013).

In a first step, patients will undergo SBRT on a priority base within 48 hours before surgery. Patients undergo a planning CT scan and MRI scan in treatment position. Patients will receive high dose, single fraction radiotherapy consisting of 18 Gy to the metastases exclusively. However, adjacent physiologic appearing bone marrow spaces may harbor subclinical disease and could potentially serve as a source for a local recurrence as reported from prospective data (Cox et al 2012). Therefore, the bony compartment will receive the conventional low dose of 8 Gy * in order to treat subclinical disease * whereas the metastasis will receive 18 Gy. To deliver this high dose safely, accurate treatment planning and positioning is needed. Treatment planning is performed on the pre-treatment CT and MRI data that are mutually registered to yield information on all relevant structures for planning assessing dose distribution using volumetric modulated arc therapy. MRI is used to delineate

the gross tumor volume (GTV), clinical target volume (CTV), planned target volume (PTV) and the organs at risk (OAR). With the aid of T1 weighted, T2 weighted and diffusion weighted imaging sequences, it is possible to delineate the GTV accurately. Dose constraints are set for the OAR and other anatomical constraints based on institution specific guidelines. These constraints are of primary concern. So, if necessary, dose delivery to the GTV will therefore by limited in order to meet these criteria.

For all patients, online cone beam CT (CBCT) data will be acquired with the patient in treatment position on the treatment table just before start of the treatment. The CBCT data yields the exact position of the bony anatomy and is also registered to the pre-treatment CT and MRI data. Given the fact that the target volume is bony anatomy, the actual re-positioning data is determined for all the pre-treatment defined relevant structures for safe dose delivery. Alignment of the patient or, more specifically, the tumor volume, with pre-treatment plan will be performed. After correction, a second CBCT will be performed. A third CBCT will be taken post-treatment to document stability of the target during treatment.

Study burden and risks

Pedicle Screw fixation
Pedicle screw fixation is a commonly performed procedure to achieve spinal fusion or stabilization for the treatment of spinal trauma, spinal deformity, degenerative disease and spinal neoplastic processes. It has gained widespread acceptance and its safety is has been well studied (Lonstein 1999, Jutte 2001, Gautschi 2011). Pedicle screw associated complications are rare, with 2.4% overall complication rate reported in a study of 875 patients with 4790 screw placements (Lonstein 1999). A recent systematic literature review of 35 630 pedicle screws showed a complication rate of 0.18% per pedicle screw for dural tears, 0.19% per pedicle screw for nerve root irritation, 0.2% per pedicle screw for pedicle fracture, one case of pneumothorax, one case of pleural effusion and no cases of vascular injuries (Gautschi 2011). These complications are mostly associated with the insertion of the pedicle screws, this recent literature study reported 92.2% screw placement accuracy. Yet, not all-inaccurate placed screws are symptomatic or clinically relevant.

Stereotactic body radiotherapy
Stereotactic body radiotherapy has evolved as an innovative treatment for the treatment of spinal metastases. Treatment of spinal metastases with SBRT is associated with risks for the patient [Lutz 2011]. In contrast with the risk low risk on late toxicities with external beam radiotherapy, ten cases of radiation myelopathy have been described associated with SBRT, 5 without prior radiotherapy and 5 cases after re-irradiation [Sahgal 2009A, Sahgal 2009B]. Furthermore, SBRT has been associated with new or progression of vertebral compression fractures, with a study from Memorial Sloan Kettering reporting a fracture progression in 38% [Rose 2009]. As a consequence patient may require

additional intervention such as surgical stabilization [Lutz 2011]. Yet, in our study the decision for surgical stabilization is already made based on the imaging and clinical parameters.
Finally, pulmonary and esophageal side effects may occur with external beam radiation therapy although they are rare. One case of fatal esophageal necrosis and one case bronchial stenosis has been described after SBRT in a series of 119 patients [Gomez 2009]. Lack of knowledge about the radiation tolerance of normal tissue has highly contributed to these toxicities. The incidence of radiation myelopathy after SBRT has already decreased due to different research projects, which have resulted in guidelines for the maximum radiation dose for the spinal cord[Lutz 2011].

Radiation therapy and Surgery
Ghogawala et al (2001) demonstrated a relation between pre-operative conventional radiotherapy and the rate of wound complications. Therefore, a minimum two-week interval between surgery and irradiation is currently considered necessary to avoid wound complications in the postoperative phase. Yet, this study was a retrospective chart review involving patients from 1970 till 1996 who underwent surgery for spinal cord compression.The systematic review of Itshayek et al (2010) reported a range of 11% to 50% for major wound complications in patients who had radiotherapy before surgical intervention. Yet, this included three retrospective studies and two very small prospective studies. In a recently conducted prospective study on adverse events in patients who underwent emergent spinal surgery for spinal metastatic disease, did not show a significant relation between conventional radiation therapy and wound complication rate (Dea 2013). Advancements in radiation treatments, surgical techniques and post-operative care may account for these differences in influence on wound complications. To our knowledge no studies describe the relationship between pre-operative stereotactic body radiotherapy and complications.

SBRT and Surgery
Being a first-in-man evaluation, there is no data available about the possible complications and risk on these complications for the combination of SBRT and surgical intervention within 48 hours. By performing preoperative high-dose irradiation (SBRT), we may experience problems in the irradiated and operated field (delayed wound healing, infection of implants). However, SBRT allows high precision irradiation, with sparing of the surrounding tissues, reducing the risk of postoperative problems in the irradiated area. Also, both treatments separately have proven to be safe. Given the huge potential benefit for the patient, we feel the experiment is justified.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Painful radiosensitive metastases from solid tumors in the thoracic or lumbar spine needing surgical stabilization
* Histologic proof of malignancy
* Radiographic evidence of spinal metastases
* Karnofsky performance status > 50
* Age > 18 years
* Written informed consent

Exclusion criteria

* Multiple spinal metastases necessitating bridging more than five vertebral levels during surgery
* Previous surgery or radiotherapy to index lesion
* SBRT cannot be delivered (Bilsky score 2 and 3 [Bilsky 2010])

* Neurological deficits (ASIA C, B or A)
* Partial neurological deficits (ASIA D) with rapid progression (hours to days)
* Inability to lie flat on table for SBRT
* Non-ambulatory patients
* Patient in hospice or with < 3 months life expectancy
* Medically inoperable or patient refused surgery

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-06-2015
Enrollment:	13
Type:	Actual

Ethics review

Approved WMO Date:	05-02-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Not approved Date:	19-04-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL51405.041.14